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IgE-based Immunotherapy of Cancer -A Comparative Oncology Approach

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Abstract

Antibody-based immunotherapies are important therapy options in human oncology. Although human humoral specific immunity is constituted of five different immunoglobulin classes, currently only IgG-based immunotherapies have proceeded to clinical application.

This review, however, discusses the benefits and difficulties of IgE-based immunotherapy of cancer, with special emphasis on how to translate promising preclinical results into clinical studies. Pursuing the “Comparative Oncology” approach, novel drug candidates are investigated in clinical trials with veterinary cancer patients, most often dogs. By this strategy drug development could be speeded up, animal experiments could be reduced and novel therapy options could be introduced benefitting humans as well as man’s best friend.

Keywords

IgE; AllergoOncology; Comparative oncology; Comparative medicine; Immunotherapy

Targeted Therapies of Cancer

Cancer is a huge burden of our societies with an overall worldwide incidence of 182,3 cases per 100.000 inhabitants and an overall mortality of 102,4/100.000 according to the International Agency for Research on Cancer of the World Health Organization (estimated age-standardized incidence and mortality rates (ASR) for both sexes). Highest incidence rates are reported for breast, colorectal and cervical cancer in women and lung and prostate cancer in men [1].

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Current treatment options comprise of surgery, chemotherapy or radiation plus more recently introduced targeted therapies. Targeted therapies aim to specifically address malignantly transformed cells while sparing healthy tissues [2]. Thus, receptors, which are important during embryonic development and readopted by cancer cells, belong to the most promising targets. One of the most prominent molecules of that kind is the human epidermal growth factor receptor-2 (HER-2). HER-2 is a receptor tyrosine kinase, mediating signals for cell proliferation, cell mobility and survival [3]. In the absence of a known ligand [4,5], activation is achieved by homo- or heterodimerization [6]. HER-2 is very important during embryonic development, e.g. it plays a role in ductal morphogenesis of the mammary gland [7], but it is almost not expressed on adult tissue, except the heart [8]. On the contrary, HER-2 is overexpressed in breast, ovarian, gastric, colorectal, pancreatic, and endometrial cancers [9].

Another closely related receptor tyrosine-kinase is the epidermal growth factor receptor (EGFR). Its overexpression is associated with head and neck squamous cell carcinoma (HNSCC), non-small-cell lung cancer (NSCLC), colorectal cancer (CRC), breast and pancreatic cancer, but also with certain types of brain cancer [10]. In contrast to HER-2, EGFR senses the epidermal growth factor (EGF) and other important growth signals, such as transforming growth factor-α (TGF-α) or amphiregulin [11-14]. EGFR is physiologically required for promoting cell proliferation and DNA repair [15], but can also lead to tumor growth, progression, and evasion of apoptosis via the activation of PLC-γ-PKC, Ras-Raf-MEK, PI-3K-Akt-mTOR and JAK2-STAT3 pathways [12,16]. Overall, EGFR and HER-2 together with HER-3 and HER-4 belong to the ErbB-family [17], which derives its name from the homology to the erythroblastic leukemia viral oncogene protein (v-erb-B, [18,19]).

Currently two forms of targeted therapies against EGFR and HER-2 are in clinical use: i) blocking the intracellular receptor tyrosine kinase with small molecules and ii) attacking the extracellular domains of the receptor with monoclonal antibodies.

Small molecules targeting EGFR comprise erlotinib (Tarceva®, Roche) and gefitinib (Iressa®, AstraZeneca) plus the dual kinase inhibitors lapatinib (Tykerb®, GlaxoSmithKline) and afatinib (Gilotrif®, Böhringer Ingelheim), the latter inhibiting HER-2 as well ([20], see Table 1). Especially the reversible inhibitors gefitinib, being FDA-approved in May 2003 [21] and erlotinib, with FDA-approval in November 2004 [22], are successfully applied in non-small-cell lung cancer [23]. Although gefitinib was recalled from that indication in the US, it is still widely used in Japan, where patients display a higher rate of EGFR-mutations in NSCLC [24], and also received marketing authorization in the European Union in 2009 [25]. Moreover, erlotinib is approved for the treatment of advanced pancreatic cancer [26] and several next generation irreversible EGFR-tyrosine kinase inhibitors, like canertinib, are under investigation for their efficacy in breast [27], colorectal, lung, pancreatic, renal, head and neck, gynecologic and prostate cancer [28].

