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OROFACIAL STEM CELLS

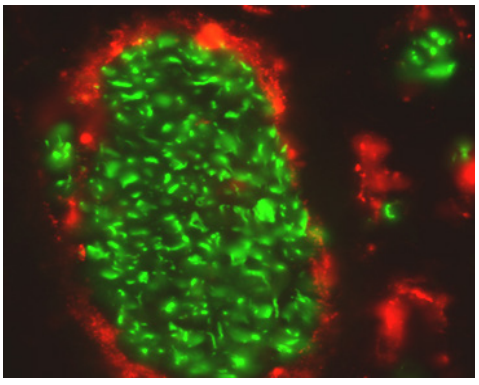
A BABY TOOTH GUIDED PENN DENTAL MEDICINE'S SONGTAO SHI TO STEM CELL INSIGHTS

ONE OF THE KEYS TO Dr. Songtao Shi's productive career in research came from a seemingly humble item: his daughter's first baby tooth.

Since isolating a population of unique stem cells from baby teeth more than a decade ago, Dr. Shi, who joined Penn Dental Medicine this fall as Professor and Chair of the Department of Anatomy & Cell Biology, has gone on to explore the great potential of stem cells as therapeutic agents to address the damaging effects of everything from tooth decay and gum disease to lupus and cancer. In coming to Penn, he hopes to foster collaborative research that spans the basic and clinical sciences as he brings the mindset of a trained clinician to the laboratory bench.

OPPOSITE: Dr. Songtao Shi joined Penn Dental Medicine this past fall as Professor and Chair of the Department of Anatomy & Cell Biology.

RIGHT: Stro-1 positive dental pulp stem cells (red) around neural fibers (green).



FROM BEDSIDE TO BENCH

Dr. Shi attended dental school at Beijing's Peking University, gained specialized training in pediatric dentistry, and then worked in the clinic for a few years before heeding the desire to pursue a research career. At that time, opportunities to conduct research alongside a clinical career were somewhat limited in China, so he and his wife moved to the United States, both earning their doctoral degrees at the University of Southern California (USC) and then pursuing postdoctoral training at the University of California, San Francisco.

In graduate school and during his postdoctoral training, Dr. Shi investigated the mechanism of cataract and osteoblast differentiation, but stepped back into clinical dentistry after taking a position at the National Institutes of Health's National Institute of Dental and Craniofacial Research in Bethesda, Md., in 1999. Encouraged to pursue research in that position, his studies turned to stem cell biology.

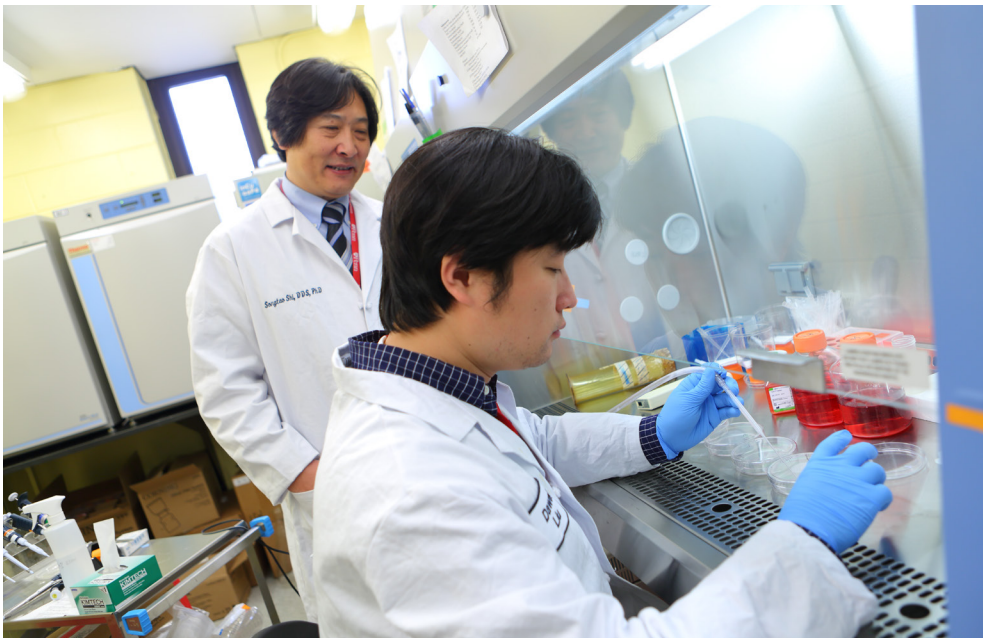
The beauty of stem cells is their versatility. Depending on their type, stem cells can differentiate to create a variety of different cell types. Some parents bank their newborn's umbilical cord blood, hopeful the stem cells within could eventually be used to correct certain diseases, such as diabetes, cardiovascular conditions, or cancers.

