Catriona Jamieson, MD, PhD: It's really a pleasure to have this spectacular event. My name is Catriona Jamieson. I go by Cat. I'm the director of the Sanford Stem Cell Institute at UC San Diego. What you can see is not only do we have spectacular views, we have spectacular science and medicine, and we bring them together very quickly because we all work together and we get everyone's input. We all have unique perspectives.

I'd really like to thank Mel Cruz for inspiring this event. She had us go to the La Jolla Playhouse when Sheldon, my husband, and I were just going to sit on the couch and binge watch Netflix. Then Mel called and said, "No. I've got tickets for you for the La Jolla Playhouse Gala." I said, "That sounds kind of fancy. I just want to relax and not do anything." She said, "You're coming.".

So we did and it was really amazing to see the level of talent in this town. You just think, how lucky are we that we get to do this? The play that we hadn't seen, The Heart, seemed really very specifically associated with regenerative medicine and all the things we aspire to do for cardiovascular disease. But it also encapsulates a thought and reparer les vivants. So reparer les vivants means repair the living. That's what we all do for each other.

It's the sense of carinoso. I'm going to mix languages here, mix metaphors, mix languages. That sense of having a heart. We're going to hear more about it from Robert Brill, but it's about grief and then guilt and gratitude and all the things that people go through when they have really tragic events happen.

But out of tragedy sometimes brings something really very special. This is what we're going to talk about today in this MIND event, which stands for Medicine Informing Novel Discoveries, all about the heart. How we can protect our hearts, enhance endogenous repair and regeneration through advanced stem cell therapies.

Not just cellular replacement therapies that I learned to do as a transplanter, but actually extracellular matrices and new kinds of technologies that are less invasive, new ways of making a sick heart heal. How you look at regeneration of the heart. So we've got a really incredible lineup, including a special representative from the La Joya Playhouse.

What we're trying to do here is combine the art of science and medicine and really bring art to the table. So I'd like to introduce our first speaker, Ehtisham Mahmud. Shami, as he's officially known. We've known each other for a long time, but somehow, I didn't know you'd gone to the University of Alberta.

I had to read your bio, finally. We looked after some people in really difficult situations for those people, but Shami always comes through as the person you want to call when you have a problem. Hello. How are you? Very personal, extremely talented, is the chief of the Division of Cardiology here. Always one of the top doctors, particularly in the interventional cardiology realm.

He's the person you want to see to say, what's coming next? Shami seems to have a crystal ball. Really remarkable talent when it comes to making sure that your heart doesn't get damaged in the first place. Really trying to avert transplant as a needed option. So thank you so much, Dr. Mahmud, for being here. We appreciate it. Thank you.

Ehtisham Mahmud, MD, FACC, MSCAI: All right. Thanks, Cat, and thank you for putting this together. It's a privilege to be in front of all of you. I'm Ehtisham Mahmud. I'm the Division Chief of Cardivascular Medicine at UC San Diego and also the Executive Director of the Cardiovascular Institute.

I'm going to take off my interventional cardiology hat for today, though I'll touch upon it just a little bit, and take a little broader hat of what we have tried and I think successfully established at UC San Diego with our cardiovascular institute.

It's a unique institute established in 2018 and the idea was that we have a multidisciplinary institute that takes care of patients who have cardiovascular disease, is involved in training and educating the next generation of physicians in cardiovascular medicine and surgery, and is involved in trials and studies, both basic science and clinical cardiovascular trials for improving health care as it relates to cardiology and cardiothoracic surgery.

I'm very pleased to share that we are now ranked number 1 in San Diego, number 3 in California and number 15 in the United States for cardiology and cardiovascular surgery. I'll tell you a funny anecdote. When I started in this job, it's been now 15 years, and we had never been ranked nationally in cardiology and cardiac surgery.

I was told you'll never be able to compete with scripts. This is 15 years ago. The first time we were ranked. Our cardiovascular center at UCSD opened in 2011. We were ranked number 42 in 2012. Now, as I mentioned, we're number 15. This is a few years ago. We were number twenty-something.

I came home and I was really pleased that we've moved from the 40s to the 20s. My boys at the time in middle school, they said, "Dad, who cares if you're twenty-something? What are you proud of about that? Nobody talks about being number twenty-something." It's like all right.

It's always nice to have your kids who set you straight. Of course, our goal, that's not where we want to stop. We were established in 2018. What's unique? Now both Michael Madani and myself have actually become sort of the go to people to figure out how this is set up.

Because in most institutions in the United States, cardiology and cardiac surgery, for one, are not combined in a single entity. Secondly, their function within their typical departments of medicine and surgery, and they don't get to make autonomous decisions. What's unique, and a number of you probably know, David Brenner, it was his vision and he's the one who put this in motion, and Pradeep Khosla was very supportive.

Here we are 15 years later and we're able to function as an entity at UC San Diego and yet we can make our own decisions and we can be nimble like a startup within a very large traditional university. My partner in crime is Mike Madani, who's the Chief of Cardiac Surgery.

The way it's set up is that Division of Cardiovascular Medicine, cardiology on the left side, and the Division of Cardiovascular and Thoracic Surgery on the right side are 100 percent within the Cardiovascular Institute.

In the middle, we have a number of programs that we collaborate with and work with together and that's what constitutes the UC San Diego Cardiovascular Institute. From a clinical standpoint, again, going back 15 years ago or so, the only place we had clinic was in La Jolla and at our Hillcrest Medical Center. If you wanted to get cardiovascular care, you had to come to one of those two locations.

Now we have outpatient locations throughout the county. In fact, we have some clinics in Las Vegas. We've had clinics and intermittent relationships in Orange County, Hawaii, and Arizona. So the idea is for patients who need advanced cardiovascular care, you don't have to come all the way here. We will come to where you are. But then when you need advanced care, you come to mothership.

We also are involved in training the next generation of specialists in cardiology and cardiac surgery. We have 42 trainees that we train and we have subspecialty trainees in every aspect of cardiovascular diseases. I won't name all of them. But what's important is, and again, I'll go back 15 years ago, patients were leaving San Diego because advanced care was not possible here in cardiovascular diseases.

