The insulin-like growth factor system and its receptors: A potential novel anticancer target

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Abstract: The current generation of novel anticancer therapies that are in preclinical and clinical development are based on exploiting our increasing understanding of the molecular and cellular basis of cancer development and progression. Accelerated rates of cell division and proliferation have been postulated to predispose to the development of malignant disease. The insulin-like growth factor (IGF) signaling system has an important physiological role in regulating cellular proliferation and apoptosis. This function has led to considerable interest in its relevance to neoplasia over the last decade. In this review, we give an overview of the IGF system physiology, discuss the epidemiological significance of IGF signaling and neoplasia, and review the preclinical and clinical studies in targeting IGF receptors as cancer therapies.

Keywords: insulin, growth factor, IGF-1, clinical trials

Insulin-like growth factor system physiology
Childhood growth in both humans and mice has been closely linked to the insulin-like growth factor (IGF) system (Liu et al 1993; Pollak et al 2004). It is largely constituted by two ligands (IGF1 and IGFII) which interact with two receptors, IGF receptors I and II (IGFIR and IGFIIIR). The complexity of the network has been significantly underlined by the identification of at least 6 IGF-binding proteins (IGFBPs), for which the functional characteristics have yet to be fully defined (LeRoith et al 2003). The presence of hybrid receptors between IGFIR and the insulin receptor (IR) has also been described (Federici et al 1997). Several proteins downstream of IGFIR have been identified, including TOR, the insulin-receptor substrate (IRS) family, AKT, MAP kinase, and S6 kinase (Pollak et al 2004). The ultimate targets of these kinase cascades are members of the Ets and forkhead transcription factor families, the regulation of which provide a mechanism by which the IGF system can elicit changes in gene expression that eventually mediate their effects on cellular proliferation and apoptosis (LeRoith et al 1995).

IGF1 is largely produced in the liver and the upregulation of IGF1 gene expression is stimulated by growth hormone (GH). It is also synthesized in extrahepatic sites (Jones et al 1995). It acts (along with IGFII) as a ligand for IGFIR, a cell-surface tyrosine kinase signaling molecule, which is highly related to the IR. It is a potent mitogen for a wide variety of cells and exerts its action by increasing DNA synthesis and by stimulating the expression of cyclin D1, which accelerates the cell cycle from G1 to S phase (Furlanetto et al 1994; Dufourny et al 1997). It also inhibits apoptosis by stimulating expression of Bcl proteins and suppressing expression of Bax (Minshall et al 1997; Parrizas et al 1997). On activation by its ligands, IGFIR phosphorylates the downstream targets mentioned above (Pollak et al 2004). Physiological activation of IGFIR and its hybrid receptors by overexpression alone is not seen, and thus, unlike with the epidermal growth factor (EGF) receptor family, activation of IGFIR requires
IGF and cancer: epidemiology studies

There are a myriad of epidemiologic studies which have investigated the IGF system and its specific relationship with different cancer types. The results of such studies demonstrate that it is difficult to identify individuals at risk of specific cancers by analysis of serum levels of the IGF system alone. Moreover, plasma levels of IGFI cannot be assumed to reflect IGF signaling given the potential for both autocrine and paracrine activation of IGFIIR. Most positive epidemiologic studies demonstrate a fairly modest increased risk of malignancy with high plasma IGFI levels. However chronic exposure to a modest risk factor may be more relevant to cancer development than infrequent exposure to a strong risk factor (Pollak et al 2004).

Prostate cancer is the malignancy that has been most studied in terms of an epidemiologic association with the IGF system. The results have been conflicting. However, the general consensus is that prospective case control studies have fairly consistently demonstrated a correlation between serum IGFI levels and prostate cancer risk. The strongest association applies to young men, with a four-fold increase in risk described for the highest compared to the lowest levels of IGFI in men under 59 years (Stattin et al 2004).

