

## Minireview

# Targeting insulin-like growth factor pathways

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Some cancer cells depend on the function of specific molecules for their growth, survival, and metastatic potential. Targeting of these critical molecules has arguably been the best therapy for cancer as demonstrated by the success of tamoxifen and trastuzumab in breast cancer. This review will evaluate the type I IGF receptor (IGF-IR) as a potential target for cancer therapy. As new drugs come forward targeting this receptor system, several issues will need to be addressed in the early clinical trials using these agents.

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There are several excellent reviews outlining a rationale for targeting the IGF system in cancer (for example Pollak *et al*, 2004). Indeed, the first clinical trials testing a monoclonal antibody directed against the type I IGF receptor (IGF-IR) are currently underway. Thus, the questions have turned away from ‘should we target this pathway?’ to several other questions concerning best clinical strategies for anti-IGF therapies. This mini-review will address questions to address in the upcoming clinical trials.

## WHAT ARE THE TARGETS?

Like many other growth factor systems, the IGF system consists of more than a single ligand interacting with a single receptor. There are three ligands (IGF-I, IGF-II and insulin) that interact with at least four receptors. In addition, the IGF system also involves six well characterized binding proteins that regulate IGF action (Clemmons, 1998). IGF-IR is a transmembrane tyrosine kinase that is highly related to insulin receptor (IR). The function for IR in health and disease is well known. IGF-IR plays an important role in childhood growth as demonstrated in both humans and mice (Liu *et al*, 1993; Abuzzahab *et al*, 2003). In addition to these holoreceptors, hybrids between IGF-IR and IR have exist (Federici *et al*, 1997). Interestingly, two splice variants of IR have been documented. The IR-A fetal splice variant is more frequently found in cancer (Frasca *et al*, 1999). The type II IGF receptor (IGF-IIR) has high affinity for IGF-II, but does not apparently transmit an extracellular signal. This receptor has been characterized as a ‘sink’ for IGF-II and its loss has been demonstrated in human cancer (MacDonald *et al*, 1988). Thus, in the extracellular space, the IGF ligands have potential interactions with four receptors and six binding proteins.

IGF-IR, IR, and hybrid receptors all function as covalently linked dimers. As such, physiologic activation of these receptors by overexpression alone is not seen, in contrast to the epidermal growth factor (EGF) receptor family members. While there are

some cell model studies demonstrating activation of IGF-IR by overexpression of receptor or intracellular tyrosine kinases (Kozma and Weber, 1990), activation of IGF-IR requires binding to ligand in most physiologic settings. This important fact has implications for anti-IGF therapy as noted below.

To date, much of the focus has been placed on IGF-IR. However, it must be remembered that IR may play a role in cancer cell biology. At physiologic concentrations of insulin, breast cancer cells are stimulated to proliferate *in vitro* (Osborne *et al*, 1976). In addition, activation of IR-A by IGF-II has been demonstrated in breast cancer cell lines (Sciacca *et al*, 1999). Thus, inhibition of both IGF-IR and IR may be required for optimal suppression of IGF signalling pathways. This possibility adds a layer of complexity to targeting the IGF system, as dysfunctional IR signalling is well understood and results in type II diabetes.

These preclinical data suggest that targeting of only IGF-IR may be insufficient to block tumor growth regulated by the IGFs and insulin. Since inhibition of IR could have profound effects on host glucose homeostasis, further definition of IR as an important target in cancer cells is needed.

## WHAT IS THE BEST STRATEGY TO BLOCK IGF ACTION?

Given the requirement for ligand activation of IGF-IR signalling, one possible strategy to block this pathway would be to lower IGF-I concentrations. During puberty, growth hormone (GH) release from the pituitary gland results in the production of IGF-I by the liver. Thus, disruption of the hypothalamic–pituitary–liver axis could result in lowered serum IGF-I levels. Several GH releasing hormone (GHRH) antagonists have been described and have antitumour activity in cancer model systems (Letsch *et al*, 2003). A pegylated mutant GH (pegvisomant) has been developed to disrupt GH signalling in patients with acromegaly, a condition of GH excess. This compound also has antitumour activity (McCutcheon *et al*, 2001). While the precise mechanisms for the antitumour activity of these compounds is not completely understood, as both GHRH and GH antagonists may have direct antitumour activity, they both result in suppression of serum IGF-I levels.