Similarly, we could not recruit the best future. People didn't come to train here at UC San Diego except for maybe cardiology and cardiac surgery. All the specialties I've now listed up there are sought after specialties. For this year for cardiology at UCSD, we have seven positions, we had 700 applications and we're interviewing 70, and we're going to accept seven.

That is what's happened for our training programs, highly sought after. We've had this T32 training grant continuously since 1976, which is how we train scientists, not just the clinicians, but scientists and how we're going to improve cardiovascular diseases of the future.

We have about 250 publications annually by our faculty. We have about 250 presentations at national and international meetings by our faculty. Here's another unique thing. Our School of Medicine was established in 1968. From 1968 to 2026, in cardiology, we've only had four chiefs of cardiology. It's been incredibly stable over 50 plus years.

I listed the four major journals in our field. All four of these journals have been at UC San Diego with our faculty being associate editors and being on the editorial boards over the last 40 years. This is my final slide. I just wanted to share what we've been able to do from a research standpoint.

Over the past five years, we've received about 80 million in federal funding in our division, 30 R01 grants, which are really prestigious grants. We've got another 75 million or so in industry awards. I mentioned the T32. We have currently over 150 clinical trials in cardiovascular diseases at the UC San Diego Cardiovascular Institute.

What this has enabled us to do is to collaborate and partner. I personally partner with Cat Jamieson in the Sanford Stem Cell Institute. The next speaker who Cat will introduce, Eric Adler, is somebody who directs our heart failure section, heart transplant program. I was able to recruit him in 2010 because his specific area of interest was stem cells.

This was one of the places in the country that he was coming to to look at and we were able to recruit talent like Eric Adler because of the collaborations we have at UC San Diego. I think what I want to highlight is a decade or 15 years ago, most of these studies, the basic science at UC San Diego could not be translated in the clinical sphere of UC San Diego.

We had to partner with other institutions. But now we can do all of this here together as a single team. We have a big clinical enterprise to not only take care of patients, but also enable the new discoveries, make sure that cutting edge clinical trials that are not available anywhere else are available to patients here at UC San Diego.

I think Cat is going to introduce Eric, who will now share with you some of the unique work that he has done and we've been able to do at UC San Diego. Thank you for joining us.

Catriona Jamieson, MD, PhD: All right. Accomplished. That's all I can say. Shockingly accomplished. This is our place because we dream big, but we also do big. You can see I'm not that sophisticated. But the people that you're listening to are. They're top innovators. Everybody works very closely together. We actually like each other. It's one of those things.

When we see each other at La Hoya shores, we saw Eric Adler walking his dog a little while ago. We're all getting over the day. Eric Adler is the director of the cardiomyopathy center that was named after Steven Strauss and Lise Wilson. They've both had a tremendous impact in the building you're sitting in right now.

It's a really important thing to consider when you look at the root cause of disease, and this is something that Eric Adler is an absolute leader in. He looks at the molecular basis of cardiomyopathy. So if you're not lucky enough to be born with the right genes or to see Dr. Mahmud if to prevent myocardial or heart damage, then you see Eric.

Together at the Speziocarovascular Institute, they've made this one of the top transplant centers in the world, which is amazing. Cardiac transplant centers. This is all because of this collaborative spirit where they really work together, Dr. Mahmud, Dr. Madani, and Dr. Adler.

Dr. Adler discovered a disease called Danon disease and said it's a genetic disorder. Why can't we fix it? Has been working with Stephanie Cherqui and the team at our institute, the Alpha Clinic, the Sanford Stem Cell Clinical Center that Sheldon Morris runs, together with Sandip Patel and our whole team that is undaunted by difficulty.

Holly is here from the Advanced Therapy Center. We really do work together to discover and deliver new therapies here. If it's not done here, if it's not invented here, don't get it. Because we're going to do better stuff. Dr. Adler will tell you about the spectacular things that he's been doing. Thank you.

Eric Adler: Cat's so humble. She said, "I don't do think she sends stem cells on rocket ships to space. It's just the simple stuff here. Well, it's amazing to be here today. We're so grateful for everyone attending. I wanted to start with defining the problem. Why are we here and what are we working towards? It's pretty daunting when you think about it. That despite all of this innovation, where are we in 2026? We still have cardiovascular disease being the leading cause of mortality.

Now, worldwide, one of our great American exports is cardiovascular disease, unfortunately. We know where we can recognize around 20 million people a year die from cardiovascular disease, 1 million hospitalizations from cardiovascular disease. Still, despite all the efforts and technology over the last 75 years, and we've made tremendous efforts. Remember, not too long ago, if you had heard a family member had a heart attack, you just assume they died. We didn't assume, gosh, you had a heart attack.

Now that's rare, thanks to Dr. Mahmud and all these innovations that we have. But despite all that progress, still 50% of people who are diagnosed with cardiomyopathy or heart failure, the syndrome that I study will be dead within five years. People don't realize that I'll see patients that have a little skin cancer, and I tell them they have

heart failure, and they're focused on this skin cancer.

When in reality, heart failure has worse prognosis, pretty much than any metastatic cancer or close to it these days. That's partially because of the advances in treating in oncology, and it's partially because we haven't made the progress that we should in cardiovascular care. The spend is just tremendous. $400 billion a year spent on cardiovascular care in the US. Despite all this, let's draw a comparison, actually to oncology.

In oncology, we know that we've radically changed, and that's a lot of the work done by people in this room. We've radically changed the approach where approach went from four drugs that treat everything, lots of side effects, maybe six drugs. Some of them are literally like mustard gas and things like that, that we use to incredibly genetically inform precise therapeutics.

Now we develop vaccines specifically for people with specific types of cancer. The root cause of the cancer is now addressed, and it's informed by the genetics and molecular biology. Unfortunately, cardiovascular disease, we really haven't done that to the extent that we should. There's only actually a handful of true, what I would define as precision therapies, therapies that treat the root cause of disease. Why is that the case?

Well, we've really focused on these broad categories of things, and that's important, and we have improved the needle in treating blood pressure, high cholesterol, blood sugar. Those have been great. The medicines to treat those things have really evolved. As a consequence of that, I think a lot of the innovation and industry focus and pharma focus has been on these large trial designs. Can we move the needle small amount, which maybe help population?

