Published in final edited form as:
Cancer Treat Rev. 2014 October ; 40(9): 1096–1105. doi:10.1016/j.ctrv.2014.07.004.

Can we unlock the potential of IGF-1R inhibition in cancer therapy?

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Abstract

IGF-1R inhibitors arrived in the clinic accompanied by optimism based on preclinical activity of IGF-1R targeting, and recognition that low IGF bioactivity protects from cancer. This was tempered by concerns about toxicity to normal tissue IGF-1R and cross-reactivity with insulin receptor (InsR). In fact, toxicity is not a show-stopper; the key issue is efficacy. While IGF-1R inhibition induces responses as monotherapy in sarcomas and with chemotherapy or targeted agents in common cancers, negative Phase 2/3 trials in unselected patients prompted the cessation of several Pharma programs. Here, we review completed and on-going trials of IGF-1R antibodies, kinase inhibitors and ligand antibodies. We assess candidate bio-markers for patient selection, highlighting the potential predictive value of circulating IGFs/IGFBPs, the need for standardized assays for IGF-1R, and preclinical evidence that variant InsRs mediate resistance to IGF-1R antibodies. We review hypothesis-led and unbiased approaches to evaluate IGF-1R inhibitors with other agents, and stress the need to consider sequencing with chemotherapy. The last few years were a tough time for IGF-1R therapeutics, but also brought progress in understanding IGF biology. Even failed studies include patients who derived benefit; they should be investigated to identify features distinguishing the tumors and host environment of responders from non-responders. We emphasize the importance of incorporating biospecimen collection into trial design, and wording patient consents to allow post hoc analysis of trial material as new data become available. Such information represents the key to unlocking the potential of this approach, to inform the next generation of trials of IGF signalling inhibitors.

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Conflict of interest statement

Dr Haluska is the recipient of research funding from Bristol-Myers Squibb, Roche/Genentech and Merck, and is an unpaid consultant for BMS, Boehringer Ingelheim, and MedImmune. Dr. Macaulay has received a research Grant from AstraZeneca and is an unpaid consultant for Boehringer Ingelheim. The other authors have no conflict of interest.

Keywords

IGF; Type 1 IGF receptor; IGF-1R cancer therapy; Therapeutic antibody; Tyrosine kinase inhibitor; Predictive biomarker

IGF-targeting: a promising start

The rationale for developing drugs to block IGF signalling has been reviewed elsewhere [1–3] and will not be repeated, except to highlight first the seminal work of Baserga in showing that type 1 IGF receptor (IGF-1R) is required for malignant transformation [4], and secondly the demonstration that low IGF bioactivity protects against development of clinical cancers [5,6]. A variety of experimental approaches was used to provide proof of principle [7–11]; strategies with clinical application fall into three categories: monoclonal anti-IGF1R antibodies, small molecule tyrosine kinase inhibitors (TKIs), and IGF ligand antibodies. Preclinical data indicate that these different classes of drug have different profiles of selectivity, efficacy and toxicity that may affect their use in clinical practice [12–22]. IGF-1R antibodies block ligand binding and induce receptor internalization and degradation [14], also resulting in insulin receptor (InsR) downregulation in cells expressing IGF-1R:InsR hybrid receptors [23]. The majority of IGF-1R TKIs described to date act by competing with ATP for binding in the IGF-1R kinase domain [18,20,24], and also inhibit InsR due to conservation of structure, particularly in the ATP-binding cleft of the kinase domain [25]. As a class effect, IGF-1R inhibitory drugs cause hyperglycemia, although this is usually mild and reversible [6,26]. IGF-1R TKIs induce hyperglycemia via direct inhibition of InsR kinase, while IGF-1R antibodies impair glucose tolerance by inducing elevated circulating levels of growth hormone and IGF binding proteins (IGFBPs), attributed to blockade of pituitary IGF-1Rs [2]. Several ATP non-competitive agents are in development, including one at an early stage of clinical testing [27,28]. IGF ligand antibodies act by neutralising IGF-1 and IGF-2, preventing receptor activation without affecting glucose tolerance [22,29]. All three classes of agent have anti-tumour activity *in vitro* and *in vivo*, although it should be acknowledged that some preclinical models were selected or designed to be IGF responsive, and relatively limited preclinical data led to an extremely large number of clinical trials [30].

