Human and computational models of atopic dermatitis

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Published in:
Journal of Allergy and Clinical Immunology

DOI:
10.1016/j.jaci.2018.10.033

Publication date:
2019

Document Version
Peer reviewed version

Link to publication in Discovery Research Portal

Citation for published version (APA):

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Human and computational models of atopic dermatitis: a review and perspectives by an expert panel of the International Eczema Council

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PII: S0091-6749(18)31573-2
DOI: https://doi.org/10.1016/j.jaci.2018.10.033
Reference: YMAI 13703
To appear in: Journal of Allergy and Clinical Immunology

Received Date: 15 August 2018
Revised Date: 10 October 2018
Accepted Date: 30 October 2018


This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.
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Conflicts of interest statement:

N. J. Reynolds has received grant support through Newcastle University from AstraZeneca, Bristol Myers Squibb, Genentech and GlaxoSmithKline. The rest of the authors declare that they have no relevant conflicts of interest.

Funding sources: The authors did not receive funding dedicated for preparation of this manuscript.

Kilian Eyerich is funded by an ERC grant (IMCIS, 676858) and the German Research Foundation (EY97/3-1); Sara Brown holds a Wellcome Trust Senior Research Fellowship in Clinical Science (106865/Z/15/Z); Bethany Perez White is supported by the Dermatology Foundation and the NIH-NIAMS (P30AR057216 and 1K01AR072773-01A1); Nick Reynolds’ research/laboratory is funded in part by the Newcastle NIHR Biomedical Research Centre, the Newcastle NIHR Medtech and in vitro diagnostic Co-operative and the Newcastle MRC/EPSRC Molecular Pathology Node. Jacob Thyssen is funded by an unrestricted grant from the Lundbeck Foundation

Word count: 3398

Number of tables: 1

Number of figures: 3
Abstract

Atopic dermatitis (AD) is a prevalent disease worldwide associated with systemic co-morbidities, representing a significant burden on individuals, their families and society. Therapeutic options for AD remain limited, in part due to lack of well-characterised animal models. To better define pathophysiological mechanisms and to identify novel therapeutic targets and biomarkers that predict therapeutic response, there has been increasing interest in developing experimental approaches to study the pathogenesis of human AD in vivo, in vitro, and in silico. This review critically appraises a range of models including: genetic mutations relevant to AD; experimental challenge of human skin in vivo; tissue culture models; integration of “omic” datasets; and the development of predictive computational models.

Whilst no one individual model recapitulates the complex AD pathophysiology, our review highlights insights gained into key elements of cutaneous biology, molecular pathways and therapeutic target identification through each approach. Recent developments in computational analysis, including the application of machine learning and a systems approach to data integration and predictive modelling, highlight the applicability of these methods to AD subclassification (endotyping), therapy development and precision medicine. Such predictive modelling will highlight knowledge gaps, further inform refinement of biological models, and support new experimental and systems approaches to AD.

Key words: Atopic dermatitis, atopic eczema, Endotype, Human models, Machine learning, Mechanistic models, Precision medicine, Tissue culture models, Skin equivalents, Systems biology

Abbreviations

ACD   Allergic contact dermatitis
AD   Atopic dermatitis
APT   Atopy Patch Test
ILs   Interleukins
IRFs   Interferon regulatory factors
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Introduction

Atopic dermatitis (AD; synonym atopic eczema) has a complex aetiology, involving multiple genetic and environmental factors\(^1\,^2\). With its very high incidence in childhood, chronicity, devastating effect on quality of life for affected patients and their families, enormous socio-economic costs, and limited therapeutic options to date, AD represents a major challenge. Furthermore, there is clear evidence that AD represents a systemic inflammatory disease with multiple comorbidities extending beyond the well-recognized atopic associations\(^3\). Consequently, a number of animal models have been developed and utilized by investigators and the pharmaceutical industry to better understand the disease and consider new pathways to target\(^4\).

However, as recently reviewed, mouse models do not adequately reflect the transcriptomic and gene pathways activated in human AD skin\(^5\) and the intrinsic difference between mouse and human skin represents a barrier to direct translation of findings from animals into human disease. Consequently, there has been increasing interest in experimental studies in humans (in part facilitated by technological and “omic” developments), cell culture models utilizing human tissue, and the use of computational or mathematical models that are developed by integrating these data. In this review article, we have used the term “human AD model” to define representations of the disease state and interventions that enable scientific insight into disease pathogenesis, disease course, and response to therapy. We delineate and critically appraise these AD modelling approaches that range from the experimental study of human skin in vivo (including challenge studies and detailed phenotyping and investigation of patients harboring specific genetic mutations), the generation of AD-relevant models using immunological, genetic and molecular methods in 2D and 3D human tissue culture, to the development of in silico computational models using a systems biology approach. Whilst a reductionist approach cannot by definition recapitulate the full spectrum of AD, these models have greatly increased our understanding of the molecular drivers of AD and provide a powerful tool for preclinical drug development and target validation. However, just as the etiology, clinical expression, and severity of AD range broadly among patients, in vitro and in silico models of AD vary widely both in how the AD phenotype is induced and how the models are evaluated. Therefore, we invited members of the International Eczema Council (IEC; www.eczemacouncil.org), a group of experts...
in AD, and associated authorities in the field to contribute to a scoping and development meeting and subsequently to evaluate and critically appraise the breadth of human AD and computational models to determine their strengths and weaknesses in how they recapitulate the pathophysiology of AD and enable therapeutics to be tested and validated.

