

Emerging role of insulin-like growth factor receptor inhibitors in oncology: early clinical trial results and future directions

A Gualberto^{1,2} and M Pollak³

¹Clinical Department, Pfizer Oncology, New London, CT, USA; ²Department of Pathology, Brown University Alpert School of Medicine, Providence, RI, USA and ³Department of Oncology, McGill University, Montreal, Quebec, Canada

Preclinical evidence that targeting the insulin-like growth factor receptor (IGF-IR) is effective in cancer treatment has been accumulating for almost two decades. Efforts to develop drugs began in the late 1990s, and initial data from clinical trials were reported in 2006. The biological rationale for IGF-IR targeting has potential relevance to many tumor types, and early results have justified expanded programs to evaluate IGF-IR-targeting agents in many areas of clinical need. More than two dozen drug candidates have been developed and clinical trials are underway for at least 12 of these. Early clinical trials reveal an acceptable safety profile together with pharmacodynamic evidence that the receptor can be successfully targeted. It is premature to draw conclusions regarding efficacy, but well-documented instances of single-agent activity were noted during phase I evaluations, and recent evidence from a phase II study suggests that co-administration of an anti-IGF-IR antibody with chemotherapy for non-small-cell lung cancer improves objective response rate and progression-free survival. With more than 70 trials involving a variety of drug candidates underway, the IGF-IR is becoming one of the most intensively investigated molecular targets in oncology. Early results justify the continuation of ongoing research across a broad range of cancer indications.

Keywords: insulin-like growth factor-I receptor inhibitors; clinical trials; targeted therapies

Introduction

Research on insulin-like growth factors (IGFs) and their receptors in cancer biology has been ongoing for over 20 years (Myal *et al.*, 1984; Pollak *et al.*, 1987; Arteaga *et al.*, 1989). Model systems provided evidence for important roles in neoplasia. Examples include genetic

alterations that reduce ligand levels (Pollak *et al.*, 2001, 2004; Baserga *et al.*, 2003; Majeed *et al.*, 2005; Hartog *et al.*, 2007; Sachdev and Yee, 2007; Samani *et al.*, 2007; Chitnis *et al.*, 2008; Weroha and Haluska, 2008; Yuen and Macaulay, 2008; Pollak, 2008a) as well as knock-down methods (Wu *et al.*, 2003). One important theme that emerged from this work was the notion that multiple oncogenes require the presence of the insulin-like growth factor receptor (IGF-IR) to achieve cellular transformation (Sell *et al.*, 1993; Martin *et al.*, 2006); another was that IGF-I signaling confers resistance to many antineoplastic therapies (Wiseman *et al.*, 1993; Lu *et al.*, 2001). Interest in IGF-IR targeting increased with the publication of evidence linking IGF-I signaling with the onset of neoplasia. Examples include evidence for associations between circulating IGF-I and cancer risk (Chan *et al.*, 1998), between IGF-I and mammographic breast density (Diorio *et al.*, 2005), between growth rate in adolescence (which is IGF-I mediated) and cancer risk (Ahlgren *et al.*, 2004), and the observation that IGF-II overexpression was among the most common molecular derangements in colorectal cancer (Zhang *et al.*, 1997).

Earlier review articles (Baserga *et al.*, 2003; Pollak *et al.*, 2004; Hartog *et al.*, 2007; Sachdev and Yee, 2007; Samani *et al.*, 2007; Chitnis *et al.*, 2008; Weroha and Haluska, 2008; Yuen and Macaulay, 2008; Pollak, 2008a) have summarized IGF-IR biology, its relevance to neoplasia and the preclinical evaluation of drug candidates targeting the IGF-IR. Recent studies have provided further evidence that IGF-IR inhibition can be useful in attenuating the malignant behavior of cancers in which KRAS (Klinakis *et al.*, 2009) or EGF receptor family members (Buck *et al.*, 2008; Huang *et al.*, 2009) play important roles in pathophysiology.

Close to 30 drug candidates targeting the IGF-IR are being investigated (Baserga *et al.*, 2003; Pollak *et al.*, 2004; Yee, 2006; Hartog *et al.*, 2007; Sachdev and Yee, 2007; Samani *et al.*, 2007; Tao *et al.*, 2007; Chitnis *et al.*, 2008; Feng and Dimitrov, 2008; Rodon *et al.*, 2008; Yuen and Macaulay, 2008; Pollak, 2008a, b). Here, we focus specifically on the available clinical trial and translational research data concerning 12 of these compounds currently in clinical trials. The large number of trials planned and in progress provide important opportunities for the incorporation of 'companion' studies that will provide serum and tissue samples for

Correspondence: Dr M Pollak, Segal Cancer Centre, McGill University, 3755, Chemin de la Cote Sainte-Catherine, Room E-763, Montreal, Quebec, Canada H3T 1E2.
E-mail: michael.pollak@mcgill.ca

analysis of patterns of gene expression, activation of signaling pathways, circulating growth factor levels, and genetic variation in the germline and within neoplastic tissue that may predict response.

Clinical trials of IGF-IR inhibitors

A12

Phase I trials evaluating the human anti-IGF-IR IgG1 antibody, A12 (cixutumumab, Imclone, New York, NY, USA), given weekly or every 2 weeks (q2weeks) at doses of 3–27 mg/kg are being conducted in patients with refractory tumors (NCT00785538, NCT00785941) (Higano *et al.*, 2007; Rothenberg *et al.*, 2007). Toxicity reported includes grade 3 hyperglycemia and grade 2 anemia, psoriasis, hyperglycemia and infusion-related reaction (Table 1). Mean half-lives of up to 211 h at 15 mg/kg/q2weeks dosing have been reported. IGF-I elevations post-A12 dosing were also observed. No objective responses have been yet seen but two disease stabilizations >9 months (one male breast cancer, one hepatocellular cancer) were reported on weekly dosing. This initial favorable profile supported the initiation of a large clinical testing program in 18 trials of A12 alone or in combination with other agents (Table 2).

AMG-479

The safety of the human anti-IGF-IR IgG1 antibody, AMG-479 (Amgen, Thousand Oaks, CA, USA), at doses of 1–20 mg/kg/q2weeks was investigated in a phase I study (Tolcher *et al.*, 2007). Grade 3 thrombocytopenia was considered dose limiting at 20 mg/kg. Additional grade 3/4 non-hematological toxicities were observed in two patients; however, no hyperglycemia greater than grade 2 was reported. Anti-AMG-479 antibodies were detected in one patient and one additional patient had an infusion reaction (grade 2). AMG-479 exhibited dose-linear pharmacokinetics reaching steady state at cycle 3 with a mean terminal half-life of 7–11 days. Pharmacodynamic studies showed a trend to dose-proportional receptor occupancy in neutrophils and elevations of serum IGF-I, and IGF-binding protein-3 (IGFBP-3). Well-documented tumor responses in patients with Ewing's sarcoma and neuroendocrine carcinoma (one each) were reported (Tolcher *et al.*, 2007). Furthermore, early data from a phase Ib combination study of AMG-479 with either panitumumab or gemcitabine have been reported (NCT00788957, NCT00630552) (Sarantopoulos *et al.*, 2008). Patients with advanced solid tumors received panitumumab (6 mg/kg/q2weeks) or gemcitabine (1000 mg/m² on days 1, 8 and 15 every 4 weeks (q4weeks)) in combination with AMG-479 at 6 or

Table 1 Summary of early clinical trial results with anti-IGF-IR drug candidates

Agent	Properties ^a	Biomarkers	Key toxicities	Preliminary activity
A12 (cixutumumab) Fully human IgG1	211 h q2weeks	IGF-I, IGFBP-3	Hyperglycemia, anemia, psoriasis, infusion reaction	Phase I: SD >9 months in two patients
AMG-479 Fully human IgG1	7–11 days q2weeks	IGF-IR, IGF-I, IGFBP-3	Thrombocytopenia, hyperglycemia, anti-AMG-479 Abs	Phase I: one CR EWS, one PR carcinoid tumor; one PR with panitumumab in cetuximab-refractory patient
AVE1642 Humanized IgG1	9 days q3weeks	NA	Hyperglycemia, hypersensitivity (grade 2)	NA
CP-751,871 (figitumumab) Fully human IgG2	20 days q3–4weeks	IGF-IR, sIGF-IR, IGF-IR CTCs, IGF-I, IGFBP-3	Hyperglycemia, anemia (myeloma), GGT elevation, urate, arthralgia, fatigue, DVT, LFTs	Phase I: one CR EWS; 9 PRs/27 myeloma patients + dexamethasone; 8 PSA PRs/20 HRPC + docetaxel; Phase II: 54% ORR + paclitaxel-carboplatin in NSCLC
MK0646 Humanized IgG1	100 h q1–2weeks	IGF-IR, FDG-PET	Thrombocytopenia, gastrointestinal bleeding, pneumonitis, LFTs	Phase I: SD > 12 months in two patients
R1507 (robatumumab) Fully human IgG1	6 days q1–3weeks	IGF-IR	Hyperglycemia, lymphopenia, CVA, bilirubin	Phase I: two PRs in EWS
Sch717454 Fully human IgG1	NA q2weeks	NA	No dose-limiting toxicity in healthy volunteers	Phase I: SD > 6 months in 7 patients
XL228 TKI IV	55 h qweek	IGF-IR, insulin receptor, Src, p56 phosphorylation	Syncope, hyperglycemia	Ph I: two CRs in CML, two PRs in ALL

Abbreviations: CR, complete response; CVA, cerebral vascular accident; DVT, deep-vein thrombosis; EWS, Ewing's sarcoma; FDG-PET, fluorodeoxyglucose positron emission tomography; GGT, gamma-glutamyltransferase; HRPC, hormone-refractory prostate cancer; IGFBP, insulin-like growth factor-binding protein; IGF-I, insulin-like growth factor type I; IGF-IR CTCs, circulating tumor cells expressing the IGF-IR; IGF-IR, IGF-I receptor; LFT, liver function test; NSCLC, non-small-cell lung cancer; ORR, objective response rate; PR, partial response; PSA, prostate-specific antigen; q2weeks, every 2 weeks; SD, stable disease.

