

# The Insulin Receptor/Insulin-Like Growth Factor Receptor Family as a Therapeutic Target in Oncology

Michael Pollak

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## Abstract

Over the past decade, encouraging preclinical and early clinical data concerning the relevance of the insulin receptor/insulin-like growth factor (IGF) receptor family to neoplasia led to ambitious clinical trial programs of more than a dozen drug candidates that target these receptors. These candidates include antireceptor antibodies, antiligand antibodies, receptor-specific tyrosine kinase inhibitors, and agents such as picropodophyllin and metformin that have novel mechanisms of action. Several recently reported phase III clinical trials of anti-IGF-I receptor antibodies have been disappointing and are sufficient to disprove the hypothesis that the antibodies tested have large favorable impacts on unselected patients with cancer. However, many of these trials were designed prior to recent insights concerning pathophysiology and predictive biomarkers. Future studies are required, but it will be important to optimize their design rather than simply repeat the approaches taken to date.

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## Introduction

Insulin and insulin-like growth factors (IGF) are potent mitogens, and the hypothesis that their receptors are important therapeutic targets in oncology has received considerable attention (reviewed in refs. 1–5). In the last decade, more than 20 drug candidates that target IGF-I receptors (IGF-IR) or both insulin and IGF-I receptors have been developed. Of these, at least 12 have been taken forward to clinical trials.

The rationale for drug development in this area included clinical and epidemiologic evidence (e.g., refs. 6, 7) that circulating levels of insulin and/or IGFs are related to cancer risk and/or cancer prognosis, as well as laboratory studies (e.g., ref. 8), which showed that interfering with signaling had inhibitory effects on neoplastic behavior. Seminal studies (9) from the laboratory of Renato Baserga showing a requirement for presence of the IGF-IR for transforming activity of a variety of oncogenes also contributed to the rationale.

This research was followed by synthesis of drug candidates. These showed activity in preclinical models and subsequently led to clinical trials (1, 2, 4, 5). In retrospect, however, it must be recognized that most preclinical studies of drug candidates showed benefit in experimental cancer models that were engineered to be IGF-IR driven or in

models chosen specifically because they were sensitive to the drugs, with relatively little attention given to studies of characteristics of the tumor or host that predicted antineoplastic activity.

The evidence from population studies is of particular interest; although it is rare for circulating ligand levels for a tyrosine kinase receptor to be related to cancer risk or prognosis, this has been shown for both insulin and IGF-I (e.g., refs. 6, 10; reviewed in refs. 1, 4, 5). For some tissue growth factors, such as epidermal growth factor or platelet-derived growth factor, circulating concentrations may have no clear physiologic significance; although the peptides are detectable, their levels are not regulated and have no known physiologic role, as they simply "leak" into the circulation from the tissues where they are expressed. Insulin and IGFs, in contrast, have credentials both as tissue growth factors and as circulating hormones, and their circulating levels are regulated by complex physiologic control systems that vary from person to person according to a variety of genetic and lifestyle factors.

Early findings (6, 11) indicating that individuals with higher circulating levels of IGF-I are at increased risk for common cancers have, in some cases, been confirmed in subsequent studies (12, 13), but for some disease sites, data are inconsistent (14–16). A poorly understood trend noted in certain data sets is that high levels of insulin (or c-peptide, often used as a surrogate) tend to be more useful in predicting prognosis among patients with cancer than cancer risk in populations, whereas variation in IGF-I levels between individuals is more useful in predicting cancer risk than in determining prognosis after diagnosis. A report (17) of unexpectedly low cancer incidence in an "outlier" population with a mutation that drastically lowers IGF-I levels is consistent with the prior studies showing cancer risk varying within the broad normal range of IGF-I.

Recent studies of cancer risk and/or cancer mortality among patients with diabetes raise many questions and are relevant to therapeutic targeting of the insulin/IGF-I receptor family to treat cancer. Certain cancers are more common among patients with type II diabetes (reviewed in ref. 18), and the basis for this is a matter of ongoing research. Direct evidence also reveals an association between hyperinsulinemia and adverse prognosis in breast cancer (10). Some experimental studies support the view that the hyperinsulinemia of type II diabetes is a key mediator of the effect of diabetes on neoplasia, as suggested by increased activation of insulin receptors (19, 20) and increased glucose uptake (ref. 21) by neoplasms in models of diet-induced hyperinsulinemia. If this is the case, then hyperinsulinemic patients with insulin-responsive tumors might be particularly appropriate candidates for therapies that reduce insulin levels and/or reduce signal transduction through the insulin receptor. However, other aspects of the pathophysiology of type II diabetes, such as elevations in inflammatory cytokines (22) or even hyperglycemia itself, may also be important mediators of the adverse effect of type II diabetes on cancer risk and/or prognosis, so caution is required in attributing the diabetes–cancer association exclusively to insulin.

