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Focus On

Drugs targeting insulin-like growth factor 1 receptor

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Over recent years, much focus has been placed on the development of targeted agents for the treatment of cancer. Breast cancer, in particular, has been an excellent model for the success of directed therapy, with the targeting of ER and HER2. Recent research findings have suggested that the insulin-like growth factor 1 receptor (IGF1R) is a promising target for the treatment of breast cancer.

Insulin-like growth factors (IGFs) are polypeptide growth factors that are ligands for IGF1R. There are two cognate ligands, IGF1 and IGF2, and insulin also has a weak affinity for IGF1R [1,2]. The receptor is composed of two disulfide-linked membrane-spanning β-subunits, each themselves linked to an extracellular α-subunit, and hence is a constitutively dimerized receptor (α2β2) (see Fig. 1). Ligand binding to the extracellular ligand-binding domain of the α-subunit activates the intracellular β-subunit tyrosine kinase, resulting in phosphorylation of substrates (e.g. insulin receptor substrate (IRS) 1 and 2) and autophosphorylation.

The IGF signaling system is further modulated by a series of at least six extracellular/circulating IGF binding proteins (IGFBPs) [3]. IGFBPs have a greater binding affinity for IGFs than IGF receptors and can, thus, exert negative signaling by competing IGFs away from receptors. IGFBPs also prolong half-life of IGFs in circulation, which can effectively serve as a signaling promoter. IGFBP-1, -3 and -7 have been reported to have tumor-suppressive properties in human breast cancer [4].

IGF signaling has a critical role in tumorigenesis as well as an anti-apoptotic role in established tumors. IGFs are important in the regulation of proliferation, differentiation, cell survival/apoptosis and transformation [1,2]. This is mediated by IGF1R that is ubiquitously expressed in normal tissues and all malignances. The necessity of IGF signaling for tumorigenesis is believed to be due to its anti-apoptotic effect, since transformed cells must evade apoptosis-inducing signals, while normal cells are under less apoptosis-inducing stress.

IGF1R activates downstream pathways that are known to serve important roles in cancer. The adapter proteins Shc and IRS1 appear to be critical signal-transducing elements. These proteins recruit members of the anti-apoptotic phosphatidylinostol 3-kinase (PI3K)-Akt (PI3K/Akt) pathway and the proliferation-inducing mitogen-activated protein kinase (ras/raf/MAPK) pathway. Downstream of Akt, mTOR and S6 kinase are known important mediators of IGF activity. IGF signaling may also utilize the Janus Kinase/Signal Transducer and Activator of Transcription (JAK/STAT) pathway [2]. A second receptor, IGF2R, does not appear to transduce signal, but rather serves as a scavenging mechanism for the IGF2 ligand and acts as a negative regulator [5]. The IGF1R pathway has a clear role in oncogenesis. IGF1R signaling appears to be necessary for cellular transformation and IGF1R deficient cells are resistant to transformation by a wide variety of oncogenes [6]. Tumor cells in mouse models in which dominant negative IGF1R expression is induced show evidence of decreased metastatic potential [7].

Breast cancer, in particular, appears to be a disease where drugs targeting IGF1R could be particularly

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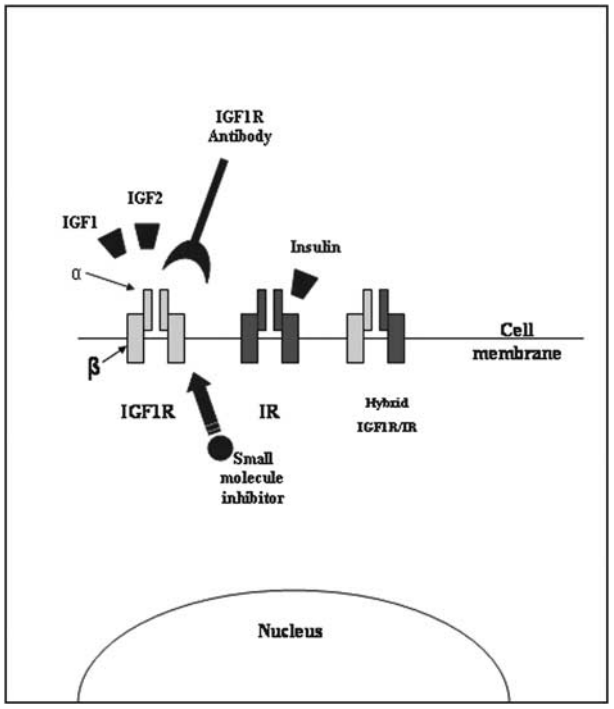

