If he develops heart disease in the future, Joseph Wu envisions his physicians selecting the ideal medication for him by first testing drugs on his “mini-me” surrogates – dishes of beating heart cells created from his own stem cells.

Growing up in Southern California, Wu helped his father grow Asian specialty pears. Now, as director of the Stanford Cardiovascular Institute in Palo Alto, California, he grows cardiomyocytes for a wide range of applications – disease modeling, drug discovery, medication safety testing, and possible regenerative therapy.

Since coming to Stanford in 2004, Wu has worked with both human embryonic stem (ES) cells and human induced pluripotent stem (iPS) cells. Using ES cells, Dr Wu’s laboratory is addressing several important technical challenges in stem cell technology, including how to improve cardiac differentiation efficiency, control potential tumorigenicity, and avoid immune rejection.

For iPS cells, his laboratory has shown that iPS cell-derived cardiomyocytes can be used to elucidate the molecular mechanisms of familial dilated cardiomyopathy and hypertrophic cardiomyopathy. In a paper designated the best basic science manuscript in Circulation in 2014, Wu used a library of iPS cell-derived cardiomyocytes to show that patterns of drug-induced cardiotoxicity differed among healthy controls and patients with long QT syndrome, hypertrophic cardiomyopathy, and dilated cardiomyopathy, indicating that the system might be a more accurate predictor of adverse drug responses than current assays and screening tests. In Circulation Research, he recently described the opportunities to use iPS cell-derived cardiomyocytes to advance the scientific understanding and treatment of sudden cardiac death. The Stanford Cardiovascular Institute is currently creating a biobank of patient-specific, deidentified iPS cell lines from healthy controls and patients with a wide range of cardiovascular diseases, which will benefit the research community and patients alike.

In 2010, Wu received a Presidential Early Career Award for Scientists and Engineers from President Obama at the White House. Among numerous other awards, Wu has been honored with the National Institutes of Health (NIH) Director’s New Innovator Award in 2008, the NIH Roadmap New Innovator Transformative Award in 2009, and the American Heart Association Established Investigator Award in 2013.

An avid reader and frequent contributor to Circulation Research since his cardiology fellowship, Wu has served on the editorial board of the journal for five years and was recently appointed associate editor. In a recent interview, he discussed his life and the multi-faceted promise of iPS cells in cardiovascular research.

Where Did You Grow Up?
I was born in Kaohsiung, Taiwan, in 1971. In the late 1970s, there was a great deal of tension between China and Taiwan. Some people in Taiwan felt unsafe, thinking that if war broke out no other countries would help defend Taiwan because it was no longer part of the United Nations. So a lot of families left the country, especially those with boys in the family, because if you had sons over a certain age there were restrictions on emigration due to mandatory conscription. We left in summer of 1980, when I was 9 years old and my brother was 10.

Did You Come Directly to the United States?
In those days, if you were wealthy enough it was easier to come directly to the United States. Our family didn’t have that kind of means, so we went first to South America, living for a year and half in Bolivia, Paraguay and Brazil before coming to California in 1981.

What Was That Transition Like for You?
I skipped 4th grade and didn’t go to school at all during the year in South America because we were moving around so much. Initially I enjoyed playing soccer with local kids, but after awhile I started asking my father when I would go back to school. When we moved to South
Pasadena, California, I had to quickly learn to speak and write English starting with the alphabet. Just like most immigrants, I worked hard. It probably took me a good five years to catch up in school.

How Did You Get Interested in Science?
I knew I didn’t want to have the same profession as my dad. He was a farmer and he grew Asian specialty pears and apples in Bakersfield, California. I used to go up there from Southern California on weekends and in the summer to help out. From an early age, I could see how demanding farming is. Not only is it hard work, it also depends on so many variables – the unpredictable weather, the variable crop yields, the water supply – and then a middle man takes out quite a chunk of the profits.

So I realized I didn’t want to do that. Also, from a young age I was quite interested in the human heart, fascinated by its constant, ceaseless beating and ability to supply blood to all the organs. By high school, I had already decided I wanted to be a doctor, to help cure diseases involving the heart.

