Researchers discover potential mole reversal therapy in rare condition

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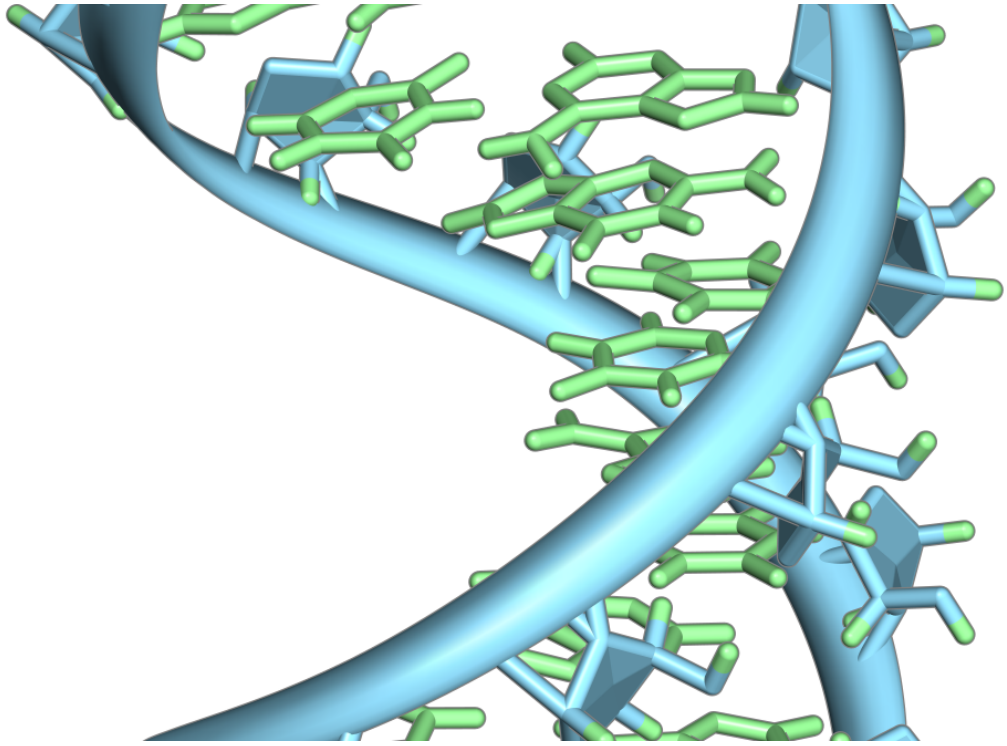

A hairpin loop from a pre-mRNA. Highlighted are the nucleobases (green) and the ribose-phosphate backbone (blue). Note that this is a single strand of RNA that folds back upon itself. Credit: Vossman/ Wikipedia

Researchers at the Francis Crick Institute, UCL Great Ormond Street Institute for Child Health and Great Ormond Street Hospital for Children (GOSH) have designed a new genetic therapy that could

alleviate debilitating giant moles in a rare skin condition.

In the future, the treatment could potentially be used to reverse the giant moles, and therefore reduce the risk of affected children and adults from developing cancer. It could also potentially reverse other more common types of at-risk moles as an alternative to surgery.

Small skin moles are common in the population, but in congenital melanocytic naevus syndrome (CMN), children are born with up to 80% of their body covered in big, painful or itchy moles, caused by mutations acquired in the womb. These moles can sometimes develop into a severe type of cancer called melanoma.

Published in the *Journal of Investigate Dermatology*, the researchers silenced a gene called NRAS, which is mutated in the cells in these moles, in cells in a dish and in mice. NRAS belongs to a group of genes (RAS genes) that, when mutated, can cause moles, and can predispose to cancer.

The team used a genetic therapy called silencing RNA, which silences the mutated NRAS in mole skin cells. The therapy was delivered in special particles directly to mole cells.

They gave injections containing the therapy to mice with CMN, which reduced the silenced the NRAS gene after just 48 hours. They also tested it in cells and whole skin sections from children with CMN. Silencing the gene triggered the mole cells to self-destruct.

Veronica Kinsler, Principal Group Leader of the Mosaicism and Precision Medicine Laboratory at the Crick, Professor of Pediatric Dermatology and Dermatogenetics at GOSH/UCL, and NIHR Research Professor, said, "CMN is physically and mentally challenging for children and adults living with this condition and for their families.

"These results are very exciting, as not only does the genetic therapy trigger self-destruction of the mole cells in the lab, but we have managed to deliver it into the skin in mice. These results suggest that the treatment in future could potentially reverse moles in people. However, more testing will be needed before we can give it to patients.

"We are very grateful to our patients at Great Ormond Street Hospital, who have been actively participating over many years to help us produce this new potential therapy. After more studies, we hope the therapy can soon enter clinical trials in people."

Jodi Whitehouse, CEO of Caring Matters Now, who helped to fund the research, said, "This breakthrough in finding a treatment for CMN could transform the lives of the families we support living with CMN. As someone who was born with CMN covering 70% of my body and having undergone 30+ operations in my childhood to try and remove the CMN because of the fear of melanoma, with no success, this news is awe-inspiring and exciting. It brings real hope to the lives of those living with CMN."

Catriona Crombie, Head of Rare Disease at LifeArc, said, "This work is part of our commitment to improving the lives of people living with rare diseases, by investing in promising research and helping scientists to overcome translational research barriers. If successful, we hope to see human clinical trials for this therapy within the next few years."

The researchers have been working closely with the Crick's Translation team to develop the technology towards patient benefit. This has included securing translational funds from LifeArc, to carry out more research in mice to understand how the treatment works over a longer period.

More information: Reference: Bryant. D. RNA therapy for oncogenic NRAS-driven naevi induces apoptosis., *Journal of Investigative Dermatology* (2024). DOI: 10.1016/j.jid.2024.04.031