

Review

Early drug development of inhibitors of the insulin-like growth factor-I receptor pathway: Lessons from the first clinical trials

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Abstract

The insulin-like growth factor-I receptor (IGF-IR) was first cloned in 1986. Since then, intense work has defined classic phosphorelays activated via the IGF-IR, which regulate cell proliferation, apoptosis, motility, and fate. The understanding of the roles of hormones in cancer and the growth hormone-IGF-IGF-binding protein axis specifically has yield to a second wave of development: the design of specific inhibitors that interrupt the signaling associated with this axis. The ability to manipulate these pathways holds not only significant therapeutic implications but also increase the chance of deeper insight about the role of the axis in carcinogenesis and metastasis. Nowadays, >25 molecules with the same goal are at different stages of development. Here, we review the clinical and preclinical experience with the two most-investigated strategies, tyrosine kinase inhibitors and monoclonal antibodies, and the advantages and disadvantages of each strategy, as well as other alternatives and possible drug combinations. We also review the biomarkers explored in the first clinical trials, the strategies that have been explored thus far, and the clinical trials that are going to explore their role in cancer treatment. [Mol Cancer Ther 2008;7(9):2575–88]

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Introduction

The past five decades have each brought about revolutionary advances in our understanding of hormone activity (1). In oncology, understanding the roles in cancer of hormones and the growth hormone (GH)–insulin-like growth factor (IGF)–IGF-binding protein (IGFBP) axis specifically has developed in a parallel fashion. Recently, discoveries of GH-IGF-IGFBP axis's actions in cancer have stimulated a second wave of development: the design of specific inhibitors that interrupt the signaling associated with this axis. The ability to manipulate these pathways hold not only significant therapeutic implications but also increase the chance of deeper insight about the role of the axis in carcinogenesis and metastasis. The GH-IGF-IGFBP axis presents multiple therapeutic targets related to cancer. Others have previously reviewed the role of the IGF-I receptor (IGF-IR) in cancer, and preclinical data are emerging related to its inhibitors (2, 3). This review is focused on the early clinical and translational data related to the first inhibitors of IGF-IR that will likely guide the future clinical development of such agents.

Molecular Biology of the IGF System and Its Role in Cancer

Abundant data garnered from diverse *in vitro* sources, animal models and clinical studies, confirm that the GH-IGF-IGFBP axis is a key regulator of postnatal growth and insulin action (4). In normal and cancer cells, insulin-like growth factors (IGF-I and IGF-II) and their high-affinity binding proteins (six known IGFBPs) comprise a major superfamily of protein hormones that regulate cell growth, metabolism, and death. IGFBPs circulate and modulate IGF activity by reducing IGF bioavailability to bind to the IGFs. In addition to other factors, the complex balance between free IGFs and IGFBPs determines the outcome for the cell among survival, growth, or death. Concomitantly, this balance between growth factors and IGFBPs is modulated by specific IGFBP proteases. Interestingly, recent data suggest that IGFBPs may also exert significant IGF-independent actions, but their role in cancer is not yet clear.

Free, unbound IGF-I exerts major actions in carbohydrate, lipid, and protein metabolism through activation of the cell surface IGF-IRs (5). This primary receptor for IGF-I is a heterotetrameric tyrosine kinase membrane receptor which displays selective binding affinity for IGF-I, although not exclusively, because IGF-IR can bind both IGF-II and insulin with less affinity. Upon binding to its

ligand, IGF-IR undergoes autophosphorylation and conformational changes that trigger an intracellular signaling cascade through the insulin receptor substrates 1 to 4 (IRS1–IRS4) and Src homology and collagen. These molecules activate the two main downstream signals of IGF-IR, the mitogen-activated protein kinase and phosphatidylinositol 3-kinase/Akt pathways (6). IGF-IIR, on the other hand, can bind these growth factors but acts as a signal decoy and does not transduce the signal intracellularly.

The last two members of the insulin receptor family are the insulin receptor (IR) and, especially in tumor cells, the

hybrid receptors IGF-IR/IR. The hybrid receptors also signal after binding IGF-I or IGF-II, similar to the function of IGF-IR. In normal conditions, both the IGF-IR and insulin receptor (IR) signaling pathways have overlapping functions and complement each other. Differences in the metabolism, availability of the ligand, receptor expression, or pharmacologic manipulations may change the equilibrium in signaling between those two pathways (Fig. 1D).

The GH-IGF-IGFBP axis is tightly regulated at different levels, as depicted in Fig. 1A-C, emphasizing its significance. The IGF-IR pathway has been implicated in

