The Marvels of Nanotechnology

A new frontier in medicine explained by one of its pioneers, **Dr. Mauro FERRARI**, President and CEO of The Methodist Hospital Research Institute

Wednesday, March 23, 2011 at 7:30 PM, Columbia University, New York, NY

Crossroads: Good evening, my name is Molly Poole. I am a medical doctor, and I would like to welcome all of you on behalf of the Crossroads Cultural Center. I would like to thank our co-sponsors: the Columbia Catholic Ministry and the MedConference.

We are very pleased to have with us Dr. Mauro Ferrari, President and CEO of The Methodist Hospital Research Institute in Houston, Texas. The story of Dr. Ferrari shows that there is nothing mechanical or automatic about the birth of a new field in science and technology. The development of ideas, the sacrifice of hard work, the willingness to take risks, the creation of a community of researchers that share the same vision—all of these steps have a deep human dimension, and require a certain type of person and a certain culture that cannot be taken for granted. This is particularly true when the motivation for research is to help others, as is the case with Dr. Ferrari and biomedical nanotechnology, one of the most fascinating disciplines in contemporary science. Crossroads is honored to host Dr. Ferrari for a wide-ranging discussion on his cutting-edge research, and also on the human and philosophical significance of scientific work.

Some biographical notes. Dr. Ferrari serves, as we said, as President and CEO of The Methodist Hospital Research Institute. He also teaches (and practices) in various hospitals and academic centers and is the President of The Alliance for NanoHealth in Houston. Dr. Mauro Ferrari is a founder of biomedical nano/micro-technology, especially in their applications to drug delivery, cell transplantation, implantable bioreactors, and other innovative therapeutic modalities. In these fields, he has published more than 200 peer-reviewed journal articles and 6 books. He is the inventor of more than 30 issued patents, with about thirty more pending in the US and internationally. Dr. Ferrari is also an academic entrepreneur, with several companies that originated from his laboratory.

Dr. Ferrari's degrees are in Mathematics (Padova, 1985, Italy), and Mechanical Engineering (U.C. Berkeley, M.S. 1987, & Ph.D. 1989). He attended medical school at Ohio State University (2002-03). Dr. Ferrari is a native of Italy, became a U.S. citizen, and he is married and has 5 children, and just to prove that he is no ordinary human being, he has not one, but two sets of twins!

I present to you Dr. Ferrari.

Ferrari: Thank you for this most gracious introduction. I'm delighted to be here and I have a few slides. We'll have a Q & A, and I'm really looking forward to the interaction with you all and I'm honored and delighted you invited me.

I took the liberty to title this talk, "NanoMedicine and Simon of Cyrene."

This is Maria Luisa. She had just turned 21. We met a few weeks earlier and of course, for reasons that are all too obvious, I had completely fallen in love with her to the point that literally within hours of meeting her I had proposed to her that we should get married. She said, "You've got to be kidding." She was 20, I was 23, and this again is a few months later. This is a picture from our honeymoon. So at that time I had just gotten an offer of a scholarship to go write my senior thesis in mathematics at the University of California, Berkeley, and I wasn't going to leave her behind in Italy with all those Italian men, so we got married and we left. I sold my car so we could eventually go for two or three days to this beautiful place. I told you Berkeley and I meant it. This is our wedding picture. I'm going to be showing you a number of pictures from my family album, if you don't mind. And here's an even more Berkelian photo. We got our degrees from Berkeley and then things were a lot of fun, and then the children came—Giacomo first, and then the twins, Kim and Chiara, at which point I got a haircut. I got a job; I was a professor at Berkeley at that time, and I stayed there for about 10 years. Maria Luisa had this great sense of humor and she had this great sweetness to her. The picture that I'm showing you comes from the albums that she would keep. This picture here is called *My Flowers*, and if you come and visit me in Texas, which I hope you will, you will still find some of these roses which have been transplanted. This is some sort of a

miracle. They've survived the transplant from California to Ohio to Washington when I was at the National Cancer Institute for a couple of years, and now Texas.

