Pioneer in Cardiovascular Gene Therapy: Seppo Ylä-Herttuala, MD, PhD, FESC

“Putting Genes into the Heart at the Same Time as Angiography or Catheterisation Is the Perfect Fit”

Seppo Ylä-Herttuala, MD, PhD, FESC, professor of molecular medicine, A. I. Virtanen Institute for Molecular Sciences and Department of Medicine, University of Eastern Finland, Kuopio, Finland, talks to Barry Shurlock, MA, PhD.

In the mid-1990s, Seppo Ylä-Herttuala, MD, PhD, FESC, professor of molecular medicine, A. I. Virtanen Institute for Molecular Sciences and Department of Medicine, University of Eastern Finland, Kuopio, Finland, became interested in gene therapy for the treatment of cardiovascular diseases and cancer. In 1995, he and his team became the first to report the successful transfer of genes to human arteries with adenoviral vectors in peripheral and coronary arteries. Later, in 2005, to increase his experience and expertise in the field, Professor Ylä-Herttuala took a 1-year sabbatical at the Salk Institute for Biological Studies, La Jolla, CA, in the Lab of Genetics with Professor Inder M. Verma, PhD, currently the American Cancer Society Professor of Molecular Biology and a leading authority on the use of lentiviruses as vehicles for gene therapy. Notable articles by Professor Ylä-Herttuala and his team since include one on the elucidation of the receptor targets of induction of angiogenesis and arteriogenesis in the myocardium by vascular endothelial growth factor B3 and another on a novel example of epigenetherapy involving regulation of vascular endothelial growth factor expression.

Speaking in July 2012, shortly after approval by the European Medicines Agency of the first gene therapy product in the Western world for the treatment of inherited lipoprotein lipase deficiency, Professor Ylä-Herttuala says, “At the Salk Institute, I wanted to learn more about all sorts of vectors, which do not all have the same efficiency, and to spend time thinking towards the future. Although many preclinical trials are now underway, it will take several years to get to products, but I am convinced that the concept of putting genes into the heart at the same time as angiography or catheterisation is the perfect fit. Also, treating elderly persons with severe heart disease with gene therapy involves fewer ethical problems than, say, treating young children. We hope to be able to use gene products to treat ischaemic disorders and perhaps cardiac dilatation. Heart failure, which is now a major problem following successful treatment of myocardial infarction, is an interesting new target for this approach and trials are underway, for example, to boost ion channels that help the heart work better.”

He points out that, whereas monogenic defects such as muscular dystrophy or cystic fibrosis require long-term expression of new genes, many vascular diseases can, in principle, be treated by transferring genes that act for relatively short periods, of the order of weeks, but long enough to effect benefits. Likely strategies include increasing secretion of proteins that stimulate angiogenesis, such as vascular endothelial growth factor and fibroblast growth...
At 55 years of age, Professor Ylä-Herttuala looks set to remain at Kuopio until retirement, and beyond. He says, “We have everything here in Kuopio—excellent basic research, excellent translational research, and a large university hospital for clinical trials. The salary may be higher elsewhere, but why would I move? If I went for more prestige in a more prestigious university, in the middle of a big city, I would lose a lot of these facilities. The Finnish system is predictable, with long-term funding, whereas I am aware, for instance, that in the United States there is often a lack of continuity and you don’t know where the next funding is coming from.” Photograph courtesy of Professor Ylä-Herttuala.

factor. Proof of concept has been achieved, but many basic issues still need to be resolved, including trial design and a better understanding of the pharmacokinetics and pharmacodynamics of gene products. Also, the efficiency of gene transfer may be a problem because it is inversely proportional to body weight and therefore much lower in humans than in small experimental animal models. Professor Ylä-Herttuala is optimistic and believes that his team has already made significant advances in vascular endothelial growth factor gene transfer, including a demonstration of increased vascularity in a lower limb artery and a safety and feasibility study of intracoronary administration to prevent postangioplasty and in-stent restenosis.