**In vivo models of AD**

To dissect the pathogenesis of AD, two general approaches using human *in vivo* models have been followed: i) the study of rare genetic variants with AD-like phenotypes; and ii) the experimental challenge of AD or non-AD subjects with allergens or irritants. Regarding the first approach, numerous studies have characterized genetic disorders that display skin barrier function abnormalities. Most often, these studies characterized ichthyosis vulgaris, a disease that allowed insights into the function of the epidermal differentiation gene *FLG* (encoding filaggrin), in which mutations show the strongest association to AD development of all known genes\(^6\) (Figure 1). Other studies have focused on disorders characterized by systemic inflammation\(^3\) and immunodeficiency with AD-like skin manifestations (Figure 1). One example is patients suffering from Immunodysregulation Polyendocrinopathy Enteropathy X-linked (IPEX) syndrome that serves as a model to study how systemic imbalances in the Treg population can drive cutaneous AD-like inflammation\(^7\). In addition, the link between type 2 immunity, transcription factors such as JAK or STAT, and high levels of IgE was investigated in immunodeficiency syndromes such as STAT3 and DOCK-8 hyper-IgE syndromes or combined immunodeficiency disorders\(^8,9\). Table S1 lists the main genetic conditions that have provided insight into AD pathogenesis to date. Whilst the study of rare variants offers the opportunity to delineate distinct molecular mechanisms and control pathways of a particular phenotype, and thus may be regarded as “human models of AD”, a limitation of this approach is that not all observed phenomena are relevant in AD, which is more complex and heterogeneous than monogenic disorders.

The second *in vivo* approach to study the pathogenesis of AD is standardized challenge with allergens or other environmental factors. The most commonly used model is the Atopy Patch Test (APT), an
epicutaneous challenge of specific allergens dissolved in vehicle, which has provided insight into the temporal development of immune phenomena in AD (Table S2). Although developed in part to define clinically relevant reactions to aero-allergens, food allergens and autoantigens, its validity and predictive value depend on a variety of factors in the protocol and the APT is not used routinely in clinical practice. Experimentally, the APT has provided insights into the temporal sequence of cutaneous cellular infiltrates. Acute skin lesions show a highly reproducible Th2 dominant infiltrate, although other cell types including Th17 cells are also present. This Th2 dominance is in sharp contrast to other inflammatory skin diseases such as psoriasis. Time course studies have shown that additional immune cell subsets, such as Th1 and Th22 cells, progressively infiltrate the skin during an ongoing APT reaction, mirroring the cellular composition of acute versus chronic human AD. The APT has also been used to characterize dendritic cells within early lesional AD skin, e.g., inflammatory dendritic epidermal cells. Furthermore, the APT has provided insights on the interaction of microbiota and our immune system, particularly the role of bacterial-derived superantigens acting as an amplifier of the allergen specific cutaneous response in AD. In all these experimental APT studies, the population of AD subjects were well defined with specific inclusion and exclusion criteria (although the precise definitions of AD varied); in most studies AD, together with specific IgE to the corresponding allergen used in the APT, was an inclusion criterion.

Hapten challenge to induce classical allergic contact dermatitis (ACD) in AD patients has also broadened our understanding of AD pathogenesis (Table S2). Whether AD patients have an increased risk of ACD remains controversial and may depend on whether they harbor FLG mutations, which may allowed increased penetration of allergens. However, attenuated ACD reactions have been reported in AD subjects compared to controls in a severity-dependent manner. This might be due to the fact that haptens induce distinct immune responses, with fragrances mimicking the Th2/Th22 dominance of AD while nickel, DNBC, or imiquimod induced Th1/Th17 skewed immune responses. Of note, AD patients show a Th2-skewed ACD reaction, and this immune deviation might account for the diminished ACD prevalence in AD. A Th2
immune reaction profile of AD patients was also observed in an aero-challenge setup\textsuperscript{29}, as well as when challenging AD patients with physical factors such as hard water\textsuperscript{30, 31}. All current challenge models have some limitations (Table S2), as they only represent acute reactions and the small areas of applications cannot reproduce the intense pruritus and sleep disturbances usually present in AD. Furthermore, to date they have not stratified for genetic differences/endotypes amongst AD patients comparing APTs in patients with and without \textit{FLG} mutations, for example, might be a useful line of future investigation. Moreover, in the future, molecular profiling of lesional skin from standardized challenge models, adjusted according to AD endotype, might be used in early clinical studies to evaluate the potential of new drugs to improve AD\textsuperscript{32}.

**In Vitro Models**

As shown in Table S3, there are several 2D cell culture and 3D organotypic models for AD that complement each other in addressing specific experimental questions. While, 2D cell culture models (by definition) do not duplicate the architecture of skin, they are amenable to high-throughput techniques for drug discovery and target validation (2D model section, Supplementary Table S3). Accordingly, Otsuka \textit{et al.} used 2D cultures to screen a chemical library for compounds that enhance \textit{FLG} transcriptional activation and mRNA expression, suggesting a potential novel therapeutic agent for AD\textsuperscript{33}. On the other hand, 3D models replicate the stratified, squamous epithelium of epidermis, but require specific expertise and are time consuming. Epidermal equivalents consist of keratinocytes without a dermal compartment, while skin equivalents have a dermis, such as fibroblast-embedded collagen (3D model section, Supplementary Table S3). Both 2D and 3D models are amenable to treatment with disease-relevant cytokines, gene knockdown, use of patient-derived cells, and/or co-culture (Figure 2 and Supplementary Table S3).

