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Jay & Margie Grosfeld Lecture: “Regenerative Medicine: A Surgeon's Perspective”

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DR. HARRISON: For the second year in the A.P.S.A. agenda, we are very proud to present the Jay & Margie Grosfeld Lecture and, I must say, we do so with great affection for the Grosfelds. Now, I am proud to introduce, Dr. Michael Longaker, Dr. Michael Longaker. Amazing guy. Played basketball for Michigan State University with Magic Johnson at the time they won the NCAA Championship in 1979, and surprisingly, was the only member of that team to go to Harvard Medical School. He completed his surgical residency at UCSF, I'm proud to say, and as a research fellow in our fetal lab, he was the most productive research fellow in history.

After years of exploring all the aspects of fetal wound healing, he made the unusual move of choosing to go deeper into the science; in more depth than our lab could provide, and went to Michael Banda's laboratory and pursued that for another couple years. Quite a commitment. After a plastic surgery fellowship at NYU and a craniofacial fellowship at UCLA, he was recruited by Tom Krummel to Stanford University. He is the director of the Children's Surgical Research Program in the Department of Surgery, Division of Plastic and Reconstructive Surgery, and at the Lucile Salter Packard Children's Hospital.

Michael is the Deane P. and Louise Mitchell Professor, and Director of Children's Surgical Research. He is the Deputy Director of the Stanford Institute of Stem Cell Biology and Regenerative Medicine and the Director of the Program in Regenerative Medicine. Michael has been a member of all the major academic surgery societies, serving as president of both the Society of University Surgeons, and the Plastic Surgery Research Council. He is one of only a handful of surgeons to be elected into the American Society for Clinical Investigation, the Association for American Physicians, and the prestigious Institute of Medicine of the National Academies.

I am not going to try to talk to you about Michael Longaker's extensive research interests and accomplishments because Michael is the master at conveying the excitement of whatever the newest and latest thing he is going after, and he is going to do that today Michael, and Melinda,

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his wife; are dedicated parents of two sons-, Daniel and Andrew. I am so proud to introduce Michael Longaker as the 2009 Grosfeld lecturer.

DR. LONGAKER: Thank you, Dr. Harrison, for a very generous introduction. I want to congratulate you on your A.P.S.A. presidency. I think it is spectacular to have you as the A.P.S.A. president, and to be able to spend time with Gretchen and your first and second generation family members at this meeting. It is for me a real pleasure to be here, and I also want to thank Jay and Margie Grosfeld. I am delighted to be the second Grosfeld lecturer. I want to comment on three things about Jay that I want everyone to know: First, Jay and I share a passion for Big 10 Basketball – although we root for different schools. Secondly, Dr. Grosfeld, was at my very first meeting abroad, when Dr. Harrison sent me to the BAPS meeting in 1988. I knew very little about what I was talking about – ‘the natural history of congenital hydrothorax.’ Jay Grosfeld listened to my talk multiple times on a boat, and on land, and kept me out of trouble. So, Jay, it is an honor to see you again. Third, and most importantly, Jay and I share a very unique bond: When Dr. Grosfeld and I both finished our training in pediatric surgery and pediatric plastic surgery respectively; we were both recruited back to NYU by the same chair, Dr. Frank Spencer.

Dr. Harrison was very generous in his introduction; but, who am I? I am a Harrison Fellow. I am in his “other family.” You have seen his beautiful family of children and grandchildren – but, I am in his laboratory family, and there must be over 100 of us as you heard about yesterday. Initially, I wanted to be a heart surgeon, when I arrived in Dr. Harrison's lab. My first topic was heterotopic heart transplantation in mini swine – a field I am not known for. Approximately 3 – 4 months into my research fellowship, it was Tim Crombleholme, Jack Langer, and I sitting there, and Mike said, “Why don't you follow up on Scott Adzick's observation and look at the way fetuses heal wounds?” Our first thought was – *Why? You're the only person on the planet making fetal wounds!* I could not understand why that would be a good project, but, as always, the professor knew more than I did and fetal wound healing has been a scientific wave that I have been riding for a long time. So, Dr. Harrison, thank you for making my career by looking at me when you asked that question in 1987.

I am going to start with a disclosure, because I changed my talk in the last few days. I want you to determine if I am biased in this presentation, but I know Mike Harrison likes gadgets and ideas; therefore, I am going to talk about new technology that we have been working on, and I think have the ability to change the way you practice surgery.

