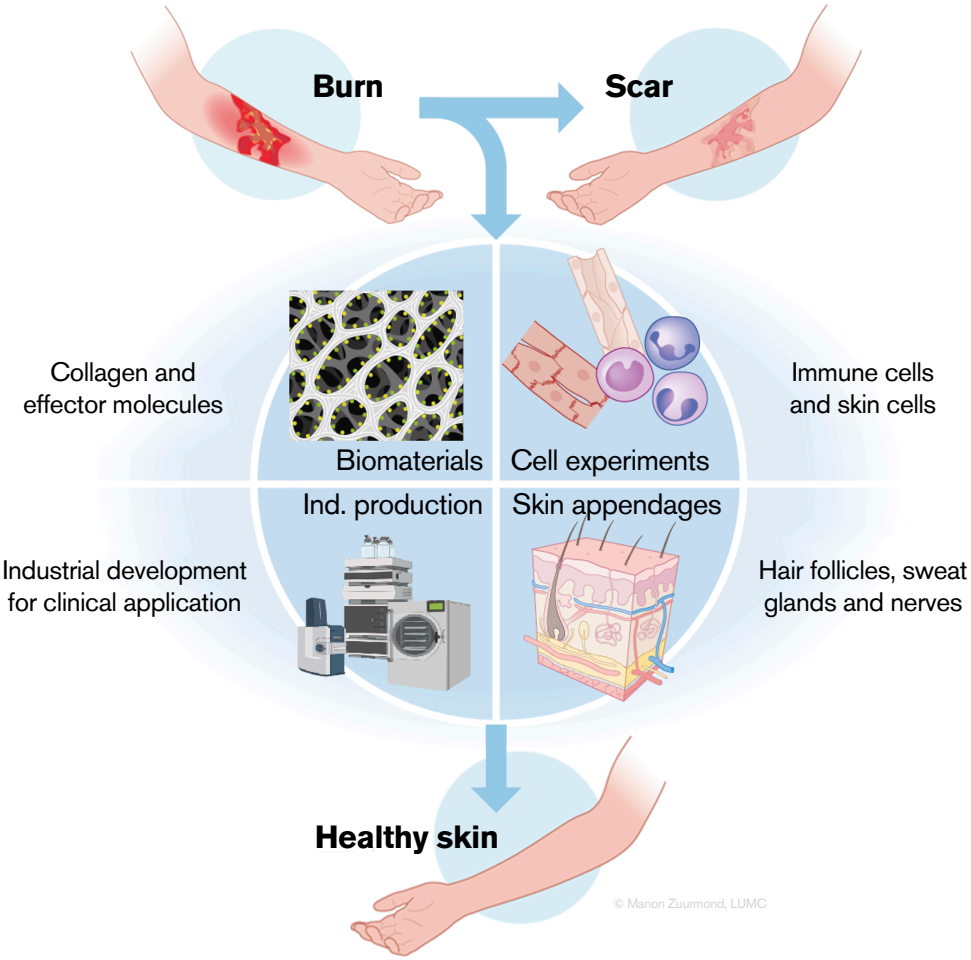
SkinTERM

Skin Tissue Engineering and Regenerative Medicine

Special issue about the experiences and research of Early Stage Researchers within the EU Innovative Training Network



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SkinTERM Consortium

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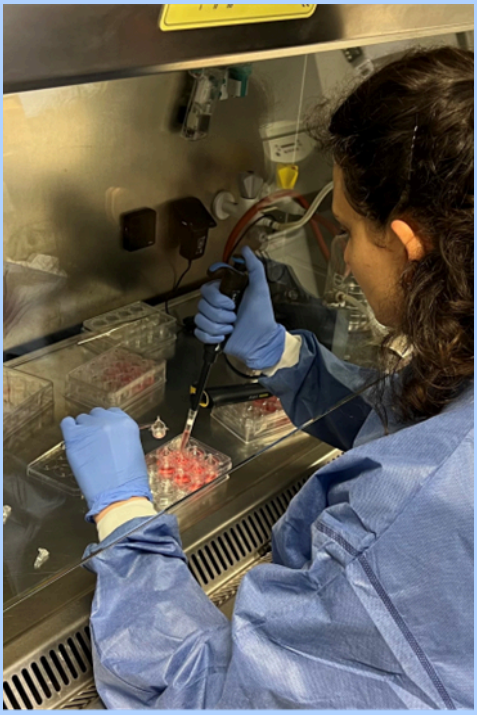
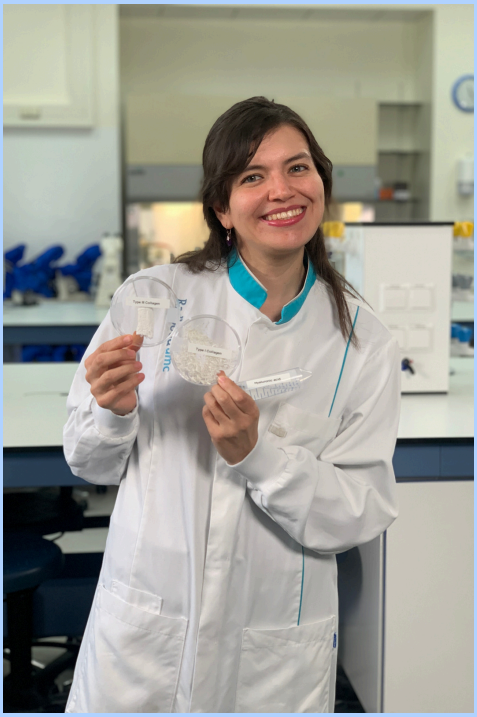
Special issue





Message from the Coordinator

A New Era in Skin Regeneration?

Welcome to the SkinTERM network, a pioneering consortium of research groups that aims to evolve the future of wound healing and tissue engineering. This collective effort brought together experts from diverse fields such as cell and molecular biology, regenerative medicine, biomaterial design, and tissue engineering, all working towards a singular, transformative goal.

At the heart of the SkinTERM project lies a bold ambition: to shift the default adult healing mechanism from repair, typically associated with scarring, towards a regenerative process that mirrors the flawless healing seen in early human development. This is no small task. However, the SkinTERM network is equipped to work on this challenge.

One of the most inspiring aspects of the SkinTERM network is its commitment to collaboration, which stands at the very core of its success. This network is not just a collection of isolated research projects but a vibrant, cross-disciplinary and cross-sectorial partnership that spans seven different countries. By pooling together diverse expertise, SkinTERM fosters an environment where ideas can cross-fertilise, leading to innovations that are greater than the sum of their parts. The collaboration between academic and industrial partners is especially noteworthy, with five industrial partners playing a crucial role in the research and training programs. These partnerships ensure that our early-stage researchers (ESRs) receive training that is both versatile and supra-disciplinary, bridging the gap between academic excellence and practical, real-world applications.

The SkinTERM research program is designed to provide outstanding training opportunities that prepare our ESRs to advance in the field of regenerative medicine. All partners deeply invested in the training process, with each leading courses and workshops that integrate cutting-edge scientific knowledge with business wit. Moreover, the international dimension of the SkinTERM network is exploited to the fullest, encouraging the translational mobility and collaboration of our researchers across borders. Our ESRs take part in at least two secondments, with those at academic institutions visiting industrial partners to gain firsthand exposure to a business environment. These secondments act more than just an opportunity for professional development; they are an essential component of our integrated approach, ensuring that our researchers are well-versed in international, intersectoral, and interdisciplinary collaboration.

Although mostly investigating scientific advances, the knowledge and technologies emerging from the SkinTERM network holds the promise of transforming how we manage scars, and engineer tissues, ultimately leading to therapies that promote true regeneration rather than mere repair.

Thank you to all twelve early-stage researchers for joining us on this journey and investing in their future by taking up a PhD project abroad. The path to perfect skin regeneration is complex, but with the collaborative spirit of the SkinTERM network and the dedication of our ESRs we are confident that we are paving the way to a future where scarless healing may just become reality.

Sincerely,

Dr.ir. Willeke Daamen
Coordinator MSC-ITN SkinTERM

Early Stage Researcher's SkinTERM Journey

SkinTERM stands for Skin Tissue Engineering and Regenerative Medicine and aims to convert skin repair to skin regeneration. Skin repair in adults results in contraction and scarring. The consortium aims for scarless skin regeneration and improvement of wound healing, which will have a significant impact on healthcare and quality of life.

This innovative training network is a EU Horizon 2020 Marie Skłodowska-Curie Actions funded project. Early stage researchers in this programme are trained to become entrepreneurial, multidisciplinary and intersectorially scientists who will be able to drive the research area further towards clinical translation in Europe.

The scientific projects of SkinTERM includes cutting-edge in vitro and ex vivo technologies and tools in molecular biology, cellular biology, proteomics, tissue engineering, biomaterial design, compound screening and model systems. Skin organogenesis is propagated by key extracellular matrix elements of foetal and non-scarring species and by employing (stem) cells from relevant cellular origins. Biomaterials and skin substitutes are being developed with functional hair follicles, sensory nerves, and sweat glands.

Twelve highly motivated early stage researchers from all over the world are working in the SkinTERM program. A versatile research training is provided on interrelated fields such as, biomaterials, tissue engineering, skin biology, regeneration, medical devices and advanced therapies medicinal products, in addition to soft skills. Industrial partners also contributed to the cross-sectorial training program.

Read about the experiences and achievements of our twelve ESRs in their SkinTERM journey

Mesenchymal Cells in Scar Free Skin

Madalena studies cells from three different origins: burn wound tissue, fetal skin and adult skin.

MADALENA PINTO GOMES

Madalena Pinto Gomes is a biomedical engineer and PhD student at the Amsterdam University Medical Center in the Netherlands. She is part of the Tissue Function & Regeneration program from Amsterdam Movement Sciences. Madalena also works in close collaboration with the Alliance of Dutch Burn Care in Beverwijk, the Netherlands.

