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Spotlight: Emilio Hirsch, PhD, FESC

Aiming to Prove the Benefits of Treating Some Cardiac Diseases With PI3 Kinase γ Inhibitors

Emilio Hirsch, professor of applied biology, Department of Genetics, Biology and Biochemistry, Centre for Molecular Biotechnology, University of Turin, Italy, talks to Jennifer Taylor, BSc, MSc, MPhil.

Proving the benefits of treating some cardiac diseases with phosphoinositide 3 (PI3) kinase γ inhibitors represents the current mission of Emilio Hirsch, PhD, FESC, professor of applied biology in the Department of Genetics, Biology and Biochemistry, at the Centre for Molecular Biotechnology, University of Turin, Turin, Italy. PI3 kinase γ has provided the focus of his career for nearly 15 years since a chance meeting with another scientist, and has led to numerous collaborations and publications.

"I Was Always Intrigued by the Mechanism of Life"

Becoming a scientist represented a break with tradition for Hirsch's family. He says, "Most of my family are industry managers, so going into science was very weird for them." But although his family supported him, he cannot say the same for his home country, in which funding and jobs remain scarce. "In Italy, it's really tough for science," he says. "The money coming from the government is not sufficient to do any science. And it's very difficult to get a position—there are very few, and they are basically only permanent positions, so it's really tough."

But science had caught Hirsch's attention at a young age—"I was always intrigued by the mechanism of life"—and the real interest began when his grandfather bought him a microscope when he was 8 years old. So he decided to pursue it as a career, and, in 1988, he graduated in biology from the University of Turin. A PhD, which he completed in 1994, followed. During that time he had 2 important mentors: the head of the department, Professor Lorenzo Silengo, who has guided Hirsch throughout his career, and Professor Fiorella Altruda, who helped him embark on his first bench work. Professor Hirsch recalls, "I think these 2 people wanted to develop mouse genetics, and I was lucky that they chose me as the one who could learn mouse genetics and mouse work while I was a student. While I was a student, I set up most of the technology here, and then, of course, I got involved in some of my beloved genes. In a way, they suggested that I start with a more technological effort, and then I think it was great luck."

"I Immediately Found the Genes He Was Proposing Extremely Exciting, and These Were the PI3 Kinases"

To enhance his technological skills, Hirsch's mentors suggested that he go to Munich for postdoctoral experience, and so, from 1995 to 1996, he worked as a postdoctoral fellow in Professor Reinhard Fässler's laboratory in the Max-Planck Institute for Biochemistry, Martinsried, Munich, Germany, where he undertook knockout mouse research. Under the mentorship of Professor Fässler, he learned how to do top-level science and how to apply genetics to problems in biology.

Everything started as a result of his postdoctoral research. Professor Hirsch says, "During my PhD, I had a lot of little papers and little stories, but actually it was after my postdoc that I had a paper in *Nature,* and this led to

On other pages...

Spotlight: Øyvind Ellingsen, MD, PhD
Øyvind Ellingsen, professor of cellular cardiology, Faculty of Medicine, Norwegian University of Science and Technology (NTNU) and consultant physician, Department of Cardiology, St. Olavs Hospital, Trondheim, Norway, received an invitation to present results in a session on groundbreaking research from *Circulation* at the American Heart Association meeting in New Orleans, La, in November 2008. He explains why he is 95% confident that interval training can improve heart function in chronic heart failure.
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many potential directions for me. And it actually opened me to new fields—particularly the field of signal transduction and inflammation—because in the end I have actually focused on these 2 processes in the past 15 years." The *Nature* article describes a gene that they found essential for the migration of stem cells during haematopoiesis.[1]

What happened next would influence the rest of Hirsch's career. He already had been thinking about returning to Italy because the University of Turin had given him an assistant professorship, but he was looking for new genes to study in Italy and for genes involved in leukocyte migration. Professor Fässler received an invitation to a meeting to present the findings published in *Nature*, but he couldn't go, so he sent Hirsch to present the data. And, at that meeting, Hirsch met Matthias Wymann, PhD, who now works in Basel, Switzerland. Professor Wyman, one of the organisers of the meeting "and a fantastic biochemist," was looking for someone to collaborate with on a more genetic approach. "I immediately found the genes he was proposing extremely exciting, and these were the PI3 kinases," says Professor Hirsch. "At the time, little was known about their in-vivo role, and mouse genetics was certainly one of the best ways to tackle in-vivo roles. And they clearly had the potential of being involved in leukocyte migration and inflammation."