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While these drugs could have activity, they do not affect IGF-II levels. Since mice and rodents do not express IGF-II during adulthood (DeChiara *et al*, 1991), it has been difficult to model IGF-II action *in vivo*. Neutralization of IGF ligands could also be effective therapeutic strategies. Pharmacologic antagonism of IGF ligands has been accomplished by neutralizing monoclonal antibodies and IGF-binding proteins (Van den Berg *et al*, 1997; Goya *et al*, 2004). Since these agents would only target the IGF ligands, insulin action would be relatively unaffected.

The bulk of drug development has been directed towards targeting IGF-IR. Several monoclonal antibodies directed against IGF-IR have been created (Li *et al*, 2000; Burtrum *et al*, 2003; Maloney *et al*, 2003; Goetsch *et al*, 2005; Wang *et al*, 2005). To date, all antibodies seem to have a similar mechanism of action and result in IGF-IR downregulation. Unlike binding of the native ligands that allow receptor recycling, several laboratories have shown that monoclonal antibody binding results in endosomal degradation of the receptor (Sachdev *et al*, 2003; Wang *et al*, 2005). While most of the antibodies also block ligand binding and inhibit the activation of the receptor, it is notable that a fully agonistic antibody also has antitumour properties (Li *et al*, 2000; Sachdev *et al*, 2003). This is presumably due to the antibody's ability to downregulate receptor expression. Thus, the agonist properties of the antibody may be less relevant than the ability to downregulate receptor levels over time.

Since IGF-IR is a tyrosine kinase, small molecule inhibitors have also been developed (Garcia-Echeverria *et al*, 2004; Mitsiades *et al*, 2004; Carboni *et al*, 2005). While these compounds show some selectivity of IGF-IR over IR in cell model systems, it is uncertain as to whether this selectivity can be seen *in vivo*. Moreover, whether or not IGF-IR selectivity is even desirable is an open question. As noted above, if IR mediates a substantial portion of IGF-stimulated tumour cell biology, especially via IGF-II activation, then cancer cell inhibition of IR would be necessary.

In addition to small molecule inhibitors, which mostly bind the catalytic site of IGF-IR, other compounds have been described that disrupt receptor function. A cyclolignan, picropodophyllin, has been shown to disrupt IGF-IR activation by interfering with substrate phosphorylation (Vasilcanu *et al*, 2004). This compound appears specific for IGF-IR and has been shown to have activity in several model systems (Girnita *et al*, 2004; Stromberg *et al*, 2006). As noted above, complete selectivity for IGF-IR would have obvious benefits for host glucose may be insufficient for complete disruption of tumour signalling. Another compound, nordihydroguaiaretic acid (NDGA) has also been shown to disrupt IGF-IR activation (Youngren *et al*, 2005). Compared to picropodophyllin, this NDGA is not specific for IGF-IR but also blocks human epidermal growth factor-2 (HER2) signalling. While this might seem undesirable, recent data suggest that IGF-IR plays a role in resistance to the anti-HER2 monoclonal antibody trastuzumab (Nahta *et al*, 2005). Thus, a drug that disrupts both pathways may be of value in specific situations.

Carefully designed clinical trials will be necessary to examine the effect on host glucose metabolism. While temporary inhibition of IR function and resultant hyperinsulinemia or hyperglycemia could be tolerated, insulin resistance over long periods of time would surely be detrimental to patients. Moreover, there are animal model systems showing that disruption of IGF-IR affects survival of the pancreatic beta cells (Withers *et al*, 1999). In a worst case scenario, long-term inhibition of IGF-IR could induce type I and type II diabetes by inhibiting insulin secretion and insulin action, respectively.

## ARE THERE BIOMARKERS FOR IGF ACTION?

The development of trastuzumab and the EGFR tyrosine kinase inhibitors have demonstrated that careful measurement of

biomarkers is necessary when only a minority of patients have 'receptor driven' tumours. In contrast, tamoxifen was initially given to breast cancer patients unselected for estrogen receptor- $\alpha$  (ER $\alpha$ ) status. Eventually it became clear that only ER $\alpha$  expressing patients responded to tamoxifen. However, the early unselected clinical trials were successful because ER $\alpha$  is expressed by the majority of tumours and a high percentage of those ER $\alpha$  positive tumours respond to tamoxifen as a single agent. Thus, biomarkers do not need to be defined if a substantial number of tumours express the target and inhibition of the target causes a clinical response in a high proportion of target-bearing tumours.

