Brussels, 27 May 2022

COST 022/22

DECISION

Subject: Memorandum of Understanding for the implementation of the COST Action "European Network for Skin Engineering and Modeling" (NETSKINMODELS) CA21108

The COST Member Countries will find attached the Memorandum of Understanding for the COST Action European Network for Skin Engineering and Modeling approved by the Committee of Senior Officials through written procedure on 27 May 2022.

MEMORANDUM OF UNDERSTANDING

For the implementation of a COST Action designated as

COST Action CA21108
EUROPEAN NETWORK FOR SKIN ENGINEERING AND MODELING (NETSKINMODELS)

The COST Members through the present Memorandum of Understanding (MoU) wish to undertake joint activities of mutual interest and declare their common intention to participate in the COST Action, referred to above and described in the Technical Annex of this MoU.

The Action will be carried out in accordance with the set of COST Implementation Rules approved by the Committee of Senior Officials (CSO), or any document amending or replacing them.

The main aim and objective of the Action is to create a scientific hub of excellence encompassing research laboratories, hospitals, industrial R&D departments, non-governmental organisations, regulatory bodies and patients 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. This will be achieved through the specific objectives detailed in the Technical Annex.

The present MoU enters into force on the date of the approval of the COST Action by the CSO.

OVERVIEW

Summary
Over the past years, investigative and experimental dermatology has developed various approaches, ranging from utilisation of ex-vivo skin tissues to establishment of reconstructed in-vitro and in-silico skin models as tools in both basic and translational skin research. These models have the strong potential to increase the significance of scientific and clinical outcomes and to reduce animal experimentation. Nevertheless, current skin models lack sophistication and standardisation, thereby hampering their wider acceptance by the scientific community and regulatory bodies. This is partly caused by a lack of cross talk between relevant stakeholders — regulatory bodies, basic scientists, clinicians, and industry — whereby advances in new technologies have not delivered their full potential in this field.

In the proposed Action, interdisciplinary and intersectoral research and coordinated initiatives will drive the development and validation of standout sophisticated cell-based and computational skin models, including the development of artificial intelligence models for dermatological research. Furthermore, the Action has ambitions to develop ethical and sustainable reagents required for the elaboration of organotypic skin models, based on a strong partnership between network academia and industries. Harmonisation of scientific and technological knowledge and an enduring bottom-up dynamic in the field will be ensured by dissemination of leading-edge know-how among research intensive and research moderate European territories. Moreover, next-generation scientists will be trained for the long-term propagation and continued development of skin models. Action outcomes will turbocharge the field of skin models to meet rising scientific, clinical, economic, environmental and regulatory expectations, making Europe the epicentre of research in this field.

Areas of Expertise Relevant for the Action	**Keywords**
● Biological sciences: Biological systems analysis, modelling and simulation ● Basic medicine: Organ physiology ● Industrial biotechnology: Biomaterials synthesis	● Skin ● 3R principles ● Skin models ● In silico skin models ● Skin bioprinting

Specific Objectives
To achieve the main objective described in this MoU, the following specific objectives shall be accomplished:

Research Coordination
● Create a favourable environment allowing the delivery of innovative and pathophysiologically relevant cell-based models recapitulating the complexity of the skin and skin diseases and the emergence of powerful in silico models by stimulating knowledge transfer within academic laboratories and between the latter and industrial partners.
● Harness all expertise within the network to share and agglomerate all fragmented knowledge and create an ad-hoc information platform compiling and implementing all documents on both cell-based and cell-free models.
● Validation of innovations elaborated within the network which requires all network expertise.
● Dissemination of results (extensive, sustained and strong towards ITCs) and educational programmes, aimed at expanding a highly cooperative European network for skin models.

● Dissemination of research results to the general public and relevant stakeholders (e.g. policy-makers, governmental organisations, NGOs, environmental and patients´ associations).
● Training the next-generation scientists (YRIs) for the long-term dissemination and development of skin models that offer powerful alternatives to animal experiments.
● Input for the future market applications via a coordinated research agenda between academic laboratories and industrial partners including SMEs of the Action to commercialise innovative skin models and composites/reagents, drug delivery systems, of new drugs/cosmetics, as well as industrial processes and software.
● Green-up the scientific practice in the field of skin models via the development of sustainable and animal-free composites and reagents by promoting interactions between industrial partners (chemistry, biology) and academic laboratories (biotechnology, chemistry, biology, computer science).

Capacity Building
● Increase intersectoral exchange via the creation of an enriched relationship between academic structures and industrial entities to transform innovations derived from basic research into marketable products.
● Empower women by ensuring gender-balance in the leadership team of the network.
● Uncover and encourage new young talents and educate the next generation of leaders in the field able to apply to ERC starting or consolidator grants.
● Create a subdivision of the European Society for Dermatological Research (ESDR) dedicated to skin models to ensure the longevity of the network.
● Upscale the network with non-European scientists, clinicians and industrial companies to contribute to the dissemination of network outcomes worldwide.
● Give rise to well-coordinated and comprehensive network for initiating follow-up grant proposals/successful joint projects(e.g. COST innovators grants, Horizon Europe, European Innovation Council, national grants, bilateral or multilateral grants).
● Stimulate cooperation and include non-governmental stakeholders such as patients, animal and nature associations or specialised in gender and diversity equality, innovation management and entrepreneurship counselling.

TECHNICAL ANNEX

1. S&T EXCELLENCE

1.1. SOUNDNESS OF THE CHALLENGE

1.1.1. DESCRIPTION OF THE STATE OF THE ART

The skin with its intricate structure and cellularity is one of the most complex organs, with multiple functions spanning from physical barrier to immune regulation (Fig.1) [1-5]. Neural projections from the spinal cord into the skin provide nerve endings that interact with cells in all skin layers. Moreover, the skin is an active neuro-immuno-endocrine interface.

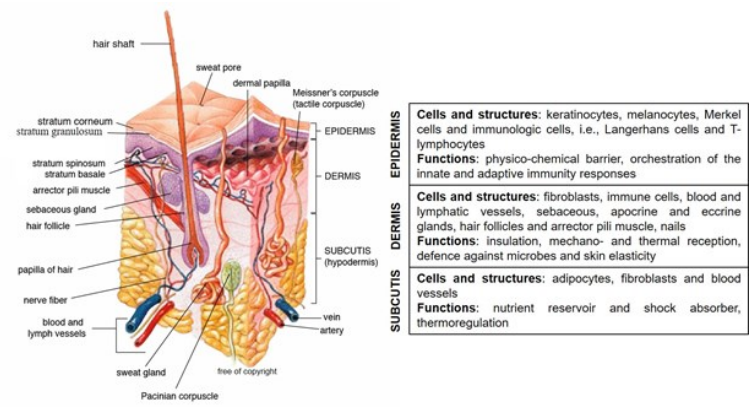


Figure 1: Organisation, cellular composition and functions of skin layers

The skin is often affected by pathological conditions such as chronic inflammatory diseases (e.g. psoriasis and eczema) and infectious diseases. Potentially life-threatening skin cancers have become a major health problem, their incidence exploding in recent decades [6]. Healing of cutaneous wounds can be impaired in diseases such as epidermolysis bullosa and diabetes. Furthermore, the skin is in daily contact with a multitude of noxious molecules that may cause irritation and allergic reactions due to local or systemic toxicity. However, the skin also offers a convenient route for the administration of medications, including topical and transdermal drug delivery.

The Directive 2010/63/EU 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 European Union (EU) to accelerate the transition to a research system that does not use animals (https://www.europarl.europa.eu/news/en/press-room/20210910IPR11926/meps-demand-eu-action-plan-to-end-the-use-of-animals-in-research-and-testing). 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. Furthermore, in addition to animal welfare issues, interspecies differences strongly encourage efforts to find alternatives to the use of animals in scientific research, including in the field of investigative dermatology [7, 8]. This highlights the urgent need to develop standout skin models able to replace live animals in most experimental contexts (3Rs: Replacement, Reduction and Refinement). Importantly, more ethical scientific practice should also include solutions to reduce plastic use via the development and validation of alternative composites, reagents and protocols (3Rs: Reduce, Reuse & Recycle).

