The XVIII Paavo Nurmi Symposium

FUTURE TECHNOLOGIES FOR HEART DISEASES – basic pathology, diagnostics and treatment

August 31 to September 2, 2016
Turku, Finland
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WELCOME

As Chairs of the Board of Paavo Nurmi Symposium, we are pleased to welcome you to the meeting on Future Technologies for Heart Diseases – basic pathology, diagnostics and treatment. The organization and we value you participation and appreciate you taking the time out of your busy schedule and join us in Turku, Finland. We hope you will be glad you found time for this meeting.

Our priority of is to provide the stimulating program and environment for sharing data, starting collaboration and hopefully finding new collegial relationships. Small face-to-face conferences represent enormous value for participants. We hope and encourage lively debate during the sessions as well as during free time and evening activities.

This is the 18th Paavo Nurmi Symposium supported by the Paavo Nurmi Foundation. The Foundation was founded 1968 to promote cardiovascular research in the form of research grants and international meetings. The Symposium is usually held in the Southern part of Finland. This year is the first time the Symposium is held in Turku where the greatest athlete in Finland Paavo Nurmi was born.

Turku is the former capital of Finland housing the oldest university in Finland. The city is located in the southwestern corner of Finland right next to the Baltic sea. The sea is unique in having thousands of small islands. We hope you have time to enjoy also the surroundings in this area during your visit.

We hope that your experience at this Symposium is valuable and memorable.

Sincerely,

Katriina Aalto-Setälä

Heikki Ruskoaho

On behalf of Organizing Committee
Paavo Nurmi Symposium 2016

The present symposium focusing on new technologies and their implications on heart diseases will be the 18th one funded by the Paavo Nurmi Foundation. The programme includes open lectures and symposium state-of-the-art lectures given by invited speakers, with a special emphasis on future aspects of cardiac diseases. The presentations will cover several timely issues including tissue and cell engineering, stem cell applications, microRNA therapeutics, gene therapy as well as personalized medicine.

The symposium and accommodation will take place in Radisson Blu Marina Palace Hotel, Turku, Finland. The Hotel places guests on the banks of the stunning Aura River and provides well-equipped, stylish rooms that showcase an intricate Baroque design. The meeting facilities overlook the Aura River and provide ample modern equipment for a successful event.

Turku is a fascinating combination of both old and new. Turku has everything for the modern urbanite, but also for tourists interested in the treasures of history. Turku offers skilled and educated workforce, modern municipal engineering, good international connections and flexible services for companies and businesses.

Social program is included in the program. It is planned with the idea 'everything is near and we reach it by walking’. The places we will visit are located by the river and in the middle of the city, which provides versatile possibilities for leisure-time activities. There will be guided cultural exercise routes for the volunteers before breakfast time. Options are Nordic walk or run and different distances. Themes are *Paavo Nurmi Stairs and Amazing Aura.*
# CONTACT INFORMATION

1. **Venue and accommodation and Symposium lectures, September 1 – 2**
   - Radisson Blu Marina Palace
     - Linnankatu 32, TURKU
     - +358 20 1234 710

2. **Get-together lunch, August 31**
   - Steamship Ukko-Pekka
     - Linnankatu 38, TURKU
     - +358 2 515 3300

3. **Opening of the Symposium, Plenary lectures, August 31**
   - Sigyn –hall (Conservatory of Turku)
     - Linnankatu 60, TURKU
     - +358 2 350 7600

4. **Welcome ceremony, August 31**
   - Town Hall of Turku
     - Aurakatu 2, TURKU
     - +358 2 362 7483

5. **Banquet dinnet, September 1**
   - Turku Castle
     - Linnankatu 80, TURKU
     - -

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Need any help?

- Katriina Aalto-Setälä
  - +358 40 582 9567
  - katriina.alto-setala@uta.fi

- Sari Sarkaniemi
  - +358 40 867 6080
  - sari.sarkaniemi@uta.fi
Plenary lectures
Wednesday 31 Aug
Sigyn -hall, Turku

Plenary lectures start with the Opening of the symposium. Lectures are open and free for general audiency up to 395 people.

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<thead>
<tr>
<th>Time</th>
<th>Event</th>
<th>Speaker</th>
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<tbody>
<tr>
<td>14:00-14:30</td>
<td>Coffee</td>
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<tr>
<td>14:30-15:00</td>
<td>Opening of the symposium</td>
<td>Kimmo Kontula (FIN)</td>
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<tr>
<td>15:00-15:45</td>
<td>Induction of pluripotency by defined factors</td>
<td>Shinya Yamanaka (JPN)</td>
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<td>15:45-16:30</td>
<td>Rebuilding the heart</td>
<td>Kenneth Chien (SWE)</td>
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<td>16:30-16:45</td>
<td>Break / tauko</td>
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<tr>
<td>16:45-17:15</td>
<td>Mitä maailma sairastaa Global health today (in Finnish)</td>
<td>Jussi Huttunen (FIN)</td>
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<td>17:15-17:45</td>
<td>Kantasoluista sydäntä – mikä merkitys potilaille tai urheilijoille Stem cell –derived cardiomyocytes - What is their benefit? (in Finnish)</td>
<td>Katriina Aalto-Setälä (FIN)</td>
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# Symposium lectures

## Thursday, Sep 1

### Session 1. Tissue and cell engineering

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<th>Time</th>
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<tr>
<td>09:00-09:30</td>
<td>Cardiac and vascular differentiation</td>
<td>Christine Mummery (NED)</td>
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<tr>
<td>09:30-10:00</td>
<td>Vascular neoformation</td>
<td>Kari Alitalo (FIN)</td>
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<tr>
<td>10:30-11:00</td>
<td>Cardiac tissue engineering for disease modelling</td>
<td>Thomas Eschenhagen (GER)</td>
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<tr>
<td>11:00-11:30</td>
<td>Modelling cardiac diseases with iPSCs</td>
<td>Katriina Aalto-Setälä (FIN)</td>
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### Coffee break

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### Session 2. Gene therapy

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<tr>
<td>13:00-13:30</td>
<td>Cardiovascular gene therapy with vascular endothelial growth factors</td>
<td>Seppo Ylä-Herttuala (FIN)</td>
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<tr>
<td>13:30-14:00</td>
<td>SERCA2a gene therapy for heart failure</td>
<td>Alexander R Lyon (GBR)</td>
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### Session 3. Stem cell applications

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<th>Speaker</th>
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<tr>
<td>14:30-15:00</td>
<td>miRNA pathway for cardiac regeneration</td>
<td>Mauro Giacca (ITA)</td>
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<tr>
<td>15:00-15:30</td>
<td>High throughput screening using stem cell-derived cardiomyocytes</td>
<td>Joseph Wu (USA)</td>
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<tr>
<td>15:30-16:00</td>
<td>Stem cell therapy in cardiac arrhythmias</td>
<td>Lior Gepstein (ISR)</td>
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<td>15:30-16:00</td>
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<tbody>
<tr>
<td>16:15-16:45</td>
<td>Genome engineering human iPSC cells to model and treat disease</td>
<td>Bruce Conklin (USA)</td>
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<tr>
<td>16:45-17:30</td>
<td>Cardiomyopathies: Genetics and towards therapies</td>
<td>Christine E. Seidman (USA)</td>
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## Friday, Sep 2

### Session 4. Regenerative therapeutics

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<tr>
<td>9:00-9:30</td>
<td>Small molecules for cardiac repair and regeneration</td>
<td>Heikki Ruskoaho (FIN)</td>
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<tr>
<td>9:30-10:00</td>
<td>miRNA in stem cell function and in the regenerative therapy of the heart (vascular)</td>
<td>Stephanie Dimmeler (GER)</td>
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<td>Coffee break</td>
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<tr>
<td>10:30-11:00</td>
<td>Individualized stratification for sudden cardiac deaths</td>
<td>Heikki Huikuri (FIN)</td>
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<tr>
<td>11:00-11:45</td>
<td>Cell therapy of cardiac diseases</td>
<td>Andreas M Zeiher (GER)</td>
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12:00 – Closing lunch

Have a nice journey back home!
Social program

Get-together Lunch
Wednesday, Aug 31 at 11:00 – 13:00
Steamship Ukko-Pekka
Lunch cruise to Turku archipelago
Attendees of the symposium, Finnish media members, athletes, politicians, influencer etc.

Welcome ceremony
Wednesday, Aug 31 at 20:00 -
City Hall of Turku
Reception by the City of Turku
Buffet

Good morning activities
Thursday, Sep 1 at 06:30 ⇒
Theme: Paavo Nurmi Stairs

Group 1: ~10km run
Group 2: ~ 5km run
Group 3: ~ 3km Nordic Walk

Banquet dinner
Thursday, Sep 1 at 19:00 -
Turku Castle

Good morning activities
Friday, Sep 2 at 06:30 ⇒
Theme: River Aura

Group 1: ~10km run
Group 2: ~ 5km run
Group 3: ~ 3km Nordic Walk

Closing lunch
Friday, Sep 2, 2016 at 12:00 -
Hotel Radisson Blu Marina Palace
Meet the Speakers

Plenary lectures
Shinya Yamanaka, MD

Professor Shinya Yamanaka is most recognized for his discovery of induced pluripotent stem cells (iPSCs), which are differentiated cells that have been reprogrammed to the pluripotent state. He is Director of the Center for iPS Cell Research and Application (CiRA), which was founded in 2008 in response to his discovery, at Kyoto University and Senior Investigator at the Gladstone Institutes.

