Minireview: Were the IGF Signaling Inhibitors All Bad?

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Preclinical studies in the 1980s defined a role for IGF signaling in the development and sustainability of the malignant process. Subsequently, antibody, tyrosine kinase, and ligand inhibitors of the IGF receptor were manufactured. In the past decade, numerous clinical trials have tested the efficacy of IGF receptor inhibitors in the treatment of advanced tumors. Early-phase trials in heavily pretreated populations showed promise with complete or partial responses in a few patients and stable disease in many more. Unfortunately, the results of the early-phase trials did not pan out to later-phase trials. The lack of use of biomarkers to define subsets of patients that may benefit from IGF receptor blockade and compensatory signaling via other growth factor receptors such as the insulin, GH, and epidermal growth factor receptors may have played a role in the lack of efficacy of IGF receptor inhibition in phase III trials. Although these trials failed to show benefit, the trials have revealed previously unknown knowledge regarding the complex nature of IGF signaling. The knowledge obtained from these trials will be useful in designing future trials studying inhibitors of growth factor signaling. **(*Molecular Endocrinology* 29: 1549–1557, 2015)**

The IGF is associated with transformation of normal cells to malignancy as well as cancer cell proliferation, growth, survival, and metastasis. IGF production by mammary tumors was first noted in 1980 (1). In the same year, a monoclonal antibody targeting the IGF-1 receptor (IGF1R) was made (2). In the years that followed, a number of preclinical studies supported the idea that IGF signaling promoted the malignant phenotype (3–5). In 2001, we stated that "translation of an anti-IGF strategy for use in breast cancer patients should determine whether the IGF system is truly a relevant target in breast cancer" (6). Since then, a number of clinical trials have tested the efficacy of inhibition of IGF-1 signaling in the treatment of cancer patients (Table 1). Early trials suggested benefit in delaying time to disease progression; however, these results were not repeatable in later, larger clinical trials. This review seeks to summarize the knowledge gained from these trials to better design trials targeting this oncogenic signaling pathway in the future.

The development of drugs inhibiting the IGF1R was based on the previous successful approach to inhibitors directed against the epidermal growth factor receptor family members. The success of these other inhibitors resulted in numerous clinical trials evaluating anti-IGF1R drugs for cancer treatment; however, thus far, none have showed significant benefit. As a result, most pharmaceutical companies have abandoned their IGF1R drug development programs. With such a clear association between IGF1R signaling and cancer biology, why have we been unable to successfully translate the preclinical work showing blockade of the IGF1R inhibits the growth of cancer into a valid targeted therapy in the treatment of malignancy? Are the clinical trials of IGF1R inhibitors wasted water down the drain, or is the knowledge gained in these trials water in an expanding reservoir that will lead to an effective way to target this oncogenic pathway?

The IGF1R and cancer

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Abbreviations: EGFR, epidermal growth factor receptor; GHR, GH receptor; IGF1R, IGF-1 receptor; IR, insulin receptor; IRS, insulin receptor substrate; NSCLC, non-small cell lung cancer; PI3K, phosphoinositide 3-kinase.

