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NETSKINMODELS: An European network—Network for skin—Skin engineering Engineering and modelingModeling

Hristijan Goreski, Dusko Ilic, Vincent Flacher, Ellen van den Bogaard, Christina Guttmann-Gruber, Reiko J. Tanaka, Gülcihan Gülseren, Christophe Marquette, Joachim Fluhr, Viviane Filor, Serghei Sprincean, CA21108 members, Sandrine Dubrac

More than 40 years of research in dermatology has led to the development of advanced skin models, including 3D organotypic cultures containing fibroblasts, keratinocytes, melanocytes, immune cells, and sensory cells; skin-on-a-chip models; bio-printed skin; and mathematics-based models, known as “in silico computational” models. These models are ~~used as~~ important tools in both fundamental and translational skin research (van den Bogaard et al., 2021). For clinical applications, clinical-grade 3D reconstructed epidermis autografts can treat extensive burns and genodermatoses after gene correction (De Rosa and De Luca, 2022). Notwithstanding the major technological advances ~~that occurred~~ over the past decades, current 3D skin models ~~are includ~~eing a limited cellular diversity.

The complex interplay between the gamut of skin cell types and commensal microorganisms, ~~which is~~ crucial for the crosstalk between the skin's physical, immunological, and microbial barriers ~~of the skin~~, is still incomplete in 3D ~~engineered~~ skin models. Therefore, these models fail to capture the complexity of the structure and function of native skin, and they only partially reflect complex processes such as skin ageing, skin pathologies, and wound healing. Additional drawbacks of most existing organotypic models are the lack of (i) cutaneous vasculature mimicking lymphatic drainage and blood supply of nutrients and incoming immune cells, (ii) innervation, which is needed to recapitulate neuro-inflammatory responses in various skin diseases, (iii) sufficient longevity of the 3D cultures, which is critical to study chronic exposure to various molecules and chronic diseases, and (iii) skin appendages and macrostructures such as sebaceous or sweat glands and hair, despite their important roles in immunosurveillance and in allowing penetration of large entities such as nanoparticles or microorganisms.

In silico computational skin models represent a promising alternative to animal experimentation and an advantageous cost-effective approach for drug/cosmetic screening, but they are still in the early stages of development. Artificial intelligence (AI) offers promising medical perspectives via analysis of the existing data and can be used to optimize research strategies. Artificial intelligenceAI methodologies such as Machine Learning and, recently, Deep Learning exhibit considerable potential for data analysis, computational modelling, and pattern recognition, facilitating enhanced diagnostic accuracy and treatment planning. Scientific and clinical outcomes of computational ~~AI~~ artificial intelligenceAI approaches in dermatology are still limited to maximize industrial development.

The Directive 2010/63/EU legislation on “the protection of animals used for scientific purposes” requires that Member States develop and validate alternative approaches (European Parliament, 2010, Recital 10). Recently, the European Parliament urged the EU to accelerate the transition to a research system that does not use animals. Moreover, testing of cosmetic ingredients in animals is banned in the EU [Cosmetic Directive 76/768/EEC; Cosmetics Products Regulation (EC) No1223/2009; chemicals REACH Regulation (EC) 1907/2006] despite the necessity for toxicity and biological action studies. In addition to animal welfare issues, interspecies differences strongly encourage efforts to find alternatives to ~~the use of~~

~~animals~~animal use in scientific research, including ~~in the field of~~ investigative dermatology. ~~This~~These points highlights the urgent need to develop sophisticated skin models able to achieve 3Rs (Replacement, Reduction, and Refinement), especially the replacement of live animals in most experimental contexts. Furthermore, reagents containing ~~non~~none or few animal-derived substances are underdeveloped in dermatological research and beyond. Importantly, more ethical scientific practice should also include solutions to reduce plastic use ~~via the~~by development~~developing~~ and ~~validation~~validating of alternative composites, reagents, and protocols (3Rs: Reduce, Reuse & Recycle).