Although hyperglycemia is a candidate risk factor, experimental systems that show that type I diabetes with hypoinsulinemia and hyperglycemia is associated with reduced rather than increased tumor growth argue against this possibility (23). Thus, important epidemiologic research associating hyperglycemia with cancer risk (24, 25) does not necessarily imply a causal relationship; hyperglycemia in these studies may serve as a surrogate for other pathophysiologic mediators. Research concerning diabetes–cancer interactions has also provided evidence that metformin treatment of patients with diabetes is associated with decreased cancer risk (reviewed in refs. 18, 26, 27). The mechanisms involved here may include the reduction of hyperinsulinemia by this agent, but preclinical evidence suggests that is only one of several relevant actions (reviewed in refs. 18, 26, 27).

If insulin can stimulate aggressive behavior of certain cancers, is it possible that insulin therapy for type II diabetes might have an adverse impact on cancer behavior? Theoretically, this outcome would be predicted, particularly as insulin levels associated with conventional subcutaneous insulin administration are higher than those of nondiabetic persons (28, 29). This situation arises not only because insulin is given at doses adequate to improve blood glucose under conditions of insulin resistance but also because the amount of insulin required to affect the liver when it is given by the subcutaneous route is considerably higher than the amount required via physiologic secretion by pancreatic beta cells. Many studies have attempted to address this issue (reviewed in ref. 27), but data to associate insulin therapy in general (or any particular insulin analog) with cancer risk are not conclusive. These studies are obviously difficult to carry out because of many potentially confounding variables and issues of dose, duration, and cotreatment. Some

studies raise concern and certainly justify further research (30). Clinical experience over decades does not suggest any major increased cancer risk associated with insulin therapy; the controversy relates to the question of no effect versus a modest effect. There is no question that insulin must be prescribed when indicated for diabetes management, but rather if diabetics in general or diabetics on insulin require enhanced surveillance for cancer.

## Progress in Physiology and Pathophysiology

The fundamental aspects of relevant physiology and pathophysiology have been reviewed previously (1, 4, 5), but certain aspects deserve emphasis in view of recent recognition of potential relevance to therapeutic targeting.

### The insulin/IGF receptor family

It was initially surprising to some endocrinologists that insulin and IGF-I receptors, previously well characterized on the normal tissues that are classically known to be responsive to these hormones, are also commonly expressed at significant levels on cancer cells derived from many organs (31, 32). However, this finding is now accepted, and it is recognized that from an evolutionary perspective insulin-like signaling in control of cellular proliferation is older than the relatively recent specialized functions in regulation of carbohydrate metabolism (insulin) and skeletal growth (IGF-I).

Although investigators sometimes find it helpful to compartmentalize their work and consider insulin and IGF-I receptors as distinct topics in oncology, it is probably more accurate to consider this receptor family in a unified fashion. Review of cancer gene expression databases reveals that most cancers express both the gene encoding the insulin receptor and the gene encoding the IGF-IR. Thus, most individual cancer cells (or epithelial cells at risk for transformation) likely express both receptors, and studies of one receptor alone may incompletely reflect physiology. Even more fundamentally, it is now understood that when both receptors are expressed, it is the rule rather than exception for "hybrid" receptors to be present on the cell surface (e.g., ref. 33; reviewed in ref. 34). Both insulin and IGF-IRs are heterodimers, in which each "half receptor" is composed of an alpha chain and a beta chain. The assembly of "half receptors" into "holoreceptors" occurs on the cell surface in a manner that does not necessarily favor pairing of identical "half receptors," so the formation of so-called "hybrid" receptors is common. In fact, if both gene products are translated at similar rates, hybrid receptors may be the dominant species on the cell surface. Although certain normal tissues express one of the receptor genes much more abundantly than the other (e.g., the liver is a classic insulin-responsive tissue, with abundant insulin receptors but few IGF-IRs), this is not generally true for neoplastic cells. In general, therapeutic antibodies directed against the IGF-IR also block hybrid receptors, but detailed studies have not been done with all drug candidates.

Additional complexity concerns the 2 isoforms of the insulin receptor (34), which arise because of alternate splicing. It is now recognized that one isoform ("IR-A") is preferentially expressed by cancers, and although it is structurally similar to the "IR-B" isoform, it has potentially important differences in ligand binding. Although the IR-B isoform is insulin specific, IR-A also binds IGF-II, which may be significant for those neoplasms in which pathophysiology involves an autocrine IGF-II loop.

Considering jointly the complexities of hybrid receptors and insulin receptor isoforms, the insulin/IGF-I receptor family actually has 6 potential members as shown in Fig. 1, and as we have seen, it is common for several of these receptor species to be expressed on a single cell. A receptor known as the IGF-II receptor must also be considered. This receptor binds only IGF-II and is structurally distinct from the other family members, with the most obvious difference being the lack of an intracellular tyrosine kinase domain. Most investigators believe this receptor does not transduce a mitogenic signal and actually acts as a growth inhibitor or tumor suppressor by binding IGF-II and sequestering it away from the IR-B or the IGF-IRs (or their hybrids), thus reducing IGF-II bioactivity (35).