Clinical trials: reality check

Given experimental data supporting a key role for IGF-1R in tumor biology, a substantial degree of optimism accompanied the commencement of clinical trials with anti-IGF-1R agents. This early enthusiasm was stimulated to a large degree by the near ubiquitous expression of IGF signalling components, including IGF-1R in most tumor types [30,31], and was reinforced by initial reports of apparently dramatic activity [32,33]. However, the data that emerged subsequently have been less impressive. Monotherapy trials of anti-IGF-1R antibodies and TKIs have generally reported disease stabilisation and minor responses, with few objective responses in common cancers [34–38]. There is, however, evidence of activity in heavily pre-treated Ewing sarcoma (EWS), other types of sarcomas, and neuroendocrine tumors, although data in the latter are conflicting [32,39–44]. In addition, IGF-1R antibodies were recently reported to have single agent activity in recurrent

ovarian cancer and relapsed thymoma, although thymoma treatment was associated with the development of autoimmune conditions including red cell aplasia [45,46]. Activity in EWS and childhood sarcomas may be a consequence of functional interactions between oncogenic fusion proteins (EWS-FLI1 and related fusion partners) and the IGF pathway [47–50].

There is as yet little evidence regarding the efficacy of ligand antibodies and non-ATP binding IGF-1R inhibitors, although of note, initial reports of the latter suggest single agent activity in non-small cell lung cancer (NSCLC) [28,51]. Otherwise, it is clear that in common cancers there is insufficient clinical support for continued evaluation of IGF-1R antibodies and TKIs as monotherapy in unselected patients. In the context of expectations generated by preclinical data, these clinical results have been disappointing. It is unclear whether limited single agent activity in common cancers reflects IGF-independent growth in established tumors, adaptive resistance mechanisms (discussed below) or the inability to sustain target blockade. The latter issue is raised by preclinical data demonstrating that IGF-1R antibodies may inadequately maintain *in vivo* IGF-1R down-regulation or suppression of PI3K-AKT signalling [52,53]. One factor that could limit efficacy was highlighted by an immuno-SPECT study showing correlation between uptake of IGF-1R antibody R1507 in responsive but not resistant IGF-1R-positive bone sarcoma xenografts [54]. These findings suggest that microenvironmental factors may limit vascular access of therapeutic antibody to tumor tissue, an obstacle that may be circumvented by small molecule drugs.

Based on reports that IGF-1R mediates resistance to other modalities of treatment [55–58], IGF-1R targeting has been evaluated in combination with an extensive range of standard and/or novel cancer treatments, including cytotoxic drugs and inhibitors of EGFR, mammalian target of rapamycin (mTOR) and steroid hormone receptors [53,59–75]. This has also met with mixed results, with Phase 2/3 trial failures in unselected patients [76]. One thing is certain: some sort of signal is needed soon, and this will require patient selection.

Can we identify who will benefit?

While negative trials led to the high profile termination of several Pharma IGF programs, a number of IGF axis inhibitors are continuing active evaluation, including small molecule inhibitors and ligand antibodies. It is important for the success of these programs that information from completed trials is utilized in translational research, because even the negative studies include patients who derived benefit from IGF-1R inhibition, providing an opportunity to characterize responsive tumors. This information has the potential to provide a basis for stratification and selection, if future trials are to be successful. Without such an approach, the clinical utility of EGFR inhibitors would not have been recognized after initial negative Phase 3 evaluation in NSCLC [77].

Although IGF-1R is almost ubiquitously expressed by human tumors, sensitivity to anti-IGF-1R therapy varies widely between patients and cancer types [26]. Large-scale cancer genome sequencing projects have identified rare *IGF1R* gene mutations reported to influence basal (ligand-unstimulated) phosphorylation of IGF-1R substrates [78]. However, these or similar mutations, comparable to those in EGFR associated with EGFR inhibitor

sensitivity, have not been reported in tumors of patients on IGF-1R inhibitor trials. Thus, it is unlikely that IGF-1R mutations will be relevant in selecting patients for IGF signalling inhibition. Therefore, there is an on-going search for predictive biomarkers, which fall generally into two groups: potential biomarkers in the IGF axis, and biomarkers in other pathways that influence response to IGF-1R inhibition (Table 1).