“In the Late 1970s, the North Karelia Project Was Launched to Improve Dietary Habits and Lifestyles. By 1995, the Rate of Cardiac Mortality Had Been Halved in Eastern Finland”

Until the 1950s, Finland was a country of farmers. It has since been industrialised and become one of the wealthiest per-capita countries in the world, with the sort of welfare and healthcare systems that only Nordic countries seem to be able to achieve. And all this from a population of only 5.4 million. Its celebrated sons include the composer Jean Sibelius and software engineer Linus Torvalds, who devised the Linux computer operating system. It is also a country of extraordinary natural beauty, with ≈180 000 lakes, and a similar number of small islands, accompanied by appropriate mythic tales to explain the coincidence. Late to escape from the last Ice Age, it is still rising out of the ocean.

Within Finland, cardiovascular research has become concentrated in its 9th-largest city, Kuopio, which has a population of ≈100 000 and is the cultural centre of East Finland. It is built beside a large lake and on several islands, is said to have the largest annual intake of medical students in the country, and has a reputation for export-led enterprise. Since 1995, at the University of Eastern Finland, Professor Ylä-Herttuala has presided over the Department of Biotechnology and Molecular Medicine at the A. I. Virtanen Institute. He leads a team of 3 associate professors and a moving raft of 12 postdoctoral students and 24 graduate students, working in 3 areas, namely, cardiovascular disease, vascular biology, and cardiovascular gene transfer technology and vector development. He is also a research professor of the Finnish Academy of Sciences and director of the Biocenter Kuopio, which is devoted to basic research across the biological spectrum, as well as translational and clinical studies.

Professor Ylä-Herttuala receives offers of posts elsewhere, but he sees no reason to move. He explains, “In the late 1950s/early 1960s, Eastern Finland had one of the highest rates in the world of death from myocardial infarction in middle-aged males, according to the Seven Countries Study carried out at the time. This finding was later confirmed by a World Health Organization study. So, in the early 1970s, the Finnish government decided to focus its cardiovascular research and prevention in Eastern Finland, and, in the late 1970s, the North Karelia project was launched to improve dietary habits and lifestyles of people [in the province of that name]. By 1995, the rate of cardiac mortality had been halved in Eastern Finland, and this example is now used by the World Health Organization to demonstrate how community-wide action can reduce cardiovascular disease.

“As a result of all this, the facilities for cardiovascular research at Kuopio are excellent. We have ≈15 000 students at the university, 3000 of them in the medical faculty, and a university hospital, 1 of only 5 in the country, that serves ≈1 million people. We have, for example, a huge animal facility with a cath lab for pigs as good as for humans, with a full range of imaging modalities, including 3-dimensional angiography, ultrasound, and magnetic resonance imaging. We can therefore carry out studies in animals and then transfer onto clinical trials, all in the one place. This is something you cannot easily do, for example, in the middle of London or New York.”

“Providing, for the First Time, Evidence in Rabbit and Man of the Presence of Oxidatively Modified Low-Density Lipoprotein in Atherosclerotic Lesions”

Professor Ylä-Herttuala came from a family with no medical tradition, but from an early age he had a strong interest in the natural sciences and says there was never any doubt that he would study medicine. He went to medical school in his hometown of Tampere, which has a metropolitan population
of ≈300 000 and is a 2-hour car ride from the capital, Helsinki. After a few months, while continuing his medical studies, he joined the Department of Medical Biochemistry at the University of Tampere, where he worked at the bench on the biochemistry of atherosclerotic lesions, the cellular uptake of lipoproteins, and atheroma. This field was new and exciting; only a few years before, Joseph L. Goldstein, MD, and Michael S. Brown, MD, had discovered cellular low-density lipoprotein receptors and receptor-mediated endocytosis at the University of Texas, Dallas, for which they received the Nobel Prize in Physiology or Medicine in 1985.

After qualifying for his MD in 1982, Professor Ylä-Herttuala continued his studies of atherosclerosis for a PhD, winning a “best thesis of the year” award for a study of arterial biochemistry. He was intending to be an internist, but in 1988, along came the opportunity to take up a National Institutes of Health Fogarty International Fellowship at the University of California, San Diego, La Jolla, where he worked for 3.5 years as a postdoctoral fellow with Daniel Steinberg, MD, and Joseph L. Witztum, MD. Within a year, he had published, as lead author, what he believes to be one of his most important scientific contributions, providing for the first time evidence in rabbit and man of the presence of oxidatively modified low-density lipoprotein in atherosclerotic lesions.

