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2nd Charles Richet et Jules Héricourt Workshop

Therapeutic antibodies and anaphylaxis; May 31–June 1, 2011; Tours, France

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The Charles Richet and Jules Héricourt workshops honor the memory of Jules Héricourt (1850–1938) and Charles Richet (1850–1935) who described the principle of serotherapy in 1888 and made the very first attempts to fight cancer with serotherapy in 1895. In 1902, Charles Richet and Paul Portier described "anaphylaxis," a discovery awarded the Nobel Prize in 1913. The first workshop, "Towards the clinical use of monoclonal antibodies with higher cytolytic efficacy in cancer" was held in Tours, France on November 20–21, 2008. The second Charles Richet and Jules Héricourt workshop, held May 31–June 1, 2011 at the University of Tours, France, was also organized by the Cancéropôle Grand Ouest. The topic of the workshop was therapeutic antibodies and anaphylaxis, a subject rarely addressed in congresses focused on mAbs. To have discussions about mAb side effects with complete objectivity, the congress was organized independently of any sponsorship from pharmaceutical companies. This academic event was motivated by the high incidence of shocks to cetuximab and the need to compile and evaluate scattered information. This growing public health concern was thus analyzed from different scientific and medical angles. The first session was devoted to acute infusion reactions, with an emphasis on deconvolution of the terms "cytokine-release syndrome," "cytokine storms," "anaphylaxis" and their epidemiology. This session concluded with the Charles Richet lecture on cetuximab anaphylaxis and anti-αGal IgE by Thomas Platts-Mills, its discoverer. In the next session, the involvement of anti-glycan antibodies in both anaphylaxis and delayed hypersensitivity reactions to therapeutic antibodies was discussed. A gala dinner was held in the gardens of the beautiful château of Villandry, which was acquired and restored by Joachim Carvalho, a pupil of Charles Richet's and great-grandfather of the present owner. The final session focused on strategies to prevent cetuximab anaphylaxis in clinical practice included a variety of topics, e.g., premedication, biobetters and biosimilars, skin testing and predictive assays. All speakers and attendees enjoyed this very stimulating and rewarding meeting, which gathered many people with divergent scientific backgrounds and medical specialties.

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Session 1: Anaphylaxis versus Acute Infusion Reactions Provoked by Therapeutic Antibodies

Philippe Solal-Céligny (Le Mans, France) introduced the meeting, relying on his practical experience of the use of monoclonal antibodies (mAbs) for the treatment of both solid tumors and hematological diseases. The incidence of infusion reactions is >75% for rituximab, ~40% for trastuzumab (associated with pulmonary metastases), <20% for cetuximab and very low for bevacizumab and panitumumab. In his opinion, it appears of utmost importance to distinguish between "cytokine-release syndrome (CRS)" and "anaphylaxis" because retreatment is possible in case of CRS, whereas it is contra-indicated for anaphylaxis. However, the task of differentiating the conditions is not easy because both frequently occur within 1 h of the first infusion, can be very severe and share many clinical symptoms. Severity grading based on defined criteria does not help, notably because there is substantial subjectivity. Almost all CRS are observed in hematological malignancies. Anaphylaxis is rarer than CRS, can be extremely brutal, and does not depend on (circulating) tumor bulk, contrarily to CRS. A previous contact is not necessary for anaphylaxis (cf. infra with cetuximab). Bronchospasm is specific to anaphylaxis whereas laryngeal edema characterizes CRS, being one of its first manifestations. Studies of CRS mechanisms are desperately scarce. Cytokine peaks occur later than the clinical manifestations, which suggests that cytokines do not play a major role despite the syndrome designation. CRS incidence seems similar with all anti-CD20 mAbs regardless of their mechanisms of action, i.e., complement-dependent cytotoxicity or antibody-dependent cell-mediated cytotoxicity (ADCC). Better clinical practices, e.g., premedication with paracetamol, anti-H1 or steroids, although there is no scientific proof that any of these is important; initial low doses and reduction of infusion rates; possibly sub-cutaneous route, have decreased the incidence of very severe or fatal cases.

