MGC-Bulletin, Nr. 52, September 2015

In dit nummer:

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The 2015 MGC workshop committee!

Leids Universitair Medisch Centrum

Het Centrum is een initiatief van het Universitair Medisch Centrum Rotterdam en het Leids Universitair Medisch Centrum

Erasmus MC Universitair Medisch Centrum Rotterdam

Onderwijs voor promovendi

Het aanbod van cursussen voor promovendi in het LUMC is tegenwoordig online beschikbaar. Deze informatie is te vinden op http://albinusnet.lumc.nl/home/.

A course "***Next Generation Sequence (NGS) data analysis*** " will be organized from *28 – 30 September 2015* in Groningen (the next edition in 2016 will be in Leiden again). The course aims at PhD students, postdocs and senior researcher who are planning or already working with NGS. Currently available technologies as well as hardware and software solutions will be presented and discussed. The focus will be on the data and way the analyse them. For more info see www.medgencentre.nl.

A course "***Functional imaging and super resolution***" will be organized from 26-30 October 2015 in Rotterdam. The aim of the course is to provide a comprehensive introduction to the field of translational cancer research. This five day course consists of lecture sessions in the morning and practical sessions in the afternoon; on some days also evening sessions with a dinner. In the final session on Friday afternoon participants will present and discuss the results of their practical work. For more info see www.medgencentre.nl

From our sister school Molecular Medicine the following courses are available:

- ***Photoshop and Illustrator CS6 workshop:*** *8 or 29 September*, a hands-on full day workshop on the programs Photoshop and Illustrator CS6. These programs are used for image enhancement and for drawing high quality graphs, tables and other figures.
- ***NGS in DNA Diagnostics Course:*** *22-24 September.* This course is aimed at Genomic Resequencing in a medical diagnostic context, i.e. to apply NGS data as diagnostic tool in the hospital and is intended for bioinformaticians, researchers and molecular and clinical geneticists.
- ***Indesign CS6 Workshop:*** *30 September*, a half-day Workshop on Adobe Indesign CS6. This program employs Photoshop and Illustrator and can be used to make high quality posters.
- ***Biomedical Research Techniques:*** *2-6 November*. A basic five-day course on several lab techniques. The program covers: Day 1: primers and probes, sequencing, SNP analysis, methylation; Day 2: Microscopy: quantitative confocal microscopy, image analysis, FRET, FRAP & computer modeling; Day 3: proteomes, mass spectrometry, special discussion program; site visit facilities labs; Day 4: (morning) cytotoxicity, ELISA & flow cytometry; (afternoon) RNA, RNA expression arrays, RT PCR, siRNA, data mining; Day 5: Applied molecular imaging: MRI, CT, nuclear, optical in vivo, Special Research Integrity and site visit proteomic labs.
- ***SNP Course****: 16-20 November*. An annual 5-day course on SNP and human diseases, including hands-on computer practicals. Basic knowledge of the central molecular biological is required.
- ***Translational Imaging Workshop by AMIE: from mouse to man:*** *24-27 November.* The aim of this 4-day workshop is to give a broad introduction into preclinical and translational molecular imaging techniques and their applications in biology and medicine.

For detailed information & registration info www.molmed.nl

Yearly courses organized by Boerhaave CME:

- **Survival Analysis:** 2-6 November. Survival analysis is the study of the distribution of life times, i.e. the times from an initiating event (birth, diagnosis, start of treatment) to some terminal event (relapse, death). During the course different types of censored data will be introduced and techniques for estimating the survival function by employing both parametric and non-parametric methods will be illustrated. Multiplicative hazards regression models, testing and inference techniques will be studied in great details. Special aspects as time-dependent covariates effects, stratification, time and prediction will be introduced. Techniques to be used to

assess the validity of the hazard regression model will be discussed.

- **Meta Analysis**: 9-11 November. Meta-analyse is een kwantitatieve samenvatting van een aantal studies binnen een systematisch literatuuronderzoek. Met deze driedaagse cursus krijgt u een overzicht van de principes van systematisch literatuuronderzoek en de statistische methoden die voor meta-analyse worden gebruikt. De statistische analyses worden geoefend met het programma STATA. Na deze cursus kunt u artikelen over literatuuronderzoek doorgronden en op kwaliteit beoordelen en kunt u zelf een (eenvoudige) meta-analyse uitvoeren.

For detailed information & registration: *www.boerhaavenascholing.nl.*

PhD Teaching Programme Committee

Since 2011 the MGC has a newly formed PhD Teaching Programme Committee. Members of the committee are: Raymond Poot and Kerstin Wendt of the Erasmus MC and Dorien Peters, Harry Vrieling and Madeleine Nivard of the LUMC. The committee will focus primarily on evaluation of the existing course program and will advise on new courses or teaching activities (Contact email address: *nivard@lumc.nl).*

MGC Promovendi Workshop 2016

The 22nd MGC-PhD workshop was held in Maastricht and was a big success. The 23rd workshop will be held in June 2016. Venue is not known yet. For more information see *www.mgcworkshop.nl*.

The MGC-PhD student workshop is a 4-day event organized every year by PhD students for PhD students.

During this workshop PhD students get the chance to:

- - exchange knowledge in an informal and relaxed way, through posters and presentations
- - build their own network during social events and free time

The workshop is meant for PhD students who are doing their research in one of the MGC departments. The attendance to the workshop is part of the PhD program and PhD students should attend at least three times during their PhD.

De prijswinnaressen tijdens de workshop: Leonie Kollenstart en Fenne Riemslagh *(beste poster) en* Malgorzata Grosbart *(beste lezing).*

Promoties

Kasper Derks is op 22 oktober 2014 in Rotterdam gepromoveerd op het proefschrift "The DNA damage respons: nucleic acid regulation in sequence". Promotoren: Prof. J. Hoeijmakers en Prof. B. van der Horst; co-promotor: Dr. J. Pothof.

Sherif Shawky Abdou is op 28 oktober 2014 in Rotterdam gepromoveerd op het proefschrift "Development of nanoparticles based assays for the direct detection of unamplified nucleic acids in clinical specimens". Promotor: Prof. F. Grosveld; co-promotor: Dr. H. Azzay.

Özge Aydin is op 29 oktober 2014 in Rotterdam gepromoveerd op het proefschrift "Chromatin remodeling in the UV-induced DNA damage response". Promotor: Prof. J. Hoeijmakers; co-promotoren: Dr. W. Vermeulen en Dr. H. Lans.

Wouter Leonhard is op 10 december 2014 in Leiden gepromoveerd op het proefschrift "Recapitulating Polycystic Kidney Disease in mice". Promotoren: Prof. D. Peters en Prof. M. Breuning.

Maikel Wouters is op 12 december 2014 in Rotterdam gepromoveerd op het proefschrift "MicroRNAs, the DNA damage response and cancer". Promotor: Prof. J. Hoeijmakers; co-promotor: Dr. J. Pothof.

