Targeting the Insulin-like Growth Factor Axis for the Development of Novel Therapeutics in Oncology

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Abstract

Insulin-like growth factors (IGF) are polypeptide hormones with potent anabolic and mitogenic effects that regulate cell growth and differentiation. Dysregulation of the IGF axis has been well documented in the development and progression of multiple types of cancer. As a result, compounds targeting the IGF axis have become an area of intense preclinical and clinical research for cancer therapeutics. The IGF axis is intimately involved with the insulin-signaling pathway because of their close homologies. This homology may explain hurdles encountered in the clinical development of IGF-targeted therapies, such as less-than-expected antitumor efficacy that may arise from compensatory increases in the activity of insulin receptor isoform A (IR-A), in response to IGF-I receptor (IGF-IR) inhibition and perturbations in glucose homeostasis, arising from the inhibition of insulin receptor isoform B (IR-B) activity. In this brief review, we compare differentiating factors that characterize the 3 major classes of IGF-targeting compounds: therapeutic antibodies that target IGF-IR, small molecule tyrosine kinase inhibitors that inhibit kinase activities of IGF-IR and IR, and antibodies that target IGF ligands.

Introduction

Insulin-like growth factors I and II (IGF-I and IGF-II) are polypeptide hormones produced mainly by the liver. They mediate the activity of growth hormone and stimulate the development of bone and skeletal muscle (for a detailed review, see ref. 1). The IGFs are also produced locally by various somatic tissues, making them the only hormones that regulate cell proliferation, differentiation, and survival via endocrine, paracrine, and autocrine pathways. The IGFs and insulin exhibit strong sequence similarities. The primary IGF receptor, namely IGF-I receptor (IGF-IR), shares almost 60% homology with the insulin receptor (IR). Both IGF-IR and IR belong to the family of receptor tyrosine kinases. As a result, the IGF-signaling system, often referred to as the IGF axis (Fig. 1A), is closely linked to insulin signaling. The IGF axis consists of ligands IGF-I and IGF-II, receptors IGF-IR and IGF-IIR, 6 high-affinity IGF-binding proteins (IGFBP) 1 to 6, and a group of proteases that degrade IGFBP. The IGFs exert their activities primarily by binding and activating IGF-IR. Phosphorylation of IGF-IR recruits the downstream signaling protein insulin receptor substrate (IRS) 1 to 3 to the cell membrane, which subsequently activates both phosphoinositide 3-kinase (PI3K)-Akt and the mitogen-activated protein kinase (MAPK) pathways. IRS proteins also mediate the effects of IR. By contrast, IGF-IR lacks intracellular kinase activity and functions as a scavenger receptor that regulates the bioavailability of IGF-II. Similarly, the bioavailability of IGFs is closely regulated by IGFBPs, which also act as carrier proteins.

Two isoforms of IR, IR-A and IR-B, result from posttranscriptional alternative splicing. IR-A is a truncated version of the IR that lacks exon 11 (36 base pairs that encode 12 amino acids toward the C-terminus of the alpha subunit). IGF-II has been shown to bind IR-A with greater affinity than IGF-I. IGF-II and insulin both stimulate IR-A, which, when activated by IGF-II, results in mitogenic effects and increased survival, motility, and invasiveness of cancer cells (2). In contrast, IR-B is activated by insulin and is mainly responsible for maintaining glucose homeostasis. Hybrid receptors composed of IGF-IR and IR, as well as IGF-IR and other receptor tyrosine kinases, such as the epidermal growth factor receptor (EGFR) and HER2, contribute to complexities of IGF signaling and may constitute pathways by which cancers resist IGF-targeted therapies.

Role of IGF Signaling in Cancer

The role of IGFs in the development and progression of a broad range of epithelial cancers is well documented (3). Although mutations of IGF-IR have not been found in cancer cells, increased IGF-signaling activity is associated with many types of cancer. In addition, downregulation of IGF-IR expression and reduced signaling have been shown to inhibit tumor growth and increase the susceptibility of cancer cells to chemotherapeutic agents in vivo (4). Increased expression of IGF-II and/or IR-A is reported during fetal development and...
IGF-binding proteins 1-6 and the scavenger receptor IGF-IIR both regulate the level of free IGF ligands.

