Editorial

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In years the Journal of Neuroimmune Pharmacology (JNIP) is still a youngster, but in the quality and number of the articles it is a fully mature journal with a solid impact factor of **4.574**. My personal involvement with the journal dates back only from May 2012, when the chief editor of the journal, professor Gendelman, invited me to become senior editor for Europe. Publications from European scientists are remarkably underrepresented in the journal, which is likely due to the low awareness of the journal that is poorly known among my colleagues. My ambition as head of the European office is to recruit more high quality publications to the journal from the old continent. In the past months I have experienced professor Gendelman's inspiring and visionary leadership, which must have been the powerful fertilizer that enabled the rapid growth of the journal and will sustain its further maturation.

Who is Bert 't Hart?

I have gladly accepted professor Gendelman's invitation to inform the readers of the journal about my scientific activities and my personal view on the future of the journal. I am a biologist by training with a specialization in cell biology and endocrinology. After graduating in 1981, I got the opportunity to work on a research project in human immunology, entitled "*the in vitro activation and differentiation of human antigen-specific B cells*". This first experience has determined my lifelong interest in the human immune system. After obtaining my PhD in 1986, I chose to work for a few years in the Pharmacognosy department of the Utrecht Pharmacy school, where I led a small research group working on the identification

of the active principles of medicinal plants. It is a great pity that immunologists have forgotten that plant molecules have powerful immunomodulatory activities. The good news is that JNIP has appointed a special section editor (dr. Raymond Chang) for natural medicine.

Our own small research group was quite successful with the identification of several new immunomodulatory compounds, of which apocynin captured most of my interest. We discovered that apocynin is a specific inhibitor of the phagocyte oxidative burst and were successful in elucidating the action mechanism in human neutrophils. We found that the o-methoxy-substituted catechol apocynin is converted by myeloperoxidase into a reactive intermediate, later identified as a quinone-methide, that prevents the assembly of the superoxide generating NADPH oxidase. The number of publications registered in PubMed in which apocynin has been used for analyzing the role of the oxidative burst in health and disease amounts now (January 2013) more than 1,300. My own favorite paper in the field of neurological disease is on the finding that orally administered apocynin attenuates neurodegeneration in SOD1 mutant mice, a model of the untreatable disease amyotrophic lateral sclerosis (Harraz et al. 2008). We recently reproduced these findings in the MPTP-induced model of Parkinson's disease in a monkey; the report by Philippens et al. will soon be published in this journal.

After 4 years working in Ethnopharmacology it was time to go back to more basic immunology. A faculty position at the Netherland's Primate Center (now known under its new name Biomedical Primate Research Centre, BPRC) offered me a unique opportunity that I could not refuse, namely to develop models of human autoimmune diseases in non-human primates. Monkeys are our closest relatives in evolution, as is illustrated by their well-established genetic and immunological proximity, and thus provide unique models of human disease. The BPRC (www.bprc.nl) has large genetically well-characterized

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colonies of macaques and marmosets, which are used for the development of relevant preclinical models of viral, parasitic and immune-mediated inflammatory disorders in the human population.

Together with a PhD student I started working on the etiopathogenesis of collagen-induced arthritis (CIA) in rhesus monkeys. The model quickly raised the interest of Pharma and Biotech companies who needed a relevant autoimmune disease model for the efficacy evaluation of biologicals, which due to species specificity did not work in lower species, monoclonal antibodies for example. The CIA model in rhesus monkeys is still operational and has now also been set up in the common marmoset.

Besides my still keen research interest in the modeling of rheumatoid arthritis (RA), I developed an interest in the modeling of multiple sclerosis (MS), an enigmatic neurological disease for which no effective cure exists. The elected animal model of MS, experimental autoimmune encephalomyelitis (EAE), had already been established in rhesus macaques. However, the acute and seriously destructive presentation of the macaque model showed only poor resemblance with human MS. I therefore welcomed the opportunity to start working with an exciting new EAE model in marmoset monkeys, which had just earlier been developed at UCSF by Luca Massaccesi, Claude Genain and Steve Hauser (Massaccesi et al. 1995). After securing the necessary financial resources, which are very substantial for preclinical research in monkeys, and obtaining permission from our ethics committee. I could set up the model in our own institute.