The immune system is a major driver of AD and \textit{in vitro} immune modulation with disease-relevant cytokines, such as interleukins (ILs), can lead to AD-like phenotypes in normal primary keratinocytes\textsuperscript{34} and
3D models (3D cytokine model section, Supplementary Table S3). Knockdown of filaggrin in culture systems can give insight into the molecular and proteomic changes associated with its loss in AD; and combining filaggrin knockdown with other perturbations, e.g., cytokine treatment, can be used to study the multifactorial drivers of AD. For example, Hönzke et al. reported that filaggrin knockdown exacerbated epidermal responses to IL-4 and 13, including increased proliferation and keratinocyte-released cytokines in 3D skin equivalents. Patient-derived cells for 2D and 3D culture or tissue for explant culture are limited by access and availability, but may be the most relevant in terms of modeling AD. Further, patient biopsies can be a source of skin cells other than keratinocytes, allowing for co-culture models. Given that multiple systems contribute to AD, co-culture models that include immune cells, dermal fibroblasts, and neurons can begin to address their interplay with keratinocytes. For example, Berroth et al. derived keratinocytes and fibroblasts from normal and AD skin and showed that AD-derived fibroblasts are sufficient to decrease FLG mRNA in normal-derived keratinocytes in 3D culture. Moreover, combining FLG knockdown with CD4+ activated T-cells uncovered direct cross-talk between keratinocytes and T-cells that resulted in T-cell migration within the dermal compartment towards the epidermis. These studies highlight the levels of complexity that can be engineered into the 3D culture models. 3D culture systems have also been used to understand environmental influences on skin, including air pollution, ultraviolet radiation exposure, and bacterial infection. These relevant environmental factors could therefore be incorporated into in vitro models of AD. The 3D cultures and skin explants can also be used to assess the comparative efficacy and practical applicability of novel drug delivery systems. Notably, despite the assorted methodologies applied in developing in vitro models of AD, there is overlap in the AD-like characteristics amongst the various models: most produce perturbed epidermal morphology, abnormal differentiation, and barrier dysfunction. Most often, disparities in reported phenotypes appear to stem, at least in part, from differences in the methodologies used in evaluating models (not necessarily because of the absence of the phenotype).
Although *in vitro* models may not mimic certain symptomatic and/or subjective aspects of the disease such as pruritus and pain, they allow monitoring of changes in epidermal morphology and differentiation, gene and protein expression, lipid synthesis, and barrier function. Histologically, AD skin sections and most 3D models of AD show profound changes in the epidermal compartment, including hypogranulosis, spongiosis, and increased cellularity due to hyperproliferation (3D model section, Supplementary Table S3). Changes in expression of genes (detected by microarray, RNA-sequencing (RNA-Seq), or qPCR) and protein (detected by liquid chromatography mass spectrometry, Western blot, ELISA, or immunohistochemistry) can be used to evaluate disturbances in differentiation and immune response in 2D and 3D models. Lipid synthesis, which is required for optimal barrier function, can be monitored by expression of related enzymes or directly by mass spectrometry. Epidermal barrier function can be monitored in 2D and 3D models, depending on the assay. We recommend that the phenotype of any AD *in vitro* model should be extensively characterized, and should include parallel analysis of epidermal morphology, differentiation status, loss or gain of key transcripts/proteins, analysis of immune components, and assessment of functional epidermal barrier parameters. Full characterization of any AD model can inform downstream evaluation of potential therapeutic agents with respect to reversing different aspects of the disease. Testing potential targets or drugs in several model types can add rigor and indicate if a signaling pathway or protein is central to the diverse manifestations of AD.

**In silico** computational models

A core element of a systems biology approach is development of *in silico* computational models (mechanistic models) by integration of different types of experimental and clinical data from multiple studies, including those associated with disease conditions. *In silico* experiments, *i.e.* computer simulations or mathematical analysis of *in silico* models, can test model-specific hypotheses, predict disease prognosis or treatment outcomes, and identify knowledge gaps, guiding future experiments and clinical trials that produce further data. This iterative process refines *in silico* models, providing holistic systems-level
mechanistic insights into how perturbations (treatments or risk factors) lead to whole-organism phenotypes.

A mechanistic model describes causative interactions between the system’s components involved in the phenomena of interest (e.g. disease or treatment outcomes). Existing mechanistic models of AD vary widely depending on the levels of interactions (tissue, cells, proteins, genes) included in the model and mathematical methods used to describe the interactions.

Domínguez-Hüttinger et al. developed a multi-scale deterministic model that delineates interactions between the environment, skin barrier integrity and immune activation by ordinary differential equations (Table 1). Two bistable “switches” are described – the first regulating the onset of AD flares and the second controlling progression to severe and persistent disease. The model predicts, for example, that genetic predisposition to barrier dysfunction (e.g. FLG haploinsufficiency) predisposes to longer flares and more persistent disease and that prophylactic emollient use may be beneficial (Table 1).

Application of optimal control theory to the hybrid mathematical model can inform the design of patient-specific optimal strategies for “proactive therapy” to prevent recurrent flares once the disease has been brought under initial control. For example, this computational model supports the need for higher topical steroid treatment dose after disease worsening and the potential need for more frequent than 2-3 days per week application of topical steroid treatment to maintain remission in patients with FLG haploinsufficiency (Table 1), presenting a readily testable stratification treatment regime based on genotype.

Polak et al. developed a stochastic Petri net model that delineates genetic regulatory mechanisms responsible for immune responses in Langerhans cells (LCs) (Table 1). The model describes reported interactions between interferon regulatory factors (IRFs), IRF transcription partners and DNA sequences in a logic-based diagram. In vitro experiments validated model predictions that LCs’ ability to present a
peptide is altered by cytokine milieu and that a PI3Kgamma inhibitor reduces the LCs’ ability to induce Th1 responses. These smaller-scale and focused mechanistic models can describe detailed interactions which are difficult to be included and validated in multi-scale models. Inclusion of the detailed interactions would make the multi-scale models too complex to interpret and to be validated, due to the current lack of quantitative dynamic data that measures the variables across different scales simultaneously.