Enrico Maggi (University of Florence, Italy) presented an overview of the pathogenic mechanisms of immediate adverse reactions to therapeutic mAbs, providing his experience in therapeutic fields other than cancer. He focused on type β (antibody-mediated) reactions,[1] underlining that pathogenic anti-infliximab

IgE antibodies could be detectable in patients who become reactive during the treatment course. He also suggested that antibody-mediated anaphylactic mechanisms, different from the IgE pathway, may also be involved in humans. In particular, basophils may be triggered also by non IgE (IgG) anti-drug antibodies. Dr. Maggi also noted that the hypersensitivity risk is detectable prior to clinical symptoms, since anti-drug antibodies are present in the sera collected immediately before the reaction. He reported unpublished data that indicated rituximab-specific IgE antibodies in the serum of a reactive patient were associated with positive intradermal skin testing and circulating drug-specific Th2 cells. He concluded that different and non-mutually exclusive mechanisms of adverse reactions toward mAbs have been shown. Since intermittent therapy or re-exposure after a free interval may be associated with an enhanced risk of reactions to biologicals, the safety of mAb infusions can thus be increased by monitoring anti-drug antibodies, skin testing and T-cell response at retreatment.

Robin Thorpe (Biotherapeutics Group, NIBSC, Hertfordshire, UK) fascinated the audience by recounting the detective and scientific investigations that followed the "TGN1412 affair" in March 2006. Preclinical safety testing in macaques failed to predict the clinical toxicity of the anti-CD28 superagonist TGN1412, which consisted of a systemic inflammatory response ("cytokine storm") in its initial phase, then continued toxicity characterized by prolonged cardiovascular shock, acute respiratory distress and multiple organ failure. A posteriori, it was observed that only immobilized (dry-coated) TGN1412 or TGN1412 with endothelial co-cultures induced massive cytokine release and lymphocyte proliferation in human peripheral blood mononuclear cells (PBMCs), but not in macaque PBMCs. The 0.1 mg/kg starting dose in the Phase 1 trial was invalid due to the absence of effect in macaques, and was close to the maximal immunostimulatory dose seen in vitro. Whereas tumor necrosis factor and interleukin (IL)-8 in vitro release by a variety of blood cells is observed with other mAbs, interferon-γ and IL-2 are TGN1412-specific, and are produced following TGN1412 stimulation of human $CD4^+$ effector memory T cells,[2] a T-cell subpopulation that does not express CD28 in macaques. Moreover, because effector memory T cells are mainly located in tissues, assay on peripheral blood may greatly underestimate potential cytokine release.

To close the session, **Aurélie Grandvuillemin** (Dijon, France) discussed infusion reactions to cetuximab (Erbitux®), their incidence and their risk factors, which are very poorly described in the Erbitux® Summary of Product Characteristics (SmPC). Adverse reactions related to cetuximab, validated and recorded in the French Pharmacovigilance Database were retrospectively studied. The 374 cases of infusion reactions identified occurred more frequently at the first cycle [OR = 13.05 (8.05–21.15)], in head and neck vs. colorectal cancer patients [OR = 2.70 (1.62–4.49)], and since 2006 ($p < 0.001$), when cetuximab was approved for the treatment of head and neck cancer. Seven lethal anaphylactic shocks have been registered in France. Considering the possibility of IgE-mediated reactions, validated tests to identify patients at risk are urgently needed.

The Charles Richet lecture was given in honor of the inventor of serotherapy and discoverer of anaphylaxis, in agreement with his descendants and in the presence of one of them. The invited speaker was **Thomas Platts-Mills** (University of Virginia, Charlottesville, VA), who played a pioneering role in establishing the mechanisms of anaphylactic shocks to cetuximab.[3] As an allergologist, he held the audience spellbound by his anecdotes of hunters, deer, ticks, cattle and cats, the main theme in common with cetuximab being anti-αGal IgE. He first described how anti-cetuximab IgE was shown to be directed against the cetuximab Fab-linked N-glycan, which is terminated with an α3-galactosyl residue, a hallmark of non-primate mammals. This "B-like" substance was first described by Landsteiner and is now known as the "Galili" or αGal antigen. This antigen can be present in mAbs produced in Sp2/0 or NS0 cells, or even sometimes in Chinese hamster ovary (CHO) cells,[4] but anti-αGal IgE do not recognize it when it is buried in the Fc, e.g., in infliximab.[5] In Tennessee, the high incidence of shocks to cetuximab has been linked to the high incidence of tick bites, which itself results from a massive rise in the population of deer, since pruritic reactions to tick bites are linked to the presence of anti-αGal IgE. These specific IgE are also responsible for red meat allergy (sometimes delayed) and some cases of allergy to cat epithelium, since secretory IgA from cat saliva express the αGal antigen. These newly discovered anti-αGal IgE-linked clinical entities are in total contradiction with the common opinion that anti-glycan IgE are not clinically relevant.

