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Inhibition of the Insulin-like Growth Factor-1 Receptor (IGF1R) Tyrosine Kinase as a Novel Cancer Therapy Approach

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1. Introduction

The initial experimental evidence for insulin-like growth factor (IGF; originally referred to as sulfation factor or somatomedin) bioactivity was demonstrated just over 50 years ago by Salmon and Daughaday.¹ The genes encoding the ligands insulin-like growth factor-1 and -2 (IGF1, IGF2) as well as insulin, and their receptors, were cloned in the 1980s,²⁻⁷ and mitogenic activity of IGF1 for breast carcinoma cells was first demonstrated in 1984.⁸ IGF1R expression was demonstrated on human cancers and the possibility of therapeutically targeting cellular signaling mediated by the receptor suggested in 1987,⁹ and antitumor activity of an IGF1R-specific antibody was demonstrated only two years later in a human breast cancer xenograft mouse model by Arteaga and colleagues.¹⁰ In the 1990s and during the first half of the current decade, both epidemiological population-based studies, which showed a correlation between circulating IGF1 levels and cancer risk (for example, see ref. 11), and laboratory-based research performed by a number of investigators, which showed that IGFs can promote the growth of multiple types of cancer (for example, see refs. 12-16), provided validation for the relevance of IGF signaling in oncogenesis. Since 2000, a number of agents that target IGF1-IGF1R signaling have been shown to possess antitumor activity in preclinical studies (for example, see refs. 17-23) and this research has led to the evaluation currently of more than 10 different drug candidates targeting IGF1 signaling in clinical trials.²⁴ Initial results from this expanding clinical trial activity were reported in 2007, with the release of results from Phase I trials of IGF1R-antagonistic monoclonal antibodies (for example, see refs. 25-30), and the clinical development has now progressed to include several Phase II trials as well as the recent launch of a Phase III trial (the latter with the fully human monoclonal antibody CP-751,871 from Pfizer) for several of these antibodies.²⁴ Although antibody-based anti-IGF1 signaling therapeutic development has been in the forefront to date, considerable work has also been undertaken on other modalities as well.³¹⁻³⁹ In this Perspective, we focus primarily on efforts to design and develop small-molecule IGF1R kinase inhibitors.

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2. Physiological functions of the IGF1R

a. Background regarding the IGF1R/IGF-1 and -2/IGFBP signaling axis

The IGF signaling system is comprised of two ligands – IGF1 and IGF2; three cellular membrane-spanning receptors – the IGF1 receptor (IGF1R), the insulin receptor (IR), and the IGF2 receptor (IGF2R); and six high-affinity IGF-binding proteins – IGFBP1-6 (reviewed in detail in refs. ^{31, 32, 35, 37-39}). The central component of the IGF system and the main focus of this review is the IGF1R, a type 2 tyrosine kinase receptor that shares 60% homology at the amino acid level with the IR.^{6, 7} The IGF1R is synthesized as a single-chain 1367-amino acid pre-propeptide that possesses a 30-amino acid signal peptide, which is cleaved after translation. This propeptide is then glycosylated, dimerized, and transported to the Golgi apparatus, where it is processed at a furin cleavage site to yield alpha and beta subunits. These subunits form a tetramer (beta-alpha-alpha-beta), linked through disulfide bonds, which is transported to the plasma membrane.⁴⁰ The fully mature cell membrane-bound IGF1R consists of two 130- to 135-kDa alpha chains and two 90- to 95-kDa beta chains, with several alpha-alpha and alpha-beta disulfide bridges.⁴¹ The alpha subunits are entirely extracellular and form the ligand-binding domain,⁴² which binds one ligand molecule.

IGF1 and IGF2 share 62% amino acid homology; in addition, there is 40% homology between the IGFs and proinsulin.⁴³ IGF2 concentrations are normally higher than IGF1 levels in both the human fetus and adult sera (5- and 3.5-fold higher, respectively).⁴⁴ Experimental evidence suggests that the binding sites for IGF1 and IGF2 on the IGF1R may be distinct.^{45, 46} Ligand-binding affinities of IGF1 and IGF2 for the IGF1R have been shown to vary somewhat depending upon cell type and experimental conditions; for example, in cultured adult bovine chromaffin cells, the IGF1R bound the two ligands with identical affinities ($K_d \sim 1$ nM) whereas recent experiments using recombinant IGF1R protein in surface plasmon resonance-based studies as well as cell-based assays suggested a difference of 4-fold in affinities, with IGF1 exhibiting a higher affinity (4.45 nM) than IGF2 (17.8 nM).^{47, 48} IGF2 and, with a much lower affinity, IGF1 can also bind to a second receptor – IGF2R, which is identical to the cation-independent mannose-6-phosphate receptor and functions as a scavenger receptor.⁴⁹ Furthermore, IGF2 can also bind the insulin receptor subtype A (IR-A) with an affinity similar to that of insulin.⁵⁰ The IR-A – a short isoform of the IR generated by the skipping of exon 11, which encodes for 12 amino acids at the C-terminal end of the IR alpha subunit – is more mitogenic than the B subtype, the latter possessing a more metabolic function; the IR-A is the predominant form expressed in normal fetal tissues as well as malignant cells.⁵⁰⁻⁵⁵ For example, IR-A increased expression has been described in breast, colon and lung tumor specimens, and on primary cultures and cell lines established from other tumors such as ovarian and thyroid carcinomas.^{50, 51, 54, 56}

The complexity of signaling mediated by the IGF system is further complicated by the existence of hybrid heterodimeric receptors in cells consisting of IGF1R and insulin receptor subunits. The basis and full significance of the preferential expression of the IR-A isoform and of IGF1R/IR-A heterodimers in malignant cells is not yet completely clear, and is a topic of ongoing investigations.⁵⁶ However, currently available data do suggest signaling generated from these heterodimeric receptors to be of pathogenic importance; for instance, in the human breast cancer cell line MDA-MB157, hybrid IGF1R/IR receptors have been shown to undergo autophosphorylation in response to IGF1, and this response exceeds the autophosphorylation of non-hybrid IGF1Rs and promotes increased cellular proliferation, suggesting that hybrid receptors are the major transducers of IGF signaling in these cells.⁵⁷ Clinical data also support a role for these hybrid receptors during carcinogenesis; for example, the expression of hybrid receptors was found to exceed that of non-hybrid IGF1R in over 75% of 39 human breast cancer specimens examined.⁵⁷ Since IGF2 is the predominant IGF in the circulation of adults, it may be that the interaction of IGF2 (rather than IGF1) with hybrid IGF1R/IR-A receptors

contributes most substantively to cancer cell growth in such settings. It also seems clear that the ability of insulin to increase the growth of neoplastic cells, an effect noted more than 30 years ago^{58, 59} and recently re-visited and confirmed by several studies, is mediated at least in part via the activation of IGF1R/IR heterodimers.⁶⁰⁻⁶⁵

The IGF1R has also been reported to form heterodimers with the HER2/ERBB2/NEU (hereafter simply HER2) tyrosine kinase and to contribute to the development of resistance to HER2 inhibition with the monoclonal antibody trastuzumab.⁶⁶ The IGF1R physically interacts with HER2 in breast cancer cells that have acquired resistance to trastuzumab but not in parental, trastuzumab-sensitive cells. Stimulation of the IGF1R results in increased phosphorylation of HER2 in resistant (but not parental) cells, and the inhibition of IGF1R kinase activity leads to decreased HER2 phosphorylation in only trastuzumab-resistant cells. Disruption of IGF1R/HER2 heterodimer formation experimentally using the anti-IGF1R antibody α -IR3 dramatically restored the sensitivity of trastuzumab-resistant breast cancer cells to the anti-HER2 antibody, emphasizing the pathophysiologic relevance of the association of the two kinases.⁶⁶

The physiological activities of the IGFs are regulated in part by their physical association with the IGF-binding proteins (IGFBPs), a six-member family of secreted proteins (IGFBP1-6) that bind both IGF1 and IGF2 with high (although varied) affinities.^{67, 68} The IGFBPs can either potentiate or inhibit IGF function, in part by maintaining a reservoir of IGFs in the circulation (a function mainly of IGFBP3) and by transporting IGFs from the circulation to peripheral tissues (IGFBP1, 2, and 4). In addition, the IGFBPs mediate IGF-independent biological effects that will not be discussed in this review (for a detailed discussion and specific example of this role for the IGFBPs, see refs. 67- 69).

b. Signal transduction downstream of the IGF1R

Ligand binding and subsequent activation of the IGF1R initiates the propagation of cell survival and proliferative signals through intracellular signaling cascades.^{70, 71} An illustration of the major signaling pathways activated by the IGF1R is provided in Figure 1. Activation of these intracellular pathways begins by ligand binding to the extracellular alpha subunits of the IGF1R.⁷⁰ Ligand binding induces a conformational change and autophosphorylation of the key tyrosine (Y) triplet residues Y1131, Y1135 and Y1136 in the activation loop of the IGF1R, leading to transphosphorylation of the opposing beta subunit; the inactive, non-ligand-bound form of the IGF1R sterically hinders the ATP-binding pocket of the kinase catalytic domain, thus preventing ready access of the receptor to ATP.⁷⁰ The intracellular portion of the beta subunit contains other domains critical for receptor activation and subsequent initiation of signaling pathways. After phosphorylation of the key triplet tyrosines in the activation loop, other tyrosine residues in the juxtamembrane region, kinase domain, and carboxy-terminus of the beta subunits are autophosphorylated, thereby generating docking sites for adaptor proteins that recognize specific sequences containing the phosphorylated tyrosines.^{32, 70} In addition to the tyrosine residues, mutations in serine (S) residues 1280-1283 (S1283 being phosphorylated during the signaling process) have been shown to abrogate the transforming ability of the IGF1R but still maintain mitogenicity;⁷² this serine quartet is involved in the activation of ERK1/2, especially in cells that do not express IRS-1.⁷³

