Evaluation of the

Hubrecht Institute

November 2014

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1. INTRODUCTION

1.1. Aims of the evaluation

The board of management of the Royal Netherlands Academy of Arts and Sciences (KNAW) commissioned an international peer review committee to evaluate the Hubrecht Institute for Developmental Biology and Stem Cell Research. Quality assessment of research is part of the assessment system for all publicly funded research in The Netherlands. In accordance with the Standard Evaluation Protocol 2009-2015 the aims of the assessment are:

- Improvement of the quality of research based on an external peer review, including scientific and societal relevance of research, research policy and research management;
- Accountability to the board of the research organisation and towards funding agencies, government and society at large.

These objectives are met by an evaluation that is both retrospective and prospective in character.

1.2. Review committee

The international review committee for the Hubrecht Institute was appointed in June 2014 and consisted of:

- Prof. Carl G. Figdor (*chair*) – Institute for Molecular Life Sciences, Radboud University Medical Center, The Netherlands.
- Prof. Roel Nusse – Howard Hughes Medical Institute Beckman Center, Stanford University Medical Center, Stanford, USA.
- Prof. Tom Look – Dana-Farber Cancer Institute, Harvard Medical School, Boston USA.
- Prof. Andreas Trumpp – Deutsches Krebsforschungszentrum, Heidelberg, Germany.
- Prof. Wolf Reik – The Babraham Institute, Babraham Research Campus, Cambridge, UK.

Secretary: Dr. Patricia Faasse – Rathenau Institute, The Hague, The Netherlands.

1.3. Scope of the assessment

The committee was asked to use the *Standard Evaluation Protocol 2009-2015 for Research Assessment in the Netherlands* (VSNU-NWO-KNAW, 2009). This protocol specifies the evaluation criteria for the assessment of the research activities of the Hubrecht Institute, both at the level of the institute as a whole and on the level of the individual research groups. Furthermore, the committee was asked to pay specific attention to two aspects: the focus and interdisciplinarity of research conducted at the Hubrecht Institute, and its societal relevance and societal impact. The Hubrecht Institute is one of the largest institutes of the Royal Netherlands Academy of Arts and Sciences (KNAW) and is located in Utrecht. The Institute will celebrate its 100 year anniversary in 2016. The period of assessment is 2008-2014.

1.4. Data provided to the committee

Prior to the site visit, the review committee received three documents: a report by the director of the Hubrecht Institute, a report by all individual groups leaders and a publication list of all group leaders. The first report provided information concerning the mission of the Hubrecht Institute, its structure, its financial situation, its building activities and its outreach activities, as well as a SWOT analysis. The latter two reports contained information about the publication records of all individual group leaders, currently working at the institute, and of their research programmes. Additional information on the financial situation of the individual research groups, currently and in the future, was provided at the committee's request.

1.5. Programme and procedure of the review committee

The assessment of the committee is based on the documentation provided by the institute, as well as on the presentations and discussions with the group leaders that took place during the site visit on November 10-11, 2014. Furthermore, the committee had discussions with a representation of junior researchers, post-docs and PhD students. The committee also spoke with the dean and

vice president of the executive board of the University Medical Centre Utrecht (UMC), the chair of the scientific advisory board of the Hubrecht Institute, the directors of the institute, and representatives from various societal relevant organisations. In addition, the committee visited some of the facilities of the Hubrecht Institute. In passing, the committee noticed that the new building is being constructed, according to the plans outlined in the documentation that was provided. The programme of the activities of the evaluation committee during the site visit is given in appendix 1.

1.6. Assessment scale

The review committee has used the ratings as outlined in the Standard Evaluation Protocol, to assess the institute as a whole and the individual research groups.

The ratings used are:

- **Excellent (5).** Research is world leading. Researchers are working at the forefront of their field internationally and their research has an important and substantial impact in the field.
- **Very good (4).** Research is internationally competitive and makes a significant contribution to the field. Research is considered nationally leading.
- **Good (3).** Work is competitive at the national level and makes a valuable contribution in the international field. Research is considered internationally visible.
- **Satisfactory (2).** Work adds to our understanding and is solid, but not exciting. Research is nationally visible.
- **Unsatisfactory (1).** Work is neither solid nor exciting, flawed in the scientific and or technical approach, repetitions of other work, etc.

The Standard Evaluation Protocol requires the review committee to assess the research performance on four criteria:

- *Quality*: international recognition and innovative potential.
- *Productivity:* scientific output.
- *Societal relevance:* societal quality and impact.
- *Vitality and feasibility:* flexibility, management and leadership.

2. THE HUBRECHT INSTITUTE

2.1. Mission

The Hubrecht Institute is one of five life science institutes of the Royal Netherlands Academy of Arts and Sciences. As such, it has no primary teaching duty, and no obligations to perform applied research. Researchers at the Hubrecht Institute can devote all their attention to fundamental research and are committed to pursue excellence in their research.