Figure 1.
IGF signaling system. IGF1 and IGF2 are the important ligands. In addition to binding the insulin receptor (IR), insulin also has a weak affinity for the IGF1 receptor. The receptor is constitutively dimerized ($\alpha 2\beta 2$) with two disulfide-linked membrane-spanning β-subunits linked to an extracellular α-subunit. Hybrid IR and IGF1 receptors are also found (adapted from Figure 1 in [89]).

useful. IGF1R levels, autophosphorylation and kinase activity were all found to be increased in breast cancer samples compared with normal breast tissue, with a 40-fold elevation in IGF1R tyrosine kinase activity [8]. In studies in human mammary epithelial cells, increased expression of a constitutively active IGF1R led to transformation of cells and promoted tumor growth in mice [9]. In-vivo studies have found that breast tumor cells without functioning IGF1R show inhibition of growth and metastasis [10], suggesting that manipulation of this signaling pathway may be a successful therapeutic target. In fact, blocking or neutralization of IGF1 has been shown to decrease cell motility in breast cancer cell lines [11].

The IGF1 pathway appears to have prognostic implications in cancer patients. In non-small cell lung cancer (NSCLC) patients, an association was found between elevated expression of IGF1R and decreased survival [12]. In breast cancer, an association has also been found with IGF1R and relapse-free and overall survival [13]. In fact, the expression of an IGF expression signature pattern in breast cancer has a strong association with poor prognosis [14]. All components of the IGF1 signaling axis have been reported to be adverse prognostic factors in breast cancer. IGFBP-2 and IGFBP-5 are predictive of the presence of metastatic disease in lymph nodes [15]. In addition, a correlation has been found between high IGF1R expression by immunohistochemistry and early ipsilateral breast tumor recurrence following lumpectomy and radiation [16].

The ligand, IGF1, is also implicated in the risk of developing cancer. A meta-analysis that evaluated IGF1 and IGFBP-3 concentrations and the incidence of several types of cancer found an association between high levels of IGF1 and premenopausal breast cancer, as well as prostate cancer [17]. A higher level of IGFBP-3 was also linked to a higher breast cancer risk in premenopausal women in this meta-analysis [17]. However, data regarding IGFBP-3 are somewhat conflicting. The Nurses' Health Study showed that in premenopausal women, mammographic density, a known breast cancer risk factor, is correlated with higher IGF1, lower IGFBP-3 and higher IGF1/IGFBP-3 ratio [18]. This does remain somewhat controversial as subsequent studies found no association between breast cancer risk and plasma IGF1, IGFBP-1 and IGFBP-3, even in premenopausal women, though premenopausal women with higher IGF1 levels had a slight increase in breast cancer risk [19,20].

The role of IGF1 in the risk and prognosis of breast cancer support its potential as a target for therapy. Transgenic mice with constitutively activated IGF1R develop mammary adenocarcinomas that are sensitive to an IGF1R-specific tyrosine kinase inhibitor (TKI) [21]. An IGF1R antagonistic murine monoclonal antibody, αIR3, decreased IGF1-activation of Akt and inhibited the growth of breast cancer cell lines in vitro [22,23]. In vivo, this inhibition was reported in an estrogen-independent breast cancer cell line, though curiously the effect was not seen in an estrogen-dependent cell line [22].

While single-agent IGF1R inhibitors may not always display in-vivo tumor activity [24], combining anti-IGF1R drugs with other agents has great potential, particularly given the anti-apoptotic function of IGF1R. Adding anti-IGF1R agents to cytotoxic chemotherapy is a logical strategy, though adding such drugs to established breast cancer targeted therapies such as anti-HER2 or anti-estrogen agents is also an attractive strategy, given known interactions between IGF1R and both HER2 and ER. This also makes IGF1R a particularly promising target for breast cancer, as opposed to other malignancies.