The engagement of the various downstream signaling cascades is mediated through the interactions of the activated IGF1R with adaptor proteins. As an example, phosphorylation of Y950 in the juxtamembrane domain of the IGF1R forms a docking site to recruit and phosphorylate the Src homology 2 domain-containing SHC (for Src homologous and collagen) adaptor protein.^{32, 74} SHC recruitment and phosphorylation in turn lead to activation of the RAS/RAF/MEK/ERK pathway through recruitment of the adaptor protein growth factor receptor-bound protein 2 (GRB2).^{70, 75} In addition to SHC, GRB2 can also be recruited by

the insulin receptor substrate (IRS)-1, another IGF1R adaptor protein.⁷⁶ Following GRB2 recruitment to the IGF1R, the guanine nucleotide exchange factor son of sevenless (SOS) is recruited and aids in the exchange of GDP for GTP on the membrane-bound small GTP-binding protein RAS.⁷⁷ GTP binding leads to a conformational change of RAS and creates a high-affinity binding site for RAF, leading ultimately to the phosphorylation and activation of the RAF serine/threonine kinase.⁷⁷ Activated RAF in turn phosphorylates the MEK dual-specificity serine/threonine and tyrosine kinases, which then phosphorylate and activate the serine/threonine kinases, ERK-1 and ERK-2.⁷⁷ Activation of the ERKs leads to both phosphorylation of cytoplasmic substrates and nuclear translocation and activation of various transcription factors (e.g., c-Myc, Ets factors, CREB, AP1) that control the expression of many genes. Ultimately, this signaling cascade culminates in the generation of pro-proliferative and anti-apoptotic effects in many cell types.⁷⁷ For example, one of the cytoplasmic substrates of ERK includes procaspase-9 – the zymogen form of the pro-apoptotic caspase-9 protein; the phosphorylation of procaspase-9 at threonine 125 by ERK has been demonstrated to prevent the conformational change of the proenzyme to active caspase-9, thus enhancing cellular survival.⁷⁸ The complexity of these signaling pathways is further amplified by the finding that different isoforms of RAS can preferentially activate different kinase signal transduction cascades. Specifically, it has been reported that Ki-RAS activates the RAS/RAF/MEK/ERK pathway, while Ha-RAS is a more potent activator of the PI3K/AKT pathway.⁷⁹ In addition to the role of RAF in the aforementioned signaling cascade, mitochondrial-associated RAF has been reported to have an anti-apoptotic effect, although the precise regulation and overall physiological relevance of the mitochondrial translocation of RAF remain to be fully elucidated.⁸⁰

The activation of the RAS/RAF/MEK/ERK pathway plays a vital role in the development and progression of cancer, with either RAS or RAF being mutated in a substantial percentage and variety of malignancies.⁸¹ Inhibition of RAS activation, by interference with its farnesylation and subsequent membrane localization, has been shown to induce cell death *in vitro* but pharmacological farnesylation inhibitors have proven to have less than optimal efficacy in clinical cancer trials performed to date.^{82–84} By contrast, the inhibition of RAF has been proven to be more promising in the clinic, as exemplified by the RAF kinase inhibitor sorafenib, **1** (BAY 43-9006, Bayer HealthCare Pharmaceuticals and Onyx Pharmaceuticals), which has recently been approved for the treatment of patients with certain malignancies such as renal cell and hepatocellular carcinomas.^{85–87} Importantly, recent data suggest that inhibition of the IGF1R (using a human IgG1 monoclonal antibody) potentiates the anticancer activity of pharmacological interference with the RAS/RAF/MEK/ERK pathway; similarly, abrogation of IGF1R activation appears to potentiate the antitumor efficacy of inhibitors of PI3K/AKT/mTOR pathway signaling (*vide infra*; see also **Section 3b**).⁸⁸ Therefore, to fully inhibit aberrant activity of these signaling pathways in malignancies, it may be necessary to target both upstream receptor tyrosine kinases, such as the IGF1R, and components within the downstream intracellular signaling cascades.

In addition to the RAS/RAF/MEK/ERK signaling cascade, activation of the IGF1R can engage the PI3K/AKT pathway. Docking of IRS-1 to either phosphorylated Y950 or the Y1131, Y1135 and Y1136 triplet motif of the IGF1R recruits the p85 regulatory subunit of phosphatidylinositol-3 kinase (PI3K), which then activates its p110 catalytic subunit.^{70, 74, 76, 89} Activated PI3K phosphorylates membrane-associated phosphatidylinositol 4,5 phosphate (PIP₂) to generate phosphatidylinositol 3,4,5 phosphate (PIP₃), in turn resulting in membrane localization of phosphatidylinositol-dependent kinase (PDK)-1.⁸⁹ The conversion of PIP₂ to PIP₃ also recruits AKT to the membrane, leading to its phosphorylation and subsequent activation by PDK1 and PDK2.⁹⁰ The AKT serine/threonine kinase itself can phosphorylate a number of targets that ultimately contribute to cellular anti-apoptotic and proliferation-enhancing effects.⁸⁹ For example, the pro-apoptotic BH3-only BCL2 family

member BAD, which can bind and inhibit the anti-apoptotic BCL2 family proteins BCL2 and BCL-XL, is phosphorylated by AKT.⁷⁰ Phosphorylated BAD is sequestered by binding to 14-3-3 proteins rather than BCL2 and BCL-XL, in turn allowing the two anti-apoptotic proteins to efficiently associate with and neutralize other apoptosis-promoting molecules and thus abrogate the pro-death signals.⁷⁰ Activated AKT can also affect cellular metabolism by phosphorylating and inactivating GSK (glycogen synthase kinase)-3 β .⁹¹ The inactivation of GSK-3 β promotes the dephosphorylation and activation of glycogen synthase (GS), which upregulates glycogen synthesis. Activated AKT plays a pivotal role as well in the regulation of translation via phosphorylation and activation of the serine/threonine kinase mammalian target of rapamycin (mTOR).⁹² Activation of mTOR is accomplished by phosphorylation and subsequent inactivation of the GTPase-activating heterodimeric protein tuberous sclerosis complex 1/2 (TSC1/2; also known as Hamartin/Tuberin, respectively) on TSC2.^{93, 94} The inactivation of TSC1/2 relieves inhibition on the RAS-family GTP-binding protein RHEB, which subsequently activates mTOR by antagonizing the endogenous mTOR inhibitor FKBP38.⁹⁵⁻⁹⁷ Key targets of mTOR affecting protein synthesis are the family of binding proteins termed eIF4E-binding proteins (4E-BPs) and the ribosomal S6 family of kinases (S6K1 and S6K2). The function of 4E-BP is to sequester and inhibit the eukaryotic initiation factor (eIF) 4E.⁹² Phosphorylation of 4E-BP proteins by mTOR causes disassociation from them of eIF4E and allows eIF4E to bind the 5' cap of mRNA and cooperate in the formation of the translational initiation complex, thereby enhancing protein translation.⁹² Several groups have demonstrated that eIF4E can function as an oncogene and possesses anti-apoptotic capabilities.^{92, 98, 99} The S6 kinases are also involved in the formation of the translation initiation complex. Phosphorylation of S6K releases it from eIF3 and S6K is then phosphorylated and fully activated by PDK1.^{92, 100} The fully activated S6K phosphorylates eIF4B, which then associates with eIF3 in the translation initiation complex.^{92, 100} Other targets of mTOR play a role in the regulation of protein translation as well, as described in recent reviews.^{92, 101} Inhibition of mTOR has also been investigated as an attractive target for antitumor agents. Analogs of the mTOR inhibitor rapamycin have demonstrated activity in clinical trials for a number of tumor types, and the first mTOR inhibitor temsirolimus (Wyeth Pharmaceuticals) for clinical use as an anticancer agent was approved by the FDA in 2007 for the treatment of advanced renal cell carcinoma.¹⁰²⁻¹⁰⁵ Recent data suggest that the inhibition of mTOR relieves negative feedback regulation of IRS-1, resulting in increased IRS-1 expression and activation of AKT.¹⁰⁶ This increased AKT activation may lead to decreased sensitivity to mTOR inhibitors, and simultaneous inhibition of the IGF1R and mTOR may be an effective combination for overcoming resistance to mTOR inhibitors (see also Section 3b).¹⁰⁶ In addition, recent studies have demonstrated that the combination of mTOR and inhibitors of other receptor tyrosine kinase inhibitors induces synergistic cell death *in vitro* and *in vivo*.¹⁰⁷⁻¹¹⁰

c. Function of IGF1R in normal development and growth, and potential negative consequences of inhibiting IGF1R function

The IGF axis fulfills critical functions during normal growth and development. Mice with deletion of either the *Igf1* or *Igf1r* genes have severe growth abnormalities,^{111, 112} and humans with functional disruption of IGF1 or the IGF1R suffer similar growth abnormalities.^{113, 114} *Igf1* knockout mice have a complex phenotype, with their birth weight averaging approximately 60% of normal and with some mice dying shortly after birth; in addition, surviving *Igf1* knockout mice suffer multiple abnormalities including underdeveloped muscles and lungs, delayed ossification, and infertility. *Igf1r* knockout mice exhibit even more severe developmental retardation than *Igf1*-null animals, with death occurring invariably at birth, severe *in utero* growth retardation with average weights only approximately 45% of normal controls, and multiple organ abnormalities (e.g., hypoplasia, abnormal skin formation, delayed bone development, anomalous central nervous system morphology). As a result of the

importance of signaling by the IGF axis during growth and development, it is therefore possible that children and adolescents could have poor growth and perhaps other developmental delays if they were treated with IGF1R inhibitors, especially for prolonged periods; these data also suggest that the administration of IGF1R inhibitors may be contraindicated during pregnancy.

While the functional importance of signaling by the IGF1R in the adult is not fully clear, aggressive and extended blockade of signaling by the receptor could potentially produce clinical signs and symptoms similar to those of severe untreated growth hormone deficiency including osteoporosis, hyperlipidemia, visceral adiposity, cardiac events, impaired physical performance, and psychological complaints.¹¹⁵ It might also be expected that inhibition of normal physiologic feedback loops mediated by the IGF1R in the hypothalamus could result in an abnormal increase in growth hormone secretion; the metabolic consequences of excessive growth hormone production in the absence of IGF1R function are unknown but one might predict that IGF1-independent effects of growth hormone (e.g., lipolysis) could be increased under such circumstances.