How Did You End Up at Yale?
I was a pre-med major at UCLA. Then I had to make a very difficult choice between staying home and enrolling in an MD/PhD program at UCLA, or going to Yale solely for an MD. I chose Yale in part because I want to experience what life is like on the east coast. Luckily, I was able to continue my interest in research there, because every student had to write a research-oriented thesis.

When I started medical school, I wanted to be a cardiothoracic surgeon, so I worked in a canine laboratory for three summers and conducted my research there with Dr Albert Sinusas. But I soon realized that cardiothoracic surgery requires a pretty exclusive focus, and that I would be better off specializing in cardiology if I wanted to be more cerebral by combining clinical medicine with basic science research.

The MD program at Yale turned out to be a good decision because I had very good mentors, experienced living on the East Coast, and met my future wife there. She was a master of public health student at that time, and now practices as an attorney.

What Drew You Back to California?
When I finished at Yale, I wanted to go back to Los Angeles, where I grew up and where my parents still lived. I also had this naïve notion that I didn’t want to associate patients with income, meaning that I wanted to talk with them as long as needed and not be forced to see excessive number of patients in order to cover overhead expenses. I thought by becoming a physician-scientist I could still see patients and, support my research with grants at the same time.

How Much of a Surprise Was Yamanaka’s Discovery?
It was a lightbulb moment. I remember distinctly when one of my colleagues called me and asked if I had seen the Cell paper showing that Yamanaka could take a skin fibroblast from a mouse and turn it into a mouse iPS cell. When I read it, I was initially skeptical. Lots of people had previously tried and failed to make cells pluripotent: How could it be so simple? But the beauty of Yamanaka’s work is its simplicity, and it’s crucial that it is readily reproducible in other laboratories. This is why he received the Nobel Prize for Physiology or Medicine in 2012, which was only 6 years after his original discovery!

How Successful Have You Been in Differentiating Cardiomyocytes From Stem Cells?
We were not the first to do it, but I think we have been instrumental in optimizing the protocols that are used. The past 10 years have seen a vast improvement in cardiac differentiation protocols, moving from 5% efficiency to 90%-4% efficiency these days.

I think the main technical limitation of the field now is that the cardiomyocytes that we get from the iPS cells are still at an...
immature state compared to adult cells (and this applies to brain, liver, skeletal, and other cell types as well). We’re now able to make large quantities of cardiomyocytes, but we still need to figure out how to “mature” the cardiomyocytes and how to make lineage-specific cells so we can study atrial cells, nodal cells, or ventricular cells. These issues will require some time to solve, but I am confident we will see significant improvements in the maturation and lineage specificity of these cells over the next 3 to 5 years.

How Are You Using Cardiomyocytes Differentiated From iPS Cells to Understand Heart Diseases?
If you have a patient who has cardiovascular disease and you want to study the source, the heart tissue, it’s not possible to do that by repeated heart biopsies. It’s too invasive and dangerous, and the patient will refuse.

Instead, what most people have done in the past is to use a transgenic mouse model. First, you figure out the mutation in the human. If the mutation is in troponin T that causes dilated cardiomyopathy, you would take that mutation and knock it in or knock it out in a mouse model to create a transgenic mouse that could simulate the same type of physiology as your patient. But the mouse and the human are two very different species, with very different cardiac physiology. For example, most human hearts beat at 60 to 80 bpm, whereas rodent hearts beat at 400 to 600 bpm.

In the future, we should be able to take a patient’s blood, create iPS cells and differentiate them to beating cardiomyocytes within two months. We actually do that routinely in the laboratory now and have several projects using this design. We’re going after interesting diseases such as hypertrophic cardiomyopathy, dilated cardiomyopathy, long QT syndrome, arrhythmogenic right ventricular cardiomyopathy, and other unusual diseases for which the mechanisms remain unclear, and for which we may achieve the greatest possible benefit on patient care.