The most prominent tyrosine kinase inhibitor (TKI) for HER-2 is lapatinib (Tykerb®, GlaxoSmithKline), the above mentioned reversible dual inhibitor of HER-2 and EGFR [29], which was FDA-approved in March 2007 for the treatment of advanced breast cancer [30].

Also in this case, irreversible inhibitors, like neratinib or again canertinib are widely investigated [31].

In contrast to small molecules that intracellularly interfere signaling via blocking the kinase activity, monoclonal antibodies directed against EGFR and HER-2 aim to extracellularly inhibit ligand binding or dimerization of these receptors, respectively [32].

For targeting EGFR, two monoclonal antibodies are currently in clinical use, cetuximab (Erbitux®, Merck KGaA), which was FDA-approved in February 2004 [33] and panitumumab (Vectibix®, Amgen), which received FDA-approval in September 2006 ([34], Table 1). In particular cetuximab, a human-murine chimeric IgG1 antibody has become an indispensable cornerstone in the treatment of advanced-stage metastatic CRC and advanced HNSCC [35,36]. Cetuximab finds its epitope within the ligand-binding site of EGFR (extracellular domain III) and can thus block binding of growth signals [37,38]. Panitumumab works mechanistically similar; it can also prevent EGF-binding via sterical hindrance [39], but on a different epitope on domain III, though partially overlapping [40]. Panitumumab is successfully applied in the treatment of metastatic colorectal cancer [41,42].

For all above mentioned therapeutics, wild type (wt) Kirsten rat sarcoma viral oncogene homolog (KRAS)-status of the patient is of uttermost importance, as it could be demonstrated, that acquired KRAS mutations lead to resistance against EGFR targeting [43]. As KRAS is a downstream effector-protein in the EGFR-signaling pathway, mutations that lead to constitutive activation of KRAS counteract growth signal inhibition of all EGFR targeting drugs [44]. Therefore KRAS-status is meanwhile routinely determined for every human patient before any EGFR-specific treatment is initiated [45].

Also in case of HER-2 targeting, two monoclonal antibody therapies are FDA-approved: trastuzumab (Herceptin®, Roche) and pertuzumab (Perjeta®, Genentech). Especially trastuzumab, being FDA approved in September 1998 [46], proved to be highly successful for the treatment of metastatic breast cancer [3] and has later received importance also for treatment of metastatic gastric cancer [47] and tumors of the gastroesophageal junction (GEJ, [48]). Trastuzumab has been so successful in breast cancer therapy, that very recently, in February 2013, also a drug-conjugated trastuzumab derivate, trastuzumabemtansine (T-DM1, Kadcyla®, Roche) was approved by the FDA for treatment of advanced breast cancer [49,50], fuelling the emerging field of antibody-drug conjugates [51].

The other HER-2 targeting antibody, pertuzumab received FDA-approval in June 2012 [52] and is also applied for treatment of metastatic breast cancer [53], as specified in Table 1.

Trastuzumab and Pertuzumab target different epitopes on HER-2: trastuzumab binds to subdomain IV on the extracellular domain (ECD) of HER-2 [54], whereas pertuzumab targets subdomain II [55]. As HER-2 has no endogenous ligand [5], the mechanisms of action of trastuzumab and pertuzumab differ from those of the mentioned EGFR-targeting immunoglobulins. Trastuzumab sterically prevents the formation of HER-2 homodimers or highly active heterodimers with other ErbB-family members [3], mainly HER-3 [56,57] and EGFR ([58,59]. Moreover, upon trastuzumab binding, HER-2 gets endocytosed and shedding of the receptor is inhibited, which otherwise would lead to an actively-signaling

p95-remnant on the cancer cell surface [3]. Pertuzumab, on the other hand, binds more distant from the cell membrane, is more efficient in preventing heterodimer formation [60] and in contrast to trastuzumab, which inhibits ligand-independent dimerization, pertuzumab especially inhibits ligand-induced HER-2 heterodimers [57].