Melvin Evers is op 7 januari 2015 gepromoveerd op het proefschrift "Developing genetic therapies for polyglutamine disorders". Promotor: Prof. G. van Ommen; co-promotor: Dr. W. van Roon-Mom.

Anita van den Heuvel is op 4 februari gepromoveerd in Rotterdam op het proefschrift "Transcriptional control during hematopoietic development; transcription factor binding and chromatin conformation dynamics". Promotor: Prof. F. Grosveld; co-promotor: Dr. E. Soler.

Jenny van Dongen is op 16 april cum laude gepromoveerd in Leiden op het proefschrift "(Epi)genetics and twins". Promotoren: Prof. D. Boomsma en Prof. P. Slagboom; co-promotoren: Dr. B. Heijmans en dr. A. Willemsen.

Loes van Cuijk is op 17 april gepromoveerd in Rotterdam op het proefschrift "Ubiquitin-mediated regulation of damage recognition in nucleotide excision repair'. Promotor: Prof. W. Vermeulen; co-promotor: Dr. J. Marteijn.

Yolande F.M. Ramos is op 26 mei gepromoveerd in Leiden op het proefschrift "Osteoarthritis, a degenerative disease of the articular joints – towards implementation of functional genomics in OA". Promotor: prof. P. Slagboom; co-promotor: dr. I. Meulenbelt.

Claudia Weller is op 2 september in Leiden gepromoveerd op het proefschrift "Unravelling genetic mechanisms in headache syndromes". Promotoren: Prof. M. Ferrari en Prof. A. van den Maagdenberg.

Dimitris Typas is op 9 september in Leiden gepromoveerd op het proefschrift "DNA damage-induced ubiquitylation: emerging regulators enforce protective mechanisms". Promotor: Prof. L. Mullenders; co-promotor: Dr. H. van Attikum.

Petros Kolovos hoopt op 22 september in Rotterdam te promoveren op het proefschrift "Developmental dynamics of transcription and genome architecture". Promotor: Prof. F. Grosveld.

Eleonora de Klerk hoopt op 30 september te promoveren in Leiden op het proefschrift "Mechanisms controlling mrna processing and translation: decoding the regulatory layers defining gene expression through RNA sequencing". Promotor: Prof. J. den Dunnen; co-promotoren: Dr. P. 't Hoen en Dr. J. Laros.

Mattijs Heemskerk hoopt op 6 oktober in Leiden te promoveren op het proefschrift "The role of energy & fatty acid metabolism in obesity and insulin resistance" Promotor: Prof. J. Willems van Dijk; co-promotor: Dr. V. van Harmelen.

Kishan Naipal hoopt op 3 november in Rotterdam te promoveren op het proefschrift "Functional ex vivo assays to guide personalized cancer treatment. From bench to bedside". Promotor: Prof. J. Hoeijmakers; co-promotor: Dr. D. van Gent.

Ileana Cantu hoopt op 4 november te promoveren in Rotterdam op het proefschrift "KLF1 in erythroid differentiation: an essential transcription factor in health and disease". Promotor: Prof. S. Philipsen; co-promotor: Dr. T. van Dijk.

Tenslotte hoopt **Nesrin Tuysuz** op 16 december te promoveren in Rotterdam op het proefschrift "Maintenance and expansion of adult stem cells: the role of Wnt3a protein". Promotoren: Prof. J. Cornelissen en Prof. E. Dzierzak; co-promotor: Dr. D. ten Berge.

De volgende OIO's hopen nog dit najaar in Leiden te promoveren:

George Kosmidis 'Human pluripotent stem cells as models for inherited arrhythmia syndromes'; promotor: Prof. C. Mummery.

Kostas Gkatzis 'Vascular differentiation of human pluripotent stem cells as a model system to study early cardiovascular development and disease'; promotor: Prof. C. Mummery.

Sabine den Hartogh 'Fluorescent pluripotent stem cell reporter lines for dissecting molecular mechanisms in cardiac differentiation and development'; promotor: Prof. C. Mummery; co-promotor: Dr. R. Passier.

Harsha Devalla 'Studying cardiac rhythm in health and disease using human pluripotent stem cell-derived cardio-myocytes'; promotor: Prof. C. Mummery; co-promotor: Dr. R. Passier.

Marcello Ribeiro 'On the path from fetal to adult- maturation and function of pluripotent stem cell derived cardiomyocytes';

promotor: Prof. C. Mummery; co-promotor: Dr. R. Passier.
Ana Melo Bernardo 'PGCs, vasculogenesis and amnion development in mouse and chicken'; promotor: Prof. C. Mummery; co-promotor: Dr. S. Chuva de Sousa Lopes.
Maria Gomes Fernandes: 'To be or not to be pluripotent: the role of BMP signaling in stem cells and early development'; promotor: Prof. C. Mummery; co-promotor: Dr. S. Chuva de Sousa Lopes.

Nieuwe medewerkers

Bij de afdeling Anatomie & Embryologie (Leiden):
Luca Scala (postdoc electrophysiologist characterizing the phenotype of human pluripotent stem cell derived cardiomyocytes and the effect of drugs on their pheneotype: CVON project Hustcare), promovendus met Richard Davis(Crispr/Cas targeting in human pluripotent stem cells).

Bij de afdeling Celbiologie (Rotterdam):
Ser van der Burght werkt vanaf maart in de groep van Gert Jansen als OIO. Ser gaat kijken of variabiliteit in de lokalisatie van eiwitten in cilia bijdraagt aan de stochasticiteit van gedrag.
Since 1 April **Shihao Ding** works as a PhD student in the lab of Niels Galjart. Shihao Ding will work on the role of the microtubule cytoskeleton in cardiomyocytes in health and disease.
Also **Mingkun Diao** joined Niels Galjart's lab (from January 1st). She will work on the in vivo role of the microtubule plus-end tracking proteins CLASP1 and CLASP2 in neural development. She got a scholarship from CSC (Chinese Scholarship Council).
Martijn Bogaerts en **Steven Heshusius** werken sinds respectievelijk 1 september en 1 november 2014 bij Sjaak Philipsen op het lab (via Sanquin Amsterdam). Ze werken aan 'developmental regulation of globin expression by the KLF1 transcription factor'.
Lennart van der Wal is op 15 januari begonnen als OIO bij Jeroen Demmers, afd. Biochemie/Genomics. Hij werkt aan het project 'A proteomic investigation of proteasome malfunctioning'.