Specific organ systems could be especially predisposed to toxicities as a result of IGF1R inhibition. For example, based on data generated using genetically engineered mice, it is now established that skeletal expression of IGF1 is critical for differentiative bone cell function, and it may also be essential for the full anabolic effects of parathyroid hormone on trabecular bone and for some aspects of biomineralization;¹¹⁶⁻¹¹⁷ in addition, low circulating levels of IGF1 in people have been associated with decreased bone mineral density (osteoporosis) and increased risk of fractures in various ethnic groups, and osteoblasts from patients with osteoporosis exhibit dysregulated IGF1R signaling.¹¹⁶⁻¹¹⁸ Furthermore, the development and extent of peak bone density during puberty in both mouse and man appears to be highly dependent upon serum IGF1 levels.¹¹⁶ Thus, IGF1R inhibition (especially for prolonged periods) may be relatively contraindicated in adolescents during the pubertal growth period or in adult patients with pre-existing severe osteoporosis. IGF signaling also plays important roles in neuronal survival throughout life,¹¹⁹⁻¹²⁰ and inhibition of IGF1R function could thus have negative effects on the central and peripheral nervous systems. IGF1 functions in the brain as a pleiotropic factor that promotes the proliferation of oligodendrocytes, myelination, neurite outgrowth, and the survival of neurons and glial cells.⁷⁰⁻¹²¹ IGF1 treatment within the initial hours following brain injury has been shown to be beneficial in limiting the extent of pathological apoptosis in experimental animal models of hypoxic/ischemic stroke; for example, ventricular infusion of IGF1 substantially reduced the infarction rate and neuronal loss induced by unilateral hypoperfusion in an adult rat stroke model.¹²² Conversely, one might predict that inhibition of IGF1 signaling via blockade of the IGF1R would potentially increase the severity of ischemic brain injury. As such, a relative contraindication to the administration of IGF1R inhibitors to specific patients might be a history of severe cerebrovascular disease and prior stroke. Similarly, neurodegenerative diseases such as amyotrophic lateral sclerosis (ALS, Lou Gehrig's disease), Huntington's disease, as well as Alzheimer's disease, which are characterized in part by pathological apoptosis, could potentially be adversely affected by IGF1R inhibition.^{70, 122-123}

Signaling by the IGF1R has also been suggested to play a role in cardiac myocyte survival.^{124, 125} In addition, IGF axis signals participate in the physiological cardiac hypertrophic responses to exercise, and play a role as well in the hypertrophic responses to hypertension.^{124, 126-131} The importance of IGF axis signals in normal cardiac function has been elegantly demonstrated by recent studies in mice with inactivation of both the insulin and Igf1 receptors in their cardiac and skeletal muscles¹³²; these double knockout mice suffer early-onset dilated cardiomyopathy and lethal heart failure within their first month of life despite having normal glucose homeostasis. Mice lacking the insulin receptor alone showed impaired cardiac performance at 6 months of age, and mice lacking the insulin receptor and one Igf1r allele had

slightly increased mortality; in contrast, animals that lacked the Igf1r or the Igf1r plus one insulin receptor allele appeared normal. These data suggest that neither the insulin receptor nor the IGF1R in muscle are essential for normal glucose control, at least during early postnatal life, but signaling by the two receptors – especially the insulin receptor – appears to be essential for normal cardiac function.¹³² Other tyrosine kinases, such as HER2 and ABL, also seem to be critical for normal cardiac function, and downregulation of signaling by these kinases in cancer patients treated with the HER2 inhibitor trastuzumab or the BCR-ABL inhibitor imatinib, 2 (STI-571, Novartis) has been associated with heart failure in occasional cases. 133-135 Signaling by phosphoinositide 3-kinase (p110alpha) may be a common feature that explains at least in part the cardiac toxicity that can occur following tyrosine kinase inhibitor therapy. PI3K (p110alpha), which phosphorylates serine/threonine residues on its substrates and is activated by the aforementioned and many other tyrosine kinases, is known to be protective of cardiac function; for example, mice deficient in PI3K (p110alpha) display accelerated heart failure in response to hypertrophic or dilated cardiomyopathies.¹²⁴⁻¹³⁶ 137 Collectively, these observations suggest that special care regarding cardiac health could possibly be warranted during the clinical use of IGF1R inhibitors, especially in patients with pre-existing cardiac disease and those treated with chemotherapeutic agents known to have heart toxicities associated with them (e.g., doxorubicin).

Adverse effects upon metabolism and homeostasis are also potential negative consequences of inhibition of IGF axis signals. Disruption of Igf1r signaling in mice with tissue-specific deletion of the *Igf1*, *Irs-2* or *Igf1r* genes has led to some degree of insulin resistance in most model systems examined (reviewed in ref. 138). It is not fully certain whether insulin resistance in these animal models is due to growth hormone overproduction or due to an IGF-dependent event. Clearly, however, liver-specific deletion of Igf1 has been shown to cause an insulin resistance phenotype.¹³⁹ Inactivation of the Igf1r, *Irs-1*, or *Irs-2* in pancreatic beta cells (the insulin-producing endocrine cells of the pancreas) has been shown to decrease beta cell mass and increase apoptotic death of these cells.¹⁴⁰⁻¹⁴² Insulin resistance, together with possible reductions of beta cell numbers and function, as a result of treatment with IGF1R inhibitors could potentially cause clinically evident diabetes. Indeed, hyperglycemia has been encountered in patients occasionally with treatment using IGF1R-specific antibodies, probably as a consequence of insulin resistance induced by high levels of growth hormone (rather than direct inhibition of the insulin receptor);¹⁴³ treatment-induced hyperinsulinemia has also been observed.²⁵ In addition, because many small-molecule ATP-competitive IGF1R inhibitors discriminate poorly between the IGF1R and the insulin receptor (due to the high homology shared by the catalytic domains of the two kinases), both hyperglycemia and hyperinsulinemia have been observed in preclinical studies using them (for example, see ref. 19). It is important to note that such iatrogenic perturbations in glucose/insulin metabolism are likely to be transient and either self-limited or amenable to medical intervention; for example, the most extreme consequences of insulin resistance such as those observed in individuals with leprechaunism associated with insulin receptor mutations (severe insulin-resistant diabetes, acanthosis nigricans, lipodystrophy, hypertrichosis, acral hypertrophy [enlargement of the ears, nose, chin, and fingertips])¹⁴⁴ would not be expected with the intermittent and relatively short-term inhibition associated with therapeutic IGF1R blockade during antitumor therapy.

3. Role of the IGF1R in oncogenesis

a. Clinical and epidemiological evidence for IGF1R signaling in tumorigenesis

The importance of the IGF signaling axis to cancer development, progression, and metastatic spread cannot be fully appreciated by simple analysis of the expression levels of the IGF1R and its ligands alone. Furthermore, the significance of IGF and IGF1R expression levels as indicators of tumor stage or disease prognosis tends to track in a tumor-specific fashion. Nevertheless, some generalizations are made below.

A wide variety of malignancies have been documented to contain increased expression of the IGF1R, IGF1, and/or IGF2 including breast cancers, cancer of the prostate, gastrointestinal tract malignancies (e.g., colorectal, hepatocellular, and pancreatic carcinomas), ovarian and endometrial cancers, glioblastomas, medulloblastomas, and neuroblastomas (see ref. ³⁸ for a comprehensive review). These reports have suggested a consistent correlation between IGF1/IGF2 expression levels and tumor progression in some malignancies (e.g., colorectal, hepatocellular, and pancreatic) but not others (e.g., breast cancers); in other cases (e.g., gliomas), conflicting results have been reported in different studies. However, considered as a whole, the above-noted studies suggest that the IGF signaling axis can play a paracrine and/or autocrine role in promoting tumor progression but that the role may differ depending on the specific tumor type, as illustrated in more detail below for the two most common malignancies, breast and prostate cancer.

In the case of breast cancer, conflicting data exist regarding the clinical and prognostic significance of IGF1R expression. For example, a study of 126 breast cancer specimens showed 39% to be IGF1R-positive; a significant correlation between IGF1R expression and estrogen receptor (ER) status was noted, and the expression of the IGF1R was found to correlate with disease-free survival;¹⁴⁵ specifically, this study suggested that patients with ER-negative/IGF1R-positive tumors suffer a worse prognosis compared to patients with ER-negative/IGF1R-negative disease. In a study of 150 breast cancer samples,¹⁴⁶ 47% of the tumors were shown to express increased levels of the IGF1R, and this increased expression was correlated with positive ER and/or progesterone receptor (Pgr) status and lower nuclear grade; in this analysis, breast cancer cases with IGF1R overexpression tended to have a better prognosis than cases without receptor overexpression among hormone receptor-positive tumors (although the difference was not statistically significant; $P = 0.09$), while IGF1R expression status was not correlated with prognosis in ER-negative and Pgr-negative cases. In another study that examined 210 formalin-fixed paraffin-embedded primary breast cancers using immunohistochemistry, IGF1R overexpression was observed in 43.8% of the specimens, but no correlation with prognosis, tumor size, lymph node status, histological grade, hormone receptor status, or HER2 status could be made.¹⁴⁷

With respect to prostate cancer as well, conflicting evidence for the role of IGF signaling in disease progression has been published. For example, a 2002 study showed a significant upregulation of the IGF1R mRNA and protein in primary prostate cancers and bone metastases compared with benign prostatic epithelium;¹⁴⁸ by contrast, an earlier study published in 1996 described decreased IGF1R mRNA expression in both high-grade prostatic intraepithelial neoplasia (PIN) and prostate cancer compared to benign tissue, thus implying that IGF1R expression was actually inversely correlated with disease progression.¹⁴⁹ In another study in which the expression of IGF1, IGF2, and their receptors was determined in 23 paired benign and neoplastic specimens, no correlation was identified between their expression and tumor grade, stage, perineural invasion, or extra-prostatic involvement.¹⁵⁰ At least a partial explanation – an explanation that reflects the aforementioned complexity of signaling mediated via the IGF axis – for these conflicting data in prostate cancer has recently been described: among various markers analyzed including serum prostate-specific antigen (PSA), IGF1/PSA ratios, and conventional TNM staging, the ratio of IGFBP3/PSA was identified as the only significant variable for relapse-free survival and was an independent predictor of survival in advanced prostate cancer patients.¹⁵¹ In other malignancies, recent data suggest that more refined analyses of several components of the IGF axis (e.g., IGF1/IGFBP ratios) may better predict disease progression than determination of one factor alone. For example, in bladder cancer, plasma IGF1 and IGFBP3 levels were not significantly different from those found in healthy individuals when compared separately; by contrast, when adjusted for serum IGF1 level, lower preoperative IGFBP3 plasma levels were found to be associated with a higher incidence of lymph node metastases and a poorer clinical outcome in these patients.¹⁵²

