Published in final edited form as:
Clin Exp Allergy. 2011 October ; 41(10): 1337–1340. doi:10.1111/j.1365-2222.2011.03764.x.

Why could passive Immunoglobulin E antibody therapy be safe in clinical oncology?

E. Jensen-Jarolim and **J. Singer**
Institute of Pathophysiology and Allergy Research IPA, Center of Pathophysiology, Infectiology and Immunology, Medical University Vienna, Vienna, Austria

Passive immunotherapy with antibodies belongs to the state of the art treatment not only in allergy, but also in rheumatology and, especially successful in oncology. These therapies are based on the concept of monoclonal antibodies and exploit (1) the epitope-specific effects of an antibody as well as (2) the effects determined by the constant domain of the immunoglobulin isotype. Thereby, monoclonal antibody therapies have the capacity to modulate biological processes. For instance omalizumab (Xolair®, Novartis, Basel, Switzerland), via binding to the Fcε3 domain of IgE [1], interferes with FcεRI binding and thus hinders allergic reactivity [2]; infliximab (Remicade®, Centocor, Ortho Biotech Inc, Malvern, PA, USA) binds tumour necrosis factor-α (TNF-α) and as a consequence dampens inflammation [3]; therapies like the anti IL-12/IL-23 antibody ustekinumab (Stelara®, Centocor) being recently FDA approved for the treatment of psoriasis, promise cure for multiple skin diseases dependent on this pro-inflammatory pathway [4].

In clinical oncology often both mechanistic aspects of monoclonal antibodies are important. For example, one growth inhibitory aspect of the FDA approved human epidermal growth factor receptor (EGFR, HER-1) monoclonal antibodies cetuximab (Erbitux®, MerckKGaA, Darmstadt, Germany) and panitumumab (Vectibix®, Amgen Inc, Thousand Oaks, CA, USA) [5] as used, for example, in colon cancer, is to interfere in an epitope-specific manner with receptor configuration and thus binding of its ligand EGF (epidermal growth factor) [6, 7]. The anti-HER-2 monoclonal antibody trastuzumab (Herceptin®, Roche, Hertfordshire, UK) which is applied in metastatic breast cancer and other HER-2 overexpressing cancer entities [8], has anti-proliferative actions because it inhibits hetero- and homodimerization of the EGFR family member HER-2 [9]. However, antibody therapies used in oncology including the examples mentioned above, also exploit immunological effector functions and stimulate immune attack specifically against the targeted cancer cells [10]. The efficacy of antibody-dependent cell-mediated cytotoxicity (ADCC) is dependent on the affinity to the antigen and its overexpression level [11]. The interaction of applied antibodies and effector cells is mediated by their Fc domains that determine not only the binding to complement, but also binding to their relevant Fc receptors. Therefore, the class or subclass of an antibody critically determines its effector function. All presently approved immunoglobulins belong to the IgG class, whereas intensive research on IgA is ongoing [12-14]. Therefore,

Correspondence: Prof. Erika Jensen-Jarolim, MD, Inst. of Pathophysiology and Allergy Research, Center of Pathophysiology, Infectiology and Immunology, Medical University Vienna. erika.jensen-jarolim@meduniwien.ac.at.

Europe PMC Funders Author Manuscripts

the today most important Ig receptors are FcγRI-III (and much less FcαRI). FcγR equipped effector cells are predominantly constituted by NK cells, macrophages, neutrophils and eosinophils, which accomplish antibody-dependent cytotoxicity (ADCC) and -phagocytosis of the tumour cell. For some monoclonal antibody therapies also complement-dependent cytotoxicity plays a role in their anti-cancer efficacy [15]. To this end, IgG antibody therapies are therefore among the most successful immunological therapies today. Needless to say that simultaneously, four of the five human immunoglobulin classes are more or less ignored. It can be anticipated that thereby, modern medicine might miss important therapy options.