^aEstimated half-life and dosing schedule.

Table 2 Summary of ongoing clinical programs for anti-IGF-IR products

Indication	Agent/combination
ACC	+ Mitotane (A12)
ALL	XL228
BC	+ Antiestrogens (A12) + Exemestane (CP-751,871) + Exemestane or fulvestrant (AMG-479) + Fulvestrant (AVE1642) + Letrozole (R1507) + Tensirolimus (A12) + Capecitabine–erlotinib (A12)
CML	XL228
CRC	Single agent (CP-751,871, Sch717454) + Cetuximab (A12) + Cetuximab–irinotecan (MK0646) + Panitumumab (AMG-479)
HCC	Single agent (A12) + Sorafenib–erlotinib (AVE1642)
H&N	+ Cetuximab (A12)
Multiple myeloma	+ Bortezomib (AVE1642)
Neuroendocrine	Single agent (MK0646) + Octreotide (A12)
NSCLC	+ Erlotinib (A12, CP-751,871, MK0646, R1507) + Paclitaxel–carboplatin (CP-751,871) + Pemetrexed–cisplatin or pemetrexed–cisplatin (CP-751,871) + Pemetrexed–cisplatin (MK0646)
Ovarian cancer	Single agent (AMG-479) + Paclitaxel–carboplatin (AMG-479)
Pancreatic cancer	+ Erlotinib–gemcitabine (A12, MK0646) + Gemcitabine (AMG-479)
Prostate cancer	Single agent (A12) + Antiandrogens (A12) + Docetaxel–prednisone (CP-751,871) + Mitoxantrone–prednisone (A12)
Sarcoma	Single agent (A12, AMG-479, CP-751,871, R1507, Sch717454) + doxorubicin (A12)

Abbreviations: ACC, adrenocortical carcinoma; ALL, acute lymphocytic leukemia; BC, breast cancer; CML, chronic myeloid leukemia; CRC, colorectal carcinoma; H&N, head and neck; HCC, hepatocellular carcinoma; IGF-IR, insulin-like growth factor type I receptor; NSCLC, non-small-cell lung cancer.

12 mg/kg/q2weeks. Grade 3/4 toxicities observed included aspartate aminotransferase/alanine aminotransferase elevations and neutropenia in four of eight patients receiving AMG-479 and gemcitabine, and several grade 3 events of hyperglycemia, stomatitis and hypomagnesemia in 10 patients dosed with AMG-479 and panitumumab. One partial response was observed in combination with panitumumab in a patient with KRAS wild-type colon cancer who

previously progressed on cetuximab. Stable disease was noted in 9 of 11 evaluable patients. A partial response was also seen in a patient with hormone-resistant prostate cancer treated with AMG-479 and gemcitabine. Panitumumab or gemcitabine did not seem to affect the pharmacokinetics of AMG-479 (12 mg/kg).

AVE1642

Two phase I studies of the anti-IGF-IR antibody, AVE1642 (Sanofi-Aventis, Paris, France), were reported. A dose escalation (3–12 mg/kg/q3weeks) was conducted in patients with refractory multiple myeloma (Moreau *et al.*, 2007). AVE1642 was well tolerated in 14 patients dosed for a median of three cycles. Two grade 3 hyperglycemias were observed in diabetic patients. No hypersensitivity or anti-drug antibodies were detected. In the second study, AVE1642 (3–12 mg/kg) was administered every 3 weeks (q3weeks) as single agent at cycle 1 and then combined with docetaxel (75 mg/m²) at cycle 2 and beyond in patients with advanced solid tumors (Tolcher *et al.*, 2008). No dose-limiting toxicity (DLT) has been yet reported. Grade 1/2 toxicity included hyperglycemia (one case) and hypersensitivity reactions (two cases). AVE1642 half-life was estimated to be approximately 9 days.

AXL1717

AXL1717 (Axelar, Stockholm, Sweden) is a small-molecule IGF-IR inhibitor investigated in phase I trials. Structurally, AXL1717 is based on a cyclolignan derivative picropodophyllin that seems to have some selectivity for the IGF-IR versus other tyrosine kinases, including the insulin receptor (IR) (Girnita *et al.*, 2004). No clinical information has yet been released.

BIIB022

BIIB022 (Biogen, Cambridge, MA, USA) is a human anti-IGF-IR non-glycosylated IgG4 antibody. A phase I dose-escalation study of BIIB022 given q3weeks to patients with relapsed or refractory solid tumors is currently underway (NCT00555724).

BMS-754807

BMS-754807 (Bristol-Myers, New York, NY, USA) is a small molecule antagonist of the IGF-IR administered orally. A multiple-dose study of the safety of BMS-754807 in patients with advanced solid tumors (NCT00569036) has been initiated with a starting dose of 4 mg/day.

CP-751,871

CP-751,871 (figitumumab, Pfizer New York, NY, USA) is a human anti-IGF-IR IgG2 antibody. Over 1000 patients have participated in CP-751,871 trials. The first-in-human study was a dose escalation (0.025–20 mg/kg/q4weeks) in patients with refractory myeloma (Lacy *et al.*, 2008). A total of 47 patients were enrolled and no DLT was observed. Grade 3 events included hyperglycemia and anemia (one case each). The effective half-life of CP-751,871 at the 20 mg/kg dose was estimated to be

20 days. Several pharmacodynamic end points were investigated. Granulocyte IGF-IR expression decreased in a dose-dependent manner together with substantial dose-dependent increases in circulating IGF-I, with >10-fold elevations from baseline at the 20 mg/kg dose (up to 1200 ng/ml), and more modest increases in IGFBP-3 (two- to three-fold). Patients with suboptimal response to CP-751,871 alone were eligible to receive CP-751,871 in combination with dexamethasone (3 × 40 mg q4weeks) or rapamycin (2 mg/day daily). A total of nine responses by European Group for Blood and Marrow Transplant criteria were noted in 27 patients receiving CP-751,871 and dexamethasone, including two patients progressing on dexamethasone regimens at study entry.

Further phase I experience involved a dose escalation of CP-751,871 (3–20 mg/kg/q3weeks) in patients with refractory solid tumors (NCT00474760) (Haluska *et al.*, 2007). In addition, two extension cohorts at the 20 mg/kg dose, one in adrenocortical carcinoma (ACC) patients ($N=21$) and another in patients with sarcoma ($N=26$), were conducted (Olmos *et al.*, 2007, 2008; Postel-Vinay *et al.*, 2008). In the dose-escalation portion of the study, 110 treatment cycles were administered to 24 patients with no DLTs observed. Grade 3 events included elevated γ -glutamyltransferase, fatigue and arthralgia. Greater than doubling of baseline growth hormone (GH) levels was observed, indicating systemic inhibition of the IGF-IR with the loss of regulatory feedback at the pituitary (discussed below), as well as modest increases in fasting glucose (Gualberto *et al.*, 2008b). Pharmacokinetic analysis revealed a dose-dependent increase in CP-751,871 concentrations with an approximately twofold accumulation on repeated dosing. No objective responses were observed but two patients experienced >1 year disease stabilization. Adverse events in sarcoma patients included one grade 4 uric acid elevation and one grade 3 deep-vein thrombosis. In ACC patients, several grade 3 elevations of liver function tests were observed. A complete response was observed in a patient with Ewing's sarcoma. Stable disease was seen in 12 of 20 evaluable sarcoma and 9 of 13 ACC patients. An additional phase Ib study investigated the safety of CP-751,871 (0.1–20 mg/kg) in combination with docetaxel (75 mg/m²) in 27 advanced disease patients (Attard *et al.*, 2006). Grade 3/4 toxicities reported were attributed to docetaxel and included neutropenia ($n=18$) and diarrhea ($n=3$). Of 20 hormone-resistant prostate cancer patients treated, eight had confirmed prostate-specific antigen responses. This study also included the enumeration and assessment of circulating tumor cells expressing the IGF-IR (IGF-IR CTCs) (De Bono *et al.*, 2007). IGF-IR CTCs were detectable in 50% of hormone-resistant prostate cancer patients and their decline post treatment seemed to be associated with prostate-specific antigen response. Furthermore, a simultaneous decrease in total CTC counts was observed in CP-751,871-treated patients, suggesting that the IGF-IR may be required for CTC migration from tumor sites, their survival in the blood stream or homing at new metastatic sites.

Safety and efficacy in combination with paclitaxel and carboplatin were investigated in a phase Ib/II study of CP-751,871 given at 0.05–20 mg/kg/q3weeks (NCT00147537) (Pollak *et al.*, 2007; Karp *et al.*, 2009). A total of 42 patients were enrolled in the phase Ib portion with no DLTs observed. Grade 3 events included γ -glutamyltransferase elevation, diarrhea, asthenia and hyperglycemia (one case each). Sustained decreases in circulating cleaved soluble IGF-IR to undetectable levels for the complete dosing period, as well as increases in the plasma concentrations of free IGF-I (5- to 10-fold) and IGFBP-3 (2- to 3-fold), were observed at doses ≥ 6 mg/kg. In all, 15 objective responses were observed in the phase Ib portion of the study, including two complete responses in non-small-cell lung cancer (NSCLC) and ovarian carcinoma patients. The phase II portion of the study was a randomization of treatment-naive NSCLC patients to paclitaxel, carboplatin, and CP-751,871 or to paclitaxel/carboplatin alone. In total, 10–20 mg/kg/q3weeks CP-751,871 dosing were investigated ($N=151$) (Karp *et al.*, 2009). A total of 42 and 54% of patients receiving, respectively, chemotherapy and chemotherapy with CP-751,871 had objective responses. Analyses by dose and histology revealed an apparent dose–response relationship for patients with squamous cell and adenocarcinoma histologies, with response rates for chemotherapy alone or with CP-751,871 at 10 and 20 mg/kg, respectively, of 33, 43 and 62%. The combination was well tolerated with a low incidence of treatment-related grade 3/4 toxicities. Grade 3/4 hyperglycemia was seen in 15% of patients receiving paclitaxel/carboplatin and CP-751,871 and 8% of patients receiving chemotherapy alone. On the basis of these results, phase III studies are being conducted in treatment-naive and refractory NSCLC (NCT00673049, NCT00596830) (Gualberto and Karp, 2009).