The bulk of data from the epidemiology literature do support a role for the IGF axis in tumor development (reviewed in refs. 37-39). For example, an increased risk for the development of multiple malignancies (bladder cancer, premenopausal breast carcinoma, colorectal carcinoma, endometrial cancer, lung cancer, and prostate cancer), presumably through paracrine activation of receptors, has been associated with elevated serum IGF concentrations (i.e., levels in the highest quartile within the normal range) and/or lower levels of serum IGFBNPs. Furthermore, an elevated incidence of precancerous colonic adenomas, as well as cervical squamous intraepithelial lesions, has been linked to higher levels of circulating IGF1, supporting a role for the IGF axis in the early stages of carcinogenesis.^{153, 154} Increased expression of IGF2, due to the loss of imprinting (LOI) also appears to be an epidemiologic risk factor for the development of certain malignancies.¹⁵⁵ The *IGF2* gene is normally maternally imprinted in humans but bi-allelic expression can occur due to LOI. LOI has been reported in colorectal carcinomas, childhood acute lymphoblastic leukemias, juvenile nasopharyngeal angiofibromas, and Wilm's tumors. Epidemiologically, LOI of the *IGF2* gene can be frequently observed in the colonic mucosa of colorectal carcinoma patients and may be an independent risk factor for developing this carcinoma; interestingly, the same genetic alterations leading to LOI found in cells of the colon are also found in peripheral lymphocytes of colorectal cancer patients, suggesting the possibility of a DNA-based blood test to follow individuals for cancer development.¹⁵⁶ Mouse modeling of IGF2 LOI and overexpression also implicates a role for IGF2 as a tumor initiator/promoter in intestinal cancers.¹⁵⁷

A number of animal models strongly support a role for aberrant IGF axis signaling in the genesis, progression and metastasis of cancer (reviewed in ref. 38). Arguably, the most compelling support from animal models for a substantive role of signaling mediated by the IGF1R itself in oncogenesis has been provided by human xenograft studies examining the efficacy of receptor inhibition. As an example, Kolb and colleagues studied the activity of a fully human anti-IGF1R neutralizing antibody against a number of pediatric tumor xenografts (including specimens representing rhabdoid tumor, Wilm's tumor, Ewing's sarcoma, rhabdomyosarcoma, medulloblastoma, ependymoma, glioblastoma, neuroblastoma, osteosarcoma and acute lymphoblastic leukemia);¹⁵⁸ although the antibody did not substantively retard the growth of cell lines *in vitro*, significantly increased event-free survivals were observed *in vivo* in 20 of 35 (57%) of the solid tumor xenografts with complete responses observed in one Ewing's sarcoma and two osteosarcoma models. By contrast, little activity was observed against eight different xenografts of acute lymphoblastic leukemia cases. Overall, this study revealed major effects in controlling tumor growth in approximately one-third of the solid tumor xenografts tested (although the objective response rate was modest given the occurrence of only three complete responses, suggesting that rationally designed combinations of IGF1R inhibitors with other anticancer agents is likely to provide optimal treatment efficacy).

b. Role of the IGF1R in mediating resistance to various cancer therapies

Cancers treated with conventional radio- and/or chemotherapy frequently develop resistance to these treatments, ultimately leading to recurrent disease that often has a more aggressive phenotype than that observed at the time of the original diagnosis. Multiple lines of evidence suggest that the IGF signaling axis contributes to the acquisition of tumor resistance to therapy. Several studies, for example, have supported a function for signaling via the IGF1R in the protection of cells from DNA-damaging agents such as ionizing and ultraviolet B irradiation and chemotherapeutic drugs; mechanistically, this protection involves IGF1R-mediated inhibition of apoptotic cell death via activation of the PI3K/AKT pathway as well as rescue from drug-induced cytostasis through the activation of MAPK pathway signals.¹⁵⁹⁻¹⁶⁵

IGF signaling appears also to directly interfere with the normal cell growth arrest and proapoptotic responses triggered by activation of the p53 tumor suppressor upon the treatment of tumor cells with anti-cancer agents. In cells experimentally subjected to chemically-induced DNA damage, the IGF1R has been demonstrated to upregulate expression of the mRNA encoding the p53 ubiquitin ligase protein MDM2 via activation of p38 MAPK; under such circumstances, this excess MDM2 protein translocates to the nucleus and facilitates p53 ubiquitination, thus targeting p53 for proteasome-mediated degradation.¹⁶⁶

Signaling mediated by the IGF system may also confer a multidrug-resistance (MDR) phenotype to cancer cells by the induction of MDR-related genes including *Mdr-1* (with increased expression of the p-glycoprotein drug efflux pump encoded by the *Mdr-1* gene) and manganese superoxide dismutase (MnSOD), a mitochondrial anti-oxidant enzyme that catalyzes the conversion of toxic superoxide radicals to hydrogen peroxide and molecular oxygen, thus leading to tumor cell protection.¹⁶⁷ Experiments using a mouse colon cancer cell line revealed that incubation of the cells with IGF1 rendered them significantly less sensitive to cell death associated with cytotoxic agents such as actinomycin D and doxorubicin, and this decreased death was accompanied by concomitant induction of *Mdr-1*, MnSOD, as well as c-H-ras, gene expression.¹⁶⁸

IGF1R signaling has been demonstrated to increase the survival of breast cancer cells treated with 5-fluorouracil, methotrexate, tamoxifen or camptothecin due to its ability to inhibit apoptosis.^{169, 170} Conversely, IGF1R inhibition using antibodies or small-molecule kinase inhibitors has been reported to enhance the cytotoxic effects of a number of conventional chemotherapy agents including gemcitabine, irinotecan, etoposide, carboplatin, adriamycin, ifosfamide, navelbine, 5-fluorouracil, and vincristine both *in vitro* and *in vivo* (reviewed in ref. 39). IGF1R signaling is also involved in radioresistance, in part by modulating ataxia telangiectasia mutated (ATM) function, which regulates the cellular response to DNA damage induced by radiation by triggering cell cycle arrest and apoptosis as well as DNA repair.¹⁷¹⁻¹⁷³ Inhibition of IGF1R signaling has been shown to enhance tumor responses to radiation in breast, gastric, colon and lung cancer models among others,¹⁷⁴⁻¹⁷⁸ and downregulation of IGF1R signals may potentially be a means to render intrinsically radioresistant tumors such as melanoma more sensitive to therapy.¹⁷¹ Thus, IGF1R inhibition may be helpful to augment the effectiveness of conventional chemotherapeutic and/or radiation therapies.

IGF1R signaling has also been found to correlate with resistance to therapies that target other kinases including the EGFR, HER2, mTOR and others. Resistance to anti-EGFR therapies has been observed in both preclinical studies (e.g., in pancreas and prostate cancer cell lines) as well as in clinical studies of lung cancer and glioblastoma patients.¹⁷⁹⁻¹⁸⁷ IGF1R overexpression correlates with decreased effectiveness of EGFR targeting at least in part due to continued activation of PI3K/AKT signaling.¹⁷⁹ Cancers such as lung tumors appear to remain dependent upon EGFR signals despite the development of resistance to EGFR inhibition.^{188, 189} Thus, co-targeting of the IGF1R and EGFR could be a potentially important means to address the problem of anti-EGFR inhibitor resistance; indeed, bispecific antibodies that inhibit both kinases have been reported to cause more inhibition of tumor growth in preclinical models than predicted with a simple additive effect.¹⁹⁰⁻¹⁹²

As mentioned above (**Section 2a**), the IGF1R can form heterodimers with the HER2 tyrosine kinase and contribute to the development of resistance to HER2 inhibition with the monoclonal antibody trastuzumab.⁶⁶ Substantial additional preclinical data support a role for IGF1R signaling in mediating resistance of tumors to HER2 inhibition.¹⁹³⁻¹⁹⁷ For example, studies by Chakraborty and coworkers using breast cancer cell lines with variable levels of HER2 and IGF1R expression showed no single receptor-targeting drug to be capable of inducing apoptosis whereas combining antagonists of both receptors resulted in a marked degree of apoptosis even

in cells in which one of the receptors was not overexpressed; specific inhibitors of one of the receptors were shown to cross-inhibit the other (due to coassociation of HER2 and IGF1R in the cells), with targeting of both providing the maximal inhibition of downstream MAP kinase and AKT signaling.¹⁹⁵ Thus, these and similar data from others suggest that drug combinations that inhibit both IGF1R and HER2 could be useful even in tumors in which single drugs produce minimal anti-neoplastic effects.¹⁹³⁻¹⁹⁷

IGF1R inhibition may also enhance the efficacy of inhibitors of other kinases such as KIT and mTOR as well. Martins *et al.* found IGF1R blockade using the small-molecule inhibitor **3** (NVP-ADW742, Novartis)¹⁷ to synergistically augment the cytostatic effects of imatinib (which inhibits an SCF-KIT autocrine loop found in a portion of Ewing sarcomas), effectively abrogating AKT/mTOR phosphorylation and reducing VEGF expression especially in Ewing's tumor cell lines with high IGF1R activation levels; the combination of **3** with **2** was associated with a significant reduction in tumor cell growth and increased apoptosis that correlated with the extent of IGF1R activation of the lines.¹⁹⁸ Importantly, the antitumor effectiveness of mTOR inhibitors such as rapamycin, temsirolimus, everolimus and others has recently been suggested to be compromised by an induction of PI3K/AKT phosphorylation/activation caused by upregulation of IGF1R-mediated signaling,^{106, 199-201} although one study has suggested that this diminished effectiveness of mTOR inhibition may also occur independent of IGF1R signaling in at least some contexts.²⁰² This enhanced IGF1R signaling has been attributed to autocrine growth loops involving IGF1 as well as increased association of the IRS-1 substrate with the IGF1R and decreased IRS-1 protein degradation. Preclinical studies indicate that IGF1R inhibition prevents the induction of PI3K/AKT by mTOR inhibitors, thus sensitizing tumor cells for growth inhibition and death and providing a strong rationale for the combination of IGF1R and mTOR inhibitors in the clinic.^{106, 199-201}