Since his breakthrough finding, he has received many prestigious awards including the Albert Lasker Basic Medical Research Award, the 100th Imperial Prize and Japan Academy Prize, Millennium Technology Grand Prize, and the Wolf Prize in Medicine. The significance of iPSCs culminated with Dr. Yamanaka being awarded the Nobel Prize in 2012.
ABSTRACT

Induction of Pluripotency by Defined Factors

Induced pluripotent stem cells (iPSCs) can proliferate almost indefinitely and differentiate into multiple lineages giving them wide medical application. Also, they can be made from various types of somatic cells. As a result, cell-based therapies, disease mechanisms and new drug development are being studied worldwide using iPSCs at an accelerated pace.

We are establishing technologies for the efficient generation of safe iPSCs that can be differentiated into cardiomyocytes for regenerative medicine, drug discovery and disease modeling. The original iPSCs were made from the retroviral transduction of four genes, Oct3/4, Sox2, c-Myc and Klf4. We have since reported an integration-free method using episomal vectors that does not cause chromosomal damage and proposed using L-Myc as an alternative to oncogenic c-Myc to reduce the risk of tumorigenicity. We have also developed a recombinant laminin-based matrix and developed a culture medium free of animal-derived constituents (xeno-free) to generate iPS cells that satisfy regulatory requirements for medical practice. Regarding quality control, we are innovating technologies to screen out low-quality iPSCs before use. This includes new miRNA technology that was used to sort cardiomyocytes differentiated from iPSCs at levels superior to antibody-dependent systems. We are also developing differentiation protocols that mix an ideal ratio of cardiomyocytes and vascular cells for optimal cardiac recovery following transplantation.

In 2014, the world’s first clinical study using iPSCs began for the treatment of age-related macular degeneration. iPSC studies have also made major progress for other disorders, giving expectation that iPSC-based regenerative medicine will be widely used in the near future. To push these efforts, we are proceeding with an iPSC stock project in which iPSC clones are being established from donors with a homologous HLA haplotype, which is associated with decreased immune response and therefore less risk of transplant rejection.
Kenneth Chien, MD PhD

Professor Kenneth Chien received a Presidential appointment as a Professor to Karolinska Institutet, in 2013. Professor Kenneth Chien was previously the Charles and Elizabeth Ann Sanders Professor in the Department of Stem Cell and Regenerative Biology at Harvard University. From 2005-2009, he was appointed as Scientific Director of the Cardiovascular Research Center at Massachusetts General Hospital in Boston.

Professor Chien graduated from Harvard College in 1973 and earned his MD in 1980 and PhD in 1983 from Temple University in Pennsylvania. After completing his internship, residency, and cardiology fellowship training at the University of Texas Southwestern Medical School in Dallas, he joined the faculty of the UCSD Departments of Medicine and Cardiology and the Center for Molecular Genetics. Subsequently, Dr. Chien became the Director of the UCSD Institute of Molecular Medicine and directed the joint UCSD-Salk Institute National Institutes of Health Molecular Medicine Training Program.

Dr. Chien is an internationally recognized leader in cardiovascular science, as well as a pioneer in developing new therapeutic strategies to prevent the onset and progression of heart failure. At Karolinska Institutet, Professor Chien leads a team of physicians and scientist on the pathways for human cardiogenesis, with a goal of finding new insights into congenital heart disease in children, as well as novel pathways and principles for regenerative medicine and the repair of damaged cardiac muscle cells.

He is a recipient of the Walter B. Cannon Award of the American Physiology Society, the Pasarow Foundation Award and a member of the Norwegian Academy of Sciences, the Austrian Academy of Sciences, and honorary doctorate of the University of Edinburgh for his work. Recently he was appointed as a Distinguished Professorship of the Swedish Research Council, and Director of the Karolinska-Wallenberg Cardiovascular Initiative.

Professor Chien has also served as a senior consultant and board member to several biotechnology and large phama over the past decade, fostering collaborative ties between academia and the private sector. Dr. Chien was also heavily involved in the establishment of the Institute of Molecular Medicine at Peking University, currently the premier site for cardiovascular science in China.
ABSTRACT
Rebuilding the heart

Over the past two decades a host of new molecular pathways have been uncovered that guide mammalian heart development and disease. The ability to genetically manipulate these pathways in vivo has largely been dependent on the generation of genetically engineered mouse model systems or the transfer of exogenous genes in a variety of DNA vectors (plasmid, adenoviral, adeno-associated viruses, anti-sense oligonucleotides, etc.). Recently, a new approach to manipulate the gene program of the adult mammalian heart has been reported that will quickly allow the high efficiency expression of virtually any protein in the intact heart of mouse, rat, porcine, non-human primate, and human heart cells via the generation of chemically modified mRNA (modRNA). The technology platform has important implications for delineating the specific paracrine cues that drive human cardiogenesis, and the pathways that might trigger heart regeneration via the rapid generation of modRNA libraries of paracrine factors for direct in vivo administration. In addition, the strategy can be extended to a variety of other cardiovascular tissues, and solid organs across multiple species, and recent improvements in the core technology have now supported moving the first in human studies of modRNA later this year (Astrazeneca/Moderna). These recent advances are reviewed along with examples of the utility of the approach into quickly delineating novel insights into new therapeutics for regenerative cardiology via the delivery of paracrine factors to drive vascular regeneration and repair post-MI. In parallel, recent advances have allowed the purification and massive expansion of human ventricular progenitor cells derived by human pluripotent stem cells that can self assemble into a 3-D functional ventricular patch in vivo. Finally, we will discuss how this new progenitor-paracrine factor technology platform could move forward in a clinically tractable manner.
Jussi Huttunen, MD PhD

Global health today (in Finnish)

A review.

Professor Jussi Huttunen is a physician (1966 University of Helsinki), scientist, and former director general of the National Public Health Institute of Finland (1978-2003). He is an internist by training, and served as associate professor of internal medicine at the University of Kuopio 1975-1978. As the first director general of the reformed (1982) National Public Health Institute he guided the institute from previously routine microbiological and clinical chemistry laboratory to an internationally recognized research institute in public health. Throughout his career Huttunen has been involved in many different organisations, and he has been a well-known health care expert often consulted by the government as well as by international and local authorities. He served as an acting director general and department chief at the Ministry of Social Welfare and Health (2000-2001). One of the longest activities is in the Finnish Medical Association Duodecim: he acted several years as editor of its journal Duodecim, and in several positions in the activities including presidency of the Association (1996-1999). He has also been president of the Finnish Diabetes Research Foundation (1985-1991), Finnish Cancer Research Foundation (1989-1990), Finnish Cancer Association (1992-1995), and Finnish Heart Association (1998-2003), among others. International assignments include presidency of the Governing Council of the International Agency for Research on Cancer (IARC, 1990-1992), Nordic Cancer Union (1991), and vice presidency of a committee evaluating the Framework Programs of the European Union (2008). He has belonged to editorial boards of several international scientific journals and was editor of Annals of Clinical Research (1984-1989).

Huttunen started his research career as medical biochemist, and presented his dissertation for doctor of medical sciences degree on sugar metabolism (1966). Subsequently his interests have been in important national diseases such as cardiovascular diseases and diabetes, as well as nutrition. Even as director general he was actively involved in epidemiological studies on cardiovascular and metabolic diseases. He has also been concerned on great health differences between social groups. He holds honorary doctorate in medicine from the University of Kuopio (2000) and many other honours.
Katriina Aalto-Setälä, MD PhD

Stem cell-derived cardiomyocytes - What is their benefit? (in Finnish)

A review.

Katriina Aalto-Setälä, M.D. is the Professor of Physiology at the School of Medicine, University of Tampere and a cardiologist at the Heart Hospital, Tampere University Hospital, Tampere, Finland.

Dr. Aalto-Setälä received her MD and PhD degrees at the University of Helsinki. Clinical training for internal medicine and cardiology she received at the University of Tampere. Dr. Aalto-Setälä did her postdoctoral training at the Rockefeller University, New York and spent a year at St Jude Children’s Hospital, Memphis TN. Later she spent a year as a visiting Professor at the Gladstone Institutes, San Francisco, USA. Currently she has a research laboratory at the University of Tampere and she also works as an invasive cardiologist and is in charge of the genetic cardiac outpatient clinic at the Heart Hospital, Tampere University Hospital.

Her research focuses on human genetic cardiac diseases such as genetic arrhythmias and atherosclerosis with the help of induced pluripotent stem cell (iPSC) technology.
Meet the Speakers

Symposium lectures
Dr. Christine Mummery, Ph.D.