Let me begin by stating that translational research is not easy. This is a cartoon from *Nature* last year talking about crossing the Valley of Death, and you heard about Dr. Harrison's struggles, not only in fetal surgery, but with magnets. So, I'll tell you a little bit about the areas where we have been trying to make progress in translational research.

First, I am representing a team. I am just one member of that team; the people I work with every day – as part of the Children's Surgical Research program at Stanford. Tom Krummel, Karl Sylvester are both pediatric surgeons. I met Tom through Mike Harrison, when he was a research fellow at UCSF – so, all roads go back again to your president. Peter Lorenz, is a pediatric plastic surgeon; Geoff Gurtner is a microsurgeon, and I will talk a lot about his work. George Yang works on keloids and cartilage, and is an adult general surgeon, and Jill Helms is a developmental biologist and dentist. Together, they are the team whose work I will describe today. I am going to talk about new technologies that address the clinical areas of skin, and bone, and blood vessels, and congenital problems.

Over 200 million incisions are made in the world each year on children and adults. They all end up in a scar, unless there is an unusual situation where we are operating on an early gestation fetus. The questions is, why don't we regenerate, and why do we always heal with either a

“normal amount of scarring” or, approximately 15% of the time, with a pathologic amount of scarring (hypertrophic scar or keloid). This is a very complicated process. We wrote a review article about a year ago and it is an incredible sequence of biologic events to go from the beginning of the wound healing process (and the macrophage dumping over 100 products into that wound alone) to a healed wound (1). The good news is that following an incision, we don't bleed to death, and we usually don't get infected. However, we have evolved for speed in repair and not quality of repair (2). The question is, “why can't we do a better job of repairing ourselves?”

Why would a fetus heal the same injury without a scar that a child would heal with a scar? Has the genome changed? The transcriptome? The proteomics? No, it's all the same DNA. The question is, what is the difference between these two scenarios?

Peter Lorenz, who directs our fetal wound healing efforts, is making progress trying to answer this question. He has narrowed the number of genes that are differentially expressed by fetal and adult fibroblasts down from beginning with thousands to approximately 100 genes. I look forward to him having the opportunity to tell you in the future about why fetal wound healing is “different” from adult wounds, and then how surgeons might be able to manipulate the repair process using genetic strategies to reduce scarring.

I am going to take a different (non-genetic) approach today in describing a strategy to reduce scarring, in the spirit of your president and his interest in devices. There are lots of ways you can manipulate wound healing; electronically, physically, chemically, etc. But, I am going to talk about mechanical forces. This is something that has been very exciting for us. My colleague, Geoff Gurtner, is the driving force in this project; again, he is a microvascular surgeon. Geoff was puzzled by the observation that mice heal with only a fine scar. In contrast, humans unfortunately do not heal with a fine scar. One of the differences is the mechanical environment – either the physiologic forces of movement and muscle or the endogenous skin strain are different between mice and humans. What Geoff did is put a distraction device across the wound and pulled it slowly apart and was able to show a dramatic increase in the amount of scar formation and, it begins to look like a human hypertrophic scar on a mouse, which was very interesting (3). In plastic surgery, we like to make incisions as you know along the lines of minimal tension. I am not going to go into the mechanics of deformation and the elastic modulus of skin, but human fetal skin is very easy to deform and adult skin is much different in its material properties (4). We have been able to show that manipulating adult mouse wounds with increased tension yields increased scarring. The question is, “what can we do in children and adults to move it the other way; reduce tension to decrease scarring. Here is something that Geoff Gurtner, Reinhold Dauskardt, Paul Yock, and me, have been working on. Reinhold is a material scientist and Paul Yock is a cardiologist who directs the Biodesign program at Stanford. It turns out that after you make an incision, collagen accumulates for three weeks, then gets remodeled, and ultimately the wound ends up at about 75% of the strength of normal skin approximately eight weeks later. During this time, the scar will spread until its strength is equal and opposite the skin strain. That is the big picture view of the mechanical environment of wound repair and scarring. The first thing we did was to prove what we are trying to avoid. So, we brought in pure bred red Duroc pigs, which are one of the few animal models that will “over heal” like children or adults. We made increasing sized excisional defects on them. These wounds were closed with increasing amounts of force and tension. If mechanical forces across a wound are correlated with scarring, and if we were correct in our hypothesis (increased tension across a wound leads to increased scar), then larger excisions should lead to larger scars. That was indeed the result. If you look at hypertrophic scars from pigs with excisional wound or human hypertrophic scars, they have the same features.