And here is where it gets a bit technical. Changing the order of the factors, the result does not change. It's a bit mathematical. [Shows photos of the twins in different positions in the baby carriers] Whichever child goes up front during the day, they take turns, very democratically. But you start to see here that even though just a few months have gone by, Maria Luisa looks different, and there is a reason for that. Even though she was living a full and apparently happy life, the little pains that she was feeling in her stomach were more than we thought they were. Actually it turned out she had very advanced cancer at the point that it was discovered. This is the last picture of Maria Luisa alive. This is the birthday of the twins, Kim and Chiara, so we are celebrating, but it is a difficult celebration. She died two weeks later. I was a mathematical physicist. My job was to do many different things, but mostly I was working on how galaxies evolve and all that stuff, and I would kind of get excited scientifically in many ways, and I don't mean to diminish the importance of that work, but after this, it became kind of difficult for me to work on things that were not related to medicine.

This is the picture, a dear picture for me, because you can see the sunshiny expression, the outlook on life that she had, a wonderful young lady, and that was the dress that she wore when she was cremated. It was her choice, so this is an important picture.

And then I asked the doctors, (I was a physicist, what did I know about medicine? I didn't know anything about medicine. I hardly know anything now.) "Come on, guys, look at her. She is playing with kids; she is doing everything, but there is this pain that will not go away. How is it that there was no sign, no evidence, nothing that could be detected? And we find out about this and we know for a fact that she is going to die. It's almost counter-intuitive unless you are in the business." And their answer was two-fold: "Number one, we were not able to catch it early enough. And number two, the disease has spread all over the place, all over her body, and when it does that, it is no longer a single disease, it is many different diseases, and essentially we don't have the ability to come up with a sufficient variation of different drugs that hit these great, regenerative diseases, this great complexity of diseases, and that is why she's going to die." And so she did.

At the time I think it is an automatic reaction for all of us, "Man, I've got to do something! What do you have? What do I have in my pockets?" I didn't have any tools that were medical, but I was a professor at Berkeley where there is a lot of great technology, a lot of great science, the beginning of the days of the micro. I said to myself, 'Come on! If you tell me that the one problem is that you cannot detect quantities that can tell you when somebody's got cancer or not, to image it, or through blood tests, or whatever, that's a technology problem. I know something about technology. If you cannot bring the right drugs in the right combinations to the right places, that's a problem of transport. That's a problem of engineering. It's a problem of physics.' And of course I was a little bit delusional when I was thinking those thoughts.

Fast forward 15 years, and it was a very emotional moment for me when from some of the considerations that took place in those years, and we had the privilege, it was a personal relief in many ways to be able to contribute to those considerations, that the advent of innovative technology to address those two exact problems—picking up things early, finding out if therapy works quickly enough, getting therapy to the right places at the right time, starts to become reality through the enabling powers of a set of technologies that were micro back in the day, and they are nano now. To go smaller is harder. It takes time, but the trajectory of evolution is almost predictable.

So what is nano? To me, nano is a set of tools. Intuitively it means working with little things. It's a set of tools that allows you to bring into reality this whole notion of personalizing medicine, and in particular, personalizing cancer medicine. That is what I've essentially spent my life on ever since...

Some more family pictures...I was very fortunate to marry Paola. Paola was a high school sweetheart of mine before I met Maria Luisa. The only thing is, Paola never knew she was a high school sweetheart of mine! About 20 years later I was able to tell her, and things kind of worked out after that. By a curious coincidence, Paola was at that time a graduate student here at Columbia University, and she's very upset that she's not here today, but she sends you her best wishes. Little would I have known, and little would she have known, that after Columbia she started working at the United Nations, and she had this great career which came to a crashing halt when she met me in a romantic sense. As if it weren't

hard enough to pick me up with the three kids, a few months later she became pregnant and we went to the doctor's office for the sonogram, and you start to see on the little video the legs, the body, the head, the other head! You can imagine poor Paola. She went from zero to 5 kids within a few short months. She used to be nicknamed "Zero to Five Lady."