Candidate predictive biomarkers in the IGF axis

The first candidate biomarker emerged from the Phase 2 figitumumab trial in NSCLC [59], with a report that high pre-treatment levels of circulating free IGF-1 were predictive of clinical benefit from addition of figitumumab to standard chemotherapy [79]. These findings were corroborated with respect to levels of free or total circulating IGFs in additional clinical trials [63,80–82]. Circulating markers present obvious advantages over tissue biomarkers: testing is minimally invasive and amenable to serial monitoring. There is novelty in the concept that tumor sensitivity to a targeted agent may be influenced by host factors; this idea is consistent with the known importance of circulating host-derived IGFs in normal and cancer biology, and the recognition that high circulating IGF-1 is associated with increased risk of developing common cancers [83,84]. However, this line of research suffered a setback when the original findings with respect to the figitumumab NSCLC data were retracted [85]. Nonetheless, more recent data support further investigation of IGF components as candidate biomarkers. Preclinical models find evidence of correlation between sensitivity to figitumumab or TKI NVP-AEW541 and expression of IRS2, IGFBP5 and MYB in colorectal cancer [86], and expression of IGF-1R, IGF-2 and IRS-1 and -2 in breast and colon models [87,88]. In breast cancer cells resistant to BMS 536924, the IGFBP-5/IGFBP-4 expression ratio was found to correlate with sensitivity to IGF-1R inhibition [89]. Clinical evidence supporting evaluation of IGF axis biomarkers comes from trials in pancreatic cancer, where sensitivity to dalotuzumab (IGF-1R antibody MK-0646) was linked with tumor IGF-1 expression, and to ganitumab with high circulating IGF-1, IGF-2 or IGFBP-3, or low IGFBP-2 [82,90].

In certain cancers, including NSCLC, breast, colorectal, EWS and rhabdomyosarcoma, tumor IGF-1R may be predictive of response [52,87,91,92]. IGF-1R expression by circulating tumor cells may correlate with tumor IGF-1R, providing a feasible approach for serial measurement [93]. This could be particularly relevant when monitoring response to IGF-1R antibody, where IGF-1R downregulation is an indicator of target engagement [14]. In rhabdomyosarcoma cell lines, there was significant correlation between elevated IGF-1R and anti-proliferative effects of an anti-IGF1R monoclonal antibody, enabling prediction of responses to IGF-1R-targeting in animal models [52]. This parameter and the finding of association with IGFs, IRS proteins and IGFBPs may indicate tumors that are more heavily dependent on IGF signalling, although evidence in this area is contradictory, with some preclinical and clinical studies reporting that IGF-1R expression or activation has no predictive value [72,94,95]. It is possible that the specific molecular context and the complexity of IGF-1R:insulin hybrid receptor biology may explain some of these contradictory results [26]. A well-designed Phase 2 study in patients with bone or soft tissue sarcomas tested the utility of IGF-1R as a predictive biomarker by measuring IGF-1R in fresh tumor biopsies pre-and post treatment [72]. The results suggested that PFS was similar

in patients with ‘IGF-1R positive’ vs ‘IGF-1R negative’ tumors, apparently challenging the assumption that lack of IGF-1R has negative predictive value, although it was acknowledged that IGF-1R could be detected by western blotting of tumor lysates in tumors that were ‘IGF-1R negative’ by immunohistochemistry, casting doubt on the sensitivity of IHC detection [72]. These data highlight the importance of establishing standardized detection protocols for IGF-1R, as for estrogen receptor (ER) and HER2, and to develop robust assays for InsR and hybrid receptors in clinical tumors.

Subcellular IGF-1R localization may also be relevant to response to IGF-1R inhibition, although there is conflict in the literature on its significance. Aberrant IGF-1R glycosylation is reported to impair insertion of IGF-1R into the plasma membrane, conferring resistance to IGF-1R antibody [96], consistent with a model in which only receptors on the plasma membrane are accessible to antibody binding. IGF-1R is known to undergo ligand-induced translocation from the cell surface to the nucleus of human tumor cells, and nuclear IGF-1R is associated with resistance to EGFR inhibitor gefitinib [97–100], suggesting a role in IGF-1R-mediated resistance to targeted therapies. Exclusive nuclear IGF-1R localization was reported by Blay and colleagues to be associated with benefit from IGF-1R antibody in unresectable and metastatic sarcomas [101]. This may suggest that nuclear IGF-1R is a marker for dependence on IGF signalling, and sensitivity to its inhibition. It also raises the question of the location of IGF-1R:antibody binding; of note, quantum dot-labelled IGF-1R antibody has been found to undergo nuclear import [102].