The IGF system is intimately linked with estrogen receptor signaling. Crosstalk between IGF1R and ER is well established [25–28]. Estrogen has been shown to induce expression of IGF1R and its

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substrates IRS1 and IRS2, with resultant enhancement of IGF1R signaling [27]. Anti-estrogens can decrease IGF1R and attenuate IGF1-stimulated growth [26]. Indeed, modulating the IGF system may be a mechanism of anti-estrogen therapy and use of tamoxifen in a breast cancer chemoprevention trial resulted in 23.5% reduction in circulating IGF1 levels [29]. IGF1R expression correlates positively with ER and PR expression and ER+ cells are more responsive to IGF-induced proliferation than ER− cells [8,30]. Furthermore, a chimeric, humanized single chain antibody to IGF1R was found to have synergistic effects in decreasing tumor growth in human breast cancer cells lines when combined with an anti-estrogen [31].

Another promising strategy is the combined targeting of the HER2 and IGF1R axis. Evidence of cooperation and cross-talk between IGFs and HER/EGFR family ligands has been well documented [32–37]. EGF can activate IGF1R, an effect that is inhibited by an IGF1R inhibitor [37]. In addition, IGF1R signaling may have a role in trastuzumab response and resistance. Inhibition of IGF signaling by dominant negative IGF1R produces synergistic cytotoxicity with trastuzumab in HER2-overexpressing breast cancer cells [38]. Furthermore, signaling by IGF1 has been linked to resistance to trastuzumab in cell culture studies. When SKBR3 cells, which possess low levels of IGF1R, were transfected with IGF1R and cultured with IGF1, they became resistant to growth inhibition by trastuzumab [39]. Other work has employed SKBR3 cells cultured for resistance to trastuzumab by continuous maintenance in the presence of trastuzumab [40]. This work used pools of such resistant cells, and comparisons were made to parental SKBR3 cells. An intimate IGF1R/HER2 interaction was noted exclusively in the resistant pools, but not in the parental cells. IGF1R and HER2 could be co-immunoprecipitated from resistant, but not from parental cells. This was independent of whether the cells were treated with IGF1 or not, though in the parental cell line a small degree of association could be induced by IGF1 treatment. Other findings included IGF1-induced stimulation of HER2 phosphorylation, and decreased HER2 phosphorylation when IGF1R was inhibited, but again only in the trastuzumab-resistant cells. Inhibiting IGF1R with an IGF1R-specific TKI or the anti-IGF1R antagonistic antibody, αIR3, restored sensitivity to trastuzumab. HER2 phosphorylation in parental cells was unaffected by the IGF1R TKI. The association between IGF1R and HER2 could be blocked by αIR3, but not by the TKI, although the TKI caused a decrease in HER2 phosphorylation, while αIR3 did not, highlighting potential differences between different types of inhibitors (antibody vs. TKI).

Some clinical evidence of the role for IGF signaling in trastuzumab resistance has been emerging, though with some inconsistencies. In a yet-to-be validated, exploratory analysis of markers predictive of response to trastuzumab-based therapies using tissues from a commercially available tissue microarray, IGF1R expression emerged as possibly predictive of non-response, especially in combination with other markers [41]. However, the accuracy and validity of the patient response data linked to the specimens in the commercially supplied tissue microarray is not documented. Another group has reported that among 72 patients with HER2-overexpressing metastatic breast cancer, IGF1R expression alone does not predict resistance to trastuzumab-based therapy [42]. Finally, we have found an association of overexpression of both IGF1R and the ligand IGF1 with primary resistance to neoadjuvant trastuzumab and vinorelbine [43]. Of note, one reason for these disparate results may lie in the fact that IGF1R immunostaining is variable, based on antibody used, conditions and scoring. We chose to score IGF1R membrane staining of 3+ (>10% of cells showing circumferential staining), based on a previous observation of an association of membrane IGF1R with trastuzumab resistance in the metastatic setting [44]. As IGF1R is widely expressed in most breast cancers, it has been difficult to determine what represents activated IGF1R in human tumors. Recent studies from the Lee laboratory at Baylor College of Medicine have used rigorous in vitro models to define a gene signature associated with IGF1 pathway activation [14]. Consideration of the global gene expression approach should be given in studying the ability of IGF1R inhibitors to modulate target pathways in breast cancer.

We have conducted preliminary in vitro studies to explore the potential of co-targeting IGF1R and HER2. We have found that HER2 antagonists and IGF1R antagonists were modestly cytostatic as single agents in breast cancer cell lines, but only their combination was able to induce apoptosis [45,46]. Others have shown that an IGF1R antagonistic antibody can potentiate the apoptotic effect of lapatinib in trastuzumab-resistant cells [47]. Similar results are found in cell lines with ER antagonists. Growth inhibition by ER antagonists is more dramatic when these agents are combined with IGF1R antagonists, and the effect of ER antagonists on apoptosis is increased by agents targeting IGF1R [45].

