Text

Description automatically generated

Significance of nuclear Insulin-like Growth Factor-1 Receptor in Cancer

London South Bank University

MRes in Human Sciences

Mavra Manzar, BSc (Hons) Bioscience

Student Number: 3532465

Supervisor: Dr. Eiman Aleem

September 2020

**Preface**

This present study was carried out at London South Bank University. The focal point of the study was my passion to learn more about cancer and to have a better understanding of nuclear insulin-like growth factor receptor 1 association with oncology.

This study was planned to be an experimental study, in which I was supposed to conduct co-immunoprecipitation and Western blot experiments, as well as kinase assay, in order to validate previous bioinformatic results by Dr. Aleem’s team. However, the major problem that I faced was due to the current Covid-19 pandemic. It was not possible to go to the lab due to the lockdown. We, therefore, decided to do a literature review instead.

The objective was to make this study as accurate as possible. I apologize, in advance, for any error found which were certainly not knowingly made. Above all, the purpose of the study will be served if it becomes source of knowledge for general public.

**Acknowledgement**

This project has been a genuine challenge to me. As both the discipline of cancer, nuclear IGF-1R and to lead a precise literature review were new to me. I persistently learned new things, and I am pleased with the knowledge and aptitudes I was able to develop with the course of time.

For the endless support I am grateful to my supervisor Dr. Eiman Aleem. I thank her for not giving up on me, for giving me the opportunity to carry the research of my interest and pushing me throughout the process. She was constantly involved in many; analytical stages of the review and I learned a lot from her expertise in this field.

On a personal note, I want to thank my parents for the countless prayers and my dad for believing in me. I want to thank my mother for being there for me in my lowest days, gave me strength and courage. Special thanks to Masab, Ahsan and Maryam and my friends as they have patiently helped in the successful completion of this work, by sharing their leisure times and knowledge with me.

**Table of Content**

Abstract--------------------------------------------------------------------------------------------------------------5

Abbreviations-------------------------------------------------------------------------------------------------------6

List of figures and tables----------------------------------------------------------------------------------------9

1. Introduction ---------------------------------------------------------------------------------------------------10

1.1 Rationale

1.2 Research question

1.3 Objectives

1.4 Background

* + 1. History of IGF-1R
    2. Receptor tyrosine kinase
    3. IGF receptors
    4. IGFs and IGFBPs in cancer
    5. Structure of IGF-1R
    6. IGF-1R Signalling pathway
    7. Functions of IGF-1R in health

2. Methods --------------------------------------------------------------------------------------------------------23

3. Results ---------------------------------------------------------------------------------------------------------26

3.1 Failure of IGF-1R clinical trials

3.2 IGF-1R expression in human cancer

3.3 Targeting IGF-1R in human cancer

3.4 IGF-1R and drug resistance

3.5 Nuclear IGF-1R

3.6 Potential functions of nIGF-1R in cancerous cells

3.7 Nuclear IGF-1R in cancer

3.8 Nuclear accumulation of IGF-1R in non-cancerous cells

4. Discussion------------------------------------------------------------------------------------------------------69

5. Conclusion and Future Directions------------------------------------------------------------------------74

6. References-----------------------------------------------------------------------------------------------------75

**ABSTRACT**

**Background:** Insulin-like growth factor receptor-1 (IGF-1R) overexpression is associated with cancer, it promotes cell migration, invasion, and proliferation. IGF-I and IGF-II ligands bind to IGF-1R and activate the signal transduction pathway. Such significant signalling pathways are essential to target in cancer. The preclinical targeting of IGF-1R was successful, however, it failed in the clinic. Recently, it has been discovered that plasma membrane IGF-1R translocates to the cell nucleus. In various types of cancer and non-cancer cells, IGF-1R accumulates in the nucleus but it is not certain whether IGF-1R nuclear translocation have alternative functions in the human body. Whilst nuclear IGF-1R topic is fairly new, the present study brings together the available research and literature published in this field.

**Aims:** IGF-1R-targetting agents include monoclonal antibodies, small molecule tyrosine kinase inhibitors and ligand binding antibodies which entered the clinical trials, however, despite the successful early phase trials of IGF-1R, the clinical trials of these inhibitors failed to show clinical benefit in cancer patients. The aim of this study is to gain an understanding of reasons behind the failure of these clinical trials. Cell membrane IGF-1R localizes to the cell nucleus predominantly in various types of cancer and in non-cancer cells as well. This study aimed to investigate the mechanism of IGF-1R nuclear translocation, nuclear IGF-1R binding proteins and potential functions of nuclear IGF-1R.

**Results:** The reasons behind the clinical failure of IGF-1R inhibitors include high homology between insulin and IGF-1R in their amino acid sequence, structure, function, and parallel growth and survival pathways, thus causing adverse side effects in patients. Another significant reason for the failure were absence of predictive biomarkers from the design of anti-IGF-1R network clinical trials. Our study demonstrates that full-length IGF-1R translocates to the nucleus. IGF-1R accumulates in the nucleus via SUMOylation and clathrin-mediated endocytosis. In addition to the canonical IGF-1R mediated functions, IGF-1R regulates additional pathways in the nucleus including transcriptional regulation and DNA damage.

**Conclusion:** The similarity that exists between IGF-1R and insulin makes it rather complex for inhibitors to target IGF-1R in cancer. Integration of biomarkers is required in all clinical investigation. IGF-1R predominately accumulates in nucleus of cancer cells, such as breast cancer, renal cancer, prostate cancer, and various types of sarcomas. Most importantly, targeting nuclear IGF-1R may successfully lead to target human cancer. The precise mechanism and functions of nuclear IGF-1R are not fully elucidated. In future, a comprehensive analysis is required to understand the functions of nuclear IGF-1R in cancer, its binding proteins which retains IGF-1R in the nucleus, and ways to target this network to overcome resistance to targeted therapies in cancer.

**Abbreviations**

ALK Anaplastic lymphoma kinase

AML Acute myeloid leukaemia

AR Androgen receptor

Areg Amphiregulin

ASO Antisense oligonucleotide

DDT DNA damage tolerance

DFS Disease-free survival

DSB Double strand break

EEA1 Early endosome antigen 1

EGFR Epidermal growth factor receptor

EMSA Electrophoretic mobility shift assay

ER Oestrogen receptor

FACS Fluorescence activated cell sorting

GD Graves’ disease

GH Growth hormone

GHRH Growth hormone-releasing hormone

HCC Hepatocellular carcinoma

HEK Human embryonic kidney

HR Homologous recombinant

IGF Insulin-like growth factor

IGFBP Insulin-like growth factor binding proteins

IGF-1R Insulin-like growth factor receptor 1

IHC Immunohistochemistry

IR Insulin receptor

IRS-1 Insulin receptor substrate-1

LEF1 Lymphoid enhancer-binding factor 1

mAbs Monoclonal antibodies

MAPK Mitogen-activated protein kinase

MS Mass spectrometry

mTORC Mechanistic target of rapamycin complex

NHEJ Non-homologous end joining

nIGF-1R Nuclear Insulin-like growth factor receptor 1

NLS Nuclear localization sequence

NPC Nasopharyngeal carcinoma

NSCLC Non-small cell lung carcinoma

OS Overall survival

PCNA Proliferating cell nuclear antigen

PDGFR Platelet-derived growth factor receptor

PFS Progression free survival

PI3K Phosphoinositide 3-kinase

PIP3 Phosphatidylinositol (3,4,5)-trisphosphate

PKB Protein kinase B

PR Progesterone receptor

RCC Renal cell carcinoma

RMS Rhabdomyosarcoma

RTK Receptor tyrosine kinase

SMS Somatostatin

SS Synovial sarcoma

STS Soft tissue sarcoma

SUMO Small ubiquitin-like modifier

TDLU Terminal duct lobular unit

TSS Transcription start site

VEGFR Vascular endothelial growth factor

**List of figures**

Figure 1. Receptor tyrosine kinase downstream signalling pathways……………………………………………………………………………………...……...13

Figure 2. Diagrammatic representation of IGF-1R and IR ……………………………………………………….………………………………………….…….14

Figure 3. The structure of IGF-1R…...…………………………………………………………….18

Figure 4. IGF-1R signalling pathway …………………………………………………...………...20

Figure 5. IGF-1R signalling pathway and drug resistance mechanism………....…………….38

Figure 6. IGF-1R nuclear translocation pathway…………………………………….…………. 49

Figure 7. Replication stress events……….……………………………………………………....53

Figure 8. EMSA displays the IGF-1R: DNA interaction….………………….………..…………60

Figure 9. Western blot analysis of nIGF-1R in osteosarcoma samples……………………….62

**List of tables**

Table 1. Upregulation and downregulation of SUMO proteins in cancer ………………….…43

Table 2. Nuclear proteins that are associated with nIGF-1R ……………………….…………55

Table 3. Association of nIGF-1R with advanced stages of prostate cancer………………….57

Appendix 1: Clinical trials involving IGF-1R and Cancer………………………………………101

Appendix 2: Primary research articles included in the study………………………………….143

**1. Introduction**

The insulin-like growth factor (IGF) is a hormone-like molecule that plays a key role in childhood growth and manifest anabolic effects in adults. The data gathered throughout the most recent three decades have evidently shown that IGF is essential in tissue growth and development. Importantly, high circulatory levels of IGF leads to potential risk of developing cancer (Cardillo et al., 2003; Sachdev et al., 2003). IGF signalling pathway activation is dependent on the effective interaction between the two ligands: IGF-I/IGF-II and membrane bound receptor IGF-1R (Pollak et al., 2004). The insulin-like growth factor receptor 1 (IGF-1R) activation is important for engendering the stimulation of mitogenesis effects of IGF signalling system. In normal human tissues, IGF-1R activation is regulated at different levels, but overexpression of IGF-1R can over-activate its signalling pathway and develop cancer (Pollak et al., 2004).

IGF-1R is a transmembrane receptor that belongs to the receptor tyrosine kinase (RTK) family. It is a tetrameric receptor comprised of the 2 subunits: α and β subunit. It induces its signalling pathway by activating mitogen-activated protein (MAP) kinase and phosphatidylinositol 3-kinase (PI3K)–Akt signalling pathway (Sehat et al., 2010), resulting in proliferation, transcription, and survival. This is known as the canonical IGF-1R signalling pathway, which is well addressed in the literature. IGF-1R preclinical and clinical studies will be discussed in the study and reasons of its failure. However, the focus of the study is the recent and interesting addition to the IGF-1R research field which is the translocation of IGF-1R to the cell nucleus.

* 1. **Rationale**

Evidence has recently accumulated showing that IGF-I ligand triggers the modification of IGF-1R by small ubiquitin-like modifier protein–1 (SUMO-1). The process of SUMOylation (Sehat et al., 2010) and clathrin-mediated endocytosis are imperative to induce IGF-1R nuclear localization (Aleksic et al., 2010). The functions of the IGF-1R in the nucleus are not yet fully elucidated. It has been reported that the IGF-1R binds to DNA and regulates transcription (Sehat et al., 2010). Additionally, IGF-1R has been shown to interact with nuclear proteins. However, we are still far from understanding the functions of the IGF-1R in the nucleus in health or in disease, specifically in cancer. So far, there are very few published review articles about the nuclear IGF-1R. For this reason, the present study is essential to critically analyse the literature about nuclear IGF-1R since its discovery in 2010. This will help researchers to gain insight into potential novel pathways regulated by the nuclear IGF-1R that may have future clinical implications.

**1.2. Research question**

The present study reviews the role of IGF-1R and its targeting in cancer but will focus specifically on the potential functions of the nuclear IGF-1R in normal and cancer cells. Through this study we attempt to answer the following research questions: (1) Why IGF-1R clinical trials failed despite the preclinical success, what are the reasons of the failure? (2) What is the significance of nuclear IGF-1R in cancer?

**Hypothesis**

We hypothesize that the nuclear IGF-1R plays an important role in cancer through novel functions in regulating transcription and nuclear proteins.

**1.3. Aims and objectives**

The overarching goal of this study is to understand the structure, functions, signalling pathways of IGF-1R and its role in cancer progression. The aim is to understand reasons behind the failure of IGF-1R inhibitors in clinic and investigate the mechanism of action of IGF-1R nuclear translocation. Following the aims described above, the present study has two objectives:

1. To review the preclinical and clinical research published so far about the IGF-1R in cancer in order to understand the reasons of why IGF-1R failed in the clinic.
2. To analyse the data published on the nuclear IGF-1R and how it may open new channels of research that may have clinical implications in cancer biomarker discovery, and in cancer therapy.

Before we present the methodological approach used in the present study, we fill first present some background about the history, structure, and functions of IGF-1R in health.

**1.4. Background**

**1.4.1 History of IGF-1 receptor**

In 1957 Salmon and Daughaday reported that growth hormones did not directly incorporate sulphate ions into cartilage tissue; rather a serum factor was necessary for this process which they named sulphation factor (Salmon and Daughaday, 1957). Later on, it was called somatomedin and ultimately changed into insulin-like growth factors (IGFs). There are two types of this factor which are conventionally identified as insulin-like growth factor-1 (IGF-I) and insulin-like growth factor-2 (IGF-II) (Brahmkhatri, Prasanna and Atreya, 2015). Originally, the term ‘insulin-like’ was emerged as IGF-I and IGF-II incited glucose uptake into the fat and muscle cells and these factors shared 50% homology with insulin (Rinderknecht and Humbel, 1978). The authors determined the complete amino acid sequence of IGF-I. Molecular weight of IGF-1 is 7649 Daltons, having single polypeptide chain of 70 amino acids interlinked by three disulphide bridges. The research in 1974 by Marshall and colleagues revealed that IGF receptor is markedly distinct from insulin receptor (IR) (Marshall et al., 1974). The IGF-1R was shown to be homodimer composed of two alpha and two beta chains strongly joined by disulphide bonds (Bhaumick et al., 1981) (Chernausek et al., 1981). IGF-1R is a 180 kDa precursor and cleavage of precursor generated α and β subunits which are formed as a mature α2β2 receptor following glycosylation and proteolysis (Jacobs, Kull and Cuatrecasas, 1983).

The next landmark was the discovery of IGF-1R as a receptor tyrosine kinase which was activated and auto-phosphorylated by the binding of IGF-I (Jacobs et al., 1983; Rubin et al., 1983). This discovery suggested that despite insulin and IGF-1R have similar molecular weight and identical mode of processing they have distinct polypeptides (Jacobs et al., 1983). In 1986, the primary structure of human IGF-1R was cloned from cDNA (Ullrich et al., 1986). In addition, the study by Abbott et al. reported that the size of human IGF-1R gene is greater than 100 kilobase pairs and includes 21 exons (Abbott et al., 1992). One of earliest studies in 1984 showed that IGFs participate in mitogenic activities (Myal et al., 1984) and they were associated with growth regulation of T-47D human breast cancer cells. The presence of IGF-I receptors was shown to promote proliferative behaviour in human colon and breast cancer (Pollak et al., 1987). 1990s onwards it was fully established that overexpression of IGF-1R is implicated in multiple types of human cancers and since then numerous researches have emerged exhibiting that IGF-1R plays a critical role in cancer formation.

**1.4.2 Receptor tyrosine kinase**

IGF-1R is a part of receptor tyrosine kinase (RTK) family of receptors, 20 distinctive RTK classes have been discovered in human, including epidermal growth factor receptor (EGFR), fibroblast growth factor receptor (FGFR), vascular endothelial growth factor (VEGF) and insulin (Heymann et al., 2015). RTKs are transmembrane proteins, they act as receptors and model the key signalling pathways to transfer signals from membrane and distinguish them into several compartments (Schlessinger, 2000).

The RTK signals are transferred through a chain of cross-link pathways (Fig 1). RTKs have their own enzymatic activity, and its kinase activity is a part of its intracellular domain (Regad, 2015). The intracellular domain acts as a tyrosine kinase which phosphorylates the amino acid tyrosine on the substrate protein. RTKs are located in the plasma membrane, the intracellular part has tyrosine amino acids, and the extracellular part has a ligand binding site where the signalling process starts. Phosphorylation is initiated by the kinase activity of the receptors. As the ligand binds to the receptor it gets auto phosphorylated, which causes the activation of Ras (a small G protein) signalling pathway and the subsequent activation of Raf kinases. Mek1/2 gets phosphorylated by Raf, which results in activation and phosphorylation of Erk1/2. Raf also induces the activation of mitogen-activated protein kinase (MAPK) (MKK4/7, MKKK3/6 and MEK5), in turn JNK1/2, p38 and ERK5 gets activated sequentially. MAP3Ks also get activated by UV radiation, oxidative stress, and inflammatory cytokines (Regad, 2015). Autophosphorylation of RTK activates phosphoinositide 3-kinase (PI3K) pathway, which causes Akt activation, which is also stimulated by mechanistic target of rapamycin Complex 2 (mTORC2) and mTORC1 is generated. Moreover, RTKs play a vital role in growth, cell survival, proliferation, differentiation, and metabolism (Regad, 2015).

A screenshot of a video game

Description automatically generated

**Figure 1:** A Receptor Tyrosine Kinase downstream signalling pathway. This figure is taken from Regad, 2015.

**1.4.3 IGF receptors**

IGF receptors include IGF-1R and IGF-2R, insulin receptors A and B and hybrid receptors IGF-1R/IR-A and IGF-1R/IR-B (Kim et al., 2009). These IGF-1R and IR hybrids are detected in all cells and tissues where both IGF-1R and IR are expressed. The two major receptors of IGF system are IGF-1R and IGF-2R and they are transmembrane glycoproteins; however, both are completely distinct in structure and function (LeRoith et al., 1995). IGF-1R, a tetramer of two identical α and two identical β-subunits, it shares ~60% of homology with IR. IGF-1R and IR can hybridize by contributing one α and one β subunit of each receptor to shape as heterodimers (LeRoith et al., 1995). They can function predominantly as heterodimer hybrids and the composition of these hybrid receptors differ in tissues and cell lines. IGF-1R binds to IGF-I and IGF-II with high affinity, it can also bind to insulin with low affinity and the insulin receptors bind to insulin with high affinity and IGFs with low affinity (Fig 2). These characteristics plays an important role for the receptors to perform their different bioactivities. Importantly, IGF-1R and IR hybrid bind to IGF-I and/or IGF-II with high affinity than insulin (Hakuno and Takahashi, 2018).

A screenshot of a cell phone

Description automatically generated

**Figure 2**. Diagrammatic representation of IGF-1R and IR. This figure is taken from Hakuno and Takahashi, 2018.

Although IGF-1R and IR are structurally homologous they have distinct pathways and activities. For example, IGF-1R is highly expressed during prenatal development and high expression of insulin is observed in liver, muscle, and adipose tissues (LeRoith et al., 1995). IGF-1R signalling pathway is implicated in cell proliferation, growth, survival, and inhibition of apoptosis. On the other hand, insulin produce short term effects and it plays a critical role in the body's metabolism. It facilitates glucose and amino acid transport, promotes protein synthesis, glycolysis, glycogenesis, lipogenesis (Hakuno and Takahashi, 2018).

The liver controls the circulatory levels of insulin-like growth factors. The production of IGF-I is controlled by liver and hepatocytes. Growth hormone (GH), is produced in the pituitary gland under the regulation of hypothalamic growth hormone-releasing hormone (GHRH) and somatostatin (SMS), gets released in the blood stream which stimulate the liver to produce IGF-1 (Pollak, Schernhammer and Hankinson, 2004). The liver is also responsible for the production of Insulin-like growth factor binding proteins (IGFBPs). Importantly, other than the endocrine source, IGFs and IGFBPs can also be produced via autocrine and paracrine mechanisms. IGF-II is not regulated by GH; however, it is expressed in liver and extrahepatic sites. The ligands IGF-I and IGF-II bind to IGF-1R, a cell-surface tyrosine kinase signalling molecule through which the intracellular signalling pathways for the cell proliferation and survival are activated. IGF-1R phosphorylation activates downstream signalling molecules including PI3Ks, AKT, TOR, and MAPK. IGF-II binds to IGF-2R and does not play a part in the signal transduction pathways.

**1.4.4** **IGFs and IGFBPs in cancer**

The six insulin-like growth factor-binding proteins IGFBP-1, IGFBP-2, IGFBP-3, IGFBP-4, IGFBP-5, and IGFBP-6 are secreted proteins of 24 to 45 kDa (Haywood et al., 2019), which interact with IGF-I, IGF-II, and other ligands as well. The IGFBPs regulate IGF actions, enhance half-life of IGFs, and perform their functions as a transport protein. IGFBPs bind to IGF-I and IGF-II with almost similar affinities, although just IGFBP-6 binds to IGF-II with high affinity (Baxter, 2014). The primary structure of IGFBPs is comprised of three domains: N-terminal, C-terminal and central linker domain. The highly conserved N-terminal and C-terminal domains administer the IGF binding. The central linker region, which is least conserved, is a site of posttranslational modifications especially phosphorylation, proteolysis, and glycosylation. All IGFBPs share 50 homologies, however, they indeed possess individual characteristics as well. IGFBPs have dual functions including tumour growth regression as well as promoting oncogenesis (Baxter, 2014).

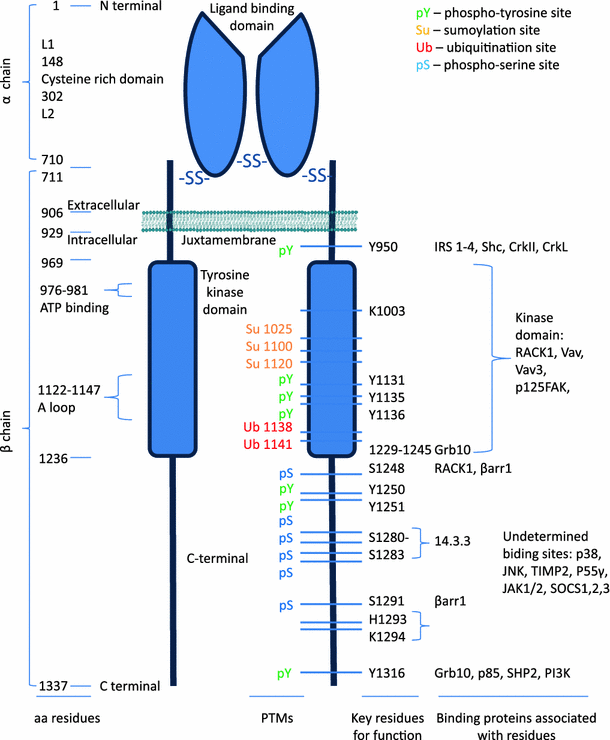
IGFBPs circulation in complex with IGF-I/II ligands reduce the bioavailability of IGFs, which can be implicated in tumorigenesis. In addition, certain studies suggest that IGFBPs can be useful as a tissue biomarker and despite the growing evidence of this notion, not much research has been carried out. Aleem et al. (2012) showed that serological levels of IGFBP3 are a better biomarker for the prediction of the development of hepatocellular carcinoma (HCC) in the chronic hepatitis C virus patients with liver cirrhosis.

IGFBP-1 was the first to be discovered in association with cancer (Baxter, 2014). Moreover, IGFBP-1, -2 and -5 might have IGF-independent functions for example, cell adhesion and migration (Jones and Clemmons, 1995). On the other hand, IGFBP-3 with IGFBBP-3, it might play a role in tumorigenesis as it stabilizes IGF-I. The study by Nickerson et al. showed that IGFBP-3 enhance mitogenic action of IGFs and also blocks their antiapoptotic effect (Nickerson, Huynh and Pollak, 1997). In contrast, IGFBP-4 and IGFBP-6 do not enhance actions of IGFs but can inhibit their mitogenic actions (Yu and Rohan, 2000). In early 1990s, increased IGFBP-2 expression in patients with ovarian cancer was associated with carcinoma antigen 125 (Flyvbjerg et al., 1997). Furthermore, no IGFBP mutations have been discovered in cancers, making it hard to understand the role of IGFBPs in carcinogenesis.

Phosphorylated IGFBP-1 is secreted in hepatoma and other cancer cell lines and it increases cell motility via binding to α5β1 integrin (Baxter, 2014). IGFBP-2 overexpression notably increases cell growth and metastasis in some cancer cell models such as ovarian prostate, bladder, and glioblastoma. IGFBP-3 can act as a tumour suppressor and is downregulated in many types of cancers, but its overexpression is linked to poor prognosis. In contrast, IGFBP-5 overexpression in some tumours is associated with antiproliferative and antiapoptotic effects, however, in some other cancers it can drive IGF-dependent and IGF-independent survival and proliferation. IGFBPs might mediate chemotherapy-induced irreversible cell cycle arrest. Preclinical results show that IGFBP-3 can potentially be used as a single-agent therapy, as it resulted in decreased growth in colorectal and lung cancer in combination with the inhibition of IGF-I-stimulated AKT phosphorylation (Baxter, 2014). Moreover, some IGFBPs can translocate to the cell nucleus. IGFBP-3 and IGFBP-5 interact with importin-β through nuclear localization sequence (NLS) motifs in the C-terminal domain to translocate to the nucleus. IGFBP-2 interacts with importin-α and this binding protein lacks the C-domain NLS motif, but it does contain functional NLS in the central domain. More importantly, IGFBPs can be implicated in drug resistance, this can be important for cancers which are caused by ligand-dependent IGF-1R activation.

**1.4.5** **Structure of IGF-1R**

The IGF-1R has a tetrameric structure which is integrated as a single chain α-β pro-receptor that is processed by proteolysis and glycosylation. The mature form of IGF-1R consists of two identical α subunits and two identical β subunits, linked by disulphide bonds (Valenciano et al., 2012). IGF-1R is known as a multi domain tyrosine kinase receptor. The α subunit is the ligand binding domain and β subunit is composed of the transmembrane domain, an intracellular domain with tyrosine kinase activity and C terminal domain (Fig 3). IGF-1R binds to IGF-I with high affinity and the circulatory levels of IGF-I is controlled by the liver, which is regulated by growth hormone. The α subunit of IGF-1R contains 710 amino acids whereas the β subunit contains 627 amino acids which are scattered around the extra cellular domain, transmembrane domain, and intracellular domain (Girnita et al., 2014). Moreover, the transmembrane and intracellular domains are further subdivided into three domains: the juxtamembrane domain, the tyrosine kinase (TK) domain, and the C-terminal (Fig. 3). The juxtamembrane region of IGF-1R contains NPXY motifs and the ATP binding motif which are required for MG-ATP binding. The IGF-1R TK domain is a cluster of three tyrosine’s which are essential for the autophosphorylation of the receptor. The C-terminal domain contains regulatory elements vital for smooth functioning of IGF-1R (Girnita et al., 2014).



**Figure 3**. The structure of IGF-1R (α and β subunits). This figure is taken from Girnita et al., 2014.

The N-terminus of the IGF-1R contains leucine-rich repeat domain (L1), a cysteine rich domain (CR), following another leucine-rich repeat domain (L2) (Menting et al., 2015; Ward et al., 2013). The Cys-rich region contains 22 cysteine residues. The C-terminal of the IGF-1R contains three fibronectin type III domains, (FnIII-1, FnIII-2, and FnIII-3). The FnIII-2 domain is the insert domain, a polypeptide sequence of ~100 residues, which have the site of proteolytic processing. Proteolysis mature the α and β precursors (Menting et al., 2015). In addition, intracellular each IGF-1R monomer consists of tyrosine kinase domain, having two regulatory regions, a juxta membrane domain (residues 930-972) and a C-terminal (residues 1230-1337) (Ward et al., 2013). The C-terminal region of the kinase domain is Phe 1229 (or shorter). Moreover, α-subunit consists of 38 cysteine residues and the β-subunit consists of total three extracellular and five intracellular cystine residues.

**1.4.6 IGF-1R Signalling Pathway**

IGF-1R regulates two important pathways: the phosphoinositide-3-kinase–protein kinase B/Akt (PI3K-PKB-) pathway and the Ras/ MAPK pathway (Fig. 4). The PI3K-PKB/AKT pathway was first described in the 1980s (Hemmings and Restuccia, 2012). Upon the activation of this highly conserved pathway, it inhibits apoptosis and induces the stimulation of protein synthesis. PKB/ Akt activates mammalian target of rapamycin (mTORC1) by phosphorylating it and inactivating PRAS40 and TSC2. The mTORC1 activation in turn phosphorylates ribosomal protein 6, therefore, resulting in protein synthesis (Hemmings and Restuccia, 2012). On the other hand, MAPK pathway activation results in cell proliferation. The Ras/Raf/MAPK pathway transduce signals to the cell nucleus where genes are activated for cell growth, proliferation, and differentiation. The insulin receptor substrate 1 (IRS1) mediates the activation of several downstream substrates such as Grb-1, SOS and SHC. PI3K along with the interaction of IRS1, produces phosphatidylinositol (3,4,5)-trisphosphate (PIP3) which recruits Akt kinase. Phosphorylated Akt regulates mTOR, which initiates the anti-apoptotic effects of the receptor by inducing phosphorylation and inactivation of BAD, which is a pro-apoptotic member. MAPK pathway regulates programmed cell death apoptosis, following RAS activation and Raf1/MAPK-independent pathways. Subsequently, IGF-1R activates RHOA which increase cell motility (Iams and Lovly, 2015).

IGF-I and IGF-II exert their effects through endocrine, autocrine, and paracrine mechanisms. Both of these ligands activate IGF-1R signalling as shown in Fig 4.

A close up of a map

Description automatically generated

**Figure 4**. IGF-1R signalling pathways. This figure is taken from Iams and Lovly, 2015.

In summary, ligand binding may occur with IGF-1R as homodimer or heterodimer with insulin receptor as isoforms A or B (INSR-A and INSR-B). The binding of ligands with IGF-1R results in activation of β subunit which then initiates downstream signalling pathways. Ligand-activated IGF-1R binds to intracellular adaptor proteins, primarily with IRS1. It can also bind to other adaptor molecules such as SHC1, GAB and CRK. Moreover, various intercellular signalling pathways are activated. On the one hand, there is IRS1-AKT1-MTOR pathway with two small molecules p85 (subunit of PI3K) and p110 right after IRS1, respectively. This pathway may end up at synthesis of specific proteins or activation of BAD which leads to blocking of apoptosis. Another signalling pathway starts at the activation of SHC via GBR2-SOS-RAS-RAF-MEK and ends at ERK. This pathway results in cell growth and proliferation (Iams and lovely, 2015). Activated IGF-1R advances cell motility through the activation of IRS2, which modifies the integrin expression through a poorly understood mechanism involving small G protein RHOA, Rho-kinase, focal adhesion kinase and PI3K (Lee et al., 1999).

**1.4.7** **Functions of IGF-1R in Health**

IGF-1R signalling pathway regulates essential processes such as growth, development, and metabolism. On the cellular level, the most significant cellular processes regulated by this pathway are cell proliferation, differentiation, survival, and glucose metabolism. This signalling pathway dysregulation is implicated in several diseases including altered metabolic processes, neurodegenerative diseases, and cancer (Jung and Suh., 2015). IGF-I promotes the progression of cell cycle from G1 to S phase thus, it has also known as a cell cycle progression factor (AsghariHanjani and Vafa, 2019). Activated pathway of IGF-1R can suppress apoptosis via inhibiting the stimulation of interleukin-1β-converting enzyme-like proteases, glycogen synthase kinase 3 and mTOR. Overactivated PI3K/Akt pathway also accelerates the ageing process (AsghariHanjani and Vafa, 2019).

IGF-I is the most essential ligand for IGF-1R and hybrid receptors. In spite of the remarkable similarity between IGF-I, IGF-II, and insulin, every ligand can bring about unique signalling outcomes. At high concentrations only, IGF-1R and insulin activate each other receptors, while IGF-II is unique it can bind to IGF-1R, hybrid-R, IR-A, and other related receptors (Denley et al., 2005). It is astounding how IGF-1R and IR can perform their own cell and physiological functions regardless of fundamentally similar homology. IGF-I is produced in somatic cells and in the liver under the endocrine growth hormone control whereas, IGF-II production is paracrine and autocrine. IGF-I and IGF-1R are abundant in fibroblasts (Lopez and Hanahan., 2002).

Overexpression of IGF-1R leads to greater risk of colon cancer (Vanamala et al., 2010) and inhibition of IGF-1R decrease cell proliferation. Carbohydrate restriction greatly reduce obesity-associated inflammation and slow cancer growth through IGF-I reduction (AsghariHanjani and Vafa, 2019). Interestingly, carbohydrate restriction leads to the increased intracell K+ ions in tumour cells via downregulating IGF-I pathway. IGF-1R is also associated with steroid hormones and their receptors, protein and DNA synthesis, proteoglycan synthesis and integrin type cells and cytokines i.e., transforming growth factor beta, which performs functions such as cell growth, proliferation, differentiation, and apoptosis (Jones and Clemmons et al., 1995).

Moreover, IGF-1R signalling pathways are major mediator of tumour progression e.g., transformation in the Ras pathway of IGF-1R drive tumorigenesis and have additionally been related to poor survival. Dysregulation of PI3K pathway is implicated in several cancer types. PI3K pathway regulates cytoskeletal rearrangements, growth, proliferation, and apoptosis (Vivanco and Sawyers., 2002). Furthermore, Akt has a variety of substrates and it is activated by the direct contact of pleckstrin-homology (PH) with PIP3 to mediate apoptosis, growth, and proliferation. PI3K also regulates PI3K-mediated tumorigenesis activity.

**Metabolic effects and Protein Synthesis**

Although IGF-I is generally viewed as a significant growth factor as it regulates the growth of almost all type, it has metabolic effects as well (Clemmons, 2012). IGF-I sends out signal to cells that sufficient nutrients are present to avoid apoptosis, enhance stimulation of protein synthesis, and cell division. Importantly, in neurons and fused skeletal myoblasts of adult tissues, IGF-I can regulate changes in cell metabolism.

The protein synthesis is modulated by IGF-1R PI3K pathway (Clemmons, 2012). This signalling pathway activation phosphorylates tyrosine’s on IRS-1 adapter protein and p85 regulatory subunit of PI3K is activated. PI3K pathway leads to the stimulation of Akt which in turn terminates tuberous sclerosis complex 2 and activates mTORC1. This series of responses activate phosphorylation of p70S6 kinase and E4B1, a translational repressor. This allows the elevation of cellular protein synthesis (Clemmons, 2012).

**Ageing**

The exact mechanism of aging is still not known but it is assumed that reduction in growth hormones like insulin and IGF-I are responsible for ageing (Anisimov and Bartke, 2013). Reduced levels of these hormones cause loss of muscle mass, reduced energy level, reduced mineral deposition in bones, etc. Especially in heart, IGF-I modulates various cellular processes, including growth, metabolism, apoptosis, autophagy, and senescence (Troncoso et al., 2013). Cardiac ageing is an inherent process which causes cardiac dysfunction, accompanied by molecular and cellular changes. IGF/IGF-1R signalling is involved in cardiac ageing. Furthermore, deletion of IGF-1R in cardiomyocytes may defer the formation of senescence-associated myocardial pathologies (Lee and Kin, 2018).

IGF-I is fundamental for neurogenesis in the adult brain, and the decrease of IGF-I with ageing leads to age-related cognitive decline (Frater et al., 2018). IGF-I is believed to play a key role in ageing as high circulatory levels of IGF-I promotes ageing through oxidative stress mechanisms. Furthermore, IGF-I is also an important regulator of vascular health, and reduction in IGF-I with age can contribute to vascular mechanisms of ageing (Frater et al., 2018).

**Craniosynostosis**

Craniosynostosis is premature fusing of the skull bones in babies (Kabbani and Raghuveer, 2004). The genetic contribution of craniosynostosis is poorly understood, with gene resequencing approach it was identified that mutations in IGF-1R may contribute to this disease and can cause single-suture craniosynostosis (Cunningham et al., 2011).

IGF-1 signalling pathway is also associated in the stimulation of tissues such as, skin and neurone through its capacity to prompt cell migration (Guvakova, 2007). Moreover, it causes adhesion to extracellular matrix proteins, which results in activation of integrins. Additionally, IGF-1 induces the upregulation of IGF-1R to focal adhesion proteins, promoting cell migration and invasion (Manes et al., 1999).

IGF-1 plays an important role in embryonic and postnatal skeletal development (Tahimic et al., 2013). In vivo, IGF-1 signalling activates osteoblast survival, growth, and development (Guntur and Rosen, 2013). Osteoblast exhibit IGF-1R and hence releases IGF-1 in the microenvironment. Therefore, in these cells, mutations of IGF-1R and IGF-1 overexpression correspond with skeletal and craniofacial defects (Guntur and Rosen, 2013). Absence of IGF-1 and IGF-1R in the mutant mice brings about extreme impediment in bone development and also, hypo mineralized skeletons (Bikle et al., 2001).

IGF-1R is expressed in normal tissues, regulates several physiological functions in growth and development. The receptor also assists the maintenance of the myocardium and brain (Yuan et al., 2018). Moreover, IGF-1R contributes to glucose metabolism and in physiology of the neutrophil. The receptor is significantly associated with the occurrence and development of cardiovascular disease and inflammation (Yuan et al., 2018). The following section will discuss the methodological approach used in this study.

**2. Methods**

Although the present study is not a systematic or a meta-analysis, the preferred reporting items for Systematic Reviews and Meta-Analyses (PRISMA) checklist was used, whenever applicable, as it is also useful for critical appraisal of published reviews (Moher et al., 2009).

**Study design:**

To accomplish the two objectives of the present study, two different sets of literature search criteria were used. The first set would serve to collect data published on the preclinical and clinical studies reporting on the canonical IGF-1R pathway in cancer. Critically analysing these data would shed light on potential reasons of the clinical failure of IGF-1R inhibitors in cancer despite its preclinical success. The second set of search criteria would serve to collect data published on the nuclear IGF-1R to gain insight about novel potential pathways regulated by nIGF-1R that may have clinical implications in cancer diagnosis and therapy.

The following box shows the steps undertaken to search literature databases, collect, analyse, extract data, and formulate results.

**Inclusion criteria**

* Full text available.
* Original research and review articles published in English Language.
* Any study including the association of nuclear IGF-1R expression with cancer or non-cancerous disease.
* The studies conducted on nuclear IGF-1R defining its binding partners, functions in nucleus, and mechanism of IGF-1R nuclear translocation.

**Exclusion criteria**

* Original studies not published in English.
* Research and/or analysis studies that included any non-disease related articles.

**Eligibility criteria:**

Searches were limited to English language and study was assessed based on the availability of full text. The inclusion and exclusion criteria were defined in advance. The search results were evaluated based on comparing title, abstract and full text against defined inclusion and exclusion criteria. Furthermore, the studies were evaluated by characterizing the literature review based on the quality, relevant research designs and topic. Two spreadsheets were made first spreadsheet including all the studies of IGF-1R and cancer and second including nuclear IGF-1R, however, the papers were narrowed down which suited best with aims of the study and inclusion criteria.

**Information sources:**

Various databases were used including PubMed, Cochrane Library, Science Direct, ClinicalTrials.gov, Google Scholar and ResearchGate. In addition, reference lists of articles were scanned. To reuse the figures and tables I contacted the publishers via email and journals via RightsLink to enquire about copyright. The original search for literature was run on 14th October 2019, all the IGF-1R/nuclear IGF-1R and cancer-related papers were included in the spreadsheet and the final literature search was run on 16 September 2020 on ClinicalTrials.gov (Appendix 1).

**Search:**

Following the Prisma Checklist presenting below the search strategy of at least one database such that it could be repeated. For the present study, the following search terms have been applied on PubMed:

1) Receptor tyrosine kinase activation in cancer

2) IGF-1R and cancer

3) IGF-1R in carcinogenesis

4) IGF-1R in cancer biology

5) Role of IGF-1R in cancer

6) IGF-1R in tumour progression

7) Functions of IGF-1R in cancer

8) Overexpression of IGF-1R in cancer

9) 2 or 3 or 4 or 5 or 6 or 7 or 8

10) Activation of IGF axis in cancer

11) IGF signalling pathway in cancer

12) IGF-1R pathway activation in cancer

13) IGF-1R signalling in carcinomas

14) IGF-1R pathway in tumour cells

15) Significance of IGF-1R pathway in cancer

16) IGF-1R mediated pathway in cancer

17) 12 or 13 or 14 or 15 or 16

18) 9 and 17

**Study selection:**

Studies were selected based on the defined inclusion and exclusion criteria. Assessed individual articles by reading titles and abstracts and comparing them against inclusion and exclusion criteria. Articles characterized as relevant were read in full text however, precisely some were excluded with reasons such as studies that included any non-disease related articles for IGF-1R however, all non-disease related articles for nuclear IGF-1R were included. The selected studies involved IGF-1R association with cancer and its functions in health. Moreover, from 1996 till 2020 there are 25 published studies of nIGF-1R either associated with cancer or non-malignant disease which are all included in this study (including all the original and review articles). No unpublished relevant articles were obtained of IGF-1R or nuclear IGF-1R.

**Data collection process**

All the individual studies were carefully read based on the full text, critically analysed, and summarized (Appendix 2). After the thorough read of research papers, both original and review articles, it was then decided whether it adds new information or perspective to the thesis. Initially all the main points of each study were listed and after the analysis it was determined which relevant detail to add. No contact was established with authors of the selected studies to extract unpublished information.

**3. Results**

**3.1** **Failure of IGF-1R clinical trials**

Early phase trials targeting IGF-1R in cancer showed positive results, however clinical trials of IGF-1R have been largely disappointing. The predominant reason for the failure was that IGF-1R inhibitors also inhibit the insulin receptor. Preclinical data showed IGF-1R inhibitors exhibited antitumour activity and disease stabilization in cancer patients (Iams and Lovly, 2015). Another significant reason was the lack of predictive biomarkers which identify patient’s response to a treatment. Predictive biomarkers help in preventing toxicity of systemic therapies in patients and nullify any false-negative signals (Iams and Lovly, 2015).

Clinical trials of single-agent anti-IGF-1R monoclonal antibody (mAbs) and IGF-1R tyrosine kinase inhibitors (TKIs) have showed almost negligible responses and disease stabilization in several types of cancer (Simpson et al., 2017), and as a result clinical trials were terminated. The reasons for the negative outcome of these clinical trials of anti-IGF-1R mAbs may include an ineffectiveness to induce inhibition of proliferation and survival signalling. Moreover, anti-IGF-1R mAbs may incorporate a failure to restrain IGF-II induced insulin receptor (INSR)-A signalling in cancer cells. On the other hand, IGF-1R TKIs promote the risk of hyperglycaemia because of the co-inhibition of INSR-B, which may limit the capacity to accomplish IGF-1R inhibition in human cancer (Simpson et al., 2017).

In addition, resistance to IGF-targeted agents can result from redundancy and crosstalk between IGF-1R and some other RTK signalling pathways such as epidermal growth factor receptor (EGFR), vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), human epidermal growth factor receptor 2 (HER2) and also including steroid hormone receptors e.g., oestrogen receptor (ER), androgen receptor (AR), and progesterone receptor (PR) (Simpson et al., 2017).

Another predominant reason for the failure of clinical trials were the absence of predictive biomarkers to permit determination of set of patients who may benefit from IGF-1R targeted therapies. There is an ongoing quest for predictive biomarkers, which is divided into two groups: (i) potential biomarkers in IGF-axis, (ii) biomarkers in other pathways that impact IGF-1R inhibition (King et al., 2014). In human cancer IGF-1R undergo nuclear translocation from the cell surface and is associated with gefitinib resistance (EGFR inhibition), suggesting that IGF-1R nuclear translocation can be a potential biomarker of IGF pathway activation (King et al., 2014).

**3.2 IGF-1R expression in human cancer**

Overexpression of IGF-1R is positively correlated with various types of cancers (Adhami et al., 2004). IGF-1R signalling pathway has three major cellular functions: cell proliferation, cell survival and blocking of apoptosis. All these cellular functions are important for cancer cells, hence overexpression of IGF-1R is associated with greater stability and longevity of cancer cells. IGF-1R’s implication in carcinogenesis was first established in fibroblast cell lines extracted from homozygous IGF-1R knockout embryos (Sell et al., 1993). Mouse embryo fibroblast are vulnerable to oncogenic mutations, but in the absence of IGF-1R signalling pathway they are resistant to these mutations and as IGF-1R is re-expressed, they become susceptible to mutations again.

Preclinical and clinical studies of IGF-1R have provided better understanding of its role in cancer biology. Overexpression of IGF-1R and its downstream signalling proteins was one of the early events in experimental hepatocarcinogenesis (2011). Reduced levels of IGF-1R signalling are associated with decreased tumour growth. Lopez and Hanahan, (2002) demonstrated in a mouse model, that expressing the oncoprotein (SV40T) in pancreatic islet β cells together with IGF-2 stimulation resulted in the initiation of tumours. The research by Carboni et al., 2005 described that transgenic mice expressing an active IGF-1R demonstrated abnormal development of mammary glands that evolved as mammary and salivary adenocarcinomas. Furthermore, in a 5T2MM (multiple myeloma) mouse model, when IGF-1R was targeted using picropodophyllin (a small molecule inhibitor of IGF-1R) it not just exhibited antitumor activity on MM tumour, but also impacted the bone marrow microenvironment, by controlling angiogenesis and bone disease (Menu et al., 2007).

The above-mentioned experiments provide evidence that IGF-1R signalling pathway promotes the malignant tumour growths and promotes proliferation and metastasis. Overexpression of IGF-1R is associated with numerous types of cancer, which is discussed below. Binding of ligand IGF-I triggers a conformational change that prompts autophosphorylation in the intracellular domain of the β-subunit. Autophosphorylation of IGF-1R elevate the catalytic domain activity and the receptor promotes proliferation and cell survival via PI3K and MAPK pathways.

**IGF-1R expression in breast cancer**

Breast cancer is one of the most abundant types of cancer, mostly affecting women. 95% of breast cancer arise from breast epithelial elements (Sharma et al., 2010). The 2 major types of breast cancer are (I) in situ carcinomas (II) invasive ductal carcinomas. The in-situ carcinomas arise in ductal or lobular epithelium and do not spread beyond epithelial boundaries. Invasive ductal carcinomas metastases and affects other areas of the body (Sharma et al., 2010). At least 50% breast cancers have an activated IGF-1R (Ekyalongo and Yee, 2017). Pian et al., 2018 observed abnormal ratio of IGF-1R and intragenic antisense [long noncoding RNA](https://www.sciencedirect.com/topics/biochemistry-genetics-and-molecular-biology/long-noncoding-rna) (lncRNA) IRAIN in breast cancer cells. IGF-1R is overexpressed whilst IRIAN is downregulated. Studies have shown that therapeutically, it is essential to target IGF-1R signalling pathway to overcome breast cancer.

Epidermal Growth Factor Receptor (EGFR) and IGF-1R contribute to cancer development through their effect on cell growth and inhibition of apoptosis. EGFR and IGF-1R are overexpressed in a variety of cancers, including breast cancer (Buck et al., 2008). Both EGFR and IGF-1R can initiate cancer development and progression by promoting cell proliferation, tumour-associated inflammation, angiogenesis, and inhibition of apoptosis. In a study by Yerushalmi et al. 65% and 22.5% of breast cancer cells overexpressed EGFR and IGF-1R, respectively, in patients with basal-like breast cancer (Yerushalmi et al., 2012). EGFR and IGF-1R collaborate on several levels, either by interceding the accessibility of each other’s ligands, downstream signalling molecules or by means of G protein-coupled receptors (Oliveira et al., 2009). In breast cancer, EGFR inhibitors, for example, erlotinib is used to repress the overexpression of EGFR. IGF-1R refutes the resistance to erlotinib by initiating one half of heterodimer in the presence of appropriate inhibitor. This procedure is alluded as crosstalk between EGFR and IGF-1R and this crosstalk is involved in anti-cancer therapy. Therefore, it is necessary to target both IGF-1R and EGFR pathways in breast cancer (Jin and Esteva, 2008).

While numerous preclinical studies have demonstrated that 87% of primary breast cancer cells showed IGF-1R activation only 50% of breast tumours show phosphorylated IGF-1R by immunohistochemistry (IHC) (Law et al., 2008). The molecular type of breast cancer falls into the luminal category. The luminal subtypes are hormone receptor positive i.e., ER+ and PR+.50% of breast cancer cases belong to the Luminal A subtype, while 10-20% are Luminal B (Eroles et al., 2012). Luminal subtypes have elevated levels of IGF-1R (Kolacinska et al., 2012). IGF-1R is exhibited in 84% and 57.5% in Luminal A and B tumours, respectively. Moreover, interestingly Luminal B breast cancer having high levels of IGF-1R have better prognosis compared to low levels of IGF-1R. It has been shown that half of all luminal tumours manifest active and phosphorylated IGF-1R (Law et al., 2008).

IGF-1R levels were reported to be 14-fold higher in human breast cancer tissue relative to normal tissue and hyperphosphorylation of IGF-1R has likewise been accounted for in breast cancer biopsies (Surmacz, 2000). It was found by Tamimi et al., 2011 that cytoplasmic IGF-1R expression was associated with the high risk of breast cancer. A total of 312 women having terminal duct lobular units (TDLU’s) epithelial cells demonstrated no or less membrane expressions of IGF-1R, however those with elevated levels of cytoplasmic IGF-1R were at the higher risk of developing breast cancer. Also, those women have 15 times greater risk of breast cancer incidence, as compared to women having no or less cytoplasmic or membrane IGF-1R expression in TDLU epithelial cells (Tamimi et al., 2011). In androgen-independent tumours cytoplasmic IGF-1 receptor was observed (Ryan et al., 2007). Jones et al., 2007 findings showed that IGF-1R is a basic regulator of mammary gland development and that anomalous levels of IGF-1R are adequate to initiate mammary epithelial hyperplasia and tumour development.

The clinical trials involving patients with different types of cancer, including breast cancer failed at phase 3 trials. The reasons include the complex structure of IGF-1R/IR and as well as lack of biological markers (Chen and Sharon, 2013). For future research it is essential to identify predictive biomarkers to improve the treatment outcome.

**IGF-1R expression in lung cancer**

IGF-I is not only produced by the liver but also by targeted tissue in autocrine/paracrine fashion. In autocrine signalling pattern, the hormones effect nearby cells whereas in paracrine mechanism, hormones are released into the blood streams where they circulate and effect far away cells and tissues. In lung cancer, this targeted secretion of IGF-I and its binding with its receptor is considered more important in development and maintenance of cancer cells (Fu et al., 2016). One of the highlights of IGF-1R signalling pathway in lung cancer is PI3K-Akt pathway activation (Isoyama et al., 2015). Resistance of malignant cells to PI3K-Akt inhibitors includes the activation of IGF-1R (Isoyama et al., 2015). About 1.5 million cases of lung cancer are determined every year of which 85% are non-small cell lung carcinoma (NSCLC) (Travis, 2011). Novel therapeutic advancements in NSCLC have brought about just minor improvement of patient results; the 5-years overall survival (OS) is just about 17% (Siegel et al., 2012). Zhao et al., 2014 performed a meta-analysis to explore the prognostic value of IGF-1R in NSCLC and the association between IGF-1R expression and clinical characteristics. Their research recommends that IGF-1R positive expression is associated with a favourable disease-free survival (DFS), and IGF-1R expression is also likewise associated with tumour size and smoking status. Another study by Huang et al., 2014 showed that the genetic variation of IGF-1R might be related with significantly increased risk of lung cancer, particularly in Asian populations.

IGF-1R signalling pathway induce (EGFR)-mutant NSCLC resistance (Lee et al., 2016). Suda., et al 2014 found that IGF-1R activation leads to erlotinib drug resistance in lung cancer. Erlotinib is a small molecule inhibitor of EGFR. IGF-1R inhibition restrains cancer cells resistance to docetaxel, carboplatin, paclitaxel and vinorelbine as well (Nurwidya et al., 2016). One of the most controversial therapy against IGF-1R in lung cancer is figitumumab. It is human-derived immunoglobulin G2 monoclonal antibody that functions explicitly against IGF-1R (Gualberto and Karp, 2009). The clinical development of figitumumab in NSCLC discontinued because of increased treatment-related deaths in the patients (Di Maio and Scagliotti, 2015). This anti-IGF-1R antibody is under review until it will help getting significant clinically relevant results.

Taken all together, high levels of IGF-1R predominantly increases the risk of developing lung cancer in the future. Activated IGF-1R has been frequently found in promoting NSCLC progression. Furthermore, activation of PI3K-Akt signal transduction pathway mediates the resistance to lung cancer therapy. Despite the disappointing results of clinical trials, it is essential to continue clinical investigations to devise strategies for lung cancer patients. As discussed above, IGF-1R activation plays a key role in resistance to several drugs. Therefore, one of the strategies to inhibit IGF-1R activation is to overcome resistance of different TKIs (Nurwidya et al., 2016).

**IGF-1R expression in prostate cancer**

High levels of IGF-1R expression manifest mostly in primary and metastatic prostate cancer. At the protein and mRNA levels, a total of 54 primary prostate tissue samples exhibited the upregulation of IGF-1R as compared to benign prostatic epithelium (Hellawell et al., 2002). Grzmil et al., 2004 reported that a direct correlation exists between the inhibition of IGF-1R gene expression and either up-regulation of IGF binding protein (IGFBP)-3 or down-regulation of matrix metalloproteinase (MMP)-2 expression in androgen-independent PC-3 cells. Evidence suggests that IGF-1R signalling contribute to the development of prostate cancer progression. Findings by Saikali et al., 2008 demonstrates that IGF-I significantly enhance the intrusive capacity of U145 (prostate carcinoma cells) in vitro, and this increase was repressed by blocking IGF-1R. Hence, IGF receptor family and their ligands likewise appear to be engaged in the carcinogenesis. IGF-1R is overexpressed in several cancer types as per reported by The Cancer Genome Atlas (TCGA) data, and gene amplification mechanism could perhaps contribute for the overexpression of IGF-1R in cancer (Chen et al., 2014).

IGF-1R is present in both benign prostate and tumour epithelium. Predominantly IGF-1R and MT1-MMP (a metalloproteinase) expressions manifest in prostate cancer (Sroka et al., 2008). Elevated levels of IGF-1R have been associated with risk of prostate metastasis even after radiotherapy (Aleksic et al., 2017). Various kinds of IGF-1R inhibitors have been tested for interrupting IGF-1R signalling pathway in prostate cancer. Luteolin has been shown to inhibit signalling pathway of IGF system in preclinical trials (Fang et al., 2007). This shows that like in all other types of cancers, elevated IGF-1R and its targeting with anti IGF-1R inhibitors has been well established.

**3.3 Targeting IGF-1R in human cancer**

The IGF pathway has been broadly studied as a significant signalling pathway in cancer. Aberrant expression of IGF-1R is implicated in many cancers. and is considered a promising therapeutic target as it shows pro-survival and strong anti-apoptotic capacities. IGF1R-targeting drugs are comprised of monoclonal antibodies, small molecule tyrosine kinase inhibitors and ligand binding antibodies.

Monoclonal antibodies (mAb) are specifically selected to block IGF-1R activity. The structural design of IGF-1R tyrosine kinase inhibitors is complex as it was discovered that the kinase domain of the IGF-1R has 85% homology to that of the IR, also the ATP-binding cleft is 100% conserved (Ullrich et al., 1986). Nonetheless, there are precise differences that can be utilized in drug design. NVP-AEW541 and NVP-ADW742 are IGF-1R inhibitors, they restrain tumour development in models of Ewing sarcoma, myeloma and fibrosarcoma, and furthermore improve tumour cell chemosensitivity (Scotlandi et al., 2005). Bell et al., 2005 generated IGF-1R inhibitors that attach to the active site of the enzymes. Inhibitors that bind to the ATP-binding cleft are not specific, substrate phosphorylation site inhibitor show significant potential for IGF-1R inhibition. Furthermore, one such inhibitor, nordihydroguaiaretic acid, additionally blocks the activation of Her2 kinase and inhibits the upregulation of IGF-1R and Her-2 in vivo (Youngren et al., 2005). Girnita’s et al., 2004 developed cyclo lignan picropodophyllin (PPP), which impedes tyrosine phosphorylation of IGF-1R kinase domain. PPP does not influence the insulin receptor or engage with ATP in in vitro kinase assays, proposing that it might inhibit IGF-1R autophosphorylation. Additionally, PPP has a microtubule binding, IGF-1R-independent mechanism that results in M phase arrest (Waraky et al., 2014).

**IGF-1R monoclonal antibodies**

The very first most readily accessible humanized anti–IGF-1R mAbs were Cixutumumab (IMC-A12), Figitumumab (CP-751, 871), Dalotuzumab (MK-0646), Ganitumab (AMG 479), R1507, SCH 717454 (19D12), AVE1642 (EM164), BIIB022, and MEDI-573 (Gombos et al., 2012). MED1-573 targets IGF-I and IGF-II, this monoclonal antibody inhibits IGF-mediated activation of IGF-1R and IR-A (Gao et al., 2011). A phase I clinical trial of AVE1642 were given to patients with advanced solid tumour (Tolcher et al., 2008). AVE1642 binds to IGF-1R with high affinity and delays the growth over which the tumour cells are developed. This study showed the safe use of this antibody in cancer patients.

A humanized monoclonal antibody dalotuzumab showed promising results in patients with aggressive solid tumours. Preclinical studies indicated that dalotuzumab inhibits IGF-I and IGF-II mediated tumour growth, also IGF-1R autophosphorylation and Akt phosphorylation (Scartozzi et al., 2010). In NSCLC and breast cancer, dalotuzumab exhibits significant antitumor activities. Additionally, dalotuzumab in combination with other anticancer drugs may appear to exhibit positive clinical results (Scartozzi et al., 2010). The first inhibitors of IGF-1R, which was tested in a clinical trial, was CP-751871 (Chen and Sharon, 2013). Pharmacokinetics and maximum tolerated dose of this inhibitor was evaluated, and later CP-751871 was named as figitumumab. Early-phase 1 trial of figitumumab was evaluated in patients with advanced nonhematologic malignancies (Haluska et al., 2007). Fifteen out of 42 patients showed stable disease response, notably two lung and ovarian cancer patients showed complete response. Twenty-nine patients with Ewing sarcoma and a group of patients with different types of sarcomas were treated with figitumumab with the dose of 20mg/kg (Olmos et al., 2010). Interestingly, half of the patients demonstrated tumour shrinkage. Out of all treated patients one Ewing sarcoma patient secured pathological complete response (pCR) and one patient with partial response. Furthermore, Pfizer showed significant development of figitumumab, other pharmaceutical companies such as Amgen and Merck showed successful advancements in the development of AMG 479, later named as ganitumab, and MK-0646, later named as dalotuzumab, respectively (Chen and Sharon, 2013). Propitious results were observed with ganitumab in clinical trials. Phase II study of ganitumab in patients with Ewing sarcoma or desmoplastic small round cell tumours exhibited promising results with 49% stable disease response and 6% partial response (Tap et al., 2012). In a xenograft mouse model, IGF-1R monoclonal antibody (A12) combined with radiation treatment, delayed the growth in an adenocarcinoma cell line (Riesterer et al., 2011). BIIB022 is a non-glycosylated, anti-IGF-1R monoclonal antibody, this antibody does not have effector functions as like other anti-IGF-1R antibodies. A multi-institutional phase I study by von Mehren et al., 2014 revealed that BIIB022 can be given to patients with relapsed and refractory solid tumours at 30mg/kg at regular intervals. BIIB022 functions as an allosteric mechanism (allosteric control) is the regulation of specific enzyme which bind to the effector molecule at a site other than the enzymes active side. Therefore, BIIB022 binds to the fibronectin III-1 domain of IGF-1R which differs from IGF-I and IGF-II bindings regions.