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 [9-13]. They are used as tools in both basic and translational skin research. In particular, clinical-grade 3D reconstructed epidermis autografts have been used to treat extensive

burns [14] and genodermatoses after gene correction [15]. Even so, current 3D skin models are elaborated with a limited number of cell types. Thus, the complex interplay between the gamut of skin cell types, which is crucial for the cross-talk between the physical, immunological and microbial barriers of the skin, is still missing. Therefore, these models fail to capture the complexity of the structure and function of native skin and they inadequately reflect processes such as skin ageing, skin pathologies and wound healing. Additional drawbacks of most existing organotypic models are the lack of (i) cutaneous vascular, lymphatic and nervous systems, which are needed to recapitulate neuroinflammatory responses in various skin diseases, (ii) relative longevity critical in many studies (e.g. chronic exposure to various molecules, chronic diseases), and (iii) skin appendages and macrostructures such as sebaceous or sweat glands and hair, despite these structures playing important roles in skin immune defence 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 early stages of development. However, artificial intelligence (AI) offers promising medical perspectives via analysis of the existing medical data and can be used to optimise research strategies. Unfortunately, AI remains underexploited in dermatology.

In this context, scientific and clinical outcomes remain limited and industrial development is not maximised. Furthermore, a significant reduction in the use of animals has not yet been achieved, and reagents containing no or few animal-derived substances are still underdeveloped in dermatological research and beyond.

1.1.2. DESCRIPTION OF THE CHALLENGE (MAIN AIM)

The main aim of the NETSKINMODELS (European Network for Skin Engineering and Modelling) Action is to create a scientific hub of excellence encompassing research laboratories, hospitals, veterinary centres, industrial R&D departments, non-governmental organisations (NGOs), regulatory bodies and patients, nature and animal associations 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. The Action will promote brain gain or circulation between research intensive and research moderate European territories with the goal to harmonise scientific and technological knowledge in the field. Indeed, the Action will be committed to efficiently and durably transfer all information to Inclusiveness Target Countries (ITCs) to initiate a long-lasting bottom-up dynamic with regard to skin models, a field with high scientific, ethical and commercial potential. Young Researchers and Innovators (YRIs) will occupy leading positions in the network and will be provided with outstanding educational and mentorship programmes. Providing YRIs with tangible opportunities to demonstrate their leadership and broaden their skills beyond the technical framework in a scholarly and kind environment will help empower and retain the next generation of researchers within the European borders and prevent brain drain.

Skin organotypic cultures are used to study various aspects of epidermal homeostasis or barrier function, to understand anomalies at the cellular and molecular levels in specific skin diseases or in skin ageing and to identify drug efficacy and adverse effects. Moreover, several European research groups and industries have ongoing studies on bioactive 3D-printed patches or are exploring the possibilities of induced pluripotent stem cells (iPSCs) and CRISPR-Cas9-mediated genome editing.
However, despite the indisputable dynamism of the field, major progress in designing and implementing relevant pathophysiological skin models is still missing because the following challenges have not yet been overcome:

- **Lack of coordinated efforts, intersectorality** and efficient bundling of available expertise for developing new technical approaches, scaffolds, composites and medium formulations to create

standout, sophisticated skin models and enable the introduction of skin appendages and macrostructures such as sebaceous or sweat glands and hair follicles into organotypic models;

- **Inaccessibility to technologies** in many European institutions, especially in ITCs owing to geographical concentration of state-of-the-art technologies/know-how;
- **Lack of a strong interdisciplinary network** in the emerging arena of computational skin models, which is indispensable for generating breakthroughs in the field;
- **Insufficient cooperation** between academia and industry to elaborate marketable sophisticated skin models as well as sustainable and ethical products.

A robust response to these challenges will allow the full deployment of alternative skin models, not only to respond to ethical injunctions, but also to enhance the relevance of scientific data, increase the success rate of clinical trials and improve patient treatments and outcomes.

The cornerstone of the NETSKINMODELS Action is to create a favourable environment allowing the delivery of innovative and pathophysiologically relevant cell-based models recapitulating the complexity of the skin and skin diseases and the emergence of powerful in silico models by stimulating knowledge transfer within academic laboratories and between the latter and industrial partners. Furthermore, NETSKINMODELS, by promoting interactions between industrial partners (chemistry, biology) and academic laboratories (biotechnology, chemistry, biology, computer science), will contribute to the development of sustainable and animal-free composites and reagents not only to respond to ethical requirements, but also to green-up the scientific practice that is currently relying on non-environmentally friendly oil-derived plastic products. This will open up new markets, provide significant economic rewards for EU states and create a virtuous cycle spiralling upwards and influencing positive change in other fields of research. As a substantial benefit, the Action will contribute to a drastic reduction of animals in dermatological research and in the manufacturing of cell culture reagents.

The overall goal of this Action will be achieved through the creation of an interdisciplinary and intersectoral network dedicated to frontier research in basic and translational sciences and their interfaces, sharing the latest technical advances in skin substitute development, optimising and generating common protocols within the community, and broadly disseminating the results to all stakeholders.

Over the long term, this Action will gather most European expertise related to the establishment of skin surrogates to make Europe a leader in the field and competitive with the traditional powerhouses, American and Asian universities and companies [16]. Besides scientific, clinical, and ethical achievements, NETSKINMODELS, by promoting public–private interactions, will contribute to sustaining the economic growth of our industrial partners within the European market, i.e. by boosting their R&D, saving costs at the levels of drug/cosmetic screening, and enhancing the effectiveness of clinical trials.

Expertise from network ITCs and YRIs will be essential to develop next-generation skin models and sustainable products. Reciprocally, the network will empower them by offering outstanding educational programmes and leading positions. Moreover, the full exploitation of COST networking activities will enable optimal transfer of knowledge towards ITCs, allowing them to develop state-of-the-art technologies in their laboratories, gain in visibility and recognition, draw strong collaborations with leading academic institutions and meet top-tier industrial partners, which is indispensable for a long-lasting and upward transformation. This win-win strategy is at the core of the network.

The Action timely fulfils criteria of scientific excellence, clinical relevance, technological advancement, economic impact, fair geographical distribution, and educational requirements to ensure European leadership in the field of skin models. The network has deep potential to be at the forefront extremely fast given appropriate resources.

1.2. PROGRESS BEYOND THE STATE OF THE ART

1.2.1. APPROACH TO THE CHALLENGE AND PROGRESS BEYOND THE STATE OF THE ART

The following points emphasise the innovative and constructive breakthrough capacity of approaches developed by the network to tackle challenges and advance the state-of-the-art in the field.

Strengths of the NETSKINMODELS Action:

► A large network of members from several research institutions and industry in COST full and cooperating members (countries), among them in ITCs and bringing together opinion leaders, top-level scientists, clinicians, technical experts, and tissue- and bio-engineers from all over Europe and beyond at all stages of professional curriculum.

► This Action has arisen at a moment when there is a strong demand from society, the scientific community and industry for skin models to carry out drug screening, develop new therapies, uncover poorly understood etiological mechanisms, switch to human-based models, reduce the use of animals in research, and to green-up experimental procedures.

► Innovation is a determining factor in advancing the cosmetics industry, an industrial sector that benefits globally from significant structural growth and whose leaders are European powerhouses.

Weaknesses in the field that will be addressed by the NETSKINMODELS Action:

► Lack of communication leading to redundant experiments in European laboratories;

► Lack of databases compiling raw data, protocols, failures, drawbacks, dead-end experiments;

► Limited access to state-of-the-art technologies and to cells (e.g. cells lines, primary cells, cells derived from iPSCs or immortalised cells, AI, computational modelling);

► Absence of validation and benchmarking technologies for many of the current skin models and cell lines;

► Simplicity of current models (simple models are useful but should coexist with complex models);

► Lack of skin-mimetic biomaterials for the fabrication of biologically functional bio-printed skin models, thus defaulting to simplistic models;

► Dependence on single-use plastic ware and on animal-based composites and reagents;

► Absence of a European-wide network.