Dept. Anatomy and Embryology,
Leiden University Medical Centre,
The Netherlands
c.l.mummery@lumc.nl

Dr. Mummery is Chair of the Department of Anatomy and Embryology and Professor of Developmental Biology at the Leiden University Medical Center (LUMC). She studied physics at the University of Nottingham, UK and earned a Ph.D. in Biophysics at the University of London. She received a postdoctoral fellowship from the Royal Society in the UK for research at the Hubrecht Institute where she became group leader and, in 2002, Professor of Developmental Biology of the Heart for the Interuniversity Cardiology Institute of the Netherlands. In 2007 she was awarded a Harvard Stem Cell Institute/Radcliffe fellowship for a sabbatical in Harvard at Massachusetts General Hospital and the department of Disease Biophysics. Dr. Mummery’s research concerns mouse development and differentiation of mouse and human embryonic stem cells. She pioneered studies differentiating and characterising cardiomyocytes from human embryonic stem cells and was among the first to inject them in mouse heart and assess their effect on myocardial infarction. In 2000, she introduced human embryonic stem cells into the Netherlands and subsequently received the first license to derive new lines from surplus IVF embryos. Four lines were later derived in her lab. Much of the work on these cells has concerned their differentiation to cardiomyocytes. Since moving to the LUMC in 2008, Dr. Mummery has continued her research on heart development and the differentiation of patient derived induced pluripotent human cells into the cardiac and vascular lineages. Immediate interest of her lab is on using stem cell derived cardiomyocytes and vascular cells as disease models, for drug discovery and future cardiac repair. In 2015 she became guest professor at the Technical University of Twente to develop organ-on-chip models of disease based on hiPSC.

Dr. Mummery is an elected member of the Royal Netherlands Academy of Science. She is a member of several Scientific Advisory Boards (Galapagos bv, Stem Cell Institute Leuven, the UK Pluripotent Stem Cell Initiative, the Australian Stem Cell Centre) and has written a popular book on stem cells. She is presently Editor-in-Chief of Stem Cell Reports (the journal of ISSCR), lead reviewer of Stem Cells, and on the Editorial Boards of Cell Stem Cell, the International Journal of Developmental Biology and Differentiation.

Dr. Mummery was an elected member of the board of ISSCR for the past 8 years and is past-president of the International Society of Differentiation. She also serves on boards of the Netherlands Heart Foundation and ZonMW (Netherlands Medical Research Council).
ABSTRACT

*Human pluripotent stem cells in understanding genetic cardiovascular disease and effects of drugs*

Derivation of many different cell types from human pluripotent stem cells (embryonic stem cells or HESCs and induced pluripotent stem cells or hiPS cells) is an area of growing interest both for potential cell therapy and as a platform for drug discovery and toxicity. Most particularly, the recent availability of methods to introduce specific disease mutations into human pluripotent stem cells and/or to derive these cells as hiPS cells by reprogramming from any patient of choice, are creating unprecedented opportunities to create disease models “in a dish” and study ways to treat it or slow down its rate of development. Understanding the underlying developmental mechanisms, that control differentiation of pluripotent cells to their derivatives and mimicking these in defined culture conditions in vitro is now essential for moving the field forward. We have used these methods to produce isogenic pairs of hiPSC lines to compare diseased and corresponding control cardiomyocytes and vascular endothelial cells and identify disease related phenotypes and mechanisms. The use of isogenic pairs has proved crucial since variability between “healthy control” hiPSC lines is often greater than the difference between a diseased cells and its isogenic control. We have also examined drug responses of hESC-derived cardiomyocytes to a variety of cardiac and non-cardiac drugs and shown that iPSC derived cardiomyocytes with mutations in ion channel genes can accurately predict changes in cardiac electrical properties and reveal drug sensitivities also observed in patients. Similar studies will be described using vascular endothelial cells from hPSC. Relevant in all cases is the development of appropriate bioassays in which to measure disease phenotypes, which may be highly cell type specific. For heart cells, this might be electrical activity or contractions force; for vascular cells, responses to fluid flow flow and inflammation. Various approaches to this will be presented.
Kari Alitalo, MD PhD

Wihuri Research Institute and Translational Cancer Biology Center of Excellence, Biomedicum Helsinki, 00014 University of Helsinki, Finland

Kari Alitalo is a Finnish medical doctor (MD) and a medical researcher. He is a foreign associated member of the National Academy of Sciences of the USA. He became famous for his discoveries of several receptor tyrosine kinases (RTKs) and the first growth factor capable to induce lymphangiogenesis: vascular endothelial growth factor C (VEGF-C). Alitalo is currently serving as an Academy Professor for the Academy of Finland and is the director of the Wihuri Research Institute.

Prof. Alitalo has mentored 46 PhD students and published over 500 original peer-reviewed publications as well as 129 reviews and editorials. In the years 1996–2007 Alitalo was Europe's second most cited author in the field of cell biology. He has received several honors and awards such as the Leopold Griffuel Prize in 2002, the 2006 Louis-Jeantet Prize for Medicine, the 2005 Eric Fernström Foundation's Nordic Prize, the 2009 In-Bev Baillet Latour Health Prize and in 2014 the Dr. A.H.Heineken Prize for Medicine.

Prof. Alitalos’s laboratory is interested in pathophysiology of cancer, tumor angiogenesis and metastasis. They have unraveled the molecular basis of lymphangiogenesis, the formation of lymphatic vessels and their involvement in tumor metastasis. They identified by molecular cloning several receptors and growth factors that govern the development and maintenance of blood vessels and lymphatic vessels. In fact, three of the currently known five vascular endothelial growth factors and two of the five endothelial-specific growth factor receptors were identified in studies of their and their collaborators.

Lymphatic vessels have been known for long, but the lack of molecular tools has prevented studies of the molecular basis of lymphangiogenesis and the development of therapeutic strategies to treat disorders where these vessels are involved. This changed with their most significant discovery concerning the growth factor/receptor system that controls the development of lymphatic vessels and lymphatic metastasis. They first discovered of the lymphatic growth factor receptor, VEGFR-3, and then isolated its first ligand VEGF-C. They greatly contributed to the characterization of the second ligand, VEGF-D, and to the discovery of VEGF-B, a coronary vessel growth factor. We used gene targeting and transgenic mouse experiments to establish the developmental and cancer-related roles of these factors. Most importantly, they initiated studies showing that lymphangiogenic factors in tumors greatly enhance tumor metastasis. Furthermore, they simultaneously showed that this can be inhibited by blocking the VEGF-C/VEGF-D - VEGFR-3 interaction and later demonstrated that such inhibition also increases the efficiency of anti-angiogenic therapy. Two antibodies from their studies are now in phase I clinical trials against cancer. They furthermore developed growth factor therapy for lymphedema that is now entering clinical trials.
ABSTRACT
Vascular Neoformation

Because of the importance of vascular neoformation, or angiogenesis, in tumor progression, the first anti-angiogenic agents have been approved for tumor therapy. Although these treatments have been successful in the treatment of many types of solid tumors, most patients are either refractory or eventually acquire resistance to anti-angiogenic therapeutics. A combination of angiogenesis inhibitors based on solid knowledge of the major interacting angiogenesis signaling pathways could be used to significantly advance the efficacy of tumor therapy. - The idea of proangiogenic therapy is to grow new functional blood vessels and thus restore blood flow to ischemic tissue. In addition to angiogenesis of blood capillaries, growth of larger arterioles/arteries (arteriogenesis, or collateral formation) is especially beneficial for this goal. Several attempts have been made to stimulate angiogenesis and arteriogenesis in tissue ischemia, with limited success. One of the obstacles has been the property of angiogenic growth factors to promote vascular leakage, leading to tissue edema and fibrin deposition. Despite intensive efforts, growth factors suitable for angiogenic therapy have not yet provided significant help for patients with cardiovascular disease. – A better understanding of the biology of the vascular growth factors may facilitate therapeutics development for cardiovascular diseases. - The growth of lymphatic vessels, lymphangiogenesis, is actively involved in a number of pathological processes including tissue inflammation and tumor dissemination but is insufficient in patients suffering from lymphedema, a debilitating condition characterized by chronic tissue edema and impaired immunity. Lymphangiogenic growth factors provide possibilities to treat these diseases. With the recent discovery of meningeal lymphatic vessels their therapeutic potential may extend also to neurodegenerative and neuroinflammatory diseases.
Thomas Escenhagen, MD

University Medical Center Hamburg Eppendorf
Experimental Pharmacology and Toxicology
t.eschenhagen@uke.de

**Keywords**: Cardiovascular pharmacology, heart failure, tissue engineering, stem cells

Thomas Escenhagen, MD, is Professor of Pharmacology and Director of the Department of Experimental Pharmacology and Toxicology at the University Medical Center Hamburg Eppendorf, Germany. He is also chair of board of directors of the German Centre of Cardiovascular Research (DZHK).

Dr. Eschenhagen has concentrated his research efforts on understanding molecular mechanisms of heart failure with a focus on β-adrenergic signaling, its adaptation in heart failure and consequences on contractile function. He is best known for his pioneering work on 3-dimensional engineered heart tissue (EHT) from primary cardiac cells, starting 1994 in collaboration with Elliot Elson, St. Louis, USA. Originally designed as an improved in vitro model for drug testing and target validation, the EHT technology has been expanded to an automated 24-well screening platform. In combination with human embryonic and induced pluripotent stem cell-derived cardiomyocyte, this technique opens new perspectives in biomedicine, e.g. medium throughput drug screening, LQT and cardiotoxicity testing, disease modeling and cardiac regeneration. Dr. Eschenhagen and his group have recently shown that EHTs survive after implantation on injured guinea-pig hearts, can couple to host myocardium and improve cardiac function.

