GENE TECHNOLOGY FORUM 2001

September 13-15 TARTU, ESTONIA

Eesti Geenikeskus
Estonian Genome Foundation

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Programme

Thursday, Sept 13, 2001

18:00-18:45 *Registration at the Vanemuine Concert Hall*

18:45-19.00 **OPENING**
Prof. Peeter Tulviste, Chairman of the Tartu City Council,
Former Rector Magnificus of the University of Tartu, Estonia

19:00-20:00 **OPENING SESSION**
Keynote **Prof. Klaus Lindpaintner**, Vice President and Director, Roche Genetics,
F. Hoffmann-La Roche AG, Switzerland
"Impact of Genetics and Genomics on Health Care: Opportunities and Challenges"

20:30 *Welcome Reception hosted by University of Tartu in the Museum of Tartu University History*

Friday, Sept 14, 2001

8:30-9:00 *Registration*

9:00-11:00 **SESSION I** Chaired by **Prof. Charles Kurland**
Dr. Andreas Braun, Chief Medical Officer, Sequenom Inc., USA
"From SNPs to Medical Utility"
Dr. Roger B Derbyshire, Associate Director, Orchid BioSciences Europe Ltd, UK
"Large Scale SNP Genotyping using Primer Extension on Multiple Platforms: Determination of Genome Wide SNP Allele Frequency Map"
Mr. Stanford (Ford) N. Goldman, Jr., Mintz, Levin, Cohn, Ferris, Glovsky and Popeo, P.C., USA
"Capital Formation: From Start-up to IPO, The American Experience"

11:00-11:20 *Coffee/tea break*

11:20-12:35 **SESSION II** Chaired by **Prof. Charles Kurland**
Dr. Ian Dunham, Sanger Centre, Hinxton, Cambridge, UK
"The Human Genome Project"
Dr. Wojciech Makalowski, Department of Biology and Institute of
Molecular Evolutionary Genetics, Pennsylvania State University, Pennsylvania, USA
"Computational Genomics - Promises and Challenges"

12:35-12:55 *Coffee/tea break*

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12:55-14.05 **SESSION III** Chaired by **Prof. Charles Kurland**

Dr. Olli-P. Kallioniemi, National Human Genome Research Institute, National Institutes of Health, Bethesda, USA

"Biochip Technologies in Cancer Research: From Genome Screening to Identification of Therapeutic Targets"

Prof. Erwin Schurr, McGill University, Montreal, Canada

"Genetic Epidemiology of Tuberculosis Susceptibility"

14:05-15.10 *Lunch*

15:10-17:00 **SESSION IV** Chaired by **Dr. Jaanus Pikani**

Dr. David G. Wang, Executive Vice President, First Genetic Trust Inc., USA

"Informatics and Genetics"

Dr. Mark S. Chee, Vice President of Genomics, Illumina Inc., USA

"Accessing Genetic Information: Technology for Large Scale SNP Genotyping"

Dr. Richard Grosse, CEO, InGene, Germany

"PHENOME™: The Clinical Database for Phenotype Driven Genotyping"

17:00-17:20 *Coffee/tea break*

17:20-19:00 **SESSION V** Chaired by **Dr. Jaanus Pikani**

Prof. Andres Metspalu, Department of Biotechnology, University of Tartu, Estonia

"Estonian Genome Project: Current Status, Permissive Technologies and Future Steps"

Dr. Kalev Kask, Stanford University, USA

"Estonian Genome Project: From Candidate Genes to Personalized Medicine"

Prof. Gisli Palsson, Director, Institute of Anthropology, University of Iceland, Iceland

"For Whom the Cells Toll: Debates About Biomedicine"

20:00 *Buffet Dinner hosted by City of Tartu in the grand hall of the Ministry of Education*

Saturday, Sept 15, 2001

9:00-11:00 **SESSION VI** Chaired by **Prof. Richard Villems**

Prof. Ralf Baumeister, Genzentrum, Ludwig-Maximilians-Universität, Munich, Germany

"C.elegans, an Animal Model for the Functional Analysis of Human Disease Genes"

Programme

Prof. Cheng Chi Lee, Baylor College of Medicine, Houston, USA
"Mammalian Circadian Clock Genes"
Prof. Charles Kurland, University of Lund, Sweden
"Vanishing Genomes, Emergent Proteomes: Evolving Mitochondria"

11:00-11:20 *Coffee/tea break*

11:20-12:40 **SESSION VII** Chaired by **Prof. Richard Villems**
Dr. Francois Cambien, Institut National de la Sante et de la Recherche Medicale (INSERM), France
"Genetics of Multifactorial Diseases"
Prof. Stylianos E. Antonarakis, Department of Medical Genetics, University of Geneva, Switzerland
"Chromosome 21; a Small Genomic Land of Fascinating Disorders"

12:40-13:50 *Lunch*

13:50-15:10 **SESSION VIII** Chaired by **Prof. Toivo Maimets**
Prof. Thomas Meitinger, Institute of Human Genetics, Neuherberg, Germany
"Complexity in Genetic Eye Disease"
Dr. Massimo Carella, Telethon Institute of Genetics and Medicine (TIGEM), Napoli, Italy
"The Genetics of Hearing Loss"

15:10-15:30 *Coffee break*

15:30-17:40 **SESSION IX** Chaired by **Prof. Toivo Maimets**
Dr. Nicholas J. Short, Chief Executive Officer, UVS Iceland Genomics Corporation, Iceland
"Clinical Genomics and the Icelandic Cancer Project"
Prof. Mart Ustav, Department of Microbiology and Virology, University of Tartu, Estonia
"Gene Therapy and Gene Vaccination"
Dr. Priit Kogerman, National Institute of Chemical Physics and Biophysics, Tallinn, Estonia.
"From Genes to Functions: the Case of CD44"
Prof. Giovanni Romeo, Director, Unit of Genetic Susceptibility to Cancer, International Agency for Research on Cancer, Lyon, France
"Genetics of Complex Diseases: the RET Protooncogene and Thyroid Cancer"

17:40 *Closing remarks*

Programm

Neljapäev, 13.september 2001

18:00-18:45 *Osalejate registreerimine Vanemuise Kontserdimajas*

18:45-19:00 **AVAMINE**
Prof. Peeter Tulviste, Tartu Linnavolikogu esimees, endine Tartu Ülikooli rektor, Eesti

19:00-20:00 **AVASESSIOON**
Põhiesineja **Prof. Klaus Lindpaintner,** asepresident ja direktor, Roche Genetics, F. Hoffmann-La Roche AG, Shveits
"Geneetika ja genoomika mõju tervishoiule - võimalused ja väljakutsed"

20:30 *Tervitusvastuvõtt Tartu Ülikooli Ajaloomuuseumis (sissepääs kutsetega)*

Reede, 14. september 2001

8:30-9:00 *Osalejate registreerimine Vanemuise Kontserdimajas*

9:00-11:00 **ESIMENE SESSIOON** Juhatab **Prof. Charles Kurland**
Dr. Andreas Braun juhatuse esimees, Sequenom Inc., Ameerika Ühendriigid
"Geneetilistelt markeritelt nende kasutamiseni meditsiinis"
Dr. Roger B Derbyshire, asedirektor, Orchid BioSciences Europe Ltd, Suurbritannia
"Suuremahuline genotüpiseerimine kasutades praimeri pikendamise tehnoloogia erinevaid võimalusi: Ülegenoomse SNP alleelide sageduse kaardi m''ramine"
Mr. Stanford (Ford) N. Goldman, Jr.,
Advokaadibüroo Mintz, Levin, Cohn, Ferris, Glovsky and Popeo, P.C. , Ameerika Ühendriigid
"Kapitali kaasamine: firma asutamisest avaliku emissioonini, Ameerika Ühendriikide näitel"

11:00-11:20 *Kohvipaus*

11:20-12:35 **TEINE SESSIOON** Juhatab **Prof. Charles Kurland**
Dr. Ian Dunham, Sangeri Keskus, Hinxton, Cambridge, Suurbritannia
"Inimese Genoomi Projekt"
Dr. Wojciech Makalowski, Molekulaar-Evolutsioonilise Geneetika Instituut, Pennsylvania Ülikool, Ameerika Ühendriigid
"Bioinformaatika ja genoomika"

12:35-12:55 *Kohvipaus*

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12:55-14:05 **KOLMAS SESSIOON** Juhatab **Prof. Charles Kurland**
Dr. Olli-P. Kallioniemi, Riiklik Inimgenoomi Uuringute Instituut, Riiklik Tervishoiuinstituut, Bethesda, Ameerika Ühendriigid
"Biokiibi tehnoloogiad v'hi uurimisel: Genoomi analüüsist teraapia märklaudade identifitseerimiseni"
Prof. Erwin Schurr, McGilli Ülikool, Montreal, Kanada
"Tuberkuloosile vastuvõtlikkuse geneetiline epidemioloogia"

14:05-15:10 *Lõuna*

15:10-17:00 **NELJAS SESSIOON** Juhatab **Dr. Jaanus Pikani**
Dr. David G. Wang, asepresident, First Genetic Trust Inc., Ameerika Ühendriigid
"Informaatika ja geneetika"
Dr. Mark S. Chee, asepresident, Illumina Inc., Ameerika Ühendriigid
"Geneetilise Informatsiooni hindamine: Tehnoloogia suuremahuliseks SNP genotüpiseerimiseks "
Dr. Richard Grosse, tegevdirektor, InGene, Saksamaa
"PHENOME™: kliiniline andmebaas fenotüübil baseeruva genotüpiseerimise jaoks"

17:00-17:20 *Kohvipaus*

17:20-19:00 **VIIES SESSIOON** Juhatab **Dr. Jaanus Pikani**
Prof. Andres Metspalu, Biotehnoloogia õppetool, Tartu Ülikool, Eesti
"Eesti Geenivaramu projekt – hetkeseis, võimalikud tehnoloogiad ja edasine tegevus"
Dr. Kalev Kask, Stanfordi Ülikool, Ameerika Ühendriigid
"Eesti Geenivaramu projekt – kandidaatgeenide kindlaksmääramiselt personaliseeritud meditsiinile"
Prof. Gisli Palsson, direktor, Antropoloogia Instituut, Islandi Ülikool, Island
"Biomeditsiini debatt"