Additional phase II studies include testing of CP-751,871 as first line treatment for hormone-resistant prostate cancer in combination with docetaxel and prednisone (NCT00313781), and a combination with exemestane in advanced estrogen receptor-positive breast cancer (NCT00372996). Initial data indicate that these combinations are well tolerated (De Bono *et al.*, 2008; Ryan *et al.*, 2008).

MK0646

The safety of the anti-IGF-IR antibody, MK0646 (Merck, Whitehouse Station, NJ, USA), was investigated in two phase I studies (NCT00282737, NCT00701103). In the first, 48 patients with IGF-IR-expressing tumors were given MK0646 weekly at 1.25–20 mg/kg (Atzori *et al.*, 2008). Sequential skin and tumor biopsies were collected and fluorodeoxyglucose positron emission tomography carried out before and on treatment. A DLT of grade 3 thrombocytopenia was noted at 5.0 mg/kg. Pharmacokinetics indicated dose-proportionality and a mean terminal half-life of approximately 4 days. Decreases in tumor IGF-IR levels and downstream signaling, and increases in circulating

IGF-I levels (twofold) were documented. Fluorodeoxyglucose positron emission tomography metabolic responses occurred in three patients but no objective responses were observed. In the second study, 29 patients were enrolled in three stages (NCT00635778) (Hidalgo *et al.*, 2008). In stages 1 and 2, patients were treated with loading doses of MK0646 (2.5–20 mg/kg) followed by maintenance doses (2.5–15 mg/kg/q2weeks). In stage three (not completed at the time of the report), patients are treated with a 15 mg/kg loading dose and 10 mg/kg/q2weeks maintenance dose. A DLT of grade 4 thrombocytopenia was observed at the 15 mg/kg loading dose in the 5 mg/kg maintenance cohort. Grade 3 toxicity included thrombocytopenia, gastrointestinal bleeding, pneumonitis and increase in the liver function tests. Pharmacokinetic analysis suggested a terminal half-life of approximately 100 h (range, 54–296). Although no objective responses were observed, two patients have had disease stabilization for > 1 year.

MK0646 is being further evaluated in a phase II/III study in combination with cetuximab and irinotecan in metastatic colorectal cancer that progressed on prior irinotecan therapy (NCT00614393) (Taberner, 2008).

OSI-906

OSI-906 (OSI Pharmaceuticals, Melville, NY, USA) is an oral small molecular weight tyrosine kinase inhibitor of the IGF-IR. Two phase I trials are underway investigating continuous (NCT00514007) and intermittent (1–3, 5, 7 days or 2 weeks) dosing (NCT00514306). A total of 30 patients received OSI-906 at 10–150 mg qd with one grade 3 hyperglycemia and one grade 3 lipase elevation reported. A total of 25 patients were dosed at 10–450 mg, days 1–3/q2weeks without severe toxicity. Disease stabilization > 6 months was observed in one thymic carcinoma, one ACC and two colorectal carcinoma patients receiving OSI-906 in continuous dosing, and one myxoid chondrosarcoma, one ACC and one refractory NSCLC patient receiving OSI-906 40 mg days 1–3 q2weeks. Trends for increases in insulin levels with increasing OSI-906 plasma concentrations were observed (Lindsay *et al.*, 2009).

R1507

The safety and pharmacokinetics of weekly and q3weeks administrations of the human anti-IGF-IR IgG1 antibody, R1507 (robatumumab, Roche, Basel, Switzerland), were explored in a phase I study in patients with advanced solid tumors or lymphomas (NCT00400361) (Rodon *et al.*, 2007). In total, 21 patients were enrolled in four dose-escalation cohorts (1–16 mg/kg) of weekly R1507. One grade 3 hyperglycemia and one grade 3 CD4-positive lymphopenia were reported. Other adverse events included infection ($n=6$) and fatigue ($n=4$). Pharmacokinetic analysis estimated a half-life of approximately 8 days. At 1 mg/kg, an average 80% reduction (range, 13–34%) in IGF-IR expression on peripheral blood mononuclear cells was seen on day 8 ($n=7$). The weekly dose escalation has been also reported (Leong *et al.*, 2007). A total of 34 patients

were enrolled at three dose levels (1–9 mg/kg). Two adverse events, a cerebrovascular accident and hyperbilirubinemia, were reported at the 9 mg/kg dose. No hyperglycemia was reported; however, glucose tolerance test abnormalities were observed in two of 17 patients at week 7. Half-life was estimated to be 6.2 days at the highest dose. Two objective responses were reported in two patients with Ewing's sarcoma in the 9 mg/kg cohort. Stable disease was reported in another two of eight evaluable Ewing's sarcoma patients. Overall, 10 patients showed stable disease of median duration 18 weeks (range, 12–48).

Sch717454

Sch717454 (19D12, Schering-Plough, Kenilworth, NJ, USA) is a human IgG1 anti-IGF-IR antibody. A phase I, single-dose study at 0.3–20 mg/kg was conducted in 32 healthy volunteers with no adverse events reported up to 8 weeks post dosing (Seraj *et al.*, 2007). Two phase II clinical trials are currently ongoing to test the efficacy of Sch717454 q2weeks. In the first of these trials, patients ≥ 11 -year-old with relapsed osteosarcoma that can be treated with surgery, will be randomized to Sch717454 administered at one of two dose levels. Patients will receive Sch717454, have surgery performed and continue to receive treatment with Sch717454. A second cohort of patients with unresectable osteosarcoma or Ewing's sarcoma will receive Sch717454 until disease progression (NCT00617890).

XL228

XL228 (Exelixis, South San Francisco, CA, USA) is a small-molecule tyrosine kinase inhibitor of IGF-IR, Src, fibroblast growth factor receptor and BCR-ABL. A phase I dose escalation of XL228 administered intravenously once or twice weekly was conducted in patients with advanced malignancies (NCT00526838) (Britten *et al.*, 2008). Data have been reported for four study cohorts (13 patients) receiving XL228 weekly at 0.45–3.6 mg/kg. No DLTs were reported. Pharmacokinetic analysis showed a slightly greater than dose-proportional increase in exposure, with mean terminal half-lives ranging from 47 to 55 h, and marked tissue distribution. There were substantial changes in phosphorylation of Src kinase substrates in peripheral blood mononuclear cell after XL228 infusion with up to 78–100% decreases in phosphoepitopes. Rapid and transient increases in plasma glucose and insulin after infusion suggest IGF-IR/IR inhibition. Twelve evaluable patients remained on study at the time of the report and continued to receive XL228 weekly; the longest time on study was experienced by patients with small-cell lung cancer (7+ cycles) and perirectal leiomyosarcoma (4+ cycles).

An additional study investigates the safety of XL228 in patients with chronic myeloid leukemia (CML) or Philadelphia-chromosome-positive acute lymphocytic leukemia (ALL; NCT00464113). Dose levels tested include 0.45–10.8 mg/kg once weekly and 3.6 mg/kg twice weekly. A total of 35 patients have received one or

more doses of XL228 and seven patients have shown signs of clinical activity: two chronic-phase CML patients showed a complete cytogenetic response, including one patient with a T315I mutation, two patients experienced a major cytogenetic response, including a patient with Philadelphia-chromosome-positive ALL harboring the T315I mutation and three patients with accelerated-phase CML have experienced a return to chronic-phase CML. Serious adverse events that were reported included tumor lysis syndrome, syncope, neutropenia, thrombocytopenia, anemia, fever and infections. DLTs of syncope and hyperglycemia were observed in the 10.8 mg/kg weekly cohort. Inhibition of BCR-ABL (including T315I), IGF-IR and Src kinase was shown by assessment of phosphoprotein epitopes in circulating leukocytes (Cortes *et al.*, 2008).

Class effects and differentiation

Safety

Early results reveal a favorable profile with most adverse events described as mild and/or manageable. Endocrine changes seem to be characteristic of the class and include elevations in circulating IGF-I, GH, insulin and glucose. These have been rarely associated with DLT, although co-administration of anti-diabetic agents has been occasionally necessary to control blood glucose.

Monitoring patients for hyperglycemia and/or dehydration is recommended. Mild elevations in blood glucose are seen in about 25% of patients treated with anti-IGF-IR antibodies. There is no evidence to support the simplistic explanation that this is a consequence of cross-reactivity with the IR. These agents were designed to spare it, and there is convincing evidence that this has been achieved. Importantly, although several antibodies target ‘hybrid receptors’ (comprising a ‘half receptor’ composed of IR- α and - β chains, complexed with a ‘half receptor’ composed of IGF-IR- α and - β chains), these are more responsive to IGFs than to insulin, and their role in the regulation of glycemia is controversial (Lammers *et al.*, 1989; Morrow *et al.*, 1994; Belfiore, 2007; Benyoucef *et al.*, 2007).