This different mode of action prompted researchers to investigate a combination therapy of both antibodies in preclinical models, resulting in more complete HER-2 blockade, and efficacy in cases where cancer had progressed after trastuzumab monotherapy [61]. Also in clinical settings, this combination therapy proved to be highly effective and peaked in June 2012 in the first FDA approval of a dual HER-2 targeting regimen for metastatic breast cancer [62].

Immunological Effects of Antibodies

The mechanism of action of monoclonal antibodies, however, cannot be confined to their growth signal inhibitory capacity only; as all mentioned monoclonal antibodies feature fully functional human constant regions, thus they are also able to attract immune effector cells to the site of the tumor and trigger immune cell mediated cancer cell death. Among the attracted immune cells are monocytes and macrophages dominant [63], which are known for their tumoricidic potential in mediating antibody-dependent cell-mediated cytotoxicity (ADCC) via insertion of granzyme B and caspase enzymes [64]. Moreover, our group could demonstrate that monocytes are also able to mediate high levels of antibody-dependent cell-mediated phagocytosis (ADCP) upon trastuzumab treatment [65]. Other attracted cell types expressing Fc-receptors for antibody binding, are NK-cells and neutrophilic granulocytes, which have been shown to bear high tumoricidic potential with regard to ADCC [66,67]. Moreover, professional antigen-presenting cells, that also express Fcreceptors such as dendritic [68] or Langerhans Cells [69] can be attracted and can induce activation of tumor-reactive T-cells upon facilitated antigen uptake and presentation. This mechanism has been demonstrated to lead to tumor regression in a xenograft model of cetuximab treatment in concert with reconstituted immune cells [70].

Upon a closer look, all mentioned EGFR or HER-2 targeting antibodies belong to the IgG class of immunoglobulins, with cetuximab, trastuzumab and pertuzumab being IgG1 antibodies [71,72] and panitumumab, being an IgG2 [73]. In fact, all currently FDA-approved monoclonal antibodies for therapy of cancer are gamma-Immunoglobulins [71]. This is indeed astonishing as the human Immunoglobulin repertoire consists of 5 different classes: IgA, IgD, IgE, IgG and IgM [74].

Based on their different constant domains, all of them bear distinct physiological properties with respect to distribution, tissue penetration and function, such as complement-activation or ADCC and ADCP mediation [75]:

IgM, the primary antibody response against pathogens [76] is highly active in opsonization, which leads to pathogen clearance by phagocytic cells [77].

IgA protects body surfaces [78], such as the respiratory, gastrointestinal or genitourinary tract [79] and is abundantly found in secrets like tear fluid [80] or saliva [78], where it exerts

neutralizing functions [81]. The function of IgA in mother's milk [82] is of special interest as it protects the infant against pathogens in the mother's environment, which are also of high risk to the child [83].

IgG is the most abundant antibody isotype in the bloodstream, as it constitutes 70% of all serum immunoglobulins [79]. IgG antibodies, which can be further subdivided in IgG1-4 in humans, exert systemic immune-protection by binding to bacteria, viruses and fungi with high affinity. In general, IgG1 and IgG3 antibodies are mainly produced in response to protein antigens, whereas IgG2 and IgG4 antibodies react against pathogens with polysaccharide capsules, like Streptococcus pneumoniae [75,79].