20:00 *Buffet õhtusöök Haridusministeeriumi suures saalis (sissepääs kutsetega)*

Laupäev, 15. september 2001

9:00-11:00 **KUUES SESSIOON** Juhatab **Prof. Richard Villems**
Prof. Ralf Baumeister, Ludwig-Maximiliansi nimelise Ülikooli Geneetikakeskus, Münhen, Saksamaa
"Inimeste geneetiliste haiguste funktsionaalne modelleerimine C. elegansil"
Prof. Cheng Chi Lee, Baylori Meditsiinikolledz, Houston, Ameerika Ühendriigid
"Imetajate rütmikella geenid"

Programm

Prof. Charles Kurland, Lundi Ülikool, Rootsi
"Hääbuvad genoomid, esilekerkivad valgud, evolutsioneeruvad mitokondrid"

11:00-11:20 *Kohvipaus*

11:20-12:40 **SEITSMES SESSIOON** Juhatab **Prof. Richard Villems**
Dr. Francois Cambien, Riiklik Tervise ja Meditsiini Uuringute Instituut, Pariis, Prantsusmaa
"Multifaktoraalsete haiguste geneetika"
Prof. Stylianos E. Antonarakis, Meditsiinigeneetika osakond, Genfi Ülikool, Shveits
"Kromosoom 21- hämmastavaid haigusi põhjustav väike piirkond genoomis"

12:40-13:50 *Lõuna*

13:50-15:10 **KAHEKSAS SESSIOON** Juhatab **Prof. Toivo Maimets**
Prof. Thomas Meitinger, Inimesegeneetika Instituut, Neuherberg, Saksamaa
"Geneetiliste silmahaiguste mitmekülgsus"
Dr. Massimo Carella, Telethoni Geneetika ja Meditsiini Instituut, Napoli, Itaalia
"Kuulmiskaotuse geneetika"

15:10-15:30 *Kohvipaus*

15:30-17:40 **ÜHEKSAS SESSIOON** Juhatab **Prof. Toivo Maimets**
Dr. Nicholas J. Short, juhatuse esimees, UVS Iceland Genomics Corporation, Islandi
"Kliiniline genoomika ja Islandi Vähiprojekt"
Prof. Mart Ustav, Mikrobioloogia ja Viroloogia õppetool, Tartu Ülikool, Eesti
"Geeniteraapia ja geenvaktsiinid"
Dr. Priit Kogerman, Keemilise ja Bioloogilise Füüsika Instituut, Tallinn, Eesti
"Geenidelt nende funktsioonideni CD44 näitel"
Prof. Giovanni Romeo, Rahvusvaheline Vähiuuringute Agentuur, Lyon, Prantsusmaa
"Komplekshaiguste geneetika - RET protoonkogeen ja türoidne kartsinoom"

17:40 *Konverentsi lõpetamine*

Klaus Lindpaintner

Vice President and Director, Roche Genetics, F. Hoffmann-La Roche AG, Switzerland

CV

Klaus Lindpaintner was born in Innsbruck, Austria, and graduates from the University of Innsbruck Medical School with a degree in Medicine and from Harvard University with a degree in Public Health. He pursued postgraduate training and specialization in Internal Medicine, Cardiology, and Genetics in the United States and Germany and holds board certifications these specialties. He practiced cardiology and pursued research in the area of cardiovascular disease genetics, most recently as an Associate Professor of Medicine at Harvard Medical School in Boston, Massachusets. He joined Roche Basel in 1997 as Head of Preclinical Research in cardiovascular diseases. Since 1998, he coordinates, as Director of Roche Genetics, the company's global efforts in genetics, genomics, and proteomics. He has co-authored more than 150 scientific paper, holds adjunct and honorary professorships at Harvard University in Boston, University of London, and Humboldt University in Berlin, and serves on the editorial board of several scientific journals. Klaus Lindpaintner lives near Basel, Switzerland; he is married to an internist, and has two daughters.

CONTACT INFORMATION

Klaus Lindpaintner, M.D., Ph.D.
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Genetics and Genomics - Impact on Health Care: Opportunities and Challenges

- Opportunity: genetic approaches will provide molecular understanding of disease and drug action - a more sophisticated and biomedically relevant level of differential diagnosis, subdividing as well as combining conventional (clinical) disease definitions;
- Opportunity: molecular disease understanding will redefine and substantially increase the role of in-vitro diagnostics;
- Opportunity: molecular disease understanding will allow better prospective risk assessment and, consequently, to shift health care emphasis from treatment to prevention.
- Challenge: while the molecular tools are available, the genetic epidemiology work that needs to be performed to understand which few thousand of millions of SNPs now known are ultimately disease-relevant is intimidatingly large and will be complex, expensive, and time-consuming;
- Challenge: public perception of common complex disease genetics - based on monogenic disease models and determinism, rather than on probabilistic assessment and odds ratios-will need to be addressed in open dialogue to provide objective information to allow acceptance of opportunities
- Challenge: need for internationally harmonized legal framework regulating what is proper and improper use of medical information, to protect individuals.

Andreas Braun

Chief Medical Officer, Sequenom, Inc., USA

CV

Dr. Braun serves as the Chief Medical Officer at Sequenom, Inc., a highly competitive industrial genomics company headquartered in San Diego, CA. He has served in this capacity since September 1999, when he was promoted from the role of Vice President, Genomics. Previously, Dr. Braun joined Sequenom GmbH, a fully owned subsidiary of Sequenom, Inc., to serve as Director of Laboratory Research in 1995. He served as Deputy Head of the Clinical Laboratory at the Children's Hospital, University of Munich from 1992. In addition to his more than 45 peer-reviewed scientific publications, Dr. Braun holds doctorate degrees in both Biology and Medicine from the University of Munich. His research focus at the University of Munich included human sex determination, population genetics of human plasma proteins, human neuro-degenerative diseases, and functional analysis of various alleles of the human bradykinin ß2 receptor. In 1996 he was honored by the German Society of Clinical Chemistry with the Garbor-Szasz Award for outstanding achievement in molecular medicine. Additional research work in functional pharmacogenomics includes the design and introduction of highly accurate molecular tests in routine medical diagnostics and quality assurance of DNA analysis in medicine. Within the past 5 years Dr. Braun has successfully lead the development of Sequenom's premier technology DNA MassArrayTM, which is now used commercially. In addition, he has developed a novel scientific concept to validate human genetic diversity with regard to its clinical importance.

CONTACT INFORMATION

Andreas Braun, M.D., Ph.D.
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Sequenom, Inc.3595 John Hopkins Court
San Diego, CA 92121, USA
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From SNPs to Medical Utility

The completion and availability of the entire human genome sequence is enabling for the discovery of genes and gene products involved in human complex disorders. The successful identification of these genes is dependent on available sample sets, a high-throughput scoring technology, and an underlying scientific hypothesis on how to use the samples and the technology. Sequenom has developed a chip-based mass spectrometry approach for the analysis of single nucleotide polymorphisms (SNPs) the most abundant genetic variations, which is complemented by a fully automated SNP assay development procedure and the rapid assessment of allele frequencies in sample pools. This allows the cost effective testing of virtually all gene-based genetic variations and the association of the results with a variety of different phenotypes. We are currently developing the world's most comprehensive set of reagents to test for SNPs. A scientific strategy using this reagent set for elucidating the major genetic factors involved in human diseases will be presented.

"Large Scale SNP Genotyping using Primer Extension on Multiple Platforms: Determination of Genome Wide SNP Allele Frequency Map"

Roger B Derbyshire

Associate Director, Orchid BioSciences Europe Ltd, UK

CV

Roger Derbyshire joined Orchid BioSciences Europe to work in pharmacogenetics business development. Prior to this he spent 15 years with Applied Biosystems, being involved with the developing Genetic Anlysis and DNA Synthesis markets in Europe. He was involved in the early applications of biotechnology at G D Searle (UK) and has a background in nucleic acid chemistry for his degree at Oxford University.

CONTACT INFORMATION

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Pharmacogenetics Business Development - Europe
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Stanford (Ford) N. Goldman, Jr.

Mintz, Levin, Cohn, Ferris, Glovsky and Popeo, P.C., USA

CV

Ford is a member (partner) of Mintz Levin, residing in the firm's Boston office, practicing in the Business and Finance Section. He has developed an extensive practice in corporate and securities law, representing businesses involved in biotechnology and high technology. Ford has handled major securities transactions, including public offerings, mergers and acquisitions, and corporate restructuring. He is frequently called on to represent boards of directors and to handle the defense of corporate control contests. He also represents clients before regulatory agencies, including the Securities and Exchange Commission and the Federal Reserve Bank. Ford received his A.B. from Cornell University (1964) and his J.D. from the Cornell Law School (1967).Mintz Levin, a law firm of approximately 500 lawyers, has been representing biotechnology companies in all aspects of their businesses since the birth of the industry in the 1970's, and today has one of the largest biotechnology practices.

CONTACT INFORMATION

Stanford (Ford) N. Goldman, Jr.
Mintz, Levin, Cohn, Ferris, Glovsky and Popeo, P.C.
One Financial Center
Boston, Massachusetts 02111, USA
ph: 617 348 4924
fax: 617 542 2241
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Capital Formation: From Start-Up To IPO, The American Experience

Will the brilliant moment in the lab (the bench) hurdle the barriers imposed by administrators, regulators, venture capitalists, investment bankers, accountants, lawyers, institutional investors, competitors, employees, family and friends (and yourself) to yield a successful IPO, thus funding the furtherance of your research….and your personal dreams?

Valuation - Understanding the determinants of a company's capitalization

- Traditional market capitalization is based on long-standing analysis of historical financial performance determined on a comparative basis.
- Valuation of emerging biotech companies, or how a quantitative judgment is derived from a qualitative analysis.

Intrinsic Value Determinants of an Emerging Biotech Venture

- Intellectual property
- Quality of management
- Cash availability

Proven Aids

- Formulate your brilliant, sophisticated, complicated, breath-taking research and prospects into a few simple words
- Utilize organizational structures investors understand and appreciate
- Gear towards liquidation events
- Engage proven professionals

The Delaware Corporation

- Time tested
- Management friendly
- Protective of shareholders
- Ease of use
- Sophisticated judicial review

The Delaware Corporation (cont'd)

- Shareholders
- Board of Directors
- Officers (Management)
- Employees
- [SAB - Scientific Advisory Board]

Basic Corporate Organization Process

- Certificate of Incorporation
- By-Laws
- Actions of Board of Directors
- Issuances of capital stock

Initial Funding

- Founders
- Friends and family
- Shareholder agreements
  - Pricing
  - Vesting
  - Registration Rights

Early Stage Professional Investors

- Venture Capitalists

vs.