Glucose Metabolism
Proliferation • Survival • Differentiation
Transformation • Metastasis

mAbs that target only the IGF-IR allow continued signaling through the IR-A homodimer.

By neutralizing IGF ligands, MEDI-573 effectively blocks both IGF-IR and IR-A signaling pathways, while sparing IR-B.

Figure 1. IGF axis and targeted therapies. A, the major components of the IGF axis. The IGF-IR/IR-B hybrid receptors are not represented. ERK, extracellular signal-regulated kinase; MEK, MAP–ERK kinase. B, IGF-IR–specific versus IGF ligand–neutralizing antibody-targeted therapy. IGF-IR–specific antibodies may also bind to IGF-IR/IR-B hybrid receptors (not represented), which may have certain impact on glucose metabolism. mAb, monoclonal antibody.

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across a broad range of cancers, including breast, lung, colorectal, thyroid, bladder, primary liver, and various sarcomas. Although posttranscriptional regulation and expression of IR-A versus IR-B is not yet fully understood, overexpression of IR-A and IGF-II (frequently caused by loss of imprinting of the maternal IGF-II allele in certain tumors) has been proposed as a potential mechanism of resistance to IGF-IR–directed therapies (5). This review focuses on 3 major classes of therapeutic compounds targeting the IGF axis currently in clinical development: antibodies that target IGF-IR, small-molecule tyrosine kinase inhibitors (TKI) that inhibit kinase activities of IGF-IR and IR, and antibodies that target IGF ligands.

**Investigational Compounds That Target the IGF Axis**

Antibodies targeting IGF-IR inhibit the binding of IGF to IGF-IR. They are furthest along in clinical development of all IGF-targeting agents. Many of these antibodies induce IGF-IR internalization and degradation upon binding to the receptor. Although these antibodies do not bind to IR, many partially modulate the activity of IR, including IR-B, by binding to IGF-IR/IR-A or IGF-IR/IR-B hybrid receptors, which may contribute to the hyperglycemia observed in clinical testing. These antibodies, however, do not inhibit the activation of IR-A homodimers by IGF-II (Fig. 1B).

TKIs are small-molecule compounds that bind to and inhibit the kinase activity of receptor tyrosine kinases. Because of the high degree of homology among the kinase domains, the majority of IGF-IR–targeting TKIs inhibit not only IGF-IR but also IR-A and IR-B (6). As a result, such TKIs can impair glucose homeostasis, as shown by transient hyperglycemia documented in clinical trials (6). Small molecules typically have short half-lives, and although adjusting the dose and schedule might minimize this adverse effect, it might also reduce efficacy by intermittent inhibition of IGF-IR and IR (Fig. 1C). Cyclolignan picropodophyllin (PPP), a unique TKI in early development, shows potential to circumvent this problem. PPP specifically decreases phosphorylation of the tyrosine residue Y1136 of IGF-IR and leads to IGF-IR downregulation without interfering with IR activity (7). This molecule apparently does not induce hyperglycemia in mice, and it was even shown to reduce serum glucose levels. It will be interesting to learn whether this molecule affects the activity of IGF-IR/IR hybrid receptors and, more broadly, to learn whether this activity translates into an improved therapeutic index in patients with cancer.