Available data are consistent with the more complex mechanism outlined in Figure 1. Anti-IGF-IR antibodies act systemically on all IGF-IR receptors, including those involved in homeostatic control of GH at the hypothalamic-pituitary axis, causing loss of feedback inhibition of GH secretion. Elevated GH levels stimulate liver IGF-I production, accounting for the observed elevations in circulating IGF-I. Furthermore, elevated GH likely leads to greater liver gluconeogenesis and insulin resistance in muscle, liver and adipose tissue (del Rincon *et al.*, 2007). This could result in hyperglycemia similar to that seen in acromegalic patients. However, in

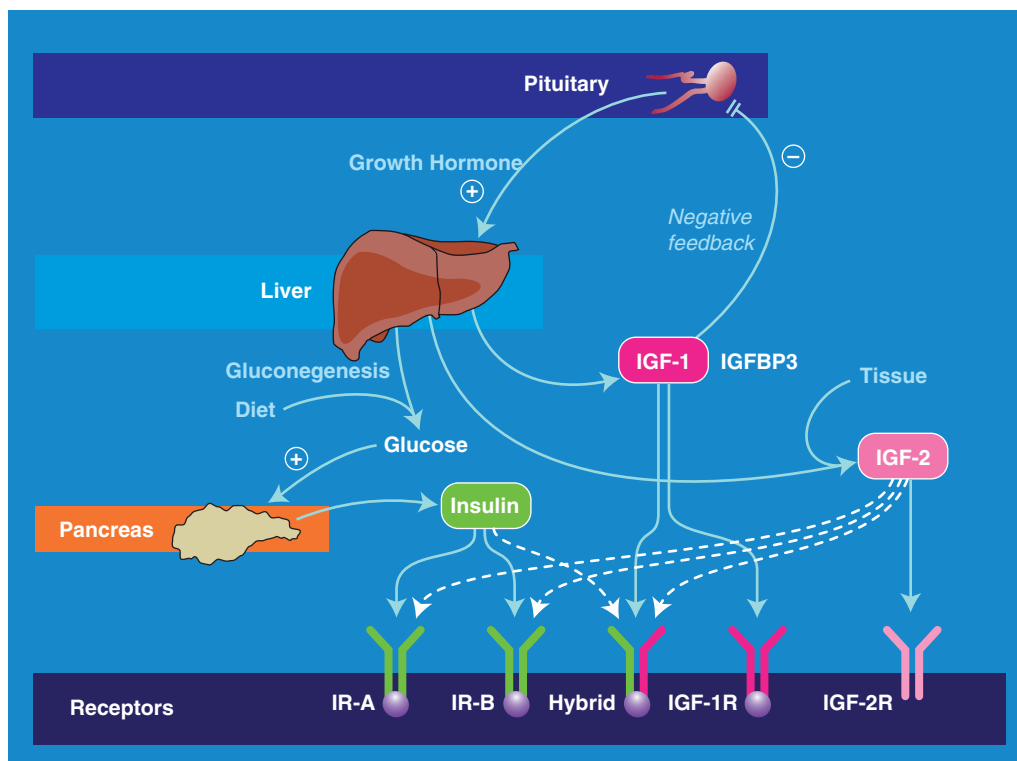


Figure 1 Regulatory interactions between the IR and IGF-IR. IGF-I receptor-targeting agents are not specific for receptors on neoplastic cells. They also block the IGF-I receptors involved in homeostatic control of the GH-IGF-I axis. Usually, IGF-I production by the liver is stimulated by GH, and IGF-I negatively regulates GH secretion by the pituitary. In the setting of IGF-I receptor blockade, this feedback inhibition is lifted, and GH and consequently IGF-I levels rise. Elevation in GH can lead to insulin resistance in classic insulin target organs, and to elevations in glucose. This in turn results in increased insulin secretion, which may vary from patient to patient, and which commonly corrects the hyperglycemia. (See text for details). GH, growth hormone; IGFBP, insulin-like growth factor-binding protein; IGF-IR, insulin-like growth factor type I receptor; IR, insulin receptor.

most patients treated with IGF-IR inhibitors hyperinsulinemia and normoglycemia are observed, suggesting that increased pancreatic secretion of insulin compensates to some extent for the insulin resistance and increased hepatic glucose production. Consequently, severe hyperglycemia is a rare event when IGF-IR antibodies are given as single agents (Haluska *et al.*, 2007; Lacy *et al.*, 2008). In contrast, up to 20% of severe hyperglycemia is seen in studies in which anti-IGF-IR antibodies are given with chemotherapy that requires pre-medication with steroids, themselves strong hyperglycemic agents (Karp *et al.*, 2009). Of note, a combination of CP-751,871 with high-dose steroids in patients with multiple myeloma did not report high frequency or severity of hyperglycemia (Lacy *et al.*, 2008). This may be due to the fact that when given at high doses in myeloma treatment, steroids significantly interfere with the GH-IGF-I axis at the hypothalamic, pituitary and target organ levels (Hochberg, 2002), further indicating the complexities of the control systems involved.

IgG2 and IgG4 antibodies (CP-751,871, BIIB022) are poor activators of antibody-mediated cytotoxicity and complement fixation and may have less hematological toxicity than those with IgG1 backbone. For example, grade 3 thrombocytopenia was considered dose limiting at 20 mg/kg for AMG-479 in a single-agent study (Tolcher *et al.*, 2007), and with MK0646, grade 3 and 4 thrombocytopenia, respectively, were encountered with a 5 mg/kg weekly regimen (Atzori *et al.*, 2008) and with a 15 mg/kg loading, 5.0 mg/kg q2weeks maintenance regimen (Hidalgo *et al.*, 2008). Furthermore, grade 3 CD4+ lymphopenia was observed with R1507 (Rodon *et al.*, 2007). However, grade 2 lymphopenia has also been seen with CP-751,871 (Olmos *et al.*, 2007), suggesting that IGF-IR targeting may contribute to hematological toxicity. If future applications involve combinations with aggressive chemotherapy, additive or synergistic hematological toxicity may become an issue. It is also possible that antibody-mediated cytotoxicity could contribute to anti-tumor activity and represent an advantage, but there is yet no clinical data supporting that hypothesis.

Pediatric trials have been initiated with five of the anti-IGF-IR monoclonals (Table 2, sarcoma). Long-term therapy would be predicted to result in growth retardation, but that would be of little significance if 'catch-up' growth occurs after completion of treatment. Of note, no growth effects have yet been described in adolescents treated with anti-IGF-IR antibodies (Olmos *et al.*, 2007, 2008).

Importantly, hypersensitivity reactions have been rare so far for anti-IGF-IR antibodies as a class. Experience with long-term (> 1 year) treatment is limited, but might be expected to associate with changes in body composition reminiscent of the syndrome of GH deficiency, including increased adiposity and decreased muscle mass. Long-term IGF-IR inhibition may also have implications in the maintenance of normal physiological functions such as atherosclerosis, increased frailty in elderly subjects and bone fractures (Ceda *et al.*, 2005). An additional particular concern would be adverse

central nervous system effects associated with those drug candidates that accumulate in the brain, as IGF-I signaling has neuroprotective effects (Russo *et al.*, 2005).

Pharmacokinetics

Target-mediated disposition has been shown for some of the antibodies (Haluska *et al.*, 2007; Lacy *et al.*, 2008; Yin *et al.*, 2008). Population pharmacokinetics conducted with one of the monoclonals identified body weight as a significant covariate for plasma clearance, whereas age, sex, and albumin or bilirubin concentrations showed no apparent effects (Yin *et al.*, 2008). These data support the continuation of body weight-based dosing. As expected, chemotherapy did not affect the pharmacokinetics of anti-IGF-IR monoclonals (Attard *et al.*, 2006; Sarantopoulos *et al.*, 2008; Karp *et al.*, 2009). It is also noteworthy that the effective half-lives of the anti-IGF-IR antibodies differ from each other. The half-life of CP-751,871 (IgG2) of approximately 20 days seems longer than others (Baserga *et al.*, 2003; Dong *et al.*, 2007). Half-life estimates of 4 days (Atzori *et al.*, 2008), 6 days (Leong *et al.*, 2007), 7–11 days (Tolcher *et al.*, 2007) and 9 days (Higano *et al.*, 2007) were reported, respectively, for MK0646, R1507, AMG-479 and A12 (Table 1). These differences could be explained in part by antibody backbone, but may also reflect target mediated disposition at low doses (Goodin, 2008).

Pharmacodynamics

IGF-IR downregulation on circulating leukocytes has been shown for several of the antibodies (Table 1), indicating target modulation, at least in a surrogate tissue. Early results with CTCs suggest similar effects on neoplastic cells (De Bono *et al.*, 2007). More detailed pharmacodynamic end points on tumor specimens were generated with MK0646 (Atzori *et al.*, 2008). At 5–20 mg/kg/week, decreases in IGF-IR, pAKT, pMAPK and pS6 were observed. These findings provide key evidence that despite the fact that many tumors have several receptor kinases upstream of pAKT and pMAPK, targeting the IGF-IR is sufficient to perturb downstream signaling.

Efficacy

To date, encouraging phase II data have been reported with CP-751,871 in NSCLC as summarized above (Karp *et al.*, 2009). Well-documented phase I responses were reported with several drug candidates in Ewing's sarcoma and other tumors (Table 1). Despite these encouraging trends, it is premature to reach formal conclusions. Considerable phase II data should become available within the next 24 months, and phase III studies of CP-751,871 and MK0646 are currently underway.

Gaps in knowledge and future research

Differences between antibodies and tyrosine kinase inhibitors

Experience with epidermal growth factor receptor inhibitors shows that it can be difficult to predict

Table 3 Critical issues

Drug structure issues	Is relative lack of selectivity of small-molecule TKIs likely to be an advantage or disadvantage with respect to efficacy? With respect to toxicity?
Development issues	ADCC may be both an advantage (tumor cell killing) and an issue (hematological toxicity) Large number of potential indications and combination regimens Limited single-agent activity Ubiquitous target
Biomarkers	Multiple mechanisms of alteration in cancer: receptor overexpression, receptor activation without overexpression, IGF-IIR inactivation, ligand overexpression
Endocrine deregulation	Metabolic effects and potential resistance mechanisms
Long-term toxicity risks	Potential CNS effects for small molecule TKIs that cross blood–brain barrier. Potential muscle wasting and increased adiposity Potential cardiovascular effects

Abbreviations: ADCC, antibody-dependent cell-mediated cytotoxicity; CNS, central nervous system; IGF-IIR, insulin-like growth factor type II receptor; TKIs, tyrosine kinase inhibitors.

differences in efficacy between anti-receptor antibodies and small-molecule inhibitors (Mendelsohn and Baselga, 2006). Small molecule IGF-IR inhibitors commonly inhibit the IR, the IGF-I receptor, and hybrid receptors, and might be expected to be more effective antineoplastic agents than the antibodies (discussed below). However, they may also have more serious metabolic toxicity (Table 3). Monoclonals that target hybrid receptors, such as Sch717454 or CP-751,871, may block any portion of insulin signaling in cancer cells mediated by those receptors (Cohen *et al.*, 2005; Sachdev *et al.*, 2006; Pollak, 2008a). Small molecule inhibitors may allow the investigation of drug sequencing and intermittent dosing more conveniently than antibodies. The question of tissue distribution of small-molecule IGF-I/IR kinase inhibitors and their metabolites is also important with respect to both potential toxicity (particularly central nervous system) and efficacy.

