



MGC-Bulletin, Nr. 45, September 2011

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De MGC AIO workshop 2011 in Maastricht was weer een groot succes!



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://intranet.lumc.nl/kwo/scholing.htm>.

A course on "**Biomedical Research Techniques**" will be given 10-14 October 2011 in Erasmus MC. PhD students (and others) often experience that not all expertise for biomedical techniques they need to perform in their research project, is available in their department. The program is set up in six half day sessions and is based on: DNA, RNA, Proteome, Cell, Tissue and organ. The topics of each day are:
Day 1: primers and probes, sequencing, SNP-analysis, methylation

Day 2: RNA, RNA expression arrays, RT PCR, siRNA, data & text mining

Day 3: site visit DNA/RNA labs; proteomes, mass spectrometry

Day 4: site visit proteome labs; ELISA, cytotoxicity, flow cytometry & phage antibody display

Day 5: Applied Molecular Imaging: Ultrasound, MRI, CT, Nuclear, Optical in vivo; Microscopy: Quantitative confocal microscopy, 4 Pi microscope, FRET, FRAP & computer modeling.

This course is free of charge for all participants from the research schools MolMed. Members of the MGC receive a discount. There is a maximum of 70 participants for this course.

A course on "**In Vivo Imaging; from Molecule to Organism**" will be given 31 October – 4 November 2011 in ErasmusMC. It is open for MolMed and MGC Phd's and Post-docs (max. 20).

The course consists of lecture sessions and practical work performed by a maximum of four groups consisting of max. five participants. Subjects: Introduction to (optical) Microscopy; image analysis; novel probes for microscopy; time-lapse microscopy; FRAP; FRET; 2-photon FLIM; STED; single molecule imaging; STORM; Deconvolution; SIM; data analysis; intravital imaging; SR single molecule and Microtubule tips & tricks. This course is a collaboration between MolMed and MGC.

For a complete programme and registration, see the link at www.medgencentre.nl or go directly to www.molmed.nl

A "**SNP Course**" will be given 21-25 November 2011 in Rotterdam. The aim of this course is to give a broad introduction in SNP techniques and applications.

The course is primarily organized for PhD students and postdocs. Other participants are also welcome on a "first-come-first-served" basis. Max 60 participants. Topics: Study design, bio informatics for SNP's and hands-on-training, genotyping techniques and DNA management, data analysis, population identification and forensics; HapMap; Bio informatics for SNP's and GWA, hands-on training, applications in diseases, genetic risk factors and meta-analysis.

This course is a collaboration between MolMed and MGC. For a complete programme and registration, see the link at www.medgencentre.nl or go directly to www.molmed.nl

A course on "**Safely working in the laboratory**" will be given 8 December 2011 (English version). The following points will be addressed: safe microbiological techniques; radionuclides; carcinogenic agents; blood, viruses; radiation. The course is also open for other new personal of the MGC. The course will be given twice a year depending on the interest in collaboration with the Department VSM of the LUMC. Apply through the MGC web site: www.medgencentre.nl or through the Boerhaave website: www.boerhaavenet.nl.

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

- The "**Ensembl Workshop**" will be given 22 & 23 September 2011. This one-and-a-half-day workshop offers participants the possibility of gaining lots of hands-on experience in the use of the Ensembl genome browser but also provides them with the necessary background information. The workshop is primarily targeted at wetlab researchers.
- A workshop "**Research management for Postdocs**" will be given 25 October & 8

November 2011. This is a popular training course on four aspects of research management: time management, project management, negotiating skills, and giving and receiving feedback. You will learn by group interactions, carrying out assignments and by applying the experience you have acquired to your own work situation. A small homework assignment is part of the course. You are required to attend the full program. This course is for Postdocs only. There is also a course for PhD-students.

- A **"Basic Course in Human Genetics: Genetics for Dummies"** will be given 3 & 4 November 2011. This 2-day course will explain the basic concepts in human genetics and more in particular in "complex Genetics". This short course is also very useful as an introduction to the SNP Course.
- A workshop on **"Basic data analysis on gene expression arrays (BAGE)"** will be given 7-9 November 2011. The program features several short, concentrated presentations on various aspects of the data analysis, followed by interactive practical sessions behind the computers.
- A new workshop on **"Microscopic Image Analysis: From Theory to Practice"** will be given 16 November 2011. In addition to the OIC Course on In Vivo Imaging, the school now organized this new hands-on one-day course on Microscopic Image Analysis. During this course, the participant will (i) obtain a deeper theoretical understanding of image analysis methods, and (ii) obtain practical experience with image analysis software tools (in particular ImageJ) and learn how to use them intelligently, on their own computer. The course is intended for PhD-students and Postdocs who want to deepen their understanding of image analysis methods and learn how to use them. No prior knowledge of image processing is required.
- A workshop on **"Research management for PhD-students"** will be given 1 & 15 December 2011. This is a popular training course on four aspects of research management: time management, project management, negotiating skills, and yearly reviews ('jaargesprekken'). You will learn by group interactions, carrying out assignments and by applying the experience you have

acquired to your own work situation. A small homework assignment is part of the course. You are required to attend the full program. This course is for PhD-students only. There is also a course for Postdocs.

For detailed information & registration info www.molecularmedicine.nl

Wijzer over DNA

Voor het vijfde achtereenvolgende jaar wordt er in Leiden in Museum Boerhaave op zondag 6 november een publieks-voorlichtingmiddag georganiseerd over 'Genetica' onder de noemer 'Wijzer over DNA', waarbij dit jaar de focus zal liggen op de toepassingen van de genomiek.

Het programma bevat 3 lezingen:

- Hoe verder als je DNA bekend is? (Marjolein Kriek – Humane en Klinische Genetica, LUMC)
- DNA en het brein (Joris Veltman – Humane Genetica, Radboud UNMC)
- Veroudering: samenspel van nature en nurture (Eline Slagboom – Moleculaire epidemiologie, LUMC)

De middag wordt georganiseerd in samenwerking met het Centre for Medical Systems Biology (CMSB) en het Cancer Genomics Center (CGC).

In de week voorafgaand aan de publieksmiddag wordt op vrijdag 28 oktober, 18:00 uur in het kader van het Leids filmfestival de film 'Gattaca' met Ethan Hawke, Uma Thurman en Jude Law in museum Boerhaave getoond. De film laat een maatschappij zien waarin het mogelijk is om vooraf de eigenschappen van kinderen te bepalen. De film zal worden ingeleid door Prof. G.J.B. van Ommen.

PhD Teaching Programme Committee

Since this year 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. The first meeting of the committee will be on 22 September. (Contact email address: Nivard@lumc.nl)

MGC Promovendi Workshop 2012

Each year the MGC is organising a workshop for their PhD students and the last four years PhD students from the Institute of Genetic Medicine from the University of Newcastle are joining them.