How can we manipulate wounds to minimize scars? What we have come up with is a technique to modulate that mechanical environment during wound repair. All wounds on children and adults get a dressing. Wouldn't it be great if that dressing minimized scar formation. Our team (Gurtner, Dauskardt, Yock, and me), has developed a dressing that does just that. A dressing applied 5 days post wounding and changed weekly, dramatically reduces scarring in pigs.

In summary, our strategy to manipulate wound healing to be more like regeneration than scar includes exploring with the fetal wound healing approach with Peter Lorenz, working at trying to whittle down genetic differences. In addition, we are also exploring taking a practical approach with a mechanical device that would be quite easy to put on beginning at five days after wound healing and keep it on for a week. We are initiating human trials in the near future to see if a similar device on patients would be affective at reducing scarring and we will see what happens.

Let's talk about a second topic which is cell-based therapy, and what types of cells are readily available in the United States in children and adults. Unfortunately, in the USA there is an abundant great natural resource – fat. As you know, hundreds of thousands of people in America each year pay to have their fat removed during liposuction and the fat is generally discarded following the procedure. Well, it turns out that there is a population of cells in the discarded fat that are quite interesting. Many labs around the world have isolated multipotent mesenchymal cells from human fat. These cells can be “coached” or differentiated into these muscle, bone, cartilage, or fat cells, and you can use them as building blocks for regenerating mesenchymal tissues (5). It turns out in the last year in top tier science journals a number of publications suggested these cells might be pericytes, the smooth muscle cells around blood vessels in adipose tissue.

We asked this simple question, of a bioengineer at UCLA, Ben Wu. I said, “Look, Ben, I'm a craniofacial surgeon and we never have enough bone. If we take this “chicken soup of cells” in fat (these are not a clonal population) and combine them with an approximate scaffold, will we be able to regenerate bone?” To make a long story short, you can make a large defect on essentially the whole parietal bone of a mouse skull, and it will never heal in the lifetime of the animal. However, if you place adipose-derived stromal cells from the groin fat pad in the mice onto a PLGA-hydroxyapatite-coated scaffold, it will regenerative the skeletal defect in eight to twelve weeks (5). These cells derived from fat are quite capable of regenerating skeletal tissue. We published this a few years back, but the question is now “how do you do this even better?” Can we accelerate the amount of bone formation? My laboratory is currently exploring multiple strategies to accelerate skeletal tissue regeneration using adipose-derived stromal cells.

Another area that we work on a lot is craniosynostosis. Approximately one in 2000 children have pathologic premature bone forming in a joint in their skull. We have been working on this area of research for over 10 years, and it turns out one of these sutures (growth plates), in mice, is the equivalent of the one that fuses in the first two months in human – the metopic suture in the middle of our forehead to protect the frontal lobes. It turns out bone morphogenetic protein (BMP) antagonists regulate BMP activity. You have BMPs everywhere in your body when you are developing, but you only form your skeleton precisely in specific areas. Even within your skeleton osteogenesis is precisely regulated as there are joints, and you don't want bone there. It turns out Noggin, a prominent BMP antagonist, is a potent negative regulator of bone formation. We published a paper a few years back showing that Noggin plays an important role in regulating cranial suture fusion in mice (6).

Given the ability of Noggin to suppress osteogenesis in a suture, we wondered if reducing Noggin, hence reducing a “brake” on osteogenesis, would accelerate osteogenesis in a skeletal

defect. To explore this question, a postdoctoral research fellow in my laboratory, Derrick Wan, used an RNA interference strategy to reduce Noggin expression in osteoblasts. The down-regulation of a BMP antagonist in osteoblasts accelerated osteogenesis *in vitro* and *in vivo* (7). We are continuing to explore ways to improve skeletal tissue engineering.

