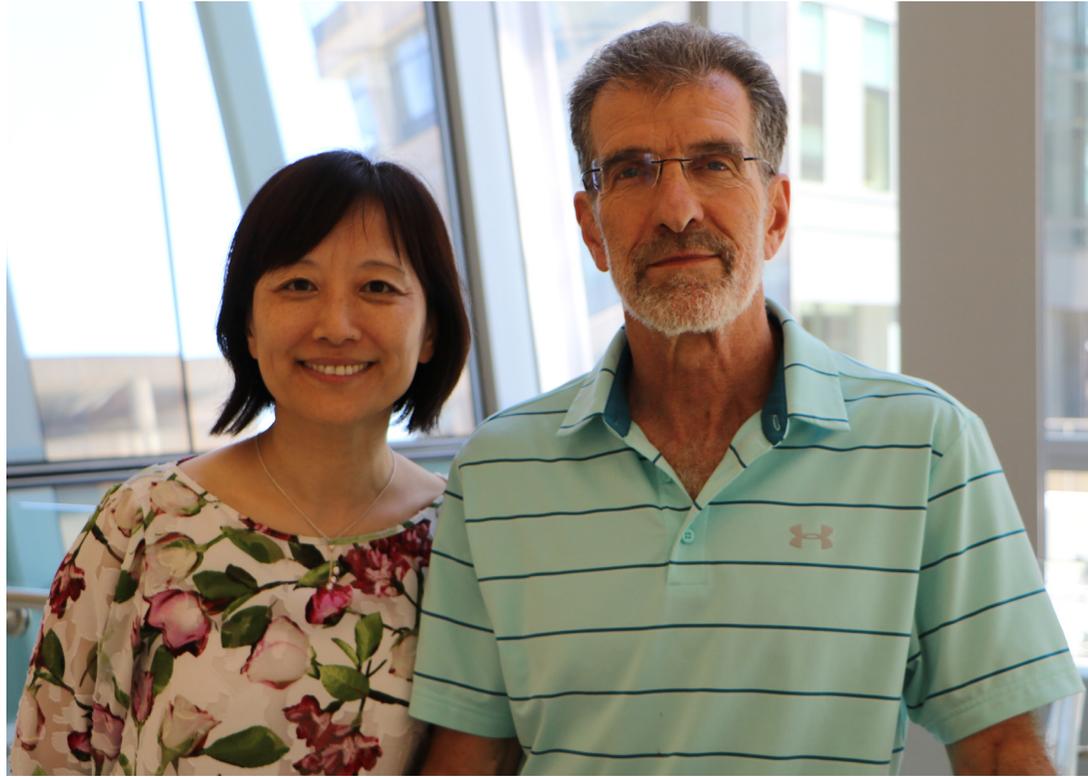


One good drug

"About a third of cancers, including leukemia and liver cancer, depend on *SALL4* being active to survive. We want to make a therapy that starves them of it."

- Li Chai, M.D., associate professor of pathology at Harvard Medical School and associate director of pathology, Brigham and Women's Hospital. Pictured with Dan Tenen, professor of medicine at Beth Israel Deaconess Medical Center and leader of the HSCI Blood Program.



Harvard Stem Cell Institute (HSCI)

Our mission is to discover cures for human diseases. We aim to:

- Stimulate healing in patients by harnessing the potential of stem cells
- Create targeted treatments by combining new gene- and cell-based therapies with traditional medicines
- Accelerate drug discovery by developing novel stem cell-based tools.

Our network of over 1,000 biomedical researchers, from across Harvard and its eight affiliated hospitals, is advancing stem cell biology and translational medicine in a way no other single entity can.

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HSCI physician-scientists Daniel Tenen and Li Chai want to turn off a gene to stop cancer without poisoning the patient.

- The ideal cancer drug would harm cancer cells without hurting normal cells.
- In their quest to discover one good therapy, HSCI scientists Dan Tenen and Li Chai have zeroed in on *SALL4*, a gene that is essential for growth in both embryos and cancers.
- A cellular therapy that deprives cancer cells of *SALL4* would stop a third of cancers in their tracks.

"I first realized I wanted to be a research scientist when I had a patient whose baby was stillborn, and the family just wanted to know why."