Variation in levels of receptor expression between transformed and normal tissue remains a topic of active investigation, although it is clear that gene amplification with greatly increased receptor numbers per cell leading to ligand-independent activation, as seen with HER2-neu, is rare. Activating mutations of the insulin or IGF-I receptors are also rare. Variation in receptor levels between tumors has been noted, and relationships may exist between receptor level and disease prognosis or response to drugs that target this receptor family (36, 37). It is important to recognize that standard immunostaining approaches with conventional antireceptor antibodies do not discriminate

between all family members. Most insulin receptor antibodies detect both the IR-A and IR-B isoforms. Furthermore, immunoreactivity with an anti-insulin receptor antibody may signify presence of insulin receptors and/or hybrid receptors, and similarly, immunoreactivity with an anti-IGF-IR antibody may signify presence of IGF-IR and/or hybrid receptors.

The first steps in the signaling networks downstream of the insulin receptor and IGF-IR are similar, although not identical (38). Both ligands have major influences on protein translation via pathways linking receptor activation to AKT and mTOR, and they also influence transcriptional programs. Although some of the important distinctions in the effects of these ligands may be attributed to differences in early steps in signal transduction pathways, many of the differences relate to the different downstream processes controlled by these networks in different cell types. For example, insulin regulates glycogen storage in liver, but it has other roles in other tissues, such as mammary gland epithelial cells. Thus, although it is true, as often stated, that insulin has dominantly metabolic effects in contrast to the dominantly mitogenic effects of the IGFs, this generalization is not universal; many cell types can respond mitogenically to insulin via its own receptor at clinically relevant concentrations (21). In contrast, pharmacologic insulin concentrations are commonly used in tissue culture media, as these may act to stimulate cell growth via insulin receptors, IGF-IRs, or various hybrid receptors.

### Ligands

IGF-I, IGF-II, and insulin obviously share evolutionary ancestry and structural features, but they have important distinguishing characteristics. One difference between insulin and the IGFs is the processing of the translated product of the insulin gene to remove c-peptide, a process that does not

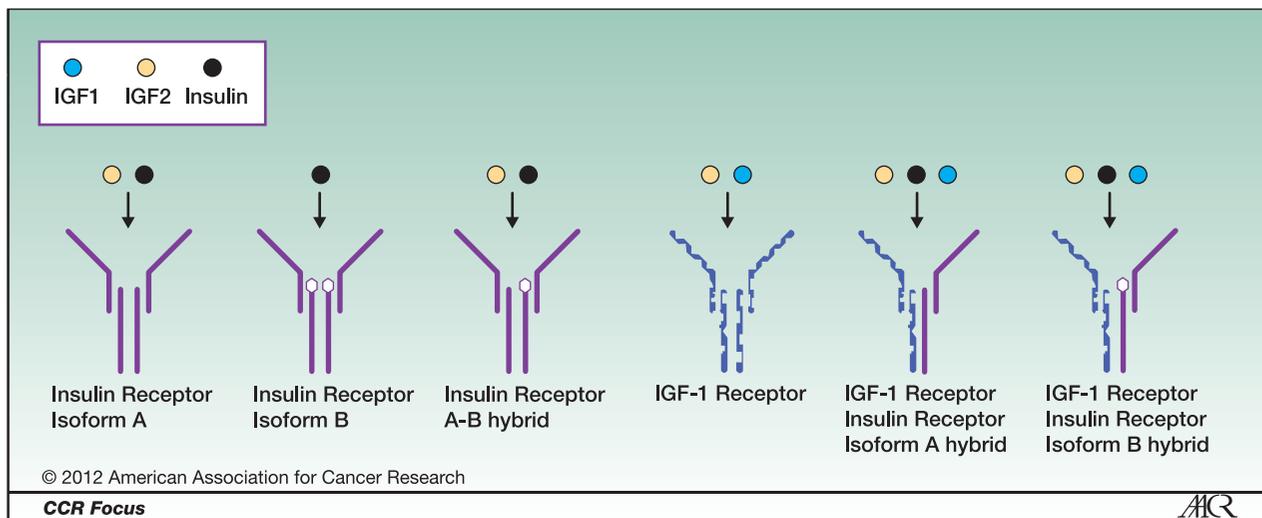


Figure 1. Members of the insulin/IGF receptor family. The insulin receptor isoform A lacks a 12–amino acid segment present at the C terminal of the alpha chain of the isoform B, which is coded for by exon 11. The dominant insulin receptor on neoplastic tissue is isoform A, but many cancers also express the IGF-IR and display multiple receptor family members, dominantly hybrid receptors. Receptors have varying affinities for the ligands IGF-I, IGF-II, and insulin (reviewed in ref. 34), and some of the more important receptor–ligand partners are depicted.