A lot of us go on these medicines, but do they help the individual? Do they really change the trajectory of disease? They often don't because they're not focused on the individual precise reason that you have the disease. There's a lot of other reasons that we could get into. We don't really use molecular phenotyping in the same way.

If you have cancer, the first thing you're doing is getting a biopsy of something. Tissue is the issue. I've heard that. Then you figure out the molecular reason, and you develop a cocktail that is for your cancer. We don't really do that in most of the time in cardiology. We're starting to, but we really haven't in a long time. There's a lot of regulatory issues. There's a lot of issues with where capital flows.

Capital has flown mostly out of cardiology in terms of investment in therapeutics. If you look at it, on average, there might be 200 trials in oncology for every one trial in cardiology. Even though we have this disease that affects a massive number of people, we still have this gap, and the gap is really around this inability to treat the molecular mechanisms disease. It's hard to. It's daunting if I have to tell a patient I need a biopsy your heart to understand the molecular mechanism.

Not many patients are excited to hear that they're going to meet me in the cath lab, and I can't tell them, I'm actually fixing something. I'm diagnosing something with this big needle I'm putting in their heart. That's been hard to get to. I'm going to talk about how we've gotten around that in a second.

But there's this huge opportunity, which I think is recognized is that, believe it or not, we tend to blame a lot of people when they get cardiovascular disease. Your behavior is wrong, you're non-compliant. You had Chinese food yesterday. You've had too many hot dogs. All these things. You're a drug addict, you're an alcoholic.

When we actually look at them and look closely and look at the molecular root cause, it is stunning how many people are born with genetic things that put them at risk, genetic mechanisms. We do that now routinely. At UCSD, we genetically sequence every patient that's getting a heart transplant.

When we do that, we actually find out about 40% of these patients have a genetic cause that is associated with it. It might not be the only thing. Certainly, they're doing other things that might help, but it puts them at a disadvantage. It's that combination, can we treat the genetic cause that I like to think about sometimes you're dealt a certain deck of cards, you have that hand. It's how do you play it. We're working on the cards you're given. Can we do this?

One of the things that we did leads me to a story I'm going to spend five minutes on, and it starts here. It starts with a patient that I was taking care of in 2010 shortly before I arrived in San Diego. This patient had this

disease, actually named after Morris Dannon, it was this rare genetic cardiomyopathy that almost no one had heard of and no treatments for it.

In this case, this boy, I never heard of this thing. It was supposed to be one patient in 10 million has this. No one's ever heard of this disease. We saw this young boy who's dying waiting for a heart transplant. Before he died, we were developing a new therapy, and this wasn't just me. This was pioneering scientists here in San Diego and in Japan and others, where we could take skin cells and we can make them into heart. We can take skin cells, make the skin cells into stem cells, and use that stemness to redirect into heart.

In this case, here, we are taking a piece of this boy's skin before he died. We brought it to our lab, and it's very surreal. Now I'm in San Diego, I'm seeing these patients. I'm rounding on their hearts beating in a dish in my lab. It seems like a science fiction thing, but this was the reality. I remember the day that we were working on this disease, Dannon, no one had ever heard of, and we were growing the skin cells into stem cells. We didn't have enough skin cells.

This boy and his mother showed up to me from New Jersey and I was like, what are you doing here? They're like, we want to help you. I'm like, what do you mean you want to help me? I'm in this lab, have some mice. I have these skin cells. She's like we want you to take our son's skin, make his cells into heart. Like, why? Because no one else is doing anything to do with this. We want to do whatever we can.

He flew all the way from Jersey. I said, I have no way of treating you. I have no idea. He's like, that's all right. We're doing what we can. That really served as an inspiration for all of these people with these various genetic disorders which get brushed aside. Individually, they are very rare, but collectively, we're almost all affected by someone that had something like that.

In this case, inspired by this boy, we made heart cells out of his skin cells. Well, here's his heart cells that are growing. This is a paper actually in a similar group of heart cells. Here are his heart cells growing in our dish. The little lines are like EKGs from his stem cells that we generated.

What we were able to do, remember, I said, we're so rarely able to develop molecular therapeutics in cardiovascular disease because we don't have access to these tissues and the technology at that time. But now with stem cells we focus a lot on treating people with stem cells, and we'll hear about that, and that shows such great promise.

But in this case, we're using the stem cells. In this boy's sense, we created a factory. We had 96 little wells of his beating heart cells in a plate. Then we stack those plates 10 high in a machine, and we screened every drug ever used by the FDA in 24 hours. You can think in the past, we used to have to make these mice, and it would take years. You would breed these mice. You can't make a mouse breed any faster despite everything. We want pregnancies.

Now, we screened every compound ever identified overnight. We took that boy, we said, I tried everything. We actually found the best way to treat him was to replace a missing gene. Fast forward to now, we have all of these tools where we can replace genes, we can edit genes, we can silence genes. Ten years ago, we were just getting at this.

But today, the way I explain it, we talk about our kids and how they inspire it, I couldn't get my kids interested. I'm like, you know about code? Like your computer code? They're like, yeah, it's like, well, we're all made of code, our genetic code. Just like you can write computer code, we can now change your human code with technology. You've heard of CRISPR and things like that. We're employing all of that.

We actually employed it for this boy and his Dannon disease, and developed a new therapy. In doing that, we're addressing a whole host of cardiovascular disease that was thought was rare, hypertrophic cardiomyopathy, but in fact, affects one in 200 people. Every time you're hearing about people doing sports, dying on the field, all these things, and this just happened in La Hoya a few months ago, a boy died at school with these syndromes. This is happening in front of us and brushed aside.

But now, because of these technologies using stem cells, we can diagnose and develop new therapies. In this case, in fact, working with my colleague and mentor, Barry Greenberg we started with a boy. We made a stem

cell, we screened the drugs. By the way, Sylvia, I can't help but look at her. She was my mentor when I first moved here, so it wasn't possible without mentorship. Having all these scientists here and amazing people like Sylvia to mentor this work is so impactful.

We took it from the very thought of this boy who passed away and this other boy who gave his cells to screening, making their cells into stem cells, growing their hearts, screening drugs on their heart, identifying, in this case, a gene therapy, and then testing that gene therapy. As Cat said so eloquently, we can do everything here within our hospital.