It has also been well documented that circulating IGFI levels are positively correlated with premenopausal (but not postmenopausal) breast cancer (Hankinson et al 1998). Other studies also have supported a positive correlation between breast cancer risk in general and IGFI levels (Peyrat et al 1993; Vadgama et al 1999), although no difference exists between cases and case controls in some studies (Favoni et al 1995). Nevertheless there does seem to be a positive association between circulating IGFI levels and mammographic density (Maskarinec et al 2003), which in itself is strongly associated with breast cancer risk (Boyd et al 2002). In colon cancer, conflicting results exist with regards to a potential association, but most studies suggested that both IGFI and IGFII plasma levels were positively correlated with cancer risk compared to controls (El Atiq et al 1994; Ma et al 1999; Palmqvist et al 2002).

Risk factor studies

Insulin and the IGF system constitute a common physiological basis for many well-defined malignancy risk factors described on an epidemiologic level, including raised body mass index (BMI), high calorie intake, higher birthweight, and lack of exercise.

The Million Women Study offers the most robust epidemiologic support for a strong association between BMI and cancer risk (Reeves et al 2007). A higher BMI was associated with a significant increase in the risk of cancer for 10 out of 17 specific cancer types examined. Among postmenopausal women in the UK, 5% of all cancers were attributable to being overweight or obese. For endometrial cancer and adenocarcinoma of the oesophagus, BMI represented a major modifiable risk factor; about half of all cases in postmenopausal women are attributable to overweight or obesity. Obesity has also been implicated in
causing up to a 20% increase in breast cancer risk in those with a BMI over 30, with a 20% increase in risk of metastasis for women who have already been diagnosed with breast cancer (Freudenheim et al 1996).

Many studies have indicated that dietary control and reduced calorie intake may have a protective effect against cancer. Increased levels of IGFI have been associated with both high levels of energy intake and high dairy intake (Giovanucci et al 2003). Prostate cancer risk, in turn, has been associated with both increased IGFI levels and increased dairy intake, leading to speculation that we may in future be able to identify individuals at high risk who may benefit from dietary restriction (Chan et al 2001; Pollak 2001). It has also been shown that intake of vegetables appears to decrease premenopausal breast cancer risk, with no isolated dietary factor explaining this effect (Freudenheim et al 1996). It is of interest that protection against carcinogenesis has been demonstrated by starvation and subsequently reversed by infusion of IGFI, suggesting a mediating role for IGFI in the protective effect of diet on carcinogenesis (Dunn et al 1997).

IGFI is very strongly associated with prenatal growth in particular. There are suggestions that high birthweight is positively associated with the risk of developing various cancer types including colorectal and prostate (Tibblin et al 1995; Sandhu et al 2002). Two large prospective cohorts have also demonstrated that high birthweight is a risk factor for premenopausal breast cancer (Michels et al 2006). An individual’s height has also been shown to contribute to a modest increase in cancer risk (Engeland et al 2003; Lawlor et al 2003), although it has not been shown to have an association with plasma IGFI levels (Landin-Wilhelmsen et al 1994).

Regular physical activity whilst healthy can lead to up to a 20% reduction in risk of breast cancer later in life (Bernstein et al 2005). Furthermore, exercise after a breast cancer diagnosis has been strongly linked to improved quality of life and mortality risk reduction of up to 6% in those who perform the most physical activity (Holmes et al 2005). There has however been no consistent demonstration that an association exists between IGFI levels and physical activity (Landin-Wilhelmsen et al 1994; Rudman and Mattson 1994).

**IGF system pathophysiology**

**IGFI and IGFIIR**

IGFIIR activation has been shown to induce proliferation and metastasis of cancer cells *in vitro*. This occurs either as an endocrine response to high levels of circulating IGFI or in response to autocrine production by tumor cells (Khandwala et al 2000). Pollak and colleagues (2004) speculated that, although there is evidence that experimental IGFI-positive cancers respond to fluctuating levels of IGFI, some malignancies probably respond to IGFI or IGFIIR produced in an autocrine or paracrine manner. This hypothesis would be consistent with the observation that IGFIIR mRNA expression was decreased in prostate cancer tissue compared with normal prostate tissue, suggesting a role for chronic stimulation by an autocrine loop (Tennant et al 1996). Such a variation in IGFIIR activation would imply that the efficacy of any treatment methods aimed to inhibit IGFIIR signaling would not be reflected by serum IGFI levels (Pollak et al 2004).