Bij de afdeling Genetica (Rotterdam):
As from January 19, **Alex Pines** started working as a postdoc in the lab of Wim Vermeulen funded by the ERC grant of Wim Vermeulen. He will be working on mechanisms and regulation of transcription-coupled Nucleotide Excision Repair.
As from April 1st, **Joyce Burger** started her PhD within the lab of Roland Kanaar. She will be working with Jeroen Essers on gene expression analysis for the detection of the molecular mechanisms of aneurysm formation (GAMMA).
As from April 15th, **Diana Putavet** started her PhD within the lab of Jan Hoeijmakers. She will be working with Peter de Keizer on targeted apoptosis of senescence and interference with SASP to improve anti-cancer treatment.
As from April 1st, **Masaki Akita** started working as a postdoc in the lab of Wim Vermeulen funded by the ERC grant of Wim Vermeulen. He will be working on mechanisms and regulation of transcription-coupled Nucleotide Excision Repair.
As from September 1st, **Stefan Roobol** started his PhD within the lab of Roland Kanaar. He will be working with Jeroen Essers on radiolabelled Nano-carriers for Customized Cancer Therapy.
As from September 1st, **Wenhao Zang** started his PhD within the lab of Dik van Gent. He will be working on ex vivo investigation of DNA damage response defects in prostate and bladder cancer.
As from September 10th, **Angela Helfricht** started working as a postdoc in the lab of Wim Vermeulen, funded by WWCR. She will be working with Hannes Lans on chromatin remodeling in Nucleotide Excision Repair.
As from September 14th, **Titia Meijer** will start her PhD within the lab of Dik van Gent. She will be working on ex vivo assays for selection of breast and ovarian cancer patients for PARP inhibitor treatment.

As of September 15th, **Jiang Chang** will start his PhD within the lab of Jan Hoeijmakers. He will be working with Joris Pothof on the development of bio-informatics approaches to identify DNA damage response defects in aging.

Bij de afdeling Humane Genetica (Leiden):
Onderzoekers
Jessica de Greef is op 1 april in dienst gekomen als onderzoeker bij de onderzoeksgroep van Silvère van der Maarel op een door het PBS gefinancierd project.
Anita van den Heuvel werkt sinds 15 juli als onderzoeker op een gezamenlijk project van Bob van de Water (Univ. Leiden) en Silvère van der Maarel, gefinancierd door de PBS Onderzoeksprijs.
Inge Lakeman is per 1 september aangesteld als arts-onderzoeker op het Horizon2020 'BRIDGES' project in de onderzoeksgroep van Peter Devilee.
Magdalena Rother is per 1 september aangesteld als onderzoeker op de ERC grant van Haico van Attikum.
Chantal Stoepker werkt sinds 1 maart op het KWF project in de onderzoeksgroep van Haico van Attikum.
Stefan White is sinds 1 januari 2015 aangesteld als hoofd van het Leiden Genome Technology Center.

OIO's
Rick Boonen werkt sinds 1 september op het KWF project in de onderzoeksgroep van Haico van Attikum.
Haoyu Wu werkt sinds 1 september 2014 als OIO in de onderzoeksgroep van Silvère van der Maarel en Lucia Clemens-Daxinger.

Overig
Daan Asscheman is per 1 november 2014 werkzaam als data-analist voor de Leiden Open Variation Database in de onderzoeksgroep van Johan den Dunnen.
Cees Burger is per 16 maart aangesteld als wetenschappelijke programmeur op het NWO-project 'ODEX' in de onderzoeks-groep van Barend Mons en Marco Roos.
Celia Dingemanse werkt sinds 16 februari als proefdieranaliste op het NIH project in de onderzoeksgroep van Niels de Wind.
Inge van Es werkt sinds 1 oktober 2014 als researchanalist op een gezamenlijk EU-project 'Myasterix' van Jan Verschuuren (Neurologie) en Silvère van der Maarel.
Janne Plugge is per 16 maart aangesteld als researchanalist in de onderzoeksgroep van Dorien Peters op een door de Nierstichting gefinancierd project.
Heggert Rebel is sinds 1 juli werkzaam op het Paradifference project onder leiding van Jean-Pierre Bayley in de onderzoeksgroep van Peter Devilee.

Bij de afdeling Moleculaire Epidemiologie (Leiden):
Yotam Raz is eind mei begonnen als arts-onderzoeker; onderzoek naar 'skeletal muscle changes in improved metabolic health'.
Sijia Chan is ook gestart als arts-onderzoeker in deze groep.

Lezingen/symposia

NKI Seminars are given at the NKI, Plesmanlaan 121, Amsterdam:
Location: Piet Borst Auditorium, 11.00 hrs.
September 11: Diana Miglioretti "Comparative modelling study of radiation-induced breast cancer and breast cancer death from mammography screening".
September 18: Jan Hoeijmakers "The impact of genome stability on health and disease".
September 25: Lee Ellis "The erosion of research integrity: the need for a culture change in academic medicine".
October 2: Meindert Lamers "The bacterial DNA replication machine caught in the act by cryo-EM".
October 9: James Hadfield "Exome sequencing in cancer research".
October 23: Neil McDonald "RET receptor tyrosine kinase architecture, ligand-recognition and disease mechanisms".
October 30: Joachim Schultze "Systems immunology: using macrophages as a model system.
November 6: Paul Baas "Translational research in mesothelioma and lung cancer".

November 13: Sjaak Neefjes "Resurrecting lost anti-cancer drugs by chemical biology and new options for patients.
November 27: John Schwabe "understanding the mechanisms of HDAC co-repressor complexes: a structural and functional approach".
December 4: Martin Klein "Neurocognitive functioning in brain tumor patients".
December 11: Edwin Cheung "Genomic analysis of nuclear receptor-mediated transcription in cancer cells".
Further info at www.nki.nl

Seminars in the lecture series ***Frontiers in Science in the low countries*****:**
October 8: Ruud Delwel 'Enhancer rearrangements in acute myeloid leukemia'.
November 5: Sander Tans 'Metabolic noise in single cells'.
December 3: Edwin Cuppen 'Genetic integrity of adult stem cells'.
January 14: Lucia Daxinger 'Paterna effect genes in the mouse'.
February 11: Henk Stunnenberg 'Systems biology of embryonic stem cells'.
March 10: Lucas Kapitein 'New light on intracellular transport: optogenetics meets optical nanoscopy'.
May 12: Cedric Blanpain 'Stem cells and cancer'.
These lectures are given in room Ee822 at Erasmus MC on Thursdays at 13.00 hrs. Further info with J.Gribnau@erasmusmc.nl or r.poot@erasmusmc.nl .

Op de jaarlijkse **LUMC Conferentie** op 26 november as. zal de gastspreker zijn: **Paulo Bianco**. De titel van zijn lezing is "expert on MSC's and what they can (and cannot!) do.

Clinical Genetics Lectures are given at 16:00 hr. in College Room 3 of the Erasmus MC:
September 17: Leonard Petrucelli, Department of Neuroscience, Mayo Clinic, Jacksonville, Florida, USA "Molecular mechanisms and therapeutic approaches in frontotemporal dementia/amyotrophic lateral sclerosis".
November 19: Lukas Pelkmans, Institute of Molecular Life Sciences, University of Zurich, Switzerland "Towards a molecular understanding of population context-determined cell-to-cell variability in human cells".