Becoming a scientist represented a break with tradition for Professor Hirsch's family. He says, "Most of my family are industry managers, so going into science was very weird for them."Photograph courtesy of Professor Hirsch.

"Proof That I Could Do Something Good at the Top Level of Science in Italy"

Together Professor Wyman and Hirsch managed to knock out PI3 kinase γ, the first PI3 kinase enzyme that anyone had knocked out. The work produced Professor Hirsch's "most beloved paper," (which appeared in *Science* in 2000[2])—he describes it as beloved in part because it remains his most-cited article, but also because it created the possibility of doing not just basic research but translational research as well. He and his collaborators showed that their mice were normal but had significantly impaired inflammatory reactions, which opened up the possibility of producing inhibitors of the enzyme that could work as antiinflammatory drugs.

Professor Hirsch says, "The *Science* paper was really exciting because this was the proof that I could do something good at the top level of science in Italy."

"The Mice That Expressed a Catalytically Inactive PI3 Kinase γ Did Not Show This Cardiotoxic Effect"

Another important article in Professor Hirsch's career, and his first as a senior author in a valuable journal, appeared in *Cell* in 2004.[3]

The team had found that cardiac function depends on PI3 kinase γ, but at the same time they were thinking about inhibiting PI3 kinase γ to generate antiinflammatory drugs. "This was a big problem because one could have expected side effects of these antiinflammatory drugs on cardiac function," says Professor Hirsch. He adds, "At the time, the Vioxx story was coming out, and everybody was very much concerned about cardiovascular side effects of antiinflammatory therapy."

The collaborators came up with the idea that knockout did not provide the best way to model the effect of a drug because drug targets do not disappear; rather, they just become inactive. They opted instead for a mouse model that expressed a catalytically inactive PI3 kinase γ.

He explains, "Of course, we were very lucky, but in the end the mice that expressed a catalytically inactive PI3 kinase γ did not show this cardiotoxic effect. And, on the other hand, their hearts were protected, as if not having the protein gives completely different results to having a catalytically inactive protein. So, we think this much better models the effect of a drug."

The findings kickstarted discussions over whether knockouts provide an appropriate model for the effects of drugs, and today scientists continue to view knockouts with more caution. Professor Hirsch describes preserving the protein rather than knocking it out as important because proteins usually play a role in protein–protein interactions, but a knockout destroys these interactions. Although drugs affect enzymatic activity, they usually do not affect protein–protein interactions.

"So, in the end, finding that mice expressing a catalytically inactive PI3 kinase γ did not develop side effects in the heart in a way boosted the search for PI3 kinase γ inhibitors to use in inflammatory diseases. And it also opened up the possibility that these inhibitors could have some beneficial effect in the cardiovascular system."

The work received the support of a Human Frontier Science Project grant. Professor Hirsch says, "If you compare it to all other grants, it was fantastic. We didn't have any auditing, and we were free to spend the money on whatever we wanted."

"For Me, and I Think in General for Italian Science, European Union Funding Is Essential"

Although European Union (EU) funding comes with an unsatisfactory amount of bureaucracy and administrative work, Professor Hirsch feels very grateful to the EU because it provides most of his grant money. "Honestly for me, and I think in general for Italian science, the European Union is essential. Without it, [research] would have been impossible because we get very, very little support from the

government." As another big plus, the EU grants have produced exciting networks. Professor Hirsch's first EU grant, FP-5, came between 2001 and 2003. It funded a small group focused on PI3 kinase and a translational approach, with the idea of finding new drugs and especially antiinflammatory drugs. The success of the network came with a large collaborative article that appeared in *Nature Medicine* in 2005, in which the authors used pharmacology to confirm the proof of concept from genetic studies.[4] This represented the first time that they had combined the genetic and pharmacological approaches. They established a model of arthritis and showed that the drug protected these mice—and normal mice—from the development of arthritis.

The work won the collaborators second place in the European Commission's 2005 Descartes Prize for Collaborative Research. Professor Hirsch says that they fell short of first place because they had not conducted the research in patients. He has since participated in the EU Grant FP-6, on a study called EUGeneheart.