How Can This Lead to Better Treatments?
I think there are several ways that you can exploit this technology. Say a drug company is about to test a new drug that might cure a specific heart disease. In the conventional model, you would typically test it in rodent models first. If it shows some efficacy, you would further do additional validation studies before going to clinical trials in humans. The problem is that mice and humans diverged evolutionarily about 75 million years ago, so the data you get in mice may not correspond to the data you get in humans. This may explain why so many clinical trials fail despite initially promising in vitro data and animal data.

In future drug discovery, I envision that in between the mice studies and human trials, we will be able to test a lead compound on a bank of human iPS-derived cardiomyocytes. With a biobank of iPS cell lines, we may finally detect be the crucial differences in drug response between men and women, among different ethnic populations, or in people with different cardiovascular diseases. By developing this “clinical trial in a dish” model, you can be much more precise in understanding how your drug mechanism works before you go to clinical trials in humans.

An alternative approach is to test drugs in heart cells differentiated from iPS cells as the first step, followed by testing the pharmacokinetics/pharmacodynamics in mice and then proceeding to phase 1 clinical trials.

In terms of other applications, for example, once you can make large quantities of atrial or nodal cells, you can help patients with atrial fibrillation, study the disease mechanism, and then come up with new antiarrhythmic drugs.

Will This Bring Us Closer to Personalized or Precision Medicine?
Yes, that’s my hope and the reason I am focusing most of our research in this area. Using myself as an example, in the event that I should develop heart disease when I’m older, I’m hoping there will be better alternatives to the current treatment paradigm. Currently, the doctor would give me a drug first without knowing whether it would work; if it didn’t, the doctor would switch me to a second or third medication. This is a wasteful and ineffective approach, and may harm patients due to side effects from multiple drugs. Instead of being the guinea pig, 20 years from now the doctors will be able to test the drugs on my “mini-me surrogates,” or my iPS-heart cells beating in a dish. Based on those results, the doctor can then prescribe me the specific optimal drugs or drug combinations. If we can do this, we will be well on our way to making personalized or precision medicine a living reality.

What Else Do You Envision for These Clinical Trials in a Dish?
All drugs being developed must be tested for cardiac safety, and we’re very interested in using these new models for safety testing. If you take a drug and get a rash, it’s worrisome but still less damaging than not waking up the next morning due to deadlier side effects such as lethal arrhythmias. Drug companies test cardiac safety by seeing whether drugs cause arrhythmias. But they don’t have access to human heart cells so they use surrogates such as Chinese hamster ovary cells or human embryonic kidney cells that overexpress the hERG (human Ether-à-go-go-Related Gene) channel. We and several other groups are now working with the Food and Drug Administration (FDA) to assess if human iPS cell-derived cardiomyocytes can be a better substitute for the current hERG testing. In the future, we hope to test drugs using iPS cell-derived cardiomyocytes from a diverse panel of patients from different sexes, ethnicities, and cardiovascular histories. Furthermore, this approach should have wider applicability in drug safety testing. For example, if you have a drug that is metabolized by the liver or exerts an effect on the brain, instead of using immortalized liver or neuronal cell lines, you may be able to test the drug on patient-specific liver cells or neuronal cells instead.

I see the systems we’re working on now as the early “beta” versions. In the future, we should be able to test not just one single type of cells alone but rather we will be evaluating a drug in a dish that has a variety of different cells, such as brain, heart, liver, skeletal, and endothelial cells, and look for the pleiotropic effects of a drug on all these organ surrogates. We will probably go beyond 2-dimensional monolayer to 3-dimensional tissue cultures and whole organ systems, as well as using in silico modeling. I don’t think there will be an “one size fits all” solution or a magic bullet for everyone. It is more likely that doctors will select the best technology or combination of approaches for treating each individual patient’s specific condition, by taking advantage of our advancing knowledge of each patient’s unique genome.

How Amenable has the FDA Been?
I think it’s a work in progress. Obviously the FDA first wants to see that we can develop a very reproducible, consistent testing method. We have been collaborating with a couple of other laboratories within the FDA to test the platform. The stakes are very high. If we can switch from the current testing model to iPS cell-derived cardiomyocytes and other iPS cell derivatives, then I think we can accelerate the drug discovery process and make it
more efficient. The downstream implication will be more affordable drugs that provide more benefit to our patients.