To optimize the therapeutic strategies, it is imperative to understand the intrinsic complexities that exist in these four receptors i.e., IGF-1R, IGF-2R, IR and hybrid receptors. The predominant complexity arises from the fact that both IGF-1R and IR can function as homodimers and can form a hybrid as well. Co-targeting strategies can prove to be effective and dual targeting of IGF-1R by the two antibodies can show optimum results. Based on this hypothesis, a study by Dong and colleagues identified BIIB4 and BIIB5 which can block both the ligands binding to IGF-1R by the means of competitive and allosteric mechanisms (Dong et al., 2010). BIIB4 and BIIB5 combined reduced tumour growth of osteosarcoma and hepatocellular carcinoma also promoted IGF-1R downregulation. As IGF-1R was downregulated this treatment proved to be an effective strategy to target the IGF-1R pathway in cancer.

In summary, IGF-1R can be inhibited through numerous approaches, one such approach has been described above. Monoclonal antibodies bind to the extracellular domain of the receptor and therefore, block the ligand binding. As mentioned earlier, several human anti-IGF-1R monoclonal antibodies demonstrate antitumour activity.

**Small molecule inhibitors**

Small molecule inhibitors target the extracellular domain, intracellular protein, and ligand-binding receptors because of their small size (Imai and Takaoka, 2006). Small-molecule tyrosine kinase inhibitors can be given orally and can cross the blood-brain barrier but if combined with other agents, it may cause drug–drug interactions and thus can be proved as toxic (Yin et al., 2010). Small-molecule tyrosine kinase inhibitors might be associated with more serious metabolic unfavourable result than monoclonal antibodies, as they can influence both IR and IGF-1R pathways (Arora and Scholar, 2005). Contrarily, small-molecule IGF1R tyrosine kinase inhibitors can potentially have advantage over antibodies as per their more extensive range of inhibition because of the incessant expression of IR in tumours (Arora and Scholar, 2005).

The combined treatment with cytostatics and small molecule tyrosine kinase inhibitors, significantly enhance the efficacy of the inhibitors, as IGF-1R is positively correlated with chemotherapy, radiation, apoptosis, and cell survival. Hopfner et al., 2006 demonstrates that NVP-AEW541 along with cytotoxic drug i.e., doxorubicin or Fluvastatin shows additive anti-proliferative effects in gastrointestinal neuroendocrine tumours. In addition, OSI-906 and BMS-754807 are the most specific small molecule TKIs, compared to others (Chen and Sharon, 2013). Moreover, an anticancer agent cyclolignan picropodophyllin (PPP) has been exhibited to have IGF-1R independent mechanisms induced by mitotic catastrophe (Waraky et al., 2014). IGF-1R TKIs manifest some IR inhibitory effect as well because of the homology between IGF-1R and IR.

The overall summary of IGF-1R targeted agents is that they operate somewhat similarly yet differ in their mechanism of action and spectrum of inhibition. For instance, anti-IGF-1R mAbs inhibit mechanism of IGF-1R and IGF-1R/IR hybrids, IGF-I and IGF-II neutralizing mAbs inhibits both homo and heterodimers of IGF-1R and IR-a and not the insulin, small molecule TKIs inhibits IGF-1R/IR signalling (Chen and Sharon, 2013).

**IGF Neutralizing Antibodies**

IGF Neutralizing Antibodies explicitly target IGF ligands IGF-I and IGF-II. Dusigitumab (MEDI-573, Medimmune) by AstraZeneca entered the clinical trial, showed the inhibition of IGF-I and IGF-II induced IGF-1R phosphorylation (Osher and Macaulay, 2019). Phase-I trial of dusigitumab showed antitumour activity via inhibiting IGF-1R signalling pathways. However, phase II trials conducted in patients with metastatic breast cancer showed no significant progression-free survival (Osher and Macaulay, 2019). Therefore, the failure of dusigitumab resulted in the discontinuation of this antibody. Another ligand binding antibody, xentuzumab (BI 836845) that bind to ligands IGF-I and IGF-II with high affinity, 0.07 and 0.8nmol/L, respectively show anti-cancer effects in human (Osher and Macaulay, 2019). Hence, xentuzumab is being clinically tested in several cancer such as lung, prostate, and breast.

**Expression of IGF1R-inhibitory proteins**

Dominant-negative proteins impede the functionality of wild-type protein usually through direct binding. The primary dominant negative IGF-1R was 486/STOP, an IGF-1R secreted with ligand-binding domain which compete for ligand binding (Riedemann and Macaulay, 2006). Similarly, 950/STOP with conserved transmembrane domain, also is a dominant-negative protein and performs its function by forming non-functional heterodimers with IGF-1R. Adenoviral-mediated delivery of dominant negative IGF-1Rs exhibit antitumor effects in a variety of cancer models. Hence, this approach can be used as an anti-IGF-1R treatment via recombinant IGF-1R dominant negatives or as a gene therapy approach.

**Antisense oligonucleotides**

Antisense oligonucleotides (ASOs) silence genes in DNA and can alter RNA molecules through several distinct mechanisms. Despite the fact that there are no particular limitations for the use of antisense, ASO-based strategies are influenced by secondary structures in target transcripts, to an extent that only 5-10% of mRNA are well-suited to interact with ASOs. The downregulation of IGF-1R expression induced by antisense results in reduced cell growth, mediates apoptosis, and defer tumour progression in several models (Riedemann and Macaulay, 2006). In addition, there has not been much progress in the use of antisense technology. ASO drug ATL1101, inhibited growth of prostate cancer xenografts however, it is not further tested in a clinical setting (Osher and Macaulay, 2019).

Phosphonothioate ASOs are resistant to nuclease attack in comparison to unmodified phosphodiester oligonucleotides, while conserving the function to target-specific RNase H-mediated cleavage (Riedemann and Macaulay, 2006). Pre-clinical studies exhibited the safe use of ASOs; however, clinical trials have not been successful (Di Fusco et al., 2019). A few ASOs have reached clinical trials, such as ASOs against Bcl-2 and c-Raf, but the efficacy of ASOs administration is constrained due to the problems in the cellular uptake (Riedemann and Macaulay, 2006).

**RNA interference**

RNA interference (RNAi) is a biological process first introduced in 1998 (Fire et al., 1998), double-stranded RNAs (dsRNA) initiate RNAi by activating the enzyme Dicer (a member of ribonuclease protein) into the short fragments of 20-25 base pairs having 2-nucleotide overhang at the 3’ end. These short-cleaved products are called small interfering RNAs (siRNAs). The siRNAs are integrated into an active multi-protein RNA-inducing silencing complex that includes the antisense strand of the siRNA, which directs towards the cleavage of complementary mRNA (Riedemann and Macaulay, 2006). RNAi is a regulatory cellular process which can promote apoptosis via stimulating dsRNA-dependent protein kinase and interferon expression. When gene silencing was induced in mammalian cells, it was clear that not all siRNAs were effective in the knockdown of target proteins. With all the information on the available transcripts on ASO efficacy, mRNA folding to induce IGF-1R silencing was examined by Elbashir et al., (2001). An oligonucleotide array-based screening enabled to make siRNAs which could interact with the specific regions on IGF-1R but not IR mRNA. The outcomes showed that siRNAs potentially can suppress IGF-1R expression and also the accessibility of target sequences; the inaccessible regions of the transcript targeted by duplexes induced slight downregulation of IGF-1R. The first approved RNAi-based therapeutic is ONPATTRO (patisiran). Eight siRNAs are undergoing clinical phase III trials including, Fitusiran, Inclisiran, Givosiran, QPI‐1002, QPI‐1007, SYL1001, Lumasiran, and Vutrisiran (Hu et al., 2019).

**IGF-1R combined with other targeted agents**

In clinical trail the use of IGF-1R inhibitors in combination with other multiple targeted agents were tested (Appendix 1). IGF-1R combined with Adriamycin, 5-fluorouracil, or tamoxifen displayed significant antitumor activity (Cohen et al., 2005). In Estrogen Receptor (ER) positive breast cancers, IGF1R-directed therapies have been used in many clinical trials. BMS-754807, an antitumor agent combined with 4-hydroxytamoxifen, fulvestrant or letrozole showed tumour regression, enhanced apoptosis, and demonstrated anti-proliferative effects (Hou et al., 2011). Phase II trial tested cixutumumab (IMC-A12) alone or in combination with anti-oestrogen therapies in breast cancer patients who have progressed on endocrine therapy (Gradishar et al., 2016). Cixutumumab with or without anti-oestrogen therapies showed positive and safe results, however, a major setback was this clinical trial did not show any further positive development. Furthermore, in contrast vast number of clinical trials have failed and showed negative results. For example, in 2011 phase II clinical trial of breast cancer patients receiving OSI-906 and endocrine therapy letrozole with or without erlotinib was dismissed because the selected patients developed severe toxicities and showed the significant sign of tumour progression (Ochnik and Baxter, 2016).

EGFR inhibitors were tested in various range of cancer such as, colorectal, head and neck, and NSCLCs (Ochnik and Baxter, 2016). In addition, IGF-1R and EGFR combined therapies were beneficial in preclinical and clinical testing. Overholser et al. reported that inhibition of IGF-1R and HER-1 (EGFR) through IGF-1R-56 and HER-1-418 peptide mimics showed potential antitumor properties (Overholser et al., 2015). Importantly, remarkable blockade of tumorigenesis was identified in OE19 EC and MDA-MB-231 TNBC cell lines. Phase 1 clinical trial of OSI-906 and erlotinib exhibited tolerable reports of these treatments which led to successful reduction in IGF-1R/InsR phosphorylation in advanced solid tumours (Macaulay et al., 2016). AMG-479 combined with centuximab, gemicitabine, and erlotinib and EGFR inhibitors demonstrated effective tumour regression (Singh et al., 2013). In non-small cell lung and human pancreatic cancer, A-928605 inhibitor along with the combination of EGFR inhibitors exhibited positive results.

Moreover, combinational treatment by EGFR inhibitor gefitinib or erlotinib with PI3K/AKT resulted in inhibiting cell growth through antiproliferative effects on basal-like lines subtype cell lines (SUM149PT and MDA‐MB‐468), however, not on mesenchymal stem-like cell lines (S578T and MDA‐MB‐231) (Yi et al., 2013). Temsirolimus combined with cixutumumab was well-tolerated in patients with Ewing's sarcoma (Naing et al., 2012). These inhibitors combined demonstrated rather effective antitumour activities.

Combining IGF-1R targeted therapies with other therapies will potentially help to achieve optimistic clinical results and in identification of significant ways to target complex signalling pathway of IGF-1R in cancer.

**3.4 IGF-1R in drug resistance**

A better understanding of how cancer cells develop resistance to targeted therapies may help to improve survival rates by overcoming resistance. Based on this, IGF-1R is intensively studied to develop tumour chemotherapeutic tolerance, however, IGF-1R mediated resistance is anticipated to be further explored. Antineoplastic agents combined with the IGF-1R monoclonal antibody has been an effective strategy to kill cancerous cells. However, not all clinical trials have shown the ideal results. In gastric carcinoma patients the correlation between IGF-1R levels and multi drug resistance-associated protein 1 (MRP1) expression demonstrated poor prognosis with adjuvant FOLFOX-4 chemotherapy (P < 0.005) (Ge et al., 2009). Notably, silencing of IGF-1R was associated with an improved response to chemotherapy in the patients with human epidermal growth factor receptor 2-negative breast cancer. Overall, 47.2% of tumours displayed reduced expression of IGF-1R during chemotherapy, however, 15.1%, a small set of tumours, displayed IGF-1R upregulation (de Groot et al., 2016). Importantly, decreased levels of IGF-1R after chemotherapy significantly link with better pathological response and long-term survival. The study by Sun et al. confirms that blocking IGF-1R signalling may allow the effective treatment of T24 bladder cancer cells that are insensitive to chemotherapy (Sun et al., 2001).

The patients who may not be well suited to undergo surgical intervention, the personalized targeted treatments are important for their survival. Furthermore, IGF-1R plays a crucial role in ovarian and prostate cancer drug resistance as well (Yuan et al., 2018). Targeting IGF-1R and PI3K signalling pathways in cisplatin-resistant ovarian carcinomas may show promising results in clinical management of this cancer (Eckstein et al., 2009). Chemotherapeutic resistance predominately generates aberrant signalling that allows cells to lose control of growth signals. Moreover, overexpression of IGF-1R also contributes to chemotherapeutic tolerance via the activation of Grb2, RAS, RAF, and MAPK pathways. These cascades function in cell survival and are a key player in activating drug-tolerant cells (Worrall et al., 2013). IGF-1R pathway induces cell proliferation, inhibition of apoptosis, and changes to ATP-binding cassette (ABC) transporter proteins and the extracellular matrix (Fig 5).

A close up of a map

Description automatically generated

**Figure 5.** IGF-1R signalling pathway and drug resistance mechanism**:** IGF-1R signalling pathway promote changes inATP-binding cassette transporter proteins and the extracellular matrix. Silencing WT1 and Mt-p53 induces loss of inhibitory effects of IGF-1R promoter. The microRNA inhibition causes the loss of IGF-1R mRNA degradation. IGF-1R upregulation promotes PI3K/Grb2/RAS/RAF pathways which enhances proliferation and anti-apoptotic activity. Therefore, IGF-1R signalling pathway plays a key role in regulating ABC genes and also alter cell responses to chemotherapy. This figure is taken from Yuan et al., 2018.

**IGF-1R in Radiotherapy**

Radiation damages the structure and function of cell; it is harmful for the DNA and ultimately causes various kinds of disease. Cells in the human body upon the exposure to such radiation produce different frequencies of electrons. The electrons disseminate energy which leads to the development of free radicals (unstable chemicals). Therefore, free radicals, upon interaction with the human body, cause minor and/or major damages to DNA. The changes in DNA structure results in nucleotide excision, single strand-, and double strand breakage. Intense radiation induces multiple DNA damages (Valenciano et al., 2012). However, the cells can cope up with the damage by the DNA damage tolerance mechanisms, which enhances the chance of survival. But if the damage is unrepairable the cells initiate apoptosis. Radiation-induced damage and genomic instability lead to double strand breaks (DSBs) in DNA which is lethal to cells. DSB damage can be repaired via homologous recombination (HR) and non-homologous end joining (NHEJ) (Valenciano et al., 2012). Homologous recombination mechanisms exchange DNA strands of with the similar or identical nucleotide sequence to facilitate strand invasion. This error-free repair pathway requires RAD52, which is a DNA end-binding component (Sallmyr, Fan and Rassool, 2008). NHEJ pathway does not require a homologous sequence to repair the damage, as it can directly do so. However, a setback of this is that NHEJ is not always quite precise and can produce small regions of non-template nucleotides called microhomologies (Sallmyr, Fan and Rassool, 2008). Importantly, IGF-1R plays an important role in response to radiation in the cancer cells. Mouse embryo fibroblast cell lines with or without the expression of human IGF-1R were exposed to gamma rays and apoptotic activity was examined (Tezuka et al., 2001). Cells not expressing IGF-1R showed higher apoptotic activity following exposure to the radiation when compared to cells overexpressing IGF-1R. Furthermore, upregulated levels of IGF-IR in tumour samples highly correlated with ipsilateral breast tumour recurrence after the lumpectomy and radiation therapy (P*=* 0.001) (Turner et al., 1997). Importantly, targeted therapies coordinated towards IGF-1R may help cure radioresistant cancer cells.

In high proliferativeER*-*positivebreast cancers IGF-1R and IRS-1 levels are overexpressed, which raises the possibility of increased radio resistance and cancer recurrence (Bartucci et al., 2001). Mutational analysis revealed that Tyr-950 of IGF-IR and C-terminal domain regulate cancer radio resistance (Wu et al., 2003). The IGF-1R signalling MEK/ERK pathway significantly contributes to the resistance and the PI3K pathway coupled with MEK/ERK pathway also induce radio resistance, however notably, the PI3K pathway alone does not drive the radio resistance. The study by Lloret and colleagues studied the cervix carcinoma patients, which ubiquitously expressed IGF-1R treated with chemo/radiotherapy (Lloret et al., 2007). 93.7% of the patients expressed IGF-1R and 83.3% of patients achieved the complete response after the treatment. The response to the chemo/radiotherapy was the important prognostic factor of survival, following the treatment the patients were clinically free of disease. However, IGF-1R expression was associated with reduced long-term local control of the cancer in patients which initially respond to the radiotherapy and chemotherapy. In patients with low levels of IGF-1R, no relapse was observed resulting in a 100% 5-year local and regional control (Lloret et al., 2007). EGFR and IGF-1R play a crucial role in the cell growth and apoptosis of nasopharyngeal carcinoma (NPC). It has been shown that EGFR and IGF-1R expression played a major role in the invasion, metastasis, and recurrence of NPC (Yuan et al., 2008). Both EGFR and IGF-1R were overexpressed by 5.3% and 56% in NPC, respectively. The tissue samples collected during biopsy and Semiquantitative scoring system determined that IGF-1R was overexpressed in 42 out of 75 tissues. EGFR and IGF-1R levels were augmented in tumours with lymph node metastases. Furthermore, a positive correlation was observed between the EGFR/IGF-1R and recurrence. Recurrence appeared in patients positive for both proteins contrarily, to the patients negative for both proteins.

Increased expression of IGF-1R in cancer cells is associated with poor clinical outcomes in breast cancer, cervical cancer, and oral cavity carcinoma patients (Valenciano et al., 2012). IGF-1R has been associated with radio resistance not only in cell lines but also in clinical setting, thereby making the receptor a predictive factor for the radiotherapy outcomes.

To sum up, IGF-1R is associated with cancer, however, IGF-1R inhibitors failed in later stage trials despite being successful in early-stage trials because the inhibitors usually inhibit insulin receptor as well. In phase I clinical trials the side effects of these inhibitors were minimal but not the same case with phase III clinical trials. In addition, not all IGF-1R inhibitors were unsuccessful. Moreover, the identification of predictive biomarkers is important to develop anti-cancer therapies and for successful clinical trials. Importantly, the rationale of the present study is to understand another aspect of IGF-1R that has not been fully covered before. Nuclear IGF-1R regulate additional pathways in the nucleus and these pathways can be targeted to inhibit cancer. The following section would thoroughly discuss nuclear IGF-1R and its implication in cancer.

**3.5 Nuclear IGF-1R**

**Discovery of nuclear IGF-1R**

The earliest findings regarding nIGF-1R were first reported by Chen and Roy (1996). Based on Western blotting results they identified that IGF-1R translocate to the nucleus in hamster kidney cells (Chen and Roy, 1996). Nuclear IGF-1R expression increased in the Syrian hamsters’ kidneys by a short-term exposure of a carcinogenic dose of stilbene oestrogen. The IGF-1R at the plasma membrane was increased by 30% upon treatment while the levels of renal nIGF-1R increased by 3 to 4-fold compared to control. This was coupled with an 8-10-fold decrease in the levels of one of the DNA repair enzymes, and with increased cell proliferation. This paper was the first to suggest an association between nIGF-1R and DNA repair that may induce carcinogenesis. However, the mechanism of IGF-1R nuclear translocation was not known.

It was not until 2010, when Sehat and colleagues (2010) reported that SUMOylation of the IGF-1R is essential for its nuclear translocation. The IGF-1R translocate to the nucleus as an intact receptor (comprised of α-and β-subunits). Besides, nIGF-1R was observed binding with enhancer-like elements in the genomic DNA which promoted transcription. The SUMOylation sites were recognized as three evolutionarily conserved lysine residues (Lys-1025, Lys-1100 and Lys-1120) of the beta subunit (Sehat et al., 2010).

SUMOylation is a type of post translational modification (PTM) that involves small ubiquitin-like modifier (SUMO) proteins. IGF-1R from human melanoma cells (DFB cell line) grown with or without serum using immunoprecipitation and Western blotting with anti-SUMO-1 antibody showed 145-kD band with the serum which suggested SUMO-1 modify IGF-1R and receptor is SUMOylated. Furthermore, the authors suppressed IGF-1R nuclear translocation via dansylcadaverine (is a lysosomotropic agent) or hypertonic medium suggesting that the receptor localizes to nucleus from the cell membrane. In addition, tyrphostin AG1024 (IGF-1R inhibitor) was used to determine whether receptor kinase activity was essential in nuclear translocation process. AG1024 decreased the nuclear accumulation of IGF-1R compared to control cells manifesting that kinase activity is essential for IGF-1R nuclear translocation (Sehat et al., 2010).

In the same year Aleksic et al., (2010) demonstrated that IGF-1R translocates to the nucleus, in various cancer cell lines, via clathrin-mediated endocytosis, which is regulated by the IGF-1 ligand. The IGF-1R nuclear localization was enhanced upon IGF-1 activation, also the translocation was relatively dependent on IGF-II and insulin. Blocking IGF-1R nuclear translocation using dansylcadaverine or the dynamin- 1 inhibitor dynasore suggested that the receptor’s translocation occurs via vesicle transport. Furthermore, IGF-1R β-subunit is a γ-secretase and in prostate cancer cells γ-secretase did not affect IGF-1R nuclear import, and full length IGF-1R was detected in the nucleus. Importantly, IGF-1R is the only receptor that predominantly translocates to nucleus as a whole receptor with its both subunits (Aleksic et al., 2010).

**SUMOylation in Cancer and Other diseases**

Post translational modification (PTM) is one of the most common and remarkable regulatory mechanisms of proteins with several cellular and biological functions. In the proteome, various proteins can be modified during or post translation. PTM include ubiquitination/ de-ubiquitination, phosphorylation/ dephosphorylation, acetylation/ deacetylation, neddylation/ de-neddylation and SUMOylation/ deSUMOylation (Bettermann et al., 2012). SUMOylation is a reversible PTM through which small ubiquitin-like modifiers (SUMO) are covalently bonded to lysine residues in a targeted protein. SUMOylation regulates the stability of various substrates and their subcellular localization. SUMOylation has gradually emerged as a significant molecular regulatory mechanism, in cell cycle, DNA repair pathways and in tumorigenesis. Proteomics screening identified cyclin-dependent kinases and cyclins as the targets of SUMOylation. SUMOylation and phosphorylation are both essential regulatory mechanisms for cell cycle progression (Alpern and Hebert, 2007). All eukaryotes express and conserve SUMO pathway and SUMOylation predominantly occurs in the nucleus (Watts, 2013). Various studies have shown that SUMOylated proteins are known to be implicated in several human diseases, proposing a significant role for SUMOylation in the disease progression. Examples include Huntington’s disease (huntingtin), Parkinson’s disease (tau, α synuclein, DJ-1), and Alzheimer’s disease (tau, APD) (Alpern and Herbert, 2007).

There are four SUMO isoforms, SUMO1, SUMO2/3 and SUMO4. In these four human SUMOs, the most common are SUMO 1-3 whilst SUMO-4 is predominantly expressed in kidney, spleen, and lymph nodes. Additionally, the size of these proteins is about ∼12 kDa. SUMO-1 is the most broadly studied out of all four (Bettermann et al., 2012). The SUMOylation process includes four enzymes: the activating enzyme E1 (i.e., SAE1, SAE2 also known as UBA2/ ASOS1), enzyme E2 (UBC9), enzyme E3 ligases and Sentrin/ SUMO-specific proteases (SENPs), which are involved in regulation of SUMO and deSUMOylation. Moreover, UBC9 is a SUMO-conjugating enzyme which plays a pivotal role in SUMOylation. UBC9 typically recognizes protein substrates and conjugates SUMO to the protein substrate (Zhang et al., 2015).

SUMO proteins are inactive precursors which undergo a cleavage by the SENP family. The cleavage process discloses a C-terminal diglycine motif, which exposes SUMO to conjugate to the lysine residues of target proteins. SUMO conjugation is mediated through E1, E2 and E3 enzymes (Wilkinson and Henley, 2010). The SUMO cycle stages include: 1) ATP-dependent mechanism provides the means of stimulating mature SUMO proteins on an active site of enzyme (E1, heterodimer of SAE1 and SAE2). A thioester bond is formed with cysteine residues in the SAE2 and C-terminal glycine residue of SUMO. 2) The SUMO is passed to the SUMO E2 conjugating enzyme UBC9 by means of thioester bonds. 3) At this stage SUMO is exposed to the target proteins via the enzyme E3. 4) SUMOylated substrate exhibits phenotypic differences to unmodified form.

IGF-1R is modified by SUMO to regulate genes associated with cellular signal transduction. The SUMOylated IGF-1R is translocated to the nucleus, where it binds to DNA and regulates transcription of certain genes (Zhang et al., 2015). This mechanism manifests the distinctive biological roles of IGF-1R and SUMO in cancer. In addition, some of the main functions of SUMO include organization of the eukaryotic genome, DNA repair, nucleocytoplasmic translocation, transcriptional regulation, DNA-protein, and protein-protein interactions (Zhang et al., 2015). Moreover, IGF-1R can be modified by SUMOylation in acute myeloid leukaemia (AML) (Zhang et al., 2015). IGF-1 increased the upregulation of IGF-1R, which increased the proliferation rate of AML cell lines, modified by SUMO-1. Disruption in SUMO proteins can lead to the development of a number of diseases such as cancer (Table. 1).

**Table 1.** Upregulation and downregulation of SUMO proteins in cancer.

|  |  |  |  |
| --- | --- | --- | --- |
| **Proteins** | **Up/Downregulation** | **Cancer types** | **Reference** |
| SUMO1 | Upregulated | Anaplastic large cell lymphoma | Villalva et al., 2002 |
| Colon | Zhang et al., 2013 |
| Liver | Guo et al., 2011 |
| SUMO2 | Upregulated | B cell lymphoma | Hoellein et al., 2014 |
| SUMO3 | Upregulated | B cell lymphoma | Hoellein et al., 2014 |
| UBC9 | Upregulated | Lung | Li et al., 2019; Moschos et al., 2010 |
| Breast | Moschos et al., 2010 |
| Prostate | Moschos et al., 2010 |
| Ovarian | Mo et al., 2005 |
| SENP1 | Upregulated | Prostate cancer | Cheng et al., 2006 |
| Downregulated | LNCaP (Prostate cancer cell line) | Kim et al., 2006 |
| SENP3 | Upregulated | Colon | Han et al., 2010 |
| SENP6 | Upregulated | Liver | Qian et al., 2013 |
| Gastric | Song et al., 2015 |
| Downregulated | Breast | Mooney et al., 2010 |

**DESUMOylation**

Highly dynamic protein SUMOylation can be reversed by the same SENP enzymes that are essential for the maturation of SUMO. In mammals there are six known as SENPs; SENP 1-3 and SENP 5-7. The SENP family plays an imperative role in managing paralogue specific SUMOylation by the removal of specific SUMO paralogues from the substrate proteins and/or take a part in cleavage of SUMO-SUMO conjugation activities (Yeh, 2009). In mammalian cell types SENPs have three main classes. Both SENP1 and SENP2 function in maturation of SUMO proteins and play a role in processing and deconjugation of SUMO-1 and SUMO 2/3. SENP1 is overexpressed in prostatic intraepithelial neoplasia and in prostate cancer tissues, while it is absent in normal prostate tissues. SENP1 leads to the development of early prostate cancer lesion into an advanced tumour. Out of all six SENPs, SENP1 is the first to play a crucial role in human disease pathogenesis (Yeh, 2009). SENP2 processes SUMO1 into the conjugatable state and also catalyses the SUMO1 deconjugation. In addition, mostly in vitro, it is hard to distinguish the activity if these two SENPs, however, SENP1 and SENP2 have different substrate specificity. Moreover, SENP3 and SENP5 select SUMO 2/3 as substrates over SUMO-1. They remove monomeric SUMO2/3 from substrates (Wilkinson and Henley, 2010). It has been recently shown that SENP3 also cooperate with nucleophosmin NPM1, a critical requirement in ribosome biogenesis (Yeh, 2009). The other two SENPs also prefer SUMO 2/3 as substrates and act as the editors for SUMO- 2/3 chains. SENP6 and SENP7 are not involved in maturation of SUMO proteins, also they are very modestly involved in deconjugation of monomeric SUMO 2/3 however, they are actively involved in deconjugation of poly SUMO 2/3 (Wilkinson and Henley, 2010).

**SUMOylation is imperative for IGF-1R internalization**

Nuclear translocation of IGF-1R is rising as a potentially significant factor in development of clinical prediction and cancer pathophysiology. But to date, its distinct role in cellular physiology is poorly understood. SUMOylation is likely a prerequisite of IGF-1R nuclear translocation. SUMOylation begins at a point when SUMO is activated by SUMO-activating enzyme such as SAE1 or SAE2. The activated SUMO is transferred to SUMO-conjugating E2 enzyme UBC9 (Desterro et al., 1999) and added to a lysine (Lys) residue of a specific protein.

Sehat and colleagues demonstrated the mechanism of SUMOylation and IGF-1R nuclear translocation (Sehat et al., 2010). The IGF-1R-deificient leiomyosarcoma SKUT-1 cells were transfected with plasmids containing WT-IGF-1R or mutant IGF-1R, analysed by Western blotting and were fractionated (Sehat et al., 2010). Three mutations displayed relatively less amount of nIGF-1R: K1025R, K1100R and K1120R by 76%, 43% and 29%, respectively. Analysis of the kinase domain of the phosphorylated IGF-1R using The Research Collaboration for Structural Biology, Protein Data Bank (code 1K3A) unveiled that Lys-1025, Lys-1100 and Lys-1120 are subjected to SUMOylation as they are the ones exposed at the receptor surface (Sehat et al., 2010). The Lys residues are in close proximity to tyrosine residue of the IGF-1R TK domain, and IGF-1R kinase activity inhibition relatively decreased the IGF-1R translocation. All of three Lys-1025, Lys-1100 and Lys-1120 predominantly contribute to SUMOylation mechanism of IGF-1R.

The IGF-1R localization in the nucleus was observed in human melanoma cells (DFB cell line) and human embryonic kidney (HEK) cell line by Western blotting analysis. IGF-1R localization was observed in human melanoma cells grown with or without the serum, in an immunoprecipitation experiment and Western blotting analysis. The results showed a 145-kD band which was identified by using an antibody directed against IGF-1Rβ. Therefore, it was determined that IGF-1R gets SUMOylated to undergo nuclear translocation. It was also determined that β subunit of IGF-1R was prone to SUMOylation and the α subunit is not modified by SUMO (Sehat et al., 2010).

**SUMOylated IGF-1R and cell proliferation**

Several studies suggest that IGF-1R nuclear translocation occurs in tumour cells and is associated with adverse outcomes and poor clinical outcomes. It was shown that SUMOylation is supremely important for IGF-1 receptor translocation (Sehat et al., 2010) and nIGF-1R was strongly related in various tumour cells (Aleksic et al., 2010). Therefore, Lin et al. sought to determine whether SUMOylated IGF-1R influence cell proliferation (Lin et al., 2017).

Cell clones expressing wild type (WT), or triple SUMO-sites mutated (TSM) were transfected with SUMO-modified IGF-1R and non-SUMO modified IGF-1R, respectively. The R-WT cells showed higher proliferation (t-test, p< 0.05 for all time points) as compared to R-TSM cells and R-puro (mock transfected cells). R-WT cells showed elevated levels of G1-S phase transition, the increase was from 12 to 38%. Hence, the data by Lin and colleagues suggested SUMOylated IGF-1R significantly induces cell proliferation. Both R-WT and R-TSM cells expressed equal kinase activity, however interestingly R-TSM cells were not found to be significantly associated with cell cycle progression and cell proliferation as compared to mock transfected cells (Lin et al., 2017). Lin et al. arrested each of the cell lines in the G1 phase by 36 hr serum starvation. They noted R-WT cells increased in S phase and decreased in G1 phase. After 16 hrs 26% increase was observed, then the decrease after 24 hrs however, the observation in R-TSM was 8% increase in S-phase after 24 hrs with no notable changes in R-puro cells. Some proteins involved in regulation and maintenance of cell cycle such as cyclin A, cyclin B1, cyclin D1, cyclin E, CDK1, CDK2, CDK4, p21, and p27 were examined. The R-WT cells exhibited the increase in G1/S cyclin D1 after 10 hrs, following an increase in S phase cyclin A after 16 hrs, and an increase in G2/M cyclin B1 after 16 and 24 hours (Lin et al., 2017). This suggests that SUMOylation of IGF-1R affects cell cycle progression.

**Nuclear accumulation of IGFBPs**

In eukaryotic cells, import of molecules into the cell nucleus occurs via nuclear pores, and is a fundamental event. By the process of diffusion, small molecules enter and exit through nuclear pore complexes whilst, large macromolecules (> 45kDa) including proteins, carry Nuclear Localization Signals (NLSs) (Iosef et al., 2008). The NLS contains a single cluster (monopartite NLS) or two clusters (bipartite NLS) therefore, the NLS are recognized by importin- α and importin- β. IGFBPs localize to the nucleus through the classical nuclear import pathway. Out of all IGFBPs, four possesses a putative NLS hence, translocate to the nucleus (Poreba and Durzynska, 2020).

The two IGFBPs -2 and -6 interact with importin-α and -3 and -5 interacts with importin-β for their nuclear translocation. IGFBP-2 is highly expressed in several human cancers, including prostate, breast, and neuroblastoma. Additionally, it is involved in intranuclear activities. Importin-α is predominately involved in nuclear uptake of IGFBP-2 as it distinguishes the NLS sequence of IGFBP-2 (Azar et al., 2014). The action of nuclear IGFBP-2 may include binding to DNA, plays a role as a transcription factor and promotes tumorigenesis. Intracellular trafficking of IGFBP-3 and -5 were shown in the nuclei of T47D breast cancer cells (Schedlich et al., 2000). The C-terminal domain of IGFBP-3 contains NLS and it has been associated with the pathogenesis of cancers. Moreover, the nuclear import of IGFBP-3 and its retention in the nucleus have been linked with phosphorylation by DNA-dependent kinase (DNA-PK) (Poreba and Durzynska, 2020). Nuclear IGFBP-5 plays a significant role in carcinogenesis. In MDA-MB-435 breast cancer cells, IGFBP-5 is translocated to the nucleus where it is linked with high proliferation and motility (Akkiprik et al., 2009). Moreover, the deletion of 5 amino acids in NLS altered the subcellular localization of IGFBP-5. IGFBP-6 nuclear internalization was observed in rhabdomyosarcoma and HEK 293 cells (Iosef et al., 2008). Within the NLS of IGFBP-6 it carries positively charged Arg and Lys residues. The mutations of one residue or in combination effects the nuclear accumulation of IGFBP-6. Importantly, all members of IGFBP family do not have similar nuclear import mechanisms.

**Nuclear translocation of IGF-1R**

It has been discovered that in genomic DNA, nIGF-1R binds to putative enhancer sites (Sehat et al., 2010). Nuclear IGF-1R binding partners are histone H3 and RNA polymerase II (Aleksic et al., 2010), brahma-related gene-1 proteins (Warsito et al., 2016), proliferating cell nuclear antigen (Waraky et al., 2017). Additionally, nuclear IGF-1R was identified to promote its own gene expression by cellular IGF-1R (Sarfstein et al., 2012).

The IGF-1 receptor lacks putative NLS (Wu et al., 2012) which is an amino acid sequence that labels a protein for the translocation to cell nucleus by nuclear transport. A protein has NLS on its DNA sequence which is comprised of at least one (or more) sequence of either lysines or arginines that are displayed on the protein surface. A signalling sequence called nuclear export signals (NES) does the opposite and exit the proteins from the cell nucleus. Therefore, for IGF-1R to translocate to the nucleus without NLS suggests that the receptor requires a binding partner to enter the nucleus.

Aleksic et al. (2010) found that the nuclear IGF-1Rβ was phosphorylated in the presence of the ligand and potential IGF-1R kinase activity is necessary for IGF-1R nuclear translocation. To test this observation, the IGF-1R inhibitors MAB391 (blocks IGF-1R autophosphorylation upon activation of IGF-1) and AZ12253801 (blocks IGF-1R activation) were used to block IGF-1R kinase activity. Both inhibitors blocked IGF-1R stimulation and in addition, MAB391 downregulated IGF-1R in the nuclear compartment. Furthermore, the authors showed by immunoprecipitation and confocal microscopy that nIGF-1R phosphorylation and its nuclear accumulation were significantly blocked by AZ12253801 (Aleksic et al., 2010). This study results suggested indeed, the IGF-1R kinase activity is an essential component for its nuclear localization.

Early Endosome Antigen 1 (EEA1) is known to play an essential role in endosomal trafficking. Phosphatidylinositol 3-phosphate binds EEA1 through its C-terminal. Immunoprecipitation and immunofluorescence data by Packham et al. (2015) showed colocalization of EEA1 and nIGF-1R (Packham et al., 2015). It was determined by Packham et al. that dynactin subunit p150Glued, which interacts with microtubules and is necessary for vesicle transportation, also mediates the nuclear translocation of IGF-1R. The authors also demonstrated that nuclear pore complexes, which connect nucleoplasm and cytoplasm, are mediated by importin- β and RanBP2. Disruption of any of these proteins leads to reduced levels of nIGF-1R expression. In H1299 and HEK293 cells, proximity ligation assays (PLA) and immunoprecipitation revealed the association of IGF-1R and p150Glued. Importin-β downstream of dynactin mediates the translocation of tyrosine kinase receptors such as EGFR and ErbB-2 and it also co-localizes with IGF-1R. Furthermore, to determine importin-β role in nuclear localization of IGF-1R, it was downregulated by siRNA transfection. Nuclear IGF-1R exhibited 46% decrease following 58% knockdown of importin-β (Packham et al., 2015).

RanBP2 is a part of nucleoporin in that it contains an active SUMO E3 ligase. RanBP2 controls shuttling of the proteins between the nuclear and cytoplasmic filaments of the cell. It contains phenylalanine–glycine repeats that attaches with importin-β. The PLA experiment revealed an association between the IGF-1R and RanBP2. The results demonstrated the significance of RanBP2 in nuclear IGF-1R, RanBP2 was downregulated by siRNA which decreased nIGF-1R expression by 70% (Packham et al., 2015). SUMOylation of IGF-1R is indeed a significant factor in its nuclear accumulation (Sehat et al., 2010). As the SUMOylation occurs near the nuclear envelope nucleoporin, RanBP2 might be E3 ligase for the receptors SUMOylation. H1299 cells were transfected with HA-RanBP2E3 or by the empty vector to determine the E3 ligase domain activity of RanBP2 on IGF-1R. Compared to the empty vector, RanBP2E3 transfected cells showed 55% increase in IGF-1R SUMOylation, which s may indicate that RanBP2E3 SUMOylates IGF-1R. As identified by Warsito et al. (2012) and Aleksic et al. (2010), in H1299 and D145 cells, the nuclear IGF-1R reaches its maximum levels upon stimulation by IGF-I after 30-60 min and 15 min, respectively (Warsito et al., 2012; Aleksic et al., 2010). This was confirmed by Packham et al. (2015) who showed that after 30 min of IGF-I stimulation the increase was observed in the interaction between IGF-1R and p150Glued or importin-β, but not in RanBP2 expression. However, RanBP2 is essential for the receptor’s stability.

Taken together, nuclear translocation of the IGF-1R takes place via a pathway in which plasma membrane IGF-1R undergoes clathrin-mediated endocytosis into EEA1-positive vesicles, dynactin/p150Glued transports IGF-1R to the nucleus, following that, importin- β spots IGF-1R and positions it at the nuclear pore complex then accordingly RanBP2 SUMOylates IGF-1R and translocates it into the cell nucleus (Fig 6).

A picture containing drawing

Description automatically generated

**Figure 6.** IGF-1R nuclear translocation pathway from the cell membrane to cell nucleus. This figure is taken from Packham et al., 2015.

A more recent study suggested that nuclear translocation of IGF-1R might be dependent on the Protein Inhibitor of Activated STAT3 (PIAS3) (Codony-Servat et al., 2017). PIAS3 also functions as a SUMO E3 ligase and maintains IGF-1R inside the cell nucleus. Immunoblot analysis of PIAS3 revealed that it increased after the treatment with ganitumab (Anti-IGF-1R mAB), NVP-AEW541 (IGF-1R inhibitor) and a combination of both in HT29-OxR cells. This led to support the association between PIAS3 and nIGF-1R. In HT29-OxR and DLD-1-OxR cells, transient transfection of siRNAs directed against PIAS3 revealed loss-of-function of PIAS3. Silencing of this protein reduced nIGF-1R expression. The data by these authors manifest that curcumin (specific inhibitor of DYRK2) reduced the nuclear translocation of IGF-1R in HT29 and HT29-OxR cells. Similar effects were observed in these cell lines upon the treatment with leptomycin B (a nuclear import inhibitor) (Codony-Servat et a., 2017). Therefore, PIAS3 might be playing a significant role in retaining IGF-1R inside the cell nucleus.

The study by Deng et al (2011) suggests that nIGF-1R is originated at the cell surface only. In MCF-7 (breast cancer cell line) the effects of figitumumab- CP-751, 871 (a human monoclonal antibody targeting the IGF-1R) on IGF-1R were analysed by Western blotting. The antibody caused the downregulation of IGF-1R. The authors sought to determine whether the nIGF-1R originate from cell surface and/or is a newly synthesized intracellular receptor. CP-751, 871 (which only affects cell membrane receptors) caused the decrease of membrane and nuclear receptors equally, however, pro-receptors experienced no change. The pro-receptors of IGF-1R were only detectable in membrane fractions, indicating no transfer occur between subcellular fractions. Furthermore, as the antibody only affect cell membrane receptors, this further indicated that nIGF-1R originates solely from the cell surface. To counter check their findings, they observed that phosphorylation-deficient receptor without phospho- Y1131, Y1135 and Y1136 residues failed to translocate to the nucleus. This suggested that sufficient phosphorylation of IGF-1R at cell membrane is required to drive its translocation to the cell nucleus (Deng et al., 2011). In contrast, another study presented that IGF-1R translocation takes place from the plasma membrane to the cell nucleus and assists its way to nuclear envelope (Packham et al., 2015). As mentioned above, nuclear translocation of IGF-1R leads its way through dynactin subunit p150Glued. Nuclear pore passage is regulated by importin-β followed by RanBP2 (this also stimulates SUMOylation of IGF-1R). Most significantly, dynactin, importin-β or RanBP2 disruption results in reduction of nIGF-1R accumulation. Additionally, UBC9, a specific SUMO-conjugating enzyme, was observed to be associated with nIGF-1R. The increased levels of UBC9 lead to the high levels of nIGF-1R and vice versa. In tumour cell lines UBC9 was 2.3-fold higher than in normal cells. The cancer cell lines surpassing 0.5 value of UBC9 expression exhibited over accumulated nIGF-1R. Furthermore, the C-terminal domain of IGF-1R influences accumulation of nIGF-1R. The cells expressing the truncated IGF-1R C terminus displayed 80% reduction in the nuclear translocation (Deng et al., 2011).

**3.6 Potential functions of nIGF-1R in cancerous cells**

**Potential function of nIGF-1R in transcription**

To discover whether nIGF-1R binds to enhancer regions and regulates the transcriptional activity, Sehat et al. (2010) used electrophoretic mobility shift assays with the biotin labelled, double stranded, 40 base pair oligonucleotides. The nucleus was extracted from the DFB melanoma cells. The electrophoretic data determined proteins binding to the DNA probe, and on the addition of an IGF-1R antibody, protein-DNA complex was super shifted. This indicated that there is an association between IGF-1R and the DNA sequence, either alone or in a complex (i.e., with other proteins). Moreover, competitive binding diminished the super shift bands. Thus, this further indicated that IGF-1R interacted with double-stranded DNA. Finally, it was concluded that DNA fragments were categorized as transcriptional regulatory elements because cells transfected with plasmid encoding IGF-1R displayed increased transcriptional activity in contrast, to cells with the empty vectors (Sehat et al., 2010). Aleksic and colleagues discovered nIGF-1R in less dense areas of DNA, which explains why nuclear IGF-1R is readily accessible to transcription factors. The IGF-treated and serum starved cells were co-stained with IGF-1Rβ and RNA poly II. The results showed that IGF-1 stimulates IGF-1R co-localization with RNA poly II and its binding to chromatin with histone H3. Hence, the results indicated IGF-1R involvement in transcriptional regulation (Aleksic et al., 2010).

Furthermore, the study in 2012 also determined that nIGF-1R binds to enhancer sites and plays a significant role as a transcriptional cofactor (Warsito et al., 2012). The nIGF-1R co-localizes with LEF1 (Lymphoid enhancer-binding factor -1), which is a transcription factor and elevates the promoter activity of LEF1 downstream target genes i.e., cyclin D1 and axin2. Moreover, the association between IGF-1R and β-catenin were observed in several human cancer cell lines, such as human melanoma (DFB), non-small lung carcinoma (H1299) and human cervical carcinoma (HeLa). β-catenin forms a complex with T cell factor (TCF) and LEF1, which in turn stimulate the transcription of these downstream target genes (Warsito et al., 2012). Furthermore, the association was determined between IGF-1R, β-catenin and LEF1. Importantly, IGF-1R and β-catenin complex was detected in both the membrane and nucleus but LEF1 colocalizes with IGF-1R exclusively in the nucleus. The IGF-1R and LEF1 interactions were dependent on the activation of ligand as serum starved H1299 cells transfected with Myc-LEF1 augmented upon the addition of IGF-1. The IGF-1R/Myc-LEF1 co-IP bands appeared shortly following IGF-1 addition. However, the IGF-1R and LEF1 co-localization is independent of β-catenin. The association was not compromised by β-catenin overexpression or by its knockdown, indicating that their colocalization is unaffected by β-catenin.

Furthermore, TSM-IGF-1R cells, which exhibit the same signalling and internalization properties as WT-IGF-1R cells, does not accumulate IGF-R in the nucleus because it is non-SUMOylated. In addition, nIGF-1R increased transcription of target genes encoding signalling downstream of LEF1. Cyclin D1 and axin2 increased by 17% and 22%, respectively in cells expressing WT-IGF-1R. Whereas, cyclin D1 and axin2 promoter activity was decreased by 7% and 20%, respectively in TSM-IGF-1R cells (Warsito et al., 2012).

**Nuclear IGF-1R binding partners**

To date, all published studies, propose that IGF-1R in the nucleus is linked with DNA binding transcription factor activity. The binding partners of IGF-1R in the cell nucleus were identified by Werner and colleagues, who designed mass spectrometry (MS) based proteomic analysis experiments to identify proteins specifically interacting with the nuclear receptor (Werner et al., 2019).

Potential proteins interactors with nIGF-1R were explored in both benign MCF10A breast epithelial cells and malignant MCF-7 breast cancer cells. MS analysis distinguished 18 proteins that were involved with IGF-1R in MCF10A cells and 11 proteins with MCF7 cells. However, more notably 4 common proteins particularly interacted with nIGF-1R in both cell lines including NOM1, ALDH18A1, TJP2 and SIPA1L1. Considering nucleolar protein NOM1 interacted with IGF-1R in both cell lines, it was marked for follow-up analysis. It is a protein that contain MIF4G domains, and functions in protein translation and apoptosis. Co-immunoprecipitation assays revealed the physical interaction between NOM1 and IGF-1R in both cell lines (Werner et al., 2019). To test whether IGF-1R expression is associated with NOM1 protein expression, the selected cell lines were introduced to pEGFP-IGF-1R or empty pEGFP-N1 plasmid. Cells that were transfected with IGF-1R containing plasmids visibly showed upregulated levels of NOM1 in nuclear fractions extracted from MCF7 cells compared with cells with pEGFP-N1 plasmid (Werner et al., 2019).

A recent study demonstrated the association of phosphorylated nIGF-1R with phosphorylated histone H3 at tyrosine 41 in HeLa cells (Warsito et al., 2016). H3 contains Y41, Y54, and Y99 (three highly conserved tyrosine residues) and H3Y41 is phosphorylated by nIGF-1R as WT-IGF-1R increased phospho-H3Y41 5-fold as compared to TSM-IGF-1R which exhibited 2.7-fold increase. Nuclear IGF-1R induced phosphorylated H3Y41 drove the stable binding of Brg1 protein to chromatin. SNAI2 gene was upregulated by nIGF-1R hence, it is considered one of the target genes of nIGF-1R. SNAI2 is a part of Snail family of C2H2 class zinc finger transcription factors and is proficient in repressing E-cadherin. The protein is notably involved in malignant cell invasion and metastasis. Furthermore, nIGF-1R and Brg1 were detected on SNAI2 promoter (Warsito et al., 2016). This notion is corroborated in a study by Aleksic et al. that showed that nIGF-1R was actively present in chromatin to directly bind with DNA at RNA polymerase II sites (Aleksic et al., 2018). In addition, JUN and FAM21 expression were augmented by nIGF-1R. JUN and FAM21 enhance the tumour cell growth and IGF-induced migration.

**Nuclear IGF-1R /PCNA interaction**

Based on identifying the binding partners of nIGF-1R, Waraky and colleagues (2017) identified proliferating cell nuclear antigen (PCNA), a nuclear protein to interact with nIGF-1R (Waraky et al., 2017). The authors used immunoprecipitated IGF-1R from human embryonic stem cells and analysed the co-immunoprecipitated proteins by mass spectrometry. They concluded that nIGF-1R phosphorylates PCNA and plays a role in the DNA Damage Tolerance pathway (DDT). DDT is a mechanism that bypasses single-stranded DNA lesions encountered by DNA polymerases during DNA replication. This prevents the stalling of DNA replication forks (Bi, 2015).

DNA replication stress originates from several different events (Fig. 7) that contribute to its initiation including as follows: 1) Unusual DNA structures 2) Mis incorporated rNTPs 3) Interference between replication and transcription on DNA 4) short of essential DNA replication constituent 5) Inaccessibility of chromatin 6) Common fragile sites 7) Dysregulated levels of oncogenes (Zeman and Cimprich, 2014).

A close up of text on a white background

Description automatically generated

**Figure 7.** The events that lead to replication stress. This figure is taken from Zeman and Cimprich, 2014.

Normal cells may experience replication stress and have the ability to combat it via DNA damage response. Cancer cells I experience chronic replication stress due to loss of proteins which restore stressed replication fork. DDT mechanisms prevent replication stress by promoting translesion synthesis (TLS) and error-free template switching (TS). Moreover, PCNA is the sliding DNA clamp and plays a critical role in regulation of DDT pathway (Waraky et al., 2017). It plays a significant role in DNA replication; it encircles around dsDNA and functions as sliding clamp to recruit other proteins.

Ubiquitination of PCNA plays a pivotal role in the regulation of mono-ubiquitination of PCNA prompts switching to low fidelity DNA polymerases, which bypass translesion synthesis, whereas PCNA polyubiquitination induces template switching (Fig. 11). The data revealed that IGF-1R directly phosphorylates three PCNA tyrosine (Tyr-60, -133, and -250) residues, which leads to mono- and polyubiquitination. This function suggests that nIGF-1R plays an important role to rescue replication fork stalling in cells exposed to DNA damage. Results indicated that IGF-1R phosphorylates PCNA, which is mediated by nIGF-1R and not via canonical signalling pathway of IGF-1R as; IGF-1R and PCNA bound solely in the cell nucleus, IGF-1R phosphorylates PCNA in the absence of other kinases. Only PCNA from cells expressing WT- IGF-1R exhibited phosphorylation whereas, TSM- IGF-1R cells did not exhibit phosphorylation, Blocking of IGF-1R canonical pathway]by specific inhibitors did not void phosphorylation and ubiquitination of PCNA (Waraky et al., 2017).

The data revealed that the IGF-1R increases tolerance to DNA damage and the link between DNA damage tolerance (DDT) and IGF-1R/PCNA has been established as IGF-1R phosphorylates PCNA. Phosphorylated PCNA is a key player in regulating DNA repair and replication. This is compatible with the finding that the Y-60, Y-133, and Y-250 mutants are important for IGF-1R/ PCNA interaction and affect ubiquitination of PCNA. Ubiquitination of PCNA significantly shown to regulate DDT. Based on this, polyubiquitination of PCNA activate the DDT pathway to prevent replication fork collapse. This could happen because of DNA damage or defects in DNA replication machinery. Furthermore, Waraky et al. demonstrated that IGF-1R is imperative for PCNA ubiquitination. Nuclear IGF-1R phosphorylates PCNA on Y-60, Y-133, and Y-250 which causes mono- and poly ubiquitination of PCNA by the DDT E2/E3 ligases. Hence, phosphorylation of these three residues is essential for the interaction between nIGF-1R and PCNA. It was noted that IGF-1R prevents replication fork stalling and support genetic stability in human embryonic stem cells (Waraky et al., 2017). Conclusively, the results suggest a role of IGF-1R in DDT.

The most recent study by Yang et al. (2020) investigated the relationship between IGF-1R and PCNA in samples of cancer tissue and cancer cells (Yang et al., 2020). The cancer tissues from clinical tumours were studied for IGF-1R/PCNA colocalization. Different types of cancers including 29 primary and 6 metastasized were studied. Tumour tissues exhibited binding of IGF-1R and PCNA in both cytoplasm and nucleus, however, weaken nuclear colocalization signals were detected in primary tumours as compared to metastasized tissues. Intense signals were noted in a small subset of clinical cancers including malignant melanoma, ovarian carcinomas, urothelial carcinomas, pulmonary carcinomas, ductal carcinomas, and squamous cell carcinoma (Yang et al., 2020).

The association between IGF-1R and PCNA may promote resistance to chemotherapy. This interaction was absent in tumour cells that survived radio- and chemotherapy. Surprisingly, the treated tumour cells showed suppressed nuclear IGF-1R-immunoreactivity and depletion in IGF-1R and PCNA signals. The 2 selective clinical cancer, invasive oropharyngeal squamous cell carcinoma and high-grade ovarian cancer examined for IGF-1R/PCNA colocalization associated with better overall survival (OS). In ovarian cancer, significantly higher IGF-1R/PCNA association cognate with better OS (p=0.037) and correspondingly better OS in oropharyngeal SCC (p=0.027). Furthermore, ex vivo irradiation in tissue sample of ovarian cancer initiated the binding of IGF-1R/PCNA and also increased the formation of γH2AX foci. This infer that colocalization of IGF-1R/PCNA is increased in presence of DNA damage and redeem stalled replication fork (Yang et al., 2020). Overall, several cancer tissues displayed nIGF-1R bind to PCNA, which supports the notion that human cancers rely on this approach to tolerate DNA damage.

To sum up, several proteins discovered act as a binding partner of nuclear IGF-1R (Table 2).

**Table 2.** The nuclear proteins discovered to date that are associated with nIGF-1R.

|  |  |
| --- | --- |
| **Nuclear proteins** | **References** |
| LEF1 (Lymphoid enhancer binding factor 1) | Warsito et al., 2012 |
| E3 SUMO protein ligase RanBP2 | Packham et al., 2015 |
| Importin-β (belongs to the family of Karyopherins | Packham et al., 2015 |
| Dynactin subunit p150Glued | Packham et al., 2015 |
| PCNA (Proliferating cell nuclear antigen) | Waraky et al., 2017; Yang et al., 2020 |
| RAD18 (E3 ubiquitin protein ligase), E3 ubiquitin-protein ligase SHPRH and Helicase-like transcription factor HLTF | Waraky et al., 2017 |
| Histone H3 | Warsito et al., 2016 |
| Amphiregulin | Guerard et al., 2018 |
| Nucleolar protein NOM1 | Werner et al., 2019 |
| Brahma-related gene-1 proteins | Warsito et al., 2016 |
| Ubc9 SUMO conjugating enzyme | Aleksic et al., 2010, Deng et al., 2012 |

**Nuclear IGF-1R enhances IGF-1R promoter activity**

Many researchers have identified upregulated expression of IGF-1R to be directly associated with breast cancer. However, the impact of IGF-1R nuclear translocation in the development of breast cancer is not well elucidated. Sarfstein et al. identified key feature of IR and IGF-1R nuclear translocation and IGF-1R gene expression in ER depleted and ER positive breast cancer cells (Sarfstein et al., 2012). Cellular IGF-1R autoregulates IGF-1R gene expression and this mechanism is categorically dependent on the ER status. Proteomic study based on DNA affinity chromatography and ChIP analyses confirmed that both receptors explicitly bind to IGF-1R promoter in ER depleted cells however, not in ER positive cells (Sarfstein et al., 2012). Co-transfection experiment indicated IGF-1R increased the IGF-1R promotor activity, and the effect of IR levels indicated that it decreased IGF-1R promoter activity in both cell lines. Western blot data and visual inspection of confocal image showed that higher IGF-1R levels were identified in the nucleus of ER positive cells, in contrast, higher IR levels were identified in ER depleted cells. Cell fractionation and confocal microscopy analysis revealed that similar to IGF-1R, the IR is also SUMOylated to undergo nuclear translocation. Moreover, the IP assays exhibited that SUMO-1 was conjugated to both IGF-1R and IR in ER positive and ER depleted breast cancer cell lines (Sarfstein et al., 2012). Importantly, nIGF-1R and not IR increased IGF-1R promoter activity. The transcription factors IGF-1R and IR exhibited completely opposite mechanisms in respect to IGF-1R gene regulation.

**3.7 Nuclear IGF-1R in Cancer**

**Nuclear IGF-1R in Prostate Cancer**

Nuclear IGF-1R in cancer has emerged as a novel topic. Not much has been published in this field. IGF-1R nuclear localization could be identified in prostate cancer, breast cancer, renal cell carcinoma (RCC) cells (Aleksic et al., 2010), and colorectal cancer (Codony-Servat et al., 2017). Nuclear IGF-1R is simultaneously associated with adverse patient outcomes in Synovial sarcoma (Palmerini et al., 2015) and in Rhabdomyosarcoma (van Gaal et al., 2013). Further research has sought to find targeted therapies for nIGF-1R, as it can cause chemotherapy and targeted therapy resistance (Codony-Servat et al., 2017).

Nuclear IGF-1R is significantly associated with advanced tumour stages in clinical prostate cancer (Table 3). Immunohistochemistry (IHC) was conducted to detect IGF-1R in the membrane, cytoplasm, and nucleus of 137 radical prostatectomies (RPs) from patients with prostate cancer (Aleksic et al., 2018). Nuclear IGF-1R was high in malignant epithelium whereas IGF-1R was significantly high in benign epithelium. This suggested nIGF-1R association with high grade tumours as stage 1 and 2 had reduced expression of nIGF-1R as compared to stage 3, PT1-2 vs. 3, P=0.011 and stage 3 vs. stage 4-5 P= 0.057.

