[Frontiers in Bioscience, Scholar, 5, 439-450, January 1, 2013]

Insulin-like growth factor receptor type I as a target for cancer therapy

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1. ABSRACT

After more than 20 years of extensive work, insulin-like growth factor receptor 1 (IGF-IR) is still an attractive target for drug development. Due to its close homology to insulin receptor, IGF-IR is of interest for antibody design while antibody great specificity allows to discriminate between the two receptors. Major efforts from a large number of pharmaceutical companies are invested to evaluate the efficacy of such molecules in human without so far an obvious success. Discovery of biomarkers associated with efficacy and patient selection is one of the main challenges that we will have to deal with in order to target the appropriate patient population that will most benefit anti-IGF-IR monoclonal antibody (Mab) and combined treatments. This review will provide an overview of the current knowledge on IGF-IR axis for development of novel therapeutics in Oncology.

2. IGF-IR AND CANCER

The type-1 insulin-like growth factor receptor (IGF-IR) was cloned in 1986(1). It is the final effector of the endocrine GHRH/GH/IGF-I axis. In normal cells, the growth hormone releasing hormone peptide (GHRH) secreted by the hypothalamus binds to GHRH receptors on somatotrophs in the anterior pituitary and regulates the synthesis and secretion of growth hormone (GH) which in turn results in IGF-I and IGF-II production by the liver. Hepatic IGF-I is the major contributor to circulating IGF-I levels. However, experiments using a Cre/loxP recombinant system to delete igf1 gene exclusively in the liver demonstrate that, in addition to the endocrine pathway, extra-hepatic normal tissue such as kidney, spleen, fat, muscle and bone produce IGF-I in addition to express IGF-IR, resulting in autocrine/paracrine regulation