Development issues

The biological rationale for IGF-IR-targeting agents suggests the possibility of indication in a wide range of cancers and combination therapies. Although this broad relevance increases enthusiasm for the target, it also presents challenges. A total of 16 tumor types and almost 30 combinations are listed in Table 2. Preclinical work does suggest that combinations with DNA-damaging cytotoxics, epidermal growth factor receptor family inhibitors, steroid hormone targeting agents mammalian target of rapamycin inhibitors, and radiation may translate to supra-additive effects and deserve prioritization (Benini *et al.*, 2001; Lu *et al.*, 2001; Cohen *et al.*, 2005; Wu *et al.*, 2005, 2006; Best *et al.*, 2006; O'Reilly *et al.*, 2006; Allen *et al.*, 2007; Barr *et al.*, 2007; Ji *et al.*, 2007; Plymate *et al.*, 2008; Wan *et al.*, 2007; Guix *et al.*, 2008). Possibilities that intermittent, pulsed or sequenced regimens with cytotoxic agents may or may not have advantages over continuous exposure remain largely unexplored for targeted therapies in general, and IGF-IR inhibitors in particular.

Study design is also challenging. IGF-IR inhibitors can be combined with other agents in ways that may

increase their activity or delay the onset of resistance. The first mechanism implies that IGF-IR is constitutively activated in tumors, and thus methods to identify baseline sensitivity to inhibition would be key in future development. The second mechanism is broader and emphasizes the importance of IGF-IR activation in acquired treatment resistance. Delays in progression-free survival by IGF-IR inhibition will be missed if studies are not powered to evaluate this end point. One interesting study design investigates the reversal of drug resistance. Patients progressing on a therapy are offered its re-administration in combination with an IGF-IR inhibitor. Reversal of drug resistance was anecdotally observed in early studies (Lacy *et al.*, 2008; Karp *et al.*, 2009), and is currently being tested in several trials of these inhibitors.

Reliable biomarkers predictive of response

IGF-IR amplification has been detected in some tumors (Natrajan *et al.*, 2006; Adelaide *et al.*, 2007; Tarn *et al.*, 2008) but does not seem to be a common event as with other receptors (Slamon *et al.*, 2001). Sensitivity to targeting could correlate with receptor activation, but methods of measurement are not yet perfected. Studies conducted in a series of blood and tumor tissues from patients with NSCLC raised the possibility that receptor and ligand levels may be independent predictors for response to anti-IGF-IR therapy (Gualberto *et al.*, 2008a,b). These pharmacologically defined groups, receptor or ligand driven, seemed to match two of three tumor differentiation phenotypes: epithelial (differentiated) and epithelial-to-mesenchymal transition (transitional). Patients with tumors belonging to a third phenotype, mesenchymal (undifferentiated), did not seem responsive to anti-IGF-IR therapy (Gualberto *et al.*, 2008a,b; Karp *et al.*, 2009). The epithelial high IGF-IR expressing phenotype included most squamous cell carcinoma tumors, whereas the transitional ligand-driven phenotype was observed in the majority of adenocarcinoma patients. Mesenchymal-like NSCLC was represented by large cell and other undifferentiated tumors that expressed the highest levels of vimentin, and

Table 4 Endocrine effects of IGF-IR inhibition

<i>Abnormality</i>	<i>Consequence</i>
Increase in IGF-I levels	Unlikely to lead to resistance to IGF-IR inhibition Attenuation of any consequences of raised IGF-I level
Increase in IGFBP-3 levels	IGFBP direct anti-tumor effects? Insulin resistance leading to hyperglycemia
Increase in GH levels	Liver gluconeogenesis increased? Increased tumor growth/survival if tumors are GH sensitive
Hyperglycemia	Consequences similar to type II diabetes Attenuation of hyperglycemia
Insulin levels increase	Metabolic syndrome symptoms such as adiposity Potential for increased tumor growth or survival?

Abbreviations: GH, growth hormone; IGFBP, insulin-like growth factor-binding protein; IGF-IR, insulin-like growth factor type I receptor.

low receptor and ligand levels (Gualberto *et al.*, 2008a, b). These data suggested that the use of differentiation markers, in addition to receptor and ligand levels, could contribute to the identification of patients susceptible to benefit from anti-IGF-IR therapy, and data emphasized the complexity of IGF-IR biology. Large variations in IGF-IR levels, comparable with that observed in cell lines, have been reported in rhabdomyosarcoma tumor specimens, and pre-clinical experiments showed that receptor number may indeed predict sensitivity to an anti-IGF-IR antibody in rhabdomyosarcoma cell lines (Cao *et al.*, 2008). In colorectal cancer and other tumors, the role of KRAS and epidermal growth factor receptor status and its relationship to the activity of IGF-IR inhibitors should be object of investigation. Similarly, more research is required to understand the potential effects of p53 and PTEN inactivation on anti-IGF-IR therapy (Hyun *et al.*, 2000; Glait *et al.*, 2006).

Endocrine deregulation

The hormonal consequences of IGF-IR inhibition could in a sense be regarded as pharmacodynamic evidence of effective targeting. Careful interpretation is needed, as these changes are likely dependent on many variables. For example, the degree to which GH levels rise for a fixed degree of IGF-IR inhibition would be expected to vary with pituitary reserve capacity (for example, elderly versus adolescent patient). Similarly, there is a likely person-to-person variability in the degree of insulin response to GH-induced insulin resistance that is not attributable to drug exposure.

The medical consequences of high GH, IGF-I, insulin and glucose levels require careful consideration (Table 4). None of these changes is desirable, but they seem tolerable. Hyperglycemia is usually controllable with metformin and other agents (Atzori *et al.*, 2008; Karp *et al.*, 2009). Metformin likely acts to lower hepatic gluconeogenesis, which reduces circulating glucose, and results in secondary decline in insulin without affecting GH or IGF-I levels (Shaw *et al.*, 2005). An alternative approach might be the use of GH antagonists, such as pegvisomant (Kopchick *et al.*, 2002). Importantly, there is no evidence that IGF-I

elevation is sufficient to overcome the desired IGF-IR inhibition (Lacy *et al.*, 2008). This may be due in part to parallel elevations of IGFBPs, which reduce IGF bioactivity (Pollak *et al.*, 2007; Rothenberg *et al.*, 2007; Tolcher *et al.*, 2007; Lacy *et al.*, 2008). In addition, despite reports of GH receptor expression in human cancers (Gebre-Medhin *et al.*, 2001), there is no clear evidence that GH has an important direct effect on neoplasia. On the other hand, insulin elevations deserve attention. There is evidence for insulin-receptor expression in human cancers (Law *et al.*, 2008; Cox *et al.*, 2009) and that insulin, acting through its own receptor, can attenuate the effects of IGF-IR targeting (Zhang *et al.*, 2007). There is also evidence that high insulin secretion is associated with adverse prognosis (Goodwin *et al.*, 2002; Ma *et al.*, 2008; Pollak, 2008a; Wolpin *et al.*, 2009). However, preliminary reports do not indicate that hyperinsulinemia post anti-IGF-IR treatment translate to worse outcome (Gualberto *et al.*, 2008a). Likewise, better outcomes are not apparent in patients who develop hyperglycemia (Karp *et al.*, 2009). Nevertheless, should hyperinsulinemia or IGF-I elevations be found to be associated with reduced clinical benefit from IGF-IR targeting, there would be clear justification for examining combinations of IGF-IR antibodies with metformin or pegvisomant, as well as exploring in more detail tyrosine kinase inhibitors that target both insulin and IGF-I signaling.

Conclusions

Early clinical trials of IGF-IR-targeting agents have been encouraging enough to justify expanded clinical trial programs. Pharmacodynamic evidence that anti-IGF-IR antibodies reduce receptor signaling is strong. Safety profiles, at least for short- and medium-term treatment durations, are favorable. It is too early to reach conclusions on efficacy. However, rare but impressive instances of major responses in phase I heavily pre-treated patients, together with early evidence of clinical benefit in combination with chemotherapy for lung cancer, have led to expanded development programs. Challenges at this stage include the multitude of potential indications, rational study design and execu-

tion, and the need for concurrent evaluation of biomarkers for resistance and sensitivity.

Two decades ago, there was speculation that it might be possible to design IGF-IR-targeting agents of utility in cancer treatment (Myal *et al.*, 1984; Pollak *et al.*, 1987; Arteaga *et al.*, 1989). Recent efforts have shown that molecular entities with the necessary pharmacological properties can indeed be developed, and the intense clinical trial and translational research activity presently underway will soon provide definite data on their value in cancer treatment.

Abbreviations

ACC, adrenocortical carcinoma; ALL, acute lymphocytic leukemia; CML, chronic myeloid leukaemia; CTCs, circulating tumor cells; DLT, dose-limiting toxicity; GH, growth hormone; IGFBP-3, insulin-like growth factor-binding protein; IGF-IR, insulin-like growth factor I receptor; IR, insulin receptor; NSCLC, non-small cell lung cancer; q2weeks, every 2 weeks; q3weeks, every 3 weeks; q4weeks, every 4 weeks.