Subramanian et al. used a pathway model that included manually-curated skin-specific pathways and relevant genes (Table 1). Pathway enrichment analysis, using transcriptomic datasets of AD patients, provided mechanistic insights into drug actions of topical betamethasone and pimecrolimus. The pathway model would allow in silico experiments, once the kinetics parameters for pathways are identified, to provide quantitative and dynamic predictions of disease progression and treatment outcomes.

Population pharmacokinetic and pharmacodynamic (PK/PD) models have also been developed to describe differences and variability in pharmacological effects observed in large clinical studies for AD treatments. The authors identified the model parameters that can best fit to the effects of nemolizumab and dupilumab measured in terms of AD severity score or pharmacokinetics (Table 1). Population PK/PD models could help achieve mechanistic understanding of pharmacological effects, if combined with mechanistic models.

One of the challenges in developing mechanistic models is identification of the components and the pathways that are relevant to the model-specific hypothesis to be tested. This can be achieved by unbiased multivariate analyses of a collection of large-scale data, for example by machine learning data analysis. Application of machine learning methods to AD-related data is relatively limited at present, but some relevant works have been already published. Thijs et al. developed a piecewise linear mixed model to predict AD severity scores after different treatments and Kiiski et al. developed a multivariate logistic regression model to predict a “good treatment response”. A sufficient level of cross-validation is crucial.
to reduce bias and to ensure the general applicability of models that have predictive power beyond mere

description of data.

All the models presented above were developed based on the published data derived from studies in which
the inclusion and exclusion criteria for AD were specified. Whilst the majority of studies utilised the Hanifin
and Rajka criteria and specified further clinical (including co-morbidities) and demographical details, it is
clear that patients with AD present with a wide spectrum of clinical and molecular features (including for
example a greater heterogeneity in transcriptomic profile of lesional skin compared to psoriasis)\(^63\).

Future developments

The development of more sophisticated human models of AD that integrate large scale clinical and ‘omic’
data offer the potential for a deeper understanding of disease endotypes, molecular mechanisms
underlying key pathogenic events and clinical hallmarks of AD, as well as prediction of therapeutic
outcomes, including comorbidity at the level of an individual patient. Accepting that, by definition, these
human models are based upon a reductionist approach, they need to reflect the complexity of AD
pathogenesis, including epidermal barrier dysfunction, altered penetration of chemicals and allergens,
host/environment interaction, type 2 immunity, and tissue remodeling. We have illustrated in this review
that the main approaches available today are \textit{in vitro} models, identification and characterization of human
inherited syndromes resembling AD, \textit{in vivo} challenges of AD patients, as well as \textit{in silico} models. Here, we
speculate how the future of AD research will likely inform the development of more refined human models
of AD.

Refinement is likely to depend, at least in part, upon methodological advances in the field and the
additional information generated by novel approaches. For example, single cell sequencing has recently
identified novel rare but important immunological subsets\(^64\) and intravital photon microscopy has enabled
visualization of cell-cell communication during inflammation\(^65\)\(^66\). Application of this technology to AD is
likely to inform the inclusion of distinct epithelial and immune cell types\(^64\) and/or genetically modified
primary human cells\textsuperscript{67}. Furthermore, small-scale spheroid organoids may enhance high-throughput
approaches in the field\textsuperscript{68}. Finally, we expect that a technological breakthrough in the development of three-
dimensional skin models will be facilitated by cell printers\textsuperscript{69,70}.

Deep neural networks are being applied as artificial intelligence tools to facilitate physician interpretation
in the field of melanoma diagnostics \textsuperscript{71} and increasingly as methods to enable large data set integration.
The first examples of disease classifiers \textsuperscript{72} and prediction of disease severity from biomarker sets \textsuperscript{61,73,74} have
recently been published, and we expect this line of development to continue while ensuring a sufficient
level of validation. We anticipate that refinement of these methods, in combination with \textit{in silico} models,
may lead to computational approaches and predictive models applied to diagnostics and therapeutic
stratification. The descriptive disease ontology of inflammatory skin diseases will need to be revised by
shifting to pathogenesis-oriented structure\textsuperscript{75} and, in the future, by better definition of disease endotypes
based on integration of multiomics data, clinical features, and clinical response to therapy in light of \textit{in silico}
models as assessed in large-scale and longitudinal cohorts\textsuperscript{76}. These advances are likely to inform the
development of many of the current models.

To achieve a substantial breakthrough, though, we expect that different approaches will need to be
combined, integrated, standardized, and performed at larger scale (Figure 3). For example, observations
made in rare human disease variants or by specific challenge models in AD patients may be validated \textit{in vitro}
and mapped to disease signatures \textit{in silico}. Validation of functional hypotheses will increasingly
depend upon cross-referencing of data derived from clinical samples with outputs from \textit{in vitro} models.
Integration of clinical, biomarker, PK/PD (topical and/or systemic) and clinical outcome data will inform
therapy development and precision medicine. Notably, all of our models depend on how precisely a
particular question is asked and the quality of the clinical input, including the clinical metadata and
integration with omics data derived from clinical samples. Finally, advanced statistical and machine
learning analysis combined with \textit{in silico} predictive modelling will be required to integrate information
throughout all described layers and data sets to elucidate underlying mechanisms (and endotypes), further highlighting the importance of data standardization and scientific networking.
Acknowledgements

We acknowledge the following IEC associates and councilors for their contributions to the concepts outlined in this article: Lisa Beck, Rochester, New York; Carle Paul, Toulouse, France; Georg Stingl, Vienna, Austria; Stefan Weidinger, Kiel, Germany. We thank Margaret Jung, IEC executive director, in organizing telephone conferences and collating responses from IEC associates and councilors.
Figure legends