While it is clear that IGFs stimulate growth of many tissues, it is difficult to show evidence of IGF-IR activation, even in the most favourable settings. In animal models of IGF action, administration of exogenous IGF is necessary to show activation of IGF signalling pathways (Pete *et al*, 1999). At a minimum, IGF-IR must be present, but beyond this requirement, the 'signature' of an IGF-driven tumour is unclear.

Measurement of key signalling pathways immediately downstream of IGF-IR offers some insight into IGF action. In model systems, the expression of insulin receptor substrate (IRS) molecules is necessary to couple IGF-IR with key downstream signalling pathways. In breast cancer cells, specific IRS adaptor proteins are activated downstream of IGF-IR that link the receptor to specific phenotypes. For example, IRS-1 activation is associated with IGF-stimulated proliferation, while IRS-2 signalling is necessary for metastatic behaviour (Jackson *et al*, 1998, 2001; Nagle *et al*, 2004; Zhang *et al*, 2004). While phosphorylation of IRS proteins has been difficult to show in primary human breast cancers, it is possible that expression of both IGF-IR and distinct IRS species could be used to identify cancers most likely to respond to IGF-IR inhibition.

## HOW SHOULD IGF INHIBITORS BE TESTED IN COMBINATION WITH OTHER DRUGS?

The combination of targeted agents with conventional cytotoxic drugs has provided important insight into the therapeutic synergy. Disruption of HER2 or EGFR enhances cytotoxic drug activity in some, but not all, cancers. Perhaps the most striking example of synergy occurs with the coadministration of trastuzumab with the taxanes. First demonstrated in metastatic breast cancer (Slamon *et al*, 2001), the synergy is even more dramatic in the adjuvant therapy of breast cancer (Piccart-Gebhart *et al*, 2005; Romond *et al*, 2005). Similarly, cetuximab in combination with irinotecan demonstrates therapeutic benefit, even when tumours have progressed beyond irinotecan alone (Cunningham *et al*, 2004). In contrast, gefitinib in combination with paclitaxel and carboplatinum in nonsmall cell lung cancer failed to show any evidence for therapeutic synergy (Herbst *et al*, 2004). Furthermore, tamoxifen given simultaneously with chemotherapy in the adjuvant treatment of breast cancer reduces the benefit for chemotherapy (Albain *et al*, 2002).

These trials show that the synergy between targeted therapies and conventional chemotherapy is not necessarily easily predicted. On one hand, the targeted therapy may induce apoptosis and lower the survival threshold of cancer cells thereby augmenting a second apoptotic stimulus. Trastuzumab, when given as a single agent, induced apoptosis in primary breast cancers (Mohsin *et al*, 2005) and this could be the mechanism of action for the observed benefit of combined therapy. In contrast, some targeted therapies, such as tamoxifen, antagonize the effects of chemotherapy, potentially by altering progression through the cell cycle or by affecting transport of drugs (Osborne *et al*, 1989).

Inhibition of IGF-IR may act in either fashion and may be dependent on the strategy used to block IGF signalling. Monoclonal antibodies directed against IGF-IR induce tumour cell

apoptosis in preclinical model systems and have been shown to synergize with chemotherapy. It has been suggested that downregulation of IGF-IR induces apoptotic cell death (Baserga, 2005). Since all of the currently described antibodies have demonstrated the ability to downregulate receptor, this may be an important mechanism of synergy. In contrast, tyrosine kinase inhibitors successfully inhibit the biochemical activity of IGF-IR and do not appear to downregulate receptor levels. Thus, the tyrosine kinase inhibitors may block progression through S-phase without inducing apoptosis. If this is the case, then the kinase inhibitors may actually interfere with the cell cycle specific effects of chemotherapy similar to the interference observed between tamoxifen and cytotoxic treatment. Careful evaluation of synergy between IGF-IR disruption and combination therapy must be studied in combination clinical trials.