This meeting was originally conceived to give graduate students the opportunity to present their work to their peers in a relaxed and informal environment and to promote subsequent discussions and interactions. During this meeting graduate students have the opportunity to participate in discussions about each other's field of research, presented by either posters or presentations. This meeting is also a great opportunity to meet fellow graduate students, who could one day become your future colleagues or collaborators. This years meeting from 14-17 June in Maastricht was again a great success and we would like to invite all MGC graduate students to join the 2012 meeting.

Pictures are posted on the website: <http://2011.mgcworkshop.nl/>

The MGC Ph.D.-student Workshop committee for the 19th edition is formed by Angela Helfricht, Steven Kunnen, Dave Lammers, LiuZhe, Joost Schimmel, and Ivo van Bostelen and Mohsin Wahid from Newcastle. As usual Madeleine Nivard will assist them in making the plans. We are still looking for one or two PhD students from the Erasmus MC who are interested to help in the organization of the workshop. Please contact Madeleine Nivard: Nivard@lumc.nl.

Promoties

Michelle Michels is op 14 januari in Rotterdam gepromoveerd op het proefschrift "Hypertrophic cardiomyopathy. Pathophysiology, genetics and invasive treatment". Promotoren: Prof. M. Simoons en Prof. B. Oostra.

Bart Bliet is op 2 maart gepromoveerd in Rotterdam op het proefschrift "Flotate related risk factors and orofacial clefting in human. Epidemiological and biological studies". Promotoren: Prof. R. Steegers-Theunissen en Prof. E. Steegers; co-promotor: Dr. J. de Klein.

Najaf Amin is op 23 maart in Rotterdam gepromoveerd op het proefschrift "A genetic epidemiological study of behavioral traits".

Promotoren: Prof. C. van Duijn en Prof. B. Oostra.

Shih-Cheng Chen is op 28 april in Leiden gepromoveerd op het proefschrift "Structural aspects of encapsidation signals in RNA viruses". Promotor: Prof. C. Pleij; co-promotor: Dr. R. Olsthoorn.

Barend Mees is op 1 juni in Rotterdam gepromoveerd op het proefschrift "Vascular remodeling: Just say NO!". Promotoren: Prof. H. van Urk en Prof. J. Hamming; co-promotor: Dr. R. de Crom.

N. Hahurij is op 8 juni in Leiden gepromoveerd op het proefschrift "Cardiac development. The posterior heart field and atrioventricular reentry tachycardia". Promotoren: Prof. A. Gittenberger-de Groot en Prof. N. Blom; co-promotor: Dr. M. Jongbloed.

Babet van der Vaart is op 8 juni in Rotterdam gepromoveerd op het proefschrift "Regulation of microtubule dynamics by protein interaction networks at microtubule tips". Promotoren: Prof. A. Akhmanova en Prof. F. Grosveld.

R. Vicente-Steijn is op 16 juni in Leiden gepromoveerd op het proefschrift "Development of the sinus venosus myocardium from the posterior second heart field". Promotoren: Prof. R. Poelmann en Prof. A. Gittenberger-de Groot; co-promotor: Dr. M. Jongbloed.

Karl Brand is op 22 juni gepromoveerd in Rotterdam op het proefschrift "Transcripts from the Circadian Clock-telling time and season". Promotoren: Prof. J. Hoeijmakers en Prof. B. van der Horst.

Luna Buijs-Offerman is op 22 juni in Rotterdam gepromoveerd op het proefschrift "Experimental therapy of airway remodeling and inflammation in Cystic Fibrosis". Promotor: Prof. F. Grosveld; co-promotor: Dr. B. Scholte.

Rita Op 't Landt-Slof is op 28 juni in Leiden gepromoveerd op het proefschrift "The genetic determinants of eating disorders". Promotoren: Prof. P. Slagboom en Prof. D. Boomsma; co-promotor: Dr. E. van Furth.

Alex Wollenschlaeger is op 29 juni in Rotterdam gepromoveerd op het proefschrift "DNA replication and cancer: a translational approach". Promotor: Prof. F. Grosveld; co-promotor: Dr. K. Stoeber (UK).

Kim Rutgers is op 30 juni gepromoveerd in Leiden op het proefschrift "Development of

affinity binders for non-invasive in vivo imaging of neurodegenerative disorders". Promotoren: Prof. M. van Buchem en Prof. S. van der Maarel.

Alireza Ghamari is op 7 september in Rotterdam gepromoveerd op het proefschrift "The role of cdk9 in transcription". Promotor: Prof. F. Grosveld.

Leonieke van Koolwijk hoopt op 16 september te promoveren in Rotterdam op het proefschrift "Genetic epidemiology of glaucoma". Promotoren: Prof. B. Oostra, Prof. H. Meij en Prof. C. van Duijn.

Herman van Haagen hoopt op 21 september in Leiden te promoveren op het proefschrift "In silico discoveries for biomedical sciences". Promotor: Prof. G. van Ommen; co-promotoren: Dr. P. 't Hoen, Dr. B. Mons en Dr. M. Schuemie.

Pavlos Fanis hoopt op 20 oktober in Rotterdam te promoveren op het proefschrift "Functional proteomics analysis of transcription factor networks in erythroid cells". Promotor: Prof. S. Philipsen.

Sahar Esteghamat hoopt ook op 20 oktober in Rotterdam te promoveren op het proefschrift "Erythropoiesis and hemoglobin regulation". Promotor: Prof. S. Philipsen.

Hans Heemskerk hoopt op 26 oktober in Leiden te promoveren op het proefschrift "Refinement of antisense oligonucleotide mediated exons skipping as therapy for Duchenne muscular dystrophy". Promotor: Prof. G. van Ommen.

Dolf Segers hoopt op 23 november in Rotterdam te promoveren op het proefschrift "Atherosclerotic plaque vulnerability in experimental models of atherosclerosis". Promotoren: Prof. A. van der Steen en Prof. R. Krams; co-promotor: Dr. R. de Crom.

Rejane Hughes Carvalho hoopt tenslotte op 22 februari 2012 in Rotterdam te promoveren. Promotor: Prof. S. Philipsen.

Nieuwe medewerkers

Bij de afdeling Anatomie & Embryologie (Leiden):

Annelot Kraima is per 1 mei als OIO gestart op het STW project "The virtual surgical Pelvis" in samenwerking met de TU-Delft (Dr. C. Botha)

Sabine den Hartogh is ook per 1 mei als OIO begonnen op het Rembrandt Institute

project, in collaboration with the AMC (Dr. V. Christoffels).

Dr. R. Vicente Steijn werkt per 1 juni als researcher aan de "Development of the cardiac conduction system".

Bij de afdeling Celbiologie (Rotterdam):

Guillaume Giraud is per 1 september in de groep van Frank Grosveld begonnen als postdoc.

Aniek van der Vaart is sinds 1 april werkzaam als postdoc in de groep van Gert Jansen en werkt aan de regulatie van intraflagellair transport in de cilia van *C. elegans*.

Marta Stolarczyk is op 16 mei begonnen als OIO bij Bob Scholte. Zij werkt aan het project "The role of ADAM metalloproteinase activity in chronic inflammatory airway disease, experimental treatment of Cystic Fibrosis with ADAM inhibitors", gefinancierd door het Astma Fonds.