Session 2: Glycans as Targets of IgE and Other Natural Antibodies, and their Involvement in Adverse Reactions to Therapeutic Antibodies

Uri Galili (University of Massachusetts, Worcester, MA) started the session by describing natural anti-αGal antibodies, which constitute 1% of circulating immunoglobulins and interact specifically with the α-Gal epitope (Galα1-3Galβ1-4GlcNAc-R) on carbohydrate chains.[6] This epitope is produced in cells of non-primate mammals by α1,3-galactosyltransferase, which is absent in humans.[7] mAbs and other therapeutic glycoproteins produced in cells containing α1,3-galactosyltransferase may carry αGal epitopes that will bind the anti-αGal antibody upon administration to humans. Patients with anti-αGal IgE may develop an allergic reaction, a concern first raised by Parekh et al.[8] who stated in 1989 that "If the recombinant form [of glycoproteins] carries Gal(α1-3)Gal, immune rejection by naturally occurring antibodies, and possible anaphylactic shock, is an immediate possibility." Identification of such epitopes on glycoproteins and on the cells producing them can be achieved by a simple immunoassay.[9] If the αGal epitope synthesis is unavoidable in the production process, passing of glycoproteins through an agarose column with bound (solid-phase) recombinant α-galactosidase results in the cleavage of the terminal α-galactosyl unit and complete destruction of αGal epitopes. Such a column can be used multiple times without loss of catalytic activity. Finally, the identification of patients who produce anti-αGal IgE can be achieved by use of an in vitro binding assay or an in vivo skin test using

a non-immunogenic allergen presenting multiple αGal epitopes, e.g., nanoparticles.[10]

Yoann Pointreau, an oncologist working with Hervé Watier's laboratory (University of Tours, Tours, France), presented a study of factors that influence the production of anti-αGal IgE antibodies in normal individuals living in the area of Tours. An immunoassay based on a polymeric α3-galactosylated antigen was developed to study anti-αGal IgE and validated using sera of patients who experienced a shock during their first cetuximab infusion. Studying anti-αGal IgE in a cohort of 300 blood donors, he reported a frequency of 6% (18/300) positive sera. Among the factors studied, i.e., age, sex, blood group and biological atopy markers (using total IgE and Phadiatop®), the only factor found to be associated with the presence of αGal IgE was the male sex, with a sex ratio at 5:1.1 ($p = 0.01$). This unexpected factor, which is rarely found in allergy, is in accordance with the higher incidence of shocks to cetuximab in head and neck cancer compared with colon cancer patients.

Jean-François Bouhours (Nantes, France), who accepted a challenge to delve into old literature about serum sickness and the involvement of the "Hanganutziu-Deicher antigen," presented the results of his investigation. The story started in the 1920s with the detection of false positive Wassermann reaction (heterospecific hemagglutinins) following serotherapy. The antigen was present in horse serum and on the red blood cells of many mammals except humans. Hanganutziu-Deicher antigens were demonstrated in the 1970s to be gangliosides containing N-glycolylneuraminic acid (Neu5Gc). Neu5Gc glycoproteins can also be the target of heterophile antibodies, as demonstrated in patients receiving anti-lymphocyte globulins. The Neu5Gc biosynthetic pathway was described later and the gene coding for the CMP-NeuAc hydroxylase (*CMAH*) was demonstrated to be inactivated in humans.

Continuing on the topic of Neu5Gc, **Ajit Varki** (University of California, San Diego, CA) emphasized that *CMAH* was specifically inactive in humans (although present in chimpanzees), an observation that could be linked to a lower expression of inhibitory Siglecs on human compared with great apes lymphocytes; this latter fact is a possible explanation for the higher sensitivity of human lymphocytes to anti-CD28 stimulation, as demonstrated by the TGN1412 history, and to immune activation as a driver of AIDs in HIV-infected individuals. Neu5Gc can incorporate into human cells through a sialic acid lysosomal transporter, constituting a dietary pathogenic mechanism in some diseases and a substantial concern in glycoproteins and cells prepared for therapy using animal culture products, due to the anti-Neu5Gc antibodies. Although all humans have anti-Neu5Gc antibodies, each individual serum recognizes a given set of Neu5GC-containing glycans, with highly variable titers. Anti-Neu5Gc IgM and IgG appear during the first year of life through the diet of mammalian foods, following Neu5Gc incorporation into bacteria. Once transferred in *CMAH* knock-out mice, human anti-Neu5Gc antibodies recognize Neu5c containing biopharmaceuticals, e.g., cetuximab, and decrease their pharmacokinetics.[11] Whether these antibodies are involved in hypersensitivity reactions is under investigation.