Several *in vivo* laboratory models of carcinogenesis have consolidated the purported relationship between the IGFI system and malignancy seen in epidemiologic research. Transgenic mice overexpressing human IGFI in basal epithelial prostate cells showed a 50% rate of prostate neoplasia by the age of 6 months (DiGiovanni et al 2000). In contrast, the incidence of prostate cancer is markedly reduced in IGFI-deficient mice (Majeed et al 2003). IGFI gene-deleted mice, which have 25% of the circulating IGFI observed in normal mice, have also been used to study breast cancer development. Following carcinogen exposure, approximately 30% of IGFI-deficient mice developed mammary tumors, compared to 60% of normal mice (Wu et al 2003). Transgenic mice that overexpress growth hormone (GH) and consequently have higher circulating levels of IGFI, also develop mammary tumors at higher frequency (Tornell et al 1991). In contrast, hepatic carcinogenesis is attenuated in mice with diminished IGFIIR signaling (Lu and Archer 2003).

In addition to involvement in carcinogenesis, it has also been proposed that IGFI has a significant role in the development of metastases. Overexpression of the IGFIIR in certain malignancies has been shown to be associated with aggressive behavior (Xie et al 1999). Evidence consistent with this includes the discovery that IGFI can upregulate VEGF gene expression and stimulate angiogenesis in a breast cancer cell line (Oh et al 2002). IGFI stimulation has also been shown to activate motility and migration of melanoma and neuroblastoma cancer cell lines (Meyer et al 2001; Satyamoorthy et al 2002).

**IGFII and IGFIIR**

IGFII is also implicated in malignancy. It has similar mitogenic and antiapoptotic mechanisms to IGFI, thereby also contributing to cell proliferation. Loss of genomic imprinting in the IGFII gene is often seen in malignancy.
(Jarrard et al 1995; Oda et al 1997), and it is the gene most overexpressed in colorectal cancer cells (Zhang et al 1997). IGFII transgenic mice have a higher incidence of hepatocellular carcinoma and lymphoma, as well as several other tumors, compared to controls after 18 months of age (Rogler et al 1994). IGFII has also been observed to have higher levels of expression in cancer cells with a strong tendency to metastasize (Guerra et al 1996).

The IGFII receptor has no tyrosine kinase activity and therefore does not transduce any signals when binding to IGFII. It is therefore postulated to function as a tumor-suppressor (or ‘sink’), exerting its influence through its affinity for IGFII which would otherwise activate the IGFIR (Oates et al 1998). Loss of IGFIIIR has been demonstrated in cancer and is correlated with increased IGFIR activation (MacDonald et al 1998).

**Targeting the IGF system: preclinical development**

Three components of the IGF system have been identified as potential targets for inhibiting its mitogenic and antiapoptotic properties: IGFIR regulators and ligands, the IGFIR itself, and downstream signaling pathways such as AKT and TOR (Figure 1).

**IGFIR regulators and ligands**

One potential upstream target in the IGF pathway is GH. Disrupting its action with the use of therapeutics such as somatostatin analogues (for example, octreotide) or GH releasing hormone antagonists has shown both anticancer efficacy in preclinical models and a reduction in plasma IGF1 levels (Pollak and Schally 1998; Letsch et al 2003). However, the results of clinical trials with these agents has been generally disappointing. This may be because GH has no effect on IGFII, which may be upregulated in response to diminished IGF1-induced IGFIR signaling. IGFII is not expressed in adult mice (DeChiara et al 1991), and it has therefore not yet been possible to model the approach of targeting the IGF system regulators and ligands in vivo accurately.

Agents generated to interfere directly with IGF1, IGFII, or the IGFBPs may represent an alternative mechanism for

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**Figure 1** Overview of initial IGFIR and IGFIIIR receptor activation and downstream signalling. Main opportunities for possible pharmacological intervention targeted towards IGFIR are also indicated. Pharmacological intervention against downstream signalling pathways such as AKT and TOC have been extensively reviewed elsewhere. IGFIIIR has no kinase domain and appears to act as a sink, preventing IGFII binding and activation of IGFIR.