For his contributions to science, he received the Fraenkel Award of the German Society of Cardiology (1997) and the Outstanding Investigator Award of the International Society for Heart Research (ISHR; 2012). He is member of the German Academy of Science Leopoldina (2008) and received an ERC Advanced Grant (2013). He is currently President-Elect of ISHR International.
ABSTRACT

Cardiac tissue engineering for disease modelling and cardiac repair

The discovery of human induced pluripotent stem cell (hiPSC) technology and improvements in protocols to differentiate cardiomyocytes from hiPSC-derived cardiomyocytes (hiPSC-CM) have opened new perspectives for cardiac biology. A current shortcoming is the limited maturity of hiPSC-CM. We have developed methods to generate 3-dimensional heart muscle strips from hiPSC-CM (engineered heart tissue, EHT) and showed that CM develop an advanced degree of cardiac maturity, both structurally and functionally. Human EHT show canonical responses to a variety of drugs with known effects on cardiac repolarization, force and contraction kinetics. Patient-derived EHTs reflect typical abnormalities in contractile function, suggesting that this approach will be useful to model complex cardiac diseases such as dilated and hypertrophic cardiomyopathies. Limitations such as clone-to-clone and intra-assay variability will be discussed. Human EHTs may also serve as patches for heart muscle repair after myocardial infarction. EHTs made from human induced hiPSC-CM and endothelial cells (hEHT) were sutured onto injured guinea pig hearts. In a large series of experiments, we compared effects of hEHTs with that of constructs made from human endothelial cells only (hEET) or cell free patches. Transplantation was done 7 days after large cryo-injury inducing a mean transmural infarct size affecting 22% of the left ventricular wall. 28 days after transplantation and double immunosuppression, hEHT-transplanted hearts showed large human heart muscle grafts within the scar that showed cardiomyocyte proliferation, vascularization and partial electrical coupling. hEHT improved echocardiographically determined LV function, while hEET or cell-free patches had no effect. Thus, the study provides the first proof of efficacy of human 3D heart muscle constructs in repairing the injured heart and suggests that this approach is an attractive alternative to cell therapy.
Katriina Aalto-Setälä, Prof. MD

Biomeditech and School of Medicine
University of Tampere
and
Heart Hospital
Tampere University Hospital
Tampere
Finland

Katriina Aalto-Setälä, M.D. is the Professor of Physiology at the School of Medicine, University of Tampere and a cardiologist at the Heart Hospital, Tampere University Hospital, Tampere, Finland. Dr. Aalto-Setälä received her MD and PhD degrees at the University of Helsinki. Clinical training for internal medicine and cardiology she received at the University of Tampere. Dr. Aalto-Setälä did her postdoctoral training at the Rockefeller University, New York in Prof. John Breslow’s laboratory and also spent a year in Prof. Malcolm Brenner’s laboratory at St Jude Children’s Hospital, Memphis TN. Later she spent a year as a visiting Professor at the Gladstone Institutes in Prof. Bruce Conklin’s laboratory and learned the iPSC technology in Prof. Shinya Yamanaka’s laboratory. Currently she has a research laboratory at the University of Tampere and she also works as an invasive cardiologist and is in charge of the genetic cardiac outpatient clinic at the Heart Hospital, Tampere University Hospital.

Her research at the Biomeditech and at the School of Medicine, University of Tampere focuses on human genetic cardiac diseases such as genetic arrhythmias and atherosclerosis with the help of induced pluripotent stem cell (iPSC) technology. The main aim of the research group is to learn more about the basic pathology of the genetic diseases as well as to test current and new pharmaceutical agents to correct the abnormalities. Her research group in collaboration with researches at the Tampere Technical University has also invented new methods to monitor and analyse the maturity and functionality cardiomyocytes.

Dr. Aalto-Setälä was for several years a member of National Medical Research Ethics committee in Finland. She has also been an active member of Basic Science working group of the Finnish Cardiac Society as well as in the Finnish Medical Society Duodecim. Currently she is the vice president of the organizing committee of the Medical Convention in Tampere.
ABSTRACT

Modelling cardiac diseases with iPSC technology

Stem cell technology is a research area, which is expected to provide new platform for drug discovery and to bring new treatment options to the currently available traditional drug and devise therapies. Induced pluripotent stem cell (iPSC) technology has provided tools to obtain genotype-specific stem cells and further differentiated these cells with the disease phenotype into the cell type of interest. Genetic defects responsible for most genetic diseases are known, but the link between molecular defect and clinical outcome is not usually clear and iPSC based cell models carrying the mutations found in patients could reveal this link. Pharmaceutical testing with these disease models would also provide more detailed information about the effects of different compounds in human cells.

Finland has been a genetic isolate and founder gene mutations have been enriched in this country. E.g. the majority of Finnish long QT syndrome (LQTS) patients carry one of the four founder mutations. However, with some diseases like catecholaminergic polymorphic ventricular tachycardia (CPVT), most families have unique mutations also in Finland. We have investigated how different ion channel mutations affect the electrical properties of differentiated cardiomyocytes carrying different gene mutations causing either LQTS or CPVT and found differences between cells with mutations in different genes but also within the same gene. We have also tested a panel of drugs and analysed their effects on the beating cells. Analysis methods and software are often the bottlenecks when analysing large quantities of cells. We have developed and improved methods to analyse more precisely findings with microelectrode array (MEA) and patch clamp as well as abnormal Ca\textsuperscript{2+} transients. An important function of cardiomyocytes, the mechanical beating behavior is easily detected with video analysis software. This automated software provides faster, but also more robust and standardized way to quantitate beating properties of the cells. The maturity of the cells is very important and thus our investigations have focused towards more rod shape cells analyzed by CytoSpectre software.

The different methods and their analyses software will be further discussed in the presentation as well as new findings when combining clinical and cell culture data to each other with special focus on LQTS and CPVT.
Seppo Ylä-Herttuala, MD, PhD, FESC

Seppo Ylä-Herttuala, MD, PhD, FESC. Professor of Molecular Medicine, A.I. Virtanen Institute for Molecular Sciences, University of Eastern Finland and Gene Therapy Unit, Kuopio University Hospital, Kuopio, Finland. Prof. Ylä-Herttuala is a world leader in cardiovascular gene therapy. His team was the first to use adenovirus-mediated gene transfer to human arteries already in 1995. Since then, he has conducted several clinical trials in cardiovascular and malignant glioma gene therapy. He is also the originator of the concept of epigenetherapy. His group has been widely recognized for basic biology, translational and epigenetic research of the vascular endothelial growth factors, especially focusing on the new members of the VEGF family. Professor Ylä-Herttuala has served as the President of the European Society of Gene and Cell Therapy and is currently the Editor-in-Chief of Molecular Therapy. His list of publications includes over 400 scientific papers and articles about vascular biology, cardiovascular diseases, malignant glioma, VEGFs, gene transfer vectors and gene therapy.
ABSTRACT

Cardiovascular Gene Therapy with Vascular Endothelial Growth Factors

Therapeutic vascular growth is a potentially useful strategy for ischemic heart disease and peripheral arterial occlusive disease. It involves generation of new capillaries, collateral vessels and lymphatic vessels in ischaemic muscles using either recombinant growth factors or their genes. Arteriogenesis is a process caused by increased sheer stress at the arteriolar level resulting in the formation of large conduit vessels from preexisting small vessels whereas angiogenesis and lymphangiogenesis refers to generation of new vascular structures in vivo. Most commonly used growth factors for therapeutic angiogenesis are members of the vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF) families. Some other cytokines and growth factors can also have angiogenic effects. Improved perfusion and functional parameters can be achieved by angiogenesis and arteriogenesis in large animal chronic ischemia models and in man. Safety of the clinical gene therapy of cardiovascular diseases has been excellent with long-term follow-up to 10 yrs after the therapy. Small non-coding RNAs can also be used for angiogenic gene therapy. Most promising results have so far been obtained with direct catheter-based intramyocardial injections of VEGF-D genes with adenovirus and AAV vectors.