## WHAT'S WRONG WITH IGF ACTION AS A TARGET?

Anti-IGF-IR trials will first be tested in patients with advanced cancers. As noted above, identifying patients with IGF-driven tumours may be difficult. In addition, IGF-IR has many effects on cancer cells that are not easily measured in a phase II clinical trial. For example, IGF-IR activation stimulates motility in many cancer cells. In some cells, IGF-IR activation does not apparently effect proliferation or survival. Thus, these types of cells have fully intact IGF-IR signalling pathways yet lack a phenotypic response to IGF inhibition that can be easily measured in clinical trials. Even the most carefully designed studies with appropriate and robust biomarker measurement would be unable to identify this type of IGF effect.

IGF-IR is ubiquitously expressed in most normal tissues (Werner *et al*, 1991). In this regard, targeting IGF-IR is different than targeting estrogen receptor where relatively limited expres-

sion of the receptor is seen. For example, IGF-IR enhances neuronal survival, maintains cardiac function, stimulates bone formation and hematopoiesis (Zumkeller, 2002; Rosen, 2004; Leininger and Feldman, 2005; Saetrum Opgaard and Wang, 2005). IGF-IR signalling has also been shown to play a role in maintaining survival of pancreatic beta cells (Withers *et al*, 1999). Thus, disruption of IGF-IR could result in many potential toxicities. Of course, these concerns could be raised about essentially every successful cancer therapy. Inhibition of basic cellular processes, such as nucleotide synthesis, tubulin function, and DNA replication have all been proven to be of value in the treatment of cancer despite many potential toxicities. The ongoing clinical trials will determine whether long- or short-term inhibition of IGF-IR results in unacceptable toxicity. Hopefully, these studies will define a therapeutic window for IGF-IR inhibition.

## CONCLUSION

There are many reasons to consider IGF-IR as a target for cancer prevention and therapy. Similarly, there are also many potential methods to disrupt IGF-IR signalling. Finally, there are numerous potential toxicities associated with disruption of IGF-IR activation in normal tissues. As clinical trials move forward, we will determine what is 'potential', what is of clinical relevance, and whether disruption of this growth factor pathway results in relevant clinical outcomes.