occur for the IGFs. Another key difference is site of production and control of release. Insulin gene expression is highly restricted to pancreatic beta cell, where it is tightly regulated according to levels of glucose in serum. Furthermore, expression of the gene encoding insulin is not sufficient for the production of bioactive insulin, as specific peptidases are needed to process proinsulin to the bioactive peptide. Insulin produced by pancreatic beta cells acts as a classic hormone, influencing physiology at distant organs, particularly liver, muscle, and fat. Ectopic production of insulin by cell types other than pancreatic beta cells is exceedingly rare.

In contrast, IGF-I and IGF-II have characteristics of tissue growth factors as well as hormones. Although most circulating IGFs are produced in the liver and circulating levels are physiologically regulated, these peptides are also widely expressed in many tissues, where they have important autocrine and paracrine actions.

The gene encoding IGF-II is imprinted (39); thus, loss of imprinting represents one of several mechanisms that can result in overexpression of this ligand. There are many reports of overexpression of IGF-I and/or IGF-II by malignant cells, and in contrast to the well-known example of HER2/neu in an important subset of breast cancers, the molecular pathology of IGF signaling in neoplasia more often involves inappropriate expression of ligands than derangement of receptors.

The bioactivity of IGFs is regulated in a complex fashion by a family of IGF binding proteins (IGFBP; ref. 40), which may increase bioactivity by prolonging half-life or decrease bioactivity by competing with receptors for ligands, depending on the physiologic context. IGFBPs are subject to degradation by various proteases, including many secreted by malignant cells; thus, secretion of proteolytic enzymes, such as prostate specific antigen (41), by transformed cells may increase local IGF bioactivity, contributing to neoplastic behavior.

It is of interest to review the circulating concentrations of insulin ( $\sim 0.5$  nmol/L), IGF-I ( $\sim 20$  nmol/L), and IGF-II ( $\sim 100$  nmol/L) in relation to the above concepts. IGF-II circulates in the highest concentration range of the 3 ligands, consistent with the fact that access to receptors that transduce its signal is restricted by competition from both the IGF binding proteins and the IGF-II receptor. Next is IGF-I, which binds to the IGFBPs but not to the IGF-II receptor. Finally, insulin, at the lowest concentration range, has a "clear path" to its target receptor without competition from IGFBPs or the IGF-II receptor.

Circulating levels of IGF-I and IGF-II vary considerably between individuals within a rather broad reference range. Twin studies have shown that both genetic and lifestyle factors contribute to this variation (42). Diseases of IGF-I excess (such as acromegaly) and deficit (such as growth hormone deficiency) are described, and it is of interest that variation both within the reference range and at pathologic extremes has been associated with cancer risk (1, 5, 17). Insulin levels vary throughout the day according to food intake to a much greater extent than IGF-I levels. Apart from

this level of variation, important differences between individuals have also been found over longer timescales; early type II diabetes, obesity, and the "metabolic syndrome" are examples of conditions in which insulin levels are higher than normal. In all of these cases, the pathophysiology involves attempted compensation by increased insulin secretion to overcome the abnormal "insulin resistance" present in classic insulin target organs, such as liver, muscle, or adipose tissue. Hyperinsulinemia has been associated with poor cancer prognosis, and experimental evidence has shown that this is related to increased insulin receptor activation in neoplastic tissue (19, 20). However, a cause-and-effect relationship is not certain, as insulin resistance is associated with many endocrine abnormalities that may influence cancer biology besides high insulin levels, including, for example, elevated levels of inflammatory cytokines (22). A key issue under study is whether insulin resistance is present in insulin receptor-positive cancers of patients who have insulin resistance in classic insulin target organs. Hyperinsulinemia due to host insulin resistance may stimulate aggressive neoplastic behavior of insulin-sensitive tumors.

## Therapeutic Strategies

### Antireceptor antibodies

Many monoclonal therapeutic antibodies against the IGF-IR have been developed. They differ from each other with respect to characteristics such as antibody subclass and serum half life. Some of these are currently in clinical trials in various combinations, and some results have been encouraging (e.g., refs. 43, 44). On the other hand, figitumumab is an example of an anti-IGF-IR antibody studied in phase III studies of unselected patients with lung cancer which revealed not only a lack of benefit but also toxicity greater than predicted on the basis of phase II studies (45), and other disappointing trials have been reported (46).