A number of strategies can be employed to interrupt the IGF signaling pathway including: (1) decreasing IGF1 levels with growth harmone-releasing hormone (GHRH) antagonists or growth

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Table 1. Drugs targeting IGF-IR.

Drug	Development phase	Class	Company	Reference
CP-751,871	Phase I–III	Fully human monoclonal antibody	Pfizer	[62,67–69]
MK-0646	Phase I	Humanized monoclonal antibody	Merck	[70,71]
AMG-479	Phase I and II	Fully human monoclonal antibody	Amgen	[72–74]
AVE1642 (humanized version of EM164)	Phase I	Humanized monoclonal antibody	Immunogen and Sanofi-Aventis	[64,78]
IMC-A12	Phase I and II	Fully human monoclonal antibody	Imclone	[61,76,77]
BIIB022	Phase I	Fully human monoclonal antibody	Biogen	[79]
R1507	Phase II	Fully human monoclonal antibody	Roche	[75]
αIR3	Preclinical	Murine monoclonal antibody		[22,23]
scFv-Fc	Preclinical	Chimeric single-chain antibody		[65]
EM164	Preclinical	Murine monoclonal antibody	Immunogen	[64]
h7C10	Preclinical	Humanized monoclonal antibody	Merck	[63]
19D12	Preclinical	Fully human monoclonal antibody	Schering-Plough	[66]
INSM-18	Phase I/II	Dual IGF1R/HER2 inhibitor	Insmed	http://www.insmed.com/oncology.php
OSI-906 (close derivative of PQIP)	Phase I	Small molecule TKI	OSI Pharmaceuticals	[60]
NVP-ADW742	Preclinical	Small molecule TKI	Novartis	[50,51,94]
NVP-AEW541	Preclinical	Small molecule TKI	Novartis	[54,56–58]
BMS-554417	Preclinical	Small molecule dual (IGF1R/IR) TKI	Bristol-Myers Squibb	[52]
BMS-536924	Preclinical	Small molecule dual (IGF1R/IR) TKI	Bristol-Myers Squibb	[59]
PPP (picropodophyllin)	Preclinical	Cyclolignan small molecule (non-ATP) competitive inihibitor	Biovitrum	[80]
PQ 401	Preclinical	Diaryl urea small molecule (non-ATP) inhibitor		[81]

TKI: tyrosine kinase inhibitor.

hormone (GH) antagonists, (2) neutralizing IGF1 with binding proteins, soluble receptors or IGF1 antibodies, (3) reducing IGF1R gene expression with drugs such as antisense agents and (4) blocking IGF1R activity with small molecular inhibitors or antibodies to IGF1R [5]. Initial drug development of small molecule inhibitors was problematic as the inhibitors that were developed had inadequate specificity, often inhibiting both IR and IGF1R [48,49]. As development has progressed, specificity has improved. Drug development strategies have been primarily focused on drugs targeting IGF1R with small molecule inhibitors or monoclonal antibodies, and many such drugs are in various stages of development (see Table 1).

Detailed analysis of an IGF1R-specific TKI, NVP-ADW742, showed numerous potentially therapeutic mechanistic effects, including decreased expression of cell cycle genes, inhibition of Rb phosphorylation, down-regulation of caspase inhibitors, inhibition of telomerase activity, down-regulation of heat shock proteins, decreased phosphorylation of Akt, p70S6K, GSK3β, FKHRL-1, MEK 1/2, src, STAT3 and FAK and decreased expression levels of Akt, p70S6K, raf, src, Bmx, IKK and PDK1, as well as other effects [50]. This agent was found to have antitumor activity in xenograft studies both alone and in combination with chemotherapy. When studied in Ewing tumor cell lines, synergism was seen with the combination of this agent with chemotherapy as well as with the targeted agent imatinib [51], which again suggests that agents targeting IGF1R have the potential to be active when combined with other targeted therapies. Another similar agent, BMS-554417, a dual kinase small molecule inhibitor of IGF1R and IR, was effective in promoting apoptotic cell death and decreasing tumor size in xenograft studies [52,53].