The biological role of IgD, however, remains still enigmatic; discovered late (in 1965) in the serum of a myeloma patient [84,85], it was long neglected, because it is only cleaved in minor amounts. Membrane-bound IgD on the surface of B-cells though, was found to regulate B-cell activation. Despite thorough investigation in recent years, the physiological and pathophysiological role of IgD is still unclear; however, an interesting aspect is, that IgD was found to bind to certain bacterial proteins with relatively high affinity, but not via its antigen binding-site, as rather through sugar residues on its constant region [86]. Moreover, it has recently been shown, that circulating IgD can activate antimicrobial, proinflammatory and B cell-stimulating effects in basophilic granulocytes [87].

IgE, finally, is the most recently discovered immunoglobulin subclass, as it was only first described in 1966 by Teruko and Kimishige Ishizaka as a novel immunoglobulin in the serum of an atopic individual [88]. At the same time, Bennich and Johannsson could purify a paraprotein from serum of a myeloma patient, which they termed "IgND" [89]. They could soon link this novel "IgND" to asthma [90] and it turned out to be the same protein as the group from Japan had found. On a meeting in Lausanne in February 1968, finally, under the guidance of the WHO Immunoglobuline Reference Laboratory, it was decided to designate this novel immunoglobuline "IgE" [91,92].

IgE plays an important role in defense against parasites [93] and is a key molecule in the pathophysiology of allergic diseases such as atopic dermatitis, asthma, food allergy or anaphylaxis [94]. Upon crosslinking of IgE-antibodies, bound to FcεRI-receptors on the surface of mast cells or basophils, histamine and leukotrienes are released leading to the manifestation of allergic symptoms [95].

IgE and Cancer

IgE is mostly known for its detrimental role in allergy, but several studies have for long pointed towards a natural tumor surveillance function of this antibody isotype [96,97]. Interestingly, large epidemiologic studies could reveal an inverse association between the history of atopic diseases and cancer [98]. In 2005, Turner et al. published a study enrolling 1.1 million US-american adults with self-reported, physician-diagnosed asthma or hay fever, who had no cancer at baseline and were followed up for 18 years. In this population, a relative-risk reduction for all cancer mortality could be observed [relative risk (RR) = 0.88; 95% confidence interval (CI) 0.83-0.93]. However, in a separate analysis of never-smokers, this effect still persisted, but was not significant anymore [99].

In a following literature analysis of studies from the MEDLINE® database from 1966 to August 2005, the same group described “strong inverse associations for pancreatic cancer and glioma, whereas lung cancer was positively associated with asthma”. However, methodical issues to these historical studies with regard to exposure assessment, confounding and bias were addressed by the authors [100].

The most recent study investigating a possible association between IgE and cancer was published in 2010: Van Hemelrijck et al. reviewed 27 studies from PubMed and EMBASE™ and surveyed a Swedish cohort of 24.820 people, who underwent IgE measurements. Here, the authors could show a weak inverse association in their cohort, and a pattern by cancer type in the meta-analysis of the historical studies [101].

Another interesting observation was made when the anti-IgE antibody omalizumab (Xolair®, Novartis) underwent clinical trials and pooled phase I to III data was evaluated. Omalizumab, which removes IgE from the circulation, is currently approved for therapy of severe persistent asthma [102]. In those mentioned phase I to III trials with allergics undergoing omalizumab treatment, a slightly higher number of malignant neoplasms was observed in the anti-IgE-treated group (20 of 4127=0.5% compared to 5 of 2236=0.2% in the control group). Malignancies that occurred in the treatment group comprised of breast, non-melanoma skin, prostate, melanoma and parotid cancer. Subsequently, Busse et al. analyzed 67 phase I to IV trials of omalizumab and could not confirm any possible association between omalizumab treatment and cancer in this extended study [103].

Summarizing all epidemiologic observations one can only state, that a possible association between IgE and cancer remains still unclear due to the lack of big prospective studies.

A more mechanistic approach, however, was pursued, when Fu et al. purified immunoglobulins from tissue surrounding pancreatic cancers. They could isolate IgE antibodies which were not only specific for a 50 kDa pancreatic cancer antigen but were indeed able to mediate ADCC of pancreatic cancer cells in vitro [104], pointing towards a benefitial role of IgE-antibodies in defense against cancer.