Although these antibodies were specifically designed to spare insulin receptors, hyperglycemia has been a commonly encountered adverse event. This is occasionally serious and associated with other metabolic derangements, such as dehydration. As shown in Fig. 2, the metabolic toxicity does not result from cross-reactivity with the insulin receptor, which was successfully avoided by antibody engineering. Rather, it is a consequence of peripheral insulin resistance that arises secondary to the high levels of growth hormone associated with administration of these antibodies. The elevations in growth hormone are likely a result of blocked signaling of IGF-IRs in the hypothalamic-pituitary control systems that regulate serum IGF-I level; perceived IGF-I deficiency leads to increased secretion of growth hormone to raise growth hormone-dependent hepatic IGF-I production. Thus, treatment with anti-IGF-IR antibodies is associated with elevations of growth hormone and IGF-I. The high IGF-I levels are without consequence due to receptor blockade, but the high levels of growth hormone lead to peripheral insulin resistance and, occasionally, to hyperglycemia and hyperinsulinemia.

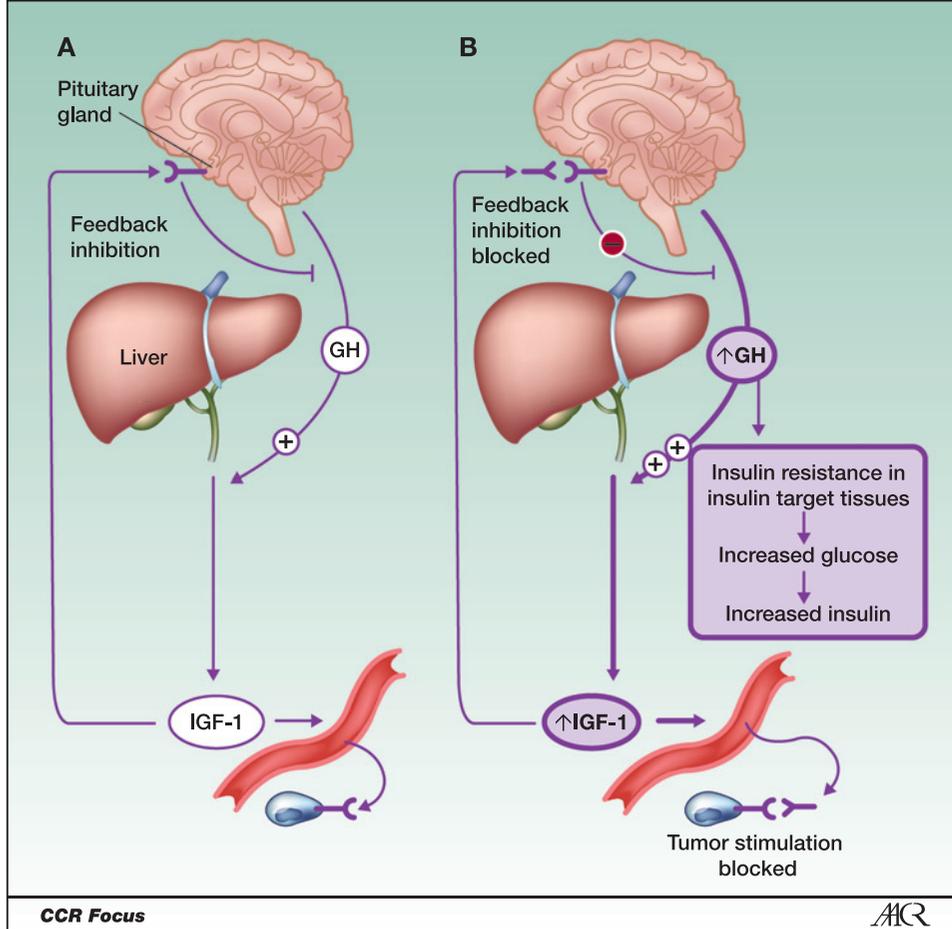


Figure 2. Mechanism of metabolic toxicity of therapies that target the IGF-IR. A, normally growth hormone stimulates hepatic IGF-I production, and circulating IGF-I exerts a homeostatic feedback inhibition on growth hormone secretion by the pituitary. B, in the presence of IGF-IR blockade, the IGF-I-induced feedback inhibition of growth hormone secretion is reduced, leading to elevations in growth hormone and in IGF-I. The high IGF-I levels have little effect in the setting of receptor blockade, but the high growth hormone levels can lead to insulin resistance, hyperglycemia, and hyperinsulinemia. Figure adapted from Pollak (1).

### Antiligand antibodies

Bevacizumab provides a precedent for a therapeutic antibody that targets a ligand (in this example VEGF) rather than the receptor. Several companies are developing high-affinity antibodies that cross-react with the ligands IGF-I and IGF-II (47). These drug candidates are at an earlier stage of development, and clinical data are not yet available, although preclinical data have been regarded as sufficiently positive to justify clinical trials. One potential advantage of the antiligand approach is that it has the potential to block the action of IGF-II at the insulin isoform A, without interfering directly with insulin action. This finding is predicted to be particularly important for the large number of cancers with IGF-II autocrine production.