NO TOOTH FAIRY

A few years after moving to Maryland, Dr. Shi's daughter, Julia, lost her first tooth at 6. Accustomed to looking after her dental-care needs, Dr. Shi examined the tooth after it came out and noticed a tiny bit of rosy tissue stuck to the root end. By the time he realized this tissue was dental pulp, the living part of the tooth, it was too late to extract any cells from it. But he couldn't shake the suspicion that the pulp of the baby tooth might contain some interesting biological characteristics. When a second tooth of Julia's began to wiggle a week later, though, he was ready with a test tube of culture medium.

"It is exciting to publish high-impact papers, but it is more exciting to see a patient who was going to die survive because of something you've done."

"I dumped that tooth in my tube and drove to my lab in the night," he says. "The amount of tissue was tiny, but I did a stem cell isolation and extracted a small number of cells. They grew slowly at first, but three days later there were so many; I couldn't believe it!"



ABOVE: Dawei Liu, a postdoctoral fellow in the Shi lab, performing culture expansion of mesenchymal stem cells.

The stem cells he was able to isolate from the dental pulp were a new breed, distinct from the stem cells other researchers had discovered in infants' umbilical cord blood and also different from adult stem cells isolated from skin, hair, blood, and heart cells.

To learn more about the baby teeth stem cells, which Dr. Shi termed SHED, for stem cells from human exfoliated deciduous teeth, he began collecting lost baby teeth from Julia's friends as well.

"If there was a birthday party, I was always there, collecting teeth," he says.

With his collaborators at NIDCR, Dr. Shi began exploring the possibilities. While the SHED cells were slow to start growing, after a short time they multiplied rapidly and were found to live longer and be more robust than previously studied adult stem cells. They were also capable of differentiating into dental pulp and neural and fat cells.

After publishing these findings in *Proceedings of the National Academy of Sciences,* Dr. Shi and his team also went on the lookout to see if stem cells were lurking in other tissues in the orofacial area. At NIDCR and at USC, where Dr. Shi was a member of the faculty for more than eight years before coming to Penn, he and his colleagues identified and characterized new types in the periodontal ligament, in the dental pulp of permanent teeth, and in tendons.

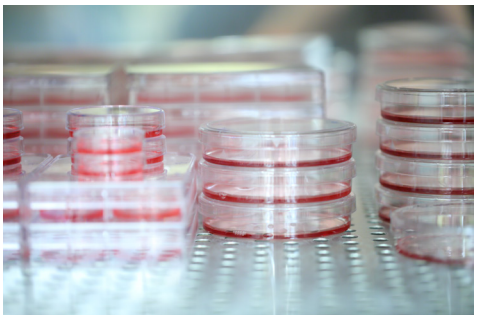
VERSATILE APPLICATIONS

Now Dr. Shi is investigating the potential of stem cell treatments in cell culture, in animal models, and in human clinical trials.

Among the first clinical trials he helped lead, a collaboration with colleagues in China, involved treating lupus patients with transplants of mesenchymal stem cells. Along with the many problems these patients faced from their condition, they also happened to have gum disease. Treating these patients using the stem cells induced lengthy remissions in their symptoms.