4. Inhibition of the IGF1R by small molecules

Diverse human diseases including cancer,²⁰³ inflammatory conditions,^{204, 205} diabetes^{206, 207} and Alzheimer's disease²⁰⁸⁻²¹⁰ have become important indications for kinase-targeted drug discovery and development. Since the 2001 FDA approval of the kinase inhibitor **2**,²¹¹ for the treatment of chronic myeloid leukemia, the widely held notion within the pharmaceutical industry that selective kinase inhibition was impossible to achieve was dispelled. By February 2009, despite the challenges in identification of novel and selective kinase inhibitors against a family of 518 proteins, pharmaceutical research and development efforts had already resulted in seven additional launched small-molecule inhibitor products for targeted cancer therapy, validating the protein kinases as a highly meaningful and tractable class of drug targets for therapeutic intervention. Gefitinib (**4**, AstraZeneca),²¹² erlotinib (**5**, Genentech/OSI),²¹³ sorafenib (**1**, Bayer/Onyx),²¹⁴ sunitinib (**6**, Pfizer),²¹⁵ dasatinib (**7**, Bristol-Myers Squibb),²¹⁵ lapatinib (**8**, GlaxoSmithKline)²¹⁶ and nilotinib (**9**, Novartis)²¹⁷ (Figure 2) have already brought substantial clinical benefit to patients with various types of cancers. Moreover, there are approximately 40 small-molecule kinase inhibitors currently at various stages of clinical investigation.²¹⁸ Protein kinases comprise the largest enzyme family, being encoded by 1.7% of the genes in the human genome.²¹⁹ The vast majority of reported kinase inhibitors bind to the highly conserved catalytic domain essential for kinase activity, competing with ATP for association with the ATP-binding pocket. As a result, selectivity is a crucial issue in the design of these inhibitors as potential drugs.

In addition to the background provided above, the complexity of the IGF signaling system and the challenges this complexity poses to the discovery and development of selective IGF1R inhibitors have been reviewed recently by others as well.^{35, 220-224} Further, Sarma and colleagues have summarized the patent literature from 2000 to early 2006 regarding the development of small-molecule inhibitors of the IGF1R.²²⁵ In addition, ongoing clinical trials

for IGF1R-targeted therapeutics in cancer were recently discussed by Ryan and colleagues.³⁶ In the following text, we attempt to provide a comprehensive review and update of both the biomedical and patent literature concerning the current state of IGF1R small-molecule inhibitor development.

a. ATP-competitive inhibitors

i. Tyrphostins—The tyrphostins are derived from a benzylidene malononitrile scaffold and were first reported as kinase inhibitors and potential antiproliferative agents in the late 1980s and early 1990s.²²⁶⁻²³⁰ Subsequently in 1997, compounds from this series of kinase inhibitors were shown to possess inhibitory effects on IGF1R and insulin receptor-stimulated cellular proliferation of NIH-3T3 fibroblasts overexpressing either receptor, and to inhibit ligand-stimulated receptor autophosphorylation and tyrosine kinase activity towards exogenous substrates.²³¹ Among the tyrphostins tested, **10** (AG1024) and **11** (AG1034) (Figure 3) showed significant selectivity against the IGF1R compared to the insulin receptor.²³¹ It was recognized early on that a potential liability of different tyrphostins was their inhibition of a variety of non-kinase enzymes; for instance, **12** (AG82), an analogue of compounds **10** and **11** in which the *tert*-butyl group of R2 in compound **11** is replaced with a hydroxyl, demonstrates inhibitory activity on guanylyl and adenylyl cyclases.²³² Studies of tyrphostins have yielded valuable information regarding the goal of achieving selective inhibition of closely related kinases. For example, 3D-QSAR studies of 50 benzylidene malonitrile tyrphostins as inhibitors of the EGFR and the homologous HER2 kinase revealed that subtle chemical differences could markedly alter kinase selectivity; representative of these studies, **13** was shown to be about 100-fold more selective against the EGFR compared to HER2 while **14** was demonstrated to be almost 1000-fold selective against HER2 compared to the EGFR.²³³ To date, the tyrphostins have served mainly as molecular tools for studying protein kinase inhibition and providing proof-of-principle concepts for the potential therapeutic feasibility of this approach.^{234, 235}

ii. Pyrrolopyrimidines and Pyrazolopyrimidines—Selected pyrrolo[2,3-*d*]pyrimidines were recently disclosed as novel, potent, and selective inhibitors of the IGF1R kinase.^{17, 22} The general structure of this series is shown in Figure 3 as represented by **3**. Warshamana-Greene and colleagues showed compound **3** to be a potent and selective IGF1R kinase inhibitor that could efficiently inhibit the growth of cells that are highly dependent on IGF1 signaling such as certain small-cell lung cancer (SCLC)-derived lines.²³⁶ In addition, synergistic antitumor responses were observed in other SCLC cell lines that possess autocrine growth loops involving stem cell factor (SCF) and the SCF/KIT receptor tyrosine kinase when they were treated with the combination of **3** and an inhibitor of KIT such as **2**, a finding consistent with previous data suggesting that IGF1R-mediated signaling could protect such cells from apoptosis induced by KIT receptor inhibition.²³⁶ Cellular kinase activity assays demonstrated **3** to be a >16-fold more potent inhibitor against the IGF1R than the IR (cellular IC₅₀ values 0.17 and 2.8 μ M, respectively)²² even though the amino acid sequence identity between the IGF1R and IR kinase domains is high (84%)⁷ and the ATP-binding site homology is close to 100%.²³⁷ In addition, compound **3** was shown to have much higher IC₅₀ values against other kinases (e.g., >10 μ M for HER2, PDGFR, VEGFR2 or BCR-ABL p210, and >5 μ M for c-KIT).²² In these studies, reported by Mitsiades and colleagues, the effect of **3** on the viability of 58 hematologic and solid tumor cell lines was assayed, with multiple myeloma lines being the most sensitive to the compound. Furthermore, **3** inhibited multiple myeloma cell growth and enhanced the survival of tumor-bearing mice and, when combined with the alkylating agent melphalan at a subtherapeutic dose, the two compounds synergistically reduced tumor burden. Compound **3** also inhibited the proliferation of Ewing's sarcoma cell lines alone and in combination with imatinib, vincristine, or doxorubicin.¹⁹⁸

Closely related to compound **3**, **15** (NVP-AEW541, Novartis, Figure 3) achieved 27-fold cellular selectivity against IGF1R over the IR (IC₅₀ 0.086 μ M and 2.3 μ M, respectively) even though the *in vitro* inhibitory activity against both of the kinases was equally potent (IC₅₀ 0.15 μ M and 0.14 μ M, respectively); the reason for this unique cellular selectivity was not determined in this report, but the suggestion is that there are conformational differences between the native forms of the two receptor tyrosine kinases that are not present in the recombinant kinase domains used for *in vitro* kinase assays.^{17, 238} Cellular selectivity over other kinases was at least 50- or 100-fold higher (e.g., >10 μ M for HER1 (EGFR), PDGFR or Bcr-Abl p210 and >5 μ M for c-KIT).¹⁷ Compound **15** was also subsequently shown to possess significant *in vitro* and *in vivo* antiproliferative activity in neuroblastoma cancer cell lines.²³⁹ In the same study, compound **15** also inhibited angiogenesis *in vivo*, presumptively due to the downregulation of *VEGF* mRNA, and decreased tumor invasiveness *in vivo* and *in vitro*.²³⁹ Similarly, compound **15** inhibited the migration, metastasis, and angiogenesis associated with the growth of Ewing's sarcoma cancer cell lines.²⁴⁰ Recently, the anticancer activity of compound **15** has also been described in several other cancer types, including hematologic malignancies and pancreatic cancer.²⁴¹⁻²⁴⁴

A high-throughput screen of Abbott's compound repository discovered a pyrazolo[3,4-*d*]pyrimidine class of compounds (which contain insertion of a nitrogen atom at the 2-position of the NVP-ADW series, Figure 3) as moderately potent IGF1R inhibitors.²²⁰ Optimization of this series led to the discovery of a compound demonstrating *in vivo* IGF1R inhibitory activity after oral administration.

A series of pyrrolopyrimidines with different substitution patterns from the Novartis series (*vide supra*) has also been designed and synthesized.²⁴⁵ As shown in Figure 3, **16** and **17** demonstrated modest activity against IGF1R with a slight selectivity over the IR. Based on the general pharmacophore model and molecular modeling, two binding modes to the active site by these molecules were proposed.^{245, 246}

4,6-Bis-anilino-pyrrolopyrimidines from GSK have been reported recently.²⁴⁷⁻²⁴⁹ In that series, substitutions varied at both the 4- and 6-positions while there was no substituent at the 2-position (refer to Figure 3 for positions). The most potent compounds exhibited single-digit nanomolar IC₅₀ values against the IGF1R with 1000-fold selectivity over JNK1 and 3.²⁴⁷ A further optimization of the series yielded both potent and acid-stable inhibitors.²⁴⁸ The optimized compounds demonstrated nanomolar potencies in both enzymatic and cellular assays as well as promising *in vivo* pharmacokinetics in the rat.²⁴⁹

iii. Benzimidazole-pyridones—Another chemotype of IGF1R inhibitors was disclosed by Bristol-Myers Squibb.²⁵⁰ As shown in Figure 3, the initial "hit" **18** was identified as an ATP-competitive inhibitor of the IGF1R kinase with an *in vitro* IC₅₀ of 3.5 μ M.²⁵⁰ Co-crystallization of **18** with a truncated IGF1R containing the kinase domain confirmed that the inhibitor bound in the ATP binding site.²⁵⁰ Further scrutinization of the crystallographic information revealed potential new interactions to explore via the 4-position of the pyridone ring and the benzimidazole methyl group, leading to a key breakthrough after a focused study of the SAR that yielded **19** *in vitro* IC₅₀ of 180 nM.²⁵⁰⁻²⁵² In order to improve the cytochrome P450 profile of compound **19**, the pendant imidazole moiety was replaced by imidazole bioisosteres including amides, amidines, imidazolines, saturated and unsaturated heterocycles. The morpholine group substitution yielded **20** (BMS-536924) and **21**, which are enantiomers of each other, that both possessed low inhibitory activity toward a panel of cytochrome P450 enzymes.^{250, 253} The difference in potency between the enantiomers was about 8-fold, as the *S*-OH isomer **20** showed an IC₅₀ of 100 nM and the *R*-OH isomer **21** had an IC₅₀ of 830 nM.²⁵⁰ Further optimization resulted in **22** (BMS-554417) that had an *in vitro* IC₅₀ of 67.9 nM against IGF1R.¹⁹ The only structural difference between **20** and **22** is the R1 pendant (Figure