Numerous other similar agents are being evaluated in vitro and in vivo, including BMS-536924, NVP-AEW541 and PQIP [54–59]. Two orally bioavailable small molecule TKIs, OSI-906 and INSM-18, are in phase I and phase I/II clinical trials, respectively. Activity of OSI-906 includes inhibiting IGF1R autophosphorylation after ligand binding, inhibiting downstream signaling pathways, and anti-tumor effects in colon cancer xenograft studies both alone and in combination with erlotinib [60]. No clinical data is yet available on either of these agents.

In addition to small molecule inhibitors, antibodies to IGF1R are in development, which may work by down-regulating IGF1R, inhibiting ligand binding or other mechanisms. Many of these have been found to inhibit tumor growth in cell lines or

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tumor xenograft studies, with drugs including CP-751,871, AVE1642, scFv-Fc, h7C10, A12, EM164 and 19D12 [61–66]. One of the agents which is currently furthest along in testing is CP-751,871 (Pfizer), a fully human IgG2 monoclonal antibody to IGF1R. This agent was found to downregulate IGF1R both in vitro and in tumor xenografts, and activity was seen in several tumor cell lines both as single agent and in combination with adriamycin, 5-fluoruracil and tamoxifen [62]. This effect was found to be dose-dependent. A phase I study of intravenous CP-751,871 administered on day 1 of a 21 day cycle in patients with advanced non-hematologic malignancies showed no objective responses, but did show disease stability in 10 of 15 patients at the maximum feasible dose [67]. Toxicities were mild and included hyperglycemia, anorexia, nausea, transaminitis, diarrhea, hyperuricemia and fatigue. Elevation of serum insulin and human growth hormone levels were noted in treatment patients.

In addition, good tolerance was found in a recently published phase I study in patients with multiple myeloma evaluating intravenous CP-751,871 either alone, or with addition of dexamethasone in patients with less than a partial response (and in some cases with rapamycin) [68]. In patients treated with CP-751,871 alone, there were no partial responses but disease stability was noted in 28 patients, all of whom were progressing when they started the study. Nine of 27 patients treated with CP-751,871 in combination with dexamethasone showed evidence of response. Toxicities in the CP-751,871 alone arm (47 patients) included: grade 1 toxicities of diarrhea 4%, thrombocytopenia 4%, nausea 4%, rash 4%, increased AST 6%; grade 2 toxicities of anemia 6%; grade 3 toxicities of anemia 2% and hyperglycemia 2%. In patients being treated with dexamethasone as well, hyperglycemia was not surprisingly seen in a higher percentage of patients (7%). Pharmacodynamic studies in patients receiving the study drug showed an inhibition of granulocyte IGF1R expression and increase in serum IGF1 concentrations, as well as IGFBP3. Based on this study, phase II studies will be carried out with a dose regimen of 6–20 mg/kg intravenously for 4 weeks.

The most promising results to date have been seen with the combination of CP-751,871 and carboplatin and paclitaxel in a phase II trial in patients with advanced untreated NSCLC [69]. Objective responses were seen in 51% of patients on the combination arm and only 36% of patients on carboplatin/paclitaxel alone. Notably 72% (13/18) of patients with squamous cell carcinoma showed response, some of which were quite impressive, including no evidence of active disease and resolution of SVC obstruction. Grade 3/4 toxicities included 11% hyperglycemia, 9% fatigue and 14% neutropenia in the arm with CP-751,871 (compared with 4%, 7% and 14% respectively in carboplatin/paclitaxel arm).

CP-751,871 is currently being investigated in additional trials in patients with lung cancer, prostate cancer, colorectal cancer and Ewing's sarcoma, mostly in phase I or II trials. In breast cancer, there is an ongoing phase I pharmacodynamic study using CP-751,871 in early stage breast cancer patients as neoadjuvant therapy. The majority of these studies are looking at the agent in combination with cytotoxic chemotherapy, though the possibility of these drugs having synergism with other targeted agents is also being evaluated. There is an active phase III trial of erlotinib with or without CP-751,871 in patients with advanced NSCLC. In addition, the drug is being studied in a phase II clinical trial in women with hormone receptor positive advanced breast cancer in combination with exemestane.