When Professor Hirsch decided to return to Italy after working in Munich, he recalls, "Many people teased me, saying 'Italy is a nice place for a vacation and to stop working'. The Science *paper was proof that I could do something good at the top level of science in Italy." Photograph courtesy of Professor Hirsch.*

"The Leducq Network Is Really Exciting"

Professor Hirsch also takes pride in his role in a grant for work on cyclic adenosine monophosphate (AMP), which has received support from the Leducq Foundation. In the *Cell* 2004 article, they had demonstrated the involvement of PI3 kinase γ in cyclic AMP regulation. PI3 kinase γ has a scaffold role independent of its activity as an enzyme. It binds proteins, and this binding controls cardiac contractility, whereas cyclic AMP, of course, modulates cardiac contractility. "The Leducq network is really exciting because it put together all the major worldwide experts in the cyclic AMP phosphodiesterase field. And then we have a very exciting interaction that goes back and forth of the 2 sides of the Atlantic Ocean." The Leducq Foundation set up the transatlantic network and is funding groups in the United States and Europe to work together. Professor Hirsch regards this putting together of all the experts in the field as the most efficient and effective way of working.

Professor Hirsch says that the network has "smoothed the competition and enhanced the collaboration" and that he has profited from it. Students from his laboratory are working in the laboratories of network members, learning new skills, and provide mouse models.

"Often, These Mouse Studies Involve a Lot of People Because Many Different Skills Are Needed"

Since the *Cell* article in 2004, Professor Hirsch's laboratory has devoted itself mainly to research in cardiovascular disease. He would like to resolve the controversy over the potential beneficial effects of PI3 kinase γ inhibitors in heart diseases and to prove the benefits of treating some cardiac diseases with PI3 kinase γ inhibitors. As a result of combining the genetic and pharmacological approaches, they published the finding that inhibition of PI3 kinase γ reduces atherosclerosis and favours plaque stability through its effects in inflammation in *Circulation* in 2008.[4]

Again, the study came about through a large collaboration between different laboratories. Professor Hirsch provided data on the mice, and Muriel Laffargue, PhD, an expert on atherosclerosis, then developed the model in Toulouse, France. Merck Serono provided experimental PI3 kinase γ inhibitors.

"Often, these mouse studies involve a lot of people because many different skills are needed," says Professor Hirsch. "We come from our background in PI3 kinase and gene targeting, but, of course, Muriel Laffargue is an expert in inflammation and vascular inflammation and she works in a department focusing on atherosclerosis."

Scientific collaborations with industry, as opposed to funding from industry, have become more common, says Professor Hirsch. He speculates that companies recognise mouse genetics as a very powerful tool but one that requires specific expensive skills, thus making it easier and more effective to collaborate with academia.

In the end, the collaborations with other laboratories and with industry have produced an exciting proof of concept. "It opens the possibility of using these PI3 kinase γ inhibitors not only in curative treatment but also in preventive treatment, and atherosclerosis is probably one of the most suitable applications for this PI3 kinase inhibition."

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Spotlight: Øyvind Ellingsen, MD, PhD

Photograph courtesy of Lasse Berre.

Ninety-Five-Percent Confident That Interval Training Can Improve Heart Function in Chronic Heart Failure

Øyvind Ellingsen, professor of cellular cardiology, Faculty of Medicine, Norwegian University of Science and Technology, Trondheim, Norway, and consultant physician, Department of Cardiology, St. Olavs Hospital, Trondheim, Norway, talks to Jennifer Taylor, BSc, MSc, MPhil.

Proving that interval training (intermittent high-intensity exercise) reverses the adverse effects of heart failure by reducing heart size represents the current goal for Øyvind Ellingsen, MD, PhD, professor of cellular cardiology in the Faculty of Medicine, Norwegian University of Science and Technology, Trondheim, Norway, and consultant physician in the Department of Cardiology, St. Olavs Hospital, Trondheim, Norway. He has just embarked (March 2009) on the SMARTEX-HF (Study of MyocArdial recovery AfTer EXercise Training in Heart Failure) study, which is randomising 200 patients with chronic heart failure into 1 of 3 exercise regimens. "What we expect to see is a nice reversal of the adverse effect of heart failure on the heart," says Professor Ellingsen. The 7 centres collaborating on the study—Antwerp, Copenhagen, Leipzig, Munich, Stavanger, Trondheim, and Utrecht—made their connections through the European Association of Cardiovascular Prevention and Rehabilitation, which operates under the auspices of the European Society of Cardiology, and Professor Ellingsen serves as head of its Section for Basic and Translational Research.