3). Both BMS compounds demonstrated very similar kinase selectivity and cellular activity against several kinases and tumor cell lines, as shown in Table 1.^{19, 250} To address issues of CYP3A4 inhibition, poor aqueous solubility, and high plasma protein binding of compound **20**, **23** (BMS-695735) was synthesized and reported to exhibit improved ADME properties, a low risk for drug-drug interactions, and *in vivo* efficacy in several xenograft models.²⁵⁴

iv. Imidazopyrazines—A novel 6/5 heteroaryl scaffold containing key pharmacophoric donor/acceptor interactions with the kinase hinge region was reported recently by OSI Pharmaceuticals.²⁵⁵ Additional advantages of the imidazo[1,5-*a*]pyrazine core over the conventional pyrrolo[2,3-*d*]pyrimidine scaffold included a slightly lower polar surface area (PSA), log*P*, and log*D*; higher basicity for potentially greater hinge-binding affinity; improved predicted solubilities; and stable attachment of both carbon and heteroatoms to C3 directly or with a methylene linker.²⁵⁵ As shown in Figure 4, **24** was found to have a biochemical IC₅₀ value of 0.606 μM. It was discovered that, in general, a 3-substitution in aromatic ring A is preferred over a 4-substitution, in terms of activity. Studies have shown that the 8-NH₂ and N₇ nitrogen of the imidazopyrazine core is involved in a conventional hinge-binding interaction with the protein, and the C3 groups project toward the P-loop, a solvent-exposed region of the protein as suggested by structural hypotheses from IGF1R models. Although the difference in biochemical activity against IGF1R between C3-cyclohexyl of **25** and C3-cyclobutyl of **24** is six-fold, there is only about a two-fold difference in cellular activity for **26** and **27**. **28** and **29** demonstrated approximately a two-fold difference in both their biochemical and cellular activity with amide and free amine functionality, respectively. Both compounds **28** and **29** were orally bioavailable with the major pharmacokinetic parameters being performed in mice.²⁵⁵ Compound **29** demonstrated selectivity against the IGF1R over 15 other protein kinases (ABL, CDK2/Cyclin A, CDK2/Cyclin E, CHK2, CK2, c-RAF, Fes, IKK-β, MAPK2, p70S6K, PDGFR-β, PDK1, PKA, PKAα and PKCα).²⁵⁵

Through structure-based design efforts utilizing IGF1R and IR co-crystal structures, the benzyloxyphenyl substituent was replaced with a bioactive, conformationally constrained 2-phenylquinolinyl moiety, resulting in a ten-fold increase in cellular potency. As a result, **30** (OSI-906, Figure 4) proved to be a potent, selective and orally bioavailable IGF1R inhibitor.²⁵⁶ **31** (PQIP, Figure 4), an analog of compound **30** bearing a methylpiperazine side chain, displayed a cellular IC₅₀ of 19 nM for the IGF1R with 14-fold selectivity over the IR. This compound showed minimal activity against a panel of 32 other protein kinases, and it abolished the ligand-induced activation of downstream phosphorylated AKT and ERK1/2 in both a cell line engineered to exogenously express IGF1R cell line and endogenous IGF1R in the GEO human colorectal cancer line.²⁰ Most recently, Wu and colleagues reported the crystal structure of the tyrosine kinase domain of IGF1R complexed with compound **31**.²⁵⁷ This structure revealed that compound **31** interacts with residues in the ATP-binding pocket and in the activation loop, which confers specificity for the IGF1R and the IR.²⁵⁷ 3-((1*S*,3*S*)-3-(Aziridin-1-yl)cyclobutyl)-1-(2-phenylquinolin-7-yl)imidazo[1,5-*a*]pyrazin-8-amine **32** (AQIP), an analog of **31** created by replacing a methylpiperazine with azetidine, was reported to exhibit strong cellular potency against IGF1R (IC₅₀ of 20 nM) with 5-fold IR selectivity, and minimal inhibition against a panel of 28 other kinases in assays performed at ATP concentrations approximating their respective *K_m* values. Once-per-day oral dosing of **32** in mouse xenograft efficacy studies led to tumor growth inhibition at a 25 mg/kg dose and tumor regression at a 75 mg/kg dosing level.²⁵⁸

v. Pyrazolotetrahydropyridines and Pyrrolopyrazoles—A series of pyrazolotetrahydropyridines was recently patented as IGF1R inhibitors.²⁵⁹⁻²⁶¹ As a representative of this series, **33** (Figure 5) inhibited the IGF1R and IGF1R-induced S6 kinase phosphorylation with IC₅₀ values of 0.34 μM and 3.05 μM, respectively.²⁵⁹ Incorporation of pyrolocarboxamide in the phenyl ring affording **34** (Figure 5) led to a seven-fold improvement

of potency in a biochemical assay against IGF1R ($IC_{50} = 0.049 \mu M$). Compound **34** also demonstrated a cellular IC_{50} value of $0.08 \mu M$.²⁶⁰

The five-member ring analogs, **35** and **36**, created by the same research group, led to the pyrrolopyrazoles. Compound **35** was reported to have an inhibitory activity against IGF1R similar to compound **33**.²⁶¹ Modifications on **33** included the change from six-member to five-member ring, removal of a sulfonamide, masking of the pyrazole nitrogen with carbamate, and the addition of a solubilizing group to the phenyl ring. Further modification of **35** yielded compound **36**, which had IC_{50} values of $0.09 \mu M$ in a biochemical assay against IGF1R and $0.30 \mu M$ in a cell-based assay.

vi. Epigallocatechin-3-gallate—It has been reported recently that the tea polyphenol, **37** (EGCG, Figure 5) is a small-molecule inhibitor of the IGF1R with an IC_{50} of $14 \mu M$.²⁶² A possible mechanism of action of compound **37** proposed that the compound may fit into the ATP-binding pocket through hydrogen-bonding interactions with residues Gln977, Lys1003, Met1052, Thr1053 and Asp1123, as suggested by a molecular modeling study. It was reported that compound **37** abrogates anchorage-independent growth induced by IGF1R overexpression and activation, including growth of the human MCF7 breast and HeLa cervical cancer cell lines, through inhibition of IGF1R downstream signaling.²⁶²

vii. Pyrrolecarboxaldehydes—Another class of IGF1R inhibitors discovered has been a pyrrole-5-carboxaldehyde series.²⁶³ As shown in Figure 5, **38** and **39** demonstrated inhibitory activity through ATP competition, forming a reversible, covalent adduct between the aldehyde moiety and a lysine residue within the IGF1R ATP-binding pocket. Crystal structure analysis confirmed the modification of the active site lysine side chain and revealed details of the key interactions between the inhibitor and enzyme. These compounds show modest selectivity for inhibition of IGF1R over the IR.

viii. Cyanoquinolines—In early 2009, Miller *et al.* from Wyeth disclosed a series of 3-cyanoquinolines as low nanomolar inhibitors of IGF1R.²⁶⁴ This series originated from Wyeth's in-house high-throughput screening and was optimized based on input from structural biology and data mining; the strategies, synthesis and SARs of the cyanoquinolines were discussed in this report. These cyanoquinoline compounds had better potency overall than a previously reported series of isoquinolinedione inhibitors of the IGF1R reported by Wyeth as potential anticancer agents,²⁶⁵ but neither series showed selectivity for the IGF1R relative to the IR.

b. ATP-noncompetitive inhibitors

ix. Picropodophyllin—A class of compounds called cyclolignans has been found to interfere with autophosphorylation of the IGF1R; this inhibition does not involve competition with ATP and has been suggested to occur at the substrate level.²⁶⁶ One of these cyclolignan compounds, **40** (PPP, Figure 6) was shown to induce apoptosis in cultured IGF1R-positive tumor cells, and to cause complete tumor regression in mice bearing several different xenografted human tumor cell lines (e.g., ES-1 Ewing's sarcoma cells, BE malignant melanoma cells, and PC3 prostate carcinoma cells). Importantly, compound **40** does not appear to affect insulin receptor function and thus would not be expected to cause iatrogenic diabetes. Unlike ATP-competitive small-molecule kinase inhibitors, **40** has been suggested to cause only minimal resistance in tumor cells exposed to the agent.²⁶⁷ In addition, **40** downregulates the receptor protein (but not several other receptor tyrosine kinases including the IR, VEGFR, EGFR, KIT, PDGFRalpha, or PDGFRbeta).²⁶⁸ Strategies that lead not only to inhibition of the tyrosine kinase activity but also downregulation of the IGF1R (such as many antibody-based therapies) have typically been associated with the strongest antitumor effects.²⁶⁹

x. 41 (AG538)—Another series of ATP-noncompetitive inhibitors is represented by **41** in Figure 6. Compound **41** belongs to the tyrphostin group of compounds with catechol functionality on both sides of the molecule, and has an IC_{50} against IGF1R of 61 nM in a cell-free kinase assay.²⁷⁰ To circumvent the sensitivity of catechol rings to oxidation, a series of **41** analogues with catechol bioisosteres have been synthesized.²⁷¹ Studies showed that these metabolically more stable **41** bioisosteres possessed similar biological properties to **41** and inhibited IGF1R by a substrate-competitive mechanism with inhibitory activity in the sub-micromolar concentration range in cell-free assays and low micromolar concentration in intact cells.