Session 3: Strategies to Prevent Cetuximab Anaphylaxis in Clinical Practice

As an introduction to the second day and the third session, **Roy Jefferis** (University of Birmingham, Birmingham, UK) gave an authoritative overview of the natural and recombinant glycoforms of human IgG-Fc. The importance of glycosylation was illustrated by the loss Fc receptor and complement effector functions exhibited by aglycosylated IgG; however, antigen binding is not affected and aglycosylated IgG offers a further therapeutic option, e.g. otelixizumab.[23] Analysis of polyclonal human IgG and myeloma proteins reveals a high diversity for IgG-Fc glycoforms (>128) and that the IgG-Fc glycoform profile is a "signature" of the producer plasma cell clone. It was posited that the immune system orchestrates the glycoform profile, in addition to the antibody isotype profile, to provide an optimal response to a given insult by pathogen. It is clear, therefore, that the IgG-Fc glycoform profile is a critical quality attribute (CRA) for therapeutic mAbs. He then pointed out that ~30 % of polyclonal human IgG also bear oligosaccharides attached to VH or VL regions; the glycosylation sequon being introduced as a result of somatic hypermutation and selection during a secondary immune response. In contrast to IgG-Fc the IgG-Fab oligosaccharide of polyclonal IgG is more fully processed, showing less heterogeneity and frequent disialylated forms, i.e. N-acetylneuraminic acid in α2-6 linkage. However, the IgG-Fab oligosaccharides attached to mAbs are very dependent on the producer cell line employed. While CHO cells add complex diantennary oligosaccharides, including N-acetylneuraminic acid and Neu5Gc in α2-3 linkage, mouse cells (NS0 and Sp2/0) produce more heterogeneous IgG-Fab glycoforms including the αGal epitope, in addition to α2-3 Neu5Gc.[12,13] This accounts for problems experienced by some patients on administration of cetuximab;[3] it is produced in Sp2/0 cells and bears the αGal epitope in the VH region of the Fab. It has recently been reported that CHO cells also have the potential to add oligosaccharides bearing the αGal epitope.[4] These experiences may deter the pharmaceutical industry from developing IgG-Fab glycosylated mAbs; however, on the positive side, it should be noted that oligosaccharides are hydrophilic and can confer solubility and stability properties on glycoproteins.[14] In conclusion, Professor Jefferis discussed the extent to which biosimilars should display similarity in glycoform profile and consideration of the potential for IgG allotype differences, between mAb and patient, to contribute to immunogenicity.[24]

Lars Stöckl (Glycotope, Berlin, Germany) discussed the GlycoExpress™ technology, which consists of a set of glyco-engineered human cell lines for the high yield production of mAbs and other biopharmaceuticals. He then presented CetuGEX™, a cetuximab "biobetter" which was produced in GlycoExpress™ that entered its first-in-man study in August 2010. CetuGEX™ and cetuximab are equivalent in terms of Fv-mediated functions in in vitro and in vivo models. Since the glycosylation of CetuGEXTM was optimized with respect to the presence of bisecting GlcNAc and reduction of α6-fucose, its ability to mediate ADCC is highly improved compared to cetuximab. Based on *FCGR3A* pharmacogenetic studies first performed in Tours,

Parma and Montpellier for rituximab, trastuzumab and cetuximab, respectively[15-17] it is known that there is a much lower clinical benefit for patients being *FCGR3A* heterozygous (158F/V) or homozygous (158F/F). Since the ADCC activity of CetuGEX compared to cetuximab is improved by ~10-fold for patients carrying the V/V allotype and up to 250-fold for the F/V and F/F allotypes (>80% of patients) an improved anti-tumor activity and clinical outcome is expected for all patients. Adjustment of CetuGEX™ sialylation with the GlycoExpress™ technology also has a significant effect on the half life of CetuGEXTM in macaques. Because it is produced in human cells, CetuGEXTM is totally devoid of αGal and Neu5Gc structures, which reduced its immunogenicity and allergenicity including anaphylactic shocks.[3]

Johannes Blatter (Merck KGaA, Darmstadt, Germany) then presented premedication strategies to limit anaphylaxis to cetuximab, stating that Merck Serono is committed to identifying and implementing any risk mitigation measure that would ensure constant monitoring of patients, as well as evaluating options that would prevent or reduced such reactions. Severe infusion related reactions are common (≥1/100 to <1/10), but rarely fatal (≥1/10,000 to <1/1,000), based on the post-marketing experience. In accordance with the SmPC, anti-H1 and steroids are required before the first infusion and are subsequently recommended. He then presented a re-analysis of premedication and infusion-related reactions[18] done by pooling the data of two major trials (CRYSTAL and MABEL) that enrolled 1,747 colon cancer patients, using the terms usually employed in patient files. Ninety five percent of patients received anti-H1 (1 in 8 different drugs), and 60% received steroids (1 in 7 different drugs) in addition to anti-H1. Grade 4 reactions were observed in 0.8% cases (0.5% anaphylaxis, 0.2% dyspnea). Addition of steroids to anti-H1 reduced the incidence of grade 3/4 reactions from 2.7–1%. In the discussion, the participants' attention was drawn to the fact that conditions of these two clinical trials were different from those likely to be encountered in real life, e.g., a selection bias in the recruitment of patients (no co-morbidity), the absence of patients from areas characterized by a high incidence of shocks to cetuximab, and more importantly, the absence of head and neck cancer patients, in whom a higher incidence of shocks has been observed.