Candidate predictive biomarkers outside the IGF axis

Given that the IGF axis engages in complex signalling interactions [103], it is predictable that candidate biomarkers will be identified outside the IGF–IGF-1R–IRS axis, and some such have been identified from tumor-specific screens. In childhood sarcoma cells, knockdowns of macrophage-stimulating 1 receptor (MST1R, also known as RON) and ribosomal protein S6 restored sensitivity to BMS-536924 in resistant cell lines [104]. Sensitivity to the dual IGF-1R/InsR inhibitor linsitinib (OSI-906) was associated with *IGF1R* gene copy number (but not IGF-1R protein) in colorectal cancer cell lines, and also with differential expression of 3 gene pairs and a trend to greater sensitivity in cells with wild-type KRAS [105]. The latter finding raises the issue of the extent to which activating mutations in IGF-1R effectors mediate resistance to IGF-1R blockade. In preclinical models, IGF-1R inhibition is capable of suppressing tumor cell growth in cells that lack functional PTEN, although there are conflicting reports of the consequences of PTEN loss in terms of the ability of IGF-1R targeting to enhance radiosensitivity [10,106,107]. While PTEN loss amplifies signalling to AKT, it does not induce constitutive pathway activation; logic dictates that constitutively activating mutations in the PI3K-AKT or RAS-RAF-ERK pathways should render cells refractory to IGF axis blockade. Indeed, preclinical data suggest that resistance to IGF-1R inhibition is observed in the context of constitutive AKT activation and high levels of activated ERKs [108–111], and sensitivity of KRAS mutant NSCLC was restored by MEK inhibition [112,113]. Consistent with this, IGF-1R antibody ganitumab was ineffective at sensitizing to FOLFIRI chemotherapy in patients with KRAS mutant colorectal cancer [114], although issues of chemotherapy scheduling may be a contributing factor (see below). In contrast, KRAS mutant NSCLC cells appear to be

sensitive to IGF-1R inhibition: mutant KRAS was found to induce IGF-dependent PI3K activation that could be suppressed by targeting IGF-1R [115]. These findings suggest that KRAS mutation may have varying significance for response to IGF-1R blockade, depending upon the tumor type and/or molecular context.

Finally, predictive information may be derived by characterizing IGF-regulated gene expression. This approach was first applied by Lee and colleagues, with reports that an IGF gene signature induced in breast cancer cells *in vitro* is associated with poor prognosis in clinical cancers, and correlates with sensitivity to IGF-1R inhibitor BMS-754807 in triple negative breast cancer (TNBC) *in vivo* [116,117]. These data provide further support for the concept that tumors that are highly dependent on IGF signalling may also be sensitive to IGF-1R inhibition. A similar approach has been taken in EWS, to identify molecular signatures associated with resistance to IGF-1R antibody or TKI drugs [118].

Thus, there is evidence from several studies that levels of circulating IGFs and IGFBPs correlate with sensitivity to IGF axis inhibition. Otherwise, there is little consensus, with a range of candidate biomarkers identified in different tumors with different classes of agent. As a consequence, phase 2/3 trials have been undertaken without patient selection, although some are now reporting post hoc identification of markers that characterize responsive patient subgroups [65,82]. In order for this research to inform clinical practice, it is of critical importance to be able to test these factors in the tumors of additional trial patients. This in turn requires that trial consents should permit future ethically-approved research on archival and trial-specific material. For example, BATTLE-FL is building on previous NSCLC BATTLE trials [119], to incorporate biomarkers into a trial adding targeted agents including IGF-1R antibody cixutumumab to first-line carboplatin/pemetrexed chemotherapy (NCT01263782). Another example is the ongoing ISPY2 (NCT01042379) breast cancer clinical trial, which is incorporating ganitumab in combination with metformin, into neoadjuvant chemotherapy, and employing a rich biomarker driven, adaptive study design [120,121]. The analysis will be used to develop both predictive and prognostic biomarkers through correlation of tumor expression profiles by DNA microarray and reverse-phase protein arrays with tumor response at the time of surgery.