Strategic Partners

- Importance of "solid" IP

Identifying and Courting VC's and Strategic Partners

Mezzanine/Later Stage Funding

Employee and Director Compensation Incentives

- Stock option programs
- Basic structures
- Tax focused
- Vesting

The IPO

- Pricing
- Underwriting agreement
- Effective time
- Initial trading
- Closing

The M&A Alternative

Epilogue

- The Company's primary assets - its people and its intellectual property

Ian Dunham

The Sanger Centre, UK

CV

POSITIONS HELD

1996 - date	The Sanger Centre, Wellcome Trust Genome Campus, Hinxton, UK. Senior Group Leader/Research Fellow
1993-1995	The Sanger Centre Group Leader
1991-1993	Division of Medical and Molecular Genetics (Paediatric Research Unit), UMDS Guys Campus, London. Wellcome Trust Postdoctoral Research Fellow
1990-1991	Division of Medical and Molecular Genetics (Paediatric Research Unit), UMDS Guys Campus, London. Research Fellow
1989-1990	Howard Hughes Medical Institute, Washington University Medical School, Dept. of Genetics, St. Louis, MO 63110 USA Postdoctoral research associate in genetics
1985-1989	University of Oxford. D. Phil.

AFFILIATIONS

Member of the Editorial Board of Molecular Medicine Today (Elsevier Trends Journals)
Member of the Editorial Board of Genome Research (CSH Press)
Member of the Editorial Board of Comparative and Functional Genomics (John Wiley)
Member of the International Advisory Board, HUGO nomenclature committee.

CONTACT INFORMATION

Ian Dunham, Ph.D.
The Sanger Centre
Wellcome Trust Genome Campus
Hinxton, Cambridge, CB10 1SA, UK
id1@sanger.ac.uk

The Human Genome Project

Knowledge of the complete catalogue of the approximately 30 000 human genes will provide a fundamental resource for study of human biology, disease and drug discovery. Furthermore natural sequence variation that exists in the human population in these genes and their control regions may be the basis for common disease and other phenomena such as differences in drug efficacy and side-effects. The human genome project (HGP) provides the complete set of genes and many of their sequence variations. The first "working" draft of the human genome sequence has now been completed, and the complete high quality sequence will be available by 2003. I will review the current status of the public domain human genome project in terms of sequencing progress, gene identification and gene maps, and maps of the repertoire of human genome sequence diversity. I will also present data from human chromosome 22 on detailed examination of human gene structure and the nature of the common haplotypes in European populations.

Wojciech Makalowski

Pennsylvania State University, Department of Biology
and Institute of Molecular Evolutionary Genetics,
Pennsylvania, USA

CV

Wojciech Makalowski graduated from Adam Mickiewicz University in Poznan, Poland with a master degree in philosophy of science and a Ph.D. in molecular biology. Very early in his scientific carrier he "discovered" that in biology nothing makes sense except in the light of evolution. With the strong molecular biology background, the molecular evolution was an obvious choice to pursue his interest. As computational biologist he went through a series of system reincarnations. The first useful for biologists program he wrote in BASIC for a ZX Spectrum machine with impressive 48 kb RAM and a cassette tape recorder as a storage device. Later, still in Poland, he moved on "real" machine - IBM PC clone and PASCAL as programming language. After a short postdoc in Montreal, Canada, he joined National Center for Biotechnology Information (NCBI) in Bethesda, Maryland, USA in 1994 where he stayed until last summer working in the Mark Boguski's group where he joined a horde of UNIX enthusiasts. Recently, he joined the Institute of Molecular Evolutionary Genetics and the Department of Biology at the Pennsylvania State University in State College, USA. He is a member of editorial board of the Gene and the Genome Research journals. His research is focused on eukaryotic genomes evolution especially influence of transposable elements on their host genome - the concept of the genomic scrap yard and comparative genomics of Eucaryotes. The latter involves development of methods for the orthologous and paralogous sequences discrimination, as well as visualization tools for large scale sequence analyses.

CONTACT INFORMATION

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Computational Genomics - Promises and Challenges

Genome science and technology has brought us to the brink of being able to describe the genetic blueprint and molecular evolutionary history of the human species. Now we can read the genomes at a frightening speed - a several-million-base bacterial genome in several days is not a problem for one of the major sequencing centers, and a billion-base eukaryotic genome can be done in several months. But reading a text and understanding it are two different things. So, would the genomic community pass the genome comprehension test? The answer to this question is vital to the whole genomic enterprise, and this is where computational analysis of genomes takes a central stage. I will discuss major goals, problems, and challenges of computational genomics.

The prevailing view of genomes is gene-centric and therefore the major effort of genomic community is to accurately annotate those important genomic features. Most of a prokaryotic genome encodes for the proteins. In contrary, protein-coding sequences in eukaryotic genomes occupy only a minute fraction of a genome. Additionally, the information about a single protein is interrupted but sometimes very long non-coding sequences. Hence, gene prediction in prokaryotic and eukaryotic genomes are of different nature. Although, the gene prediction problem in prokaryotic genomes can be considered as solved, the gene prediction in eukaryotic genomes is one of the biggest bioinformatics challenges. The extent of the problem is such that it is not likely that can be solved by computational methods only. With the human genome in hand we look toward other mammalian genomes for help. We will need several genomes of different evolutionary distances along with the information on expressed sequences (ESTs, full-length mRNAs, etc.) to accurately annotate our genome. Once the predicted proteome for a given genome has been defined, the major task is to analyze and interpret it. Again, comparative genomic is a major force here. Database searches became everyday task of most molecular biologist. I will discuss current efforts to improve homology search sensitivity including domain profiles based approaches.

Although most of an eukaryotic genome does not encode proteins, these sequences are not useless. They carry a biological treasure hidden from most current methods. Only by comparing syntenic regions of several organisms we can detect regions which are subject of stabilizing evolution which in turns indicates functional importance of a revealed region.

The problems outlined above are just the tip of the iceberg that bioinformatics has to deal with. The comparative genomics is a central approach in most of the cases. Ergo, the most important achievement of the Human Genome Project is fact that it has spawned sequencing of other genomes from different branches of the tree of life, including multiple species of bacteria, archaea, fungi, plants, and animals. Genome comparison is crucial in interpreting of any particular genome.

Olli-P. Kallioniemi

National Human Genome Research Institute, National Institutes of Health, Bethesda, USA

CV

EDUCATION:

1985 M.D., University of Tampere, Finland
1988 Ph.D., University of Tampere, Finland

Post-graduate training and fellowship appointments:

1985-1990 Resident and Research Scientist, Dept. Clinical Chemistry, Tampere University Central Hospital, Tampere, Finland
1990-1991 Visiting Fellow, Dept. Laboratory Medicine, University of California, San Francisco, CA

FACULTY APPOINTMENTS:

1995-1996 Professor of Cancer Biology, Institute of Medical Technology, University of Tampere
1996-2000 Investigator, Section Head, NIH, National Human Genome Research Institute, Cancer Genetics Branch
2000-present Senior Investigator, Head of Translational Genomics, Cancer Genetics Branch, NHGRI, NIH

AWARDS AND HONORS:

1994 Young Scientist Award, European Ass. for Cancer Research
1998 Anders Jahre Young Scientist Award, Oslo, Norway
2000 NIH Director's lecture
2000 Highly Cited Breast Cancer Researcher of the 1990's (ISI, Institute of Scientific Information)

Patents held: 8 issued patents.

EVALUATIVE AND EDITORIAL POSITIONS:

1993 - Cytometry, associate editor
1997 - Genes Chrom Cancer, editorial board
1997 - Cytogenetics Cell Genetics, editor
1999 - Anal Cell Pathol, editorial board
2001- Cancer Biology and Therapeutics, editorial board (new journal)
2001- Molecular Cancer Therapeutics, editorial board (new journal)

SELECTED PUBLICATIONS IN 2001

Kallioniemi OP, Wagner U, Kononen J, Sauter G. Tissue microarray technology for high-throughput molecular profiling of cancer. Hum Mol Genet. 7:657-62, 2001.

Kallioniemi OP. Biochip technologies in cancer research. Ann Med. 33:142-7, 2001.

CONTACT INFORMATION

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Biochip Technologies in Cancer Research: From Genome Screening to Identification of Therapeutic Targets

Development of high-throughput "biochip" technologies has dramatically enhanced our ability to study cancer biology and explore the molecular basis of this disease. This forms a logical basis for development of targeted therapeutics. Biochips enable molecular analyses to be carried out in a miniaturized, massively parallel format with a very high throughput. Many different kinds of biochips are applicable in cancer research, such as: 1) Single nucleotide polymorphism (SNP) microarrays for research on genetic predisposition and pharmacogenomics, 2) cDNA microarrays for analysis of global gene expression patterns, 3) Comparative genomic hybridization (CGH) microarrays for surveys of genetic alterations in cancer cells, 4) proteomics microarrays for the analysis of concentrations, functional activities or interactions of proteins, 4) tissue microarrays for analysis of the clinical significance of candidate molecular targets in cancer, 5) biochip techniques for analyzing gene functions.

We are applying several different biochip technologies to study cancer development and progression. Specifically, we have performed genome-level screening of cancer cell lines using cDNA and CGH microarrays in order to identify amplified and overexpressed genes that may represent primary genetic alterations driving cancer progression. Such genes are also ideal therapeutic targets. Candidate genes are then validated for their involvement in vivo using tissue microarrays and the gene targets are selected for functional evaluation.