**Where Do You See Things Going Next With Regenerative Therapy?**

Our laboratory has four major research foci – disease modeling, drug discovery, personalized (precision) medicine, and regenerative medicine. I think the first three will be accomplished first, followed by cell therapy once we figure out how best to deliver the cells to intended organs and ensure that they survive after transplantation.

Regenerative medicine is a much more complicated process because you need to show that stem cells are efficacious and safe, and that they offer an added benefit compared to current medical treatment regimens for our patients. Necessity is the mother of invention here, because there aren’t that many treatment options for patients besides surgery, drugs, antibodies, gene therapy, and stem cell therapy. The approach makes sense because we are, after all, the product of our stem cells. When you see an infant grows into a child and then an adult, that’s stem cells in action. Conversely, when we grow old and develop multiple debilitating diseases, it’s often due to stem cells becoming senescent and losing their reparative capabilities. In the end, one may not need to inject stem cells themselves but rather deliver drugs that activate or coax the existing endogenous stem cells. So there are many exciting possibilities in the future, and we are just scratching the surface.

**Are You and Others in the Cardiac Field Keeping a Close Watch on Yamanaka’s Current Work on Macular Degeneration?**

Yes, in 2014, Masayo Takahashi and Shinya Yamanaka took skin cells from a Japanese woman with macular degeneration, made iPSCs, and differentiated them into retinal pigment cells. The team then put a sheet of retinal pigment cells back into the same woman. The hope is that the new cells will function normally and the patient will regain her sight. We’re very interested to see if it works, but keep in mind that the eye is an easier target because it’s localized. You can put the retinal pigment cell sheet into the eye socket. By comparison, in the human heart, it’s very difficult to deliver cells directly to the heart and have them stay there. Because of the mechanical stress, the inflammation, and the ischemia, in our experience cell survival in the heart has been quite poor thus far. It’s clear that we have many more obstacles to deal with than treating heart disease. Luckily, there are many groups with similar interests, and collectively I think we will find the best solutions in the end.

**What Mix of Clinical Practice and Research Is There in Your Current Worklife?**

When I first came to Stanford, I was seeing adult congenital heart disease patients, reading in the echocardiography laboratory, and attending in the inpatient general cardiology service. But because of growing research demands in my laboratory, and now as director of the Stanford Cardiovascular Institute, I have many more administrative and leadership responsibilities. Hence I have had to cut back on my clinical practice. Currently, I have half a day of clinic once a month, seeing general cardiology patients and some adult congenital heart disease patients. I also attend in the inpatient cardiology service 2 weeks a year.

**How Hard Do You Work?**

Like any physician scientist, I wear many hats and try to balance a busy work schedule. Unless I’m traveling for work, I work on Saturdays half day and Sundays half day after church. On those days, I focus on writing grants and papers. I really enjoy what I am doing now, so I don’t really consider it “work.”

**What Do You Do in Your Free Time?**

I used to play recreational basketball, but as I’ve gotten older the weekend-warrior aches and pain have caught up with me. So these days I swim whenever I can. I love to hang out with my wife and my son and daughter, ages 11 and 9. I enjoy reading nonfiction, favoring military history books. I am currently reading a biography on Winston Churchill, who I think is one of most courageous figures in the 20th century.

**What Is Your Advice to Young Scientists?**

When young scientists join the laboratory, the first thing I tell them is you need to work hard, work smart, and work together. Among the three prescriptions, I would say that team work is the most important. Even if they don’t learn anything else from my laboratory, as long as they understand these three precepts, I hope it will serve them well no matter what field or career they end up in.

I am deeply committed in making sure my trainees succeed. This is a great privilege as well as responsibility because they are looking to you for guidance. Over the years, I’ve learned just as much from them as they have from me. I encourage all of them to think outside the box and give them as much freedom as possible to pursue unconventional projects. After all, scientific discovery is always about pushing the envelope, and I look forward to what the next generation of scientists and thinkers will bring us.

**References**

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