We don't hand it off to some pharma company and hope they look, why should I invest in this? I'll invest in that? Why don't we just make another drug for weight loss? Why don't we make another drug for hair growth. We can hold onto it and develop the value. We did the whole trial at UCSD, from soup to nuts, from the first cells, all the way, the first bag of drug going into the patient, the millions of viral particles to that patient living.

To the trial being published in New England Journal, and hopefully the drug being approved, all really because of this ability to make stem cells from patients and think about molecular techniques. There's more than 80 gene therapies now like this in development. We're seeing all of these things really rapidly coming to the clinic.

I think we're the leading center for genetic trials in the United States right now. Pretty much every company now comes to us to do their trials here, and we're developing in-house a ton of trials with all of our collaborators. This is very exciting. All this being said, and I think I speak for all of us in the front row, it's funny we're talking about a play because even just today I was talking to some investors thinking about investing in research.

When we advance research, we can think about it like a play. We think about the producers. Those are people, whether that's philanthropic folks who donate or investors that are trying to do something as the producers. Then we as directors are trying to put it together, and then the patients are the actors. They're living the story, and we're counting on them.

When it's really magic, we all work together. We all are envisioned together. Things like this, when they really become magical is when the philanthropy is supported by people who care about the cause. I have to call out Steve Straus, who doesn't just talk the talks, but he walks the talk, too, and who stepped up and helps us fund this great work that we're doing here in the Straus Center.

Investigating hypertrophic cardiomyopathy, this cause of death with this boy had, and looking forward to the new cares. So grateful to be here. Thanks for the opportunity, and look forward to the rest of the time.

Catriona Jamieson: You're getting it. I just like to practice French. Fix the living. Thank you for doing that. We're going to move on to fixing the living, different strategies. This base editing molecular scissors, CRISPR strategy is very clever. It's been invented here, applied here. The ball is now being dropped. It keeps going running down the field. What I should say with Dr. Mahmud and with Dr. Adler, they run to where the ball is going to be.

Or in hockey terms like Wayne Gretzky, he always skated to where the puck was going to be, and that's what they're doing. The other person who is doing that is Karen Christman. Dr. Christman is a professor of bioengineering. She was recently inducted into the Academy of Inventors here in the US for being one of the top inventors. Very talented, keeps being trying to be recruited or they're trying to recruit you to Germany, I think, because I know the people there.

International reputation for thinking about things slightly differently. You see this is a common thread here with all of our speakers. Dr. Christman had the idea that, well, you may not be able to prevent cardiac damage. You may not be able to fix a gene that has gone awry, but maybe you can take what you've got there and make it work better.

Karen has invented an extracellular matrix hydrogel. Very clever. It sounds simple, but it actually isn't. But she's very clever at making these matrices as a bioengineer and really realizing where the best place to apply these new therapies is. She's worked with Tach Mahmoud before on peripheral artery or peripheral vascular disease. That looks extremely exciting.

What you're seeing are these teams just get together iteratively to come up with new solutions, and that's how we roll here. Creative. We like to work together. I think that this is what Eric was talking about. We're undaunted

by difficulty, perhaps encouraged by difficulty. If it's not hard, we don't want to do it. It's a thing. I don't know whether it's a San Diego thing, but I think everybody in this room has that. Dr. Christman will tell us about new discoveries. Thank you so much for being here.

Karen L. Christman: Thank you, Cat, for the introduction. I'm a little short, so I'm going to stand, I think, over to the side. But it's a great pleasure to be here to tell you about some of our work. It's humbling to go after both of the clinicians, which I am not one, but I went into bioengineering really with the goal of eventually affecting patient lives and so that, folks like you just heard from, can apply new technologies and hopefully, while I don't treat patients, our goal is to really impact them. Just required disclosures, and we'll talk about some of the works related to Ventrix Bio.

You've already heard a lot about heart disease. I'm going to talk specifically about myocardial infarction or a heart attack, which, as Eric had said, we've exported, cardiovascular disease around the world. It's a huge problem. When you have a loss of blood supply to the region of the heart, you have a cascade of events that happens that leads into heart failure.

That initial stage, it's actually a lot of inflammation and so you get cardiomyocyte or cardiac muscle death, but you also get the blood vessels become very leaky, a lot of inflammatory or immune cells in, and creates an environment that really is very hostile to cardiac muscle survival. That's the first initial days, and then eventually you get scar tissue formation. The same thing, probably everyone has a scar somewhere on their knees or something from when they're a kid. If you get an injury big enough on your skin, it'll get a scar.

But the same process will happen essentially when you have a heart attack is that eventually that inflammation will turn into scar tissue since the heart doesn't have a regenerative capacity like the skin does. Then the heart undergoes what's called this negative left ventricular remodeling process where it will get larger, and then have difficulty pumping blood effectively to the body leading to heart failure.

My lab has been very interested in developing therapies to treat heart attacks along the spectrum to the early stages where you maybe trying to treat that leaky vasculature and the inflammation and salvage the heart or heart muscle to the later stages where we're trying to reverse or prevent some of those remodeling processes.

A lot of traditional regenerative strategies have involved stem cell therapy. We take what I like to think as an opposite approach. Instead of delivering the cells that are lost, what's also lost is the extracellular matrix of the natural scaffolding of your heart. We work on acellular proregenerative biomaterials.

What these are traditionally have been implantable scaffolds, you can see some of those cartoon images, where you create this open porous and fibrous network that allow the body's own cells to colonize it, particularly immune cells. If you design a material appropriately, you shift an immune cell from inflammatory to pro-reparative or pro-regenerative.

This has been used for, say, hernia repair, diabetic foot ulcers, there's a new vascular graft that's also been approved, but they're mostly by and large, implantable and so my lab has been designing more injectable approaches that can be delivered minimally invasively, particularly to the heart, minimally invasively via catheter that doesn't require surgery.

The idea is that we harness the body's own cells and immune response to driver general response. One of the benefits of this is it can be much more cost effective. Particularly the materials we work with are about a couple orders of magnitude cheaper than, say, cell therapies or some other biologic therapies.

Then, particularly compared to a cell therapy, it's not living. It can be stored on a freezer shelf or some of the materials can be stored just on a shelf, and you don't have to worry about whether the cells are living if they've changed with storage or freezing or injection. There's a lot of advantages with this approach.