A phase I study of another IGF1R humanized monoclonal antibody, MK-0646, given intravenously every 2 weeks in patients with advanced solid tumors found that the drug was well tolerated with adverse events including fatigue, nausea, vomiting, constipation, diarrhea, weight loss and abdominal pain [70]. There was one dose limiting toxicity, which was grade 4 thrombocytopenia. Results with the same drug were reported in another abstract and confirmed safety in a group of 48 patients with advanced solid tumors, 11 of which were breast cancer patients [71]. Dose-limiting, grade 3 purpura was reported in one patient. Grade 1–2 hyperglycemia was noted in 10% of patients. Correlative studies showed reduction in expression of IGF1R and inhibition of the downstream signaling. Stable disease in three patients for more than 3 months and mixed response on imaging in one patient were noted.

In addition, abstract data is available on AMG-479, a fully human IGF1R monoclonal antibody, which is currently being evaluated in phase I and II clinical trials. Tumor regression in pancreatic xenograft studies was seen with this agent in combination with gemcitabine and the anti-EGFR agent panitumumab, while only tumor stasis was observed with panitumumab and gemcitabine alone [72]. A phase IB study of AMG-479 in combination with panitumumab or gemcitabine in patients with advanced solid tumors showed tolerability and evidence of activity in refractory disease [73]. In addition, a phase I study in 16 patients with advanced tumors reported one partial response, five stable disease and one mixed response (in a breast cancer patient). Again, toxicity was mild with one grade 3 thrombocytopenia, two grade 3/4 non-hematologic toxicities and hyperglycemia of grade 2 or less [74]. AMG-479 is also being evaluated in postmenopausal

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women with hormone receptor positive locally advanced or metastatic breast cancer in combination with exemestane or fulvestrant.

R1507 is a fully human monoclonal antibody that was studied in every 3 week dosing in 21 patients with advanced cancer, with almost half of the patients (10) showing stable disease [75]. No dose-limiting toxicities or serious adverse events were noted. Half-life in that study was found to be approximately 8 days. A subsequent phase I study with weekly dosing evaluated 34 patients with advanced solid tumors and showed disease stability in nine patients and minimal side effects (most commonly seen were fatigue, anorexia, weight loss) (unpublished data, http://www.genmab.com/ScienceAndResearch/ProductsinDevelopment/R1507.aspx). This agent is currently being evaluated in a phase II study in sarcoma patients.

IMC-A12 is a fully human IgG1 monoclonal antibody targeting IGF1R, which has been found to be effective in the inhibition of tumor growth in breast, lung, colon and pancreas in xenograft studies [76]. A phase I study of the drug in 11 patients with advanced solid tumors showed good tolerance with toxicities including grade 1 pruritis, rash, discolored feces; grade 2 anemia, psoriasis, hyperglycemia, infusion reaction; grade 3 hyperglycemia [77]. A phase II randomized study of HER2-positive stage IIIB-IV breast cancer being treated with capecitabine and lapatinib with and without IMC-A12 is currently underway. Other antibodies including BIIB022 and AVE1642, both of which are in phase I clinical trials, are also currently under evaluation. A phase I study of AVE1642 in 14 patients in combination with docetaxel found good tolerance with no serious adverse events and grade 1/2 toxicities of one hyperglycemia, two hypersensitivity reactions, two asthenia, one anemia, one nail disorder, one paresthesia and one pruritus [78]. Four patients with stable disease after four cycles were reported and one patient with metastatic breast cancer with skin nodules was found to have a decrease in skin manifestations [78]. BIIB022 has been found to enhance anti-tumor activity of erlotinib and rapamycin in lung cancer and sarcoma cell lines, respectively [79], but clinical trial data is not yet available.

In addition to development of antibodies and small molecule TKIs, other strategies are also being employed in the development of drugs targeting the IGF system. A catechol bioisoteres which serves as an IGF1R substrate-competitive inhibitor has been developed which inhibits IGF1R kinase activity and inhibits ability of prostate and breast cancer cell lines to form colonies [49]. Autophosphorylation of the IGF1R can also be interrupted by cyclolignans serving as substrates. One such agent, picropodophyllin, inhibited IGF1R activity, had an apoptotic effect on IGF1R positive cells and decreased tumor size in mouse xenografts and allografts [80]. Interaction with the IR was not observed. PQ401, a non-ATP competitive small molecule inhibitor, is another novel agent with potential therapeutic effects [81]. This diaryl urea compound interfered with growth of breast cancer cell lines in culture and mouse xenograft studies. The above agents have been found to induce apoptosis by reducing signaling through the Akt anti-apoptotic signaling cascade [80,81]. Strategies with antisense oligonucleotides have also been employed and found to decrease level of IGF1R mRNA and inhibit proliferation in cell lines [82,83]. None of these agents are currently in the clinical trial phase of development.