Among the few monoclonal antibodies (mAb) that target IGF ligands instead of the IGF-IR, the only one that has been
clinically tested to date is MEDI-573, an investigational human monoclonal IgG2a antibody that specifically binds to both free IGF-I and IGF-II [dissociation constant (Kd) = 294 and 2 picomolar units]. MEDI-573 recognizes epitopes that are essential for IGF binding to IGF-IR, IR-A, and IGFBP3 and, thus, renders the IGF ligands biologically inactive (8). MEDI-573 inhibits IGF-stimulated phosphorylation of IGF-IR, IR-A, and the downstream signaling proteins IRS-1, Akt, and extracellular signal-regulated kinase 1/2 (ERK1/2). Importantly, it does not affect insulin-stimulated phosphorylation of IRSs and their downstream signaling. MEDI-573 inhibits IGF-II–induced proliferation of cells that express only IR-A with the same potency as cells that express only IGF-IR, as well as heterogeneous cell populations that express both receptors. An IGF-IR–specific antibody tested in the same studies did not inhibit IGF-II activity mediated by IR-A, including in MDA-MB-231 breast cancer cells, which express high levels of IR-A along with moderate levels of IGF-IR that can hybridize with IR-A receptors. In in vivo studies, MEDI-573 showed close to 90% tumor growth inhibition in mouse 3T3 tumors dependent on autocrine IGF signaling by ectopically overexpressing human IGF and IGF-IR. In these IGF-IR–dependent mouse models, the activity of MEDI-573 was shown to be comparable to that of IGF-IR–specific antibodies.

In summary, both IGF-IR and IR-A are involved in IGF signaling and play significant roles in the development and progression of cancer. As a result, dual inhibition of IR-A and IGF-IR may improve therapeutic efficacy against IGF-driven cancers. Antibodies specific for IGF-IR block IGF-IR and IGF-IR/IR-A (or IGF-IR/IR-B) hybrid receptors, but IGF-II stimulation of IR-A homodimers remains intact. Furthermore, because IGF-IR–specific antibodies induce internalization and degradation of IGF-IR, a stoichiometric shift toward formation of IR-A homodimers may occur and may contribute to the less-than-expected efficacy signals emerging from clinical trials to date. Small molecule TKIs achieve antitumor effects by inhibiting both IGF-IR and IRs, and diabetogenic effects have been documented in clinical trials. Whether a ligand-neutralizing antibody like MEDI-573 sufficiently overcomes IGF activity and compensatory pathways by inhibiting both IGF-IR and IR-A and, thereby, improves clinical outcomes, without limiting adverse effects, remains a provocative hypothesis. Selective binding of IGFs by IGFBPs, although still in early development, shows potential as an alternative to IGF-IR targeting that also spares IR. IGFBPs regulate IGF bioavailability and bioactivity, and high IGFBP levels have been associated with decreased IGF signaling and the antitumoral activity. Thus far, IGFBP3 has shown the greatest promise owing to antiproliferative and proapoptotic activities in certain in vitro and in vivo models (9).

Highlights of Clinical Trial Results

The IGF axis has become an increasingly attractive target for cancer research. Nine large and 6 small molecules have been tested across approximately 150 phase I to III trials in 16 solid tumor types and certain hematologic malignancies (e.g., multiple myeloma and leukemia; Table 1). Objective response to IGF-IR–targeting mAb monotherapy is rare, with notable occurrences in approximately 10% of patients with various sarcomas, in particular the Ewing subset (34). Objective responses, in some cases durable ones, have been reported in phase I and phase II studies of mAbs that target IGF-IR (e.g., figitumumab, R1507, and ganitumumab) in adults and children with heavily pretreated sarcomas. Nevertheless, disease stabilization, defined as lack of objective response or progressive disease at 12 weeks, remains the overwhelming efficacy signal (34). IGF-targeting agents are generally expected to show their full potential by augmenting the efficacy of endocrine, cytotoxic, or other targeted therapies, possibly by mitigating the development of resistance to otherwise effective interventions.