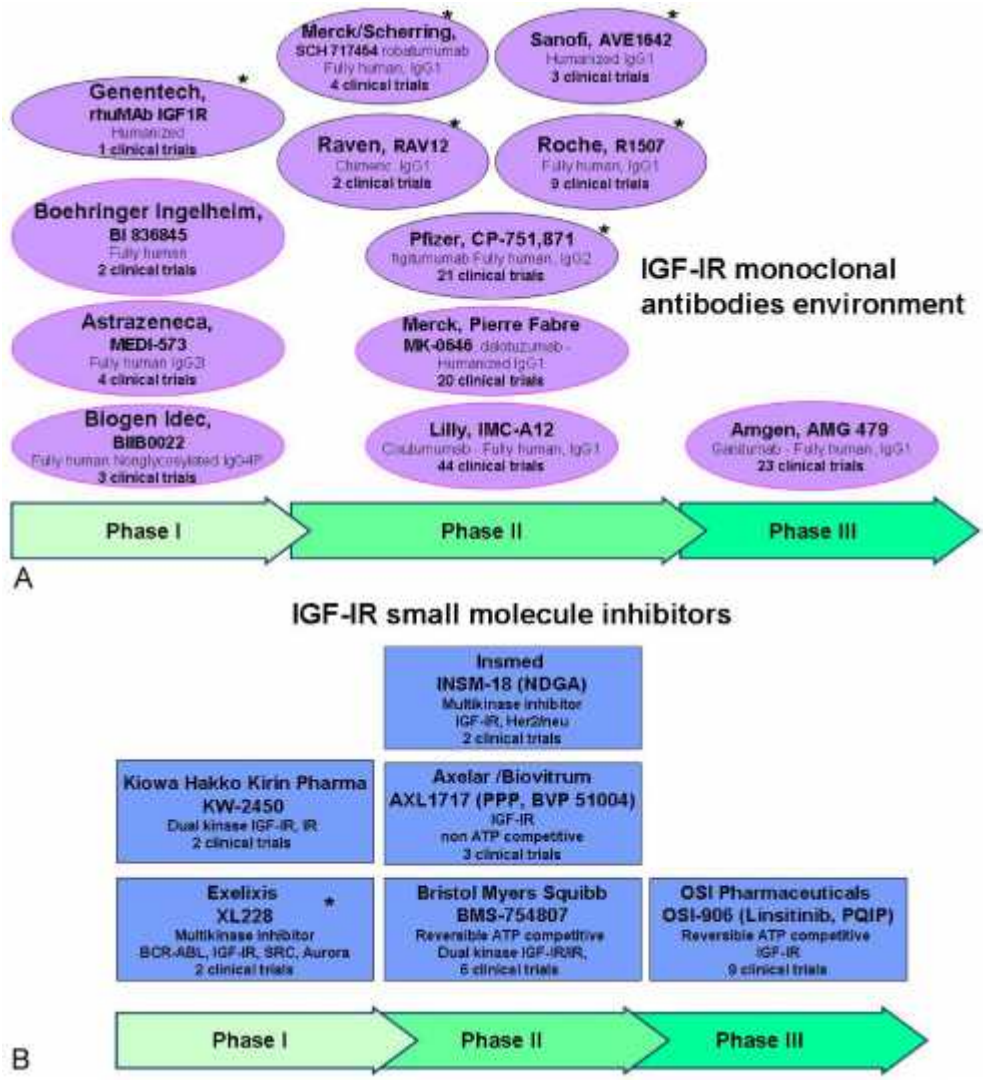

Figure 1. List of molecules currently in clinical trails (A for mabs and B for small molecule inhibitors) Stars indicate that clinical trials has been stopped.

pathways(2). Finally, the binding of IGF-I and IGF-II to IGF-IR is the key regulator of post-natal growth(3).

IGF-IR belongs to a tyrosine kinase receptor family including insulin receptors (IR-A and IR-B, two isoforms that differ by the presence of a twelve residue segment inserted at position 716 of the B isoform) and the insulin receptor-related receptor (IRR). These receptors are disulfide-linked homodimers composed of two extracellular α- and two transmembrane β-subunits. Each α-subunit contains a ligand binding domain whereas the tyrosine kinase (TK) domain bearing an ATP-binding site (lysine 1003), is located in the β-subunit.

At the cellular level, IGF-IR is modulated by a complex network including two ligands, IGF-I and IGF-II, and six known high-affinity circulating binding proteins (BP) that regulate the bioavailability of these ligands to IGF-IR and determine the survival, growth or death of cells. The balance between growth factors and IGFBPs is modulated by specific IGFBP proteases (Figure 1A). IGF-IIR, a cation-independent mannose-6-phosphate receptor, is also involved in this regulation as it plays the role of decoy by sequestering IGF-II and as such behaves as a tumor suppressor(4-5). Finally, a third modulation system is linked to the formation of hybrid receptors (HRs). Due to the high homology between IRs and IGF-IR (50% overall amino acid sequence homology and approximately 85% homology in the tyrosine kinase domain), hybrid insulin/IGF-I receptors occur in cells and tissues co-expressing both receptors(6-7). These receptors are heterodimers formed by assembly of one IR α- and β-chain and one IGF-IR α- and β-chain(8). Within IR isotypes, the IR-A one is the most expressed in cancer diseases(9), consequently IGF-IR/IR-A (HR-A) are the most commonly occurring hybrid receptors found in such pathologies, potentially conferring a significant advantage in terms of mitogenic and anti-apoptotic signals to cancer cells(10) in

response to IGF-I and insulin as well as IGF-II which binds to HR-A with very high affinity(11-12). Binding of ligands to HR-A leads to autophosphorylation and presumably tyrosine kinase activation of both β-subunits(13). Although the biological role of HRs has not been fully elucidated, recent data provide strong evidence that hybrid formation could significantly interfere with the IGF system(14).

IGF-IR signals in response to its ligands. Upon ligand binding, the receptor is trans-autophosphorylated by the dimeric subunit partner on three tyrosine residues (1131, 1135 and 1136) located within the TK domain(15-16). This phosphorylation results in conformational changes that in turn trigger the phosphorylation of other tyrosine residues along the receptor and subsequently activates multiple cytoplasmic substrates such as insulin receptor substrate-1 to 4 (IRS1-4), Shc (Src homology collagen), Grb10 and Src(17). These molecules activate the two main downstream signals of IGF-IR, the mitogen-activated protein kinase (MAPK) and the phosphatidyl inositol-3-kinase (PI3K)/Akt pathways(18-19) (Figure 1B).

In normal cells, IGF-IR pathways are crucial in mediating development and growth from the embryo through adulthood and aging in response to pituitary growth hormone. IGF-IR/IGF-I axis is also involved in regulating differentiation of most cell types and in cellular survival processes(20). Knock-out mice for IGF-IR are minimally viable and show severe growth retardation (45% of normal)(21). KO mice usually die at birth of respiratory failure and display severe muscle hypoplasia as well as abnormality of the central nervous system and epidermis(21-22). Conversely a 30% growth increase is observed in transgenic mice over expressing human IGF-I(23).