References:
Alexander Lyon, MA BM BCh PhD FRCP

Dr. Alexander Lyon is a British Heart Foundation Senior Lecturer in Cardiology at Imperial College London and a Consultant Cardiologist at the Royal Brompton Hospital. Alex studied medicine at Oxford University where he gained a first class degree, and studied for his PhD thesis in myocardial gene therapy at Imperial College London. He continued his gene therapy research during a postdoctoral research year in the laboratory of Roger Hajjar at Mount Sinai Hospital in New York. His clinical interests are in the field of heart failure, chemotherapy cardiomyopathy and the cardiovascular complications of modern cancer therapies, Takotsubo syndrome, and the development of novel therapeutics including gene therapy for chronic heart failure. Alex is the theme leader for heart failure research in the NIHR-funded Biomedical Research Unit at the Royal Brompton Hospital, and he is the UK national lead investigator for two gene therapy trials for chronic heart failure (CUPID2 and SERCA-LVAD), which are the first gene therapy trials for heart failure in the UK. Alex is the clinical lead for the Cardio-Oncology service at the Royal Brompton Hospital since 2011, specialising in surveillance and cardioprotection from modern cancer drugs, risk stratification and treatment of all cardiac complications of cancer treatment. Alex is president of the British Cardio-Oncology Society (formerly the UK Cardio-Oncology Consortium) and he is the cardiology advisor to Macmillan Cancer. He is a member of the International Cardio-Oncology Society and is a co-author of their guideline document for the clinical community. Dr. Lyon leads both a laboratory research programme understanding the influence of stress and high catecholamine levels upon myocardial function, and he is coordinating both a national and European strategy to advance knowledge and improve care for individuals with Takotsubo syndrome. He runs a specialist clinic for patients with Takotsubo syndrome focusing on risk prediction and management of refractory symptoms.
ABSTRACT

SERCA2a gene therapy for heart failure

Chronic heart failure is a major health burden resulting from many factors including the growing e molecular and cellular changes occur in the chronically failing heart, but one common feature is disturbance of cardiomyocyte intracellular calcium regulation. This is multifactorial including increased diastolic calcium leak from ryanodine receptors and the reduction in the expression of the cardiac sarcoplasmic reticulum calcium ATPase (SERCA2a) enzyme, disrupting myocardial calcium regulation, resulting in impairment of contraction, relaxation, energetics and increases arrhythmogenesis. Twenty-five years of preclinical studies have demonstrated beneficial effects of SERCA2a gene transfer to the failing heart in a variety of preclinical models and assays. This underpins the CUPID clinical trial programme, which has evaluated the safety and efficacy of AAV1.SERCA2a gene therapy in patients with advanced heart failure on top of optimal medical care. The contrasting results of the initial phase 2a CUPID study and the larger multicentre, international phase 2b CUPID2 trial will be reviewed, and the SERCA-LVAD trial in the UK. Other gene therapy approaches including S100A1 and SDF-1 will be presented, and future directions in this field will be discussed.
Mauro Giacca

International Centre for Genetic Engineering and Biotechnology (ICGEB)
Trieste, Italy

Mauro Giacca, MD PhD, is the Director-General of the International Centre for Genetic Engineering and Biotechnology (ICGEB), an international organization in the United Nations system for advanced research and education, with laboratories in Trieste, Italy, New Delhi, India and Cape Town, South Africa (www.icgeb.org). He is Full Professor of Molecular Biology at the University of Trieste. He has served on the Boards of various scientific organizations in Italy and abroad, including the National Committee for Biotechnology, Biosafety and Life Sciences (CNBBSV), an advisory body to the President of the Council of Ministers of the Government of Italy, the Scientific Council of the National Center for Genetic Engineering and Biotechnology (BIOTEC), Bangkok, Thailand and the International Governing Board of the International Centre for Biotechnology at the University of Nigeria Nsukka (UNN) of UNESCO.

His research interest focuses on the development of novel biotherapeutics for cardiovascular disorders, with particular reference to the identification of growth factors and microRNAs inducing cardiac regeneration after myocardial infarction. He also maintains a strong interest in the molecular biology of HIV-1 infection. He has published over 290 papers in peer-reviewed, international journals. He is also active in promoting scientific outreach for the general public.

Further information: http://www.icgeb.org/mauro-giacca.html
ABSTRACT
Small RNA and protein therapy for cardiac regeneration

There is an impelling need to develop innovative therapies that promote cardiac repair and regeneration in patients with myocardial infarction and heart failure. In contrast to other species that are able to regenerate the heart throughout their entire life, post-natal damage to the myocardium in mammals is repaired through formation of a scar. Copious evidence nonetheless indicates that the capacity for myocardial renewal, albeit limited, also exists in adult individuals. During the last several years, my laboratory has become deeply interested in developing methods to search for factors able to foster this cardiac regenerative capacity. We follow two parallel approaches, both based on unbiased, functional screenings. In one approach, we generated a cDNA library corresponding to the secretome (all secreted factors encoded by the genome, including growth factors, interleukins and chemokines, hormones, extracellular matrix proteins, etc.; approximately 1200 proteins); with each factor coding region individually cloned into an AAV vector. We developed a procedure (named FunSel) for the functional selection of therapeutic factors after in vivo administration of this library to the heart after myocardial infarction. FunSel has so far generated a number of novel and, in some cases, unexpected molecules able to protect the heart and, in other instances, able to induce its regeneration.

With the other approach, we searched for small RNAs inducing cardiac regeneration by the ex vivo, high throughput screening of miRNAs and miRNA-inhibitors able to promote primary cardiomyocyte proliferation using whole genome libraries. We identified at least 8 microRNAs that increase cardiomyocyte proliferation in mice, rats and pigs as well as in human cardiomyocytes from fetal hearts, or derived from ES and iPS cells. Delivery of two of these miRNAs in vivo, either using AAV9 vectors or as synthetic mimics after myocardial infarction markedly reduced infarct areas and improved cardiac function in both mice and pigs. These microRNA function by directly activating the proliferative potential of differentiated cardiomyocytes thus bypassing the requirement of stem cell expansion and differentiation. Taken together, these results indicate that finding novel biotherapeutics for myocardial infarction and heart failure is an attainable goal, including proteins or small RNAs capable to induce cardiac regeneration.
High Throughput Screening Using Stem Cell-Derived Cardiomyocytes

Abstract:
Heart disease is the most significant cause of morbidity and mortality in the industrialized world, accounting for nearly 33% of all deaths in 2008 within the United States alone. While the use of human induced pluripotent stem cell (iPSCs) in regenerative medicine is a long-term goal, a growing body of studies has shown promising results in the fields of drug discovery, development, and toxicity screening. Specifically, recent technological advancement has enabled the generation of patient-specific and disease-specific human induced pluripotent stem cell-derived cardiomyocytes (iPSC-CMs) in vitro. These iPSC-CMs carry all the genetic information from the individuals from whom they are derived and hence may be an ideal platform for elucidating disease modeling, drug screening, and cell therapy. Here I will discuss recent advances in this technology in the cardiovascular field.

Biography:
Joseph C. Wu, MD, PhD is Director of the Stanford Cardiovascular Institute and Simon H. Stertzer, MD Professor of Medicine (Cardiology) and Radiology at the Stanford School of Medicine. Dr. Wu received his MD from Yale University School of Medicine. He trained in internal medicine and cardiology at UCLA followed by a PhD in the Dept of Molecular Pharmacology. His clinical interests involve cardiovascular imaging and adult congenital heart disease.

Dr. Wu has published >300 manuscripts. His lab works on biological mechanisms of patient-specific and disease-specific induced pluripotent stem cells (iPSCs). The main goals are for (i) understanding basic cardiovascular disease mechanisms, (ii) accelerate drug discovery and screening, and (iii) develop personalized medicine and "clinical trial in a dish" platforms. His lab uses a combination of genomics, stem cells, cellular & molecular biology, physiological testing, and molecular imaging technologies to better understand molecular and pathophysiological processes.

Dr. Wu has received numerous prestigious awards, including Burroughs Wellcome Fund Career Award for Medical Scientists (2007), National Institutes of Health Director’s New Innovator Award (2008), NIH Roadmap Transformative Award (2009), American Heart Association Innovative Research Award (2009), Presidential Early Career Award for Scientists and Engineers given out by President Obama (2010), AHA Established Investigator Award (2013), and BWF Innovation in Regulatory Science Award (2015). He also received the Best Basic Science Award in Circulation twice (2006 & 2014), Best Manuscript Award in Circulation Research (2013), and the William Parmley outstanding paper award in JACC (2009). In addition, he received the inaugural Joseph A. Vita Award (2015) at the AHA meeting which is given to an investigator whose body of work published in the last 5 years has had transformative impact on basic, translational, or clinical cardiovascular research.

Dr. Wu is an Associate Editor for Circulation Research. He is Senior Guest Editor for JACC: Cardiovascular Imaging. He is also on the editorial board of Journal Clinical Investigator, Circulation Cardiovascular Imaging, Human Gene Therapy, Molecular Therapy, Stem Cell Research, Journal of Nuclear Cardiology, Physiological Genomics, and Scientific Report. He is a council member for the American Society of Clinical Investigation (ASCI), a member of Association of University Cardiologists (AUC), and a member of American Association of Physicians (AAP).
ABSTRACT
High Throughput Screening Using Stem Cell-Derived Cardiomyocytes

Heart disease is the most significant cause of morbidity and mortality in the industrialized world, accounting for nearly 33% of all deaths in 2008 within the United States alone. While the use of human induced pluripotent stem cells (iPSCs) in regenerative medicine is a long-term goal, a growing body of studies has shown promising results in the field of drug discovery, development, and toxicity screening. Specifically, recent technological advancement has enabled the generation of patient- and disease-specific iPSC-derived cardiomyocytes (iPPS-CMs) in vitro. These iPSC-CMs carry all the genetic information from the individuals from whom they are derived and hence may be an ideal platform for elucidating disease modeling, drug screening, and cell therapy. Here I will discuss recent advances in this technology in the cardiovascular field.
Lior Gepstein. MD, PhD

Rappaport Faculty of Medicine and Research Institute, Technion – Israel Institute of Technology, Haifa, Israel

Prof. Lior Gepstein graduated his MD studies at the Rappaport Faculty of Medicine, Technion- Israel Institute of Technology, Haifa, Israel and conducted his PhD thesis at the same institute. During this period he was involved in the development of a three-dimensional electroanatomical mapping techniques (CARTO system), which became the state-of-the-art technology for the treatment of complex cardiac arrhythmias. Dr. Gepstein completed his internship and residency in internal medicine at Rambam Health Care Campus as well as a Cardiology fellowship at the same institution. He then spent a two-year fellowship in Cardiac Electrophysiology at the University of California San Francisco (UCSF).