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## REFERENCES

- Abuzzahab MJ, Schneider A, Goddard A, Grigorescu F, Lautier C, Keller E, Kiess W, Klammt J, Kratzsch J, Osgood D, Pfaffle R, Raile K, Seidel B, Smith RJ, Chernausk SD (2003) IGF-I receptor mutations resulting in intrauterine and postnatal growth retardation. *N Engl J Med* **349**: 2211–2222
- Albain KS, Green SJ, Ravdin PM, Cobau CD, Levine EG, Ingle JN, Pritchard KI, Schneider DJ, Abeloff MD, Norton L, Henderson IC, Lew D, Livingston RB, Martino S, Osborne CK (2002) Adjuvant chemohormonal therapy for primary breast cancer should be sequential instead of concurrent: initial results from intergroup trial 0100 (SWOG-8814). *Proc ASCO*, Abstract 143
- Baserga R (2005) The insulin-like growth factor-I receptor as a target for cancer therapy. *Expert Opin Ther Targets* **9**: 753–768
- Burtrum D, Zhu Z, Lu D, Anderson DM, Prewett M, Pereira DS, Bassi R, Abdullah R, Hooper AT, Koo H, Jimenez X, Johnson D, Apblett R, Kussie P, Bohlen P, Witte L, Hicklin DJ, Ludwig DL (2003) A fully human monoclonal antibody to the insulin-like growth factor I receptor blocks ligand-dependent signaling and inhibits human tumor growth *in vivo*. *Cancer Res* **63**: 8912–8921
- Carboni JM, Lee AV, Hadsell DL, Rowley BR, Lee FY, Bol DK, Camuso AE, Gottardis M, Greer AF, Ho CP, Hurlburt W, Li A, Saulnier M, Velaparthy U, Wang C, Wen ML, Westhouse RA, Wittman M, Zimmermann K, Rupnow BA, Wong TW (2005) Tumor development by transgenic expression of a constitutively active insulin-like growth factor I receptor. *Cancer Res* **65**: 3781–3787
- Clemmons DR (1998) Role of insulin-like growth factor binding proteins in controlling IGF actions. *Mol Cell Endocrinol* **140**: 19–24
- Cunningham D, Humblet Y, Siena S, Khayat D, Bleiberg H, Santoro A, Bets D, Mueser M, Harstrick A, Verslype C, Chau I, Van Cutsem E (2004) Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. *N Engl J Med* **351**: 337–345
- DeChiara TM, Robertson EJ, Efstratiadis A (1991) Parental imprinting of the mouse insulin-like growth factor II gene. *Cell* **64**: 849–859
- Federici M, Porzio O, Zucaro L, Fusco A, Borboni P, Lauro D, Sesti G (1997) Distribution of insulin/insulin-like growth factor-I hybrid receptors in human tissues. *Mol Cell Endocrinol* **129**: 121–126
- Frasca F, Pandini G, Scalia P, Sciacca L, Mineo R, Costantino A, Goldfine ID, Belfiore A, Vigneri R (1999) Insulin receptor isoform A, a newly recognized, high-affinity insulin-like growth factor II receptor in fetal and cancer cells. *Mol Cell Biol* **19**: 3278–3288
- Garcia-Echeverria C, Pearson MA, Marti A, Meyer T, Mestan J, Zimmermann J, Gao J, Brueggen J, Capraro HG, Cozens R, Evans DB, Fabbro D, Furet P, Porta DG, Liebetanz J, Martiny-Baron G, Ruetz S, Hofmann F (2004) *In vivo* antitumor activity of NVP-AEW541-A novel, potent, and selective inhibitor of the IGF-IR kinase. *Cancer Cell* **5**: 231–239
- Girnita A, Girnita L, del Prete F, Bartolazzi A, Larsson O, Axelsson M (2004) Cyclolignans as inhibitors of the insulin-like growth factor-I receptor and malignant cell growth. *Cancer Res* **64**: 236–242
- Goetsch L, Gonzalez A, Leger O, Beck A, Pauwels PJ, Haeuw JF, Corvaia N (2005) A recombinant humanized anti-insulin-like growth factor receptor type I antibody (h7C10) enhances the antitumor activity of vinorelbine and anti-epidermal growth factor receptor therapy against human cancer xenografts. *Int J Cancer* **113**: 316–328
- Goya M, Miyamoto S, Nagai K, Ohki Y, Nakamura K, Shitara K, Maeda H, Sangai T, Kodama K, Endoh Y, Ishii G, Hasebe T, Yonou H, Hatano T, Ogawa Y, Ochiai A (2004) Growth inhibition of human prostate cancer cells in human adult bone implanted into nonobese diabetic/severe combined immunodeficient mice by a ligand-specific antibody to human insulin-like growth factors. *Cancer Res* **64**: 6252–6258
- Herbst RS, Giaccone G, Schiller JH, Natale RB, Miller V, Manegold C, Scagliotti G, Rosell R, Oliff I, Reeves JA, Wolf MK, Krebs AD, Averbuch SD, Ochs JS, Grous J, Fandi A, Johnson DH (2004) Gefitinib in