xi. 42 (SBL02)—A series of secondary or tertiary amines branched out with at least one catechol ring has been identified as ATP non-competitive IGF1R inhibitors.²⁷² Within the combinatorial chemical libraries synthesized, one of most potent compounds, **42** shown in Figure 6, demonstrated inhibitory activity against the IGF1R with an IC_{50} of 170 nM in a cell-free kinase assay. Compound **42** was found to inhibit IGF1R auto-phosphorylation and substrate phosphorylation at the low micromolar range in cellular assays.

c. Miscellaneous

xii. Diarylureas—After screening of a chemical library against the IGF1R in the human MCF7 breast cancer cell line, **43** (PQ401, Figure 6) was identified as a potent inhibitor of IGF1R signaling.²⁷³ Although the mechanism of kinase inhibition has not been elucidated, compound **43** might act as an indirect inhibitor of ATP binding, similar to heterocyclic urea inhibitors of the p38 mitogen-activated protein serine-threonine kinase.^{274, 275} Compound **43** inhibited autophosphorylation of the IGF1R in cultured human MCF7 cells with an IC_{50} of 12 μ M and autophosphorylation of the isolated kinase domain of the IGF1R with an IC_{50} < 1 μ M.

xiii. Lapatinib—The dual EGFR/HER2 kinase inhibitor **8** (Figure 2) was approved to treat metastatic HER2-positive breast cancer that has progressed following standard therapy, to be used in combination with capecitabine (Roche) in March 2007 by the FDA.²¹⁶ Recently, compound **8** was reported to also inhibit some of the functional consequences of IGF1R signaling, an effect thought to contribute to its ability to induce apoptosis in trastuzumab-resistant breast cancer cells.²⁷⁶ This study showed that compound **8** induces apoptosis in HER2-overexpressing breast cancer cells that are either naïve or refractory to trastuzumab; in addition to blocking HER2 and EGFR signaling, **8** reduced IGF1R signaling in HER2-overexpressing breast cancer cells, and co-treatment with an IGF1R-targeted antibody increased **8**-mediated growth inhibition yet further. It is important to emphasize that lapatinib is very selective for EGFR and HER2 and does not directly inhibit the IGF1R;²⁷⁷ rather, these effects occur due to inhibition of EGFR/HER2 signaling, which can undergo cross-talk with the IGF1R.^{278, 279} These results help to explain the mechanisms that enable compound **8** to be an effective therapy in trastuzumab-resistant cancers and suggest that **8**-mediated cytotoxicity may be due in part to its indirect effects on the IGF1 signaling pathway.²⁷⁶

xiv. 44 (NDGA)—It has recently been reported that nordihydroguaiaretic acid **44** (Figure 6), a naturally occurring compound isolated from creosote bush (*Larrea divaricata*), inhibits IGF1R and HER2 kinase activity.²⁸⁰ Compound **44** inhibited IGF1R kinase activity at an IC_{50} of 0.9 μ M and also inhibited lipoxygenase activity at an IC_{50} of 3.8 μ M.²⁸¹ Analogs of **44** with increased specificity for IGF1R over lipoxygenase have been described. It is currently unknown whether **44** competitively inhibits the ATP-binding pocket of IGF1R.²⁸⁰ The anticancer activity of **44** and its analogs is being investigated in clinical trials.^{282, 283}

xv. Simvastatin—Recently, a group of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors known as statins, simvastatin **45** (Figure 6) have been found to decrease IGF1R plasma membrane expression.²⁸⁴ This effect has been attributed to a decrease in dolichyl phosphate, a nonsterol isoprenoid derivative in the mevalonate pathway, that is decreased following inhibition of HMG-CoA reductase.²⁸⁴ Dolichyl phosphate plays an important role in the N-glycosylation of several proteins;²⁸⁵ glycosylation of the IGF1R is required for targeting of the receptor to the plasma membrane.^{284, 286} Demonstrating the importance of the isoprenoid pathway in statin-induced cell death, cell death induced by the **45** in C2C12 mouse myoblast cells can be blocked by co-treatment with mevalonate and other intermediates in the isoprenoid pathway.²⁸⁷ **45** has been shown to block IGF1-mediated proliferation of PC-3 prostate cancer cells.²⁸⁸

xvi. Heat shock protein 90 (HSP90) inhibitors—Heat shock proteins play a vital role in the chaperoning and trafficking of receptors to the plasma membrane.^{289, 290} Heat shock proteins have been implicated in mediating the proper folding and membrane targeting of IGF1R.^{34, 291} Recently, heat shock protein 90 (HSP90) inhibitors have become valuable tools in research and a promising class of anticancer therapeutics.²⁹⁰ Although not direct inhibitors of IGF1R activity, HSP90 inhibitors may indirectly reduce IGF1R expression and, therefore, mediate overall activity. As one example of the effectiveness of HSP90 inhibition, treatment of pancreatic cancer cell lines with the HSP90 inhibitor 17-AAG decreased IGF1R phosphorylation and total protein expression and, in an orthotopic model, pancreatic tumor growth and vascularization were both significantly reduced upon Hsp90 inhibition.²⁹² In addition to antitumor efficacy, HSP90 inhibitor therapy may potentially be associated with toxicities that involve interference with normal IGF1R-mediated signaling as well; for example, IGF1-induced proliferation of articular chondrocytes has been shown to be decreased by HSP90 inhibitor treatment.²⁹³

5. Conclusions and further considerations

In summary, in addition to other therapeutic modalities that target IGF1 signaling, there are at least a dozen chemotypes of small-molecule inhibitors of the IGF1R (Table 2). These include either ATP-competitive or ATP noncompetitive inhibitors, or small molecules that possess a mechanism of inhibition not yet elucidated. As these IGF1R inhibitors progress forward, some key issues need to be addressed. For instance, what is the therapeutic window for inhibition of the IGF1R versus the IR? What approaches are required to fully optimize the physicochemical properties of the currently described IGF1R inhibitors to achieve adequate pharmacokinetic and pharmacodynamic profiles? How can potential metabolic liabilities best be addressed?

Notably, the majority of kinase inhibitors reported to date have been identified from high-throughput screens of libraries containing large molecular weight compounds. Hit-to-lead and lead optimization performed around “hits” identified in this manner usually add, rather than remove, more functional groups or rings to increase the binding affinity of the inhibitors. With advances in technologies such as X-ray crystallography, NMR-based screening, surface plasmon resonance, mass spectrometry and isothermal calorimetry, fragment-based and structure-guided approaches are becoming increasingly common.²⁹⁴ Compounds obtained from fragment-based and structure-guided approaches may result in novel kinase inhibitors characterized by a greater “fine-tuning” of their selectivity and more optimal physicochemical properties; thus, the authors (as well as others) favor these approaches to improve new kinase inhibitor discovery and development in the future.^{295, 296}

With regard to IGF1R small-molecule inhibitor design, the authors predict that optimal clinical utility may actually be obtained with compounds that are not necessarily highly selective for the IGF1R but that also inhibit other kinases such as the EGFR that can signal in parallel (since

tumor cells can switch in their “preference” for a given upstream kinase) and/or kinases such as mTOR that signal downstream of IGF1R (since IGF1R signaling can diminish the antitumor effects of mTOR inhibition). Efforts toward the design and preclinical testing of such “dirty” inhibitors are warranted to assess the effectiveness of the simultaneous inhibition of the IGF1R with these and other kinases (see ref. ²⁹⁷ for a recent review concerning kinase inhibitor selectivity). With respect to the design and optimization of future IGF1R inhibitors regarding their pharmacokinetic/pharmacodynamic characteristics, it may also be relevant to take into account experimental and clinical data suggesting that compounds associated with long half-lives and near-continuous kinase inhibition *in vivo* are not necessarily required (nor, perhaps, preferred) for clinical effectiveness.²⁹⁸ These recent findings run counter to the general prevailing assumption that continuous kinase inhibition is a requirement for clinical anticancer success, and they suggest that high-dose pulse therapy with a kinase inhibitor might still be effective while also allowing one to minimize toxicities (e.g., iatrogenic diabetes in the case of a dual IGF1R/IR small-molecule inhibitor) that could complicate or preclude continuous therapy.

There are also questions to be addressed from the biology/oncology viewpoint. For example, is IGF1R downregulation (which occurs with certain therapeutic antibodies but not with small-molecule inhibitors – a notable exception being the cyclolignan compound **40**)²⁶⁸ required for optimal antitumor responses in the clinical setting? This question will be answered only upon the entry of small-molecule IGF1R inhibitors into clinical trials. Nonetheless, considerable experimental data indicate that IGF1R downregulation is probably necessary to induce tumor cell apoptosis – without downregulation, growth inhibition but no apoptosis occurs (reviewed in ref. ²⁹⁹). Whether these preclinical observations hold true in the clinic remains to be seen, but the authors consider this to be a point that could be a relative “make or break” issue for the overall clinical applicability of small-molecule inhibitors of the IGF1R. Does the optimal strategy for IGF1R-targeted therapy involve the use of small molecules that specifically target the IGF1R alone or rather less selective compounds that show concomitant IR inhibition (in a trade off for the possible enhancement of antitumor efficacy against increased toxicity)? What are the optimal combinations and sequencing of IGF1R-targeted agents with other targeted therapies (e.g., EGFR and/or HER2 inhibitors; inhibitors of the downstream RAS/RAF/MEK/ERK and PI3K/AKT/mTOR signaling pathways) and with conventional chemo- and radio-therapy? As described above in this Perspective, experimental results suggest an important role for the IR, especially the IR-A in the form of hybrid receptors with the IGF1R, in transducing tumor growth-promoting signals. Likewise, substantial experimental data support the combination of IGF1R-targeted therapy with other treatments as a means to enhance antitumor responses, especially due to inhibition of the strong antiapoptotic signaling that is normally mediated by the IGF1R. Unfortunately, these experimental results provide only general guidance, and definitive answers for these two latter questions must await actual clinical experience with small-molecule IGF1R inhibitors; however, results from ongoing and future trials examining anti-IGF1R antibodies may help to presage at least some of the possible clinical characteristics of anti-IGF1R small molecules.