Ellingsen's scientific life began during his childhood in a rural district near Sandefjord, a small city in Southern Norway, where his mother and grandparents raised him. His grandfather, who taught all subjects to students between the ages of 7 and 14 years, allowed him to have a science laboratory in the basement. He recalls. "I created quite a few firework items in that lab, but also some pH measurements."

Between 1971 and 1973, Ellingsen studied physics at the Norwegian University of Science and Technology. During that time, he took a part-time job with a researcher working on ultrasound. And when a doctor came into the laboratory to carry out some investigations on a patient, Ellingsen says, "I knew then that I wanted to deal with patients." He gained acceptance into the University of Oslo, Oslo, Norway, and became an MD in 1980.

Even before his PhD studies, Ellingsen had carried out his first scientific study, which led to his first article—a small clinical trial comparing different medications in angina. He found inspiration in his supervisor, cardiologist John Kjekshus, MD. Professor Ellingsen considers him "a very good example of a person who starts out doing some basic research and takes what he learns from basic research back to the patients." They remain in touch—Professor Kjekshus sits on the end-point committee of the SMARTEX study.

"You Bring Something Home That You Didn't Know You Were Looking For"

For his PhD at the University of Oslo, which he received in 1989, Ellingsen studied myocardial potassium balance during adrenergic stimulation. He describes his supervisor, Arnfinn Ilebekk, MD, PhD, as a mentor who "taught me to make high-quality physiological measurements and the tedious work of doing technically good science."

Ellingsen shared his office with David Rutlen, MD, FACP, FACC, a professor visiting from Yale, who convinced him that he should go to the United States for a postdoc—specifically to the laboratory of Thomas W. Smith, MD, at Brigham and Women's Hospital, Cardiovascular Division, Harvard University, Boston, Mass. Professor Smith had a reputation as a very good mentor, and he was doing groundbreaking work. "He was probably one of the first people who brought cellular cardiology and molecular medicine into contact with cardiology, which I think had been for many years mostly occupied with haemodynamics and the biochemical aspects of the heart," says Professor Ellingsen.

Having an excellent place to go helped Ellingsen win a Fogarty international research fellowship for 2 years, from 1990 to 1992. His application benefited from the fact that he had already had some good publications, and his interests made a good match for the laboratory at Harvard. For 5 years, he had been working on potassium balance in the intact heart in experimental pig models, and Professor Smith's laboratory conducted cellular experiments on the sodium potassium pump and the effect in isolated myocytes. Professor Ellingsen says, "I think it was probably obvious from the project I had proposed that Harvard would take me from the level of the whole organ to the cellular level within the field that I was interested in."

But Ellingsen ended up doing something completely different. He recalls, "I had imagined that I would continue the work on the sodium potassium pump that I had been doing for my PhD thesis in Norway, and to work on sodium, potassium, and maybe calcium regulation in the heart. But, at that time, these ideas were a little bit old for the lab. It was working on mechanisms of hypertrophy and molecular biology which was quite new in basic cardiology research at that time. So, it was an introduction to a new way of looking at the heart and heart disease." He became trained in isolating cardiac myocytes, and in carrying out cell culture

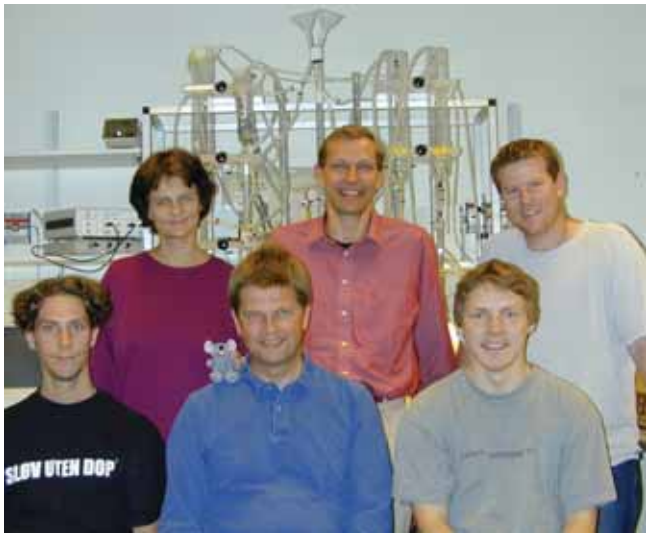
and contractility measurements, which proved highly beneficial because, as he says, "You bring something home that you didn't know you were looking for."

