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editorial

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Disease models – one size does not fit all

Because proof of principal studies in disease models often gate for important 'go/no go' decisions in discovery projects, it is vital that the correct disease model is selected. Projects might be compromised should the wrong model be selected because of the lack of knowledge relating to the human disease or chosen target. In the search for new opportunities, both the pharma and biotech industries often repurpose within cluster indications – frequently resulting in costly errors in terms of both wasted time and wasted resources because of the inappropriate use of disease models.

Psoriasis is now perceived as a highly immune-mediated disease, characterized by disturbed morphology of the skin, cutaneous infiltration of inflammatory cells and increased dermal angiogenesis. Furthermore, there is an upregulation of a variety of different cytokines, chemokines and growth factors leading to a characteristic immune response.

Most new effective treatments, either on the market or in the pipeline, are directed against cytokines or immunological targets. Increased understanding of the disease within this indication has led to several new transgenic psoriasis mouse models. Within such models the animals develop phenotypes that are considered closely similar to human psoriasis. Various companies have created several screening models derived from such transgenic mice and are employing them in the search for new treatments of psoriasis; however, to consider all such models to be mice representing/displaying human psoriasis might compromise important project decisions.

Scenario: a pharma/biotech wishes to repurpose an anti-CD4 antibody but lacks informed knowledge of new indication (psoriasis) it wishes to target. To test the concept, three different procedures, each requiring a different transgenic mouse (disease model), are adopted

(a) A mouse with overexpression of VEGF in the skin [1,2].
   – The antibody treatment arguments disease [3].
(b) A model with expression of integrins in the suprabasal layers of the skin [4].
   – The antibody does not affect disease [5].
(c) A model with overexpression of TGF-beta in the skin [6].
   – The antibody possibly delays the onset of the disease [7].

In short, to use the same antibody treatment in the three procedures would afford three different answers.

Even if the data are taken out of context, the above example illustrates that even where models have many similarities to the human condition, investigation of the same targets will often lead to strikingly different conclusions in the different disease models. Thus, knowledge and understanding of a human disease is essential to selecting the most appropriate disease model when entering new indications.

When compared to any other indication, psoriasis perhaps has the best and most established humanized mouse model. In the model's simplest version, skin biopsies from human psoriatic lesions are removed and grafted onto the back of immune-deficient SCID mice. The graft is not rejected by the mice but survives and retains the psoriatic phenotype. Thus, the effect of new drugs can be tested for a long period in an *in vivo* situation with human material, quite unique when it comes to animal models.

Even with sophisticated humanized mouse models, however, there are pitfalls where a pharmacologist is not very familiar with the model. In this case, the T cells in the graft lose or downregulate their CD4 receptor rapidly after removal from the patients [8]. Thus, the effect on the primary readout of an anti-CD4 treatment would be very limited. The end result is little or no effect in the disease model and, consequently, no clear answer whether the company should invest in the development of the antibody for psoriasis.

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If disease models are to add value to projects, they need to be validated well, to know what can and – in particular – what cannot be done with the model. Familiarity with models serves to simplify apparently complex questions.

For example, here are the preferred choices when targeting
(a) angiogenesis in the skin: the VEGF model;
(b) keratinocyte hyperproliferation: the integrin model.

But none of the models are suitable to test whether CD4 depletion would benefit psoriasis patients. Because psoriasis is only found in humans, major questions can only be addressed using human subjects and disease models can only address certain aspects of the disease. Success is dependent on an informed choice.

References

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