Another consideration for the clinical development of anti-IGF1R therapies: which tumors are most likely to respond to treatment? With the exception of selected malignancies (such as Ewing’s sarcomas, in which the IGF1R is constitutively activated by autocrine production of IGF1), the majority of primary tumors may exhibit only minimal-to-modest antitumor responses to IGF1R-directed therapy (at least when administered as monotherapy without other concomitant treatments). The IGF1R is required for anchorage-independent growth of tumor cells (scored experimentally as colony formation in soft agar), which is considered by investigators to be an *in vitro* biological counterpart in at least certain respects of metastatic capability and the occurrence of metastatic spread (reviewed in ref. ²⁹⁹). Furthermore, experimental targeting of the IGF1R has much greater effects on the viability of cells in

anchorage-independent as compared to adherent growth conditions, and several *in vivo* cancer models have demonstrated metastases to be very susceptible to IGF1R targeting (reviewed in ref. 299). These observations argue that IGF1R-targeted therapies (especially administered as monotherapy) could have a substantive role in the prevention and/or treatment of metastatic cancer (perhaps being of greater efficacy in this setting than for the monotherapy of most primary cancers). In the opinion of the authors, serious consideration should be given to the performance of clinical trials that address this hypothesis; one very common clinical setting that could be employed to test this possibility would be for the prevention of liver metastases in colon cancer patients post-resection of their primary tumors. Metastatic colon tumors in the liver are the main cause of mortality in patients with colon cancer, and cancer cells in the liver are awash in IGF1 (which is produced in large amounts by the liver) and may be addicted to it for their viability, especially before they are established as discrete metastatic tumor masses.

Yet another clinically relevant question concerns identification of the most informative biomarkers that allow prediction of the robustness of antitumor efficacy of IGF1R inhibition, as well as the clinical monitoring of antitumor responses.³⁰⁰ Rather than overexpression, expression (even at low levels) of the IGF1R is the requirement for cellular transformation in general; thus, the amount of IGF1R in a given tumor cannot be used as a reliable predictor of response to IGF1R-targeted therapy. Baserga has suggested that the status of IRS1 in a particular tumor may possibly presage responsiveness to anti-IGF1R therapy, given that without IRS1, the IGF1R does not send a mitogenic signal but rather a differentiation signal in cells.³⁰⁰ Thus, expression of IRS1 (especially nuclear IRS1, which can function as a transcriptional cofactor) may be a requirement for IGF1R-driven tumorigenesis and could potentially serve as a biomarker for sensitivity to IGF1R targeting; as such, assessments of IRS1 status should be considered for incorporation into clinical trial designs in the authors' opinion.

Despite a number of unanswered questions, it does now appear clear that the IGF1R signaling system is an important component of the development, progression, and therapeutic responsiveness of a number of cancer types.^{32, 34, 36-39, 56, 221, 222, 224, 279, 301, 302} Furthermore, experience from early-stage clinical trials has thus far suggested that the toxicities associated with IGF1R inhibition can be managed effectively and tolerated by the patient.³⁰¹ Now slightly more than fifty years after the initial recognition of signaling by the IGF1 pathway, and roughly 20 years following the initial suggestions of possible antitumor efficacy of the targeting of this pathway, we are finally poised to fully test the clinical usefulness of IGF1R-inhibitory agents for cancer therapy.

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Abbreviations

ER	estrogen receptor
HSP90	heat shock protein 90
IC ₅₀	inhibitory concentration at 50% control growth

IGF1R	insulin-like growth factor 1 receptor
IGFBP	insulin-like growth factor binding protein
IR	insulin receptor
mTOR	mammalian target of rapamycin

Figure 1.

The major signaling pathways activated by the IGF1R. The RAS/RAF/MEK/ERK and PI3K/AKT pathways are depicted above. The IGF1R is activated by binding of either IGF1 or IGF2. Binding of ligand induces a conformational change and autophosphorylation of key residues in the β subunits of the receptor, and docking proteins then interact with the phosphorylated residues of the activated receptor. Activation of the receptor and transduction of the intracellular signaling kinase cascades culminates in cell proliferation and anti-apoptotic effects. Detailed descriptions of the regulation of IGF1R activation and of these signaling pathways can be found in Sections 2a and b.

1 sorafenib **2** imatinib **4** gefitinib **5** erlotinib **6** sunitinib **7** dasatinib **8** lapatinib **9** nilotinib

Figure 2.
Structures of kinase inhibitors approved for cancer therapy.

- 10** R1 = Br, R2 = ^tBu, R3 = CN
11 R1 = OH, R2 = ^tBu, R3 = CN
12 R1 = OH, R2 = OH, R3 = CN
13 R1 = OH, R2 = H, R3 = CONHBn
14 R1 = ^tBu, R2 = ^tBu, R3 = CSNH2

- 16** R = H, IC₅₀ for IGF1R = 6.1 μM
 IR > 20 μM
17 R = Cl, IC₅₀ for IGF1R = 7.4 μM
 IR > 20 μM

Figure 3.
Structures of ATP-competitive inhibitors (I).

Figure 4.
Structures of ATP-competitive inhibitors (II).

Figure 5.
Structures of ATP-competitive inhibitors (III).

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Figure 6.
Structures of ATP-noncompetitive or “mechanism unknown” inhibitors.

Table 1Enzyme and cellular activity of **20** - **23**

Enzyme or cellular activity	IC ₅₀ (nM)		
	20 (BMS-536924) ²⁵⁰	22 (BMS-554417) ¹⁹	23 (BMS-695735) ²⁵⁴
IGF1R	100	68	34
IR	73	51	72
FAK	150	94	165
MEK	182	356	-
Lck	341	>1500	140
RD-1 (sarcoma)	202	146	
MDA PCa-2b (prostate)	194	188	
Colo205 (colon)	212	120	
MCF-7 (breast)	460	234	

Table 2

IGF1R signaling inhibitors at various stages of development

Therapeutic agent	Type	Company/Institution	Phase	Therapeutic Indication	Comments
Anti-IGF-1R/BIIB022 ANT-429 ^{*,†} AMG 479 AMG 655 ATL1101 AVE1642 CP-751,871	SMI	Abbott	PC	Cancer	ATP-competitive kinase inhibitor.
	SMI	Calbiochem/ The Hebrew University of Jerusalem	ND	RT	ATP-noncompetitive kinase inhibitor.
	mAb	Amgen	I, II	Solid tumors, NHL, sarcoma	Fully human monoclonal antibody.
	Peptide	Antyra	PC	Pancreatic cancer	Receptor ligand antagonist.
	mAb	Biogen Idec	PC	Solid tumors	Fully human monoclonal antibody.
	AS	Antisense Therap. Ltd.	I	Psoriasis, HRPc	Blocks translation of the IGF1R.
	mAb	Immunogen, Sanofi-Aventis	I, II	Solid tumors	Humanized antibody.
	SMI	Bristol-Myers Squibb	PC	Cancer	ATP-competitive kinase inhibitors. Inhibit several kinases.
	mAb	Pfizer	I, II, III	Breast and prostate cancers, NSCLC, Rheumatoid arthritis	Fully human monoclonal antibody.
	SMI	Various companies/institutions	I, II, III	Diabetes, Cancer	Natural product. Focus of clinical trials is on prevention.
GSK 621659A ^{*,†} MK-0646	mAb	Merck, Pierre Fabre Medicament	PC	Cancer	Recombinant humanized monoclonal antibody.
	mAb	Imclone Systems	I, II	Colorectal cancer, prostate cancer, solid tumors	Fully human monoclonal antibody. Also, exists as a Diabody with the EGFR antibody IMC-11F8.
	SMI	Insmed, University of California, San Francisco	II	Breast and prostate cancers, and neuroblastomas	Kinase inhibitor. Also inhibits human epidermal growth factor receptor (HER2/neu).
	SMI	GlaxoSmithKline	PC	Cancer	Kinase inhibitor.
	mAb	Merck	I, II	Breast, pancreatic, and prostate cancers, and MM	Monoclonal antibody.
	SMI	Novartis Pharma AG	PC	Cancer	ATP-competitive kinase inhibitor.
	SMI	OSI Pharmaceuticals	I	Solid tumors	ATP-competitive kinase inhibitor.
	SMI	Axelar	I,II	Cancer	ATP-noncompetitive kinase inhibitor. Natural product.
	SMI	OSI Pharmaceuticals	PC	Cancer	ATP-competitive kinase inhibitor.
	mAb	Genmab A/S, Roche Holdings Ltd	I, II	Lymphoma, NHL, sarcoma, solid tumors	Fully human IgG ₁ recombinant antibody.
SCH-717454 (19D12)/Robatumumab	SMI	The Hebrew University of Jerusalem	ND	RT	ATP-noncompetitive kinase inhibitor.
	mAb	Schering-Plough/Medarex	II	Osteosarcoma, Ewing's sarcoma, colorectal cancer	Fully human monoclonal antibody.

Therapeutic agent	Type	Company/Institution	Phase	Therapeutic Indication	Comments
45	SMI	Various companies/institutions	II	Breast and prostate cancers. NSCLC, SCLC. Multiple sclerosis.	Indirect inhibition of IGF1R by inhibition of the HMG-CoA pathway.
	XL228 ^{†,*}	Exelixis	I	Hematologic and solid tumors	ATP-competitive kinase inhibitor. Also inhibits BCR-ABL, including drug-resistant T315I mutant, as well as SRC, FGFR 1-3, and Aurora kinases. [§]

mAb- monoclonal antibody
 SMI- small molecule inhibitor
 AS- antisense
 NA- Not applicable
 RT- research tool
 PC- Preclinical
 ND- Not currently in clinical development
 MM- multiple myeloma
 HRP- hormone-refractory prostate cancer
 NSCLC- non-small cell lung cancer
 NHL- non-Hodgkin's lymphoma

[†] References 31 and 301 also contain further information regarding these and other novel therapies targeting the IGF signaling axis, as well as completed, current or planned clinical trials testing these agents.

* Structures not disclosed.

[§] These inhibitors have been reported to be in development by the designated companies but minimal data are currently available.

[§] Minimal information (see references 303 and 304) is presently available on this compound.

[‡] See ref 305.