Li Chai, a transfusion medicine specialist and associate professor of pathology, talks about her research in the busy, jumbled office of her colleague Dan Tenen, who leads HSCI's Blood Program.

"I looked into it with the help of another resident physician, and we found that a gene mutation had been the cause, not an inherited

disease. So I could tell the parents they should not worry too much about the same thing happening again if they wanted to try to have another baby.

“That was a real gift, to be able to tell someone that. It was also how I got hooked on studying genes during fetal cell development. How could one gene be so important that one little mistake could lead to disaster?”

The embryo-cancer connection

“I want to know what is so special about our genetic activity as embryos, and why we see some of that same activity in cancer,” says Chai.

“Once we have that knowledge, could we influence the genetic program in adult tissues to maintain a healthy state? Could we use it to stop cancer from growing? That’s what our work is about.”

Blood: our most abundant organ

Chai and Tenan study the body’s most abundant, accessible organ and use what they learn about healthy and leukemia cells to advance research on many other organs and diseases.

“Blood may not look as solid as a heart or brain, but it is an organ. And because it is so accessible, we probably know more about each of its cell types, genes, and proteins than we do about any other organ,” explains Chai.

Tenen, a professor of Medicine at Harvard Medical School and Director of the Cancer Science Institute of Singapore, is clear about the team’s objectives:

“Our goal is to find one good, targeted therapy – one drug that makes a positive difference in people’s lives. If we are going to do that, we need to figure out how genes are regulated –

why some cells fight bacteria and others move your body, when they all have the same genes.

“We need to know how this works in healthy cells at all stages of life, and how it works in cancer cells. You can see that cancer cells only think about themselves, they take whatever they want: all the nutrition, everything. They drain their host, starve its organs. That sounds a little bit like a developing fetus—and there is a connection.”

A time to grow

“When human embryos are growing, the *SALL4* gene is active, but at a certain point it shuts off permanently,” adds Chai.

“So, consider this: about a third of cancers, including leukemia and liver cancer, depend on *SALL4* being active to survive. We want to make a therapy that starves them of it.

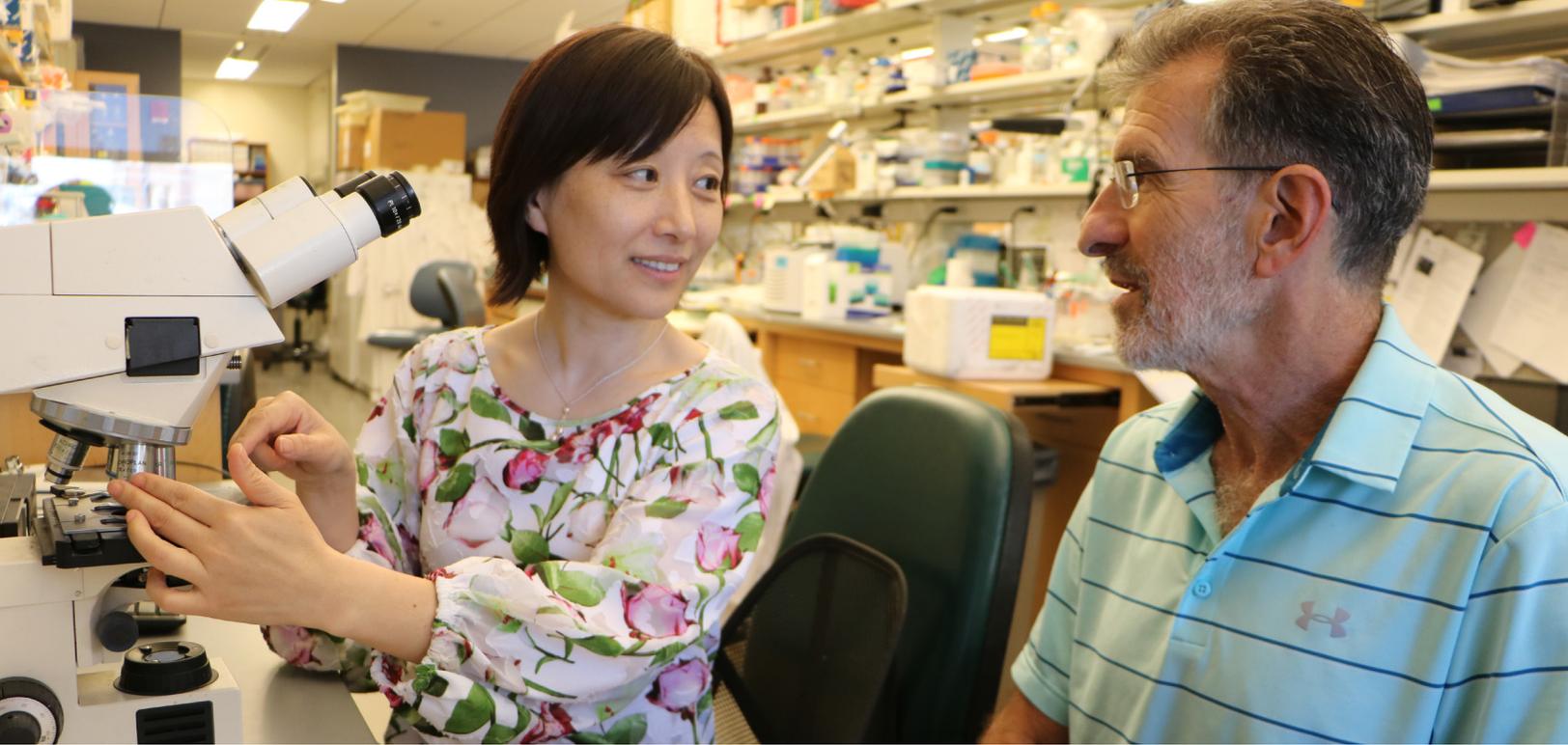
“And of great interest to me is that our results indicate that the same type of therapy that might block the growth of leukemia cells would enhance the ability of normal blood stem cells to produce normal blood cells. We can use that for cellular therapy.”