Table 1. Summary of IGF1R Inhibitor Clinical Trials

Author/Year	Treatment	Phase	Advanced Malignancy	ORR (CR + PR)[a]	SD[b]
Atzori et al, 2011 (25)	Dalotuzumab	I	Solid tumors	0%	8%
Reidy-Lagunes, 2012	Dalotuzumab	I	Neuroendocrine tumors	0%	NR
Brana, 2014	Dalotuzumab + MK-2206, ridaforolimus, or MK-0752	I	Solid tumors	0%/0%/0%	37%/50%/0%
Doi, 2013	Dalotuzumab + cetuximab and irinotecan	I	Colorectal	15%	NR
Ellis, 2014	Dalotuzumab + cisplatin and etoposide	I	SCLC	67%	17%
Di Cosimo et al, 2015 (26)	Dalotuzumab + ridaforolimus	I	Solid tumors	7%	46%
Moran et al, 2014 (32)	Dalotuzumab + erlotinib	I/II	NSCLC	3%	57%
Olmos et al, 2010 (19)	Figitumumab	I	Sarcoma	7%	29%
Haluska et al, 2007 (17)	Figitumumab	I	Solid tumors	0%	67%
Haluska et al, 2010 (18)	Figitumumab	I	Adrenocortical carcinoma	0%	57%
Juergens, 2011	Figitumumab	I/II	Ewing sarcoma	14%	24%
Chi, 2012	Figitumumab	II	Prostate	94%[c]	NR
Becerra, 2014	Figitumumab	II	Colorectal	0%	NR
Schmitz, 2012	Figitumumab	II	HNSCC	0%	12%
Goto, 2012	Figitumumab + carboplatin and paclitaxel	I	NSCLC	39%	44%
Karp et al, 2009 (20)	Figitumumab + carboplatin and paclitaxel	I	Solid tumors	36%	38%
Karp et al, 2009 (21)[d]	Figitumumab + carboplatin and paclitaxel	II	NSCLC	54%	NR
Langer et al, 2014 (31)	Figitumumab + carboplatin and paclitaxel	III	Nonadeno-NSCLC	33%	37%
Lacy et al, 2008 (16)	Figitumumab + dexamethasone	I	Multiple myeloma	33%	48%
Molife and colleagues, 2010 (19)	Figitumumab + docetaxel	I	Solid tumors	10%	31%
de Bono, 2014	Figitumumab + docetaxel and prednisone	II	Prostate	52%[e]	NR
Scagliotti et al, 2015 (33)	Figitumumab + erlotinib	III	Nonadeno-NSCLC	5%	39%
Quek, 2011	Figitumumab + everolimus	I	Sarcoma and solid tumors	6%	83%
Murakami, 2012	Ganitumab	I	Solid tumors	0%	37%
Strosberg, 2013	Ganitumab	II	Carcinoid and pancreas	0%	34%
Tap et al, 2012 (24)	Ganitumab	II	Ewing and desmoplastic	6%	49%
Robertson, 2013	Ganitumab + exemestane or fulvestrant	II	Breast cancer	8%	35%
Cohn, 2013	Ganitumab + FOLFIRI	II	Colorectal	8%	59%
Kindler, 2012	Ganitumab + gemcitabine	II	Pancreas	10%	51%
Okusaka, 2014	Ganitumab + gemcitabine	I	Pancreas	0%	80%
Van Cutsem, 2014	Ganitumab + panitumumab	I/II	Colorectal	22%	61%
Rosen, 2012	Ganitumab + sorafenib, panitumumab, erlotinib, or gemcitabine	I	Solid tumors	9%	66%
Puzanov et al, 2015 (29)	Linsitinib	I	Solid tumors	1%	36%
Jones et al, 2015 (30)	Linsitinib	I	Solid tumors	3%	41%
Fassnacht et al, 2015 (35)	Linsitinib	III	Adrenocortical carcinoma	3%	32%
Bendell and colleagues, 2015 (26)	Linsitinib + everolimus	I	Colorectal	0%	NR
Mahadevan, 2014	R1507	I	Solid tumors	36%	40%

Abbreviations: CR, complete response; HNSCC, head and neck squamous cell carcinoma; NR, not reported; ORR, overall response rate; PR, partial response; SCLC, small-cell lung cancer; SD, stable disease. Data are from clinical trials investigating the efficacy of inhibition of the IGF1R in the treatment of various types of advanced malignancy.

[a] CR and PR were determined by Response Evaluation Criteria In Solid Tumors criteria.

[b] Duration of SD varied by study.

[c] Partial response was measured by a greater than or +25% decrease in serum prostate-specific antigen.

[d] Partial response was measured by decrease in prostate-specific antigen.

[e] Study was retracted in 2012.

tor proteins are subsequently phosphorylated, resulting in the stimulation of a number of oncogenic pathways known to be involved in cancer cell proliferation, survival, and metastasis. Downstream effectors activated by the IGF1R include insulin receptor substrates (IRS), phosphoinositide 3-kinase (PI3K), protein kinase B (Akt), mammalian target of rapamycin, and MAPKs. Preclinical in vitro studies show that the IGF1R activation of these oncogenic proteins increases tumor cell invasion, survival, and metastasis (7, 8). The malignant potential of IGF1R signaling has also been verified in preclinical in vivo studies. Transgenic IGF1R overexpression in mouse models leads to increased tumor growth (9). Conversely, down-regulation of the IGF1R leads to regression of tumors in vivo (10).