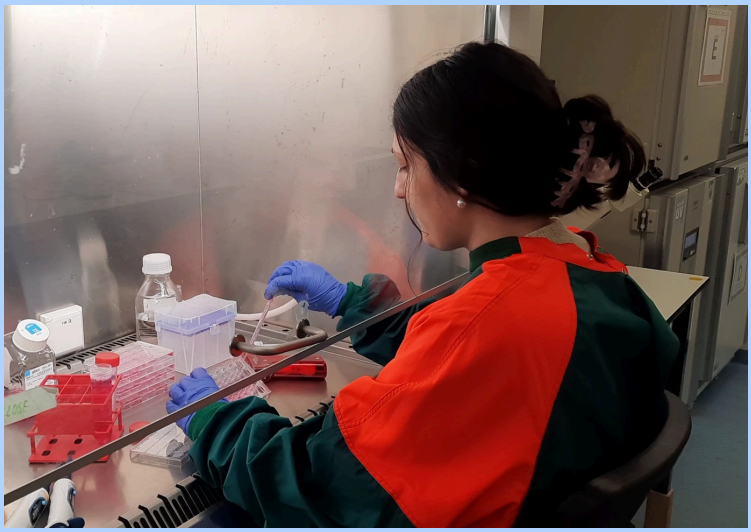
When an injury occurs, skin tissue is lost in the damaged area. Mesenchymal cells build new tissue by creating new extracellular matrix which acts as support for skin cells to populate the wound area. In the lab, Madalena investigates how mesenchymal cells and their extracellular matrix can steer scarless wound healing. Madalena focuses on studying cells from three different origins: burn wound tissue, fetal skin and adult skin.

The devastating consequences of burn wounds

Every year, 11 million people worldwide suffer from burns requiring medical care. Beyond the immediate pain, survivors face a lifetime of scars, which can bring a panoply of long-term problems. For example, restrictions in movement, itching, discomfort, impaired sweating and temperature regulation, emotional distress, and even social stigma. Madalena studies mesenchymal cells isolated from the tissue of these burn wound patients while they are still healing and no scar has yet formed. This creates opportunities to steer research results towards improving the quality of life of these patients.

The miracle of fetal regeneration

The human fetus can regenerate its skin completely up to week 22 of gestation. All skin layers, hair follicles and sweat glands come back as if nothing happened. But how does this phenomenon happen? What are the secret factors that allow a scar free healing? These are the questions Madalena is trying to answer with her research. The aim is to apply this knowledge to create novel regenerative therapies to treat burn wound patients and possibly other skin defects.



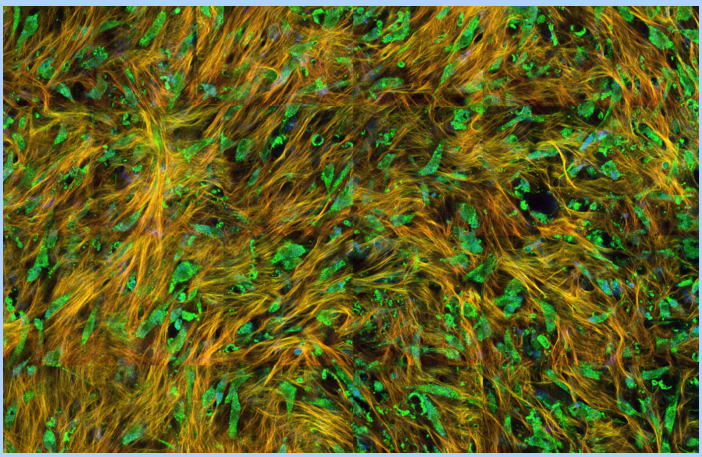
Scar free healing: secret ECM components

Madalena cultures mesenchymal cells stimulating them to produce extracellular matrix, abbreviated as ECM. Madalena showed that fetal ECM, opposed to wound tissue derived ECM, led to a more scar free "finger print" of mesenchymal cells. Depending on the origin of mesenchymal cells, ECM has a different composition and structure.

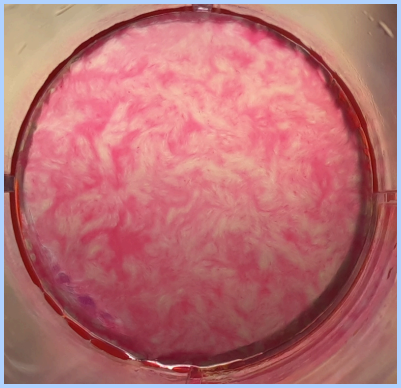
Madalena focused on comparing the composition of the ECM of three different mesenchymal cell populations: burn wound tissue, fetal skin and adult skin. Which components are unique, highly abundant or minimal in fetal skin? And in wounded skin? By answering these questions Madalena could identify several components that might promote skin regeneration if added to or inhibited in the wound area. By comparing mesenchymal cells, Madalena also identified cellular mechanisms that potentially contribute to scar free healing.

Building a novel dermal substitute

From the identified components, Madalena selected the one which held the highest promise for scar free healing and that had not been explored in the pharma and medical devices industry yet. Madalena is currently working on creating scaffolds functionalized with such components and aims to test these in the lab. If successful, this scaffold could lead to a new dermal substitute in the future.



Fetal mesenchymal cells and their produced ECM



ECM stained with eosin

“In this last stage of my PhD, I have focused on only one component from all those I identified as potentially interesting. I really hope other researchers can focus on other possible novel components identified through this work.

Science is never finished, there is always improvements to be made, new knowledge to be unraveled. We support and trust in each other's work to advance science. SkinTERM is exactly that. We work and learn together with one main goal: skin regeneration. I am truly happy we can contribute to this immense millennia-long chain reaction we call science.

SkinTERM seeks to apply this knowledge to industry, because the true beauty of science lies not on its pursuit but in the profound changes it brings to society.”

Further reading

Gomes MLNP, Krijnen PAJ, Middelkoop E, Niessen HWM, Boekema BKHL. Fetal Skin Wound Healing: Key Extracellular Matrix Components and Regulators in Scarless Healing. J Invest Dermatol. 2024 Aug 16:S0022-202X(24)01863-3. doi: 10.1016/j.jid.2024.05.027. Epub ahead of print. PMID: 39152955.

Making Skin Elastic Again

The elastic fibre network is lost with severe wounds and not restored as it was prior wounding.

ROMAN KRYMCHENKO

Collagen-elastin skin substitutes

Roman Krymchenko works on identification and application of specific elastin hydrolysates for scarless skin regeneration at Radboud university medical center (Nijmegen, the Netherlands).

Roman's research in skin regeneration field

As a chemist and biologist, Roman has always been curious about how we can improve people's lives by making them healthier and free of medical problems. The development of every medicinal product or medical device is a unique and fascinating journey. It starts from the first spark of an idea and progresses through research, discoveries, and large-scale manufacturing to eventually help countless people in need.

One major issue in healing of severe wounds is the limited elasticity of healed skin, which can restrict movement in the affected areas and have an unpleasant appearance. The elasticity of our skin depends on elastic fibers. These fibers are a crucial component found in organs that undergo repetitive stretching, such as the lungs, blood vessels, and skin. Unfortunately, once elastic fibers are destroyed, our body cannot properly regenerate them. This is where this research project aims to make a significant difference.

Roman's research started with the preparation of soluble elastin substances designed to stimulate the regeneration of elastic fibers. The initial steps involved identifying how to create different compounds and determining the best approaches to achieve this. Once the compounds were developed, he conducted extensive analyses to confirm their purity and composition. Furthermore, it was ensured that procedures were reproducible, consistently yielding the same compounds.

After developing these active molecules, he moved on to testing their effects. Before thinking about human trials, more knowledge needed to be obtained in the lab.. He cultivated fibroblasts and macrophages and evaluated the substances' effects on extracellular matrix production, fibrosis markers and differentiation of macrophages. Dermal fibroblasts showed that collagen deposition was not altered with elastin preparations. Specific elastin preparations showed potency to stimulate macrophage differentiation.

After identifying the best candidates, he created special skin substitutes. These substitutes underwent rigorous mechanical and chemical testing, followed by further testing with human cells and small live organisms.

The largest challenges in Roman's research

He is confident that the project will definitely bring us a step closer to achieving scarless skin regeneration. While he is doing his best to make the elastin solutions effective, research is not always about success. It involves numerous attempts and learning from each one. Each try can illuminate other aspects that are not well-known, guiding other researchers and helping them avoid the difficulties or mistakes that were encountered. So, his solutions are definitely worthy to investigate.

One of the biggest challenges in our research is ensuring that the regenerated elastic fibers function like the natural ones. While substances can be created that stimulate regeneration, replicating the complex structure and properties of natural elastic fibers is a significant challenge. Additionally, translating findings from the laboratory scale to clinical applications and large scale production involves rigorous testing and regulatory approvals, which can be time-consuming and complex. Despite these challenges, the potential benefits for patients is a key driver to persevere and innovate continuously.

“I am incredibly proud that our SkinTERM project is both multidisciplinary and international. This collaboration allows me to learn new techniques and approaches, and I have the incredible opportunity to cooperate with other researchers from around the world. I have completed three secondments at different institutions in various countries, which has enormously broadened my horizons.”

Futher reading

Krymchenko R, Coşar Kutluoğlu G, van Hout N, Manikowski D, Doberenz C, van Kuppevelt TH, Daamen WF. Elastogenesis in focus: navigating elastic fibers synthesis for advanced dermal biomaterial formulation. Adv Healthc Mater. 2024 Jul 11:e2400484. doi: 10.1002/adhm.202400484

Hair Follicles in Skin Constructs

Masi is working to engineer new hair follicles to incorporate into skin grafts.

MASOUME YOUSEFI

Masi Yousefi is a PhD candidate at Durham University, Durham, UK. As an early stage researcher, she is undertaking one of the most long-standing challenges in human skin tissue engineering.