Scientific, clinical, educational and industrial opportunities will emerge from NETSKINMODELS Action:

► Creation of robust and fully characterised cell-based and computational skin models, as well as establishment of guidelines for skin model and cell line validation;

► Creation of databases (publications, protocols, dead-end experiments, pitfalls, information related to skin models, reagents/composites) and a registry including all biological material collected by Action participants;

► Interaction between mathematicians, biologists, veterinarians and clinicians within the network will allow the development of powerful computational methods/models creating a favourable environment for the advancement of new therapeutic and cosmetic approaches;

► Improvement and acceleration of preclinical research and drug development pipelines by understanding the disease physiopathology in order to identify and validate new drug targets;

► Development of an educational programme that includes theoretical knowledge and hands-on training, with specific attention to ITCs. This is foundational to support a continuous and mutual flow of benefits within Europe and to open opportunities for educational exchanges and economic growth;

► Emergence of the next-generation scientists and leaders in Europe by stimulating, listening, encouraging and supporting ECIs via network activities, including a mentoring programme;
► Creation of tangible opportunities for quick transfer of knowledge and responding to questions related to products by connecting academia, clinics and companies;
► Implementing R&D that facilitates constant crosstalk between network scientists, clinicians and industrial partners leading to drug/product development in a setting of optimal market transfer;
► Possibilities to create spin-offs or start-ups (with focus on the ones developed in ITCs and by YRIs) and an innovative industrial base within Europe consisting of intermediate structures between academic laboratories and industry partners;
► Stimulate sustainable research by developing alternative products and create a dynamic that will inspire other European scientific communities. The broad dissemination of results related to this activity should inspire other branches of science, which will not only benefit society, but also science per se.

Threats that should be averted by NETSKINMODELS Action:
► Sophisticated skin models have huge economic and ethical potential that might be pre-empted by America and Asia, hence creating economic imbalance and scientific disparities in the field and even beyond. Allowing European academic institutions and industry to capture significant intellectual properties (IP) via the Action will increase market share and competitiveness and boost the socioeconomic and environmental impact of European research. Thus, the objectives of NETSKINMODELS respond to strategic interests;
► Lack of significant progress in the field of skin models in Europe leading to unsatisfactory scientific, clinical, ethical and commercial outcomes; NETSKINMODELS is sized and equipped to respond to such threats.

NETSKINMODELS will encourage a bottom-up approach to scientific collaboration by bringing together all members of the scientific community related to skin models. The synergy of goodwill, energy and common cause within the network will lead to rapid advances in the state-of-the-art and culminate in sustained dermatological breakthroughs in Europe.

1.2.2. OBJECTIVES

1.2.2.1 Research Coordination Objectives

The ambitious objective of the Action is to optimally transfer technologies, material and knowledge across Action participants. Indeed, NETSKINMODELS represents an ideal instrument which will bring together many groups and experts from diverse fields of investigative dermatology and beyond. **Only an extensive and well-coordinated network of tenured senior and junior academic researchers and clinicians in association with industrial R&D departments can take up the challenge to (1) rapidly elaborate highly competitive skin models on the international stage and (2) bring ITCs into the fold.** Thus, the objectives of NETSKINMODELS are manyfold and will be organised according to four main axes: scientific, educational, environmental and commercial.

1 Scientific: A data management system will be created at the start of the Action to efficiently distribute and share results from many studies and to accelerate data dissemination to every network participant, including industrial partners. NETSKINMODELS will be a reservoir for innovation and will rigorously develop and share protocols via **an Atlas** including all validated protocols, descriptions of cell lines and computational models developed by Action partners, and dead-end experiments/pitfalls. The Atlas will be accessible as public data or as a restricted space only available for participants (at least until patenting or publication). Action participants will contribute to the creation of an **initial database** that will compile all publications and information on existing models, protocols, reagents and

composites. Moreover, the Action will also provide **guidelines for validation** of models and cell lines that will be based on interdisciplinary and intersectoral synergies within the network. An inter-laboratory ring test will ensure the reproducibility of 3D skin models and proper dissemination of information. Action innovations (models, protocols, technologies, biological and non-biological material) will be evaluated to set up strategies necessary for their improvement. All Action partners, as well as external observers, will contribute to data curation. This is a prerequisite for delivering high-quality models and reagents and providing the scientific community with relevant and reproducible data and protocols that can be further exploited for preclinical or clinical research, or for commercial purposes.

2 Educational: The gained expertise and the new models or composites/reagents will be integrated into **strategic dissemination** (extensive, sustained and strong towards ITCs) and **educational programmes** (including in University Master and PhD programmes), aimed at expanding a highly cooperative European network for skin models. Next-generation scientists (ECIs) will be trained within the network for the long-term dissemination and development of skin models that offer powerful alternatives to animal experiments. Short-Term Scientific Missions (**STSMs**), **training schools** and the elaboration of a **mentoring programme** will be powerful Action educational tools. Dissemination of research results to the general public and relevant stakeholders (e.g. policy-makers, governmental organisations, NGOs, environmental and patients´ associations) will be ensured via participation to Action activities and invitations to Action conferences and via general media (e.g. journals, YouTube channels, social media), interviews, website and industrial partners, hence increasing societal awareness to scientific advances and the importance of skin models.

3 Environmental: The Action possesses a reservoir of talented intersectoral bioengineers who will develop ethical and green products designed for the elaboration of 3D 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. Moreover, high-performance computational models have a significant environmental and ethical impact by being an alternative to animal experiments. Thus, **the Action timely responds to the 3Rs on animal and waste management.**

4 Commercial: A coordinated research agenda between academic laboratories and industrial partners including SMEs of the Action will ensure the **commercialisation** of innovative skin models and composites/reagents, drug delivery systems as well as of new drugs/cosmetics. **Patents** may be applied and **spin-offs** created, expanded or reinforced. Moreover, **novel industrial processes**, and **software** (e.g. for monitoring progression of skin conditions) will be developed and commercialised.

1.2.2.2 Capacity-building Objectives

NETSKINMODELS already has the requisite critical mass of expertise and of interdisciplinary and intersectoral participants, hence ensuring long-lasting European leadership in the research area. However, NETSKINMODELS will likely arouse the interest of additional academic and industrial partners firstly in Europe and then potentially worldwide, but most probably initially in the American, Australian and Asian continents. The capacity building of the Action is described in Fig. 2.

NETSKINMODELS Action will eventually:

► Create a large, world-leading but flexible interdisciplinary and intersectoral collaborative network in Europe, driven by excellent scientists, outstanding clinicians and top-tier industries to stimulate a bottom-up dynamic regarding skin models and preponderant breakthroughs. This will make Europe the epicentre of excellent research in the field;

► Increase intersectoral exchange via the creation of an enriched relationship between academic structures and industrial entities to transform innovations derived from basic research into marketable products;

►Empower women by ensuring gender-balance in the leadership team of the network;

► Uncover and encourage new young talents and educate the next generation of leaders (ECIs) in the field able to apply to European Research Council (ERC) starting or consolidator grants;
► Create a subdivision of the European Society for Dermatological Research (ESDR) dedicated to skin models to ensure the longevity of the network;

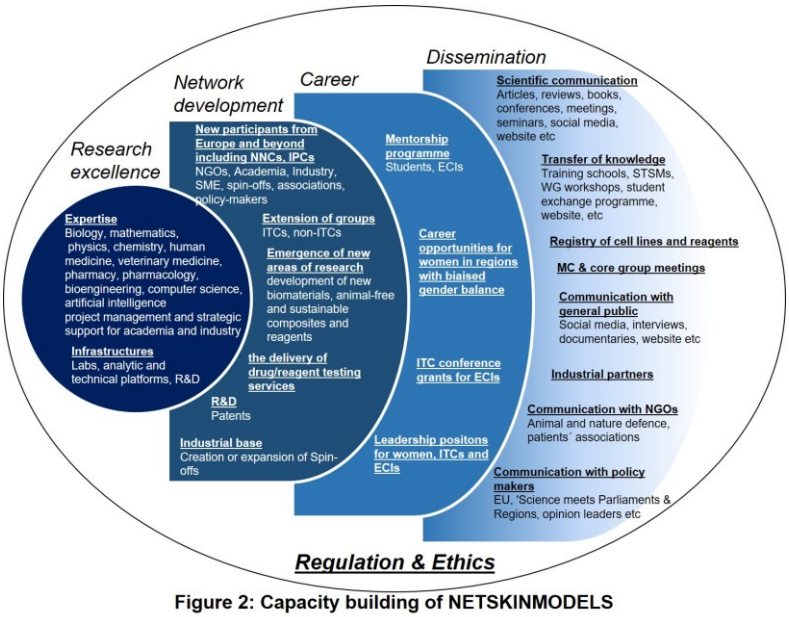


Figure 2: Capacity building of NETSKINMODELS

► Upscale the network with non-European scientists, clinicians and industrial companies to contribute to the dissemination of network outcomes worldwide;
► Give rise to well-coordinated and comprehensive network for initiating follow-up grant proposals/successful joint projects (e.g. COST innovators grants, Horizon Europe, European Innovation Council, national grants, bilateral or multilateral grants).
► Stimulate cooperation and include non-governmental stakeholders such as patients, animal and nature associations or specialised in gender and diversity equality, innovation management and entrepreneurship counselling.