As Cat mentioned, we work a lot with extracellular matrix materials where we take a tissue and decellularize it, meaning you take the tissue and you essentially strip out all the cells, leaving behind that natural scaffolding or framework, which is the extracellular matrix. I have a quick video that hopefully will play that it's one of my former PhD students who's actually now a cardiologist at Vanderbilt showing just so you can get a quick visual about our cardiac extracellular matrix material and how it's.

Jean Wang: My name is Jean Wang, and I'm a first year MD PhD student in the Christman lab, and this is how we make our therapy for treating heart attacks. We get heart tissue, and the first step is we chop it up into tiny pieces, and we put it into a bath like a beaker right here, and stir it up with a detergent so to remove all the cellular contents.

After a couple of days, we rinse it out to remove all the detergents, and all we really have left are the structural proteins that make up a tissue. We take that and we freeze dry it into this styrofoam-like substance. It's really light and crispy so it's freeze dried, and then we take this and we mill it into a fine powder that looks like this.

We take that and digest it with an enzyme to liquefy it. You can see that there's liquid at the bottom of this and this little bead is just stirring it up and keeping everything well mixed. Then finally, we take the liquid form of this and we inject it into the heart into damaged heart tissue, and once the liquid hits body temperature, it forms a gel that looks like this, and it no longer flows anymore.

Karen L. Christman: That hopefully gives you a little visual on what that looks like. We've now since really scaled up the process. We have a clinical grade process, but it still follows generally those simple steps. When you inject the material into tissue where the arrow is pointing or a skinny electron microscope on the bottom, you can see it goes from a liquid to this porous and fibrous scaffold that does a great job of recruiting the body's own cells to help repair.

We injected directly into the heart attack region and get the body's own cells to come in and help repair that region. What we found, like other decellularized materials, it's anti-inflammatory, so it does promote that pro-remodeling immune environment as opposed to a heart attack is an inflammatory environment.

Then we basically, I like to think of it as create a healing wound inside of the heart and promote development of all the different cell types and tissues that are in the heart. We don't fully regenerate it. It's not unfortunately a perfect heart yet. We're working on that, but it's better than what it was started with.

We encourage blood vessel development, cardiac muscle or cardiomyocyte survival and development, we decrease scar tissue so on the right is from one of our large animal studies. Red is cardiac muscle, blue is scar or fibrosis, and we get significant increases in the cardiac muscle and less scar tissue.

Then we also have some recent data showing that are likely that we encourage nerve development, also lymphatic develop, so basically all components of the tissue. In animal studies that improve cardiac function as well, so that led to Ventrix, the company, co-founded doing a phase 1 clinical trial. That's what the material looks like. It's called ventrigel.

It comes just as a dried powder. You add sterile water, and then you can inject it minimally invasively with a catheter that basically snaked from the femoral artery up through the aorta, and then you're inside the left side of the heart, the left ventricle, and you have a needle that you can inject multiple locations specifically at the infarct.

Fifteen patients were treated between 60 days and three years after their heart attack, and comparing baseline after six months showed encouraging signs of improvements in exercise capacity and decreases in heart volumes, indicating less less of that negative remodeling. But of course, it's a phase 1 trial. It needs to be examined in larger randomized controlled trials.

But going back for the last couple of minutes to my lab, a lot that's still undergoing development, but we took a lot what we learned, I thought about how can we redesign this material to make it easier to apply? For Shammy to make it easier to apply in the cath lab using techniques that he uses every single day.

That catheter approach that I mentioned with the needle is not something that's used all the time. It's just basically used for clinical trials. But what's used every day when somebody comes in with a heart attack, typically is they get an angioplasty with a balloon, often getting a stent, and so what you can do with that same catheter is you can blow it up again, and then you can infuse material at the end of that catheter and go into directly in the vasculature in the region of the heart.

As I had mentioned, if you remember, I said the vessels are very leaky. We wanted to see, could we take advantage of that to target material to those leaky blood vessels to try to reduce the edema or fluid that comes

in that is known to cause cardiomyocyte death. It's also known to increase inflammation. We want to see, could we deliver material like that, have it target those regions and then damaged blood vessels in the heart?

We basically took that same material I showed you, that's a hydrogen and we fraction into smaller components that were better for this to go into the bloodstream, and then we found we can get it to target the heart. On the top, we tagged it or actually all the images, we tagged it with a fluorescent dye. It's just in grayscale on the top set of images, and we found where you're seeing it localizes where the heart attack was.

Then on the bottom, you're looking at three different blood vessels, and in red is what we call our new infusible or iECM and it binds to the gaps between the endothelial cells or the cells that line the blood vessel. What that does, it has still a lot of the same effects that our other ECM materials had.

We found that it really accelerated healing, and particularly, we found reduction in that leakiness of the blood vessels. Again, a shift to more pro-reparative versus inflammatory immune cells, and we increased cardiac muscle cell survival that led to improvements and reductions in that remodeling process.

The top images are MRIs so on the right side is sailing at 24 hours or five weeks after delivery. The iECM is on the left, so you can see the right four hearts basically are larger than the left four hearts, indicating we're able to reduce remodeling. We're really encouraged by these results. This is a small animal. We've done larger animal, and now we're in the midst of doing clinical grade manufacturing and really trying to push this to patients.

As I said in the beginning, I really went into bioengineering because I want to get and want to help develop technologies that will help patients and so we are very focused on getting all of these arrows further to this side and getting these technologies into additional trials. The top one is the original hydrogel. We actually are going to start two new trials within the year.

One that's actually here at UCSC with Dr. Madani and also Dr. Demaria on CABG patients, so bypass grafting patients that can't be fully bypassed, injecting into the region that can't be bypassed to stimulate new blood vessels. We also have a new trial in hypoplastic left heart syndrome patients who undergo right ventricular failure, congenital heart defect.

As Cat mentioned, Shammy and I are pushing hard to try to hopefully in the near future start a trial for interment clottination patients. Then we have some other things in women's health that I'm not going to talk about today, but we're really hoping to push these things more into patients. That's really all thanks to a team of outstanding trainees that I've had in my lab post PhD students and postdocs, and I've bolded.