For many years, researchers have been creating skin constructs that replicate the two main layers of skin, an underlying dermis with epidermis on top. More recently much greater focus has been on seeking to better represent the true anatomical and physiological complexity of skin by the inclusion of other key tissue and cellular components. Of these, hair follicles are arguably the most important missing structures. Masi's research aims to combine key cell types in three dimensions to create proto-follicles that can be incorporated into skin grafts and which, when transplanted with the grafts, will make hair.

The role of hair follicles

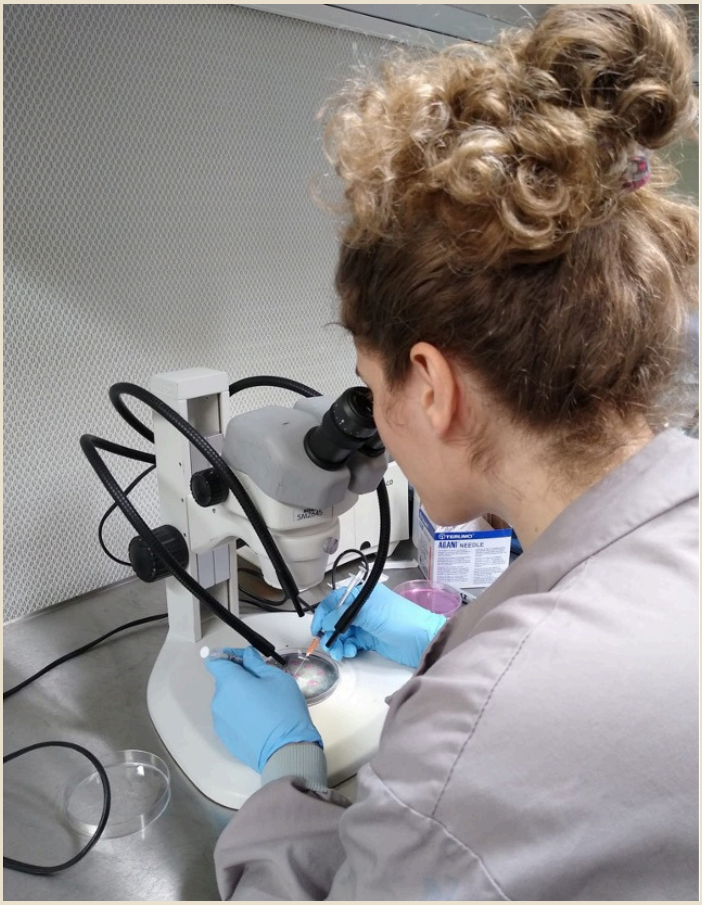
Until relatively recently the role of hair follicles in human skin was considered to be more cosmetic than functional, but recent work has demonstrated that follicles play a key role in skin physiology. In a wound healing context there is strong evidence that they reduce scar formation and can even elicit nerve and blood vessel formation. Introducing follicles into grafts therefore has the potential to produce an incremental improvement in skin replacement surgery.

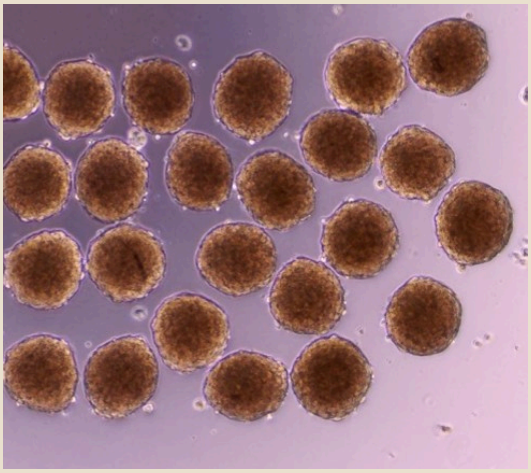
"My research is dedicated to one fascinating goal: creating new hair follicles in the lab. Hair follicles do much more than just grow hair. They play a crucial role in keeping our skin healthy and healing wounds. By recreating these tiny, complex structures, I hope to improve skin grafts as well as to open doors to new treatments for hair loss."

Masi's research strategy

Masi works with a special developed technique to create early-stage hair follicles, called “proto-follicles.” To build these, she starts with small clusters of cells derived from hair follicles, known as dermal papilla cells. She carefully grows these clusters to form a spherical shape, mimicking how hair follicles naturally develop. After a few days, epithelial cells are added to create layered structures that resemble the end-bulb or “engine room” of real hair follicles.

The results so far are very promising. In her structures after 3 to 7 days, Masi observed that the cells started to organize themselves in a way that closely mimicked how real hair follicles form. They began to create important layers, with one layer showing signs of active growth, just like in natural hair follicles. These models also produced key components that are essential for hair growth, including specific proteins that help structure and support the hair. In particular, she detected the presence of a particular protein, trichohyalin, which indicates the start of hair fibre development and differentiation.





Dermal papilla spheres

Double layered sphere with epithelial cells covering dermal papilla sphere

Masi visited the University of Zurich to incorporate the hair model into a skin construct. She is currently working on defining the most suitable construct for her models. Together with the CUTISS AG company she will develop a standard operating procedure for the developed technology.

Future directions

Masi aims to perform preclinical experiments to assess whether incorporation of proto-follicles follicles in grafted skin models will generates robust hair growth and to assess to what extent these follicles influence the cellular and extracellular environment in surrounding skin.

Scarless Healing in Acomys

The African spiny mouse has a unique ability to heal its skin without scarring.

HAARSHAADRI JAYAPRAKASH

A colony of African spiny mice, known as Acomys

Haarshaadri Jayaprakash is a PhD researcher at the University of Algarve, working in the faculty of medicine and biomedical sciences. His research focuses on the African spiny mouse, also known as Acomys, which has a unique ability to heal its skin without scarring. This remarkable regenerative capability provides a natural model to understand how mammals, including humans, might improve their own healing processes.

Decoding scarless healing in Acomys

Unlike most mammals, Acomys can regenerate its skin without leaving scars. This makes it a valuable model for studying how to achieve similar results in humans. During wound healing, Acomys manages inflammation better compared to ordinary mice (Mus). This controlled immune response is crucial for effective healing. The distribution and activity of immune cells like macrophages, as well as the expression of proteins called cytokines, differ between Acomys and Mus. Understanding these differences helps in decoding the mechanisms behind scarless healing.

The extracellular matrix (ECM) is a network of proteins that supports various cell functions. In Acomys, the ECM is geared towards regeneration. Recent studies have identified specific signaling pathways and activation states of fibroblast — cells crucial for tissue repair — that are unique to Acomys. By comparing the skin healing processes of Acomys with Mus, researchers aim to uncover fundamental differences that could revolutionize our approach to scarless healing. This involves using decellularization methods, which removes cells from skin tissues to leave behind the ECM. Studying this residual matrix allows researchers to conduct detailed experiments on how it interacts with cells.

“The SkinTERM collaboration helps in pushing forward research and personal growth in the skin regeneration field. It expands knowledge on how different labs across Europe function and how questions and problems in biology are tackled in academia and in industry.”

Exploring the ECM interactions in Acomys and Mus

The process of decellularization is a technique that removes cells from skin tissues while preserving the essential structural proteins of the ECM. This method not only helps to prevent immune rejection in animal studies but also allows researchers to conduct precise experiments on how cells interact with the matrix. After decellularization, the ECM from both Acomys and Mus is repopulated with fibroblasts from each species. Initial studies have revealed that fibroblasts from Acomys perform better on their native matrix, suggesting that the Acomys ECM offers a superior environment for regeneration.

The next phase of research involves surgically implanting decellularized tissues from one species into the other. By analyzing the infiltrated cells through techniques like RNA sequencing and histology, Haarshaadri aims to uncover deeper insights into the regenerative mechanisms at play.

Collaborations with cutting-edge labs

Funding from the EU Horizon program has been instrumental in advancing Haarshaadri’s PhD research, offering him an unique opportunity to collaborate with leading experts across Europe. Through this consortium, Haarshaadri has had the privilege of accessing state-of-the-art labs and benefiting from specialized knowledge that has significantly enriched his work.

Haarshaadri's journey took him to Helmholtz Munich, where he explored the use of omics technologies to advance his research objectives. His visit to the Netherlands, specifically the Association of Dutch Burn Centres, allowed him to refine his techniques in decellularization and experimental assays. In Zurich, at CUTISS AG, Haarshaadri delved into human precision medicine for skin wound healing and gained a deeper understanding of the regulatory frameworks involved.

Potential impact of Acomys research

This research sheds light on the regenerative potential of mammals, offering valuable insights for medical treatments of wounds, burns, and degenerative diseases in humans. By decoding how Acomys achieves scarless healing, strategies could be developed in the future that could enhance human healing processes, minimize scarring, and boost tissue regeneration.

Pigmented Skin Substitute

ZUZANA OULEHLOVA

“Skin pigmentation is not only responsible of the color of our skin, but also provides essential protection against UV light, functioning as a natural suncream. Without pigmentation, the skin is more susceptible to sunburns and to disorders associated with premature aging of the skin; such as skin thinning and wrinkling, and also increased risk of cutaneous cancers.”

Zuzana’s goal is to develop a pigmented skin substitute for patients with severe skin burns

Zuzana Oulehlova is an industrial PhD student at the University of Zurich, doing her PhD project at CUTISS AG, a Swiss tissue engineering start-up company. Zuzana’s goal is to develop a pigmented skin substitute for patients who suffered severe skin burns.