The recently introduced concept of AllergoOncology [16] deals with exactly this problem and aims to address the opportunities vs. possible pitfalls of IgE-mediated and Th2-biased cellular responses in malignant diseases. Previous pioneer studies and current work have collected *in vitro* and *in vivo* evidence that engineered anti-cancer IgE antibodies may be comparable, or even superior to their IgG counterparts [17-22]. In these studies IgG and IgE with exactly the same variable domains and antigen affinity, but with either γ or ε constant domains, have been compared head-to-head in functional assays, which combine oncologic and allergologic readouts. For instance, effector cells such as mast cells or macrophages, which express both FcγRI and FcεRI, can be sensitized with anti-tumour-specific IgG or IgE. Bound to these effector cells they could be shuttled into the tissue site. Consequently, instead of a soluble antigen or allergen, a tumour cell overexpressing the specific epitope of the antibody can be used as the target. The released mediators are further tested for their tumoricidal effects. For instance, TNF-α has been early proposed to lyse tumour cells upon ADCC [23]. As can be seen from the name, TNF-α had been originally identified in necrotic tumour tissue before its pathophysiological role in inflammation including allergy was recognized [24].

In spite of numerous elegant studies and the accumulating evidence that IgE could have beneficial roles in clinical oncology, studies with IgE anti-tumour antigen antibodies have so far not risen above preclinical proof of concept studies. This might be due to serious concerns in respect to the role of IgE antibodies in anaphylaxis. In sensitized organisms minute levels of allergen may be sufficient to trigger IgE-armed allergy effector cells, and lead to potentially deleterious systemic hypersensitivity reactions. In this context it is worth mentioning that anaphylactic reactions are well known in routine clinical oncology, because allergic reactions to biologicals [25] or chemotherapy are relatively common side-effects [26]. Oncologists try to prevent them by pre-medication with anti-allergic drugs.

Interestingly, clinical and immunohistochemical studies have shown that IgE specific to tumour antigens and with tumoricidic properties can be found in tumour patients in the circulation and the tumour tissue [27, 28]. In a recent diagnostic study we compared the IgE levels in 96 serum samples from oncology patients to those in 688 samples from allergic subjects. The comparative prevalence of IgE levels for instance for EGFR was four times higher in cancer patients [29]. However, anaphylaxis has not been observed in any of the above mentioned studies on naturally occurring IgE antibodies in head and neck cancers, pancreatic, ovary, breast or colon cancers. The question arises how tumour-specific IgE may

be beneficial without increasing the anaphylactic risk. This knowledge could be exploited for the design of IgE-based cancer immunotherapeutics.

The most important basic principle in Type I allergy is that only allergens which are able to target more than one IgE bound to FcεRI on effector cells will lead to productive crosslinking and mediator release [30]. According to that principle, IgE towards tumour antigens also need to be cross-linked by tumour antigens to be tumoricidal. When comparing thus the requirements of an allergen to those needed for an overexpressed tumour antigen, the critical point seems to be epitope-spacing and -rigidity. More than any other immunoglobulin class IgE antibodies are tightly fixed to their receptor in a bent form [31]. This geometry determines the minimal requirements for epitope spacing on the triggering antigen for successful IgE bridging. More than at least two epitopes have to be minimally 40Å and maximally 240Å apart, and they have to be displayed rather rigidly [32]. These requirements are excellently fulfilled by most potent allergens forming covalent multimers, but may also be achieved by non-covalent complexing of molecules by aggregation. The capacity of cellular antigens to bridge cytophilic IgE has thus to follow strict geometrical rules and in principle, two different scenarios can be considered: (i) at low-level antigen expression, for instance such as levels of growth factor receptors on healthy cells, IgE bridging cannot be achieved; (ii) in contrast, overexpressed tumour antigens, tightly packed on the whole cell membrane or packed in lipid rafts, obviously may achieve bridging requirements because they form tumour-associated molecular patterns [32]. This implicates that at the site of the tumour, IgE may fully exert all effector functions via FcεRI on shuttle cells, such as macrophages, mast cells and eosinophils. All these cell types have been observed previously in tumour tissues [33, 34].

Ideally, an engineered tumour-specific IgE antibody may, like natural anti-tumour IgE, exploit the specific effector mechanisms at the site of the tumour where the highest target antigen expression is found, but not systemically.