2. NETWORKING EXCELLENCE

2.1. ADDED VALUE OF NETWORKING IN S&T EXCELLENCE

2.1.1. ADDED VALUE IN RELATION TO EXISTING EFFORTS AT EUROPEAN AND/OR INTERNATIONAL LEVEL

A European network harnessing all actors able to contribute to the elaboration of sophisticated skin models and able to capitalise on the accelerated development of these tools is still missing. Despite enormous expectations of the scientific community and of business enterprises, no European or international large-scale networks have been created for the sole purpose of advancing skin models. Despite various initiatives for peer-to-peer networking (e.g. annual meetings), the scale and scope of collaborations currently formed, typically micro- to mini-scale, often lack interdisciplinarity and intersectorality, which are indispensable for creating scientific breakthroughs and transformative medical outcomes in the field. Moreover, effective collaboration between mathematicians, computer scientists, biologists and clinicians is still clearly missing to create *in silico* models and AI models to be further exploited in projects related to dermatological research. Indeed, only a large-scale network can be expected to launch this type of endeavour, by bringing together a great variety of outstanding experts in Europe**. Teams from large number of European countries will participate in this Action with the contribution of ITCs, supporting a strong demand in the development of skin models and related innovations.** Intensive circulation of researchers, ideas, protocols and biological materials within the network, and infrastructure sharing will be supported by Action networking tools such as STSMs,

Training Schools, various meetings, conferences, website, registry and databases. They are unique opportunities to engage in a transregional scholarly exchange programme within a non-hierarchical academic/industrial framework. They represent tangible opportunities to implement the network via integrative and leveraging approaches and are essential for addressing the key challenges in this Action. NETSKINMODELS includes opinion leaders and industrial partners who will ensure the wide dissemination of network outputs. Moreover, this Action represents the first step towards preparing large-scale international projects and the creation of a novel scientific society, which will radiate beyond our European borders.

2.2. ADDED VALUE OF NETWORKING IN IMPACT

2.2.1. SECURING THE CRITICAL MASS AND EXPERTISE

NETSKINMODELS will encompass top academic experts with a broad spectrum of competences (clinical, scientific, technical, educational) and industrial partners dispersed in teams from COST member countries and cooperating state and other countries as well (International Partner Countries e.g. Brazil, a very dynamic South American country in activities related to the field). This is the first time that such a large network dedicated to skin models has been created. Moreover, NETSKINMODELS includes opinion leaders, experienced researchers and promising young researchers and innovators (high involvement of YRIs and female researchers is expected). Participants of the network have extensively published papers related to skin models in top specialised journals and/or patented key discoveries related to the network topic. Several industrial partners have an international dimension. Moreover, all participants have major interests in keeping the network cohesive because of reciprocal benefits. Furthermore, NETSKINMODELS will generate a scientific vortex attracting new participants (e.g. scientists, clinicians, industries), hence creating over the long term “a skin model galaxy” centred in Europe. This will generate a gravitational force for all network actors, which will secure its critical mass and expertise, while promoting intensive and internal network movements, exchanges and emulations.

2.2.2. INVOLVEMENT OF STAKEHOLDERS

The Action includes stakeholders split into four bodies:
1) **The academic entity** consists of biologists (e.g. cell and molecular biologists, biochemists, physiologists, lipidologists, immunologists, neuroendocrinologists, microbiologists), computer scientists, mathematicians, physicists, chemists, pharmacists, pharmacologists and bioengineers from basic and applied science and includes senior scientists, top experts, opinion leaders and YRIs. Network clinicians are outstanding healthcare professionals with expertise in dermatology, plastic surgery, dentistry, oncology and veterinary medicine, and most also engage in intense research activities.
2) **Industrial partners** include top-tier European companies with international branches but also SMEs providing Omics and testing services, innovative and sustainable composites, cosmetic and pharmaceutical products. One SME is specialized in strategic support for academia and industry.
3) **Regulatory bodies** are internal strategy institutions protecting the IP and ethics organisations (Universities, legal departments of industrial partners) to ensure high scientific good practices and industrial exploitation compliance.
4) **NGOs including associations of patients, nature animal defence and policy makers**. Policy makers and representatives of NGOs and associations will be approached by the Management Committee (MC) and invited to contribute to the Action as guest speakers at conferences. The European Union Joint Research Centre for Alternatives to Animal Testing (EURL ECVAM) platform (including EURL ECVAM Stakeholder Forum (ESTAF), https://ec.europa.eu/jrc/en/eurl/ecvam) is complementary

(yet not redundant) with current Action activities and will be contacted for maximising impact at the European level and translating results into policy-making, notably via the programme 'Science meets Parliaments & Regions'.

Such a large network needs **coordinators** for (1) STSMs, (2) ITCs, (3) YRIs, (4) mentorship programme, (5) gender balance and diversity, (6) scientific communication including conferences, interviews (7) communication with industry including issues related to IP, (8) dissemination including sub-coordinators for (a) the implementation of Atlas and databases and (b) website, social media and general public and (9) training schools.

Interactions between all network bodies will be supported by **participant mobility, regular meetings,** and the establishment of a **dissemination platform** (description under point 3.2.2) and a **mobile intranet**.

2.2.3. MUTUAL BENEFITS OF THE INVOLVEMENT OF SECONDARY PROPOSERS FROM NEAR NEIGHBOUR OR INTERNATIONAL PARTNER COUNTRIES OR INTERNATIONAL ORGANISATIONS

NETSKINMODELS will be recognised beyond European borders and will attract participants from many countries. Brazil participates in the Action because it is very active in the field of 3D organotypic skin research. It is a reciprocal benefit for Brazilian research and NETSKINMODELS to be connected as it will increase the visibility and expertise mass of both parties. Moreover, NETSKINMODELS will weave novel international collaborations especially in the USA, Australia, China, Japan and Korea, hence further enhancing grant opportunities for all participants and accelerating knowledge sharing. Furthermore, integration of participants from International Partner (IPCs) and Near Neighbour Countries (NNCs) will provide the Action with broader visibility worldwide, hence demonstrating European strength, innovation potential and leadership in the field. Whereas the initial goal of NETSKINMODELS is to create a world-leading network producing standout skin models, this will not preclude us from entering into potential fruitful collaborations with our American, Australian and Asian colleagues. The scientific community as a whole has largely embraced the concepts of “Team Science” [17] and “collective intelligence” (developed by James Surowiecki) to attain greater achievements for the superior benefit of science and medicine. Thus, they will definitively be interested in participating to the network. Moreover, all current Action participants and those to be are well aware of the potential socioeconomic impacts of the network and the great opportunity it presents to translate outcomes into changes in regulation, ethics and policies with respect to animal experimentation and sustainable research globally.

3. IMPACT

3.1. IMPACT TO SCIENCE, SOCIETY AND COMPETITIVENESS, AND POTENTIAL FOR INNOVATION/BREAKTHROUGHS

3.1.1. SCIENTIFIC, TECHNOLOGICAL, AND/OR SOCIOECONOMIC IMPACTS (INCLUDING POTENTIAL INNOVATIONS AND/OR BREAKTHROUGHS)

Scientific and medical impact:
Short term: The development of standout skin models will advance the field of dermatology and likely beyond, by providing the scientific community and society with clinically relevant models that could be

translated into novel research strategies, therapeutic approaches, patient care and prediction of disease evolution and comorbidities. The use of sophisticated 3D skin models will also help optimise drug delivery through human skin, which will accelerate the development of new innovative drug delivery systems. Advanced computational methods including AI will allow us to create predictive models for specific medical conditions and to optimise/tailor treatment strategies.
Mid- and long term: Tailoring these skin models towards engraftment in patients with large wounds, burns, oncological plasty or genetic disease will be of immeasurable benefit. Furthermore, the utilisation of gene editing technology in 3D skin models will increase our understanding of the physiological and pathophysiological roles of genes in the skin, and thereby facilitate the identification of targets for therapies to treat skin diseases, for which today no cures exist. Computational models will revolutionise scientific practice by considerably reducing the use of experimental animals, animal- and oil-derived reagents, and patient and animal biopsies and repeated blood sampling. In the long-term perspective, skin models generated within the Action will increase the quality, relevance and soundness of the research and foster translation into clinical applications.