**Abbreviations:** IGFIR, Insulin growth factor receptor I; IGFIIIR, Insulin growth factor receptor II; IGF1, insulin growth factor I; IGFII, insulin growth factor II; IRSI, insulin receptor substrate I; TOR, phosphoinositide-3-Kinase; PI3 K, target-of-rapamycin.
inducing anticancer activity. One recent exciting example of this possible therapeutic intervention involves curcumin, an agent with anticarcinogenic and chemo-preventive properties found in high levels in turmeric. This agent has shown an ability to down-regulate the IGF1 axis in MCF-7 cell lines (Xia et al 2007). The purported mechanism for this effect is increased sequestration of IGF ligands by IGFBP3, rendering IGF1 unavailable for binding to and activation of IGFR. Moreover, curcumin in combination with 5FU/oxaliplatin chemotherapy in vitro produced greater inhibition of growth and stimulation of apoptosis in colon cancer cells compared to 5FU/oxaliplatin alone (Patel et al 2008).

**IGFIR**

Monoclonal antibodies currently constitute the majority of agents that have been developed to target IGFIR, and were the first agents that target IGFIR to enter clinical trials. Several antibodies directed against IGFIR have been developed and have shown a common anticancer mechanism of IGFIR down-regulation (Li et al 2000; Burtrum et al 2003; Maloney et al 2003). CP-751,871 is a fully human IgG2 antibody with high affinity for human IGF-1R, which has now entered human clinical trials (see below). It has been shown in preclinical studies to block binding of IGF1 to IGFR, IGF1-induced receptor autophosphorylation, and induce the downregulation of IGFIR in vitro and in tumor xenografts. It has also demonstrated significant antitumor activity both as a single agent and in combination with adriamycin, 5-fluorouracil, or tamoxifen in multiple tumor models (Cohen et al 2005). Sachdev and colleagues (2003) examined in vitro and in vivo mechanisms of the monoclonal antibody, scFv-Fc, on MCF-7 breast cancer cells, and proposed that it potentially downregulates the IGFR via the endosomal endocytic pathway. It was also noted that, aside from blocking IGFR activation, scFv-Fc appeared to have direct antitumor properties, possibly by altering the distribution of cell cycle components. Another fully human antibody that targets IGFR, IMC-A12, has shown antitumor effects in a number of cancers in vivo (breast, renal, pancreatic, multiple myeloma) by inducing IGFR internalization and degradation, resulting in a significant reduction in cell surface receptor density (Rowinsky et al 2007; Wu et al 2007).

Small molecule tyrosine kinase inhibitors of IGFIR have also been developed and recently entered human clinical trials. Potent antitumor effects of small molecule inhibitors have been demonstrated in preclinical studies for a variety of cancer types. Activity of the tyrosine kinase inhibitor, NVP-ADW742, has been demonstrated against multi-drug resistant multiple myeloma cell lines (Mitsiades et al 2004). In vivo, the orally bioavailable compound, NVP-AEW541, inhibited IGFR signaling in tumor xenografts and significantly reduced the growth of IGFIR-driven fibrosarcomas (Garcia-Echeverria et al 2004). Another recent study utilized an alternative IGFR kinase inhibitor, PQIP, for once daily oral administration, and showed robust antitumor efficacy in colorectal cancer xenografts which was correlated with the degree and duration of inhibition of tumor IGFR phosphorylation by the compound (Ji et al 2007). Moreover, a novel class of IGFR/IR receptor inhibitors have also shown potential clinical application with their antiproliferative and proapoptotic activity leading to significant inhibition of the growth in vivo (Haluska et al 2006). One potential concern regarding inhibition of IGFR tyrosine kinase is the close homology of IGFR to the IR, and the possibility of drug-induced hyperglycemia. However, early results in clinical trials have so far been favorable with regard to potential detrimental effects on glucose metabolism (see below).