Erwin Schurr

Associate Professor, Departments of Human Genetics and Experimental Medicine, McGill University, Montreal, Canada

CV

EDUCATIONAL BACKGROUND:

Albert-Ludwigs University, Freiburg, Germany, B.Sc., 1979, Biology/Chemistry
Albert-Ludwigs University, Freiburg, Germany, M.Sc., 1981, Physical Chemistry
Albert-Ludwigs University, Freiburg, Germany, M.Sc., 1983, Parasitology
Albert-Ludwigs University, Freiburg, Germany, Ph.D., 1986, Cell Biology
McGill University, Dept. Biochemistry, PDF, 1986-89, Molecular Genetics

ACADEMIC APPOINTMENTS:

1990-96 Assistant Professor, Depts. of Experimental Medicine and Biochemistry, McGill University
1990-present Member, McGill Centre for the Study of Host Resistance
1993-present Medical Scientist, The Montreal General Hospital (MGH)
1996-present Associate Professor, Depts. of Experimental Medicine and Biochemistry, McGill University
1997-present Chairman, Research Advisory Committee, MGH Research Institute
1998-present Associate Professor, Dept. of Human Genetics, McGill University
1999-present Leader, Infection and Immunity Axis, McGill University Health Centre
2000-present Associate Director, McGill Centre for the Study of Host Resistance

SELECTED AWARDS:

1986-89 Postdoctoral Fellowship, Deutscher Akademischer Austauschdienst (DAAD) Sonderprogramm Moleculare Parasitologie
1990 Fraser-Monat-McPherson Award, Faculty of Medicine, McGill University
1991 ICAAC Merck Young Investigators Award of the American Society for Microbiology and the American Academy of Microbiology
1991-96 Scholar Award of the Medical Research Council of Canada
1992 Canada-USSR Exchange Award, Association of Universities and Colleges of Canada
1993 Fellowship Award, WHO/PAHO and the Canadian Society for International Health
1996-2000 Senior Researcher Award, Fonds de la Recherche en Santé du Québec
1996-2000 Dr. Phil Gold Research Award, MGH Research Institute
2000-05 Investigator Award, Canadian Institutes of Health Research

RESEARCH AREA:

Host genetics of susceptibility to infectious diseases with focus on tuberculosis and leprosy.

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Genetic Epidemiology of Tuberculosis Susceptibility

Tuberculosis (TB) is an infectious disease caused by Mycobacterium tuberculosis. TB, which has ravaged humankind since neolithic times, is easily transmitted by aerosol droplets from person to person. It is this easy mode of transmission that most likely explains the persistence of TB as one of the most pressing health problems of today.

Not all individuals exposed to M. tuberculosis are at equal risk of contracting TB. There is ample evidence from both experimental models of M. tuberculosis infection and studies of M. tuberculosis exposed human populations that the host genetic background is an important determinant for development of disease. However, little is known about the range and diversity of genes involved in tuberculosis susceptibility and how genetic variability and racial diversity affect immune responses to M. tuberculosis.

The genetic component of tuberculosis susceptibility has been studied employing both genome-wide approaches and candidate gene analyses in either population-based case-control designs or by enrolling TB families. In most studies the effect of selected candidate TB susceptibility genes was found to be modest. In some studies, however, a strong genetic effect of selected candidate genes on TB susceptibility was noticed. Possible reasons for the varying strength of genetic effects detected in different studies will be discussed.

In the absence of a universally efficacious vaccination against TB, the disease remains a global health emergency. Understanding the host genetic components that favor (or prevent) the spread of M. tuberculosis through an exposed population will give us new and until now little explored avenues to stem the spread of the disease.

David G. Wang

Executive Vice President of Strategy, Technology and Operations, First Genetic Trust, Inc., USA

CV

David Wang was most recently director of applied genomics and bioinformatics at Motorola Life Scieneces and Chairman of the TSC Scientific Management Committee. Prior to his tenure at Motorola, Dr. Wang was head of human genetics at Bristol-Myers Squibb [BMS] and researcher at Whitehead Institute/MIT Center for Genome Research and head of SNP Identification, Mapping and Genotyping Project. He holds a M.D. from Beijing Medical University, and a Ph.D. in development biology from the California Institute of Technology.

The TSC is a two-year, $50 million initiative, funded by the Wellcome Trust, ten major pharmaceutical companies and two technology companies: Aventis, Bayer Group AG, Bristol-Myers Squibb Company, Glaxo Wellcome PLC, IBM, Monsanto Company, Motorola, Novartis AG, Pfizer Inc, Roche Holding Ltd., SmithKline Beecham PLC, and Zeneca Group PLC.

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Informatics and Genetics

Accessing Genetic Information: Technology for Large Scale SNP Genotyping

To enable large-scale SNP genotyping we have combined a multiplexed oligonucleotide ligation-based assay with read-out on miniaturized arrays of universal capture probes. The probes are attached to beads, which are assembled into arrays on the ends of optical fiber bundles. By formatting these miniaturized arrays into a matrix that matches a 96-well microtiter plate, many samples can be processed simultaneously and efficiently in an automated fashion. This combination of technologies provides a novel and versatile system for genetic analysis that has the capacity to match the needs of analysis on a genomic scale. Fundamental aspects of the technology will be reviewed, and the application of these arrays to SNP genotyping will be discussed.

Mark S. Chee

Vice President of Genomics, Illumina Inc., USA

CV

Mark Chee received his B.Sc. in Biochemistry from the University of New South Wales in 1985 and his Ph.D. in Molecular Biology from the University of Cambridge in 1991. Dr. Chee was a postdoctoral fellow at the Stanford Yeast Genome Center and at Affymax Research Institute. At Affymax, and subsequently at Affymetrix, Dr. Chee contributed to the development of oligonucleotide arrays for the analysis of complex genetic samples. Dr. Chee was a co-founder of Illumina and is currently Vice President of Genomics at Illumina.

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Richard Grosse

CEO, InGene, Germany

CV

PROFESSIONAL EXPERIENCE

1999 - present Chief Executive Officer and Founder
Institute of Genetic Medicine Ltd.
Development of a Clinical-Phenotypic Database
(Phenomene™ for phenotype based gene validation

1994 - present Chief Executive Officer and Founder
Institute of Medical Molecular Diagnostic Ltd. (IMMD), Berlin
Leading German Genetic Testing Laboratory

1993 - 1995 Professor University of Bergen, Medical Faculty, Norway

1991 - 1993 Scholar-in-Residence
International Fogarty Center, NIH, Bethesda, USA
Honorary Award for contributions to cell biology

1991 - 1992 Head of Laboratory
Max-Delbrück-Center, Berlin-Buch
Molecular and cellular biochemistry
Regulation of cell growth

1978 - 1992 Head of Laboratories and Departments,
Associate director Central Institute of Molecular Biology, Berlin-Buch
Cellular and Molecular Biology
Cell growth mechanisms

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PHENOME™: The Clinical Database for Phenotype Driven Genotyping

InGene is establishing a human phenotype database (PHENOME™) based on a 10 year population-wide data collection study approved by an independent ethic's committee and the German Federal Data Protection Agency. This database contains up to 1000 clinical, environmental and life style parameters, as well as DNA and serum from tens of thousand individuals of a diverse European population.
Contrary to other data collection projects phenotype data are linked to PHENOME`s biomedical knowledgebase to screen for patient cluster distinguished by specific features. For each phenotype cluster available DNA / serum samples allow phenotype selected proteotyping, genotyping and SNP profiling.
In silico matching links phenotype cluster to annotated genome databases (matching analysis). A match is found when

- presumed functions of defined genes can be associated with known or newly defined clinical-phenotype clusters;
- more than one gene is linked to one phenotype cluster thus revealing a new polygenic background.

Collected data from questionnaires and laboratory analysis cover most medical fields, and include behaviour, life style and genealogical information. Questionnaires are designed to provide universal standards for phenotyping diseases. The PHENOMETM-technology is inherently flexible, hypothesis independent and expandable.

We report about

- Certified ethical, data protection and data security standards;
- Data collection by using a network of hospitals and clinics, and universal standards for phenotyping diseases;
- Universal data structure for phenotyping (heart disease, gastroenerology, gynecology, asthma, nephrology, rheumatology, pulmonology and others);
- Data processing tools;
- Database design for PHENOME™;
- Designs for knowledgebase and phenotype-cluster analysis.

PHENOME™ provides access to phenotype-selected genetic targets for diagnostics and drug design.

Andres Metspalu

Department of Biotechnology, University of Tartu, Estonia

CV

EDUCATION:
M.D., Tartu University. Date of graduation: June 1976.
Ph.D., in Molecular Biology 1979. "Structure and function of the eukaryotic ribosome". Institute of Molecular Genetics, Ukrainian Acad. of Sciences, Kiev.
POSTDOCTORAL RESEARCH:

1. Columbia University, New York, USA. Prof. Alex Tzagaloff laboratory. From August 1981 to February 1982. Yale University, New Haven, USA. Prof. Joan Steitz laboratory. From March 1982 to May 1982.
2. European Molecular Biology Laboratory (EMBL), Heidelberg, Germany. Prof. Riccardo Cortese laboratory. Fellowship from European Society of Biochemistry (FEBS) 1985.
3. Max-Planck Institute of Molecular Genetics, Wittman, Berlin, Germany. Fellowship from European Molecular Biology Organization (EMBO) 1988.
4. Visiting scientist at University of Tampere, Finland. From October to November 1991.
5. Visiting scientist at Hamburg University, Dept. of Molecular Biology, Germany. Prof. Joachim Kruppa laboratory. Fellowship from DAAD, 1991-1992.
6. Research grant in 1993 from EC to study hRP protein S6 gene at University of Hamburg.

PROFESSIONAL HISTORY:

1976-1980	Junior scientist at the Laboratory of Molecular Biology, Tartu University.
1981-1982	EREX fellow in USA, Columbia University, New York, and Yale University, New Haven.
1982-1984	Senior scientist at laboratory of Molecular Biology, Tartu University.
1985-1992	Head of Laboratory of Gene Expression, Tartu University.
1986-1992	Research Director of the Estonian Biocentre.
July 1992 -	present. Full professor of Biotechnology at Tartu University
October 1993 - December 1994	Visiting professor faculty at Baylor College of Medicine, Dept. of Molecular and Human Genetics with Prof. C.T. Caskey.
February 1996 -	present. Head of Molecular Diagnostics Center at Children's Hospital of Tartu University.
1999-2000	IARC, Lyon France, The Visiting SCIENTIST AWARD

Main interest is to develop highly parallel and roboust arrayed primer extension technology for DNA microchips.
AT PRESENT, MY RESEARCH INTERESTS ARE:

1. Fundamental questions of gene structure, function and organization. Special interests are human disease genes.
2. Developing new oligonucleotide array - based SNP genotyping methods and applying DNA diagnostics for detecting human genetic diseases, gene expression and resequencing.