**Figure 1.** Diagrammatic representation of ‘Human knockout’ monogenic models providing insight into the pathomechanisms of AD. Specific genetic variants affecting the structural and/or immune functions of skin or other organs recapitulate features, but not the entire phenotype, of atopic inflammation and AD. *CARD11*, caspase recruitment domain-containing protein 11; *CDSN*, corneodesmosin; *CTLA4*, cytotoxic T lymphocyte-associated protein 4; *DOCK8*, dedicator of cytokinesis 8; *DSG1*, desmoglein 1; *DSP*, desmoplakin; *FLG*, filaggrin; *FOXP3*, forkhead-box-protein 3; *IL2RA*, interleukin-2 receptor alpha; *IL4RA*, interleukin 4 receptor alpha; *IFNGR1*, interferon gamma receptor 1; *MALT1*, mucosa-associated lymphoid tissue lymphoma translocation protein 1; *PGM3*, phosphoglucomutase 3; *RAG1*, *RAG2*, recombination-activated gene 1 and 2; *SPINK5*, serine protease inhibitor Kazal type 5; *STAT3*, signal transducer and activator of transcription 3.

**Figure 2.** Human *in vitro* models of AD. *In vitro* models can be designed to address specific experimental questions based on the input materials of the cultures. Assessment of the cultures, or output, depends on the type of culture. HEE, human epidermal equivalent; HSE, human skin equivalent (inset: fibroblasts in collagen); *FLG*, filaggrin; *IVL*, involucrin; *KRT10*, keratin 10; *DSG1*, desmoglein 1; *CDSN*, corneodesmosin; *TSLP*, thymic stromal lymphopoietin; TEER, trans-epithelial electrical resistance.

**Figure 3.** Interconnected multi-layer networks: the future of human AD modelling. To answer clinically relevant questions such as identification of distinct disease endotypes, elucidation of molecular pathomechanisms, or prediction of therapeutic response, a combination of innovative *in vitro* and *in silico* models obtained by a systems biology approach and machine learning algorithms will be needed.
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<td>Models developed based on published pathways.</td>
<td>A pathway model including 35 manually-curated skin-specific pathways and 2600+ genes.</td>
<td>Pathway enrichment analysis using transcriptomic datasets of 10 AD patients treated with betamethasone valerate and pimecrolimus predicted mechanism of action of both drugs on human skin.</td>
<td>58</td>
</tr>
<tr>
<td>Population PK/PD models</td>
<td>Understanding of differences and variability in pharmacological effects among a target population from clinical trials data</td>
<td>Prediction of optimal dose regimen. Testing effects of weight, gender etc.</td>
<td>Requires a large clinical data to have sufficient predictive power</td>
<td>PK/PD model for serum nemolizumab and pruritus VAS developed from 299 patients’ time course data</td>
<td>An appropriate flat dose regimen that is independent of body weights.</td>
<td>59</td>
</tr>
<tr>
<td>Machine learning predictive models</td>
<td>Unbiased analyses of differences between disease and non-disease (including treated) tissue/patients and prediction of clinical outcomes (prognostic and therapeutic)</td>
<td>Identification of disease and therapeutic targets. Findings can feed into mechanistic models</td>
<td>Causative mechanisms remain largely unknown. Machine learning applications to atopic eczema relatively limited at present</td>
<td>Piecewise linear mixed models to predict EASI scores at 3 future timepoints from baseline biomarkers. Developed from data of 150 serum biomarkers measured in 193 AD patients.</td>
<td>Combination of TARC, IL-22 and S1L-2R provides a good predictor for future EASI</td>
<td>62</td>
</tr>
</tbody>
</table>

**Table 1**
References


Multi-system atopic inflammation:
- Lungs
- Elevated IgE
- Skin
  - SPINK5 – Netherton syndrome
  - IL4RA
  - CARD11

Skin barrier dysfunction
- FLG – ichthyosis vulgaris
- CDSN – peeling skin syndrome
- IFNGR1 – AD and eczema herpeticum

Barrier dysfunction in bowel
- DSG1, DSP - severe dermatitis, multiple allergies and metabolic wasting (SAM)

Immunodeficiency syndromes
- Omenn syndrome e.g. RAG1, RAG2
- Wiskott Aldrich syndrome – WAS
- Hyper-IgE syndromes e.g. STAT3, DOCK8, PGM3
- Immunodysregulation polyendocrinopathy enteropathy X-linked (IPEX) e.g. FOXP3, MALT1, IL2RA, CTLA-4
### Input

<p>| | |</p>
<table>
<thead>
<tr>
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<tbody>
<tr>
<td><strong>a</strong></td>
<td>Normal Keratinocytes: *primary/*immortalized</td>
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<tr>
<td><strong>b</strong></td>
<td>Gene (e.g., FLG) knockdown: <em>siRNA/shRNA/CRISPR</em></td>
</tr>
<tr>
<td><strong>c</strong></td>
<td>Co-Culture: <em>T-cells, neurons, fibroblasts</em></td>
</tr>
<tr>
<td><strong>d</strong></td>
<td>Patient-derived tissue/cells: <em>immune, keratinocytes, etc.</em></td>
</tr>
<tr>
<td><strong>e</strong></td>
<td>Cytokine treatment: <em>interleukin(s)</em></td>
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### In Vitro Model

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### Output

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<thead>
<tr>
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<tbody>
<tr>
<td><strong>1</strong></td>
<td>Epidermal Morphology: <em>e.g., spongiosis</em></td>
</tr>
<tr>
<td><strong>2</strong></td>
<td>Differentiation: <em>FLG, IVL, KRT10, LOR, DSG1, CDSN, etc.</em></td>
</tr>
<tr>
<td><strong>3</strong></td>
<td>Keratinocyte / immune cell factors: <em>TSLP, Th2 cytokines</em></td>
</tr>
<tr>
<td><strong>4</strong></td>
<td>Barrier Function: <em>Lipid profile, TEER, permeability</em></td>
</tr>
<tr>
<td><strong>5</strong></td>
<td>Key Transcript and Protein Changes <em>immune, barrier, etc.</em></td>
</tr>
</tbody>
</table>
Integrative predictive models