- combination with paclitaxel and carboplatin in advanced non-small-cell lung cancer: a phase III trial—INTACT 2. *J Clin Oncol* **22**: 785–794
- Jackson JG, White MF, Yee D (1998) Insulin receptor substrate-1 is the predominant signaling molecule activated by insulin-like growth factor-I, insulin, and interleukin-4 in estrogen receptor-positive human breast cancer cells. *J Biol Chem* **273**: 9994–10003
- Jackson JG, Zhang X, Yoneda T, Yee D (2001) Regulation of breast cancer cell motility by insulin receptor substrate-2 (IRS-2) in metastatic variants of human breast cancer cell lines. *Oncogene* **20**: 7318–7325
- Kozma LM, Weber MJ (1990) Constitutive phosphorylation of the receptor for insulinlike growth factor I in cells transformed by the src oncogene. *Mol Cell Biol* **10**: 3626–3634
- Leininger GM, Feldman EL (2005) Insulin-like growth factors in the treatment of neurological disease. *Endocr Dev* **9**: 135–159
- Letsch M, Schally AV, Busto R, Bajo AM, Varga JL (2003) Growth hormone-releasing hormone (GHRH) antagonists inhibit the proliferation of androgen-dependent and -independent prostate cancers. *Proc Natl Acad Sci USA* **100**: 1250–1255
- Li SL, Liang SJ, Guo N, Wu AM, Fujita Yamaguchi Y (2000) Single-chain antibodies against human insulin-like growth factor I receptor: expression, purification, and effect on tumor growth. *Cancer Immunol Immunother* **49**: 243–252
- Liu JP, Baker J, Perkins AS, Robertson EJ, Efstratiadis A (1993) Mice carrying null mutations of the genes encoding insulin-like growth factor-I (IGF-1) and type-1 IGF receptor (IGF1r). *Cell* **75**: 59–72
- MacDonald RG, Pfeffer SR, Coussens L, Tepper MA, Brocklebank CM, Mole JE, Anderson JK, Chen E, Czech MP, Ullrich A (1988) A single receptor binds both insulin-like growth factor II and mannose-6-phosphate. *Science* **239**: 1134–1137
- Maloney EK, McLaughlin JL, Dagdigian NE, Garrett LM, Connors KM, Zhou XM, Blattler WA, Chittenden T, Singh R (2003) An anti-insulin-like growth factor I receptor antibody that is a potent inhibitor of cancer cell proliferation. *Cancer Res* **63**: 5073–5083
- McCutcheon IE, Flyvbjerg A, Hill H, Li J, Bennett WF, Scarlett JA, Friend KE (2001) Antitumor activity of the growth hormone receptor antagonist pegvisomant against human meningiomas in nude mice. *J Neurosurg* **94**: 487–492
- Mitsiades CS, Mitsiades NS, McMullan CJ, Poulaki V, Shringarpure R, Akiyama M, Hideshima T, Chauhan D, Joseph M, Libermann TA, Garcia-Echeverria C, Pearson MA, Hofmann F, Anderson KC, Kung AL (2004) Inhibition of the insulin-like growth factor receptor-1 tyrosine kinase activity as a therapeutic strategy for multiple myeloma, other hematologic malignancies, and solid tumors. *Cancer Cell* **5**: 221–230
- Mohsin SK, Weiss HL, Gutierrez MC, Chamness GC, Schiff R, Digiovanna MP, Wang CX, Hilsenbeck SG, Osborne CK, Allred DC, Elledge R, Chang JC (2005) Neoadjuvant trastuzumab induces apoptosis in primary breast cancers. *J Clin Oncol* **23**: 2460–2468
- Nagle JA, Ma Z, Byrne MA, White MF, Shaw LM (2004) Involvement of insulin receptor substrate 2 in mammary tumor metastasis. *Mol Cell Biol* **24**: 9726–9735
- Nahta R, Yuan LX, Zhang B, Kobayashi R, Esteva FJ (2005) Insulin-like growth factor-I receptor/human epidermal growth factor receptor 2 heterodimerization contributes to trastuzumab resistance of breast cancer cells. *Cancer Res* **65**: 11118–11128
- Osborne CK, Bolan G, Monaco ME, Lippman ME (1976) Hormone responsive human breast cancer in long-term tissue culture: effect of insulin. *Proc Natl Acad Sci USA* **73**: 4536–4540
- Osborne CK, Kitten L, Arteaga CL (1989) Antagonism of chemotherapy-induced cytotoxicity for human breast cancer cells by antiestrogens. *J Clin Oncol* **7**: 710–717
- Pete G, Fuller CR, Oldham JM, Smith DR, AJ DE, Kahn CR, Lund PK (1999) Postnatal growth responses to insulin-like growth factor I in insulin receptor substrate-1-deficient mice. *Endocrinology* **140**: 5478–5487