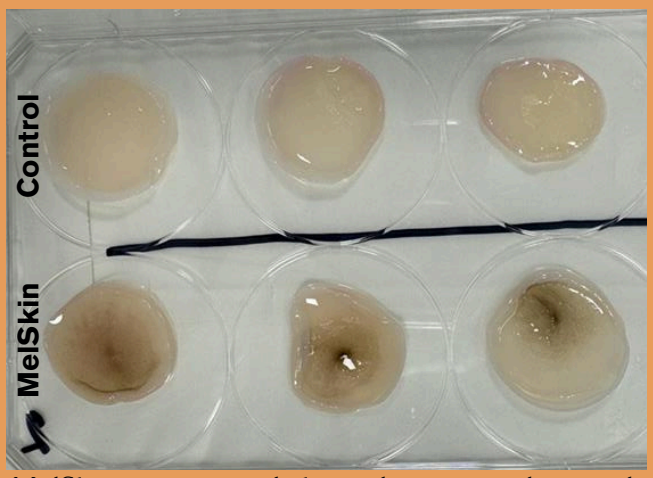
Personalized skin grafts

Rapidly available skin grafts are crucial for improving the outcome of severe burn patients and are vital in reducing the incidence of atrophic scars. CUTISS AG has developed denovoSkin™, a personalized skin tissue currently under clinical evaluation. The skin engineered grafts are manufactured using patient’s own cells, namely keratinocytes and fibroblasts, combined with a collagen hydrogel matrix.

While the denovoSkin™ results in a functional skin tissue, it lacks pigmentation component of the skin. Burn injuries treated by transplantation of denovoSkin™ can remain unpigmented. Despite the lack of pigmentation, the benefit of rapid transplantation with this engineered skin remains highly favorable. Additionally, the standard treatment of large burn injuries, based on autologous transplantation of meshed skin, also comes with pigmentation disorder.

Addressing the pigmentation gap

Zuzana’s research mainly focuses on adding melanocytes to denovoSkin™. Melanocytes are specialized cells that are responsible for producing melanin - the pigment that determines skin color and acts as a UV filter. Zuzana aims to establish a manufacturing protocol for bioengineered skin consisting of patient’s own melanocytes, keratinocytes and fibroblasts embedded in a collagen matrix. Before the first human trial, the pigmentating capacity of melanocytes in bioengineered skin must be characterized in vitro as well as in animal models. Safety studies to rule out any tumorigenicity risk associated with melanocytes are required as well.



MelSkin - pigmented skin substitute and control

Manufacturing challenges

To manufacture the bioengineered skin substitute, it is necessary to first isolate and expand the patient's cells. Establishing a primary culture of human melanocytes can be challenging. This is because the number of melanocytes in human skin, and consequently in the starting skin biopsy, is very low as melanocytes represent about 1% of the epidermal cells versus a majority (99%) of keratinocytes. Furthermore, melanocytes tend to proliferate quite slowly. When cultivated outside of their natural micro-environment, they also tend to lose their original shape and their ability to produce melanin.

Zuzana's project focuses on optimizing the isolation and in vitro culture conditions of human primary melanocytes, as well as the process of incorporating them into the bioengineered skin substitute. A broad range of analytical techniques, including flow cytometry, western blot, quantitative PCR, immunofluorescence, and histology staining, are employed to thoroughly characterize and evaluate the phenotype, functionality, and safety of both the in vitro expanded melanocytes and the engineered skin substitute.

The aim of Zuzana's research is to develop cell therapy addressing pigmentation disorders associated with burn injuries. Achieving this not only requires tissue engineering innovation but also strict adherence to good manufacturing practice standards to ensure the consistent efficacy, quality, and safety of the engineered tissue, as well as compliance with the quality standards of national drug evaluation agencies.

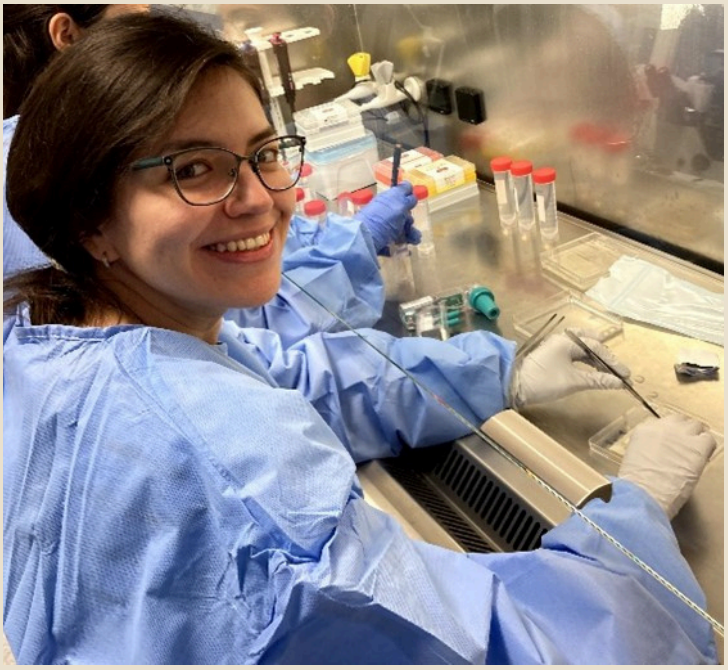
Future outlook

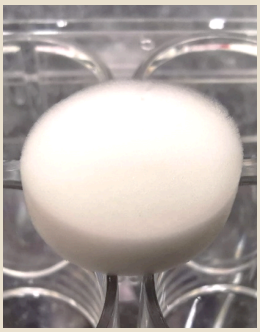
Beyond burn injury, cell therapy with melanocytes to restore skin pigmentation can also be extended to other pigmentation disorders of the skin, like vitiligo. Vitiligo unpigmented lesions result from local loss of melanocytes. Some vitiligo lesions can remain localized but can also extend to the whole body resulting in generalized depigmentation. This dermatological disorder affects between 0.5 and 1.5% of the population worldwide. By creating a homogeneously pigmented skin graft, Zuzana and the CUTISS AG team hope to extend the scope of the melanocytes cell therapy solution to patients suffering vitiligo disease.

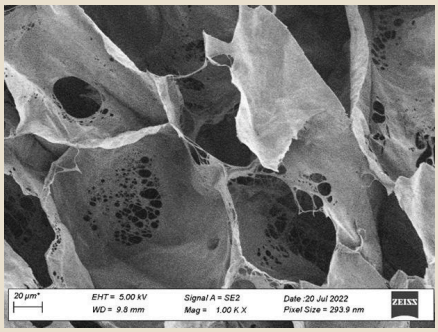
Mimicking Fetal Skin

Nancy creates skin substitutes that mimic the properties of fetal skin to promote scar-free healing

NANCY AVILA MARTINEZ







Collagen scaffold with fetal components and its inner porous structure

Nancy Avíla is a tissue engineer at Radboud university medical center in Nijmegen, the Netherlands. In the Matrix Biochemistry research group, focus lies on the creation of biomaterials to restore damaged tissues. Likewise, her groundbreaking work aims to revolutionize burn treatment by preventing scarring. Deep and extensive burns often result in severe skin loss, requiring skin replacements.

Unfortunately, current market solutions fail to restore skin functionality and cause scars and contractures that may limit patient mobility. Remarkably, our skin can heal without scars during pregnancy while we are in the womb. Nancy's innovative research seeks to replicate this scar-free healing by mimicking some aspects of fetal skin, potentially transforming burn recovery and improving patients' lives.

The secret of scarless fetal skin healing

Our skin's primary building block is a thick fibril called type I collagen. In contrast, fetal skin has a different structure with an abundancy of thinner type III collagen fibrils, hyaluronan (a sugar that keeps our skin moisturized), and sonic hedgehog (a growth factor aiding in a.o. hair growth). In Nancy's research, she bound the last compound with a linker called RGTA (ReGenerating Agent), a polysaccharide provided by the company OTR3 in France.

She investigates whether these components foster a softer and regenerative environment making it easier for cells to close the wounds efficiently.

“When I was 17, I participated in a competition to raise funds for children with burns. That experience opened my eyes to the profound impact burns have on people's lives, emotionally, economically, and functionally. As adults, our skin heals with scars, but before 24 weeks of gestation, fetal skin regenerates mostly scar-free. Research has shown that the composition of our skin varies at different life stages. This discovery could lead to significant improvements in the treatment and outcomes for burn victims.”

Fetal-like skin substitutes for regeneration

In the lab, Nancy produced skin substitutes using a base of type I collagen with the fetal components incorporated. After meticulously examining these biomaterials for morphology, chemical composition, and mechanical properties to ensure they meet rigorous quality standards, she assessed their biological activity by adding skin fibroblasts and macrophages to the substitutes, evaluating their safety, gene expression, and immune profile. Finally, promising candidates undergo preclinical trials in small animals to simulate a wound and observe the healing process.

The power of collaboration: driving innovation in scar-free healing

After extensive testing, she discovered that fetal-like skin substitutes moved towards reduced scarring genes and increased pro-healing cells at the cellular level. Initial findings revealed improved wound closure with less contraction. This progress owes much to collaboration with academic and industry partners both in the Netherlands and abroad, including the SkinTERM consortium and colleagues at Radboudumc. Thanks to these collaborative efforts, new techniques have been applied to this research.

Future directions

Unfortunately, adult human skin cannot yet heal without scars, but if we can provide surgeons with a readily available product that closes wounds as if we were back in our fetal stage, patients may restore their mobility and rejoin an active society. This research still needs further validation both preclinically and at the clinical level, and collaborations with hospitals and burn centers will be essential for these trials. With continued support and innovation, we can bring this innovative solution closer to reality, offering new hope for burn victims worldwide.

Futher reading

Avila-Martinez N, Gansevoort M, Verbakel J, Jayaprakash H, Araujo IM, Vitorino M, Tiscornia G, van Kuppevelt TH, Daamen WF. Matrisomal components involved in regenerative wound healing in axolotl and Acomys: implications for biomaterial development. Biomater Sci. 2023 Sep 12;11(18):6060-6081. doi: 10.1039/d3bm00835e

Fibroblasts in Skin Organoids

George investigates fibroblast development and their response to wounding using skin organoids.