Professor Ylä-Herttuala comments, “There were several connections between Finland and San Diego, and some of the techniques in biochemistry that we had developed in Finland were useful to those working in the lab in California. It was a ‘hot’ place for the oxidation of lipoproteins at the time, and for me it marked a point of no return: I wanted to stay in research, which was so exciting, and not go into internal medicine. However, it was important that I had already had enough exposure to clinical medicine, because in directing the work on ischaemia, it meant that we were always 1 step ahead [of the pure scientists] because we could look at clinical applications. It was a great time. I still have connections with several people in the lab. It is important to see other environments. You cannot be ‘world-famous’ in a small place! The scientific community cannot only communicate by e-mail. You need to know the people if you are to develop new concepts. Exposure to the international community is the only way to move forward, remain competitive, and get international funding.”

“The Competition Is Tough, but the European Research Council Is One of the Best [Funding] Developments That Has Happened in Europe”

Professor Ylä-Herttuala has benefited hugely from the European Union (EU) via its Framework Programmes. These ambitious blueprints have sought to define major themes of research in medicine and other areas, and they have made large financial grants to those with the ideas to deliver. He has also more recently benefited from the European Research Council, which invites investigators to propose ideas instead of imposing objectives on them.

Grants have often been made to large consortia, such as the Bone-Marrow Derived Mononuclear Cells for Acute Myocardial Infarction (BAMI) Consortium, which has been provided with €5.9 million of funding over a 5-year period by the EU Commission of the European Communities to trial the use of stem cells from bone marrow for the treatment of acute myocardial infarction. Professor Ylä-Herttuala’s team at the University of Eastern Finland has a share of €100 000 and is 1 of 21 partners from 11 European countries in a group coordinated by Professor Anthony Mathur, FRCP, PhD, professor of cardiology, Queen Mary’s Hospital, London, England.

The team also has a share of €770 000 in the Biodegradable Magnetised Stent for Coronary Artery Luminal Regeneration (BIOMAGSCAR) Consortium, set up to trial a novel magnetised biodegradable coronary stent designed to attract the patient’s stem cells dosed with iron nanoparticles and thereby repair the intima of the diseased.
In his leisure time, Professor Ylä-Herttuala likes to ski or run, or take to roller skates (which he calls “skiing in the summer”). He also plays the piano and is in great demand at parties because although classically trained he “plays almost anything.” Photograph courtesy of Professor Ylä-Herttuala.

artery. It involves 5 partners in 8 European countries and has been awarded an EU grant of €5.3 million over 4 years. The coordinator is Professor John Martin, MD, FRCP, FESC, FMedSci, University College London, London, where Professor Ylä-Herttuala holds a visiting professorship.

Additionally, Professor Ylä-Herttuala has been awarded a European Research Council grant of €2.2 million over 4 years for his work in Kuopio on gene therapy, and he has secured a share of €1.6 million over 4 years granted to the CosmoPHOS Consortium for a study of nanotechnology-enabled, fluorescence molecular imaging and endovascular targeted photodynamic therapy of atherosclerotic heart disease using near-infrared radiation.

All these grants add up to a secure future at Kuopio for the next few years. Despite its AAA stable credit rating, the Republic of Finland is, however, one of those countries where a breakup of the Eurozone, and more widely the EU, would be a disaster that would turn the clock back to 1995, when it achieved membership of the EU, or to 1999, when it joined the Eurozone (the Euro went into general circulation 3 years later).

Commenting on the current economic climate, Professor Ylä-Herttuala says, “EU funding is critical for us, but I am positive. You have to remain highly competitive. The Euro won’t collapse in the near future, though the amount available for funding research might not increase so much. Over the past 10 years, the EU has been a major source of funding for us, contributing ≈70% of our grant income. We have also received ≈10% each from the Finnish Academy of Sciences, international grants such as the Leducq Foundation and the University of Eastern Finland. The economic difficulties in Europe so far have not affected Finland much, and some of our grants are long-lasting, but if there are problems they could be starting soon. The European Research Council gives good grants. The competition is tough, but its creation is one of the best developments that has happened in Europe, and it gives us something like the National Institutes of Health in the United States. ‘Top down’ schemes like the Framework Programmes never work well in scientific discovery.”