Let's switch gears to another topic; using small molecules, chemical biology, or chemical genetics, to stimulate a very specific type of tissue regeneration. On this project, we collaborated with Tom Wandless, who is an associate professor in The Department of Chemical and Systems Biology at Stanford. Matt Kwan, who was a research fellow in my laboratory and is now a chief resident in surgery at Stanford, and Mark Sellmyer, a MD/PhD student at Stanford, brought the two labs together because Tom had this very neat system where he could regulate protein function using small molecules or drugs. He developed a construct with a destabilizing domain, and a leader sequence. We inserted FGF-2 in to the construct, and I'll tell you a little bit about that in a second. If you do not give drug, FGF-2, is destabilized and degraded as if you don't have FGF-2. In the presence of a small molecule, the destabilizing domain is bound by drug leading to a constitutive overexpression of FGF-2. What we are talking about is turning on protein *in vitro* or in an animal and then turning it off (as the drug is metabolized), which is a very clever way to control protein function.

We chose FGF-2, which you may remember Dr. Folkman's laboratory isolated after heparin-binding column years ago as basic FGF. We chose it because you could stimulate a mesenchymal cell population derived from fat to proliferate for over 10 passages and maintain the multipotency (8). If we take osteoblasts, bone-forming cells, and treat them with mitomycin so they can't divide and transfect them with the Wandless construct, now they are going to be "factories for FGF-2" when they are exposed to the small molecule but they can't proliferate. The FGF-2 goes on and off with drug or without drug respectively, in a very tunable system *in vitro*. We wanted to determine if we had that "factory" of FGF-producing bone cells and added in green labeled fat-derived stromal cells; would they respond to the FGF-2 and increase their number as a result of the FGF-2 made by the bone cells. The answer is yes. Clearly, this is a system that could work if our biology was correct.

But we don't operate on cells in a dish. We wanted to go *in vivo*, and in this case we, as a first step, put a luciferase construct downstream so when you give the small molecule intraperitoneally to the animal and put these bone cells onto a scaffold in a skull defect, you can follow the expression of luciferase using molecular imaging. Using this strategy we can turn on and off FGF-2 and titrate the dose of small molecule to regulate FGF-2 in the animal. Here is the experiment: We put less than the number of green-labeled cells previously used to regenerate the skull defects. Those are green labeled fat stromal cells. We also added in the bone cells which make FGF-2 only in response to drug and put both types of cells into PLGA-hydroxyapatite-scaffold. When we give the small molecule intraperitoneally into the nude mice, the drug stimulates expression of FGF-2 by the osteoblasts. The FGF-2 stimulates proliferation of adipose-derived stromal cells to proliferate and regenerate the skull defect. That is exactly what happened as the animals receiving the small molecule (and the resulting FGF-2 expression) had the most skeletal regeneration. I think this is a very clever idea that Tom Wandless came up with and it shows you how surgeons are interacting with lots of different disciplines, particularly in University centers. This is one of the things that we would think about for children and adults. That is, that you would aspirate fat in a child or adult in the operating room, sort for the cell population you most desire depending on the tissue needs, seed the cells in a scaffold that provides the approximate inductive micro-environment (niche) for tissue engineering and put that construct right back in that patient. This is a vision for bedside tissue engineering.

I know you are pediatric surgeons and may be thinking who cares about bone? You are interested in lung, esophagus, midgut, hindgut and help is on the way with the observation of Shinya Yamanaka and James Thomson, that you can reprogram adult cells, a fibroblast, for example, back to an embryonic-like state (9,10). These reprogrammed cells are referred to as induced pluripotent stem cells (iPS). Joe Wu is a collaborator of mine who is an assistant professor of cardiology at Stanford. Joe wondered if the adipose-derived stromal cell is multipotent, we might not have to back it up as far to be in a pluripotent state. In other words, it might be very efficient to reprogram a multipotent, readily available source of cells from any child or adult, that is, fat-derived stromal cells, back to an embryonic state so that you would use them for regenerative strategies for all types of cells. You can use the four factors described by Yamanaka, or three factors, or two factors. You may know that Sheng Ding's group at Scripps recently used small molecules to create iPS cells (11). What this potentially means for pediatric surgeons is reprogramming a fat cell back to an embryonic-like pluripotent state so that it could be differentiated into any type of cell you desire. The translation of this work is becoming more realistic as we are now using non-integrating viral approaches to generate iPS cells and avoiding the homologous recombination consequences of gene therapy.