Clinical studies also demonstrate a strong association of IGF-1 and cancer. High circulating IGF-1 levels are associated with an increased risk of developing a number of malignancies including breast, colon, and lung cancers (11–13). Overexpression of the IGF1R in cancer is associated with a poor prognosis characterized by shorter progression-free and overall survival (14, 15).

Success of IGF1R inhibitors in early-phase clinical trials

IGF1R-targeting drugs have included monoclonal antibodies and small molecule tyrosine kinase inhibitors. Antibodies against the IGF ligands have also been developed. The first inhibitor of the IGF1R to enter clinical trial was CP-751871, a fully human IgG2 monoclonal antibody to the IGF1R. The early phase I trial evaluated the pharmacokinetics and maximum tolerated dose of CP-751871, later named figitumumab, in the treatment of 47 patients with relapsed or refractory multiple myeloma. In the trial, nine patients demonstrated a partial response to therapy and another 28 demonstrated stable disease, for an overall response rate of 78% (16). In a second early-phase trial of figitumumab in the treatment of nonhematological malignancies, 10 of 15 patients showed stable disease, two of which achieved long-term stability (17). Figitumumab went on to be tested in other malignancies; including in the treatment of patients with adrenocortical carcinoma and unselected sarcoma and Ewing's sarcoma in which figitumumab showed response rates of 57% and 36%, respectively (18). In the latter sarcoma trial, a complete response in one patient was noted (19).

The early-phase trials of figitumumab in the treatment of lung cancer yielded some of the most promising data supporting the inhibition of the IGF1R in the treatment of cancer. The phase I trial of figitumumab in combination with carboplatin and paclitaxel in patients with advanced or metastatic solid tumors showed 15 of 42 objective responses, with two complete responses noted in a lung and ovarian carcinoma patient (20). The phase II trial of figitumumab plus carboplatin and paclitaxel in the treatment of treatment naïve non-small cell lung cancer (NSCLC) showed 54% of patients in the figitumumab arm with objective responses compared with 42% in the carboplatin- and paclitaxel-only arm. Patients in this trial who were nonresponders to carboplatin and paclitaxel were then allowed to cross over to the figitumumab treatment arm, and in the extension cohort, 16 of 23 patients demonstrated response (21). This early evidence of antitumor activity raised excitement over the potential of IGF-1 blockade in the treatment of cancer. However, it was subsequently learned that the data collection and measurement of responses could not be confirmed; therefore, this manuscript was subsequently retracted 3 years later (22).

Around the same time that Pfizer began development of figitumumab, a number of other companies developed their own IGF1R antibodies. Among these, Amgen and Merck began development of AMG 479, later known as ganitumab, and MK-0646, later known as dalotuzumab, respectively. Like figitumumab, ganitumab and dalotuzumab showed moderate percentages of stable disease and occasional partial and complete responses in patients with previously treated cancer. In the earliest-phase trial of single-agent ganitumab, one Ewing sarcoma patient sustained a durable complete response for longer than 28 months (23). The phase II trial of ganitumab in the treatment of Ewing family tumors or desmoplastic small round cell tumors demonstrated a 6% partial response and a 49% stable disease response (24). Likewise, dalotuzumab also showed phase I clinical activity in patients with advanced solid tumors, further supporting the idea that antibodies to the IGF1R had antitumor activity (25). Results from a phase I trial of dalotuzumab in unselected patients with advanced solid tumors showed antitumor activity in a number of malignancies including three partial responses. Of note, in the breast cancer patients enrolled in this trial, there was a greater than 50% stable disease rate in patients with estrogen receptor-positive, high proliferative disease, suggesting a subset of patients were more likely to benefit from this treatment (26).