In retrospect, the choice to develop a disease model for MS and later also for RA in marmosets has been very rewarding (for review: (Vierboom et al. 2005; 't Hart and Massaccesi 2009)). Moreover, the now firmly established integration of exploratory research into pathogenic mechanisms and applied research on new therapies has proven to be a powerful strategy for obtaining unique insights into the mechanisms of human autoimmune disease (Fig. 1).

Fig. 1 Translational research should be bidirectional. The integration of forward (from animal model to patients) and reverse (from patient to animal model) translation is essential for the development of effective therapies for immune-mediated inflammatory disorders

Of mice and man

My major interest in science is translational neuroimmunology and immunotherapy development. In immunological research the mouse is the dominant animal model and working horse. There is nothing wrong with this situation as most fundamental immunological principles have been discovered and developed in well-defined laboratory mouse strains. The advantages of the mouse are obvious: relatively low cost per animal, low interindividual variation within inbred strains due to genetic homogeneity and defined microbial status and the availability of a wide array of genetically modified variants of the B6 strain. However, it cannot be ignored that the (forward) translation of immunological knowledge into effective therapies for patients suffering from immune-mediated inflammatory disorders has been notoriously difficult. In each of the three main categories of immunological diseases, i.e. asthma/allergy, transplant rejection and autoimmunity, there is a long list of new treatments that fail to replicate promising effects observed in mouse models, when they were tested in patients. Some even showed detrimental effects. With reference to Fig. 1 the question is warranted why the reverse-translation of a failed treatment in the clinic to the mouse model, questioning the relevance of a critical pathogenic mechanism observed in the animal model for the human disease, is so rarely made. Scientists observing that a monoclonal antibody modifying a pathogenic mechanism in mouse EAE models does not work, usually have no problem with the conclusion that the targeted pathogenic mechanism might be less relevant than anticipated. However, when such a therapeutic monoclonal antibody fails to work in the patient such a conclusion is rarely drawn.

The accumulating number of promising therapies that have been lost in translation show that there may be something fundamentally wrong with the assumption that immunopathogenic mechanisms developing in an immunologically immature 12 weeks old SPF raised inbred laboratory mouse are to a high level comparable with those in the ageing pathogen-educated human immune system. Transplantation immunologists have already discovered this discrepancy as new immunomodulatory treatments suppressing graft rejection in mouse models need to be tested first in non-human primates before they can be entered into clinical trials (Sachs 2003). In my view there is no rational argument why the therapy development policy should be different in neuroimmunology or neuroimmune-pharmacology.

Relevant autoimmune disease models in non-human primates are indeed rare. However, my team at the Biomedical Primate Research Centre has shown throughout the years a strong ambition to develop such models in non-human primates, which are increasingly used by the scientific community. We concentrate on models of

multiple sclerosis and Parkinson's disease, as prototype models for neuroinflammatory ('t Hart et al. 2011) and neurodegenerative disease (Philippens et al. 2010).

My vision on the future of the journal

The journal operates in an exciting field, where in future years many important developments can be expected. The late prof. Ralph Steinman, posthumous winner of the 2011 Nobel Prize for Physiology and Medicine for his groundbreaking work in immunology, wrote a memorable Science article on the relevance of human immunology research as a basis for immunotherapy development (Steinman and Mellman 2004). In this article he complains that editors of leading journals often hesitate to open the pages for studies in human immunology. My personal experience with getting results from immunology studies in non-human primates published in high-ranked journals are equally frustrating. It is too easily forgotten that our thinking about immunological mechanisms in health and disease is mainly based on the laboratory mouse and that our insights into the functioning of the human immune system in health and disease are much more limited.

The research of our group in a non-human primate model of multiple sclerosis, EAE in the common marmoset, shows that the pathogenic mechanisms leading to disease in a pathogen educated immune system differ fundamentally from the classical EAE models in inbred/SPF mice ('t Hart et al. 2011). The main pathogenic pathway leading to MS-like pathology does not even exist in the mouse EAE model. Nevertheless, when we submitted our findings to a high impact journal, the editor responded that we should first prove that the pathway exists in mice.

The discussion about which is the better model is not so interesting as the relevance of any model is determined by

its intended use. As stated by the statistician George Box "all models are wrong, but some are useful" (Box and Draper 1987). For new discoveries in immunology the inbred/SPF laboratory mouse has been and will remain to be very useful. However, the demonstration that the newly discovered immunological mechanism operates in a similar fashion in the pathogen-educated primate immune system, i.e. that of monkey and man, is also important and deserves a warm welcome in the high impact journals.

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