Currently, he holds the position of Professor of Physiology and Medicine (Cardiology) at the Technion’s Faculty of Medicine and holds the Edna and Jonathan Sohns Chair in Tissue Engineering and Regenerative Medicine. He also serves as an attending electrophysiologist specialist at Rambam. More recently, he was appointed as the Director of the Cardiology Department at Rambam Health Care Campus, Haifa.

Prof. Gepstein's research activities focus on the areas of basic and clinical cardiac electrophysiology, stem cell biology, studying of inherited cardiac disorders, and establishment of novel gene and cell-based strategies for the treatment of different cardiac disorders. Dr Gepstein’s group was among the pioneers in developing unique cardiomyocyte differentiation strategies from human embryonic stem cells and human induced pluripotent stem cells and utilizing the generated heart cells for cardiac disease modeling, drug discovery, and regenerative medicine applications.

Dr. Gepstein was awarded a number of prestigious awards for his achievements in cardiology including the American College of Cardiology Douglas P. Zipes distinguished award, the European Society of Cardiology outstanding research achievement award and the Mirowski award from the Israel Cardiology Society. More recently he was elected to the Israeli Young Academy of Science.
ABSTRACT

STEM CELL AND GENE THERAPY STRATEGIES FOR CARDIAC ARRHYTHMIA

One of the most exciting scientific developments in recent years involves the use of stem cells for several research areas including developmental biology, drug discovery, disease modelling, and regenerative medicine. In the current presentation, we will focus on the possible implications of this emerging discipline in the field of cardiac electrophysiology and specifically for better understanding and treatment of cardiac arrhythmias.

Initially, efforts from our laboratory in establishing and coaxing the cardiomyocyte differentiation of patient-specific hiPSCs derived from patients with a number of familial arrhythmogenic disorders (long QT syndrome and catecholaminergic polymorphic ventricular tachycardia) will be described. These disease states may lead to the development of malignant arrhythmias and sudden cardiac death in otherwise healthy individuals. The ability of the hiPSCs approach to recapitulate the disease phenotype in the culture dish, to provide novel insights into disease mechanisms and to evaluate potential disease aggravators and novel customized treatment options will be described. We will next describe our efforts in using novel cell and gene therapies for the treatment of different cardiac arrhythmias. First, we will demonstrate the ability of human pluripotent stem cells to differentiate into sinoatrial node like pacemaker cells and to serve as biological pacemakers for the treatment of bradyarrhythmias. We will next describe the possible applications of using similar strategies for the treatment of common tachyarrhythmias through overexpression of different ion channels, connexins, or their modifiers. These approaches are based on direct myocardial gene delivery or on utilizing cell grafts engineered to express specific ionic channels to modify the myocardial electrophysiological substrate (enhancing conduction and/or prolonging refractoriness) and therefore rendering this area incapable of supporting the development of re-entrant arrhythmias. Finally, we will describe our efforts in developing a unique optogenetics approach, by which the expression of light-sensitive proteins can be used to pace the heart ("optogenetics-based biological pacemaker approach"), to induce electrical and mechanical ventricular synchronization ("optogenetics-based biological cardiac resynchronization therapy approach"), or even to induce cardiac defibrillation.
Bruce R. Conklin is an Senior Investigator at the Gladstone Institutes and a Professor in the UCSF Division of Genomic Medicine. Dr. Conklin’s research focuses on human genetics that lead to human diseases such as cardiomyopathy and blindness. His major model system is induced pluripotent (iPS) cells that are engineered to test the role of specific genetic changes on disease. Dr. Conklin began his research career by working for two years with Julius Axelrod, Ph.D., (Nobel Laureate) at the National Institutes of Health. He then completed his residency at Johns Hopkins Hospital and a postdoctoral fellowship in the laboratory of Henry Bourne, M.D. at UCSF. In 1995 Dr. Conklin joined the Gladstone Institutes and the UCSF faculty where he has advanced to become a Senior Investigator at Gladstone, and a Professor at UCSF. Dr. Conklin is also the Gladstone Scientific Officer for Technology and Innovation. Dr. Conklin is the founder of several public stem cell and genomics projects including BayGenomics, GenMAPP, AltAnalyze and WikiPathways. Dr. Conklin pioneered the field of using designer G protein coupled receptors (RASSLs) for tissue engineering. He was the founding director of the Gladstone Genomics Core and the Gladstone Stem Cell Core. He has a leadership role in the Innovative Genomics Initiative (IGI) headed by Jennifer Doudna. Dr. Conklin founded the Gladstone Stem Cell Training Program, is the principle investigator on multiple research grants from NIH and serves on multiple advisory boards including the Allen Institute for Cell Science. He is a member of several honorary societies including the American Society for Clinical Investigation, and is a Fellow in the California Academy of Sciences.
ABSTRACT
Therapeutic Approaches to Genetic Disease

CRISPR-Based Screens in Human Cardiac Disease Models: We have developed efficient methods to edit one residue at a time in human induced pluripotent stem (iPS) cells. These “isogenic” lines form models that are yielding phenotypes that help to explain the molecular basis of several human diseases. We are constructing collections of these lines that carry a range of severe (rare) to moderate (common) forms of cardiomyopathy disease mutations.

Surprisingly, little is known about many genes associated with heart failure, from cardiomyopathy to heart arrhythmias. Until recently, modeling gene variants in human cardiac tissue was impossible. Human iPS cells now allow us to produce cardiovascular tissues that are identical except for a single gene alteration using genome engineering. Our efforts have already been used to uncover multiple disease phenotypes and targets for drug therapy. Recently, we developed CRISPR-inhibition (CRISPRi) cell lines for high throughput gene inactivation of thousands of genes. CRISPRi screens can be used to identify the molecular basis of development, so that we can construct more mature human tissues and improved disease models. These studies will also allow us to identify drug targets that could treat cardiomyopathy and other major diseases. We are also focused on finding new pathways to enhance cardiac regeneration. In the future, other CRISPR systems could be used to activate genes and control the epigenetic state of the genome.

Precise Genome Editing for Human Therapy: The rapid development of genome engineering, such as the CRISPR system, allows us to contemplate using these tools for human therapy. “Fixing” a gene using genome editing could permanently correct the disease. However, challenges remain to ensure that the fixes are ‘on-target’, and without “off-target” DNA damage that could lead to cancer. We focused on therapeutic editing for diseases of the heart and retina, because each tissue has unique challenges and opportunities. The retina has the advantage of being a non-vital organ and has a limited number of cells that need to be targeted for therapy. Blindness caused by many gene mutations that currently have no therapy can be cured by genome engineering. We are developing proof-of-concept therapeutic editing methods in the retina that can be expanded to other tissues, such as the heart.

Future Directions: We are developing new genome engineering methods in human iPS cells to identify targets and to develop strategies for therapeutic genome editing for cardiac disease. The combination of human iPS cells and genome editing provide unprecedented opportunities to explore new areas of biology and discover new therapies for disease.
Christine Seidman, MD

Christine Seidman, MD is the Thomas W. Smith Professor of Medicine and Genetics at Harvard Medical School and Brigham and Women’s Hospital and an Investigator of the Howard Hughes Medical Institute. She was an undergraduate at Harvard College and received a M.D. from George Washington University School of Medicine. After clinical training in Internal Medicine at John Hopkins Hospital she received subspecialty training in cardiology at the Massachusetts General Hospital. Dr. Seidman is a faculty member of Brigham and Women’s Hospital, where she serves as Director of the Brigham Research Institute. She is the founding Director of the BWH Cardiovascular Genetics Center.

Dr. Seidman’s laboratory uses genomic strategies to define causes of human cardiovascular disease, including congenital heart malformations and cardiomyopathies. By exploiting model systems to identify pathways impacted by mutations, these studies have enabled gene-based diagnostics and novel strategies to limit the deleterious consequences of human mutations. Dr. Seidman also leads multi-institution consortium that assess rare and common variants involved in cardiovascular phenotypes and that explore the clinical utility of genomic variation in early diagnosis and prevention of cardiovascular disease.