GEORGE VOGELAAR

George Vogelaar is a biomedical doctoral researcher at the Institute of Regenerative Biology and Medicine (IRBM) at Helmholtz Munich and Ludwig-Maximilians University of Munich, Germany. As part of the SkinTERM consortium, George aims to better understand the intricacies of skin fibroblasts, which are cells that play a crucial role in scarring.

George is motivated by his natural curiosity for science and his drive to help people with severe scarring, like his uncle who suffered severe burns after a gas-station explosion. He hopes that with his research, reconstructive surgery can reach new heights and help people like his uncle.

Unlocking the secrets of fibroblast development

Fibroblasts are cells that are responsible for producing the extracellular matrix, the supportive framework that gives skin its strength and elasticity. Despite their crucial role, much about fibroblast development remains a mystery, and their subtypes are still a topic of scientific debate. Understanding these cells better is key to advancing future treatments for scars and burns, paving the way for more effective healing strategies.

To research human skin fibroblast development trajectories, a human skin organoid model was created derived from induced pluripotent stem-cells (iPSCs). These lab-grown skin organoids are incubated for 30 to 150 days and closely studied. By employing advanced techniques such as single-cell transcriptomics to analyze gene expression, imaging with antibodies to track developmental markers, and protein extraction to observe key changes over time, George is uncovering the intricate processes that shape fibroblast development.

“We are currently entering a new era of medical research, where mini-organs with human cells can be made to test treatments and to analyze their makeup. I could never have done this without the network created by the SkinTERM project. Learning directly from the experts in the field has progressed by career considerably and I’m sure to develop my network and my skills in the future.”

The future of skin research: organoids

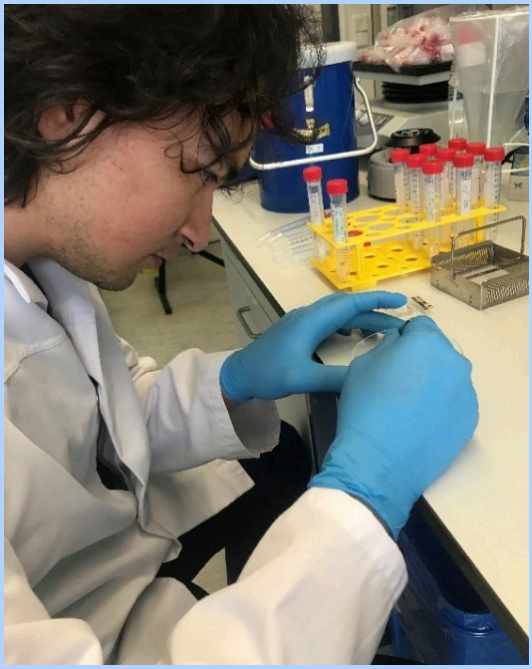
George believes the human skin organoid model will become a pivotal tool in skin science. Not only does it have the potential to reduce reliance on animal testing, but it also generates data that more accurately reflects human biology. One of his key findings revealed that the most significant changes in fibroblast behavior occurred over a short period of just 10 days.

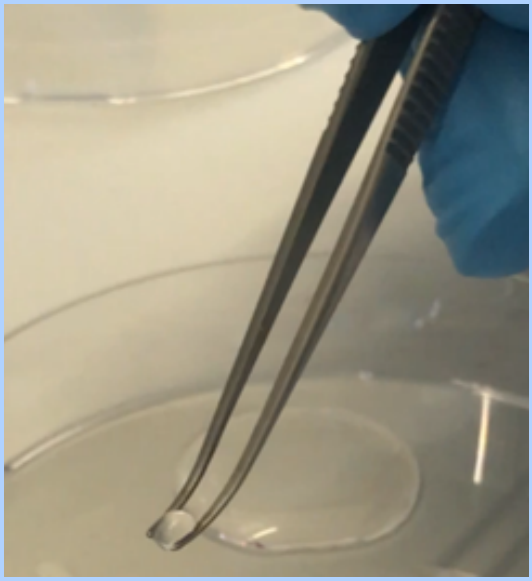
In his experiments, George discovered that fibroblasts within these organoids respond to wounding—mimicked by a needle puncture—by transforming into myofibroblasts and migrating toward the wound site, much like they do in real human skin. However, these organoids lack an immune system, which normally influences the healing process. To better simulate this natural environment, George introduced macrophages after wounding and observed something remarkable. When macrophages were present, the number of fibroblasts remained consistent between wounded and unwounded samples. In contrast, without macrophages, the number of fibroblasts surged, suggesting that even in vitro, with just a single immune cell type, human cells can influence the process of skin repair.

Challenges and hope for the future

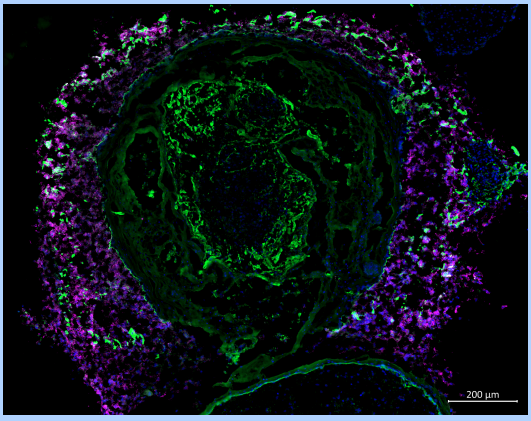
George's biggest challenge now lies in managing the vast amounts of data generated by his methods, which create extensive databases that require meticulous curation. Fortunately, with the support of data science experts, he is confident he will successfully navigate this hurdle before completing his PhD.

Currently, George is focused on analyzing single-cell transcriptomics data from 75-day-old human skin organoids, comparing a control group with four conditions that influence fibroblast development. He hopes this data will hold the key to unlocking a regenerative rather than a scarring phenotype. This breakthrough could pave the way for new medical treatments that help doctors heal severe scars and burns more effectively.





An organoid being moved with pincers



Fluorescent image of skin organoid

Restoring Touch and Life

Mahrukh develops advanced skin substitutes that restore natural sensation and hair growth.

MAHRUKH RIAZ

“It is a mission filled with hope and compassion. Imagine the pain and isolation of losing the ability to feel the touch of a loved one, or the warmth of the sun. For many people with severe skin injuries, this is a harsh reality—living with skin that may look healed on the outside but is numb and lifeless beneath the surface. This innovation could mean regaining the ability to feel and respond to their environment—something that current treatments fail to offer.”

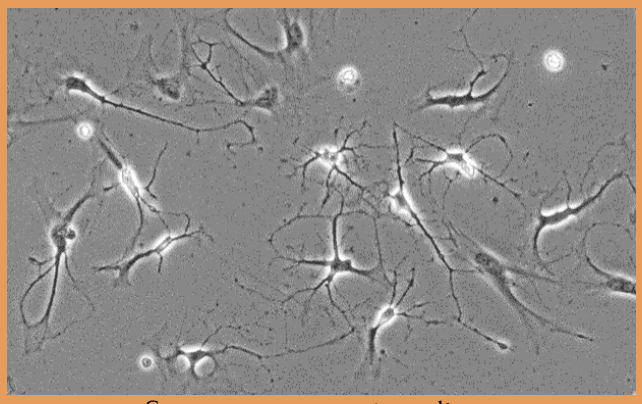
Mahrukh Riaz is at the cutting edge of skin regeneration research at the Tissue Biology Research Unit of the Children’s Hospital Zurich, Switzerland. Her work focuses on developing advanced skin substitutes that not only cover wounds but also restore critical skin functions, including sensation and hair growth. By exploring the interactions between blood vessels, sensory nerves, and hair follicles, Mahrukh aims to create skin substitutes that mimic natural skin, with the ultimate goal of bringing these innovative solutions to the market.

The sensation challenge in skin regeneration

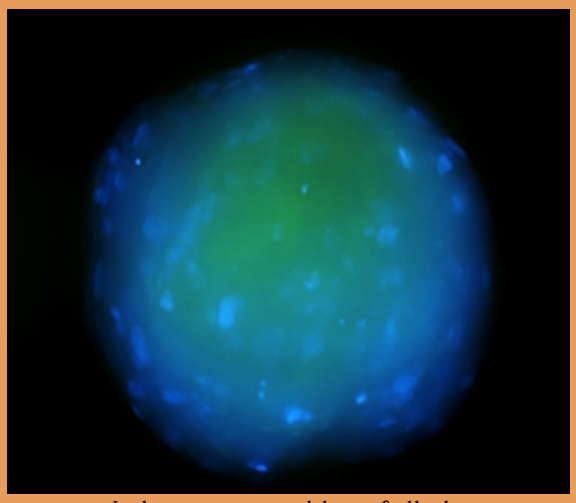
Severe skin injuries disrupt the intricate network of nerves, hair follicles, and blood vessels essential for normal skin function. These structures are crucial for sensation and hair growth, enabling the skin to detect subtle environmental changes, such as a light breeze or a gentle touch. However, deep skin injuries sever these connections, impairing the skin's ability to sense and respond to its surroundings. Existing skin grafts often fail to restore these functions, leaving patients with skin that looks healed but lacks sensation and hair growth.

Mahrukh’s innovative approach

Mahrukh is determined to address this challenge in skin regeneration. Her research focuses on developing skin substitutes that include deeper structures like nerves and hair follicles. The goal is to create a skin graft that closely mimics natural skin, restoring both sensation and the ability to grow hair in patients with deep skin injuries. This work holds the potential to provide a solution that goes beyond surface healing to fully restore skin functionality.



Sensory neurons in culture



Lab engineered hair follicle

The journey of creating advanced skin substitutes

Mahrukh's approach to skin regeneration begins with using natural human skin as a foundation. She carefully isolated various skin cells-such as fibroblasts, keratinocytes, and endothelial cells, each of which plays a crucial role in creating different layers of skin and forming blood capillaries. She cultivated these cells under controlled laboratory conditions to form distinct skin layers based on collagen hydrogels that closely resemble the natural structure of human skin.