"In Heart Failure the Heart Tends to Grow. With Exercise Training We Were Able to Reverse Those Changes"

On returning to Norway, Ellingsen felt energised, but he found the transition moving on from his postdoctoral post disappointing. He could not find any available positions, so he opted out of research and took up a post in clinical cardiology. Eventually, in 1995, he took up his current position of professor of cellular cardiology. He describes his specialty as a kind of translational cardiology, looking at cell physiology but with a clinical perspective.

Professor Ellingsen's first task involved establishing a laboratory of cellular cardiology, which he found very rewarding. He says, "I was, for the first time, able to try out some of the ideas I had gotten from Harvard—that the cellular aspects of heart function would lead us to new discoveries and new therapies."

He considers himself fortunate that he had a couple of very bright, talented, and inspiring PhD students there from the start—in particular Ulrik Wisløff, PhD, a sports scientist who now runs his own group as a tenured professor in the same department. Together, they found that in the rat model of heart failure, interval training (exercise with a high intensity) had a very powerful beneficial effect on heart muscle function.[1] Interval training increased the function of the heart and also reversed some of the adverse effects of heart failure on the heart morphologically. Professor Ellingsen explains, "In heart failure, the heart tends to grow. With exercise training, we were able to reverse those changes, at least to the same extent as the most powerful medical therapy."



The Norwegian University of Science and Technology Research Group in Cellular Cardiology in 2001. Back row, left to right: Ingerid Arbo, MSc, technician, now PhD student; Jan Pål Loennechen, MD, PhD, student, now associate professor of cardiology; Ulrik Wisløff, MSc, PhD student, now professor of cardiovascular physiology. Front row, left to right: Vidar Beisvåg, MSc, PhD student, now postdoc; Øyvind Ellingsen, MD, PhD, professor of cellular cardiology; Ole Johan Kemi, MSc, PhD student, now lecturer in biomedical sciences, University of Glasgow, Glasgow, Scotland. Photograph courtesy of Professor Ellingsen.

"One of the Hottest Labs in Molecular Cardiology"

The discovery that interval training both increased the function of the heart and also reversed some of the adverse effects of heart failure on the heart morphologically produced a desire for tools to figure out the molecular mechanisms behind it, and partly for this reason Professor Ellingsen spent his first sabbatical, from 2003 to 2004, as a visiting scholar in the laboratory of Kenneth R. Chien, MD, PhD, in the Institute of Molecular Medicine, University of California, San Diego. The location had a reputation as "one of the hottest labs in molecular cardiology" with a lot of transgenic mice models to work on.

Professor Ellingsen came away from his sabbatical with the tools he needed, but not in the way he had expected. "I had thought that I would learn the details of doing molecular biology, and what I ended up doing was establishing contacts I could collaborate with," he says. It provided the start of a collaboration with Gianluigi Condorelli, MD, a professor at the Parco Scientifico San Rafaele in Rome, Italy. Professor Ellingsen's laboratory continues to do exercise training, at the level of experimental models in mice and rats, and also in people, and then gets help with molecular analyses from Professor Condorelli and other skilled scientists.

Professor Ellingsen had hoped to learn more than he accomplished in his sabbatical year, but he realised when he returned to Norway that a small laboratory like his should, perhaps, specialise on a few aspects and not try to cover everything. He says, "I think one of the lessons I learned from that experience is that science is really about people, and one of the most important aspects is establishing good collaborations and having good communication."

When asked whether he thinks laboratories spread themselves too thin by trying to do too much Professor Ellingsen says, "It depends on the resources—if you are a large lab, as in those that I've visited and spent some time in, in the United States, you can probably cover most of what you need. But I also think that if you look at some of the best articles, many of them are collaborative, meaning 2 or 3 excellent groups who work together. You cannot be at the cutting edge of all the areas that you need."