IgE-based Immunotherapies of Cancer - Pioneer Studies

Pioneer studies with IgG and IgE antibodies of the same epitope specificity tested head-to-head revealed a higher potential of the IgE in terms of cytotoxicity. The very first studies were performed with Mov18IgG and IgE [105], antibodies that target the folate receptor (FR)-α. FR-α (also known as folate-binding protein, LK26 trophoblastic antigen or GP38) is a glycosylphosphatidylinositol (GPI)-anchored membrane protein that binds folic acid and is regarded as a tumor-associated-antigen (TAA) in gynecologic malignancies [106], due to its overexpression in more than 90% of epithelial ovarian cancers and in a subpopulation of uterine carcinomas. As folate is a necessary micronutrient of replicating cells, overexpression of FR-α facilitates enhanced growth of cancer cells [107].

For targeting of this receptor, Gould et al. could demonstrate in an ovarian cancer model, that Mov18IgE was able to mediate ADCC of FR-α expressing tumor cells in vitro and in vivo. In a mouse model using xenografted human FR-α overexpressing cells, mice that

received Mov18IgE treatment developed in the presence of human peripheral blood mononuclear cells (PBMCs) significantly smaller tumors than those treated with Mov18IgG [105]. In a follow-up study, it could further be demonstrated, that also cytotoxic killing by monocytes can be efficiently triggered with IgE. In a subsequent nude mouse study, where again FR-α overexpressing tumors were grafted and PBMCs were reconstituted, the IgE-treated group had shown monocytic infiltration of the tumor xenografts, which was still persistent after 3 weeks and led to significantly longer survival. Moreover, upon a closer look in an in vitro flow cytometric model, specific ADCC of tumor cells, executed by monocytes upon Mov18IgE stimulation could be displayed. Finally phagocytosis of FR-α positive tumor cells by monocytes armed with FR-α specific IgE could be displayed by fluorescence microscopy [108].

Subsequently, we could demonstrate similar results for the HER-2 system in close collaboration with Prof. Gould and Dr. Karagiannis: upon generation of a recombinant trastuzumab-like IgE, constituted of the same variable regions as original trastuzumab (being an IgG1), it was shown in a flow cytometric assay, that the IgE antibody is highly effective in mediating ADCC of monocytes against HER-2 overexpressing cells. Interestingly, in this model, the IgE antibody mediated high levels of ADCC but only background ADCP, whereas the picture was completely opposite for the IgG, which mediated killing of tumor cells almost exclusively via ADCP [65]. This could be a first hint towards distinct mechanisms of tumor cell killing mediated by different immunoglobulin classes; however, this still has to be confirmed in more extensive experiments and has to be investigated also for other cancer types.

Possible Advantages and Pitfalls of IgE-based Cancer Immunotherapies

Apart from a possibly higher potential for mediating ADCC, IgE-based immunotherapies of cancer could have other beneficial effects: first, IgE antibodies have a uniquely high affinity to their receptors on immune cells (Ka~ 1010/M for FcεRI and Ka~ 108-109/M for the CD23 trimer complex), which significantly exceeds the affinities of IgG1-4 to their high-affinity receptor FcRI [94,109]. Thus, due to its rapid binding to Fcε-receptors on cells, IgE is quickly removed from the circulation, which is advantageous in terms of side-effects because of the short duration of the compound in the bloodstream. Moreover, potential IgE-immunotherapies would be effectively distributed to tumor tissues, as IgE antibodies bound to Fcε-receptors on e.g. mast cells can use those cells as shuttle systems to penetrate malignancies and as mast cells are tissue-resident immune cells [110], this transport would be highly efficient.