**Drug Endotypes**
- Preclinical efficacy prediction
- Responder prediction
- Treatment of comorbidity
- Secondary loss of efficacy
- Risk of adverse events

**Molecular Mechanisms**
- S. aureus
- AMP’s
- Th17/22
- Inflammasome
- IL-31
- Epicutaneous barrier
- Neuro-inflammation
- (Auto-) IgE
- Mast cells
- Dendritic cells
- Hapten/allergen
- Type 2 cytokines

**Disease/Prognostic Endotypes**
- Allergic asthma
- Inflammatory bowel disease
- Allergy
- Rhino-conjunctivitis
- Relapsing-remitting
- Progressive
- Self-limited
- Allergic asthma

Integration of data by systems biology and machine learning

- *In silico* models
- Integrative predictive models
- *In vitro* models
<table>
<thead>
<tr>
<th>Genetic disease</th>
<th>Gene and mutation type(s)</th>
<th>Phenotype(s)</th>
<th>Mechanistic insights</th>
<th>Clinical utility</th>
<th>Limitations</th>
<th>Pathway relevance for drug development</th>
<th>Refs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin barrier dysfunction</td>
<td>FLG: Loss of function mutations semi-dominant in IV and complex trait in AD</td>
<td>Early onset, severe and persistent AD with &amp; without other atopic diseases; predisposition to eczema herpeticum (EH)</td>
<td>Understanding that skin barrier dysfunction predicts atopic inflammation</td>
<td>Illustrates importance of barrier repair</td>
<td>Molecular mechanisms and control pathways remain unclear</td>
<td></td>
<td>1, 2</td>
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<tr>
<td>Ichthyosis vulgaris (IV)</td>
<td>CDSN: Loss of function mutation autosomal recessive</td>
<td>Ichthyosiform erythroderma, pruritus and food allergies</td>
<td>Confirms the role of corneodesmosin in epidermal adhesion</td>
<td>Understanding that skin barrier dysfunction predicts atopic inflammation</td>
<td>Helps to explain why a subset of AD patients suffer recurrent EH</td>
<td>Protease inhibitors</td>
<td>3</td>
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<tr>
<td>Generalised peeling skin</td>
<td>IFNGR1: Loss of function mutation Complex trait</td>
<td>AD and eczema herpeticum (EH)</td>
<td>Defective systemic IFN-gamma immune response accounts for disseminated viral skin infections</td>
<td>Understanding that skin barrier dysfunction predicts atopic inflammation</td>
<td>Does not explain all cases of EH</td>
<td></td>
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<tr>
<td>Netherton syndrome</td>
<td>SPINK5: Loss of function mutation Autosomal recessive</td>
<td>Congenital ichthyosis, severe atopic disease, elevated IgE, hypereosinophilia, infections</td>
<td>Single nucleotide variants associated with AD. Illustrates role of epidermal protease inhibitors and kallikrein proteases in regulating epidermal barrier function</td>
<td>Understanding that skin barrier dysfunction predicts atopic inflammation</td>
<td>Protease inhibitors</td>
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<td>5</td>
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<tr>
<td>Systemic atopic inflammation</td>
<td>IL4RA: Gain of function Complex trait</td>
<td>Elevated IgE with &amp; without AD</td>
<td>Mutation found in severe cases is also a common risk allele in the population</td>
<td>Evidence of role for IL-4 in atopic inflammation</td>
<td>Unclear whether this mechanism plays a role in prevalent AD</td>
<td></td>
<td>6, 7</td>
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<tr>
<td>Atopic disease</td>
<td>CARD11: Heterozygous mutations Loss of function and dominant negative effect</td>
<td>Severe AD with &amp; without infection</td>
<td>Illustrates importance of lymphocyte receptor signalling</td>
<td>mTORC1 and IFN-gamma production defects can be partially rescued by glutamine supplementation</td>
<td>Evidence of role for IL-4 in atopic inflammation</td>
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<tr>
<td>Severe atopic disease</td>
<td>DSG1: Homozygous loss of function mutations</td>
<td>Ichthyosiform erythroderma, atopic disease and failure to thrive</td>
<td>DSG1 mutations lead to loss of cell-cell adhesion in epidermis</td>
<td>Structural epidermal defects lead to atopic inflammation</td>
<td>Other DSP mutations cause different phenotypes without atopic manifestations</td>
<td></td>
<td>9</td>
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<tr>
<td>SAM (Severe dermatitis, multiple Allergies and Metabolic wasting)</td>
<td>DSG1: Homozygous loss of function mutations</td>
<td>Ichthyosiform erythroderma, atopic disease and failure to thrive</td>
<td>DSG1 mutations lead to loss of cell-cell adhesion in epidermis</td>
<td>Structural epidermal defects lead to atopic inflammation</td>
<td>Other DSP mutations cause different phenotypes without atopic manifestations</td>
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<tr>
<td>SAM</td>
<td>DSP: Heterozygous mutation</td>
<td>Ichthyosiform erythroderma, atopic disease and failure to thrive</td>
<td>DSG1 mutations lead to loss of cell-cell adhesion in epidermis</td>
<td>Structural epidermal defects lead to atopic inflammation</td>
<td>Other DSP mutations cause different phenotypes without atopic manifestations</td>
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<tr>
<td>Skin inflammation and gastrointestinal inflammation</td>
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<tr>
<td>SAM</td>
<td>STAT3: Dominant negative mutations</td>
<td>AD-like skin inflammation, elevated IgE, immunodeficiency leading to infection</td>
<td>Illustrates role of STAT3 in signal transduction for multiple cytokines</td>
<td>Biologic treatments targeting IgE have limited clinical efficacy for AD</td>
<td>Immunodeficiency is not a prominent feature of AD</td>
<td></td>
<td>10</td>
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<tr>
<td>Ommenn syndrome</td>
<td>D0C8: Autosomal recessive loss of function mutations</td>
<td>AD-like skin inflammation, elevated IgE, immunodeficiency leading to infection</td>
<td>Aberrations of T cell and NK cell migration to skin can cause atopic inflammation</td>
<td>Antiviral and antibacterial prophylaxis, immunoglobulin replacement and HSCT</td>
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<tr>
<td>Hyper-IgE like syndrome</td>
<td>PGM3: Autosomal recessive loss of function mutations</td>
<td>AD-like skin inflammation, atopy, immune deficiency, autoimmunity and neurocognitive impairment</td>
<td>Role of glycosylation in immune regulation and systemic atopy</td>
<td>Requires HSCT</td>
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<tr>
<td>Wiskott-Aldrich</td>
<td>WAS: X-linked mutations</td>
<td>AD-like skin inflammation, severe immunodeficiency, autoimmunity and malignancy</td>
<td>Systemic imbalances in Treg populations can drive cutaneous AD like inflammation</td>
<td>Immunosuppressive treatment or HSCT</td>
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<tr>
<td>IPEX and IPEX-like syndromes</td>
<td>FOXP3, MALTF1, IL2RA, CTLA-4: Autosomal recessive</td>
<td>Immune dysregulation, polyendocrinopathy, enteropathy and AD-like skin inflammation</td>
<td>Role of autoimmunity in AD-like inflammation</td>
<td>Role of autoimmunity in AD-like inflammation</td>
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<td>Immunodeficiency syndromes</td>
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<td></td>
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<td>15, 16</td>
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</tbody>
</table>
References