Although combinations of large or small IGF-targeting molecules with various standard-of-care therapies have generally shown a reasonable toxicity profile, this strategy has yet to translate preclinical promise into therapeutic efficacy. Few of the IGF-IR–targeting antibodies under investigation have progressed to or completed phase III testing. As recently as 2010, 2 phase III clinical trials were testing figitumumab (CP-751,871) globally, one in conjunction with paclitaxel plus carboplatin [first line for stage IV or recurrent nonadenocarcinoma non–small cell lung cancer (NSCLC)], and another with erlotinib (second line or greater for refractory and/or relapsed stage III or IV nonadenocarcinoma NSCLC). Both of these pivotal ADVancing IGF-IR in Oncology (ADVIGO) trials were discontinued after data showed an imbalance of serious adverse events, including mortality, in the arm testing figitumumab and a low likelihood of meeting the primary endpoint of improved overall survival (17). Prior testing did not expose the potential for untoward events to undermine the mAbs’ therapeutic benefits. The phase II study of figitumumab plus paclitaxel plus carboplatin versus paclitaxel plus carboplatin alone yielded improved objective response rates in the figitumumab plus paclitaxel plus carboplatin versus paclitaxel plus carboplatin alone treatment arm (54% vs. 42%), and subset analysis suggested that the addition of figitumumab (20 mg/kg) to the paclitaxel plus carboplatin regimen might boost progression-free survival (PFS; hazard ratio of 0.56, P = 0.0153) as well as response rate (62% compared with 33%, P = 0.0578) in patients with adenocarcinoma or squamous cell histology (14). The phase II to III randomized, double-blind, placebo-controlled trial of dalotuzumab (MK-0646) with cetuximab and irinotecan in patients with KRAS wild-type stage IV colorectal cancer was stopped prematurely owing to worsened PFS and overall survival in patients randomized to the dalotuzumab arm (35). A phase III randomized, double-blind, placebo-controlled trial of ganitumab (AMG-479) was recently initiated to test the mAb coadministered with gemcitabine in 825 patients with stage IV pancreatic cancer. Only 1 IGF-targeting TKI has progressed into advanced clinical testing; linsitinib (OSI-906), an oral small molecule, is being tested in a phase III randomized, double-blind, placebo-controlled monotherapy trial in 135 patients with locally advanced or metastatic adenocortical carcinoma.