Sectie 'DNA herstel-mechanismen'
De volgende bijeenkomst zal plaatsvinden op vrijdag 25 september in Rotterdam, LUMC, aanvang 9.30 uur. Deze sectie komt ca. 1 x per 2 maanden bijeen op een vrijdagochtend, alternerend in Leiden en Rotterdam. Coördinatoren: Haico van Attikum (☎: 071-5269624) en Wim Vermeulen (☎: 010-7043194).

Sectie 'Lysosomal Storage Diseases'
Eens per week overleggen betrokkenen van de afdelingen Kindergeneeskunde, Klinische Genetica, Neurologie, Interne Geneeskunde, Ziekenhuis Apotheek en andere afdelingen van het Erasmus MC over de lopende zaken wat betreft patiëntenzorg en onderzoek aangaande lysosomale stapelingsziekten. Hierbij staat de toepassing van enzymvervangings-therapie en daaraan gerelateerd onderzoek centraal (ziekte van Pompe, ziekte van Hurler, ziekte van Hunter en Maroteaux-Lamy).
De bijeenkomsten worden gehouden in het Sophia kinderziekenhuis, Dr Molewater-plein 60, Rotterdam. Voor meer informatie kunt U terecht bij Pim Pijnappel: 010-7043357; w.pijnappel@erasmusmc.nl.

Verkregen subsidies
Richard Davis (Anatomie & Embryologie LUMC): ERC starters grant; "STEMCARDIORISK - Stem Cells for Cardiac Arrhythmia Risk Assessment"
VID; "ILLUMINATE - Linking Genetics to Cardiac Arrhythmias through Stem Cells and Light"
Peter Devilee (Humane Genetica LUMC) heeft een Horizon 2020 project gehonoreerd gekregen, Breast Cancer Risk after Diagnostic Gene Sequencing (BRIDGES). Toegekende subsidie bedraagt € 6.460.000 voor een consortium van 17 partners wereldwijd.
Monique Jongbloed (Anatomie & Embryologie LUMC): Toekenning LUF/ Gratama fonds subsidie voor het project

getiteld “3D printing van aangeboren hartafwijkingen: de hand op het hart”.
Martijn Luijsterburg (Humane Genetica LUMC) heeft een LUMC Research Fellowship toegekend gekregen voor 4 jaar.
Paul Gobée, **Marco de Ruiter** (Anatomie & Embryologie LUMC) and Daniël Jansma of Maastricht University, in collaboration with the other departments of Anatomy in the Netherlands and Flanders (Belgium), received a grant from the Dutch Ministry of Education in its 2015 program for Open Online Learning, to develop an open anatomical educational platform under the name ‘Topic Oriented Open Learning (TOOL) platform’. The platform will contain a combination of openly accessible anatomical educational materials (such as images, virtual microscopy slides) and educational tools (such as quiz creation).

Personalia/Prijzen

Emmeline Calkoen (Anatomie & Embryologie LUMC) won op hetzelfde congres de prijs voor het Beste imaging abstract getiteld “Disturbed Intra-cardiac Flow Organization after AtrioVentricular Septal Defect Correction as assessed with 4DFlow MRI and Quantitative Particle Tracing”. Het abstract werd gepresenteerd door kindercardioloog Arno Roest.
Wouter Leonhard (Humane Genetica LUMC) heeft bij de Nederlandse Federatie voor Nefrologie 2014, de prijs voor de beste presentatie gewonnen.
Gert Jan van Ommen (Humane Genetica LUMC) is per 1 januari toegetreden tot het bestuur van de American Society of Human Genetics (ASHG). De ASHG is de grootste en meest invloedrijke organisatie op het gebied van humane genetica.

Samen met de European Society of Human Genetics speelt de ASHG een centrale rol in de huidige ontwikkeling rondom de implementatie van next generation sequencing in de gezondheidszorg.
Valeria Orlova (Anatomie en Embryologie LUMC) won the first prize for best oral presentation at the HHT meeting for the hiPSC model for HHT. It took place in Florida, June 2015.
Svetlana Pasteuning (Humane Genetica LUMC) heeft tijdens de Cold Spring Harbor-conferentie over RNA en therapie met oligonucleotiden de 'Young Investigator Award' toegekend gekregen. Deze prijs van 10.000 euro is beschikbaar gesteld door AUM Technologies.

Pasteuning (rechts op de foto) mag het geld besteden aan de aanschaf van anti-sense-oligonucleotiden voor haar onderzoek naar een mogelijke behandeling van Duchenne spierdystrofie en andere spierziekten.
Marcelo Ribeiro (Anatomie & Embryologie LUMC) won the 3rd prize for oral presentation in the DSSCR meeting Friday April 24th, with the project “Improved function of pluripotent stem cell-derived cardiomyocytes by defined physiological factors facilitates disease modelling”.
Julie Rutten (Humane Genetica LUMC) heeft bij het najaarssymposium van de Nederlandse Vereniging voor Humane Genetica 2014 de prijs voor de beste presentatie gewonnen.
Marcel Tijsterman (Humane Genetica LUMC) is per 1 oktober 2014 in Leiden benoemd tot hoogleraar 'Genoomstabiliteit'.
Rebecca Vicente Steijn (Anatomie & Embryologie LUMC) won op het congress European Association for Paediatric & Congenital Cardiology in Praag (21-25 mei 2015) de Moderated Poster Competition met poster: “Regional differences in WT-1 and Tcf21 expression during ventricular development: implications for myocardial compaction”.

MGC-Bulletin no. 53

Het drie-en-vijftigste MGC Bulletin is gepland voor september 2016. **De sluitingsdatum voor kopij is gesteld op 15 augustus 2016.** Mededelingen, nieuws, agendapunten en andere wetens-waardigheden gaarne per e-mail inleveren bij Madeleine Nivard of Ingrid Braxhoven, , Nivard@lumc.nl/ I.Braxhoven@lumc.nl, af-deling Humane Genetica.