Consistently, we would like to quote the review “Problems of Delivery of Monoclonal Antibodies” by Reilly et al., who wrote that “the clinical success of monoclonal antibody-based cancer diagnosis and therapy depends, however, on solving a number of pharmacokinetic delivery problems. These include: (i) slow elimination of monoclonal antibodies from the blood and poor vascular permeability; (ii) low and heterogeneous tumour uptake” [111], and state that those two substantial challenges of anti-tumor immunotherapy could be simply addressed by using IgE.

Other possible advantages include the high sensitivity of IgE-effector cells to activation by antigens and the speed and amplitude of the response, which can most impressively be seen during allergic and anaphylactic reactions, typically beginning within minutes upon allergen exposure.

That is at the same time also the biggest concern of using IgE-based immunotherapies against cancer: recombinant IgE, applied intravenously, always bears the risk of anaphylactic reactions; therefore, careful selection of the target epitope is of uttermost importance in this regard.

During an anaphylactic reaction, preformed IgE, that is bound to Fcε-receptors on the surface of mast cells or basophilic granulocytes is cross-linked by allergens, which induces release of stored granules, containing vasoactive amines (e.g.: histamine) or lipid mediators (e.g. Prostaglandin D2, Platelet-activating factor, or leukotrienes) [112]. This rapid release can lead within minutes to fatal symptoms like asphyxiation from laryngeal swelling, circulatory collapse from hypotensive shock, cardiac arrest, or respiratory failure because of bronchoconstriction [113].

In order to prevent such effects, the target structure for designing passive immunotherapies with IgE-antibodies should not be expected to be cross-linking, which means, that the epitope should be

- monovalent and
- it should not circulate in the blood, or if,
- it should only circulate in a monomeric form [114].

These requirements are fulfilled for the mentioned anti-FR-α antibody “Mov18IgE”, but also for the anti-HER-2 antibody “trastuzumab-like IgE”. For both antibodies it could be demonstrated, that monomeric target molecules do not trigger mediator release of mast cells, which were preloaded with their specific IgE-antibodies, respectively [65,115]. Furthermore, Rudman et al. could demonstrate, that although serum levels of FR-α were increased in ovarian cancer patients (up to 40 ng/ml) compared to healthy controls (mean=1,73; SD=3,45), basophilic granulocytes loaded with Mov18IgE were not significantly activated upon incubation with FR-α even at a concentration of 300 ng/ml [115].

On the other hand, both antibodies were shown to mediate mast cell degranulation upon incubation with tumor cells, displaying high numbers of target molecules in a repetitive manner on their surface [65,115]. Here, cross-linking of Fcε-receptors is highly efficient, and therefore local anaphylaxis at the tumor site could be expected, which would again be beneficial, as it results in initiation of a strong immune response. As mast cells also store tumorinhibiting agents in their granules, e.g. tumor necrosis factor (TNF)-α [116], this degranulation could also result in direct tumor cell killing. Moreover, also other cells involved in anaphylactic reactions, such as eosinophils, have been shown to execute tumoricidic functions, e.g. via secretion of granzyme A [117] or eosinophilic peroxidase [118].

Another big challenge of current immunotherapies with IgG antibodies is that not all human Fcγ-receptors are immune-activating, but one among them, FcγRIIb is -inhibiting [119]. Therefore, the tumoricidic effects of IgG-based immunotherapies also depend on the net ratio of binding to activating and inhibiting receptors. As it has recently been shown for IgG4, a subclass that shows relatively high binding affinity to FcγRIIb [120], this antibody is not able to trigger immune cell-mediated tumor cell killing in vitro, despite being TAA-specific. Moreover it was demonstrated, that IgG4 antibodies significantly impaired the killing potential of IgG1 antibodies of the same specificity in vitro and in vivo [121]. Strategies to overcome this limitation include modification of the posttranslational glycosylation of the IgG-constant regions' heavy chains, as these sugar residues have been identified to be of high relevance for distinct binding affinities to different Fc-receptors [75]. For IgE on the other hand, there are no inhibitory receptors [114], so again this isotype could contribute to overcome a current challenge of immunotherapies of cancer.