MEDI-573 is the only mAb in clinical testing that exerts its effects by neutralizing IGF-I and IGF-II ligands instead of by directly binding to the IGF-IR receptors. Distinct from other
Table 1. Efficacy signals from clinical studies testing monoclonal antibodies that target the IGF axis

<table>
<thead>
<tr>
<th>Agent</th>
<th>Disease</th>
<th>Dose/schedule (i.v. mg/kg)</th>
<th>Clinical activity</th>
<th>Clinical trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Figitumab</td>
<td>Sarcoma ($n = 15$); Ewing ($n = 14$)</td>
<td>20 Q3W (3–20)</td>
<td>1 CR and 1 PR (Ewing); 8 SDs $&gt; 4$ mo</td>
<td>Ph I (10)</td>
</tr>
<tr>
<td>Figitumab</td>
<td>Adrenocortical cancer ($n = 14$)</td>
<td>20 Q3W</td>
<td>8 SDs</td>
<td>Ph I (11)</td>
</tr>
<tr>
<td>Figitumab + dexamethasone</td>
<td>Multiple myeloma ($n = 47$)</td>
<td>0.025–20 Q4W</td>
<td>9 responses in 27 patients</td>
<td>Ph I (12)</td>
</tr>
<tr>
<td>Figitumab + docetaxel</td>
<td>Solid tumors ($n = 46$)</td>
<td>0.1–20 Q3W</td>
<td>4 PRs, 12 SDs $&gt; 6$ months; CRPC: 6/10 had CTCs drop from $&gt; 5$ to $&lt; 5$; 9 of 10 had $&gt; 30%$ decline in CTCs</td>
<td>Ph I (13)</td>
</tr>
<tr>
<td>Figitumab + T/C</td>
<td>Solid tumors ($n = 42$)</td>
<td>0.05–20 Q3W up to 6 cycles; option to continue F alone</td>
<td>2 CRs (ovarian, NSCLC); 14 of 15 ORs (NSCLC); 16 SDs (NSCLC; median 2 months), 6 SDs $&gt; 6$ mo on single-agent F</td>
<td>Ph I (14)</td>
</tr>
<tr>
<td>Figitumab + T/C</td>
<td>NSCLC, nonadenocarcinoma ($n = 56$)</td>
<td>20 Q3W up to 6 cycles $\geq$ SD option to continue F alone</td>
<td>1 CR; 7 PRs; median 4 cycles; 46% patients received F alone beyond cycle 4; higher IGF-IR expression in responders (trend)</td>
<td>Ph I (14, 15)</td>
</tr>
<tr>
<td>Figitumab + T/C</td>
<td>NSCLC, treatment naive ($n = 159$)</td>
<td>20 Q3W</td>
<td>Median PFS 2.73 vs. 6.53 months (T/C vs. T/C + F) in patients with high free-plasma IGF-I at baseline</td>
<td>Ph I b–2 (16)</td>
</tr>
<tr>
<td>Figitumab + T/C or T/C alone</td>
<td>NSCLC, locally advanced or metastatic ($n = 158$)</td>
<td>2:1 randomization T/C; T/C + F 10–20 Q3W</td>
<td>OR T/C + F vs. T/C: 54% vs. 42%; 16 of 23 evaluated patients in extension cohort responded, especially squamous: T/C, T/C + F 10, T/C + F 20 in squamous or adenocarcinoma (combined): 33%, 43%, and 62%, respectively</td>
<td>Ph II (14)</td>
</tr>
</tbody>
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### Table 1. Efficacy signals from clinical studies testing monoclonal antibodies that target the IGF axis (Cont’d)