The recipient of many honors, Dr. Seidman is a Distinguished Scientist of the American Heart Association, Fellow of the American Academy of Arts and Sciences, and member of the Institutes of Medicine and the National Academy of Sciences. She is also President of the Association of American Physicians.
ABSTRACT
Cardiomyopathies: Insights From Mutations that Inform Mechanisms and Therapies

Extraordinary technologic advances have provided unparalleled opportunities to sequence DNA, identify pathogenic mutations, and recapitulate disease in model organisms and human cells. These strategies have fueled the discovery of genetic causes and mechanisms for human heart disease – and pose a new opportunity – to target individuals at risk for disease with interventions that delay or prevent clinical expression. Genetic cardiomyopathies provide a paradigm for fulfilling these opportunities. Hypertrophic cardiomyopathy (HCM) is characterized by left ventricular hypertrophy, diastolic dysfunction with normal or enhanced systolic performance and a unique histopathology: myocyte hypertrophy, disarray and fibrosis. Dilated cardiomyopathy (DCM) exhibits enlarged ventricular volumes with depressed systolic performance and with variable amounts of myocardial fibrosis. Both HCM and DCM increased risk for arrhythmias, sudden death, and heart failure. Human molecular genetic studies demonstrated that these unique pathologies both result from dominant mutations in genes that encode protein components of the sarcomere, the contractile unit in all striated muscles. Ascertainment of the spectrum of human pathogenic mutations, in concert with biophysical studies and transcriptional analyses in model organisms and in human cardiomyocytes derived from induced-pluripotential stem cells provide unexpected molecular mechanisms for HCM and DCM. This presentation will discuss how human genetic discoveries inform fundamental knowledge about sarcomere biology, provide insights into clinical manifestations of cardiomyopathies, and provide new strategies to delay or prevent the emergence of HCM and DCM.
Heikki Ruskoaho MD, PhD

Division of Pharmacology and Pharmacotherapy, Faculty of Pharmacy, University of Helsinki, Finland

Heikki Ruskoaho is Professor of Pharmacology and Drug Development at the University of Helsinki. He was the Professor of Molecular Pharmacology in 1996-2012, the Dean of Faculty of Medicine in 2001-2005 and served as the Vice-President for Science and Research during years 2006-2009 at the University of Oulu. Heikki Ruskoaho received his doctorate in 1983, after which he performed postdoctoral training as an Alexander von Humboldt Foundation Research Fellow at the Department of Pharmacology and German Institute for High Blood Pressure in Heidelberg, Germany 1984-1985. His research group was a member of Finnish Center of Excellence for Cardiovascular and Type 2 Diabetes Research, funded by the Academy of Finland for 2008-2013. Currently, Heikki Ruskoaho is the coordinator of Tekes funded Large Strategic Research Opening, 3iRegeneration - Innovative Induction Initiative. His research interests include cardiovascular drugs, natriuretic peptides and the identification of signaling pathways and targets for the treatment of heart failure and myocardial infarction.
ABSTRACT
Small molecules for cardiac repair and regeneration

Cardiovascular diseases are today the major causes of death and disease in developed as well as developing countries. Ischemic heart disease alone is responsible for almost 10 million deaths worldwide. Finland is no exception, since ischemic heart disease is responsible for 1 out of 5 deaths. The key pathophysiological process in ischemic heart disease and myocardial infarction is the loss of functional cardiomyocytes, leading to heart failure. Multipotent cardiac stem/progenitor cells that reside in the heart have been shown to differentiate into cardiac myocytes, smooth muscle cells, and vascular endothelial cells. These cardiac stem cells have the potential to actively regenerate the heart. However, these endogenous stem cell repair mechanisms are underpowered for tissue repair in ischemic diseases. Thus, there is intense interest in developing therapeutic strategies to enhance the endogenous regenerative potential of adult human myocardium, including proliferation and differentiation of cardiac progenitor cells, proliferation of pre-existing cardiomyocytes, and reprogramming of cardiac fibroblasts.

Our focus is to enhance regeneration of damaged myocardium by inducing new cardiac cells locally in the heart with novel pharmaceuticals. The primary test assays used for screening of small molecule compounds are spontaneous and directed differentiation of mouse embryonic stem (ES) cells and mouse cardiac fibroblasts. For in vitro screening, we have developed a novel dual mouse ES reporter line for ventricular and atrial cell types. Candidate molecules have been tested in a number of confirmatory in vitro assays, including neonatal rat cardiomyocytes. For the improved cardiac function, the most potent compound has been evaluated in vivo in animal models of myocardial remodeling and repair to provide insight into the potential therapeutic effects. Finally, to improve the functional outcome of the small molecule compounds, we have designed a multifunctional nanosystem composed by a core of porous silicon (PSi) nanoparticles, decorated with different peptides for heart targeting. Qualitative and quantitative cellular uptake studies revealed a significant increase in the accumulation of atrial natriuretic peptide (ANP)-modified nanoparticles in primary cardiomyocytes, non-myocytes and H9c2 cells, and in hypoxic primary cardiomyocytes and non-myocytes, highlighting the potential of these peptide-modified nanosystems for future cardiac regenerative applications.
Stefanie Dimmeler

Institute for Cardiovascular Regeneration, University Frankfurt, Germany


ABSTRACT

miRNA in stem cell function and in the regenerative therapy of the heart (vascular)

In the last years, it has become evident that the majority of the genome is transcribed, while only about 2% codes for proteins. These so-called non-coding RNAs gained increasing attention as multifactorial regulators of gene expression. MicroRNAs (miRs) are small non-coding RNAs that bind to target mRNAs thereby inducing degradation or translational repression, whereas long non-coding RNAs act as epigenetic regulators of gene expression or by modulating splicing. Several miRs were shown to regulate cardiovascular repair and regeneration. Particularly, inhibition of miR-34a prevented age-related impairment of cardiac function, improved the repair capacity of bone marrow-derived progenitor cells and extends the postnatal regeneration window of the heart after injury. Moreover, first evidence suggests that long non-coding RNAs also play critical roles in cardiovascular diseases. The presentation will summarize the therapeutic perspectives of antimiRs and additionally will provide some recent insights into newly identified long non-coding RNAs in cardiovascular disease.
Heikki Huikuri, PI

Professor of Cardiology,
Director of Medical Research Center
University of Oulu, and University Hospital of Oulu, Finland

The research activity of the cardiology research group of the University of Oulu, directed by professor Heikki Huikuri has focused on the problem of sudden cardiac death, especially on research aimed at finding new risk markers of sudden cardiac death. The group has lead the field of research on risk markers of sudden cardiac death since late 1990s. The group has published over 500 original articles in the peer-reviewed international journals, many of them in the top cardiology journals with an impact factor >10, such as Circulation (n=21), Journal of the American College of Cardiology (n=19), and European Heart Journal (n=23), as well as in the top general medical journals, such as Lancet (n=4), New England Journal of Medicine (n=7), Nature (n=2) and Nature Genetics (n=3). A total of 31 medical dissertations (PhD degrees) have been completed under the supervision of the PI, 17 of them within the last 10 years. From his students 14 have received the degree of Adjunctive Professor and four have been nominated as Professors of Cardiology.

The publications of Prof. Huikuri within the past 10 years includes 232 original articles, 44 reviews or editorials, 8 chapters in textbooks, and more than 300 congress abstracts. The current H-index of Prof. Huikuri is 73 (Web Of Science) and his studies have been cited 21144 times with an increasing trend during the past 10 years. The Cardiovascular Research group directed by professor Huikuri received the highest rank (6/6) in the international Research Assessment Exercise of the University of Oulu in the most advanced science category (“Vici” category). The international panel commented the research group as follows: “The research is internationally very competitive and either outstanding or at least excellent. Surely the center is comparable to other well established research centers internationally given the reputation and achievements of its senior researchers with an eminent position with regard to their main topics. At the national level, there is no doubt that it is the top center in cardiovascular diseases”.

Professor Huikuri has collaborated with several international and national research groups creating a large research network focusing on the problem of sudden cardiac death. He has been an invited speaker 34 times in the major international conferences during the past 10 years. A fruitful collaboration has been active with the group of Professor Robert Myerburg from the University of Miami. He has been the PI of a large European multicenter study (CARISMA) assessing the risk factors of sudden cardiac death among patients with depressed left ventricular function after myocardial infarction. Currently he is the European PI of the REFINe-ICD study randomizing the patients with moderately depressed left ventricular function and abnormal autonomic and electrical function to implantable cardioverter-defibrillator therapy vs. standard therapy. Prof.
Huikuri is also in the executive committee of the large EU-funded EU-CERT study assessing the benefits of cardioverter-defibrillator therapy. Prof Huikuri is currently the director of the Medical Research Center (MRC) Oulu and one of the nine focus research groups of the MRC. The cardiology research group has started the collaboration with the group of Professor Kerkelä from the Department of Pharmacology aimed at studying the mechanisms and background of myocardial fibrosis as a cause of sudden cardiac death. The group of Prof. Kerkelä is also one of the research focus groups of the MRC Oulu.

**ABSTRACT**

**Individualized stratification for Sudden Cardiac Death**

Major advances have been achieved in understanding the etiology of cardiovascular diseases and concomitant reduction in cardiovascular disease-related mortality. The mechanisms of sudden cardiac death (SCD) are still largely unknown, however, and the incidence of SCD has remained unchanged for decades affecting younger people in general (mean age ~ 65 years) than the other causes of cardiovascular mortality. Several reasons have been identified as responsible for our inability to significantly improve the outcome of our patients at risk for premature unexpected SCD, such as the inability to understand the role of genetic, environmental and other modifiers of the phenotype and the lack of good risk stratification parameters.