However the Fcε-receptor-biology differs considerably between humans and mice, as the high affinity IgE receptor FcεRI is only expressed on mouse basophils and mast cells [122], whereas it has been described in humans on mast cells, basophils, eosinophils, monocytes, Langerhans and dendritic cells [123,124]. This is a huge limitation of current mouse models in displaying all mentioned in vivo benefits and risks of IgE-based immunotherapy of cancer and the great benefit of using a "Comparative Oncology" approach.

Comparative Medicine

Although human and veterinary medicine share the same goals and aims, namely to treat patients and promote health, currently both of them are distinct sciences with distinct studies taught on separate universities. Research is presently going on in one or the other, but there is little crosstalk between the two specialties.

The concept of Comparative Medicine, however, aims to study naturally occurring diseases across species to improve both human and veterinary medicine [125,126]. There is in fact no explicit reason for a strict separation of studies for humans or other mammals, as many pathophysiological processes have been shown to be similar and highly comparable, or as the german pathologist Rudolf Virchow stated: "Between animal and human medicine there are no dividing lines - nor should there be. The object is different but the experience obtained constitutes the basis of all medicine" [127].

This view, which is also in line with the wider concepts of "One Medicine", or "One Health", bringing together aspects of health of humans, animals and also their environment [128] is not really novel. Browsing through the history of medicine, this approach appears at many points, starting with Hippocrates and Plato in ancient Greece [129]. Even further back in time, physicians in Ancient India were trained to treat humans and animals, especially cattle, elephants and horses [130] and in Ancient China, medical treatment for horses was highly elaborated as well [131].

Also in Europe and North America human and veterinary medicine were closely interconnected for a long period of time, peaking in the 18th, 19th and early 20th century. Many important findings were made by comparative observation and experimentation

during that time, for instance Edward Jenner (1749-1823) noted that milkers who had been in contact with cowpox-infected cows did not develop smallpox (variola minor) but only the milder cowpox. He also observed that this protection could be mediated by inoculation of a small amount of pus from cowpox blisters, a method he called “vaccination” because of the Latin word for cow, vacca [132]. Similarly, Louis Pasteur (1822-1895) worked on cholera in humans and chicken [133], Robert Koch (1843-1910) researched on human and bovine tuberculosis [134], and the mentioned Rudolf Virchow (1821-1902) worked on trichinella infections in humans and pigs [135].

Besides Virchow, the most important proponent of Comparative Medicine was Sir William Osler, a Canadian physician (1849-1919), who studied, worked and taught in London, Berlin, Vienna, Toronto and Montreal, and was one of the four founding professors of Johns Hopkins Hospital in Baltimore. Osler lectured at McGill University for medical students as well as for students from the Veterinary Medical College with emphasis on comparative topics. His research in this field concentrated on infectious diseases in dogs, pigs and cattle and his deep interest is documented in many editorials of the “Journal of Comparative Medicine and Surgery” [136].

Recent developments are no longer dependent on distinguished individuals, but comprise the establishment of special departments for Comparative Medicine within universities, such as at Stanford, Yale or at the University of California, Davis. Whereas Comparative Medicine focused mainly on infectious diseases in previous centuries, modern approaches tend to tackle another big burden of our societies, cancer, via the principle of “Comparative Oncology”.

Comparative Oncology

The Comparative Oncology approach aims to speed up drug development simultaneously for human and animal cancer patients via clinical trials in pet patients, primarily cats and dogs [137]. Although murine models have been proven to be highly effective with regards for understanding basic principles of malignant transformation, cancer signal transduction pathways or drug resistance formation, these models often poorly mimic human cancer for drug testing [138]. For many compounds, the translation of a safe and efficacious agent in mice into an actual drug fails [139], due to the poor presentation of key features of human cancer in murine tumor models, such as genomic instability, long latency periods or the lack of intra-tumor heterogeneity [140]. Moreover, the concept of toxicity studies, which are conducted in healthy animals, followed immediately by Phase I and Phase II trials in humans, often leaves many important questions unanswered, before treating a relatively high number of human patients [140,141].

