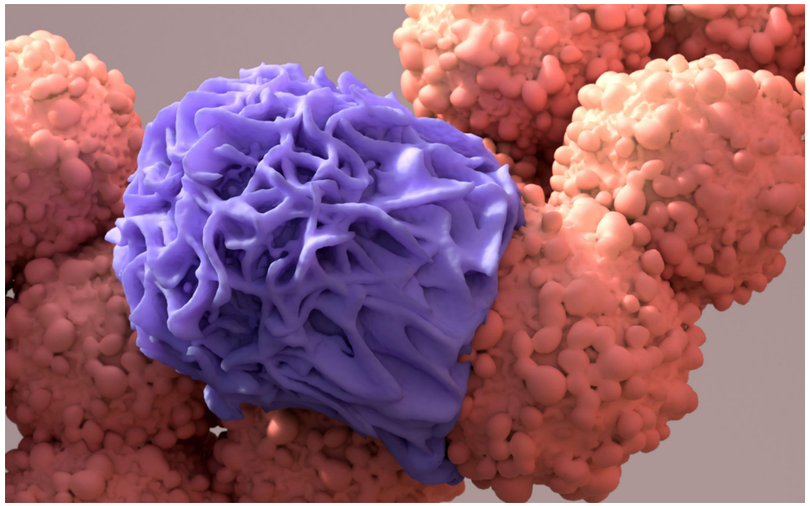
BRINGING THE BODY'S 'BIG EATER' CELLS TO THE TABLE

ENGINEERED MACROPHAGES could treat hard-to-treat tumours, as well as liver cirrhosis, osteoarthritis and other diseases.

When the zoologist Elie Metchnikoff discovered how certain cells could devour and digest cell debris and foreign bodies, he coined the perfect name: macrophages. That's Greek for 'big eaters'. Although Metchnikoff worked with invertebrates, he quickly became convinced that macrophages underpin a broad-acting immune system across species. Powerful 19th-century contemporaries, including Louis Pasteur, opposed the idea, but Metchnikoff's ideas prevailed, and he was awarded the Nobel Prize in 1908.

More than a century later, scientists are looking again at macrophages, taking advantage of their versatility to target difficult-to-treat solid tumors. Macrophages are also being developed to help battle a range of other diseases, including fibrosis of the lung and liver, as well as inflammatory diseases such as arthritis and asthma.

Clinical applications remain some ways off, but many scientists see huge therapeutic potential for these big eaters. As well as consuming debris and foreign bodies, macrophages naturally target and penetrate solid tumours; they specialize for the tissue they reside in, and they regulate immune function in several ways. "Macrophages allow you to almost take an engineering approach to treating disease," says Stuart Forbes, who works on regenerative medicine at the University of Edinburgh. "There's huge interest in this."



DESIGN CELLS/SPL/ALAMY

▲ Unlike other cell therapies, macrophages can infiltrate solid tumors and kill the cancer cells inside.

Front-line defence
Macrophages are a central player in the innate immune system, which includes a diverse group of cells and acts as a first line of defence against microbial pathogens and cancer. As with any front-line troops, the innate immune system detects and fights threats, and calls for backup. As key players in this system, macrophages carry out each of these roles.

"MACROPHAGES ALLOW YOU TO ALMOST TAKE AN ENGINEERING APPROACH TO TREATING DISEASE."

Because they can consume debris, macrophages are also good at healing wounds and helping restore injured tissue to health. For example, Forbes and his team have shown in mice that macrophages can reverse liver fibrosis, an early stage of liver cirrhosis in which healthy liver tissue is replaced by dead scar tissue, degrading the organ's function. "We've seen that a particular type of macrophage is very good at going to a damaged liver, eating the dead material, promoting repair and reducing inflammation," Forbes says.

These same capabilities could also enable macrophage therapy for osteoarthritis, says Sowmya Viswanathan of the University Health Network in Toronto. A macrophage type called M2 produces cell signals that reduce inflammation in, say, a damaged knee joint. Modifying the local microenvironment in this way, "can act as a bit of a circuit breaker" to relieve pain, Viswanathan says.

Experiments like these, as well as recent discoveries about the natural role of macrophages in targeting tumours and killing cancer cells, have raised hopes that macrophages derived from a patient's own immune system could effectively treat tumours. But these cells are hard to engineer, and they do not proliferate naturally — challenges that could make this approach difficult to scale. There are only so many macrophages that can be withdrawn from a patient, modified, and reinjected as therapy — especially if several injections are required for effective treatment, Viswanathan says. "I'm getting away with this now, but I'm quite sure we are going to run into problems as we start figuring out dosage."