So what are the pieces that we call personalizing medicine? Let's take a look at the broader perspective of things. I told you about identifying signatures of disease possibly from the blood, from fluids, in ways that are non-invasive. You cannot poke holes into people to look at tissue all the time. You cannot give people x-rays all the time, and even if you could, you don't have the resolution to look deep enough and small enough. So the whole notion of extracting information from things in a non-invasive fashion—a little drop of blood, or from sputum, biological fluids, and finding a way to identify markers of disease. Now there was a thought a number of years ago, Dr. Renzo Canetta is a great expert, a dream that it would be possible to find individual markers of disease, some sort of a magic molecule that if you find in your body it means, man, you've got cancer, and by the way, it's in this place and it does this, that, and the other.

It turns out cancer is health out of whack, out of balance. A number of the fundamental processes become disorganized. Some become over-expressed; some become under-expressed. So it is a matter of loss of balance in processes that have to do with health, so you don't find the magic blue molecules that say, "Look, I'm blue; I've got cancer." But it is a different intensity, so you have to track many different molecular channels to understand if somebody's got a disease, or not, and how they respond to treatment. That's one thing. Another thing, the notion of getting drugs to the right place, using drugs at the right time, mimicking what the body does with the glands. They secrete things in the body to maintain health or to fight a disease in both. And no matter what you do in medicine, it's always a good idea to find the way to work with the body's regenerative capabilities and healing capabilities, and help it bridge and do the things that it can't do by itself. Those are the four things.

So I'm not going to be giving you any lecture about nano in any academic or formal sense. I'm going to continue to show you pictures from my family album, and in this case the family is going to be folks in the lab and the things that we do. There are many other smarter people out there, but these are the things that we do. I know them best because they are done in my lab. I have a big lab. About 100 people are in my lab.

Nano is not new to the world of cancer. As a matter of fact, the first nano-drugs, define nano any which way that you want, you will always be able to identify the things that we call liposomes as nanoparticles, little fat globules, 100-115 nanometers across. You see one there with a drug inside. Why do you want to encapsulate a drug in a little nano-capsule? Because it may give you an advantage in bringing the drug in greater concentration to the cancer that you want to treat than the simple naked drug would do by itself. They just inject it in your bloodstream. Case in point, this first nano-drug approved is called Doxorubicin which is still used very widely in all sorts of fields of oncology. It's a drug that is very potent, very effective, but of course doesn't have great specificity for cancer cells, so it can hit and damage other parts of the body, in particular the heart. Now it turns out somebody discovered if you put Doxorubicin in the nanoparticle, and inject this nanoparticle, this liposome...look what happens. These are blood vessels that feed the tumor, and these others are blood vessels in a healthy part of the body. Do you notice any difference? There are these things here which we call *fenestrations*. The real word would be *holes*, but in medicine you like to use big words with 4 syllables. If in medicine the word has more than 4 syllables, it means it's a disease that you don't know how to cure. So fenestrations, if you make the particles the right size, they are going to be able to find a way through the hole and stick to the cancer a bit longer. So you get a bit more Doxorubicin in the drug. This was approved in the mid-90s, so it is not even off-patent, and it is a very simple example of a nano-drug. If you look at the overall market, science has to be crass in the way we look at impact; nano-drugs in the U.S. have exceeded a 5-billion-dollar-a-year threshold in 2006 and are now approaching a 10-billion-dollar-a-year threshold, which makes it a significant player. So we don't have to wait for the Martians to land and the little green men to come out and bring nano to the world of medicine. It has been there for a long time, and there are many other examples.

Again, I don't want to be too formal about this story, but conceptually, how can you make sure that you bring more and more drugs to the right places and less and less to the wrong places? There has been a school of thought that says if you can put molecules in the little particles that conjugate preferentially with other molecules that are preferentially expressed at cancer sites, you would be able to get greater concentrations. It was a great theory, but unfortunately it's meeting with a

very sad reality that it doesn't really work. Why? Because distributionally the loading is not governed by recognition as much as it is by the ability to penetrate biological barriers in the body. Let me elaborate. The body is built like a medieval fortress—it's got the big walls, the mote, the crocodiles, the guys on top with the arrows, the caldrons, the boiling oil, and all those things. So to get to the treasure room...once you get to the treasure room it's easy to recognize; you open it up, pick it up, whatever you want to do. That's easy. The hard part is to get there without getting killed. So metaphorically speaking, these are some of the barriers that you've got to play with, very, very, very scary. And of course we are in Houston, Texas. You've seen the movie *Apollo 13*? To get to the moon is a very difficult trick with many barriers. The people at NASA realized that they couldn't do it with a single cannon ball. They had to do it with a rocket at multiple stages. Each stage was designed for a part of the trip. That's what we do. So we came out with this notion of multi-stage vectors where the first stage lands on the blood vessel wall that feeds the tumor. The second stage penetrates to the tumor. The third stage localizes inside of the cell, and so on and so forth. Multi-staged systems.