Approaches to design rational combination therapies

Given the large number of signalling pathways that converge on those activated by IGF-1R [103], it was in retrospect unlikely that IGF-1R targeting would have dramatic impact as monotherapy, except in specific cancers that are highly IGF-dependent. Predictive biomarkers serve an important purpose in identifying potentially responsive patients, but they do not make treatments more effective *per se*. To achieve that goal, it is necessary to understand how to combine novel drugs most effectively, and how to schedule targeted drugs with standard treatments. A large body of literature has highlighted the ability of IGF-1R to mediate resistance to other treatment modalities, and conversely has identified proteins capable of compensating for IGF-1R blockade. These findings provide the rationale for designing trials of IGF-1R inhibitory drugs in combination with other targeted agents, and with chemotherapy.

Trials of IGF-1R inhibitory drugs with targeted agents

IGF-1R signalling is involved in extensive cross-talk with other receptor tyrosine kinases (RTKs) and their downstream effectors, such that compensation from other pathways is likely to mediate resistance to inhibition of a single class of receptor [122]. For IGF-1R, the most closely-related candidate is InsR, with evidence that resistance to IGF-1R antibody therapy results from IGF-1R:InsR heterodimer formation, and IGF-2 signalling via the variant InsR isoform A (InsR-A) that is frequently expressed by human tumors [96,123–125]. Of note, InsR-A may be the more important IGF signalling receptor in hormone-resistant breast cancer [126–128]. This source of compensatory signalling may be blocked by IGF ligand antibodies and dual IGF-1R/InsR TKIs such as linsitinib and BMS-754807 [20,129]. Trials currently in progress will clarify whether this conceptual advantage translates to improved efficacy.

Cross-talk has been demonstrated between IGF-1R and other cell surface and nuclear receptors including epidermal growth factor receptor (EGFR), platelet-derived growth factor receptor α (PDGFRα), Src and ER [130–136]. Preclinical studies implicate RTKs such as EGFR, HER2, PDGFRα and cMET in adaptive resistance to IGF-1R inhibition [133,137,138]. In particular, it is well-recognized that EGFR and IGF-1R are capable of providing reciprocal compensation, via receptor upregulation, enhanced PI3K-AKT signalling, and altered function of cell cycle regulators, patterns of chromatin modification and gene expression [55,87,130,139,140]. This recognition prompted trials of combined IGF-1R:EGFR inhibition, alone or with standard cancer treatments. Phase 1 evaluation suggests that such combinations are tolerable, with evidence of activity in non-adenocarcinoma NSCLC [61]. However, outcomes were not improved by the addition of IGF-1R antibodies ganitumab to EGFR antibody panitumumab in colorectal cancer, or cixutumumab to EGFR TKI erlotinib with gemcitabine in unselected patients with pancreatic cancer [67,73]. This and other IGF-1R:EGFR combination trials, such as the Phase 2 NSCLC trials of linsitinib and erlotinib (NCT01221077, NCT01186861) have been conducted in erlotinib naïve patients, whereas the ability of IGF-1R to mediate resistance to EGFR inhibition was identified preclinically in NSCLC cells induced to be erlotinib resistant [130]. Due to the paucity of trials that have to date incorporated post-treatment biopsies, it is unclear to what extent the mechanisms identified preclinically contribute to clinical resistance to IGF targeted therapy.

Components of downstream signalling pathways may also modulate response to IGF-1R inhibition [141]. While anti-IGF-1R antibodies down-regulate IGF-1R and inhibit activation of AKT, S6 and ERKs, at least acutely, it is recognized that AKT can be reactivated despite sustained IGF-1R down-regulation, leading to tumor progression [52,142]. Thus there is interest in combining IGF-1R inhibition with small molecule inhibitors of the PI3K/AKT pathway [143]. Given the redundancy in RTK signalling cascades, a logical therapeutic strategy would be to target the points at which these pathways converge. Inhibition of the mTOR complex 1 (mTORC1) by rapamycin and rapalogues everolimus and temsirolimus has been found to activate PI3K-Akt via a pro-oncogenic feedback loop that can be suppressed by IGF-1R blockade [21,144,145]. This could be an effective approach in tumors that harbor mutant LKB, in which expression of IGF axis components is upregulated [146],

and in sarcomas where RPS6 has been shown to mediate resistance to IGF-1R inhibition [104]. Indeed, anti-tumor effects have been observed preclinically using rapamycin with figitumumab, ganitumab or ligand antibody BI 836845 in sarcoma models [21,147,148]. This strategy is being explored in clinical trials including NCT00927966, NCT00678769, NCT01016015, with promising evidence of durable disease control in metastatic adrenocortical cancers and sarcomas including EWS [70,72,149,150], findings that clearly merit further follow-up. IGFs regulate cell cycle progression by influencing the activity of cyclin-dependent kinases (CDKs), and IGF-1R inhibition has been shown to synergize with CDK4/6 inhibition in models of pancreatic ductal carcinoma and dedifferentiated liposarcoma [151,152].