Anne Moneret-Vautrin (Epinal, France) first reminded the audience that anaphylaxis can also be IgG-mediated (dextran infusion).[19] Starting with anti-αGal anaphylaxis, she performed cetuximab intradermal testing (IDT) in two patients referred for recurrent idiopathic anaphylaxis who recovered after avoidance of mammalian meat.[20] IDT with cetuximab at 5, 50 and 500 μg/mL, as well as anti-αGal IgE measurements (Genclis), performed in 13 cases of anaphylaxis to beef and offals, in ten cases of idiopathic anaphylaxis and in 14 controls demonstrated the high specificity and sensitivity of the method (>90%). Such a high performance can be explained by the fact that each cetuximab molecule expresses αGal epitopes on its two Fab arms, constituting an excellent bridging allergen ("haptenic brush"). To avoid syndromic reactions, prick tests must be performed first (up to 500 μg/mL) then IDT, starting at 5 μg/mL. Positive IDT to cetuximab (a doubled diameter of the papula) very nicely correlated with the presence of anti-αGal IgE. In vitro inhibition experiments showed that a synthetic αGal structure was more convenient to detect anti-αGal IgE than cetuximab. She concluded by telling the audience that patients at risk of anaphylaxis to cetuximab could be detected just before starting a cetuximab infusion if there is a collaboration between an allergologist well-trained for skin testing and the oncologist.

The next topic was validation of in vitro assays for anti-glycan IgE detection. **Anita Kober** (Phadia, Uppsala, Sweden) first mentioned that clinical symptoms in allergy result from multiple factors, the specificity and concentration of IgE antibodies being only one of them. The quantitative assays for the detection of anti-αGal IgE were developed under the validated standards, i.e., excess of allergen, calibration traceable to WHO, parallelism, precision and a low level of detection. She illustrated how Phadia has developed a test for measuring anti-αGal IgE antibodies by using bovine thyroglobulin as marker for αGal antigen. By using sera from patients allergic to beef, she demonstrated that this test gives good correlation with cetuximab and αGal-human serum albumin (neoglycoconjugate) derivatives.

After reminding the audience that the frequency of severe anaphylactic reactions to cetuximab varies from 1.2–3.5%, but may be as high as 22–33% in some geographic areas, **Benoît Dupont**, an oncologist working with Brigitte Le Mauff's laboratory (Centre Hospitalier Universitaire, Caen, France) focused on the necessity of identifying patients at risk. He presented a retrospective analysis of 213 patients who received cetuximab, identifying 21 cases of anaphylaxis (9.9% frequency). Anti-cetuximab IgE, measured using an in-house ELISA, were detected in 10 out of 14 pretreatment available sera (OR >11).[21] To demonstrate that this assay is suitable for detecting patients at risk of anaphylactic reaction to cetuximab, a prospective multicentric study called IgES started in 2010. The main goal is to reduce the incidence of severe anaphylactic reaction in anti-cetuximab IgE negative patients. Positive patients are clinically re-evaluated then either treated with another mAb when possible or treated with cetuximab in an intensive care unit. Ninety patients (of a total of 180 planned) have already been included. The final results are now awaited!

Maya Jerath (University of North Carolina, Chapel Hill, NC) discussed the case of a patient with a refractory metastatic breast cancer who presented an anaphylactic shock to cetuximab and anti-αGal IgE in her serum.[22] Although anaphylaxis reaction to cetuximab is usually an absolute contraindication to cetuximab re-administration, the fact that there was no treatment alternative prompted the medical team to proceed with cetuximab re-administration in an intensive care unit, under a "desensitization" protocol: premedication, starting with a very low dose (0.001 mg), dose doubled each step, with 15 min break time between steps, and slow infusion rates (5 ml/min). The patient received the complete cetuximab dose within 10 h without any event except maculo-papular rashes. At subsequent infusions, administration with an increased rate protocol was uneventful. She concluded that this desensitization protocol enabled the patient to "tolerate" the drug and could be helpful in patients presenting anti-α3Gal IgE antibodies.

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