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Feature

Reality check for stem cell cures

Four decades after the first preparation of embryonic stem cells, early hopes for regenerative medicine have failed to convert to real world applications. While rogue clinics try to cash in on unproven treatments, the real cures are still in medical trials and new avenues like the use of animals as intermediate hosts are still being explored. Michael Gross reports.

The initial success of cultivating embryonic stem cells, published in 1981 for mouse and then in 1998 for human cells, inspired naïve hopes of regenerative medicine. With the right sort of guidance, these cells could be brought to develop into replacement tissues and organs in the patient. However, fundamental problems including the risk of cancer formation and tissue rejection, along with the ethical objections against the use of human embryos for research have slowed down progress.

Instead, stem cell research advanced in different, often unexpected directions. The dogma of the one-way street from embryonic stem cells to fully differentiated somatic cells fell with the cloning of Dolly the sheep in 1996. Somatic cells can be de-differentiated by implantation into an enucleated egg cell, in cloning, or by switching on a specific combination of regulatory genes.

The resulting induced pluripotent stem (iPS) cells are a way of bypassing the ethical concerns, and they can be produced from a patient’s own cells, which provides better immune compatibility. Still, the cancer worries remain — and they were highlighted by the fact that, in the first recipe for generating iPS cells, one of the four factors needed was a known oncogene.

As yet, the interface of stem cell development and carcinogenesis still needs to be elucidated more comprehensively before one can be entirely certain that stem cells implanted into patients aren’t going to become cancerous. This problem hasn’t stopped some rogue clinics from offering miracle cures based on stem cells.

False promises

Anybody typing ‘stem cells’ into a search engine will be flooded with offers of therapies for everything from skin ageing and sport injuries to multiple sclerosis and Parkinson’s disease. These offerings often come from dubious clinics, many of which are based in the US and operating on the edge of legality. They use the language of real stem cell research, but they don’t tell you that whatever they are offering is at best an unproven, experimental treatment.

Part of the problem is that stem cells can’t be filled into bottles or pressed into pills and offered as a ready-made and thoroughly tested medication for a given ailment. This has already scared the pharmaceutical industry away from the field, as companies find it more difficult to protect their revenue given the complexities of cell therapies. It also means that the US regulatory authority for medicines, the FDA, does not normally get involved with stem cell treatments. If clinics remove cells from a patient and reinject them elsewhere, that doesn’t count as a product requiring FDA approval. Instead, it is seen as akin to a blood transfusion.

To the uninitiated consumer, the advertised therapies appear to be fulfilling the promises of miracle cures that were made since the late 20th century. As decades have passed since the first reports of stem cell lines, it would be entirely plausible to expect that cures have by now been developed. In reality though, proven treatments are very few, and only a handful of others are now in clinical trials.

What really works

Proven stem cell therapies do exist — the most widely used is haematopoietic stem cell transplantation, more widely known as a bone marrow transplant. Developed in the 1950s to 1970s, this method is now routinely used against life-threatening cancers like multiple myeloma and leukaemia. More recently, its use has been expanded to autoimmune diseases...
such as multiple sclerosis. In some cases, haematopoietic stem cells for treatments can also be extracted from umbilical cord or peripheral blood. If the cells are not derived from the patient to be treated, the compatibility between cell donor and recipient is a major concern that often limits the use of the technique.

A rare example of a new and genuine stem cell treatment already available for a specific group of patients in the EU is Alofasel, a preparation based on adipose-derived stem cells, which under the name of Cx601 were successful in a phase 3 clinical trial (Lancet (2016) 388, 1281–1290). In March 2018, the European Medicines Agency (EMA) approved its use for the treatment of complex perianal fistulas (abnormal narrow tunnels forming between the gut and the skin) in Crohn’s disease that have proven intractable with at least one conventional treatment. Alofasel was developed by the spin-out company TiGenix based in Leuven, Belgium, which has since been bought up by the Japanese pharmaceutics company Takeda.

Pigs are similar to humans in many ways to the extent that growing human organs in a pig host is a realistic avenue currently under investigation, although many challenges remain. (Image: Kenneth Schipper Vera.)

Pigs to the rescue

The naïve hope of injecting stem cells into a patient and watching them grow to replace a damaged tissue or organ may turn out to have been misguided. There is a chance, however, that part of the process can be outsourced to other species as demonstrated through the development of a whole mouse pancreas in a recipient rat. Paul Fairchild, whose team investigates the immunobiology of stem cells at the University of Oxford, expressed guarded optimism for the approach: “The prospect of developing replacement human organs in a species such as the pig may provide hope for some patients with end-stage organ failure. Even though the patient’s own stem cells would be used, contributions from the recipient pig, such as leukocytes and blood vessels may still pose a risk of rejection.”