The use of dominant-negative IGFR is an alternative therapeutic strategy which is at an earlier stage of preclinical development, but has also shown promise. The development of metastases from breast cancer cells has been shown to be inhibited by a truncated dominant-negative IGFR. By transfecting a dominant-negative form of IGFR into metastatic breast cancer cell lines, Dunn and colleagues (1998) showed that metastases were significantly decreased, although this method did not significantly suppress primary tumor growth. These findings were supported by an in vivo study of colon cancer which showed decreased tumor growth, cell proliferation, and vascular endothelial growth factor (VEGF) expression in nude mice who were transfected with an alternative truncated dominant-negative form of IGFR (Reinmuth et al 2002). Moreover, tumor formation and metastatic abilities were reduced and survival increased with the use of this method in vivo in Ewing’s sarcoma cells (Scotlandi et al 2002).

Antisense RNA and gene disruption also constitute preclinical strategies with early success. Reduction in IGFR expression, cancer cell growth, and proliferation have been shown in vivo with the use of this method (Sell et al 1994; Bohula et al 2003). Chernicky and colleagues (2000) also demonstrated in vivo efficacy of this method in mammary tumors: injection of IGFR antisense RNA into nude mice led to both a delay in tumor formation and a dramatic reduction in tumor size. As with the studies examining dominant-negative IGFR, the studies looking at antisense RNA as a therapeutic
strategy have suggested that IGFIR particularly plays a role in progression and metastasis of cancer.

**Downstream targets**

Downstream proteins in the IGF system such as AKT, TOR, or MAP kinase represent alternative targets for inhibition of IGFIR signaling, and may not be associated with compensatory mechanisms for decreased IGFIR signaling which could exist further upstream. The rationale for such ‘cross-talk’ further upstream is validated by the observations that resistance to HER2 inhibition is associated with increased IGFIR signaling (Nahta et al 2005), and also that suppression of IGFIR signaling led to inhibition of non-small cell lung cancer proliferation by gefitinib (Morgillo et al 2007). A number of agents which target these downstream proteins are in preclinical and clinical development and have been extensively reviewed elsewhere.

**Targeting the IGF system: clinical development**

All the clinical trials that have been published to date have involved strategies aimed at blocking the IGFIR. Targeting IGFIR represents a conceptually different therapeutic approach compared to the rationale employed for the use of some other biological treatments, such as imatinib, which acts on single molecular targets that are unique or overexpressed in tumor cells compared to normal cells. Although the IGF system is expressed in a wide range of malignancies, it is also expressed ubiquitously in normal human tissue. Thus it is likely that agents which target IGFIR will have a therapeutic window with the optimal dose being that which inhibits IGFIR function that sustains tumor cell growth without compromising survival of normal cells. Currently there is relatively little clinical data arising from the large body of preclinical research in this area. Published literature (mostly abstracts) on clinical trials of IGFIR inhibitors have begun to emerge during recent years, and it is likely that mature clinical data will continue to emerge for these studies in the near future. Almost all of the published clinical information arises from early phase clinical trials. These trials utilize IGF1R inhibitors either as monotherapy or as part of combination therapy regimens. Clinical studies with somatostatin analogues, AkT, TOR, and MAP kinase inhibitors have been extensively reviewed elsewhere. In this section, we focus on the emerging clinical studies with IGFIR inhibitors.

**IGFIR inhibitors: Single agent studies**

Three phase I studies of monoclonal antibodies targeted against IGF1R have been published (Lacy et al 2006; Haluska et al 2007; Higano et al 2007). CP-751,871 is a fully human IgG_2_ monoclonal antibody (mAb) antagonist of IGF-1R used in two of the studies (Lacy et al 2006; Haluska et al 2007). The other trial studied IMC-A12, a fully human IgG_1_ mAb also directed against IGF-1R (Higano et al 2007).

