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Improvement of preclinical animal models for autoimmune-mediated disorders via reverse translation of failed therapies

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The poor translational validity of autoimmune-mediated inflammatory disease (AIMID) models in inbred and specific pathogen-free (SPF) rodents underlies the high attrition of new treatments for the corresponding human disease. Experimental autoimmune encephalomyelitis (EAE) is a frequently used preclinical AIMID model. We discuss here how crucial information needed for the innovation of current preclinical models can be obtained from postclinical analysis of the nonhuman primate EAE model, highlighting the mechanistic reasons why some therapies fail and others succeed. These new insights can also help identify new targets for treatment.

The past few decades have been an era of enormous progress in our mechanistic understanding of AIMID. Much of the research into the processes underlying the initiation and progression of AIMID has been obtained in EAE, the elected preclinical model of multiple sclerosis (MS), most often induced in rodents. In several cases, new knowledge obtained in EAE has been successfully translated into effective treatments for patients with MS, such as small molecules (e.g. fingolimod), cytokines (interferon β) or various monoclonal antibodies (mAbs) [1]. Examples of mAbs showing significant clinical efficacy include natalizumab, targeting anti-α4β1 integrin; anti-CD52 (alemtuzumab), targeting a glycoprotein expressed on all mature lymphocytes; and several mAbs against CD20 (rituximab, ofatumumab and ocrelizumab), targeting a surface molecule that is broadly expressed in the B cell lineage. However, the translation of a pathogenic mechanism discovered in an animal model into a safe and effective treatment for patients often fails; a problem that is sometimes referred to as 'the valley of death' [2,3].

The limited predictive validity of the currently used animal models for the safety and efficacy evaluation of a new therapeutic biological agent in the clinic is the Achilles heel of preclinical research [4,5]. For this reason, new research programs funded by the European Commission, such as Horizon 2020 and Innovative Medicine Initiative 2, stimulate the generation of better predictive animal models for preclinical research as a priority strategy that should help the drug development industry to cross the valley of death. However, how can scientists working in preclinical research be expected to improve their animal models when they do not know why and where they fail?

In this review, we postulate that such strategic information can be obtained from a critical 'postclinical' analysis of the reasons why some treatments succeed in the clinic, where others fail. We discuss examples from work in the field of MS where such strategic information has been obtained from 'reverse translation analysis' of failed and successful therapeutic mAbs in well-validated nonhuman primate (NHP) models of the disease. Although the discussion is focused on MS and its elected animal model EAE, we envisage that this strategy could serve as a template for several types of treatment in a broader range of autoimmune inflammatory disorders, such as rheumatoid arthritis (RA), diabetes and others.

MS and EAE

MS is an enigmatic autoimmune inflammatory disease that targets the human central nervous system (CNS), comprising the brain

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and spinal cord. The pathological hallmark of MS is the lesion, a usually sharply edged focal area of inflammation within the CNS white matter, which results in a variable degree of injury to oligodendrocyte–myelin (demyelination) or neuron–axon complexes (neurodegeneration). The early phase of MS is clinically characterized by alternating episodes of neurological dysfunction (relapse) and recovery (remission). Relapses are caused by the activation of T cells that mediate inflammation and antibodies mediating demyelination. Remissions are thought to be induced by the activation of T regulatory cells, which suppress the inflammatory T cells, and by repair of the injury through formation of new myelin sheaths (remyelination). Most patients with relapsing remitting disease (RRMS) transit to secondary progressive disease (SPMS), where symptoms worsen progressively and remissions occur less frequently and, ultimately, disappear. The mechanisms that drive this late phase of the disease are currently unknown and, therefore, effective treatments are lacking.

The factor(s) that trigger(s) the activation of autoreactive T and B cells are poorly understood. Opposing views exist, namely that autoimmunity is elicited by the interaction of genetic susceptibility factors with infection by environmental pathogens (outside-in paradigm), or that autoimmunity is a response to self-antigens released from injured target tissue (inside-out paradigm) [6]. A 'response-to-injury' concept has been proposed for MS that harmonizes these opposite views, stating that autoimmunity in MS results from immune hypersensitivity against self-antigens released from CNS injury and that the hypersensitivity is caused by effector memory cells against chronic infection with herpesviruses [e.g. cytomegalovirus (CMV) and Epstein-Barr virus (EBV)] [7].