After the early success of the monoclonal antibodies, the development of small-molecule tyrosine kinase inhibitors of the IGF1R followed. Due to the homology between the intracellular domains of the IGF-1 and insulin receptors (IRs), these tyrosine kinases showed dual IGF1R and IR inhibition. Because compensatory IR signaling has been shown to be a pathway of resistance to IGF1R inhibitors, the ability to inhibit both receptors was

promising (27, 28). The benefit of these tyrosine kinase inhibitors was confirmed in a phase I trial of OSI-906, later named linsitinib, in the treatment of advanced solid tumors. The trial demonstrated stable disease in 36%; one patient with melanoma had a partial radiological response and was found to have no evidence of viable tumor on resection (29). Likewise in another phase I trial of linsitinib in the treatment of patients with metastatic solid tumors refractory to established treatment, 41% of patients showed stable disease. Seven of these patients exhibited stable disease for longer than 6 months. Two patients with adrenocortical carcinoma demonstrated partial response (30).

Surprisingly, none of the phase I trials of IGF1R inhibitors were limited by adverse effects. In fact, maximum tolerated doses were often not reached due to a lack of dose limiting toxicity at the maximum feasible dose (17). Common side effects of IGF1R inhibitors include hyperglycemia, fatigue, nausea, diarrhea, mild increases in transaminases, thrombocytopenia, and prolonged QTc interval. Side effects to IGF1R therapy in the early-phase clinical trials were minimal, with very few grade 3 or 4 adverse effects noted in any given trial. Although the efficacy of these agents is questioned, the safety of the use of IGF-1 inhibitors in humans is established.

Failure in later-phase clinical trials

As noted above, excitement over IGF1R blockade in the treatment of cancer was sparked by the annual meeting of the American Society of Clinical Oncology in 2008 during which the promising results of a phase II study of figitumumab in combination with carboplatin and paclitaxel in the treatment of advanced, treatment-naïve squamous cell lung cancer were reported (21). These data were subsequently retracted. However, the timing of the initial reporting of these results and subsequent retraction was critical. Excitement regarding the initial phase II results resulted in a race to complete registration trials from many pharmaceutical companies including a confirmatory phase III figitumumab trial. This phase III trial was based on the previous phase II success of figitumumab in the treatment of nonadenocarcinoma NSCLC (31). Knowing what we know now about the phase II trial, the failure of the phase III trial might have been predicted. It was discontinued early due to the lack of survival benefit and more adverse events in the treatment group. Similar outcomes were seen in the phase II trial of dalotuzumab with erlotinib and the phase III trial of figitumumab and erlotinib in the treatment of NSCLC (32, 33). Unlike many trials, most studies did not collect correlative biomarker data. For those studies in which such data were collected, most have not been analyzed due to the withdrawal of corporate cooperation and sponsorship when IGF1R antibody programs were discontinued (Yee, D., personal observation).

A similar story is that of ganitumab in the treatment of metastatic pancreatic cancer. Early trials suggested the efficacy of ganitumab in the treatment of metastatic pancreatic cancer; however, in the phase III trial of ganitumab combined with gemcitabine as a first-line treatment of unselected metastatic pancreatic cancer patients, the trial was stopped early because of a preplanned futility analysis demonstrating no progression-free or overall survival benefit (34).

Dual small-molecule tyrosine kinase inhibitors of the IGF1R and IR have also fallen short of the desired outcomes in larger phase III trials. For example, in the phase III trial of linsitinib vs placebo in the treatment of advanced adrenal corticocarcinoma, the study was unblinded at an early date due to failure of the drug to prolong either progression-free or overall survival (35).

Failure to demonstrate a clinical benefit of IGF1R inhibitors in the larger phase III trials has shut down development programs of specific IGF1R inhibitors and has sparked controversy as to whether funding should continue to support the development of others. On the other hand, many have argued that the failure of these trials can be attributed to a number of factors including the enrollment of unselected patient populations, a lack of biomarkers used to predict response, and compensatory signaling of other growth factor pathways.

Biomarkers to identify those that may benefit from IGF1R blockade

Most early clinical trials examining inhibitors of the IGF1R involved a population of unselected patients. Trials often measured serum IGF-1 levels to determine adequate blockade of the IGF1R, however, failed to quantify other biomarkers to predict response to treatment. In a trial of IGF1R inhibition in the treatment of osteosarcoma, IGF1R mRNA expression, copy number, cell surface expression, and mutation status were not associated with responsiveness to IGF1R therapy (36). An exploratory analysis of serum biomarkers suggested that elevated levels of ligands and IGF binding proteins, potentially as a result of adequate IGF1R blockade, were associated with improved responses to ganitumab in the treatment of pancreatic cancer (37). However, later trials could not confirm this observation and found no correlation between levels of IGF-1 as a potential biomarker of activity, suggesting that perhaps other biomarkers or a stringent definition of high vs low levels need to be studied (34).

