Professional Development Dermatology

UCD CHARLES INSTITUTE SEMINAR SERIES

UCD School of Medicine
Scoil an Leighis UCD
Charles Institute of Dermatology

The naked truth about human health research

Attendees at UCD's Charles Institute Seminar Series heard a presentation from expert in stem cell biology and regenerative medicine Dr Andrei Mardaryev on insights into human health via the unique physiology of the naked mole rat

The Charles Institute, Ireland's national dermatology research and education centre, played host to a range of guest speakers who covered a variety of topics ranging from skin cancer to psoriasis, among others. The series, which was sponsored by RELIFE (part of the A.Menarini group), was designed to provide expert advice from a range of distinguished national and international experts in their respective fields and was chaired by Prof Desmond Tobin, Full Professor of Dermatological Science at UCD School of Medicine and Director of the Charles Institute of Dermatology. The seminars were broadcast to attendees with a special interest in dermatology in other locations, who accessed the talks remotely via an audio-visual link.

Attendees at the series heard a presentation from Dr Andrei Mardaryev, a researcher with international expertise, and currently Lecturer in Biomedical Sciences and Senior Lecturer in Stem Cell Biology and Regenerative Medicine at the University of Bradford, UK. Much of Dr Mardaryev's current work is focused on better understanding the physiology of naked mole rats (NMRs), long-lived mammals that demonstrate a marked resistance to cancer and other age-related pathologies, and which have more morphological similarities to humans than mice.

Both humans and NMRs demonstrate similar molecular changes during the skin ageing process, however NMRs have the ability to regenerate and heal skin wounds without scarring and are resistant to chemically-induced skin tumours. Dr Mardaryev told the seminar that the NMR is a unique adult mammalian model for studying mechanisms of scar-free wound-healing and cancer resistance.

Fascinating models

"For decades, traditional laboratory animals such as mice and rats have been widely used and they have been very helpful in identifying fundamental principles which were then proven to be true in humans as well," Dr Mardaryev told the attendees. "But if you want to study ageing or long-living organisms such as us humans, short-living animal models are not good enough for that. So a very important question arises: To what extent can we extrapolate data generated in mice and rats to long-living mammals, such as humans? We probably need to start looking at more adequate models and that is why we turned to naked mole rats a few years ago and found that they are fascinating models to study."

NMRs are the longest-living rodent known to science and the older ones can live for up to 30 years, he explained, and are unable to maintain their own body temperature, which is due mostly to their subterranean lifestyle. "These animals have unique features," Dr Mardaryev told the seminar. "They are highly resistant to cancer and other diseases such as diabetes and cardiovascular diseases — they do not get these conditions. They can also survive without oxygen for up to 18 minutes without incurring any brain damage; they can survive a hypoxic condition for hours with no damage due to their unique metabolic activity; they use their anaerobic metabolism in a hypoxic environment, so they can actually 'rewire' their metabolism to survive in these conditions."

These animals also barely ever feel any pain and maintain a high fertility level until the very latest stages of their lives, explained Dr Mardaryev, who presented an overview of research conducted in his laboratory and published studies, and added that a real understanding for the molecular basis for their longevity has only been looked at carefully in recent years.

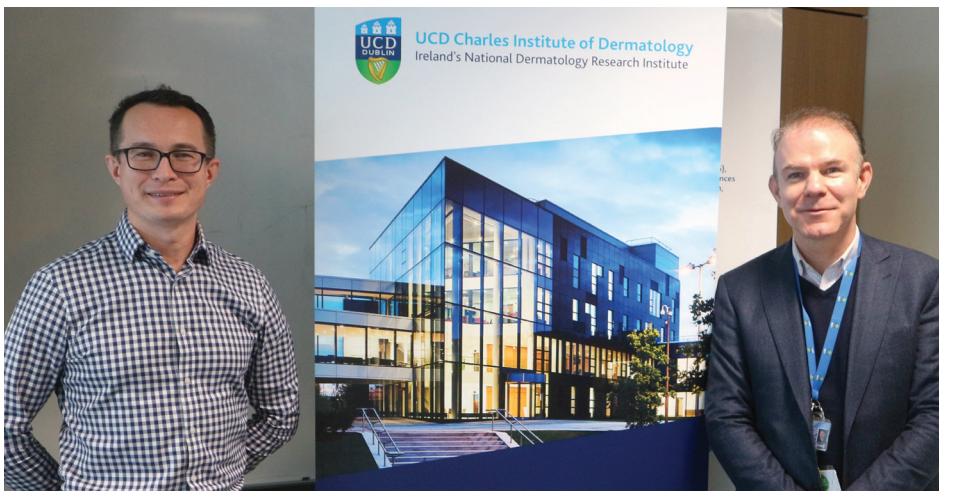
In terms of the unique skin characteristics of NMRs, Dr Mardaryev explained that they have a thicker dermis than mice, for example, and this feature makes their skin composition more similar to humans. In addition, they share key structural proteins with humans, such as keratins 14 and 10. "Architecturally, we believe naked mole rats' skin is morphologically more similar to humans than mice or rats… they also have stem cells that are similar to humans."