- Piccart-Gebhart MJ, Procter M, Leyland-Jones B *et al.* (2005) Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. *N Engl J Med* **353**: 1659–1672
- Pollak MN, Schernhammer ES, Hankinson SE (2004) Insulin-like growth factors and neoplasia. *Nat Rev Cancer* **4**: 505–518
- Romond EH, Perez EA, Bryant J, Suman VJ, Geyer Jr CE, Davidson NE, Tan-Chiu E, Martino S, Paik S, Kaufman PA, Swain SM, Pisansky TM, Fehrenbacher L, Kutteh LA, Vogel VG, Visscher DW, Yothers G, Jenkins RB, Brown AM, Dakhil SR, Mamounas EP, Lingle WL, Klein PM, Ingle JN, Wolmark N (2005) Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. *N Engl J Med* **353**: 1673–1684
- Rosen CJ (2004) Insulin-like growth factor I and bone mineral density: experience from animal models and human observational studies. *Best Pract Res Clin Endocrinol Metab* **18**: 423–435
- Sachdev D, Li SL, Hartell JS, Fujita-Yamaguchi Y, Miller JS, Yee D (2003) A chimeric humanized single-chain antibody against the type I insulin-like growth factor (IGF) receptor renders breast cancer cells refractory to the mitogenic effects of IGF-I. *Cancer Res* **63**: 627–635
- Saetrum Opgaard O, Wang PH (2005) IGF-I is a matter of heart. *Growth Horm IGF Res* **15**: 89–94
- Sciacca L, Costantino A, Pandini G, Mineo R, Frasca F, Scalia P, Sbraccia P, Goldfine ID, Vigneri R, Belfiore A (1999) Insulin receptor activation by IGF-II in breast cancers: evidence for a new autocrine/paracrine mechanism. *Oncogene* **18**: 2471–2479
- Slamon DJ, Leyland-Jones B, Shak S, Fuchs H, Paton V, Bajamonde A, Fleming T, Eiermann W, Wolter J, Pegram M, Baselga J, Norton L (2001) Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med* **344**: 783–792
- Stromberg T, Ekman S, Girnita L, Dimberg LY, Larsson O, Axelson M, Lennartsson J, Hellman U, Carlson K, Osterborg A, Vanderkerken K, Nilsson K, Jernberg-Wiklund H (2006) IGF-1 receptor tyrosine kinase inhibition by the cyclolignan PPP induces G2/M-phase accumulation and apoptosis in multiple myeloma cells. *Blood* **107**: 669–678
- Van den Berg CL, Cox GN, Stroh CA, Hilsenbeck SG, Weng CN, McDermott MJ, Pratt D, Osborne CK, Coronado-Heinsohn EB, Yee D (1997) Polyethylene glycol conjugated insulin-like growth factor binding protein-1 (IGFBP-1) inhibits growth of breast cancer in athymic mice. *Eur J Cancer* **33**: 1108–1113
- Vasilcanu D, Girnita A, Girnita L, Vasilcanu R, Axelson M, Larsson O (2004) The cyclolignan PPP induces activation loop-specific inhibition of tyrosine phosphorylation of the insulin-like growth factor-1 receptor. Link to the phosphatidylinositol-3 kinase/Akt apoptotic pathway. *Oncogene* **23**: 7854–7862
- Wang Y, Hailey J, Williams D, Lipari P, Malkowski M, Wang X, Xie L, Li G, Saha D, Ling WL, Cannon-Carlson S, Greenberg R, Ramos RA, Shields R, Presta L, Brams P, Bishop WR, Pachter JA (2005) Inhibition of insulin-like growth factor-I receptor (IGF-IR) signaling and tumor cell growth by a fully human neutralizing anti-IGF-IR antibody. *Mol Cancer Ther* **4**: 1214–1221
- Werner H, Woloschack M, Stannard B, Shen-Orr Z, Roberts C, Le Roith D (1991) The insulin-like growth factor receptor: molecular biology, heterogeneity, and regulation. In: *Insulin-like Growth Factors: Molecular and Cellular Aspects*, Le Roith D (ed) pp. 18–48
- Withers DJ, Burks DJ, Towery HH, Altamuro SL, Flint CL, White MF (1999) IRS-2 coordinates IGF-1 receptor-mediated beta-cell development and peripheral insulin signalling. *Nat Genet* **23**: 32–40
- Youngren JF, Gable K, Penaranda C, Maddux BA, Zavodovskaya M, Lobo M, Campbell M, Kerner J, Goldfine ID (2005) Nordihydroguaiaretic acid (NDGA) inhibits the IGF-1 and c-erbB2/HER2/neu receptors and suppresses growth in breast cancer cells. *Breast Cancer Res Treat* **94**: 37–46
- Zhang X, Kamaraju S, Hakuno F, Kabuta T, Takahashi S, Sachdev D, Yee D (2004) Motility response to insulin-like growth factor-I (IGF-I) in MCF-7 cells is associated with IRS-2 activation and integrin expression. *Breast Cancer Res Treat* **83**: 161–170
- Zumkeller W (2002) The insulin-like growth factor system in hematopoietic cells. *Leuk Lymphoma* **43**: 487–491