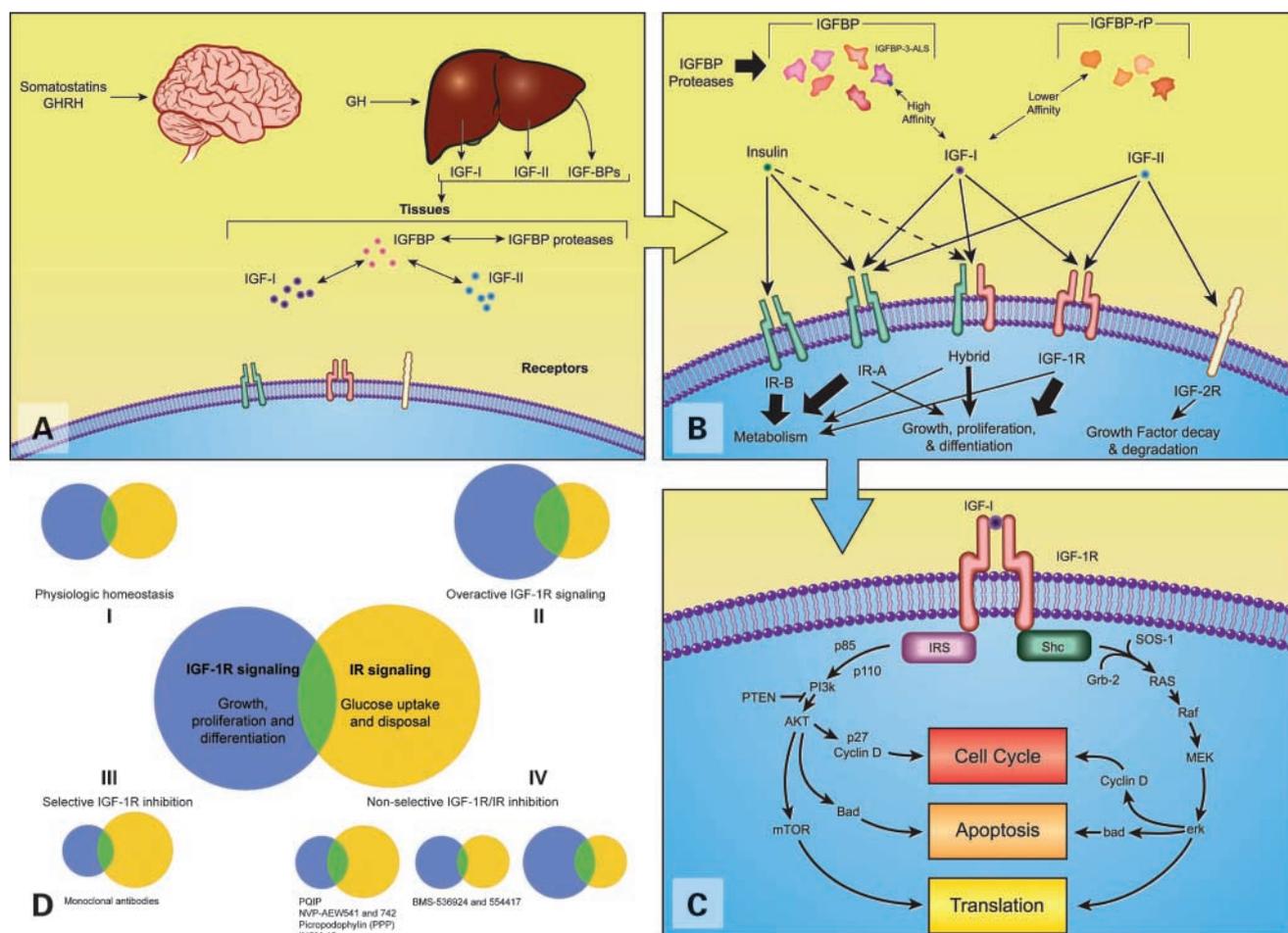


Figure 1. The three levels of regulation of the IGF-IR pathway and its components. **A**, systemic regulation at the endocrine level. The GH-IGF-IGFBP axis is directed by the hypophysis where GH is produced. In the liver, GH stimulates the secretion of its main effector, IGF-I, as well as IGF-II and IGF-BPs. **B**, at the tissue level, the levels of the free ligands (IGF-I and IGF-II) are regulated by the presence of the six different IGF-BPs, which bind the growth factors with high affinity, and by IGF-BP-related proteins, which bind IGF-I and IGF-II with lower affinity. The formers are regulated by specific proteases. Insulin, IGF-I, and IGF-II bind to the different receptors (insulin receptors A and B, IGF-IR, and IGF-IIR) with diverse affinities, and each receptor triggers different intracellular signaling cascades. Hybrid receptors are composed by one α -subunit and one β -subunit of the IGF-IR and one α -subunit and one β -subunit of the insulin receptor. **C**, at the cellular level, binding of IGF-I to its receptor triggers the autophosphorylation of the later and of the adaptor proteins IRS1 to 4 and shc/Grb-2. Activation of each of these proteins prompts different signaling cascades through the phosphatidylinositol 3-kinase/Akt and ras/raf/mitogen-activated protein/extracellular signal-regulated kinase pathways. The GH-IGF-IGFBP axis controls, through these three levels of regulation, mediators of the cell cycle, apoptosis, and translation that regulate cell growth, proliferation, and differentiation, as well as energetic metabolism. **D**, overlapping in function between IGF-IR and IR signaling. I, in normal conditions, both pathways complement each other and there is an equilibrium in signaling between the energy and metabolic pathways and pathways that drive growth and proliferation. II, in tumor cells, IGF-IR signaling is frequently overactive, and the signaling predominance of IGF-IR turns the cells to survive apoptotic signals and to proliferate. III, specific inhibition of IGF-IR with monoclonal antibodies can switch the equilibrium toward a predominance of the insulin pathway, having significant metabolic effects. IV, tyrosine kinase inhibitors differ in specificity against IGF-IR and IR, and each drug has a different profile of toxicity-efficacy. GHRH, growth hormone releasing factor; IGFBP-rP, IGF-BP-related proteins; IR-A, insulin receptor A; IR-B, insulin receptor B; PI3K, phosphatidylinositol-3-kinase; Shc, src homology 2 domain-containing.

tumor genesis, mitogenesis, metastasis, angiogenesis, and antiapoptosis. These effects are mediated by multiple mechanisms, conferring resistance to chemotherapy, radiation therapy, and agents targeting HER-2 and epidermal growth factor receptor (EGFR; ref. 7).

The molecular mechanisms by which the GH-IGF-IGFBP axis is deregulated in malignant cells is complex, and abnormalities at each of the levels depicted in Fig. 1A-C have been described in different tumors. Overexpression of the growth factors (IGF-I or IGF-II) or the receptor, by either gene amplification, loss of imprinting, or overexpression of convertases or transcription factors, have been observed in different tumor samples, as well as posttranslational modifications of the IGF-IR by glycosylation. Also, modification of the concentration of IGF-BPs (especially IGFBP-1, IGFBP-3, and IGFBP-5) or of the insulin receptor can modify the overall activation of the pathway. Finally, loss of IGF-IR, a negative regulator of IGF signaling that works by as a decoy by binding the growth factor, could drive cells into an IGF-IR-dependent growth (6, 8, 9).