References

- Adelaide J, Finetti P, Bekhouche I, Repellini L, Geneix J, Sircoulomb F *et al.* (2007). Integrated profiling of basal and luminal breast cancers. *Cancer Res* **67**: 11565–11575.
- Ahlgren M, Melbye M, Wohlfahrt J, Sorensen TI. (2004). Growth patterns and the risk of breast cancer in women. *N Engl J Med* **351**: 1619–1626.
- Allen GW, Saba C, Armstrong EA, Huang SM, Benavente S, Ludwig DL *et al.* (2007). Insulin-like growth factor-I receptor signaling blockade combined with radiation. *Cancer Res* **67**: 1155–1162.
- Arteaga CL, Kitten LJ, Coronado EB, Jacobs S, Kull Jr FC, Allred DC *et al.* (1989). Blockade of the type I somatomedin receptor inhibits growth of human breast cancer cells in athymic mice. *J Clin Invest* **84**: 1418–1423.
- Attard G, Fong PC, Molife R, Reade S, Shaw H, Reid A *et al.* (2006). Phase I trial involving the pharmacodynamic (PD) study of circulating tumour cells, of CP-751,871 (C), a monoclonal antibody against the insulin-like growth factor 1 receptor (IGF-1R), with docetaxel (D) in patients (p) with advanced cancer. *J Clin Oncol* **24**: 126s.
- Atzori F, Taberner J, Cervantes A, Botero M, Hsu K, Brown H *et al.* (2008). A phase I, pharmacokinetic (PK) and pharmacodynamic (PD) study of weekly (qW) MK-0646, an insulin-like growth factor-1 receptor (IGF1R) monoclonal antibody (MAb) in patients (pts) with advanced solid tumors. *J Clin Oncol* **26**: 157s.
- Barr S, Buck E, Thomson S, Haley J, Gibson N, Ji Q *et al.* (2007). The combination of small molecule inhibitors of EGFR and IGF-1R is synergistic in HNSCC and ovarian cancer cell lines. *Proc Am Assoc Cancer Res* **48**: 608.
- Baserga R, Peruzzi F, Reiss K. (2003). The IGF-1 receptor in cancer biology. *Int J Cancer* **107**: 873–877.
- Belfiore A. (2007). The role of insulin receptor isoforms and hybrid insulin/IGF-I receptors in human cancer. *Curr Pharm Des* **13**: 671–686.
- Benini S, Manara MC, Baldini N, Cerisano V, Massimo S, Mercuri M *et al.* (2001). Inhibition of insulin-like growth factor I receptor increases the antitumor activity of doxorubicin and vincristine against Ewing's sarcoma cells. *Clin Cancer Res* **7**: 1790–1797.
- Benyoucef S, Surinya KH, Hadaschik D, Siddle K. (2007). Characterization of insulin/IGF hybrid receptors: contributions of the insulin receptor L2 and Fn1 domains and the alternatively spliced exon 11

Conflict of interest

Dr Pollak received research funds from Pfizer Inc., and has consulted for OSI, BMS, Amgen, and Pfizer. Dr Gualberto is an employee of Pfizer Inc.

Note added in proof

18 additional reports concerning IGF-IR targeting strategies in cancer treatment were presented at the 2009 Annual Meeting of the American Society for Clinical Oncology in May 2009 and published in *Journal of Clinical Oncology* **27**: 15s (2009) after acceptance of this paper but prior to its publication, and most of these could not be cited in this review.

Acknowledgements

We thank D Yee and numerous colleagues for constructive criticism and encouragement. Editorial assistance was provided by ACUMED, Tytherington, UK and was funded by Pfizer Inc. This study was supported by funding from Pfizer Inc.

- sequence to ligand binding and receptor activation. *Biochem J* **403**: 603–613.
- Best CJ, Ludwig DL, Steeg PS. (2006). Breast cancer cell lines resistant to either tamoxifen or Herceptin exhibit sensitivity to the anti-IGF receptor antibody A12 *in vitro*. *Proc Am Assoc Cancer Res* **47**: 290.
- Britten C, Smith D, Bui L, Clary D, Hurwitz H. (2008). A phase I dose de-escalation study of XL228, a potent IGF1R/src inhibitor in patients with advanced malignancies. Presented at the 20th EORTC-NCI-AACR symposium on Molecular Targets and Cancer Therapeutics Congress, 21–24 October 2008, Geneva, Switzerland.
- Buck E, Eyzaguirre A, Rosenfeld-Franklin M, Thomson S, Mulvihill M, Barr S *et al.* (2008). Feedback mechanisms promote cooperativity for small molecule inhibitors of epidermal and insulin-like growth factor receptors. *Cancer Res* **68**: 8322–8332.
- Cao L, Yu Y, Darko I, Currier D, Mayeenuddin LH, Wan X *et al.* (2008). Addiction to elevated insulin-like growth factor I receptor and initial modulation of the AKT pathway define the responsiveness of rhabdomyosarcoma to the targeting antibody. *Cancer Res* **68**: 8039–8048.
- Ceda GP, Dall'Aglio E, Maggio M, Lauretani F, Bandinelli S, Falzoi C *et al.* (2005). Clinical implications of the reduced activity of the GH-IGF-I axis in older men. *J Endocrinol Invest*. **28**(11 Suppl): 96–100.
- Chan JM, Stampfer MJ, Giovannucci E, Gann PH, Ma J, Wilkinson P *et al.* (1998). Plasma insulin-like growth factor-I and prostate cancer risk: a prospective study. *Science* **279**: 563–566.
- Chitnis MM, Yuen JS, Protheroe AS, Pollak M, Macaulay VM. (2008). The type 1 insulin-like growth factor receptor pathway. *Clin Cancer Res* **14**: 6364–6370.
- Cohen BD, Baker DA, Soderstrom C, Tkalcovic G, Rossi AM, Miller PE *et al.* (2005). Combination therapy enhances the inhibition of tumor growth with the fully human anti-type 1 insulin-like growth factor receptor monoclonal antibody CP-751,871. *Clin Cancer Res* **11**: 2063–2073.
- Cortes J, Paquette R, Talpaz M, Pinilla J, Asatiani E, Wetzler M *et al.* (2008). Preliminary clinical activity in a phase I trial of the BCR-ABL/IGF-1R/aurora kinase inhibitor XL228 in patients with Ph⁺ leukemias with either failure to multiple TKI therapies

