# The tricky path for using stem cells to treat coronavirus-ravaged lungs



he coronavirus pandemic has unleashed a wave of repurposing efforts, from old malaria drugs prescribed off-label to anti-virals stalled in development from past scourges, like <u>remdesivir</u> for Ebola, SARS, and MERS. Stem cells are finding new niches too, in helping to heal the devastation the novel coronavirus can leave in its wake.

It's understandable in the face of such a swift killer as COVID-19 to desperately try any treatment that makes even a bit of sense. But as many experts have insisted, only a controlled clinical trial can produce reliable information on efficacy.

"One advantage of a randomized controlled clinical trial is that if you find something that doesn't work, you get it off the table quickly. I've been through this before in the early HIV years, when there wasn't any therapy at all. There was the tension between doing a trial and just giving someone something," said Anthony Fauci. MD. director of the National Institute of Allergy and Infectious Disease and unofficial guru



*rk* webinar.

Some patients are joining clinical trials already in progress to

assess stem cells for other conditions that are rapidly being retooled to embrace the new disease. Others may participate in new trials, or their families may be asked for permission to enroll them if matters turn dire.

Finding legitimate offerings can be tricky. Beware claims of direct-to-consumer stem cell treatments, warns Leigh Turner, a bioethicist at the University of Minnesota Center who specializes in "stem cell tourism."

"I'm concerned that individuals purchasing these supposed 'therapies' for COVID-19 will be scammed. I'm also worried that they'll be injured as a result of being given products that haven't been adequately tested, or that they'll forgo measures like social distancing because they've paid for a product that they think will protect them from being infected or getting sick," he said. Dr. Turner published "Preying on Public Fears and Anxieties in a Pandemic: Businesses Selling Unproven and Unlicensed 'Stem Cell Treatments' for COVID-19" in *Cell Stem Cell*.

But there are trials underway with real promise for coronavirus patients. Many of the stem cell treatments

being evaluated in clinical trials are using mesenchymal stem cells (MSCs), which are well-studied "adult" stem cells. ClinicalTrials.gov (run by the US but international) lists only one entry outlining use of the controversial human embryonic stem cells to treat COVID-19, from <u>Beijing YouAn Hospital</u>.

# MSC are widespread in the body



Bone marrow is rich in mesenchymal stem cells

Bone marrow is rich in MSCs, but they also gather as pockets of unspecialized cells, tucked into nooks and crannies. When injury strikes, they are mobilized and migrate to the scene. There, in response to chemical signals, MSCs divide and specialize, forming connective tissue and its derivatives – bone, blood, and fat – while also maintaining "stemness," the ability to make more of themselves.

A dividing MSC produces two daughter cells. One is another stem cell, quiescent until it's needed, while the other divides further and specializes into one or a few types of cells. Such "self-renewal" is essential to growth and healing.

MSCs may fight the deadly lung inflammation of COVID-19, quieting it enough to permit tissue repair, because they naturally home to the lungs. They protect the delicate cells lining the air sacs (alveoli), while dampening growth of strangling connective tissue. Researchers hope that the cells will also prevent the out-of-control "cytokine storms" that kill, and boost production of the types of white blood cells that prevent infection by other pathogens, like bacteria.

All sorts of body parts, some considered "medical waste," harbor MSCs. The versatile cells have been in clinical trials for various conditions for many years. To tame SARS-CoV-2, the virus behind COVID-19, MSCs come from bone marrow, umbilical cords, blood vessel linings, placentas, and even teeth and fat. Most applications are from donors.

### **Umbilical cord stem cells**

An umbilical cord houses two arteries and a vein within a mushy substance, <u>Wharton's jelly</u>. It has the consistency of fatty chicken soup that's been left in a too-cool fridge, and it has connective tissue proteins and MSCs. One umbilical cord can supply 10,000 to 15,000 doses.