Abbreviations

EH, eczema herpeticum; HSCT, haematopoetic cell transplantation; IPEX, Immunodysregulation Polyendocrinopathy Enteropathy X-linked; IV, ichthyosis vulgaris; SAM, Severe dermatitis, multiple Allergies and Metabolic wasting
<table>
<thead>
<tr>
<th>Table S2. Human in vivo Models of AD</th>
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<tr>
<td><strong>Atopy Patch Test</strong></td>
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<td><strong>Epidemiology</strong></td>
</tr>
<tr>
<td><strong>Validity/relevance</strong></td>
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<td><strong>Reproducibility</strong></td>
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<tr>
<td><strong>APT: clinical usage</strong></td>
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<tr>
<td><strong>APT: immunological relevance</strong></td>
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<td><strong>Th2 immunity</strong></td>
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<tr>
<td><strong>Dynamics/kinetics of immune response</strong></td>
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<td><strong>Specificity</strong></td>
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<td><strong>Contact allergens</strong></td>
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<tr>
<td><strong>Patch testing: clinical usage</strong></td>
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<tr>
<td><strong>Epidemiology</strong></td>
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<tr>
<td><strong>Immunological relevance</strong></td>
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<tr>
<td><strong>Contact allergens</strong></td>
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<tr>
<td><strong>Patch testing: clinical usage</strong></td>
</tr>
</tbody>
</table>
to different haptens (n=24 ACD patients w/o AD) Patch tests in AD patients (n=18) and healthy volunteers (n=10) Repetitive application of hapten Repetitive hapten challenge caused a switch in immune response towards Th2 immunity including barrier damage them might mimic AD AD patients show a Th2 skewed ACD reaction Small cohort (n=16 AD patients); experimental hapten Immune responses towards a hapten might change after repetitive challenge Murine study

Other challenge models
System Interplay/ Application Key Findings Scientific Merit/ Limitations Clinical Relevance Reproducibility

Aero-challenge Treatment Standardization
Pollen chamber challenge of sensitized AD patients Application of vehicles and/or topical treatments in AD patients Application of established AD triggers (AD patients) AD patients sensitized to grass pollen reacted with IgE might play a role in AD Barier restoration might also repair immune abnormalities in AD No direct causal link to IgE No evidence for a specific effect of petrolatum Experimental design does not mimic real world exposure

Triggers challenge
System Interplay/ Application Key Findings Scientific Merit/ Limitations Clinical Relevance Reproducibility

Other challenge models
System Interplay/ Application Key Findings Scientific Merit/ Limitations Clinical Relevance Reproducibility

Abbreviations: APT: Atopy Patch Test; SPT: Skin Prick Test; LIT: Lympohocyte Transformation Test; ACD: allergic contact dermatitis; TSS: total sign score; TEWL: transepidermal water loss; DC: dendritic cell; CD: contact dermatitis

References:


Supplementary Table 1. Human In vitro Key Findings

<table>
<thead>
<tr>
<th>Limitations</th>
<th>Ref</th>
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<tbody>
<tr>
<td>No assessment of lipids or barrier function; no rescue experiment</td>
<td>(6)</td>
</tr>
<tr>
<td>No evidence changes in protein expression under AD phenotype</td>
<td>(15)</td>
</tr>
<tr>
<td>Epidermal thinning; immune component not assessed; no rescue experiment</td>
<td>(17)</td>
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<tr>
<td>Epidermal barrier not assessed; no rescue experiment</td>
<td>(22)</td>
</tr>
<tr>
<td>Primary keratinocytes not used; IL-4 alone effects shown not to reduce FLG in NHEK (30)</td>
<td>(23)</td>
</tr>
<tr>
<td>Barrier not assessed; desmazemohase or tacrolimus did not reverse phenotype</td>
<td>(32)</td>
</tr>
<tr>
<td>Changes in keratinocyte immune cell signaling not assessed</td>
<td>(33)</td>
</tr>
<tr>
<td>Most experiments performed with HaCaT cells</td>
<td>(36)</td>
</tr>
<tr>
<td>Barrier function not assessed</td>
<td>(38)</td>
</tr>
<tr>
<td>Role of membrane lipid domains not clear in AD; no change in keratinocyte TSLP</td>
<td>(39, 40)</td>
</tr>
<tr>
<td>No change in histamine-treated explant cultures</td>
<td>(43)</td>
</tr>
<tr>
<td>Barrier function not assessed</td>
<td>(44)</td>
</tr>
<tr>
<td>No system perturbations</td>
<td>(44)</td>
</tr>
<tr>
<td>Use of skin explants and emulsifier technology</td>
<td>(45)</td>
</tr>
<tr>
<td>AD skin samples not used; barrier function or differentiation status not tested</td>
<td>(46)</td>
</tr>
</tbody>
</table>