TEACHING:
1980-present. I have supervised diploma works, M.Sc., M.D. and Ph.D. students.
1989-present. I have lectured in, and I am currently in charge of the Molecular Biotechnology and Molecular Diagnostics and Gene Therapy courses at Tartu University.

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Estonian Genome Project: Current Status, Permissive Technologies and Future Steps

The Estonian Genome Project (EGP) has developed in leaps and bounds since the last Gene Forum meeting. First of all "Human Genome Research Act" was passed by the Estonian parliament in December 2000. This is one of the most comprehensive legal documents in the world regulating population based genomic studies and a main cornerstone of the EGP. Passing the law by the Estonian parliament resulted in state funding provided for the implementation of the EGP, in founding of special non-profit and for-profit organizations and in working out legal documents aimed at regulating complex interactions between different bodies involved.

As of today, 25 people are working for the project in Estonia and USA, preparing the pilot phase of the EGP (10 000 individuals to the database by July 2001), looking for funding and transforming the EGeen (commercial partner for the EGP) into a successful genomics company. According to the recent poll people are supporting the EGP: ~ 40% would like to join, ~36% would like to get more information before decision and 6% said definite no.

Technologies are maturing also and the prices are decreasing to the level which will make genotyping of the pilot project samples feasible in year 2002. And again, the EGP is supposed to benefit from the developments at the global level. International haplotyping consortium was formed with the task to build the human LD and haplotype map. The latter will help to select the right set of the SNPs for the EGP without a need for constructing the relevant map ourselves. The genotyping data of Estonians and the others and LD map of the human chromosome 22 demonstrate clearly that there are only minor differences between European populations. Meaning that if the new drug will be based on the genetic data of Estonians, it can be used as a drug for other Europeans as well.

Future of the EGP depends on two major factors: i) how many Estonians would like to be a part of it and ii) level of trust of the public institutions and private investors in the EGP and the project team working hard to make it happen.

Kalev Kask

Department of Neurobiology, Stanford University, USA

CV

Graduated from Tartu University, completed Ph. D. studies at Stockholm University.
Postdoctoral work with Prof. Peter Seeburg at the Max-Planck Institute for Medical Research, Heidelberg, Germany.
Prior to Stanford was a senior scientist at AGY Therapeutics, South San Francisco, USA

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Estonian Genome Project: From Candidate Genes to Personalized Medicine

Sequencing of the human genome has catapulted biology to where chemistry was when the table of periodicity was discovered. Like with the chemical industries in mid-1900s, systematic advances in biomedical research enabled by genomics are expected to take place and revolutionize medicine in the near future. The outcome based "what disease have you got?" approach is likely to give way to a preventive "what diseases are you likely to get?" kind of healthcare. The Estonian Genome Project is likely to play a globally significant role in that conversion by enabling massive identification of disease genes for diagnostics and drug development. At the completion of the project, citizens of Estonia may be first ones on the planet to enjoy the benefits of personilized medicine. Locally, The Estonian Genome Project is likely to enliven biomedical research environment and boost economic opportunities in high and biotechnology at an unprecedented scale.

Gísli Pálsson

Director and Professor of Anthropology, Institute of Anthropology, University of Iceland, Reykjavík, Iceland

CV

Professor Gísli Pálsson was born in the fishing community of the Westman Islands, Iceland, on December 22, 1949. After receiving his BA-degree in Social Science at the University of Iceland in 1972, he studied Social Anthropology at the University of Manchester, England (M.A. 1974, Ph.D. 1982). He has been married to Dr. Guðný Guðbjörnsdóttir, Professor of Educational Psychology, since 1973. Dr. Pálsson and his wife have two children, Páll Óskar Gíslason (25) and Rósa Signý Gísladóttir (18).

Since he finished his postgraduate studies, Dr. Pálsson has been employed by the University of Iceland. In 1992 he was granted Professorship and in 1998 he was appointed Director of the Institute of Anthropology. He has lectured at several other universities, including the University of Caloifornia at Berkeley, the University of Copenhagen, the University of Iowa, and the University of the Sea, Spain.

Dr. Pálsson has contributed extensively to anthropological books and journals. His writings focus on a range of issues, including human-environmental interactions, fishing communities, the human body in social theory, the social aspects of language, and the anthropology of the Icelandic sagas. He is the author, editor, or co-editor of 15 academic books and he is the author or co-author of approximately 80 articles in reviewed journals and edited books. His main books are The Textual Life of Savants (1995), Coastal Economies, Cultural Accounts (1991), Nature and Society: Anthropological Perspectives (1996, co-editor), and Images of Contemporary Iceland (1996, co-editor).

Currently, Dr. Pálsson's research focuses on the social implications of biotechnology and concerns about the collection, storing, and exchange of human bodily material and medical information. Also, he is engaged in research on ecological knowledge and the social implications of climatic change. Dr. Pálsson has done anthropological fieldwork in Iceland and The Republic of Cape Verde. He has participated in several international research projects, including a project organised and funded by the Beijer Institute at the Swedish Academy of Science in Stockholm (1993-1997).

Dr. Pálsson is a member of several international scientific societies and he has held important international responsibilities. He was a member of a scientific committee established by the National Research Council of the United States and the US Congress to review the implications of individual quotas in fishing. He has also actively participated in public discussions on the role of practical knowledge in fishing, the social aspects of resource management, public policy on language and culture, and the social implications of biotechnology.

In 1995, Dr. Pálsson was invited as Research Fellow at the Swedish Collegium for Advanced Study in the Social Sciences (SCASSS), Uppsala, Sweden. In April 2000, he was awarded the Rosenstiel Award in Oceanographic Science at the Rosenstiel School of Marine and Atmospheric Science, the University of Miami, for excellence in the field of marine affairs, specifically in world wide marine policy.

CONTACT INFORMATION

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For Whom the Cells Toll: Debates About Biomedicine

In this paper I analyze recent debates on a central medical database on Icelanders. My aim is to situate these debates in the domestic context, focusing on the contribution of anthropology to the understanding of central issues at the intersection of biotechnology and society. Events in Iceland call attention to similar developments in the larger world. Modern biotechnology and bioinformatics have opened up an entirely new world in which a multitude of different kinds of human bodily components as well as genetic and medical information can be isolated and used for commercial, medical, and scientific purposes. While these developments are generally met with heavy criticism and organized opposition, responses vary from one context to another. In order to explore current moral debates on biotechnology I suggest the perspective of moral landscapes recently developed in anthropology. Such a perspective, I think, helps to understand the topography of moral debates and, consequently, to define the options available for informing public decisions on contested issues such as those surrounding modern biotechnology.

Ralf Baumeister

Genzentrum, Ludwig-Maximilians-Universität, Munich, Germany

CV

Education:

1982-1987	Student of Biology, FA University Erlangen/Nürnberg
1987	Diploma (Biology), emphasize on Microbiology, Human Genetics and Computer Sciences, University of Erlangen/Nürnberg.
1988-1992	Doctoral thesis: "Molecular mechanisms of the regulation of tetracycline resistance determinants", major supervisor: Prof. Dr. Wolfgang Hillen
1992-1995	Postdoctoral research fellow in the lab of Professor Gary Ruvkun at the Harvard Medical School / Mass. General Hospital, Boston MA, working on the role of the gene unc-86 for the specification and differentiation of the C.elegans nervous system
1995-2000	Group leader at the Genzentrum of the Ludwig-Maximilians-University of Munich
since Nov. 2000	Professor of Biochemistry at the University of Munich, Medical Faculty

Research visits:

1989	Karolinska Institute Stockholm, Sweden. Work in the lab of Prof. Dr. Alexander von Gabain on the translation initiation and decay of tetR mRNA
1991	Institute of Crystallography, Free University of Berlin. Molecular modelling of Tet repressor-tet operator interactions in the lab of Prof. Dr. Wolfram Saenger.

Awards and Prizes:

1987	Eva-Schleip Stipend, awarded from the University of Erlangen
1993	VAAM-Promotionspreis (Graduation Prize) 1993, awarded by the "Vereinigung für Allgemeine and Angewandte Mikrobiologie e.V.", Germany
2001	Philip-Morris-Research Prize, Europe

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C.elegans, an Animal Model for the Functional Analysis of Human Disease Genes

The different genome projects have resulted in an exponential increase in sequence information available in the databases. At the same time, the number of functionally characterized genes is only increasing linearly. How can we increase the speed of functional genomics to make full use of the data mining? Model organisms have helped significantly to understand the roles of particular genes in an organism. The classical approaches to address gene function first involves the inactivation of a given gene and the monitoring of the resulting consequences. For single factors, this method was successfully used in the model organisms Drosophila melanogaster and mouse. However, in order to upscale this knock-out methodology and subsequent analysis, these models have a significant disadvantage: the time and effort to perform even single targeted gene manipulations is significant, and the complexity of the organism prevents in many cases the detailed analyses of the KO consequences. Here, the nematode C. elegans offers several advantages: 40-60 % of the human disease genes are represented by homologues in C. elegans. In addition, the animals are small enough to be kept in large numbers in a format that allows mass manipulations (microtiter plates) and knock-outs of candidate genes can be obtained in a matter of 4-6 weeks. Animal facilities are cheap, and C. elegans is the only multicellular organism for which the development of each single cell and the entire connectivity of its nervous system are known. At the same time, the cellular diversity of the C. elegans nervous system is in the same range as that of a vertebrate brain, although the total number of neurons is only 302. Remarkably, C. elegans neurons use the same neurotransmitters as humans, and the receptor pharmacology is astonishingly similar.

In this seminar, examples of functional conservation of human genes and their C. elegans counterparts/homologues will be discussed. In particular, I will focus on genes involved in human neurodegenerative diseases and discuss the contribution C. elegans models can make to understand the function of the relevant human disease genes.

Cheng Chi Lee

Baylor College of Medicine, Houston, USA

CV

Assistant Professor, Department of Molecular & Human Genetics
BSc, University of Otago, New Zealand, 1981
PhD, University of Otago, New Zealand, 1986
Postdoc, Baylor College of Medicine, 1990

Research Interests:

A major area of my laboratory research is focused on how genes control mammalian behavior. I have chosen to study circadian rhythm, a behavior that is highly reproducible and easily monitored. Circadian rhythm controls our sleep-wake cycle and many of the physiological changes that accompanies the daily rhythm. My laboratory was instrumental in the identification of two genes, mPer1 and mPer2 that plays a major role in the mammalian circadian clock core mechanism. My laboratory has shown at a molecular and genetic level that mPer1 and mPer2 plays a central role in maintaining circadian rhythm in mice. These discoveries have now open this area of mammalian behavior to detail analysis by genetic and molecular tools. In addition to study of the core mechanism of the circadian clock, the future calls for a better understanding of how the many physiological process are linked together by the clock mechanism. Towards these goal, the laboratory is focused on using genetic and microarray tools to identify key genes under the control of the clock mechanism that are involved in these physiological processes.