### Receptor tyrosine kinase inhibitors

Receptor tyrosine kinase inhibitors were initially developed as IGF-IR-specific inhibitors (48), but it is now recognized that *in vivo*, they broadly inhibit the entire receptor family. In view of this property, the theoretical risk for serious metabolic toxicity is relatively high. However, these agents may have important advantages over the other approaches in that insulin receptor-mediated resis-

tance to IGF-IR targeting has been described (49) and is less likely with these broader spectrum inhibitors.

It is of interest that in early clinical trials, severe metabolic toxicity of these agents has not been seen despite the blockade of insulin signaling, which might be expected to cause a clinical picture similar to untreated diabetes. This tolerability is the subject of ongoing research, but some preclinical models suggest that pharmacokinetic factors may provide an explanation. Evidence indicates that the drugs accumulate only to suboptimum therapeutic levels in muscle (23), which is an important site of insulin-mediated glucose uptake. Therefore, severe hyperglycemia may not occur as frequently as was predicted because even at therapeutic serum drug levels, insulin-mediated glucose uptake by muscle takes place. However, other theoretical metabolic hazards must be taken into account with these agents, as there is evidence that their use is associated with hyperinsulinemia, and sudden cessation of therapy or a skipped dose could therefore lead to hypoglycemia.

### Metformin

Metformin is commonly used in type II diabetes treatment, where it lowers both hyperglycemia and

hyperinsulinemia. These properties, particularly the latter, have led to proposals that it be evaluated as a drug candidate for treating or preventing cancer (reviewed in ref. 26). Interestingly, these proposed mechanisms do not require a direct action of the drug on neoplastic cells but only in liver, a key site for its therapeutic effect in diabetes. Retrospective epidemiologic studies suggesting reduced cancer burden among patients with diabetes on metformin compared to patients with diabetes on other therapies have generated interest. However, caveats for using metformin to treat cancer are that it has negligible effects on IGF-I levels and that it only lowers insulin levels if they are elevated at baseline (reviewed in ref. 26).

On the other hand, this agent, if it accumulates at sufficient concentration in neoplastic tissue, may have additional "direct" mechanisms of action. One of these mechanisms involves inhibition of signaling downstream of the insulin/IGF-I receptor family by AMPK-dependent inhibition of mTOR (50). Metformin indisputably has a favorable safety profile but important gaps in knowledge to study include factors influencing metformin accumulation in tumors and the pros and cons of metformin compared with other biguanides (such as phenformin) for potential oncologic indications. Many clinical trials with this off-patent agent are in progress.

### **Picropodophyllin**

Picropodophyllin has an interesting history and credentials as an IGF-IR inhibitor, although other modes of action have not been excluded with certainty (51–53). Preclinical and early clinical results have been favorable, and expansion of the clinical trials program is planned.

### **Clinical Trials to Date**

More than 100 clinical trials relevant to the hypothesis that insulin and IGFs represent therapeutic targets are listed in ClinicalTrials.gov, and it is beyond the scope of this review to assess them individually. Although reviews of the status of the trials tend to quickly become outdated, the reader is referred to several recent summaries (e.g., ref. 54). Table 1 lists some trials representative of the extensive ongoing clinical evaluation programs.

In general, toxicity of anti-IGF-IR antibodies has been greater than originally predicted, particularly in large phase III trials carried out in part in nonspecialist centers. Metabolic adverse events of IGF-IR–targeting agents, such as hyperglycemia, are treatable if promptly diagnosed, and metformin has been used for this purpose. However, for some oncologists, these adverse events differ from those commonly encountered with approved cancer treatments, so clear algorithms must be provided to enable optimum screening for adverse events and effective management of complications.

What can we conclude from clinical trials to date? Although well-documented anecdotal reports of benefit of IGF-IR–targeting agents, particularly in Ewing sarcoma, and also some encouraging phase II results have emerged,

negative phase III results clearly must be regarded as more definitive.

However, careful consideration must be given to the generality of conclusions from these trials. One view would be that the negative phase III data now available are sufficient to justify abandonment of further investigation of therapeutic targeting of the insulin/IGF-I receptor family for all indications, regardless of targeting strategy. At the opposite extreme, to use the figitumumab example (45), some would limit the conclusion to the specific demonstration that this particular drug candidate has no utility in unselected patients with non–small cell lung cancer when added to a specific cytotoxic regime, but they would not extend this conclusion to other possible figitumumab indications and certainly not to other antireceptor antibodies or to other targeting strategies, such as small molecule kinase inhibitors.

The wide spectrum of opinion on this issue is illustrated by the fact that some pharmaceutical companies are closing drug development programs, whereas others are initiating or continuing trials. Although in some drug development programs, disappointing clinical trial results have led to the recognition that the original rationale was flawed (55), this is not the case for the insulin/IGF-I receptor target.