25th MGC-SYMPOSIUM

Thursday, September 10, 2015
Building 3, LUMC

Program 25th MGC Symposium

8.45 Coffee and registration

9.30 Opening: Prof.dr. Leon Mullenders
Chairman: Prof.dr. Bob van de Water
9.35 **Claudia Ruivenkamp**: "BRAIN: a tool to rationalize the biology behind genes for disorders (ID as example)" (Clinical Genetics, LUMC)
9.55 **Arjan Theil**: "New paradigms for understanding the rare progeroid DNA repair disorder trichothiodystrophy" (Genetics, Erasmus MC)
10.15 **Steven Hiemstra**: "Systems microscopy to unravel the signaling network that controls the KEAP1/Nrf2 antioxidant adaptive stress response pathway" (LACDR, UL)

10.35 *Best lecture of the MGC PhD Workshop 2015*
Malgorzata Grosbart: "DNA repair complex MRE11/RAD50 exhibits ligand-specific conformation changes linked to function" (Genetics, Erasmus MC)

10.55 Coffee/tea

Chairman: Prof.dr. Robert Hofstra
11.15 **Silvana Jirka**: "Enhancing the delivery of antisense oligonucleotides for Duchenne muscular dystrophy" (Human Genetics, LUMC)
11.35 **Tobias Messemaker**: "A novel long non-coding RNA in the rheumatoid arthritis risk locus TRAF1-C5 regulates C5 mRNA levels" (MCB/Reumatologie, LUMC)
11.55 **Virginie Verhoeven**: "Genetic pathways in human myopia" (Clinical Genetics, Erasmus MC)
12.15 **Wouter Leonhard**: "Mechanistic insights into autosomal dominant polycystic kidney: the role of TGFβ, activins and cysts themselves human genetics" (Human Genetics, LUMC)

12.35-14.00 Lunch

Chairman: Prof.dr. Jan Hoeijmakers
14.00 **Saskia Hiltemann**: "Discriminating somatic and germline mutations in tumour DNA samples without matching normal" (Bioinformatics, Erasmus MC)
14.20 **Arnoud Boot**: "Imprinted cell survival genes drive thyroid cancer cells to maintain heterozygosity on chromosome 7" (Pathology, LUMC)
14.40 **Peter de Keizer**: "Targeted apoptosis of senescent cells (TASC) against cancer and aging" (Genetics, Erasmus MC)

Chairman: Prof.dr. Silvère van der Maarel
15.00 **Sreya Basu**: "A novel role for dynamic microtubules in the control of stem cell fate" (Cell Biology and Genetics, Erasmus MC)
15.20 **Georgios Kosmidis**: "Human pluripotent stem cell derived cardiomyocytes to study the read through of nonsense mutations in the sodium channel gene SCN5A" (Anatomy and Embryology, LUMC)
15.40 **Petros Kolovos**: "Genome structure and hematopoietic development" (Cell Biology, Erasmus MC)

16.00 Coffee/tea

Chairman: Prof.dr. Danny Huylebroeck
16.30 MGC Symposium Lecture:
Timm Schroeder: "Long-term single cell quantification: new tools for old questions" (Department of Biosystems Science and Engineering, ETH Zurich, Basel, Switzerland)

17.30 Drinks and snacks

BRAIN: a tool to rationalise the biology behind genes for disorders (ID as example)

Claudia Ruivenkamp
Clinical Genetics, LUMC

Whole Exome Sequencing (WES) has revolutionized the field of clinical genetics, and is more and more routinely used as a diagnostic approach for detecting genetic causes of complex diseases such as intellectual disability (ID). Conclusive genetic diagnoses will be obtained for patients with mutations in or around known ID genes. Nevertheless, variants affecting candidate genes as found by WES and not yet explicitly linked to a certain phenotype are posing an enormous evaluation challenge. Published information on indirect evidence for the involvement of the gene in the phenotype, locus specific databases such as LOVD, GWAS studies, transcriptomics evidence and a plethora of potentially relevant model organism databases is scattered and difficult to find and interpret. This results in a rapidly growing and inhibitory imbalance between tour ability to obtain information on the variants in a persons' genome and our capacity to interpret all potentially relevant variants. The final decision on which candidate genetic variants to pursue further will, however, continue to depend on many factors, but in most cases it requires input and interpretation from so many different sources, in many formats and scattered around the world that classical methods simply fail.
There is a growing international effort (Lead by infrastructures such as ELIXIR-EUROPE, GA4GH and BD2K in the USA) to make data sets increasingly Findable, Accessible, Interoperable and Reusable (i.e. FAIR). Based on these principles, preconfigured semantic environments can be built that enable much faster evaluation of clinically observed gene-phenotype combinations. To increase the ability and capacity of our group in making timely and evidence based follow up decisions on potentially relevant variants we used the BRAIN (Bio Relations and Intelligence Network) knowledge discovery platform from Euretos. BRAIN contains millions of unique scientific associations from different data sets and those are interactively forming a knowledge representation graph (the MindMap) of all connecting concepts between the gene (or the variant if already described earlier) and the phenotype observed. Via one- and two-step indirect relations, via physiology, anatomy, chemicals/metabolites, genes/proteins and other diseases, it is now a matter of minutes rather than hours to get a first impression about the likelihood that the detected variant might cause the observed phenotype. The latest development that will be shown is the so called SEED article, a 'scientific article-style' PDF that systematically lists and displays the various relations with all supporting evidence from the different databases as 'references' at the end of the article. We have created many of these articles already for gene-disease combinations that have a high likelihood of being functionally associated.
The combination of the BRAIN MindMap and the SEED articles derived from the knowledge graph form a highly valuable addition to our arsenal of tools to speed up clinical genetic diagnosis.

New paradigms for understanding the rare progeroid DNA repair disorder trichothiodystophy

Arjan Theil
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The human syndrome Trichothiodystrophy (TTD) is a rare, autosomal recessive disorder, characterized by a low content of sulfur-rich proteins in both hair and nails in addition to neurodevelopmental and premature aging features. The clinical symptoms observed among TTD patients are very variable in expression and severity, including: photosensitivity, ichthyosis, brittle hair and nails, intellectual impairment, decreased fertility and short stature and stretches from very mild forms of the disease,¬ characterized by normal development with only brittle hair and scaling skin (typical TTD-features) to very severe cases, characterized by high mortality at young age combined with severe developmental and progressive neurologic defects. Approximately 50% of TTD patients are photosensitive and carry inactivating mutations in either the XPB, XPD or TTDA genes, each of which encode for subunits of the transcription factor IIH (TFIIH). TFIIH is essential for both transcription initiation and nucleotide excision repair (NER). The affected NER function by these mutations explains the photosensitivity as NER is the main DNA repair process in mammals to remove UV-induced DNA lesions. Progressive premature aging features, including neurological decline are thought to be derived by the inefficient repair of endogenously produced DNA lesions. The more developmental abnormalities are suggested to be caused by a subtle TFIIH-dependent transcription deficiency. Mutations in the TTDN1 gene are associated with the non-photosensitive form of TTD, although the function of TTDN1 remains elusive. However, the causative gene(s) for the majority of non-photosensitive TTD patients (approximately 80%) has not yet been identified.

In order to dissect the contribution of DNA lesions from affected transcription function in photosensitive TTD patients with respect to aging and developmental problems, it is important to identify the genes and their function causing the non-photosensitive form of TTD. We have selected a group of unrelated non-photosensitive patients, with unequivocal TTD-specific features and without a mutation in TTDN1 for massive parallel whole genome sequencing. Among others, we have identified a novel potential pathogenic mutation in the General Transcription Factor IIE Subunit Beta (GTF2E2/TFIIEβ). Functional defects in TFIIEβ have being verified in patient cells. Currently, the effect of the identified TFIIEβ mutation on transcription is being analyzed. In transcription initiation TFIIE is directly coupled to the action of TFIIH, but in contrast to TFIIH is TFIIE not linked to a DNA repair function.