The challenge in Mahrukh's research

One of the greatest challenges in Mahrukh's work is isolating and cultivating sensory nerve cells, a task that has long stymied researchers due to its complexity. These cells are crucial for restoring skin sensation, yet extracting and growing them outside the body is notoriously difficult. To overcome this, Mahrukh employed a specialized technique where she provided skin cells with specific nutrients, guiding them to develop into sensory nerve cells. She characterized these sensory nerves in terms of morphology and gene expression markers to compare with naturally occurring nerves. After confirming identity of sensory nerves, she integrated these nerves into her skin substitutes along with blood vessels.

Moreover, she incorporated hair follicle structures by employing dermal papilla cells isolated from the human scalp, enabling hair production in the regenerated skin.

Future impact

Through this innovative approach, Mahrukh is not just healing surface wounds but restoring essential sensory functions and the natural appearance of the skin. Her work offers a more comprehensive solution for those with deep skin injuries, potentially transforming lives.

Futher reading

Iqbal MZ, Riaz M, Biedermann T, Klar AS. Breathing new life into tissue engineering: exploring cutting-edge vascularization strategies for skin substitutes. Angiogenesis. 2024 Jun 6. doi: 10.1007/s10456-024-09928-6. Epub ahead of print. PMID: 38842751.

Proteomics in Rodent Models

Prerna researches key healing differences between the African spiny mouse and the ordinary mouse.

PRERNA KARTHAKA

Prerna Karthaka is a biomedical doctoral researcher at the Institute of Precision and Regenerative Medicine (PRM) at Helmholtz Munich and Ludwig-Maximilians University of Munich, Germany. At PRM, they employing cutting-edge multi-omics technologies and advanced pre-clinical models to explore the cellular and molecular processes behind lung fibrosis and regeneration. Their ultimate goal is to translate these discoveries into breakthrough therapies for prevention and regeneration. Similarly, Prerna's research focuses on uncovering the critical events that occur during the phases of wound healing by comparing two distinct rodent models: the scarring-prone ordinary mouse and the regenerative African spiny mouse.

Prerna's motivation in skin regeneration

As a biotechnologist hailing from India, Prerna has always been intrigued by the complexity of every aspect of all living organisms, every theory hypothesized and proven, every scientific discovery and marveled at the brilliance behind every innovation.

Her major incentive for pursuing the field of regenerative and tissue engineered wound healing therapies was her deep compassion for victims of pyro and acid attacks in India, being one of the top 10 countries facing this issue, and wanted to find a way to improve the lives of these victims and prevent their ostracization by society caused by their disfigurements.

The African spiny mouse – a marvel in the regenerative medicine field

It is a well-known fact that fetal organisms are capable of scarless regenerating entire limbs, an ability that is lost in adult mammals which undergo scarring processes known as fibrosis. In the context of deep cutaneous wounds, we are often left with a disfiguring fibrotic scar that can sometimes cause pain and limit mobility, thereby affecting quality of life.

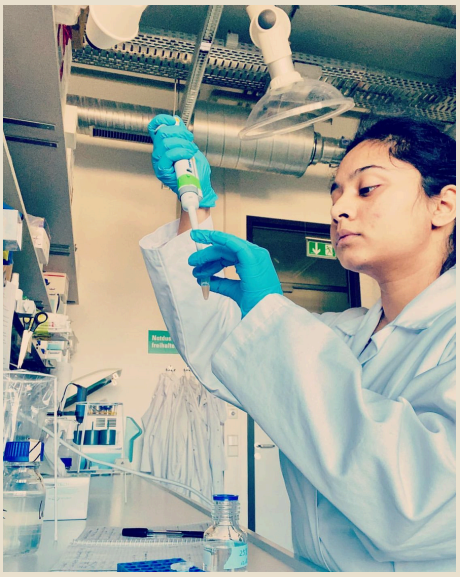
However, there are some mammals that have shown remarkable regenerative potential, such as the African Spiny mouse, otherwise known as Acomys cahirinus. These rodents have demonstrated the ability to scarlessly regenerate a variety of tissues (kidney, heart, spinal cord, muscles, skin) after grave injuries. Understanding the underlying molecular mechanisms (cells, genes, proteins and pathways) and identifying key therapeutic targets driving this regeneration is what Prerna's project aims to address.

“When I was a little girl, I came across a horribly disfigured woman begging on the dusty streets of Mumbai, India. Terrified, I asked her what had happened to her, to which she replied that someone had thrown acid on her face and due to her disfigurement, she was ostracized by society and had to beg on the streets. This opened my eyes to the very real issue faced by countless people in India and this is when I knew I needed to contribute in some way to helping these people. With a lot of pride I can say that the SkinTERM project has helped me achieve my dreams both personally and professionally.”

Prerna's proteomic analyses

Prerna’s research began with designing a time course wound healing experiment comparing the ordinary mouse and Acomys. The initial steps involved performing full thickness punch biopsies in these mice and collecting samples over a time course of 3, 5, 7, 14, 21 and 42 days post-wounding. Once the samples were collected, she conducted extensive bioinformatic analyses using data generated from proteomics, single cell transcriptomics and histology experiments to identify these molecular events occurring at each phase of the wound healing – hemostasis, inflammation, proliferation and remodeling.

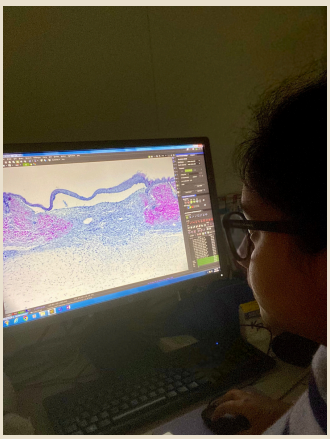
Proteomics results indicate certain wound healing proteins being differentially expressed in both species. Some pro-fibrotic proteins are being upregulated in Mus and downregulated or absent in Acomys. Results also indicate signaling pathways related to lipid metabolism and calcium regulation being regulated in Acomys, which suggests a regenerative phenotype. However, more research must be conducted to gather further knowledge before any functional trials.



The biggest challenges Prerna faced so far

Even though Acomys has been discovered and researched for its amazing healing potential in various tissues, it is still not extensively studied and is therefore a non-model organism without an established reference genome. There were significant challenges in optimizing experimental protocols in sample preparation as well as establishing bioinformatic pipelines in the analysis of the experimental data.

Prerna is confident that we are a step closer to achieving scarless wound healing having already identified key processes that potentially drive regeneration in this animal model. Moreover, performing functional experiments to validate her findings and also translate these results into a bench-to-bedside therapeutic will take time and patience.



Macrophages in Skin Healing

Different macrophages subtypes either promote scarring or support tissue regeneration

MUHAMMAD ZOHAIB IQBAL

“Macrophages are essential to how our bodies heal wounds. By steering these cells to promote healing with fewer scars, we can develop better treatments that help people recover more effectively from serious skin injuries. Our research goes beyond just closing wounds; it is focused on enabling the body to heal in a way that minimizes scarring and enhances quality of life."

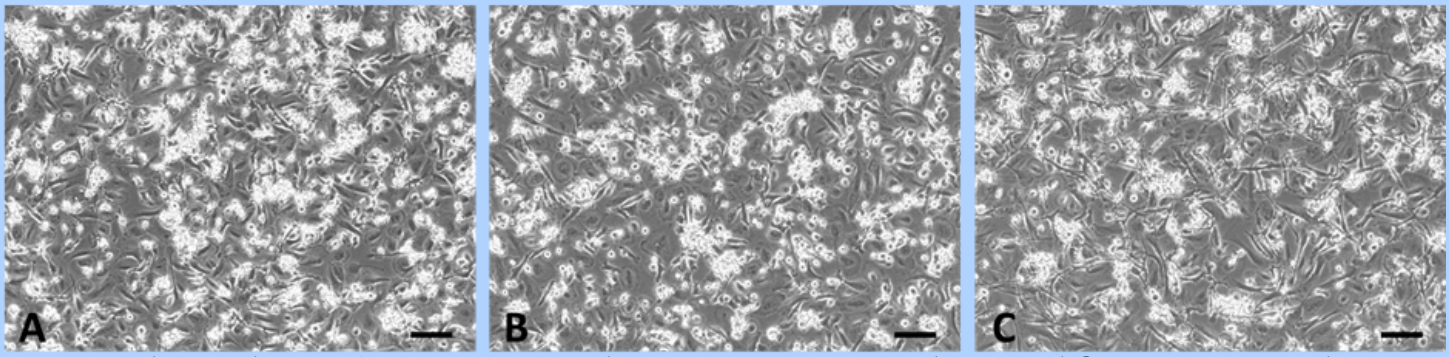
Zohaib Iqbal is a PhD student at the Tissue Biology Research Unit of the Children’s Hospital Zurich in Switzerland. His research is focused on enhancing skin healing to minimize scarring and improve outcomes for individuals with chronic wounds and severe skin injuries.

At the center of Zohaib’s research are macrophages, immune cells that are crucial to the body’s response to injury. These cells can either contribute to scarring or support tissue regeneration. Zohaib aims to better understand how different types of macrophages influence the healing process, with the ultimate goal of guiding them toward a response that favors scar-free healing.

Key challenges in Zohaib’s research

One of the most significant challenges in Zohaib’s research is translating promising laboratory results into effective real-world therapies. While it is possible to manipulate macrophages in a controlled lab environment, translating these results into human patients is far more complex. The human immune system is highly variable, with different patients responding in unpredictable ways to specific treatments. This variability makes it difficult to develop a general one-size-fits-all therapy for scar-free healing.

Another major challenge is to ensure that the treatment is safe and effective over the long term. Manipulating immune cells like macrophages involves intricate biological processes, and there is always a risk of severe side effects in human body. Therefore, Zohaib's project investigates the potential benefits of promoting regeneration with no harmful immune responses.