Preclinical and clinical data with the anti-IGF1R agents have found that hyperglycemia is a common toxicity. The IGF1 ligand has an important role in the metabolic pathway of glucose. Recombinant IGF decreases blood glucose levels and increases sensitivity to insulin [84]. Studies in rats have showed that IGF1 can produce insulin-like effects, though with only 2% of the potency of insulin [85]. Thus, altering the IGF1 pathway has the potential to induce glucose intolerance. The small molecule TKIs likely exert their hyperglycemic effects through the blockage of insulin receptor (IR) signaling. IR and IGF1R have been showed to form hybrid dimers [86]. In addition, IGF1R and IR have 84% homology in the tyrosine kinase domains and 100% homology in the ATP binding regions [87]. Thus, cross-reactivity is a potential issue. This cross-reactivity may be beneficial in some respects. Insulin can act as a growth factor stimulating proliferation of breast cancer; therefore, co-targeting IR and IGF1R may have some advantages [88].

The mechanism of hyperglycemia secondary to receptor antibodies is less clear. Hyperglycemia secondary to direct insulin receptor binding is less likely as the monoclonal antibody CP-751,871 apparently does not cross-react with the insulin receptor, though it does recognize heterodimers of IGF1R and IR [62]. Studies with IGF1R antibodies in breast cancer cell lines showed that these agents could downregulate the IR in cells that had at least moderate expression of the IGF1R [89], an effect that could impact on glucose levels. However, given redundancy in signaling by IGF1R and IR, and the existence of IGF1R/IR hybrid receptors, some have argued that targeting both of those receptors may be necessary to achieve maximal anti-tumor effect [88]. Another toxicity that has been observed with some agents is anemia. IGF1 increases proliferation of erythroid progenitors [90] and is a potent activator of erythropoietin in cell lines [91].

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IGF1 may also act synergistically with erythropoietin to stimulate hematopoiesis [92]. With numerous ongoing trials evaluating agents targeting IGF1R, the toxicities as well as mechanisms of toxicity will likely become clear.

The differing toxicities between the classes of targeting agents are one factor that will impact on which agents ultimately enter into the clinical arena. While the antibodies exert much of their effect by downregulating the receptor or inhibiting ligand binding, TKIs more directly inhibit downstream signaling. At this time, neither mechanism has proved to be better. In general, antibodies have the advantage of long half-life, while the small molecule TKIs have the advantage of oral bioavailability. Perhaps both antibodies and TKIs will each have a role, as we have seen with agents targeting VEGF, HER2 and EGFR.

Strategies to target the IGF1R have great potential, particularly in breast cancer, given the overexpression in this disease, well established cross-talk with both ER and HER2, and vital role in transformation and anti-apoptosis for all types of malignancy. The synergistic activity seen with the combination of anti-IGF1R with other targeted agents invites cautious optimism. Though breast cancer treatments have been greatly aided by therapies targeting ER and HER2, thus far, these drugs have been ineffective in breast tumors that lack ER or do not overexpress HER2. We have shown in vitro that combining trastuzumab with IGF1R inhibitors not only dramatically enhances the anti-tumor effect of trastuzumab against HER2+ breast cancer cells, but the combination also induces apoptosis in HER2-normal level human breast cancer cells [46]. If such synergism occurs clinically, this would have the potential to extend the benefits of HER2-directed therapy to a wider population of breast cancer patients, regardless of a tumor's HER2 status.

IGF1R represents a promising target in the search for novel and more effective agents to treat cancer. The key will be to develop measures to identify which patients are likely to benefit from these agents and candidate markers for sensitivity are actively being sought [93]. Strategies that use global pathway profiling may have advantages over less reliable single gene markers [14]. Though clinical data is limited at this time, there is currently much focus on developing these agents and testing them in clinical trials. Data thus far shows that drugs targeting IGF1R are well tolerated, with a notable side-effect of hyperglycemia. The bulk of the benefit with these drugs may be in combining these agents with cytotoxic chemotherapy or other targeted agents. The potential to combine these agents with targeted therapy in order to overcome resistance is particularly exciting. Synergism in cell lines has been reported with anti-estrogens, anti-HER2 agents and EGFR inhibitors [31,38,45,46,72,93] and clinical trials are further evaluating efficacy of these combinations. Overall, the results thus far with drugs targeting IGF1R are promising and further data is eagerly awaited.

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