On the other hand, also more and more extensive studies in animals cannot be the solution, as it would increase the ethical dilemma that potential benefits for humans stand against the costs sustained by animals. Thus, legislators and regulatory bodies state in their directives on drug development that the “3Rs” should be applied on animal experiments [142], which are: Replacement, Reduction, and Refinement [143,144].

In line with these concepts, clinical studies in animal patients, which suffer from spontaneously developed tumors, would allow the investigation of drug effects on malignancies that developed naturally within intact immune systems, in the context of their original tumor microenvironment in pet animals that share similar environmental factors as their owners, for instance pollution. Such trials in veterinary patients could replace many preclinical experiments, refine our models and ultimately reduce animal experiments. The information obtained from these studies would be highly relevant and valuable, while the treated veterinary patients would be provided with cutting edge research simultaneously [140].

Studies in this field of Comparative Oncology with treated dog patients, led to the advancement of surgical techniques, like limb sparing for sarcoma patients, elucidating hyperthermia or evaluating novel delivery strategies, like inhalation of cytokines or chemotherapies [137].

This development peaked recently in the formation of the “Comparative Oncology Trials Consortium” (COTC), a multicenter initiative of twenty Comparative Oncology centers throughout the USA. Founded and centrally managed by the National Cancer Institute of the National Institutes of Health (NIH), 11 clinical trials have been conducted so far, ranging from all fields of cancer therapy attempts like “Evaluation of RGD Targeted Delivery of Phage Expressing TNF-alpha to Tumor Bearing Dogs” (COTC001, closed trial) via “Preclinical Comparison of Three Indenoisoquinolines Candidates in Tumor Bearing Dogs” (COTC007b, open trial) to “Evaluation of the mTOR inhibitor Rapamycin in Dogs with Metastatic Osteosarcoma” (COTC008, closed trial) [145].

One of the most successful example of a recent clinical Comparative Oncology trial was published in 2009, in which the tyrosine kinase inhibitor toceranib phosphate (Palladia®, SU11654, Pfizer), targeting kit, vascular endothelial growth factor receptor 2 (VEGFR2) and platelet derived growth factor receptor-beta (PDGFRβ) [146] was tested in dog cancer patients with recurrent mast cell tumors. This large clinical phase III trial could demonstrate significant effects of toceranib phosphate with regard to overall response rates, median duration of objective responses and time to tumor progression [147], which has finally led to the approval of toceranib phosphate for mast cell tumors in dogs [148] and to the approval of sunitinib (Sutent®, SU11248, Pfizer), a similar compound, for therapy of human renal cell cancer and gastrointestinal stromal tumors (GIST, [149,150]).

Also for evaluation of IgE-based immunotherapies of cancer, trials in dog cancer patients would be highly valuable, due to the fact that dogs, in contrast to mice, share important principles of the IgE-biology with humans [151,152], underlined by the clinical observation that dogs also suffer from IgE-mediated diseases, such as atopic dermatitis [153] or food allergies [154]. Thus, the introduction of passive immunotherapy in veterinary clinical oncology would be highly valuable to elucidate the full potential of IgE-based Immunotherapy of Cancer. We contributed to this strategy by our recent molecular characterization of canine EGFR and the generation of a recombinant canine IgE of the exact cetuximab specificity [155, 156].

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Table 1

Overview of indications for approved targeted therapies against EGFR and HER-2.

Cancer Type	EGFR expression	HER-2 expression	Approved Targeted Therapy
Breast Cancer	Yes	Yes	Lapatinib, trastuzumab, pertuzumab, T-DM1
Colorectal Cancer	Yes	Yes	Cetuximab, panitumumab
Gastric Cancer (GEJ)	No	Yes	Trastuzumab
HNSCC	Yes	No	Cetuximab
NSCLC	Yes	No	Afatinib, Erlotinib, Gefitinib
Pancreatic Cancer	Yes	Yes	Erlotinib