Joke van der Meulen is per 1 augustus als analist begonnen in de groep van Frank Grosveld (Harbour Antibodies).

Maria Mikropoulou en **Ileana Cantu** zullen in oktober als nieuwe AIO's beginnen in de groep van Sjaak Philipsen. Zij gaan werken aan de regulatie van hemoglobine expressie.

Bij de afdeling Genetica (Rotterdam):

Yanto Ridwan started on June 1st as a technician on the project "Dilating versus stenosing arterial disease; identification of the genetic factors involved in aortic aneurysm formation" supervised by Jeroen Essers.

Inger Brandsma will start in September as a PhD student on the EU-funded project DDRresponse, supervised by Dik van Gent. Her research will especially focus on the balance between Non-homologous End-joining and Homologous recombination repair of DNA double strand breaks.

Kishan Naipal will also start on the EU-funded project DDRresponse as a PhD student under supervision of Dik van Gent. he will start in October and his main focus will be on analyzing DNA damage response defects in breast and ovarian cancers, for which he will develop several novel ex vivo repair assays.

Karin Thijssen will start on October 1st as a research technician in the group of Wim Vermeulen. Here she will work on the role of

Nucleotide Excision Repair in *C.elegans*, together with Hannes Lans.

Ingrid van der Pluijm will start on November 1st as a senior postdoc on the project "Dilating versus stenosing arterial disease; identification of the genetic factors involved in aortic aneurysm formation" supervised by Jeroen Essers.

Bij de afdeling Humane Genetica (Leiden):

Onderzoekers:

Kristina Hettne (projectleider Marco Roos). Kristina is aangesteld op een EU-FP7 project 'Workflow for ever'. Zij ontwikkelt computer methoden als hulpmiddel voor een beter en sneller inzicht in de genetische ontrafeling van het metabool syndroom en andere aandoeningen.

OIO's:

Mireille Schaap (projectleider Silvère van der Maarel). Mireille doet onderzoek naar de rol van macrosatellite repeat (MSR) in de epigenetische regulatie van het menselijk genoom.

Lianne van Beek (projectleider Ko Willems van Dijk). Lianne is aangesteld op een samenwerkingsproject met Frits Koning van de LUMC afdeling Immunohematologie en Bloedtransfusie. Zij houdt zich bezig met de rol van ontsteking in het vetweefsel in het ontstaan van het metabool syndroom. Zij richt zich met name op de rol van de verschillende subpopulaties T-cellen.

Irina Pulyakhina (projectleider Peter-Bram 't Hoen). Irina zal nieuwe bioinformatica algoritmes ontwikkelen ten behoeve van de analyse van next generation sequencing data.

Analisten:

Marina Ventayol Garcia (projectleider Johan den Dunnen). Marina werkt sinds 1 augustus 2011 als researchanalist bij het Leiden Genome Technology Center.

Overig

Zuotian Tatum (projectleider Peter-Bram 't Hoen). Zuotian is aangesteld als wetenschappelijk programmeur en zal onder directe leiding van Jeroen Laros werken aan de ontwikkeling van software op het gebied van de bioinformatica.

Bij de afdeling Klinische Genetica (Rotterdam):

Luna Buijs-Offerman is per 1 augustus als onderzoeker aangesteld op het project "Aneurysm mouse models".

Linda Koster is per 1 juni aangesteld op het project "Next generation sequence analyses".

Bij de afdeling Moleculaire Epidemiologie (Leiden):

Nils Bömer is per 1 juni in dienst getreden als OIO op het EU Project "IDEAL" – Integrated research on developmental determinants (Prof. P. Slagboom).

Wouter den Hollander is per 1 juni in dienst getreden als OIO op het Reumafondsproject Molecular Aspects of OA cartilage biology (Dr. I. Meulenbelt).

Bij de afdeling Pathologie (Leiden):

Onlangs is **Maurits de Vries** als OIO begonnen om in samenwerking met de afdeling KNO onderzoek te gaan doen naar klinisch-genetische en pathologische aspecten van Schwannomen in het hoofd hals gebied.

Bij de afdeling Toxicogenetica (Leiden):

Ons chromosomale DNA is met behulp van histon-eiwitten verpakt tot chromatine. Wanneer het DNA beschadigd raakt vormt chromatine een obstakel voor de efficiënte detectie en reparatie van schade. **Martijn Luijsterburg** is per 1 juli aangesteld als postdoctoral fellow in de groep van Dr. H. van Attikum. Hij zal bestuderen op welke wijze chromatine remodeling complexen helpen om beschadigd DNA in chromatine te detecteren en te repareren (FEBS gesubsidieerd onderzoeksproject en VENI subsidie).

Evelina Papaioannou has started working as a postdoc in the group of Marcel Tijsterman on a project funded by the ERC, entitled: "Developmental and genetic analysis of double-strand break repair".

Jordi Carreras Puigvert has started working as a postdoc in the group of Marcel Tijsterman on a FP7 funded project on DNA Damage Responses.

<http://www.ddresponse.eu>

Lezingen/symposia

Leidse Genetische Colloquia :

Nog niet alle sprekers zijn bekend, wel de meeste data.

October 19: spreker nog niet bekend.

November 16: Maria Yadzanbakhsh "Immunomodulation by Helminth Parasites - a Molecular and Cellular Dialogue".

January 18: Tom de Boer "Cognitive chronobiology: effects of sleep loss and clock genes on waking performance.

February 15: spreker nog niet bekend.

LGC lezingen beginnen om 16.00 uur, tenzij anders aangegeven; minisymposia and Technology Platform Presentations beginnen om 13.30 uur. Locatie: één van de LUMC collegezalen. Voor informatie: R.H.Buitelaar@lumc.nl

Frontiers of Science in the Low Countries

Deze lezingen worden gehouden om 11.30 in het Erasmus MC Faculteitsgebouw, ruimte Ee 10-24):

September 21: Jacques Neefjes "Data-based systems biology to understand and manipulate MHC class II-dependent immune responses".

October 19: Hans van Bokhoven "Genetic and epigenetic networks in cognitive dysfunction".

November 16: Piet Borst "Mechanisms of drug resistance in mouse models for mammary cancer resembling human tumors".

December 14: René Medema "Recovery from a DNA damage-induced arrest.

Deze lezingenserie wordt georganiseerd door Joost Gribnau en Raymond Poot.

JNI Oncology Lectures 2011-2012:

October 26: Owen Sansom "Investigating the interplay between Apc, KRAS and p53 mutations in mouse models of intestinal cancer".

November 23: Ugo Cavallaro "Adhesion molecules in cancer: an old story with new players and mechanisms".

January 25: Jason S. Carroll "Understanding estrogen receptor function in breast cancer".

February 22: Gerhardt Attard "Biomarker-driven therapeutic strategies for castration-resistant prostate cancer.

March 28: Sakari Kaupinnen "Targeting of microRNAs for therapeutics".