Ongoing preclinical data combined with clinical data studying inhibition of the IGF1R in the treatment of cancer have begun to elucidate subsets of patients more likely to benefit from IGF1R blockade. In a trial of IGF1R inhibition in NSCLC, researchers subcategorized subsets of NSCLC as epithelial, transitional, or mesenchymal to determine whether the phase of epithelial-to-mesenchymal transition influenced the response to IGF1R inhibition. Patients with e-cadherin intermediate/IRS1 high tumors, considered a transitional subset of NSCLC, had an increased response rate compared with the mesenchymal subset (e-cadherin low/IRS1 low) (21, 38).

A number of other studies have sought to find biomarkers predicting response to anti-IGF1R therapies. Analysis of 93 cancer cell lines of breast, colon, and lung origin for biomarkers predicting sensitivity to figitumumab found that only 15 of the cell lines were sensitive to figitumumab. Nine of these cell lines were colon in origin. Increased expression of IRS2, IR, and GH and decreased expression of IGF-binding protein-5 were all associated with figitumumab sensitivity (39). In vitro work with BMS-754807 in colorectal carcinoma cell lines also sought to determine biomarkers predictive of response. These studies found that cancer wild type for both KRAS and BRAF with higher RNA expression levels of IR-A or low levels of IGF binding protein-6 were most sensitive to BMS-754807. KRAS mutant cell lines with IRS2 gain or high IGF1R expression levels were also sensitive (40). These preclinical studies suggest additional biomarkers outside serum IGF-1 levels and tissue IGF1R expression need to be utilized.

Compensatory signaling via the insulin receptor in the setting of IGF1R blockade

An important factor in the failure of IGF1R blockade might be the compensatory actions of other growth factor receptors such as the IR. The IR and IGF1R are highly homologous. There are also hybrid-IGF1R/IRs to which both IGF-1 and insulin may bind. Insulin binding to the insulin or hybrid receptors activates kinases, such as Akt, PI3K, and MAPK, which are common to both the insulin and IGF-1 receptors. In the setting of IGF1R blockade, IGF-1 oncogenic pathways remain activated by insulin and IGF1R/IR hybrid receptors. High IR to IGF1R ratios are associated with increased resistance to IGF1R inhibitors (41) and IGF1R inhibitor-resistant tumors demonstrate increased expression of IR and increased binding of insulin to the IR (15). Furthermore, the numbers of holo- vs hybrid receptors may predict benefit from IGF1R antibody therapies based on the ability of the antibodies to down-regulate these receptors (42).

In vitro studies confirm the ongoing activity of the IR in the absence of IGF1R activity. Insulin stimulates the proliferation and cell cycle progression of cancer cells independent of the IGF1R (27). In breast cancer, the down-regulation of the IR decreases cell proliferation, angiogenesis, lymphangiogenesis, and metastasis (43). Growth of endocrine-resistant breast cancer cells that lose IGF1R expression is not inhibited by IGF1R blockade; however, the growth of these cells is inhibited by dual-IGF1R and -IR blockade (44). Furthermore, studies using a hyperinsulinemic mouse model demonstrate that both endogenous and exogenous insulin increase xenograft tumor growth (45). Down-regulation of the IR reduces growth of xenograft tumors, whereas the blockade of the IR will resensitize tumors to IGF1R inhibition (15, 43).

Compensatory signaling via GH and epidermal growth factor receptors in IGF1R blockade

In addition to the IR, other growth factor receptors such as the growth hormone receptor (GHR) and the epidermal growth factor receptor (EGFR) also activate oncogenic signaling pathways in the absence of IGF1R activity. Growth Hormone (GH) and its activity via the GHR is involved in the production of hepatic IGF-1. GHRH from the hypothalamus stimulates GH release from the pituitary gland during puberty. GH, in turn, stimulates the production of IGF-1 from the liver. This GH/IGF-1 axis is involved in normal human growth, development, metabolism, and longevity.