**Toxicity analyses**

Safety and tolerability has to date been favorable with the use of these agents in phase I studies. One of the phase I studies of CP-751,871 did not define the maximum tolerated dose (MTD) of CP-751,871 as it exceeded the maximum feasible dose (MFD) of 20 mg/kg (Haluska et al 2007). There were no treatment-related toxicities greater than NCI-CTC grade 3 observed in this study. One grade 3 episode of fatigue and arthralgia occurred at the maximal dose administered. Grades I/II toxicities included hyperglycemia, anorexia, elevated AST/GGT, diarrhoea, hyperuricemia, and fatigue. Two patients received at least 16 three-weekly cycles without demonstrating evidence of cumulative toxicity, and patients were able to tolerate repeated cycles of CP-751,871 at doses several orders of magnitude above the minimal biologically effective concentration (Cohen et al 2005).

These toxicity findings were consistent with the observation from two other monotherapy studies of IGFIR antibodies (Lacy et al 2006; Higano et al 2007). No dose-limiting toxicities (DLTs) were reported in the phase I study of CP-751,871 in patients with advanced multiple myeloma (MM). One DLT (grade 3 hyperglycemia) was observed in the phase I study of IMC-A12, but otherwise toxicities were again limited to grade 1 (pruritis, rash, discolored feces) and grade 2 (anemia, psoriasis, hyperglycemia, infusion-related reaction) levels despite a more intensive weekly dosing regimen with this IGFIR inhibitor.

Prior to clinical evaluation, hyperglycemia was considered to be the likely drug-related toxicity in clinical trials, and certainly it is the most common laboratory related abnormality from current evidence (albeit nearly all at grade 1 or 2 level). However, at a preclinical level, it was anticipated that monoclonal antibodies were specific enough to avoid inhibition of the IR despite its extensive homology with IGFIR. Furthermore, Haluska and colleagues (2007) established that the C_{max} with repeated dosing of CP-751,871 in their trial was less than a third of what earlier investigation had shown to be the concentration necessary for binding to the IR (Cohen et al 2005; Haluska et al 2007).
The above data has therefore led to an alternative hypothesis which does not attribute raised glucose levels to IR-binding by IGFIR inhibitors. Alternatively it has been suggested that IGF1 has an important role in regulation of glucose homeostasis, whereby inhibition of its ligand action on IGFIR could lead to hyperglycemia. Data consistent with this theory includes the finding that IGF1 administered to humans results in hypoglycemia (Guler et al 1987; Schmitz et al 1991), as well as the knowledge that recombinant IGF1 has been shown to improve glucose control in type II diabetics by increasing insulin sensitivity (Moses et al 1996). This potential shift in conception of the causality of hyperglycemia could have significant implications in the long-term for use of monoclonal antibodies over small molecule tyrosine kinase inhibitors in the targeting of IGFIR, as the main purported advantage of immunological treatments is that they are more specific to the IGFIR. Small molecule inhibitors already have the advantage of being available as a convenient oral therapy. Furthermore, there is a body of preclinical evidence that suggests IR (as well as IGFIR) potentially has a role in carcinogenesis itself, thereby suggesting that CP-751,871 does not reach appropriate pharmacologic concentrations to achieve an optimal anticancer effect on human insulin receptors.

An interesting observation in the endocrine analysis of three-weekly administration of CP-751,871 is that insulin levels cumulatively increased in patients who received prolonged administration. This was therefore proposed as a potential compensatory mechanism for control of hyperglycemia caused by IGF1 inactivation (Haluska et al 2007). Further endocrine studies are required in future clinical trials for further characterisation of all of the above findings.

**Clinical responses**

Although a secondary endpoint for phase I studies, encouraging clinical responses have been observed in preliminary data from studies of IGFIR inhibitors as single agents. Weekly administration of IMC-A12 induced stable disease in 2 of 11 patients for over 9 months at the time of reporting, with another three patients showing disease stability after their first 4-weekly cycle with dose escalation continuing (Higano et al 2007). Furthermore, there was 1 near complete response (CR) and 2 partial responses (PRs) seen in patients with MM treated with CP-751,871 in combination with dexamethasone (Lacy et al 2006). Haluska and colleagues (2007) reported that 7 of 12 patients with advanced solid tumors receiving CP-751,871 at 20 mg/kg had small reductions in measurable tumor size. Furthermore, two patients had prolonged disease stabilization for over 48 weeks. These findings are encouraging given the advanced refractory disease of patients who enter into early phase clinical trials.