All lectures will be held at the Josephine Nefkens Institute, Erasmus MC, Room Ae-406 at 11.00 hrs. Further information at www.erasmusmc.nl/pathologie or contact

Marieke Bootsma: c.bootsma@erasmusmc.nl NKI Seminars are given at the NKI, Plesmanlaan 121, Amsterdam:

Location: Dc Auditorium, 11.00 hrs.

September 16: Steve Elledge "Adventures in human genetics".

September 23: Wolfram Goessling "Fishing for novel regulators of liver development and cancer".

September 30: Ton Schumacher "Dissecting T cell immunity in mice and men".

September 30: Keith Baggerly, title to be announced. **15:00** hrs at Room Z4.

October 7: Piet Gros "Molecular mechanisms underlying complement activation and regulation".

October 21: Peter Verrijzer "Undercover transcription factors in development and disease".

October 28: Antoni Ribas "TCR engineering and BRAF targeted therapy for melanoma".

November 4: Ron Heeren "Pathway imaging mass spectrometry: multiplexed label-free detection of molecular signals on biological surfaces".

November 9: Gustavo Leone "Pten and p53 pathways in the tumor microenvironment".

November 10: Maria Masucci "Highjacking of Ub and UbL signalling in Epstein-barr virus infection".

November 18: Nancy Hynes "Targeting signalling pathways in breast cancer". **15:00** hrs.

November 25: Maria Soengas, title to be announced.

December 9: David Barford "Structural basis for the subunit assembly of the anaphase promoting complex".

December 16: Rob Wolthuis "Mechanisms of cell division: the Be All and the End All.

Further info, also for the programme after December, at www.nki.nl

Bridge Meetings on Bio Informatics are held every second Tuesday of the month at the Erasmus MC, room Ae-4.06 around **11 o'clock** and will close off with an informative lunch for all participants.

Further info at www.molmed.nl

Sectie 'DNA herstel-mechanismen'

De volgende bijeenkomst zal plaatsvinden op vrijdag 4 november in Leiden, LUMC, aanvang 9.30 uur. Deze sectie komt ca. 1 x per 2 maanden bijeen op een vrijdagochtend, altemeerend in Leiden en Rotterdam. Coördinatoren: Leon Mullenders (☎: 071-5269600) en Jan Hoeijmakers (☎: 010-7043199).

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 Molewaterplein 60, Rotterdam. Voor meer informatie kunt U terecht bij Arnold JJ Reuser: 010-7043153; a.reuser@erasmusmc.nl.

Personalia

Mihaela Crisan (Celbiologie, EMC), postdoc bij het Erasmus Stemcel Instituut, heeft een VENI beurs verworven, getiteld "Role of pericytes during hematopoiesis in mouse embryo".

Dr. P. Gobée, Dr. D. Jansma en Prof. M. de Ruiter (Anatomie & Embryologie, LUMC) hebben van het Den Dulk-Moermans Fonds een subsidie ontvangen voor het project "Het Leids Web-platform Anatomical Terms".

Dr. M. Jongbloed (Anatomie & Embryologie, LUMC) heeft een ZON-MW subsidie binnengesleept met het project "Tracing and characterization of the cardiac conduction system; contribution of the second heart field".

Dr. Martijn Luijsterburg (Toxicogenetica, LUMC) heeft een VENI beurs verworven met het project "Elucidating the role of chromatin remodelling in the DNA damage response".

De OIO's **Maaïke van Putten** en **Menno Schut** (Humane Genetica, LUMC) hebben

ieder een fellowship van de Bontius Stichting toegekend gekregen.

Prijzen

B. den Adel (Anatomie & Embryologie, LUMC) heeft de poster award ontvangen op de ESMI conference 2011 met de poster "Molecular MRI of atherosclerosis by a scavenger receptor A1 targeted contrast agent".

Gert-Jan van Ommen (Humane Genetica, LUMC) zal op 23 september de ZonMW Parel uitgereikt krijgen. Gert-Jan neemt deze Parel in ontvangst namens de onderzoeksgroep die al jarenlang werkt aan de ontwikkeling van gentherapie voor de ziekte van Duchenne.

Overige Mededelingen

The "DOREMI" project "Low dose gene expression signature and its impact on Cardiovascular disease – LoGiC" has been funded by the EC. Projectleaders are Jeroen Essers, Dik van Gent, Jan Hoeijmakers and Roland Kanaar.

Academische Jaarprijs 2011

De Academische Jaarprijs is bestemd voor de beste vertaling van wetenschappelijk onderzoek naar een breed publiek. Het team met het meest creatieve communicatieplan ontvangt de hoofdprijs van 100.000 euro om het ingediende plan te realiseren.

'Leve DNA!' is één van de drie finalisten voor de Academische Jaarprijs 2011

Het team is een samenwerking van het Leiden Genome Technology Center, het Forensische Laboratorium voor DNA Onderzoek (beide van de afdeling Humane Genetica), NCB Naturalis, Netherlands Bioinformatics Center en de Hogeschool Leiden.

Met 'Leve DNA!' wil het team laten zien wat er met DNA kan en niet kan. Toegepast op de mens en alles wat leeft. Jongeren zijn de voornaamste doelgroep, omdat zij in de toekomst zeker met DNA technologie te maken zullen krijgen. De basis van het plan is dat het Nederlandse publiek onderzoeken mag bedenken. De onderwerpen mogen serieus zijn, of gewoon uit interesse. Iedere maand maakt een middelbare school een keuze uit de lijst met voorstellen. Die gaat

het team dan uitvoeren. Zo zet het team iedereen aan tot nadenken over DNA. Meer informatie is te vinden op: www.levedna.nl. Iedereen mag ideeën aandragen (ook als je niet meer op de middelbare school zit). Voor inspiratie, volg ons op twitter: @leveDNA. Vertel ons over je idee op: info@LeveDNA.nl. We zijn ook te vinden op facebook, onder de naam: dnA-team.

MGC Kerstkaart 2011

Ongetwijfeld zal het MGC bestuur, traditie getrouw, ook dit jaar een kerstkaart laten maken. Heeft U een voorstel voor een passende prent, dan kunt U die zenden aan

M.J.M.Nivard@lumc.nl. We zoeken een wetenschappelijk verantwoorde illustratie met esthetische kwaliteit òf een kunstwerk met wetenschappelijke inslag.