Clinical Development of IGF-IR Inhibitors

The IGF-IR was first cloned in 1986. Since then, intense work has defined classic phosphorelays activated via the IGF-IR, which regulate cell proliferation, apoptosis, motility, and fate. Drug development aimed to inhibit the IGF-IR has lagged, although less pursued over concerns with toxicity related to the high homology between IGF-IR and the insulin receptor. Only very recently and encouraged by the success of other targeted drugs, pharmaceutical companies began to pursue compounds to inhibit the IGF-IR. Now, >25 molecules with the same goal are at different stages of development, engaging big pharma and highly specialized small biotechnology companies (see Table 1).

The two most investigated strategies in preclinical models use specific tyrosine kinase inhibitors and monoclonal antibodies, recapitulating the development of drugs which targeted the EGFR and vascular endothelial growth factor receptor (VEGFR) pathways (10). As reviewed here, both strategies possess advantages, and it seems reasonable to develop both drug classes. Moreover, as learned from the experience with EGFR, tyrosine kinase inhibitors and antibodies display different activity profiles, and they can be combined to attain major inhibition of a specific pathway.

Small Molecules versus Monoclonal Antibodies

The differences between small molecules and antibodies have been addressed already in other fields, say comparing erlotinib and cetuximab (both inhibitors of EGFR) or lapatinib and trastuzumab (inhibitors of HER2; ref. 10). The differences between tyrosine kinase inhibitors versus antibodies against IGF-IR resemble those between the aforementioned agents.

One of the most important differences is the disparity in selectivity. Since the IGF-IR is homologous to insulin receptor (sharing 84% amino acid identity in the intracellular tyrosine kinase domains), IGF-IR presents a formida-

ble challenge for the development of specific small molecule inhibitors of IGF-IR tyrosine kinase activity (11). Antibodies are more likely to be selective for the target. Selectivity could be an advantage, because sparing inhibition of the insulin receptor may avoid toxicities like hyperglycemia.

On the other hand, nonselective inhibitors may have a different profile and alternative benefits. Some tyrosine kinase inhibitors inhibit other kinases, like Src (XL-228) or HER2 (INSM-18), and this can expand the activity of the agent (12), as that with sorafenib and the inhibition of both ras and VEGFR (13, 14). It could also add toxicity mediated by target and off-target effects, complicating the combination of those therapies with other agents.

Selectivity is also important when considering the degree of involvement of the IR and the hybrid IGF-IR/IR receptors in IGF signaling. The role of the IR in carcinogenesis is still debated (15, 16), but IR represents a portion of IGF signaling. IR is frequently overexpressed in tumor cells (15–19), and the potential coactivation of the insulin pathway through their coexpression or through hybrid receptors (IGF-IR/IR) is under intense study. Hybrid IGF-IR/IR receptors are found in cells that express both receptors, and they consist on one half of the receptor formed by one IGF-IR α -subunit with one IGF-IR β -subunit and the other half of the receptor formed by one insulin receptor α -subunit and one insulin receptor β -subunit (20). Hybrid receptors behave more like IGF-IR than IR, exhibiting affinities for IGF-I and IGF-II similar to the IGF-IR homodimer (heterotetramer formed by two complexes, each containing one IGF-IR α -subunit and one β -subunit).

Because IR and IGF-IR share 95% of homology at the ATP-binding site of the tyrosine kinase domains, small molecules will certainly inhibit the insulin receptor to some degree. Targeting IR by nonspecific tyrosine kinase inhibitors may inactivate also the hybrid receptors. Down-regulation of those receptors can also be achieved by some of the monoclonal antibodies (21), because they can bind to the IGF-IR component and cause their internalization, potentially down-regulate IR signaling (20, 22).

Additional differences between small molecules and antibodies depend on the pharmacologic characteristics of each approach. Differences in molecule size and metabolism between antibodies and other drugs, such as chemotherapy and other targeted drugs, facilitate the safe combination at full doses. Small molecules, on the other hand, can be given orally and may cross the blood-brain barrier, but when combined with other agents, they could present pharmacokinetic drug-drug interactions and overlapping toxicities. Pharmacokinetic and pharmacodynamic differences among monoclonal antibodies will be probably minor and reduced to differences in domain specificity (23), potency of induction of internalization and degradation, antibody-dependent cell-mediated cytotoxicity (depending on the class of immunoglobulin), and inhibition of IGF-IR/IR hybrid receptors (depending on the specific epitope for

Table 1. Inhibitors of IGF-IR by drug class

Drug	Company	Class	Status			Notes	Citations
			PRE	IND	I II III		
Monoclonal antibodies							
CP-751,871	Pfizer	Fully human IgG2 mab				Ongoing trials: phase I/II for pediatric patients with Ewing's sarcoma family of tumors. Phase Ib with docetaxel in HRPC. Phase II with exemestane in breast cancer, with Carbo/Taxol in NSCLC, with docetaxel/prednisone in HRPC. Phase II single agent in metastatic CRC.	(29, 76, 86, 88, 95, 96)
IMC-A12	Imclone	Fully human IgG1 mab				Development with NCI-CTEP. Ongoing trials: phase I/II. Phase II single agent in HRPC and in Ewing's sarcoma family of tumors, in combination with cetuximab for CRC and H&N cancer.	(25, 28, 97–99)
R1507	Roche	Fully human IgG1 mab				Previously known as RO4858696. Ongoing trials: phase I in pediatric patients. Phase II single agent in sarcomas.	(26, 27, 100)
AMG-479	Amgen	Fully human mab				Phase II single agent in Ewing's sarcoma family of tumors and in combination with gemcitabine for pancreatic cancer.	(30, 101, 102)
SCH-717454	Schering-Plough	Fully human mab				Previously known as 19D12 (Medarex). Phase I trial done in healthy volunteers. Phase II single agent for CRC	(85)
AVE-1642	Sanofi-Aventis	Humanized mab				Previously known as EM164 (ImmunoGen)	(22, 103–105)
MK-0646	Merk/Pierre Fabre	Humanized mab				Previously known as A2CHM, F50035, 7C10, or 7H2HM. Ongoing trials: phase II in combination with irinotecan/cetuximab in CRC.	(21, 106–108)
BIIB022	Biogen Idec	Fully human nonglycosylated IgG4.P antibody				Devoid of Fc-effector function to eliminate potential Fc mediated toxicity to the normal vital organs.	(109, 110)
Tyrosine kinase inhibitors							
INSM-18	Insmid and UCSF	Reversible ATP-competitive				Ongoing phase I/II. Inhibits IGF-IR and HER2, and it could act as an inhibitor of transcription (blocking also cdc2, survivin, and VEGF). Initially developed by Erimos Pharmaceuticals (EM-1421 or Terameprocol).	