My laboratory is also interested in the association of genes to human disorders. One major contribution my laboratory has made is the identification of the gene that causes spinocerebellar ataxia type 6 (SCA6) The SCA6 gene encodes for the a1A Calcium Channel and the mutation associated with this disorder is caused trinucleotide repeat expansion. One goal of our research is to better understand the pathogenesis of SCA6, and the role of polyglutamine expansion in animal model. The gene that responsible for SCA6 was identified by a strategy based on association studies. Together with the new information generated by the human genome projects, the laboratory is using similar approach to study other polygenic disorders in human.

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Mammalian Circadian Clock Genes

Circadian rhythms are an evolutionarily conserved property of many biological processes in diverse life forms. Endogenous oscillators in response to daily environmental cues control the physiology and behavior of diverse organisms including human. My laboratory identified two mammalian period homologue, *mPer1* and *mPer2*, and recently provided genetic and molecular evidences that *mPer1* and *mPer2* are key players in the mammalian circadian clock. Loss of function mutation of *mPer2* gene result in the loss in control of circadian rhythmicity. The loss of mPer1 gene affects the precision control of the clock period but the mutant animals retained circadian rhythmicity. However, a loss of both *mPer1* and *mPer2* results in a complete absence of circadian clock activity. Our studies using cDNA Microarray technology revealed that *mPER1* and *mPER2* have differential control on the mammalian clock. Using Northern and *in situ* hybridization methods we confirmed the genes identified by microarray methods to be either clock or clock controlled genes. The identification of new genes in the clock pathways further adds to the understanding of the mammalian clock mechanism.

Charles G. Kurland

University of Lund, Sweden

CV

Charles Kurland received his PhD in Biochemistry from Harvard University in 1961, and did postdoctoral work at the Microbiology Institute of the University of Copenhagen. Since 1971, he has been a Professor of Molecular Biology at Uppsala University, Sweden. Professor Kurland has been a member of the European Molecular Biology Organization since 1994, and has represented Sweden on the Councils of both the EMBC and the EMBL (1989-1992). He has been chairman of several national councils and committees, and is a member of the Royal Science Society, Uppsala, the Royal Academy of Sciences, Stockholm, the Royal Academy of Sciences, Copenhagen, the Estonian Academy of Science, Tallinn, and the Royal Physiographical Society, Lund. Professor Kurland has published more than 170 scientific papers, among them a series of signal papers on the biochemistry and biophysics of the ribosome. His prominence in this field was witnessed by his contribution to the authoritative text ŒThe Ribosome[1]. Kurland's study of the E. coli ribosome is, however, but part of a career devoted to the molecular biology of bacteria, the most recent avenues of which have led him to study the evolution of endoparasitic bacteria and cellular organelles. Professor Kurland continues to be an enthusiastic promoter of molecular biology, whilst taking a keen interest in the communication of science to the public. As well as chairing the EMBO committee on Science and Society, he co-wrote the EMBO statement on genetically modified organisms and the public, which was published in February this year, and which is the starting point for the EMBO on-line discussion forum on GMOs.

CONTACT INFORMATION

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Vanishing Genomes, Emerging Proteomes: Origins of Mitochondria

The genomes of mitochondria are miniscule and can encode as few as 2 proteins or as many as 67 proteins. Recent genomic sequence determinations with ?-proteobacteria such as Rickettsia and Bartonella have been useful aides to the analysis of mitochondrial origins. Phylogenies based on ribosomal RNA as well as mitochondrial proteins have shown rather clearly that mitochondria are sister clades of ?-proteobacteria such as Rickettsia.

The endosymbionts that were the direct ancestors of mitochondria were in all probability descendents of free living ??proteobacteria. These must have had genome sizes sufficient to code 1000 to 2000 proteins if the facultative endocellular parasite Bartonella is a reliable guide. Where have all these genes gone during the evolution of mitochondria?

Yeast has at least 400 mitochondrial proteins encoded in its nuclear genome. But of these only ca 50 can be identified with confidence as descendents of ?-proteobacterial ancestral sequences.

The largest group of proteins in the yeast mitochondrial proteome is in fact not made up of bacterial descendents. They are eukaryotic proteins with no allignable homologues in bacteria or in archaea. Some of the characteristic organelle-specific functions such as ATP export are carried out by such eukaryotic add-ons to the mitochondrial proteome.

The laboratories of Thorsness and Fox have demonstrated that there is a mechanism in yeast cells to transfer genes from mitochondria to nuclear genomes; the reverse process is not detectable. Such a biased transfer mechanism supported by mutations that can inactivate coding sequences in mitochondria would drive an evolutionary process in which genes would tend to be transferred from mitochondria to nuclei. Nevertheless, circa 1000 protein-coding sequences from the ancestral bacterial genome have simply vanished from mitochondrial lineages.

Thus, coding sequences of the ancestral bacterium that are not required by the organelle have vanished. A majority of the small number of bacterial proteins that remain has been transferred to the nucleus. In parallel, the proteome of an efficient ATP producing organelle has evolved within the nuclear genome of eukaryotic hosts.

Andersson, S. G. E., and C. G. Kurland. 1998a. Reductive evolution of resident genomes. Trends Microbiol. 6:263-268.

Berg, O. G., and C. G. Kurland. 2000. Why mitochondrial genes are most often found human genome. Nature Genetics 19: 19-24.

Karlberg, O., B. Canbaeck, C. G. Kurland, and S. G. E. Andersson. 2000. The dual origin of the yeast mitochondrial proteome. Yeast 17:170-187.

Kurland, C. G. and S. G. E. Andersson. 2000 Origin and Evolution of the Mitochondrial Proteome. Microbiol. Molec. Biol. Rev. 64: 786-820.

Thorsness, P. E., and T. D. Fox. 1990. Escape of DNA from mitochondria to nucleus in Saccharomyces cerevisiae. Nature (London) 346:376-379.

Francois Cambien

Institut National de la Sante et de la Recherche Medicale (INSERM), France

CV

Epidemiologist, geneticist, Director of INSERM Unit 258 "Molecular and Epidemiological Genetics of Cardiovascular Diseases" and of INSERM SC7 "INSERM DNA Bank for Cardiovascular Research".

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Genetics of multifactorial diseases

The etiology of mutifactorial diseases is characterized by a complex interplay between genetic and environmental determinants. Atherothrombosis, diabetes, hypertension, obesity, cancer, rheumatologic, neurodegenerative, pulmonary, digestive and most other common disorders are multifactorial; even infectious diseases are known to be strongly influenced by genetic predisposition. A number of environmental factors contributing to these conditions have been identified, such as infectious agents, smoking, excess or specific patterns of food intake, sedentarity, stress of different nature ... The conviction that genetic factors contribute to most common disorders is based on the observation that these diseases aggregate in families in a specific way that is compatible with genetic transmission and on the discovery of associations between particular gene variants and the risk to develop the disease. Identifying the precise genetic determinants of multifactorial diseases is considered important for 2 reasons: 1. On the short term, from a clinical perspective, it may help identify individuals at increased risk and provide a rational to tailor drug prescription, providing better efficacy and reduced risk of adverse effects; 2. For the long term, from a more basic perspective, a global understanding of the contribution of gene variability to etiology and pathophysiology through the study of major biological functions may be a prerequisite to ultimately control diseases and maintain health and well-being of human until an advanced age. Obviously, the first reason above constitutes the major stimulus for present research. Genetic factors having strong effects may be identified by a systematic exploration of the genome; however many expectations may not be fulfilled, because many genes may be involved, the genetic effects may be weak, important interaction may exist ... In several research programs, the assumed models linking genes to multifactorial diseases may be much too simplistic (as for example in the proposals for whole genome associations studies) or the question of which model to assume may even not be considered. Despite the availability of the almost complete human genome sequence, we still know very little of the distribution and structure of polymorphisms across the human genome. An important goal for the next few years will be to generate (in an appropriate way that needs to be discussed !) a catalogue of 'all' common polymorphisms of functional sequences (genes and non-gene) in

the human genome. A second goal which is implicit for the global understanding mentioned above will be to develop models of relevant functions that will allow the direct evaluation of naturally occurring gene variants reliably and with high throughput using proteomic tools and cellular arrays. Interestingly biological systems and the functions to which they contribute are not specie-specific; there is therefore good reasons to investigate them in relation to the genetic variability of their protein components in different species simultaneously. The evolutionary and functional information gained from these comparative-genomics studies is expected to provide a powerful source of inspiration for drug development or other rational ways to maintain health. As recently stated by Richard Lewontin "The greatest methodological challenge that population genetics now faces is to connect the observations between outcome of evolutionary processes to the tradition of experimental functional biology". We believe that it is not only the challenge of population geneticists but of most scientists trying to understand multifactorial diseases. Epidemiology and Mendelian genetics may be helpful in this context but may also obscure the specificity of this area of research which has to develop its own concepts and tools.

Stylianos E. Antonarakis

Professor of Medical Genetics, Division of Medical Genetics, University of Geneva Medical School, Geneva Switzerland.
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CV

EDUCATION
Athens University School of Medicine, 1969-1975
M.D. degree (magna cum laude) 1975
Athens University School of Medicine
Doctoral Thesis (magna cum laude) 1983

INTERNSHIP AND RESIDENCY
Internal Medicine, 1976-1978
King Paul's University Hospital, Dept. of Medicine (Prof. G. Daikos)
Hellenic Air Forces Gen. Hospital, Dept. of Medicine (Dr. G. Psimenos)
Pediatrics, 1978-1980
Kozani General Hospital, Dept. of Pediatrics (Dr. P. Economopoulos)
Patras Children's Hospital, Dept. of Pediatrics (Prof. Th. Giogarakis)
Aghia Sophia University Children's Hospital, Dept. of Pediatrics (Prof. N. Matsaniotis)

LICENSES TO PRACTICE MEDICINE
Athens, Greece 1975
State of Maryland, USA, 1984 License # D304
Post-Doctoral Fellowship
The Johns Hopkins University School of Medicine ; Department of Pediatrics, Genetics Unit (Jul 1980 - Mar 1983)
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Chromosome 21; a Small Genomic Land of Fascinating Disorders

Chromosome 21 is the smallest human chromosome, three copies of which are associated with Down syndrome. The determination of the nucleotide sequence of 33.5 Mb of DNA of the (almost) entire long arm was achieved after an international collaborative effort in 2000. The total number of genes of chromosome 21 has not yet been accurately determined, but the current estimate is approximately 240. In addition, a considerable sequence variation has been determined.