MGC-Bulletin no 46

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21th MGC-SYMPOSIUM

Thursday, September 15, 2011
Building 3, LUMC

Program 21th MGC Symposium

8.45 coffee and registration

9.30 opening: F.G. Grosveld

Chairman: F.G. Grosveld

9.35 Vanessa French: "NPHP4 Variants are Associated with Congenital Heart Malformations and Heterotaxy" (Clinical Genetics, Erasmus MC)

9.55 Eskeatnaf Mulugeta Achame: "Y chromosome lost: the *Ellobius lutescens* genome" (Reproduction and Development, Erasmus MC)

10.15 Twinkal Pansuriya: "Mutations in *XXX* cause enchondroma formation in Ollier disease and Maffucci syndrome" (Pathology, LUMC)

10.35 Jun Wang: "The identification of mutations in *ZBTB24* in ICF syndrome" (Center for Human and Clinical Genetics, LUMC)

10.55 coffee/tea

Chairman: B. v.d. Water

11.15 Raju Kandimalla: "Genome-wide analysis of CpG island methylation in bladder cancer identifies novel biomarkers for diagnosis and prediction of progression" (Pathology, Erasmus MC)

11.35 Petra Schwertman: "Identification of *KIAA1530/UV^SSA* in a SILAC-based proteomics screen for ubiquitinated complexes" (Genetics, Erasmus MC)

11.55 Anastasia Shtylik: "Replication stress at endogenous DNA damage induces premature aging" (Toxicogenetics, LUMC)

12.15 Louise von Stechow: "Identifying novel DNA damage signaling networks using a systems biology approach" (LACDR - Toxicology)

12.35 -14.00 lunch

13.35-13.55 De 'Perskamer': 'Hitting the headlines: how to write your scientific data for a broader audience' an informative meeting about a workshop that will be given in two half day sessions (for those interested)

Chairmen: L.H.F. Mullenders

14.00 Milena Bellin: "Induced pluripotent stem cells: generation of disease models" (Anatomy and Embryology, LUMC)

14.20 Marie-Jose Goumans: "TGFbeta signaling is necessary for cardiovascular progenitor cell differentiation" (Molecular Cell Biology, LUMC)

14.40 Yaser Atlasi: "Wnt/?-catenin Signaling in Embryonic Stem Cell Self-renewal and Differentiation: the role of *Tcf3*" (Erasmus MC)

Chairmen: B. Oostra

15.00 Dorota Kurek: "Enhanced self-renewal and suppression of spontaneous differentiation of epiblast and human embryonic stem cells by Wnt signaling inhibition" (Stem Cell Institute, Erasmus MC)

15.20 Ralph Stadhouders: "Dynamic long-range chromatin interactions control Myb proto-oncogene transcription during erythroid development" (Cell Biology, Erasmus MC)

15.40 Mijke Visser: "Functional genetics of common phenotypes; *HERC2* rs12913832 modulates human pigmentation by attenuating a long-range enhancer of *OCA2* expression" (Forensic Molecular Biology, Erasmus MC)

16.00 coffee/tea

Chairman: F.G. Grosveld

16.30 MGC Symposium Lecture: Prof. dr. Danny Huylebroeck: "Mouse models for studying TGFbeta family signalling" (Laboratory of Molecular Biology, Center for Human Genetics, K.U.Leuven)

17.30 drinks

18.30 - ~22 h dinner at Boerhaaveplein (building 1)

Abstracts 21st MGC Symposium

NPHP4 Variants are Associated with Congenital Heart Malformations and Heterotaxy

Vanessa French

Clinical Genetics, Erasmus MC

Congenital heart malformations are a major cause of morbidity and mortality especially in newborns and young children. Failure to establish normal left-right (L-R) asymmetry often results in cardiovascular malformations and other laterality defects (heterotaxy). Using a genome-wide linkage analysis and gene sequencing, we identified mutations in NPHP4 in patients with cardiac laterality defects from a consanguineous family. The patients had various combinations of defects that included dextrocardia, transposition of great arteries, double outlet right ventricle, atrio-ventricular septal defects and caval vein abnormalities. We then investigated 146 unrelated individuals with similar cardiac laterality defects. Forty-one percent of these patients also had laterality defects of the abdominal organs, including abdominal situs inversus, asplenia or polysplenia, midline liver and intestinal malrotation. Mutation analysis of NPHP4 in this cohort identified eight additional missense variants that were absent or very rare in control populations. To study the role of *nphp4* in establishing L-R asymmetry, we used antisense MOs to knockdown *nphp4* expression in zebrafish. Depletion of *nphp4* disrupted L-R patterning as well as cardiac and gut laterality. We show that *nphp4* is involved in the formation of motile cilia in Kupffer's vesicle, which generate asymmetric fluid flow necessary for normal L-R asymmetry. The linking of NPHP4 to L-R axis determination and laterality defects will help dissect the complex genetic composition of heterotaxy and related cardiovascular malformations.



Y chromosome lost: the *Ellobius lutescens* genome

Eskeatnaf Mulugeta Achame

Reproduction and Development, Erasmus MC



Evolution of the heterologous sex chromosomes in placental mammals, giving rise to XX female and XY male karyotypes, is associated with X chromosome inactivation in female cells (XCI) which functions in gene dosage compensation between female and male somatic cells. In addition, this evolution has resulted in silencing of the sex chromosomes in the XY body in male meiotic prophase, and drives the origin of autosomal retrogenes replacing X chromosomal genes in spermatogenesis. With the progressive loss of a meiotic recombination partner, the Y chromosome has lost most of its genes, but it has kept the male sex determining gene *Sry* and a handful of genes that are required for spermatogenesis. The X chromosome, in contrast, has a meiotic partner during oogenesis and has gained importance, now carrying more than 1000 genes. The bizarre evolution of X and Y has taken a special course in the Transcaucasian mole vole *Ellobius lutescens*. In this rodent species, both females and males have a 17,X karyotype and the Y chromosome appears to be lost.

From Illumina short reads (~110-fold coverage, raw data) we have assembled the draft genome of a male *E. lutescens* (N50 of ~10kb, and ~100kb maximum contig length). The first analysis of this genome confirms previous observations that the *Sry* gene is not detected, so that a new mechanism for sex determination must have evolved, in which a pair of autosomes may have been recruited to become a new pair of sex chromosomes. Several other Y-chromosomal genes are present in the genome, possibly located on autosomes in both females and males. The *E. lutescens* X chromosome lacks a meiotic pairing partner but

still contains some 5% of the haploid DNA. In the footsteps of the mammalian Y chromosome, the X chromosome of *E. lutescens* must have entered an evolutionary pathway of decay, accumulating deleterious mutations and losing genes in an irreversible manner. Offspring with an 18,XX karyotype has never been reported, which indicates that this is a lethal condition, probably because XCI is compromised. However, the *Xist* gene, a key factor in the XCI machinery, is still present, implying that *E. lutescens* has abandoned proper regulation of this gene or other aspects of the XCI mechanism. The present sequencing and assembly will be followed by sequencing of related *Ellobius* species with XX/XX and XX/XY female/male karyotypes. Taken together with more detailed analysis of the *E. lutescens* genome, we expect to gain much information about the evolutionary dynamics of mammalian sex chromosomes and their roles in sex determination and gametogenesis.