**Table 3.** Association of nIGF-1R with advanced stages of prostate cancer. This table is taken from Aleksic et al., 2018.

|  | Internalized IGF1R | | |
| --- | --- | --- | --- |
|  | IGF1R ≤ 6 | IGF1R > 6 | P |
| Stage | | | |
| Stage pT1–2 | 40 | 27 | 0.293 |
| Stage pT3 | 35 | 34 |  |
| Grade | | | |
| Gleason grade 6 + 7(3 + 4) | 59 | 39 | 0.057 |
| Gleason grade 7(4 + 3) + 8–9 | 16 | 22 |  |
| PSA | | | |
| 0–10 | 60 | 43 | 0.422 |
| >10 | 15 | 15 |  |
|  | Nuclear IGF1R | | |
|  | IGF1R = 0 | IGF1R > 0 | P |
| Stage | | | |
| Stage pT1–2 | 50 | 17 | 0.011 |
| Stage pT3 | 37 | 32 |  |
| Grade | | | |
| Gleason grade 6 + 7(3 + 4) | 64 | 34 | 0.602 |
| Gleason grade 7(4 + 3) + 8–9 | 23 | 15 |  |
| PSA | | | |
| 0–10 | 67 | 36 | 0.612 |
| >10 | 18 | 12 |  |

The role of nIGF-1R in human DU145 prostate cancer cells was investigated and the distance of IGF-1R as well as RNA pol2, H3K4me1 and H3K4me3 (regulatory elements) from transcription start site (TSS) was calculated by ChIP-seq. The peaks for each RNA pol2, H3K4me1/3 was identified as 16,239, 19,759 and 21,782, respectively. RNA pol2, H3K4me1/3 peaks were identified within the range of 300 kb of TSS whilst IGF-1R peaks appeared to cluster around TSS. Most of the sites of IGF-1R recruitment were detected with the peaks of RNA poly2 and H3K4me1 i.e., out of 62 regions of IGF-1R binding, 95% coexisted with RNAPol2 peaks, 87% with H3K4me1 peaks, and 50% with H3K4me3. The significant sites were detected within JUN and FAM21A/C genes which was also associated with RNAPol2 and H3K4me1 peaks in both DU145 cells and SK-N-MC (Ewing sarcoma cells). The significant difference between the previous reports and Aleksic et al. is that they did not identify IGF-1R on any of the promoters previously discovered, thus proposing cell type specific differences (Aleksic et al., 2018).

To corroborate that IGF-1R attaches directly to DNA, electrophoretic mobility shift assay (EMSA) was performed using probes corresponding to ChIP-seq–identified IGF1R binding peaks, which represented IGF-1R binding region with JUN and FAM21A promoters (Fig 8). Upon the addition of recombinant human IGF-1R protein the probe mobility was retarded (Aleksic et al., 2018).