Technological impact, breakthroughs and innovation:
Short term: In dermatology, the use of AI methods opens up new possibilities for treating patients and gaining novel insights into specific diseases. Some of the existing (and upcoming) approaches use smartphone applications for quick assessment of skin conditions [e.g. basocellular carcinoma (BCC), melanoma, psoriasis or healing of wounds], and they work as an excellent additional tool for clinicians, allowing telemonitoring of patients. Skin bio-printing will benefit from the development or amelioration of scaffolds based predominantly on abundant non-animal-based polysaccharides (e.g. alginate, carboxymethyl cellulose, nanofibrillar cellulose) or fully synthetic polymer matrices that are fabricated by advanced manufacturing approaches or techniques (e.g. multidimensional dynamic model using a bioreactor fluidic system).
Mid- and long term: Big data analysis, such as the medical records of many patients suffering from a specific medical condition or data generated by multi-omics approaches, may offer insights such as forecasting the progress of a disease, the efficacy of a treatment approach or the development of specific co-occurring diseases. Modelling of skin diseases and wound repair — or even skin ageing — associated with machine learning will allow: (i) improved understanding of the underlying causative events, (ii) prediction of skin condition evolution, (iii) anticipation of potential adverse effects of newly developed drugs/cosmetics, and (iv) anticipating the development of associated comorbidities. Moreover, the elaboration of sophisticated 3D skin models as well as of computer-based models is at the pinnacle of technological innovations, and lessons from their elaboration will extend to fields well beyond dermatology.

Socioeconomic impact: End users of skin models including skin substitutes for burn victims are on all continents and the market is enormous [incremental growth of 3.65 billion dollars expected for permanent artificial skin between 2019 and 2023 (Global Skin Models Sales Market Report 2021)].
Short term:
(1) The skin model market segment comprises different types of models such as ones for ageing skin and hair loss, skin burn, acne, normal skin, and skin cancer. This market represents an increasing part of the valuation related to dermatological research. Therefore, the creation of high-end skin models will significantly contribute to the expansion and diversification of this market. (2) The full commitment of female participants to projects and at leading positions in the network will, within a few years, contribute to equilibrating the gender balance in the profession at all levels as well as locally in universities/companies. (3) The development of skin models and new composites, reagents, drugs, cosmetics and delivery systems potentially subjected to patenting will strengthen R&D and help the economic development of industrial partners, including in ITCs. Industrial partners of NETSKINMODELS will benefit from the network to develop their product portfolio, broaden their customer reservoir and find new market opportunities. Moreover, network outcomes might stimulate partners to create spin-

offs/start-ups and, eventually, enrich their local industrial base. (4) The development of green and vegan products will benefit society and open/support new markets with high potential for development within Europe (e.g. vegan cosmetics).

Mid- and long term:

(1) Network activities and leading opportunities will allow ECIs to acquire all competences to run for outstanding positions in European institutions and industries and create spin-offs or start-ups, a prerequisite to retain them in Europe. (2) Network activities and outcomes will facilitate the further development of educational and entrepreneurial bases in ITCs. (3) The socioeconomic burden linked to skin diseases (e.g. occupational hand eczema) as well as to patients with skin burns and scars amounts to several billions of euros per year as direct costs (medical care) and indirect costs (e.g. unworked days) [18]. Thus, creating new models able to drastically and rapidly advance scientific and medical knowledge as well as medical follow-up via AI using smartphone applications will significantly improve patients´ lives and reduce costs for families and societies. (4) Cosmetic and pharmaceutical industries will benefit from the creation of novel skin models recapitulating skin morphology, function and response. Prediction of toxicological effects and drug/cosmetic testing/screening using computer-based models will reduce development costs and time investment for companies, hence increasing product profitability for businesses and lowering buying costs for patients/customers.

3.2. MEASURES TO MAXIMISE IMPACT

3.2.1. KNOWLEDGE CREATION, TRANSFER OF KNOWLEDGE AND CAREER DEVELOPMENT

Knowledge creation: Sophisticated, cell-based models of healthy and diseased human skin — i.e. models which include skin appendages and related tissues — do not yet exist. Nor do computational skin models. Indeed, innovation in this domain requires collaboration and input from many different disciplines at the knowledge frontier. NETSKINMODELS will allow the creation of such models by harnessing domain experts, motivated YRIs and industrial partners. The establishment of sophisticated skin models will tremendously extend the knowledge in the field by facilitating a better understanding of all normal and pathophysiological skin processes, including ageing, wound healing, tumour evolution, inflammation, itch, infection and interactions with the skin microbiota. Cellular biology approaches, clinical assessment and computational models will synergise to elucidate scaffold disease evolution, comorbidities, disease relapse, and best therapeutic approaches. Moreover, the process of skin model development will generate many pitfalls and challenges to be solved before reaching completion and this itself will create novel knowledge at various levels: cell-cell interactions, optimal culture conditions, medium composition, the reaction of cells to a novel composite material, model inference, treatment of measurement variability, etc., some possibly spun-off to other disciplines or to commercialisation.

Transfer of knowledge: A cornerstone of NETSKINMODELS is the transfer of knowledge between participants, the scientific community (transversal transfer to other disciplines), to industrial partners as well as to policy-makers and various associations but, very importantly, towards ITCs (strengthening or initiating firm collaborations) and YRIs. Interactions between academia and industrial partners/SMEs will create a bidirectional transfer of knowledge, favourable for the development of industrial R&D and of spin-offs and start-ups. Indeed, the success of the Action relies on the capacity of the network to efficiently diffuse knowledge between all network bodies. The Action will be poised to give unrestricted access to information (technical, theoretical, industrial, clinical, ethical and educational) to all its members to allow optimal dissemination of crucial data. Social media, website, live and e-meetings, conferences, workshops, STSMs, and training schools will contribute to knowledge diffusion. Exchange programme (STSMs) will enable YRIs to visit network laboratories and industrial partners to establish strong relationships between eminent experts and those rising, and to create job opportunities and leadership qualities in early stages of careers. The mentorship programme will also benefit YRIs, who

will be supported in their career development via informed advice (transmission of leadership and management qualities).

Career development: NETSKINMODELS will encourage ECIs to vie for leading positions by offering them outstanding training, networking opportunities, support and an accompanying framework to develop their own projects and own groups. Moreover, this large network will indubitably give birth to smaller clusters potentially enriched with women and members from ITCs, with capacity to initiate new joint grant proposals/successful projects, hence boosting participant careers. NETSKINMODELS will comprise many ITCs with high involvement of women researchers. This is an incredible opportunity to boost their careers and to radiate this talent beyond national borders. Stimulating YRIs, especially women, for professional mobility and leadership is not enough. NETSKINMODELS will help YRIs with young children to attend training schools, meetings, STSMs etc.

3.2.2. PLAN FOR DISSEMINATION AND/OR EXPLOITATION AND DIALOGUE WITH THE GENERAL PUBLIC OR POLICY

Because expeditious dissemination of NETSKINMODELS breakthroughs to both specialised groups and the general public is crucial for optimised exploitation of the results, the Action will establish as soon as possible a **detailed data management plan** in coordination with all network participants to organise data collection, curation, sharing, and archiving, complying with the "FAIR" (Findable, Accessible, Interoperable, Reusable) principles.