Beyond important ethical considerations, there is a need to provide the research community with relevant models to lead not only to scientific breakthroughs but also to the validation of new therapeutic drugs in the absence of animal testing. Towards this goal, a group of researchers (Dusko Ilic, Sanja Kezic, Ellen van den Bogaard, Michel Simon, Yves Poumay, Sandrine Dubrac) have created an ambitious network funded for 4-four years (2022—2026) by the European Union through the European Cooperation in Science and Technology (COST Action CA21108: <https://www.cost.eu/actions/CA21108/>; Action Chair Sandrine Dubrac, Action co-Chair Hristijan Goreski). ~~Their aim is~~They aim to create a scientific hub of excellence to foster, in Europe, the scientific and industrial capacity to develop, share, and produce sophisticated cell-based and computational models of healthy and diseased skin. Only a large consortium including a broad spectrum of complementary expertise will allow the field to make a giant step forward. Moreover, the Action will promote brain gain or circulation between research-intensive and research-moderate European territories with the goal to harmonize scientific and technological knowledge in the field.

The COST Action called NETSKINMODELS includes nearly 350 participants distributed in 37 European countries as well as in Israel, the USAU.S., Argentina, and Brazil. It encompasses research laboratories, hospitals, veterinary centers, and non-governmental organizations (NGOs). Moreover, 17 industrial partners have joined the network (Almirall, CELLnTEC, DermAb.io, Essity, Group Rocher, IMD Pharma, Keratify, Monasterium Laboratory, Paprika-Bioanalytics BT, Labskin, MatTek Life Science, Prion, ReprocCell, River D, StratiCELL, Unilever, and Wepredic). The network gives prominence to female scientists and clinicians (60%), to junior fellows (40%), and to European low-income countries (43%).

NETSKINMODELS ~~is articulated~~articulates around the following 5-five working groups:

WG1: Sophistication of cell-based healthy skin models made with keratinocytes and fibroblasts, including bio-printed models by including immune cells, other skin cell types (e.g. for example, sensory and endothelial cells, melanocytes), skin appendages (e.g. for example, hair follicles, sebaceous and sweat glands) and connected with other compartments (e.g. for instance, lymph nodes, lymph vessels, vascular system) and complex- skin microbiota and models with satisfactory native-like lipid barrier (current skin models differ substantially in lipid composition and organization with each other and with native skin) (Leader Dusko Ilic, co-leader Vincent Flacher).

WG2: Sophistication of cell-based models of skin diseases (e.g. for instance, psoriasis, atopic dermatitis, vitiligo, ichthyoses), skin infections (e.g. for example, Herpes simplex, Staphylococci, Pseudomonas spp., Malassezia, Streptococci, Leishmania spp., Trypanosoma spp., chiggers, cytomegalovirus, papillomavirus), skin cancers (melanoma, squamous and basal cell carcinomas), wound (repair) and ageing, as well as the development of novel transdermal and topical drug application systems, such as micro-needles, deformable

liposomes, biological vesicles or lipid-based nanocarriers, advanced wound dressings with and without incorporated functional nanoparticles (Leader Ellen van den Bogaard, co-leader Christina Guttman-Gruber).

WG3: Advancing ethical and sustainable practices in dermatological research involves accountability for plastic waste reduction, boosting research on alternative scaffolds, including melt-electrospun writing, bio-inks from renewable sources (e.g., for instance, natural polymers), and optimized hydrogels, which do not influence the immune response or cell phenotype. Moreover, the development of vegan products (e.g. like cosmetics) or reagents containing none or few animal-derived substances (e.g. such as less fetal calf serum) will be enhanced. Furthermore, it entails the development of in silico models addressing predictive, prognostic, and therapeutic outcomes of skin diseases, smartphone applications for patient's follow-up and disease monitoring, and algorithms that predict skin ageing and disease processes to respond to exponential societal demand (Leader Reiko Tanaka, co-leader Gülcihan Gülseren).