(Continued on the following page)

Table 1. Inhibitors of IGF-IR by drug class (Cont'd)

Drug	Company	Class	Status					Notes	Citations
			PRE	IND	I	II	III		
OSI-906	OSI Pharmaceuticals	Oral small molecule. Reversible ATP-competitive		█				Derived from compound-1, also known as PQIP.	(111–114)
XL-228	Exelixis	Oral small molecule		█				Inhibits bcr-abl, scr and IGF-IR. Ongoing phase I for CML and ALL. Also known as XL-2280	(115, 116)
NVP-ADW742	Novartis	Reversible ATP-competitive		█					(39, 40, 117)
NVP-AEW541	Novartis	Reversible ATP-competitive		█					(37, 41, 93, 118–120)
AG-1024	Merk	Non-ATP-competitive		█					(121)
BMS-536924	Bristol-Myers Squibb			█					(84)
BMS-554417	Bristol-Myers Squibb	Oral small molecule. Reversible ATP-competitive		█					(122)
BVP-51004	Biovitrum	Oral small molecule. Non-ATP-competitive		█				Also known as Cycloignan PPP. Causes IGF-IR down-regulation, probably through the induction of ubiquitination.	(123, 124)
Other									
ATL-1101	Antisense therapeutics	Topical Antisense oligonucleotide		█				Developed for the treatment of psoriasis.	—
ANT-429	Antyra	HotSpot pharmaphores		█					—

Abbreviations: mab, monoclonal antibody; HRPC, hormone refractory prostate cancer; NSCLC, non-small cell lung cancer; CRC, colorectal cancer; NCI-CTEP, National Cancer Institute–Cancer Therapeutics Evaluation Program; H&N, head and neck; Fc, fragment crystallizable region; CML, chronic myelogenous leukemia; ALL, acute lymphocytic leukemia; PPP, picropodophyllin.

each antibody). Small molecules on the other hand will probably represent a broad spectrum of specificity against IGF-IR and IR (Fig. 1D) and a unique “profile” of toxicity efficacy for each drug (24).

Therefore, it is easy to envision for the near future a profusion of preclinical and clinical information of different TKI inhibitors with some overlapping in efficacy and toxicity. In this sense, the early experience with monoclonal antibodies described here can serve as gold standard and as a reference to select the best small molecules for further development.

Other approaches different from antibodies and small molecules are being developed, like peptides, proteins, or antisense oligonucleotides that antagonize IGF-IR but have

not reached the clinic yet. They will need to prove additional advantages over antibodies and tyrosine kinase inhibitors, because these types of drugs have already set a paradigm in cancer treatment.

Early Clinical Experience in Targeting IGF-IR

Many drugs that inhibit the IGF-IR pathway have been filed to the Food and Drug Administration for an Investigational Drug Application (Table 1). Of those, monoclonal antibodies have reached the clinic much earlier than the tyrosine kinase inhibitors, and several phase I trials have already been reported.

More than 150 patients have been treated in seven reported clinical trials concerning monoclonal antibodies

targeting IGF-IR (IMC-A12, R1507, AMG-479, SCH-717454, and CP-751,871). The treatments were given i.v. following several schedules that ranged from once a week to once every 4 weeks.

As depicted in Table 1, slight differences in immunoglobulin class, glycosylation, or the species of origin differentiate some of them. CP-751,871 differs from the rest in being the only IgG2 subtype available thus far and, as such, a poor activator of cellular immune response. Tumor growth inhibition in preclinical models with this antibody seems to be as good as with the rest, so it remains to be determined whether efficacy of targeting IGF-IR with antibodies is linked to the antibody-dependent cell-mediated cytotoxicity. On the other hand, the potential longer half-life of an IgG2 antibody and the effect in the safety profile of this class of antibodies does not seem to be clinically significant thus far.

The pharmacokinetic behavior was also similar among antibodies, with minimal differences in half-life across studies (the half life of those monoclonal antibodies ranged from 7 to 11 days) and similar to those reported with other non-IGF-IR--targeting antibodies. The clearance decreased with increasing doses, showing saturation in the elimination of the antibodies. The treatments were well tolerated, and the dose-limiting toxicities were scarce. Therefore, dose recommendations were frequently based on information from preclinical xenograft models (IC₅₀ or IC₉₀), pharmacokinetic variables, or pharmacodynamic data like maximal receptor occupancy.

Apart from monoclonal antibodies, there is only clinical information available about the small molecule nordihydroguaiaric acid. Initially developed by the University of California in San Francisco and currently developed with Insmid (and named INSM-18), it is an orally available, small molecule, tyrosine kinase inhibitor. Although it was described as an IGF-IR inhibitor, its mechanism of action is not clear. It directly inhibits the activation of both IGF-IR and c-erbB2/HER2/neu receptor, but also may induce apoptosis by activating stress-activated protein kinases, via both survivin-dependent and survivin-independent pathways, may inhibit arachidonic acid 5-lipoxygenase and may prevent the release of reactive oxygen species. It is currently being studied in patients with prostate cancer and rising PSA.