Mutations in XXX cause enchondroma formation in Ollier disease and Maffucci syndrome

Twinkal Pansuriya

Pathology, LUMC

In Ollier disease and Maffucci syndrome patients have multiple enchondromas in their skeleton without (Ollier) or with (Maffucci) haemangiomas. Enchondromas are benign cartilage forming tumours with PTH1R mutations in 8% in Ollier disease, whereas the genetic cause of Maffucci syndrome is unknown. Enchondromas can transform to malignant chondrosarcoma in up to 30-50% of the cases. Twinkal has sequenced three genes in 56 tumours (enchondromas and chondrosarcomas) of 40 patients and found somatic heterozygous mutations in 95% of enchondromas. These mutations are located at a single amino acid residue position. These mutations are absent in normal tissues for example, blood, saliva and muscle tissues. Using immunohistochemistry for the mutated protein we showed presence of wild type and mutated protein in the chondrocytes of the tumour lesion. This suggests presence of mosaicism in these benign enchondromas. Mutated protein was also found in surrounding normal tissues of these patients but at very low frequency. Together with the observation that tumours within one patient did not show different mutations, this could suggest germ line mosaicism. The frequency of mutations decreases with increasing histological grade in chondrosarcoma, which confirms that these mutations are an early event, and suggest that other hits are needed for progression towards chondrosarcoma, and that these other hits not necessarily occur in the mutated cells but can also occur in the wild type cells of the benign enchondroma precursor.



The identification of mutations in ZBTB24 in ICF syndrome

Jun Wang

Center for Human and Clinical Genetics, LUMC



A utosomal recessive immunodeficiency, centromeric instability and facial anomalies syndrome (ICF; MIM 242860) is a rare immune disorder characterized by recurrent, often fatal, respiratory and gastrointestinal infections. About half of ICF patients (ICF1) carry mutations in the DNA methyltransferase 3B (*DNMT3B*) gene rendering specific repetitive DNA sequences in their genome hypomethylated. The remaining ICF patients (ICF2) are *DNMT3B* mutation negative but share with ICF1 patients the same immunological and epigenetic features including hypogammaglobulinemia and hypomethylation of juxtacentromeric regions. By a combination of homozygosity mapping,

whole exome sequencing and Sanger sequencing we identified mutations in the zinc finger and BTB domain containing 24 (*ZBTB24*) gene in four consanguineous ICF2 patients, in an affected sibling pair and in one patient of whom consanguineous descent was unknown. *ZBTB24* is part of a family of transcriptional repressors that includes members with prominent regulatory roles in hematopoietic development and malignancy. FACS-sorting followed by quantitative RT-PCR analysis showed that *ZBTB24* is ubiquitously expressed with highest mRNA levels in human peripheral blood B cell subpopulations, especially in naive B cells. These data thus suggest that *ZBTB24* is involved in DNA methylation of juxtacentromeric DNA and in the development and/or function of B cells. As *ZBTB24* is a putative DNA binding protein highly expressed in the lymphoid lineage, we predict that the identification of mutations in *ZBTB24* in a proportion of ICF patients will expand our understanding of the molecular pathophysiology of ICF syndrome.

Genome-wide analysis of CpG island methylation in bladder cancer identifies novel biomarkers for diagnosis and prediction of progression

Raju Kandimalla

Pathology, Erasmus MC

Cancers of the urinary bladder (BC) present as muscle-invasive (MI) or non-muscle invasive (NMI). Major problems with NMI-BC are that 70% of the tumors will recur and 10-20% will eventually progress to MI-BC. These patients require life-long surveillance by cystoscopy. Over 50% of patients with primary or secondary MI-BC die of their disease. Cancer-associated hypermethylation is often found in CpG islands (CGIs). Consequently DNA modifications may serve as useful biomarkers, both for diagnostic and prognostic purposes. We aimed to identify DNA methylation markers as a prognostic tool to predict progression, survival and to enable detection of recurrent tumors in urine. In this study, we performed a genome wide screening for DNA methylation in different subtypes of bladder cancer with the aid of differential methylation hybridization (DMH) coupled with Agilent 244k human CpG island microarrays. We have found 731 significant probes to be more methylated in bladder tumors than in blood, which represents 392 unique CGIs. The adjacent CpG dinucleotides within a CGI were co-methylated in most of the significantly methylated CGIs. In contrast, CGIs neighboring a methylated island were usually not methylated. Extensive methylation indicative of a CGI methylator phenotype was observed in *FGFR3* wild-type NMI-BC. Most *de novo* methylated genes in bladder cancer are known targets of repression by polycomb group proteins in embryonic stem cells. CGI markers for the detection of recurrences and prediction of progression were validated in an independent set of 90 FFPE tumors on a 384-plex custom Illumina Golden Gate Methylation Assay (GGMA). We identified 110 CGIs that are differentially methylated between tumor cells and control urine and 8 of these were further investigated. This led to the identification of 3 CGIs that are able to detect recurrent and primary bladder cancer in urine with a high sensitivity and specificity. In addition, we identified CGIs that predicted progression in NMI-BC. Four of these were validated in an independent series of tumors. In summary, DNA methylation markers were identified that will help to predict disease progression and help to stratify patients for personalized follow-up. In addition, a vast number of markers were selected to employ in urine-based tests in order to reduce cystoscopy frequency.



Identification of KIAA1530/UV^SSA in a SILAC-based proteomics screen for ubiquitinated complexes

Petra Schwertman

Genetics, Erasmus MC



Nucleotide Excision Repair (NER) is a versatile DNA-repair pathway, which removes a wide variety of helix distorting DNA damages including those induced by UV-light. Two different lesion recognition pathways can be distinguished in NER; the transcription coupled NER (TC-NER) and global genome NER (GG-NER). Post translational modifications play an important role in regulating the DNA damage response (DDR). An example of this is the covalent attachment of ubiquitin, a small highly conserved protein of 76 amino acids. The importance of ubiquitination in regulating NER has been shown for several proteins in both sub-pathways; for example DDB2, XPC and RNAPol2.

To study the role of ubiquitination within the UV-DDR, we performed an unbiased proteomics screen to identify UV-dependent changes in ubiquitin modifications. SILAC (Stable Isotope Labeling with Amino-acids in Cell culture) in combination with tandem Mass Spectrometry was used for the quantitative identification of differential ubiquitinated proteins and protein-complexes. Since only a fraction of all proteins is ubiquitinated, enrichment of these proteins greatly improves the sensitivity of the detection. Immunoprecipitations (IP) were performed under native conditions using an antibody recognizing mono- and polyubiquitylated proteins (FK2).

Several NER proteins that are known to be differentially ubiquitinated in response to UV, like DDB2, XPC and RNAPol2, were identified and illustrate the validity of our selection procedure and quantitative proteomics approach. Of the identified proteins with an unknown function within UV-DDR, KIAA1530 showed the highest fold change in response to UV. KIAA1530 is a highly conserved uncharacterized protein containing a VHS- and DUF2043-domain. Live cell imaging and chromatin immunoprecipitation experiments indicate that this protein is a novel TCR-factor. In addition, different NER assays showed that knockdown of KIAA1530 closely resembled the TCR-deficient phenotype of cells derived from UV-sensitive syndrome group A (UV^SS-A) patients, a rare autosomal recessive disorder characterized by photosensitivity and mild freckling. Expression of KIAA1530 in UV^SS-A patient cells rescued the UV sensitive phenotype, indicating that KIAA1530 is the causative gene for UV^SS-A.