These achievements now provides unprecedented opportunities to understand the molecular pathophysiology of trisomy 21, elucidate the mechanisms of all monogenic disorders of chromosome 21, and discover functional sequence variations that predispose to common complex disorders. All of that requires the functional analysis of gene products and the determination of the sequence variation of this chromosome.

Thomas Meitinger

Institute of Human Genetics, Neuherberg, Germany

CV

EDUCATION:

1973-1981	Biology, Ludwig-Maximilians-Universität München (LMU)
1978-1982	Medicine, Ludwig-Maximilians-Universität München (LMU)
1982-1983	Final year medical student, Bharagwanath Hospital, Soweto, University of Witwatersrand, Johannesburg
1983	MD thesis, "Sequence and copy number of a repetitive element in the mouse genome" - Institut für Physiologische Chemie der Universität München

(Prof. Dr. H.-G. Zachau)

DEGREES:

1991	Diploma, Biology, LMU München
1983	MD, LMU München
1993	Board Certification for Medical Genetics
2000	Professor of Human Genetics, Technische Universität München

POSITIONS HELD:

1981	Research Fellow, Institut für Physiologische Chemie der Universität München (LMU) (Prof. Dr. H.-G. Zachau)
1982	Final year student, Gold Fields West Hospital, Westonaria, Johannesburg
1984-1985	Assistent, Kinderchirurgische Klinik, Karlsruhe, Akad. Lehrkrankenhaus der Universität Freiburg (Prof. Dr. W. Maier).
1985-1988	DFG/Royal Society fellowship, Genetics Laboratory, Dept. of Biochemistry, University of Oxford (Prof. J. Edwards)
1988-2000	Head, Molecular Genetics Laboratory, Department of. Medical Genetics, Kinderklinik der LMU München (Prof. J. Murken)
Oct. 2000	Director, Institute of Human Genetics, Klinikum rechts der Isar, Technische Univeristät München Director, Institute of Human Genetics, GSF National Research Centre, Neuherberg

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Complexity in Genetic Eye Disease

Over the past decade, remarkable progress has been made on molecular genetic characterisation of the eye. More than 50 genes with mutations causing retinal degenerations have been identified, many more have been mapped. Allelic heterogeneity is also a common theme with for instance more than 100 different mutations known in the rhodopsin gene. Experimental strategies used for the elucidation of monogenic disease are now being adapted to the study of multifactorial disease such as glaucoma and age related macular dystrophy, with limited success so far. This is hardly surprising given the underlying heterogeneity observed in monogenic disorders which is augmented by phenomena such as phenocopies and clinical misclassifications. The identification of genes involved in degenerative eye disorders has increased our knowledge base about mechanisms of neurodegeneration but in general it has still not provided clues for individual therapies. There is hope however that a unifying concept of neuroprotective strategies will emerge to combat the complex issue of genetic eye disease.

Massimo Carella

Researcher, TIGEM, Italy

CV

1991-92	Student at Microbiology Institute of the University of Bari, Italy; Supervisor: Prof. E.Jirillo.
1993-99	Fellow at Medical Genetics Service of IRCCS-"CSS" Hospital, San Giovanni Rotondo (FG), Italy; Supervisor: Dr. L.Zelante
Sep95-Jul96	Project fellow at Telethon Institute of Genetics and Medicine (TIGEM), Milan, Italy; Supervisor: Dr. B.Franco
1998	Research Associate at Department of Pediatrics of the Children's Hospital of Philadelphia, Philadelphia, PA, USA; Supervisor: Prof. P.Fortina
Nov99-Oct00	Researcher at BIRD (Baschirotto Institute for Rare Diseases), Costozza di Longare (VI), Italy
Nov00-present	Researcher at Telethon Institute of Genetics and Medicine (TIGEM), Naples, Italy; Director: Prof. A. Ballabio.

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The Genetics of Hearing Loss

Hereditary hearing loss comprises a broad spectrum of forms ranging from simple deafness to genetically determined syndromes. The incidence of prelingual hearing loss is 1/1000 births. The most common forms of genetic deafness are the non-syndromic neurosensory autosomal recessive deafness (NSRD) accounting for >75%, autosomal dominant inheritance accounts for a further 10 to 20% of cases, while X-linked inheritance accounts for 2-3%. We largely contributed to the identification of one common gene, named connexin 26 (CX26 or GJB2) and to the description of one very common mutation (35delG). Then, we defined the high worldwide carrier frequency of 35delG mutation in 3,270 random controls from 17 European countries, detecting a carrier frequency of 1 in 35 in southern Europe and 1 in 79 in Central and Northern Europe. In addition, 35delG was detected in 5 out of 376 Jewish subjects of different origin, but was absent in other non-European populations.. as regards to 35delG hystorical tracing. our studies suggest either a single origin for 35delG somewhere in Europe or in the middle East, and the possible presence of a carrier advantage together with a founder effect. The identification of families linked to DFNB1/DFNA3 but negative for GJB2 mutations within CX26, suggested the possible presence of other deafness genes within these loci. Mouse connexin-30 has been cloned and mapped to mouse chromosome 14 in a region syntenic to human chromosome 13q12. It is expressed in the cochlea and partly colocalize together with CX26. All these findings made the human homolog of mCX30 a good candidate gene for deafness. Thus, we have cloned the human connexin-30 gene and detected a missense mutation in a family affected by NSAD. The mutation affects a residue highly conserved across species. CX30 message, found at high levels in the trachea, thymus and thyroid gland, occurs also in the mouse embryos inner ear. Functional electrophysiological studies measuring the conductances of either wild-type and mutant in Xenopus oocytes clearly demonstrate a) the role of this mutation in affecting the protein function, b) its trans-dominant effect on the wild type providing a molecular explanation for the dominant effect.

Finally, a proportion of cases, yet to be defined is due to mutations in mitochondrial DNA, which play a significant role in both syndromic and non-syndromic sensorineural hearing impairment. All mutations apart one are in general specific and rare, while a large proportion of Spanish families with late-onset sensorineural deafness carries a mithochondrial DNA mutation named A1555G. This mutation has an age-dependent penetrance for deafness that is enhanced by the treatment with aminoglycosides. Until few years ago genetic deafness was a "mare magnum" in which the absence of knowledge was the main feature. Successively, several loci have been described and the presence of genetic heterogeneity, previously only hypothesized, was clearly demonstrated. Molecular biology techniques applied to the genetics of hearing loss shed a new light on old questions regarding hearing and deafness and already led to a better understanding of the biology of normal and abnormal hearing. These discoveries have major implications in terms of early molecular diagnosis, genetic counseling and possible prevention. For example, despite the large genetic heterogeneity in hearing loss, the identification of GJB2 as a major gene accounting for at least half of the cases of hearing loss and the identification of a very common mutation within it, make possible to provide at risk families and sporadic cases with a simple DNA test to ascertain whether one is carrier or not of 35delG mutated allele. This finding makes either risk calculations or genetic counseling more accurate, and hopefully will allow faster treatment of affected children. In addition, the identification of the above mentioned genes will facilitate development of animal models, which should be useful for studying pathophysiology as well as for development of new strategies for therapeutic intervention, such as gene therapy.

Nicholas J. Short

CSO, Iceland Genomics Corporation, Iceland

CV

Nicholas J. Short is the Managing Director and Chief Scientific Officer of Iceland Genomics Corporation, a privately held company working to develop new diagnostic tests, therapeutic targets and drugs for cancer. After completing his Ph.D. at the University of Cambridge, he moved to London, where he continued his work on the control of eukaryotic transcription at King's College. In 1992, he became the Chief Editor for the Biological Sciences at the journal Nature, where he and his team published papers on topics ranging from cloned sheep and feathered dinosaurs to new drugs and genetically modified crops. While there, he was also responsible for supplements on genomics, drug discovery and new forms of therapy, in addition to organizing seven conferences and helping to launch four new journals in the Nature stable. In 1999, he left to become the founder and Senior Partner of Short & Co., a consulting firm providing scientific advice for the banking, venture capital, biotechnology and pharmaceutical communities, before joining Iceland Genomics in 2000.

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Clinical Genomics and the Icelandic Cancer Project

Populations that have remained substantially isolated since their foundation offer major advantages for genetic studies, as the relatively homogenous genetic background reduces the number of disease alleles in the population and hence increases the relative risk conferred by each allele. One of the best studied such populations is that of Iceland, which was founded in the 9th century. Iceland Genomics Corporation enjoys preferential access to Icelandic cancer patients by virtue of its close relationship with the clinicians treating cancer in the country and its collaborations with the Icelandic Cancer Registry and the National Hospital System. But how can identifying disease-causing alleles be used to maximize benefit to the patient? Iceland Genomics is using a 'clinical genomics' approach to correlate the molecular biology of patient tumors with the mutations that give rise to them, giving the first integrated picture of cancer across an entire nation. The Company is also developing an integrated platform with which to validate promising targets and screen for drug leads directed against them. This 'post-genomics' strategy should produce drugs with increased effectiveness against tumor types that are refractory to current treatment, while at the same time minimizing undesirable side effects.

Mart Ustav

Department of Microbiology and Virology,
University of Tartu, Estonia

CV

Mart Ustav, born in 1949, received his B.Sc. in organic and bioorganic chemistry in 1972 and the degree of candidate (Ph.D.) in 1980 in Molecular Biology. He was awarded the Estonian State Prize for his research into the biosynthesis of proteins in 1980 and for his research in the field of papillomaviruses in 1996. He held a postdoctorate at the University of Uppsala from 1982-1985 and was a visiting scientist at the Cold Spring Harbour Laboratory, NY, USA from 1989 to 1992. He has been working at the University of Tartu since 1992 as the Professor of Microbiology and Virology. His research interests lie in molecular biology, virology and diagnostics, also gene therapy and vaccination.