### **What Are the Major Unanswered Questions?**

#### **Are there candidate predictive biomarkers that might guide further trials, and is this worth investigating?**

There are clear precedents where the use of a predictive biomarker has been essential to define a subset of patients for whom a particular therapy is applicable. Examples include the classic case of trastuzumab, which is useful for the ~30% of breast cancers that are HER2 positive and the more recent example of crizotinib for the small (~5%) subset of lung cancers that are driven by alk fusion proteins (56). In some cases, the candidate predictive biomarker was obvious, but at the time of initiation of clinical trials of agents that target the insulin/IGF-I receptor family, no predictive biomarkers for these drugs had been described. By mid-2011, however, candidate predictive biomarkers had been identified. Some of these are supported by early clinical evidence, but none are formally validated. In retrospect, review of preclinical models does not suggest anything approaching dependency of 100% of neoplasms on the insulin/IGF-I receptor family; perhaps 25% is a more reasonable estimate.

This issue is of central importance in further development of agents that target the insulin/IGF receptor family, now that emerging phase III data are showing lack of activity in unselected patients, at least for certain indications. It is not necessary that predictive biomarkers perform perfectly, but rather that they allow enrichment of clinical trials with patients more likely to respond and/or exclude patients more likely to experience toxicity.

Among candidate predictive biomarkers is the pretreatment level of circulating free IGF-I (57–59). The early data

**Table 1.** Representative clinical trials

Reference no.	Agent	Class	Trial description	Comments
77	Dalotuzumab (MK0646)	Anti-IGF-IR	Phase I with PK and PD endpoints	<ul style="list-style-type: none"> <li>• Well tolerated</li> <li>• Decreases in tumor proliferation observed</li> <li>• 18FDG-PET metabolic responses observed</li> </ul>
78, 79	XL228	TKI with activity against BCR-ABL and IGF-IR	Phase I	<ul style="list-style-type: none"> <li>• CRs and PRs observed</li> </ul>
80, 81	Robatumumab (R1507)	Anti-IGF-IR	Phase I	<ul style="list-style-type: none"> <li>• PRs seen in Ewing sarcoma</li> </ul>
82	BMS-754807	Insulin/IGF-I receptor TKI	Phase II in progress	<ul style="list-style-type: none"> <li>• Ongoing study of this TKI with letrozole in metastatic ER+ breast cancer</li> </ul>
46	Figitumumab	Anti-IGF-IR	Phase III	<ul style="list-style-type: none"> <li>• Unexpected toxicity</li> <li>• No benefit</li> </ul>

Abbreviations: CR, complete response; ER, estrogen receptor; FDG-PET, 2[18F]fluoro-2-deoxy-D-glucose positron emission tomography; PK, pharmacokinetic; PD, pharmacodynamic; PR, partial response; TKI, tyrosine kinase inhibitor.

to support this candidate come from relatively small phase II rather than phase III studies, so no definitive conclusions are available, but evidence that confining treatment to subjects with higher free IGF-I levels would both reduce toxicity and increase efficacy is intriguing. The rationale offered for these findings is that tumors that developed in hosts with higher ligand levels were more likely to become dependent on or even addicted to IGF-IR activation and, therefore, more likely to respond to interruption of signaling.

Additional candidate predictive biomarkers include receptor levels and the presence of autocrine loops. The presence of autocrine loops is relatively easy to assess in tumor specimens by measuring expression of receptors and ligands. Consideration of this candidate predictive biomarker leads to the question of efficacy of agents for tumors that may be stimulated by circulating ligands from the host ("endocrine" sources) compared with those that are stimulated by locally produced ligands. Various drug candidates may differ in their efficacy depending on ligand source. For example, higher tissue levels of antiligand antibodies may be required to inhibit growth of tumors that have strong autocrine production compared with those that rely on circulating ligands. Although it is likely that the presence of autocrine loops indicates a degree of dependency of tumors on the signaling pathway, it may be a marker of sensitivity for those agents capable of interrupting such loops, or it may be a marker of resistance for agents that are capable only of attenuating receptor activation related to circulating ligands.

Other candidate predictive biomarkers are under investigation, including, for example, the presence of certain transforming fusion proteins that seem to have a requirement for IGF-IR activation (60). In contrast, although not

investigated in clinical trial specimens, it is highly plausible that the presence of activating mutations downstream of the IGF-IR, such as those resulting in constitutive rather than ligand-dependent activation of phosphoinositide 3-kinase, would confer resistance to receptor targeting.