Systems microscopy to unravel the signalling network that controls the KEAP1/Nrf2 antioxidant adaptive stress response pathway

Steven Hiemstra
LACDR, Leiden University

Reactive oxygen species (ROS) are major inducers of cellular stress and cell death in various pathologies. An important extrinsic cause of increased ROS are adverse effects of drugs and their reactive metabolites. In the liver, ROS formation induced by drugs contributes to cell death and subsequent Drug-Induced Liver Injury (DILI). The Nrf2 anti-oxidant response pathway is a key mechanism in protecting cells against ROS-mediated toxicity. To monitor the entire KEAP1/Nrf2 signaling pathway we apply live cell imaging with GFP-tagging of individual Nrf2 pathway components (e.g. KEAP1, Nrf2, Srxn1, HMOX1 and NQO1). Using high throughput confocal imaging we have quantified the dynamics of Nrf2 activation and established the concentration time course dynamics of Nrf2

pathway activation by, amongst others, iodoacetamide, diethylmaleate and CDDO-me, which already directly target KEAP1. In order to provide full understanding of the upstream regulators of the Nrf2 pathway, we applied a Dharmacon Smartpool siRNA-based knock-down screen using the Srxn1-GFP reporter as a downstream target of Nrf2. We screened all individual kinases, phosphatases, ubiquitinases and transcription factors for their involvement in Nrf2 activation, a total of ~3300 individual genes. After knock-down, CDDO-me was used to activate Nrf2 followed by quantification of Srxn1-GFP expression using automated high throughput imaging and image analysis. Candidate Nrf2 pathway regulators that upon KD enhanced (58 genes) or inhibit (19 genes) the CDDO-me-induced Srxn1 upregulation were validated with single siRNAs. Candidate hits included BRD4, ATF3 and RXRA which have previously been associated with Nrf2 regulation. To assess DILI relevance, the candidate hits were further validated with drugs known to induce DILI in the clinic: acetaminophen, azathioprine and diclofenac. This work contributes to more elaborate understanding of the signaling networks that control Nrf2 signaling in the context of DILI.

Best lecture of the MGC PhD Workshop 2015

DNA repair complex MRE11/RAD50 exhibits ligand-specific conformation changes linked to function

Malgorzata Grosbart
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The MRE11/RAD50 (MR) complex is an essential element of DNA double strand break (DSB) repair process. Highly conserved through evolution, it participates in homologous recombination (HR), telomere homeostasis, checkpoint activation and immune system development. In double strand break repair MR is involved in many tasks, including damage recognition, DNA ends processing and DNA tethering. Extensive studies of the complex throughout numerous years of research did not lead to a definitive understanding of how it performs such a variety of functions. Recent crystallographic data suggest that MR appears in a broad variety of conformation forms, which can be influenced by binding one of its ligands (ATP, double stranded DNA, single stranded DNA). Unfortunately, as it is impossible to crystalize full-length MR complex, these results are fragmentary and do not provide an overall understanding of MR conformation states and their relevance for HR. Therefore, we employ Scanning Force Microscopy as a tool for imaging full-length human MR complex with nanometer resolution. Our findings suggest that Wild Type human MR indeed appears as a mixture of distinct conformation forms, suggesting great flexibility of individual domains. Conformation of MR is stabilized upon ligand binding, and each form appears to be characteristic for binding a specific ligand. Our data provide new insights on MR complex architecture and the impact of conformation changes on its function in DNA repair.

Enhancing the delivery of antisense oligonucleotides for Duchenne muscular dystrophy

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Duchenne muscular dystrophy (DMD) is a severe X-linked muscle wasting disorder affecting 1:5000 newborn boys. DMD is caused by reading frame disrupting mutations in the DMD gene leading to an absence of dystrophin protein. Dystrophin is an important protein in muscle since it stabilizes the muscle during contractions. Without a functional dystrophin protein, muscles are chronically damaged and eventually replaced by fibrotic and adipose tissues, which is accompanied by loss of muscle function. In general DMD patients become wheelchair dependent before the age of 12. Later they develop respiratory and cardiac problems, which leads to premature death for most patients around the age of 30 in the Western world. Restoration of the reading frame would allow the production of a shorter but partly functional dystrophin protein as seen in the less severely affected Becker muscular dystrophy patients. Antisense oligonucleotides (AON) can induce skipping of specific exons from the pre-mRNA during splicing, thereby restoring the open reading frame. Exon skipping is a therapeutic approach currently evaluated in clinical trials.
Since the human body consists of 30-40% muscle, systemic treatment is necessarily and appeared feasible. While sufficient amounts of AON are taken up by skeletal muscle to induce exon skipping, increasing the delivery of AON to muscle and heart is anticipated to improve the therapeutic effect. Tissue specific homing peptides could help increase the uptake of AONs to target tissues. Phage display biopanning is a well-known technique to identify target specific peptides. However, this approach is not without challenges and pitfalls. We used this technique, for the first time in combination with next generation sequencing analyses, to select candidate peptides for skeletal and cardiac muscle delivery of AONs. Here we present our new insights in phage display technology and delivery of AONs to the tissue of interest.

A novel long non-coding RNA in the rheumatoid arthritis risk locus TRAF1-C5 regulates C5 mRNA levels

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MCB/Reumatology, LUMC

Long non-coding RNAs (lncRNAs) can regulate the transcript levels of genes in the same genomic region. These locally acting lncRNAs have been found deregulated in human disease. However, to our knowledge they have not been linked to the transcription of candidate risk genes in loci associated to complex genetic diseases, like autoimmune disorders. We hypothesized that regulatory lncRNAs may play a role in autoimmune risk loci that harbor multiple candidate disease genes, especially when these are known as eQTL genes. To test this we analysed the TRAF1-C5 risk locus that is associated to rheumatoid arthritis (RA) for transcription of non-coding sequences. We identified a non-coding transcript (C5T1lncRNA), intergenic of the disease candidate genes C5 and TRAF1. RA-relevant cell types express the lncRNA and transcription is under immune regulation as expression is induced by specific immune stimuli. Expression correlates with TRAF1 or C5 indicating transcriptional co-regulation, which is directly dependent of the expression of the lncRNA. Overall our data show the presence of a novel lncRNA in a genetic risk locus influencing transcript levels of flanking candidate disease genes. Similar mechanisms may be more common to other genetic risk loci than previously anticipated.