During the last decade a major involvement of IGF-IR in cancer development and progression has been demonstrated. The IGF-IR pathway was shown to play a role in tumor genesis, mitogenesis but also metastasis, angiogenesis and anti-apoptosis(24). Both clinical sample analysis and experimental studies of cell lines have shown that IGF-IR is over- expressed in many cancer cell types when compared to normal tissues(25-27). Likewise, increased expression of IGF-I and IGF-II has been documented in various human tumors suggesting that the IGFs play a paracrine and/or autocrine role in promoting tumor growth(19). Epidemiological studies also provide evidences for a role of IGFs in tumor development. Large prospective studies in breast(28),prostate(29), lung(30) and colorectal(31) cancers indicate that high plasmatic concentrations of IGF-I or IGFBP-3 are linked to an increased risk of cancer. The IGF-IR has also been shown experimentally to be crucial for the establishment and maintenance of cellular transformation as exemplified by the ability of IGF-IR$^+$ cells to grow under anchorage-independent conditions(32) and to form tumors in mice(33). Another essential finding that clearly demonstrated the major role played by the IGF-IR in cellular transformation was the demonstration that knock-out mouse embryo cells for this receptor (3T3-like fibroblasts described as R$^-$ cells) are refractory to transformation by viruses, oncogenes and other over-expressed growth factor receptors; each of these conditions readily transforming R$^-$ cells after reintroduction of IGF-IR(33-34). Moreover, in the TRAMP (transgenic adenocarcinoma of the mouse prostate) model, selective over-expression of human igf1 gene in the basal epithelial cells of the prostate resulted in over-expression of IGF-IR in these cells and spontaneous development of prostate cancer(35).

Another key point of the role of IGF-IR in tumorigenesis is its anti-apoptotic function. Over-expression of IGF-IR protects cells from UV irradiation-, cytokine-, and gamma radiation- induced apoptosis(36-38). On the other hand, IGF-IR down-regulation leads to massive apoptosis of tumor cells *in vitro* in anchorage-independent conditions and *in vivo* when grown as tumors in mice(36-39-42). In addition to its role in the establishment of primary tumors, IGF-IR activation is also involved in invasion and metastasis(43) by deregulation of E-cadherin expression or function(44), reduction of cell-cell adhesion, secretion of matrix metalloproteinases(45) which results in stimulation of cell motility and migration. Numerous experiments using dominant negatives mutants of IGF-IR support the significant role of this receptor in the metastatic process(46-47).

Finally, studies have suggested that the IGF-IR signaling pathway can influence other growth factors. The molecular alteration that results in enhanced activation of IGF-IR may represent one mechanism of resistance to trastuzumab, a humanized antibody targeting HER2/neu(48-49). More recently, it has been shown that gefitinib resistant cells exhibit markedly reduced IGFBP-3 and hyperphosphorylation of IGF-IR leading to a constitutive association of IRS-1 with PI3K(50). Addition of IGFBP-3 or inhibition of IGF-IR signaling restored the ability of gefitinib to down-regulate signaling and to inhibit cell growth suggesting that IGF-IR is involved in the gefitinib resistance process. These observations are in agreement with synergies observed with combined anti-EGFR and anti-IGF-IR treatments(51) and with the abrogation of gefitinib drug resistance when administered with an anti-IGF-IR therapy(50). Another cross talk has been identified between IGF-IR and vascular endothelial growth factor (VEGF). Elevated VEGF levels correlate with increased progression and poor prognosis of head and neck squamous cell carcinomas (HNSCC). For this cancer type, the presence of an IGF-I-regulated VEGF autocrine loop has been suggested(52).

Taken together, all these data emphasize the interest of IGF-IR as a target for cancer therapies.

3. STRATEGIES FOR TARGETING IGF-IR AND ONGOING CLINICAL TRIALS

The original strategies used to demonstrate that targeting IGF-IR *in vivo* impairs tumor growth involved either dominant negative mutants(53) or antisense oligonucleotides directed against IGF-IR mRNA(54) that down-regulates IGF-1R and results in massive apoptosis of