Tenen chimes in: “We want to know the *SALL4* gene inside and out, and not just to learn about cancer. If we knew exactly how it influences healthy growth in the embryo, we could perhaps develop a method to program adult stem cells to regenerate - and that would be a radical change.

“If we could artificially, intentionally, tell cells what to do in order to maintain health, if we understood how healthy genes are regulated, and could manipulate other cells into copying that pattern, then we could basically keep a person healthy.”

“When you study blood, you are really studying everything,” adds Chai. Tenen nods agreement.

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Blood as a drug, blood banks as pharmacies

“Cellular therapy always comes back to blood,” says Chai. “My speciality is transfusion medicine, so to me this is not so new. What is different now is that we are trying to fix your own cells, rather than giving you someone else’s, and trying to make more of them outside your body. If we can make this work, blood banks would become the new pharmacies.”

“Think about it: you probably don’t see of a bag of blood as drugs. We do. In the future, we see it as life-saving drugs at around \$200 a bag.” adds Tenen.

“It might sound straightforward to culture cells, change them, and make them fit for transfusion, but it isn’t. You cannot just make this in your backyard and give it to people,” he cautions. “This has to be done with extreme care and attention to detail. Each step along the way is more complicated than it first appears, and it takes a lot of resources. We are doing this in an academic setting, so we do not have the big team sizes you might find in a company. Our collaborations, for example with our colleagues in Singapore, are absolutely essential to making progress.”

The dream

When asked what his big dream is, Tenen is unequivocal: “You should not have a bucket list – you should be living it, and that is what I am doing. I love this work. You have to, because most times, Mother Nature is smarter than you. So, we are working on targeting this gene, *SALL4*. You give me that? I can treat one third of human cancers. That is the dream.”

About the HSCI Blood Program

Researchers in the HSCI Blood Program investigate how the self-renewal of blood stem cells is turned on and off. To regenerate damaged tissues, self-renewal must be turned on. But it must be turned off to stop blood cancers like leukemia and lymphoma from growing. Using genetic screens, mouse models of disease, bioinformatics, and comparative cell analyses, the HSCI Blood Program explores how genes influence blood stem cell self-renewal, whether different tissue types share similar stem cell regulators, and whether it’s possible to screen for chemical compounds to control self-renewal.