Macrophage subtypes: A represents M0 subtype, B represents M1 subtype, and C represents M2 subtype

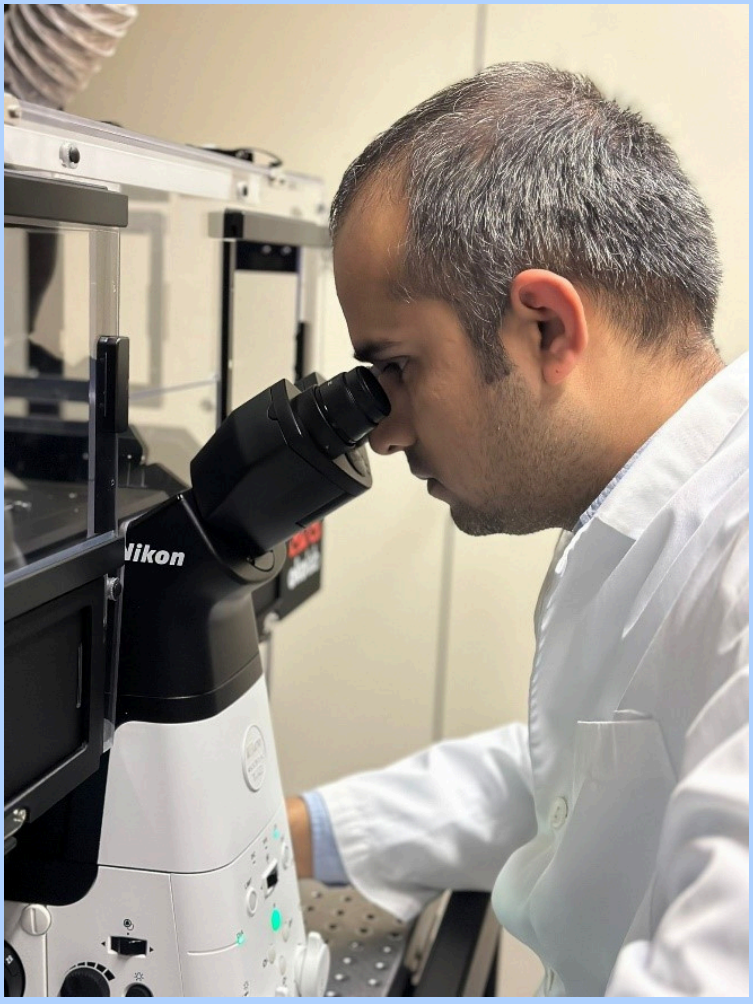
Lastly, the transition from experimental research to clinical application is a lengthy and costly process. Even if Zohaib's findings are successful in the lab, there will be significant hurdles in testing, refining, and eventually bringing these therapies to patients. Overcoming these challenges requires not only scientific innovation but also strong collaboration with clinicians and industry partners.

Future collaborations and potential impact

Zohaib's research is supported by collaborations with leading European institutions, including the University of Algarve in Portugal and MedSkin Solutions and Helmholtz Zentrum München in Germany. These partnerships are vital, providing access to advanced technologies and diverse expertise.

Zohaib's work could lead to new therapies that reduce scarring, offering improved healing options for patients with severe skin injuries. The potential to improve quality of life for these individuals makes this research an important step in the field of regenerative medicine.

Zohaib's research represents a significant effort to push the boundaries of regenerative medicine. While challenges remain, the potential impact of his work on the treatment of skin injuries is both promising and inspiring.



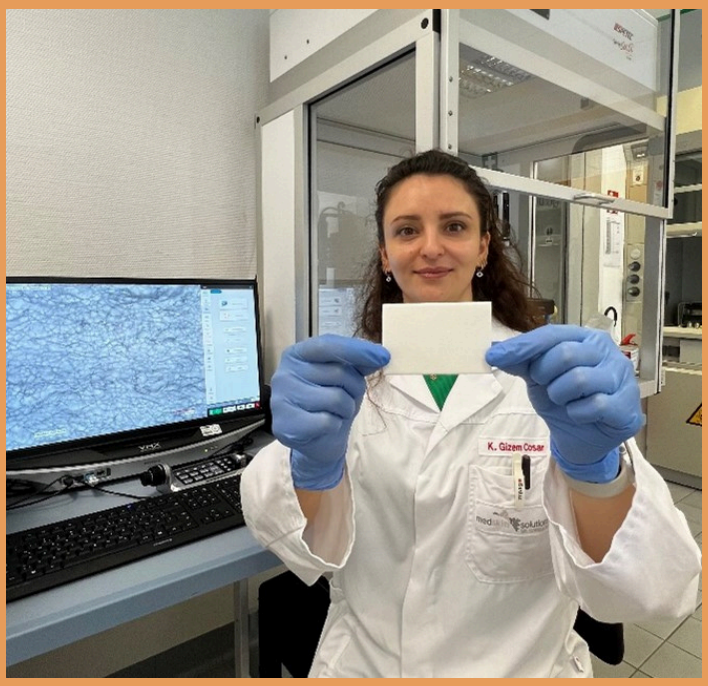
Futher reading

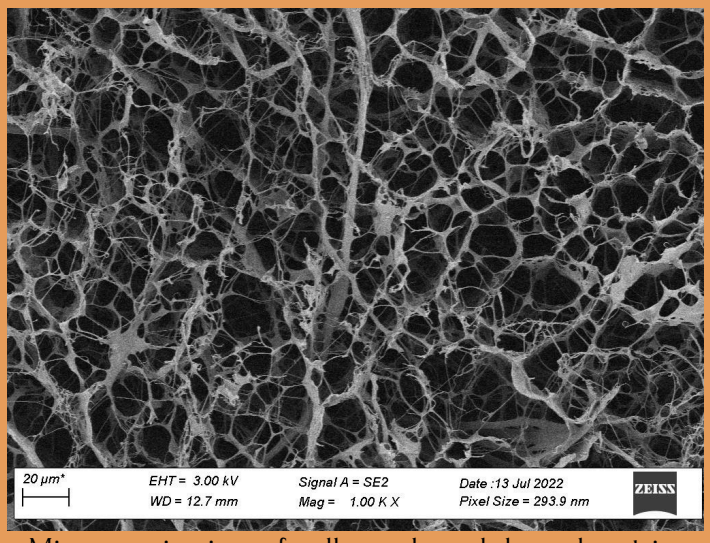
Iqbal MZ, Riaz M, Biedermann T, Klar AS. Breathing new life into tissue engineering: exploring cutting-edge vascularization strategies for skin substitutes. Angiogenesis. 2024 Jun 6. doi: 10.1007/s10456-024-09928-6. Epub ahead of print. PMID: 38842751.

New Generation Dermal Matrices

Gizem explores the key fetal regenerative elements, aiming to incorporate them into dermal matrices for improved healing.

GIZEM COSAR KUTLUOGLU





Microscopic view of collagen based dermal matrix

Gizem Cosar Kutluoglu, is a bioengineer employed at MedSkin Solutions Dr. Suwelack AG in Germany, and a PhD candidate at Radboud university medical center in the Netherlands.

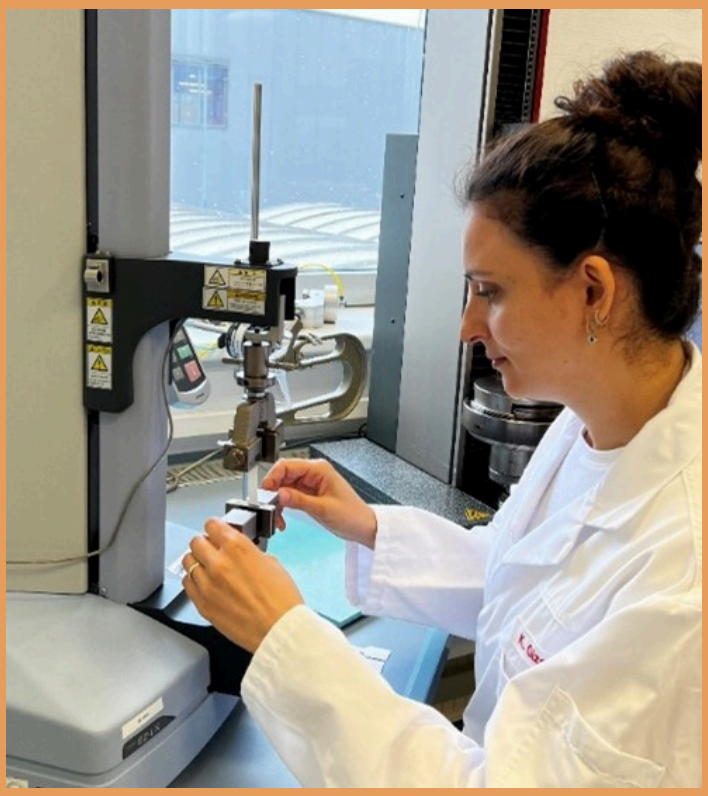
Gizem's research delves into the world of dermal matrices used to treat wounds that are too large or complex for natural healing. Currently available dermal matrices, primarily composed of collagen, provide structural support and contribute the healing but often fall short in promoting regeneration. Contraction and resulting scarring remain persistent challenging, causing both physical and emotional distress in patients. Gizem focusses on dermal matrices aimed at enhancing burn wound healing.

Mimicking fetal wound healing

The visual impact of scars is a prominent concern for many, but their effects extend far beyond appearance, particularly when they form on joints or the face. In these sensitive areas, scars can severely impact movement, functionality, and overall quality of life. Imagine a world where individuals with facial or joint burns not only see their skin repaired but also regain the full functionality and comfort they deserve.

The answer might lie in nature itself. Gizem's research focuses on mimicking fetal wound healing —a remarkable scarless process. Her work explores the key elements present in the regenerative environment of fetal tissue, aiming to incorporate them in dermal matrices. By harnessing these regenerative properties, Gizem seeks to develop advanced treatments that not only repair the wounded skin but also minimizes scar formation and restores the skin's natural elasticity .