#### What resistance mechanisms have been proposed?

Many advanced cancers have likely evolved to a degree that their behavior is constitutively aggressive and uninfluenced by growth signals. For such neoplasms, targeting the insulin/IGF-I receptor (or any other receptor kinase) will be ineffective. Similarly, some cancers are driven by other receptors (e.g., HER2/neu) to such an extent that insulin/IGF-I receptor signaling becomes irrelevant, and these would also be predicted to be resistant. Finally, as mentioned above, situations may exist in which cancers are dependent on insulin receptor or IGF-IR activation, but due to processes such as insulin receptor-mediated resistance to IGF-IR targeting or the presence of a strong autocrine loop, particular drugs may not be effective. Many model systems exist that provide examples of cancers that are sensitive to insulin/IGF-I receptor family targeting, but further research is needed to allow estimates of the percentage of clinical cancers that exhibit this sensitivity. Although it is likely that a majority of cancers are indeed resistant, examples of successful drug development programs in the era of "personalized medicine" involve agents active in <10% of patients (56).

#### Are there important differences between the targeting strategies or between drug candidates in a particular class?

As mentioned above, several classes of agents target the insulin/IGF-IR family, and some of these classes

(particularly the antireceptor antibodies) have many individual drug candidates. Most investigators would agree that the various classes of agent that involve different therapeutic strategies are distinct from each other, to the extent that toxicity or efficacy data about one class will not necessarily apply to the others. However, the significance of differences between agents within a strategic class (e.g., antireceptor antibodies) is less clear. Many drug candidates were developed for commercial competitive reasons, and although they are clearly nonidentical in potentially important areas, including pharmacokinetic profile, it is a matter of controversy whether results with any one member of a class are relevant to the other members of the class. This is a matter of practical importance, as it is crucial to avoid repeating large phase III trials of agents that are highly likely to yield results already obtained with similar drug candidates, whereas at the same time, it would be unfortunate if a superior drug candidate were not taken to the clinic on the basis of a prior negative clinical trial experience with an inferior member of a therapeutic class.

#### **Are there rational combination therapies to be explored?**

Many targeted therapies are routinely used in combination with other agents. A classic example is trastuzumab, which is given with cytotoxic chemotherapy. Others, such as crizotinib, are active as single agents. Most trials with agents that target insulin/IGF-I receptors have involved combinations. In general, these combinations have not been selected on the basis of specific synergy shown preclinically but rather on a pragmatic approach involving the addition of a drug candidate to a current "standard" therapy that has some activity, but where there is an obvious clinical need to improve efficacy.

Further preclinical studies may guide clinical trial design in this area and offer advantages over a strictly pragmatic approach. For example, synthetic lethality experiments suggest cotargeting partners for agents that inhibit insulin and/or IGF-I signaling (61). It is possible that common resistance mechanisms to approved targeted therapies, radiotherapy (62), or cytotoxic agents involve insulin and/or IGF-I signaling (63–68), and such information suggests specific clinical trial designs. Data concerning roles for the insulin/IGF-I receptor family in resistance to mTOR inhibitors (69) and BRAF inhibitors (70–72) are of particular interest. Several trials combining IGF-IR blockade and mTOR inhibition are ongoing.

Cotargeting steroid receptors and the insulin/IGF-I receptor family may offer specific opportunities. For example, recent preclinical data indicating that insulin can stimulate local androgen production by prostate cancer cells (73)

suggest the possibility of combinations with castration and/or inhibitors of androgen synthesis.

#### **What Next?**

In the search for new cancer therapies, it is well known that investigation of most targets initially considered promising does not justify drug development, that preclinical investigation of most drug candidates does not justify clinical evaluation, and that a great majority of drug candidates that are evaluated in clinical trials do not lead to approved indications. It is also clear that among approved drugs, many have therapeutic activity that is clearly documented but is small in magnitude and/or confined only to small subgroups of patients. Progress by small increments is more common than major leaps forward.

In the case of drug candidates that target the insulin/IGF receptor family for indications in oncology, initial phase III trials have been disappointing, and the best-case scenario proposed by optimists 10 years ago, namely, broad spectrum activity for unselected patients with many kinds of advanced cancer, has been disproven. However, it remains to be seen whether these results represent the beginning of the end for this therapeutic target or whether further studies will reveal specific contexts in which targeting this receptor family will lead to clinical benefit. It has been pointed out that, in general, clinical trials should take into account the possibility of benefit confined to patient subgroups (74), and this has not been explored in detail in the case of therapies that target the insulin/IGF-I receptor family. This issue is a common one in cancer drug development (75, 76).

Prominent among current lines of investigation are the search for rational rather than arbitrary drug combinations, the identification of predictive biomarkers, and clarification of the pros and cons of the various classes of targeting agents in terms of safety and efficacy.

#### **Addendum**

Two recent reports (83, 84), together with ref. 73 and a prior report (32), add to the rationale for investigating combinations of insulin receptor/IGF-IR kinase inhibitors with agents that target steroid hormone signaling. We apologize to those who contributed to this field whose work could not be cited due to space limitations.

#### **Disclosure of Potential Conflicts of Interest**

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