At the University of Miami Miller School of Medicine, 24 patients with COVID-19 are receiving intravenous infusions of umbilical cord MSCs that head straight to the lungs, where 95% of them become trapped. The cells were already in clinical trails to treat Alzheimer's disease and type 1 diabetes, diseases whose progression seems leisurely compared to the onslaught of the viral infection.

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"Patients who die from COVID-19 have a median time of just 10

days between first symptoms and death. In severe cases oxygen levels in the bloodstream drop, and the inability to breathe pushes patients towards their end very quickly; any intervention that might prevent that trajectory would be highly desirable," said Camillo Ricordi, MD, director of the Diabetes Research institute and Cell Transplant Center at the university, who is leading the <u>clinical trial</u>.

The non-profit <u>Cure Alliance</u> is turning all its efforts to the virus, including funding the Florida work. The protocol is being shared with several other institutions.

"When COVID exploded, we communicated with collaborators around the nation and asked if they'd tried the cells to treat COVID-19. And they have been, with remarkable initial results. But it is critically important to do a solid, prospective clinical trial to claim efficacy," Dr. Ricordi told MSNBC.

The first patient was treated April 23 on a compassionate use basis. Signs that the stem cells are working should appear within three months. Researchers at Stem Cells Arabia from Amman, Jordan, are conducting a similar <u>clinical trial</u>.

### Teeth

Dental pulp is another repository of MSCs. Investigators at Renmin Hospital of <u>Wuhan University</u> gave 20 patients with severe pneumonia from COVID-19 injections of either MSCs or saline, three shots three days apart. The study is triple blinded – patient, doctor, and outcomes assessor don't know who received the cells and who got the salt water.

The study is tracking time to clinical improvement, lung CT findings, immune function (types of antibodies and lymphocyte counts), negative PCR viral test, blood counts, the inflammation marker C-reactive protein, vital signs, and side effects.

px connective tissue adipose

Image not found or type unknown Adipose tissue (fat) contains valuable stem cells.

### Fat

"DEFENSE AGAINST COVID-19. PROTECTING OUR HEROES" reads the banner on the opening webpage for the <u>Hope Biosciences</u> Stem Cell Research Foundation, based in Sugar Land, Texas. They have three clinical trials to investigate the use of MSCs from adipose tissue, aka fat, to prevent and treat COVID-19.

The goal is to "provide immune support against coronavirus disease."

One trial will deliver 50 million, 100 million or 200 million donor MSCs intravenously at 5 timepoints within 14 weeks to 100 patients, and assess new symptoms and test for COVID-19.

A <u>second trial</u> is enrolling 56 people who will test their own previously donated and banked MSCs, to evaluate prevention.

A <u>third trial</u> is enrolling 110 patients hospitalized for COVID-19. They'll receive four infusions of donor MSCs or placebo. Also, some patients will receive hydroxychloroquine and azithromycin and some will not, unless those arms are stopped pending other studies.

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Image not found or type unknown Merrit the horse had a good experience with a type of stem cell now being tested to protect against COVID-19 in people.

Stem cells from fat is more advanced in the veterinary world. Check out the "pet success stories" of <u>VetStem Biopharma</u>. <u>Merrit</u>, for example, suffered a disintegrated right hind fetlock but was restored to health courtesy of stem cells derived from fat. Kirby the corgi found relieve from arthritic hips and knees while Trinity the cat reported improvement in her kidney disease.

## Exosomes - tiny bubbles of healing

A novel approach to stem cell therapy is to inhale tiny fat bubbles containing immune system signaling molecules, using a nebulizer similar to receiving an asthma treatment. The bubbles, called exosomes, are fleets of tiny packages that many types of cells use to ferry various molecules, like proteins and RNA, through body fluids. MSCs spawn exosomes.

Researchers at Jinyintan Hospital in China collect <u>"mesenchymal stem cell-derivied exosomes,</u> trademarked "MSCs-Exo"s. The bubbles have been tested for anti-inflammatory effects in traumatic brain injury, seizures, and stroke. To treat or control COVID-19, exosomes might deliver immune system proteins that reduce inflammation in lungs.