Replication stress at endogenous DNA damage induces premature aging

Anastasia Shtylik

Toxicogenetics, LUMC

The stochastic component of aging has been associated with unrepaired endogenous DNA damage. DNA lesions progressively interfere with protein binding, transcription and replication but also induce mutations that alter gene regulation or protein function. Both replicational arrests at unrepaired DNA damage and mutations have been proposed as causes of stochastic aging. Endogenous DNA lesions that arrest processive replication can be bypassed by error-prone translesion synthesis (TLS) polymerases, at the expense of induced mutations. Here we have investigated the roles of replicational stress and mutagenesis in aging using mice with a disruption of the key TLS polymerase Rev1. In a global-genome



nucleotide excision repair (GG-NER)-deficient background, Rev1 deficiency results in stochastic segmental progeria, characterized by atrophy of tissues with a high proliferation rate and by a simultaneous predisposition to lymphomagenesis. This is accompanied by

DNA damage responses, senescence and apoptosis as well as hypersensitivity to the oxidative DNA damage-inducing agent Paraquat, and a defect in mutagenic TLS at an endogenous lipid peroxidation DNA adduct. Unlike cells, deficient in the transcription-associated NER subpathway, no compensatory suppression of the somatotrophic axis was observed in response to DNA damage. In conclusion, our data provide evidence that replication stress at endogenous DNA damage, rather than mutagenesis, can contribute to organismal aging, whereas escape from senescence contributes to aging-related cancer. This, and related, models may aid in the identification of endogenous DNA damage types that induce aging, as well as of preventive strategies.

Identifying novel DNA damage signaling networks using a systems biology approach”

Louise von Stechow

LACDR – Toxicology



Delineating the cellular response to DNA damage is of great clinical relevance, both to better understand the mechanisms underlying the process of cancer formation, as well as to improve genotoxic cancer therapy. We explored the DNA damage response in embryonic stem cells treated with cisplatin. Transcriptomics and phospho-proteomics analysis was combined with gene-family wide RNAi screening for kinases, phosphatases, (de)ubiquitinases, and transcription factors. Bioinformatics integration of the datasets, pointed to high confidence signaling networks implicated in the DNA response. In addition to well-known networks, such as p53-signaling, additional pathways were identified, including a signaling network centered around Wnt. Validation of these networks and novel DNA-damage response modifying genes in other cell types including cancer cells is ongoing.

Induced pluripotent stem cells: generation of disease models

Milena Bellin

Anatomy and Embryology, LUMC

BACKGROUND. Long-QT syndrome (LQTS) and catecholaminergic polymorphic ventricular tachycardia (CPVT) are heritable diseases associated with lifethreatening arrhythmia leading to syncope and sudden cardiac death at a young age.

METHODS. We generated induced pluripotent stem cells (iPSCs) from i) two patients affected by LQTS type 1 (LQT1), carrying an autosomal dominant mutation in the *KCNQ1* gene, and ii) one patient with CPVT, carrying a mutation in the *RYR2* gene. Dermal fibroblasts were obtained from the patients and from healthy controls and infected with retroviral vectors encoding the human transcription factors OCT3/4, SOX2, KLF4 and c-MYC to generate induced pluripotent stem cells. These cells were then directed to differentiate into cardiac myocytes.

RESULTS. Electrophysiological single-cell analysis on LQT1 iPSC-derived cardiomyocytes identified cells with a ventricular, atrial, or nodal phenotype as confirmed by the expression of cell-type-specific markers. The action potential duration was markedly prolonged in ventricular and atrial cells derived from LQT1 patients compared to control cells. Further characterization of the specific *KCNQ1* mutation revealed a dominant-negative trafficking defect associated with a 70-80% reduction in I_{Ks} current. Moreover, we demonstrated an increased susceptibility of LQT1 myocytes to catecholamine-induced tachyarrhythmia and the effect of beta-blockade in attenuating this phenotype.



In CPVT iPSC-derived cardiomyocytes, catecholaminergic stress led to elevated diastolic Ca^{2+} concentrations and to a reduced SR Ca^{2+} content compared to control myocytes. In these conditions also an increased susceptibility to arrhythmia was observed.

CONCLUSIONS. This study demonstrates that human iPS cells can be used to model the specific pathology seen in a genetically inherited cardiac disease. As such, they represent a new strategy to study disease mechanisms, screen drug compounds for individual risk stratification and develop patient-specific therapies.

TGFbeta signaling is necessary for cardiovascular progenitor cell differentiation

Marie-Jose Goumans

Molecular Cell Biology, LUMC



Until recently, the heart was considered a post-mitotic organ without resident stem cells. However, dividing cell populations with various molecular identities have recently been detected in rodent and human hearts and termed cardiac or cardiomyocyte progenitor cells (CMPCs). Recently we developed a protocol for efficient isolation and propagation of these cells from human fetal heart and adult biopsies. In order to test the cardiomyogenic potential of CMPCs in vitro, we treated CMPCs with 5-azacytidine for three consecutive days, followed by culture in medium containing a mix of growth factors. Within 3-4 weeks, spontaneously beating cells. Despite its potent effect, the efficiency of cardiomyogenic differentiation with 5-azacytidine treatment is relatively low (13.5 %) and therefore we exposed cells to cardiogenic inducing growth factors. Interestingly, when we added TGFbeta1 and/or BMP6 after 5-azacytidine treatment, the CMPC differentiation efficiency was greatly increased (up to 95%). Furthermore, adding TGFbeta to our differentiation culture without 5-azacytidine treatment hardly resulted in cardiac differentiation. Inhibiting the TGFbeta type I receptor ALK-5 abolished CMPC differentiation into cardiomyocytes as well. In conclusion, TGFb signalling through ALK5 is necessary for cardiac differentiation of CMPCs.

Wnt/?-catenin Signaling in Embryonic Stem Cell Self-renewal and Differentiation: the role of Tcf3

Yaser Atlasi

Erasmus MC

Wnt signaling has been implicated in maintenance of pluripotency and self-renewal of embryonic stem cells although the exact mechanism is to date still controversial. Recent reports implicate that Tcf3, the member of Tcf/lef family and a component of the core self-renewal circuit is the dominant downstream effector in mouse ESCs. Tcf3 co-occupy Oct4/Nanog/Sox2 DNA binding sites and displacing the chromatin-bound-Tcf3, either by loss of function experiments or by inducing stabilized β -catenin, can enhance self-renewal in ESCs. This suggests that Wnt signalling exert its function in part by Tcf3 displacement as well as via β -catenin signalling.