In 1997, Professor Ylä-Herttuala founded Ark Therapeutics PLC, a company listed on the London Stock Exchange, as a vehicle for raising venture capital for the clinical trials he could not fund with academic grants. It employs 60 people and is situated near his lab in Kuopio. He says, “It produces adenoviral gene products for third parties. There are not many companies in this field and sooner or later, when gene therapy drug submissions become successful, we will be well placed to take advantage of the situation. It is a different life to academic research, but there has to be an understanding from both sides—how to produce the products, on the one hand, and how to use them in animals and humans, on the other.”

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Barry Shurlock is a freelance medical journalist.
After 4 productive years as a postdoctoral fellow in the lab of Professor Victor Dzau, MA, MD, first at Brigham and Women’s Hospital, Boston, MA, and then at Duke University, Durham, NC, Massimiliano Gnecchi, MD, PhD, assistant professor in cardiology, University of Pavia, Pavia, Italy, head, Lab of Experimental Cardiology for Cell and Molecular Therapy, and attending physician, Intensive Coronary Care Unit, Fondazione IRCCS Policlinico San Matteo, Pavia, returned to his native Italy in 2006 and rejoined the Department of Cardiology directed by Professor Peter J. Schwartz, MD, in Pavia. His plan was to work as a physician at the San Matteo Hospital and, at the same time, set up a basic science lab to continue the pioneering stem cell therapy research he had started in the United States.

“In the United States, We Showed That Mesenchymal Stem Cells Produce and Release Soluble Factors That Act in a Beneficial Manner on Ischaemic Myocardium”

Dr Gnecchi says, “In the United States, I became specialised in adult stem cell and gene therapy. I worked with mesenchymal stem cells genetically modified to overexpress Akt, or protein kinase B, which plays a key role in many cellular processes. Using this cell model we discovered what we named the ‘paracrine hypothesis,’ which then became a proven mechanism of stem cell action.”

“We were the first to show that mesenchymal stem cells repair infarcted hearts more through paracrine mechanisms rather than direct regeneration. We showed that stem cells produce and release soluble factors that act in a beneficial manner on ischaemic myocardium to preserve global ejection fraction and improve left ventricular remodelling by decreasing the number of apoptotic events, increasing the number of vessels, and producing a beneficial effect on cardiac metabolism. Our first article on the concept of the paracrine mechanism was published in Nature Medicine in 2005.¹ We confirmed our results in FASEB in 2006.² The Nature article has been cited >500 times and the FASEB article >300 times. Then came the isolation of a putative paracrine factor, Sfrp2, which we published in 2007,³ and in 2009, we proved that these cells act positively on cardiac metabolism, preserving the storage of phosphocreatinine and the pH.”

“At the Window of My Office I Can See Where I Was Born and This Helps Me to Remember Where I Come From and Why I Came Back. I Believe That the Best People Should Bring Back Home What They Have Learned Abroad”

Dr Gnecchi recalls, “It was a difficult decision to return to Italy because I was working in one of the best medical centres in the world and I had other good offers from the United States and Canada. Furthermore, I knew that the system there helps you in your daily research work like nowhere else. Nevertheless, I decided to return, mainly because Italy is my home country and certain bonds are hard to break. Each time I have difficult moments or doubts, from the window of my office I can literally look at the room where I was born and this helps me remember where I come from and why I came back. I believe that the best people should bring back what they have learned working abroad to act fairly to their fellow citizens and their family who have made efforts to allow them to study.”

“The infrastructures and system are completely different in Italy compared with the United States where everything is straightforward and standardised and you step into the lab and start working. In Italy, I had to create a completely new lab. I did everything, also working with the technical office to achieve the characteristics needed. Designing the lab was interesting, but the bureaucracy behind each step slowed the process and was frustrating. “In general, the concept of physician scientist is not standardised and well developed in Italy, so I had to...
find my own way. In particular, it is difficult, if not impossible, to negotiate protected full days or weeks for research as occurs in the United States. I see patients every day until 2 p.m, then I take care of the lab until late evening.”