A dissemination platform (interactive and dynamic Action website, Fig. 3) will be created with links to:

► **Scientific outcomes:** (1) the Atlas compiling validated protocols but also negative results, pitfalls, troubleshooting, drawbacks etc; (2) databases with all published data related to the field split into two categories: (i) past publications (initial database) and (ii) publications of Action participants as research and review articles in open-access peer-reviewed journals (including *https://www.coalition-s.org*) as well as (e)-books to increase global scientific knowledge; (3) a network registry for biological material; (4) Biobanking and BioMolecular resources Research Infrastructure (BBMRI-ERIC) (extra-network biobank); (5) each Working Group (WG, detailed below). Moreover, each deliverable will have a dedicated page, in which the most recent developments, protocols and validation guidelines will be summarised by participants and linked to related papers. Associated tutorials and podcasts will be included;

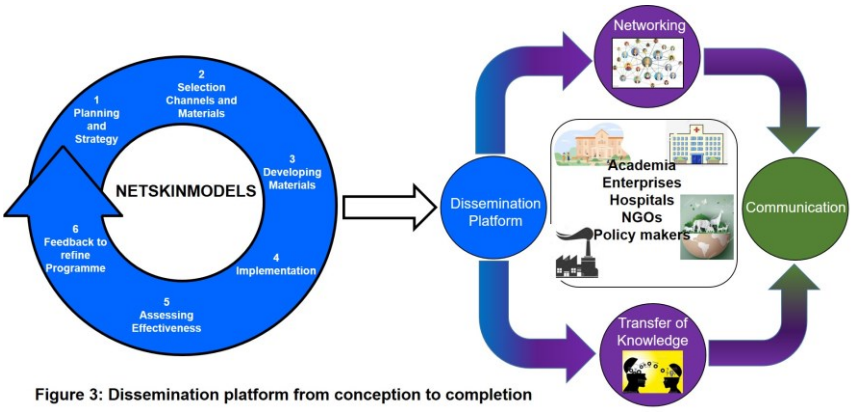


Figure 3: Dissemination platform from conception to completion

► **Educational programmes:** (1) STSMs; (2) WG meetings, conferences, training schools, seminars, workshops; (3) Mentoring programme. Videos and interviews will be included;

► **Internal and external partners' websites** (industry, SMEs, NGOs and patient groups and nature and animal defence advocates that will have accepted to be associated to the Action). This partnership will enhance dissemination of network outcomes to specific and general public audiences alike;

► **Social media** (e.g. Twitter, Instagram, ResearchGate, LinkedIn, Facebook), videos (e.g. YouTube), and **general media** (e.g. TV and radio interviews, newspapers, documentaries) showing network activities or outcomes;
► **Annual meetings** of research and medical networks related to the fields, at European and international levels;
► **Contact details of all network experts** will be included to promote rapid communication and enable quick answers to urgent questions;
Action industrial partners, NGOs, participant institutions (e.g. websites) and conferences attended by Action participants will be important for the dissemination of network outcomes via their websites and product portfolios.

4. IMPLEMENTATION

4.1. COHERENCE AND EFFECTIVENESS OF THE WORKPLAN

4.1.1. DESCRIPTION OF WORKING GROUPS, TASKS AND ACTIVITIES

The Action will be managed by the Management Committee (MC), supported by WG leaders and coordinators to address challenges and facilitate decision-making. Four WGs (WGs 1 to 4) are dedicated to scientific innovations and one WG (WG5) deals with regulation issues, including IP and ethics, dissemination, and educational programmes, including towards ITCs and YRIs.
The Action MC will adopt the following policies to support the Action objectives: (1) Fair regional contribution (50% ITCs at all levels of Action management), (2) Balanced generational representation [enrichment in YRIs (25%) at leading positions] and (3) Gender and diversity equity (50% females in decision-making bodies).
The interrelations between all WGs will promote information sharing during WG meetings and the annual Action conference.

The objectives of NETSKINMODELS include advancing state-of-the-art cell-based and computational skin models and developing new through-the-skin delivery systems, sustainable composites and vegan reagents. The generation of 3D skin models requires biological material that can be a limiting factor in many laboratories. NETSKINMODELS will enhance biological material sharing by creating a registry (available on the network website) where all network participants will deposit information on available biological material [e.g. primary cells, iPSC and immortalised cells subjected or not to gene editing as well as senescent cells with down-regulated or overexpressed specific genes (including dedicated vectors), skin biopsies, micro-organisms, Peripheral Blood Mononucleated Cells (PBMCs), hematopoietic stem cells etc.] from healthy human donors and patients [e.g. psoriasis, atopic dermatitis, vitiligo, melanoma, squamous cell carcinoma (SCC), BCC, ichthyosis, viral/bacterial/fungal/parasite infection, wound defects, and fragile aged skin] and from healthy and diseased pets/livestock (e.g. eczema, infection, cancer). Fair distribution of this biological material will be ensured by specific and unanimously validated Material Transfer Agreements (MTAs). Moreover, a link to the BBMRI network (https://www.bbmri-eric.eu) will be added to the Action website to enhance network resources in biological material.

To achieve Action goals, the scientific work plan will be organised in five tightly interconnected WGs:

WG1- Sophistication of cell-based healthy skin models

This WG is dedicated to the sophistication of current 3D skin models, including bio-printed models. For the latter, a range of alternative scaffold materials or extracellular matrix mimetics based on natural (e.g. pectin, elastin, hyaluronic acid, chitosan etc.) as well as synthetic materials (e.g. PEG, PVA, PLA, PLGA etc.), or blends thereof, will be exploited and shaped by advanced manufacturing techniques including but not limited to electrospinning (e.g. salt-leaching, gas foaming). The objectives of WG1 are to jointly generate:

Task 1.1: Immunocompetent models including immune cells such as Langerhans cells, dermal dendritic cells, lymphocytes, macrophages and mastocytes. Immune cells will be generated from PBMCs and haematopoietic stem cells or isolated/expanded from skin biopsies;

Task 1.2: Models containing various other skin cell types (e.g. sensory and endothelial cells, melanocytes) derived from primary cells, iPSCs or immortalised cell lines;

Task 1.3: Models with skin appendages (e.g. hair follicles, sebaceous and sweat glands) and connected with other compartments (e.g. lymph nodes, lymph vessels, vascular system);

Task 1.4: Models with satisfactory native-like lipid barrier (current skin models differ substantially in lipid composition and organisation with each other and with native skin).

Task 1.5: Models with skin microbiota;

WG2: **Sophistication of cell-based models of skin diseases, wound (repair) and ageing**

Skin bio-printing will be utilised in this WG in addition to other methods to generate cell-based skin models of diseases. According to the scheme and development in WG1 (fostered through tight collaborations between WG1 and WG2 participants), the objectives of WG2 are to create sophisticated 3D skin models of:

Task 2.1: Skin ageing;

Task 2.2: Skin diseases (e.g. psoriasis, atopic dermatitis, vitiligo, ichthyoses);

Task 2.3: Skin infections (e.g. Herpes simplex, Staphylococci, Pseudomonas spp., Malassezia, Streptococci, Leishmania spp., Trypanosoma spp., chiggers, cytomegalovirus, papillomavirus);

Task 2.4: Skin cancers (melanoma, SCC, BCC);

Task 2.5: Wounds such as observed in epidermolysis bullosa. Moreover, the effect of mechanical stimuli will be studied by using mechanical bioreactors (cell stimulator) to uncover the roles of mechanical cues in wound contraction, regeneration, disease remission or progression.

Task 2.6: Develop 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 (e.g. superparamagnetic) nanoparticles.

WG3: Towards ethical and sustainable research in dermatology

To meet ethical and environmental but also scientific and clinical requirements, WG3 will be composed of the following tasks:

Task 3.1: *Increase accountability for plastic waste reduction* while advancing the quality of research by supporting innovation for a replacement strategy for plastic-based products and boosting research on alternative scaffolds, including melt-electrospun writing, bio-inks from renewable sources (e.g., natural polymers) and optimised hydrogels, which do not influence the immune response or cell phenotype. The development of bioreactor fluidic systems will be included in this task.

Task 3.2: Follow guiding principles for reducing the use of animals by enhancing the development of vegan products (e.g. cosmetics) or reagents containing none or few animal-derived substances (e.g. less FCS). This should include chemically defined components offering accurate and highly reproducible models and highly certified media to support the development of clinical applications.