Despite growing criticism [8–12], the prevailing concept in preclinical MS research is still the outside-in paradigm, as is recapitulated in the elected animal model EAE. For this reason, the immunopathogenic mechanisms identified in mouse EAE models still form the conceptual basis of most translational research in MS.

An immunological gap between mice and humans

Most preclinical researchers use 10–12-week-old mice from a limited number of inbred and/or SPF strains (e.g. C57BL6, SJL or Balb/c) in their EAE models [12]. However, do these models sufficiently reflect the complexity of the human disease to serve as a reliable preclinical model?

The observation that the disease concordance among identical twins is more than fivefold higher than in nonidentical twins (±25% vs. 5%) suggests a strong genetic influence [13,14]. Moreover, environmental factors have a substantial influence on the disease, which might even be stronger than that carried by genes. Well-documented environmental factors influencing MS susceptibility include infections, such as with EBV, or noninfectious factors, such as smoking or low serum vitamin D levels. The standard laboratory mouse has been bred and raised under SPF conditions and experiments are performed in a clean animal house. The minimal environmental influence on the models is a clear advantage when the effect of an environmental factor on a biological process is studied. However, it is a disadvantage in preclinical studies based on the assumption that the model is a faithful representation of the human disease.

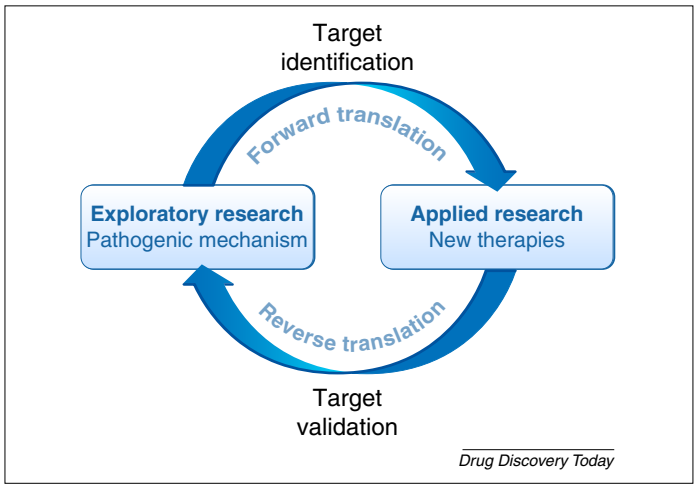

FIGURE 1

Optimization of the translational validity of preclinical animal models for a certain disease is a reiterative process. New pathogenic concepts are forward translated into new therapies, which are tested in the patient. Failed therapies are reverse translated to a suitable animal model in which mechanistic information of the reason of failure can be obtained.

The mouse strains used are also inbred, meaning that all mice of a certain strain are genetically identical. This lack of genetic variation sharply contrasts with the genetic complexity of the MS patient population, which receives input from more than 90 different risk genes [15].

Last but not least, there are many well-documented fundamental immunological differences between a laboratory mouse and a human [16]. It is rather remarkable that most immunologists have a much deeper understanding of the murine than of the human immune system [17,18].

Translational research refers to the development or translation of new insights and discoveries in the laboratory into products that are applicable for patients. In this review, we distinguish two aspects of translational research, namely 'forward translation', being the preclinical translation of a concept from the animal model to the human patient, and 'reverse translation', which is the analysis in a suitable animal model of therapies that failed in the clinic (Fig. 1). Below, we discuss different treatments based on mAbs that failed to reproduce promising effects observed in mouse and monkey EAE models when they were tested in patients with MS. It is important to emphasize here that treatments failing in RRMS were nevertheless relevant in other autoimmune diseases.

Therapies lost in translation

Here we describe a selection of new therapeutic antibodies that failed to show efficacy in RRMS clinical trials. Analysis of the mechanism of action in a nonhuman primate model provided new insights into pathogenic mechanisms in MS.

Example 1: ustekinumab

Ustekinumab is the trade name for a fully human immunoglobulin (Ig)G1κ mAb against the shared p40 subunit of two pro-inflammatory heterodimeric cytokines, namely interleukin (IL)-12 (p35/p40) and IL-23 (p19/p40) (Fig. 2). An impressive body of literature data indicates that the two cytokines have a key pathogenic role in mouse EAE models (reviewed in [19]). In brief, IL-12 produced by

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