Cross-talk between IGF and endocrine pathways has prompted clinical trials of IGF-1R inhibition with hormone therapy in breast and prostate cancer. IGF-1R was identified in a kinome-wide screen as a key mediator of resistance to endocrine therapy in hormone receptor positive breast cancer [153], but outcomes were not improved in this patient population by addition of ganitumab to the aromatase inhibitor exemestane or ER antagonist fulvestrant [154]. An earlier trial using figitumumab had similarly found no overall benefit from addition to exemestane, but a possible responsive subgroup based on glycemic control, with HbA1c <5.7% [155]. Additional preclinical data suggest that complete blockade of IGF signalling through IGF-1R and InsR A isoform is required for reversing resistance to endocrine therapy in ER+ breast cancer [156]. An ongoing study of BMS-754807 alone or with letrozole (a non-steroidal aromatase inhibitor) in patients with metastatic breast cancer is collecting post-treatment biopsies to evaluate potential mechanisms of resistance (NCT01225172). TNBC may also be an appropriate focus for this approach, given the adverse prognostic significance of IGF-1R expression in TNBC, and the sensitivity of TNBC cells to IGFs and IGF-1R inhibition [117,157,158]. In prostate cancer, preclinical data indicate that IGF-1R antibody cixutumumab caused significant delay in development of androgen resistance, and early trial results suggested benefit from IGF-1R blockade in men with this disease [93,159]. These data have prompted two neoadjuvant trials: figitumumab monotherapy [160], and cixutumumab with endocrine therapy (bicalutamide and goserelin) prior to radical prostatectomy [161].

Clinical trials combining IGF-1R inhibitory drugs with chemotherapy

The addition of IGF-1R inhibition to chemotherapy is supported by preclinical evidence that IGF-1R protects tumor cells from killing by cytotoxic drugs [68,162]. Further mechanisms that may be relevant include the ability of IGF-1R inhibition to suppress chemotherapy-induced IGF-1R activation and DNA damage repair [107,112,163–165]. Phase 1 trials suggested that IGF-1R inhibition is tolerable with chemotherapy, with evidence of clinical activity in heavily pre-treated patients [71,74,75,166–170]. The first reported Phase 2 trial with chemotherapy tested effects of figitumumab with paclitaxel and carboplatin in NSCLC. The initial results generated considerable enthusiasm when the trial found highly significant benefit in terms of objective responses and progression-free survival (PFS, hazard ratio 0.56) for patients receiving the higher dose of figitumumab [59]. However, it was subsequently determined that a substantial number of responses proved to be unconfirmed by RECIST criteria, and a later retraction stated that the differences in response rates were

more modest, and without PFS prolongation [171]. Meanwhile, this trial had prompted a Phase 3 study that was prematurely discontinued after interim analysis favoured the paclitaxel/carboplatin only arm [172]. Unfortunately this pattern has been repeated, with failed trials being followed by subgroup analysis characterizing responsive patients. IGF-1R antibody ganitumab showed a trend to improved 6 month and overall survival when combined with gemcitabine in a Phase 2 trial in patients with pancreatic cancer [173]. This led to the Phase 3 GAMMA trial (NCT01231347) in unselected pancreatic cancer patients that was terminated prematurely due to lack of benefit [76]. Subsequently, as highlighted in the previous section, biomarker studies suggested that analysis of circulating IGFs and IGFBPs may identify subsets of ganitumab-responsive patients [82]. Two trials have evaluated addition of IGF-1R antibody to irinotecan-containing combination therapy in colorectal cancer: ganitumab with FOLFIRI chemotherapy in KRAS mutant cancers refractory to fluoropyrimidine- and oxaliplatin-based chemotherapy [114], and dalotuzumab with EGFR inhibitor cetuximab in chemorefractory KRAS wild-type or mutant cancers [64]. The latter suggested that addition of dalotuzumab actually worsened progression-free and overall survival. However, subsequent molecular analysis identified differential IGF expression and mesenchymal phenotype as potential markers of benefit from dalotuzumab [65,112]. It may also be relevant that these trials involved sustained antibody-mediated IGF-1R blockade, which could protect tumor cells from the toxicity of phase-specific cytotoxic drugs. Consistent with the concept that effects of IGF-1R inhibition on DNA repair play a major role in chemosensitization, no clinical activity has been seen in trials combining IGF-1R antibodies with taxanes, which do not damage DNA [174,175]. Furthermore, preclinical data suggest that the most effective inhibition of tumorigenesis occurs when the anti-IGF-1R agent is applied after DNA-damaging chemotherapy [176,177], which was not the design employed in the failed trials. These findings suggest that greater emphasis should be placed on the class of cytotoxic drug(s) with which IGF-1R agents are combined, and the scheduling of IGF-1R inhibition with chemotherapy; this will be more readily achieved using IGF-1R TKIs or short-half-life antibody therapeutics. Scheduling appears not to be critical for combination with radiation therapy, which causes DNA damage in all phases of the cell cycle, and to which IGF-1R inhibitory drugs have been shown to sensitize in head and neck, prostate and lung cancers [53,69,107,178], although this approach has not been tested clinically.