GH has been shown to regulate the malignant phenotype. GH is a mediator of chemotaxis and motility (46) as well as a mediator of apoptosis and cell survival in cancer. A group of approximately 100 adults in Ecuador have a mutation in the GHR yielding them insensitive to GH, a condition known as Laron syndrome. These patients have a dramatically decreased lifetime incidence of cancer compared with a control population (47). Serum from a patient with Laron syndrome is protective against DNA breaks and shows increased apoptosis in response to reactive oxygen species compared with healthy controls (48).

The ability of GH to induce oncogenic Akt, PI3K, and MAPK activity has been demonstrated in the absence of IGF1R (49). GH activates janus kinase and signal transducer and activator of transcription-5 in mammary epithelial cells. The signal transducer and activator of transcription-5 signaling positively regulates PI3K/Akt activation (50). Inhibition of the IGF1R in both in vitro and in vivo models leads to compensatory pituitary negative feedback increases in GH (51). Likewise, the inhibition of the IGF1R in humans has also been shown to increase serum levels of GH (18).

The elevation of GH due to the disruption of inhibitory endocrine feedback mechanisms has additional implications for cancer therapy. Early development of IGF1R inhibitors showed that their administration resulted in not only increased GH but also IGF-1 and insulin (17, 23). Because GH excess has been linked to insulin resistance due to the increased release of hepatic free fatty acids and lipids (52), the IGF1R inhibitors may result in a paradoxical effect of increasing signaling by up-regulating the ligands involved in receptor activation.

The EGFR has also been linked to resistance to IGF1R inhibition. IGF1R inhibitor resistant cell lines show the up-regulation of EGFR (53). The IGF1R and EGFR have been shown to heterodimerize in response to IGF-1 signaling, and stimulation of cancer cells with IGF causes the phosphorylation of both IGF1R and EGFR (54). Epidermal growth factor binding to the EGFR is able to directly phosphorylate IRS and activate Akt and MAPK pathways independently of the IGF1R (55). Treatment of cells with combinatory IGF1R and EGFR inhibitor therapy is synergistic (53). Retrospective clinical data suggest that patients with high IGF1R expression have improved outcomes on treatment with an EGFR inhibitor (56). High coexpression of both IGF1R and EGFR in lung cancer correlates with decreased disease-free survival (57). Based on this evidence, multiple clinical trials have combined anti-IGF1R with anti-EGFR therapy. As described previously, the larger phase trials of IGF1R inhibitors in combination with either gefitinib or erlotinib failed to show benefit; however, notably biomarkers for response were not used.

IRS1, a commonality of growth factor receptor signaling

Many recent approaches to cancer therapy has focused on the disruption of enzyme function to block downstream signaling. Growth factor receptors, as tyrosine kinases, have been particularly attractive. In addition, other enzymes downstream of growth factor receptors, such as the molecules involved in PI3K or MAPK, are also attractive targets. It needs to be recognized that the first step in many of these signaling cascades is the phosphorylation of nonenzyme adaptor proteins. Adaptor proteins have the potential to link cell surface signaling events to multiple downstream molecules. IRS1 is the prototype of such an adaptor protein that plays a key role in transmitting signals from multiple receptors. As the name implies, the IRS proteins were first identified to be substrates for the IR, but subsequent research showed that the IGF1R also uses IRS1 to activate oncogenic Akt and MAPK pathways (58).

Cells that express high levels of both IGF1R and IRS1 are more sensitive to IGF1R inhibitors (59). In addition to IRS1 activation by the IR and IGF1R, IRS1 has been shown to be phosphorylated by the GHR, and the ErbB family of receptors in the absence of IGF1R. Other proteins with oncogenic potential such as proinflammatory cytokines and anaplastic lymphoma receptor tyrosine kinase also are able to activate IRS1 (60, 61). Preclinical data have also shown the direct phosphorylation of IRS1 and the activation of its downstream oncogenic pathways by ErbB3. Blockade of the IGF1R enhances this interaction, suggesting a resistance mechanism when solely IGF1R is targeted (62).