WG4: Validation and prospective standardization of skin models, including cellular components and computational models. This encompasses a comprehensive evaluation and benchmarking of primary cells, induced Pluripotent Stem Cells (iPSCs), and immortalized cell lines. Emphasis is placed on these cell lines' genetic stability, phenotypic fidelity, and functional consistency of these cell lines, hence ensuring accurate replication of key aspects of human skin physiology. Additionally, WG4's tasks include is tasked with the development of developing robust, standardized protocols for the delivery systems, bio-composites, and biochemical reagents used within the scope of skin engineering. This initiative will draw upon existing published protocols, refining and consolidating them into a cohesive set of guidelines. These guidelines aim to standardize methodologies across research entities, thereby enhancing the comparability and reproducibility of dermatological research. The overarching goal is to establish a unified framework that assures quality control and methodological consistency in skin model development and application (Leader Christophe Marquette, co-leader Joachim Fluhr).

WG5: All activities should consider Regulatory, ethics, education, dissemination, and technology transfer should be taken into account in all activities. In addition, it is essential to promote the dialogue between academia and industry has to be promoted to make the field to progress in the field progressing. Key tasks include addressing ethical and legal challenges, facilitating theory and technology transfer, implementing an interdisciplinary education programme, establishing internal communication platforms, and creating a dissemination platform to communicate results and influence policy (Leader Viviane Filor, co-leader Serghei Sprincean).

An essential mission of this COST Action is to provide the community with opinions papers, guidelines, cell lines, various materials, algorithms, models, and protocols critically reviewed by multiple experts of in the field. Current research in dermatology is still heavily relying-relies on animal experimentation despite clear differences with human physiopathology, which might hamper the relevance in-of the research outcome. For example, mouse epidermis is much thinner than human epidermis, and researchers have observed some transcriptomic differences have been evidenced, and clear differences in the mouse skin immune system and microbiota composition display clear differences etc when compared to human tissue. Notwithstanding the historical/historic importance of animal models to our field, and the many discoveries that animal models have facilitated, current technological advancement should enable us to develop and implement engineered human skin models. However, When

~~researchers validate and standardize engineered skin models and replicate results between model systems,~~ support for studies solely based on engineered skin models will increase ~~when models will have been well validated and standardized, and when results between model systems will have been replicated.~~ The COST Action NETSKINMODELS aggregates scientists and clinicians with diverse backgrounds. Some working with animals, ~~who wants~~ to increase the significance of their research by working in a human context or to slowly transition to ~~an~~ animal-free research. Others have been advocating for animal-free research for years. Without judgement and in a dispassionate atmosphere, we will work hand-in-hand to eventually change the mentalities ~~on-of~~ animal experiments and increase community awareness ~~of the community.~~ This will increase the positive evaluation rate ~~rate of positive evaluation~~ of scientific research ~~that is only~~ only based on skin models or utilizing a combination of skin models and animal experiments.

Moreover, ~~computational models,~~ as a mathematical description of the knowledge base, computational models are an alternative to animal experiments with a significant environmental and ethical impact. Furthermore, the COST Action NETSKINMODELS aims to green up experimental dermatology, ~~and~~ advocate for a reductioning of plastic waste in research, ~~and for the development of~~ environment-compatible products. A reservoir of talented intersectoral bioengineers will develop ethical and green products designed for the elaboration of organotypic skin models but with potential applications beyond the field to increase accountability for plastic waste reduction efforts and reduction of animal use for biological research. Besides scientific, clinical, and ethical achievements, NETSKINMODELS promotes public-private interactions, ~~which will contribute to~~ boosting R&D ~~in~~ industrial partners.

To join the COST Action or get more information, please contact Sandrine Dubrac, cost21@i-med.ac.at.

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