tumor cells *in vivo*. Interestingly, in addition to the apoptotic effect, antitumor responses elicited by antisens in syngeneic immunocompetent animals protected them from subsequent tumor challenge and caused regression of established tumors with no further recurrence. This latter observation suggested the involvement of an immunological response in addition to the direct effect on IGF-1R(55). A pilot study involving the use of this antisens oligodeoxynucleotide in patients carrying malignant astrocytomas gave the first line of evidence on the importance of IGF-IR. In this clinical assay, no side effects were noticed and eight out of twelve patients including three cases of distal recurrence showed unexpected spontaneous or post-surgical regression at either the primary or the distant intracranial site(56). Murine monoclonal antibodies(57-59) were also described. The best known is the αIR3 Mab(60). Many other approaches including suppression, sequestration of the ligand(61) or interference with IGF binding proteins(62) have been explored. However, there was a twenty years lag and a tremendous amount of work between the discovery of IGF-IR and the development of drugs targeting IGF-IR by pharmaceutical companies. As discussed by K. Garber(63), the two possible reasons for this delay are i) the risk of targeting the homologous IR with non-selective inhibitors and ii) the ubiquitous expression of IGF-IR in normal tissues(63). The success of targeted therapies against tyrosine kinase receptors such as Her2/neu and EGFR probably contributed to an increased interest of many drug companies in the IGF-IR. This review will focus on humanized or human antibodies and small molecule tyrosine kinase inhibitors (TKIs) which represent the most advanced compounds being developed to target IGF-IR.

3.1. Current agents targeting IGF-IR

Two classes of molecules have been developed by pharmaceutical companies in order to block IGF-IR signaling: tyrosine kinase inhibitors (TKI) and antibodies. What was initially a potential advantage of targeting IGF-IR with antibodies was the high specificity of these compounds that allows a clear discrimination between IGF-IR and IR could ultimately be a problem as it was reported that IR isoform A through dimerization with IGF-IR may provide mitogenic stimuli to cancer cells through activation via IGF-2. Recent data have suggested that it could be a mechanism of resistance to therapies in particular anti-IGF-IR Mabs(64-65). The development of antibody humanization, recent advances in genetically engineered mice and the availability of human antibody phage libraries resulted in the emergence of a new class of products: humanized and fully human Mabs that overcome the major problems occurring with immunogenicity of murine antibodies. Currently, the development of anti-IGF-IR Mabs is the focus of many pharmaceutical companies with 12 identified antibodies in the preclinical or clinical stage of development (Figure 1A). These antibodies could be divided into two groups depending on their ability to activate effector functions such as ADCC (antibody-dependent cell cytotoxicity) and CDC (complement-dependent cytotoxicity). MK-0646(51), AVE 1642(66), IMC-A12(67), R1507(68), AMG 479(69), SCH 717454(70) are humanized or fully human IgG1 antibodies that may activate effector functions in addition to their direct effect on signaling and down-regulation of IGF-IR. RAV12(71), a chimeric antibody directed against a glycotope of IGF-IR, is a murine Fv domain engineered onto a human IgG1-Fc domain and may also activate the immune component.

Alternatively, CP-751,871(72) and BIIB022(73) are two fully human antibodies that probably act as poor or non activators of the cellular immune response. CP-751,871 is the only IgG2 antibody being developed in this field and as such is a poor activator of the cellular immune response. However, as an IgG2, CP-751,871 could display a potentially longer circulating half-life. Finally BIIB022, a fully human non gylcosylated IgG4P antibody totally devoid of Fc-effector function and engineered with a gamma 1 like hinge region has been developed by Biogen Idec.

All these antibodies are described as specific and high affinity binders for IGF-IR. They i) block IGF-IR/IGF interaction, ii) inhibit cell proliferation and induce apoptosis by blocking IGF-IR signaling and by internalizing and degrading IGF-IR. Within the signaling cascade, the anti-IGF-IR Mabs are described as very efficient blockers of IRS-1, IRS-2, Akt and ERK1/2 phosphorylation. All of them demonstrate significant *in vivo* activities in various xenograft and orthotopic models including breast, colon, NSCLC, pancreatic cancers and sarcomas(51-66-70-72). Moreover, it has been shown that MK-0646, IMC-A12 and CP-751871 enhance the activity of cytotoxic therapeutics, biological therapeutics(51-69-72-74-75) and radiations(76). MK-0646, IMC-A12, CP-751,871 and SCH 717454 are described as Mabs binding to the heterodimeric IGF-IR/IR hybrid receptors(67-70-72-77).

One antibody was selected below to illustrate the safety profile and the type of responses observed when targeting IGF-IR. Several very recent reviews have summarized the state of art regarding clinical benefit of anti-IGF-IR treatments(78-79) and are summarized in the Figures 1A and 1B.