Conclusion

While many studies have not yet reported results, IGF-1R inhibitory antibodies and TKIs have not to date demonstrated significant benefit in unselected patients recruited to Phase 2/3 trials. This may be due, at least in part, to the lack of robust predictive biomarkers. Following the initial transition from bench to bedside, there is a clear need to look critically at the preclinical evidence, so that new trials are conducted in tumors with the appropriate molecular context. For example, IGF-1R inhibitory drugs may be more appropriately tested in triple negative rather than hormone receptor positive breast cancers [117,154,157,158], and in KRAS-mutant rather than wild-type colorectal and lung cancers [65,115]. Completed IGF-1R trials represent an opportunity to investigate the characteristics of responding and resistant subgroups, provided tumor tissue was collected. This in turn requires trial consents

to be written with sufficiently broad scope to allow future translational research, so that newly identified biomarkers can be tested, and if validated, incorporated into future studies. There is as yet little consistent evidence regarding candidate tissue biomarkers for response to IGF-1R antibodies and TKIs, and it is not clear at this stage whether the same parameters will influence sensitivity to IGF ligand antibodies, which are still at a relatively early stage of development. However, enough trials have highlighted the association between response to IGF-1R inhibition and circulating IGFs, IGFBPs, and indicators of glycemic control [63,80–82,86,87,155] to support inclusion of these parameters in future trials of agents that remain under active investigation, for example [21,22,51,165]. Even amongst the failed trials, there are subsets of patients who have obtained durable benefit from IGF-1R inhibition. The challenge is to identify and characterize those patients, and use that information to increase the efficacy of this approach in cancer therapy.

Acknowledgments

The authors' work is supported by NIHR Oxford Biomedical Research Centre, Prostate Cancer UK, Breast Cancer Campaign, Rosetrees Trust, UCARE-Oxford, Cancer Research UK (VMM), and by United States National Institutes of Health Grant CA136393, Mayo Clinic SPORE in Ovarian Cancer and the CA116201 Mayo Clinic Breast SPORE (PH).

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Table 1

Candidate biomarkers of sensitivity to IGF-1R inhibitory drugs. PC, preclinical; CT, clinical trial; WT, wild-type; SCLC, small cell lung cancer; NSCLC, non-small cell lung cancer; EWS, Ewing sarcoma; NET, neuroendocrine tumor; ER, estrogen receptor; MAb, monoclonal antibody; TKI, tyrosine kinase inhibitor.