Early Signs of Activity

In the five single-agent trials with monoclonal antibodies that are reported, there have been seen early signs of activity in a variety of tumors. Long stable disease has been observed in tumors where IGF-IR is thought to play a significant role: breast, liver, colorectal, prostate, leiomyosarcoma, cervical and endometrial cancer, prostate, and pancreatic cancer. In carcinoid and pancreatic endocrine tumors, stabilizations of disease, one minor response and one partial response have been reported (25–30). In addition, one patient with Ewing sarcoma had a spectacular complete response (AMG-479), two had

partial responses (R1507), and one case of pheochromocytoma had also long stable disease, indicating that the broad family of neuroectodermal tumors may be susceptible to this approach.

In combination with carboplatin and paclitaxel, the monoclonal antibody cp-751,871 was well tolerated, and the efficacy of the combination in non-small lung cancer looks promising. With a 46% response rate, the combination exceeded the criterion for further study (set at least 40%), although the role of the IGF-IR inhibition is difficult to dissect from the chemotherapy at this point (31).

Toxicity in the First Clinical Trials with IGF-IR inhibitors: Comments on Hyperglycemia as a Mechanism-Related Toxicity

By comparing the toxicities from the reported studies, one can dissect class-specific toxicities from the particular ones of each compound and the advanced disease itself. By doing this, one recognizes hyperglycemia, mild skin toxicities (rash, flushing, pruritus, acne), and fatigue as common toxicities of these antibodies. Other observed toxicities, like reduction in CD4+ lymphocytes, thrombocytopenia, and transaminitis, do not seem to be related with the mechanism of action but with specific antibodies.

Hyperglycemia seems to be frequent (around 20%) but tolerable, mild to moderate (grades 1 and 2), reversible, and manageable with an oral hypoglycemic drug, such as sulfonylureas. Patients with previous glucose intolerance or with concomitant steroids were more susceptible to developing hyperglycemia. Of note, cancer patients with diabetes were excluded in those initial studies. On the other hand, when investigators treated healthy volunteers with one dose of the monoclonal antibody SCH-717454, they did not see an increase in glycemia when compared with baseline levels (85).

The degree of hyperglycemia seems to be, directly or indirectly (increase of GH, up-regulation of IGF), related with IGF-IR inhibition and could constitute a mechanism-based toxicity. The Common Terminology Criteria for Adverse Events considers a serum glucose level above 250 mg/dL as grade 3, which may result in declaring it a dose-limiting toxicity while being clinically insignificant. Common Terminology Criteria for Adverse Events have been useful guidelines for uniformly report chemotherapy-related toxicities but they seem to fail when applied to toxicities of targeted drugs. This raises the need of reviewing the Common Terminology Criteria for Adverse Events or developing specific guidelines for the management of tolerable, mechanism-based toxicities.

Finally, when treating hyperglycemia in cancer patients, one should have in mind that thiazolidinediones (rosiglitazone and pioglitazone), which are frequently added to the treatment with sulfonylureas, are known PPAR- γ inhibitors. The role of PPAR- γ in cancer is not well understood but some studies suggest that it may have angiogenic or antiangiogenic effects depending on the cellular context. Therefore, because its inhibition could be either detrimental or beneficial, we recommend to avoid this kind of agents (32–36).

It is still early to evaluate long-term toxicity of IGF pathway blockage, but several patients in our center have been on treatment for more than a year and no significant changes in weight or body fat have been observed (data not published).

Clinical experience with small molecules is still very limited. Based on pharmacologic studies *in vitro*, the selectivity of those molecules for IGF-IR and IR varies from drug to drug. These differences in selectivity translate *in vivo* to different performance in the glucose tolerance test. Some of them, like OSI-906, NVP-AEW541, picropodophyllin, and INSM-18, seem to be more selective for IGF-IR. On the other hand, drugs, like BMS-554417, have comparable potency toward both receptors. The different selectivity for each receptor will define a specific therapeutic window for each drug.

Looking Back at the Preclinical Experience for Clues of the Future Development

Preclinical data of the antitumoral activity of IGF-IR inhibition in breast, lung, colorectal, and prostate cancer is consistent across tumor models and regardless the use of monoclonal antibodies or small molecules, as seen in Table 2. This body of experimental evidence confirms what epidemiologic studies and analysis of tumor samples in these diseases were suggesting; that is to say, the IGF pathway plays a major role in at least a significant subset of these tumors. Considering how consistent all these studies are when analyzed together, it seems very logic to consider them prime candidates for IGF-IR targeting.

Combining IGF-IR Inhibitors with Cytotoxic Agents

IGF-IR is tightly linked with cell survival, apoptosis, and resistance to the cytotoxic effects of chemotherapy and radiation, suggesting the benefit of using IGF-IR inhibitors in combination with either cytotoxic (chemotherapy or radiation) or cytostatic treatments. A phase I trial of the combination of cp-751,871 with docetaxel has been already reported, and another one with the combination of AMG-479 and gemcitabine is ongoing. The only *in vivo* data to date of small molecules targeting IGF pathway in combination with chemotherapy was puzzling. Whereas in several tumor models the combination of NVP-AEW541 or NVP-ADW742 with chemotherapy was synergistic (37–41), NVP-AEW541 combined with doxorubicin or cisplatin in a Ewing's sarcoma xenograft had subadditive effects and warrant further studies (41).