Task 3.3: Develop *in silico* models to address (1) predictive, prognostic, and therapeutic outcomes of skin diseases to tailor therapeutic and prevention (comorbidities) strategies and, in turn, advance

precision medicine in the clinic, (2) smartphone applications for patient´s follow-up and disease monitoring and, (3) skin ageing processes and prevention to respond to exponential societal demand.

WG4: Validation of models, cell lines, delivery systems, composites and reagents

Increasing the balance between value vs. noise in scientific outcomes relies on scientific rigor, which, in the frame of this Action, requires the validation of innovations elaborated in WGs1-3. Of note, part of the activity of WG4 will be dedicated to the standardisation and reproducibility of models destined to industrial partners, complying with their legal, economic and ethical constraints. Careful, exhaustive and precise validation of innovations will be carried out as described in the following tasks:

Task 4.1: Validation — potentially standardisation — of sophisticated cell-based models for skin architecture and function and physiological (alternatively pathological) processes via assessment of (1) skin morphological architecture, (2) epidermal barrier function, (3) lipidomics, (4) immunological and cancer environment, (5) transcriptomic, metabolomic and proteomic profiling and (6) microbial composition. Functional assays will complete the battery of validation tests. High-resolution profiling is indispensable to validate models and will be achieved via Omics platforms at participants´ institutions or by Omics service partners. Validation will be assured by comparison with published data, evaluation by scientific/clinical network expert panels, and parallel analyses with patient skin biopsies.

Task 4.2: Validation of cell lines — authentication, purity and sterility — from healthy and diseased subjects (e.g. iPSCs, immortalised cells, cells after gene editing) will be carried out via, inter alia, full phenotyping including genetic, transcriptomic and proteomic analyses and via functional assays.

Task 4.3: Validation of computational models will be based on wet-lab experiments, published literature and expertise from scientists/clinicians within the network. When dealing with such models including AI models, interpretability and trustworthiness are of key importance, to ensure their acceptance by patients and clinicians.

Task 4.4: Validation of pathologic/ageing/wound models regarding response to treatments. The validation of diseased skin models involves the confirmation of suitable responses to well-known treatments (e.g. cortisone, tacrolimus, chemotherapeutics) to verify the appropriate resolution process of the skin condition and will be based on strategies developed in Task 4.1.

Task 4.5: Further innovations (composites, vegan reagents and delivery systems) will be tested for performance in cell-based models and subjected to extensive validation according to schemes described in Task 4.1. This task will be carried out with industrial partners (validation for further industrial exploitation).

WG 5: Regulatory, ethics, education, disseminating and technology transfer

NETSKINMODELS aims to become a think tank and a business incubator for technology related to patentable skin models and related products. This requires a conduit for permanent information flow between academia and industries under the guidance of ethical and regulatory bodies. Moreover, the development capacity of NETSKINMODELS lies in the opportunity for academic laboratories and industrial partners to develop an educational programme together with a clear dissemination strategy as follows:

Task 5.1: The MC will tackle ethical and regulatory challenges with regards to background and foreground IP, technical innovations, biobank, MTAs and access to Atlas to ensure the preservation of IP and patentability of products in compliance with current European and international laws. The Action will secure the exploitation of inventions. The Action will also adopt the European Code of Conduct of Research Integrity [1] and follow the recommendation on IPR (Intellectual Property Rights) as described

[1] European Code of Conduct for Research Integrity, https://allea.org/code-of-conduct

[2] https://www.cost.eu/uploads/2022/02/COST-094-21-Annotated-Rules-for-COST-Actions-Level-C-2022-02-15.pdf

in the Annotated Rules for COST Actions[2]. In- and out-licensing technologies created within the network will be accessible to internal but potentially to external partners as well and will also provide learning opportunities. Confidentiality, Non-Disclosure, or Data Use Agreements may be necessary for data sharing. Thus, a memorandum on the accessibility of unpublished data and on discoveries as well as on personal data [according to General Data Protection Regulation (GDPR) compliance] will be elaborated. Legal departments of network members (academia and industries) will oversee patent management between all implicated parties to ensure respect of IP and to avoid spoliation. Potential litigations might be solved with further support from the European IP Helpdesk. External counselling (e.g. attorney firms, NGOs, the World Intellectual Property Organization (WIPO) Arbitration and Mediation Center) could be consulted if necessary.

Task 5.2: Theoretical and technology transfer will be ensured by (1) live/hybrid/e-conferences, workshops, seminars, WG meetings, (2) videos, podcasts and tutorials on the network website, (3) STSMs, (4) the website (details in section 3.2.2). Moreover, live seminars/workshops with world-leading scientists, industrial partners and young scientists (pre-/post-PhD) will be organised to stimulate exchange of information, networking, brainstorming, debate, academia-industry interactions, mobility of PhD students and post-doctoral fellows, mentorship spirit, and career development. These small-scale meetings will also be designed to encourage ECIs, especially women, to acquire more self-confidence in promoting and defending their ideas, projects and leadership.

Task 5.3: The educational programme includes interdisciplinary training schools and mentoring programme. Specific attention will be brought to ITCs desiring to develop 3D skin models in their laboratories. Hands-on training and lectures will be given by network partners based on interdisciplinarity and intersectorality. A mentorship programme including recommendations on career development, grant and CV writing and unconscious gender bias will be elaborated at the beginning of the Action. Specific talks on these topics will be included in network seminars and workshops. Master and PhD programmes at participant institutions will be implemented with network innovations as soon as they will have been thoroughly validated. This will likely start at the end of the Action and will pertain after the Action ends to ensure long-lasting educational outcomes.

Task 5.4: Internal information will be ensured by creating a platform (mobile Intranet) based, for example, on Microsoft SharePoint.

Task 5.5: A dissemination platform, as detailed in section 3.2.2, including the Action website will be created to communicate outcomes from the network taking into account the questions related to IP protection. Decision-makers and opinion leaders of the network will translate network outcomes into public policy, and facilitate information transfer to NGOs and various associations related to patients, animals and environmental defence.

4.1.2. DESCRIPTION OF DELIVERABLES AND TIMEFRAME

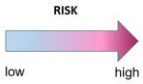
4.1.3.

WG	Description of deliverables	timeframe (months)
WG1	D1.1 Registry for biological material (constantly updated)	7-48
	Up-to-date information and recommendation on 3D skin models including several cell types:	
	D1.2 e.g. keratinocytes, fibroblasts, melanocytes, immune and sensory cells	25-48
	D1.3 and capillaries or vasculature	37-48
	D1.4 and sweat and sebaceous glands	37-48
	D1.5 and hair follicles	37-48
	D1.6 and lymph vessels and skin lymph nodes	37-48
	D1.7 and skin microbiota	25-48
	D1.8 and recapitulating native-like lipid barrier composition	25-48

WG2	Up-to-date information and recommendation on 3D skin models including several cell types and modelling:	
	D2.1 microbial skin infections	25-48
	D2.2 skin diseases (e.g. atopic dermatitis, psoriasis, vitiligo, ichthyoses)	25-48
	D2.3 skin wounds	37-48
	D2.4 skin ageing	25-48
	D2.5 melanoma, BCC, and SCC	25-48
	D2.6 Up-to-date information and recommendation on new drug delivery systems	13-48
WG3	Up-to-date information and recommendation on:	
	D3.1 sustainable composites	13-48
	D3.2 vegan reagents	13-48
	D3.3 in-silico models of skin diseases	37-48
	D3.4 in-silico models of skin wound	37-48
	D3.5 in-silico models of skin ageing	37-48
	D3.6 smartphone apps	25-48
WG4	Up-to-date information and recommendation on validation (guideline) of:	
	D4.1 cell lines and models from WG1	13-48
	D4.2 cell lines, models and delivery systems from WG2	13-48
	D4.3 in-silico models and smartphone apps from WG3	33-48
	D4.4 new sustainable and vegan products from WG3	17-48
	D4.5 standardisation and reproducibility of models from WG1and WG2	37-48
WG5	D5.1 Data management plan	4-6
	D5.2 Memorandum on ethics	4-6
	D5.3 Creation of Intranet platform	4-6
	D5.4 Elaboration/update of interdisciplinary programme of training schools and mentoring programme	6/24
	D5.5 Organisation plan for conferences, seminars, WG meetings, workshops	6/24
	D5.6 STSMs	5/16/28/40
	D5.7 Dissemination platform (constantly updated) including website, social media, tutorials, databases, atlas, peer-reviewed articles, academic volumes etc	6-48 6-48

4.1.4. RISK ANALYSIS AND CONTINGENCY PLANS

NETSKINMODELS is a large interdisciplinary and intersectoral network with top experts, opinion leaders, outstanding clinicians and industry partners of various sizes, which will ensure the feasibility of the work plan and the resilience of the network. However, as a large, distributed entity, NETSKINMODELS will have to tackle challenges at individual, WG and network scales.