**IGFIR inhibitors: combination therapy studies**

Synergy between biological treatments and chemotherapies is not necessarily easily predicted. Successes such as trastuzumab in combination with taxanes (Slamon et al 2001) are outweighed by other failed combination attempts (Herbst et al 2004). It has been suggested that IGFIR inhibitors may act in either way and this could be dependent on the strategy used: monoclonal antibody treatments are thought to potentially synergize with chemotherapy by lowering the apoptotic threshold of cancer cells, while it is speculated that tyrosine kinase inhibitors may interfere with the cell cycle specific effects of chemotherapy by blocking progression through to S-phase (Yee 2006).

Two trials involving IGFIR inhibitors in combination with chemotherapy have been reported. One phase I trial analyzed the combination of varying doses of CP-751,871 administered with docetaxel (75 mg/m2) at 3-weekly intervals in patients with advanced cancer (Attard et al 2006). Again the MTD had not been reached in this trial and toxicities experienced in patients were felt to be attributable to the chemotherapy. Only a transient grade 1 episode of hyperglycemia was noted, and this had occurred following steroid use prior to taxane administration. No cardiac toxicity was observed on serial echocardiograms. Response rates were again encouraging with 5 patients receiving CP-751,871 alone reported as having stable disease.

Phase II evidence has now begun to emerge with an interim analysis of paclitaxel and carboplatin with or without CP-751,871 in stage IIIb/IV NSCLC recently being reported (Karp et al 2007). Impressive response rates were observed in the 73 patients analysed, although more data with regard to toxicity emerged. The response rate was 46% in the IGFIR inhibitor group compared with 32% in the chemotherapy alone group, and it was noted in particular that 52% of the nonadenocarcinoma patients responded to treatment. Furthermore, a PR was observed in a patient who received single agent CP-751,871 following progression on chemotherapy alone. Hyperglycemia (20% vs 10%), fatigue (15% vs 8%), and neuropathy (10% vs 4%) were, however, found to be more prevalent in the IGFIR inhibitor group.

**Biological markers**

It is clear from this review that the IGF system has a role implicated in several cancer types including breast, prostate,
multiple myeloma, and sarcoma. However it is likely that different subtypes of patients with each of these cancers (for example, premenopausal breast cancer) may respond to IGFR1 blockade more than other subtypes. It is therefore of great importance to discover molecular markers that can predict a high probability of clinical benefit from such treatment. Studies performed of cells which are IGFR1 activated and yet lack a phenotypic response would suggest that this may not be straightforward (Yee 2006). Furthermore, as already discussed, IGF-related tumors are not necessarily associated with overexpression of IGFR1 (as is the case with HER2), and plasma levels of IGF1 and IGFII do not reflect IGFR1 activation given that autocrine and paracrine mechanisms are likely to be involved also.

The most interesting biomarker study reported so far details the detection of circulating tumor cells (CTCs) with CP-751,871 blockade of IGFR1 (de Bono et al 2007). IGFR1 expression is detectable by immunofluorescence on CTCs. CTCs were commonest in advanced hormone-refractory prostate cancer patients, with detectable IGFR1 expression on the CTCs showing an association with higher frequency of PSA declines by over 50%. However, it was not possible to establish a dose-effect relationship with only 33% of patients having detectable CTCs at initiation of treatment. This lack of sensitivity represents the main limitation of this technique as a biomarker, and therefore its current use appears to be most promising in patients with large tumor burdens.

**Future developments**

Several phase II trials involving IGFR1 inhibitors are now underway, the results of which are eagerly anticipated. Prostate cancer has been an area of particular interest. However, continuing research is also focused on trying to identify cancers at a biological level which might be susceptible to IGFR1 antibody therapy, with the further characterization and early clinical trial use of appropriate biomarkers of particular importance.

**Disclosure**

The authors report no conflicts of interest in this work.

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