![A close up of a device

Description automatically generated](data:image/jpeg;base64,/9j/4AAQSkZJRgABAQEBLAEsAAD/4S/GRXhpZgAATU0AKgAAAAgABgALAAIAAAAmAAAIYgESAAMAAAABAAEAAAExAAIAAAAmAAAIiAEyAAIAAAAUAAAIrodpAAQAAAABAAAIwuocAAcAAAgMAAAAVgAAEUYc6gAAAAgAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAFdpbmRvd3MgUGhvdG8gRWRpdG9yIDEwLjAuMTAwMTEuMTYzODQAV2luZG93cyBQaG90byBFZGl0b3IgMTAuMC4xMDAxMS4xNjM4NAAyMDIwOjA3OjEyIDE0OjI2OjIxAAAGkAMAAgAAABQAABEckAQAAgAAABQAABEwkpEAAgAAAAM5NgAAkpIAAgAAAAM5NgAAoAEAAwAAAAEAAQAA6hwABwAACAwAAAkQAAAAABzqAAAACAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAMjAyMDowNzoxMiAxNDoyNToyOAAyMDIwOjA3OjEyIDE0OjI1OjI4AAAAAAYBAwADAAAAAQAGAAABGgAFAAAAAQAAEZQBGwAFAAAAAQAAEZwBKAADAAAAAQACAAACAQAEAAAAAQAAEaQCAgAEAAAAAQAAHhoAAAAAAAAAYAAAAAEAAABgAAAAAf/Y/9sAQwAIBgYHBgUIBwcHCQkICgwUDQwLCwwZEhMPFB0aHx4dGhwcICQuJyAiLCMcHCg3KSwwMTQ0NB8nOT04MjwuMzQy/9sAQwEJCQkMCwwYDQ0YMiEcITIyMjIyMjIyMjIyMjIyMjIyMjIyMjIyMjIyMjIyMjIyMjIyMjIyMjIyMjIyMjIyMjIy/8AAEQgBAADxAwEhAAIRAQMRAf/EAB8AAAEFAQEBAQEBAAAAAAAAAAABAgMEBQYHCAkKC//EALUQAAIBAwMCBAMFBQQEAAABfQECAwAEEQUSITFBBhNRYQcicRQygZGhCCNCscEVUtHwJDNicoIJChYXGBkaJSYnKCkqNDU2Nzg5OkNERUZHSElKU1RVVldYWVpjZGVmZ2hpanN0dXZ3eHl6g4SFhoeIiYqSk5SVlpeYmZqio6Slpqeoqaqys7S1tre4ubrCw8TFxsfIycrS09TV1tfY2drh4uPk5ebn6Onq8fLz9PX29/j5+v/EAB8BAAMBAQEBAQEBAQEAAAAAAAABAgMEBQYHCAkKC//EALURAAIBAgQEAwQHBQQEAAECdwABAgMRBAUhMQYSQVEHYXETIjKBCBRCkaGxwQkjM1LwFWJy0QoWJDThJfEXGBkaJicoKSo1Njc4OTpDREVGR0hJSlNUVVZXWFlaY2RlZmdoaWpzdHV2d3h5eoKDhIWGh4iJipKTlJWWl5iZmqKjpKWmp6ipqrKztLW2t7i5usLDxMXGx8jJytLT1NXW19jZ2uLj5OXm5+jp6vLz9PX29/j5+v/aAAwDAQACEQMRAD8A9/ooAKKACigAooAKKACigAooAKKACigAooAKKACigAooAKKACigAooAKKACigAooAKKACigAooAKKACigAooAKKACigAooAKKACigAooAKKAKmpapYaNYyX2pXcNpax/elmcKo9PxqvoviHSPEVs9xo+o297EjbXaJs7T6EdR+NAGnRQAUUAFFABRQAUUAFFABRQAUUAFFABRQAUUAFFABRQAUUAFFAHnPxSaG31Hwjf6mu7QrbU918WXKISuI2Yf3Q2a0vC+o+FdX8W6rd+HbUyTLBHHdahb8W8pzlUGDhnA7gdO9AHaUUAFFABRQAUUAFFABRQAUUAFFABRQAUUAFFABRQAUUAFFABRQAySKOaNo5UV42GGVhkH8Kbb20FpEIraCOGMdEjQKPyFAEtFABUS3MLXUlsHzNGiyMuOisWAP4lW/KgChL4h0uEopuGeR5ZIkiiieR2aM4fCqCSFPU4xUR8U6TmBUmnledXZI4bWWR8IwV8qqkrhiAcgc0ASv4i0mMXe+8VWs7cXNzGVbfDGQSCy4yDgHgjPtUlnrVjfXRtYXmW4EfmCOe3khYpnG4B1GRkjp6igDQooAKKAI5p4rdVaVwgZ1QE92Y4A/EkVJQAVHFPFM8qRuGaF9kgH8LYBwfwIP40ASUUAFFAEX2qD7X9k81ftHl+Z5ffbnGfpmpaAGSSJDE8sjBURSzMewHU0RSxzwxzRMHjkUMjDoQeQaAH1HBcRXMXmwSB0yV3D1BIP6g0ASUUAFFABRQAUUAVtQikn026hi/1kkLqnOOSCBXGf8IUyaYVisYRdx6daRQvuG5Z0d2kbd6nIJbvQBMmiavpeqPq0FoLpi15EYI5VWQJLMJEdC3y5wOQcdvTFQ2vhXV7/WrO81a5u4o0guRut7sRypveIojNGF3cKxOBjOOTQBo694euLuPXEsoUH23STbI24KXly/U+vI5NP0nw9caP4ne6MtzfW01qI1murkyPbMDkoMn7rcHgZyvORjAB1FMlTzYXj3Mm9Su5DgjPcH1oAisrX7HarB588+3P7yd9zn6mrFAGTrnh2w19IFvYyxgkV1IYjowYjg98YrTjjSGJIoxhEUKoz0AoAcQCCD0NY+j+GdO0O7vLmziKvcvuOWJ2jaoxyf8AZz+NAGzUN1B9qtpIPNli3jHmRNtZfoaAHQReRbxxeZJJsULvkbLN7k9zUlAGH/wimm/8JP8A295Z+0+XtxubG7Od3X8MdK3KAKWraXbazps1jdKWilUjgkYPY8U3R9JttE0uGwtFIjiUDJJO44AJ59cUAWri3iureS3mXdFIpVlyRkH6Vn6D4fsvD1m1tZqQHdnZiSc5Ynue2cUAatFABRQBwuqapLbWPjaJr547iNwLRTLh13W8YXZzkZfdjHfPeq2teJNaWDVv3lsloJruxiESMJlKW7yiTfuxnK4xj3zQBFqnjHUY7yWzheNrNhLamRYyrJIts0mfMLglgR0CEYP3s05fF2tWWmW1uHs7+5nS0MNxBHlUEqvwwaQB2/d8HcuSw47EAT/hLdaAWVIF+23Igttg2OiMJLoM4TzQuWEQGPM4JAycYMeo+KNZv9DL/aLSwaEWxnUffmL3BjzGyyEKPk6fN94rnjNAHQ+Jde1DTtWis7K4sIEFhPeu10jMW8op8owwxnccnnGOhqjH4j168mjCNY2cd3dtbQGeBmMO2Mud/wA4yxxtAGMYJyelAGZH4u1VrmbVUuLLyY7O1MtoQzeeTPNGTCdw27sAgkNn5RWp4V8XarresJFd2Cw2lzFNLF9xXi8twuD+8Zm68nauCMd6AO3pkztHDI6RtK6qSsakAsfQZwOfegCGxuJ7q0Sa4s5bOVs5hlZGZefVSR+tWaAKeo3dzZ26yWunT37ltpiheNSBzzl2UY/HPNWxyASMe1AC1i6Tca5LquoR6jaW8VokgEDRzljjYp4BRcjJbnPB4oA2qgvZ5ra0kmgtJLuVR8sMbKrPz2LED8zQA+CR5beOSSFoXZQWjcglD6EgkfkakoAppd3LapJatp0626puW7Lpsc8cAbt2fqMcVcoAgvXuktJGs4opbgD5UlkKKfxCt/Ks3wrcavdeGrGbXIEiv2gQyANyTtGSw2rtbOcqM49aANhiQpIUsQOAO9VdOuri8tvNutPmsZNxHlTOjNj1yjMP1oAt0UAFFAFabTrK4uo7qazt5LiL/VyvGCy/QnkU9rS2cENbxMGYsQUBySME/Ug4oAxPE4tdI0S/1iHT7J7yOMEPLAGzyF5xyQAfWsHT9ctFhu7K9t9JNuLmJZ3gs2jjcOrE7o35yNn3uQfqDQBPfeKdLXTIYovD8jrPLaxR208CIJIJJQiyKucYBJwpwQSMgZzT18RaL9m0+S60nztkUbefDaL5dskkjRp1OVG5Ogz69KAJ9cv9BGvWU81nLql2trP5aW6JKsaK0bOxyeCCUx3645pZfFOiX/n2kelXGoQmRFGy3Ro55XRZFVdxAJ2NuycAAHJoArt4m0r+1Fmk0Vzb2ttHIbj7Ku+zIkkjYPz8oUp/DnuenNXtM8R+H5/Ec1lZwJHdzPIn2hUQC4eM/OMg7sjB+8BnBxmgDp6gu7qOytZLiUSFEGT5cbO35KCT+VAFTQdag1/R7fUII5Y1lRWKSRspUlQcfMBkc9RxWlQBla1r1toccDXEc7+dKkYEUDvjcwXJKqemenftWnG6yxrIudrAEZBBwfY8igB1ZGmeIbTVNRvLKGO4V7ZwpaS3kQN8qnOWUAfexjPOM9KANesvxBrcHh7RbnUp45ZVhjZwkaMxYgE4JAO0cdTxQBdtLqK9tUuIRII36eZGyN/3ywBH5VPQBiS+J7SLxPFoZiuTLJE0nmC3kKghlGM7cY+b72cDHNbdAEF5dxWNq9zMJDGnXy42dvyUEn8qo+HNdh8R6Ha6nBFLEs8auY5EZdpKg4BIG4c9RwaANRmCqWYgKBkk9qrWGpWOqW/2jT7y3u4NxXzIJA65HUZHegC1RQAUUAFFAFPVdNi1fTJ7CZ5EjmABaMgMMEEEZBHUelZR8IWc8jy393d30ztGWknZBlUD7VwqgY/eN2zz1oAi/wCEKsmgSOW9vZXiECwTOyF4VhcOgHy4PzAZJBJxyasDwlpw057HdP5TxRRE7hnEcjSL29WNAFXUPCKXOvWd1ZSDTraO1uYZhaIqPIZTF/skYwh565xirUfhKwtrdorOSe1P2lLmJ4iMxOsSxALkEY2LjBB6mgCBvBVmwdTfX2yePy7pd64uR5jyHd8uRlnbO3HBxViw8K2Onaob2CSYAPLIkHyhFaQ5Y8AMeScAkgZ4oAu6nrenaOYRfXHlGbPlgIzFsYzwoPqKoHxnoGObx/8AwGl/+JoAZD4u8OW0EcMNyY4o1Coi2soCgdABt6U//hNNAPS8f/wGl/8AiaAGy+LfDsyqJbhnVWDANaynBByD93qDTv8AhNNA/wCf1/8AwGl/+JoAP+Ez0H/n8k/8Bpf/AImmp4t8OxvI6XLK0h3OwtZcscAZPy+gA/CgB3/CaaD/AM/j/wDgNL/8TTJ/Fnhu6gkt57gyxSqVdHtZSGB6gjb0oAf/AMJpoHT7a/8A4DS//E0v/CZ6D/z+Sf8AgNL/APE0ARHxZ4aNytybgmdUKCT7LLuCkgkZ29MgflUn/CaaB/z+P/4DS/8AxNAB/wAJloJGDeP/AOA0v/xNR2/ivw3a20dvbzmKGJQkcaWsoVVHAAG3gUAS/wDCZaDjm8k/8Bpf/iaaPGPh6FCRdsiDk4tZQB/47QBvI6yIrocqwyD6inUAFFABRQAUUAFFABRQAUUAcR47/wCQrov+7cfySsBiOhoATb8ooHTAoAUkjAzUbNzxQAo96GJx1NAACSP50A4Ix1FADTwSBRuwMmgBpmGRyKkUg0APPB/DmkL+mOKABXBGar3zf6BcDPHlN/I0Aer2H/IOtv8Arkv8hVigAooAKKACigAooAKKACigDh/Hv/IT0X/duP8A2SufJoAMnFNZtsZJPSgDOlvWX+PrwCKbZXhlmZGkDDsMcigC/uA+tOZtygUAKh+X0oyOeDQAgZCSoOSBk1BcMFTBOAT1oAoNcbfuj8atadcGbfyRtOKALzE546Um7IoAMNnI+76VDff8g+49PKb+VAHrNh/yDrb/AK5L/IVYoAKKACigAooAKKACigAooA4fx7/yFNF/3bj/ANkrnSB1oAX8aztYufsumzy/3VJzQBwkGuvM2/dyOgNS6Hqrv4hWIsSrk8e9AHfnkAmjeAO7UAOTpwenWnggDB5oATIBxWbrd0Le03E4yeKAMyO7BjDE9RxWjobh4JGGN2855oA0vMG/aaWgCQHioL1s6fcjH/LJv5UAes2H/IOtv+uS/wAhVigAooAKKACigAooAKKACvPPEfxl8J6HHKsN+t5d29wIZrVEcOAG2vgkYJXk9ecUAHirU7PWD4e1HT50ntZ4p3jkQ8EYT9fasfqcnrjigAU7ulc341kaLw9dYPUY/WgDyy1nbbt3Y9DWr4XLP4mt8sSQT3oA9ccHywc02L5SG6jNADlOSTjqakYgD9KAI9/r0rnPF0yw2MbPnG+gDnjfARRjcDxwc10nhSdZLWc/xb+c0AbpYF8frTl465xQBOxATP41VvTnTrj08pv5UAeu2H/IOtv+uS/yFWKACigAooAKKACigAooAK+dvGPwE1N7q+1bTtUW8uLy9Lpai32bRI+SS+48KDknHagDq28H2/gfS/D+kQTPO4FxJNKxOGkIjyQOw46f1pWzu/woAch9OK5zxyufDlxz6fzoA8jjYYxjit7wWM+I4Wxkd6APWXHbjBpucdqAHRn5c96czZJBOKAG/wAQxXLeOlJ02I9AJOaAOIWRjtVjwBXZeCGZoLkejigDqiGD1IpI465NAE56AVXvf+PC4/65N/KgD1yw/wCQdbf9cl/kKsUAFFABRQAUUAFFABRQAUUAcP4851TRf924/wDZK5qThsetACggDFc/40j3eG7k8nAB/WgDyeCzklYbQcHrxXTeCrOSHxChcYAB60AenTA4GKjZc4PXigBU4XkZoIPPHfNAC4DECsLxfD5ulKjDPzcUAcTJYbdhxnjBFdb4LtvJtJztIzJQB0jD5mz3o2tkBTg9qALCj5RxzUN8ubC4+X/lk38jQB61Yf8AIOtv+uS/yFWKACigAooAKKACigAooAKKAOI8d/8AIV0X/cuP5JXMyklx6UAM3AnFV9WgW70yWEjIYUAcuuhRogwoH0FXtG05LbUC4U5GetAHSuORk1Ecg47etAEkQ+X8abtyXwSBnFACqAH5PNV9VtftFttPrQBitpC5HGcVr6XaLb25VehOaALmwnJNN2EEcUAWB9zpzUF4D/Z9wf8Apk38qAPV7D/kHW3/AFyX+QqxQAUUAFFABRQAUUAFFABRQBw3j3/kJ6L/ALtx/wCyVykhZSAT9KABWGeTxU8qhoW6/hQBR8ng8E/hTrePE3oKALM3bk4qJiVb5aAJrfmPPfNIxwDnHWgAUDzBzUk2XTFAEQjBH3anhQKmAOaAEKndzRjpQBL24qveg/2fc5/55N/I0AerWH/IOtv+uS/yFWKACigAooAKKACigAooAKKAOI8d/wDIV0X/AHbj/wBkrlbn5XB60AQIwJxz1q7/AA80AR5AOCKjAIk4x+FAEkpOxfeo9h3jI6igCeFQueeKrSnLkZ70AKhPmrVp+OlADOjcEmplHy596AI+5z60A8rQBNVe+50+4z2ib+VAHqth/wAg62/65L/IVYoAKKACigAooAKKACigAooA4jx3j+1dFz/duP8A2SuWvPvLigCBMK2T+FXCfkoAj6DJximRj97n8qAHyZAH1pMjAzkGgB8PKMB61UmIE5BBoAWNx5qKPWrjcDmgBBwalT7uc8UAMPWkU5YGgCbtVe+/5B9z/wBcm/kaAPVbD/kHW3/XJf5CrFABRQAUUAFFABRQAUUAFFAHEeO+dU0X/cuP/ZK5K9ONpoArJJ8wB9av7sRDI7UARZyoI9elKhbzcGgB9wQEBOeDUDOcA+vagC1ak7CT61n3Tf6a3OSOlADIj/pkYHftWnOxAHFAEO48VahO6PnuaAImOWI9Kb3XtzQBbA4qve/8g+5x/wA8m/kaAPVLD/kHW3/XJf5CrFABRQAUUAFFABRQAUUAFFAHEePP+Qpov+7cf+yVxmpvtVTng0AZUVx+8BzkZxW+rFoAT6UANIAXgUKpaZTnofWgB13gxgCqy5yAfSgC5bEspGPwrOuAPtr4PTrQAsQ/0yPAGfetKZSV96AIgDjt9asRD5DzQBGVwWz600DDL14NAFraar3uBYXP/XJv5UAeqWH/ACDrb/rkv8hVigAooAKKACigAooAKKACigDh/Hv/ACE9Fz/duP8A2SuE11WIjZR0NAGZDCSVJUgV1MalrdeB0oAYRhM4+XPNKpzIuOlACXnEQwO/IqoC2RmgC7ZHdn2NUZFJupM+tADoFIu1Y1pSH5RigBhFSxkeXyPyoAiPJ9qTpgUATjtz1qC+/wCPC5/65N/I0AeqWH/IOtv+uS/yFWKACigAooAKKACigAooAKKAOH8ef8hTRc/3bj/2SuTvYhJGMjpQBXjthgfL9K1FQJF07dBQBARvx+lORcOABQA+dVK4NV/KUcgdKAJLfKgn3qEqPtDE96AHxqBKOelWn+7gGgBmM1Io+U0ARtjJoC55xQBMOlQ3xH9nXIx/yyb+VAHqVh/yDrb/AK5L/IVYoAKKACigAooAKKACigAooA4fx5/yFNF/3bj+SVzc/wBwselAFdZVAAHbg1dV90WfagCtvAGfU1KuPMyPTmgBZwCnNRZGNvtQA6Dpx0qrLJi4OaAHwsHuFGauPnbx60AGQo96VCSKAGHqaM9KAJRgEGoL/wD48bnH/PJv5UAeqWH/ACDrb/rkv8hVigAooAKKACigAooAKKACigDiPHeP7U0XPTbcf+yVy98cWxI4AoAy/N+UEVsQYMKkntQBE49BSqf3gBOM0ALcMQo64FQMRkc9e9AE9scoe1Z87f6W2KAJLZt1yoJ5rQmPAA/GgBozjrx7VJHjB4zQAwkFjSDqBnPegCZfmwfeor7H9n3X/XJv5UAep2H/ACDrb/rkv8hVigAooAKKACigAooAKKACigDh/Hn/ACFNF/3bj/2SuR1Z2Fk+0gfWgDEtyxjUAnJrpohm2CZ/hoAqlSqjJ5zSxNul9qAHXh/dryetVCTxzQBcsyfLZj64rKuZMag3PWgCxZyKbxee1acxGOuKAIQcMBntU8JymaAGN94mouSwOeAaALgHGe1Q3/8AyD7nP/PJv5GgD1Sw/wCQdbf9cl/kKsUAFFABRQAUUAFFABRQAUUAcN49/wCQnov+7cf+yVymoD/Q2z6c0AY1ptJzn9a6SHiJT7UAVZWVuQeajiB88c4+vegCW8H7tfrVLqwoAvWuPKP1rnr9yNWdf9nigB+m7v7SQHge9dDcgCMdTzQBWMnIq1bcoaAI5mwzD0qGI/z6UAaI6VXvz/oFwOv7lv5GgD1aw/5B1t/1yX+QqxQAUUAFFABRQAUUAFFABWK97qWoW4bToFg/fFRLKwYEKxByo5wcfXmgDmPFl6t5qWj5QxzRC4SaFjko2I+PoeoPcVyninUEsNEmmAywGAPWgDzO08VXETDeq7c816jbXaz6Slyh+Vo9woA5+XxBBFsDSAFmxWjYarDcX6wqctjNAFzWLpLS28xzgZ4NYf8AblsHQFxluetAG3pF5HdwM6NlQcVh29zBdeNZbaX+FePc0AdFdwW8N1A4KqxOAPWk1K5S2iUuwwTQBktq0Ql2kgZrV0q6F1AzI2QDgmgBLqZVlbNUhexRhWdwoz3oA2redLiJZInV0PdTmm33/IPufXym/lQB6rYf8g62/wCuS/yFWKACigAooAKKACigAooAKx5LC/srcLpl0zHzS3lzBdgDMS3IXPGc9aAOW8YWaWd/o6hmeRxcPLK33pGxHyf6DsMAVxfiu3S40GcOeAM0AeW21na3Fxs3HbgZx2r1zTbVYdFigX7ojAH5UAc3ceDUeQvvY85Aq9o3htrDURctKWAHQ0AaWu6Z/adoIckc5zXPHwYp2t5h460AdBpGlppFkYkbgknrXmGr6jJH4juLq1kKOkhAYe1AE9n4jvrvXbOa8mLhXAwOBzxXp2pWq3lqueehBFAGLNo4fAIz6GtrQrQWVsY+etAC3UG+dsDrWVfaML22kgZiofjI7UAaegaMuh6aLVZWlOSxLVevM/2bccf8sm/kaAPVbD/kH23/AFyX+QqxQAUUAFFABRQAUUAFFABRQBheIfDn9uy2kq3jW0ltvAIjDBg2M9f90Vzup/DI6rZtaz65MsbdfLt1B/nQBgRfATToWDpr16GHQ+UnFdNB8PZIIViXXJGCjALWy5/nQA8+AZf+g0//AIDL/jSjwFMOmtP/AOAy/wCNACt4EmbrrTf+Ay/40w+AZf8AoNv/AOAy/wCNACnwBKVwdafH/Xsv+NcxcfAbTbm4kmfXLwM7biFhTGaAEh+AmmwTJKuu3hKMGAMSYrqP+EAl2bf7afH/AF7L/jQA3/hXz/8AQZf/AMBl/wAakXwHMowNabH/AF7L/jQA0+ApScnWnz/17L/jR/wgMv8A0GW/8Bl/xoAf/wAILP8A9Bpv/AZf8aZL4ClmheJtafa6lTi2XofxoA7KGMQwRxA5CKFBPfAp9ABRQAUUAFFABRQAUUAFFABTXUvGyhihIIDDqPegDnfBtv8AZLPU7cTTTeXqUy+ZM5d26ckmukoA5zxpeaPY6NHPrTboBOojtzIqi4kwdqNuIUjvycDbk9Kf4LgS38NxrHe290ryyyA20nmRRbnLeUh/upnb+HQdKAOgrgviN/Z5srndcwRanFZtJCLlmXCAnJgPQTZwARkjjIwRQB29rIZrOGUo6F41Yq/3lyOh96q65dXtlo1zPp1o91eKoEUSgEkkgZwSMgZyRnoKAOb+HEkh07V4ZYr1Wj1ObL3YG9ycE5wTznqOgzxXaUAebzvFa+OZr1Z9Nv7qbVYrf7G1uwuYE8tV3KxPRQC5wuCCea9IoA5HxyHkbRoHms4bOW6YTyXq7oQfLYqGXcobnoCQM49MVpeEJRL4VsmVY1UB1XymZkYB2AZCxJ2EDK88AigDWu4ree0liuo0kt2UiRXGQV75rmvAVhaJoz6zbW4t/wC12F0sSgKscRH7pQBwPkwT7saAOrooAKKACigAooAKKACigAooAKKAECqudoAycnA60tADJYYp1CyxJIAcgOoNEcUcKbIkVFH8KjAoAfUckEUxQyxI5Q7kLKDtPqPSgCSigBFVVztUDJycDqaWgCPyIvO87yk83G3ftG7Hpn0qSgBksUc0ZjljWRG6q4yD+FOACgAAADgAUAL1GDSKoRQqgBQMAAcCgBaKACigD//Z/+Ex6Gh0dHA6Ly9ucy5hZG9iZS5jb20veGFwLzEuMC8APD94cGFja2V0IGJlZ2luPSfvu78nIGlkPSdXNU0wTXBDZWhpSHpyZVN6TlRjemtjOWQnPz4NCjx4OnhtcG1ldGEgeG1sbnM6eD0iYWRvYmU6bnM6bWV0YS8iPjxyZGY6UkRGIHhtbG5zOnJkZj0iaHR0cDovL3d3dy53My5vcmcvMTk5OS8wMi8yMi1yZGYtc3ludGF4LW5zIyI+PHJkZjpEZXNjcmlwdGlvbiByZGY6YWJvdXQ9InV1aWQ6ZmFmNWJkZDUtYmEzZC0xMWRhLWFkMzEtZDMzZDc1MTgyZjFiIiB4bWxuczp4bXA9Imh0dHA6Ly9ucy5hZG9iZS5jb20veGFwLzEuMC8iPjx4bXA6Q3JlYXRvclRvb2w+V2luZG93cyBQaG90byBFZGl0b3IgMTAuMC4xMDAxMS4xNjM4NDwveG1wOkNyZWF0b3JUb29sPjx4bXA6Q3JlYXRlRGF0ZT4yMDIwLTA3LTEyVDE0OjI1OjI4Ljk1NjwveG1wOkNyZWF0ZURhdGU+PC9yZGY6RGVzY3JpcHRpb24+PC9yZGY6UkRGPjwveDp4bXBtZXRhPg0KICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgIAogICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgCiAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAKICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgIAogICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgCiAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAKICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgIAogICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgCiAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAKICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgIAogICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgCiAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAKICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgIAogICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgCiAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAKICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgIAogICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgCiAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAKICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgIAogICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgCiAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAKICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgIAogICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgCiAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAKICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgIAogICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgCiAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAKICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgIAogICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgCiAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAKICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgIAogICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgCiAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAKICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgIAogICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgCiAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAKICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgIAogICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgCiAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAKICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgIAogICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgCiAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAKICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgIAogICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgCiAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAKICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgIAogICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgCiAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAKICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgIAogICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgCiAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAKICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgIAogICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgCiAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAKICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgIAogICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgCiAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAKICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgIAogICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgCiAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAKICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgIAogICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgCiAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAKICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgIAogICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgCiAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAKICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgIAogICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgCiAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAKICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgIAogICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgCiAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAKICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgIAogICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgCiAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAKICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgIAogICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgCiAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAKICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgIAogICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgCiAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAKICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgIAogICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgCiAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAKICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgIAogICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgCiAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAKICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgIAogICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgCiAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAKICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgIAogICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgCiAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAKICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgIAogICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgCiAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAKICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgIAogICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgCiAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAKICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgIAogICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgCiAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAKICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgIAogICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgCiAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAKICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgIAogICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgCiAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAKICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgIAogICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgCiAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAKICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgIAogICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgCiAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAKICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgIAogICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgCiAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAKICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgIAogICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgCiAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAKICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgIAogICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgICAgPD94cGFja2V0IGVuZD0ndyc/Pv/bAEMAAwICAwICAwMDAwQDAwQFCAUFBAQFCgcHBggMCgwMCwoLCw0OEhANDhEOCwsQFhARExQVFRUMDxcYFhQYEhQVFP/bAEMBAwQEBQQFCQUFCRQNCw0UFBQUFBQUFBQUFBQUFBQUFBQUFBQUFBQUFBQUFBQUFBQUFBQUFBQUFBQUFBQUFBQUFP/AABEIAv0C0AMBIgACEQEDEQH/xAAfAAABBQEBAQEBAQAAAAAAAAAAAQIDBAUGBwgJCgv/xAC1EAACAQMDAgQDBQUEBAAAAX0BAgMABBEFEiExQQYTUWEHInEUMoGRoQgjQrHBFVLR8CQzYnKCCQoWFxgZGiUmJygpKjQ1Njc4OTpDREVGR0hJSlNUVVZXWFlaY2RlZmdoaWpzdHV2d3h5eoOEhYaHiImKkpOUlZaXmJmaoqOkpaanqKmqsrO0tba3uLm6wsPExcbHyMnK0tPU1dbX2Nna4eLj5OXm5+jp6vHy8/T19vf4+fr/xAAfAQADAQEBAQEBAQEBAAAAAAAAAQIDBAUGBwgJCgv/xAC1EQACAQIEBAMEBwUEBAABAncAAQIDEQQFITEGEkFRB2FxEyIygQgUQpGhscEJIzNS8BVictEKFiQ04SXxFxgZGiYnKCkqNTY3ODk6Q0RFRkdISUpTVFVWV1hZWmNkZWZnaGlqc3R1dnd4eXqCg4SFhoeIiYqSk5SVlpeYmZqio6Slpqeoqaqys7S1tre4ubrCw8TFxsfIycrS09TV1tfY2dri4+Tl5ufo6ery8/T19vf4+fr/2gAMAwEAAhEDEQA/AP1TooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigApm/tT6+W/wDgo98cr34E/swa5f6PcNaa/rU0ei2NxG2GhaQM0kinHVY0f8cUAcz+0T/wVF+FvwJ1668PWMd5438QWrmO4g0koLeBx95HnJ27l7qobHcivH/Cf/BbPwdfaokPiT4d6xo1iz7TdWN/Fdsg9TGyxn9a+ff+CYv7FPh/9o3UNc8c+PbZtT8L6PcrZwacXZVvbraHcyMCCUVWTgHkuM9DX3n8dv8Agm38G/iT8O9V07w14L03wj4jS3dtN1PSYzAyTAZQOAdroT8pyCeeKAPoT4T/ABg8KfG7wfaeKPBmsw61o9xkCWLho2HVHU8qw9DXa1+W/wDwTR+An7QH7OvxnvbXxb4Pu9L8C63ZyLfPJdwSRxXCLuhl2JIW3Ertzjndz0FfqRQAUUUUAFFFFABRRRQAUUUUAFFFFABRRRQAUUUUAFFFFABRRRQAUUUUAFFFFABRRRQAUUUUAFFFFABRRRQAUUUUAFFFFABRRRQAUUUUAFFFFABRRRQAUUUUAFFFFABRRRQAUUUUAFFFFABRRRQAUUUUAFFFFABRRRQAUUUUAFFFFABRRRQAUUUUAFFFFABRRRQAUUUUAFFFFABRRRQAUUUUAFFFFABRRRQAV+dH/Ba63uZPgX4FuIwTaxeIispHQMbaXbn8mFfovXhX7aHwAP7Sn7PfiPwba7U1rat5pjyHCi5iO5AT2DfMmf8AaoA8F/4I53lpc/so3lvCwa6tfEV156g8qWjhK/8AjuD+Jr7pO1Tk9AeM9jjOfavwb/Y8/a48SfsG/ETxH4e8VeHLyfRrubyNX0SQCG7tbiP5RIgbo2Dgg8EdDxX1H+0J/wAFh/DeufDvVNF+Gnh/WYdd1K3e3/tHWFihSzDLhnVVdi7AfdztoA/TG18RaVqEywW+p2dzM3SKK4R2OBk4AJzge1a1fk7/AMEg/wBmnWj4o1D4x+I7aa102G1ay0NbjINw8h/eTqD/AAKqlQe+4kfd5/WKgAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigApuxfSnUUAeS/GP9lX4VfHxkl8beDNP1i9RdiXwDQXKr2HmxlWI9ia848Ff8E2f2efBOqR6haeAYdQuYmDp/al5Ndxow6Hy3cqfxBr6g2j0paAK9pp9tp9pDa20EdvbQqEihiUKiKOgUDgAdgOlWKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigBjM3GP8KaZCrcntn6e9eI/tueIdT8I/sofEzWNE1C40rVLPSmkt7y0kMckTb1GVYdDgmvm/wDZW/Z7+KXxg0X4b/Gfxn8ZfEcN1IltdReHbGRltpLNPupId/LSABmYg53c5oA9u/Yz/aI8UfHz/haP/CRw2Ef/AAjXim40Wy+wxGPdDH3fLHLe/Ar6RRy3Ht6f171+UP7H/wAGvG3xy8cfG/Rbbx/q3gX4f2vi+8mvl8OsIr2+umkYKhlxlEVFB78nmvYfg7L44/Ze/ba0z4O6h451fxx4D8UaPLqFi2uzGae1kXdxvPTmNh9DQB6n8X/2oPFvgb9tj4WfCjTItOk8M+JrFri9kmgLXAcGYYjcOAP9UOorsv2rv2sNH/Zf8M6dJLZTeIfFetzfZdF8P2vMt1LwPmxyqAkc85JAFfOP7S2P+Hp/7P2Rn/iWMOf964p15ax/E7/grpBaawouLLwd4b+1adby/MiS7QQwHqGlLf8AAR6CgDo7DUv26PGliNbgtfAXg2GUebDod7G8s4XrskbnDdq6r9nf9sTxbrPxbufg58Z/C1v4P+IscDXNlPZyZs9TjA6x7icNgMQNxzg9Ole9/Gj41eEvgF4LfxX40v303REuEtWmjgeb94+do2rzzivnHSf2xP2WPjF8Z/Bd/b3a6v8AECKYafod9JpdwksLynAVWIAGST1z94+tAGT+1B+1B8bfC/7VGhfCH4T2Phu7udU0gX0X9uQuuXBkLDzPMUdE9Kb/AG9+31/0Lnwz/wC/7f8Ax2vLP2sviNe/Cb/gpb4G8Uaf4W1bxncWnhvYuj6LGXuZt3nrlQAem7P4V7BH/wAFFPFjyKv/AAzL8TRuOP8AjzP/AMRQB7r4c+K+r/C34H2nib49ahofhnXrdJG1JrGX/R8h22LEMkuxTbwPWvJf2K/209S/ax+InxOjSwgsPCeiyW/9kAxlbhonLrulJbGWKZxjjNes/Ef9nPwL+0NrHgzxN450efUW0SBprXRbqUi2WSURsTNEMbmXbjB4r5t/YNtYLH9r79qe2toY7e3h1mKOOKJAqookmwoA6D2oA6/9t79pz4o/Bz4lfC/wb8M7bQrjUfGEz2o/tuFnQS+Yip8yuNoO7uDWT/a37eqEk6L8L3A7eZLz/wCP151/wU48XL8Pv2kv2c/Ezadd6uNKvZbv7HYpuuJ9k0TbI/VjgCup17/grZ4f8L26y6r8I/HWlo52RtqFukAZ/wCFctxk/WgDv/2Zf2xPF3jX4wa18Hfi14UtvCHxE0+2+125spC9vexAAkqCSeh39elfXdfBH7Nvw5+Ivx2/avuP2ivHXhk+BdEt9N+waBo8sqvcTRshUSSAZP3WOSQAcgDha+96ACiiigAooooAKKK8e/aN/aX0H9mfw/pmr6/pGt6zb6hcm1ji0O1W4kRgu7LAsML2zQB7DRXzf+z5+3L4R/aN8bT+F9C8N+KtIvobOS8abWtPEEO1WVdu4MfmO7OMdq+kKACiiigAooooAKr3lz9ls5p8bhHG0mAeuBmrFfI3x38A/tVax44129+H/wAQ/DGi+C3jzaWF9aB50URjcGYxHqwPegD1X9lv9oeL9pj4c3Hiu30aTQo4tSuNO+yyTrMf3RwX3ADqa9jr8k/2H/Af7UOu/Bu5ufhn8QvDeheHf7ZvEe01K1EkhuA37w58o/KWr9UvCdvq1r4X0mDXbmK71pLWNL24gXbHJOFG9lGOAWz0oA26KKKACiiigBv4/pXjHxf/AGkIfhL8W/hh4Hl0STUZPHF5NaR3iziMWpRVOSpB39e2K6j45aT491r4b6ha/DXWLLQfFztH9lvdQjDwoN3zArg9vavzL/aC8C/tO6d8fvghaeLPiB4b1HxZd6hcJ4dvrS32RWsoVdzTDyhuB9waAP10z+P4UtfOv7Nvg79ofwz4k1Sf4xeNvD/ijR3tgtnDpFr5Ukc27kk+WnG2voqgAooooAKKKKACiivkL4kf8FLfAXwy8ea34U1Hwh42u77SblrWWax0lZIZGXujGQEqfXFAH17RXFfCD4pWHxl+HWj+MtKs73T9P1SNpIrfUohFPGFZl+dQTj7ueveu1oAKKKKACiiigBvI9xXjP7Nf7SEH7Rdh4xubfQ5NFHh3XJ9FYSXCzecY+sgwBgH0NcJ8fvAv7T+v/EKW7+Fvj/w34c8Jtbxqllqdt5kyyD77bvKPX0zgV8W/sZ+Bf2nNa034iN8OfH/hzQ4ofFN1Hqw1G2En2i9H+slT90cKfT+VAH66Utcr8M7HxPpfgDQbXxlf2uqeKYrVV1K8s02Qyz/xMq44H4V1VABRRRQAU3d+Yp1cb8WtP8W6t8O9ctPAupWukeLZodun3t9GHhhk3D5mXBzwDxigDiP2hv2kIPgHrHw7sZ9Fk1f/AIS/W49FV45xF9mL4xIcg7gM9Otez547/lX5GftbeBf2ndI8RfCFPH/j/wAOaveXPiiJNBextti2178u2WTEQyvtX21+zx4I/aV8OePJLr4s+O/DviPwx9kkVbTS7Ty5vPyu07vLT5fvd+9AH03RRRQAUUUUAZfiLWP+Ef8AD+p6m0fnCytZbryweXCKWxn8K87/AGY/jxF+0l8H9K8eW+kyaLFfSzRfY5JxMUMchjJ3ADqQa8B/aC+H/wC1fqGreNr7wx8RfC+m+BJIp5bbTbq03Tpa+VhkZvKPON3fvXzv+xN4C/an1z9n3QLz4b/EPwxong9p7j7Pp+o2vmTKRK3mbmMR6tu7/lQB+r1FUtLW8j020S+kWW9WJRcSRrhWfb8xA+tXaACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigD57/b8y37G/xXGQP+JOxPHbzF+lb37H//ACaz8KWPJ/4Ryx54P/LJc855Fen+KvCejeOPD19oOv6db6to19H5VzZXSb4plyDhh3GQKm8P+HdM8K6LY6Ro9jDpumWMKwW1rbrtjhjUYCqOwAFAHxZ/wTDwW+P2SCf+E/vOcgn6Zz+h5pnxh/5SkfBpguGHhy7B7H/lr7cjk19g+Dfhr4W+Hf8Aan/CM6FZ6H/al099e/Yo/L+0Tt96RsdWPrRf/DPwrqnjbTvGF3oNjceKNPha3tNWkiBuIY2zuVW6gHJ/OgD4a/aVb/jad+z91x/ZbHJBH8Vzx79B09auftkeHfEf7PH7T/hD9pXw7o9xr2gw2/8AZHiizs4y0kcJUr5mB22t94cBkGetfaWr/Cfwdr3jjS/GOo+G9OvPFOlp5dlq0sANxAvJwrdup/OumubK3vLeSC4hjngkUo8cqhlZT1BB6g+lAHz/AKN+2h+z38TvCkd9c+PPDc1gyiZrLXGSKSNh0DxS9Gr4/wDi58TPAn7SX7XvwQ0r4MaN/bkXhXXFv9b1LR9MEdoIvNjJcyKBuVBG3zEYOeDX2j4g/Yb+A/ijVpNS1D4XaC15I255IbfyQx9SqED9K9P8B/DHwl8L9IGl+EvDmm+HtPyD5Gn2yxKSOhOByfrQB8SfE5d3/BXL4asVJ2+GX/h/2bjnnqOe1foDiuVvPhT4P1Dx5ZeNbnw5p83iyyhNvb6w8ANxFGQQVVuw5P511dACbRnNfB/7Dalf2xf2qyobH9uR9u/mS8Z/+sK+8a5bwz8LfCPg3xDrmu6H4d0/StY1yQS6nfWsISW7cEkGRh1OSaAPib9vRc/tkfssE9P7bA5HH/HxF/npX2h8VPhb4e+MfgbVfCXiawj1DSdQhaN1dQTGSPldD2YHuKm8UfCjwd418RaJr2veG9P1bWdDk83Tb66gDy2jbg2Y2P3TlQfwrq9o9KAPzt/Yq+J3iH9mv45a1+zF8RtRmnto5Gm8H6pdE4uISS6wgnPysvKjsQ6jqK/ROuK8Y/BbwL8QvEOla94k8KaXrOs6UQbG+u7cPNb4bcNrdRhuR6Gu1oAKKKKACiiigAprRo4wyhh/tDNOooAjWCOPIWNVHfaMVJRRQAUUUUAFFFFABVe6tlureWIkhZE2Fge3P+NWKSgDy/8AZ9+Amhfs5eBpfCvh67vruxlv59Q337q0m+VssPlAGAa9Q2gUm0HPX16mnUAFFFFABRRRQAm0V5V8TP2fdC+KXxJ+H/jTU7u+i1LwXdyXVjFbOgikZwBiTIzjgcCvVqTaOOM46UAJtHTHHSnUUUAFFFFABRRRQAVGYIyCCikHk8dfr61JRQA1UC4wOnT2p1FFABRRRQAUUUUAJivKvgP+z7oPwBs/FFv4fvL68TxBq82tXLXro22aXqF2gfL9ea9WpNo9KADaPSloooAKKKKACm7RwcdOlOooA8p+Nn7Pmg/HDUvBN9rd7f2snhLV11mzFpIiq8y/dD5B+Xjtg16rtA6DFJtA6DFOoAKKKKACiiigDN1vSU13Rb/TZneOG8gkt3aP7wVwRn8ia4j4A/BPRv2efhlp3gjw/dXl5pljJK6S3rq0pMkhc5KgD+I9q9I2juM/WjaDQAbf85paKKACiiigAooooAKKKKAPGf2tvjtffs5fAvXPHmnabbavdae8KpaXMpSN98gTkjnvXb/CfxpP8Rfhj4S8UXFulnca1pdrqElvGdyxmWNXKg9+uK+ev+Cow/4wt8ajP/LW1P8A5MLXsf7L4/4xx+GHb/im9P8A/SdKAOF/bF/ah1T9mXTPAl1pui2etN4i1yPSZVu5mi8pHGd646sPSvoaOUsgY46A8HNfB/8AwVkyvh34LYyD/wAJrbngn+7XWf8ABR745eOfgT4D+HOq+BL5rfULzxHFZy2+1WF6hjZhCcg4DEDkYPvQB9jZOMg9q8V/bA+Pl/8As0/ArWPHum6Zba1d2M9vEtpdSmONvMlWPqOeM5r5u+K/wo/ab8JfDPWvipJ8epE8SaVaPqs/hm0sI10yONE3vApPXABG4j8axf2qvjHc/Hv/AIJWw+OL+KODUNTNkbyOEYjWZLoRuVHoSpP40AfoD4T1qTxF4X0bVZYxC9/Zw3JiXnaXRWx+Ga1dwxkHNfOnxg8bfEfwT+y/4bm+FfhqTxJ4wvLGxtLcLFvSzVoF3XDr3C+leP8AjX9nD9oTwr8P77xe/wC0zqx8WWdk949hLYxRaczIu4xDrgHpux+FAH0z+038Xr34D/Avxb48sLCHVLvRbdJo7W4YpHITIiYJHI+9XSfCfxtP8Rfhj4U8U3EEdnPrOl21/JbxNlImljVyoOTnGcV8SeOPjhrH7Q3/AASj8W+Mtfihj1maxa2u2hULHJJFdxp5gXtuADY6CovgJ8FP2hPjB8B/CfiI/GS6+G6x6Pax+HvD+kWSSQCCONVikuSxyWkAyRnvQB+h3NIrZ5/w4+tfKH7Hn7Uuu+NvCfxD0P4oCC18a/Da4lt9auLZQsdxEgcidVAAHEbdAOgryv4U6n8bP26LbVvH1r8Ubz4Q/D77ZNbaFpmi28clzcRo2PNmdiDz0+oPpQB+ge4seuCP8814B+zP+0tqXx28cfF3Qb7R7TS4vBOvHSLea3lZ2uU3SDewPRv3fQeteZ/s8/Gz4i/Dv9o3UPgB8Wdcg8XXkth/avh7xRHEsUl5BzmOVF438Mf+AN6iuG/Y58dWHwz8UftkeLNWdhpui+Kbi+n2/eKobg4/HGPxoA/QUN8pOePUUm49f6dPrXwH8JND+PX7Ynhf/hZuofGO8+FOg6k8kmh+H9BtImKQBmVHmdmyd2B613P7L/7Q3jTRfil44+Cvxe1G11fxP4VsRqdn4jtIljXUrEAMzso4DAMvA/2vSgD7DD5/kenH1r59uv2mtSh/bStvgiNHtP7Mm8P/ANsnVDMRMr/N8gXpjivn/wCFOqfGv9u688QeOdJ+J998J/h3aX8ljoVnotqkk935ZwZZS5B9OCccnjiuN+CNp8RNH/4KgWmk/Eu9tta17TPCc9rBrNrD5I1C1HMczL0DfMQwAGNtAH6b0zcfx/z+tPr4H/ak+MXxqsf21PCnws+GGtx2UHiDw6GZbuBZILNzLKHu+hYlEQcHj2oA+9GbaMnH6c/SlV+/UV8AfGqH46fsSaRp/wATB8V9Q+K3hO3uoYvEWja9aRxusTsFMkBXpycduorS/bY/aW+IXhPxR8A3+EmpqR42Myx2Uyq0N2ZBCIS5IJG0y54PPfNAH3YZOnP48YpVLYBPX8q+GdT1r4t/sN/CXx18Qvij8Tm+KEk0EFto+ktAYo49QkcrjOM7eh47K3FN8I/AH9pr4meC7Xxtrfx71Dwn4q1G3F9a+HbGwj+wWodQ0cUg78cHuKAPt/VLt7HTrq5VdxhiZ9p74Ga8S/Y0/aM1H9p74ODxpqekWuiXP9pXNibW1lZ0xGVCt8wzzmuF/ZD/AGkfEnxk8I/EDwd8QraCx+I/geSXT9WFqAI7hdrBZlXHGSjDjA4FfJ3/AAT3+Gvxk+MHwYutK0H4i3Hwv8BaXqt15V1pFokt7qNy5UudzEAInA4x1oA/WHJPQ/596Utt6j9K+MP2c/jR8R/hz+0hrHwA+Lmtx+KrptP/ALW8O+JvJEUl5bgZZJAABuAD/ijeork/DvxA+LH7cnxK8Zw+CvH8nwr+FPhq9bS4b7TbZJb7Up16t854X3BHUUAfffzH2p1fDfgb4qfE79mP9pLwt8KfiX4wT4jeD/GasmheI54Fhu7e5XOIZdpwQflHf7wr7koAKKKKACiiigAoornfF3xA8N+ALOC68TeINM8P208hiim1O6jt0kfGdqs7AZxQB0VFcb4T+MXgfx3qR0/w54w0PXr9Ymma202/iuJNgIBbajE4yRXZUAFFFFABRRRQAUUVleI/E2leEdIn1XW9StdJ02DHm3V5KsUaZIAyx4HJFAGrRXAaL8fPht4i1S203S/H/hvUtRuW2QWlpq1vJLKx6BVD5J9hXf0AFFFFABRRRQAVx3xM+LPhb4P+H49c8X6xFoulSXEdolzIjyKZXOFXCKT1rX8Xa7ceHPC2r6raWE2rXNlayXEdjBjzJ2RS2xfc9K/Kz9uL9rjxx8Wvg3Z6NrnwN8UeBrNNatLoalqoby2aNsiPBjX5iaAP1oimWeNJEbKOoYH69Klr5G+BP7Ynjv4leOtC8Max8BvFXhDTLqNkk1zUNwgh8uMsC2YwOcY696+uaACiiigAooooAKKK84uv2jPhbp91NbXPxH8KwXELmOSGTWLdWRgcEMN+cg5oA9HoqlpmrWmtaZbahp93De2NzGJoLqBw8ciEZDBhwQR6VdoAKKKKACiiigAornPGHxC8NfD+1t7jxL4i0zw/DcMUhk1S7jt1kYDJClyBnFUvCfxe8E+PL+Sx8N+LtE1+9jiMz2+m38Vw6oCAWIRjgZIoA7CiiigAooooAKKKp6lfPY6bd3UcLTvDC0ixL95yFzj8elAGD8R/iZ4c+EnhK68T+LNTTSNCtSonvJI3dY9zBRkIpPUit7S9Tg1jT7W+tJRNa3USzQuoxuRgCp/I1+WX7bX7X3jn4pfs8+JvDGtfAfxT4N0+6lh3a1qQbyYvLmVvmBjHXbj8a9//AGef2yfHnim+8B+ELz4B+K9I0i4htrJvEVwG+zRIsYUSn93jb8oP3u9AH21RRRQAUUUUAFFc/wCLvHnh3wFYxXviTXtN0C0lk8qObUrqOBHfBO1WcgZwDWX4V+M3gTxxqg03w74y0LXdRMZl+y6bqEVxJsGMttRicDIoA7SiiigAooooAKKKKACiiigD54/b28A6l8S/2TPiFo+k27XmoLZC8ht4hueQwyLJtUdyVVvzrnv2G/2lPAvj79nLwTZr4k0yx1rRdKh07UNNu7pIpYHhUR5IYjg7Qc9Oa+pmjVlKlQVPBFfNPxI/4J1/Af4meIZ9c1Pwathqdw++ebSrqS1WVv7xRW2598UAfPP7eXxA0b9ob44fBH4TeB9StfEep2viKPU9UfTZRMlrGrKCGdeAdm9sew5ruP8AgqMqpofwOXPXx/YjBOB/FX0R8EP2Vfhd+zytw/gbwtb6ZeXC7Zb6R2nuZF/u+Y5JC+wwK6X4ofBfwh8ZIdEi8XaSNXTRb+PU7FTNJH5Vwmdr/IwzjPQ5HtQBjftQfL+zl8TWB2/8U7fDJP8A0xavzt8RZ/4cuaeev+kwj/yoetfqf4o8Nad4w8OanoWrwfatL1G2ktLmEsy+ZE67WXKkEZBPIINeeT/sufDS5+DEfwqk8Nq3gSNlddK+0TYDCTzAd+/f9/n73t04oA+bf21vjf4u+E/7Pfwf0fwjq/8Awi03i+Wx0u78R7QRYQtDHuYN2J3Zz1wrVznxY/Y9+D/wv+EeveMviV8TfFPjWaKxmmjk1bxC3lXdyyHywkUfLlnIAGT+NfaXxB+Cfgv4o+AF8F+KNBt9X8OxxxxxWs5YmPYAqFXB3KQABkHPX1ryr4ef8E/Pgf8ADfWodWsPCTajeW5zb/2vdyXiQMAAGVHYrkYGDjI7UAfGnwuuln/4IzeNUTkwyXSNkdD9sibGc8dRX2t+yP8AGrwj4u/Zd8Fazb65YxWelaPb2motcXCr9jlhjVZFlyfkI25GT3rqNK/ZV+GWh/C3XPhzZeHBD4M1qZ577S/tkxR3ZlZiGL7l5ReFIHFcD4q/4Jz/AAF8W6lb3tz4ONo0UUcEken300EdwqKFXzVVgGOAMt1PcmgD52/Zf8NXfx68T/tdePfDyy/2J4wWfR9EuDkLdsElUSKfTO3/AL7rh/2C/wBmf4NfGv4ULp/ifU/EWmfELQ7qa01bSIvEE1mYyJW2ssII2jBHT+IH3r9QPBvgnQfh74dstB8N6Xb6No9mnlwWdqu2NB9O59zzXi/xa/YT+DXxl8SzeItf8LGDXJ/9ffaXdSWj3Hu4RgGPuRmgDwD4K/Db9nrwr+2VbeG/Atv4r8Q+NvDdlJdTa6+sNe6dZgqymKVmbk4dRgfxN7GvP/hb4N1L4heC/wBvHw9o8TTape67ciCFTlpGRrhgnHc7cfjX318F/wBnnwB+z7o9xp3gfw7b6Mly2+5uAWknuG9Xkclj9M1ofD/4L+EPhbrHijVfDWkjTb7xNe/2hqsonkfz58sd5DMQvLNwuBz0oA/Pj9in9mH4E/Hf4FaFqF3rfiK28U2ERtNY0+PxJNbfZ7hGZSRED8iN1HAxXXfA/wCFvwJ1P45fEjw38K7bxPrHinS9AutOufE91qzXmnfvovL8oOzHLhm2/wDAWI4FfQPxI/4J8/BD4neKLnxFqXhRrDVrwlrqbSbuS0FwT1LKjBee/HPevVfhF8EfBPwK8Nf2F4I0C20GwZ/MkEAJeZ/7zuxLMee5NAHyt/wSu8c6ZpPwLv8A4bancxad4w8J6vdwahptw4SUK0hZZAp6r1Gf9mue8P8AxK0D4j/8FZIf7AvYNSt9H8Jz6fPeW7BkeZfmdQwOG27tpx3GK+ivjH+xD8H/AI4+Jv8AhI/EvhkprrjZNqOnXMlpLOuOjlGG76nmtz4d/sm/Cr4T+JtL8Q+FPCNto2r6bYtp1vcW8kgPlMctuBbDMSeWYFj60AewV+ffxu+JOhfCz/gqd8O9T8RXcOnabe+E200Xk7hI4pJJJtm5jwq5AXJ/vV+glfn58bvAOgfE7/gpz4R8O+KNIg1rRLzwLPHcWl0m5W5nIOc8MCBggg9KAO5/4KcfE7QtO/Zl1fwjBeQX3iXxVNb2Gl6XbSq807GZCWC+gx9OleW/Gbwfc+Afit+wt4avjuutKmW1mVjz5iR2wI/MGvpn4UfsJfBj4O+KYvEugeFfN1qHm2u9SupLtrYf9Mw7EKffGa9L8bfBnwj8QvFvhTxNr2lfbda8L3DXWk3PnSIbeRtuW2qwVvurwwI4oA+b/wDgql4K1LxZ+yne3el2813JoWp2upzW8AyTCrFXbHoobP4GvdvhP8cvBXjr4P6P4ysPEGnJoY0+OW4nmuUjFoQgLrJk4Qr05xXpd1Y299bS29zBHcW8qlJIpVDK6nqCDwRz0NfL+sf8E1PgBrevS6o/g+azE0jSyWNlfzw2rMTk/u1YAD2GBQB49+w9fP8AE741ftOfFfS4SPC2uXK2enXbKQtx5ayfMp7jAXOO7Vd/4JG/FDw5efs+X/hAalbQa9o+r3U81pI4Rmhlbcsignleo46ba+3PCvgLw94H8LweG9A0i10jQ4IzFHY2ibI1UjB6dz69a8G1z/gnX8Bta0Gw0tfBQsFsWd4bixvJornDnLK0u/cy57MSB2xQB4pPfWnx8/4Kfade+E7hb/RfAvhqe31TVbQ7oBcSLIvlBwcEgyr+Kt6V4f8AsW/s0/C7xt4i+IvgD4l32uaH8RdD12cCwttaksEubY4xIkYbDY2nJ7qykV+mfwe+Bngj4C+Gzofgjw/b6HZO3mStHlpZ39XdiWb8TXI/Gr9jn4T/AB81aHWPF3hlJdbiUIuqWMz2twQOgZkI3Y/2s0AfKlx8E/2cPh3+1N8PfBOkweL/ABX48juBqFu1vrcl3DpRRg4ecM3yj5R09PpX6M14/wDBH9lP4X/s9vcz+C/DUVnqN0oSbUrmVrm7kUfw+Y5JA9hjpXsFABRRRQAUUUUAFeffGD4D+Bfj1pNlpnjvQIfENhZzG4ggmkkRUkIwW+Rhnj1r0GigDx34Tfsi/CT4G+JpfEHgfwba6Bq8kDWzXMM0rsY2IJXDuQASo7dq9ipMD0paACiiigAooooAK5f4i/DXw38WPCN74Y8WaZHrGh3m3z7SZmVX2sGHKkEcgdDXUUUAeB+Cf2FPgZ8OvFemeJfDvgC003WtNmFxaXUdzOWikHRgGkIP4ivfKKKACiiigAooooAbtHHtXz3+2x8A/EH7RXwhtPC3hueyttQi1i01Bn1CRkTy4nywyqsdxFfQ1N2j096AK9jbm3s4ImOXjRVLdzj/APVVqkxS0AFFFFABRRRQAV86av8A8E9f2fte1W81K/8AhzZXN9eTPcTztdXAZ5HJLNxJ3JPTp2r6LpNooAyPCfhTS/BHhvTNA0WzTT9J023S1tLWMkrFGgwqjJJ4HrWxRRQAUUUUAFFFFAHnnxi+AfgL4+aZYaf488PQ+IbOxlae3imkkQRuRgt8jLnj1rC+Ev7JPwm+BfiKbXfA3g+28P6pNA1tJcQzSuWjJBK4dyOqjt2r2CkwPSgBaKKKACiiigApMUtFAHhX7ZnwX139oH9nvxD4G8PT2lvq2oPA0Ul87JF+7lRiGKq3XBr1jwXo8/h/wfoWl3Lq9zY2MFrKycgskYUkeuSDW5tFJtA7e9ADqKKKACiiigDg/i58D/BHx20G20bx1oMPiDTLaf7TFbzO6BZMFd2UYHOCa5X4V/sefB/4J+K18S+CvBVroOtLDJbi7hmmZvLfG5cM5GDgduO1ey4owPSgBaKKKACiiigAooooAKKKKACkxS0UAIVB6jNGB6UtFACUYHpS0UAJtHpRgUtFAHwh+2V8dfjP4f8A2qvhz8K/hd4m07w//wAJPp5fdqFjHPGJfMk+YllYj5U6Dj2p2q+Ef26fCem3OrQ/EDwP4oe1Qzf2WLAIZwoyVDGJBk/71ebft5eIPEnhL/goH8FNZ8I+Hf8AhK/ENrpbNZ6L5wi+1P5ky7dx6feJ59K7T4i/tUftbr4T1I6d+zf/AGRceQ6/bvtwvmgO3l1iUgtj9aAPoX9jX9pr/hqX4Op4nlsV0nXbOd9P1OxU5jiuEAO5e+1gQcHmug/ZttfitaeDtTX4vXun32vtqk5tH03yxGtnx5QPlqBn73Xn1rxT/gmP/wAILbfs63Nt4R1W61PXBfzT+I/t0HkXMd+4BZTF/CoAAX1215D+yp8edS+EP7C3xh8fXV1Nquo6R4jvxZC+naTMjGFIkJbOAGYHHTrQB+jk15BbyBZZ4kdj8qswBJ9OvNPWTcuchh2IHBHUc9+Pwr4C+BP7CGl/Hj4X6T8QvjJ4o8TeJPGnii3XUllh1WW3SwWRdyLGq4G4KQemPar/AOy3qnifwf8AGj4nfsueO/EWoeJ9ItdN+2aFrFzMy3gspVAKGTqDtkXvwytigD2/4A/tKaj8ZvjX8YvCUul2+naX4JvYbC2kVi01yT5m6RuwHyDgZrpfgTa/Fq1134gn4mXmn3emy6w7+GVsfLzHYgthZNig78bPvZNfEX7CP7N/hU/tU/Ghjea5nwP4ih/sr/iaygS/NLzOP+W3Qfer2X/gndrWo6t8Qv2lUvr+6vUtfG80cC3EzSCJd03yqCflHsKAPtCWdYYXd5VjVRks52gDtn0/zxS29xHdRCSKRZUboyEMOenIPNflj+xf+z/f/tUWvxEPj3xl4jk8A6N4ou4rTQtP1J4FnuGYtJJLJnJVVKAKOmT0r0b9n/RL79l39v69+DOieIdV1bwBrXh7+1ILDVbg3H2SVQSArHpgI/50AfohVBrGyfUI71ra3N8qGOO4aNTJt64VuuOTxXC3H7SPwptLiaCb4k+FIpoWZXjfWbcFSDgg/P618b/t2yeKfHf7Uv7Pug/D7xfc6E3iSzu411PT7g7Ps7lTJMMHa5EW7bwaAP0IjvIJpXjSVHkTlkDAsv1HUVIzFR/+r8q/Pr9oj9iPTf2ffhPqHxL+EnibxJoPjjwpCNSmvLjVJbhdUVAPMWVWYjJXLdMe1U/22PjhqfxK/wCCd/gX4h6PdTaTqusalps8ptJmQpMBIsqZB6b0xj2oA/Q1LtHmaISxmRMFkDfMB1GR2yKLi8t7Ur50scRY4XzCAT9PWvhrw5+zRY/sv+F9R/aG8S+MPEnirx5pmhXGpahDeXYFrdXLxH5AgAOFYhQCcVzX7N37IEH7V3w3tfiz8bfEmv8AiLWvFAe7srG11KS2ttPhLEIERCMHj/8AXQB+h6yFgD6/5/ya+Wf2GPjt4s+NGl/FW48Zapb3q6B4rutLs3WGOJYrZPuq20AE/wC0TXm37M+ueKv2cf2uNY/Z31vxHfeKvB99pZ1jw3dam5kntlHzGIseSMBxjp8teJ/sZ/svf8NFeKPi63i/xFq8Xw+07xjfGPw/pt49st5emRt0sjLhsKuwYz3oA/ViC4juI0kidXjccOrAg/QjrSyyiONmLBQoyWJwB+P/ANevz88J6fqv7EH7ZXgz4faV4i1XV/hR8Q4JIrTTdUuWuDpt2pIARychd20f8DrnPjd8UNM/aI/a68R/DTxx8Sf+FffCbwXFGl3aw6kLKTWLxsfIXJG4DLZx0CHuc0AfpHBdxXUQlilSSM9WVsirNflD8U9e+HH7HOveF/iF8A/irHqtj/aUNnr3g3+3Pt8d5bNktIu5icjHXPda/VHS9Si1fTrW9tn329zEk0b8YKsMjH4UAXaKKKACiiigArI8VeIofCfhfVtcuUklttNtJbuVIx8xWNSxA/AGtevhf9ozXP2vfL+IUWi+HfBc3w9W3vFhup5wLprLy3+bb5n3tmTQB9TfAn4zaX8fvhfo/jnQ7W6stL1RXaGG+VVlG1ivzbWYdjXoVflh+xjrn7W1r+z74Qi+Hnh7wbeeBB5os7nU5wLhk85g5YeZ2bf+VfqNZtcNaRG4CrcbF8wL03dxQBZooooAKKKKACoLq4FrazTNyI1LHHsM1PXyJ8ePEH7W1r4316L4d+HfBt34HWP/AEWfVJwtwV8sbyw8zs2aAPav2e/2gNE/aO8BzeKvD9nfWVjFfT6eY9QVFkMkRwxwjNwTXqNfkj+xDrX7Vlj8GblfhZoHhC/8NjWbwvNrE2yYXG796uCy/KGr9VPCc2sTeGNKfX0gh1w2sZvY7Zt0Sz7RvCn+6GoA2qKKKACiiigAryz9oX9oLRP2cfAsHinxBZX19YzX0GniLT1RpBJKcK2HZeBXc+LpdZh8LarJ4eSC41xbWRrGO5O2JptvyBj/AHS1flX+2/rf7Vd98G7MfFPQPCFh4b/tqzMc2jzB5jcb8xLwzfKTQB+tFtcC5t4pl+7IoYe2Rmpq+RvgTr37W11450KL4j+HfB1l4IMbfa59LmDXAHlnZtHmd2219c0AFFFFABRRRQAV5T4n/aI0Lwr8ePCnwpurG+fXfEVlNf211GqfZlSPOVY7t2eD/DR+0RqHxX0/wLHJ8ILHSNR8U/aow8OtuEgEHzbmyWX5vu1+cXxA1j9qeT9s74az6voHhGP4lrpF0uj2sM+bOS3+bzWkbd9773egD9c6K8I/Zn1b496h/bv/AAuzSfDullPL/sz+wZd+/wC95m/DNjHyfnXu9ABRRRQAUUUUAFeU/Cn9obQ/i346+IPhXTbO+tL/AMF362F9JdqipK5B+aPDHj5T1rh/2kNY/aU0/wAVaenwZ0XwvqWgm0zdSa7MEkW43NwvzL8u3bXw1+zZrH7U9v8AGb43t4I0HwjceJZNYjbxJDfT7YYrja21Yfm5X71AH650VwPwVvPH158N9Jl+Jlrp9j4zO/7bDpTBrcfM23aQW/h2mu+oAKKKKACiiqepNdrp1ybIK14Im8hZPul9vyhvxoA4P4+/G7Sf2efhfqnjnXbS8vtM08xiWGxVDKS7hRt3so712vh7WovEfh/TdWtw6QX1vHcxrIMMFdQwB/Aivy3/AG1tc/ayvP2fPE0XxN8PeD7HwQ0kIu7jS5w1wv75dm0GTudte/8A7POu/teTah4Dh8TeHPBsHw/8i3W6ubWcNdC08rCsB5nLYC/lQB9uUUUUAFFFFABRXmXx1/aH8Ffs4+G7TXvHOpTabpl1cfZYpYbZ5yZNpbBVRnHFcV8FP26vhF+0F40HhTwTr91qOt/Z3ufIm06aEeWmNx3MuMjPSgD6CooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKAPzR/bg+Img/Cn/goh8DvFvia8+waHpmltLd3HlNJ5aeZOudq5YnJHavc77/gqZ+ztZWM08Hi67vpUQMlrb6ZcGSQ/3V3KFz+NfTmv+AfDPiu5iuNa8O6Vq9xEuyOW+so5nReeAWUkDk9PWqNv8IvAtnOs0Hgvw/DMpyskelwKwPqCFzmgD4y/4JreEPEGpeIPjN8WdR0abw1oXjbU/M0rS518s+WpkfzNmOmJFH4NXmn7M/wkv/jZ/wAE9vjT4R0qPzdWu/EuoS2cefvzRGGRVz0OdoH41+oMcEcMaxxoI0UAKqcAAdAMdBVLRfDmk+G7WS20jTLPSreRzK8NlAsKM56sQoAyfXrQB8Z/sq/t1fC/RfgboPhzx74jtvA3i/wnZR6Tqek6wrQzBoV8sMgI+bIUHA556Vh/sgPf/tCftjfEn4+2un3Vh4HOnx6DolxcwmI3qjYTIFPOMLuz0+evsPxN8Evh/wCNNWXVNe8FaDrGpL/y93mnxSSnnPLFcnp3rrbHTbTS7SK1s7aG0tYhtjhgQIiD0CjgD2oA/PD9lv4teFvhD+2x+0J4W8X6ouia34o8R26aTBcRsBdMzyYCnGOfMTBOBzXZ/wDBN/8A5KL+05xj/iuZT7/em4P/ANb1r7B1L4a+Eta1631vUPDOk3us25Bh1C4so5J4yOhVyMjHbnjtWlpPhrSNBmu5dM0uz06W8kM1y9rbpEZ5D1dyoG5vc80AfFn/AASn/wCScfFQdx46vjx/uxfqeayvEaq3/BX7w8CgI/4Qxssev3JRnP4ivujRfDek+G45o9J0uz0uOeQzSpZQJCsjnqzBQMk46nmmv4X0aTXE1ptJsW1lI/KXUTbp9oCf3fMxuxz0zigDwW//AOCd/wCzzql/cXt18NbKa5uJWmlka6uPmdjkkjzMde3Svmj9uDxZpf7Of7Vn7M+q6fpE0ug+HbG6hGn2MbSvHaDbG3lrySVjLH/gNfpLXxr+0p4A8Q+JP25P2dtdsdCvtQ0HTY75dQvorctBBuXgSNjAB9KAOf8A2t/23Phx43+AuseEfhvr0Pjrxh4ytTpem6VpCNNMPN+VzIuPk2gn71ee/tlfCu4+C/8AwTY+HHgy9wdQ0vVNLS629PtDCV3H0DMwz7V9++Hfg/4F8I6xNq2ieD9D0rU5m3SXlnp8UcpPruC5re1rw3pPiWy+x6vplnqtpvD/AGe+gWaPcOjbWBGR60AedfHP4bz/ABc/Z18VeDrV1F3rGiNbwMx+XzdgKZ+rAV8wfsU/tieAPhr8E9M+GnxM1q38AeM/BiPpt3YazmEyqjtteMkYbjHSvvMRqFCgYUDAA4xXH+Lvgz4D8fXiXfiTwdoeuXSfdnv7CKVx/wACZc0AfFnwD1q4/aq/b41f4x6FZ3Ufw58LaKdF03VJ4WiS/lbcC0e7qvzyHj/Zrg/2Cv2pPB3wZ8V/F/wt471EeGLHUfF19d6frN8GS0lkEjLLAZMYDgBG567q/TTSdF0/QbCKx02xt9PsohiO3tYlijT6KoAFYGq/CXwTrmkz6Xf+EdEu9OnnNzJay6fEY3lJyZCNv3j3bqaAPh6+8WWP7an7eHw71TwOkmp+AvhrDLd33iIQkW89ySSI43I+YbhH0/2jXHeOPDPgL9n79u/xzqfxs8J6fq/w+8fRx3mla/quni6gsbn5d0ZYg7OQwPsF7V+k3hnwfoXgrTI9O8P6PY6JYR/dtdPt1hjH/AVAFP8AEfhPRfGGmvp+u6TZazYvy1tfwLNGf+AsCKAPz0+KHxK/Z2bxZ4U8H/BT4S+Bfir4v1q7RJYLLTE+z2lucbpHkVcAjjr0xziv0U0+zWzsLeBYkt1ijCLFF9xABgAfQVgeDvhP4L+HrSN4Y8KaPoEkmd8mnWUcLtnsWUA49q6rFAC0UUUAFFFFABWF408Or4v8I6zockzWyalZzWhnQAmMSIV3frW7SUAeYfs4/BWD9nv4O6D4Ct9Tk1eHSVkVbySLymk3SM/IB/2sV6ftFJ5a+lOoAKKKKACiiigAqteWou7WeHOwSoV3fX/9dWaSgDxz9mL9nu3/AGZfhxP4Ttdal1uGXUrjUPtU0KwtmVs7cA+1exbR6Y+nFLS0AFFFFABRRRQAm0V43+1B+z1bftNfDq38KXeszaHDFqVvqX2mGFZmzESdmCfevZaSgCC1txa20UWSwjTbu/z9KsUlLQAUUUUAFFFFACba8X8Xfs6W3iz9o/wZ8XZNZlt7jw1p1xYJpaQjZOJd3zM+7g/N2Fe00m0daAE2j/Jp1FFABRRRQAUUUUAJtFeL/Bj9nW2+DXxI+JviyLW5dTl8cajHfyWssKxralQw2Ickt972r2mm7RnNABtB68/jTqKKACiiigApNopaKAPKP2lvgbB+0Z8H9Z8B3WqzaNDqLRlryKISsmyQScAn2FegeGtEXw34d0rSUkaZLC1itvNbgsEQLnj6Vq7QeCM0u2gBaKKKACiiigDP1jw9pXiC3WDVdNtNTgVt6x3kCzKG9QGBANU9J8DeHNBu/tWmaBpenXO0p51pZxxPtPUblUHHFblFABRRRQAUUUUAFFFFABRRRQAUUUUAFFFFABRRRQAUUUUAFFFFABRRRQAUUUUAFFFFABRRRQAU3aOeOe9OooAKKKKACiiigAooooAKKKKACiiigAr5g/bX/aO8b/AX/hX1l4G03SNR1XxTqcmnBdYLiNCI9wOUIr6fr4i/4KNZHjj9nrB/5mib/wBEYoA5n/hp79qr/oV/h99fPn/+KpV/ac/aq/6Fj4ef+BM//wAVXRbXb5egpMDd0X8qAObb9p/9qpWC/wDCM/D36/aJ/wD4qkf9qT9qZCAfDPw7+v2qf/GujaNXGW4FVp18zIyxwcDk0AY7ftP/ALVG3cPDPw9Pt9on/wDiqb/w1J+1PtJ/4Rn4e/8Af+f/AOKrUhk+dQcgVYkUKcY4oAwF/ap/am6/8Iz8Pfp9on/+Koi/ao/amm4Hhf4fqf8ArvP/APFVstbiP5uvtS7SNrKMGgDL/wCGnP2qtv8AyLHw9/8AAif/AOKob9p79qlf+ZY+Hv8A4ET/APxVb4YiPmm+Ysmc7fl/WgDD/wCGnf2qP+hZ+Hf/AIFT/wCNPb9pb9qv/oWvh1/4FT/41uLIWTO45+tOa4x1c0Ac8f2nf2qF6+Gfh3/4FT/41H/w1J+1O2ceGPh7x1/0if8A+KrpVmEjcEt+NVmXy87V3Z60AYf/AA1F+1Tu/wCRY+Hv/gRP/wDFUf8ADUX7U/8A0LXw9/7/AM//AMVWwxCnHf1pnnKpUlePSgDM/wCGoP2p1/5lr4dn/t6n/wAab/w1F+1Pt/5Fr4e/9/5//iq2N27kOw9s01pBGwUjNAGUv7UH7VO7/kWPh7/4ET//ABVL/wANPftVf9Cv8Pf+/wDP/wDFVsxsDggbhUjXnfZ+FAGK37Tn7VW3/kWPh7/4ET//ABVRf8NRftUf9C18Pf8Av/P/APFVutdlt2ExUCzfvNpUD3oAyf8AhqL9qj/oWfh7/wCBE/8A8VTv+GoP2qNqt/wjHw9A/wCu8/8A8VWspDLuqZpvMt1yq9c/hQBg/wDDUn7VH/QsfD0f9vE//wAVT/8Ahp39qpl3jwz8Pcen2if/AOKrVk8qT7ppysyrtzQBiL+1H+1Qcn/hGfh7j/rvP/8AFVK37Tf7VapvPhr4dhf+vif/AOKrW3ERuBjOMirQaKfSQsh/fFsBelAHMt+1P+1MOf8AhGfh7j/r4n/+KoT9qj9qWTp4a+Ho/wC28/8A8VWm2fILEceZsAx+tSRmNVoAyP8Ahqb9qb/oWvh7/wB/5/8A4qnf8NRftUf9Cz8Pf/Aif/4qtksh6AUiMrdaAMn/AIai/ao/6Fj4e/8AgRP/APFU5v2nf2qQuT4Z+HgHr9pn/wDiq11Hy9KAdjblQMfpQBhf8NT/ALUzKWHhn4e/Tz5//iqcv7UX7U//AELPw9/7/wA//wAVW5uRUZhx+FQxyB2GPxoAym/ai/ao/wChY+Hv/gRP/wDFU3/hqT9qf/oWvh7/AN/5/wD4qtptpxg02OEsmc80AZK/tQftUs23/hGPh79ftE//AMVTv+Gn/wBqr/oVvh7/AOBE/wD8VWwrLGM5B9qmE24YA5HU4oAwj+07+1Suc+Gvh1x1/wBKn/xoT9p79qmTkeGPh7j/AK+J/wD4qt2RW5O7IPWktSQQg6DrQBhN+1B+1Qv/ADLHw9z6faJ//iqd/wANOftUs2P+EY+HoHr9on/+Krd8tZZN2ealZSy45AoA51v2nP2qu3hn4dn/ALeJ/wD4qm/8NPftU9P+EZ+Hf1+1T/410KxheM8+tL821sH9aAOf/wCGmv2qf+hZ+Hv/AIET/wDxVH/DTX7VTf8AMs/D0f8AbxP/APFVtxMS21ql8pnIIPHegDnV/ae/aobp4Z+HZ/7ep/8AGn/8NMftVbN58NfDsD0+1T/41tTM65UMQ3akt5ZFjILuT2oAx/8Ahpj9qvr/AMIx8Pcf9fE//wAVVjwP+2D8dLb44fDjwh488PeELTSfFWoyWRl0mWV5k2xs3c47CtLztuEJrzzxIAP2pP2dMHg+Ibo8f9e7UAfpRRRRQAUUUUAFFFFABRRRQAUUUUAFFFFABRRRQAUUUUAFFFFABRRRQAUUUUAFFFFABRRRQAUUUUAFFFFABRRRQAUUUUAFFFFABXxD/wAFHOPHH7PWf+hom/8ARNfb1fEH/BR7/kdf2ev+xom/9EUAJJGd2VPyetJwvUVFHcbVqWQbl96AEMyxJjoPzoZlZWYFRxnHvVaRWjjz19qiVlkj3KWPbpQBYt1XzM9vpSTRyMzZFSWvzDPQU5jzjvQBAiuGyRxTmYIy0528tCSMiq0k26RVx+NAFtgGjzn8KreWVx904qSNdzN8+Fqb5P4BuoAjhUqADxjruomX5evPrUkhJiLnkmqrSNt2kZFADofmGRuzStcP5m3FRxyiLAyfm/SkZlbkNgf7VAEMkpaRkK4qPl5gOKbv2zE43D/Z5qa12O+SMCgB0M26YBhxU0iISMNuFRjYTgbcL79aeGjK7Qy5oAczbUIAwB0pJoWVl5zUcnzLgfnUrwsuC4YDtQAuF+xs+G8yqPmBRnvVjczKedvtVZofM+QnafWgCxaq2Mn86kkuPlMeFyBgVF5aQRrGZNzei1KFjfDdSetADY1Yfd+X/eFSfxcmnMrpy4x7VD8p3ZLfLQA9449pw2WAx1oVDKsap97OahVk3DAPPWp7VR5qk/zoAJiNqx4+7/OqrMNmCwBqxNjew981Vt28v5pY1xQAkk6QOAeQ/T2qdUZVDkcbckVFPDHcIJBkVMzl1I6Z4IoAcswZc4wPSmtcYPC/L/eqJplVlyM1UurpbeQFuR6ZoAt/aPl6VFGzQ546jH41Vh1CPJDjcMY/GoZL7cM7h1zigDUt1Y4YvuX0q1HIsXyk59Pesq3vIlXjlv7tXIZhIrFhgelAFvcrY+WrSRgQEhSSwyapJIApwOlWLcFdxyduMdaAHRjbHyahyyAhTyetWGlRVBzlT0qGPAkz2oAljkbjPH4VXnJVSRIfpRNOrEAHkdaiMi5IG7nocUAP3PJGo6O3b0pn2hl6DNORSOpH51VuWYPgHAoA0HbdHleTT7cny25rNsd/yqTgNu4zV9ZBDgEcHrQAsjbpA27kUrMse3PP+6ahNx97imtJ5jdk5zx6UAEjZkBHSuB18bf2pv2c8f8AQwXH/pO1d3uG0DHNcDrTFv2qP2dQTnHiC45/7dmNAH6X0UUUAFFFFABRRRQAUUUUAFFFFABRRRQAUUUUAFFFFABRRRQAUUUUAFFFFABRRRQAUUUUAFFFFABRRRQAUUUUAFFFFABRRRQAV8Q/8FHf+R2/Z6/7Gib/ANJ6+3q+If8Ago5/yO37PX/Y0Tf+k9AFHcG3YqVZmHVahUBd2eOcYqT72Pvc9KAHPL8uXVQnrmq+1WXKMNnrTpHWJMyf98tTdyM2AqhfSgCaNyvAGE9akuWMbg4xVP5+vQ0+Ri2ec46UAPkuPkK5pIVU53bTj3qF1BUgfd3YBpYInbqKALR4HG3FVHm8lMglTux1q3GGWHG0ZrPv1BQguu7OdtADm1KJV/eNt5zjPaqY1QCQ8ZVf1rEnYvI284OcZ9qqnUEj4zytAG9f+JYLZf3m1MjHzdzUEniSCPAkYCP+81c9fFNQWMyL5mw5wKw/EOn/ANpWYt1kZAemD0oA9OhvIrqMvByB1xT/AOHk7T6VyXhXdp9vDG8hxGMEseprspJBc7H6Z68UANjCIyZ5z+lKfLVvlKimrwCW+QjripF8nnpk9PagBfMG1h/Duxmrsc3mYSTLY6VmSAE5jye+KnW8VnxHz70AO1CRY5vRsKcCqLXBSTKruHpV26bJzgE7aqsoZ2bGHHagCWMGZV3DZztHv71Yj+VcDrUVvcAjJG4YxipVbnJGDnFAB57SSMrffznHtQ2Ru/2utSOqi4YkZOMZqFpBu4NAEcNs2x2wxC9GpzTSRt8oxViFoI7csJGEhblW9KgjzcSEAcetAEe4sxyc/hU7xqwwRkU/bg8gCiQYHJx70AVZF7D7npVdQ7y7mNXGxtAzz3qvu3KMDLDqKAIbmZYI2bG49q528nee6UspRPTNa2sM32f+79Kz3TzId5XO2gBkO5mbae+eacrxgEscGq32vf04NUX1JYzg9KANv7ZGY+Cc/SnW2pSQzAEZB61z0d42S25fzqvDrKtIAzBW3YHNAHpNrdLcW3mAVfW5RoTCnfpWHpTMLdSBmHGTWxaqj5dugGRQBIflt4wUwAcn6VXFxt6LViW6aaMBQDkYNZphl5IbjdgCgC15gbc2OaPugfJlR3qOGT76kY29/Wj7R5coH3hQBYbP90VB5Ylm+YfLjNOZ/lyx20oYM2QcjpQAjSCJkdjtZfakjuhcTfK25VouF83ds+YVSgs3hkfacA0AaDKQxwu6nwqu45GOMVGqk7ee2PxpSd2Md+u2gB0m3zPk4rz3Whj9qb9nX/sYLj/0mYV3wOGB9Otef6wT/wANTfs6/wDYwXH/AKTtQB+mNFFFABRRRQAUUUUAFFFFABRRRQAUUUUAFFFFABRRRQAUUUUAFFFFABRRRQAUUUUAFFFFABRRRQAUUUUAFFFFABRRRQAUUUUAFfEX/BRvA8cfs856f8JRN/6T19u18P8A/BR7/kdv2eh/1NE3/oigCldIzTbhzuOfpUiKUVWLfd7UwjbvxUDQhnILHBoAlW4iaTexVh6Gk86B/lCndUDwpGilVwW/SiFfm80daALDL5nHSnxwk7ue2PxoTmPdSeaVY49c0AM25YheSDkUqyPFIV2Zx1OaQMxORw3ekG75+N2Bg89TQBYlkCxblO6uY1m8WFuBj8a255G27Oi+leceMtYNpcMoNAGhJqiLj+LJycCsq6vo8SlRhj0LVydx4lBYIZgrez1myeIFmugiycN/Fn5RQB2NnfP5bNuPLYrHk1d47hg0ny5xtqS11i2js9uGaVVz+NeceIdbaHUiQ+UD5PPWgD2DS9c8+6jQ8ndXo1lcC4t0XHzEZHtXzb4Z8YpNqkMaMrNu+dc9K+gdHY+XG7Pwy0AbQDRIQRuJ6mqTTGOTAGSwzVgNIIefTNVbq38yUMD04FAE2XyCOtWY/lOD8tUGd7fHzjjrVozADO5SaAH9jnk4x1pryDawPU9KXcGJPemzQ8Bs9KAFtj5cu0nnOfwq95vkKvy5Gc7qx4ZHmut5j28YzV6a5ViABxQBa81W42sKpLGfM2559af5h/jOKUFS28dKAHfZ0PzZZz3xzimrIVUqeD3xVpYwyqM4PtxmoGjaGRyVwD+NAFK+1B7WxmnjUyNEuStJ4b1ZtYsUaSJoD3DipoMTSfOMjptAqwqrbriL5TjH40AI1wEZtyn8qZ9naaOT7wO3NS268c9c5/CpC/l5bdjPBoA5rVA6wH5W/wCBVitqjpFJGBW/4iYwQE7ty+teeXWrSRTPGi9TigDWhnWUEqST2qvNCXcnqMY/GkgvI2jQIMsOpqSK4KsQy8ZzQBTaGRVYK4IrHhkb+1UDhQu7ha6PUrkxL+7jWud0+N7jXEyM4bigD1vQZCdPCngkYxW8rJbwbSVA6Vj6ZA+1dqDpmtRGWSHY2M0AFuQyts+6rY+tReWY5ULbgCcj2pGZoyUU8Kc/WlWZuQ3JPQ0AFwv3cPsGMYx3qMfu2yeTTpGZthIwc5NN56nj2oAfMy4EZ5yMg1JCyqreWc1Ubd5OANxUYFOgmfcAwUE9VoAuwqcGP+ItgGnyQmNuTn/dqNHKsGH3h0+tTMS/3m2/SgCAqACB1ByKkt1Eig9KRsLJnqMYNTRBY14GKAIZECvjOfU153rH/J037Ov/AGMFx/6TtXpYXJIK9evIrzfW1C/tU/s6gDj/AISC5/8ASdqAP0uooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAr4g/4KPf8jr+z1/2NE3/oivt+viD/AIKPf8jp+z1/2NE3/pPQBUAB3Anmmsokw2MZ/SmxKVdi/BpQ4DEHqe9AEci/u8NwaSD5I/m49qkLZxUUz7m3dqALCUYP8fDVH5hVemaQ3G75hQA/nJPc1BNlVyZB1zVjd+73dfaqskqSL0wvrigCndXQgTch59+a8D+LniQ2Mw5ZVJwW4r3PVofMhLltoHUCvkj9oLWj/aSQq/zMc/KelAFCHV4blvN87H+9Wjp2qLuc7/MQ9NteUabfMyOjSbkHRq6jRdZW3h8kjPutAHcR6tKiuIpWKnsTXIeKLp5pEbcy45IzWgb5LiDfHkP69K4rxBdPNdMGd1GM0AbvhfWPs2uwZP3m5PpX2N4Xuhc6XbsG3fKtfA+lXUkerWmPmQOoBr7k+Gv7zQ7fLZ7UAdyzvg/K3l4wGpqse4xUy7WhCkvuBztpszybGJ2qaAIWhWbAPBPU1ZW1t1TAbJqpN5iwxnbn15pBctGxAU57cUATwyBZGSQ4/wB2kkuQ2Ywc56VWvE24bpIeqinWtlLuDYwo/vUAXLWQRxbSfmpky4aML65J9qrHImwRg/WtWFkWNd4+bGKAI3UdR+VG0JH05zn8KRn2/OOnpU8kgaFXVchhj6UAWdi/u5Q2SlQ7xcSFTwp6VWRnmyoYAd6CzcBBkCgB9xCtszMN2fUCmxru+cnjOcUTTXEiFdnFVo5JEl8sjouTQBe85eufmxjFRN+8bJ6U35QMAbqSZisYI5DfpQBzfiq5aC2kyVKrXlEmqreXjLu2t1212XxC1T7PpszA9sH3NeH22pia63ZJO7Gc0AeqafeeZhFDZPfIrRS58kkscZ6Vy2kuJEVjxVma+8twCenvQBqaxfs0TOvAXt61l+C9Ve51hW8vHOOfWq17fGSHjJFQ+FdUSDVIhgAl8kUAe/WshWNX3FB0wam/jySRVTR5DcW65G7jPPatLzFj5C/N/doArXF1jG75sDHy1FC/nFhu+VO1RXO4rkDBzn8KrWs/lyHAyR3oA22j/cgqMnvzVeK4VPmlP4VHZznySrnbk4zUjTRHkw4P+9QA5Qsg8zdtRv4fSnW7Q/wnO3+93pkgVFKllqOOQR443YoAsrC3mb9wxnOM1YZfemxR7o925emMUM22TaRn3oAd/EV9ab9qDHA6U1pgr4xx61FCv7znigCcswb5RmuE11Sv7Uv7Oh6n/hILj/0nau6Iz836VwGsA/8ADUv7OuWzjxDcD/yXagD9MaKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiikoABSFj9aZMSIXI6hSRXxJ+w9+3tbfGLxLrPwz8a3Udn42029uYtPunIVNUgSRgFA4xKqjoPvAZHpQB9wV8Qf8ABR7/AJHT9nr/ALGib/0nr7c3Hp+fr9a+JP8Ago9/yOn7PX/Y0T/+k9AFL+KnfK0OT1qtcSum0qQMtz7CmzB5Icof3npQBCyyrIoA3CrEcaPGTngDBHvT7Z92GkAyOvaqzeZCWKrgMc/N2oAs7/m2Y59aFhXPeq+4cfMSw68U+FpW3ZI/OgCQtsxt/GqzfKxBOB2qW4h85CQrZPWqt8pKhRxj+9QBk6tfNDE+SrxkZzXwv8eNS+2eL5UG7CtjKV9p+LM22nyO3B29q+BfireG68S3hdSo3dATQBnabdIkm3PCnI+ldJDfhcBBgZy2P4RXAWpYM3Pzba6HTZTjY2emGORQBtya5JDD8r99uM/rWRqOrmVSdpYkYGSKm+zSSBjj7gwxxWFc7RcsG6fw8UAXNFvJZ9RgdhgB1IC191/Cu4K6BaluTXwtoMJe8hYnjfghe1fdHwvTboduvspoA9RW6h8vOeaqzSKkLcbqesZ8sfLn1pLq33wuEOSv60AUvN+6qOW4x+NV1kZbgqc7h0NSsr2sy5GBnORT9qmQu1AEkSySbi3VWxzW/bxo9qG6461gTAx9GO2Tk1fivjDYkZPPegCpqEYa8/dqxNWLcjaOW468VXgndVzu4/vd6tIoRDtbJNAClRIuBwc5/CrHnC3t1iVWfP3jjpUC4Y5B5UYPvVmS8HkodhAzlRjqKAG2ao2842k9qryK235eGqTceHUNktg1E0zbd23j1oAW3ZwuH9c/hStHmdznqvWoJnaR/lkAbGNtNEjgHccj7tAEsxLbSOnrTJLj92VHzA1NJj7MFC7cHJ57VRkY+Wx/9BoA8n+METvpeyNsHOeK8W09hbbQRg9a9l+K115FqSx59K8Pj1KHUJtkZ+dWx8wxmgD0nRb5vsxzyo6NVa6umlmPzYrJs7qaCFMJhSMtVa51ApJuPrjrQBqm+mHyiRQnpiq3h2dpvEkK9fm9axptUKsHKkjt83Wrng+5ibxBCxkVdzfKM0AfVHh1vLgKvwWXrWmWbdkLgVk6KyeTActgLz71oPOzttHC7sUANklMlxsVcNt61B9nMq/JwakkIhk8w9emaghvClx8gxQAqy+XHhkyM5pfPGMiPAqWRyV4XJqJiduCePpQBZuWMy4jQNUthERuEi596hsyF43c1bhZemfwoAmVDu+78tJL5q/MeB6VIv3T+lG8betAFZjuXB+YUsOWkBU8DrmmTOjPhTkUbl5BzzQBI8jKeBzXn+pMT+1N+zrk/wDMwXB/8l2ru04XnrXC6lj/AIan/Z1/7GC4/wDSdqAP01ooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAK/H/9pz/gpp8bPhX+0B468IaDe6MmkaPqctrapPpqyybBjAY7vev2Ar+c79uj/k7z4r/9hyb/ANloA9gb/grt+0CylTe6CQRg/wDErX/GvkNfF+q2/io+JLS8kstZ+1m+W6tiUeOUtu3KR0O454rEpdxHegD92f8Agn3+3ZYftMeF4/DPiSeGx+I2mQ4mjOFXUYhx58Q45/vKOh5AxWd/wUe/5HT9nr/saJv/AEnr8j/2Y/Bfj/xz8aPDVj8NDcweK47lZoL6FiFtFXG6WQ9kAzkHhhxX6wft/wAOo2+tfs2Q6vcQ3epx+IJBdXEMZjjklFsoZ1GThSSeOtAEdxG3lyAqPmqSGH7Pbgk5B/iz0p+F65prEuu0/iKAK0lw7YAVST1qe6zDCRtLtjk+9VIrpI7oKR0XJpDJM29Rk5ORQAW8km4uwKgnGM1bXG3d03dvSoYYSFG45PXFWGVGJy3J7UATw5Vaz7lCJclCR71oxzRsvf8AMVWv25zggemaAOH8Ybv7IuTjhV4Ffn38TCZPFV6OmG6+tfoV403PpdyQMjbX58fEmMf8JJd5O1hJigDmbMkyHP8AdrRhmMbNuKkbumKoWqhWGQw3cdOlaVvDGzDzG+Y80AbUGs/ZQIQEYn+9WFqVwrTbk3Fc43VLep5NxlRwoyDWXeyA7fL55z1oA2fCEvna5DDJny/NzxxX3r8ObdTo9ukRYjaOa+E/h+AusQO4JhDc8fMTX3v8Nbd4dCgZdxi28UAd600cMREbbiRj8ajupYFUbSy461TZljxuO3ccr7069+eMY79aAKNzLjjd8vY1LZyDbyMfWo3hZnjZgpWp/LC8D86ALSqJlIYhAejNUTlorfyy6nnPQdKgXzN4HBUdATUt62MNx0x0oAZGv7zAOB/tVPtU/eOPpVSGQO24Kx+bHUVfjXdHuHB9KAHWyxqp3Ehs5/CrE0gmwVGFxjDcUQFYmAADEjBzReL5bDdgJuoAimkf7KpDc7ulUvPdmORjb+tWWnRYCe4Oap7WdvvfSgCTzF2McAHORupInMluwBw6tu+tJJaszbic01d6SMoHbANAD7eYtIExwRg0TKFhYDkflU1tsZMng1HeMi7lHH0oA8I+OBaKHdnG736V81afqlxa6tlHJRG575r6J/aDnW3sWJY8jA+tfM9nMkJdm5BbigD1aLWDLGkokAJGOKxtT1IG4UAsGzkjNZ+l332e2RnQKv8AtHpUFxereSYyv/AaANptQSfESYyaZ4fmNp4ktAE3FW9axVLecGINXPDl5I3iISnGN3ye9AH2f4XujNpdsz8sFrdkuAYBtHO6uT8JXDTaXaj/AGea6ddqx4UZPWgCKeR5Bg9KrxACai48xjkOMUW/zSc0Aacc0QZmPy+lNMMbhwTg9qr+aqtsI3CpI2ZW6UASSWojkOzd9akThwR96pFug0eCCr+lKsPyq4zv/u0AXlb/AOtQzHadhU56UkY3KO2KR2CxFhwo6GgDHnupY7wKF+WtGHzLg5KBBSGFJGDEGnxsUGB8n60AI0e1Q2e+K4HUl/4yo/Z1/wCxguP/AEnau7ffLEQOMciuG1Vgv7U/7Oq9W/4SC4yf+3dqAP00ooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAK/M/wCPn/BJHXPjN8ZfF/jeD4g6fpsGuX8l6tpJYyO0QbsSG56V+mFNCgcAYFAH5ISf8ERfEMcbN/ws/TOBn/kGS/8AxVfAPhv4QeIfG3xQXwH4bspNa12S/ksIY4AcMVcoXP8AdQYJLHiv6aplLROB1K181fshfsZaH+zbHrWvXqQ6n45125mnvNS25EEbuSIIs8heeT1PftQBe/Yw/Y+8P/sm/D9bKFYdQ8W6givq+sheZWHPlIeojU9B+NeV/wDBR9QvjL9nzAxnxROTj2gB/mBX2/tHpXxD/wAFHl3eNf2el/6mif8A9J6AKO5mbbjDelV5WkWTDcE9TUu0ltnzY9aRkVjl+AvvQBTYBpM45bj6VYt/3OQ/IFQtgSOq8ZbANI0bOAe5680ATSSB5N0fPpUsX7yLJ61UWMx4ycYq2v8Aq/8AZoAnt1Xa3yj8qaEZpmJHy5z+FJDMI1cMMk9KdJMjRlPmywwD6UAcn46jH9j3AHB2t0r89PiHEzeIr18c78c+tfoV4umgGlzYbfuVuvavz4+KWZPE146fKvm5wTQBy/2oOwGWUkYPA606MtHIXJBjUYHuapxSNF84O45zVqOYMAQMopzlqALV1dNJHINqjbx161mxQ+ZxkfXNXJMurAYO39aoqzq33crjH40AdJ4KYrr9rA2eHyT6V+g3w7mWXQLUxbiPL6e9fCHwz0+C61F53kDXLt8sa9q+4/hqrWvh+AsCMLwW4oA6++i8yNQB83b2qq0cnlnPbpWgrLIob+L+KqckjMzqvQNg0ANmkKw/NGQOxqLzgGUDgVNvd0EbA4HSmSWzeWr7SD/tUASLInlluDUNxdZVUZcmlWUL0QLhct3pssgkUNQAaSq/aHUc45Ga0Wk8khyMGs21jJY7SFY9ea0G+/ndkLQAqyMzhhxTZvmucs3Gc05PMk4Qrt9ahuiFkwy5980ASyKG39TnpxTFkK4ITgVD5ghj3M5FS/bjtxjI+lAD45i0mWAxjH41ThWQs+ZAFHQ1blkKxkgcE5BxUTYyxwAW/SgCTBjVfnB5xTiAytsBPOeR2pLcb1AGM9aRlmVTuj+UjAbNAHzp+0Vi4tY4EUmbOfl5r5z+wt9lkUkK8bfnX1V8brVY7GaVlVXVfkPpXynA7NeOWYYLc80AXIrh1tpIXJO71qS0jYyMAVB25pLtFWIHJVz6jpSW0jK29QFOMUAaUijbv+bHpVDR5jFrQJyR5mBzUzXD+TJlgPTmm6XDu1S1A5LNk0AfZ/w/jMuiW0mesea62P8AfKQOHrlvhsu3QbfPHyKK7KC0wwdTjPWgDLuUljwAvHeoY5Gjm7GtORm82UOufSoI4UJyV+agAhict8oz7mpDHIOpXH97NCv93LgJ3FSM3mKkoGM9aAEmZoYgepHWpbS6aZQACOc59qrkE7lDDA6+9aNnCY0zgYxigC4PlUd/WqzTFs/Jip2kC5296gGHYLnG7u3agBDxweRnPXtVhfuA9x196hdRCpZjjjC/7VTN8sCv225AoAbbybtwb5RXn+qLt/aq/Z4/7GC4/wDSdq7xGCsdy4rhdWbd+1T+zuQcj/hILj/0nagD9M6KKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigBKTaKdRQAV8Rf8FGv+R4/Z6P/U0Tf+iK+3a+If8Ago9x42/Z6I6/8JRP/wCiKAKPG5uefSq90rMp8sYz13VaYgMWJAY9KaWIjPH50AUgzCMAsmRyRUTF41BHT0pzRszNJwu7pwKj3HdnqKAJrON7hAW4LevarS/KoXbkHpzVcghRg4z1qRChiQh8Y7UAS/KFdmGCOlVprho41YAHPQetTb1YkKd2epo2qu3gYoA5PxZCv9lzgpglM8V+f3xGjX/hJr5Dlhvzya/RDxF5bWMwyudmK/P34rII/F18cYG/FAHnZyc4OB2qxYkLvycqfUVYW3EqqMZXbkbactqFUrGN2f4vSgBCokWQeWxx90g9aqwZ3bcBuN3410enaPL9lmdlZgF3t9PSsqS123WQAF29KAOy+E/kx+IoQRhm9x1r7z8Ewq+kxZUj5M818I/CzRzN4stSq/x5z7elffXg6EPpiR5YMEwTQBtxwiMYUjFZt8yqz4GctzWjxD935t3TnpWdfw7zuPAznFAFWVvMmUowCdzmrk2fsqu8haqHk+S2dtabR7tNyTj2oAy7dkUyhmDFkx+NSNGnGOOM0n2cxfNsGcZp0jNtw67W6UANtf8AWNir8ahgVIyT1NZ9qsizdM1oKwibJORQA1LNlkLAN5f96o7xSysy81P5zfKoYhM4IqrNLJEMIMr9KAJGybFCQuScGmwld2AuKW6yLVARtUHJFJA6sg3ffoAmjK7iSRkdN1V5ldpSduSeu2rOwr1X9KBnOcY+vFAENrAqruVju+tW1m8zasj5XdjGKj275PkAI9aTyS0yA9ByaAPJvjhYiaxm2jPytXyPJprrdAAZG5s8dK+yfiw5j0+bdHuGMblr5f1OzSPUJ403bmfOAO1AFAWD/wBnBXXeSckkdqyLa3MkwU5Thh+Neiwaf5tiBsw5GAK52+0/7DIMcc56UAYlxp/7krghyMAN60/wzZtL4ht41BbDc89K6B5N0KExMzAZLcdad4NtVbxFE+3AVuKAPrbwdD9l0iGPr8q11tucxrtX9axPCkif2fGCjAbV5xW9CwlgBA2ndigCheTDzGw2KZGGVemW9aW+gyx3ZU/SnWjIY9rGgCtIG3fMN3rxVld+0fN8o6DAp33WbA+93pbiMxldv93NAFZpEVlA+/6Vaj1JW/cdHznrUHk/MNwy30pkejr5wlLHzPTdQBtRR74t4fnGalkhMYBHzg9ajt4fK2LnOeD7VPcMTlfugdMUANaMzKADnHRSKcy4VY9vTgbeaSOTMShiOuDzQOVz39qAIWgUR5XlvrXn+oQvD+1P+ztnp/wkFx/6TtXfvuLYrg9Uyf2pv2dc/wDQwXH/AKTtQB+mlFFFABRRRQAUUUUAFFFFABRRRQAUUUUAFFFFABRRRQAUUUUAFFFFABRRRQAUUUUAFFFFABRRRQAUUUUAFFFFABRRRQAUUUUAFfEP/BR4FvG37PQHX/hKJ/8A0nr7er4i/wCCjX/I8fs8Hv8A8JRN/wCk9AES7GA5UEdKjmAWM8UrQnzMqVIp9woaPmgDBuFaVWIOFj/i9aW0UtDyuakumEEJXaTv6e1QQsY4xjp6UASlx3INDTouM81NHs3BSBmoJowCxHI9KAH29yu5UVfxq3s3DB2kdqzk+8CdqkdcVqR5JUlQAentQBha9bjyZlCZG372RXwN8ZLFl8WXqKGyTkE461+hmpxq1jICoxjFfIXxJ8JLfeLLiR1UKemRQB4TptizRgHnavBUVs6T4fFzdSA8bujYr0TT/CcPK+WqLjHFXYvC8drNI/3sLlcUAcppmhiFbiJiwhcYJqhd+G4RfBIzu3JnOOntXoNrpW5tuDisq60OaO4J2soLUAVvAWmfY/Elosbcqyu+RjFfZvhaYLYpsViTwTXzT4B8PtJr0czQsO3PtX03ocYhsxHkDHTmgDU8nz1+XrVK4TaOX+bGNuKvMx2j+GqV4iTISTx2oAo/ZzjL5B+tWEaT7OyAbvrTjhiQDxUazM7fKR70ALMh+RQOcYJzTLqHbIrM27jNSqhbln/CoZgigDcC/TbmgBLRVVslualJ3DBAxUFvG3m52mtVWX/nmKAKBTzDhckdakbMWBgFj0WtGSFRanC4Y9Kw7jzVnjGBlTgnNAFhGNxw6bQ3ai808R3C7Xx8ucUGUpMHGD5YyR61C999quo35HbpQBI7OckyAD8aW3y6Esee2abcEbSgYk+tLE7FRlenagC/bsqrtK5NSSRrIAVGAait45GYnKgVMytHCx/75FAHlnxejkk05wmMnrXgX9lPJelim7HVj3r6Y8bWourX51z+FePahYmK4EajgegoA5+SPZajbH0GB6Z+tYl/ZDUEJ27ZV/h9a9Cj0xBH8wyM5xjis+40AtMrKcN/exQBxCaWRHs8vA6da1PB+jqNciU924BFdPJoStDgDJ+lbngjR0hu4XO1yDkbhmgD2jQoBDpaI7AErx7Vo7QrLhj69Kq6V81rwp54GRVlGwucYNAFW4UTTAnr/dzTJbcBhtPl/WpWX3yvZu9OS3DffJYr60ARLlY15XFSMw8tXZW29KbJhlCqCAOvFJueMk/eQfw0AC3XmT7yuD9KuLHDJ90c9mqnJEZJt6bSPSrNvL5KhNvI70AWY0Kt8xwrdak43Nz0bB96ljgDKPWneT06cc0AQrHFnbg4605YhJt2tgYx+NN3bQTjO3t60qyFQQFwAcjdQBM1um7bnn1rzvXkC/tTfs64GP8Aiobof+S7V6EsjNLyMr/ergPEA/4yk/Zz/wCxhuj/AOS7UAfpTRRRQAUUUUAFFFFABRRRQAUUUUAFFFFABRRRQAUUUUAFFFFABRRRQAUUUUAFFFFABRRRQAUUUUAFFFFABRRRQAUUUUAFFFFABXxD/wAFHTt8a/s84/6Gib/0nr7er4g/4KPf8jt+z1/2NE3/AKIoAjnfy0U4yW/SqtxK7xdOauHAjAJ+pqlKyFSVLD03UAYt1MW6Kf8AgRq5Gu2NWwPpUTbmbkD8ab2AzzQA+ZljkUn5TUfn8kjrUUxb5cnJpFO3k8p60AaFuse5mIXe3vVv1z901lR3B3DauMVoCcbSr8GgCO9kE1rIoHNeMeNdB8zUGlVQxPTivaPJK7jnjGa4jxBYtd3BYbcDoKAPNbHw3Fswy8f7tWZPDC265fgYxXZw6YOQ3G3r70SWKSoytlv92gDjLTQY4SBt3Y69Kp3Gmgy4KDHXpXZWtischRRknqSKr3+k/vW27n/CgCr4ZsfKukIUgDq1er6SzSx7AoA/2hiuC0HT5luNzMBXoNvEPJTrz1oA0byMmRVU/LjNVbvbEojOWx3xVxF2wqSecYrOvF+bZ0X60AS/ZWij81sYbtVSYiNSyrnPWp4Z9u1GIJ7c0ybZI3zNtoAqLNnczdunvU626yRlsDPY1HcGGSOMJlStAhkWFcKw/EUAOtQftGC34VpiFTtI4H1rKt1bgEbTnJ+lbCx+ZGMZ2hck0AKGMmF3cCsrUpERvu981pbVjXcp3f7tZGoAy3BXHFAF3TLcyrvIDBl49qbHEVUfINw6cVOZIobFRGzZ2ZNRRyZUFmyaAIYFUKSetTR4EisoyKScxLG2CarLdBm2YwfWgDWi2MpCKWP+zTpNwjyRmm2Tbm+Xj6Vdkj8uPLDI9KAOW8RQm4tyCuQehxXnknh4PPuxla9Z1aEfYSMcjpXK+T820LkUAcxcaGnlYQbjVBtIdGAKcDqcV3Mlp5apx161DJZmRCDyD7UAcnDpKBl4+WtfR9Dihuw2AgHAAq7NZC3X5ea0dFhD3HzDmgDehiZrdFTggcY9afNn7pG2rFriNABwc5pxUshYjLetAGZG22QHOQParatu3ZG3zOntTljVQoC81MI0DNnptyKAKMjBSy4yfWoVc4J4FX3ZfMOAtEiKYshQT9KAM77uTkZHUVJbjdled9TcM3mMAN3UYqzHGgjBB5PU4oAs26+XGCzZY9Kl2grkGqwjJxj+HpU0cbeTg9aAKwk2YJG4j+7U8LeZuyM0xrfdwvy+9Swho2PFAESxj7RkHiuC8Qf8nSfs5/8AYxXQ/wDJdq9IUKp715r4gz/w1L+zmO3/AAkNwf8AyXagD9K6KKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAK+IP+CjuB42/Z6z/0NE3/AKIr7fr4g/4KQD/is/2e/wDsaJ//AEnoAz9Qm8uMiPcQeu6qMN3ujCs4GPWrc0Jm3D+ZrEu7dlkwBgUAS3F2DIAM4HU+tNS6DHJHNQtMVUIy8joahVgvWgC1LcbSpAwf9qpYbhSpDIC/Zah2hkUsu4/Wkhi3yAA4A70AWra3DTbWO2tHyRuHv1qrYzruy5B9qvR/vAT0x0oAY/MbDH41yeoErcNxn8K7Jgu1lJ+Wud1K3hW6ba+7nP4UAYm/dI6kLg9NtAhCuADgnvVxrVWnU549uKma3Xj2oAypLUCRmUVB5LKSW7da0STDJsxz6VHL8yvkdaAG2A/eDIwPpXVwwny48ZrmIVLFBjHvXY2akwqScfLmgBcutqSfnI/u1l3cnmSAuOnXbWx5RkVg3ynGeKx7wCGMsepON1AFdrjdKgC9KlkkGRzT7eFOGdsntTrhQsYYD8KAIDcxowBXLGrEl2lvCN672PQZrJklVZt2MmnsWkUK42gdKALljMLiRwoZCRgd607KJ8ySFiO2M1k6aq282S/Nbmx5FZUIQt3oAeqhlZ+g9BWexS4vAMYJ6irUgaOHDFVP1qo0XzRAJknrzQBYuYQ1lvXg4x+FVvs52RlTkYzUk67bNtm8/Nj5qhgmmzGiqNvSgBixovDSMRUTW6hlwcvnJHtVqW3URs5YHb15ot40mZtpxxj5qAL2mjacDg+taLP5n3utZseUTGeak5lXfnPOKAG6rzbtg5rmn3eYMcfhXQXSlY27ru/SsoW235jIp/A0ADW8jqhwcfSmrZybsbeKsiV2jCITn1qeNtseHFAFG5s0jjPPzUaRZMZRJ+dWJYftEhb9Kt2MX2fdzQBdW3fdkDj0p/MMbAjJqVZPLXzM59qryuPvMPwoAoNJMrL8q5HWlVmOdwzgYqaSNWcnOCarxRySM2VoAcFYruG3OMY96mf5o2HemswhUqT+9JyBipDGW5HTvQBXZPLwOrf3asW/VR2pGUNjJqxDGi7WHNAEy47Lim4qd1znCmo3XHRTQBHL8kbY/wDHqjMrYyME0MzdD8wzn8KLYM3BQfWgCRRuXcefbNed+IGLftTfs5/Lj/ioLr/0navRNyqcAgH1rzzxF/ydN+zn6f8ACQXP/pO1AH6VUUUUAFFFFABRRRQAUUUUAFFFFABRRRQAUUUUAFFFFABRRRQAUUUUAFFFFABRRRQAUUUUAFFFFABRRRQAUUUUAFFFFABRRRQAV8Qf8FH/APkdP2eu/wDxVE//AKT19v18Q/8ABRsZ8bfs8/8AY0Tf+k9AGa6k9AajkiEkZBHNaGwrwV5qlK+zcSM0Ac5qAy+Ad3tUSruVSzVYucm73HhafKqtGNik0AV/NKlUB4qbzDEp469DVPdu24GavsZPso+UbR/FQA21VpJshcCugjygAPy571h2bHcqqufetiKd5FwY+KAJ2bzMKOFPWsi/0/8A0kk5RdvWtP3qGaMyNl2ycYoAxZbZht8vk/7VWGs5QuTxVuFA0mHKgbc1I+ZMq3OOtAGRLpbBW+dSy1UljRYz/FW5LCTllOAfvVRntULFcHA60AV4Y0YKAM1uLM4XDKVPT5eazY2W1G4Dgdq0o3jZQzls7d3y/wAqALC72yyknjFZl1BJcZb15AWtXzVkCqAfmGfpVS7+U4jG0r3NAGaVkBQYwB0qeZgy/fzUNwzMyor5H0okIijOeKAK0karIfnyewxRJAzryR/wGiGEzTrJj93/AHquXAiLKqE/gKAKWk4jvFSXLDdjBIrqGlPmbQoHpiudaNVKqEw/XcRW7asVVC3JHWgB1xCskZaQN7VUuU8kRyR84GDk9DWoXd4w33ArY+bvWHqzbrqJJXCwg5JSgB00rx6eWZz8xyo9apafL8wySGHQZqTUpUkhVV4T1qjDIqyKuD9aANm4uEij27M7utVYpmtcHGcnFElyssarg5qoW/0gBvlUnIoA6JJFljDgYp2dseH4PXio7RkZdqnK08cY9utACTKXhbOFGcVR2FQxIyavtKqx7ChI69KhZ+WI5X0oAgCjaCQwH0qzbQhh5Z5b1qNnLLszgUkNxsl9fegBXteC0efM/u1Nbx5XaDmT0pwyTIQGzQse4570AWo+VVW5qVbdBk5waj2ng96SRTtPNAEMmJGIU4K9/Wmbiv1qJZAIxu4IbFPIMiMV5OMD60AIcSMHYbsDANPjkZgwC4FMiHl2pjYbSvf1p0Hyq2/g0ADQ+YydsdakaNtyqo+SmHdxgFif7tTxbkTb1oAn5VjliaSRd0md5VfSm88Nj8Kd93nrQA1ev4YpcFSo7UowMZ/i/Sn7euD06UARlVzgrx9K878RAf8ADUv7OYByP+Eguv8A0nau/uJnSRlIA+prz3XFA/ai/ZyYEn/ioLr/ANJ2oA/SuiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACviL/go0Qvjj9nn0Hiib/wBEV9u18Qf8FHv+R0/Z6/7Gib/0RQAx2V5MjpjH41VuImU5PIqSE7VIJGc5qSRg2csNtAHKX7q0hA4FM84LHjPP1qxqSBLhsD+LFZqQecjH5if9mgAknRsADmrUM6TQ4LgfjWaq/PnvSpg8AHP0oA3LFjC6gPx9BWnC2WYdh1PpWNZsWVUK8+tbkcKqu3dQALycfrTJGUrnLflU8keDhRgVBIu1W6H5sdaAKrKFbco3dqZ9qPKjv1p7fM+Qe2PxqsoPmkAYPrQBbh3eXLvQj0rPnEoDuSNp75qxCzrjcxK4wfrTbqWNl64NAFFfMkkKsFK4zWrDthVcFqorIvmeWB2xmr/kyfZwwFAFq1jbcHDDBGKrX0zwmQdQ3TvVuzk2wgbPmxjb71Q1WMqisOaAKSyBuWIPtVlsyRueidiRTI4Qdp2Dd6VoPaL5fznCqMfjQBlRXD7dqphV/WrVnbsdzscntUMyiOICM5AbFXo5gsKLjGOp9aAGIu7LsMkNjOKu2cfnsyllxVTzFyqDaVY5xnpWjZxxwqXKGgCxeQjYIyrcHI5rn76MSZJUZFaUlw8yliuz0rC1CRlm544x+NAFe6w2AGyaBJngDmmrs8zdu/CpIgokbP4UAPRQwBySaryn98PbpVzcJOCdp9qrTRnzM9qAN6zI8ngYrRYHyzgYY1S0sB4ck/8AAavPcbg2Qfu56UAUpizKVVsY61Xi+XGcc1M0TMztuHPUVEy4dgdqBRj6mgCy0MZj681UVVVeB+FSyXAHVcVFCoWTeDuHpQBYt2Ejuys2T03VZteZNtV0hKtvB49KtWoG5sg+1AFkwMq8nH9ary4EeQwNW7qbzI48cbelVuNuMqKAMo/K23r81Wyc7COFzkioV8pPvrj5qkjJbhRk+tACTTFVHGcHP4U9cNGG9etRyLmPjrjFLDnyVHQUANG+SQDOPdTV+3kPl881lSbuqnHsK0bVSIFPQ0AWGUZyOfekPDYpQ21di4YUjYZ8g4FAEe1Sp5PNAmWPsz7v0py/McdBTtu3JznPagBVwylnXd9a848RPu/ak/Zz4x/xUF1/6TtXpG7ax3cV5z4mz/w1N+zl/wBjBdf+k7UAfpPRRRQAUUUUAFFFFABRRRQAUUUUAFFFFABRRRQAUUUUAFFFFABRRRQAUUUUAFFFFABRRRQAUUUUAFFFFABRRRQAUUUUAFFFFABXxD/wUcG7xz+zyO3/AAlE3/oivt6viL/goyQvjr9nknp/wlE3/omgCJVbLHYM4x0psnePYN3rU7zbVHGM9ahPMmT1oA5XUpPLumUnnd96qdsGG5kfmtLXgMthQT1rJt1ywIOCetADjGB90ZNLHGUbccClnyjAjle7CrFuyK2xxgUAaVsqGONicbv0q/8AM2HC5FZnnRhVA5NadtJ+5CI+T6YoAlLHqy7apTSNHIVwCM5qy0jMjHPNUrgBmbnD+lACxSJsLHg5z0poAkxjgnvUP2VmLAHNPVZlYJ8uA2DQAPC0KsoGfm61TmQM3zjbWhLI0eUHPOaz5t235+GoAitVV2xjit+FSYQvb0rGswq87f8AgVa8bMF+U5GM0AMMgjcj7vORUd6wEaKeVqWS3+07S/J/Kql1lVCEcCgCPcFU7TnHSrNvcearQvyrHO6qEJS3QglmNWbdlaQLnp0oAFtQzOrIdoORzTEla4jZVGBH0q3IyiFxlg386ia3RrcsJPLI64oAgt/lkblTW/bg+X8ziufh2RuFxlycGt1Y1Ma7cjjNAEDZZgBwwbAFYOrWsk0pccRg5Nb3PIPTOayNSlKsTnGeq9qAMZWPmE++KsrtI3gEntVaN0SYGQfKWq79qjl284/CgBsKtHJkN83pTrifDKmOaazx/wB6q1zcAycCgDptPXbbjnNWmZ2UKP8AWHgiqekqZLfrire3bJ6nd1oAT7qgj73eq3+sXc7gHOelWiA2dp603AY4woH0oAgT73HP1p8agyYbpTpkjxndk1Cg2yAsQR9aALbdWC8DtToZGWQZ+XPTdTCcKp7npSLG88g4+7QBdmcsqBSvHWiZdyjgfd54pyx4pGY+WfcYNAFOZ419++KjabdtA4H8XtSNGGkyWwcY/Ghk3eVhsY68UASUMu5T2x0pskgjKnGR3quWMisQce1ACxfMwzzWhEcqCeq9fes+P5F+bAf0rSjTavXNACtwjEfw9vWnsw8tWDA+22lVQy5xilbtnt1oAiwzNlduPTNEayK2WHFIyhmyTzUzOOVJzt/WgBjbG+ZGz7V534iYt+1J+zkT/wBDBdf+k7V6K0axnIGK858RZ/4am/Zz/wCxiuh/5LtQB+lNFFFABRRRQAUUUUAFFFFABRRRQAUUUUAFFFFABRRRQAUUUUAFFFFABRRRQAUUUUAFFFFABRRRQAUUUUAFFFFABRRRQAUUUUAFfEH/AAUe/wCR0/Z6/wCxon/9EV9v18Q/8FHOfG/7PQPT/hKJv/RFAFSD5iQeQOlNlmaOTH61M6pb87uaguGEgBXk0Ac/qjj7Sw3cVSVY05LbfarOuXEdvOUfgY/Ws4P5jZAwD0oAtq0ceQx3A1JPAscRZH3Mei1nrPtLZGasm4MluCygsP4VNAFm1ulaRQVOfXFbVqp8sKeB7Vhwwszbd6r+BrfsJI4oRk7moAfkMhePr3qneS7mO2PFW+PnwduetVbrG7J6UALYtt3bjmlndUZuc85qrxGp4Zv92oZZCGbJNADTdMJvlB/3ak5mjLt8vOMU1Mu2BgD1p8jY+VSGGcnr1oASJSnzHk1owS+arLwO1Z0d0pjwBubditG2AClhjcelAE6iqOqRrGWbn2q6uV4PWszWd0i45xQBEkamMMOasW9pHHIrhs+1ULZmjYIFbI71YnuCWCoPnHWgB14DuRsnYOhpgbzGcD7h7UNKbhVXr9aIVWNeaAGtK29gfm5yOK2raRpI0yT93msa3mVJVB/OuhtE3W+dqntnNABJaMVJU5Nc74it3Sz3lhmurS6SSM5OMda5jxVcI1u3b/eoA5mGQfZyWOSG4qwrfLntWZCPMXIbvmr6yDy1THPrQBMwOwP/AA+tVmkEjDacmlmYqqgHDf3e1Z0Mw+1bcc+tAHoWj4+yA96v+X8ue3Ws3QSZLVARle5WtlvkXH3hQBm3K7YwQ+COtV9uDg/McZ61bmwzbChA71my5ZslyD04oAueXGp37smmr5bbVkGDTHaNF+UF2qEyiRlIHOc8+lAF55gdqgfd6VYsZS8svy4B6VQiZmbJ61Ys5vMkKKpBAzn1oA1WH3ahY/KeambG1cHNVNp+bhqAIFZEkfPQHIpfkbBD8N29KcwQo+4/hVNVCuSOM/3qAJZmDL8pz7NUK/fwemc/hSSKFm5Oac5A7fNjFAEsirMvbNXYQBH13ViMrrliw8v1Y4rR0y4DR4PJ/wBmgDR42jg570MRsYnktTtgBBJ+Y9eaTaGAC8AdKAIooQ2R1f0qPyW3qe+7FTyMh3fwt7UjDgHvnNAEkkZlIIPA615t4iVh+1N+znn/AKGC6P8A5LtXo8cwTIxgHrXnPiSbzP2p/wBnPAwP+Ehuh/5LtQB+k9FFFABRRRQAUUUUAFFFFABRRRQAUUUUAFFFFABRRRQAUUUUAFFFFABRRRQAUUUUAFFFFABRRRQAUUUUAFFFFABRRRQAUUUUAFfEP/BRv/keP2ev+xom/wDRNfb1fEP/AAUc/wCR4/Z5/wCxom/9E0AVbqNvMLk5B6Cq7N/3zV+by5FOdxYdKz2iZjjcAKAOf16FfNZpFLDOcVl+cyDBG0D7tafiSV1kIBz71gxtlT5h6dKAJZJAmT2p7XjbQqlQPYVUaZfuY/WkadY8fxf7ooA3beZ5jvPJrasH2rzxXNabdJsBKtu3YrqYbdWtw+evSgCa4c7TtHPrWfJI8keHBBq4I3kGwjisrUmlWRgDQAqTMzBIxznGWNWLriPldr/3qpWZZ23AHrn56t3F4PugBvegClbtyFJJps83ku3zMM9K0LeJI5lfbkelF7CsyhgoBHSgDOiZpJOFx3rds4j5aux5Wsa1RvNyxwK3EVlVVT5s/eoAn8wMc4waoapMu3OMf71XT+87Mm7p7VT1W1xFvLZHoaAM1W8sBwTk/pT9PczLJkKG9ayIZh5hy5K/WtKLEcbMpPzUAQ3SnzBtJH0oa46qTyv60y6ZxN8p3fhTI41faznBoAsWqNM/zLtHaut090jtRERyelc/Yr+8RQCVPTkcVvRxqsaHGSKAJFVNrD+93rlPF0QjjKOMk9K6r7Ui7RhcLXIeNrwtCWIGVbA4NAHPWaiPqatRSbsZGRWVbzGRecKfStaIAx8UAEmHb0HrWU8ix3A2j5t2K1JkZojxisKN5GviMfKDkGgD0nw2w+zjHyk9a15ncSY+Yj6Vm+HIUa1Yk/P/AAitfLHO4Yfs1AGLfSlWYkkj61nxt5m4jco9K0L6IZI7VnqitI2Gbpj8aAJY1ZTu3fLTpWRsbn2ZGBQqlV8thUMli0zLh87aAJGmNuqselXdO/1isHb0qmYSEKnkDpV/T4wiigDcbHy8cUzJCtjmo1mDR7c/vPSn3GVjGOSWx6UAZd4w3E4Oe9Q7mBHy7veobiFpM7ZSMtg7qlgMkcYT75HXFADZsbsoMnOKcJ9/O3L/AN2lfDcMdpzmlVo42zuz+FAEMzK0LBg34ir9jCuMx5FUbhg5DBmKnquKv6cPMj+9g0AXfKkkZSKsNF8vynFRofJAG6pI5UbjOF9aAIpF2yfKBUed33fmFK2PMz2+tCjb14z0oAdtDNllyK838Rf8nTfs54Klf+Eguj8v/Xu1emBvl2j5m/u15n4ijWP9qb9nMKMD/hILr/0nagD9KaKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAK+If+Cjn/I7/s8/9jRN/wCiK+3q+If+Cjn/ACPH7PX/AGNE3/oigCBc7jVa4YBmboq1YeQwhiVyaqTf6TB6LJ3oA5bWZTJIx++q/wB3vXKXF8WZwEIFdHrkK2DbY3yK5a51KEF8LzQBGL5tpLODJ/dqS1vBJ8pDZ9ay5mRpjgEf71Sx3DWvPUUAddpzbY1Y+ua7axmDadGf7vavONN1AvGqsMCuz0i5Z4QuRsPegDUNxtXHU5xVC9gabLDgHoat5VTk9c5qvN/rl54/u0AVFt2VPnY7fWrHkiGLPDGplkAbnbt9DSOuFOOVoAgt5mkweAR1p9zcL5hVSAQMEe9V1kaKQkBcmrHkhrrzAoO4ZP1oAx9ShuNo8lwrbufpXR6J5k1viQ4asZl3XDbRn3rZ09PMXLZB9qANLyTnO7I+orH1jPCEEL3NbF4VsbWLbGGlZsn/AHfWsvWJ1ltz79aAOWmCRybVq1bzKqrljVWQbvu9akjjbap2HFAE0sjmZcLn5sVcVY7hQGXAHVqoRKiSxks2OtaM/kq25SRuXP0oAkgBtGXIAjb+L0rftZFkjXae2a5S3lNw3lIcjOOa6Syk+ywhmAOBg0ASPCr7mAwK5HxerSbBk4BzXaRqXUHcu09RXJeLjHC4hDbvduKAOStdkb5K5Natv9zPb0qhDDukUKOPWtOKFlVccH/aoAWWMsCCeKx47fy9UPPynpWvPmNeTnnP4VlsrtqSlm+X0oA9H0SFYbZVDcYzuq1JP5bBQOnesfSY5pAjqxjCL8ydc1t7NwyRn2oAzNQjVV3ZzWYJjHJwv3ufpW3Pta3AbkjrWWsWZGKjI9aAJ48zyMDgU5reMsctsz6VACpBIBzTvMDDOOaAFeRY2MYOcdeDzViCYKcD8qjt4y0gI5A9anif/SFwgoA04R8qtjB9ar3W+aRADgMc/Sr+0sg2jcKrupJYBDigDFkLrcNHtB5zU8ifMwX9KhnjEdwWy3IwKtRcKp7t+lAFW6Yrl0HOMCkj/wBXuYZarU0IjKlT5gWonZVZcL2zQBVbHmle46HNbFnGyw5wC3+zWa8Ko4Y8seorSgx5I8vhvagCUsvc7P8Aep0fzPwwFPigDLiYb39qcMRqeAW7cUAROpVcH5j/ALNRTNLKybV4HWrKkNuJVs1MMRr92gCvb7mk5FefeKAv/DUn7OXHzf8ACRXX/pO1eixtluTivN/E/wDydR+zmc5H/CQXJ/8AJdqAP0mooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAr4g/4KPceNP2eyOv/AAlE/wD6T19v18Q/8FHvm8afs9D/AKmif/0noAoeYW3iQ/w5Aqt5hjzv5B+6PSrEah28w8cYqK/jMyb4+ndqAOM8YXUEZJGQR+tcLNdKqtLtDCtjx07KANrEj3rjbW43LsZdynrz0oAfb6xDcXBSN2ZwcHeKv+Z8mN26qVvDHGDIIhycnpRJvkbaDQB0GgSGS48sFitelaJGwH3cHGcdq8x8No8dxGWPDda9h0tXayIULnbxQBJcR7fv1l3TBbpTnitcwtJ1NZt5bln5XaaABdlwPMPCf3aVY8r8nMff+9TfuKQBVjcIYGLA5bvQBVSzQSKd+VzjFRXTSK21cY6daljVlO4cjOcVYW3+UuQQT03CgCOGNYcFVLAjGPetW3ZrWPYEBb+9WTNdeVcKOgzmtW1hWeHKSZ9jQA5pGdGVhkt0PpWNf27qNxf5fpWvLGIztBy3oao6pOPJ8rG1v71AHP7QkgOMk9Ktxw/KBn5PXNUTL5bDIzjpU8N3nOeKAIZodrIN341eaFZITh8P0xWebnzjzVxmKqB+ZoAda25hZGwRk5LV0djtMZyM5rm4ZDI6liVA966SxTdCSOlAF9YUaIELXA+NGMc+PvV3wk8uFjjivP8AxMwuLqT0Vc/WgDK0+UNGMDaF/Wr9u7PMo25G7HBzVKzl8yEYXGOlXYVMJWT8eKAJbwKqMAOcYrEgl/4mKDHNaN3M8gJA5qjYx+ZfI7DlevvQB6Po/wAsJBXnGNtXWJXnrUGmyGa3yOAenFW1Re4zQBTuAcMNq/N3qk1uy2pVzhvatK9ZI1AByRVNZBI3SgCtHI0G1dmfU1IzIF3FePSpVjVeKhjxIQrI23+9QA9pY4RgjafUU6zi8yZMHHqaftTGGwRV3T4xwNp5oAsxyiOPYwycYz70wbuQWwtSmIHoe+aq3YaNR29aAKTW4cE5wUOKUqI4evPpTJPToc5qEu7FS3NACeYEUEttRuppdu5TIGyBwFxR5ZZHJ+UHrUkCrHnnGelAETW8mwBquaWvksN7MF+gqvNI28gcirNureWPmy3egDTeQNCU+VCehFNijDAFjkjpVaSQeWMLyKlSQhFBXmgCYBFU4br0qrIx2gZ5qZV6ZGMVHJFukBWRcfQ0AJtrzbxAwP7VH7Og5B/4SG6G3/t3avTXUKFIkX6V5v4m2/8ADU37Oe0Ef8VBdHp/07tQB+k9FFFABRRRQAUUUUAFFFFABRRRQAUUUUAFFFFABRRRQAUUUUAFFFFABRRRQAUUUUAFFFFABRRRQAUUUUAFFFFABRRRQAUUUUAFfEP/AAUc48bfs9f9jRN/6T19vV8Q/wDBR7jxp+z0e/8AwlFx/wCk9AFOaZuAFGR1qrcySrbsAMn/AGak3FmJxgmmSSbYy2PwPFAHmHjpXVc4JavOYjLazMrfMJP7vavXvGMOY9wH4157NpRbDfcagCsk22P5AH9sVbt7f94rMauWOg+WyliS5/hrQaxRsdsdaAJ9NtlVkyVXHTmvQdFWXy4wG46da4XTbULMnLFR14r0HS7mKGNFKkAdeKALrKWkaIEhv71Vr8PCw3qxfu1au5HuDsOffFQXSpIGBb95nOPagDNhkjLgZ3EjB+tMvWJTa5Ix0qSO3WSZCnOG5q5dJAyyMW+Zf1oAqafIIVzIc+1NubwtIBu2oO/WqMk2xvl5FPhkjWRWk5b+7QA24ZZZAc7iBg/Wtq1j8qDchBOM9ax2QNcNhfvfNW1aqGiwBz0oAlhmypBHHbNZXiJGEXmY+XGPxrUkXYqsefQVn62wl0/Y3y/N1oA5MTFpOT3z+FTiNmGB1bv6VHJa+VIvzdsVdj2KrAtnPSgCju8tlGMmrzTL5QHc9arBNzluuOlT/ZWbB2kDtQAW8hdgoGMV1mnSEW4AGQetcdHA8c3A/wC+q7HST+4X7q0AX7hCtqeB8zY+btXnviIbbmUAdOAK9EWPzIyp5B5OTXCa8oW+c4yScGgDJssiEfJj/dq4ysYxgfSmRQgjAbA9q0/s7eRG+VIAxj3oAx5IyFycqKjgh/0neGwa1W+7s25qC3t914oYYf8Au0Addo7AQBOwGRWm3zYxg467WrLtcNDtfjtkVbit1jyQVAPWgBLzy25yA/pVTA3gqcCp7sNIQqoD6mqywuuOKALEhCoCetRSZZV2nBqS4AaDI4NMWQLgkNigCDBbAI571Ys3mXGCai8/52PeprNgz+goA2I7gbRnr3qC9YSKdvOetRNsydrdagnaQNtA+X+9QBXu/mmyOlQiNpGAVWba2D71Oyu+GKYG7GFNKkJUZRmJzmgCPzF/1Z6n+GkW1DsN56e9P2HqQC3rRMoIJ3bT2oAjaNVJQHj61NaTFVOFHLYPNVpHEMe5V8wetWbWMJGWAxzmgDSjhVl5qOb5ZVA6UpYlRikkzuUjrQA91BUH8+abuK4UDp1NSDBVs1CsT87R1oAI1G8HHFeeeJB/xlN+zn/2MF1/6TtXoqqwGMfjXnXiT/k6T9nM/wDUw3Q/8l2oA/SeiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACviD/AIKOMP8AhOP2eQfu/wDCUTf+iK+36+H/APgpAo/4TT9ns/8AU0T/APpPQBSe2z827C5zj2pu3PBOfrVlmLR5P92qbEhsgZNAHOeJrESt91s1x1xo7qy7TuavRdYjaWFSobNc1JBtkGT0bBoAyLbTJPMQsxXHWry6X5xYqMirQhZGZetaKRBbdSBg4y1AGbZ6aUk2rwfWussbPbCB0J9ax7Mt5g+XLeldRYwtcLucbRuwKAHww7Wxuz+FRXVu7fOvpitBYhF83b0as3ULxGjPz+XQBXWaO33KcCT0rPmQ3DOzMVHarCwxyOG+9nrkmnNIu4oFyB0oAqJbKPusRznp2qU2scTAnJ4x+NKYGdjjpjFTf8s138knPzcUAMhWViHKjIGPl9Kv2gZcjG33qo25ZGKZxnI7cVesV3KTgkelAEpw2Mjp0qpqEaNCEPIzk1oSR+Xjg1VvlDRDtu6igDmJbXM/IX/dp500wwiQ/MM52+1a0kMZyAp3Zz+FRxq7Bw/AAwPegDHt4fvDawHvVp1aODc+dv8ADVq4gW5fOWjHsKimuMQmErnHSgClDlplx831rpYOI9pxXPQsscgLDb9K2Y4NybskUAa32tYI8g7vX2rjdchZJi7Dvmuom8iWzQodx781zt9G0i4IGcY5NAFC1t8EluB2rQW3ZY2Qeuaht7c4Uc1piFcMPmz60AZyL5bc8tjH40jQtJMjD5X7mrX2V95OcnORtp1uskcw+XrQBq2bM0O0/KfpV9Y98a4AOagt4kVYzgk96sFVGcn5R0oAY4wpyvzGs3zy3WrkyyNI3zYWq/k7c989KAJJxut8DrUPBQDcfpTtzdzmn7QzZwc0AQeSrZYdPSpY1CnAXAqaBdv+s+Whj+9wnAoAsRQqsfA+amL8zHg1NFluAc8ZzUfllSwJ5oAqSR+c7Anywpzx3qDcwwqgqQMEsetWJBslyem7FK0ileRll6UAVHhmByTk1IsMgxv4UUnmvuIHGOtO3SbfX2oANo3Egcdqls8Hcud3OM1EpO3pj0q1GqrH/vHNAEq/dAHWngKrdd4qJGIkFWmTHBFAEPtVhYtv8X8OajSPLkk80+a52/8ALM+lADsHlR2715j4lUr+1N+zmD/0MF1/6TtXpf2pRlc815r4mfd+1N+zn/2MN0P/ACXagD9JaKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAK+IP+Cj3/I6fs9D/AKmif/0nr7fr4g/4KQceM/2ez/1NFx/6T0AV8HlccdKY0LQhT2qVZD5Y+b5j14qO4+dMUAZ98ouIQGJU+1c3ewnzCB1Jrp5ldW6qR3HpWTeW+JPkO8+tAEKW/wC5DHv1qzHblkBBUqTil0uINGPMPTrU0Z+xux2lxu4GKALNvarbsOOK2LP/AFQA4A5FZS5kZVzitW3dFjHVucGgCbhl+X5vrWTf2vysXxt9MVo7m28AioZVG35jndQBhfdIA4FS3CM23j7ox+NNuwlvJx81WI42kDMflDHOKAJbTnI74x+NRXke2QHPy+tPR/Ik3ds5ouopJcfL16UAQRAXTbVLLxj5uK0rO3FvuYsx9qzLd/Jm2kZk9K1oWfaGxgmgCaSYyj5d2P71ZepN+8zvOPpWlJ+8+YcGqWpbWxyqUAZq3TNPv34DDGPSnuv2jA3jI6Gs+WMwyfMBub7oB61q2eyNMPGBQA6OQ/KAuaqXkQVySy89DVq4wSrLwaq3ls00K8UAMs8RzKRhh7jNbdr+8h+b7tYVtGbdhzWtb3G6Ip2oAd9lEO7Y21fzrM1aHaqkfK1a8MiqjcfL61k646yNlTkdqAKEcjSsAHAq75pjXYTuLd/SsiFiq8DFXoi+ws520AT3EohWM5IaooZ2eaNm+VTRczedbrGVUt/smqluWLKgDMd2KAOnt5Crk5yduRVpp3YAGPr1qrZw7lBJwQtWuw9R1oAHDSQlWGxv7tVNxXG7jHSp7iYxoS3Izn8KpxyLMpBba/pQBNho1DYznoKI2+cDccVJ5bSY2/w9Kctq4OcHP0oAfIp+tEdueBnFBlEWCcY+hqNrxmxtIoAvrMG+UD2zVeRX8wnrRHcDAULg+tD/ALzdnmgCnK3nYO75c5NR7WVmLJkVLIuJDg9aZ5jNuHQd/agBmwPk4xnqM1Nbr+8OAx9DTdxbJ6GnFXwATtA6YoAstHGygkcDtQi7WCgqMdN1VN7bl5+9+lOjjaTO0bvrQBZXmQnoB0qwZi3Uq3+7VfaQnJUmiH5Zt1AE20qCc80pkY9TUnlh16VDIrKw/WgBF2ZznmvOPES7f2pv2c/+xhuj/wCS7V6JuAmz3rzvxNJu/ap/Z1GP+Zguv/SdqAP0oooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAr4g/wCCj3/I5/s9/wDY0T/+k9fb9fEP/BRxd3jf9npc4z4om/8ASegCgsL4Un5QGwafNIrcYpHfy2MY+bPNOEO7BHT0oAqSQkkuCvFZ0lwY3IKqRW3MgjiY44rk9QuHjmcALlfbrQBdtbr7OrIcAnoaWaaS4bcHUc5rDlnL43jGPepI7sYwM4oA2YX3SZEuTWrpcgkV9pJ+bvXMpcDcrH5fYVu6bdHGQuBnNAGsxaNlAJxUF437sH06VbUxsN24D8azr7eyny+ec/hQBnLmSds8jGPxqw2+JQEZcjpuqlb3HlyfNg85p8uJZPlO5sZ20AT+Zu4kdc/7NX5rorHHtwD2NYkUZe4+7j8RWlIzNbx4jG1TjdQARrum3Hls5z7Vps4CjPHtWfakRycntip7ht8vr70AWgSQM8VXvdgTJIz24qwFMi5NVNSiO0KcDHegCntjZlUoc+tJI0cQyCcVGjSyMWJwB0FOacLExkUY7CgByyK6hl59KjkchfmPyetV1cMQc4A6VNdESR8N+FADI2DkjYc1o28RjXBwOM4rJtWPnHmtyxbktlS/TFAAynYxxiud1guAAOgrqriVGjKryw61yutZVM45oAzI3x944FaEUySR7eo+tYkN0skmzoKuQ/vHVQKANB5ljibAX/ZANR2i77rJbBzng1VnXy2yOaSymMd0g9aAO6tYxFGuOPlpVbbvZhnPSkt3M0KsP7vSnZOc0AQ3SnyTu54xVOyQHIxgk4Bq/qUyrH8pqvHII4UbPR8nigCWBTA3zHirDzBd+w7tvTnrUDyNN8u5SfWopA8aoSCfpQAy4mnmjO7KgdBSQ5Vcn73pikad1b5lanowdMDgUAW1xsUk5P0pVcMrdqIWX1wtOkkRUwBz3oAot8zelKXLNnbtFLdRtHyOn96mSSCOPAGTQAu31OaGVlkwGyKZGxIHGG7inw8xnNAAzCPG4ZzU1nIGZvlx+NVLlyrKrcVPboY5Njfe9qALcMe5uuKc8e2TAIA/2jTU+9wcUhkDHJ60AXLebzFwF59uaimkaOQjbnNMjYw8qwB9qWRi5z3oAYSxdiOPavN/EH/J1H7OZ7/8JBdf+k7V6N5JbLE81514gI/4am/ZzGOf+Eguuf8At3agD9KqKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAK+IP+Cj//ACOn7PWP+hnuP/Sevt+viH/go5/yPH7PI7f8JRN/6IoAqx2pnXc3Wpli8thk5I609pFjOBkCoPMZyTkYNAEOrSiO0YLwa4W8mYTb5GI+prstYWR7ZiOtcJfSeXMzyfOPQ0ATKuW5ORUsjrbruVgR6NVFLsSrhODUcv76NtzcYzigC5HIdwwK63S8/Zie/auCs7ovIBjmu+0fDW45OBQBeW3LpgbcUskcqR/Lt6Yq1HD5ZwCcfSkmfy4+E+X+9QBiLCo+/hW+lOMKRRs5OeMVPIwYqe+M1QusqMHhcYx70ANt2TzjuXr0NTs0qxyJ/CHyB6ioZo1VYzu5P8PpSzfNGjAkn60AOaYsy/wHOT9KvxNmHgiqOY1bcynpiti12tCu2OgCRoyse7dn2Wsu8mIUjJAX72a0JsIvBx7Vk6l/q1fPC0AVftXTA5PWm7S/y8ls5/CmRSK21hzu6D0q75ccLeaz44xQBTKpGhEm4e1Hyt86tx6VEZDNcuGYYPSnyBVjUjgUATW+PMGO/SuisCIYzkLnvXKWs22VMnKjoa6WG28xmYP96gCWRgzO4HBXOK5TxBcMqtxxXTyKttDvdt46ZxXJ+JmHktty1AHP2+TMHAwO9bVnIkMgdm+lYVvIrZUbsGrofzscdOlAFyScNuot+Z1J2g1VbheKmsJT9oUFQTQB2enypDGoO4npla0o4TIo7N6VTtbUyQqQCF9K02kCwkZ5HSgDMvFjxjzOKzEkDbwzYVDk7e9W9WhQKuNxqvboiw8DG7rQBNHsVAVbcalhlK/MHOf7p5qvHC0a+q1PDyoQjBxuJ/pQA24lM2N/FOhUNGT0NSpGo64P41FG2Szjp6UAaKoGUc0eSqhiRk/7NJHOVKgL2zRNOWBP3RQBTkVtzbyBxnGahjLSNzzU0lwq/Owz23UQujKWVqAIJMLlBwT3zTLe62syuOM4qRoy0mR8woEKwhmxnnNABP8AMFPUe9W7RgIVy2aoSXSz/IVb/gNWFhEca7QzL60AX/mX0NRS27u3BwKZBIXdQ3yip5owOA5z/doAWGPjJXIqby16K/NJCP3f96o5o3X5u9AEohI+XOfevNfEWR+1L+zmOg/4SC6/9J2r0u3LpD+84avNfE0gk/am/Zz4x/xUF1/6TtQB+k1FFFABRRRQAUUUUAFFFFABRRRQAUUUUAFFFFABRRRQAUUUUAFFFFABRRRQAUUUUAFFFFABRRRQAUUUUAFFFFABRRRQAUUUUAFfEP8AwUb/AOR4/Z6/7Gib/wBE19vV8Q/8FHuPG37PRHX/AISif/0RQBVkg85shsDGOvenKu1MDk1DbsWkaMk43das/wCoYj16Fu1AFW+VjaSM4wPRea8x8QXRhdjtwK9E1q5MNqzB/k/u15N4ovg0wQsMHrQBcs7tBzxn2qaSTzPmT5R0Irk9LujDwMlM43da3xdRopHUmgC7Z2589Dnp1rvdFVltVwT8wzj0rzW31KX7YNq/ujXpugyGS3BIy5GMUAbVvGzRq5Jz35qhfX3zbejZzt9q1VnXYRjmue1pWQiUjahGAe9ADknV1DA47UrgMhJbIzmsS3uGZmUjnsaszSusZX2x+NAFpdszEZwD1NSNF5ceU+ZPWs+xTarAP+FSXUnkoELYPfFADJZmjYEfN6nNb9jKzwqB12564rEtZo3WSPAb3rTt87A6swHTGKALU0DudwqnqShbck9+1XVmdlCgYz0rI16TyoQN3zd6AMdoWWQfN3z+FaKXQNvslHOc5rGaaTd+GKka7fbt46YzQA64ZWf5DkfSrLKJIVQttPrWb5jebsJ4xj8acshVuTlV/WgC7bxqrAlvm7V1Gn3Q2gFcEdK5GKcvKhC4x2rrtHjV41dn+f8Au0ATXBdlG1R97HzVxPiT9xI6OcJ7V3t0yFgqHdxmvPPFn/LTJ3CgDDs4xvyGyPrWuu1VGDXN6bdLHkPwS2BW/bzBo2287f1oAdIT5bcgc4FM0qRjeDJ53dadccr0zzmoNHkLXmOAM5oA9LsCTag5PtzTrrPzFT+FJZKwt4+OPRakkIjwdrE/xe1AGbcp5y/K5O2q8bBUUdh1q1dOIw5CNg1ltN94bT+YoA2I51kh4GKXzFbJB6nOKzbWZ1iJbgfSm28u2fzGbj+7QBbYKrKMtv8ASnQ71mA25z1RabI3nfvE+UL2bvT7Wb96D3oA0hCMhg2BjGKZdAlMN8w/2aWb5VU+Ww9ql2htwJxQBlXfCZPJznHtUVpIB91N3rU90v7zIOVxjNVbNTH5oxjb3bvQBdkZunyj1PpUMkzrGw+Uio7kMVDFsKvUetVvtBk/hxQBN5sfmZAYGrzY/h3dMjmsCZxGz/N9NxrTsFWQKxc46YyaANGFJEkXeyhf71WN28feDU3cvl8nH4UiTJJuK8+2KALS58vHeoWV8ZLZFN2kHO/8KlkZWjx3oARpGC5J+T1rzjxCwP7Un7Ofr/wkF1/6TtXojNuxnlfSvOPEH/J1H7Ovp/wkFx/6TtQB+ldFFFABRRRQAUUUUAFFFFABRRRQAUUUUAFFFFABRRRQAUUUUAFFFFABRRRQAUUUUAFFFFABRRRQAUUUUAFFFFABRRRQAUUUUAFfEP8AwUb+bxx+z0O3/CUTf+iK+3q+If8Ago5/yPH7PX/Y0Tf+iaAKzyC3IC455NLI+6MsfmyM1FdY3Dimq7LHsG30oAy9YjNxZuqjHpzXiXii0nnv22H5Izjd617ZfKfJcd4+vvXj3ixpPtjomA3UgUAVtJZc7c55ztXmtlYhI52tj5c1kaTFmL5Rh8Yz05rXh3pIAe4waALWjRb7gLt3HtXp+ix/ZoEUjr0NcFpMYWRHAxhsV6BprlrVc87elAGkqkybR0xndWb4ks5LmMEAlV/hWr1q25d5Hz9KW5BkyuTtJycelAHNWkC7ASPmHWprqHcM9CTkVa+zpEW4b5v0rPvbg5wDkL0oAbDmGYO2CD1C1BM6M7AszCl/1i7uh7VA0JjfA6+tAE8MJVjg9etdDahhbowbOeornLWYeaoywH0rpFx5a46UASsw3RleAvesfX23Z27WJ71rAZBbpjqPWsbVwyqAwVRjNAHPtnJHfOfwqyw3R8A/kKqsSGZj6Yqz5wCrQBFtyc985qJjjI9OlPkm2qvOOcUvk7ow+eD1FACWLGaZT0rtrOBo7ONgQGrjrCEC4UA5967USAWqpHydufmoAZN8vA4O2uD8THbHJuNdtJdKzMeN+3pXCeLpv9GkYnFAHLW0qtMoK4+bqTW9bs3RelcfZzC8kwDuI5PbFdDDefY7dQx570Aa8t1HEoyc+tGhyRSXgOcN6VjyXsT5B5zU2j3UEM8YVtz5xigD121b/R42UkfSpTuZQG5IrK024MkaHJC1d3BpV5OKAK9wzfMp6VRkiHmEKgxU+pfuxuBxVK3uPlxnP9aAJlPmZjf5BUNvaiC4zneKkm3eWSOTVaOR5ZSFHA60AaNwv3fnXd6UtruSXLnAqC5Qm3RhycYP1ptiy+b+/DbPWgDoImcnJORSShQp+bNJHhhhOB9aRlGzA60AZ8mVk3e2cUgBPSRcemKWVmZwSOehpV8hW43FvpQBDI2xHKruA6AmqUf7zhVwafc3RWYgfKp67qih1ERyZ2qP96gA8lZHy3I9xWha25UKFcH2xUcu2OPhR0zT9L+WYkE8d80Aa8a5VR1LfpSrEIzlRinxkNKCOAamkjCr1zQBA3380gXaMmkjYyTMD0BxU0q/LxxQAkcYmBC9ulebeIhj9qb9nQf9TFdD8rdq9FVj5gHRT1rzrxGw/wCGqP2dQB/zMV1/6TtQB+lNFFFABRRRQAUUUUAFFFFABRRRQAUUUUAFFFFABRRRQAUUUUAFFFFABRRRQAUUUUAFFFFABRRRQAUUUUAFFFFABRRRQAUUUUAFfEP/AAUcIHjf9nonp/wlE3/oivt6viD/AIKQD/isv2e/+xon/wDSegDPk/eSNk0xWG3kc0SIWY7VY0tuzRt86EUAUbxiIXbbvJrzLxDHGszPsA/3q9T1NzHbsoHzV5lr6+c0gcYfsDQBgw7lbgYBOQwrUsbSS6kyx4/2aoQyDcnsta9jM6xg/oKANmxi8lth57132imNbX72fauChJ3qcV2+ix/ud2OaANGNSpzU80iiLg9sdKhJJ6U25kCR5PSgChMyLI/zA5rFvYTJIwAwM5/CtpmhkYsAFqvcINq7SPmGPpQBjKdsYU/eHemSTMsbMefSnuuJCu8EVDcbVXo2aAGrIysrZzXS6fIXhGTkVzdqhucKiba6Oxt2SFEzgnqaALTRythgeB2rG1rftzt4Xj610KqiMys3zdlrE1kHyiDuXHQNQBy+S0jZGan9F/Wm/dJOKFk+RgRzuxQBBIom4c55yO3NTru27VOBTMjjjpViFfkz1NAFnT4iCpDYP0rp44xHGpY/N0z1rl7T/XDGM/WurjhPlopORQAxoVlUgKF4xnFeaePrhYbdo2XNenXTfL8nCr1968t+Im2S1lZjgjpQBwmkyhbzK52r7VtyTpzg9OvvXKaBNJ9omRiG/wB01v8Ap7UAOlnVW5bbxmnaTN5mqRRg8buao3j+W3H92pPDW99RWQ9d1AHuuiMJrBccGtBWYSbcD61S8Nwq1ijcrntWo0Cr0/nQBk65DhAobORkVlWageWFP3a2dWmj25Xl1GAKw1ulYhhtU96AL3ncNgZk9KgWdbdXEgwX6Y7VBbyAbv4uc/hUFzcb5CgHzHo1AGhFKXV1BxzkVLbqzDcW3H0qlCwWHl+asafKVZeaAOltVHl570zcVOMc+tNtCWj+Ublq35ayL6UAZEzRxyPubOelQSP5l0CvCAZNLqUKrIoB5qmJHXBP3DwWxQBDcyCZmzxhsVWKqxweRS3zp1Bxu5+lQw/vJOnFAGisxk+Xdz0rQ0tS0bDPOc8+lU7VR5mWUYq1pzfaJmZ/l4xxQBsrx7N6Uu44HNI3zcGlPagBGZxlVGOc5qzId8OM4b1quvpT5WVl2/d96AGyADCsfxrzjxB/ydN+zn/2MV1/6TtXe+dyQCCK8+1pmf8Aam/Z1JIwPEVz/wCk7UAfpfRRRQAUUUUAFFFFABRRRQAUUUUAFFFFABRRRQAUUUUAFFFFABRRRQAUUUUAFFFFABRRRQAUUUUAFFFFABRRRQAUUUUAFFFeQfAT9pTw18fE1+20uQ2euaBfTWOo6VMR5seyRkWVR/FG+3gjoeDzQB6/XxB/wUg48Zfs9nr/AMVRccf9u9fb9fD/APwUe+Xxt+z1j/oaJv1goApm3ZkLbinpT1tnZc85Xr71pWapJjzDtxVmK3jZtseWFAHN6hG3ktIU7ZryPxp8r/K5Vs5x7V7NrH7u2lGenArwj4la3BY53bUwvJzQBk2upB5PvZ2jFdHY6kqqteP6V40tkmlyy4JyDntXV2vjC0khBVsDs1AHqmn3okmVXAYf7Nd9o8w8kBR16c14noPiCK8lVFkUjGdwNewaFtuLWI5wR15oA3I2XfjPG39apajMPsfLLU6R4jYgZG71rn9fuvJhZEOaAK/2oszLuwO1RfaWP3mY1nx3PmfNvDbWx8tRXF95ZYk8bc9aANhDG7EjGaZdRxls7zisix1NWZQOTV+a4DR80APtrhreQsi7l/vV1NjIbq1RsYauTsGWSUAng9RXXWOIYwRtPtQBLgqw+X5h1NY2vs0kh3HNa8kkfzMxIJ6beawNaVlYsx+Q9DQBmyrjvmqbKd3T361HJflZMDkU1rjcw2jp15oAlkxGw5zzircEqxxjHNZckiyMO2OTVvcscSgDn60AaGnyq02SNprplYyhTGuQox171xlneBWUgc5xXY2Mg+zqw+UMck0AT7FxtYnpj8a8w+Inl29rIzHivTbqJY4vMBbdjd83rXkXxcugtiegz1oA830m8QXUjR/IWGMe9dppdi11GSw3E9K8+8H6bLq2qRsuQpbnHavozw/4RC2ccnH5UAea6louI/mRg397npVbQN0Woon8O7nivatQ8LwNZ8sC+MYxXmuoaU+m6kDjgt1AoA9N0mYfZIwNy+4rWideOfru4rB8PqVsUbO9K2Jm3ZHc0AVdWRFjJx8vpXNzKGLBRzW1q10WOwjislAscjElVH1oAR42VfTjBxVZsrjjOKkkuFgB7qe+ahNx/d54x+NAEobdj5sfhWlp6g4Lrj8ayJrjbg44q5ptwVxuOaAOxtV/d/Icp608YRWzVS3uFSEfNU3nNIwB5UnFAGRqkeyZVQsW9aptN+78vcoq7rCu1wRuAx0Oax5lDMVPHuKAIbn94WI4FJYsdxw3TtRdAqg5xlsGq1u/lkuPlY96ANNJSxAJYCtTSdgmVFBYd6577Sdpz94dK2NCZ8gt1NAHRLyMd/WpCPXimKy7cZwKcjbunNACAN2GaZID5PvT3VvlAbB9aXaW5PNAFa3jT5vkx/vVwOvAL+1L+zmAMD/hIrr/ANJ2r0VQfmzzXnOvMG/am/Z1/wCxguD/AOS7UAfpZRRRQAUUUUAFFFFABRRRQAUUUUAFFFFABRRRQAUUUUAFFFFABRRRQAUUUUAFFFFABRRRQAUUUUAFFFFABRRRQAV4JqX7V6jxr4p8N6D8NfGviyXw5eCxvrzR7S3eASmNZAFLzoTww7V73Xzz+zOB/wALc/aF45/4S+Lnv/x4wf4CgC9/w05r/wD0Qv4lf+AVr/8AJFeNfC39nPxbJ8JrXxjo+nTeBfi7put6pqWnR6kqqbq1nupJhZ3gXho3Dcd0PIIPNfblJ5a9McUAebfBH412Xxk8O3EwtZNF8SaXL9i1zw/d8XGm3S/ejcd1PVHHDLyPSvmv/go9/wAjr+z1/wBjRN/6Ir0j9qrw+vwvib45eGdRs9B8U6BCseoQXTlINftM4+yTAfek/wCebgFg3HSvHP26fEjeMJv2Yddk0+70dtQ1xrtrG/j8ua332obY47MMkUAb8JDdTketWYphbghGy3rWWPkjCo4OOtNld48AtknrQBX8WX+2zlZlC/Lnivhn49eOJJr+W1gfAT5WBHWvr7xxqDW+kznGSF45r89/iFdSXniK9lYswWRsbu9AGXHrE0cTkM2VX161es/FF9tQxySFB33Vz67vKPGVAx8vNS20xSBymMr0oA9f8A/EL7DqsAunzuGCRgCvsjwLrEOsaassfKMuQM1+a1lfN9oO9ixzlcc5r7m/Z31I3/h62JbedvYmgD29WVYCFLDPIFcR4yvv7Pt8vwSv6118jOrgp0Bz+FedfFr5bEvnIHWgDmrDWXj2ru4Y5PNRax4lhRT+9VMDBDV5T/wmcltOF34wcjjtXK+KfG0kjPh2LMcnnoKAPe/Dfia3uZNyy/d+8M9K6HUPEkcUIKOo9RivmLwP4tkgk/eHDZycnqK7nXPFjyaY4TcuDk4PUUAewaP4k8+7VGkUD2Fer6TIskYIAPCmvkXwL4klm1SNFd2XOCDX1J4Uk3WIk5L9AM0AdBMo2jAC4Ga5TxJqHlREuMKOldPLL+5YucHpXn3xO1P7JpZZQAoXJagDjdS8Q/6UoiGBVq31s+Q7sRvJyB7V4ZqHjBvtbZkYlf7pq9D8Qo4bfyhvcbaAPWpvFyJIoygcthlzWjH4iXy1Z0w3pmvm268bmS9Xy2LjOSxIrfk+I6Q6aheRwe3vQB75pOvRSXm0OpbdwMV6bpMkbWsUnK46jrXyT4F8arqWrq6OwcNwuetfUXheQy2IJyQRkc0AdHPIsiug6gYG6vnH49awNNtyjSjPYZr6BuC1ursDu+XPNfIn7Sl41xff3drYxQBc+A+uJfXgWSQKzyYwc19kaHCv2GPKkDGa/OH4X+Im03xRabnZI/M9etfoH4R16LUNJhKyctH3PSgDpLi2EiMARtFcT4s0+JGjfHGc11MmpJa2rNKwH41498QfiPa294tukuxt2OaAPSPDqLLbhVNaM0flt1yfWuQ8A6ubyxWUc7u9dZJKZIdxXbQBz/ia4SEkq37uuS/tpWXIcMucU34iao0TsQSBXmlrrDyNyGHzUAeg3+uKucHk9D6VSt/ERkfbISDnPWuT1DUplt3KAEmuYXXpo7kk7iQMHJoA9obWE8n7w/OpfD2qG6naMke3NeRSeLlWDABJ+tangPWZtQ1T5ztbdgKDQB9GWPzW645960o9qwnnkDIqjoKq2mqCCTV64fygRsPPAOKAOe1uQNN8hzxg/WsVLoW8hDnIq3rTFJm5x81c/dTbpN2eKALepagHjz0GcioobpZo15rG1Kab7ORjlelUItUMK/NxQB1k11HGAWPJ61raTe/Ip3ZNeU65rMkfzoTj61x9/wDHiz8L3BRpGlZfvf7NAH1dDG9yoYfd/vVNDA0K8HndivIfhb8cNP8AGCrHFJiXOSp7CvZI2LqCOpGR9aAEXKxgHk0sKq8mzoPrSDI60u0jpx9KAJZI/Lz3rzDXQF/ao/Z1A6f8JBcf+k7V6Wz9fMNeceIFA/am/Z0Pf/hILj/0nagD9KqKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACvkfwT481X4LfGD4znVPh1451e11zxFHf2N7omiNc28sQtYUJ3hh3Vq+uKTaPSgDwn/hq+L/olHxS/wDCYf8A+LrqPBH7QnhLxt8KLz4hi6uNE8O2L3Ed3JrMP2eS3eBykqupP3gwIwDyeBzXp1fCn7NPwN8VfFCG5g+IFmdO+GWi+JtT1HTdBkyG1y4a8ldbi5U9YEyCqfxMNzZoA9R+H/hfVf2mvF2m/EzxpYz6f4I01xP4R8KXgKtKR93ULuP++w+4hyFHOM8153/wUeUL40/Z6IHJ8UXGff8A0cV9uLCirtCAL0wB7Y/lXxH/AMFHst40/Z6A6/8ACUT/APpPQBQ8887UUZoZt7ZZgpqwGVPvBRUJUMVKAEUAcj42sy+lzqB1VsV8MfE7Qnj1qQgKo35+UV+gfiC3jnsyJAwBX+dfI3xq0mCC/dlwuOuKAPA59BmtlWZwV3fwrwD+dNi0uWTbGkXPYV2esTLc6PbSvHuRDjcORUWiIstwJk+9Gu9g3YUAcnaeG5Zrx41jcPnBbGMV9n/AvRzpHh20AJOEUFunNeW+FV07XPLdUQS78kqOtfRfgexjjsYURQPpQB3UciqgY8jGMVwHxIsGvdJmXOCfuj1r0GFSIzuQlR0NYevWovIzjkFsbcUAfF2reH7z7e+xmIAwK5ybwnd3MyhsvtGMkV9f33gexmkZ/JALVl3vw/gjyUgyT9KAPlqx8I3ELgljlRjrS3VvqMO5dzFcYAr6Tj+H8aux8lSzHPQU+b4ZmVdxgQn+7igDwz4d2lxHrADkqQ24+9fZPgyNl0OPPLeprzXw38MY7e8E0kYLjgc4r2Cxto7PT4oQMNjPHegBzpvUqBXmnxU0+SeyaGM7t3Hzdq9RVmW3JAOfpXI+IrH+0PMD4wOue9AHxbqGhzR6rOoQswOCwzU1v4eupFB2gJjGa+i3+HsEl3JJ5apu5Jxmrn/CA2tsvEasP7oFAHyrdeGrmOTzBACuMZ24qyfCkt5DtO4bunXivpq5+Hsd0pk8rav+7Uuk+AIY3IeNXGcDIFAHiPwx8GXFvqSOVwF5Ga+sfDsUlnYwoT7dK5zS/CKWkyGJBgtzx2rt47f7PtUdFGPxoAj1a42w4yPTNfHf7QS/8TZt3O45619ca6ypaHP3vSvij49a99r8TNbg8xjJBoA8nivJNP1BZIy5+fKn0r3j4a/tCPodvHBeElMY3Ma8EmkMjqRyEGSPU1EyjaQDg/w7u1AH1Z4s/aThutO2W7L5jep6V4PqXjzUNc1hZ5rn593Y5WuK8toslSzE/wB+nI23bnr1296AP0C+D90k3hu2CvvOMmvTUxJbsg4PrXzp+zP4mF9pAi3ZZPlJNfRkcf8AoqsD94ZoA898daC19AzBa8nTSZYZtpH8VfQmsRmS3IYqBtziuEm0cSXTKUG3qOKAOH+xtjlRnvWHqnhdpJGmHybvSvUp9BfzjtChT7VmyWMpkMZT5QcjjtQB5ReeF5vLbB/Piui+HGhvYagrFzg8jjOK7I6GWjOQG/CtHw5on2e48zZ9aAPUND3RWoByfStpk8yFc87apWnlw2ce0fw5q9G26EYOM9aAOI8RQ/6QyZ5znNc99lz97muw1xVkm/6aelc/JACzbTmgDBuLPejFgW9smsqSzPmY2bV/Ouv+xnaxxVWXTvMUnOzPSgDg/EGlmW02rkHb1HrXyr470u60zV7pp4t6t6ivuP8AsdPJ2sN3vWZJ8LdK1yQ/a7VZdzYoA+cf2Z9Fvr7xcksassAGDkYBr7qtFaPAkDDaMYrB8H+B9J8LKFtLUIydOAK6lv8AXFxwCMEe9AEM2CMJ1+tOtv3fJ5FR3HBU9T7U+3ztCk8etAEhUBeledeIP+Tpv2c/+xguv/Sdq9IHzLjvXmuvPu/ao/Z14xjxDdD/AMl2oA/SuiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKYsKL0XA7U+igAr4i/wCCjX/I8fs8f9jRN/6T19u18J/8FM9dsPDfiL4Balql3HZWFr4lnkmuJuFjUQYyfxoAkulEjAONnrUEcpVdpT8a85uv2nvhPIx/4r3Ryp/6bH/4mmt+058J8YHjvR8f9dm/+JoA7vXrgfY3Zv3YQYPvXxn8dtehXUJomk2k9xXt3jH9pj4Zy6VKtp400u4crwizHr/3zXxV8RPiVpPiTWprmK/ieP8A5ZkZP9KAIpNZuVtPsyzh7cPlQo4NbHhLWEtbxXcb0ZNkimvPofEGnF3X7ZHGG/2j8v6VqaXrGktM5bWLaEIcqzE/N+lAHv8A4Tkjk1i3GmK32YbcgA7ga+rfAx/4l8bZ2sq55XrXwB4P+MVj4b1AMdSgeEnLHJz/ACr6j+H/AO0t4Bt7K3N54t063fo6SSN8v6UAfRQnKL3NVbjaFyFXHXdXnX/DTXwpC/8AI96P/wB/m/8AiaST9pj4Ut/zPWjf9/T/APE0AegT2sbTKCFz64FRXGlrJt2YNeezftMfCtpVC+OtHx6+a3/xNJ/w0t8LOP8Aiu9H/wC/zf8AxNAHerpdtG6kkZqdLJXuQw3Be9ebyftI/CqRg/8AwnWkB/7vmt/8TUsf7TXwtVj/AMVvpO09f35/+JoA9Kh08W8xbAq8qOe3XgV5d/w098KwcHx3o5H/AF1b/wCJq2P2oPhV8mPHuijHT98f/iaAPSfs79cH6ZqpfWcci5ljxtGd2etcR/w098J+v/CfaL/3+b/4mqF5+038J5JQf+E70dgBj/Wn/wCJoA7iW0gCjEZOetOtYIRN+8jytef/APDTPwpUgf8ACc6OR/12b/4mmXH7T3wsSH93430Zj6ea3/xNAHo91ChlwFUI3aq8lpCskOIwM8151J+058LmUY8a6PuHT963/wATTv8Ahpb4VyBGPjjScjp++P8A8TQB6nC6KyqFAPY0l03lqON2Tk15iP2mPhWskZHjrR8KP+ezf/E1JL+0x8Kyox460f8A7/H/AOJoA6DxlqX2fTZHAJ+XNfAPxGvpbzxleTuMksygMe1fYPiX9oT4XahYOkXjfSGYpwnnHr/3zXxl8SPE3h6fxE91p+sWl3Exzujcnk/hQBlSSb2UttUkKOKjEjeYxA3cbsH+VZ//AAkmlt1vovz/APrVA3iLS9+ReoOc9f8A61AGrEzM7KzZ9Kfj+ec98fWsiLxFpnzyG8iDL0+Y8/pT28TaWv8Ay/RHjHf/AAoA+l/2XZmjnuIkc7d27bX2VZMTZBWOcL8tfDP7OvxD8F+Fbia51fxRYWRk4CyuePyFfTUX7THwqjwv/Cd6PgDH+ub/AOJoA9FuoEkTGAe2a5+axDOR0IrnpP2nPhUEwfHGjEf9dT/8TWbcftKfCzzCw8a6S3/bY/8AxNAHZfYVX7zkGqk2mZlbJyMYrnZP2ivhRJJuk8c6P/3/AD/8TTJf2iPhSIyR480cv/d80/8AxNAHTrp+0YFaGn2Lqx8uE5PU5rh7f9o74VxthvHWjH/tq3/xNXbf9pb4UQ8f8Jzo3/f0/wDxNAHqtrbGOMeYcYGKsDaqnAbaOleYr+098J8YPj3RyP8Arsf/AImj/hpz4T7cf8J9o+P+uzf/ABNAHd6parJJvC1hRw+Y7KFyc5zjGRXNXH7THwoaPI8e6Pv/ALvmn/4mqbftLfCtZk/4rrRsAYz5p/8AiaAO/wDsreWQUAFVjZpJtVV74+biuO/4aa+FSpj/AITnSCf+u5/+Jpf+GlvhOyAf8JzowOc/65v/AImgDr5LEtE4UcJ196u6Lb7bhSY8Ipz0rgh+0p8KFBA8c6Pg9f3zf4VLD+038KI5Djx5o4U/9NT/APE0AesSYaQMq4ApM7mXPPOa8y/4ag+FDdfHuj/9/T/8TTP+Gn/hRx/xXmj/APf1v/iaAPTXj3PhTkL+tTLBHJCBlgvpXlh/ae+FBYY8e6OMf9Nj/wDE05P2o/hQnJ8e6Ofbzm/+JoA9TjI34IwfWvOPEqhf2qP2dMH/AJmK6/8ASdqrv+1B8J2Tj4gaLn/rqf8A4muY0z4q+EPiJ+1Z+z9H4Y8RWOuSWuv3DzLaOW2BrdgCcgY5oA/VaiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACsXxN4K8PeNIYYfEGhabrkMLFo49StI7hUJGCQHBAraooA4UfAf4bD/mn/hj/wAFFv8A/EUv/Cifhv8A9CB4Y/8ABPb/APxFdzRQBw3/AAon4b/9CB4YH/cHt/8A4ik/4UT8Nx08AeGR9NIt/wD4iu6ooA4b/hRPw2/6EDwx/wCCe3/+IpP+FEfDbn/i3/hj/wAE9v8A/EVL4m+MHhLwf418OeEtY161svEXiJ3TTNObPm3O0EsQOwAHU8HtXa0AcN/wor4b/wDQgeGP/BPb/wDxFJ/wof4anOfh/wCFz9dHtz/7JXdUUAcL/wAKJ+G3/QgeGP8AwUW//wARS/8ACifhv/0IHhj/AMFFv/8AEV3NFAHDf8KJ+G44/wCEA8Mf+Ce3/wDiKP8AhRXw3/6EDwx/4J7f/wCIruaj3+/6fjQBxP8Awon4bf8AQgeGf/BRb/8AxFL/AMKJ+G3/AEIHhj/wT2//AMRXEeNv21vgh8O9efRdf+JOi2Wpxvskt0kacxsOocxqwX/gWK9N8E/EHw78SNBh1rwvrdlr2lTDKXVhMsidM4OPun2PNAGT/wAKJ+G//QgeGP8AwT2//wARSf8ACiPht/0T/wAMf+Ce3/8AiK7qigDhf+FE/Db/AKJ/4Y/8E9v/APEUf8KJ+G3/AEIHhj/wT2//AMRXdUUAcN/won4b/wDQgeGP/BPb/wDxFJ/won4bdf8AhAPDH/gnt/8A4iu6ooA4b/hRPw3/AOhA8M/+Ci3/APiKT/hRHw24/wCLf+GP/BPb/wDxFZfxX/aU+GXwPkgi8ceNNM8PXMy747W4ctMw9fLQM+PfFavwv+Nfgf4zaW+oeCvFOneJLaPHmfYpgzx57MvVfxoAP+FF/Df/AKEDwx6f8ge3/wDiKP8AhRPw26f8K/8AC/8A4J7f/wCIruaKAOG/4UT8Nv8Aon/hj/wT2/8A8RR/won4b8Y8A+GRj00i3H/sldzRQBw3/Cifht/0IHhj/wAE9v8A/EUf8KJ+G/8A0IHhn/wUW/8A8RXc0UAcN/won4bcf8UB4Y46f8Si3/8AiKP+FE/Df/oQPDP/AIKLf/4ij/hdHg0/E5fh3/wkVl/wmhtmvP7GViZhEBu3HjC/L82Dziu5oA4b/hRPw2/6J/4X/wDBPb//ABFH/Cifht/0IHhj/wAE9v8A/EV3NFAHC/8ACifht/0IHhj/AMFFv/8AEUf8KJ+G3/RP/DH/AIJ7f/4iu6ooA4X/AIUR8Nv+if8Ahf8A8E9v/wDEUv8Awon4bf8AQgeGP/BPb/8AxFXfiD8UvCnwp0eHVfF/iGw8PafLL5CXOoSiNGkwTtB+gP5VwP8Aw2j8DP8Aoqnhf/wYLQB2P/Cifhv1/wCEA8Mf+Ce3/wDiKT/hRHw2/wChA8Mf+Ci3/wDiK6jQfEGn+KNFsdX0m9i1DTL6ET211AdySxsMqwPpitKgDhf+FE/Db/oQPDH/AIKLf/4ij/hRPw2/6J/4Y/8ABPb/APxFd1RQBw3/AAon4b/9CB4Y/wDBPb//ABFJ/wAKJ+G3A/4QDwx/4KLf/wCIruqq3uoQafazXN1PHa20Sl5JpmCJGo6lmPAx6mgDj/8AhRPw2/6J/wCF/wDwT2//AMRR/wAKJ+Gx/wCZA8Mf+Ci3/wDiK8/X9uz4CN4h/sQfFHQf7Q3eX/rm8nd6ebt2Z/GvcLe8jvLeOa3lW4hkQPHJEQyupGQVPQgjoRxQByH/AAon4b/9CB4Y/wDBRb//ABFH/Civhv8A9CB4Y/8ABPb/APxFdzRQBwv/AAon4bf9CB4Y/wDBRb//ABFL/wAKK+G//QgeGP8AwT2//wARXc0UAcKPgT8Nh/zIHhj/AMFFv/8AEUf8KJ+G3X/hAPDH/gnt/wD4iue8Q/tY/B/wnrl/o2tfEjw9puq2ErQXNpcXqrJC46qw7Gs8ftpfAzk/8LW8LnAycagnT6ZoA7H/AIUR8Nv+if8Ahj/wT2//AMRVzSfhB4F0HUoNQ03wZoGn38B3RXVrpkMcqHBGQyqD0Nbmg+INP8T6JZ6vpN7Ff6ZeRCa3u4TujlQjIYH0NaVABRRRQAUUUUAFFFFABRRRQAUUUUAFFFFABRRRQAUUUUAFFFFABRRRQAUUUUAFFFFABRRRQAUUUUAFFFFABRRRQAUUUUAFFFFABRRRQAUUUUAFeTftJfEzxn8MPh1JqPgHwfL448U3FzFZ2mmodqIz7v3sh7KMd8D3r1mm+WCMY9+tAH5CWfgH4neD/wDgop8ENW+LWvw6z4x8RO2oS21ucw6dHiVEgXttGD0r9fa/Pb9qY/8AG0D9nH/ryYfhvnP9TX6E0AFFFFABRRRQAV5b+0lovjfxH8EfFekfDuSKDxjf2htrOaWfyRHvKh2D4OCFzXqVRjIBzn/PpQB8u/sy/sN/D74V/CHRdK8VeC9G17xfc2yz63fapbx3kkty3MgDuD8oJ2jHXGa8G/Zf0yz+C/8AwUg+Jnw08CTNH4Bn0s31zpiszw2V0BEdq8kAgsw57HHUCvWv2rf217jwb4gT4UfCCw/4TP4vaofISG0HmQ6XnJLysOC6jnYeB1YjpXV/sX/sjj9nHw7q2teIb8698SvEzfadc1hyXO4sW8pGPJUEkk9z9BQB9NUUUUAFFFFABTWztO3k06mdic4HOf8AGgD48+B/7DK2fxQ8f/EP4zw6J4/8Ta5qLPp3nRNPb2doCSAEkXaDg4xj+H3rxrxV4f8AD/wn/wCCnXw4074QRQac+sWTjxVo+jkLbRoPMO6RFyqnABPTHGMZOfuz4u/DWz+Nnw/1DwvNrup6Na3cqGW80K58m4XY6syCQZwSRg/Wvz38VeAL7/gmP8ePCPijw7qTeLPAnji+XTNTj1mFJNQgYsPu3AUHo+R67DnNAH6j0UyOQSxq6nKsMg0+gAooooAK8c/ah/aH079m/wCFV54kul+26zcMLPRtLXBkvrx/ljjAHJAJy2OgB9RXr00y28LyucIgJY1+Wfhf9qr4WfG/9qvU/iV8VvGFnoPhjwXM1l4P8N3kcjF5A3zXsgQMMn0Oe392gDO/ZT+H3i3wH/wUi0mTx5qT6l4017wxNruqZ/5d550JMP8AwBQF/Sv1ir8qbz9rP4USf8FLrP4jr4wtT4KTwv8AYG1bZJ5Yn2sNuNu7P4V+oPhvxJYeLtB07WtJulvNM1CBLm3uE6PGwyrD2IoA1aKKKACiiigD8+f+Cln9n+PvjD+z98MtWlhj0bUNXl1LVPOkEcYtkKqzMxICgJ5uTXTeFfg3+wz448Snw9oVh4G1LW92wWUOoPvZv7q5kwx/3Sa9A+Pv7Cvgn9pD40eH/G3jHV9QubfSbT7N/wAI9GwSG4UMTlmHzgFnGQOoAz1NcB+11+wL8Jrj4E+JdX8IeF7LwZ4j8PWE2p2Wo6TuhbMSFyrgHkELjPWgD7G8L+GdK8G+HdO0DRLNNP0jTYEtLW0jzsijRcKozk4xWzXzb/wT5+LGrfGb9lPwfr+uzPc6vCJtOnuZDl5zA5QOT3JUCvpKgAooooAK+F/+Cj3iTWfG/ij4T/AbQ9Sl0o+PNSJ1WeFiHNlGVDLx2OXJHQ7K+6K/MD/gpR4d1vxP+2h8CtF0PVJ9BvdYsW0yLVIfvwCW4aORk9GCOeRzyKAPfde+BP7Kd54KuPhLEfA9nqv2VrOBhcwf2lHNt2rIZM+ZvDc8n9OK9W/ZI+Dfij4CfBfTfBXinxRF4sn06SRbS+hR1CW7HKRneTkL27AcdK8m8V/8Eu/gfqnw1udB0vw7Jp3iBbUrB4j+1yveC4Aysr5baST7Y9qrf8Eufi14g+IPwN1bQvFF2+p6r4P1aTR1vpGLPLCACuWPXHI9cCgD7OooooAKKKKAPC/Fn7D/AMDPHXiTUfEGvfDnS9S1jUZ2ubu8maXfLI3VjhxXwX8Wv2a/hf8AHL9rLSvgj8JvBmn+G9J8Nt9u8X+IrHezquQTboWYgHBC+u4/7Jr9G/2kPixF8Dfgf4y8bSMpl0nT5JLZX5D3BG2JT9XZRXz/AP8ABL74Qz+DvgS/j3Ww0/i3x9dPq97dS/6xoi7eUM+hBaT/AIFQB9Z+E/Cum+CfDWl6Bo1qtlpem2yWtrAmQqRoMKv4D1rapKWgAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigAooooAKKKKACiiigD4f/AGivhb4u8Sf8FC/gT4u0vw3qV/4a0i0ZL/VILdnt7Zt8x/ePxt4Za+4KTaOmOKWgAooooAKKKKACvD/2w/F3jzwf8BtfuPhpod7rvjK6C2dlFYwNLLD5hw8wXHVRzz3r3CmrGqrhRtHoOPegD8kv2VfFHxe/Ze0O8a2/ZZ8S+IfF2pytLqniS+Mgubgs3yqAYyUTPvyeTX2H+z3+098W/il8RodB8YfAfWPAGiPbSytrd5K7RI68omCgHzfXjtX1UqhVAAwB2FG0UAOooooAKKKKACobi3W6t5InBKOu04JHH1FTUlAH5wfD9vix/wAE9/HfjDR5fAmu/FH4Va5fvqOn6hof+kXVk2ASjITkfLtG04yVyDyal1rwf8T/APgoH8ZPBOq+JfBGofDb4ReEbs6iketjZe6lKHBIC9vuhfRRuwTX6MrGq9BikMatyVyffnp0oAVY1RQAMBRgCnUUUAFFFFADWjVlKkZUjBBrzOT9mH4RzSNI/wAN/DLyMxdmbTIiSxOSSdvJ6/mfWvTqKAPz6vP2TNPb/govaXq/C+1/4Vb/AMI1sZxpa/2b9q2tx93Zvr7603SbPRtPtrCxto7Syto1iht4V2pGgGAoA6ACrOxc5wM9adQAUUUUAFFFFAHwr+1b8K/ip8OP2ifD3x/+FunXHi23tbcWeueFlnIMqBShaNM45UgfLkhkBrnPjD+0b8ZP2qPBdx8M/hx8F/E/hC616EWmq674oQW8NpA4xJsI9Rxu6/7NfoX5a5zjn60u0f56UAea/s7fBnT/AIA/Bvw14EsH89dKtwk1xjHnTN80kn1LEmvS6btFOoAKKKKACvlL9vD9mnxF8Z9B8K+L/AMqQ/EPwRfrqOlpI+0XK5UtEG7HKKRng496+rab5ajnHNAHwXrX7cHxo8ReCZ/C+j/s8eLbD4m3MRsjNNCRptvKw2tP5mOinkBsD/ar239h39m+6/Zr+CFvomszLc+J9TupNU1iSN8p9okABQHuFUAeh5PvX0PtHp7UeWvp7/0oAdRRRQAUUUUAfHn/AAU+8G+NPiN+z3ZeF/BOg6lr91qOtW32uHTYWlZYFDMWIXPy7tv5V9ReA/DcXhHwT4f0OFBHDpthBaKqjAASMLx+Vb+xeuOelLQAtFFFABRRRQAUUUUAFFFFABRRRQAUUUUAFFFFABRRRQAUUUUAFFFFABRRRQAUUUUAFFFFABRRRQAUUUUAFFFFABRRRQAUUUUAFFFFABRRRQAUUUUAFFFFABRRRQAUUUUAFFFFABRRRQAUUUUAFFFFABRRRQAUUUUAFFFFABRRRQAUUUUAFFFFABRRRQAUUUUAFFFFABRRRQAUUUUAFFFFABRRRQAUUUUAFFFFABRRRQAUUUUAFFFFABRRRQAUUUUAFFFFAH//2Q==)