Dr Gnecchi is employed by both the hospital and the university. He explains, “I went back as the winner of a national initiative that may be translated as ‘Brain Drain Return.’ I was one of the first cardiologists to benefit from it. It provided a salary for 4 years and some funding to set up the lab. At the same time, I got the contract with the San Matteo Hospital, which also provided funding to create the lab. After 4 years, I achieved the expected results, so I was promoted to a tenured track position as assistant professor and attending physician. I am now in the process of obtaining the habilitation to be promoted to associate professor. The process sounds smooth now, but it was a lot of trouble because I was ‘opening up a new way.’ The concept was new for the university and the hospital, but I hope that from now on other people will be able to follow a similar path.”

Lab staff are funded in a variety of ways. “Some funding is provided by the hospital and some PhD students are paid by the university, but most of the costs are covered by my grant money. The initial grant from the government was not enough to employ several people, but fortunately I have been successful in getting additional extramural funding,” says Dr Gnecchi.

“You Cannot Wake up in the Morning and Work Hard if You Do Not Believe in What You Do. It Will Be a Long but Exciting Journey”

“Sometimes I have wondered what I might have achieved if I had stayed in the United States,” reflects Dr Gnecchi. “Workwise, returning to Italy has not been simple. On top of my clinical and research work I also have teaching duties, so it is hard. However, I feel that I have ‘made it’ in a way. I have an up and running lab, and in the past 5 years I have received >2 million Euros in funding from the Ministry of University, the Ministry of Public Health, the Ministry of Foreign Affairs, and the Cariplo Foundation. I have 7 staff members who are either PhD students or postdocs between 24 and 33 years of age. We also have students (I teach at the medical, biotechnology, and pharmacology schools), who work on their thesis in the lab and stay for 18 to 24 months. Clinical Lab staff fellows help with the translational work. In the lab we are trying to cover all aspects of adult stem cells, both differentiation and paracrine aspects, and recently we started to get involved with induced pluripotent stem cells, but mainly for disease modelling.

“In general, the scientific community will need at least another 10 years to understand better whether this therapy can work and how. My feeling is that the magic bullet will probably be a combination of tissue engineering with the right cell type and with the right protocol to drive cell differentiation. We now need to prove it, and that is what we are trying to do in Pavia. Of course we think we can. You cannot wake up in the morning and work 12 to 14 hours a day if you do not believe in what you do. It will be a long but exciting journey. The future is work, work, work. Right now our pace of research is quite good. We have published some articles and have other exciting articles in preparation, particularly on amniotic mesenchymal stem cells. The main goal for 2013 is to get most of the research we have done over the past 3 years published. At the same time, we have other interesting ongoing projects. Following a small collaborative project, we have started an official partnership with Cardiocentro Ticino, Lugano, Switzerland, a state-of-the-art cardiac centre directed by Professor Tiziano Moccetti, MD, PhD. We aim to develop standardised protocols and clinical grade products for the patients and also to exchange researchers, students, and clinical fellows.

“Recently, I have been appointed honorary senior lecturer at the University of Cape Town, Cape Town, South Africa, where, in collaboration with Neil Davies, PhD, we are studying how to improve cell therapy efficacy using specific biomaterials. Other projects will start soon with Professors Bongani Mayosi, MD, PhD, chief of medicine, and Karen Sliwa, MD, PhD, director of the Hatter Institute. Working in the same institution where Chris Barnard carried out the first human heart transplantation is inspiring!”

“I took a big risk in coming back but now I am happy with my decision. Things are working out and I experience, on a daily basis, that besides several contradictions and economic restraints, Italy is full of resources, particularly in terms of brilliant and flexible people. Not to forget that in my opinion Italy is among the most beautiful places on earth and the quality of life is unique. My aim for the future is to do good science, to be happy with my lab fellows, and feel that I am doing something new and of value for the community. Treating patients is rewarding and our primary goal as cardiologists, but it is also important to get involved with science and think outside the box to create new ways to treat our patients, otherwise we will never improve.”

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European Perspectives

Circulation. 2012;126:f139-f144
doi: 10.1161/CIR.0b013e31827ed66c
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2012 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/126/24/f139.citation

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