Interspecies transfer of stem cells leading to organ development has already been demonstrated in several examples. Recently, the...
group of Daniel and Mary Garry at the University of Minnesota at Minneapolis has prepared iPS cells from human skin cells and implanted these into pig embryos. Their goal is for the pigs to grow blood vessels that present a human-like interior surface to the blood and thus to the immune system, avoiding the risk of transplant rejection. If this approach succeeds, it may enable the transplantation not just of blood vessels, but possibly also of entire organs, which will hopefully be compatible with the patient’s immune system thanks to the nature of the blood vessels. The researchers have recently reported results of an experiment in which the pig embryos were allowed to develop for 27 days (Nat. Biotechnol. (2020) 38, 297–302). They are now looking for clearance for longer developmental timescales.

The obvious advantage for the patients would be that the risk of stem cells misbehaving and forming tumours would be delegated to the pigs. Only if the cells develop the tissue correctly and without malformations will it be transplanted into the patient. The concern with inter-species transplantation on the other hand is that one might transplant some sort of pathogen, such as a dormant retrovirus, that could not only harm the recipient but jump the species barrier and spread in the human population. In the year of the Covid-19 pandemic, we are all too aware of the dangers that such a zoonotic transfer can bring (Curr. Biol. (2020) 30, R191–R194). The group of Luhan Yang at the company eGenesis in Cambridge, USA, has therefore used CRISPR gene editing to delete all identified retroviral sequences in the pig genome (Science (2017) 357, 1303–1307).

Thus, where some people are placing misguided hopes on miracle cures, the reality is much more complicated because many risks need to be addressed simultaneously. However, progress is being made and patients will reap the benefits eventually.

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Book review

A feast in the desert

Thomas S. Collett

Desert Navigator: The Journey of an Ant
Rüdiger Wehner
(Belknap Press, Cambridge, MA; 2020)
ISBN: 978-0-674-04588-0

Reduce your bulk to that of an ant and imagine that, to gain a good living, your forefathers left the overcrowded regions of the world and slowly migrated towards the emptier areas of the desert. For the past half century, Rüdiger Wehner has studied such adaptations in carnivorous, thermophilic ants from just about every imaginable perspective. His superbly illustrated book contains a fascinating and vivid account of how the ants are able to thrive and navigate in desert conditions. The examples below give a flavour of the book and come from him or the many researchers he has attracted to his field site in Tunisia. Here, ant colonies are found on sand flats, fortunately by the sea, near what was a welcoming coastal village 50 years ago and is now a busy town.

Most of the ants’ food comes from locating other insects or small animals that have succumbed to the heat or perished in some other way. By scavenging when it is hot, ants avoid competitors and some potential predators. Thus, Cataglyphis bombycina is subject to predation by a lizard. The foragers tend to emerge in a bunch just after the ground has become so hot that the lizard has sought shade and just before the ground temperature is lethal for the ants. In these deserts, morsels of food are rare, so the ants must often travel long distances (hundreds of metres) to find them. They then navigate accurately across the desert, carrying or dragging the prey back to their inconspicuous nest as nourishment for larvae.

There are many species of thermophilic ants that have colonised a variety of deserts. In extreme conditions where food is particularly scarce so are mates. It is then safer to mate within your colony than to look beyond. Winged virgin queens stay close to the nest where they were born and release pheromones to attract and mate with several winged but usually walking males, which normally come from the same nest. The mated queen then flies away to found a new nest, carrying enough genetic variability in the sperm from different males for the new colony to cope with environmental uncertainties and the varied tasks performed in a mature colony. In addition to the near certainty of finding a mate, this reproductive strategy preserves special adaptations that have made the species successful in these particular surroundings. Thermophilic species in less extreme surroundings with nests closer together follow the usual practice, with males and females dispersing simultaneously in flight before mating. Males that are often produced in profusion may become food once mating is complete. Foragers can be seen to come out in force directly after mating is over to collect dead males and take them home.

How do ants cope with heat when the ground temperature is around 50°C? Many thermophilic species have unusually long legs. Temperature drops rapidly with height above the surface, being 10 to 15 degrees lower at ant height than at the surface. The ants

Cataglyphis velox: A long-legged desert ant from southern Spain photographed in the laboratory while it pauses after drinking from a drop of sugar water. (© Cornelia Buehlmann.)