Inhaling the tiny fat bubbles is safer than injecting the whole cells that produce them, which can lodge in damaged narrow blood vessels. The researchers are treating 30 people who have COVID-19 pneumonia with the preparation 5 times, along with standard treatment.

### MSCs from around blood vessels

Mesoblast Limited plucks its product, remestemcel-L, from around blood vessels, where the stem cells secrete growth factors that keep the linings in good condition.

Called "mesenchymal precursor cells," these are the developmentally earliest MSCs. They've already shown promise in phase 3 clinical trials for acute graft-versus-host-disease (GVHD), which happens when a transplant attacks the recipient's body, and for chronic obstructive pulmonary disease (COPD), including bronchitis and emphysema.

This variation on the MSC theme calms things down. The cells tweak the balance of cytokines to dampen inflammation and secrete mediators and growth factors that help to heal damaged tissue.

A <u>clinical trial</u> just began enrolling 300 patients at up to 30 medical centers in North America who have moderate-to-severe acute respiratory distress syndrome (ARDS) due to COVID-19, the complication that necessitates mechanical ventilation. The patients, on ventilators, will receive either two IV infusions of remestemcel-L within five days or a placebo.

All participants will receive standard supportive care. The researchers will assess mortality within 30 days or the number of days off the ventilator.

### **Placental stem cells**

A placenta, the organ that connects pregnant woman to fetus, is another medical waste that harbors valuable stem cells. The organ oversees exchange of gases, nutrients and wastes; incubates new blood cells; and quells the maternal immune response.



cs has been tapping these cells to treat several conditions.

For peripheral artery disease the cells clear the way for new blood vessels to extend

into blood-starved muscles. They fight muscle atrophy by inducing specialization of muscle cells while blocking connective tissue build up, reducing scarring. The placental cells are also used to treat GVHD, bone marrow failure, acute radiation syndrome, and to reduce inflammation.

The company's PLX (Placental eXpanded) cells can modulate a recipient's immune response and secrete the recipe of biochemical (a balance of cytokines, chemokines, and growth factors) that repair damaged tissue. The cells travel in the bloodstream like a hormone or act locally where injected.

In response to the coronavirus, the placental cells summon from the immune response the big blobby macrophages that digest debris and regulatory T cells (T-regs) – changes that fight cytokine storms and reverse lung inflammation. The Jerusalem Post reported that March 30 was the first compassionate use of the cells in 3 patients in Israel, who were older and on ventilators. A week later, 7 patients had been

treated and all survived, four improving and three at that time weaning off the vent.

On April 13 the first patient in the US was treated at Holy Name Medical Center in New Jersey.

### **Bone marrow**

<u>Athersys Inc</u>. had already been testing its proprietary "MultiStem clinical product" to treat ARDS, which can develop from several underlying conditions, when COVID-19 came along, so patients were able to join a phase 1 clinical trial. The company plans to enroll up to 400 patients with the new disease in a double-blinded, placebo-controlled trial at University Hospitals Cleveland and the Cleveland VA Medical Center.

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The terminology is a tad confusing – it seems backward. The "MultiStem" product, according to the website, is derived from "multipotent adult progenitor cells." But a stem cell is a precursor to a progenitor cell, not the other way around. When a progenitor cell divides, it gives rise to more progenitor cells and possibly specialized cells – but not stem cells. The trademark must mean that the company adds something to the brew to send the cells back in developmental time to regain their stemness.

Where will stem cells fit in?

Picture the US, picture the world, a year or two from now.

Herd immunity is building from increasing numbers of people who've survived COVID-19 and others who have been vaccinated.

Anti-virals shorten the sickness, easing the burden at hospitals.

For those who still get sick, perhaps stem cells will come to the rescue. Stem cell technology's time may have finally come, in a way that many of us could never have imagined.

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