<table>
<thead>
<tr>
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</tr>
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<tbody>
<tr>
<td>Figitumumab</td>
<td>NSCLC, squamous, large cell, adenocarcinoma</td>
<td>20 Q2W</td>
<td>Arm A: F Q2W + erlotinib Study terminated early on the basis of low likelihood of significant improvement in OS in F-treated arm</td>
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<tr>
<td></td>
<td>NSCLC, squamous, adenocarcinoma</td>
<td></td>
<td>Ph II (19)</td>
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<tr>
<td></td>
<td>Sarcomas and other advanced solid tumors</td>
<td>20 Q2W</td>
<td>G1 (20)</td>
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<td></td>
<td>Thymoma, thymic carcinoma</td>
<td>20 Q2W</td>
<td>G1 (21)</td>
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<tr>
<td></td>
<td>CRPC, metastatic</td>
<td>20 Q2W</td>
<td>G1 (18)</td>
</tr>
<tr>
<td></td>
<td>Solid tumors (n = 3; 1 CR, Ewing/PNET &gt; 30 months, 1 PR, Ewing)</td>
<td>G1 (18)</td>
<td>G1 (18)</td>
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<tr>
<td></td>
<td>Solid tumors (n = 12; 6 PR, endometrial cancer, 6 PR, NSCLC)</td>
<td>G1 (18)</td>
<td>G1 (18)</td>
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<tr>
<td></td>
<td>Solid tumors (n = 13; 6 PR, breast, endometrial cancer, 6 PR, NSCLC)</td>
<td>G1 (18)</td>
<td>G1 (18)</td>
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<tr>
<td></td>
<td>Solid tumors (n = 25 total; 6 or 12 Q2W)</td>
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<td>G1 (18)</td>
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<td></td>
<td>Solid tumors (n = 12; erlotinib, n = 13 sorafenib)</td>
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<td>G1 (18)</td>
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<td>G1 (22)</td>
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</tr>
</thead>
<tbody>
<tr>
<td>Ganitumab + AMG 655</td>
<td>Solid tumors (n = 9)</td>
<td>18 Q3W (3 cohorts with AMG 655)</td>
<td>3 SDs &gt; 120 days</td>
<td>Ph I (23)</td>
</tr>
<tr>
<td>Ganitumab + panitumumab or gemcitabine</td>
<td>Solid tumors (n = 18)</td>
<td>6 or 12 Q2W</td>
<td>1 PR (CRC KRAS WT, 12 + panitumumab); 5 SDs (panitumumab); 4 SDs (gemcitabine)</td>
<td>Ph Ib (24)</td>
</tr>
<tr>
<td>Ganitumab</td>
<td>Ewing (n = 19); desmoplastic small round cell tumors (n = 16)</td>
<td>12 Q2W</td>
<td>2 PRs (1 each); 5 SDs &gt; 24 weeks</td>
<td>Ph II (25)</td>
</tr>
<tr>
<td>Ganitumab + gemcitabine or placebo</td>
<td>Pancreatic cancer (n = 75)</td>
<td>12 or 20 Q2W</td>
<td>PFS and OS increased ~2-fold</td>
<td>Ph II (26)</td>
</tr>
<tr>
<td>Dalotuzumab</td>
<td>Solid tumors (n = 48)</td>
<td>1.25–20 QW</td>
<td>3 PDG-PET metabolic responses; 1 mixed radiologic response (Ewing); 3 SDs &gt; 3 mo</td>
<td>Ph I (27)</td>
</tr>
<tr>
<td>Dalotuzumab + erlotinib</td>
<td>NSCLC, relapsed (n = 16; 11 evaluable)</td>
<td>5 or 10 QW</td>
<td>No ORs; median time on drug: 4 weeks (A) and 5 weeks (B)</td>
<td>Ph I/II (28)</td>
</tr>
<tr>
<td>Dalotuzumab + cetuximab/irinotecan</td>
<td>CRC, chemorefractory metastatic (n = 10 [A]; n = 8 [B])</td>
<td>Arm A: 10 QW; Arm B: 15 loading dose &amp; 7.5 QOW</td>
<td>Radiologic response 33% (A) and 14% (B); 5.8 months (A) and 3.9 months (B) median time on study drug</td>
<td>Ph II (29)</td>
</tr>
<tr>
<td>Dalotuzumab + gemcitabine or gemcitabine/erlotinib</td>
<td>Pancreatic cancer, metastatic (n = 28; ongoing)</td>
<td>5 or 10 QW</td>
<td>6 PRs (including 1 hepatic CR); 8 SDs</td>
<td>Ph I (30)</td>
</tr>
<tr>
<td>AVE1642 + sorafenib</td>
<td>HCC (n = 13)</td>
<td>1, 3, or 6 Q3W</td>
<td>11 SDs (median 13.2 weeks)</td>
<td>Ph I (31)</td>
</tr>
<tr>
<td>BIIB022</td>
<td>Solid tumors (n = 24)</td>
<td>1.5–39</td>
<td>No ORs; 3 FDG-PET metabolic responses</td>
<td>Ph I (32)</td>
</tr>
<tr>
<td>MEDI-573</td>
<td>Solid tumors (n = 18; ongoing)</td>
<td>0.5, 1.5, 5, 10, or 15 QW</td>
<td>No ORs; 7 SDs ≥ 3 months (3 sarcoma)</td>
<td>Ph I (33)</td>
</tr>
</tbody>
</table>

