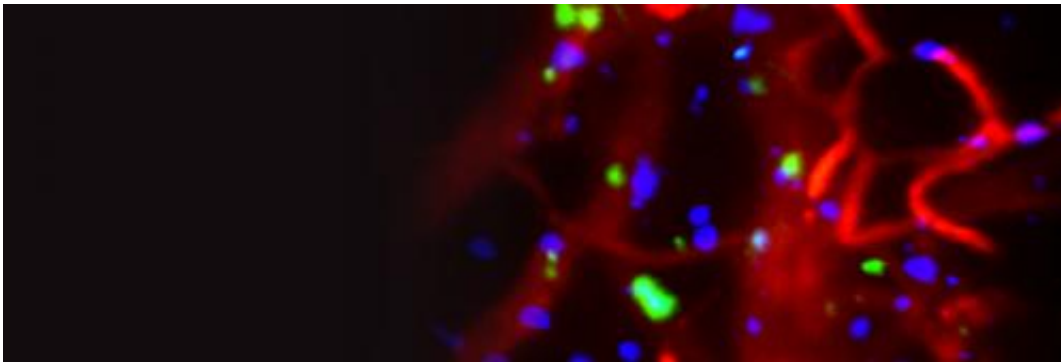


Small molecule helps get stem cells to sites of disease and damage

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Researchers identified a small molecule that can be used to program mesenchymal stem cells (blue and green) to home in on sites of damage. Credit: Oren Levy, Brigham and Women's Hospital

Bioengineers from Brigham and Women's Hospital (BWH) with collaborators at the pharmaceutical company Sanofi have identified small molecules that can be used to program stem cells to home in on sites of damage, disease and inflammation. The techniques used to find and test these small molecules may represent important tools in advancing cell-based therapy, offering a new strategy for delivering cells to the right locations in the body. The results of their work appear online this week in *Cell Reports*.

Through a collaborative research project, the research team tested more than 9,000 compounds, and used a multi-step approach - including a

sophisticated microfluidics set up and novel imaging technique - to narrow in on and test the most promising compounds.

"There are all kinds of techniques and tools that can be used to manipulate cells outside of the body and get them to do almost anything we want, but once we transplant cells we lose complete control over them," said co-senior author Jeff Karp, PhD, an associate professor at BWH, Harvard Medical School, and principal faculty at the Harvard Stem Cell Institute. "Through this collaboration, we've been able to identify [small molecules](#) that can be used to treat cells outside of the body, programming them to target blood vessels in diseased or damaged tissue."

Small molecules offered the team several advantages including the ability to use a safe and relatively simple procedure to pre-treat the cells before injecting them intravenously.

"There's a great need to develop strategies that improve the clinical impact of cell-based therapies," said co-first author Oren Levy, PhD, an instructor in medicine at BWH. "If you can create an engineering strategy that is safe, cost effective and simple to apply, that's exactly what we need to achieve the promise of cell-based therapy."

Karp's team at the Brigham had previously found that it is possible to use bioengineering techniques to chemically attach molecules to the surface of a cell that act as a GPS, guiding the cell to the site of inflammation. These findings indicated that targeted delivery of cells was possible, but a scalable approach would be needed to impact patients.

"At BWH, we had laid the groundwork. Our collaborators at Sanofi have complementary expertise in screening for small molecules, deep understanding of the biology and unmet needs, and an exceptional ability to bring new therapeutics to the clinic," said Karp. "Defined goals and

both teams working seamlessly together created perfect synergy. We learned so much from each other."

The Sanofi team screened thousands of compounds, looking for ones that activated telltale molecules on the surface of the MSCs, as well as verified that the active compounds did not alter mesenchymal stromal cell viability or the profile of secreted immunomodulatory protein factors.

There are currently more than 450 clinical trials ongoing or completed using [mesenchymal stem cells](#) (MSCs) to treat a range of diseases including heart attacks, Crohn's disease, lupus, multiple sclerosis and more, but many trials fail to meet clinical endpoints. One of the key challenges has been getting MSCs to arrive at - and stay at - sites of damage.

Researchers found six promising molecules, including one known as Ro-31-8425, the most potent of the group. Karp's lab then tested these compounds further by pre-treating cells with them, and then flowed the cells onto a microfluidic device - a glass slide with tiny channels only big enough to allow small groups of cells to flow through at a time. The channels were coated with an Intracellular Adhesion Molecule (ICAM-1), which is also found on the surface of [blood vessels](#) at inflamed tissue within the body. Cells pre-treated with Ro-31-8425 stuck - a sign that they might be able to home in on sites of inflammation.

The team further tested its results with the help of collaborator and co-corresponding author Charles Lin, PhD, a faculty member at Wellman Center for Photomedicine at Massachusetts General Hospital. The research team systemically injected cells that had been pre-treated with Ro-31-8425 into a mouse model that had one inflamed ear. Lin, who specializes in optical imaging techniques, then examined the ears using intravital microscopy, a technique that allows researchers to capture

images of tissue in live animals. The researchers observed that the [cells](#) treated with the compound not only homed in on the inflamed ear, but also reduced inflammation.

"We were uniquely positioned to achieve this as a result of our collaborations with partners both in industry and academia," said Karp. "Together we are tackling one of the major challenges facing cell-based therapy, ultimately achieving targeted delivery of [stem cells](#)."

Provided by Brigham and Women's Hospital

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