Genetic pathways in human myopia

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Purpose: Myopia is widely recognized as a multifactorial, complex genetic disorder. Recently, multiple loci for refractive phenotypes were identified separately by the Consortium for Refractive Error and Myopia (CREAM) and investigators from 23andMe, Inc. We aimed to identify additional genetic loci that explain the genetic architecture of refractive error using higher power and denser imputation by meta-analyzing data from CREAM and 23andMe.
Methods: We conducted a genome-wide association study (GWAS) meta-analysis of refractive error including 63,697 individuals (49,808 Caucasians; 13,899 Asians) from the CREAM consortium using a linear regression model. Age-at-onset of myopia for 104,294 individuals from the 23andMe dataset was analyzed using survival analysis (Cox proportional hazards model). GWAS regression results from both studies were meta-analyzed by z-scores using a fixed effects model. We performed pathway analyses using Ingenuity IPA and public databases.
Results: Over 80 regions across the genome reached genome-wide significance at P-value < 5.0x10-8. The most significant P-value was 2.74x10-54 for rs670352 near the known refractive error gene GJD2. We confirmed association with all but 2 from 36 previously reported CREAM and 23andMe genes. We identified 71 new hits for refractive error and myopia. These SNPs explain ~12% of the variance of all common SNPs for SE. The results confirm over-representation of known pathways, such as extracellular matrix, ion channel activity, and glutamate signaling but also suggest potentially new mechanisms, including signaling of calcium, VEGF and TGF-β, mitochondrial function, and apoptosis.
Conclusions: This study is the largest meta-analysis on refractive error known to date. This large catalogue of genetic variants opens up new insights in myopiagenesis.

Mechanistic insights into autosomal dominant polycystic kidney: the role of TGFβ, activins and cysts themselves

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Autosomal Dominant Polycystic Kidney Disease (ADPKD) has a prevalence of approximately 1 in 1000 individuals and the patients carry a germline mutation in PKD1 or PKD2, which leads to massive renal cyst formation and to renal failure around the age of 50-60 years.
Based on the Cre-LoxP system, we previously generated a Tamoxifen-inducible-kidney-specific-Pkd1-deletion-mouse-model for ADPKD. By varying the dosage and timing of Pkd1-deletion, several remarkable features of cyst formation were uncovered. Notably, we found that Pkd1-deletion in a limited number of kidney cells in adult mice, initially, only led to incidental cyst formation over a period of six months. However, with increasing size, the cysts chronically stimulated PKD-related signalling specifically in the surrounding tissue, which locally accelerated the phenotype. This led to a 'snow-ball' effect, which culminated in massive PKD.
Like in human ADPKD, the delayed and massive onset of PKD is accompanied by renal fibrosis, suggesting a role for the TGFβ pathway. In fact, the TGFβ pathway has been suggested before to also play a role in driving cyst formation. This was shown by increased SMAD2/3 dependent signalling, which lies downstream of the TGFβ pathway. However,

when we conditionally ablated the TGFβ receptor I (Alk5) in PKD mice, there was hardly any effect on cyst formation. This suggested the involvement of another pathway. Activins are members of the TGFβ superfamily and have been shown to elicit similar effects on SMAD2/3 dependent signalling. The expression of ActivinA and ActivinB were increased in mice with PKD. We therefore treated two distinct PKD mouse models with an Activin ligand trap and found that the treatment effectively inhibited disease progression.
Collectively, we were able to recapitulate human ADPKD in mice and show that cysts themselves are the principal trigger for a 'snow-ball' effect driving the formation of new cysts. In addition, the Activin signalling pathway is important in driving cyst formation and can be therapeutically targeted. Since several Activin-ligand traps are being tested in the clinic for various other purposes, these results might become relevant to ADPKD patients.

Discriminating somatic and germline mutations in tumour DNA samples without matching normals

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Tumour analyses commonly employ a correction with a matched normal (MN), a sample from healthy tissue of the same individual, in order to distinguish germline mutations from somatic mutations. Since the majority of variants found in an individual are thought to be common within the population, we constructed a set of 931 samples from healthy, unrelated individuals, originating from two different sequencing platforms, to serve as a virtual normal (VN) in the absence of such an associated normal sample.

Our approach removed over 96% of the germline variants also removed by the matched normal sample, and a large number (2-8%) of additional variants not corrected for by the associated normal. The combination of the VN with the matched normal improved the correction for polymorphisms significantly with up to ~30% as compared to matched normal and ~15% as compared to VN only. We determined the number unrelated genomes needed in order to correct at least as efficiently as the matched normal is ~200 for SVs and ~400 for SNVs and indels. In addition, we propose that the removal of common variants with purely position-based methods is inaccurate and incurs additional false positive somatic variants, and more sophisticated algorithms, which are capable of leveraging information about the area surrounding variants, are needed for optimal accuracy.
Our VN correction method can be used to analyse any list of variants, regardless of sequencing platform of origin. Somatic variants identified by our method are annotated with a confidence score derived from considering the ratio of full calls vs half-calls and no-calls at the locus across the CG-sequenced VN samples. This VN methodology is available for use on our public Galaxy server.

Imprinted cell survival genes drive thyroid cancer cells to maintain heterozygosity on chromosome 7

Arnoud Boot
Pathology, LUMC

Oncocytic follicular thyroid carcinomas (FTC-OV) frequently show a pattern of genome-wide haploidisation, resulting in almost genome-wide loss of heterozygosity (LOH). Remarkably, LOH of chromosome 7 is never observed. This suggests that retention of heterozygosity is important in tumorigenesis of these tumors and that tumor cells with LOH at chromosome 7 do not survive. A possible explanation could be that cell survival genes across chromosome 7 are mono-allelically expressed from either the paternal or the maternal allele, regulated through epigenetic silencing of one of the alleles. When LOH of chromosome 7 occurs, gene expression is lost, resulting in either cell cycle arrest or cell death.

The aim of our study is to identify the genes which are driving FTC-OV cells to retain heterozygosity at chromosome 7.

Using Infinium HumanMethylation450 BeadChips we generated DNA methylation profiles of 7 genomically stable FTC and 7 FTC-OV showing the genome wide haploidization and included two non-thyroid samples with LOH of chromosome 7 as controls.

All hemi-methylated sites were mapped to investigate the presence of mono-allelically expressed genes on chromosome 7. After rigorous filtering for background signals and false-positive hemi-methylation, 3 distinct regions were identified, associated with the 3 known imprinting clusters on chromosome 7. To these imprinting clusters 15 genes are annotated which were further investigated. After allele specific gene expression analysis, 6 candidate genes remained. siRNA mediated knockdown experiments were performed to mimic loss of these genes in thyroid cancer cell lines, showing the importance of these genes in for thyroid cancer cells.

Targeted apoptosis of senescent cells (TASC) against cancer and aging

Peter de Keizer
Genetics, Erasmus MC

DNA damage drives aging and promotes age-related diseases including cancer. Cellular senescence is a state of permanent cell cycle withdrawal closely linked to both processes. It can be induced within days after DNA-damaging insults as radio- and chemotherapy, or upon wound healing. Senescent cells are notoriously resistant to apoptosis, and inefficient clearance results in their accumulation with age. Given that senescence is associated with a chronic pro-inflammatory state termed the Senescence-Associated Secretory Phenotype (SASP), they are thought to negatively influence tissue homeostasis in time. Indeed, senescence has been associated with numerous pathologies and clearance of senescent cells in a genetic fashion was shown to be beneficial in a mouse model for aging. Unfortunately however, therapeutic options to counter senescence are currently lacking. This is in part because it remains unclear how damaged cells favor senescence over apoptosis. We set out to identify such molecular pivots in order to develop methods to selectively target senescent cells, something which we dubbed Targeted Apoptosis of Senescent Cells (TASC).