Hopefully, you can see, many of the physicians here at UCSC in cardiovascular medicine and cardiothoracic surgery that I have worked with really very closely over the past almost 20 years now, and it's really because of them and this close connection, and also now, particularly with the Stanford Stem Cell Institute and Advanced Therapy Center, which I helped co-direct and the clinical center, being able to really accelerate more of these technologies into patients and getting those arrows further advanced to hopefully becoming real therapies one day, so thank you very much.

Catriona Jamieson: As you heard from the last three speakers, this is where the rubber meets the road or the ECM meets the heart. We're really thrilled to have Robert Brill here. He's a professor in our Department of Theater and Dance, and he focuses on scenic design and actually has been put up for four Tony Awards. I didn't meet him until Mel Cruz had to sit right next to each other. What a thrill. What you've heard about here is the heart of creativity and innovation, and this play about the heart got my attention.

The idea that you can repair the living pie des vivant, but sometimes people have to give the ultimate gift, and their families have to make that decision to do that. This is what this play is about. It's about the grief that turns into guilt, but then gratitude from the person that accepts that ultimate gift.

Robert was explaining how he designed the set for this and how to have the impact, the gravity task that this needs. I know that we have this opportunity to have the La Jolla Playhouse be one of the leading centers in the world for really incubating new plays, and that's thanks in large part to Debbie Jacobs and others who were involved with the La Jolla Playhouse.

You see the arts coming together right here. Art matters as much as science. Yes, Steve, I think it actually

does. Steve Strauss is up there. Anyway, I think we'd like to hear what Robert has to say about The Heart. Thank you.

Robert Brill: I feel so unqualified to be in this room right now. Thank you for having me. It's a pleasure to be here and to be with this group of folks that are doing amazing research. We like to think that I teach in theater and dance and that our theaters are our labs as well.

The work that we're doing there- I should start off probably by saying that I was actually an undergrad here at UCSD back when dinosaurs were roaming the campus. To come back years later and to be teaching here and to have San Diego as my home base really means a lot to me.

This is the La Jolla Playhouse has been always known as a home for artists, and their collaboration and relationship with UCSD and with theater and dance has always been very strong. As an undergrad and now as a practitioner, I get a chance to collaborate with La Jolla Playhouse frequently.

This is a project that I worked on with Christopher Ashley. We've done numerous projects together. This paper that I'm holding right now are not my notes for this evening, so don't worry. This happens to be the current draft of the script for The Heart, which is now currently we just started rehearsals in New York two days ago for the New York production of The Heart, which will then transfer to Broadway in the winter. We're very, very excited about that. Thank you.

But really, it is I am grateful to the opportunities that La Jolla Playhouse has offered me over the years, and, of course, now teaching and introducing students to that institution means so much. I'm going to just take you through a little bit of the process of how we go about creating space and creating space for telling a story.

I'm going to show you a little bit of a clip from the production from last year. But the thing that I want to start with, of course, is that, Roger Ravel had always said that there is this unique relationship between arts and science and sciences. That relationship of how they are committed to the work and how they evolve their work, that that's a very unique relationship between their research and their practice.

To be able to work on a piece here to tell this story, and then to be able to also have access to what UCSD offers the world in medicine was really important to the entire creative team. There were so many folks that we reached out to that worked with us to consult with us, along with other folks that were consulting on the pit in all ways so that we get it right.

One of the things that I want to mention that actually is from the script was that there is a line in the script where they talk about and I'm sorry, I did not take Latin in school, but the line non-sibist omnibus, which is not for oneself, but for all, is actually a lyric in the piece. In many ways, it talks about the sense of community.

I mean, as collaborators, it's a really important thing because we feel like we are doing this not just for the art, for the group that we're making work for or for the commercial aspect of it, but we're also doing it for a community.

When you find a piece that actually has that depth and resonates with a community, so many times you don't know who your audience is, but it was really gratifying to be able to do the work here in the San Diego area. Now we get to share it with a whole another region. I'm going to show you a few images here.

This basically we did a lot of research. First off, we start with story. For those of you that don't know the piece, the piece was inspired by the creative team, the music, much of the music. There's a lot of different music in the piece, but it started from the idea of EDM, which is electronic dance music.

While there are a lot of different styles of music in the piece, it starts with the idea of heartbeat. In fact, there's a line in it about two of the characters are meeting and talking in a club about the idea of the difference 60-70 heartbeats a minute versus EDM, which can be up to 120 or 130 beats a minute. That is a recurring theme throughout.

That was really one of the touch points in terms of design was how to create a liminal space that could serve the play, take us on a journey, be many different places, but also be an experience for the audience. Are we in a club space? Are we in a medical environment? Are we at the beach?

The goal was to create an environment really for sound. Chris Ashley had this brilliant idea, and I can't take responsibility for it, which was that we want to tell this story in a very simple, fluid way. We're going to do it maybe in a 20 or 25 foot square space. But we're going to do it with a company of folks and artists present telling that story.

We start off by doing research, and, of course, we have a lot of research available to us here. It was amazing to see how many spaces start to feel like, oh, there's video everywhere. There's electronics. Some of the spaces almost start to resonate with theatrical club spaces, electronics, video, LED technology, all those kinds of things. Of course, it takes place at the ocean.

The idea of how waves are represented and how waves are both sound waves are waves of the ocean, and also even the wave of EKG. Where those things work together, working with our projection designers and all the designers on the team, we created a space that was very active and a very, very electric.

This was a particular image that Chris and I landed on and then trans created a space that looked very much like this. When the audience walked in, you weren't exactly sure where you were, but it was a space for storytelling.

These are various storyboard images where you can see how lines and grids and a very efficient space was created to tell this story in. What I'm going to do now is I have just a little bit of video that I'm going to share with you of the moment of early in the play within the first few minutes, spoiler alert.

Our central character, Simon, is in a car accident, and he is taken to the emergency room. It really is an amazing amazing five minute sequence where his community expands. It's not just about his parents and his family, but it's about this community of people that are now taking care of him, caring for him, and making decisions with his family about the next steps. It's about how that community works and is committed to their daily life. I'm going to just play this for you.

FEMALE_1: 5:55 AM, and everything races out of control.

MALE_1: TBI Glasgow 3, no spontaneous reaction to auditory, visual, or tactile stimuli.

FEMALE_1: Pupils fixed and dilated.