Abbreviations: AP-1: activator protein 1; CGRP: calcitonin gene-related peptide; CALI: carbonic anhydrase II; CASP14: caspase 14; CDSN: corneodesmin; DSG1: desmoglein 1; FLG: filaggrin; GM-CSF: granulocyte-macrophage colony-stimulating factor; HMGB1: high-mobility group box 1; HSE: human skin explants; IL: interleukin; KRT: keratin; LOR: lactoferrin; NELL2: neural epidermal growth factor-like 2; NHEK: normal human epidermal keratinocytes (primary); NMF: natural moisturizing factor; NT-4: neurotrophin 4; PBMC: peripheral blood mononuclear cell; STAT6: signal transducer and activator of transcription 6, Tj: tight junction; TEER: transepithelial electrical resistance, TGM1: transglutaminase 1; TSLP: thymic stromal lymphopoietin


33. Yuki T, Tobishii M, Kusaka-Kikushima A, Ota Y, Tokura Y. Impaired Tight Junctions in Atopic Dermatitis Skin and in a Skin-Equivalent Model Treated with Interleukin-17. PloS one. 2016;11(9):e0161759. Epub 2016/09/03. doi: 10.1371/journal.pone.0161759. PubMed PMID: 27588419; PMCID: PMC5010286 Kao Corporation, a commercial company, during this study. There are no patents, products in development or marketed products to declare.


Human Models of Atopic Dermatitis: A Review and Perspectives by an Expert Panel of the International Eczema Council

Kilian Eyerich is funded by an ERC grant (IMCIS, 676858) and the German Research Foundation (EY97/3-2).

Sara J. Brown holds a Wellcome Trust Senior Research Fellowship in Clinical Science (106865/Z/15/Z) and reports honorarium from the British Society for Paediatric Dermatology and other from the British Association of Dermatologists.

Bethany Perez White reports grants from Dermatology Foundation Research Career Development Award, and from the National Institute of Arthritis, Musculoskeletal, and Skin Diseases K01 Mentored Research Career Development Award and P30 Skin Disease Research Center Grant.

Reiko J. Tanaka reports grants from EPSRC, Royal Society, and British Skin Foundation.

Robert Bissonnette is an Investigator, Consultant, Advisory Board Member, Speaker for and/or receives honoraria from Aquinox Pharma, Antiobix, Asana, Astellas, Brickell Biotech, Dermavant, Dermira, Dignity Sciences, Eli Lilly, Galderma, Glenmark, GSK-Stiefel, Hoffman-LaRoche Ltd, Kiniksa, Leo Pharma, Neokera, Pfizer, Regeneron, Sienna and Vitae. R. Bissonnette is also Shareholder of Innovaderm Research.

Sandipan Dhar has no relationships to disclose.

Thomas Bieber is a consultant for Dermavant, AbbVie, Kymab, and Glenmark and a lecturer and consultant for Sanofi, Novartis, Lilly, Pfizer, and Allmiral.

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Emma Guttman-Yassky is a consultant and/or advisory board member for and/or received grants and/or personal fees from Novartis, Pfizer, Regeneron, Asnan, Dermira, Sanofi, Eli Lilly, Asana Bioscience, Kyowa Kirin, Allergan, Escalier, AbbVie, Celgene, Gladerma, Glenmark, LEO Pharmaceuticals, Novartis, Pfizer, Regeneron, DS Biopharma, Janssen Biotech, Innovaderm, Ralexar, Novan, Dermavant, Mitsubishi Tanabe, Concert, Amgen, and DBV.

Alan Irvine has no relationships to disclose.

Jacob Thyssen is funded by an unrestricted grant from the Lundbeck Foundation.
Christian Vestergaard has no relationships to disclose.

Andreas Wollenberg reports personal fees and/or grants and/or non-financial support from Almirall, Anacor, Astellas, Beiersdorf, Biderma, Celgene, Chugai, Galderma, GSK, Hans Karrer, Leo Pharma, L'Oréal, MEDA, MSD, Novartis, Pierre Fabre, Pfizer, Regeneron, and Sanofi.

Amy Paller is an investigator or consultant with honorarium for and receives personal fees from AbbVie, Anaptysbio, Eli Lilly, Galderma, Incyte, Leo, Janssen, Novartis, Sanofi-Regeneron, Amgen, Asana, Dermavant, Dermira, Galderma, Forte, Matrisys, Menlo, Morphosys/Galapagos, and Pfizer.

Nick J. Reynolds has received grant support through Newcastle University from AstraZeneca, Bristol Myers Squibb, Genentech and GlaxoSmithKline. Nick Reynolds’ research/laboratory is funded in part by the Newcastle NIHR Biomedical Research Centre, the Newcastle NIHR Medtech and In vitro diagnostic Co-operative and the Newcastle MRC/EPSRC Molecular Pathology Node.