Pediatric surgeons frequently perform anastomoses; bringing together hollow tubes, such as blood vessels. In terms of clinical problems relating to blood vessels, I like to think of scenarios involving either too many or too few. You know what the problems are when there are "too many" blood vessels – vascular anomalies, cancer. In contrast, "too few" blood vessels are the problems we struggle with in plastic surgery, such as the tip of the ischemic flap that is failing. That is the biggest deal in the world to a plastic surgeon. So, here is a thought process for everyone – what makes an anastomosis difficult? Is it the size? Is it the quality of the vessels? Usually that comes up in an adult diabetic patient with calcified vessels. That's not the case for the most part in children. Is it space constraints? Certainly this is the case with the microscope. So Geoff Gurtner began to work with Gerry Fuller, a professor in the Department of Chemical Engineering at Stanford. Geoff, as a microsurgeon, understands the challenge of doing anastomoses on tiny blood vessels. He was trying to make the process much easier from a technical standpoint.

The improvement in technology that Geoff and Gerry Fuller, developed was to use a poloxamer that is FDA approved. This unique substance would be a liquid at room temperature and would convert to a more solid, thick gelatin-like substance, at a higher temperature. Once the temperature was reversed down to room temperature, the solid would become a liquid again. In general, this would be analogous to going from water to ice to water again. Working together, Dr. Gurtner and Dr. Fuller developed the technology such that a blood vessel, for example the rat aorta, could be divided and each of the divided ends could be filled with the poloxamer. Then, using various techniques the operative field temperature would be raised a few degrees and the poloxamer would turn into a solid. Now, you would simply align the two ends of the rat aorta and then, using a glue on the outside of the vessels, you could rapidly perform a sutureless anastomosis. Once the vascular clamps are removed, and the operating field heating source is taken away, the temperature would decrease rapidly and the poloxamer reverts back to liquid nanoparticles that would be removed from the anastomotic site with the re-establishment of blood flow.

Dr. Gurtner and his laboratory perfected this technique such that they were able to routinely perform anastomoses on rat aortas using microsurgical technique, and it was significantly faster to use the sutureless anastomosis than to perform a hand sewn anastomosis. This was true whether you were an experienced microsurgeon or a beginning research fellow. Perhaps more importantly than the speed of repair, it appears that without the use of sutures, the foreign body reaction is significantly diminished and perhaps the quality of the repair is improved compared to using sutures. This potentially represents an important advance in microsurgery because not

only do you perform the anastomosis more quickly, but if you can also minimize the cicatricial reaction and scar formation at the site of the anastomosis, this would also be a tremendous advantage of the sutureless technique. For pediatric surgeons, this is a potentially exciting new technology to trivialize how you put hollow tubes together. Dr. Gurtner is continuing to develop this technology for future clinical use.

What about cancer? Cancer is an enormous clinical burden in children and adults. You keep seeing and reading about personalized medicine approaches and how this may make an impact on the future of caring for cancer patients. It is not trivial to obtain a diagnosis for some tumors. Depending on the anatomic location of a mass, it may be difficult or not possible to obtain enough tissue on a biopsy to establish a tissue diagnosis. This is where another colleague of mine, Howard Chang, an assistant professor of Dermatology at Stanford, along with Eran Segal and Michael Kuo, developed a novel technology that derives the genomic signature of a tumor from a CT scan without touching the patient (12). When Howard told me about this technology, I thought it sounded a little bit like "Star Wars." It turns out that they were serious and can take the features of a liver tumor on a CT scan and can predict almost 80% of the genome signature of the tumor. As you can imagine, to use a business term, this technology is pretty disruptive to current approaches to diagnosis and treatment. Currently, when a patient has a CT scan, you see a mass you try to obtain a biopsy which becomes a big deal if it is a brain tumor, located near the breathing center. Getting a biopsy is not always easy depending on where the tumor is and surgeons know this better than anyone. If you are successful in obtaining a tissue biopsy, the pathologist looks at the anatomic features under the microscope and usually makes a diagnosis. In addition, you can grind up the sample and you can derive a genomic expression pattern with a microarray analysis. This "wet lab" approach is expensive. What if you didn't have to touch the patient to derive the genomic signature of the tumor? What if you could look at all 30,000 genes? Essentially Howard Chang and his colleagues have come up with a way to do this. They evaluated patients with liver tumors on CT scans and using a software program and the features reported by a radiologist, they were able to derive approximately 80% of the genome expression of the tumor (12). Imagine how this technology, if commercialized, could be used to improve diagnoses and guide individual therapy. For pediatric surgeons who frequently deal with solid tumors, this technology could have a considerable translational impact.