There is, however, a last concern before clinical studies with therapeutic IgE can be initiated: The possible crosslinking capacity of soluble forms of tumour antigens. This important concern is carefully addressed by Rudman and co-workers in this issue [35]. For most tumours, antigen shedding is a well-known mechanism as a sign of immunological escape [36]; moreover some soluble tumour antigens may regulate tumour growth for instance by modulating angiogenesis or lymphangiogenesis [37], or by interaction with specific receptors [38]. Alternatively metalloproteinases like ADAM15 may shed functional ectodomains of membrane antigens that stabilize heterodimerization and, as a result lead to receptor activation [39]. Therefore, soluble tumour antigens in the circulation may potentially trigger anaphylactic effector cells via tumour-specific IgE before it has been shuttled to the cancer tissue, if it has capacity to crosslink IgE.

In line with their previous fundamental work on anticancer IgE in this issue Rudman et al. tackle this question by a series of elegant *in vitro* assays. Their work is the logical consequence of a series of studies, in which they repeatedly could demonstrate the superior *in vitro* and *in vivo* efficacy of a recombinant anti-folate receptor α (FRα) IgE antibody Mov18 [17-20]. FRα is very specifically overexpressed in ovarian cancer and represents

therefore an interesting target [40], but it is also found in a monomeric form in the circulation. The potential IgE crosslinking capacity of soluble FRα represents thus an important safety aspect that needs to be answered in readiness for clinical application of IgE for cancer treatment.

Indeed, the authors add convincing evidence for safety of a humanized IgE-anti-tumour antibody: In line with the *in silico* stereometric arguments above, they demonstrate that FRα overexpressed on tumour cells, but not soluble FRα is able to crosslink the engineered anti-FRα IgE antibody when fixed to effector cells. This effect could be reproduced using a rat basophil leukaemia cell line transfected with human FcεRI [41]. More close to the clinical setting, the effects could be reproduced with patients' primary human basophils either isolated or within whole blood which also did not get activated by Mov18 IgE in context with monomeric soluble FRα. This observation held true although levels of soluble FRα were significantly elevated in ovarian cancer patients' sera as compared to healthy controls. Their data suggest that the extent of FRα overexpression on the tumour cells and the density of tumour cells determine the IgE-crosslinking capacity. Therefore, circulating tumour cells will most likely not be able to trigger mediator release. The truly innovative aspect of this highly interdisciplinary work is that not only assays are used which support a research hypothesis, but also material from cancer patients suffering from ovarian cancer of various stages which supports the clinical relevance of the observations.

The work by Rudman et al. [35] may open up avenues to novel anti-cancer therapeutics based on IgE antibodies in clinical oncology. For the allergy field, studies on this specific topic may contribute to the basic understanding of IgE biology possibly offering a rationale for the survival of IgE immunoglobulins.

Acknowledgements

This work was supported by grants of the Austrian Science Fund FWF, 23398-B11, APW 01205 FW and by Biomedical International R+D, Vienna, Austria.

References

1. Zheng L, Li B, Qian W, et al. Fine epitope mapping of humanized anti-IgE monoclonal antibody omalizumab. Biochem Biophys Res Commun. 2008; 375:619–22. [PubMed: 18725193]
2. Corren J, Casale TB, Lanier B, Buhl R, Holgate S, Jimenez P. Safety andtolerability of omalizumab. Clin Exp Allergy. 2009; 39:788–97. [PubMed: 19302249]
3. Danese S, Colombel JF, Reinisch W, Rutgeerts PJ. Review article: infliximab for Crohn's disease treatment – shifting therapeutic strategies after 10 years of clinical experience. Aliment Pharmacol Ther. 2011; 33:857–69. [PubMed: 21320139]
4. Kurzeja M, Rudnicka L, Olszewska M. New interleukin-23 pathway inhibitors in dermatology: ustekinumab, briakinumab, and secukinumab. Am J Clin Dermatol. 2011; 12:113–25. [PubMed: 21348542]
5. Saif MW, Kaley K, Chu E, Copur MS. Safety and efficacy of panitumumab therapy after progression with cetuximab: experience at two institutions. Clin Colorectal Cancer. 2010; 9:315–8. [PubMed: 21208847]
6. Li S, Schmitz KR, Jeffrey PD, Wiltzius JJ, Kussie P, Ferguson KM. Structural basis for inhibition of the epidermal growth factor receptor by cetuximab. Cancer Cell. 2005; 7:301–11. [PubMed: 15837620]