Ageing

He continued: "Their genome is more similar to humans than either mice or regular lab rats are to humans and the ageing in the naked mole rat's skin has features that have more in common with the chronological ageing in human skin," said Dr Mardaryev. "For example, there is a decrease in thickness of the epidermis, reduction in proliferation, down-regulation of keratins and collagen genes, depigmentation, and a decrease in the number of immune cells. These are typically not found in mice or regular rats, probably because they live for a much shorter time and that's why we think the skin of the naked mole is much better suited for the study of ageing in human skin."

"Wound-healing in naked mole rats occurs without visible contraction and the healing of injured skin is associated with a higher expression of collagen 3, which we think is linked to scarless healing in these animals," Dr Mardaryev told the seminar. Also, when the skin is wounded, collagen 3 is highly expressed in the skin immediately after wounding and normally, in the remodeling stage, it is replaced by mature collagen 1. That is how normal scar tissue is formed in human skin," said Dr Mardaryev, "whilst collagen 3 is more typical in fetal skin, which as we know heals without any scarring and we think one of the reasons why naked mole rats show minimal or no scarring is because they express immature collagen at later stages during the remodeling phase of wound-healing. We are studying this at the moment and preliminary data suggest that the TGF-beta pathway, which is in humans and mice, stimulates collagen 1 production and leads to scarring, compared to naked mole rats, where that pathway stimulates collagen 3 production," he said.

He also told the attendees that NMRs express high levels of DNA repair genes, cell cycle inhibitors and other characteristics that are thought to be the basis for resistance to skin cancer in these animals. Skin cancer was induced in NMRs in the laboratory but unlike mice, the NMRs did not develop any tumours when exposed to the same concentration, he explained.



Prof Tobin and Dr Mardaryev

"We have shown that naked mole rats have a high resistance to chemical carcinogenesis and this is an intrinsic, tissue-autonomous property of their skin cells," said Dr Mardaryev. "Despite changes in the epidermis, such as increased proliferation and thickness, they do not develop papillomas if you administer highly-potent chemical carcinogens.

"Naked mole rats are more suitable for studying human ageing and age-related pathologies, including cancer, and we think that by studying animals that are naturally more resistant to diseases, that will be a way forward to understand and develop new solutions for the treatment of medical conditions."

Cancer resistance

During a lively Q&A session following the presentation, Prof Tobin asked Dr Mardaryev to expand on the biological characteristics of naked mole rats compared to other mammals commonly used in the laboratory, such as mice and common rats, and the significance in terms of cancer resistance. "The junction between the dermis of the engrafted naked mole rat's skin with the mouse skin is distinct," said Prof Tobin. "But when the papillomas in the adjacent mouse skin start to become potentially squamous cell carcinomas and therefore more metastatic, are they capable of getting into the dermis of the engrafted naked mole rat's skin?" Dr Mardaryev replied: "That is an area that we have not yet looked at but studies have shown that the naked mole fibroblast produces a higher molecular weight hyaluronic acid compared to that produced by human or mice. They do prevent the spread of cancerous cells when the cancerous cells are injected into the subcutaneous tissue, so it seems like the environment that they create has a protective function."

Speaking to the ***Medical Independent (MI)*** following his presentation, Dr Mardaryev commented on the paradox of a subterranean species developing a resistance to skin cancer, when in theory, they should be more susceptible to the UVB to which they are exposed. "It does sound strange but the unique environment in which they live has forced them to develop new adaptations," he said. "Somehow, these adaptations became beneficial in terms of disease prevention. This has allowed them to live longer, but also to withstand harmful influences from the outside — it's an adaptation step and anything extra that this adaptation provides helps them to live longer."

Dr Mardaryev was also asked about the potential for the naked mole rat to provide insights into a wide range of possible therapies for human illnesses. "I believe there is enormous potential there, not just in skin conditions, but systemically," he told ***MI***. "Some aspects [of the animal], such as high molecular weight hyaluronic acid, have started to be used in clinics for the treatment of arthritis — not purely because of the naked mole rat, because all those studies were done before our research on the mole rat. These are anti-inflammatory molecules and the more we learn about the naked mole rats, how they function, how they behave — we hope that will provide new clues and understanding, and then we are hoping that it will be possible to translate this research to clinical application and the development of new approaches for the treatment of skin, as well as other diseases."

Bearing in mind the protective benefits of the animal's biology, are there any indications of potential protection from cognitive decline also? "Studies done by others show that signs of neurodegeneration, such as dementia, are not very typical for naked mole rats, even at their oldest age," said Dr Mardaryev. "Very old naked mole rats do not show signs of neurological problems. Even damage caused by hypoxia, for example, does not damage the animal's brain. They can survive for 18 minutes without oxygen — for a human, that would result in irreversible brain damage, but they are able to withstand that kind of oxygen deprivation.

"They use different chemical pathways to get energy to keep cells alive; switching from glucose to fructose is one way they do this, but there are probably other mechanisms at work too that we don't yet know about."

RELIFE has had no input into the content of this article or series of seminars