Sudden unexpected cardiac death (SCD) occurs most commonly in previously asymptomatic subjects. The cumulative number of SCDs is smaller in patients with advanced cardiac disease but its incidence is substantially higher. Therefore, the recognition of an elevated risk for SCD in both asymptomatic subjects and patients with a known cardiac disease is of major importance for clinicians and scientists in attempts to prevent these events.

Relatively little information is available about the risk factors of SCD in general population. The most common cause of SCD is acute coronary event among the subject over the age of 40 years. Traditional coronary risk factors, such cholesterol and blood pressure, do not identify those at specific high risk for SCD. Observational follow-up studies, e.g. the Framingham study, have recognized some risk variables, such as elevated heart rate and body mass index, impaired vital capacity and signs of left ventricular hypertrophy on electrocardiogram (ECG) as risk factors of SCD in general population. Our own studies in a large Finnish population cohort have identified several other ECG variables as predictors of SCD in middle-aged subject during a long follow-up. Some genetic variants have also been identified as risk factors of SCD in meta-analyses of large sample sizes.

In 1999, our research group started to collect a consecutive series of victims of SCD caused by an acute coronary event in collaboration with the Forensic Department of our university (cases) aimed at comparing phenotype and genotype profiles of victims of SCD (FinGesture study). We have now collected 4500 cases of SCD until the end of 2014. We have shown that 70% of the SCDs are due to ischemic heart disease and 30% of the victims have a non-ischemic etiology. In recent years the proportion of non-ischemic etiology is increasing. In the latter group, idiopathic myocardial fibrosis is the most common autopsy finding among the subjects experiencing SCD under the age of 40 years. Our current research is focusing on studies of molecular and genetic background of SCD caused by idiopathic fibrosis in young victims of SCD.
Andreas M Zaiher, MD

Dr. Zeiher is Professor of Medicine and board-certified in internal medicine and cardiology. He has served on the faculties of Albert-Ludwigs-Universität of Freiburg from 1990-1995 as director of interventional cardiology and – since 5/1995- Dr. Zeiher is the Chairman of Medicine in the Department of Cardiology / Angiology /Nephrology at the J. W. Goethe-University of Frankfurt, Germany.

Dr. Zeiher is the recipient of numerous awards, honors and grants and has published more than 400 original articles and reviews with over 50,000 citations. His current h-index is 117. According to Thomson Reuters analysis, Dr. Zeiher belongs to the Highly Cited Researchers, ranking among the top 1% most cited for the field of Clinical Medicine.

He is a fellow of the European Society of Cardiology. Dr. Zeiher is past chairman of the Working Group on Interventional Cardiology of the European Society of Cardiology. He served on the editorial boards of several journals, including Circulation, Circulation Research, European Heart Journal and others. Dr. Zeiher is currently the Co-Chairman of the Excellence Cluster Cardio-Pulmonary System (ECCPS) of the German Research Foundation (DFG).

His research interests include basic and clinical aspects of vascular biology and atherosclerosis, the role of stem and progenitor cells for endogenous cardiovascular repair as well as their therapeutic application for regenerating cardiovascular function, and the use of biomarkers for risk prediction and therapeutic stratification of patients with acute coronary syndromes.
Paavo Nurmi Foundation

Runner
No athlete this century has evoked such universal admiration as Paavo Nurmi - the Finnish runner supreme.

The son of a carpenter, Nurmi was born in Turku, on Finland's south-west coast, in 1897. At various stages of his amazing athletic career Paavo Nurmi won a total of 40 world records, including every race from 1500 metres to 20 kilometres. During the course of three Olympic Games he won nine gold medals and three silvers.

Although he took great care of his physical health, he suffered from myocardial infarction at the age of 60 and later also from stroke, despite the absence of all the known risk factors. He died from multiple complications of atherosclerosis at the age of 76. As Nurmi realized that the causes of atherosclerosis were far from being understood, he created a foundation in his name in 1968 for the purpose of financing research on cardiovascular diseases.

Activities
Nurmi involved himself intensely in the new foundation's activities, and the first grants were awarded in the same year. At the ceremony the recipients were awarded their grants by the great man himself. In his presentation to honour the occasion Professor Pentti Halonen said: 'Paavo Nurmi achieved greatness in his early years by running Finland into the consciousness of the world. By establishing the Paavo Nurmi Foundation in his later years he has made another great achievement which will prove to be of historical importance'.

In only its second year of life the new foundation organized an international symposium in Helsinki on Thrombosis and Coronary Heart Disease, which was attended and addressed by numerous Finnish and foreign scientists. Over the years since then the Paavo Nurmi Foundation has concentrated on two principle activities - sponsoring individual investigators for sabbatical terms, and organising international symposia on topics of current interest in cardiovascular diseases.

These two activities had their origins in the contemporary Finnish context. Professor Pentti I Halonen (1914-83) was the father of cardiology in Finland as
well as being Paavo Nurmi’s key mentor in planning and crystallizing the structure and aims of the Paavo Nurmi Foundation. He served as the foundation's first vice-chairman and took over as chairman after Nurmi's death. Halonen had long been acutely aware of the problems faced by many of his junior clinical research students in finding time for research while heavily committed to clinical duties. In the Finland of 1968, no institution provided sabbatical terms for research, and not even the university hospitals were able to award salaries or part-time remuneration for exclusively clinical research. There was thus a pressing need for this type of sponsorship in medical research. Although much less so than in 1968, Finland is still relatively remote from the major world centres of medical research. While a young doctor, Halonen developed a passionate devotion to cardiology, including the desire to know more about cardiovascular research in the international context. In the late 1940s he visited London's Hammersmith Hospital, where he quickly developed a close friendship with John McMichael, the leading British cardiologist of the day and founder of the Royal Postgraduate Medical School at Hammersmith Hospital. McMichael was eventually awarded a knighthood for his work and came to be known affectionately as 'Sir John'. His rounds of medical research establishments abroad and discussions with Sir John and others convinced Pentti Halonen of the urgent need for Finnish medical scientists to develop contacts, dialogue and cooperation with colleagues in other countries. Thus is was that a priority activity of the Paavo Nurmi Foundation from day one was to organise symposia in Finland every two years for the purpose of inviting prominent foreign medical research specialists to address the meetings and discuss topical issues with Finnish scientists.

The foundation also set out to create or support initiatives that could later be adopted and expanded by larger institutions or society in general. In 1972 the foundation funded the launch of cardiac resuscitation units in emergency ambulances with an attending specialized physician, while in 1973 the establishment of a renal dialysis unit was funded. The Paavo Nurmi Foundation is also a co-founding sponsor of the prestigious Tiede 2000 (Science 2000) journal, which presents and discusses the latest research findings in a format accessible to the public. In recent years Estonian cardiologists have been supported for visiting research tenures in Finland, and Finnish scientists for visits to foreign laboratories.
Symposia topics through the years

I Paavo Nurmi Symposium
"Thrombosis and Coronary Heart Disease"
25-27 September 1969, Haikko Manor, Porvoo

II Paavo Nurmi Symposium
"Early Diagnosis of Coronary Heart Disease"
9-11 September 1971, Haikko Manor, Porvoo

III Paavo Nurmi Symposium
"Physical Activity and Coronary Heart Disease"
18-20 September 1975, Haikko Manor, Porvoo

IV Paavo Nurmi Symposium
"Sudden Coronary Death"
15-17 September 1977, Haikko Manor, Porvoo

V Paavo Nurmi Symposium
"Thrombosis and Blood-Vesel Wall Interactions in Coronary Heart Disease"
20-22 September 1979, Haikko Manor, Porvoo

VI Paavo Nurmi Symposium
"Neurogenic and Psychological Factors in Coronary Heart Disease"
17-19 September 1981, Haikko Manor, Porvoo

VII Paavo Nurmi Symposium
"Management of Angina Pectoris"
6-8 October 1983, Haikko Manor, Porvoo

VIII Paavo Nurmi Symposium
"Modern Aspects in Hypepretension Research"
16-18 June 1986, Haikko Manor, Porvoo

IX Paavo Nurmi Symposium
"Lipoproteins and the Pathobiology of the Arterial Intima"
7-9 September 1989, Haikko Manor, Porvoo

X Paavo Nurmi Symposium
"Role of Infection and Inflammation in Vascular Disease"
27-29 August 1992, Unitas Institute, Helsinki
XI Paavo Nurmi Symposium
"Diabetes and Atherosclerosis"
18-19 September 1995, Haikko Manor

XII Paavo Nurmi Symposium
"Myocardial Response to Disease, Hormones and Training"
13-14 June 1997, Haikko Manor

XIII Paavo Nurmi Symposium
"Arterial Thrombosis - from Mechanisms to Treatment"
1-3.9 2000, Hanasaari, Espoo

XIV Paavo Nurmi Symposium
"Genetic and Molecular basis of Cardiac Arrhythmias"
27-29.8 2003, Biomedicum, Helsinki

XVII Paavo Nurmi Symposium
"Future directions of hypertension: Tailor-made diagnostics and treatment"
7.-9.9.2011, Porvoo, Finland