Abbreviations: CR, complete response; CRC, colorectal cancer; CRPC, castration-resistant prostate cancer; CTC, circulating tumor cell; cTTP, median time to composite progression; DSMB, Data and Safety Monitoring Board; F, figitumumab; FDG, [18F]fluoro-2-deoxy-D-glucose; HCC, hepatocellular carcinoma; HR, hormone receptor; OR, objective response; OS, overall survival; PD, progressive disease; PDG, pregnanediol-3-glucuronide; PET, positron emission tomography; Ph, phase; PNET, primitive neuroectodermal tumor; PR, partial response; QOW, every other week; QW, every week; Q2W, every 2 weeks; Q3W, every 3 weeks; Q4W, every 4 weeks; SABCS, San Antonio Breast Cancer Symposium; SD, stable disease; T/C, paclitaxel/carboplatin; WT, wild-type.

*Figitumumab, CP-751,871; cixutumumab, IMC-A12; ganitumab, AMG 479; dalotuzumab, MK0646.
IGF-IR–targeting mAbs under development, MEDI-573 specifically inhibits IGF signaling through IGF-IR and IR-A, as well as through their hybrid receptors. The ongoing phase I clinical trial has shown stabilization of disease $\geq3$ months in 7 of 16 patients, most of whom had chemoresistant cancers (33). Importantly, preliminary data strongly suggest that MEDI-573 might achieve this result without inducing hyperglycemia (33). If confirmed, this observation would be consistent with expectations about ligand-versus receptor-based targeting of the IGF axis, specifically with respect to the clinical consequences of sparing IR-B and its various hybrid receptors, each of which has potential to alter glucose metabolism via interactions with insulin.

Transient hyperglycemia has been among the most common treatment-related toxicities reported for every IGF-IR–targeting antibody and several TKIs. Serious glycemic complications have been rare, and on the basis of published data, treatment-induced hyperglycemia is unlikely to be a serious developmental liability for agents targeting the IGF axis. Nevertheless, the impact of hyperglycemia and associated increases in insulin levels may mitigate or potentially override antitumoral effects of drugs that target IGF-IR. One plausible mechanism for resistance to IGF-IR–targeting therapies may relate to the unopposed effects of compensatory increases in insulin levels and associated increases in IGF-I and glucose levels. This finding has prompted recommendations to boost efficacy and reduce toxic consequences through coadministration of a growth hormone antagonist or glucose-lowering agents. If IGF-I and IGF-II ligand–neutralizing antibodies directly achieve the same goal of antitumoral activity with negligible impact on glucose homeostasis, then studying MEDI-573’s dual-targeting approach becomes even more compelling, particularly in tumors that overexpress IGF-IR or IR-A, either together or alone.

MEDI-573 recently completed the weekly dose-escalation phase of first-time-in-human testing (exclusively solid tumors), in which preliminary data have shown negligible perturbations of glucose homeostasis in nondiabetic patients and no dose-limiting toxicities. Treatment-related adverse events from this ongoing study have been hematologic (anemia, leukopenia), gastrointestinal (abdominal pain, diarrhea, nausea, vomiting), and metabolic and/or nutritional (decreased appetite) disorders, as well as fatigue, all of which have been grade 1 or 2 in severity (33).

Predictive Biomarkers

The 3 major classes of IGF-targeting compounds currently under development differ in their mechanisms of action, ranges of target specificity, preliminary efficacy, pharmacokinetics, and safety profiles. A growing clinical database suggests that efficacy and toxicity of these compounds may be predicted by quantifiable factors such as tumor IGF-IR or circulating IGF ligand levels. Target expression levels such as these, if validated, would serve as relatively straightforward predictive biomarkers for identifying patient subpopulations likely to respond to IGF-targeted therapies. For IGF-IR antibodies, elevated tumor IGF-IR expression and circulating IGF-I have both been shown to correlate to some degree with responses in early clinical trials. As noted above, data from the phase II study testing the IGF-IR–specific mAb fitigumumab in combination with paclitaxel plus carboplatin in NSCLC showed a higher objective response rate in the subset of patients with squamous cell carcinoma histology ($78\%\pm11\%$ of 14). Despite the limited sample size, these data are particularly compelling in light of biomarker analysis showing the highest IGF-IR expression in the squamous subtype. In addition, a higher response rate to the combination of paclitaxel plus carboplatin and fitigumumab was observed in epithelial-to-mesenchymal transitional tumors (71%), defined by intermediate E-cadherin and high IRS-1 expression, compared with those in the mesenchymal-like subset (32%), defined by low expression of both E-cadherin and IRS-1. By contrast, sample analysis showed high plasma levels of free IGF-1 and vimentin predictive of clinical benefit in the adenocarcinoma subtype.