7. Schmitz KR, Ferguson KM. Interaction of antibodies with ErbB receptor extracellular regions. Exp Cell Res. 2009; 315:659–70. [PubMed: 18992239]
8. Lordick F. Trastuzumab: a new treatment option for HER2-positive metastatic gastric and gastroesophageal junction cancer. Future Oncol. 2011; 7:187–99. [PubMed: 21345138]
9. Ghosh R, Narasanna A, Wang SE, et al. Trastuzumab has preferential activity against breast cancers driven by HER2 homodimers. Cancer Res. 2011; 71:1871–82. [PubMed: 21324925]
10. Yan L, Hsu K, Beckman RA. Antibody-based therapy for solid tumors. Cancer J. 2008; 14:178–83. [PubMed: 18536557]
11. Tang Y, Lou J, Alpaugh RK, Robinson MK, Marks JD, Weiner LM. Regulation of antibody-dependent cellular cytotoxicity by IgG intrinsic and apparent affinity for target antigen. J Immunol. 2007; 179:2815–23. [PubMed: 17709495]
12. Cohen J, Wilson A. New challenges to medicare beneficiary access to mAbs. MAb J. 2009; 1:56–66.
13. Reichert JM, Wenger JB. Development trends for new cancer therapeutics and vaccines. Drug Discov Today. 2008; 13:30–7. [PubMed: 18190861]
14. Lohse S, Derer S, Beyer T, et al. Recombinant dimeric IgA antibodies against the epidermal growth factor receptor mediate effective tumor cell killing. J Immunol. 2011; 186:3770–8. [PubMed: 21317397]
15. Weiner LM, Surana R, Wang S. Monoclonal antibodies: versatile platforms for cancer immunotherapy. Nat Rev Immunol. 2010; 10:317–27. [PubMed: 20414205]
16. Jensen-Jarolim E, Achatz G, Turner MC, et al. AllergoOncology: the role of IgE-mediated allergy in cancer. Allergy. 2008; 63:1255–66. [PubMed: 18671772]
17. Gould HJ, Mackay GA, Karagiannis SN, et al. Comparison of IgE,IgG antibody-dependent cytotoxicity in vitro andin a SCID mouse xenograft model of ovarian carcinoma. Eur J Immunol. 1999; 29:3527–37. [PubMed: 10556807]
18. Karagiannis SN, Wang Q, East N, et al. Activity of human monocytes in IgE antibody-dependent surveillance and killing of ovarian tumor cells. Eur J Immunol. 2003; 33:1030–40. [PubMed: 12672069]
19. Karagiannis SN, Bracher MG, Hunt J, et al. IgE-antibody-dependent immunotherapy of solid tumors: cytotoxic and phagocytic mechanisms of eradication of ovarian cancer cells. J Immunol. 2007; 179:2832–43. [PubMed: 17709497]
20. Karagiannis SN, Bracher MG, Beavil RL, et al. Role of IgE receptors in IgE antibody-dependent cytotoxicity and phagocytosis of ovarian tumor cells by human monocytic cells. Cancer Immunol Immunother. 2008; 57:247–63. [PubMed: 17657488]
21. Karagiannis P, Singer J, Hunt J, et al. Characterisation of an engineered trastuzumab IgE antibody and effector cell mechanisms targeting HER2/neu-positive tumour cells. Cancer Immunol Immunother. 2009; 58:915–30. [PubMed: 18941743]
22. Kershaw MH, Darcy PK, Trapani JA, MacGregor D, Smyth MJ. Tumor-specific IgE-mediated inhibition of human colorectal carcinoma xenograft growth. Oncol Res. 1998; 10:133–42. [PubMed: 9700724]
23. Pullyblank AM, Guillou PJ, Monson JR. Interleukin 1 and tumour necrosis factor alpha may be responsible for the lytic mechanism during anti-tumour antibody-dependent cell-mediated cytotoxicity. Br J Cancer. 1995; 72:601–6. [PubMed: 7669568]
24. Green S, Dobrjansky A, Carswell EA, et al. Partial purification of a serum factor that causes necrosis of tumors. Proc Natl Acad Sci USA. 1976; 73:381–5. [PubMed: 54919]
25. Buttel IC, Chamberlain P, Chowers Y, et al. Taking immunogenicity assessment of therapeutic proteins to the next level. Biologicals. 2011; 39:100–9. [PubMed: 21353596]
26. Romano A, Torres MJ, Castells M, Sanz ML, Blanca M. Diagnosis and management of drug hypersensitivity reactions. J Allergy Clin Immunol. 2011; 127:S67–73. [PubMed: 21354502]
27. Fu SL, Pierre J, Smith-Norowitz TA, et al. Immunoglobulin E antibodies from pancreatic cancer patients mediate antibody-dependent cell-mediated cytotoxicity against pancreatic cancer cells. Clin Exp Immunol. 2008; 153:401–9. [PubMed: 18803764]