And a movie is worth a thousand words. This movie is courtesy of French National TV. [Shows movie] These are nanoparticles that make it across this barrier and identify the cancer cell. Actually the particles are particles that we also put on the cover of *Nature* journal and on which we have done a lot of work. It turns out that particles are not the particles that we all have in our fantasy of what nanoparticles should be like. As a matter of fact, like you wouldn't dream of building a plane first and then try to find out if it flies, that was the Wright Brothers' philosophy, now people do mathematics, people do laboratory experiments, and then they see if it works. Finally in the nano-world, not only do we make things, but we're also able to do the math so that we can predict the behavior of the nanoparticles, and it turns out that its vertical shape is the very worst possible that you can have, which of course does not make me very popular in nanotechnology meetings, and if you make things like these "half-coconuts" or disc-like, you can actually identify the best size and shape to get places. How do you know? Remember this notion of personalizing treatment by picking the right combination of drugs to hit the great molecular diversity of cancer? I think of cancer like malignant snowflakes. You cannot find two of them that are alike. You are going to have to convince me that one day going the molecular therapeutics route, you are going to build a very sufficient number of different molecularly recognizing compounds to kill everybody's cancer. I am not a believer in that right now.

But I have another idea which may not work either, but you have to try different things. [shows moving image] So now you are looking inside of the blood vessel of a living animal, which is florescent green. There are animals like that. And actually the guy that cannot be distracted from making the animals florescent green or other colors won a Nobel Prize for that. So this is the blood vessel wall and you see these particles zooming by. They have different colors. We can follow the trajectory in the animal. From the image observation of the blood flow, I can identify the characteristics of the flow; I can even track particles, and with the cohort of mathematicians, back-calculate information about the trajectories, and based on this, and here's the point, I can personalize the carrier to the specific lesion that I'm observing. And then what drug I carry is not important. Killing cancer cells is very easy. You can do that with water. You can drown cancer cells. The problem is not what drug to use. The difficult part is making sure they don't kill everything else. So the notion of carrying the drug to the right place, as simple as it sounds coming from a simple engineer, may have some advantage to it.

I work with some great people who actually have the ability to image pretty much every blood vessel, including the smallest blood vessel that feeds the tumor, so we have in our room imaging, in another room as an observation we do the mathematics that we have developed to generate the code that gives you the ideal size and shape to get the particle to the right place. And then you have to make it the right size and shape. It's not simple in the nano-world. And then I have a big group of people in my lab, molecular biologists, and you see here some images...You have to study how these particles interact with the cells. We don't have time to describe the whole story, but it's fascinating to see how cells react to stimuli that are encoded. I don't want to belabor the point tonight. I just want to give you an idea.

So we are able to do things that nobody else can do, as far as I know. We are able to target places that are very difficult to get at, such as the pancreas. 95% of the people who get pancreatic cancer are dead in 6 months. So nobody should ever over-promise, but I think there are hints of innovation that perhaps can help.

I like happy-ending stories and this is another example of that. These are mice that had very deadly, triple-negative breast cancer, and they are now collecting social security checks! They are so happy. They've been going on for months and months and months, and they were only expected to live just a few weeks.

I started looking at cancer in a different way, not in terms of the six traditional hallmarks of cancer, but as a disease of mass transport dysregulation. It's a disease of multi-scale. So we put together major centers funded by the National Cancer Institute, and we do multiple different things along those lines. That's the first part.