“From observer to innovator: having previously witnessed the use of dermal matrices in burn surgeries, I am privileged to now contribute to the development of dermal matrices. The ultimate goal? A revolutionary dermal substitute that promotes complete wound healing, minimizes scar formation and restores skin’s natural elasticity.”

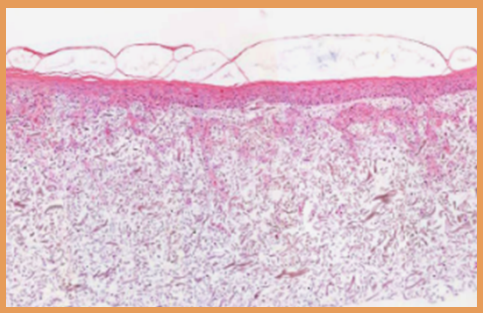


Prototype development

Gizem has pioneered the creation of various prototypes by integrating regenerative elements from fetal wounds into a collagen based matrix. The initial phase involved mechanical characterization to ensure these prototypes offered adequate structural support and were user-friendly for surgeons. Following this, the prototypes underwent rigorous biological testing in an in vitro setting, where artificial skin models were crafted using cells isolated from burn patients. These tests not only demonstrated biocompatibility but also successfully produced artificial skins with both epidermal and dermal layers across all prototypes.

Among the different prototypes, variations were observed in the formation and contraction of the epidermal and dermal layers. These differences provided valuable insights, enabling a detailed comparative analysis of various dermal substitute formulations in an in vitro burn-mimetic model. This comprehensive process has identified the most effective prototype for advancing to the next stage of medical device development.

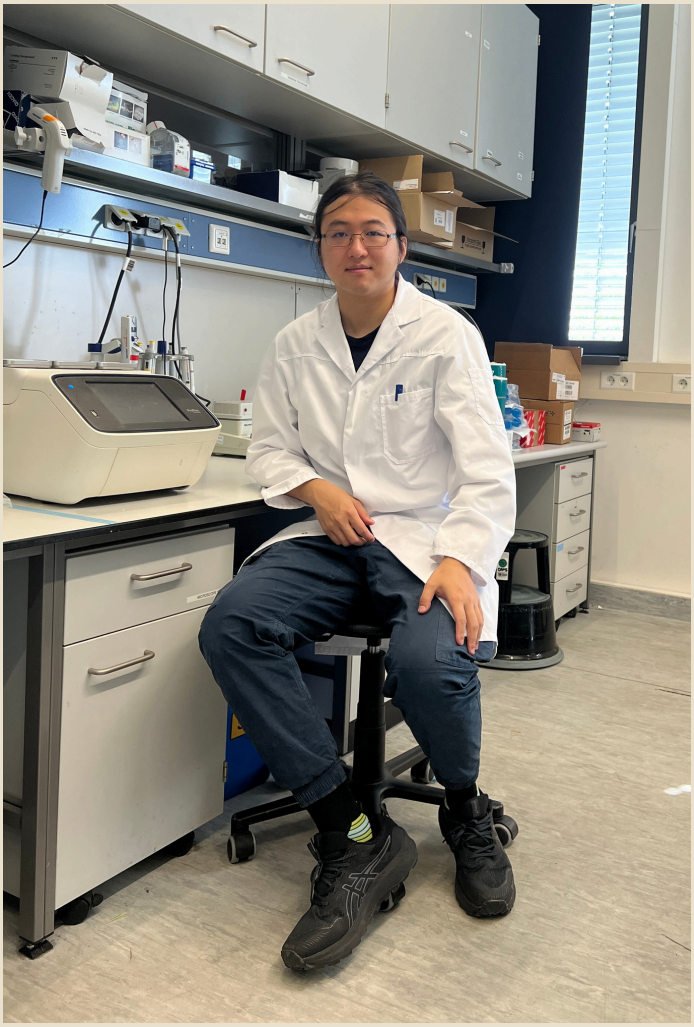
Artificial skin model



Succesful epidermis and dermis formation

Sweat Gland Regeneration

JIAZHENG LAI



“The life as an ESR in SkinTERM is invaluable for me, not only the communication with other ESRs, the training and activities we had, but also making progress of my project independently. I think these memorable experiences will assist my career in the future.”

Organoids could be potentially used to regenerate sweat glands in skin healing strategies.

Jiazheng Lai explores the potential of organoids in sweat gland regeneration in skin regeneration strategies as PhD candidate at Helmholtz Munich in Germany.

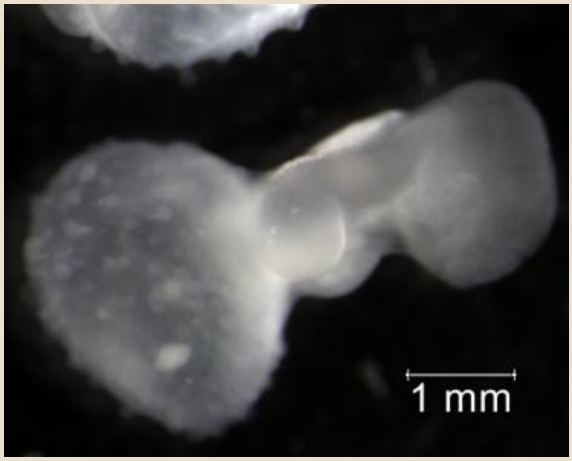
The importance of sweat glands

When the skin suffers a severe burn, a deep wound forms, and over time, scar tissue begins to develop. While the skin eventually heals, there's much more happening beneath the surface than just the visible recovery.

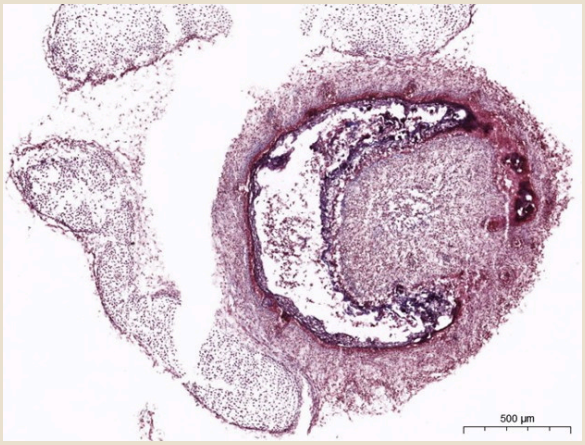
What many people don’t know is that an essential component—the sweat glands—are missing in this newly regenerated skin. These tiny, tube-like structures with coiled roots deep within our skin share a developmental process with hair follicles early in life. While they differentiate from hair follicles before birth, their role extends far beyond just keeping us cool. Sweat glands are crucial for maintaining skin's moisture, promoting overall skin health, and even protecting against harmful bacteria by secreting natural antibiotic components.

Unfortunately, sweat glands do not regenerate after injury. The absence of these glands can have serious consequences. Without them, patients become more susceptible to overheating, making it difficult to regulate body temperature. This loss of thermal regulation not only limits physical activity but can also significantly diminish the quality of life for burn survivors.

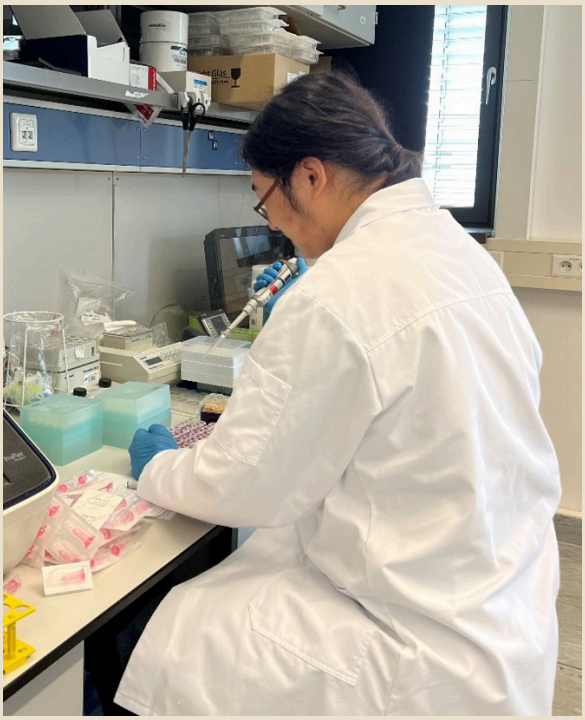
Therefore, the aim of Jiazheng’s research is to pioneer a way to generate these sweat glands outside the body and investigate possible mechanisms that decide the fate choice between sweat gland and hair follicle development in human.



Sweat gland organoid



Sweat gland organoid section



Pioneering sweat gland regeneration

Jiazheng's research faces two major challenges. First, no prior studies have attempted to induce sweat glands from stem cells without gene editing. Second, while sweat gland development has been studied in mice, much about the process in humans remains unclear. As a result, the research begins with the establishment of a protocol to induce sweat glands.

Starting with stem cells, mini-skin structures called organoids are cultivated in culture dishes using protocols adapted from hair-growing organoid research. These skin organoids are then exposed to various chemicals—candidates identified in previous research as key factors in sweat gland development—at different concentrations and timepoints. Once the organoids reach maturity, they are subjected to detailed analysis, including sectioning, trichrome staining, and immunostaining to detect sweat gland markers. The structure and morphology of the sweat glands are also quantified to assess their development.

Through rigorous experimentation and optimization, Jiazheng successfully developed a protocol for inducing sweat gland organoids. Stained sections revealed gland-like structures expressing sweat gland-specific markers, and even peptide secretions were observed—clear indicators of success. The organoids also showed notable morphological changes, further suggesting that sweat gland formation had been achieved.

Future directions

While Jiazheng successfully developed a protocol for creating sweat gland organoids, their functionality and viability in living organisms remain untested. The next phase of this research will involve transplanting these lab-grown sweat glands into animal models, with the ultimate goal of human application in the future. If successful, this innovation could one day offer new hope to patients around the world who lack functional sweat glands, potentially improving their quality of life.

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