**Figure 8.** EMSA displays IGF-1R: DNA interaction. JUN lane 2 and FAM21A lane 5, whereas lane 3 and 6 contain excess unlabelled probe. This figure is adapted from Aleksic et al. (2018).

Subsequently, serum starved DU145 cells were exposed to IGF-1, ChIP-qPCR was performed for amplification of the receptor’s peaks in JUN and FAM21A/C promoters. The IGF-1R recruitment to these promoters increased upon the treatment with IGF-1 whereas it was inhibited by xentuzumab. Therefore, this manifests that IGF-1R binds to the regulatory regions of DNA, which is enhanced upon the treatment with the ligand. As nuclear IGF-1R discovered around the TSS region of JUN and FAM21A/C promoters this implies that it can have regulatory functions. To confirm this finding, JUN promoter was cloned into a luciferase reporter. DU145 cells transfected with JUN reporter displayed luciferase activity higher than in empty vector controls, and IGF-1 enhanced the reporter activity in serum-starved cells. Furthermore, JUN and FAM21A/C promoters represented GATA-2, KU80 and AP-1 binding motifs (Aleksic et al., 2018). In addition, an association was found between nIGF-1R and RNA poly2 and co-IP data determined that nIGF-1R exists in the protein complexes and may induce RNA poly2 recruitment to chromatin. However, the authors suggested that this recruitment is not dependent on nIGF-1R.

In addition, ChIP-qPCR experiment was conducted on fresh frozen prostate cancers, which identified IGF-1R on JUN and FAM21A promoters and determined high signal in the tumours with increased nIGF-1R. The IHC performed for JUN in adjacent FFPE tissues of the RP revealed the relationship between nIGF-1R and JUN expression. However, this relationship was absent with total IGF-1R thus, signifying the importance of nuclear IGF-1R in upregulation of this protein (Aleksic et al., 2018). Conclusively, IGF-1R nuclear translocation enhance gene promoters of clinical prostate cancer and is directly correlated with JUN expression. Nuclear IGF-1R binds to dsDNA effectively and collaborates with the transcriptional regulators, it promotes RNA poly2 recruitment and genes that have the capability for sustaining proliferative signalling in cancer cells.

**Nuclear IGF-1R in Renal Cell Carcinoma (RCC)**

Aleksic and colleagues discovered IGF-1R nuclear translocation in many different types of cancer e.g., prostate, renal and breast cancers (Aleksic et al., 2010). The authors detected nIGF-1Rβ in primary RCC cultures, formalin-fixed RCC and prostate cancer, however, prostate cancer showed heterogenous staining. In addition, nIGF-1R was also detected in tumours such as lung, ovary, and ductal carcinomas in situ. In clear RCC cells, 94 out of 195 cells exhibited IGF-1R nuclear accumulation. The multivariate data analysis showed that patients with high levels of nIGF-1R expression have poor prognosis (p = 0.005) (Aleksic et al., 2010).

**Nuclear IGF-1R in Sarcomas**

It is well known that in several tumours IGF-1R pathway enhances cell proliferation of tumour cells, regulates tumour cell motility, and inhibits apoptosis, including sarcomas. High levels of IGF-1R are directly associated with a variety of human malignancies. IGF-1R monoclonal antibodies (mAbs) are associated with anti-tumour activities in various preclinical models of sarcomas. For example, R1507 monoclonal antibody induced complete response in patients with osteosarcoma and rhabdomyosarcoma. Treatment with IMC-A12 resulted in growth inhibition of rhabdomyosarcoma xenografts (Asmane et al., 2012). Disrupting the IGF-1R signalling is also a potential therapeutic approach. Asmane and colleagues determined nuclear internalization of IGF-1R is a biomarker associated with better progression free survival (PFS) and overall survival (OS) for advanced soft tissue sarcomas (STS) patients. Phase I/II trials of patients with STS established prolonged stable disease. A small set of patients with advanced sarcoma was treated with IGF-1R monoclonal antibody therapy was investigated for prolonged PFS and OS. All the 16 patients having STS, ES and osteosarcoma treated with IGF-1R inhibitors were assembled. The histopathological test of STS showed six diverse sarcomas characterized as liposarcoma (n= 6, whereas one myxoid liposarcoma and one pleomorphic liposarcoma), osteosarcoma (n= 4), ES (n= 3), pleomorphic rhabdomyosarcoma (n= 1), desmoplastic small round cell tumour (n= 1) and synovial sarcoma (n= 1). Moreover, the subcellular localization of IGF-1R was observed. The IGF-1R staining varied between tumour and patients with no distinct significant difference in different histotypes, however, as compared to others stronger nuclear staining was observed in osteosarcoma and liposarcoma. IGF-1R IHC staining was exclusively nuclear in 56% samples, cytoplasmic in 25% samples and nuclear + cytoplasmic in 19% samples.

Progressive disease was examined in the group of tumour samples with nuclear + cytoplasmic staining (n= 3, 19%), cytoplasmic staining (n=4, 25%) and nuclear staining (n= 9) had 5 stable diseases (60%) and one partial response (10%). Furthermore, PFS was evaluated in patients and unlike cytoplasmic and nuclear + cytoplasmic staining, exclusive nuclear staining was associated with overall significant PFS (median = 10.1 vs. 1.6 months, P= 0.01) and OS (median= 28.3 vs. 6.6 months, P= 0007) (Asmane et al., 2012). In order to confirm the presence of IGF-1R in the nucleus of tumour cells, Western Blot analysis (Fig 9) was performed on frozen specimens of patients with advanced stage of osteosarcoma after R1507 treatment. MCF-7 breast cancer cell line was used as a positive control, whereas SK-UT1 cells were used as a negative control. DAPI fluorescent stain was applied on cells to locate nuclei. IGF-1R nuclear accumulation was detected in metastatic osteosarcoma sample, and in primary tumour samples.

A picture containing food

Description automatically generated

**Figure 9.** Western Blot analysis showing nuclear localization of IGF-1R protein in the metastatic osteosarcoma samples. β-actin and poly ADP-ribose polymerase 1 expression were chosen as the loading control for cytoplasmic and nuclear fractionated samples. This figure is taken from Asmane et al. (2012).

IGF-1R functions have been established in Rhabdomyosarcoma (RMS). RMS is a type of sarcoma that builds in soft tissues and is present predominantly in children. Alveolar RMS (aRMS) is the aggressive form of RMS, which has poor prognosis and high metastatic rate regardless of several targeted therapies discovered in cancer. This type of cancer is of exigent need for new treatments and as RTKs are practised as targeted therapies in cancer, Aslam and colleagues investigated whether 2 such RTKs are associated with aRMS. They developed a mouse model of aRMS via genetic engineering to target PDGF-receptor- α (PDGFRα) and IGF-1R to explore potential treatment options (Aslam et al., 2013). They were able to detect that murine aRMS tumour cells displayed a dynamic cell surface expression of PDGFRα and IGF-1R.

Using fluorescence activated cell sorting (FACS), cells sorted for high IGF-1R/ PDGFRα were designated as IGF-1Rhi / PDGFRαhi, and low levels for each as IGF-1Rlo/ PDGFRαlo. Sorted subpopulations of positive and negative for PDGFRα and IGF-1R expression exhibited a drastic change in their cell surface expression within 48 hrs. The data by Aslam et al. (2013) determined that PDGFRα and IGF-1R expression is associated with cancer cells in a dynamic manner as identified by FACS profiling. The cancer cells, however, showed significantly slower growth in vivo in PDGFRαhi and IGF-1Rlo as compared to PDGFRαlo and IGF-1Rhi (Aslam et al., 2013). Furthermore, the cells with high levels of nuclear IGF-1R expression were associated with aggressive tumour growth in vivo but, nuclear PDGFRα role in tumour growth in vivo was otherwise. Importantly, IGF-1Rhi cells with upregulated levels of nuclear IGF-1R expression also had increased phospho-IGF-1Rβ levels. IGF-1R silencing induced by RNA interference in IGF-1Rhi and IGF-1Rlo cells demonstrated reduced formation of anchorage independent colony by 45% and 27%, respectively. On the other hand, as murine aRMS suggested, human aRMS also manifest nIGF-1R expression. Thirty-one sections of human aRMS were analysed and approximately 84% of them displayed nIGF-1R expression. While pancreatic and skeletal muscle tissues were the positive control for IGF-1R, they represented only cytosolic IGF-1R staining and no nuclear IGF-1R staining was observed (Aslam et al., 2013). In conclusion, this suggests that nIGF-1R is predominantly expressed in human aRMS.

Moreover, IGF-1R and anaplastic lymphoma kinase (ALK) expressions were detected in patients with RMS (van Gaal et al., 2013). Co-expression of IGF-1R and ALK was observed in embryonal RMS (eRMS) but more prominently in aRMS. Clinical trials so far have not shown effective ideal results in sarcoma patients. Van Gaal et al. revealed significant data regarding clinical aspect of IGF-1R in RMS (van Gaal et al., 2013). In total, 112 primary tumours were assembled. Eighty-six were eRMS and 26 aRMS. Specific RMS cell lines included Rh30 and Rh41 for aRMS and Rh18 and RD for eRMS. IGF-1R and ALK expressions were detected i.e., 72% of IGF-1R and 92% of ALK in aRMS, and 61% of IGF-1R and 39% of ALK in eRMS. Importantly, co-expression was detected in 68% samples of aRMS and 32% samples of eRMS. Subsequently, follow-up data of 72 patients in which 18 aRMS and 54 eRMS were collected. The median follow-up time was 24.7 months for aRMS and 60.3 months for eRMS. In particular, nIGF-1R expression had no significant prognostic effect for aRMS (n= 18) however, an adverse prognostic effect in eRMS (n= 53, 5-year disease specific survival 46.9 ± 18.7 vs. 84.4 ± 5.9%, p= 0.006). In aRMS and eRMS cell lines, the effect of inhibitors NVP-TAE684 of ALK, R1507 of IGF-1R and the combined treatment was monitored. NVP-TAE684 caused decreased cell growth in Rh41 and Rh30 cell lines, whereas, to a lesser extent in Rh18 and RD cell lines. The inhibition of IGF-1R by R1507 caused decreased cell growth in Rh41 cell line. Furthermore, simultaneous treatment in aRMS cell lines with both inhibitors showed a synergistic effect in vitro. Therefore, targeting both IGF-1R and ALK can act as a potential therapeutic target in RMS (van Gaal et al., 2013). Importantly, the presence of IGF-1R in the nucleus of eRMS and aRMS was identified, 10% and 4% respectively (van Gaal et al., 2013).

Synovial sarcoma (SS) is also a type of soft tissue sarcoma and represents approximately 5% to 10% of overall soft tissue sarcomas. SS cell lines displayed 78% of activated IGF-1R and the receptors signalling promoted SS cell migration (Friedrichs et al., 2008). The type of treatment varies in this form of sarcoma depending on whether it has metastasized. Survival rate is from 62 to 83%, with significantly better results for patients with < 5 cm small tumours and with dismal survival when metastasized. The standard treatment of SS includes surgical removal of the lesion, chemotherapy, and radiotherapy (Palmerini et al., 2015). IGF-1R is highly expressed in many human cancers including sarcomas. The SS cells exhibited upregulated expression of IGF-2, these cells also manifest IGF-1R and therefore, SS is associated with IGF-1R expression. Palmerini and colleagues showed a significant association between IGF-1R expression and synovial sarcoma (Palmerini et al., 2015). Eighty-eight SS samples were selected samples of 45 were female and 43 males. Tumour size was >5cm in 60 patients, ≤ 5 cm in 24 patients and unknown in 4 patients. The patients sustained surgery, out of all 65% underwent adjuvant chemotherapy and 56% adjuvant radiation therapy. Chemokine receptor CXCR4 was positively associated with 74 patients, however nuclear staining was observed in 31 patients. The IGF-1R expression was detected in 55 patients with 34 cytoplasmic and 21 patients presented nuclear expression. The 5-year OS was 63% in patients exhibiting nIGF-1R expression, whereas patients with negative nIGF-1R the OS was 73%. Furthermore, the multivariate analysis determined that both nuclear IGF-1R and nuclear CXCR4 expression manifested independent adverse prognostic factors for overall survival in patients with SS. The patients with nIGF-1R expression who did not undergo adjuvant chemotherapy were associated with poor survival. Contrarily, CXCR4/ nuclear negative expression was associated with poor prognosis, however just in patients who received chemotherapy (Palmerini et al., 2015). In general, nuclear expression of IGF-1R and CXCR4 were predictive of poor prognosis in the SS patients who underwent adjuvant therapy, underlining the potential role of these receptors in drug resistance.

**3.8** **Nuclear accumulation of IGF-1R in non-cancerous cells**

The IGF-1R translocation is not limited to cancer cells rather can be established in normal non-transformed cells and can have physiological relevance. IGF-1R nuclear translocation was detected in Graves’ disease (GD) (an autoimmune disorder). Confocal immunofluorescence microscopy revealed that in thyroid-associated ophthalmopathy (TAO) fibroblasts, IGF-1R undergoes nuclear localization in response to IGF-1 and GD-IgG of GD fibroblast. IGF-1Rα translocates to the cell nucleus in this disease whilst IGF-1Rβ is scattered peripherally before and following the treatment with IGF-1. The steroid dexamethasone can inhibit IGF-1 effect on the nuclear translocation of IGF-1Rα in GD fibroblasts. 1H7 (anti IGF-1R mAb) treatment with or without GD-IgG completely block the nuclear accumulation of IGF-1Rα (Hoa et al., 2012). This suggested that GD-IgG impact on IGF-1R translocation is mediated by IGF1-R itself.

Furthermore, IGF-1 and GD-IgG treatment stipulated IGF-1R protein accumulation in the nucleus of GD fibroblasts. The fibroblasts were treated with vehicle control and 16 hr treatment with IGF-1 followed by Western immunoblot analysis. The nIGF-1R migrating with a pace of 110kDa band was elevated upon the treatment with IGF-1 whereas the results were otherwise in cytosol. The same was seen with the GD-IgG treatment that IGF-1R nuclear content increased in GD fibroblasts, however, control orbital fibroblasts exhibited no change before or following IGF-1 or GD-IgG treatment. Interestingly, IGF-1Rβ was undetectable in the nucleus (Hoa et al., 2012). Both the control and GD fibroblasts had high levels of ADAM metallopeptidase domain 17 (ADAM 17) as assessed by Western blot. TAPI-1, an inhibitor of ADAM17 activity appeared to block the IGF-1Rα accumulation in combination with IGF-1. In short, ADAM17 appeared to play an active role in IGF-1Rα nuclear translocation. Additionally, phosphorylation of IGF-1Rβ can drive the translocation of IGF-1Rα. NVP-AEW541, a tyrosine kinase inhibitor which blocks IGF-1R phosphorylation coupled along with IGF-1 inhibited the IGF1-Rα translocation in GD fibroblasts. This finding suggested that IGF-1R phosphorylation is fundamental for nuclear translocation in non-cancer cells unlike in cancer cells (Hoa et al., 2012).

IGF-1R can accumulate in the nucleus in a variety of cells such as normal diploid fibroblasts. In MCF10A cells (a non-malignant breast cell line) cell fractionation experiment was conducted of cytoplasmic and nuclear proteins, followed by Western blot analysis. IGF-1R siRNAs were used, which induced profound IGF-1R knockdown. The results showed that IGF-1R was readily present in the nucleus fractions of MCF10A cells but was absent from the cytoplasmic fractions. Before and following IGF-1R siRNA treatment no prominent difference was observed in SUMO-1 levels of both cytoplasmic and nuclear fractions. Confocal microscopy analyses were conducted in breast cancer cell lines both benign (MCF10A) and malignant (MCF7). For 48 hrs, these cell lines were transfected with IGF-1R siRNA or NT siRNA. Serum starved cells were then exposed to IGF-1 for 7 hrs. IGF-1R was detected in the cytoplasm and nucleus of both cells, Treatment with IGF-1 caused reduced levels of IGF-1R, especially observed in perinuclear areas (Solomon-Zemler et al., 2017). Therefore, this study supports that IGF-1R nuclear translocation is an IGF-1 independent process. The authors also showed IGF-1R nuclear translocation occurs in another normal, non-transformed cells. Fluorescence confocal microscope analysis in primary human fibroblasts displayed IGF-1R nuclear translocation.

Previously it was identified that the inhibition of the receptor internalization with dansylcadaverine repress its nuclear accumulation (Aleksic et al., 2010) by inhibiting clathrin, which plays a critical role in nuclear endocytosis. Solomon-Zemler et al. (2017) also identified that in breast and prostate cancer cell lines treatment with dansylcadaverine reduced the IGF-1R levels in the nuclear fractions of these cells (Solomon-Zemler et al., 2017). As dansylcadaverine inhibits IGF-1R nuclear accumulation, it also reduces cell proliferation and migration. It can be deduced from the results that nIGF-1R can cooperate with other proteins associated with cell proliferation and migration. In addition, this treatment effect on proliferation was more robust in cells expressing IGF-1R than cells with no IGF-1R expression. Further studies are required to establish a role of IGF-1R nuclear translocation pathway in normal cells.

Furthermore, a heterodimer hybrid of IGF-1R/INSR (Hybrid-R) localize to the nucleus of human corneal epithelial cell line (hTCEpi) (Wu et al., 2012). Reciprocal co-immunoprecipitation assays in hTCEpi cell line detected Hybrid-R presence in whole lysates and confocal microscopy confirmed its presence in the nucleus. IGF-1 activated the phosphorylation and signalling of Hybrid-R, it also induced the proliferation through the canonical IGF-1R/Akt signalling pathway and not the insulin. The hTCEpi cells stimulated by IGF-1 showed 58% increase in cell growth as compared to non-treated cells. The use of αIR3 antibody which reacts with IGF-1R homodimer inhibited the proliferation induced by IGF-1 in corneal epithelial cells, which suggests that cell growth is mediated by IGF-1R homodimer and not by Hybrid-R (Wu et al., 2012). As IGF-1R does not possess NLS it is suggested that IGF-1R translocates to the nucleus with INSR via importins (transfer proteins to the nuclear through nuclear pore complex).

**Clinical significance of nuclear IGF-1R**

In the most recent decade, nuclear translocation of several RTKs has become a major focus for scientists. Cell surface receptors localize to the nucleus after endocytosis. There are only few known functions of nuclear translocated RTKs in cancer development and this field remains to be further explored. Importantly, in cancers, RTK targeted therapies have shown clinical efficacy. However, the use of these therapies is limited due to intrinsic resistance. Several new studies have emerged demonstrating nuclear translocation of IGF-1R leading to resistance towards specific drugs in cancer. Very recently, gefitinib treatment, an EGFR inhibitor was  associated with increased nuclear accumulation of IGF-1R in hepatocellular carcinoma mahlavu cells and the authors also showed nIGF-1R expression to be linked with drug resistance (Bodzin et al., 2012). Hepatocellular carcinoma is the predominant type of liver cancer, which accounts for over half a million deaths worldwide. Upon treatment with gefitinib, the cells show augmented levels of IGF-1R and Akt phosphorylation demonstrating the upregulated cancer associated signalling pathway. Nuclear IGF-1R reportedly undergoes nuclear localization in gefitinib treated cells. Moreover, gefitinib enhanced the translocation of the receptor, and the effects appeared in a dose-dependent manner (Bodzin et al., 2012). The IGF-1R accumulation in the nucleus after treatment with gefitinib may propose the mechanism of acquired drug resistance. Another study showed that gefitinib facilitated the nucleus translocation of IGF-1R in invasive mucinous lung adenocarcinoma cell line (Guerard et al., 2018). Interestingly, neither gefitinib affected cellular expression of IGF-1R, nor it influenced EGFR nuclear accumulation suggesting, gefitinib predominantly targets nuclear localization of IGF-1R. Nuclear IGF-1R was also identified in lung adenocarcinoma, as well as in some basal cells of bronchial epithelium. The nuclear expression of the receptor was also detected in normal pneumonocytes (Guerard et al., 2018).

Furthermore, amphiregulin (Areg), an EGFR ligand, contributes to the receptor’s translocation induced by gefitinib both in vitro and in vivo. Areg neutralization by siRNA prevented the nuclear translocation of IGF-1R. The combination of both gefitinib and Areg silencing intercepted the translocation process (p= 0.0046) as compared to the treatment by gefitinib alone (Guerard et al., 2018). Previously, Packham et al. (2015) reported the importance of association between importin-β1 and IGF-1R nuclear translocation upon IGF-1 activation (Packham et al., 2015

). Guerard and colleagues investigated this association. The PLA experiment confirmed the association of importin- β1 and IGF-1R and this interaction distinctly increased with gefitinib treatment. However, Areg knockdown suppressed gefitinib-induced interaction between IGF-1R and importin- β1. Importantly, as gefitinib effected the interaction between Areg and IGF-1R, it also prompted the association between Areg and importin- β1. Hence, it is evident that this drug induced nuclear transport of IGF-1R via establishing IGF-1R, importin- β1 and Areg complex. The nuclear import of IGF-1R is associated with p21Waf1-dependent cell cycle arrest, which is linked toinhibition of apoptosis. Nuclear expression of the receptor promotes cell cycle arrest through upregulated levels of p21Waf1 and inhibition of apoptosis in response to gefitinib (Guerard et al., 2018). Furthermore, Areg contains NLS which allows its binding to importin-β1. It is an NLS containing protein which can interact with IGF-1R and importin-β1 to promote the nuclear internalization of IGF-1R.

The nuclear IGF-1R expression after targeted IGF-1R therapy was studied in colorectal cancer (CRC) cell lines, a parent HT29 cells and a chemo-resistant version, designated as HT29-OxR effect of ganitumab (a human monoclonal antibody against IGF-1R), TIMP1 (metallopeptidase inhibitor 1) and sorafenib (kinase inhibitor) on IGF-1R signalling was evaluated. Only ganitumab inhibited the activation of AKT and IRS-1 signalling. Significant reduction in IGF-1R signalling pathway activated apoptosis in HT29 cell lines, whereas apoptosis was not activated in HT20-OxR cells. In addition, this led to investigate the effects of ganitumab and NVP-AEW541, a tyrosine kinase inhibitor of IGF-1R on the receptor. Nuclear and cytosolic IGF-1R were extracted from HT29 and HT29-oxR cell lines and subjected to immunoblot analysis, which displayed that after treatment with ganitumab, cytosolic IGF-1R levels decreased whereas nuclear IGF-1R expression increased in HT29-OxR cells but not with NVP-AEW541. Confocal microscope analysis in HT29-OxR cells further determined that membrane bound IGF-1R was inhibited by ganitumab, while this treatment’ s effect on nIGF-1R was otherwise. In addition, cetuximab (epidermal growth factor receptor inhibitor), dasatinib (tyrosine kinase inhibitor) and dynasore (blocks endocytosis) also elevated the presence of nIGF-1R in HT29-OxR cells (Codony-Servat et al., 2017). In conclusion, no such treatment has emerged so far which target nIGF-1R, since RTKs targeted therapies can cause an increase in nuclear translocation of IGF-1R, this suggest that nIGF-1R may play a role in therapy resistance in cancer.

Since the last decades mounting evidence is present on the canonical actions of IGF-1R in cell proliferation, differentiation, and survival, also IGFBPs are well described. However, in recent years it has been unfolded that IGFBPs and IGF-1 receptor enters the nucleus. These components particularly need a direct signal transmission to undergo the nuclear translocation. The current understanding of IGF-1R nuclear translocation lies with some known factors associated with this receptor. Firstly, one familiar aspect discovered is that IGF-1R is associated with transcriptional regulation. Another known characteristic of IGF-1R is its implication in DNA damage tolerance pathways and this mechanism involves translesion synthesis and error-free template switching. Furthermore, only SUMOylated IGF-1R translocate to the nucleus and IGF-1R colocalizes with some proteins to manifest its action in the nucleus.

**4. Discussion**

IGF-1R plays a significant role in several physiological processes including, cell growth, differentiation, and apoptosis. It plays an essential role in cancer progression and metastasis. IGF-1R downstream signalling pathways also interact with other RTK’s such as EGFR, VEGFR, and PDGFR to regulate cancer cell proliferation and differentiation. Identification of IGF-1R as a significant contributor of carcinogenesis, has stimulated the development of inhibitors targeting IGF-1R including, anti-IGF-1R mAbs and small molecule inhibitors. IGF-1R or IGF-1R/INSR hybrid receptors mediate cell cycle progression and proliferation via MAPK and PI3K/Akt pathways. The canonical pathway of plasma membrane IGF-1R can be modified by small ubiquitin-like modifier proteins which drive the nuclear translocation of IGF-1R. This study was conducted to provide an overview about the potential functions of the nuclear IGF-1R (nIGF-1R) in non-transformed cells and in cancer cells. Additionally, the study aimed to understand the reasons behind the failure of IGF-1R targeting in the clinic despite its preclinical success.

IGF-1R is a potential target for anticancer drugs. It was assumed that interventions in signalling pathway of IGF-1R would be successful in suppressing various types of cancer. The rationale was to interrupt growth, proliferation, and survival of the cancerous cells by disrupting signalling pathways of IGF-1R. Researchers in the last four decades attempted to develop IGF-1R inhibition based on the given rationale. However, they developed antibody, tyrosine kinase, ligand inhibition of IGF-1R and a significant number of these drugs showed positive results in preclinical research but failed in clinical trials. In few patients, early-phase trials showed complete or partial response with stable disease. Unfortunately, in the later-phase trials, due to complex nature of IGF signalling, the trials failed.

One of the possible reasons for this failure might be the compensatory action of some other growth receptors such as IR. IR is structurally homologous to IGF-1R and this potentially increases accumulation of IGF-1R/IR hybrids which leads to activation of Akt, PI3K, and MAPK pathways. Therefore, it is possible that blockade of IGF-1R has no effect due to disrupted signalling by other growth hormones. Dual targeting of the IGF1R and IR was unsuccessful in phase III trials, because of failure of drugs to optimize progression-free or overall survival. Another reason is the lack of robust predictive biomarkers. IGF-1R is an epi-driver gene, it is not the primary cause of tumour development rather is anonymously expressed in various forms of cancer. Therefore, predictive biomarkers are needed for selection of patients in clinical trials. No protein biomarker has emerged till now. Protein or radiologic predictive biomarkers may allow clinically significant outcomes in cancer patients.

Due to clinical failure of IGF-1R inhibitors, most of the pharmaceutical companies terminated the manufacturing of these drugs. The companies considered other possible ways for targeting IGF-1R such as targeting common signalling pathway of IGF-1R and other growth hormones including IRS proteins which act as substrate for both IR and IGF-1R and also EGFR. However, these approaches have not been much successful either. Thus, researchers sought to discover effective aspects of targeting IGF-1R. Recently, it has been discovered that IGF-1R translocate to cell nucleus in various types of cancers. The mechanism of IGF-1R nuclear translocation is associated with advanced stage tumours. Targeting nuclear IGF-1R could potentially inhibit cancer cells growth and proliferation.

Although the nIGF-1R was first reported in 1996, it was not until 2010, when several studies started characterizing it. As many as 18 RTKs have been demonstrated to accumulate in the nucleus from the cell surface membrane. In addition to IGF-1R, the IR, EGFR, FGFR, HER2 and ErbB-4 were reported to translocate to the nucleus and the process was well characterized. Since IGF-1R does not contain NLS, it is translocated to the nucleus with the help of other proteins, as characterized by Packham et al (2015). Larsson’s lab corroborated that IGF-1R undergoes nuclear translocation and that this process is dependent on SUMOylation of the receptor and stimulation by IGF-1. SUMOylation is required for the receptor’s stability. This finding was supported by another study in colorectal cancer, where the protein inhibitor of activated STAT3 (PIAS3), a SUMO E3 protein ligase, was the key mediator contributing to IGF-1R nuclear sequestration (Codony-Servat et al., 2017). However, the study by Lin et al. (2017) reported that an IGF-1R construct lacking the residues necessary for SUMOylation (TSM-IGF-1R) can still translocate to the cell nucleus, albeit to a lower extent compared to WT‐IGF‐1R. This indicates that SUMOylation of IGF‐1R is not an absolute requirement for its nuclear localization. Additional studies are warranted to investigate how IGF-1R translocate into the nucleus in the absence of SUMOylation. Phosphorylation of IGF-1R was found to be indispensable for subsequent nuclear internalization as essentially phosphorylation-deficient receptor without Y1131, Y1135 and Y1136 residues failed to translocate to the nucleus (Deng et al., 2011).

It has been also shown that nIGF-1R binds to DNA-regulatory elements that activate/regulate transcription (Sehat et al., 2010). In 2012, a study by Sarfstein and colleagues determined that IGF-1R autoregulates its own gene expression in human breast cancer MCF7 (ER positive) cells and MCF7 derived C4.12.5 (ER depleted) cells. Importantly, although IR is also capable to undergo nuclear translocation it does not influence IGF-1R gene expression. Whilst nIGF-1R enhances the gene expression, IR supresses IGF-1R promoter activity (Sarfstein et al., 2012). The structural homology between IGF-1R and IR is 80% (Lin et al., 2017). The similarity between these two receptors might underlie the failure of IGF-1R targeted therapy in the clinic because most inhibitors will also inhibit the insulin receptor causing hyperglycaemia in patients. However, (Werner et al., 2017) deduced that IGF-1R and IR have different internalization pathways. With respect to these two highly homologous molecules it was shown that heterodimerize form of IGF-1R/INSR hybrid (Hybrid-R) localizes to the nucleus of human corneal epithelial cells. Interestingly, only Hybrid-R was observed in the nuclear extracts, but not the presence of IGF-1R/IGF-1R. Identification of nuclear Hybrid-R suggests that IGF-1R not as a homodimer rather a heterotetrametric complex traffics to the nucleus and plays a role which is yet to be discovered. A noticeable distinction observed is that IGF-1 but not insulin resulted in the phosphorylation of the Hybrid-Receptor, IGF-1 also activated PI3K/Akt signalling and enhanced cell growth through IGF-1R activation, which was independent of Hybrid-R (Wu et al., 2012). This shows a significant aspect of IGF-1 in stimulating proliferation. Furthermore, IR but not IGF-1R contains the NLS thereby, IR might assist IGF-1R internalization to the nucleus through importin system, thus further research in this area is warranted. The primary structure of the receptor shows a single potential nuclear localization sequence ERKRRD detected in the IGF-1Rβ amino-terminus, but it is still unknown whether this sequence is associated with IGF-1R nuclear translocation (Hoa et al., 2012).

Overall, the findings of nIGF-1R are significantly associated with cancer cells compared to normal cells. IGF-1R translocates to the nucleus in cancer cells following clathrin-mediated endocytosis and cognates with poor survival. Nuclear IGF-1R was associated with aggressive clinical outcome of renal cancer. The authors also determined that full length IGF-1R translocates to cell nucleus with both stable α and β subunits rather than being cleaved (Aleksic et al., 2010). This finding is rather intriguing because of the large size of the receptor.

Diminished levels of the nIGF-1R have been associated with decreased levels of nucleolar NOM1 protein, which correlates with nIGF-1R in the breast cancer cells. As identified nuclear proteins co-localizes with IGF-1R in benign and malignant cells, close attention is required to discover how these interactions are manifested in the disease development (Werner et al., 2019). Importin-α also co-localizes with IGF-1R. Packham et al. identified the significance of importin-β as it functions independently of importin-α (Packham et al., 2015). Further investigations are expected to arbitrate precise mechanism by which importin-β as well as importin- α attaches to the IGF-1R. Moreover, RanBP2 is significant for the stability of IGF-1R, more studies are essentially required to illustrate the role of RanBP2 in SUMOylation of IGF-1R and its nuclear localization. Additionally, nuclear accumulation of IGF-1R associated with the binding to importin- β was promoted by amphiregulin, which induced cell cycle arrest by directly upregulating the levels of p21Waf1- (Guerard et al., 2018). The study by Warsito et al. showed that nIGF-1R binds to transcription factor LEF-1 and thus, activates the LEF-1 downstream target genes (Warsito et al., 2012).

The fact that nIGF-1R enhances transcription by binding to enhancer-like regions, might explain the pathway by which it modifies gene regulation. It would be interesting to further investigate how the accumulation of nIGF-1R in the cancer cells influence cancer growth and metastasis. Mounting evidence has been shown that nIGF-1R has essential roles in cancer growth and development. For instance, Aleksic and colleagues discovered that IGF-1R is present in clinical cancers and nuclei of cancer cell lines (Aleksic et al., 2018). In benign prostate tumour, IGF-1R was localized in the membrane but malignant epithelium displayed explicit nuclear localization of IGF-1R. Hence, nIGF-1R is significantly correlated with advanced/cancer metastasis. Importantly, the IGF-1R binding sites were determined around transcription start sites of JUN and FAM21. JUN and FAM21 increases tumour cell survival. Conclusively, the relationship of nIGF-1R over-accumulation in cancer cells is an intriguing topic requires further exploration.

IGF-1R mediates its action in cancer development, enhancing cancer cell proliferation, migration, invasion, and metastasis. IGF-1R is overexpressed in tissues where it mediates tissue growth such as in sarcoma. For example, 10% to 40% of sarcoma patients show promising effects from anti-IGF-1RAbs with prolonged progression free survival (Olmos et al., 2010). It is of utmost importance to develop new therapeutic strategies to improve survival of sarcoma patients. A small subset of STS, ES and osteosarcoma patients were targeted with different anti-IGF-1RAbs. Nuclear IGF-1R was correlated with increased PFS (p=0.01) and OS (p=0.007) for selected patients. IGF-1R nuclear translocation transpire in patients with advanced stage of sarcoma (n = 16, 75% nuclear staining) however, treated with IGF-1R antibody therapy have better progression-free and overall survival (Asmane et al., 2012). The presence of IGF-1R in the nucleus of eRMS and aRMS was identified, 10% and 4% respectively (van Gaal et al., 2013). Nuclear translocation may be a predictive factor in sarcoma patient as the response to anti-IGF-1RAb in soft tissue sarcomas. Therefore, understanding the mechanism of IGF-1R nuclear translocation is necessary to discover its potential role as a biomarker.

From the above studies, there seems to be discrepancy regarding whether IGF-1R is associated with aggressive cancer (for example in prostate cancer, Aleksic et al (2018) or with a good prognosis as is the case with sarcomas (Asmane et al., 2012). Further studies are warranted to investigate the association of nIGF-1R with clinical outcome of cancer patients.

In this century, personalized cancer therapy clinical trials, biomarkers, precision, personalized and stratified medicine is of paramount importance. It is important to recognize IGF-1R mediated activities that are unequivocally essential for malignant cell growth. Such discoveries may prompt improvement of targeted treatments. An interesting phenomenon still unknown is whether small molecule inhibitors, which inhibit the kinase activity of RTKs, can inhibit function of another RTK i.e., IGF-1R and its nuclear translocation.

Given the complexity of IGF-1R/IR family, for future it is essential to develop novel approaches to target IGF-1R in cancer cells. IGF-1R localizes to the cell nucleus of several cancer and non-cancer cells thus, to prevent this one potential approach could be targeting different points of its translocation process. For future trials two or more proteins within IGF-1R signalling cascade can be co-targeted. Furthermore, to take advantage of successful phase I clinical trials, more research and effort can be put into the biomarker discovery for successful outcome of phase III trials.

The present study has potential notable limitations.

* This study may subject to biases that perhaps have influenced the research involuntarily. More studies can be added to cover every aspect of IGF-1R signalling pathway and functions in health. However, this review pools and scan all the available information on nuclear IGF-1R.
* The present study does not cover all the research data published on IGF-1R and cancer. This could be attained by expanding the research topic and field of study. However, this review answers all the aims and objectives initially decided.

**5: Conclusion and Future Directions**

IGF-1R has emerged as an attractive target in cancer biology. Several in vitro, in vivo, and clinical studies have shown that IGF-1R contributes to resistance to targeted therapies. The receptors expression enhances upon the binding of IGF-I therefore, this relation is a key factor to promote oncogenic pathways. IGF-1R overexpression and overactivation induces tumour growth, thus it is implicated in almost every type of cancer. Hence, greatly contributing to invasion, metastasis, and cancer cells angiogenesis.

Our research group will further explore that how exactly nIGF-1R promotes carcinogenesis and its mechanism of action. The future research would determine how initiation of nuclear localization of IGF-1R plays a pivotal role in clinical pathology. Predominantly the focus of the research would be to identify the binding partners of IGF-1R which promote its nuclear translocation and retains the receptor inside the nucleus. Such research could contribute to discover novel strategies and patterns of use that relate to improved treatment strategies. The newly emerging field of nIGF-1R would lead to the discovery of novel potential pathways regulated by nIGF-1R in the nuclei of cancer cells that can be clinically targeted, thus improving clinical outcome in aggressive cancers.