Second story, do you remember that we talked about the notion of picking up signatures of disease from peripheral blood, for instance? Because of a number of biological considerations we said that upstream of that, essentially looking into the garbage can of the blood, the degraded proteins and peptides, and looking at differences, this is the ultimate problem of the needle in the haystack. And we're looking at this, looking at the overall protein populations in the blood stream. The sequencing of the genome has been a lot of fun, and a lot of great technology and a lot of great science that has come from that, and much more will come. But the problem of completing the understanding of the genome is many orders of magnitude easier than the real difficult problem of figuring out the proteome, the complexity of the proteins that come out of that. And look, same gene on different proteome. You can get remarkably different creatures. So it's very difficult, a needle-in-the-haystack type of problem. So very fundamental tools in genomic technology are the same tools that have been used for making computer chips that transform the world, the use of metography in making computer chips, or for making DNA, micrabase.

Some of you may remember Gordon Moore, a very famous entrepreneur on the computer technology side who predicted that every 18 months computer power will double, "Moore's Law." He said that in 1965, so it has been true for 50 years. Why can computer guys double the power every 18 months? It's unbelievable! Because they can make things smaller and smaller on the chip—that's all it is, from micro to nano. Now every piece of electronics that we use is nano-electronics. Nano used to be a small part of electronics; now any piece of electronics that you want to use is nano. I am thinking that medicine will suffer the same fate.

Here is the equivalent of DNA chips; these are nano chips. It used to be that DNA chips...I remember when I was consulting 15 years ago...the smallest domain that they could make was 100 microbes. These, say 10 nanometers, if you do the numbers, I can get 100 million times more information...than half a matrix could 15 years ago. Look at the level of control over the dimensions of the space; it's a different technology. It gives you the idea of the computer power equivalent in the world of biology, and here are some of the things that we can do in the clinic: A drop of blood (this is a retrospective study), and look, these are folks in the context of cancer of the colon, of the rectum. This group of people here has polyps, so you want to keep monitoring them, but they're not going to die unless these things evolve into something else that is bad. These others have early-stage cancer. If you give them what you've got, they will be saved. These others have late-stage disease; no matter what you do to them, they are pretty much going to die. From a drop of blood, that is the type of power. Don't take this to the clinic; don't take this home. This is a retrospective study. A lot more has to be done. I just want to point you in a direction.

I have shown you two types of nano things: I've shown you nanoparticles and I've shown you nanosurfaces. Now I'm going to show you nanochannels. This blood line here is a nanochannel. You are looking at a cross-section, so start moving across this nanochannel, and molecules will move. How small is this thing? You see the control of the dimensions. I'm claiming that it is 3.6 nanometers. How do I know that? Do you know what each of these dots is right here? Each of these dots is an individual atom. And we know in a silicon light... is the distance between one atom and the next, so it's perfectly healthy; there is no messing around with the laws of nature here. Boom! So I know exactly what this is. I can make hundreds of hundreds of millions of completely identical nanochips, nanochannels like this, and I can use them to deliver drugs following a time released profile that mimics what the body does. I'll come back to this in a minute. This is the highest production of a nanostructure anywhere, and we have 5 products that are going to the clinic, and here is the story right here, but these are essentially glands that are going in the body.

The only thing I'm going to tell you about this next slide is that we are actually going in space with this and this is supposed to be done in April. We won this award and so we get to take this in space for certain scientific reasons, but the

fun part about this is that we've got the chips and these guys just have to finish up the rockets. I don't know what's wrong with them. These are people that rent from NASA. This qualifies the first scientific experiment at work...[inaudible] spacecraft.

I'm going to conclude my nano-stories with the notion of regeneration of tissue. We are working on the regeneration of bone and the soft tissue that goes with that in the context of a large, multi-institutional program which is osteo-regeneration of sheep being fixed up through this technology where the fourth form of nanotechnology is a component of a biological hybrid material that helps regeneration. The typical problem that you have with new technologies as they come into existence in medicine is that they are very expensive, and the south of the world, if you will, and the north of the world, never have license to that. And then sometimes the pharmaceutical companies or medical device industries will donate. It turns out that pharmaceutical companies are the largest donors of medical help, more than countries, so it's unbelievable how much they do. Nevertheless, it is a strategy that perhaps can be re-thought with charity, the idea of exporting new technologies so that they will be directly addressing the difference in provisional health care to the haves and have-nots of the world. Developing them so that they will be reducing the differentials is something that is being done in different places.