Although the rationale for combining radiation therapy and an IGF-IR inhibitor is strong, this area is far less explored than the combination with either chemotherapy or other targeted agents. The only two interventional works studying the effect of IGF-IR inhibition and the enhancement of the sensitivity to DNA-damaging agents that are published to date involve silencing of the IGF-IR gene (42) and inhibition of the receptor with the monoclonal antibody IMC-A12. In the later, *in vitro* studies (clonogenic survival, anchorage-independent colony formation, radiation-induced apoptosis, and double-stranded DNA damage), as well as *in vivo* studies (with the non-small cell lung carcinoma H460 xenografts), confirmed the synergism of combining both therapies. Although still premature,

these promising data, consistent with the effect seen with chemotherapy, justify its investigation in cancer types like prostate cancer, advanced head and neck cancer, and locally advanced pancreatic cancer where radiation therapy forms part of the main initial treatment (42–44).

Exploiting the Cross-Talk between the IGF-IR Pathway and Other Growth Pathways to Overcome Resistance

Recent evidence suggests that one mechanism of resistance to the anti-HER2 therapies may be due to activation of IGF-IR signaling in those cancers (45–48). These observations have been confirmed in experimental *in vivo* models (Table 2). In the clinical setting, combining these two strategies could be developed as first line in HER2-positive breast cancers or as second line therapies, after resistance to trastuzumab has developed.

The cross-talk between EGFR and IGF-IR is well supported by a growing understanding of the molecular biology of those pathways. Several studies showed that tumor cells may gain resistance to anti-EGFR therapies through several mechanisms, including the phosphatidylinositol 3-kinase/Akt pathway (like akt mutations) or up-regulation and activation of other proliferative and/or antiapoptotic activities, like IGF-IR. Inhibition of IGF-IR may preclude resistance, at least in a subset of tumors (49). Tumors in which both pathways are active can survive the inhibition of one receptor by shifting the cellular equilibrium toward reliance on the uninhibited receptor. This is suggested by the observation that treatment of cells with an IGF inhibitor enhanced phosphorylation of EGFR and, conversely, treatment with erlotinib enhanced phosphorylation of IGF-IR.

This cross-talk may be mediated at the intracellular level, through feedback loops between the phosphatidylinositol 3-kinase pathway and the ras/raf/akt pathway: treatment with erlotinib reduced phosphorylated extracellular signal-regulated kinase and increased phosphorylated Akt through inhibition of the S6K-IRS-1–negative feedback loop (50, 51). Again, this is confirmed by *in vivo* experimental data of different drug combinations tumor models, providing the translational clinical trialists a strong rationale to combine inhibitors of both pathways. Based on the interaction between EGFR and IGF-IR, Imclone has designed a bispecific antibody molecule that targets both EGFR and IGF-IR by combining in a di-antibody the variable regions of IMC-11F8 (antibody that binds to EGFR) and IMC-A12 (which binds IGF-IR; ref. 52).

The possible cross-talk of IGF-IR with other pathways like angiogenesis are less studied in animal models. It has been observed that the direct inhibition of IGF-IR modulates VEGF in pediatric sarcoma; that IGF-IR, VEGF expression, and angiogenesis are inhibited by IMC-A12 in a myeloma model; and that angiogenesis is also inhibited by h7C10, another monoclonal antibody, in breast cancer cell lines. In another study, 11 s.c. xenograft models with a variety of human cancer cell types were treated with DC-101 (VEGFR inhibitor), cetuximab (EGFR inhibitor), and IMC-A12 (IGF-IR inhibitor), achieving significant synergism with the three drugs (53).

Table 2. Preclinical *in vivo* studies of IGF-IR inhibitors by tumor model and treatment

Tumor type	Cell line	Treatment		Effect	Citations
		IGF-IR inhibitor	Other agent		
Single agent					
Breast cancer	MCF-7	NVP-ADW742, XL820, IMC-A12, h7C10, and cp-751,871	—	Active	(60, 97, 106, 115)
Breast cancer, HER2+ trastuzumab resistant	SKBR3-Her10	IMC-A12	—	Active	(125)
Colorectal cancer	Colo-205, GEO, SW620, NCI-H322M, HT29	XL820, OSI906, IMC-A12, R1507 and cp-751,871	—	Active	(24, 97, 113, 115)
NSCLC	A549, NCI-H322M	XL820, OSI906, R1507, and h7C10	—	Active	(100, 106, 115, 126)
Prostate cancer	LuCaP35, LuCaP 23.1	IMC-A12	—	Active	(127)
Ewing sarcoma	TC-71, SK-ES-1 and SK-NEP-1	AMG-479, NVP-AEW541, and NVP-ADW742	—	Active	(23, 39, 41, 92, 93)
Pediatric sarcomas/ other tumors	ns	BMS-536924, CP-751871	—	Active	(76, 84, 103, 105)
Pancreatic cancer	BxPC-3	IMC-A12, AVE-1642, AMG-479	—	Active	(97, 101, 103)
Drug combinations					
NSCLC	A549	MK-0646	Vinorelbine	Synergism	(106)
NSCLC	A549	h7C10	Cetuximab	Synergism	(106)
Ovarian cancer	NS	PQIP	Erlotinib	Synergism	(128)
Breast cancer, HER2+ trastuzumab resistant	SKBR3	IR- α (murine antibody)	Lapatinib	Synergism	(46)
Breast cancer	BT474	NVP-ADW541	Trastuzumab	Synergism	(119)
Breast cancer ER+	MCF-7	h7C10	Tamoxifen	Less than additive effect	(106)
Pancreatic cancer	BxPC-3, MiaPaCa	AMG-479, MK-0646	Gemcitabine, erlotinib, panitumumab	Synergism	(101, 103)
Head and Neck	TU159	IMC-A12	Cetuximab	Synergism	(98)
Colorectal cancer	GEO, HT29	OSI-906	Erlotinib	Synergism	(50)
Pediatric sarcomas	EW5, ES2, ES8, OS1, OS9, Rh18	CP-751871	Rapamycin	Synergism	(76)
Other	Several	Several antibodies, NVP-ADW742	Melphalan, vinorelbine, docetaxel, adriamycin, 5-fluorouracil, doxorubicin, and gemcitabine	Synergism	(54, 90, 96, 129, 130)
Combination with radiation					
NSCLC	H460	IMC-A12	Radiation	Synergism	(131)

The estrogen pathway and its relation with IGF has been explored in tamoxifen-resistant breast cancer models. This resistance is in part mediated by IGF-IR/mitogen-activated protein kinase signaling pathway and

c-Src seems to be one of the critical elements. Thus, the small molecule XL-228, tyrosine kinase inhibitor of both Src and IGF-TK seems a good candidate for development in this setting.