MALE_1: Suspected brain herniation intubated on the scene. Vitals are holding steady with support. Positive ID. Simon Lamar. He is things.

FEMALE_1: Let's do a full neuro check. Bring in two.

MALE_1: Trauma two. [Music]

FEMALE_1: Hello. Good morning, everyone. Nineteen-year-old male, a car accident near Tourmaline Beach, unconscious on arrival. Vitals, blood pressure and heart rate are stabilized. Have the parents been contacted.

MALE_1: Not yet.

FEMALE_1: Cordelia right away. [Music] We have another day of [inaudible 00:55:21] parents. The mothers on our way.

FEMALE_2: I'm looking for my son, Simon Lamar.

FEMALE_3: Sign in and stay in the waiting area.

FEMALE_2: This is an emergency.

FEMALE_3: Oh, in the emergency room. We're doing the best we can.

FEMALE_2: Sean, pick up. I just got here. They said it's urgent, but they won't let me get through. I need you here now. This place is assumed. Pick up David for standing us up. No letting the sound. When I need an answer, you shut down like a ghost town. [Music]

FEMALE_1: Dr. Ramus, we have Simon Lamar perfusion scans.

FEMALE_3: Who?

FEMALE_1: Trauma two.

Dr. Ramus: What are we looking at?

FEMALE_1: What are you doing here?

Dr. Ramus: I'm doing a bypass in an hour. I stopped on my way to check on a golfing buddy. What happened?

FEMALE_1: Car crash, 19-years-old.

Dr. Ramus: What's a 19-year-old doing awake at 6:00 AM.

FEMALE_1: Surfing, apparently. No blood flow. Brain dead. Get neurology to confirm.

Dr. Ramus: Organ donor.

FEMALE_1: Not on his license.

FEMALE_3: He's on call at OPO?

FEMALE_1: Driscoll, I think.

Dr. Ramus: Good. He likes to challenge. [Music]

Robert Brill: That just gives you a little off of it. Thank you.

Catriona Jamieson: We were riveted, Robert. That was amazing. If you just take a seat up here, we're actually going to transition to the panel, the Q&A. Sylvia Evans, a professor in pharmacology here, who's also the co-director of our Sanford Stem Cell Discovery Center will join us on the panel.

She has extensive experience in myocardial regeneration and really understanding what makes the heart tick pun intended, and the metabolic rate of the heart. I'm not sure we're going to have any EDM up here. A new term for me, Robert.

We really just wanted to open it up to the audience now to see if you have any questions for our erudite panel members here. You've heard about people who are creators. They get things done in a way that I've never seen before, and it's pretty dramatic.

But we know that there are problems that still need to be fixed and ways that we can work together to do that. I wanted to actually ask a question of Sylvia. She and I started our careers at the University of British Columbia as did my sister Christina Jamison, who's out here somewhere in the bright lights, who thought science was cool. We didn't know that. But we were making rockets in the backyard. Our parents kept buying us chemistry sets, and we'd literally make rockets.

But Sylvia, what got you into science and looking at myocardial regeneration and how you get the heart to repair itself? How did you think about that as a molecular biologist?

Sylvia Evans: Really, I was always interested in regeneration. I think I was always interested in biology as a kid. I used to love reading about it, but I was always interested in regeneration. I thought it was so amazing that some animals could lose their limb and it would grow right back. Why couldn't we do that? Then I was very interested that a lot of animals can regenerate their hearts. Axolotls do it, zebrafish do it. Why can't we do it?

I think that's really one of the things that got me very interested in studying the heart, was, how can we regenerate it? I came from a field of earlier studying skeletal muscle, which can regenerate itself. It has an endogenous stem cell. You can injure your skeletal muscle and has an amazing ability to repair, but that's not true for the heart. That's how I got into it.

Catriona Jamieson: Sylvia is one of the best teachers I've ever met. We've talked about discovery, innovation, and training, and they all go together. A lot of people you hear these days when you watch the news talk about commercialization first. I don't know what you're commercializing. You have to start with discovery, innovation, training, whether you're in theater or whether you're here working at the forefront of medicine. Karen, what got you into all this?

Karen L. Christman: Similarly, I was always interested in science, and I really liked medicine and chemistry. I

thought I wanted to go into chemical engineering. Then I grew up in Houston and went and saw I think a plant in DuPont. It was like days since last injury won. I was like, this is not what I want to do. Then I was an athlete. I thought maybe I'll be an orthopedic surgeon and treat athletes.

Then I luckily found out about biomedical engineering when I was an undergrad at Northwestern. I was like, this gets to combine all the things that I really like, and I really like the idea of developing new technologies. I switched tracks. I actually went into engineering, and then became really fascinated by tissue engineering.

At the time when I went to grad school, nobody was working in the heart. People had been looking at bone and cartilage for quite some time, but my advisor had a project on trying to do it in the heart. I thought that was really fascinating. I had a family history of cardiovascular disease. Did a little bit of a roundabout pathway, but I did always have an interest as a kid in science and math.

Catriona Jamieson: Very cool. Eric

Eric Adler: I think I was always drawn to cardiovascular medicine, partially because I had family members affected, partially because the cardiovascular system and physiology in general, in med school, it was the one thing you didn't have to memorize a ton of stuff. It just made sense. You could think about it and understand. I was really drawn to that.

In terms of stem cell biology, I was fortunate when I was coming through training was right around the time that the pivotal discoveries around embryonic stem cells were being made. I was training in New York with a scientist, Gordon Keller, who was trying to make blood cells, actually. He was making the hemangioblast. He thought he had the secret to making blood, and they made a wrong turn.

They came in one day and someone forgot to change some media, and they left in some growth factors too long, and the whole dish started beating. What am I going to do with this? He called my boss, and they said, you know someone interested in research? I was there. I saw this thing, this beating. I said, this is incredible. Then leads to where we are today.

Catriona Jamieson: Amazing. Shammy.

Ehtisham Mahmud, MD, FACC, MSCAI: Cat, for me, and I think it's a common theme here, same thing, I liked science and biology. I wanted to be a cardiologist. It was sixth grade. I still remember that. That's when I decided. Then when I was in medical school, I really liked surgery. I didn't like the fact that surgeons got up early morning. I'm not a morning person, and I was like, trying to get to work at 5:30 every morning is not going to be fun for the rest of my life.