Made-to-order macrophages
A better way to produce macrophages is to make them to order from induced pluripotent stem cells (iPSCs), Viswanathan says. This approach is being pioneered by Shoreline Biosciences, a San Diego-based biotechnology company, which is developing iPSC-derived macrophage therapies for solid tumours.

"We've harnessed recent advances in iPSC biology and gene editing to efficiently generate potent tumor-directed macrophages as an off-the-shelf therapy to treat many patients," says Robert Hollingsworth, Shoreline's chief scientific officer.

Since iPSC-derived macrophages are easier to engineer than patient-derived macrophages, they can also be altered to improve their function and persistence. This could make them a more powerful therapy against cancer — and, when engineered differently, it could give them improved abilities to tackle fibrosis of the liver, lung and other tissues, as well as battle infections.

iPSC-derived macrophages also leverage another macrophage trait — their ability to find and infiltrate solid tumours, some of which actively lure macrophages because they can help the cancer cells survive. Perhaps counterintuitively, this homing ability could give macrophage cell therapies for cancer a head start. "Macrophages could be a way of targeting tumours and getting cells directly to that area to influence the cancer cells," Forbes says.

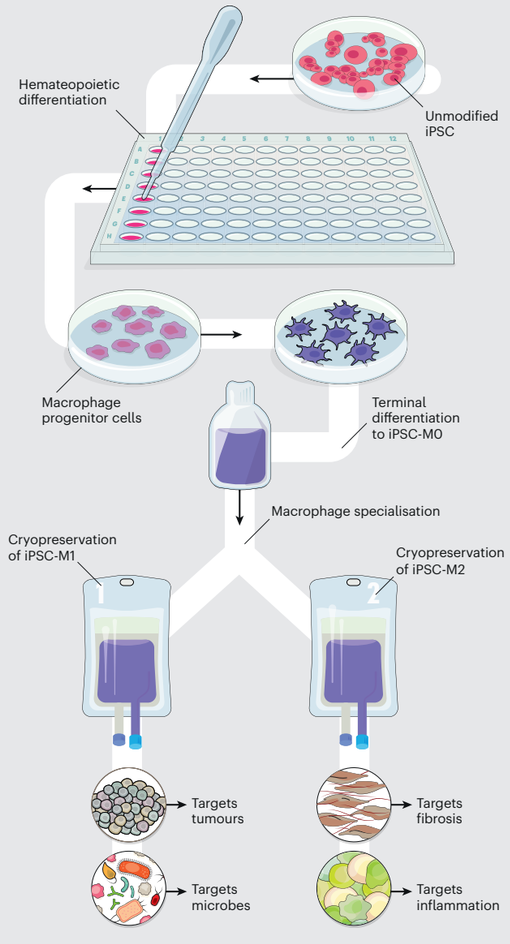
Turning cold tumours hot
Once inside a tumour, the macrophage takes a command role, which allows it to fight cancer in additional ways. "A macrophage is a master regulator of the immune response at a local level," says David Rodgers, Shoreline's director of macrophage biology. These big eater cells also actively recruit and activate other immune cells and bring them to bear on the tumour. "We can direct these cells to eat tumours, but I think that's only part of the story. The main story is the effect on the broader immune response against the tumour."

Because of their versatility and power, macrophages could help overcome the limitations of previous immunotherapies, among them engineered white blood cells called CAR T-cells. Although CAR-T therapy has had some success treating blood cancers such as multiple myeloma, the approach has not proven effective against solid tumours. Researchers think this is because solid tumours are 'cold', meaning they are broadly resistant to anticancer immune defences and impenetrable to T-cells.

Shoreline believes that iPSC-derived macrophages could prove effective at infiltrating solid tumours and killing cancers, turning cold tumours hot, Rodgers says. These cells also have an additional advantage. Because they aren't sourced from a specific individual, iPSC-derived macrophages can be prepared in advance and then given to all who need them. "The cost goes down and the barriers to treatment go down. You no longer need to be in a specialist hospital," Rodgers says. "You can start to push this out to community clinics. You start to make this cell therapy way more accessible to the broader population. ■

OFF-THE-SHELF IMMUNE REINFORCEMENT

SPECIALIZED MACROPHAGES engineered from induced pluripotent stem cells (iPSCs) are plentiful and potent enough to treat tumours and a range of other conditions.



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