The example selected among Mabs under clinical trial evaluation is MK-0646 (dalotuzumab). This humanized IgG1 Mab blocks IGF-I and IGF-II induced signaling with a significant effect on IRS-1, IRS-2 and Shc phosphorylation. A one hour incubation of cells with MK-0646 totally abolishes activation of PI3K activity, phosphorylation of Akt and various MAPKs effectors including ERK1/2, JNKs and p38. Another key point of the activity of MK-0646 both in *in vitro* models and in *in vivo* xenografts is its ability to down-regulate IGF-IR(51-80) but also HR-A and B(77). Its efficiency has been shown as a single therapy in many xenograft models and combination studies have demonstrated that it synergizes with Vinorelbine and Cetuximab(51). In addition to its direct action on IGF-IR signaling, MK-0646 also has the potential to elicit ADCC activity. First in man studies on chemo-refractory solid tumors(81) investigate two aspects. The first one was to determine the safety profile and

pharmacokinetic parameters of MK-0646. Secondary criteria selected for this first phase I trial were i) to assess changes in molecular markers of the IGF-IR pathways in serial tumors and skin biopsies, ii) to follow the clinical activity (RECIST criteria) and iii) to study tumor metabolism using ^{18}FDG-PET/CT. The most frequently observed drug-related adverse event was a hyperglycaemia in 10% of treated patients. Chills, tumor pain, purpura, nausea, rash, asthenia and pyrexia were also observed. Three patients experienced grade 3 hyperglycaemia beyond the DLT period and were treated successfully with metformin, an anti-hyperglycaemic agent. MTD was not reached at a dose of 20 mg/kg/week. PD studies on tumor biopsies showed an IGF-IR signaling inhibition after MK-0646 treatment with significant inhibitions of pMAPK, eIF4-E, p4EBP-1 and pS6. For doses of MK-0646 ≥ 5 mg/kg, a significant decrease in Ki67 was observed. As demonstrated in preclinical studies, a significant down-regulation of IGF-IR was shown in patients infused with MK-0646. A mean IGF-I plasma level increase was observed in all patients following MK-0646 treatment. FDG-PET metabolic responses occurred in three patients. One patient with Ewing's sarcoma showed a mixed radiological response and 3 patients had stable disease for ≥12 weeks (24, 16 and 13 weeks respectively). A multicentre phase Ib study was conducted in parallel to the first in man study. Interim results, presented at the 2008 ASCO meeting, confirmed the safety profile of MK-0646 and the evidence of signaling modulation after MK-0646 treatment. Based on these results, additional phase I trials were planned to assess safety of combined therapies and phase II trials are ongoing in lung, pancreatic, colon and metastatic neuroendocrine tumors. Last year, the phase II/III randomized double-blind, placebo-controlled trial of dalotuzumab with cetuximab and irinotecan in patients with KRAS wild-type stage IV colorectal cancer was stopped owing to worsened PFS and overall survival in patients randomized to the dalotuzumab arm (82).

Side effects described for MK-0646 are representative of those described for the other tested Mabs and early signs of activity were observed in all clinical trials(83-88). Long term stable disease, minor or partial responses have been reported with a particular focus on sarcoma which seems to be particularly sensitive to IGF-IR targeting. In addition to what was described above for MK-0646, a spectacular complete response was observed in an Ewing's sarcoma patient treated with AMG-479(89) and two partial responses were observed in the same indication with R1507(83). Theses evidences of single agent activity in sarcoma patients are consistent with previous studies highlighting the critical role of IGFs/IGF-IR axis in this tumor type(90-91). So far two molecules have moved to phase III: AMG-479 in combinaison with gemcitabine in stage IV pancreatic cancer patients for antibody and OSI-906 (linsitinib), an roal small molecule in a phase II randomized double-blind, placebo controlled trial in 135 patients with locally advanced or metastatic adrenocortical carcinoma.

Six years after initiation of clinical trials with molecules targeting IGF-IR and a lot of expectations, only few companies are still running clinical trials in the IGF-IR axis. Several hypotheses are now explored in order to improve clinical benefit of such compounds.

3.2. IGF-IR: which population to target ?

The success of clinical development of targeted therapies depends on the identification of susceptible patients in whom the target is absolutely necessary for tumor pathogenesis and progression. Lessons from EGFR modulators have demonstrated that they are only efficacious in tumors that exhibit genetic alterations of the receptor itself (92) or that do not bear mutated K-ras(93-95). The main challenge that is currently being faced is to identify with appropriate biomarkers those tumors that may respond to IGF-IR inhibition and how to detect as earlier as possible if target inhibition has been achieved.