Realising the benefits of collaboration has helped Professor Ellingsen deal with the frequent frustration of having an idea but not having the resources to pursue it. For several years he felt that he could not properly explore the molecular mechanisms behind the beneficial effects of exercise on the heart. But now, through the collaboration with Professor Condorelli, he believes they will untangle some of those mechanisms. So far, the mechanism seems different from those behind medical therapy, which means that uncovering the pathway could unearth targets for new heart failure drugs and, perhaps, also for high performance in sports medicine.

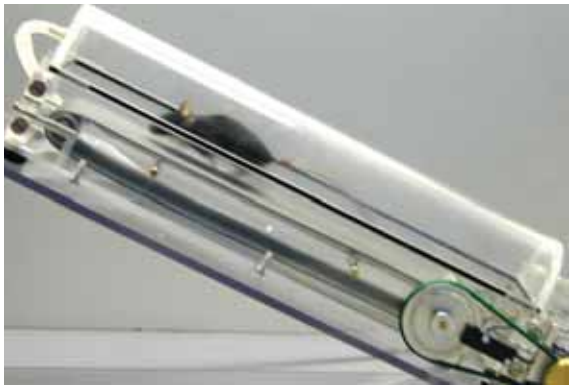
"If You Do Higher-Intensity Training, Like Interval Training, Then You Have More Than Twice the Beneficial Effect"

After returning from San Diego in 2004, Professor Ellingsen contributed to an article in *Circulation* showing a very close relation between fitness (as measured by performance on a treadmill) and myocardial function.[2] Professor Ellingsen and his colleagues trained rats, then stopped training them, and found that the beneficial effects went away.

The same idea also came through in a *Science* paper in 2005,[3] which a new collaboration had made possible. Professor Steven Britton, Medical College of Ohio, Toledo, Ohio, had seen an article about the work in Professor Ellingsen's laboratory and sent him an e-mail, asking whether he could test some of his animals, to prove that they had a higher level of fitness and a higher oxygen uptake. The laboratory in Toledo had been selectively breeding, for 10 generations, the best and the worst performers on the treadmill.

Through the collaboration they reinforced the concept that improved level of fitness has a correlation with the muscle function of the heart. They also showed that, at least in skeletal muscle, that correlation had to do with energy metabolism and metabolism related to mitochrondria.

The importance of intensity in exercise provided the next big finding.[4] Professor Ellingsen explains, "If you exercise at moderate intensity, you certainly have a nice effect on the arteries and also on the heart. But, if you do higher-intensity, training, like interval training, then you have more than twice the beneficial effect."



Professor Ellingsen says, "For the past 10 years Professor Wisløff has been the most influential researcher that I've been in contact with because he introduced me to the exercise training perspectives. He was very keen on training rats and mice and insisted that we should get treadmills. And he was right." Photograph courtesy of Professor Ellingsen.

Professor Ellingsen's contribution to research in exercise training and cardiology gained recognition in 2005 with the Ole Storstein Award for excellence in cardiovascular science from the Norwegian Society of Cardiology. Professor Ellingsen says, "Ole Storstein was an early Norwegian cardiologist and scientist, and though it's not a huge amount of money, the honour and the recognition was quite nice."

The basic research was becoming practical, because if the same proved true in people, then patients with heart failure could gain a greater effect from exercise training after a myocardial infarction if they exercised more intensely. So, a clinical study came next. In a relatively small number of heart failure patients, the group directly compared moderate-intensity exercise with interval training, and also with the recommended level of exercise given by general physicians. Their finding that high-intensity exercise had a much larger effect, particularly on the heart, appeared in *Circulation* in 2007.[5] It generated so much interest that they received an invitation to present the results in a session of groundbreaking research from *Circulation* at the American Heart Association meeting in New Orleans, La, in November 2008.

Their findings have had a mixed response. People feel excited about the large effect, but also think it seems too good to be true. And some have concerns about safety. So, SMARTEX-HF represents the next step, which will test exercise training on a larger cohort of patients and look for side effects, to see whether more or fewer complications appear. Professor Ellingsen says, "I think when we have completed that study with a year of follow-up we should be able to either convince ourselves that this was not a good idea or convince the world that this is a good idea and that it's also safe to try and do this." At this stage, Professor Ellingsen feels 95% confident in characterising it as a good idea, because of the evidence that improving heart function improves prognosis and the fact that doing this type of exercise improves cardiac function.

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