Lastly, let's talk about congenital problems. Cleft lip/palate is the second most common birth defect in the world. Depending on your racial incidence, it could be 1 in 500 to 1 in 2000 births. As a result of fetal diagnosis and therapy, many cases are now referred *in utero* so pediatric plastic surgeons are seeing an ultrasound and then counseling the parents about the operations that the unborn child is going to have in the years ahead. Karen Liu was a post-doc at Stanford working in Gerald Crabtree's laboratory when we met to discuss the idea of using a small molecule to prevent cleft palate in a transgenic mouse model. Karen is now an assistant professor in London, and doing very well. If you knock out a gene (and many people in the room have done this) and look at developmental consequences, if the gene is really important, you cripple some developmental process. Using standard or inducible knock-out technology, when you delete the gene, it is gone forever in that animal. Karen's strategy was different and would allow her to stabilize a protein *in vivo* whenever and wherever it would be normally made. Dr. Crabtree published a paper describing the biochemistry *in vitro* of this novel strategy (13), but Karen did not know if it would work *in vivo*. Karen Liu was able to make it work.

Karen, along with other members of Dr. Crabtree's laboratory, designed a transgenic mouse which knocked out the gene GSK3-beta. These knock-out mice developed with a cleft palate. She also designed a transgenic mouse using Dr. Crabtree's chemical genetic strategy which modified the GSK3-beta in such a way that if you did not treat the animal with a small molecule that would stabilize the GSK3-beta protein, it would be degraded immediately. That is to say,

in the GSK3-beta mouse they designed, if they were not treated with a small molecule or drug the GSK3-beta would be immediately degraded everywhere it was being made in the developing embryo and potentially mimic the knock-out mouse. Indeed that was the case as the GSK3-beta transgenic mice that did not receive the drug via maternal injection, the fetuses developed a cleft palate (14). Karen then took the bold step of asking that if we were to treat the fetuses with the analogue of ribohmycin, would it cross the placenta and perfuse the fetuses, leading to stabilization of the GSK3-beta protein? If this were the case then, in theory, whenever and wherever the fetus was producing GSK3-beta, it would now be a stable protein that would perform its biologic function. Her theory was that if you gave this drug to the pregnant mother during the window of palate formation (approximately 12.5 to 14.5 days gestation; mice are born at 19.5 days gestation), could you prevent or rescue cleft palate formation? It turns out that Karen was correct. When the small molecule or drug was delivered to the pregnant mother during the two days that the palate was forming, the mice that received the drug indeed had either partial or complete rescue of their palate (14). It was extremely interesting from a developmental biology standpoint that if you gave the drug prior or after to the 48 hour window of palate organogenesis, the palate was not rescued. This is strong evidence that there is a precise competency window when you can rescue a developing organ or tissue. From a pediatric surgery standpoint, it was also interesting that another midline structure, the sternum, was also rescued in this system. In addition to the cleft palate in transgenic mice that did not receive drugs, they also developed a cleft of the sternum. The sternum develops approximately between days 15 – 17 of gestation. If drug was given to the pregnant mother during those two days, the GSK3-beta would stabilize and this also would be able to partially rescue the clefting of the sternum. Because Karen had the bold vision to try this approach, she was able to publish this paper in *Nature* and, as I mentioned earlier, has now gone on the lead a very productive laboratory in London (14). This is a particularly powerful example of an interdisciplinary approach where a developmental biology laboratory and a surgery laboratory are brought together by an outstanding post-doc to ask a very far-reaching question. I encourage all surgery residents in the room and pediatric surgery faculty to pursue interdisciplinary research programs where surgery labs are collaborating in very different fields to answer difficult questions.

Finally, you hear a lot about stem cell biology and when is it going to impact clinical surgery. Children and adults die everyday due to cellular, tissue, or organ dysfunction or deficits. In this lecture, I hope I have described how through new technology development, with or without cells, one can potentially improve clinical care of children and adults. I want to emphasize that clinical leadership is important for clinical problems. Through either new technology and/or stem cell biology, we are not trying to put pediatric surgeons out of business. In contrast, I think pediatric surgeons can play a leadership role in regenerative medicine.

In conclusion, I do want to thank Dr. Harrison, my mentor, for his kind invitation. I also want to say how thrilled I am to be able to deliver this Grosfeld Lecture. Thank you.

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