In summary, we can easily foresee the incorporation of IGF-IR inhibitors to conventional treatments like chemotherapy or radiation therapy. In the same way, combining those drugs with other biological agents, one could overcome resistance to HER2, EGFR, or estrogen receptor inhibition. Finally, targeting IGF-IR could become an additional strategy to antiangiogenic therapy, in addition to VEGF, VEGFR, angiopoietin, or HIF-1 α inhibition (54, 55).

Translational Development: Key Issues in IGF Inhibition

Two decades of research in the role of IGF in growth and development, endocrine homeostasis, carcinogenesis, and tumor resistance opened a milieu of unresolved questions that will need to be addressed in the next years. In the meantime, pharmaceutical companies will rush for drug approval.

Thinking Beyond the Surface Receptor: Upstream and Downstream Approaches to Inhibition of the IGF Pathway

The current boom in drug development to target the IGF pathway is focusing in how to inhibit the interaction of IGF-IR with its ligand or the subsequent receptor activation. Still, the pathway is far more complex and other strategies could be considered. These other strategies can be divided in those that target upstream of the receptor (mainly by altering the IGF-I bioavailability) and those that target signaling molecules that are downstream of the receptor and transduce the signal from the receptor to the effector molecules.

The potential strategies to modulate ligand bioavailability include the use of soluble IGF-IR, IGF-binding proteins, or monoclonal antibodies against IGF-I or IGF-II, as well as calorie restriction and the administration of either somatostatin analogues or GH releasing hormone and GH antagonists, like pegvisomant (56–58).

Because limited access to interstitial fluid in solid tumors is a major problem for the efficacy of intact antibodies, targeting the ligand could be a useful strategy for treatment of solid tumors. The success of bevacizumab, antibody against the VEGF, has validated this strategy in a different setting (59). Recently, others report the development of monoclonal antibodies that target IGF-II (60, 61) or both IGF-I and IGF-II (such as KM1468; ref. 62), which could inhibit not only its binding to the IGF-IR but also its binding to the insulin receptor. On the other hand, the IGF-BP family is composed by at least six different proteins that bind IGF-I with a variable affinity, buffering serum concentrations of the ligand. Recombinant forms of IGFBP-3 protein are available for i.v. use (63) and are beginning clinical testing.

The role of calorie restriction may not seem very appealing for the management of metastatic disease, but hypothetically it could have a role in preventing recurrence after surgery, because studies in rodents have shown its potential benefit in preventing tumor development (64–66). The administration of somatostatin analogues has been, on the other hand, studied in the treatment of metastatic disease, including breast cancer, neuroendocrine tumors,

and prostate cancer (67–71). It is thought to exert its antitumoral effects by binding to specific high-affinity receptors on the cell. Nonetheless, part of its effect could be due to indirect mechanisms, such as inhibition of the GH-IGF axis, as suggested by *in vivo* studies (72–74). A more potent suppression on GH signaling can be achieved by GH antagonists (75).

Targeting downstream signals of the IGF-IR pathway has the potential benefit of inhibiting, at the same time, the potential crosstalk with different surface receptor pathways, like EGFR or VEGFR. Selective inhibition of mTOR, phosphatidylinositol 3-kinase, akt, or b-raf is nowadays a reality—thanks to the development of specific kinase inhibitors. *In vivo*, a comparison of combined inhibition of IGF-IR, akt, and mTOR (76) has been studied in cell lines derived from pediatric rhabdomyosarcoma and neuroblastoma. Moreover, some neuroendocrine tumors have responded to mTOR inhibition (77, 78), and phase III trials analyzing this strategy are ongoing. The potential effect of mTOR inhibition on IGF-IR signaling could account for part of the observed clinical activity of these compounds and supports the rationale for the combined use of IGF-IR inhibitors and mTOR inhibitors. Finally, IGF-IR and other surface receptors are client proteins for both heat shock proteins and the proteasome. Inhibitors of these targets are already available and have been tested *in vivo* as potential mechanisms of IGF pathway inhibition (79).

We Are Targeting IGF-IR but... Are We Targeting the Right Population? Comments on Biomarkers

Thanks to the recent efforts in the clinical development of IGF-IR inhibitors, novel biomarkers have been explored *in vivo* and in the clinic to further understand which tumors could respond to IGF-IR inhibition (predictive markers) or to detect early on if the target inhibition is achieved (pharmacodynamic markers).

Predictive markers. The translation of the experience with other targeted therapies in the biomarker field to the study of the IGF pathway has produced confusing data. This is probably because there may be multiple molecular mechanisms by which the IGF pathway can be altered in tumors. Some authors have explored the phosphorylation status of the IGF-IR or IRS-1 as a marker of the overall activation of the pathway. In addition, the evaluation of heterodimers or the IGF-IR/IR ratio may prove to be a useful predictor of the clinical response of anti-IGF-IR therapeutic antibodies (21).

Because those mechanisms are heterogeneous, preselection of patients to therapeutics that target IGF-IR with a single marker may not work. Conversely, a profile of the pathway or an algorithm that takes into account the whole axis (including the two growth factors, receptors, the IGF-binding proteins, and IRS-1) may be more comprehensive methods to select patients.