**6. References**

1. Abbott, A.M., Bueno, R., Pedrini, M.T., Murray, J.M. and Smith, R.J., 1992. Insulin-like growth factor I receptor gene structure. Journal of Biological Chemistry, 267(15), pp.10759-10763.
2. Abdel-Wahab, R., Varadhachary, G.R., Bhosale, P.R., Wang, X., Fogelman, D.R., Shroff, R.T., Overman, M.J., Wolff, R.A. and Javle, M., 2018. Randomized, phase I/II study of gemcitabine plus IGF-1R antagonist (MK-0646) versus gemcitabine plus erlotinib with and without MK-0646 for advanced pancreatic adenocarcinoma. Journal of hematology & oncology, 11(1), p.71.
3. Adhami, V.M., Siddiqui, I.A., Ahmad, N., Gupta, S. and Mukhtar, H., 2004. Oral consumption of green tea polyphenols inhibits insulin-like growth factor-I–induced signaling in an autochthonous mouse model of prostate cancer. Cancer research, 64(23), pp.8715-8722.
4. Agnelli, G., Prandoni, P., Santamaria, M.G., Bagatella, P., Iorio, A., Bazzan, M., Moia, M., Guazzaloca, G., Bertoldi, A., Tomasi, C. and Scannapieco, G., 2001. Three months versus one year of oral anticoagulant therapy for idiopathic deep venous thrombosis. New England Journal of Medicine, 345(3), pp.165-169.
5. Akkiprik, M., Hu, L., Sahin, A., Hao, X. and Zhang, W., 2009. The subcellular localization of IGFBP5 affects its cell growth and migration functions in breast cancer. BMC cancer, 9(1), p.103.
6. Aleem, E., Elshayeb, A., Elhabachi, N., Mansour, A.R., Gowily, A. and Hela, A., 2012. Serum IGFBP‑3 is a more effective predictor than IGF‑1 and IGF-2 for the development of hepatocellular carcinoma in patients with chronic HCV infection. Oncology letters, 3(3), pp.704-712.
7. Aleksic, T., Chitnis, M.M., Perestenko, O.V., Gao, S., Thomas, P.H., Turner, G.D., Protheroe, A.S., Howarth, M. and Macaulay, V.M., 2010. Type 1 insulin-like growth factor receptor translocates to the nucleus of human tumor cells. Cancer research, 70(16), pp.6412-6419.
8. Aleksic, T., Gray, N., Wu, X., Rieunier, G., Osher, E., Mills, J., Verrill, C., Bryant, R.J., Han, C., Hutchinson, K. and Lambert, A.G., 2018. Nuclear IGF1R interacts with regulatory regions of chromatin to promote RNA polymerase II recruitment and gene expression associated with advanced tumor stage. Cancer research, 78(13), pp.3497-3509.
9. Aleksic, T., Verrill, C., Bryant, R.J., Han, C., Worrall, A.R., Brureau, L., Larré, S., Higgins, G.S., Fazal, F., Sabbagh, A. and Haider, S., 2017. IGF-1R associates with adverse outcomes after radical radiotherapy for prostate cancer. British journal of cancer, 117(11), pp.1600-1606.
10. Alpern, R.J. and Hebert, S.C. eds., 2007. Seldin and Giebisch's The Kidney: Physiology & Pathophysiology 1-2. Elsevier.
11. Andrews, D.W., Resnicoff, M., Flanders, A.E., Kenyon, L., Curtis, M., Merli, G., Baserga, R., Iliakis, G. and Aiken, R.D., 2001. Results of a pilot study involving the use of an antisense oligodeoxynucleotide directed against the insulin-like growth factor type I receptor in malignant astrocytomas. Journal of Clinical Oncology, 19(8), pp.2189-2200.
12. Anil, C., Akkurt, A., Ayturk, S., Kut, A. and Gursoy, A., 2013. Impaired glucose metabolism is a risk factor for increased thyroid volume and nodule prevalence in a mild-to-moderate iodine deficient area. Metablism, 62(7), pp.970-975.
13. Anisimov, V.N. and Bartke, A., 2013. The key role of growth hormone–insulin–IGF-1 signaling in aging and cancer. Critical reviews in oncology/hematology, 87(3), pp.201-223.
14. Arora, A. and Scholar, E.M., 2005. Role of tyrosine kinase inhibitors in cancer therapy. Journal of Pharmacology and Experimental Therapeutics, 315(3), pp.971-979.
15. AsghariHanjani, N. and Vafa, M., 2019. The role of IGF-1 in obesity, cardiovascular disease, and cancer. *Medical journal of the Islamic Republic of Iran*, *33*, p.56.
16. Aslam, M.I., Hettmer, S., Abraham, J., LaTocha, D., Soundararajan, A., Huang, E.T., Goros, M.W., Michalek, J.E., Wang, S., Mansoor, A. and Druker, B.J., 2013. Dynamic and nuclear expression of PDGFRα and IGF-1R in alveolar Rhabdomyosarcoma. Molecular Cancer Research, 11(11), pp.1303-1313.
17. Asmane, I., Watkin, E., Alberti, L., Duc, A., Marec-Berard, P., Ray-Coquard, I., Cassier, P., Decouvelaere, A.V., Ranchère, D., Kurtz, J.E. and Bergerat, J.P., 2012. Insulin-like growth factor type 1 receptor (IGF-1R) exclusive nuclear staining: a predictive biomarker for IGF-1R monoclonal antibody (Ab) therapy in sarcomas. European journal of cancer, 48(16), pp.3027-3035.
18. Atzori, F., Tabernero, J., Cervantes, A., Prudkin, L., Andreu, J., Rodríguez-Braun, E., Domingo, A., Guijarro, J., Gamez, C., Rodon, J. and Di Cosimo, S., 2011. A phase I pharmacokinetic and pharmacodynamic study of dalotuzumab (MK-0646), an anti-insulin-like growth factor-1 receptor monoclonal antibody, in patients with advanced solid tumors. Clinical Cancer Research, 17(19), pp.6304-6312.
19. Azar, W.J., Zivkovic, S., Werther, G.A. and Russo, V.C., 2014. IGFBP-2 nuclear translocation is mediated by a functional NLS sequence and is essential for its pro-tumorigenic actions in cancer cells. Oncogene, 33(5), pp.578-588.
20. Bartucci, M., Morelli, C., Mauro, L. and Surmacz, E., 2001. Differential insulin-like growth factor I receptor signaling and function in estrogen receptor (ER)-positive MCF-7 and ER-negative MDA-MB-231 breast cancer cells. Cancer research, 61(18), pp.6747-6754.
21. Baserga, R., 1995. The insulin-like growth factor I receptor: a key to tumor growth?. Cancer research, 55(2), pp.249-252.
22. Baxter, R.C., 2014. IGF binding proteins in cancer: mechanistic and clinical insights. Nature Reviews Cancer, 14(5), pp.329-341.
23. Bell, I.M., Stirdivant, S.M., Ahern, J., Culberson, J.C., Darke, P.L., Dinsmore, C.J., Drakas, R.A., Gallicchio, S.N., Graham, S.L., Heimbrook, D.C. and Hall, D.L., 2005. Biochemical and structural characterization of a novel class of inhibitors of the type 1 insulin-like growth factor and insulin receptor kinases. Biochemistry, 44(27), pp.9430-9440.
24. Bettermann, K., Benesch, M., Weis, S. and Haybaeck, J., 2012. SUMOylation in carcinogenesis. Cancer letters, 316(2), pp.113-125.
25. Bhaumick, B., Bala, R.M. and Hollenberg, M.D., 1981. Somatomedin receptor of human placenta: solubilization, photolabeling, partial purification, and comparison with insulin receptor. Proceedings of the National Academy of Sciences, 78(7), pp.4279-4283.
26. Bi, X., 2015. Mechanism of DNA damage tolerance. World journal of biological chemistry, 6(3), p.48.
27. Bikle, D., Majumdar, S., Laib, A., Powell‐Braxton, L., Rosen, C., Beamer, W., Nauman, E., Leary, C. and Halloran, B., 2001. The skeletal structure of insulin‐like growth factor I‐deficient mice. Journal of Bone and Mineral Research, 16(12), pp.2320-2329.
28. Bliss, J.M., Robison, L.E., Webster-Smith, M.F., Emson, M.A., Kilburn, L.S., Smith, I.E., Robertson, J., Dowsett, M., Bundred, N.J., Cameron, D.A. and Vidya, R., 2011. OT2-03-04: A Trial Model for the Future in the Search for Personalised Medicine–The UK POETIC and EPHOS-B Perioperative Trials Experience.
29. Bodzin, A.S., Wei, Z., Hurtt, R., Gu, T. and Doria, C., 2012. Gefitinib resistance in HCC mahlavu cells: Upregulation of CD133 expression, activation of IGF‐1R signaling pathway, and enhancement of IGF‐1R nuclear translocation. Journal of cellular physiology, 227(7), pp.2947-2952.
30. Bonath, K., 1975. The halothane inhalation anesthesia in birds and its clinical control. Berliner und Munchener tierarztliche Wonchenschrift, 88 (15), pp.299-301.
31. Brahmkhatri, V.P., Prasanna, C. and Atreya, H.S., 2015. Insulin-like growth factor system in cancer: novel targeted therapies. BioMed research international, 2015.
32. Brandes, A.A., Scelzi, E., Salmistraro, G., Ermani, M., Carollo, C., Berti, F., Zampieri, P., Baiocchi, C. and Fiorentino, M.V., 1997. Incidence and risk of thromboembolism during treatment of high-grade gliomas: a prospective study. European Journal of Cancer, 33(10), pp.1592-1596.
33. Bridda, A., padoan, I., Mencarelli, R. and Frego, M., 2007. Peritoneal mesothelimo: a review. Medscape General Medicine, 9(2), p.32.
34. Buck, E., Eyzaguirre, A., Thomson, S., Mulvihill, M., Barr, S., Brown, E., O'Connor, M., Yao, Y., Pachter, J., Miglarese, M. and Epstein, D., 2008. Feedback mechanisms promote cooperativity for small molecule inhibitors of epidermal and insulin-like growth factor receptors. Cancer research, 68(20), pp.8322-8332.
35. Cage, T.A., Lamborn, K.R., Ware, M.L., Frankfurt, A., Chakalian, L., Berger, M.S. and McDermott, M.W., 2009. Adjuvant enoxaparin therapy may decrease the incidence of postoperative thrombotic events though does not increase the incidence of postoperative intracranial hemorrhage in patients with meningiomas. Journal of neuro-oncology, 93(1), p.151.
36. Capdevila, J., Teule, A., Barriuso, J., Castellano, D., Lopez, C., Manzano, J.L., Alonso, V., Garcia-Carbonero, R., Dotor, E., Matos, I. and Custodio, A., 2019. Phase II study of everolimus and octreotide LAR in patients with nonfunctioning gastrointestinal neuroendocrine tumors: the GENTNE1003\_EVERLAR study. The oncologist, 24(1), p.38.
37. Carboni, J.M., Lee, A.V., Hadsell, D.L., Rowley, B.R., Lee, F.Y., Bol, D.K., Camuso, A.E., Gottardis, M., Greer, A.F., Ho, C.P. and Hurlburt, W., 2005. Tumor development by transgenic expression of a constitutively active insulin-like growth factor I receptor. Cancer research, 65(9), pp.3781-3787.
38. Cardillo, M.R., Monti, S., Di, F.S., Gentile, V., Sciarra, F. and Toscano, V., 2003. Insulin-like growth factor (IGF)-I, IGF-II and IGF type I receptor (IGFR-I) expression in prostatic cancer. Anticancer research, 23(5A), pp.3825-3835.
39. Carpentier, A., Laigle-Donadey, F., Zohar, S., Capelle, L., Behin, A., Tibi, A., Martin-Duverneuil, N., Sanson, M., Lacomblez, L., Taillibert, S. and Puybasset, L., 2006. Phase 1 trial of a CpG oligodeoxynucleotide for patients with recurrent glioblastoma. Neuro-oncology, 8(1), pp.60-66.
40. Cella, D., Butt, Z., Kindler, H.L., Fuchs, C.S., Bray, S., Barlev, A. and Oglesby, A., 2013. Validity of the FACT Hepatobiliary (FACT-Hep) questionnaire for assessing disease-related symptoms and health-related quality of life in patients with metastatic pancreatic cancer. Quality of Life Research, 22(5), pp.1105-1112.
41. Chalasani, P., Stopeck, A., Clarke, K. and Livingston, R., 2014. A pilot study of estradiol followed by exemestane for reversing endocrine resistance in postmenopausal women with hormone receptor-positive metastatic breast cancer. The oncologist, 19 (11), p.1127.
42. Chaput, N., Schartz, N.E., André, F., Taïeb, J., Novault, S., Bonnaventure, P., Aubert, N., Bernard, J., Lemonnier, F., Merad, M. and Adema, G., 2004. Exosomes as potent cell-free peptide-based vaccine. II. Exosomes in CpG adjuvants efficiently prime naive Tc1 lymphocytes leading to tumor rejection. The Journal of Immunology, 172(4), pp.2137-2146.
43. Chen, C.W. and Roy, D., 1996. Up-regulation of nuclear IGF-I receptor by short term exposure of stilbene estrogen, diethylstilbestrol. Molecular and cellular endocrinology, 118(1-2), pp.1-8.
44. Chen, H.X. and Sharon, E., 2013. IGF-1R as an anti-cancer target—trials and tribulations. Chinese journal of cancer, 32(5), p.242.
45. Chen, Y., McGee, J., Chen, X., Doman, T.N., Gong, X., Zhang, Y., Hamm, N., Ma, X., Higgs, R.E., Bhagwat, S.V. and Buchanan, S., 2014. Identification of druggable cancer driver genes amplified across TCGA datasets. PloS one, 9(5).
46. Cheng, J., Bawa, T., Lee, P., Gong, L. and Yeh, E.T., 2006. Role of desumoylation in the development of prostate cancer. Neoplasia (New York, NY), 8(8), p.667.
47. Chernausek, S.D., Jacobs, S. and Van Wyk, J.J., 1981. Structural similarities between human receptors for somatomedin C and insulin: analysis by affinity labeling. Biochemistry, 20(26), pp.7345-7350.
48. Chiappori, A.A., Otterson, G.A., Dowlati, A., Traynor, A.M., Horn, L., Owonikoko, T.K., Ross, H.J., Hann, C.L., Hejleh, T.A., Nieva, J. and Zhao, X., 2016. A randomized phase II study of linsitinib (OSI-906) versus topotecan in patients with relapsed small-cell lung cancer. The oncologist, 21(10), p.1163.
49. Chugh, R., Griffith, K.A., Davis, E.J., Thomas, D.G., Zavala, J.D., Metko, G., Brockstein, B., Undevia, S.D., Stadler, W.M. and Schuetze, S.M., 2015. Doxorubicin plus the IGF-1R antibody cixutumumab in soft tissue sarcoma: a phase I study using the TITE-CRM model. Annals of Oncology, 26(7), pp.1459-1464.
50. Codony-Servat, J., Cuatrecasas, M., Asensio, E., Montironi, C., Martínez-Cardús, A., Marín-Aguilera, M., Horndler, C., Martínez-Balibrea, E., Rubini, M., Jares, P. and Reig, O., 2017. Nuclear IGF-1R predicts chemotherapy and targeted therapy resistance in metastatic colorectal cancer. British journal of cancer, 117(12), pp.1777-1786.
51. Cohen, B.D., Baker, D.A., Soderstrom, C., Tkalcevic, G., Rossi, A.M., Miller, P.E., Tengowski, M.W., Wang, F., Gualberto, A., Beebe, J.S. and Moyer, J.D., 2005. Combination therapy enhances the inhibition of tumor growth with the fully human anti–type 1 insulin-like growth factor receptor monoclonal antibody CP-751,871. Clinical cancer research, 11(5), pp.2063-2073.
52. Cosaceanu, D., Carapancea, M., Alexandru, O., Budiu, R., Martinsson, H.S., Starborg, M., Vrabete, M., Kanter, L., Lewensohn, R. and Dricu, A., 2007. Comparison of three approaches for inhibiting insulin-like growth factor I receptor and their effects on NSCLC cell lines in vitro. Growth Factors, 25(1), pp.1-8.
53. Chaput, N., Schartz, N.E., André, F., Taïeb, J., Novault, S., Bonnaventure, P., Aubert, N., Bernard, J., Lemonnier, F., Merad, M. and Adema, G., 2004. Exosomes as potent cell-free peptide-based vaccine. II. Exosomes in CpG adjuvants efficiently prime naive Tc1 lymphocytes leading to tumor rejection. The Journal of Immunology, 172(4), pp.2137-2146.
54. Cunningham, C.C., Holmlund, J.T., Schiller, J.H., Geary, R.S., Kwoh, T.J., Dorr, A. and Nemunaitis, J., 2000. A phase I trial of c-Raf kinase antisense oligonucleotide ISIS 5132 administered as a continuous intravenous infusion in patients with advanced cancer. Clinical Cancer Research, 6(5), pp.1626-1631.
55. Cunningham, M.L., Horst, J.A., Rieder, M.J., Hing, A.V., Stanaway, I.B., Park, S.S., Samudrala, R. and Speltz, M.L., 2011. IGF1R variants associated with isolated single suture craniosynostosis. American Journal of Medical Genetics Part A, 155(1), pp.91-97.
56. Dasari, A., Phan, A., Gupta, S., Rashid, A., Yeung, S.C.J., Hess, K., Chen, H., Tarco, E., Chen, H., Wei, C. and Anh-Do, K., 2015. Phase I study of the anti-IGF1R antibody cixutumumab with everolimus and octreotide in advanced well-differentiated neuroendocrine tumors. Endocrine-related cancer, 22(3), pp.431-441.
57. Davidson, A. and Diamond, B., 2001. Autoimmune diseases. New England Journal of Medicine, 345(5), pp.340-350.
58. de Bono, J.S., Piulats, J.M., Pandha, H.S., Petrylak, D.P., Saad, F., Aparicio, L.M.A., Sandhu, S.K., Fong, P., Gillessen, S., Hudes, G.R. and Wang, T., 2014. Phase II randomized study of figitumumab plus docetaxel and docetaxel alone with crossover for metastatic castration-resistant prostate cancer. Clinical Cancer Research, 20(7), pp.1925-1934.
59. de Groot, S., Charehbili, A., van Laarhoven, H.W., Mooyaart, A.L., Dekker-Ensink, N.G., van de Ven, S., Janssen, L.G., Swen, J.J., Smit, V.T., Heijns, J.B. and Kessels, L.W., 2016. Insulin-like growth factor 1 receptor expression and IGF1R 3129G> T polymorphism are associated with response to neoadjuvant chemotherapy in breast cancer patients: results from the NEOZOTAC trial (BOOG 2010-01). Breast Cancer Research, 18(1), p.3.
60. Deng, H., Lin, Y., Badin, M., Vasilcanu, D., Strömberg, T., Jernberg-Wiklund, H., Sehat, B. and Larsson, O., 2011. Over-accumulation of nuclear IGF-1 receptor in tumor cells requires elevated expression of the receptor and the SUMO-conjugating enzyme Ubc9. Biochemical and biophysical research communications, 404(2), pp.667-671.
61. Denley, A., Cosgrove, L.J., Booker, G.W., Wallace, J.C. and Forbes, B.E., 2005. Molecular interactions of the IGF system. Cytokine & growth factor reviews, 16(4-5), pp.421-439.
62. Desterro, J.M., Rodriguez, M.S., Kemp, G.D. and Hay, R.T., 1999. Identification of the enzyme required for activation of the small ubiquitin-like protein SUMO-1. Journal of Biological Chemistry, 274(15), pp.10618-10624.
63. Di Fusco, D., Dinallo, V., Marafini, I., Figliuzzi, M.M., Romano, B. and Monteleone, G., 2019. Antisense Oligonucleotide: basic concepts and therapeutic application in Inflammatory bowel disease. *Frontiers in pharmacology*, *10*, p.305.
64. Di Maio, M. and Scagliotti, G.V., 2015. The lesson learned from figitumumab clinical program and the hope for better results in squamous lung cancer. *Translational lung cancer research*, *4*(1), p.15.
65. Dong, J., Demarest, S.J., Sereno, A., Tamraz, S., Langley, E., Doern, A., Snipas, T., Perron, K., Joseph, I., Glaser, S.M. and Ho, S.N., 2010. Combination of two insulin-like growth factor-I receptor inhibitory antibodies targeting distinct epitopes leads to an enhanced antitumor response. Molecular cancer therapeutics, 9(9), pp.2593-2604.
66. Dorn, A. and Kippenberger, S., 2008. Clinical application of CpG-, non-CpG-, and antisense oligodeoxynucleotides as immunomodulators. Current opinion in molecular therapeutics, 10(1), pp.10-20.
67. Eckstein, N., Servan, K., Hildebrandt, B., Pölitz, A., von Jonquières, G., Wolf-Kümmeth, S., Napierski, I., Hamacher, A., Kassack, M.U., Budczies, J. and Beier, M., 2009. Hyperactivation of the insulin-like growth factor receptor I signaling pathway is an essential event for cisplatin resistance of ovarian cancer cells. Cancer research, 69(7), pp.2996-3003.
68. Ekman, S., Harmenberg, J., Frödin, J.E., Bergström, S., Wassberg, C., Eksborg, S., Larsson, O., Axelson, M., Jerling, M., Abrahmsen, L. and Hedlund, Å., 2016. A novel oral insulin-like growth factor-1 receptor pathway modulator and its implications for patients with non-small cell lung carcinoma: A phase I clinical trial. Acta oncologica, 55(2), pp.140-148.
69. Ekyalongo, R.C. and Yee, D., 2017. Revisiting the IGF-1R as a breast cancer target. *NPJ precision oncology*, *1*(1), pp.1-7.
70. Elbashir, S.M., Harborth, J., Lendeckel, W., Yalcin, A., Weber, K. and Tuschl, T., 2001. Duplexes of 21-nucleotide RNAs mediate RNA interference in cultured mammalian cells. *nature*, *411*(6836), pp.494-498.
71. Ellis, P.M., Shepherd, F.A., Laurie, S.A., Goss, G.D., Olivo, M., Powers, J., Seymour, L. and Bradbury, P.A., 2014. NCIC CTG IND. 190 phase I trial of dalotuzumab (MK-0646) in combination with cisplatin and etoposide in extensive-stage small-cell lung cancer. Journal of Thoracic Oncology, 9(3), pp.410-413.
72. Eroles, P., Bosch, A., Pérez-Fidalgo, J.A. and Lluch, A., 2012. Molecular biology in breast cancer: intrinsic subtypes and signaling pathways. Cancer treatment reviews, 38(6), pp.698-707.
73. Evan, Y.Y., Li, H., Higano, C.S., Agarwal, N., Pal, S.K., Alva, A., Heath, E.I., Lam, E.T., Gupta, S., Lilly, M.B. and Inoue, Y., 2015. SWOG S0925: a randomized phase II study of androgen deprivation combined with cixutumumab versus androgen deprivation alone in patients with new metastatic hormone-sensitive prostate cancer. Journal of Clinical Oncology, 33(14), p.1601.
74. Fan, Z. and Mendelsohn, J., 1998. Therapeutic application of anti-growth factor receptor antibodies. Current opinion in oncology, 10(1), pp.67-73.
75. Fang, J., Zhou, Q., Shi, X.L. and Jiang, B.H., 2007. Luteolin inhibits insulin-like growth factor 1 receptor signaling in prostate cancer cells. Carcinogenesis, 28(3), pp.713-723.
76. Fassnacht, M., Berruti, A., Baudin, E., Demeure, M.J., Gilbert, J., Haak, H., Kroiss, M., Quinn, D.I., Hesseltine, E., Ronchi, C.L. and Terzolo, M., 2015. Linsitinib (OSI-906) versus placebo for patients with locally advanced or metastatic adrenocortical carcinoma: a double-blind, randomised, phase 3 study. The lancet oncology, 16(4), pp.426-435.
77. Fire, A., Xu, S., Montgomery, M.K., Kostas, S.A., Driver, S.E. and Mello, C.C., 1998. Potent and specific genetic interference by double-stranded RNA in Caenorhabditis elegans. nature, 391(6669), pp.806-811.
78. Flyvbjerg, A., Mogensen, O., Mogensen, B. and Nielsen, O.S., 1997. Elevated serum insulin-like growth factor-binding protein 2 (IGFBP-2) and decreased IGFBP-3 in epithelial ovarian cancer: correlation with cancer antigen 125 and tumor-associated trypsin inhibitor. The Journal of Clinical Endocrinology & Metabolism, 82(7), pp.2308-2313.
79. Frater, J., Lie, D., Bartlett, P. and McGrath, J.J., 2018. Insulin-like Growth Factor 1 (IGF-1) as a marker of cognitive decline in normal ageing: A review. *Ageing research reviews*, *42*, pp.14-27.
80. Friedrichs, N., Küchler, J., Endl, E., Koch, A., Czerwitzki, J., Wurst, P., Metzger, D., Schulte, J.H., Holst, M.I., Heukamp, L.C. and Larsson, O., 2008. Insulin‐like growth factor‐1 receptor acts as a growth regulator in synovial sarcoma. The Journal of Pathology: A Journal of the Pathological Society of Great Britain and Ireland, 216(4), pp.428-439.
81. Fu, S., Tang, H., Liao, Y., Xu, Q., Liu, C., Deng, Y., Wang, J., Wang, J. and Fu, X., 2016. Expression and clinical significance of insulin-like growth factor 1 in lung cancer tissues and perioperative circulation from patients with non-small-cell lung cancer. Current Oncology, 23(1), p.12.
82. Gao, J., Chesebrough, J.W., Cartlidge, S.A., Ricketts, S.A., Incognito, L., Veldman-Jones, M., Blakey, D.C., Tabrizi, M., Jallal, B., Trail, P.A. and Coats, S., 2011. Dual IGF-I/II–neutralizing antibody MEDI-573 potently inhibits IGF signaling and tumor growth. Cancer research, 71(3), pp.1029-1040.
83. Ge, J., Chen, Z., Wu, S., Chen, J., Li, X., Li, J., Yin, J. and Chen, Z., 2009. Expression levels of insulin-like growth factor-1 and multidrug resistance-associated protein-1 indicate poor prognosis in patients with gastric cancer. Digestion, 80(3), pp.148-158.
84. Girnita, A., Girnita, L., del Prete, F., Bartolazzi, A., Larsson, O. and Axelson, M., 2004. Cyclolignans as inhibitors of the insulin-like growth factor-1 receptor and malignant cell growth. Cancer research, 64(1), pp.236-242.
85. Girnita, L., Worrall, C., Takahashi, S.I., Seregard, S. and Girnita, A., 2014. Something old, something new and something borrowed: emerging paradigm of insulin-like growth factor type 1 receptor (IGF-1R) signaling regulation. Cellular and molecular life sciences, 71(13), pp.2403-2427.
86. Goldfine, I.D. and Smith, G.J., 1976. Binding of insulin to isolated nuclei. Proceedings of the National Academy of Sciences, 73(5), pp.1427-1431.
87. Gombos, A., Metzger-Filho, O., Dal Lago, L. and Awada-Hussein, A., 2012. Clinical development of insulin-like growth factor receptor—1 (IGF-1R) inhibitors: At the crossroad?. Investigational new drugs, 30(6), pp.2433-2442.
88. Goss, P.E., ., Smith, I.E., O'Shaughnessy, J., Ejlertsen, B., Kaufmann, M., Boyle, F., Buzdar, A.U., Fumoleau, P., Gradishar, W., Martin, M. and Moy, B., 2013. Adjuvant lapatinib for women with early-stage HER2-positive breast cancer: a randomised, controlled, phase 3 trial. The Lancet Oncology, 14(1), pp.88-96.
89. Gradishar, W.J., Yardley, D.A., Layman, R., Sparano, J.A., Chuang, E., Northfelt, D.W., Schwartz, G.N., Youssoufian, H., Tang, S., Novosiadly, R. and Forest, A., 2016. Clinical and Translational Results of a Phase II, Randomized Trial of an Anti–IGF-1R (Cixutumumab) in Women with Breast Cancer That Progressed on Endocrine Therapy. Clinical Cancer Research, 22(2), pp.301-309.
90. Grzmil, M., Hemmerlein, B., Thelen, P., Schweyer, S. and Burfeind, P., 2004. Blockade of the type I IGF receptor expression in human prostate cancer cells inhibits proliferation and invasion, up‐regulates IGF binding protein‐3, and suppresses MMP‐2 expression. The Journal of Pathology: A Journal of the Pathological Society of Great Britain and Ireland, 202(1), pp.50-59.
91. Gualberto, A. and Karp, D.D., 2009. Development of the monoclonal antibody Figitumumab, targeting the insulin-like growth factor-1 receptor, for the treatment of patients with non–small-cell lung cancer. Clinical lung cancer, 10(4), pp.273-280.
92. Guerard, M., Robin, T., Perron, P., Hatat, A.S., David-Boudet, L., Vanwonterghem, L., Busser, B., Coll, J.L., Lantuejoul, S., Eymin, B. and Hurbin, A., 2018. Nuclear translocation of IGF1R by intracellular amphiregulin contributes to the resistance of lung tumour cells to EGFR-TKI. Cancer letters, 420, pp.146-155.
93. Guntur, A.R. and Rosen, C.J., 2013. IGF-1 regulation of key signaling pathways in bone. BoneKEy reports, 2.
94. Guo, W.H., Yuan, L.H., Xiao, Z.H., Liu, D. and Zhang, J.X., 2011. Overexpression of SUMO-1 in hepatocellular carcinoma: a latent target for diagnosis and therapy of hepatoma. Journal of cancer research and clinical oncology, 137(3), pp.533-541.
95. Guvakova, M.A., 2007. Insulin-like growth factors control cell migration in health and disease. The international journal of biochemistry & cell biology, 39(5), pp.890-909.
96. Hakuno, F. and Takahashi, S.I., 2018. 40 years of IGF1: IGF1 receptor signaling pathways. Journal of molecular endocrinology, 61(1), pp.T69-T86.
97. Haluska, P., Shaw, H.M., Batzel, G.N., Yin, D., Molina, J.R., Molife, L.R., Yap, T.A., Roberts, M.L., Sharma, A., Gualberto, A. and Adjei, A.A., 2007. Phase I dose escalation study of the anti–insulin-like growth factor-I receptor monoclonal antibody CP-751,871 in patients with refractory solid tumors. Clinical Cancer Research, 13(19), pp.5834-5840.
98. Han, Y., Huang, C., Sun, X., Xiang, B., Wang, M., Yeh, E.T., Chen, Y., Li, H., Shi, G., Cang, H. and Sun, Y., 2010. SENP3-mediated de-conjugation of SUMO2/3 from promyelocytic leukemia is correlated with accelerated cell proliferation under mild oxidative stress. Journal of Biological Chemistry, 285(17), pp.12906-12915.
99. Haywood, N.J., Slater, T.A., Matthews, C.J. and Wheatcroft, S.B., 2019. The insulin like growth factor and binding protein family: novel therapeutic targets in obesity & diabetes. Molecular metabolism, 19, pp.86-96.
100. Hellawell, G.O., Turner, G.D., Davies, D.R., Poulsom, R., Brewster, S.F. and Macaulay, V.M., 2002. Expression of the type 1 insulin-like growth factor receptor is up-regulated in primary prostate cancer and commonly persists in metastatic disease. Cancer research, 62(10), pp.2942-2950.
101. Hemmings, B.A. and Restuccia, D.F., 2012. Pi3k-pkb/akt pathway. Cold Spring Harbor perspectives in biology, 4(9), p.a011189.
102. Heymann, D., Segaliny, A., Tellez-Gabriel, M. and Heymann, M.F., 2015. Receptor tyrosine kinases: Characterisation, mechanism of action and therapeutic interests for bone cancers.
103. Higano, C.S., Berlin, J., Gordon, M., LoRusso, P., Tang, S., Dontabhaktuni, A., Schwartz, J.D., Cosaert, J. and Mehnert, J.M., 2015. Safety, tolerability, and pharmacokinetics of single and multiple doses of intravenous cixutumumab (IMC-A12), an inhibitor of the insulin-like growth factor-I receptor, administered weekly or every 2 weeks in patients with advanced solid tumors. Investigational New Drugs, 33(2), pp.450-462.
104. Hoa, N., Tsui, S., Afifiyan, N.F., Hikim, A.S., Li, B., Douglas, R.S. and Smith, T.J., 2012. Nuclear targeting of IGF-1 receptor in orbital fibroblasts from Graves' disease: apparent role of ADAM17. PLoS One, 7(4).
105. Hoellein, A., Fallahi, M., Schoeffmann, S., Steidle, S., Schaub, F.X., Rudelius, M., Laitinen, I., Nilsson, L., Goga, A., Peschel, C. and Nilsson, J.A., 2014. Myc-induced SUMOylation is a therapeutic vulnerability for B-cell lymphoma. Blood, The Journal of the American Society of Hematology, 124(13), pp.2081-2090.
106. Hopfner, M., Baradari, V., Huether, A., Schofl, C. and Scherubl, H., 2006. The insulin-like growth factor receptor 1 is a promising target for novel treatment approaches in neuroendocrine gastrointestinal tumours. Endocrine-Related Cancer, 13(1), pp.135-149.
107. Hou, X., Huang, F., Macedo, L.F., Harrington, S.C., Reeves, K.A., Greer, A., Finckenstein, F.G., Brodie, A., Gottardis, M.M., Carboni, J.M. and Haluska, P., 2011. Dual IGF-1R/InsR inhibitor BMS-754807 synergizes with hormonal agents in treatment of estrogen-dependent breast cancer. Cancer research, 71(24), pp.7597-7607.
108. Hu, B., Weng, Y., Xia, X.H., Liang, X.J. and Huang, Y., 2019. Clinical advances of siRNA therapeutics. *The journal of gene medicine*, *21*(7), p.e3097.
109. Huang, C.H., Williamson, S.K., Neupane, P., Taylor, S.A., Allen, A., Smart, N.J., Uypeckcuat, A.M., Spencer, S., Wick, J., Smith, H. and Van Veldhuizen, P.J., 2016. Impact study: MK-0646 (Dalotuzumab), insulin growth factor 1 receptor antibody combined with pemetrexed and cisplatin in stage IV metastatic non-squamous lung cancer. Frontiers in oncology, 5, p.301.
110. Huang, X.P., Zhou, W.H. and Zhang, Y.F., 2014. Genetic variations in the IGF-IGFR-IGFBP axis confer susceptibility to lung and esophageal cancer. Genet Mol Res, 13(1), pp.2107-2119.
111. Hubbard, S.R., 1999. Structural analysis of receptor tyrosine kinases. Progress in biophysics and molecular biology, 71(3-4), pp.343-358.
112. Iams, W.T. and Lovly, C.M., 2015. Molecular pathways: clinical applications and future direction of insulin-like growth factor-1 receptor pathway blockade. Clinical Cancer Research, 21(19), pp.4270-4277.
113. Imai, K. and Takaoka, A., 2006. Comparing antibody and small-molecule therapies for cancer. *Nature Reviews Cancer*, *6*(9), pp.714-727.
114. Iosef, C., Gkourasas, T., Jia, C.Y., Li, S.S.C. and Han, V.K., 2008. A functional nuclear localization signal in insulin-like growth factor binding protein-6 mediates its nuclear import. Endocrinology, 149(3), pp.1214-1226.
115. Isoyama, S., Kajiwara, G., Tamaki, N., Okamura, M., Yoshimi, H., Nakamura, N., Kawamura, K., Nishimura, Y., Namatame, N., Yamori, T. and Dan, S., 2015. Basal expression of insulin‐like growth factor 1 receptor determines intrinsic resistance of cancer cells to a phosphatidylinositol 3‐kinase inhibitor ZSTK474. Cancer science, 106(2), pp.171-178.
116. Jacobs, S., Kull, F.C. and Cuatrecasas, P., 1983. Monensin blocks the maturation of receptors for insulin and somatomedin C: identification of receptor precursors. Proceedings of the National Academy of Sciences, 80(5), pp.1228-1231.
117. Jacobs, S., Kull, F.C., Earp, H.S., Svoboda, M.E., Van Wyk, J.J. and Cuatrecasas, P., 1983. Somatomedin-C stimulates the phosphorylation of the beta-subunit of its own receptor. Journal of Biological Chemistry, 258(16), pp.9581-9584.
118. Jin, Q. and Esteva, F.J., 2008. Cross-talk between the ErbB/HER family and the type I insulin-like growth factor receptor signaling pathway in breast cancer. Journal of mammary gland biology and neoplasia, 13(4), pp.485-498.
119. Jones, J.I. and Clemmons, D.R., 1995. Insulin-like growth factors and their binding proteins: biological actions. Endocrine reviews, 16(1), pp.3-34.
120. Jones, R.A., Campbell, C.I., Gunther, E.J., Chodosh, L.A., Petrik, J.J., Khokha, R. and Moorehead, R.A., 2007. Oncogene, 26(11), pp.1636-1644.
121. Jung, H.J. and Suh, Y., 2015. Regulation of IGF-1 signaling by microRNAs. Frontiers in genetics, 5, p.472.
122. Kabbani, H. and Raghuveer, T.S., 2004. Craniosynostosis. American family physician, 69(12), pp.2863-2870.
123. Kim, J.H., Choi, H.J., Kim, B., Kim, M.H., Lee, J.M., Kim, I.S., Lee, M.H., Choi, S.J., Kim, K.I., Kim, S.I. and Chung, C.H., 2006. Roles of sumoylation of a reptin chromatin-remodelling complex in cancer metastasis. Nature Cell Biology, 8(6), pp.631-639.
124. Kindler, H.L., Richards, D.A., Garbo, L.E., Garon, E.B., Stephenson Jr, J.J., Rocha-Lima, C.M., Safran, H., Chan, D., Kocs, D.M., Galimi, F. and McGreivy, J., 2012. A randomized, placebo-controlled phase 2 study of ganitumab (AMG 479) or conatumumab (AMG 655) in combination with gemcitabine in patients with metastatic pancreatic cancer. Annals of oncology, 23(11), pp.2834-2842.
125. King, H., Aleksic, T., Haluska, P. and Macaulay, V.M., 2014. Can we unlock the potential of IGF-1R inhibition in cancer therapy?. *Cancer treatment reviews*, *40*(9), pp.1096-1105.
126. Kolacinska, A., Chalubinska, J., Zawlik, I., Szymanska, B., Borowska-Garganisz, E., Nowik, M., Fendler, W., Kubiak, R., Pawlowska, Z., Morawiec, Z. and Szemraj, J., 2012. Apoptosis-, proliferation, immune function-, and drug resistance-related genes in ER positive, HER2 positive and triple negative breast cancer. Neoplasma, 59(4), p.424.
127. Langer, C.J., Novello, S., Park, K., Krzakowski, M., Karp, D.D., Mok, T., Benner, R.J., Scranton, J.R., Olszanski, A.J. and Jassem, J., 2014. Randomized, phase III trial of first-line figitumumab in combination with paclitaxel and carboplatin versus paclitaxel and carboplatin alone in patients with advanced non–small-cell lung cancer. Journal of clinical oncology, 32(19), p.2059.
128. Law, J.H., Habibi, G., Hu, K., Masoudi, H., Wang, M.Y., Stratford, A.L., Park, E., Gee, J.M., Finlay, P., Jones, H.E. and Nicholson, R.I., 2008. Phosphorylated insulin-like growth factor-i/insulin receptor is present in all breast cancer subtypes and is related to poor survival. Cancer research, 68(24), pp.10238-10246.
129. Lee AV, Jackson JG, Gooch JL, Hilsenbeck SG, Coronado-Heinsohn E, Osborne CK, et al. Enhancement of insulin-like growth factor signaling in human breast cancer: estrogen regulation of insulin receptor substrate-1 expression in vitro and in vivo. Mol Endocrinol. 1999;13:787–96.
130. Lee, C.Y., 2013 The effect of high-fat diet-induced pathophysiological changes in the gut on obesity: what should be the ideal treatment?. Clinical and Translational Gastroenterology, 4(7), p.e39.
131. Lee, W.S. and Kim, J., 2018. Insulin-like growth factor-1 signaling in cardiac aging. Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease, 1864(5), pp.1931-1938.
132. Lee, Y., Wang, Y., James, M., Jeong, J.H. and You, M., 2016. Inhibition of IGF1R signaling abrogates resistance to afatinib (BIBW2992) in EGFR T790M mutant lung cancer cells. Molecular carcinogenesis, 55(5), pp.991-1001.
133. LeRoith, D., Werner, H., Beitner-Johnson, D. and Roberts Jr, C.T., 1995. Molecular and cellular aspects of the insulin-like growth factor I receptor. Endocrine reviews, 16(2), pp.143-163.
134. Li, J., Choi, E., Yu, H. and Bai, X.C., 2019. Structural basis of the activation of type 1 insulin-like growth factor receptor. Nature communications, 10(1), pp.1-11.
135. Lin, E.H., Lenz, H.J., Saleh, M.N., Mackenzie, M.J., Knost, J.A., Pathiraja, K., Langdon, R.B., Yao, S.L. and Lu, B.D., 2014. A randomized, phase II study of the anti‐insulin‐like growth factor receptor type 1 (IGF‐1R) monoclonal antibody robatumumab (SCH 717454) in patients with advanced colorectal cancer. Cancer medicine, 3(4), pp.988-997.
136. Lin, Y., Liu, H., Waraky, A., Haglund, F., Agarwal, P., Jernberg‐Wiklund, H., Warsito, D. and Larsson, O., 2017. SUMO‐modified insulin‐like growth factor 1 receptor (IGF‐1R) increases cell cycle progression and cell proliferation. Journal of cellular physiology, 232(10), pp.2722-2730.
137. Liu, X., LoRusso, P., Mita, M., Piha-Paul, S., Hong, D.S., Fu, S., McQuinn, L., Asatiani, E., Doyle, L.A., Chen, H.X. and Hess, K.R., 2014. Incidence of mucositis in patients treated with temsirolimus-based regimens and correlation to treatment response. The oncologist, 19(4), p.426.
138. Lloret, M., Lara, P.C., Bordón, E., Pinar, B., Rey, A., Falcón, O., Molano, F. and Hernández, M.A., 2007. IGF-1R expression in localized cervical carcinoma patients treated by radiochemotherapy. Gynecologic oncology, 106(1), pp.8-11.
139. Longo, V.D. and Finch, C.E., 2003. Evolutionary medicine: from dwarf model systems to healthy centenarians?. Science, 299(5611), pp.1342-1346.
140. Lopez, T. and Hanahan, D., 2002. Elevated levels of IGF-1 receptor convey invasive and metastatic capability in a mouse model of pancreatic islet tumorigenesis. Cancer cell, 1(4), pp.339-353.
141. Macaulay, V.M., Middleton, M.R., Eckhardt, S.G., Rudin, C.M., Juergens, R.A., Gedrich, R., Gogov, S., McCarthy, S., Poondru, S., Stephens, A.W. and Gadgeel, S.M., 2016. Phase I dose-escalation study of linsitinib (OSI-906) and erlotinib in patients with advanced solid tumors. Clinical Cancer Research, 22(12), pp.2897-2907.
142. Magbanua, M.J.M., Roy, R., Sosa, E.V., Weinberg, V., Federman, S., Mattie, M.D., Hughes-Fulford, M., Simko, J., Shinohara, K., Haqq, C.M. and Carroll, P.R., 2011. Gene expression and biological pathways in tissue of men with prostate cancer in a randomized clinical trial of lycopene and fish oil supplementation. PloS one, 6(9), p.e24004.
143. Mañes, S., Mira, E., Gómez-Mouton, C., Zhao, Z.J., Lacalle, R.A. and Martínez-A, C., 1999. Concerted activity of tyrosine phosphatase SHP-2 and focal adhesion kinase in regulation of cell motility. Molecular and cellular biology, 19(4), pp.3125-3135.
144. Marshall, J., 2006. Clinical implications of the mechanism of epidermal growth factor receptor inhibitors. Cancer, 107(6), pp.1207-1218.
145. MARSHALL, R.N., UNDERWOOD, L.E., VOINA, S.J., FOUSHEE, D.B. and VAN WYK, J.J., 1974. Characterization of the insulin and somatomedin-C receptors in human placental cell membranes. The Journal of Clinical Endocrinology & Metabolism, 39(2), pp.283-292.
146. McCaffery, I., Tudor, Y., Deng, H., Tang, R., Suzuki, S., Badola, S., Kindler, H.L., Fuchs, C.S., Loh, E., Patterson, S.D. and Chen, L., 2013. Putative predictive biomarkers of survival in patients with metastatic pancreatic adenocarcinoma treated with gemcitabine and ganitumab, an IGF1R inhibitor. Clinical Cancer Research, 19(15), pp.4282-4289.
147. Menting, J.G., Lawrence, C.F., Kong, G.K.W., Margetts, M.B., Ward, C.W. and Lawrence, M.C., 2015. Structural congruency of ligand binding to the insulin and insulin/type 1 insulin-like growth factor hybrid receptors. Structure, 23(7), pp.1271-1282.
148. Menu, E., Jernberg‐Wiklund, H., De Raeve, H., De Leenheer, E., Coulton, L., Gallagher, O., Van Valckenborgh, E., Larsson, O., Axelson, M., Nilsson, K. and Van Camp, B., 2007. Targeting the IGF‐1R using picropodophyllin in the therapeutical 5T2MM mouse model of multiple myeloma: beneficial effects on tumor growth, angiogenesis, bone disease and survival. International journal of cancer, 121(8), pp.1857-1861.
149. Mo, Y.Y., Yu, Y., Theodosiou, E., Ee, P.R. and Beck, W.T., 2005. A role for Ubc9 in tumorigenesis. Oncogene, 24(16), pp.2677-2683.
150. Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G. and Prisma Group, 2009. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS med*, *6*(7), p.e1000097.
151. Mooney, S.M., Grande, J.P., Salisbury, J.L. and Janknecht, R., 2010. Sumoylation of p68 and p72 RNA helicases affects protein stability and transactivation potential. Biochemistry, 49(1), pp.1-10.
152. Moschos, S.J., Jukic, D.M., Athanassiou, C., Bhargava, R., Dacic, S., Wang, X., Kuan, S.F., Fayewicz, S.L., Galambos, C., Acquafondata, M. and Dhir, R., 2010. Expression analysis of Ubc9, the single small ubiquitin-like modifier (SUMO) E2 conjugating enzyme, in normal and malignant tissues. Human pathology, 41(9), pp.1286-1298.
153. Murakami H, Doi T, Yamamoto N, Watanabe J, Boku N, Fuse N, et al. Phase 1 study of ganitumab (AMG 479), a fully human monoclonal antibody against the insulin-like growth factor receptor type I (IGF1R), in Japanese patients with advanced solid tumors. Cancer Chemother Pharmacol. 2012;70:407–14.
154. Myal, Y., Shiu, R.P., Bhaumick, B. and Bala, M., 1984. Receptor binding and growth-promoting activity of insulin-like growth factors in human breast cancer cells (T-47D) in culture. Cancer research, 44(12 Part 1), pp.5486-5490.
155. Myhre, H.O., 1997. Surgical treatment of aorto-iliac atherosclerosis. Acta chirurgica Scandinavica, 143(1), pp.15-20.
156. Naing, A., LoRusso, P., Fu, S., Hong, D.S., Anderson, P., Benjamin, R.S., Ludwig, J., Chen, H.X., Doyle, L.A. and Kurzrock, R., 2012. Insulin growth factor-receptor (IGF-1R) antibody cixutumumab combined with the mTOR inhibitor temsirolimus in patients with refractory Ewing's sarcoma family tumors. Clinical Cancer Research, 18(9), pp.2625-2631.
157. Nickerson, T., Huynh, H. and Pollak, M., 1997. Insulin-like growth factor binding protein-3 induces apoptosis in MCF7 breast cancer cells. Biochemical and biophysical research communications, 237(3), pp.690-693.
158. Nurwidya, F., Andarini, S., Takahashi, F., Syahruddin, E. and Takahashi, K., 2016. Implications of insulin-like growth factor 1 receptor activation in lung cancer. The Malaysian journal of medical sciences: MJMS, 23(3), p.9.
159. O’Byrne, K.J., Edwards, J.G. and Waller, D.A., 2004. Clinico-pathological and biological prognostic factors in pleural malignant mesothelioma. Lung Cancer, 45, pp.S45-S48.
160. Ochnik, A.M. and Baxter, R.C., 2016. Combination therapy approaches to target insulin-like growth factor receptor signaling in breast cancer. Endocrine-related cancer, 23(11), pp.R527-R550.
161. Oliveira, S., Schiffelers, R.M., Storm, G., Henegouwen, P.M.P. and Roovers, R.C., 2009. Crosstalk between epidermal growth factor receptor-and insulin-like growth factor-1 receptor signaling: implications for cancer therapy. Current cancer drug targets, 9(6), pp.748-760.
162. Olmos, D., Postel-Vinay, S., Molife, L.R., Okuno, S.H., Schuetze, S.M., Paccagnella, M.L., Batzel, G.N., Yin, D., Pritchard-Jones, K., Judson, I. and Worden, F.P., 2010. Safety, pharmacokinetics, and preliminary activity of the anti-IGF-1R antibody figitumumab (CP-751,871) in patients with sarcoma and Ewing's sarcoma: a phase 1 expansion cohort study. The lancet oncology, 11(2), pp.129-135.
163. Osher, E. and Macaulay, V.M., 2019. Therapeutic targeting of the IGF axis. *Cells*, *8*(8), p.895.
164. Overholser, J., Ambegaokar, K.H., Eze, S.M., Sanabria-Figueroa, E., Nahta, R., Bekaii-Saab, T. and Kaumaya, P.T., 2015. Anti-tumor effects of peptide therapeutic and peptide vaccine antibody co-targeting HER-1 and HER-2 in esophageal cancer (EC) and HER-1 and IGF-1R in triple-negative breast cancer (TNBC). Vaccines, 3(3), pp.519-543.
165. Packham, S., Warsito, D., Lin, Y., Sadi, S., Karlsson, R., Sehat, B. and Larsson, O., 2015. Nuclear translocation of IGF-1R via p150 Glued and an importin-β/RanBP2-dependent pathway in cancer cells. Oncogene, 34(17), pp.2227-2238.
166. Palmerini, E., Benassi, M.S., Quattrini, I., Pazzaglia, L., Donati, D., Benini, S., Gamberi, G., Gambarotti, M., Picci, P. and Ferrari, S., 2015. Prognostic and predictive role of CXCR4, IGF-1R and Ezrin expression in localized synovial sarcoma: is chemotaxis important to tumor response?. Orphanet journal of rare diseases, 10(1), p.6.
167. Pappo, A.S., Patel, S.R., Crowley, J., Reinke, D.K., Kuenkele, K.P., Chawla, S.P., Toner, G.C., Maki, R.G., Meyers, P.A., Chugh, R. and Ganjoo, K.N., 2011. R1507, a monoclonal antibody to the insulin-like growth factor 1 receptor, in patients with recurrent or refractory Ewing sarcoma family of tumors: results of a phase II Sarcoma Alliance for Research through Collaboration study. Journal of Clinical Oncology, 29(34), p.4541.
168. Peralta, E.A., Brewer, A.T., Louis, S. and Dunnington, G.L., 2009. Vitamin E increases biomarkers of estrogen stimulation when taken with tamoxifen. Journal of Surgical Research, 153(1), pp.143-147.
169. Peralta, E.A., Murphy, L.L., Minnis, J., Louis, S. and Dunnington, G.L., 2009. American Ginseng inhibits induced COX-2 and NFKB activation in breast cancer cells. Journal of Surgical Research, 157(2), pp.261-267.
170. Peralta, E.A., Viegas, M.L., Louis, S., Engle, D.L. and Dunnington, G.L., 2006. Effect of vitamin E on tamoxifen-treated breast cancer cells. Surgery, 140(4), pp.607-615.
171. Perez, E.A., Jenkins, R.B., Dueck, A.C., Wiktor, A.E., Bedroske, P.P., Anderson, S.K., Ketterling, R.P., Sukov, W.R., Kanehira, K., Chen, B. and Geiger, X.J., 2011. C-MYC alterations and association with patient outcome in early-stage HER2-positive breast cancer from the north central cancer treatment group N9831 adjuvant trastuzumab trial. Journal of clinical oncology, 29(6), p.651.
172. Pian, L., Wen, X., Kang, L., Li, Z., Nie, Y., Du, Z., Yu, D., Zhou, L., Jia, L., Chen, N. and Li, D., 2018. Targeting the IGF1R pathway in breast cancer using antisense lncRNA-mediated promoter cis competition. Molecular Therapy-Nucleic Acids, 12, pp.105-117.
173. Piccart-Gebhart, M., Holmes, E., Baselga, J., De Azambuja, E., Dueck, A.C., Viale, G., Zujewski, J.A., Goldhirsch, A., Armour, A., Pritchard, K.I. and McCullough, A.E., 2016. Adjuvant lapatinib and trastuzumab for early human epidermal growth factor receptor 2–positive breast cancer: results from the randomized phase III adjuvant lapatinib and/or trastuzumab treatment optimization trial. Journal of clinical oncology, 34(10), p.1034.
174. Pollak, M., 2001. Insulin-like growth factors and prostate cancer. Epidemiologic reviews, 23(1), pp.59-66.
175. Pollak, M.N., Perdue, J.F., Margolese, R.G., Baer, K. and Richard, M., 1987. Presence of somatomedin receptors on primary human breast and colon carcinomas. Cancer letters, 38(1-2), pp.223-230.
176. Pollak, M.N., Schernhammer, E.S. and Hankinson, S.E., 2004. Insulin-like growth factors and neoplasia. Nature Reviews Cancer, 4(7), pp.505-518.
177. Poręba, E. and Durzyńska, J., 2020. Nuclear localization and actions of the insulin-like growth factor 1 (IGF-1) system components: Transcriptional regulation and DNA damage response. Mutation Research/Reviews in Mutation Research, p.108307.
178. Qian, J., Luo, Y., Gu, X. and Wang, X., 2013. Inhibition of SENP6-induced radiosensitization of human hepatocellular carcinoma cells by blocking radiation-induced NF-κB activation. Cancer Biotherapy and Radiopharmaceuticals, 28(3), pp.196-200.
179. Rajan, A., Carter, C.A., Berman, A., Cao, L., Kelly, R.J., Thomas, A., Khozin, S., Chavez, A.L., Bergagnini, I., Scepura, B. and Szabo, E., 2014. Cixutumumab for patients with recurrent or refractory advanced thymic epithelial tumours: a multicentre, open-label, phase 2 trial. The lancet oncology, 15(2), pp.191-200.
180. Regad, T., 2015. Targeting RTK signaling pathways in cancer. Cancers, 7(3), pp.1758-1784.
181. Riedemann, J. and Macaulay, V.M., 2006. IGF1R signalling and its inhibition. Endocrine-related cancer, 13(Supplement\_1), pp.S33-S43.
182. Riesterer, O., Yang, Q., Raju, U., Torres, M., Molkentine, D., Patel, N., Valdecanas, D., Milas, L. and Ang, K.K., 2011. Combination of anti-IGF-1R antibody A12 and ionizing radiation in upper respiratory tract cancers. International Journal of Radiation Oncology\* Biology\* Physics, 79(4), pp.1179-1187.
183. Rinderknecht, E. and Humbel, R.E., 1978. The amino acid sequence of human insulin-like growth factor I and its structural homology with proinsulin. Journal of Biological Chemistry, 253(8), pp.2769-2776.
184. Rosen, N., Yee, D., Lippman, M.E., Paik, S. and Cullen, K.J., 1991. Insulin-like growth factors in human breast cancer. Breast cancer research and treatment, 18(1), pp.S55-
185. Rubin, J.B., Shia, M.A. and Pilch, P.F., 1983. Stimulation of tyrosine-specific phosphorylation in vitro by insulin-like growth factor I. Nature, 305(5933), pp.438-440.
186. Ryan, C.J., Haqq, C.M., Simko, J., Nonaka, D.F., Chan, J.M., Weinberg, V., Small, E.J. and Goldfine, I.D., 2007, March. Expression of insulin-like growth factor-1 receptor in local and metastatic prostate cancer. In Urologic Oncology: Seminars and Original Investigations (Vol. 25, No. 2, pp. 134-140). Elsevier.
187. Sachdev, D., Li, S.L., Hartell, J.S., Fujita-Yamaguchi, Y., Miller, J.S. and Yee, D., 2003. A chimeric humanized single-chain antibody against the type I insulin-like growth factor (IGF) receptor renders breast cancer cells refractory to the mitogenic effects of IGF-I. Cancer research, 63(3), pp.627-635.
188. Saikali, Z., Setya, H., Singh, G. and Persad, S., 2008. Role of IGF-1/IGF-1R in regulation of invasion in DU145 prostate cancer cells. Cancer cell international, 8(1), p.10.
189. Sallmyr, A., Fan, J. and Rassool, F.V., 2008. Genomic instability in myeloid malignancies: increased reactive oxygen species (ROS), DNA double strand breaks (DSBs) and error-prone repair. Cancer letters, 270(1), pp.1-9.
190. Salmon, W.D. and Daughaday, W.H., 1957. A hormonally controlled serum factor which stimulates sulfate incorporation by cartilage in vitro. The Journal of laboratory and clinical medicine, 49(6), pp.825-836.
191. Sarfstein, R., Pasmanik-Chor, M., Yeheskel, A., Edry, L., Shomron, N., Warman, N., Wertheimer, E., Maor, S., Shochat, L. and Werner, H., 2012. Insulin-like growth factor-I receptor (IGF-IR) translocates to nucleus and autoregulates IGF-IR gene expression in breast cancer cells. Journal of Biological Chemistry, 287(4), pp.2766-2776.
192. Scartozzi, M., Bianconi, M., Maccaroni, E., Giampieri, R., Berardi, R. and Cascinu, S., 2010. Dalotuzumab, a recombinant humanized mAb targeted against IGFR1 for the treatment of cancer. Curr Opin Mol Ther, 12(3), pp.361-371.
193. Schedlich, L.J., Le Page, S.L., Firth, S.M., Briggs, L.J., Jans, D.A. and Baxter, R.C., 2000. Nuclear import of insulin-like growth factor-binding protein-3 and-5 is mediated by the importin β subunit. Journal of Biological Chemistry, 275(31), pp.23462-23470.
194. Schlessinger, J., 2000. Cell signaling by receptor tyrosine kinases. Cell, 103(2), pp.211-225.
195. Schwartz, G.K., Tap, W.D., Qin, L.X., Livingston, M.B., Undevia, S.D., Chmielowski, B., Agulnik, M., Schuetze, S.M., Reed, D.R., Okuno, S.H. and Ludwig, J.A., 2013. Cixutumumab and temsirolimus for patients with bone and soft-tissue sarcoma: a multicentre, open-label, phase 2 trial. The lancet oncology, 14(4), pp.371-38
196. Scotlandi, K., Manara, M.C., Nicoletti, G., Lollini, P.L., Lukas, S., Benini, S., Croci, S., Perdichizzi, S., Zambelli, D., Serra, M. and García-Echeverría, C., 2005. Antitumor activity of the insulin-like growth factor-I receptor kinase inhibitor NVP-AEW541 in musculoskeletal tumors. Cancer research, 65(9), pp.3868-3876.
197. Sehat, B., Tofigh, A., Lin, Y., Trocmé, E., Liljedahl, U., Lagergren, J. and Larsson, O., 2010. SUMOylation mediates the nuclear translocation and signaling of the IGF-1 receptor. Sci. Signal., 3(108), pp.ra10-ra10.
198. Sell, C., Rubini, M., Rubin, R., Liu, J.P., Efstratiadis, A. and Baserga, R., 1993. Simian virus 40 large tumor antigen is unable to transform mouse embryonic fibroblasts lacking type 1 insulin-like growth factor receptor. Proceedings of the National Academy of Sciences, 90(23), pp.11217-11221.
199. Sharma, G.N., Dave, R., Sanadya, J., Sharma, P. and Sharma, K.K., 2010. Various types and management of breast cancer: an overview. *Journal of advanced pharmaceutical technology & research*, *1*(2), p.109.
200. Siegel, R., Naishadham, D. and Jemal, A., 2012. Cancer statistics, 2012. CA: a cancer journal for clinicians, 62(1), pp.10-29.
201. Simpson, A., Petnga, W., Macaulay, V.M., Weyer-Czernilofsky, U. and Bogenrieder, T., 2017. Insulin-like growth factor (IGF) pathway targeting in cancer: role of the IGF axis and opportunities for future combination studies. *Targeted Oncology*, *12*(5), pp.571-597.
202. Singh, I., Amin, H., Rah, B. and Goswami, A., 2013. Targeting EGFR and IGF 1R: a promising combination therapy for metastatic cancer. Front Biosci (Schol Ed), 5, pp.231-246.
203. Solomon-Zemler, R., Sarfstein, R. and Werner, H., 2017. Nuclear insulin-like growth factor-1 receptor (IGF1R) displays proliferative and regulatory activities in non-malignant cells. PloS one, 12(9).
204. Song, J.G., Xie, H.H., Li, N., Wu, K., Qiu, J.G., Shen, D.M. and Huang, C.J., 2015. RETRACTED ARTICLE: SUMO-specific protease 6 promotes gastric cancer cell growth via deSUMOylation of FoxM1. Tumor Biology, 36(12), pp.9865-9871.
205. Songdej, N. and von Mehren, M., 2014. GIST treatment options after tyrosine kinase inhibitors. Current treatment options in oncology, 15(3), pp.493-506.
206. Sroka, I.C., McDaniel, K., Nagle, R.B. and Bowden, G.T., 2008. Differential localization of MT1‐MMP in human prostate cancer tissue: Role of IGF‐1R in MT1‐MMP expression. The Prostate, 68(5), pp.463-476.
207. Suda, K., Mizuuchi, H., Sato, K., Takemoto, T., Iwasaki, T. and Mitsudomi, T., 2014. The insulin‐like growth factor 1 receptor causes acquired resistance to erlotinib in lung cancer cells with the wild‐type epidermal growth factor receptor. International journal of cancer, 135(4), pp.1002-1006.
208. Sun, H.Z., Wu, S.F. and Tu, Z.H., 2001. Blockage of IGF-1R signaling sensitizes urinary bladder cancer cells to mitomycin-mediated cytotoxicity. Cell research, 11(2), pp.107-115.
209. Surmacz, E., 2000. Function of the IGF-I receptor in breast cancer. Journal of mammary gland biology and neoplasia, 5(1), pp.95-105.
210. Tahimic, C.G., Wang, Y. and Bikle, D.D., 2013. Anabolic effects of IGF-1 signaling on the skeleton. Frontiers in endocrinology, 4, p.6.
211. Tamimi, R.M., Colditz, G.A., Wang, Y., Collins, L.C., Hu, R., Rosner, B., Irie, H.Y., Connolly, J.L. and Schnitt, S.J., 2011. Expression of IGF1R in normal breast tissue and subsequent risk of breast cancer. Breast cancer research and treatment, 128(1), pp.243-250.
212. Tang, J., Flomenberg, P., Harshyne, L., Kenyon, L. and Andrews, D.W., 2005. Glioblastoma patients exhibit circulating tumor-specific CD8+ T cells. Clinical Cancer Research, 11(14), pp.5292-5299.
213. Tap, W.D., Demetri, G., Barnette, P., Desai, J., Kavan, P., Tozer, R., Benedetto, P.W., Friberg, G., Deng, H., McCaffery, I. and Leitch, I., 2012. Phase II study of ganitumab, a fully human anti-type-1 insulin-like growth factor receptor antibody, in patients with metastatic Ewing family tumors or desmoplastic small round cell tumors. Clin Oncol, 30(15), pp.1849-1856.
214. Tetri, S., Hakala, J., Juvela, S., Saloheimo, P., Pyhtinen, J., Rusanen, H., Savolainen, E.R. and Hillbom, M., 2008. Safety of low-dose subcutaneous enoxaparin for the prevention of venous thromboembolism after primary intracerebral haemorrhage. Thrombosis research, 123(2), pp.206-212.
215. Tezuka, M., Watanabe, H., Nakamura, S., Yu, D., Aung, W., Sasaki, T., Shibuya, H. and Miura, M., 2001. Antiapoptotic activity is dispensable for insulin-like growth factor I receptor-mediated clonogenic radioresistance after γ-irradiation. Clinical cancer research, 7(10), pp.3206-3214.
216. Toi, M., ., Iwata, H., Fujiwara, Y., Ito, Y., Nakamura, S., Tokuda, Y., Taguchi, T., Rai, Y., Aogi, K., Arai, T. and Watanabe, J., 2009. Lapatinib monotherapy in patients with relapsed, advanced, or metastatic breast cancer: efficacy, safety, and biomarker results from Japanese patients phase II studies. British journal of cancer, 101(10), pp.1676-1682.
217. Tolcher, A.W., Patnaik, A., Till, E., Takimoto, C.H., Papadopoulos, K.P., Massard, C., Mery-Mignard, D., Deslandes, A., Ozoux, M. and Soria, J., 2008. A phase I study of AVE1642, a humanized monoclonal antibody IGF-1R (insulin like growth factor1 receptor) antagonist, in patients (pts) with advanced solid tumor (ST). Journal of Clinical Oncology, 26(15\_suppl), pp.3582-3582.
218. Travis, W.D., 2011. Pathology of lung cancer. Clinics in chest medicine, 32(4), pp.669-692.
219. Troncoso, R., Díaz‐Elizondo, J., Espinoza, S.P., Navarro‐Marquez, M.F., Oyarzún, A.P., Riquelme, J.A., Garcia‐Carvajal, I., Díaz‐Araya, G., García, L., Hill, J.A. and Lavandero, S., 2013. Regulation of cardiac autophagy by insulin‐like growth factor 1. IUBMB life, 65(7), pp.593-601.
220. Turner, B.C., Haffty, B.G., Narayanan, L., Yuan, J., Havre, P.A., Gumbs, A.A., Kaplan, L., Burgaud, J.L., Carter, D., Baserga, R. and Glazer, P.M., 1997. Insulin-like growth factor-I receptor overexpression mediates cellular radioresistance and local breast cancer recurrence after lumpectomy and radiation. Cancer research, 57(15), pp.3079-3083.
221. Ullrich, A., Gray, A., Tam, A.W., Yang‐Feng, T., Tsubokawa, M., Collins, C., Henzel, W., Le Bon, T., Kathuria, S. and Chen, E., 1986. Insulin‐like growth factor I receptor primary structure: comparison with insulin receptor suggests structural determinants that define functional specificity. The EMBO journal, 5(10), pp.2503-2512.
222. Valenciano, A., Henríquez-Hernández, L.A., Moreno, M., Lloret, M. and Lara, P.C., 2012. Role of IGF-1 receptor in radiation response. Translational oncology, 5(1), pp.1-9.
223. Vanamala, J., Reddivari, L., Radhakrishnan, S. and Tarver, C., 2010. Resveratrol suppresses IGF-1 induced human colon cancer cell proliferation and elevates apoptosis via suppression of IGF-1R/Wnt and activation of p53 signaling pathways. *BMC cancer*, *10*(1), p.238.
224. van Gaal, J.C., Roeffen, M.H., Flucke, U.E., van der Laak, J.A., van der Heijden, G., de Bont, E.S., Suurmeijer, A.J., Versleijen-Jonkers, Y.M. and van der Graaf, W.T., 2013. Simultaneous targeting of insulin-like growth factor-1 receptor and anaplastic lymphoma kinase in embryonal and alveolar rhabdomyosarcoma: a rational choice. European journal of cancer, 49(16), pp.3462-3470.
225. Villalva, C., Trempat, P., Greenland, C., Thomas, C., Girard, J.P., Moebius, F., Delsol, G. and Brousset, P., 2002. Isolation of differentially expressed genes in NPM‐ALK‐positive anaplastic large cell lymphoma. British journal of haematology, 118(3), pp.791-798.
226. Vivanco, I. and Sawyers, C.L., 2002. The phosphatidylinositol 3-kinase–AKT pathway in human cancer. Nature Reviews Cancer, 2(7), pp.489-501.
227. Vogelzang, N.J., Rusthoven, J.J., Symanowski, J., Denham, C., Kaukel, E., Ruffie, P., Gatzemeier, U., Boyer, M., Emri, S., Manegold, C. and Niyikiza, C., 2003. Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. Journal of clinical oncology, 21(14), pp.2636-2644.
228. von Mehren, M., Britten, C.D., Pieslor, P., Saville, W., Vassos, A., Harris, S., Galluppi, G.R., Darif, M., Wainberg, Z.A., Cohen, R.B. and Leong, S., 2014. A phase 1, open-label, dose-escalation study of BIIB022 (anti-IGF-1R monoclonal antibody) in subjects with relapsed or refractory solid tumors. Investigational new drugs, 32(3), pp.518-525.
229. Waraky, A., Akopyan, K., Parrow, V., Strömberg, T., Axelson, M., Abrahmsén, L., Lindqvist, A., Larsson, O. and Aleem, E., 2014. Picropodophyllin causes mitotic arrest and catastrophe by depolymerizing microtubules via insulin-like growth factor-1 receptor-independent mechanism. Oncotarget, 5(18), p.8379.
230. Waraky, A., Lin, Y., Warsito, D., Haglund, F., Aleem, E. and Larsson, O., 2017. Nuclear insulin-like growth factor 1 receptor phosphorylates proliferating cell nuclear antigen and rescues stalled replication forks after DNA damage. Journal of Biological Chemistry, 292(44), pp.18227-18239.
231. Ward, C.W., Garrett, T.P., Lou, M., Mckern, N.M., Adams, T.E., Elleman, T.C., Hoyne, P.A., Frenkel, M.J., Cosgrove, L.J., Lovrecz, G.O. and Sparrow, L.G., 2013. The Structure of the Type 1 Insulin-Like Growth Factor Receptor. In Madame Curie Bioscience Database [Internet]. Landes Bioscience.
232. Warsito, D., Lin, Y., Gnirck, A.C., Sehat, B. and Larsson, O., 2016. Nuclearly translocated insulin-like growth factor 1 receptor phosphorylates histone H3 at tyrosine 41 and induces SNAI2 expression via Brg1 chromatin remodeling protein. Oncotarget, 7(27), p.42288.
233. Warsito, D., Sjöström, S., Andersson, S., Larsson, O. and Sehat, B., 2012. Nuclear IGF1R is a transcriptional co‐activator of LEF1/TCF. EMBO reports, 13(3), pp.244-250.
234. Watts, F.Z., 2013. Starting and stopping SUMOylation. Chromosoma, 122(6), pp.451-463.
235. Werner, H., Sarfstein, R. and Bruchim, I., 2019. Investigational IGF1R inhibitors in early stage clinical trials for cancer therapy. Expert opinion on investigational drugs, 28(12), pp.1101-1112.
236. Wilkinson, K.A. and Henley, J.M., 2010. Mechanisms, regulation and consequences of protein SUMOylation. Biochemical Journal, 428(2), pp.133-145.
237. Worrall, C., Nedelcu, D., Serly, J., Suleymanova, N., Oprea, I., Girnita, A. and Girnita, L., 2013. Novel mechanisms of regulation of IGF-1R action: functional and therapeutic implications. Pediatric endocrinology reviews: PER, 10(4), pp.473-484.
238. Wu, J., Haugk, K. and Plymate, S.R., 2003. Activation of pro-apoptotic p38-MAPK pathway in the prostate cancer cell line M12 expressing a truncated IGF-IR. Hormone and metabolic research, 35(11/12), pp.751-757.
239. Wu, Y.C., Zhu, M. and Robertson, D.M., 2012. Novel nuclear localization and potential function of insulin-like growth factor-1 receptor/insulin receptor hybrid in corneal epithelial cells. PLoS One, 7(8).
240. Yang, C., Zhang, Y., Chen, Y., Ragaller, F., Liu, M., Corvigno, S., Dahlstrand, H., Carlson, J., Chen, Z., Näsman, A. and Waraky, A., 2020. Nuclear IGF1R interact with PCNA to preserve DNA replication after DNA-damage in a variety of human cancers. PloS one, 15(7), p.e0236291.
241. Yeh, E.T., 2009. SUMOylation and De-SUMOylation: wrestling with life's processes. Journal of Biological Chemistry, 284(13), pp.8223-8227.
242. Yerushalmi, R., Gelmon, K.A., Leung, S., Gao, D., Cheang, M., Pollak, M., Turashvili, G., Gilks, B.C. and Kennecke, H., 2012. Insulin-like growth factor receptor (IGF-1R) in breast cancer subtypes. Breast cancer research and treatment, 132(1), pp.131-142.
243. Yi, Y.W., Hong, W., Kang, H.J., Kim, H.J., Zhao, W., Wang, A., Seong, Y.S. and Bae, I., 2013. Inhibition of the PI 3K/AKT pathway potentiates cytotoxicity of EGFR kinase inhibitors in triple‐negative breast cancer cells. Journal of cellular and molecular medicine, 17(5), pp.648-656.
244. Yin, S., Girnita, A., Strömberg, T., Khan, Z., Andersson, S., Zheng, H., Ericsson, C., Axelson, M., Nistér, M., Larsson, O. and Ekström, T.J., 2010. Targeting the insulin-like growth factor-1 receptor by picropodophyllin as a treatment option for glioblastoma. Neuro-oncology, 12(1), pp.19-27.
245. Youngren, J.F., Gable, K., Penaranda, C., Maddux, B.A., Zavodovskaya, M., Lobo, M., Campbell, M., Kerner, J. and Goldfine, I.D., 2005. Nordihydroguaiaretic acid (NDGA) inhibits the IGF-1 and c-erbB2/HER2/neu receptors and suppresses growth in breast cancer cells. Breast cancer research and treatment, 94(1), p.37.
246. Yu, H. and Rohan, T., 2000. Role of the insulin-like growth factor family in cancer development and progression. Journal of the National Cancer Institute, 92(18), pp.1472-1489.
247. Yuan, J., Yin, Z., Tao, K., Wang, G. and Gao, J., 2018. Function of insulin‑like growth factor 1 receptor in cancer resistance to chemotherapy. Oncology letters, 15(1), pp.41-47.
248. Yuan, Y., Zhou, X., Song, J., Qiu, X., Li, J., Ye, L., Meng, X. and Xia, D., 2008. Expression and clinical significance of epidermal growth factor receptor and type 1 insulin-like growth factor receptor in nasopharyngeal carcinoma. Annals of Otology, Rhinology & Laryngology, 117(3), pp.192-200.
249. Zeman, M.K. and Cimprich, K.A., 2014. Causes and consequences of replication stress. Nature cell biology, 16(1), pp.2-9.
250. Zhang, H., Kuai, X., Ji, Z., Li, Z. and Shi, R., 2013. Over-expression of small ubiquitin-related modifier-1 and sumoylated p53 in colon cancer. Cell biochemistry and biophysics, 67(3), pp.1081-1087.
251. Zhang, J., Huang, F.F., Wu, D.S., Li, W.J., Zhan, H.E., Peng, M.Y., Fang, P., Cao, P.F., Zhang, M.M., Zeng, H. and Chen, F.P., 2015. SUMOylation of insulin-like growth factor 1 receptor, promotes proliferation in acute myeloid leukemia. Cancer letters, 357(1), pp.297-306.
252. Zhao, S., Qiu, Z., He, J., Li, L. and Li, W., 2014. Insulin-like growth factor receptor 1 (IGF1R) expression and survival in non-small cell lung cancer patients: a meta-analysis. International journal of clinical and experimental pathology, 7(10), p.6694.
253. Zimmerman, R.A., 1991. Imaging of adult central nervous system primary malignant gliomas. Staging and follow‐up. Cancer, 67(S4), pp.1278-1283.
254. Zucali, P.A., De Pas, T., Palmieri, G., Favaretto, A., Chella, A., Tiseo, M. and Caruso, M., 2018. Phase II study of everolimus in patients with thymoma and thymic carcinoma previously treated with cisplatin-based chemotherapy. J Clin Oncol, 36(4), pp.342-249.
255. Zwick, E., Bange, J. and Ullrich, A., 2002. Receptor tyrosine kinases as targets for anticancer drugs. Trends in molecular medicine, 8(1), pp.17-23.

