Hitting the 'cellular sweet spot'—new delivery system for regenerative therapies

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One of the main stumbling blocks in regenerative medicine has been the inefficient delivery of targeted treatments to control how cells behave—one way is to regulate the genes inside damaged cells by efficiently delivering specific molecules. With the emergence of gene editing and reprogramming many scientists are working towards enhancing the ways in which these technologies can be used inside cells and correct the genome of patients with genetic disorders such as muscular dystrophy and cystic fibrosis.

Now a team of experts led by The University of Nottingham have developed a highly efficient system using small proteins that target the cell's sugar coating (heparan sulphate). The tethered therapeutic molecules are delivered at high dosages inside cells meaning that they have much more effect.

The research, published in the academic journal *Proceedings of the National Academy of Sciences* (*PNAS*), has shown that their simple protein based system could deliver any number of therapeutic molecules into damaged cells and lead to a new class of potential therapies and drugs for a variety of diseases and disorders.

The outside of the cell membrane has a dense lawn of heparan sulphate sugars in which many types of protein sit. Most approaches try to target these proteins and not the sugars. Specifically targeting heparan sulphates is a novel concept for drug delivery.

Lead author, Dr James Dixon, from the School of Pharmacy, said: "In this study we show that we can directly and efficiently deliver a variety of therapeutic molecules attached to proteins that can control the gene expression of stem cells and programme their fate."

This new, highly controlled and efficient 'delivery' system has the potential to target specific cells and reduce side effects. Because it is a simple protein that targets the cells surface sugars it may be easily modified to target specific organs and cell types and therefore specific diseases.

Dr Dixon said: "We've taken natural molecules that have evolved to interact with cells in this way and exploited their activity to design our technology. There are more versions of this sugar molecule (heparan sulphate) than the complexity of the human genome. Some types are only present on diseased cells, some on healthy tissue, some specifically in the heart, some in brain… If we can target these specific types we have the potential to create a very powerful therapy that could deliver therapeutic molecules and drugs directly to where we want them in the body, and very efficiently."

The Nottingham team is part of the UK's Regenerative Medicine

Platform (UKRMP), funded by the Biotechnology and Biological Sciences Research Council, the Engineering and Physical Sciences Research Council, and the Medical Research Council, to build on the UK's expertise in regenerative medicine and develop novel and efficacious approaches to regenerative medicine. The University of Nottingham is leading the hub for Acellular (smart materials) for therapeutic delivery.

Dr Dixon said: "Controlling stem cells in this way may be important, not just for regenerative medicine, but also for drug safety, the reduction of animal testing and personalised medicine approaches. We hope technologies like this and those developed with our collaborators in the UKRMP will allow us to build functional tissues from stem cells as replacements for diseased organs. Hopefully this work will also allow us to make drugs safer and smarter by specifically designing them for individual patients and removing the use of animals by testing them on patient tissue engineered in the lab."

The future of regenerative medicine is to ultimately get the patients cells to regenerate the diseased tissue themselves. The team is aiming to control the fate of cells directly in the human body—for instance the regeneration of new cells or repurposing existing cells to repair problems such as heart defects. The technology has been licensed to a University of Nottingham spin-out company, Locate therapeutics Ltd, with the hope that this fundamental research can be translated quickly to the clinic.

Dr Dixon said: "We still need much further work to test its safety, stability and activity inside the body and ensure we can get the drugs to the right place. We've shown this can be done in-vitro but it needs to be achieved before this technique can be trialed in patients. We are however very hopeful that this powerful technology can be used to help people as soon as possible."

More information: James E. Dixon et al. Highly efficient delivery of functional cargoes by the synergistic effect of GAG binding motifs and cell-penetrating peptides, *Proceedings of the National Academy of Sciences* (2016). DOI: 10.1073/pnas.1518634113