But also, when I was in medical school is when this whole idea of angioplasty had just taken off. People said, this is a field. It's in its infancy. I was just fascinated by you don't have to open up the body, and you can fix these things using catheters. It was very, very early. I've just been really lucky in my career to see how moving from a surgical area for cardiovascular disease, we've gone to much less invasive approaches.

Now we can put stents and open up heart arteries. We can put heart valves without opening up the chest. We can obviously do stem cell injections and see if we can get heart function to get better. It's been an incredible journey to see the marriage between technology, innovation, science, and something that can directly impact patient care. That's what I feel lucky about every single day, what I get to do as rewarding on a daily basis.

Catriona Jamieson: Are you cool to your kids now that you're number one?

Ehtisham Mahmud, MD, FACC, MSCAI: Not nationally, but we will be.

Catriona Jamieson: Then Robert, what got you into putting a heartbeat to a play and making us feel things like this?

Robert Brill: Again, so undeserving to be on this panel right now. When I was a kid, I had an interest, of course, like everyone, in puppets, in graphic design. I was also really interested in magic. I got involved in theater as a way to be able to do magic, oddly. That turned into I also had an interest in architecture.

I was very fortunate in my high school they had a fantastic vocational arts program. I had four years of architecture and drafting training. I apprenticed with an architect firm. The great thing now is that I feel like I'm

doing all of those things just in a different way. Every day is different.

Catriona Jamieson: Going to Broadway. They'll come back here. They'll go, I'm going to San Diego. I wanted to open it up for questions because I know a lot of people have a real interest in everything to do with the heart. I think you can hear the carinhoso here, the emotional intelligence, but I think that the networked intelligence on this stage is pretty amazing.

You hear a lot about AI. Natural intelligence can't be trumped. It's regenerative and it's networked. That's my plug for tonight. Does anybody have a question? I think we have microphones out there, if you have any questions. Steve Strauss, any questions?

Steve Strauss: Dr. Mahmud, you mentioned some numbers regarding funding and sources from grants and industry and things like that. I was just wondering if any of you want to comment on how you navigate funding from NIH, from industry, potential conflicts of interest there. Also, as Dr. Christman mentioned, new companies that you might form. There's a navigation process that runs through your research and looking for various sources of funding. I was wondering if any of you would like to comment on that.

Ehtisham Mahmud, MD, FACC, MSCAI: I can start. Eric and I think Karen can comment as well. Obviously, all the sources that you identified are crucial. I'll add to that, by the way, philanthropy, because all of those areas help us differentiate and move forward. When it comes to conflict of interest, the best way to deal with that, obviously, is to completely disclose it and be transparent about it.

I often say, any faculty member who has no conflict in an area of interest, especially in my field or in the cardiovascular diseases field, is probably not a valid expert. Because you really need to work very closely with industry and the private sector because that's often where a lot of things are developed in addition to obviously working with the NIH and federal sources.

It is a challenge at all times, but I will say the thing that has helped us the most in enabling acceleration is that when we get philanthropic support, we can leverage that into supporting younger faculty, getting their careers off the ground, and then they can go ahead and get independent funding.

For me and in my current role, I think that's been the biggest challenge because to get young people started in this environment today is very challenging. Established investigators have many ways to continue their support and funding. It's really getting careers off the ground. Eric, you want to comment on that?

Eric Adler: I think it's a great question. It's a very pertinent question given what's been happening in the last several years around funding. I think we have a traditional model in which mechanistic work and the important questions and exploratory work was funded by the federal government largely through the National Institute of Health and through philanthropic support.

Then when things got closer to what we call translational medicine where you're making that jump from the lab and from this mechanistic work into the clinic, frankly, just the resources you need are so large that it was handed off to industry. I think we shared this, Karen and I, that, for me, the adage is I think about actually musical, I think about Hamilton, which is be in the room where it happens. That's where you have to be.

When you're doing the basic mechanistic work, you traditionally rely on either philanthropy and NIH. That's where those have come from. That's the ground for everything else. Then when it's time to move into these trials that cost $50 million, $100 million, that's when industry has traditionally stepped in.

I think, frankly, we're at a strange time where people are questioning whether we need the support from the National Institute of Health and from things like that. I don't think folks recognize it's like pulling the rug out from under us because if we don't have that support for the basic mechanistic things, that's the seeds which everything else will grow.

It's a very daunting time when you see people shrug their shoulders because what's happening is that for the first time ever, we're seeing in huge waves the epicenter of research not being in the US anymore, which is our secret sauce for the 20th and 21st century, but going abroad. The ramifications of that are to be determined right now, but it's certainly a daunting time.

Karen L. Christman: I'll just add a couple of things. I agree, but I'll just say that the conflict of interest, I think

when I was a junior faculty, I was very concerned about this. But I think as long as you're transparent and you disclose everything in or out in the open, it's all manageable. I think we're all transparent about that.

Then the funding, as Eric said, it is a challenging time. I will say, as you mentioned in your talk too for cancer, there's a lot of funding for early stage trials, but funding for cardiovascular disease, unless you're in a couple of niche things, really, the large scale investors have moved to they don't want to fund it until it's at a Phase 3 trial.

Right now, it's, I think, trying to figure out amongst all these sources, how do you fund that translational? CIRM has been great in California to fund some of that, but I think we're going to see more philanthropy or angel investing needing to bridge those really translational first-in-man, maybe even Phase 2 studies to get us there.

Eric Adler: I think, and Shammy and I talked about this, is that traditionally in academia, on the other hand, we give things away way early and don't let them accrue value. In some ways, there's going to be an opportunity here where we can hold on to things, figure out how to do things, and make that translational step sooner, deliver more value, and then return that to academia and to the institutions that support us.

I think for too long, we've just given things. You'll give us $10,000 for next thing, we'll take it, and signing on the bottom line and giving away. That literally happened to me. I think there's actually opportunity in crisis to change that paradigm.

Catriona Jamieson: Never let a crisis go to waste. I think that's the heart of the matter. We really appreciate everyone being here. We do have some appetizers outside and some very nice wine. We'd like to thank everybody for really getting to hear the brilliant, bold, brave discoveries that our audience members get to listen to and I get to marvel at. Robert, thank you so much for showing us how to have heart.