- or with T315I mutation. Presented at the 50th ASH Annual Meeting and Exposition, San Francisco, USA, 6–9 December 2008, <http://ash.confex.com/ash/2008/webprogram/Paper13204.html>.
- Cox ME, Gleave ME, Zakikhani M, Bell RH, Piura E, Vickers E *et al.* (2009). Insulin receptor expression by human prostate cancers. *Prostate* **69**: 33–40.
- De Bono JS, Attard G, Adjei A, Pollak MN, Fong PC, Haluska P *et al.* (2007). Potential applications for circulating tumor cells expressing the insulin-like growth factor-I receptor. *Clin Cancer Res* **13**: 3611–3616.
- De Bono JS, Attard G, Adjei A, Pollak MN, Fong PC, Haluska P *et al.* (2008). Activity of the anti-IGF-IR antibody CP-751,871 in combination with docetaxel as first-line treatment for castration-resistant prostate cancer in a randomized phase II trial. Presented at the *Molecular Targets and Cancer Therapeutics Congress*, 21–24 October 2008, Geneva, Switzerland.
- del Rincon JP, Iida K, Gaylann BD, McCurdy CE, Leitner JW, Barbour LA *et al.* (2007). Growth hormone regulation of p85 α expression and phosphoinositide 3-kinase activity in adipose tissue: mechanism for growth hormone-mediated insulin resistance. *Diabetes* **56**: 1638–1646.
- Diorio C, Pollak M, Byrne C, Masse B, Hebert-Croteau N, Yaffe M *et al.* (2005). Insulin-like growth factor-I, IGF-binding protein-3, and mammographic breast density. *Cancer Epidemiol Biomarkers Prev* **14**: 1065–1073.
- Dong MQ, Venable JD, Au N, Xu T, Park SK, Cociorva D *et al.* (2007). Quantitative mass spectrometry identifies insulin signaling targets in *C. elegans*. *Science* **317**: 660–663.
- Feng Y, Dimitrov DS. (2008). Monoclonal antibodies against components of the IGF system for cancer treatment. *Curr Opin Drug Discov Devel* **11**: 178–185.
- Gebre-Medhin M, Kindblom LG, Wennbo H, Tornell J, Meis-Kindblom JM. (2001). Growth hormone receptor is expressed in human breast cancer. *Am J Pathol* **158**: 1217–1222.
- Girnita A, Girnita L, del PF, Bartolazzi A, Larsson O, Axelson M. (2004). Cycloignans as inhibitors of the insulin-like growth factor-I receptor and malignant cell growth. *Cancer Res* **64**: 236–242.
- Glaït C, Tencer L, Ravid D, Sarfstein R, Liscovitch M, Werner H. (2006). Caveolin-1 up-regulates IGF-I receptor gene transcription in breast cancer cells via Sp1- and p53-dependent pathways. *Exp Cell Res* **312**: 3899–3908.
- Goodin S. (2008). Development of monoclonal antibodies for the treatment of colorectal cancer. *Am J Health Syst Pharm* **65**: S3–S7.
- Goodwin PJ, Ennis M, Pritchard KI, Trudeau ME, Koo J, Madarnas Y *et al.* (2002). Fasting insulin and outcome in early-stage breast cancer: results of a prospective cohort study. *J Clin Oncol* **20**: 42–51.
- Gualberto A, Karp DD. (2008). Development of a monoclonal antibody against the IGF-IR for the treatment of non small cell lung cancer (CP-751,871). *Clin Lung Cancer* June 2009 (in press).
- Gualberto A, Melvin CL, Dean A, Ang AL, Reynolds JM, Lee AV *et al.* (2008a). Characterization of NSCLC patients responding to anti-IGF-IR therapy. *J Clin Oncol* **26**: 424s.
- Gualberto A, Melvin CL, Dean A, Ang AL, Reynolds JM, Lee AV *et al.* (2008b). IGF-IR markers in NSCLC patients on anti-IGF-IR therapy. *Ann Oncol* **19**: viii62.
- Guix M, Faber AC, Wang SE, Olivares MG, Song Y, Qu S *et al.* (2008). Acquired resistance to EGFR tyrosine kinase inhibitors in cancer cells is mediated by loss of IGF-binding proteins. *J Clin Invest* **118**: 2609–2619.
- Haluska P, Shaw HM, Batzel GN, Yin D, Molina JR, Molife LR *et al.* (2007). Phase I dose escalation study of the anti insulin-like growth factor-I receptor monoclonal antibody CP-751,871 in patients with refractory solid tumors. *Clin Cancer Res* **13**: 5834–5840.
- Hartog H, Wesseling J, Boezen HM, van der Graaf WT. (2007). The insulin-like growth factor 1 receptor in cancer: old focus, new future. *Eur J Cancer* **43**: 1895–1904.
- Hidalgo M, Tirado Gomez M, Lewis N, Vuky JL, Taylor G, Hayburn JL *et al.* (2008). A phase I study of MK-0646, a humanized monoclonal antibody against the insulin-like growth factor receptor type 1 (IGF1R) in advanced solid tumor patients in a q2 wk schedule. *J Clin Oncol* **26**: 158s.
- Higano CS, Yu EY, Whiting SH, Gordon MS, Lorusso P, Fox F *et al.* (2007). A phase I, first in man study of weekly IMC-A12, a fully human insulin like growth factor-I receptor IgG1 monoclonal antibody, in patients with advanced solid tumors. Presented at the 2007 Prostate Cancer Symposium, Orlando, USA, 22–24 February, 2007 (Abstract 269) http://www.asco.org/ASCO/Abstracts+%26+Virtual+Meeting/Abstracts?&vmview=abst_detail_view&confID=46&abstractID=20331.
- Hochberg Z. (2002). Mechanisms of steroid impairment of growth. *Horm Res* **58**(Suppl 1): 33–38.
- Huang F, Greer A, Hurlburt W, Han X, Hafezi R, Wittenberg GM *et al.* (2009). The mechanisms of differential sensitivity to an insulin-like growth factor-1 receptor inhibitor (BMS-536924) and rationale for combining with EGFR/HER2 inhibitors. *Cancer Res* **69**: 161–170.
- Hyun T, Yam A, Pece S, Xie X, Zhang J, Miki T *et al.* (2000). Loss of PTEN expression leading to high Akt activation in human multiple myelomas. *Blood* **96**: 3560–3568.
- Ji QS, Mulvihill MJ, Rosenfeld-Franklin M, Cooke A, Feng L, Mak G *et al.* (2007). A novel, potent, and selective insulin-like growth factor-I receptor kinase inhibitor blocks insulin-like growth factor-I receptor signaling *in vitro* and inhibits insulin-like growth factor-I receptor dependent tumor growth *in vivo*. *Mol Cancer Ther* **6**: 2158–2167.
- Karp DD, Paz-Ares LG, Novello S, Haluska P, Garland L, Cardenal F *et al.* (2009). Phase II study of the efficacy of the anti-insulin-like growth factor type 1 receptor antibody CP-751,871 in combination with paclitaxel and carboplatin in previously untreated, locally advanced, or metastatic non-small cell lung cancer. *J Clin Oncol* **27**: 2516–2522.
- Klinakis A, Szabolcs M, Chen G, Xuan S, Hibshoosh H, Efstratiadis A. (2009). Ig1r as a therapeutic target in a mouse model of basal-like breast cancer. *Proc Natl Acad Sci USA* **106**: 2359–2364.
- Kopchick JJ, Parkinson C, Stevens EC, Trainer PJ. (2002). Growth hormone receptor antagonists: discovery, development, and use in patients with acromegaly. *Endocr Rev* **23**: 623–646.
- Lacy MQ, Alsina M, Fonseca R, Paccagnella ML, Melvin CL, Yin D *et al.* (2008). Phase I, pharmacokinetic and pharmacodynamic study of the anti-insulinlike growth factor type 1 Receptor monoclonal antibody CP-751,871 in patients with multiple myeloma. *J Clin Oncol* **26**: 3196–3203.
- Lammers R, Gray A, Schlessinger J, Ullrich A. (1989). Differential signalling potential of insulin- and IGF-1-receptor cytoplasmic domains. *EMBO J* **8**: 1369–1375.
- Law JH, Habibi G, Hu K, Masoudi H, Wang MY, Stratford AL *et al.* (2008). Phosphorylated insulin-like growth factor-i/insulin receptor is present in all breast cancer subtypes and is related to poor survival. *Cancer Res* **68**: 10238–10246.
- Leong S, Gore L, Benjamin R, Warren TL, Eckhardt SG, Camidge DR *et al.* (2007). A phase I study of R1507, a human monoclonal antibody IGF-1R (insulin-like growth factor receptor) antagonist given weekly inpatients with advanced solid tumors. Presented at the *AACR-NCI-EORTC Molecular Targets and Cancer Therapeutics Meeting*, San Francisco, USA, 22–26 October 2007, http://www.aacr.org/Uploads/DocumentRepository/2007conf/moltar/mt07_postera.pdf.
- Lindsay CR, Chan E, Evans TR, Campbell S, Bell P, Stephens AW *et al.* (2009). Phase I dose escalation study of continuous oral dosing of OSI-906, an insulin like growth factor-1 receptor (IGF-1R) tyrosine kinase inhibitor, in patients with advanced solid tumors. *J Clin Oncol* **27**: 15s (suppl; abstr 2559).
- Lu Y, Zi X, Zhao Y, Mascarenhas D, Pollak M. (2001). Insulin-like growth factor-I receptor signaling and resistance to trastuzumab (Herceptin). *J Natl Cancer Inst* **93**: 1852–1857.
- Ma J, Li H, Giovannucci E, Mucci L, Qiu W, Nguyen PL *et al.* (2008). Prediagnostic body-mass index, plasma C-peptide concentration, and prostate cancer-specific mortality in men with prostate cancer: a long-term survival analysis. *Lancet Oncol* **9**: 1039–1047.