Ancillary data from the NSCLC study of fitigumumab (described immediately above) showed improved PFS among patients with high pretreatment-free IGF-I levels (at least 0.54 ng/mL; PFS $>6$ months, $P = 0.007$) compared with patients with low pretreatment-free IGF-I levels (PFS $<3$ months, $P = 0.026$), pointing to the potential role of this ligand as a predictive marker (36). These intriguing data are indirectly supported by interim results from a phase I to II study of fitigumumab in 31 patients with relapsed sarcoma, which suggested that pretreatment plasma levels of IGF-I $>110$ ng/mL conferred a significant treatment advantage compared with lower levels (10.5 vs. 4.5 months overall survival, $P < 0.001$). In aggregate, these data suggest the value of evaluating circulating IGF-I as a possible predictive marker in studies of IGF-targeting agents and opportunities for enriching future study populations (34). A growing body of nonclinical and clinical data provide valuable lessons for the development of ligand-based approaches (such as MEDI-573) in terms of patient selection. In particular, they provide a compelling rationale for a priori identification of patients with tumors that overexpress IR-A and IGF-II in addition to IGF-IR, which may prove a critical determinant of clinical response to monotherapy or combination regimens in molecularly defined subpopulations. This hypothesis has been supported by preclinical studies (8, 37) in which high levels of IR expression and elevated mRNA levels of IR-A compared with IR-B have been found in most of the cancer cell lines tested. Other molecular markers may also predict tumor response to IGF-targeting compounds. IRS-1 expression levels have been positively correlated with sensitivity of preclinical models to IGF-IR targeting (38). Increased VEGF production by cancer cells following rapamycin treatment has been shown to correlate with synergistic responses to rapamycin and IGF-IR antibody–combined therapy in certain sarcoma tumor models (39). Finally, elevated genomic signatures associated with IGF-1 signaling, evaluated by whole-genome array analysis, have been associated with worse prognosis in patients with estrogen receptor–positive compared with estrogen receptor–negative breast cancer (40). Among the cancers associated with dysregulation of the IGF axis, increased IGF-II/IR-A signaling has been best.
documented in breast cancer, in which conventional criteria (e.g., estrogen receptor and/or progesterone receptor and/or HER2 status, stage, grade, luminal type A vs. type B) together with IR-A signatures may enable identification of and enrichment for subpopulations likely to respond to dual targeting of IGF-IR and IR-A (41). MEDI-573 has been shown to inhibit IGF-induced proliferation of cells expressing IGF-IR or IR-A, either together or alone, pointing to a distinct theoretical advantage over IGF-IR-targeting antibodies in selected populations. A global clinical trial is currently testing whether MEDI-573 in conjunction with an an aromatase inhibitor enhances therapeutic outcomes in patients with advanced estrogen receptor–positive, HER2-negative breast cancer. Whether these markers achieve the level of validation required to predict for sensitivity to different types of IGF-targeted agents has yet to be confirmed by clinical testing.

Conclusions

The IGF axis has emerged as a meaningful therapeutic target for oncology drug development that is strongly supported by preclinical studies and promising results from early phase clinical trials. Nevertheless, this complex system presents distinct developmental challenges, and demonstration of meaningful clinical benefit remains elusive. The 3 major classes of IGF-targeted therapeutic compounds (i.e., IGF-IR–specific mAbs, small molecule TKIs targeting IGF-IR and IR kinase domains, and an IGF-I and IGF-II ligand–neutralizing mAb) differ in the range of target inhibition based on their ability to block activation of IGF-IR, IGF-IR/IR-A hybrid, and IR-A. They also exhibit distinct safety profiles, most notably with respect to modulation of glucose metabolism, as well as through changes in circulating levels of IGF, insulin, and growth hormone. Although agents that target the IGF axis typically have acceptable toxicity profiles alone and in combination with chemotherapy, no specific factors have been conclusively associated with improved clinical outcomes. The identification of patient subsets likely to respond to IGF-targeting strategies and selection of rational companion therapeutics are expected to pave the way for significant improvements in clinical outcomes and provide critical direction for multifunctional, pathway-driven approaches to cancer treatment.

Disclosure of Potential Conflicts of Interest

B. Jallal and J. Viner are employees of MedImmune, LLC. J. Gao and Y.S. Chang are former employees of MedImmune, LLC.

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