

# **Synopsis: What is the most important advance in dermatology in the last 25 years?**

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One's choice of the most important advance in dermatology depends on the criteria used for making that selection. The key criterion in this essay was that the advance needed to have significantly increased dermatological knowledge over the last 25 years (and should have the capability to continue doing so). This is because increasing dermatological knowledge aids in the development of clinical interventions; bringing us closer to the ultimate ambition of achieving 'healthy skin for all'.

The three advances perceived to be most successful at meeting the criteria were: gene-targeted mice, tissue microarrays, and genome-wide association studies. I believe gene-targeted mice have been the most successful out of these. I will offer my reasons for this, and then compare gene-targeted mice to the other advances mentioned above.

## **Gene-targeted mice**

Gene-targeted mice can be described as either knockout or knockin. In knockout mice, the gene of interest has been deleted.<sup>1</sup> In knockin mice, the gene has been inserted at a specific locus, replacing an existing DNA sequence.<sup>2</sup> Observation of the effects of altering specific genes allows for a greater understanding of the integumentary system in health and disease, as much of the molecular processes between mice and humans are similar.

Gene-targeted mice have played an important role in developing diagnostics. For example, by greatly assisting in the identification of *COL5A2* gene mutations as a cause of Ehlers-

Danlos syndrome, gene-targeted mice have helped make the confirmatory diagnosis and pre-implantation diagnosis of Ehlers-Danlos syndrome possible.<sup>3,4,5</sup>

Gene-targeted mice have also aided in the development of current treatments. For example, gene-targeted mice were necessary in clarifying the role of CTLA-4.<sup>6,7</sup> This allowed for the development of a biologic called ipilimumab, a CTLA-4 inhibitor, which is used in the treatment of metastatic melanoma.<sup>7</sup>

In addition, gene-targeted mice have been used to develop fully-humanised monoclonal antibodies.<sup>8</sup> The aim of this is to reduce the side-effects of treatments, as antibodies with mouse components have a higher immunogenicity than fully-humanised antibodies.<sup>9</sup> A number of biologics (e.g. ustekinumab) have been produced through this method.<sup>10</sup>

Gene-targeted mice are likely to aid in the emergence of future dermatological treatments. They have already been used to identify a number of therapeutic targets, and also to evaluate the potential of particular treatments; some of which are now in clinical trials.

### ***Tissue microarrays***

Tissue microarrays allow the assaying of hundreds of small quantities of patients' tissues at a time. This has been useful in understanding the molecular pathogenesis of particular dermatoses, and has identified potential therapeutic targets.<sup>11</sup>

So far, clinical applications of knowledge from this source have not been evident, whereas information discovered using gene-targeted mice has already been applied to develop clinical interventions.

### ***Genome wide association studies (GWAS)***

In dermatology, GWAS have validated many existing therapeutic targets, and identified novel disease-associated loci, providing new candidate disease-susceptibility genes.<sup>12</sup> For example, a GWA-study associated psoriasis with a (previously unidentified) locus containing the gene *IL28RA*, which encodes for the alpha-subunit of the IL-28 receptor.<sup>13</sup>

To date, there does not appear to have been any clinical interventions derived from GWAS in dermatology. Additionally, GWAS has identified fewer novel therapeutic targets than gene-targeted mice. This prevents GWAS from being considered as the most important advance.

### **Conclusion**

‘Healthy skin for all’ is a goal of enormous ambitions, which will require the development of better diagnostics and treatments if it is to be achieved. The advances discussed are catalysts for this. Of these, gene-targeted mice have demonstrated the most success. Therefore, on consideration of the criteria, it is legitimate to state that the applications of gene-targeted mice make it the most important advance in dermatology of the last quarter-century.

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