- Majeed N, Blouin MJ, Kaplan-Lefko PJ, Barry-Shaw J, Greenberg NM, Gaudreau P *et al.* (2005). A germ line mutation that delays prostate cancer progression and prolongs survival in a murine prostate cancer model. *Oncogene* **24**: 4736–4740.
- Martin MJ, Melnyk N, Pollard M, Bowden M, Leong H, Podor TJ *et al.* (2006). The insulin-like growth factor I receptor is required for Akt activation and suppression of anoikis in cells transformed by the ETV6-NTRK3 chimeric tyrosine kinase. *Mol Cell Biol* **26**: 1754–1769.
- Mendelsohn J, Baselga J. (2006). Epidermal growth factor receptor targeting in cancer. *Semin Oncol* **33**: 369–385.
- Moreau P, Hulin C, Facon T, Boccadoro M, Mery-Mignard D, Deslandes A *et al.* (2007). Phase I study of AVE1642 anti IGF-1R monoclonal antibody in patients with advanced multiple myeloma. *Blood. ASH Annual Meeting Abstracts*, <http://abstracts.hematologylibrary.org/cgi/content/abstract/110/11/1166?maxto show=&HITS=10&hits=10&RESULTFORMAT=&fulltext=AVE1642&searchid=1&FIRSTINDEX=0&volume=110&issue=11&resourcetype=HWCIT>.
- Morrow LA, O'Brien MB, Moller DE, Flier JS, Moses AC. (1994). Recombinant human insulin-like growth factor-I therapy improves glycemic control and insulin action in the type A syndrome of severe insulin resistance. *J Clin Endocrinol Metab* **79**: 205–210.
- Myal Y, Shiu RP, Bhaumick B, Bala M. (1984). Receptor binding and growth-promoting activity of insulin-like growth factors in human breast cancer cells (T-47D) in culture. *Cancer Res* **44**: 5486–5490.
- Natrajan R, Reis-Filho JS, Little SE, Messahel B, Brundler MA, Dome JS *et al.* (2006). Blastemal expression of type I insulin-like growth factor receptor in Wilms' tumors is driven by increased copy number and correlates with relapse. *Cancer Res* **66**: 11148–11155.
- O'Reilly KE, Molife R, Okuno S, Worden F, Hammer G, Yap T *et al.* (2006). mTOR inhibition induces upstream receptor tyrosine kinase signaling and activates Akt. *Cancer Res* **66**: 1500–1508.
- Olmos D, Molife R, Okuno S, Worden F, Hammer G, Yap T *et al.* (2007). Safety, tolerability and preliminary efficacy of the anti-IGF-1R monoclonal antibody CP-751,871 in patients with sarcomas and adrenocortical tumors. *Presented at the AACR-NCI-EORTC Molecular Targets and Cancer Therapeutics Meeting, San Francisco, USA, 22–26 October 2007*, [http://www.aacr.org/Uploads/Document Repository/2007conf/mol tar/mt07_postera.pdf](http://www.aacr.org/Uploads/DocumentRepository/2007conf/mol tar/mt07_postera.pdf).
- Olmos D, Okuno S, Schuetze SM, Pacagnella ML, Yin D, Gualberto A *et al.* (2008). Safety, pharmacokinetics and preliminary activity of the anti-IGF-1R antibody CP-751,871 in patients with sarcoma. *J Clin Oncol* **26**: 553s.
- Plymate SR, Haugk K, Coleman I, Woodke L, Vessella R, Nelson P *et al.* (2007). An antibody targeting the type I insulin-like growth factor receptor enhances the castration-induced response in androgen-dependent prostate cancer. *Clin Cancer Res* **13**: 6429–6439.
- Pollak M. (2008a). Insulin and insulin-like growth factor signalling in neoplasia. *Nat Rev Cancer* **8**: 915–928.
- Pollak M. (2008b). Targeting insulin and insulin-like growth factor signalling in oncology. *Curr Opin Pharmacol* **8**: 384–392.
- Pollak M, Blouin MJ, Zhang JC, Kopchick JJ. (2001). Reduced mammary gland carcinogenesis in transgenic mice expressing a growth hormone antagonist. *Br J Cancer* **85**: 428–430.
- Pollak M, Eisenberg P, Karp D, Cohen R, Kreisman H, Adjei A *et al.* (2007). Safety and tolerability of the anti-IGF-1 receptor antibody CP-751,871 in combination with paclitaxel and carboplatin in patients with advanced solid tumors. *AACR Meeting Abstracts (abstract LB-343)*, http://www.aacrmeetingabstracts.org/cgi/content/meeting_abstract/2007/1_Annual_Meeting/LB-343?maxto show=&HITS=10&hits=10&RESULTFORMAT=1&author1=Pollak&title=paclitaxel+carboplatin&andorexacttitle=&and&andorexacttitleabs=&and&searchid=1&FIRSTINDEX=0&sortspec=relevance&fdate=1/1/2007&tdate=12/31/2007&resourcetype=HWCIT.
- Pollak MN, Perdue JF, Margolese RG, Baer K, Richard M. (1987). Presence of somatomedin receptors on primary human breast and colon carcinomas. *Cancer Lett* **38**: 223–230.
- Pollak MN, Schernhammer ES, Hankinson SE. (2004). Insulin-like growth factors and neoplasia. *Nat Rev Cancer* **4**: 505–518.
- Postel-Vinay S, Okuno S, Schuetze SM, Pacagnella L, Yin D, Gualberto A *et al.* (2008). Safety, pharmacokinetics and preliminary activity of the anti-IGF-1R antibody CP-751,871 in patients with sarcoma. *Presented at the 20th EORTC-NCI-AACR symposium on Molecular Targets and Cancer Therapeutics Congress, 21–24 October 2008, Geneva, Switzerland*.
- Rodon J, DeSantos V, Ferry Jr RJ, Kurzrock R. (2008). Early drug development of inhibitors of the insulin-like growth factor-I receptor pathway: lessons from the first clinical trials. *Mol Cancer Ther* **7**: 2575–2588.
- Rodon J, Patnaik A, Stein M, Tolcher A, Ng C, Dias C *et al.* (2007). A phase I study of q3w R1507, a human monoclonal antibody IGF-1R antagonist in patients with advanced cancer. *J Clin Oncol* **25**: 160s.
- Rothenberg ML, Poplin E, Sandler AB, Rubin EH, Fox F, Schwartz J *et al.* (2007). Phase I dose-escalation study of the anti-IGF-1R recombinant human IgG1 monoclonal antibody (Mab) IMC-A12, administered every other week to patients with advanced solid tumors. *Presented at the AACR-NCI-EORTC Molecular Targets and Cancer Therapeutics Meeting, San Francisco, USA, 22–26 October 2007*, http://www.aacr.org/Uploads/DocumentRepository/2007conf/mol tar/mt07_posterc.pdf.
- Russo VC, Gluckman PD, Feldman EL, Werther GA. (2005). The insulin-like growth factor system and its pleiotropic functions in brain. *Endocr Rev* **26**: 916–943.
- Ryan PD, Neven P, Dirix LY, Barrios CH, Miller WH, Fenton D *et al.* (2008). Safety of the anti-IGF-1R antibody CP-751,871 in combination with exemestane in patients with advanced breast cancer. *Presented at the 31st Annual San Antonio Breast Cancer Meeting, San Antonio, USA, 10–14 December 2008*.
- Sachdev D, Singh R, Fujita-Yamaguchi Y, Yee D. (2006). Down-regulation of insulin receptor by antibodies against the type I insulin-like growth factor receptor: implications for anti-insulin-like growth factor therapy in breast cancer. *Cancer Res* **66**: 2391–2402.
- Sachdev D, Yee D. (2007). Disrupting insulin-like growth factor signaling as a potential cancer therapy. *Mol Cancer Ther* **6**: 1–12.
- Samani AA, Yakar S, LeRoith D, Brodt P. (2007). The role of the IGF system in cancer growth and metastasis: overview and recent insights. *Endocr Rev* **28**: 20–47.
- Sarantopoulos J, Mita AC, Mulay M, Romero O, Lu J, Capilla F *et al.* (2008). A phase IB study of AMG 479, a type I insulin-like growth factor receptor (IGF1R) antibody, in combination with panitumumab (P) or gemcitabine (G). *J Clin Oncol* **26**: 173s.
- Sell C, Rubini M, Rubin R, Liu JP, Efstratiadis A, Baserga R. (1993). Simian virus 40 large tumor antigen is unable to transform mouse embryonic fibroblasts lacking type I insulin-like growth factor receptor. *Proc Natl Acad Sci USA* **90**: 11217–11221.
- Seraj J, Tsai M, Seiberling M, Cutler D. (2007). Evaluation of safety and pharmacokinetics of a fully human IGF-1 receptor antibody, SCH 717454, in healthy volunteers. *Presented at the AACR-NCI-EORTC Molecular Targets and Cancer Therapeutics Meeting, San Francisco, USA, 22–26 October 2007*, http://www.aacr.org/Uploads/DocumentRepository/2007conf/mol tar/mt07_postera.pdf.
- Shaw RJ, Lamia KA, Vasquez D, Koo SH, Bardeesy N, Depinho RA *et al.* (2005). The kinase LKB1 mediates glucose homeostasis in liver and therapeutic effects of metformin. *Science* **310**: 1642–1646.
- Slamon DJ, Leyland-Jones B, Shak S, Fuchs H, Paton V, Bajamonde A *et al.* (2001). Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med* **344**: 783–792.
- Taberero J. (2008). The role of the IGF-1R inhibitor in CRC. *Presented at the 33rd ESMO congress, Stockholm, Sweden, 12–16 September, 2008*, http://www.esmo.org/fileadmin/media/presentations/977/1976/Taberero_ESMO%20symposium%202008_slide%20presentation_d02b.ppt.pdf.

- Tao Y, Pinzi V, Bourhis J, Deutsch E. (2007). Mechanisms of disease: signaling of the insulin-like growth factor I receptor pathway—therapeutic perspectives in cancer. *Nat Clin Pract Oncol* **4**: 591–602.
- Tarn C, Rink L, Merkel E, Flieder D, Pathak H, Koumbi D *et al.* (2008). Insulin-like growth factor I receptor is a potential therapeutic target for gastrointestinal stromal tumors. *Proc Natl Acad Sci USA* **105**: 8387–8392.
- Tolcher AW, Rothenberg ML, Rodon J, Delbeke D, Patnaik A, Nguyen L *et al.* (2008). A phase I study of AVE1642, a humanized monoclonal antibody IGF-1R (insulin like growth factor I receptor) antagonist, in patients (pts) with advanced solid tumor (ST). *J Clin Oncol* **26**: 173s.
- Tolcher AW, Patnaik A, Till E, Takimoto CH, Papadopoulos KP, Massard C *et al.* (2007). A phase I pharmacokinetic and pharmacodynamic study of AMG 479, a fully human monoclonal antibody against insulin-like growth factor type I receptor (IGF-1R), in advanced solid tumors. *J Clin Oncol* **25**: 118s.
- Wan X, Harkavy B, Shen N, Grohar P, Helman LJ. (2007). Rapamycin induces feedback activation of Akt signaling through an IGF-1R-dependent mechanism. *Oncogene* **26**: 1932–1940.
- Weroha SJ, Haluska P. (2008). IGF-1 receptor inhibitors in clinical trials—early lessons. *J Mammary Gland Biol Neoplasia* **13**: 471–483.
- Wiseman LR, Johnson MD, Wakeling AE, Lykkesfeldt AE, May FE, Westley BR. (1993). Type I IGF receptor and acquired tamoxifen resistance in oestrogen-responsive human breast cancer cells. *Eur J Cancer* **29A**: 2256–2264.
- Witt K. (2008). OSI Pharmaceuticals Oncology Portfolio: R&D Strategy and Update on Pipeline. Securities and Exchange Commission OSI Pharmaceuticals Inc. 8-K form for 11/26/2008, Exhibit 99.1.
- Wolpin BM, Meyerhardt JA, Chan AT, Ng K, Chan JA, Wu K *et al.* (2009). Insulin, the insulin-like growth factor axis, and mortality in patients with nonmetastatic colorectal cancer. *J Clin Oncol* **27**: 176–185.
- Wu JD, Haugk K, Coleman I, Woodke L, Vessella R, Nelson P *et al.* (2006). Combined *in vivo* effect of A12, a type I insulin-like growth factor receptor antibody, and docetaxel against prostate cancer tumors. *Clin Cancer Res* **12**: 6153–6160.
- Wu JD, Odman A, Higgins LM, Haugk K, Vessella R, Ludwig DL *et al.* (2005). *in vivo* effects of the human type I insulin-like growth factor receptor antibody A12 on androgen-dependent and androgen-independent xenograft human prostate tumors. *Clin Cancer Res* **11**: 3065–3074.
- Wu Y, Cui K, Miyoshi K, Hennighausen L, Green JE, Setser J *et al.* (2003). Reduced circulating insulin-like growth factor I levels delay the onset of chemically and genetically induced mammary tumors. *Cancer Res* **63**: 4384–4388.
- Yee D. (2006). Targeting insulin-like growth factor pathways. *Br J Cancer* **94**: 465–468.
- Yin D, Paccagnella ML, Lacy MQ, De Bono JS, Haluska P, Gualberto A *et al.* (2008). Population pharmacokinetics of CP-751,871, a monoclonal antibody against IGF-I receptor, in patients with multiple myeloma or solid tumors. *J Clin Oncol* **26**: 118s.
- Yuen JS, Macaulay VM. (2008). Targeting the type I insulin-like growth factor receptor as a treatment for cancer. *Expert Opin Ther Targets* **12**: 589–603.
- Zhang H, Pelzer AM, Kiang DT, Yee D. (2007) Down-regulation of type I insulin-like growth factor receptor increases sensitivity of breast cancer cells to insulin. *Cancer Res* **67**: 391–397.
- Zhang L, Zhou W, Velculescu VE, Kern SE, Hruban RH, Hamilton SR *et al.* (1997). Gene expression profiles in normal and cancer cells. *Science* **276**: 1268–1272.