By taking advantage of a set of ES cell lines carrying different *Apc*-hypomorphic alleles previously developed in our laboratory, we found that Tcf3 is specifically downregulated in *Apc* mutant ESCs, an observation that was subsequently validated by Wnt3a treatment and by specific inhibition of glycogen synthase kinase-3 (Gsk3) in wild type ESCs. To test whether Tcf3 down regulation mediates the phenotype of *Apc*-mutant ESCs, we rescued

Tcf3 expression in *Apc*-mutant background and evaluated the self-renewal/ differentiation potential of these cells by means of different *in vitro/ in vivo* assays. We found that, similar to *Apc*-mutant ESCs, Tcf3 rescued cells fail to undergo neural differentiation *in vitro* and could be cultured in the absence of GSK inhibitor in N2B27 medium supplemented with LIF and MEK inhibitor. However, Tcf3 expression, could partially rescue the neuroectodermal differentiation in teratoma assay. Our results indicate that overexpressing Tcf3 in Wnt context has limited effects on the differentiation/ self-renewal potential of ESCs supporting the model according to which Wnt signaling is the main factor in enhancing self-renewal and inhibiting differentiation despite the constitutive repressive influence of Tcf3.

Enhanced self-renewal and suppression of spontaneous differentiation of epiblast and human embryonic stem cells by Wnt signaling inhibition

Dorota Kurek

Stem Cell Institute, Erasmus MC



Murine epiblast stem cells (EpiSCs) and human embryonic stem cells (hESCs) exist in pluripotent state that is different from the pluripotent state of mESCs and both are dependent on bFGF and Activin signaling for their self-renewal. Recent findings suggested that EpiSC cultures comprise heterogeneous subpopulations of cells with distinct potency. Here we examine the possible role of Wnt signaling in the nature of this heterogeneity. We show that endogenous Wnt signals are active in EpiSCs and hESCs and that EpiSC cultures exhibit heterogeneous cell populations with distinct levels of Wnt pathway activation and signs of mesodermal differentiation. Furthermore we show that activation of Wnt signals in EpiSC positively correlates with expression of mesodermal marker Brachyury. By inhibiting Wnt signals in EpiSCs we are able to suppress this mesodermal gene expression induction. Moreover we show that inhibition of Wnt signals enhances self-renewal of EpiSCs. Importantly inhibition of Wnt signaling improves self-renewal and suppresses spontaneous differentiation of hESCs. By modulating Wnt signals in EpiSCs and hESCs we are able to restrict cells to one developmental stage and suppress undesired differentiation which can improve control of differentiation process towards desired cell types.

Dynamic long-range chromatin interactions control Myb proto-oncogene transcription during erythroid development

Ralph Stadhouders

Cell Biology, Erasmus MC

The *Myb* proto-oncogene is a key regulator of hematopoietic stem and progenitor cells, and precise regulation of its expression is essential for coordinating proliferation and differentiation. Since *Myb* transcriptional regulation remains poorly understood, we used an integrative approach combining ChIP-Sequencing and 3C-Sequencing technologies to characterize the structural and protein-binding dynamics of the *Myb* locus during erythroid differentiation. In proliferating cells expressing *Myb*, enhancers and CTCF-bound elements within the *Myb-Hbs1l* intergenic region were shown to form an active chromatin hub (ACH) containing the *Myb* promoter and first intron. Upon erythroid differentiation, *Myb* expression is downregulated and the ACH destabilized, concomitant with a loss of associated transcription complexes. A model is proposed for *Myb* activation by distal enhancers dynamically bound by KLF1 and the GATA1/TAL1/LDB1-complex, which may function as a transcription elongation element through chromatin looping.



Functional genetics of common phenotypes; *HERC2* rs12913832 modulates human pigmentation by attenuating a long-range enhancer of *OCA2* expression

Mijke Visser

Forensic Molecular Biology, Erasmus MC



Pigmentation of skin, eye and hair reflects some of the most evident common phenotypes in humans. Several candidate genes for human pigmentation are identified, and the SNP rs12913832 has strong statistical association with human pigmentation. It is located within an intron of the non-pigment gene *HERC2*, 21 kb upstream of the pigment gene *OCA2*, and the region surrounding rs12913832 is highly conserved among animal species. However, the exact functional role of *HERC2* rs12913832 in human pigmentation is unknown. Here we demonstrate that the *HERC2* rs12913832 region functions as an enhancer regulating *OCA2* transcription. In darkly pigmented human melanocytes carrying the rs12913832 T-allele, we detected binding of the transcription factors

HLTF, LEF1 and MITF to the *HERC2* rs12913832 enhancer, and a long-range chromatin loop between this enhancer and the *OCA2* promoter which leads to elevated *OCA2* expression. In contrast, in lightly pigmented melanocytes carrying the rs12913832 C-allele, chromatin-loop formation, transcription factor recruitment and *OCA2* expression are all reduced. This is the first demonstration that allelic variation of a common non-coding SNP located in a distal regulatory element not only disrupts the regulatory potential of this element but also affects its interaction with the relevant promoter. We provide a novel paradigm describing how allele-dependent differences in chromatin-loop formation (i.e. structural differences in the folding of gene loci) results in differences in allelic gene expression that affects common phenotypic traits.

MGC Symposium Lecture

Mouse models for studying TGF β family signalling

Prof. dr. Danny Huylebroeck

Laboratory of Molecular Biology, Center for Human Genetics, K.U.Leuven

We are interested in the *in vivo* functions of TGF β family signaling and how the receptors and Smads exert their multiple functions in co-operation with Smad-interacting proteins, including many transcription factors. Many of these genes/proteins are studied through using conditional knockout mice. In addition to our work on BMP receptors and the downstream proteins Smad1/5, we also intensively study Sip1 (also named Zeb2, Zfx1b). Sip1 binds to the TGF β /nodal/activin Smads2/3 and the BMP-Smads1/5/8 in ligand-stimulated cells. However, many of Sip1's functions may be Smad-independent, which points at multiple mechanisms of action. Sip1 is a zinc finger DNA-binding transcription factor that represses target gene transcription through binding with each of its two zinc finger clusters to a separated repeat of CACCT(G) in gene regulatory regions. Full-length Sip1 binds to the co-repressor CtBP and the chromatin-remodeling corepressor complex NuRD, but can become an activator by binding to P300/PCAF. Recent progress in this work, with emphasis on Sip1's role in embryonic and adult systems (CNS, PNS, hematopoiesis) in mice and aspects of which link to Mowat-Wilson syndrome in humans, and the role of Sip1 as both a repressor and activator of transcription, will be presented.



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Heelkunde, LUMC (Prof. Dr. R.A.E.M. Tollenaar)
Neurologie, groep neurogenetica, LUMC (Prof.dr. R.A.C. Roos en Prof.dr. M.D. Ferrari)
Huid- en geslachtsziekten, groep erfelijke melanomen, LUMC (Prof. R. Willemze, Prof.dr. W. Bergman, Dr. F. de Gruijl & Dr. N.A. Gruis)
Pathologie: moleculaire tumorpathologie, LUMC (Prof.dr. P.C.W. Hogendoorn, Prof.dr. J. Morreau, Dr. A.M. Cleton-Jansen en Dr. J.V.M.G. Bovee)
Medische Statistiek en Bio-informatica: Moleculaire epidemiologie, LUMC (Prof.dr. T. Stijnen en Prof.dr. P.E. Slagboom)
Anatomie en Embryologie, LUMC (Prof.dr. C.L. Mummery)
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[n.b. verbeteringen voor deze lijst gaarne doorgeven aan het secretariaat]

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