Risk 	Contingency measures
	At the individual level
Difficulties to involve ECIs in leadership roles	Mentoring programme and financial (ITC-ECI conference grants) and organisational support (childcare) will thwart mobility issues, thus allaying potential conflicts between professional and personal achievements, and will reinforce self-confidence.
	At the WG level
Delayed activities, tasks and deliverables	WG leaders will evaluate the level of contribution of each group twice a year via regular communication [WG (e-)meetings] and updates (publications, activities in social media, website, participation at workshops, conferences etc). They will oversee slowing/barring factors,

	and find solutions in agreement with all actors, including at higher levels of network management or via ethical and regulatory bodies.
Differences in priorities and expectations from industrial partners	During the kick-of meeting, industrial partners will present their enterprise and their expectations. Open discussions with all participants will be organised to promote fruitful collaborations. Moreover, the memorandum on ethics will secure the conditions of co-development of products between academia and industries.
Differences in priorities and expectations from academic groups	A satisfaction questionnaire will be sent once a year to all participants with the opportunity to express specific comments, suggestions, wishes and criticisms.
Technical difficulties	These will be solved via monitoring of activities and regular meetings: (1) Minor: consultation of website, Atlas and databases, (2) Medium: consultation with network experts, and (3) Major: emergency e-meeting with WG participants, internal and external experts
	At the network level
Travelling restriction	E-meetings, asynchronous seminars and workshops, small-scale training schools and deferred STSMs (if necessary) will allow time for the lifting of restrictions.
Coordination issues for such a large network	Challenge will be tackled by regular meetings of MC, e-meetings and extensive utilisation of the intranet platform.

4.1.5. GANTT DIAGRAM

4.1.1.

	Year 1				**Year 2**				**Year 3**				**Year 4**			
Quarter:	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
MC meetings	K		M		M		M		M		M		M		M		M
WG meetings		M		M		M		M		M			M			
Network workshops			W			W			W			W			W	
Network seminars		S	S	S	S	S	S	S	S	S	S	S	S	S	S	
Network conference							C			C			C			C
Training schools		T		T		T		T		C		T		T		
WG1: Up-to-date information and recommendation on cell-based healthy skin models																
D1.1 Registry			X	X	X	X	X	X	X	X	X	X	X	X	X	X
D1.2 Several cell types									X	X	X	X	X	X	X	X
D1.3 Capillaries/vasculature													X	X	X	X
D1.4 Sweat/sebaceous glands													X	X	X	X
D1.5 Hair follicles													X	X	X	X
D1.6 Lymph system									X	X	X	X	X	X	X	X
D1.7 Skin microbiota									X	X	X	X	X	X	X	X
D1.8 Native-like lipid barrier																
WG2: Up-to-date information and recommendation on cell-based models of skin diseases, wound (repair) and ageing																
D2.1 Skin infections									X	X	X	X	X	X	X	X
D2.2 Skin diseases									X	X	X	X	X	X	X	X
D2.3 Skin wounds													X	X	X	X

D2.4 Skin ageing									X	X	X	X	X	X	X	X
D2.5 Skin cancer									X	X	X	X	X	X	X	X
D2.6 New drug delivery systems					X	X	X	X	X	X	X	X	X	X	X	X
WG3: Up-to-date information and recommendation on ethical and sustainable innovations																
D3.1 Sustainable composites					X	X	X	X	X	X	X	X	X	X	X	X
D3.2 Vegan reagents					X	X	X	X	X	X	X	X	X	X	X	X
D3.3 Comp. mod. skin diseases													X	X	X	X
D3.4 Comp. mod. skin wound													X	X	X	X
D3.5 Comp. mod. skin ageing					X	X	X	X	X	X	X	X	X	X	X	X
D3.6 Smartphone apps																
WG4: Up-to-date information and recommendation on validation of innovations																
D4.1Cell lines/innovations WG1					X	X	X	X	X	X	X	X	X	X	X	X
D4.2Cell lines/innovations WG2					X	X	X	X	X	X	X	X	X	X	X	X
D4.3 Innovations WG3 (1)						X	X	X	X	X	X	X	X	X	X	X
D4.4 Innovations WG3 (2)													X	X	X	X
D4.5 Standardisation																
WG 5: Regulatory, ethics, education, disseminating and technology transfer																
D5.1 Data management plan		X														
D5.2 Memorandum on ethics		X														
D5.3 Intranet platform		X														
D5.4Training schools/mentoring		X						X								
		X				X				X				X		
D5.5 Organisation meetings		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
D5.6 STSMs		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
D5.7 Dissemination platform																

C: conference; Comp. mod.: computational model; K: kick-off meeting; M: meeting; MC: management committee; S: seminar; T: training school; W: workshop; WG: working group

REFERENCES

1. Zaidi Z., Lanigan S.W. Skin: Structure and Function. In: Dermatology in Clinical Practice 2010. Springer, London. https://doi.org/10.1007/978-1-84882-862-9_1
2. Quiroz FG, et al. Liquid-liquid phase separation drives skin barrier formation. Science 2020; 367(6483): eaax9554.
3. Vidal Yucha SE, Tamamoto KA, Kaplan DL. The importance of the neuro-immuno-cutaneous system on human skin equivalent design. Cell Prolif 2019; 52(6): e12677.
4. Gur-Cohen S, et al. Stem cell-driven lymphatic remodeling coordinates tissue regeneration. Science 2019; 366(6470): 1218-1225.
5. Ellis SJ, et al. Distinct modes of cell competition shape mammalian tissue morphogenesis. Nature 2019; 569(7757): 497-502.
6. Sung H, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin 2021; 71(3): 209-249.
7. Gerber PA, et al. The top skin-associated genes: a comparative analysis of human and mouse skin transcriptome. Biol Chem 2014; 395(6): 577-91.
8. Guerrero-Aspizua S, et al. The importance of immunity in the development of reliable animal models for psoriasis and atopic dermatitis. Immunol Cell Biol 2020; 98(8): 626-638.
9. Phua QH, Han HA, Soh BS. Translational stem cell therapy: vascularized skin grafts in skin repair and regeneration. J Transl Med 2021; 19(1): 83.
10. Choudhury S, Das A. Advances in generation of three-dimensional skin equivalents: pre-clinical studies to clinical therapies. Cytotherapy 2021; 23(1): 1-9.
11. Roy V, et al. Human Organ-Specific 3D Cancer Models Produced by the Stromal Self-Assembly Method of Tissue Engineering for the Study of Solid Tumors. Biomed Res Int 2020; 2020: 6051210. eCollection 2020.
12. Neupane R, et al. Alternatives to Biological Skin in Permeation Studies: Current Trends and Possibilities. Pharmaceutics 2020; 12(2): 152.
13. Yu JR, et al. Current and Future Perspectives on Skin Tissue Engineering: Key Features of Biomedical Research, Translational Assessment, and Clinical Application. Adv Healthc Mater 2019; 8(5): e1801471.
14. Rowan MP, et al. Burn wound healing and treatment: review and advancements. Crit Care 2015; 19: 243.
15. Baker C, Hayden MS. Gene editing in dermatology: Harnessing CRISPR for the treatment of cutaneous disease. F1000Res 2020; 9: 281. eCollection 2020.
16. Lee J, et al. Hair-bearing human skin generated entirely from pluripotent stem cells. Nature 2020; 582(7812): 399-404.
17. Bennett LM, Gadlin H. Collaboration and team science: from theory to practice. J Investig Med 2012; 60(5): 768-75.
18. Chu S, et al. Burden of skin disease and associated socioeconomic status in Europe: An ecologic study from the Global Burden of Disease Study 2017. JAAD Int 2020; 1(2): 95-103.