A different approach is to analyze the tumor epithelial-mesenchymal transition. This is a fundamental process governing not only morphogenesis in multicellular organisms but progression of carcinomas, and it is

defined by the expression of mesenchymal markers, such as vimentin or fibronectin. Various epithelial-mesenchymal transition inducers have been described, including EGFR, Met, and IGF-IR. A correlation between expression of mesenchymal markers and sensitivity to EGFR or IGF-IR inhibitors has been proposed by some authors (80–83) and could be used as predictive markers.

Finally, high-throughput analysis using DNA microarray and mass spectrometry–based protein profiling has been used *in vitro* to identify candidate molecular biomarkers that predict response to the small molecule BMS-536924 by comparing sensitive and resistant rhabdomyosarcoma cell lines. The authors identified several candidate pathways, including EGFR, mitogen-activated protein kinase, SRC, and cathepsins, which may be related with sensitivity to the drug, but their validation is still pending (84).

None of the mentioned markers has been validated yet, and there is no clinical data available at this point. But because it is common nowadays in clinical trials to systematically collect archived tumor tissue, it is expected that soon there will be more information regarding their value.

Pharmacodynamic markers. Biomarkers of drug effect or pharmacodynamic markers reflect the interaction of novel therapies with their intended target. In early clinical drug development, they can be used to optimize the dose and schedule, as well as to obtain crucial mechanistic information regarding success or failure (“hitting the target”) of a drug.

The interaction of monoclonal antibodies with the receptor has been studied by different methods: down-regulation of IGF-IR, either in the tumor or in peripheral blood cells (85–87); changes in the phosphorylation status of the receptor; or the receptor occupancy by the antibody on neutrophils (30) are the reported ones. Whether the measurement of IGF-IR down-regulation in circulating blood cells reflects or not the concentrations required to penetrate the tumor and to affect the growth of solid tumors is still unknown. Alternatively, circulating tumor cells, which have a short half life, may reflect better the status of the IGF axis of the tumor. Treatment with CP-751,871 decreased both total circulating tumor cell count and IGF-IR–positive circulating tumor cell count, suggesting that circulating tumor cells could be used as a biomarker of drug effect (88). Another approach that has been clinically tested are the changes in serum concentrations of IGF-I and IGFBP-3 (28) or IGF-IR (86).

In another clinical trial, molecular imaging with FDG-PET showed that 17 of 26 patients treated with AMG-479 had some decrease in metabolic activity. It is not clear, though, if this effect reflects antitumoral activity or if it is due to the effect on glucose metabolism of the inhibition of IGF-IR (30). Other events, such as hyperglycemia, could be a mechanism-related toxicity, and as such, it could serve as a marker of target inhibition. The use of mechanism-based toxicities, like hyperglycemia, hypertriglyceridemia, or hypercholesterolemia, has also been suggested as markers of mTOR inhibition, a pathway that is highly related with IGF-IR (89).

Academic and Pharmaceutical Industry Agendas in the Development of IGF-IR Inhibitors

Expression of the IGF-IR has been reported in a broad panel of tumor types. Being so ubiquitous and the fact that, after many years of research, its role in cancer remains so uncertain is intriguing. This suggests that IGF-IR could play different roles in different tumor types or cellular contexts. Some tumors may be dependent on IGF-IR signaling for survival, and its inhibition might trigger apoptosis and a subsequent cytotoxic effect. This could probably be the mechanism behind the dramatic responses observed in tumors like Ewing sarcomas. Some other tumors, though, may rely on IGF-IR for proliferation, like neuroendocrine tumors. Inhibiting IGF-IR will produce a cell cycle arrest and, thus, a cytostatic effect. Other tumors may have IGF-IR overexpression as a survival mechanism against cytotoxic insults, and combining chemotherapy with an IGF-IR inhibitor may overcome this mechanism of resistance (90). This could be the case of the observed synergy between chemotherapy or radiotherapy and IGF-IR inhibition, as well as with targeted therapies like trastuzumab, EGFR inhibitors, and hormone therapies.

In this context, the agenda of pharmaceutical companies and of academic investigators may diverge, following different approaches. Some may want to introduce the use of IGF-IR inhibition on the treatment of the four big killers (breast, prostate, colorectal, and lung cancer) in the advanced refractory disease. Such a big market has been always the preference of pharmaceutical companies. Others will consider that IGF-IR inhibitors may potentiate the effect of chemotherapy, radiotherapy, hormone therapy, or even other targeted agents, and these combinations will be tested, although some of the most reasonable ones may be difficult to test outside non-profitable institutions. On the other hand, small niche markets have been shown to be profitable for pharmaceutical companies in the past (91), and this setting is probably more rationally driven. Early clinical data indicate that IGF-IR inhibitors could be efficacious as single agents in infrequent tumors like neuroendocrine carcinomas or Ewing or synovial sarcomas (41, 92–94). This, if shown, would be the proof of principle that validates the pathway as a therapeutic target. As well, by subclassifying tumors according to molecular events in smaller entities like trastuzumab-resistant, “wild-type akt” tumors, or EGFR-positive tumors, one could better select patients that are more likely to have benefit to a specific agent. This later strategy has been successfully pursued (scientifically and financially) in the case of trastuzumab for breast cancer, erlotinib for lung cancer, or panitumumab for colorectal cancer.

Whatever strategy may sponsors pursue, what experience indicates is that everybody benefits from Food and Drug Administration approval. Scientific endeavor is intensely stimulated, and many other settings, may be less profitable, can be tested once the drug is approved and available. As well, the success of one drug encourages the competing companies to invest efforts in the development

of better drugs or to look for alternative indications for their candidate. On the other hand, if the first clinical studies fail, research in the field may lose momentum. Because of that, a joint effort between academia and pharmaceutical companies seems to be in the best interest of all, patients first, even in such apparently competitive environment.

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