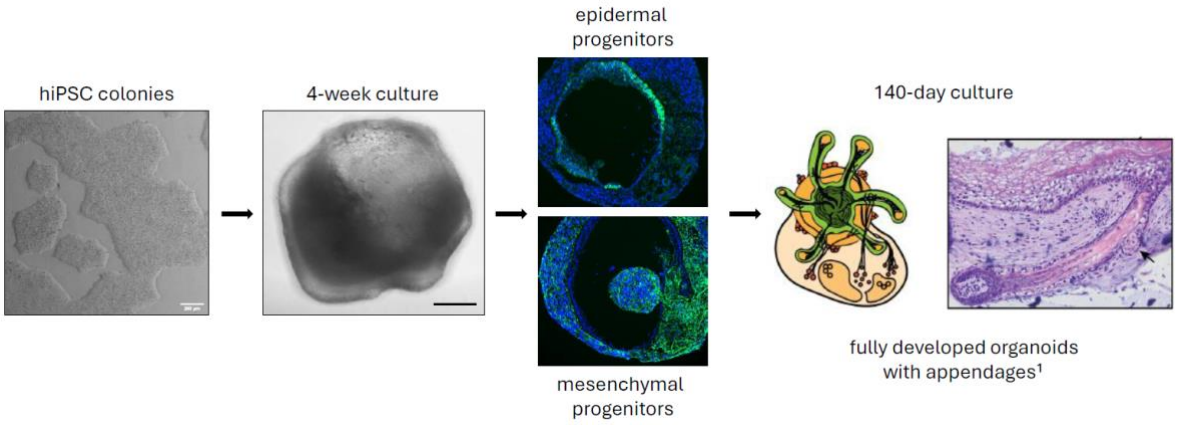
INFRAFRONTIER Complex *In Vitro* Models:

Advanced 3D Skin Models as Innovative Platforms for Biomedical Testing and Research

Brief description:

Skin organoids are three-dimensional models that recapitulate key structural and functional features of native skin tissue. Because they closely mimic the physiological processes of skin development and wound healing, they represent a valuable tool for biomedical research.

To introduce non-animal preclinical models at the Czech Center for Phenogenomics, we have been establishing an *ex vivo* submerged skin organoid model. This system is based on the reprogramming of human pluripotent stem cells (hiPSC) derived from various primary sources, such as dermal fibroblasts. The reprogramming protocol is well defined and highly effective, as it enables hiPS cells to form spherical structures containing not only all major skin layers, but also skin appendages, including hair follicles, Merkel cells, and early sweat gland structures, depending on the duration of cultivation (from weeks to months).



This unique model can subsequently be applied to the investigation of tissue regeneration mechanisms, disease modeling, and preclinical drug screening.

How is the model generated?

1. Human induced pluripotent stem cells (hiPSCs) under feeder-free conditions are first induced into ectodermal lineage commitment by dual SMAD inhibition to promote surface ectoderm fate.

2. Cells are subsequently guided toward epidermal and dermal progenitors using a timed combination of growth factors such as FGF and WNT modulators, followed by aggregation into 3D spheroids in low-adhesion conditions.

3. These aggregates are embedded in an extracellular matrix (Matrigel) and cultured long-term in differentiation media that supports the development of layered epidermis and dermis-like structures. Over several weeks, the organoids mature with keratinocyte differentiation, fibroblast emergence, and in hair follicle-like structures, making them suitable for downstream biomedical testing applications.

Potential applications:

Skin organoids will be derived at CCP from human iPSCs, pre-characterized and provided by the requestor. The organoids will serve as a versatile in vitro platform for functional testing across multiple applications: to evaluate (1) the effects of small-molecule compounds on skin differentiation and maturation, (2) the affinity, uptake, and structural stability of organoids during antisense oligonucleotide therapy, and (3) the biological impact of chemical modulators such as retinoids on skin development and homeostasis. Together, these studies will enable controlled, human-relevant assessment of pharmacological and molecular interventions in a physiologically representative 3D skin system.

Who provides this model?

Czech Centre for Phenogenomics

The Czech Centre for Phenogenomics (CCP) is a leading European research infrastructure for functional genomics and preclinical model development, operated by the Institute of Molecular Genetics of the Czech Academy of Sciences. CCP provides an integrated pipeline covering advanced genome engineering, generation of transgenic and disease models, and comprehensive in vivo phenotyping under specific pathogen-free (SPF) conditions. Within CIVM, CCP provides expertise in the generation of human iPSC-derived 3D skin organoids as complex cellular models that recapitulate key aspects of human epidermal differentiation, development and patophysiology. Such models are designed for studying rare genetic skin disorders, functional genomics, and therapeutic testing in a controlled human-relevant context. To ensure robustness and translational relevance, CCP integrates these in vitro models with complementary validation pipelines. This combined approach enables mechanistic insight, predictive modelling, and preclinical validation within a single infrastructure, while supporting the transition toward reduced animal use.

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References:

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2. Garriga-Cerda L, et al. IPSC-derived organoid-sourced skin cells enable functional 3D skin modeling of recessive dystrophic epidermolysis bullosa. J Tissue Eng. 2025 Dec 1;16: 20417314251397594.

INFRAFRONTIER, the European Research Infrastructure for Modelling Human Diseases, is a non-profit organisation dedicated to advancing disease understanding and treatment through cutting-edge models. Operated by a network of over 20 leading biomedical research institutes, it empowers research on human health and disease. Committed to excellence, INFRAFRONTIER adheres to rigorous scientific benchmarks and prioritises animal welfare. Through collaboration with other infrastructures, it fosters global data sharing and contributes to tackling significant health challenges. INFRAFRONTIER serves as a platform for innovative technologies and knowledge exchange, leveraging the power of disease modelling to improve human health.