Here, we show that senescent cells are primed to undergo apoptosis, but execution of the death program is restrained by a molecular brake. We observed FOXO4 to be elevated in senescence and show FOXO4 to be critical for maintaining senescent cell viability. Targeting FOXO4 in a therapeutic fashion cleared senescence and reduced SASP in vivo. Excitingly, this counteracted chronic features of aging and damage-induced organ toxicity. Thus, FOXO4 is a weak-spot in senescent cell viability that may be employed to improve the healthspan of senescence-related diseases through TASC.

A novel role for dynamic microtubules in the control of stem cell fate

Sreya Basu
Cell Biology and Genetics, Erasmus MC

Our research is aimed at understanding basic mechanisms underlying cell structure and shape in health and disease. We focus on the role of the microtubule (MT) cytoskeleton and its associated proteins. We study MT plus-end tracking proteins (+TIPs), as these factors behave in a fascinating manner and are exquisitely positioned at the ends of MTs to regulate MT fate and interactions. We have found that CLASP2, a +TIP that selectively stabilizes MTs upon reception of signalling cues and that helps nucleate MTs at the Golgi apparatus, regulates multiple cellular processes, including intracellular transport, cell polarization, and migration. Previous studies in mouse hematopoietic stem cells (HSCs) have shown that the loss of CLASP2 adversely affects HSC maintenance in a manner consistent with the disruption of an organized MT network. Using fluorescence-based microscopy techniques (including live cell imaging), in combination with high throughput methods (RNA-Seq, mass spectrometry), we have now discovered a new role for CLASP2 and dynamic MTs in the regulation of a key step in the protein secretory pathway. Our current data suggest that this novel CLASP-dependent mechanism regulates both signaling and transcription in embryonic stem cells, suggesting that CLASP2 plays a role in a conserved process required for stem cell maintenance and development.

Human pluripotent stem cell derived cardiomyocytes to study the read through of nonsense mutations in the sodium channel gene SCN5A

Georgios Kosmidis
Anatomy and Embryology, LUMC

The SCN5A gene encodes the primary subunit of the cardiac sodium channel, a key ion channel responsible for the generation of the action potential upstroke in cells of the working myocardium and of the cardiac conduction system. In essence the propagation of the electrical signal in heart tissue and the maintenance of a normal heart rhythm is bestowed upon the proper function of the cardiac sodium channel. Patients with mutations on the sodium channel exhibit progressive conduction disease, dilated cardiomyopathy and a series of cardiac arrhythmias that include long QT-3 and Brugada syndrome all of which can lead to sudden cardiac death. A subset of patients with SCN5A mutations are carriers of nonsense mutations. Nonsense mutations cause premature stop codons in the gene, leading to premature termination of translation and production of truncated proteins with aberrant function. Several compounds have been shown to promote translational readthrough of premature stop codons and lead to the production of a full-length protein.

Human induced pluripotent stem cell derived cardiomyocytes (hiPSC-CMs), originating from patients carrying nonsense mutations, provide an attractive in vitro model to evaluate the efficiency of readthrough promoting drugs.
In this study we generated hiPSC lines from patients carrying the R1638X or W156X mutations in SCN5A and from a healthy individual (control), using the integration-free Sendai virus approach to deliver the four reprogramming factors. After their pluripotency status was confirmed, we effectively differentiated the lines into the cardiomyocyte lineage with a monolayer based protocol under defined conditions. Patch clamp experiments performed in single CMs, revealed a significant reduction in sodium current densities in the mutated CMs compared to wild-type control CMs. Accordingly, action potential measurements showed a significant decrease in maximal upstroke velocity (Vmax) in the mutated CMs. However treatment with readthrough promoting compounds such as gentamycin and PTC-124 did not restore their functional electrophysiological profile to control levels. Taken together, these results recapitulated in-vitro the electrophysiological phenotype of the patients, illustrated the limitations of the readthrough promoting approach as a treatment strategy and highlighted the validity of hiPSC-CMs as a model to study sodium channel related cardiac diseases.

Genome structure and hematopoietic development

Petros Kolovos
Cell Biology, Erasmus MC

The first hematopoietic and endothelial progenitors are derived from a common embryonic precursor termed the hemangioblast. At the molecular level, lineage choice and differentiation of multipotent cells to mature progeny are characterized by dynamic changes in gene transcription under the control of transcription factors (TFs). LDB1, TAL1 and GATA2/1 are TFs involved in the hematopoietic development. Here, we study their dynamics in development; both independent as well as a protein complex termed the LDB1 complex. Our study shows that LDB1, TAL1 and GATA2 control different biological processes, acting mainly independently of one another at the hemangioblast stage, whereas at later stages as a complex. Their collective and collaborative action as a protein complex is associated with important functions for the hematopoietic development and coordinates the expression of important genes encoding key hematopoietic transcriptional regulators. Our study provides fundamental new insight into how combinatorial TF function controls a complex cell-developmental process and we propose a model where the LDB1 complex acts differently depending on the co-localizing TFs. Finally, we postulate a model which controls that process and offer thoughts for the shape of the chromatin during that procedure.

MGC Symposium Lecture

Long-term Single cell quantification: new tools for old questions

Timm Schroeder
Department of Biosystems science and engineering, ETH Zurich, Basel, Switzerland

Stem cell systems are highly complex and dynamic, and consist of large numbers of different cells expressing many molecules. Despite intensive research, many long-standing questions in stem cell research remain disputed. One major reason is the fact that we usually only analyze populations of cells - rather than individual cells - at very few time points of an experiment. Tracking of individual cells would be an extremely powerful approach to improve our understanding of molecular cell fate control. We are therefore developing imaging systems to follow the fate of individual cells over many generations. We program new software to help recording and displaying the divisional history, position, properties, interaction, etc. of all individual cells over many generations. Our approaches also allow continuous long-term quantification of protein expression or activity in individual living cells. The resulting novel kind of continuous quantitative single cell data is used for the generation of improved models describing the molecular control of stem cell fates. I will discuss how we try to find answers for long standing questions in stem cell research.

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Huid- en geslachtsziekten, groep erfelijke melanomen, LUMC (Prof.dr. R. Willemze, Prof.dr. W. Bergman, Dr. F. de Gruijl en Dr. N.A. Gruis)
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Medische Statistiek: Moleculaire epidemiologie, LUMC (Prof.dr. P.E. Slagboom)
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