Research from 2000

Mechanisms of papillomavirus DNA replication during the viral life cycle

The p53 protein is a transcriptional regulator of genes involved in growth control, and it plays a central role in modulating the processes that lead to apoptosis and DNA replication. We have shown with transient replication assays that the p53 protein specifically blocks the amplificational replication of bovine (BPV1) and human (HPV11, HPV18) papillomavirus origins. This inhibitory effect can be detected in the number of cell lines. Domain mapping by point mutations and deletions showed that the central core domain and oligomerization domain are necessary and sufficient for p53 replication suppression activity. Cell cycle analysis of the transfected cells showed that this activity is not an indirect consequence of a p53-dependent cell cycle block or apoptosis, nor is the phenomenon mediated by transactivation or transrepression activities of p53 protein. We tested the effect of p53 on papillomavirus and Epstein-Barr virus latent origin replication. We showed that both latent replication modes are insensitive to p53 action, which suggests that the inhibitory effect of p53 is specific to the type of DNA replication mode represented by papillomavirus amplification. Papillomavirus genomes are maintained as multicopy nuclear plasmids in transformed cells. We found that plasmids of BPV1 origin are tightly associated with chromatin throughout the cell cycle. We showed that the minichromosome maintenance element (MME), composed of oligomerized E2 binding sites, is the only cis element required for this activity. Our data show a perfect correlation between episomal maintenance and the ability of these plasmids to associate with chromatin. We identified by mutational analysis the specific pocket in the E2 transactivation domain that is responsible for binding of the E2 to the metaphase chromosomes. Our data suggest that E2-mediated MME chromatin association provides the mechanism for partitioning and segregating the plasmids in the dividing cells during latent papillomavirus infection.

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Gene Therapy and Gene Vaccination

Priit Kogerman

National Institute of Chemical Physics and Biophysics, Tallinn, Estonia

CV

EDUCATION AND PROFESSIONAL DEVELOPMENT

2001:	Head of the Laboratory of Molecular Genetics, National Institute of Chemical Physics and Biophysics (NICPB)
1999:	Senior Research Scientist, NICPB and Associate Professor, Tallinn Technical University Gene Technology Center
1999:	Assistant Professor, Karolinska Institute, Department of Biosciences at Novum
1997-98:	postdoctoral training at Karolinska Institutet, Department of Biosciences at Novum (Advisor Prof. Rune Toftgård)
1992-96:	Case Western Reserve University, Department of Molecular Biology and Microbiology, Ph. D. (1997). "Significance of CD44s for tumor progression of a murine fibrosarcoma model". Advisor Dr. Lloyd Culp
1991-92:	University of Helsinki, Department of Biochemistry and Institute of Biotechnology.
1988-91:	University of Tartu, Faculty of Biology, Department of Biochemistry Cum Laude Diploma in Biology and Biochemistry, Diploma. Thesis: "Nucleotide Sequence of the Potateo Leafroll Virus (Russian Isolate) coat protein gene and its constructs in plant expression vectors". Advisor Prof. Mart Saarma.
1985-88	Moscow State University, Faculty of Biology

AWARDS

2001:	President of Estonia, Young Scientist Award
1999:	Paul Kogerman Memorial Medal
1997:	Visby Scholar, Swedish Institute
1995:	Jüri Lellep Memorial Award, Nikolai Küttis Memorial Award
1993:	Rotalia Foundation Award
1991:	Rector of the University of Helsinki, Outstanding Foreign Student Award

ACADEMIC DUTIES

Board Member: Estonian Genome Project Foundation, Estonian Society of Human Genetics
Member of the Scientific Council: NICPB and TTU Gene Technology Center

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From Genes to Functions: The Case of CD44

The postgenomic era offers enormous new opportunities for uncovering the genes involved in complex human diseases. However, such genes have been discovered and their functions elucidated even in pregenomic times. Recent history offers numerous examples of breakthrough discoveries creating elevated expectations about immediate benefits in the clinic which have gone through a painful reality check only to reemerge at a more realistic level. One such example that has gone through the full cycle is CD44, a cell surface receptor for the glycosaminoglycan hyaluronan. Discovered 10 years ago by Herrlich and colleagues as the molecule capable of conferring metastatic behavior to rat pancreatic carcinoma cells, it was expected to have enormous potential in early detection of metastatic cancers. However, the numerous studies in the mid-nineties gave contradictory results resulting in considerable confusion and disappointment about this molecule. However, our results to be presented show that CD44 has a dual role in cancer progression: it is important for metastatic spread, but is inhibitory for angiogenesis, a process absolutely necessary for local growth of both primary and metastatic tumors. These results present an explanation for the conflicting data in the literature, establish CD44 as a novel type of metastasis molecule and offer a new strategy for simultaneously interfering with angiogenesis and metastasis, both critical processes in malignant tumor progression.

Giovanni Romeo

Director, Unit of Genetic Susceptibility to Cancer, International Agency for Research on Cancer, Lyon, France

CV

PROFESSIONAL EMPLOYMENT

1995-to date	Chief, Unit of Genetic Cancer Susceptibility, International Agency for Research on Cancer, Lyon, France
1986-1995	Professor of Human Genetics - University of Genoa Medical School - Director of the Laboratory of Molecular Genetics and Laboratory of Clinical Cytogenetics, Istituto G. Gaslini
1978-86	Associate Professor of Molecular Genetics - University of Bologna Medical School
1978-82	Lecturer in Genetics and Assistant Professor - University of Bologna
1976-78	Visiting Scientist in the Department of Genetics-Stanford Medical School - Laboratory of Prof. L.L. Cavalli-Sforza
1972-78	Lecturer in Genetics - University of Naples
1972-76	Group leader of the Laboratory of Human Genetics - International Institute of Genetics and Biophysics (I.I.G.B.) Naples
1968-71	Fellowship awarded by the Leukemia Society of America for research on somatic cell genetics and biochemical genetics in the Division of Genetics of the Department of Pediatrics of the Johns Hopkins Medical School, Baltimore, MD - Laboratories of Dr. E.Y. Levin and of Dr. B.R. Migeon
1966-69	Internship and residency in Pediatrics, University of Bologna Medical School
1965	Certificate of the Educational Council for Foreign Medical Graduates (ECMFG) M.D. degree (with honours) from the University of Bologna Medical School

HONOURS:
- Graduated cum Laude in Medicine, University of Bologna (1965)
- Lepetit prize 1966, for M.D. thesis
- A.I.R.H. prize 1988, for work in human genetics

MEMBER OF THE FOLLOWING SCIENTIFIC SOCIETIES:
European Society of Human Genetics
- President for 1991-1992
- Member of the Board (1990-95)

American Society of Human Genetics (ASHG)
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Genetics of complex disorders: The RET Protooncogen and Thyroid Cancer

Giovanni Romeo, Raffaella Corvi, Fabienne Lesueur and James McKay International Agency for Research on Cancer (Lyon) and University of Bologna Medical School Centre for Genetic Medicine

Non-Medullary Thyroid Carcinoma (NMTC) accounts for ~90% of all thyroid cancers (prevalence adjusted for age=0,5-5/100,00 in most populations) and originates from the follicular cells of the thyroid. Papillary Thyroid carcinoma (PTC) and Follicular Carcinoma (FC) represent the two main variants of NMTC. Epidemiological studies demonstrate that a familial clustering of NMTC does exist. Familial NMTC (FNMTC) has been repeatedly observed clinically and it is characterized by a more aggressive behaviour than the sporadic cases. It follows an incompletely penetrant autosomal dominant mode of inheritance, and it is thought to represent ~5% of all cases of thyroid cancer. Very little is known about genetic predisposition to NMTC. On the other hand RET is found activated in 66% of sporadic PTC observed in Ukraine and Belarus 10 years after the Chernobyl accident. This activation derives from somatic mutations, namely chromosomal translocations or inversions resulting in rearrangements of the protooncogene RET with different genes.

In order to map genes predisposing to NMTC an International Consortium for the Genetics of FNMTC has been organized by IARC and 225 pedigrees have been collected. Two loci predisposing to FNMTC have been already identified: TCO (MIM [603386]) on 19p13.2, in a French family with an unusual form of NMTC with cell oxyphilia and PRN1 (MIM [605642]) on 1q21 in a US family with the most common from of NMTC, Papillary Thyroid Carcinoma (PTC) and Papillary Renal neoplasia. However, neither of these loci, nor the MNG1 (MIM [138800]) locus on 14q identified in a large Canadian family with multinodular goiter and low recurrence of NMTC account for a significant fraction of FNMTC pedigrees.

More recently in a large Tasmanian pedigree (Tas1) with recurrence of the most common form of NMTC, Papillary Thyroid Carcinoma (PTC), an extensive genome wide scan revealed a common haplotype on chromosome 2q21 in seven out of the eight PTC patients. In order to verify the significance of this 2q21 locus, linkage analysis was performed in an independent sample set of 80 pedigrees yielding a multipoint HLOD of 3.07 (a=0.42), NPL=3.19, (p=0.001) at marker D2S2271. Stratification based on the presence of at least one case of the follicular variant of PTC (fvPTC), the phenotype observed in the Tas1 family, identified 17 such pedigrees which showed a maximal HLOD score of 4.17 (a=0.80), and an NPL=4.99 (p=0.00002) at markers AFMa272zg9 and D2S2271 respectively. These results indicate the existence of a new major susceptibility locus for FNMTC on chromosome 2q21.

In addition, six candidate genes, RET, TRK, MET, TSHR, APC, PTEN as well as TCO abd MNG1 were excluded as major susceptibility genes in a large sample of families families by using microsatellites that are positioned in or in close proximity to these genes. In order to determine if some variants of RET or a combination of them might predispose to PTC we looked for association of RET haplotype(s) in PTC cases and in controls matched for sex, age and population. Four single nucleotide polymorphisms (SNPs) across the RET coding sequence were typed and haplotypes reconstructed for sporadic PTC cases and controls using the Arlequin algorithm. Eleven unique haplotypes were obtained, which show a different breakdown in cases vs controls. Our data suggest that some variants of RET and some specific haplotypes are associated with predisposition to sporadic as well as familial PTC.

NOTES

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