	Candidate biomarker of sensitivity	Preclinical/clinical	Tumor type	Anti-IGF-1R strategy	Ref.
Tumor expression of IGF axis components	High IGF-1R expression	PC – cell lines, xenografts	Rhabdomyosarcoma	MAb h7C10	[52]
	High expression of IGF-1R, IRS-1, IRS-2	PC – cell lines	Breast, colorectal	MAb h10H5	[87]
	IGF-1R upregulation, increased gene copy number	PC – cell lines	NSCLC	MAb R1507	[91]
	Circulating tumor cell (CTC) IGF-1R expression	Phase 1 CT	Hormone refractory prostate	MAb figitumumab	[93]
	IGF gene signature	PC – cell lines, xenografts	Triple negative breast	TKI BMS-754807	[117]
	Nuclear IGF-1R localisation	Single-centre – tumor samples	Soft tissue, EWS, osteosarcoma	MAb, various	[101]
	IGF-1R/IR heterodimerization, N-linked glycosylation	PC – cell lines, xenografts	Gastric, hepatocellular	MAb figitumumab	[96]
	High tumor expression of IGF-1, low IGF-2	Phase 2/3 CT	Metastatic colorectal (WT KRAS)	MAb dalotuzumab	[65]
	IRS-2 amplification, low IGFBP-5 expression	PC – cell lines	SCLC, NSCLC, breast, colorectal	MAb figitumumab	[86]
	Low IGFBP-5/IGFBP-4 ratio	PC – cell lines, tumor cohorts	Breast	TKI BMS-536924	[89]
	High tumour IGF-1 expression	Phase 2 CT	Advanced pancreatic	MAb dalotuzumab	[90]
	High IGF-1R gene copy number, pathway expression	PC – cell lines	Colorectal	TKI linsitinib	[105]
	High IGF-1, IGF-2, IGF-1R, low IGFBP-3 and -6	PC – cell lines	Various sarcoma, neuroblastoma	TKI BMS-536924	[92]
Host factors	High pre-treatment circulating free IGF-1	Phase 2 CT	NSCLC	MAb figitumumab	[79]
	High pre-treatment circulating free IGF-1	Phase 1/2 CT	NSCLC	MAb cixutumumab	[63]
	High pre-treatment circulating free IGF-1	Phase 1 CT	NSCLC	MAb figitumumab	[80]
	High baseline IGF-1, IGF-2 & IGFBP-3, low IGFBP-2	Phase 2 CT	Metastatic pancreatic	MAb ganitumab	[82]
	High pre-treatment circulating free IGF-1	Phase 2 CT	NSCLC	MAb R1507	[81]

	Candidate biomarker of sensitivity	Preclinical/clinical	Tumor type	Anti-IGF-1R strategy	Ref.
	HbA1c <5.7%	Phase 2 CT	ER-positive breast	MAb figitumumab	[155]
Compensatory signalling by alternative kinases	Low level of EGFR pathway activation	PC – cell lines	Various sarcoma & neuroblastoma	TKI BMS-536924	[92]
	Low HER2 expression, high AKT	PC – cell lines	HER2 positive breast	TKIs BMS-536924, NVP-AEW541	[94]
	Low level of PDGFRα pathway activation	PC – cell lines	Rhabdomyosarcoma	TKI BMS-754807	[133]
	Low insulin receptor expression	PC – cell lines, transgenic mice	Pancreatic NETs, breast cancer cells	MAb cixutumumab	[124]
Downstream molecules	RAS/MAPK activity reduced by IGF-1R targeting	PC – cell lines	Oesophageal	TKI NVP-AEW541	[109]
	Tumour expression of WT EGFR and K-RAS	PC – cell lines	NSCLC	TKIs PQIP, linsitinib	[113]
	Mutant K-RAS	PC – cell lines	NSCLC	TKIs, various	[115]
	Mutant K-RAS	Phase 2 CT	NSCLC	MAb R1507	[81]
	WT K-RAS	PC – cell lines	Colorectal	TKI linsitinib	[105]
	WT PTEN	PC – cell lines	Prostate	TKI NVP-AEW541	[106]
	Low baseline ERK phosphorylation	PC – cell lines, xenografts	SCLC	TKI linsitinib	[111]
	High IRS-1 expression	PC – cell lines	Breast	TKI NVP-AEW541	[88]
Cellular phenotype	Mesenchymal phenotype	Phase 2/3 CT	Metastatic colorectal (WT KRAS)	MAb dalotuzumab	[65]
Screens for resistance/sensitivity mediators	RPS6, MST1R	PC – cell lines	Ewing family	TKI BMS-536924	[104]
	MYB amplification	PC – cell lines	SCLC, NSCLC, breast, colorectal	MAb figitumumab	[86]
	k-TSP classifier gene pair expression	PC – cell lines	Colorectal	TKI linsitinib	[105]
	Insulin, MAPK, endocytic pathway gene expression	PC – cell lines	Ewing's sarcoma	figitumumab, AVE-1642, NVP-AEW541	[118]
	CDK4/6	PC – cell lines	Dedifferentiated liposarcoma	MAb R1507	[152]
Imaging	Uptake of indium-111-labelled R1507	PC – xenografts	Osteosarcoma	MAb R1507	[54]