If some approved targeted agents work by targeting the “oncogene addiction” of cancer, other therapies such as trastuzumab target breast cancer HER2 gene amplification. So far, no specific mutations, translocations or amplifications of IGF-IR in cancer have been reported. Fortunately, tremendous work has been performed in the IGF-IR/IGF-I field and novel potential biomarkers have been proposed based on extensive basic research work. The expression level of IGF-IR has recently been proposed to predict the response to Mab therapy in rhabdomyosarcoma cell lines expressing high levels of IGF-IR in which 80 to 90% of Akt signaling depends on elevated IGF-IR(75). Constitutively activated Akt would thus circumvent the inhibitory effect of anti-IGF-IR Mabs. Other parameters may be of importance in the tumor sensitivity to anti-IGF-IR Mab treatment like i) the presence or the absence of IGF-IR/IR hybrid receptors(96), ii) HER receptor since its signaling confers resistance to the IGF-IR inhibitor BMS-536924(97), iii) or interaction with integrins(98-99). Recently, Byron *et al*(100) reported that anti-IGF-IR Mab was ineffective in T74D-YA breast cancer cells until IRS-1 and IRS-2 were introduced into the cells. The transfected cells became sensitive to IGF-I and therefore responded to anti-IGF-IR treatment. Other factors proposed from preclinical data like IRS-1 (Baserga(101)), PTEN status is(69-102-103) and K-ras status has been investigated in response to anti-IGF-IR treatment in mice but are still under further discussion in human.

In clinical trials, as already reported in preclinical studies(51-67-70-72-104-106), down-regulation of IGF-IR has been reported in humans on circulating blood cells(107), circulating tumor cells(108) and on tumor biopsies(81). After treatment with CP-751,871, a decrease both in circulating tumor cells and IGF-IR positive tumor cells was reported suggesting that the treatment could have a cytotoxic effect. After treatment with MK-0646, inhibition of IGF-IR has been reported (decrease in pAkt, pMAPK and pS6). It remains to be demonstrated that changes in receptor number or phosphorylation of signaling proteins correlate with efficacy and clinical benefit. Changes in IGF-I level, hyperglycaemia have also been reported in clinical

trials(81-107) but remain to be explained and correlated to either efficacy or toxicity.

3.3. IGF-IR: Are we dealing with the right target ?

At high concentration, IGF-I is known to bind to both IGF-IR and IR. Targeting IGF-IR has been reported that IR-A and IR-B were up-regulated and interestingly, targeting both IGF-IR and IR blocked tumor growth. Initial design of drugs targeting IGF-IR was focused on potential safety issues if IR would be also blocked. Thus antibodies, selected to only bind to IGF-IR appeared to be the preferred approach for such target. More than 100 clinical trials have been performed using either TKI or antibodies or tumor. Bypass of IGF-IR pathway via IR-A is an option that has been proposed (79). Antibodies block IGF-IR and some also interfere with hybrid receptors but IR-A is not affected. Thus TKIs might be ultimately a better approach since they block both IGF-IR and IR signals (109-110). On going clinical trials hopefully will bring some information.

4. FUTURE PERSPECTIVES

IGF-IR is a major factor in tumor growth and agents that interfere with this receptor will be of importance for cancer treatment and patient benefit in the coming years. Since the cloning of IGF-IR in 1986, a considerable number of scientific publications were generated bringing a strong scientific rationale to target IGF-IR with Mabs. Clinical trials and translational research will help to address scientific questions that are still unexplained, in particular the existence and the exact role of hybrid receptors, the importance of cross-talk with other growth factor receptors, EGFR in particular and the effect of combined therapies. One can expect that following the ongoing clinical trials, we will more clearly understand the biology of the receptor in humans and will define useful biomarkers of efficacy and predictivity.

In the next few years, exciting clinical trials and translational research will provide information and explanations in order to identify biomarkers for anti-IGF-IR treatments, thus allowing the targeting of populations that will most benefit from anti-IGF-IR Mabs and combined treatments.

5. ACKNOWLEDGEMENT

We acknowledge Claire Catry for helping in manuscript preparation

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Key Words: IGF-IR, Cancer, antibodies, Tyrosine Kinase Inhibitors, Biomarkers, Translational Research, Review

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