Additional aspects of Dr. Shi's work also have found impact beyond the dental field. In a recent study published in the *Journal of Experimental Medicine* with colleagues from Penn, USC, Nanjing University in China and elsewhere, Dr. Shi helped identify the signaling pathway that is involved in deficiencies in the differentiation of bone marrow mesenchymal stem cells that can result in a chronic autoimmune disease known as systemic sclerosis. This condition involves, among other symptoms, an overgrowth of connective tissues and patients have problems with their bones.

The researchers' study showed that treating mice that had systemic sclerosis with rapamycin, a drug commonly used to reduce the likelihood of organ rejection in kidney



ABOVE: Mesenchymal stem cells are cultured in vitro. These cells will be used to regenerate orofacial bones and treat autoimmune diseases, such as lupus and osteoporosis, in animal models.

transplant patients, reversed the stem cell problems and improved their bone density.

"We're very excited by these results and hope that a phase I trial can be initiated to bring this treatment to human patients," Dr. Shi says.

Still other trials involving stem cells are now in the works in China to see if stem cells from dental pulp and periodontal ligament could help regrow dental pulp. Down the line, this approach could offer patients new therapies for dental and orofacial tissue regeneration.

Alongside these clinical trials, Dr. Shi is leading laboratory work to discern the mechanism by which stem cells may have their beneficial effects. Such investigations could reveal even more opportunities to put stem cell therapy to work in the orofacial field. For example, cell therapy could involve re-growing jaw bone that is damaged from trauma or tumors.

"Right now if you have to replace jaw bone, a surgeon has to take bone from another area, like the tibia," Dr. Shi says. "Re-growing the mandible would eliminate this need. There is huge demand in this area, and we are glad to see we have already started in the game."

Also, a recent study published in the *Cell Stem Cell* with collaborators from the Capital Medical University, Peking University, and the NIH identified that hydrogen sulfide plays a crucial role in controlling mesenchymal stem cell function.

GLOBAL APPROACH

Part of this effort involves deep partnerships with colleagues in China. Dr. Shi has been instrumental in plans for a collaborative center for dental research with his alma mater, Peking University School of Stomatology. In March, he traveled to Beijing as part of the Penn Dental Medicine delegation with Dean Denis Kinane that joined representatives from throughout the University of Pennsylvania to help celebrate the launch of the Penn Wharton China Center.

The stem cells Dr. Shi was able to isolate from dental pulp were a new breed. Dr. Shi termed the stem cells SHED, for stem cells from human exfoliated deciduous teeth.

Dr. Shi is collaborating with Dr. Anh Le, Chair and Norman Vine Endowed Professor of Oral Rehabilitation in Penn Dental Medicine's Department of Oral and Maxillofacial Surgery/Pharmacology, to use the principles of stem cell therapy to treat osteonecrosis, a condition that arises in some people who take bisphosphonate drugs that are used to treat melanomas or to prevent osteoporosis.

"We're hoping to find a drug that is already FDA-approved that has a similar mechanism of action to the cell therapy," Dr. Shi says.

Through work in human patients, in animal models, and in the lab, Dr. Shi is making good on the promise of translational medicine.

"We're using these various tracks to work hard to study how stem cells work so we can push these therapies to the patient," he says. "We're on our way."

While there, Penn Dental Medicine also renewed a memorandum of understanding with Peking University School of Stomatology and announced plans for the National Center for International Research, a collaborative program between the two schools that aims to encourage an exchange of training and research opportunities.

"Through the center we'll have young faculty from China come to Penn to train and focus on translational research," Dr. Shi says. "We're opening the door to opportunities to solve clinical problems."

Fundamentally, Dr. Shi hopes to realize the power of translational medicine to save and improve lives by capitalizing on the potential of stem cell biology.

"One day we were working and my collaborator in China told me something that has made me feel differently about my work," Dr. Shi says. "He said, 'You know, it is exciting to publish high-impact papers, but it is more exciting to see a patient who was going to die survive because of something you've done.'" ■

—By Katherine Unger-Baillie