28. Neuchrist C, Kornfehl J, Grasl M, et al. Distribution of immunoglobulins in squamous cell carcinoma of the head and neck. Int Arch Allergy Immunol. 1994; 104:97–100. [PubMed: 7950411]
29. Zennaro, D.; Capalbo, C.; Scala, E., et al. IgE, IgG4 and IgG response to tissue-specific and environmental antigens in patients affected by cancer. 30th Congress of the European Academy of Allergy and Clinical Immunology; Istanbul. 2011;
30. Larche M, Akdis CA, Valenta R. Immunological mechanisms of allergen-specific immunotherapy. Nat Rev Immunol. 2006; 6:761–71. [PubMed: 16998509]
31. Perez-Montfort R, Metzger H. Proteolysis of soluble IgE-receptor complexes: localization of sites on IgE which interact with the Fc receptor. Mol Immunol. 1982; 19:1113–25. [PubMed: 7144755]
32. Jensen-Jarolim, E.; Mechtcheriakova, D.; Pali-Schoell, I. The targets of IgE: allergen-associated and tumor-associated molecular patterns. In: Penichet, M.; Jensen-Jarolim, E., editors. Cancer and IgE: introducing the concept of AllergoOncology. Humana Press; New York: 2010. p. 231-54.
33. Brigati C, Noonan DM, Albini A, Benelli R. Tumors andinflammatory infiltrates: friends or foes? Clin Exp Metastasis. 2002; 19:247–58. [PubMed: 12067205]
34. Legrand F, Driss V, Delbeke M, et al. Human eosinophils exert TNF-alpha and granzyme A-mediated tumoricidal activity toward colon carcinoma cells. J Immunol. 2010; 185:7443–51. [PubMed: 21068403]
35. Rudman SM, Josephs DH, Cambrook H, et al. Harnessing engineered antibodies of the IgE class to combat malignancy: initial assessment of FcεRI-mediated basophil activation by a tumour-specific IgE antibody to evaluate the risk of type I hypersensitivity. Clin Exp Allergy. 2011; 41:1400–1413. [PubMed: 21569129]
36. Black PH. Shedding from normal and cancer-cell surfaces. N Engl J Med. 1980; 303:1415–6. [PubMed: 7001235]
37. Pavlakovic H, Becker J, Albuquerque R, Wilting J, Ambati J. Soluble VEGFR-2: an antilymphangiogenic variant of VEGF receptors. Ann N Y Acad Sci. 2010; 1207(Suppl. 1):E7–15. [PubMed: 20961309]
38. Weichselbaumer M, Willmann M, Reifinger M, et al. Phylogenetic discordance of human and canine carcinoembryonic antigen (CEA, CEACAM) families, but striking identity of the CEA receptors will impact comparative oncology studies. PLOS Curr. 2011; 3:RRN 1223.
39. Najy AJ, Day KC, Day ML. The ectodomain shedding of E-cadherin by ADAM15 supports ErbB receptor activation. J Biol Chem. 2008; 283:18393–401. [PubMed: 18434311]
40. Clifton GT, Sears AK, Clive KS, et al. Folate receptor alpha: a storied past and promising future in immunotherapy. Hum Vaccin. 2011; 7 Epub ahead of print.
41. Dibbern DA Jr, Palmer GW, Williams PB, Bock SA, Dreskin SC. RBL cells expressing human Fc epsilon RI are a sensitive tool for exploring functional IgE-allergen interactions: studies with sera from peanut-sensitive patients. J Immunol Methods. 2003; 274:37–45. [PubMed: 12609531]

Europe PMC Funders Author Manuscripts