APPENDIX 1: Table showing clinical trials involving IGF-1R and Cancer (searched on 16/09/2020)

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Sr#** | **Status** | **Study title** | **Target** | **Interventions** | **Phase** | **Biomarker/ therapeutic** | **Reference** |
| 1 | NCT00763607  Completed | Retrospective Study Evaluating IGF1R And p95HER2 as Prognostic Factors in Non-Small Cell Lung Cancer (NSCLC) | Non-small cell lung cancer | Genetic: Protein expression by immunohistochemistry and immunofluorescence |  | Biomarker |  |
| 2 | NCT00882674  Completed | A Study to Evaluate the Biological Activity of R1507 in Women with Operable Breast Cancer | Breast cancer | Drug: RG1507 | I | Therapeutic |  |
| 3 | NCT00774878  Completed | Study of AVE1642 (IGF-1R/CD221) in Combination With Fulvestrant (Faslodex®) in Postmenopausal Patients With Advanced Hormono-dependent Breast Cancer | Breast cancer | Drug:AVE1642  Drug: Fulvestrant | II | Therapeutic |  |
| 4 | NCT01013506  Completed | Phase 2, Endocrine Therapy + OSI-906 With or Without Erlotinib for Hormone-sensitive Metastatic Breast Cancer | Breast cancer | IGF1R inhibitor OSI-906, Erlotinib hydrochloride,Goserelin, letrozol | II | Therapeutic |  |
| 5 | NCT00555724 | Phase 1 Study of BIIB022 (Anti-IGF-1R Monoclonal Antibody) in relapsed/refractory Solid Tumors | Refectory Solid tumors | Drug: BIIB022 | I | Therapeutic | von Mehren et al., 2014 |
| 6 | NCT01779336  Suspended | Clinical Study of Oral IGF-1R inhibitor in subjects with advanced refractory Solid Tumors | Refectory Solid tumors | Drug: PL225B | I | Therapeutic |  |
| 7 | NCT02711865 | Predictive Biomarkers for IGF1R Targeted Therapy in Ovarian Cancer | ovarian cancer | Biological: IGF1R antibody MK0646  Other: Saline solution |  | Therapeutic |  |
| 8 | NCT01466647  Completed | A Study of the IGF-1R Inhibitor AXL1717 in Combination With Gemcitabine HCL and Carboplatin to Treat Non-small-cell Lung Cancer (NSCLC) | Non-small cell lung cancer | Drug: AXL1717 | I | Therapeutic |  |
| 9 | NCT00898898  Completed | Studying Tissues Samples From Women With Breast Cancer Who Were Treated on Clinical Trial NCCTG-N9831 | Breast cancer |  |  | Biomarker | Perez et al., 2011 |
| 10 | NCT02719041  Unknown | Predictive Biomarkers for IGF1R Targeted Therapy in Ovarian Cancer: a Retrospective Study | ovarian  cancer | Other: Immunohistochemistry staining method |  | Biomarker |  |
| 11 | NCT00718523  Terminated | Study of Adding AMG 479 to First Line Chemotherapy in Patients With Optimally Debulked Epithelial Ovarian Cancer | Epithelial ovarian cancer | Drug: AMG 479Drug: AMG 479 Placebo | II | Therapeutic |  |
| 12 | NCT02045368  Completed | Study of Insulin-like Growth Factor (IGF)-Methotrexate Conjugate in the Treatment of Advanced Tumors Expressing IGF-1R | Various types of cancer | Drug: IGF-Methotrexate conjugate | I | Therapeutic |  |
| 13 | NCT02780401  Active | Vaccine Therapy in Preventing Cancer Recurrence in Patients With Non-Metastatic, Node Positive, HER2 Negative Breast Cancer That is in Remission (WOKVAC) | Various types of cancers | Other: Laboratory Biomarker Analysis Biological: pUMVC3-IGFBP2-HER2-IGF1R Plasmid DNA Vaccine Biological: Sargramostim | I | Therapeutic |  |
| 14 | NCT00869752  Completed | MK-0646, Etoposide, and Cisplatin in Treating Patients With Extensive-Stage Small Cell Lung Cancer | Small cell lung cancer | Biological: anti IGF1R  recombinant monoclonal antibody MK-0646  Drug: cisplatin  Drug: etoposide | I and II | Therapeutic | Ellis et al., 2014 |
| 15 | NCT00778167 | Erlotinib Hydrochloride With or Without Cixutumumab in Treating Patients With Stage III or Stage IV Non-Small Cell Lung Cancer | Non-small cell lung cancer | Biological: cixutumumabDrug: erlotinib hydrochlorideOther: laboratory biomarker analysis | I and II | Therapeutic |  |
| 16 | NCT00799240  Completed | MK-0646 Insulin Growth Factor 1 Receptor Antibody in Stage IIIb or IV Metastatic Non-Squamous Lung Cancer (IMPACT) | Non-squamous lung cancer | Drug: Arm A: Pemetrexed CisplatinDrug: Arm B Pemetrexed, Cisplatin and MK-0646 | II | Therapeutic | Huang et al., 2016 |
| 17 | NCT01725555  Completed | A Study to Assess the Effect of Food on the Bioavailability of the IGF-1R Inhibitor AXL1717 in Patients With Advanced Malignant Tumors | Solid tumors | Drug: Fasted treatment: AXL1717Drug: Fed treatment: AXL1717 | I | Therapeutic |  |
| 18 | NCT01205685  Terminated | Endocrine Therapy + OSI-906 With or Without Erlotinib for Hormone-Sensitive Metastatic Breast Cancer | Breast cancer | Drug: OSI-906  Drug: Erlotinib  Drug: Letrozole  Drug: Goserelin | II | Therapeutic |  |
| 19 | NCT01062620  Completed | A Dose Escalating Clinical Trial of the IGF-1 Receptor Inhibitor AXL1717 in Patients With Advanced Cancer | Solid tumors | Drug: AXL1717 | I | Therapeutic | Ekman et al., 2016 |
| 20 | NCT00719212  Completed | Study of AMG 479 as Second Line Therapy in Patients With Recurrent Platinum-sensitive Ovarian Cancer | Ovarian cancer | Biological: AMG479 | II | Therapeutic |  |
| 21 | NCT01122199  Completed | Study of RAD001 + AMG479 for Patients With Advanced Solid Tumors | Solid tumors | Drug: RAD001+ AMG479 | I | Therapeutic |  |
| 22 | NCT01479179  Completed | Trastuzumab in Combination With AMG 479 in HER-2 Overexpressing MBC Progressing on Trastuzumab | Breast cancer | Drug: AMG479  Drug: Trastuzumab | I and II | Therapeutic |  |
| 23 | NCT01061788  Completed | A Trial of AMG 479, Everolimus (RAD001) and Panitumumab in Patients With Advanced Cancer - QUILT-3.007 (RAP) | Non-small cell lung cancer | Drug: AMG479, everolimus, panitumumab | I | Therapeutic |  |
| 24 | NCT02134340  Completed | A Safety and Biodistribution Study of [I-124]-CPD-1028 Injection in Solid Tumours | Solid tumors | Drug: [I-124]-CPD-1028 Injection  Biological: CPD-1061 | I | Therapeutic |  |
| 25 | NCT00551213  Completed | A Study to Determine the Activity of Robatumumab (SCH 717454, MK-7454) in Participants With Relapsed or Recurrent Colorectal Cancer (P04721, MK-7454-003) | Colorectal cancer | Biological: robatumumabDrug: irinotecanbiological, Cetuximab, Capecitabine, Folfox, Capeox/xelox, Folfiri | II | Therapeutic | Lin et al., 2014 |
| 26 | NCT00759785  Completed | A Study of Dalotuzumab (MK-0646) in Breast Cancer Patients (MK-0646-013) | Breast cancer | Drug: Dalotuzumab | I | Therapeutic |  |
| 27 | NCT00609141  Completed | IMC-A12 in Treating Young Patients With Relapsed or Refractory Ewing Sarcoma/Peripheral Primitive Neuroectodermal Tumor or Other Solid Tumor | Recurrent Ewing Sarcoma/Peripheral Primitive Neuroectodermal Tumor  Unspecified Childhood Solid Tumor | Biological: cixutumumab  Other: pharmacological study  Other: laboratory biomarker analysis | I | Therapeutic |  |
| 28 | NCT00684983  Completed | Capecitabine and Lapatinib Ditosylate With or Without Cixutumumab in Treating Patients With Previously Treated HER2-Positive Stage IIIB-IV Breast Cancer | Breast cancer | Drug: Capecitabine Biological: CixutumumabDrug: Lapatinib Ditosylate  Other: Quality-of-Life Assessment | II | Therapeutic |  |
| 29 | NCT00880282  Completed | Cixutumumab and Temsirolimus in Treating Younger Patients With Solid Tumors That Have Recurred or Not Responded to Treatment | Solid tumors | Biological: cixutumumabDrug: temsirolimus Other: pharmacological study Other: laboratory biomarker analysis | I | Therapeutic |  |
| 30 | NCT00678769  Completed | Cixutumumab and Temsirolimus in Treating Patients With Locally Advanced or Metastatic Cancer | Malignant Neoplasm | Drug: CixutumumabOther: Laboratory Biomarker Analysis  Other: Pharmacological Study  Drug: Temsirolimus | I | Therapeutic | Liu et al., 2014 |
| 31 | NCT00563680  Completed | QUILT-3.025: A Phase 2 Study of AMG 479 in Relapsed or Refractory Ewing's Family Tumor and Desmoplastic Small Round Cell Tumors | Askin's TumorsDesmoplastic Small Round Cell Tumors  Estraosseous Ewing's TumorEwing's Family Tumor  Ewing's Sarcoma  Primitive Neuroectodermal Tumors (PNETs)  Sarcoma | Drug: AMG479 | II | Therapeutic | Tap et al., 2012 |
| 32 | NCT00560144  Completed | A Multiple Ascending Dose Study of R1507 in Children and Adolescents With Advanced Solid Tumors | Solid tumors | Drug: RG1507 | I | Therapeutic |  |
| 33 | NCT00811993  Terminated | A Study of R1507 in Combination With Multiple Standard Chemotherapy Treatments in Patients With Advanced Solid Tumors | Neoplasms | Drug:RG1507  Drug: RO1507 Drug:  bevacizumab [Avastin]  Drug: capecitabine [Xeloda] Drug: carboplatin Drug: cetuximab Drug: docetaxel Drug: erlotinib [Tarceva] Drug: etoposide  Drug: gemcitabine Drug: irinotecan Drug: mFOLFOX6 Drug: paclitaxel Drug: pemetrexel Drug: sorafenib Drug: temozolomideDrug: trastuzumab [Herceptin] | I | Therapeutic |  |
| 34 | NCT00985374  Terminated | A Multiple Ascending Dose Study of the mTOR Inhibitor (RAD001) in Combination With R1507 in Patients With Advanced Solid Tumors | Neoplasms | Drug: RAD001 Drug: RG1507 | I | Therapeutic |  |
| 35 | NCT01182883  Withdrawn | A Phase I Study of IMC-A12 in Combination With Temsirolimus in Pediatric Patients With Recurrent or Refractory Solid Tumors | Brain Stem Neoplasms Glioma Pinealoma | Drug: IMC-A12 Drug: Temsirolimus | I | Therapeutic |  |
| 36 | NCT01533181  Completed | Linsitinib or Topotecan Hydrochloride in Treating Patients With Relapsed Small Cell Lung Cancer | Small cell lung cancer | Other: Laboratory Biomarker Analysis Drug: Linsitinib Other: Pharmacological Study  Drug: Topotecan Hydrochloride | II | Therapeutic | Chiappori et al., 2016 |
| 37 | NCT00887159  Completed | A Randomized Phase II Study of Cisplatin and Etoposide in Combination With Either Hedgehog Inhibitor GDC-0449 or IGF-1R MOAB IMC-A12 for Patients With Extensive Stage | Small cell lung cancer | Drug:Cisplatin Biological: CixutumumabDrug: Etoposide Other: Laboratory Biomarker Analysis Drug: Vismodegib | II | Therapeutic |  |
| 38 | NCT00831844  Completed | Cixutumumab in Treating Patients With Relapsed or Refractory Solid Tumors | Solid tumors | Biological: cixutumumabOther: laboratory biomarker analysis | II | Biomarker |  |
| 39 | NCT00635778  Completed | A Dose-finding Study of Dalotuzumab in Subjects With Advanced Solid Tumors (MK-0646-002) | Solid tumors | Drug: Dalotuzumab | I | Therapeutic |  |
| 40 | NCT00769483  Completed | MK-0646 and Gemcitabine +/- Erlotinib for Patients With Advanced Pancreatic Cancer | Pancreatic cancer | Drug:  MK-0646  Drug: Gemcitabine Drug: Erlotinib | I and II | Therapeutic | Abdel-Wahab et al., 2018 |
| 41 | NCT02507583  Active | Antisense102: Pilot Immunotherapy for Newly Diagnosed Malignant Glioma | Malignant glioma  Neoplasms | Drug: IGF-1R/AS ODN; Surgery with tissue harvest and implantation 20 diffusion chambers in the rectus sheath with IGF-1R/AS ODN within 24 hours of craniotomy, implanted for 48 hours. | I | Therapeutic | Andrews et al., 2001 |
| 42 | NCT03384914  Active | Vaccine to Prevent Recurrence in Patients With HER-2 Positive Breast Cancer | Breast cancer | Biological: DC1 Vaccine Biological: WOKVAC Vaccine | II | Therapeutic |  |
| 43 | NCT01008566  Completed | Cixutumumab and Sorafenib Tosylate in Treating Patients With Advanced Liver Cancer | Hepatocellular carcinoma and liver carcinoma | Biological: Cixutumumab Other: Laboratory Biomarker Analysis  Drug: Sorafenib Tosylate | I | Therapeutic |  |
| 44 | NCT02755844  Active | Safety and Efficacy of Metronomic Cyclophosphamide, Metformin and Olaparib in Endometrial Cancer Patients (ENDOLA) | Endometrial cancer | Drug: Olaparib Drug: metformin Drug: metronomic  cyclophosphamide | I and II | Therapeutic |  |
| 45 | NCT00639509  Completed | IMC-A12 in Treating Patients With Advanced Liver Cancer | Hepatocellular and Liver carcinoma | Biological: cixutumumabProcedure: computed tomography Procedure: contrast-enhanced magnetic resonance imaging | II | Therapeutic |  |
| 46 | NCT04329065  Active | Concurrent WOKVAC Vaccination, Chemotherapy, and HER2-Targeted Monoclonal Antibody Therapy Before Surgery for the Treatment of Patients With Breast Cancer | Breast cancer | Biological: pUMVC3-IGFBP2-HER2-IGF1R Plasmid DNA Vaccine  Drug: Paclitaxel Biological:  Trastuzumab Biological: Pertuzumab | II | Therapeutic |  |
| 47 | NCT00845039  Terminated | A Study of Irinotecan and Cetuximab With or Without IMC-A12 for Treatment of Participants With Colon or Rectum Cancer Who Got Worse After Their First Treatment With Oxaliplatin and Bevacizumab (FC-4) | Colon and rectum cancer | Biological: Cetuximab Drug: Irinotecan Biological: IMC-A12(cixutumumab) | II | Therapeutic |  |
| 48 | NCT01026623  completed | Cixutumumab and Temsirolimus in Treating Patients With Metastatic Prostate Cancer | Prostate cancer | Biological: CixutumumabOther: Diagnostic Laboratory Biomarker Analysis Drug: Temsirolimus | I and II | Therapeutic |  |
| 49 | NCT00402285  Completed | Lycopene or Omega-3 Fatty Acid Nutritional Supplements in Treating Patients With Stage I or Stage II Prostate Cancer | Prostate cancer | Dietary Supplement: lycopene supplement Dietary Supplement: fish oil supplement Other: Placebo | Not applicable | Therapeutic | Magbanua et al., 2011 |
| 50 | NCT00785538  Completed | A Study of IMC-A12 in Participants With Tumors Who No Longer Respond to Treatment or For Whom No Treatment is Available | Solid tumors | Biological: IMC-A12 | I | Therapeutic | Higano et al., 2015 |
| 51 | NCT01721577  Unknown | Phase I/II Trial of Safety and Anti-tumor Efficacy of AXL1717(Picropodophyllin) in the Treatment of Recurrent Malignant Astrocytomas (AXL1717) | Glioblastoma Gliosarcoma Anaplastic Astrocytoma Anaplastic Oligodendroglioma  Anaplastic Oligoastrocytoma  Anaplastic Ependymoma | Drug: AXL1717 | I and II | Therapeutic |  |
| 52 | NCT00785941  Completed | A Study of IMC-A12 Every 2 Weeks in Patients With Tumors Who No Longer Respond to Treatment or No Treatment is Available | Solid tumors | Biological: IMC-A12 | I | Therapeutic |  |
| 53 | NCT00526838  Terminated | Study of XL228 Administered Intravenously to Subjects With Advanced Malignancies | Cancer  Lymphoma | Drug: XL228 | I | Therapeutic |  |
| 54 | NCT00699491  Completed | Cixutumumab and Temsirolimus in Treating Patients With Locally Recurrent or Metastatic Breast Cancer | Breast cancer | Biological: CixutumumabOther: Laboratory Biomarker Analysis Other: Pharmacological Study Drug:  Temsirolimus | I and II | Therapeutic |  |
| 55 | NCT01061749  Completed | Selumetinib and Cixutumumab in Treating Patients With Advanced Solid Malignancies | Adult solid neoplasms | Biological: CixutumumabOther: Laboratory Biomarker Analysis Other: Pharmacological Study  Drug: Selumetinib | I | Therapeutic |  |
| 56 | NCT00617708  Completed | S0727 Gemcitabine Hydrochloride and Erlotinib Hydrochloride With or Without Monoclonal Antibody Therapy in Treating Patients With Metastatic Pancreatic Cancer That Cannot Be Removed By Surgery | Pancreatic cancer | Biological: cixutumumabDrug: erlotinib hydrochlorideDrug: gemcitabine hydrochloride | I and II | Therapeutic |  |
| 57 | NCT02454517  Active | Diet and Exercise Program to Promote Weight Loss and Improve Health in Men With Low- or Low-Intermediate-Risk Prostate Cancer (PALS) | Prostate adenocarcinoma Stage I Prostate Cancer AJCC V7 Stage IIA Prostate CancerAJCC v7 | Behavioral: Behavioral Dietary Intervention Behavioral: Exercise Intervention Other: Informational Intervention Other: Laboratory Biomarker Analysis Other: Quality-of-Life Assessment Other: Questionnaire administration | III | Therapeutic |  |
| 58 | NCT00701103  Completed | Dose Escalation Trial of Dalotuzumab (MK-0646) in Advanced Solid Tumors and Multiple Myeloma (MK-0646-001) | Solid Tumor Multiple Myeloma | Drug: Dalotuzumab | I | Therapeutic | Atzori et al., 2011 |
| 59 | NCT02916394  Active | In Vivo IGF-1R Molecular Imaging Using [68Ga]- Labelling Anti-IGF-1R Affibody Molecule |  | Radiation: 68Ga-NODAGA-ZIGF-1R:4: 40 | Not applicable | Biomarker |  |
| 60 | NCT00630552  Completed | QUILT-2.019: A Study of AMG 655 or AMG 479 in Combination With Gemcitabine for Treatment of Metastatic Pancreatic Cancer | Pancreatic cancer | Other: Placebo Drug: AMG479  Drug: AMG655 | I and II | Therapeutic | Cella et al., 2013; Kindler et al., 2012; McCaffery et al., 2013 |
| 61 | NCT00970580  Completed | A Study of BIIB022 in Combination With Paclitaxel and Carboplatin in Subjects With Non-Small Cell Lung Cancer | Non-small cell lung cancer | Drug: BIIBO22 with paclitaxel and carboplatin | I | Therapeutic |  |
| 62 | NCT01142388  Active | Paclitaxel With or Without Cixutumumab as Second-Line Therapy in Treating Patients With Metastatic Esophageal Cancer or Gastroesophageal Junction Cancer | Gastroesophageal Junction Adenocarcinoma and Esophageal Adenocarcinoma | Biological: CixutumumabOther: Laboratory Biomarker Analysis Drug: Paclitaxel Other: Pharmacological Study | II | Therapeutic |  |
| 63 | NCT01614795  Completed | Cixutumumab and Temsirolimus in Treating Younger Patients With Recurrent or Refractory Sarcoma | Refractory sarcoma | Biological: CixutumumabOther: Laboratory Biomarker Analysis  Drug: Temsirolimus | II | Therapeutic |  |
| 64 | NCT02145559  Completed | A Pharmacodynamic Study of Sirolimus and Metformin in Patients With Advanced Solid Tumors | Breast Neoplasms  Lung neoplasms  Cancer of Liver Lymphoma Cancer of Kidney | Drug: Metformin XR Drug: Delayed Metformin Drug: Sirolimus | I | Therapeutic |  |
| 65 | NCT00974896  Completed | QUILT-2.016: Study of AMG 479 With Biologics or Chemotherapy for Subjects With Advanced Solid Tumors | Solid tumors | Drug: AMG479 | I | Therapeutic |  |
| 66 | NCT01560260  Completed | Linsitinib in Treating Patients With Gastrointestinal Stromal Tumors | Carney Complex chondrosarcoma Gastrointestinal Stromal Tumor Paraganglioma | Other: Laboratory Biomarker Analysis Drug: Linsitinib Other: Pharmacological Study | II | Therapeutic | Songdej et al., 2014 |
| 67 | NCT00596830  Terminated | Carboplatin And Paclitaxel With Or Without CP-751, 871 (An IGF-1R Inhibitor) For Advanced NSCLC Of Squamous, Large Cell And Adenosquamous Carcinoma Histology | Carcinoma, Squamous Cell Carcinoma, AdenosquamousCarcinoma, Large Cell Carcinoma, Non-Small-Cell Lung | Drug:  CP-751,871 (figitumumab)  Drug: Carboplatin Drug: Paclitaxel | III | Therapeutic | Langer et al., 2014 |
| 68 | NCT00791544  Terminated | Dose Finding Study of AVE1642 in Patients With Advanced or Metastatic Liver Carcinoma | Liver carcinoma | Drug: AVE1642 Drug: sorafenib Drug: erlotinib | I and II | Therapeutic |  |
| 69 | NCT00976508  Terminated | Figitumumab Combined With Pegvisomant For Advanced Solid Tumors | Colorectal Neoplasms Lung neoplasms Breast Neoplasms Prostatic Neoplasms Sarcoma | Drug: figitumumab Drug: pegvisomant | I | Therapeutic |  |
| 70 | NCT01949519  Completed | Docetaxel and Lycopene in Metastatic Prostate Cancer | adenocarcinoma of the Prostate | Drug: Lycopene and Docetaxel | I | Therapeutic |  |
| 71 | NCT01561456  Completed | Study of AXL1717 Compared to Docetaxel to Treat Squamous Cell Carcinoma or Adenocarcinoma of the Lung | Non-small-cell Lung Cancer Squamous Cell Carcinoma Adenocarcinoma of the Lung | Drug: AXL1717 Drug: Docetaxel | II | Therapeutic |  |
| 72 | NCT00560573  Completed | Study Of CP-751,871 In Combination With Cisplatin And Gemcitabine In Chemotherapy-Naïve Patients With Advanced Non-Small Cell Lung Cancer | Non-small cell lung cancer | Drug: CP751,871 Drug: Cisplatin Drug: Gemcitabine Drug: Pemetrexed | I | Therapeutic |  |
| 73 | NCT00986674  Completed | Carboplatin and Paclitaxel Combined With Cetuximab and/or IMC-A12 in Patients With Advanced Non-Small Cell Lung Cancer | Non-small cell lung cancer | Biological: cixutumumabDrug: carboplatin Drug: paclitaxel Biological: cetuximab | II | Therapeutic |  |
| 74 | NCT00977561  Terminated | A Study Of Cisplatin (Or Carboplatin) And Etoposide With Or Without Figitumumab (CP-751,871) In Patients With Extensive-Stage Small Cell Lung Cancer | Small cell lung cancer | Drug: figitumumab Drug: Cisplatin (Or Carboplatin) Drug: Etoposide | II | Therapeutic |  |
| 75 | NCT01427205  Withdrawn | Phase II Study of Cetuximab With or Without OSI-906 in Head and Neck Squamous Cell Carcinoma (HNSCC) | Head and neck cancer | Drug: Cetuximab Drug: OSI-906  Other: Placebo | II | Therapeutic |  |
| 76 | NCT01708161  Terminated | A Phase Ib/II Study of the Combination of BYL719 Plus AMG 479 in Adult Patients With Selected Solid Tumors | Solid tumors | Drug: BYL719  Drug:  AMG 479 | I and II | Therapeutic |  |
| 77 | NCT01233895  Completed | Study of AVE1642 Anti-IGF-1R Monoclonal Antibody in Patients With Advanced Multiple Myeloma | Multiple Myeloma | Drug: AVE1642  Drug: Velcade | I | Therapeutic |  |
| 78 | NCT01120236  Completed | Bicalutamide and Goserelin or Leuprolide Acetate With or Without Cixutumumab in Treating Patients With Newly Diagnosed Metastatic Prostate Cancer | Prostate cancer | Drug: Bicalutamide Biological: CixutumumabDrug: Goserelin Acetate  Other: Laboratory Biomarker Analysis  Drug: Leuprolide Acetate  Other: Pharmacological Study | II | Therapeutic | Evan et al., 2015 |
| 79 | NCT00881725  Terminated | A Study of Pre-operative Metformin in Prostate Cancer (ANIMATE) | Prostate cancer | Drug: Metformin | II | Therapeutic |  |
| 80 | NCT03746431  Active | A Phase 1 Study of [225Ac]-FPI-1434 Injection | Solid tumors | Drug: [111In]-FPI-1547 Injection Drug: [225Ac]-FPI-1434 Injection | I | Therapeutic |  |
| 81 | NCT00617890  Terminated | A Study to Determine the Activity of Robatumumab (SCH 717454) in Participants With Relapsed Osteosarcoma or Ewing's Sarcoma (MK-7454-002/P04720) | Osteosarcoma Sarcoma, Ewing's Peripheral Neuroectodermal Tumor | Biological:  Robatumumab | II | Therapeutic |  |
| 82 | NCT01365962  Completed | Biomarker in Tumor Tissue Samples From Patients With Rhabdomyosarcoma | Rhabdomyosarcoma | Genetic: gene expression analysis  Other: immunohistochemistry staining method  Other: laboratory biomarker analysis  Other: mass spectrometry |  | Biomarker |  |
| 83 | NCT01204476  Completed | Cixutumumab, Everolimus, and Octreotide Acetate in Treating Patients With Advanced Low to Intermediate Grade Neuroendocrine Carcinoma | Neuroendrocrine carcinoma | Biological: CixutumumabDrug: Everolimus Other: Laboratory Biomarker Analysis Drug: Octreotide Acetate  Other: Pharmacological Study | I | Therapeutic | Dasari et al., 2015 |
| 84 | NCT02306161  Active | Combination Chemotherapy With or Without Ganitumab in Treating Patients With Newly Diagnosed Metastatic Ewing Sarcoma | Ewing sarcoma | Drug: Cyclophosphamide  Drug: Doxorubicin Drug: Doxorubicin HydrochlorideDrug: Etoposide Drug: Etoposide Phosphate Radiation: External Beam Radiation Therapy Biological: Ganitumab Drug: Ifosfamide Radiation: Stereotactic Radiosurgery Procedure: Therapeutic Surgical Procedure Drug: Vincristine Drug: Vincristine Sulfate | III | Therapeutic |  |
| 85 | NCT00965250  Completed | Multicenter Phase II Study of IMC-A12 in Patients With Thymoma and Thymic Carcinoma Who Have Been Previously Treated With Chemotherapy | Thymoma and thymic carcinoma | Drug: IMC-12 | II | Therapeutic | Rajan et al., 2014 |
| 86 | NCT00313781  Completed | Study of CP-751,871 in Combination With Docetaxel and Prednisone in Patients With Hormone Insensitive Prostate Cancer (HRPC) | Prostate cancer | Drug:  CP-751,871  Drug: docetaxel  Drug: prednisone | II | Therapeutic | de Bono et al., 2014 |
| 87 | NCT00889382  Completed | A Study Evaluating Intermittent and Continuous OSI-906 and Weekly Paclitaxel in Patients With Recurrent Epithelial Ovarian Cancer (and Other Solid Tumors | Epithelial ovarian cancer | Drug:  OSI-906  Drug: Paclitaxel | I and II | Therapeutic |  |
| 88 | NCT01550523  Completed | Pilot Immunotherapy Trial for Recurrent Malignant Gliomas | Gliomas | Drug: IGF-1R/AS ODN  Device: biodiffusion chamber | I | Therapeutic | Andrews et al., 2001; Agnelli et al., 1998; Agnelli et al., 2001; Baserga et al., 1995; Brandes et al., 1997; Cage et al., 2009; Carpentier et al., 2006; Chaput et al., 2004; Cosaceanu et al., 2007; Cunningham et al., 2000; Davidson and Diamond, 2001; Tang et al., 2005; Tetri et al., 2008; Zimmerman, 1991; Dorn and Kippenberger, 2008 |
| 89 | NCT01312467  Completed | Trial of Metformin for Colorectal Cancer Risk Reduction for History of Colorectal Adenomas and Elevated BMI | Adenomatous Polyp Colorectal Cancer Obesity | Drug: Metformin hydrochloride | II | Therapeutic |  |
| 90 | NCT01231347  Completed | QUILT-2.014: Gemcitabine and AMG 479 in Metastatic Adenocarcinoma of the Pancreas (GAMMA) | Adenocarcinoma of the pancreas | Drug:  AMG 479  Drug: PlaceboDrug: gemcitabine | III | Therapeutic |  |
| 91 | NCT00807612  Terminated | QUILT-2.017: Phase 1b/2 Study of AMG 479 in Combination With Paclitaxel and Carboplatin for 1st Line Treatment of Advanced Squamous Non-Small Cell Lung Cancer | Non-small cell lung cancer | Biological: AMG 479  Drug: Carboplatin  Drug: Paclitaxel | I and II | Therapeutic |  |
| 92 | NCT02042495  Withdrawn | Endometrial Cancer Biomarker Changes Following Exposure to Metformin | Endometrial cancer | Drug: Metformin | II | Therapeutic |  |
| 93 | NCT00897663  Completed | Improving the Selection of Patients With Glioblastoma Multiforme for Treatment With Epidermal Growth Factor Receptor Inhibitor Therapies | Brain and central nervous system tumors | Genetic: gene expression analysis  Genetic: microarray analysis Genetic: protein expression analysis Other: diagnostic laboratory biomarker analysis Other: immunohistochemistry staining method |  | Biomarker |  |
| 94 | NCT00678626  Withdrawn | Phase 2 Trial Of CP-751,871 And Docetaxel In Advanced Breast Cancer | Breast cancer | Drug: CP751,871  Drug: Docetaxel | II | Therapeutic |  |
| 95 | NCT00560560  completed | Study Using CP-751,871 In Patients With Stage IV Colorectal Cancer That Has Not Responded To Previous Anti- Cancer Treatments | Colorectal neoplasm | Biological: CP-751, 871 | II | Therapeutic |  |
| 96 | NCT00320411  Completed | GW572016 In Patients With ErbB2 Over - Expressing Advanced Or Metastatic Breast Cancer | Breast cancer | Drug: Lapatinib | II | Therapeutic | Toi et al., 2009 |
| 97 | NCT00753207  Completed | Lapatinib and Epirubicin in Treating Patients With Metastatic Breast Cancer ICORG 06-30 | Breast cancer | Drug: epirubicin hydrochlorideDrug: lapatinib ditosylate  Other: biomarker analysis  Other: immunohistochemistry staining method  Other: liquid chromatography  Other: mass spectrometry | I | Therapeutic |  |
| 98 | NCT00372996  Terminated | Study Of CP-751,871 In Combination With Exemestane In Postmenopausal Women With Hormone Receptor Positive Advanced Breast Cancer | Breast neoplasms | Drug:  CP-751,871  Drug: exemestane  Drug: Fulvestrant | II | Therapeutic |  |
| 99 | NCT01497626  Terminated | Lapatinib and Bortezomib in Patients With Advanced Malignancies | Solid tumors | Drug: Lapatinib and bortezomib | I | Therapeutic |  |
| 100 | NCT01413191  Completed | Cixutumumab in Treating Patients With Metastatic Melanoma of the Eye | Melanoma of the eye | Biological: CixutumumabOther: Laboratory biomarker analysis | II | Therapeutic |  |
| 101 | NCT00885755  Completed | A Study of Herceptin (Trastuzumab)and Biomarkers in Patients With HER2-Positive Metastatic Breast Cancer | Breast cancer | Drug: Standard taxane therapy  Drug: capecitabine [Xeloda] Drug: trastuzumab [Herceptin] | II | Therapeutic |  |
| 102 | NCT01104571  Active | Trastuzumab or Lapatinib Ditosylate in Treating Women With Early Breast Cancer (EPHOS-B) | Breast cancer | Biological: trastuzumab Drug: lapatinib ditosylate Other: laboratory biomarker analysis Procedure: adjuvant therapy Procedure: neoadjuvant therapy Procedure: therapeutic conventional surgery | III | Therapeutic | Bliss et al., 2011 |
| 103 | NCT00631852  Completed | A Phase II Biomarker Trial of Gelatin Encapsulated Extract of American Ginseng Root (LEAG) in Breast Cancer | Breast cancer | Drug: American Ginseng root | II | Biomarker | Peralta et al., 2009; Peralta et al., 2009; Peralta et al., 2006 |
| 104 | NCT01536145  Completed | CP-751,871 Treatment For Patients With Multiple Myeloma | Multiple myeloma | Drug:  CP-751,871 | I | Therapeutic |  |
| 105 | NCT01653158  Completed | CP-751,871 In Combination With Docetaxel In Advance Non-hematologic Malignancies | Advanced Non-Hematologic Malignancies | Drug:  CP-751,871  Drug: Docetaxel | I | Therapeutic |  |
| 106 | NCT01385280  Completed | Pilot Study Estradiol Followed by Exemestane Hormone Receptor + Metastatic Breast Cancer | Breast cancer | Biological: therapeutic estradiol  Drug: exemestane Other: laboratory biomarker analysis  Other: enzyme-linked immunosorbent assay |  | Biomarker | Chalasani et al., 2014 |
| 107 | NCT00720174  Completed | Cixutumumab and Doxorubicin Hydrochloride in Treating Patients With Unresectable, Locally Advanced, or Metastatic Soft Tissue Sarcoma | Soft tissue sarcoma | Biological: CixutumumabDrug: Doxorubicin HydrochlorideOther: Laboratory Biomarker Analysis | I | Therapeutic | Chugh et al., 2015 |
| 108 | NCT00562380  Completed | AMG-479 in Treating Patients With Advanced Solid Tumors or Non-Hodgkin Lymphoma | Lymphoma Prostate Cancer Sarcoma Small Intestine Cancer Unspecified Adult Solid Tumor | Biological: ganitumab  Other: laboratory biomarker analysis  Other: pharmacological study  Procedure: biopsy | I | Therapeutic |  |
| 109 | NCT02049047  Unknown | Study of Everolimus in Patients With Thymoma and Thymic Carcinoma Previously Treated With Chemotherapy (ONC-2010-001) | Thymoma and thymic carcinoma | Drug: Everolimus | II | Therapeutic | Zucali et al., 2018 |
| 110 | NCT01567488  Completed | Phase II Study of Everolimus Combined With Octreotide LAR to Treat Advanced GI NET (EVERLAR) | Gastrointestinal neoplasm | Drug: Everolimus Drug: octreotide LAR | II | Therapeutic | Capdevila et al., 2019 |
| 111 | NCT02538627  Terminated | Phase 1 Combination Study of MM-151 With MM-121, MM-141, or Trametinib | Colorectal Cancer Non-small Cell Lung Cancer Squamous Cell Carcinoma of the Head and Neck | Drug:  MM-151  Drug:  MM-121  Drug:  MM-141  Drug: trametinib | I | Therapeutic |  |
| 112 | NCT01430585  Terminated | Pre-Operative Study of PF-4691502 With Letrozole Compared To Letrozole Alone In Patients With Early Breast Cancer | Breast cancer | Drug:  PF-04691502  Drug: PF-04691502 in combination with Letrozole  Drug: Letrozole | II | Therapeutic |  |
| 113 | NCT00147537  Completed | Combination Study Of CP-751,871 With Paclitaxel And Carboplatin In Advanced Lung Cancer | Non-small cell lung cancer | Drug:  CP-751,871 Drug: paclitaxel Drug: carboplatin Drug: erlotinib | I and II | Therapeutic |  |
| 114 | NCT03085368  Active | A Randomized Controlled Trial of HER-2 Positive Breast Cancer Patients Treated With Lapatinib vs Herceptin | Breast cancer | Drug: Herceptin/lapatinib | II and III | Therapeutic | Piccart-Gebhart et al., 2016; Goss et al., 2013 |
| 115 | NCT00246571  Completed | Study Of SU011248 Versus Chemotherapy For Patients With Previously Treated Triple Receptor Negative Breast Cancer | Breast cancer | Drug: SU011248 Drug: Chemotherapy | II | Therapeutic | Curigiano et al., 2013 |
| 116 | NCT01041027  Completed | Radiation Therapy, Paclitaxel, and Carboplatin in Treating Patients With High-Risk Endometrial Cancer | Uterine corpus  Cancer | Drug: Paclitaxel Drug: Carboplatin Radiation: Internal Radiation Therapy Radiation: External Beam Radiation Therapy Other: Laboratory Biomarker Analysis | II | Therapeutic |  |
| 117 | NCT01672736  Terminated | A Trial of ASP7487 (OSI-906) in Combination With Bortezomib for the Treatment of Relapsed Multiple Myeloma | Multiple myeloma | Drug: ASP7487, Velcade, Dexamethasone | I and II | Therapeutic |  |
| 118 | NCT00673049  Terminated | Trial Of CP-751, 871 And Erlotinib In Refractory Lung Cancer (NSCLC) | Non-small cell lung cancer | Drug: CP 751,871 (figitumumab)Drug: Erlotinib | III | Therapeutic |  |
| 119 | NCT01156545  Unknown | BIBW 2992 Plus Simvastatin vs. BIBW 2992 in Previously Treated Patients With Advanced Non-adenocarcinomatous NSCLC | Non-small cell lung cancer | Drug:  BIBW 2992  Drug: simvastatin | II | Therapeutic |  |
| 120 | NCT01733004  Completed | A Phase 1 Study of MM-141 in Patients With Advanced Solid Tumors | Hepatocellular carcinoma | Drug:  MM-141 | I | Therapeutic |  |
| 121 | NCT00474760  Completed | Study Of Anti-IGF-IR CP-751,871 In Patients With Solid Tumors | Ewing’s sarcoma | Drug:  CP-571, 871 | I | Therapeutic | Asmane et al., 2012; Olmos et al., 2010 |
| 122 | NCT01594177  Completed | Dual Blockage With Afatinib and Trastuzumab as Neoadjuvant Treatment for Patients With Locally Advanced or Operable Breast Cancer Receiving Taxane-anthracycline Containing Chemotherapy (DAFNE) | Breast cancer | Drug: Afatinib  Drug: Trastuzumab  Drug: Paclitaxel Drug: Epirubicin Drug: Cyclophosphamide | II | Therapeutic |  |
| 123 | NCT03041701  Active | Insulin-like Growth Factor 1 Receptor (IGF1R) Antibody AMG479 (Ganitumab) in Combination With the Src Family Kinase (SFK) Inhibitor Dasatinib in People With Embryonal and Alveolar Rhabdomyosarcoma | Alveolar Rhabdomyosarcoma | Drug: Dasatinib  Drug: Ganitumab | I and II | Therapeutic |  |
| 124 | NCT03300557  Active | Exemestane in Treating Patients With Complex Atypical Hyperplasia of the Endometrium/Endometrial Intraepithelial Neoplasia or Low Grade Endometrial Cancer | Atypical Hyperplasia Endometrial Intraepithelial Neoplasia and Endometrial Endometrioid Adenocarcinoma | Drug: Exemestane  Other: Laboratory Biomarker Analysis  Other: Pharmacokinetic Study  Other: Questionnaire administration | II | Therapeutic |  |
| 125 | NCT00642941  Completed | A Study of R1507 in Participants With Recurrent or Refractory Sarcoma | Refractory sarcoma | Drug: RG1507 | II | Therapeutic | Asmane et al., 2012; Pappo et al., 2011 |
| 126 | NCT01016015  Completed | Temsirolimus and Cixutumumab in Treating Patients With Locally Advanced, Metastatic, or Recurrent Soft Tissue Sarcoma or Bone Sarcoma | Metastatic Osteosarcoma Recurrent, Adult Soft Tissue Sarcoma, Recurrent Osteosarcoma | Biological: CixutumumabOther: Laboratory Biomarker Analysis  Drug: Temsirolimus | II | Therapeutic | Schwartz et al., 2013 |
| 127 | NCT02056691  Completed | EDICT - Exercise induced Changes In Colorectal Cancer Tissues (EDICT) | Colorectal cancer | Procedure: Exercise programme Procedure: Muscle biopsy | Not applicable | Therapeutic |  |
| 128 | NCT00957853  Completed | Preoperative Treatment With Cetuximab and/or IMC-A12 | Head and neck squamous cell carcinoma | Drug: Cetuximab  Drug:  IMC-A12  Procedure: Surgical tumor resection | II | Therapeutic |  |
| 129 | NCT02546544  Completed | Eurosarc Trial of Linsitinib in Advanced Ewing Sarcoma (LINES) | Ewing’s sarcoma | Drug: Linsitinin | II | Therapeutic |  |
| 130 | NCT00778817  Terminated | IMC-A12 With Mitotane vs Mitotane Alone in Recurrent, Metastatic, or Primary ACC That Cannot Be Removed by Surgery | Adrenocortical Carcinoma | Biological: IMC-A12  Drug: mitotane | II | Therapeutic |  |
| 131 | NCT02110641  Active | Lifestyle, Exercise and Nutrition Study 2 (LEAN 2) (LEAN 2) | Breast cancer | Behavioural: weight loss counselling | Not applicable | Therapeutic |  |
| 132 | NCT04199026  Active | Implantable Microdevice for the Delivery of Drugs and Their Effect on Tumors in Patients With Metastatic or Recurrent Sarcoma | Sarcoma | Drug: Doxorubicin Drug: Doxorubicin HydrochlorideDevice: Drug Delivery Microdevice Drug: Everolimus Biological: Ganitumab  Drug: Ifosfamide Drug: Irinotecan  Drug: Pazopanib Drug: Polyethylene Glycol  Drug: temozolomide  Drug: TemsirolimusProcedure: Therapeutic Conventional Surgery  Drug: Vincristine | I | Therapeutic |  |
| 133 | NCT01160458  Completed | Phase II Study of IMC-A12 in Patients With Mesothelioma Who Have Been Previously Treated With Chemotherapy | Pleural Mesothelioma  Peritoneal Mesothelioma | Drug:  IMC-A12 | II | Therapeutic | Bridda et al., 2007; Vogelzang et al., 2003; O’Byrne et al., 2004 |
| 134 | NCT04485949  Active | A Phase 2b Clinical Study With a Combination Immunotherapy in Newly Diagnosed Patients With Glioblastoma Multiforme (GBM) - the ImmuneSense Study | Glioblastoma Multiforme Glioblastoma | Biological: IGV-001 Cell Immunotherapy  Biological: Placebo  Procedure: Standard of Care (SOC): Radiation Therapy  Drug: SOC: Temozolomide | II | Therapeutic |  |
| 135 | NCT00923325  Completed | Blood and Tissue Study of Patients in NIH Protocol 08-C-0800 | Sarcomas |  |  | Biomarker | Bonath, 1975; Myhre, 1977; Rosen et al., 1991 |
| 136 | NCT01465815  Withdraw | Phase I/II Study of Postoperative Adjuvant Chemoradiation for Advanced-Stage Cutaneous Squamous Cell Carcinoma of the Head and Neck (cSCCHN) | Cutaneous Squamous Cell Carcinoma of the Head and Neck | Drug: erlotinib hydrochlorideDrug: linsitinib  Drug: placebo  Radiation: radiation therapy  Procedure: therapeutic conventional surgery  Other: laboratory biomarker analysis | I and II | Therapeutic |  |
| 137 | NCT03029481  Not available | Single Patient Expanded Access to Ganitumab for Metastatic Ewing Sarcoma | Ewing’s sarcoma | Drug: Ganitumab |  | Therapeutic |  |
| 138 | NCT00956436  Completed | Sorafenib With BIIB022 in Hepatocellular Carcinoma (HCC) | Hepatocellular carcinoma | Drug: BIIB022  Drug: Sorafenib | I | Therapeutic |  |
| 139 | NCT01901666  Completed | Assessment Of Gh-Igf-1 Axis In Children With Chronic Myelogenous Leukemia (CML) In Remission | Chronic Myelogenous LeukemiaShort Stature | Drug: growth hormone | IV | Biomarker |  |
| 140 | NCT02824133  Completed | Treatment With AZD4547 for Recurrent Malignant Glioma Expressing FGFR-TACC Gene Fusion" (TARGET) | Glioma | Drug: AZD4547 | I and II | Therapeutic |  |
| 141 | NCT01327781  Completed | Z-Endoxifen Hydrochloride in Treating Patients With Metastatic or Locally Recurrent Estrogen Receptor-Positive Breast Cancer | Breast cancer | Other: Laboratory Biomarker Analysis  Other: Pharmacological Study  Other: Questionnaire administration  Drug: Z-Endoxifen Hydrochloride | I | Therapeutic |  |
| 142 | NCT01652547  Completed | A Phase I, Exploratory, Intra-patient Dose Escalation Study to Investigate the Preliminary Safety, Pharmacokinetics, and Anti-tumor Activity of Pasireotide (SOM230) s.c.Followed by Pasireotide LAR in Patients With Metastaticmelanoma or Metastatic Merkel Cell Carcinoma | Metastatic Merkel Cell Carcinoma | Drug: Pasireotide sub-cutaneous formulation  Drug: Pasireotide lon acting release formulation | I | Therapeutic |  |
| 143 | NCT04393285  Active | Abemaciclib and Letrozole to Treat Endometrial Cancer | Endometrial cancer | Drug: Abemaciclib  Drug: Letrozole | II | Therapeutic |  |
| 144 | NCT01055314  Completed | Temozolomide, Cixutumumab, and Combination Chemotherapy in Treating Patients With Metastatic Rhabdomyosarcoma | Metastatic Rhabdomyosarcoma | Biological: CixutumumabDrug: Cyclophosphamide  Biological: DactinomycinDrug: Doxorubicin HydrochlorideDrug: Etoposide  Drug: Ifosfamide  Drug: Irinotecan HydrochlorideOther: Laboratory Biomarker Analysis  Drug: Temozolomide  Drug: Vincristine Sulfate Liposome | II | Therapeutic |  |
| 145 | NCT00924989  Completed | A Study of OSI-906 in Patients With Locally Advanced or Metastatic Adrenocortical Carcinoma (GALACCTIC) | Adrenocortical Carcinoma | Drug:  OSI-906  Other: Placebo | III | Therapeutic | Fassnacht et al., 2015 |
| 146 | NCT04506398  Active | Heterogeneity and Evolution of hepatoceLlular Carcinoma in Post-transplant HCC Recurrence (HELP-2020) | Hepatocellular Carcinoma RecurrentLiver Transplant; Complications | Procedure: liver transplant  Diagnostic Test: ctDNA  Diagnostic Test: whole exome sequencing |  | Biomarker |  |
| 147 | NCT04298684  Active | Efficacy of Metformin Versus Sitagliptin on Benign Thyroid Nodules in Type 2 Diabetes (METNODTHYR) | Diabetes Mellitus, Type 2Thyroid Nodule (Benign) | Drug: METFORMINDrug: Sitagliptin | IV | Therapeutic | Anil et al., 2013 |
| 148 | NCT03813381  Active | Calorie and Protein Restriction Program in Barrett's Esophagus Patients (CARE-PRO). (CARE-PRO) | Barrett's EsophagusOverweight and Obesity | Behavioral: Calorie and protein restriction diet | Not applicable | Therapeutic | Lee, 2013 |

APPENDIX 2: Selected primary research articles included in the present study.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Year** | **Author** | **Title** | **Key findings** | **Study selection process** |
| 1978 | Rinderknecht and Humbel | The amino acid sequence of human insulin-like growth factor I and its structural homology with proinsulin | IGF-I shares ~50% homology with pro-insulin and its molecular weight is 7649 Daltons | This study describes IGF-1R and Insulin similarity |
| 1983 | Rubin et al | Stimulation of tyrosine-specific phosphorylation in vitro by insulin-like growth factor I | IGF-1R is activated and phosphorylated upon the IGF-I binding | The binding of ligand IGF-I activate IGF-1R |
| 2012 | Murakami | Phase 1 study of ganitumab (AMG 479), a fully human monoclonal antibody against the insulin-like growth factor receptor type I (IGF1R), in Japanese patients with advanced solid tumors | A fully human monoclonal antibody against IGF-1R exhibited promising and acceptable safety against solid tumours | A phase I study, exhibits the safe use of ganitumab against IGF-1R |
| 2011 | Tamimi et al | Expression of IGF1R in normal breast tissue and subsequent risk of breast cancer | High levels of cytoplasmic IGF-1R in the epithelial cells, have up to 15 times increased BrCa incidence | IGF-1R is associated with high risk of breast cancer |
| 2010 | Aleksic et al | Type 1 insulin-like growth factor receptor translocates to the nucleus of human tumor cells | After 1996, it was one of the first article to validate that IGF-1R translocates to the nucleus | First study since 1996 to identify IGF-1R translocate to cell nucleus |
| 2010 | Sehat et al | SUMOylation Mediates the Nuclear Translocation and Signaling of the IGF-1 Receptor | IGF-1R nuclear translocation is dependent on SUMOylation. Nuclear IGF-1R binds with enhancer-like elements | The importance of SUMOylation in the nuclear translocation of IGF-1R and nIGF-1R binds to DNA-regulatory elements |
| 2011 | Deng et al | Over-accumulation of nuclear IGF-1 receptor in tumor cells requires elevated expression of the receptor and the SUMO-conjugating enzyme Ubc9 | IGF-1R translocation is dependent on SUMO-conjugating enzyme (Ubc9) | nIGF-1R originate from cell surface only and phosphorylation of IGF-1R is essential for its nuclear translocation |
| 2017 | Codony-Servat et al | Nuclear IGF-1R predicts chemotherapy and targeted therapy resistance in metastatic colorectal cancer | Nuclear IGF-1R can cause chemotherapy and targeted agent resistance | This study determines IGF-1R is a major cause of chemotherapeutic resistance in colorectal cancer |
| 2015 | Packham et al | Nuclear translocation of IGF-1R via p150 Glued and an importin-β/RanBP2-dependent pathway in cancer cells | Nuclear pore passage is moderated by importin-β followed by RanBP2 | This study is important as it characterizes IGF-1R nuclear translocation pathway from the cell membrane to cell nucleus. |
| 2012 | Warsito et al | Nuclear IGF1R is a transcriptional co‐activator of LEF1/TCF | Nuclear IGF-1R increases protein levels of cyclin D1 and axin2. LEF1 is a nIGF-1R transcriptional cofactor | A strong association of nIGF-1R and LEF1. nIGF-1R binds to enhancer sites and plays a key role as a transcriptional cofactor |
| 2016 | Warsito et al | Nuclearly translocated insulin-like growth factor 1 receptor phosphorylates histone H3 at tyrosine 41 and induces SNAI2 expression via Brg1 chromatin remodeling protein | Phosphorylated nIGF-1R is rather essential in cancer disease than unphosphorylated nIGF-1R | This study identifies the association of nIGF-1R with phosphorylated histone H3 at tyrosine 41 |
| 2017 | Waraky et al | Nuclear insulin-like growth factor 1 receptor phosphorylates proliferating cell nuclear antigen and rescues stalled replication forks after DNA damage | PCNA regulates DNA damage tolerance (DDT) pathway | This study shows the importance of IGF-1R/ PCNA interaction to regulate DDT pathway |
| 2012 | Sarfstein et al | Insulin-like growth factor-I receptor (IGF-IR) translocates to nucleus and autoregulates IGF-IR gene expression in breast cancer cells | IGF-1R promotor to exhibit its own expression | Depending on the ER status cellular IGF-1R autoregulates IGF-1R gene expression |
| 2015 | Palmerini et al | Prognostic and predictive role of CXCR4, IGF-1R and Ezrin expression in localized synovial sarcoma: is chemotaxis important to tumor response? | Nuclear IGF-1R is significantly associated with adverse patient outcomes | In synovial sarcoma IGF-1R is highly expressed |
| 2013 | Aslam et al | Dynamic and Nuclear Expression of PDGFRα and IGF-1R in Alveolar Rhabdomyosarcoma | Human alveolar RMS exhibit nIGF-1R | In RMS high levels of nIGF-1R expression is associated with aggressive tumour growth |
| 2012 | Asmane et al | Insulin-like growth factor type 1 receptor (IGF-1R) exclusive nuclear staining: a predictive biomarker for IGF-1R monoclonal antibody (Ab) therapy in sarcomas | Nuclear IGF-1R expression increase the cell proliferation and effects the therapeutic response | In advanced soft tissue sarcomas IGF-1R nuclear localization is a potential biomarker |
| 2018 | Aleksic et al | Nuclear IGF1R interacts with regulatory regions of chromatin to promote RNA polymerase II recruitment and gene expression associated with advanced tumor stage | Nuclear IGF-1R interact with RNAPol2 to upregulate the expressions of JUN and FAM21 | nIGF-1R drive the tumour progression of prostate cancer and IGF-1R binding sites are around transcription start sites of JUN and FAM21 |
| 2013 | van Gaal | Simultaneous targeting of insulin-like growth factor-1 receptor and anaplastic lymphoma kinase in embryonal and alveolar rhabdomyosarcoma: a rational choice | In Rhabdomyosarcoma nIGF-1R is associated with adverse patient outcomes | IGF-1R and ALK expressions is detected in patients with RMS. Prominently in aRMS IGF-1R is highly expressed. |
| 2017 | Lin et al | SUMO‐modified insulin‐like growth factor 1 receptor (IGF‐1R) increases cell cycle progression and cell proliferation | SUMOylation of IGF‐1R is not an absolute requirement for nuclear translocation | This study highlights that SUMOylated IGF-1R induce cell proliferation |
| 2015 | Zhang et al | SUMOylation of insulin-like growth factor 1 receptor, promotes proliferation in acute myeloid leukemia | IGF-I ligand increases the upregulation of IGF-1R modified by SUMO-1 | UBC9 plays a pivotal role in SUMOylation and in AML, IGF-1R can be modified by SUMOylation |
| 2012 | Hoa et al | Nuclear targeting of IGF-1 receptor in orbital fibroblasts from Graves' disease: apparent role of ADAM17 | IGF-I along with GD-IgG mediates the nuclear accumulation of IGF-1R in Graves' disease | IGF-1R also translocate to the nucleus in an autoimmune disease |
| 2019 | Werner et al., | Identification of nucleolar protein NOM1 as a novel nuclear IGF-1R interacting protein | NOM1 acts as an interacting protein for nIGF-1R | NOM1 is a significant binding partner of nIGF-1R |
| 2012 | Wu et al | Novel nuclear localization and potential function of insulin-like growth factor-1 receptor/insulin receptor hybrid in corneal epithelial cells. | Nuclear IGF-1R plays a key role in gene regulation and nuclear receptor interacts with DNA | In a non-cancerous cell line, heterodimer hybrid of IGF-1R/INSR localize to the nucleus |