And here are the funding acknowledgments. [shows slide] These are the companies that we have started. I have a financial interest in all three of them: one is public-related, two are public. And here's a list of names of all the people I work with. They come from all different backgrounds.

With this, I'll take you back to where everything starts from and the reason why we do what we do. [shows slide of Maria Luisa and 3 children] And now I think it's time for the Q & A. Thank you.

Question: In the title, you mention Simon of Cyrene. Why?

Ferrari: Simon of Cyrene is the reason. Do you want the short answer or the long answer? Long answer? This is a difficult concept. It's so difficult that I never write things and I actually wrote this one down. Would it be okay if I read it? It gets worse because it is in Italian and I will do my best to translate.

It's about *Fratello Dolore*, Brother Sorrow. It kind of sounds more like it's supposed to be in Italian, so I will read and translate:

Let us then allow ourselves to contemplate Fratello Dolore. He is not a brother to seek, a brother whose company we should pursue. If we did that, it is not an affliction to cause to oneself or others, like for Sister Death, *Sorella Morte*, if we did that, that would be evil, that would be mental disease, that would be contrary to Divine Precept. Brother Sorrow is very difficult to love; he's very difficult to tolerate, to understand, to bring to oneself, to introduce to our friends as a traveling companion in our earthly experience. It is very difficult to integrate him in our lives in ways that are harmonious with the Precept itself. He is a source of extraordinary strength and of interminable energy, but it is very difficult to be thankful for his presence which still is a central guide to all aspects of our life. Life requires the guidance of the Fratello.

To a sudden light after darkness, our eyes respond with pain, with *doloro*, but that is how they acquire true vision. The Lord does not want us to suffer, and He does not want us to die. He wants our hands, in difficult moments such as those, as He's waiting to welcome us with a smile at the first light following the final birth. And I was never able to be upset with the Lord for the encounters with the Fratello and the Sorella, despite their unbearable intensity. I do have my faith, but certainly I have no credentials whatsoever to discuss the meaning of life, but from the trenches it seems to me that I'm fairly certain that it has a lot to do with the ability to transform a wrong pain into a force of good for our neighbor, our biblical neighbor, whomever and wherever he or she may be. Of course each of us has our different ways to do that and none is necessarily better than the others. For me, it's research. Others have other ways that are just as good, if not better, for their own vital catharsis. Research is just one of the many ways, but for me research is a process of salvation, a transformation of the horror in front of the mystery of evil, into vital energy, to beautiful energy and to energy of hope.

The ulterior beauty is that for me research is exactly prayer to the Lord Almighty. Like prayer, when we do research, we cannot even begin to stammer a few words without a declaration of humility in front of what we are, with humility daring to contemplate its majestic beauty. In the physical universe of the world studied in the various sciences, I find everywhere little secret divine signatures and love messages, post-its, hidden in the most unexpected of places, and more often than not they are hidden in places that are very visible to everybody. Research for me is adoration of the majesty expressed in the physical world. It is a humble collecting in the worn wicker baskets of the mind the luminous cycles of the Spirit and the fluid harmonies. As we do when we pray, when we do research, it is essential to confess our own limits, and of these we cannot be forgiven without forgiving the limits of the others. If you get mathematicians, engineers, physicists, biologists together, how do you get them to work together? I have to tell you, I don't know how.

We have set up a program at Methodist; on Fridays we get together at 4 p.m. and then again at 5 p.m., and then, at 6 p.m. we go and drink beer together, which is another great thing about Houston, Texas. So at 4 p.m. we have "Open Mic Friday" where everyone comes in to talk about their research. It's a way to train. At 5 p.m., the program is called, "Houston, I Have a Problem," and people stand up in front of the mic and say, "Let me tell you what I've done now. Let me tell you where I've gotten stuck." In front of 200 people, National Academy members or whoever they may be—it takes heart, it takes guts, but unless you're able to do that, unless you're willing to make a leap in the dark, expecting that somebody with a different background will pick you up, you cannot really make true progress or as much progress.