Based on the above mentioned data, it is reasonable to postulate that IRS1 plays a significant role in resistance to IGF1R inhibitors and potentially other therapies. An example of this is in aromatase inhibitor-resistant breast cancer, which demonstrates decreased levels of IGF1R expression. Despite low levels of IGF1R, the levels of IRS1 remain the same as pretreatment, suggesting ongoing signaling via IRS1 in endocrine-resistant disease (63). Thus, if methods or drugs could be developed to inhibit IRS function, this might be a superior strategy to receptor inhibition. One such molecule has been described (64, 65), and additional studies will be necessary to determine whether these findings can be translated into a clinical strategy.

Conclusion

Fifteen years ago we suggested that "whether the IGF system is truly a relevant target in breast cancer" depended on the outcomes of clinical trials designed to block this system. These studies have focused on only the targeting of IGF1R. The failure of the IGF1R inhibitors in clinical trials might be interpreted as a lack of relevance of the IGF system to breast cancer.

However, one could argue that the IGF1R trials were instructive on several levels. In early-phase trials, IGF1R inhibitors have clearly demonstrated activity in the setting of both treatment naïve and heavily pretreated patients as demonstrated by the complete and partial responses in a few patients and stable disease in up to one-third to half of patients. Despite the success in multiple phase I clinical trials, IGF1R inhibition in the treatment of cancer has failed to show benefit in larger phase III randomized trials. This fact suggests that we have not yet clearly identified a subpopulation that will benefit from such therapy.

Furthermore, the targeting of the IGF system has not yet been tested. In the excitement of impressive preclinical data suggesting the benefit of inhibiting the IGF1R in the treatment of cancer, perhaps the clinical trials were performed in haste. Phase III trials enrolled patients with a

specified malignancy but paid no attention to tumor subtypes that had demonstrated an increased response to therapy in the earlier-phase trials. The success of targeted therapy in the treatment of cancer over the past decade has brought to light the importance of biomarkers for selecting a patient population that is more likely to benefit from any given treatment. Multiple preclinical trials have found potential biomarkers for response to IGF1R inhibition that have yet to be tested.

Many of the phase III trials were performed in combination with approved therapies for cancer. In the case of endocrine-resistant breast cancer, preclinical and clinical data suggest that IGF1R is down-regulated in tamoxifen-resistant breast cancer (44, 66); thus, an IGF1R inhibitor would be unlikely to be successful in this patient population. There are also data that combination of IGF1R inhibitors could either enhance or inhibit response to DNA-damaging agents (67, 68), but little thought was given to the optimal drug combinations or sequencing effects in the phase III studies.

Both preclinical and trial data have shown the importance of compensatory growth factor signaling in resistance to IGF1R therapy. The insulin, GH, and EGFRs all demonstrate some redundancy with IGF1R signaling, making blockade of a single receptor unlikely to be effective. Perhaps combinatory receptor targeting or targeting a common point in these pathways, such as IRS1, will increase the efficacy of inhibitors of growth factor receptors. One such strategy is being tested in the Investigation of Serial Studies to Predict Your Therapeutic Response With Imaging and Molecular Analysis 2 clinical trial (69). In this study, the IGF1R monoclonal antibody ganitumab is administered with metformin and paclitaxel in the neoadjuvant treatment of locally advanced breast cancer. Because ganitumab induces insulin resistance via the upregulation of GH and hepatic gluconeogenesis, metformin was included to hopefully reduce this complication. Whereas other strategies, such as the use of peroxisome proliferator-activated receptor-γ agonists might have been used, metformin has an established safety profile in nondiabetic subjects and does not induce hypoglycemia (70). It is hoped that metformin can reduce the compensatory hyperinsulinemia associated with the administration of this antibody.

Although multiple clinical trials testing inhibitors of the IGF1R have failed to show definitive clinical benefit, the knowledge obtained from these trials has given us a better understanding of tumor biology and how we may improve on the design of future trials. We understand that IGF1R is only one part of a complex signaling pathway. Furthermore, disruption of IGF1R with existing therapies is insufficient to block the system associated with pathway activation. Whereas the initial failure of these drugs is disappointing, it was not all bad. Lessons were learned about the complexity of this system and future efforts will be guided by these first attempts.

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