So you have to confess your limits, and of these you cannot be forgiven unless you are willing to forgive those of others. The great examples of progress in the sciences were born from thoughts that overcame traditions, disciplines and their artificial barriers, and these require mutual trust among diversities of knowledge, and a profession of the impossibility of being successful by ourselves, and mutual forgiveness.

As we pray, we give thanks and we offer before we present petitions. And I was without any merit whatsoever. I was blessed with a great many joys in my life. I also met Fratello Dolore, and from each encounter I was transformed irreversibly. Without ceasing, I give thanks for the joys and I give thanks for the gift of having been able to learn at least a miserable little bit to transform terminal dolore to forces of good. It is a lot harder to be thankful for the pain itself, but the trial I can. It is an experience that is similar to forgiveness, which often is not natural; it doesn't come easy to allow it to concede. But when we allow ourselves to forgive, we free our own spirit; the spirit of the forgiver is freed as much as, if not more than that of the forgiven. I believe that if you find yourself in the fortunate condition that you can make a difference for your neighbors, even though you realize that it is not because of your own merits that you are in that position, then you have an ethical imperative to do that. If you don't complete the mission, it is an ethical transgression.

Simon of Cyrene wasn't even from Jerusalem. He was from Cyrene. And he found himself in the crowd probably by coincidence, and maybe he got curious to see what was going on as he happened to be on the Via Dolorosa of our Lord. I imagine that some Roman soldier maybe told him something like, "Hey you, come on over here. Look, this guy here is not able to carry this cross anymore. Pick it up and carry it a little ways." Simon had nothing to do with that whatsoever, but in my imagination he didn't say, "Now why me? Look, this other guy here is bigger than I am, and he looks stronger than me, and besides, I've got something to do...I've got an appointment at the barbershop; I wasn't even supposed to be here, plus I didn't study to be a cross-bearer. I studied for something else." He didn't do that. He didn't say that. He took the cross, put it up on his shoulder, even though he was there by happenstance. And after all, most of the important things in life happen by coincidence. He didn't say, "I didn't study to be a cross-bearer." Maybe he thought, 'He called me. He Himself called me. And think about how crazy it is; He called me through a Roman soldier.' And he responded to the call. That's why I've always liked Simon of Cyrene.

If the mysterious circumstances of life brought me, without any merit whatsoever, to find myself in a place where I can contribute something to research in medicine, and to be able to help create instruments that one day may be able to save lives and save people from suffering, then I think it's a duty to do that. That way you can start thinking, 'Look, it's going to take 20 years to get anywhere.' I don't have a choice. What am I going to do? Not do it? If you think it's going to work, sooner or later it's your duty. You cannot do anything else. It's like prayer—just get down on your knees and then do what you can. That's the way it works.

So the pain that I feel when we're not able, when we don't succeed, when we are in front of cases that we cannot solve, when the shame comes in when we recognize that we have been distracted by the more superficial parts of life, then this strong pain that we feel is guidance, is energy, is a resource. Physical pain allows us to avoid danger and death; spiritual pain brings us back to Him from being lost in the wilderness, and to get up one more time once we have been knocked down on the canvas.

Lord, all of the things that I could have done to help those who are suffering and who have suffered, and that I have not been able to do, that's my confession. And it is my offering. The pain itself, the stinging, irreversible pain of these unforgivable shortcomings, I'm offering to You. And accept as an instrument that I will use with everything I have, to help bring Your Precept of love to completion. We will give birth with pain, as You have told us, pain that is not a punishment for daring to want to be able to distinguish good from evil, but it's a guidance so that we are able to do this. And we will give You thanks for the new life that is being born. So Lord, my first petition to You is to give me the strength to be able to do whatever I can that is positive and helpful. The second is to help me struggle and resist the overwhelming floods of pain with the guiding lighthouse of Your mission as guide to the poor sailor surviving the shipwreck and who finds himself or herself in the ice cold water, in the churning waters of the suffering of the world. The third is to be able to receive from You as a gift the strength to guide the great energies that come from the mystery of pain without losing control or rightful navigation.

And this is dedicated to Maria Luisa, to Antonio, to Federico, to Mina, to Ricardo, to Guillermo, to Camilla, to Your images in our neighbor, whomever our neighbor may be, whether he may be suffering or he may be a bearer of relief.

Thank you for your patience.