The central mission of the Hubrecht Institute is to perform fundamental research in the field of developmental biology, with an emphasis on the biology of stem cells. Researchers at the Hubrecht Institute study a variety of biological processes, mainly concerning the developmental biology of animals. Developmental biologists are interested in the mechanisms by which an organism grows from a single fertilized egg into a fully formed adult. This encompasses many areas, from basic (pre-)embryonic processes, such as the establishment of a body plan, to the specifics of organ growth in adult animals. Closely linked to developmental biology is stem cell research. Embryonic, fetal, adult and cancer stem cells are all subjects of study in the Hubrecht Institute. Most recently this knowledge resulted also in the development of so called organoids as physiological representations of organs in a 3D context grown from stem cells.

The Hubrecht Institute aspires to be a world leader in this field. Given its citation impact score of 2.86, which makes it internationally comparable to EMBL Heidelberg (2.98), Harvard (2.40) and MIT (2.45), the Hubrecht Institute impressively succeeds in this aspiration. It currently ranks as one of top institutes worldwide in the field of developmental biology and stem cell research.

While the Hubrecht Institute investigates basic mechanisms of development, there are numerous translational and clinical ramifications of the research program. One example is the recently established Foundation Hubrecht Organoid Technology (HUB), which aims to use organoid technology, developed at the Hubrecht Institute, for translational and clinical applications. Another example is a company called Cergentis, established in 2012, which is based on the structural genomics technology that Wouter de Laat developed at the Hubrecht Institute. These initiatives serve to demonstrate that the Hubrecht Institute succeeds in converting the advances made in its research program to practical goals.

Since 2008, the Hubrecht Institute has an official affiliation with the University Medical Centre Utrecht, in an agreement to last for 10 years. To accommodate this collaboration, additional research space is necessary. The KNAW has recognized this need, which has led to an expansion of the laboratory buildings and facilities (see also 2.3).

2.2. Structure and organization

Over the past six years, a number of significant changes have been realized at the organizational level. A new managing director, Mariëtte Oosterwegel, was recruited to the institute replacing Jos Koelman. When Hans Clevers accepted the position of president of the Royal Netherlands Academy of Arts and Sciences in 2012, Alexander van Oudenaarden was appointed as institute director. The current board consists of Mariëtte Oosterwegel (managing director), Jeroen den Hertog (deputy director research), and Alexander van Oudenaarden (institute director). The Hubrecht Institute has maintained a flat overall organizational structure.

The organization has been further simplified. At present, the *institute director* holds responsibility for the entire institute. The director is also a group leader. The *managing director* is in charge of the non-scientific service departments: she is directly responsible for the IT-, finance and personnel department, as well as for the technical and domestic service, general facilities (media kitchen, canteen, security, reception, cleaning) and communication. The *deputy director of research* is responsible for the research infrastructure; he is a group leader as well. He is directly responsible for the animal facilities, research infrastructure, coordination of master and PhD students and Intellectual Property and he serves as scientific sparring partner. The Hubrecht Institute currently hosts 18 senior and junior group leaders. They directly report to the director.

Group leaders are responsible for their group finances and hiring, and are scientifically fully independent. *Senior group leaders* are tenured and supported by a technician. When a senior group leader earns a professor position at a university (either at Utrecht University or elsewhere in the Netherlands), the institute provides the senior group leader with extra funding to recruit a graduate student. *Junior group leaders* are offered 5-6 year contracts and get support to recruit a PhD student and a technician. At the end of their contract, junior group leaders are evaluated in a transparent process by an expert peer review committee that includes international scientists. Junior group leaders are advised in practical and strategic matters by senior colleagues in a "buddy" system.

The institute strives to provide cutting-edge research facilities at low cost for the individual research groups. A nominal fee is charged for animal care and sequencing. Histology, imaging and cell-sorting services are free. All research facilities are centrally organized. However, group leaders are held responsible for running the facilities. For example, Van Rheenen, is responsible for running the microscopy facility.

Between 2008 and 2014, 15 new group leaders were appointed (Rabouille, Van Rheenen, Geijsen, De Rooij, De Koning, Creyghton, MacInnes, Knipscheer, Van Oudenaarden, Guardavacco, De Laat, Van Rooij, Kind, Kops, and Robin), of whom 6 are appointed as (part-time) professors at UMC Utrecht (Van Rheenen, Robin, Van Rooij, Rabouille, Van Oudenaarden, De Laat). Two lines of research (or groupleaders) were actively terminated. Furthermore two group leaders retired (Meijlink, Jongejan-Zivkovic) and 4 left the institute for positions elsewhere (Tijsterman, Ketting, Berezikov, Schulte-Merker). This has resulted in a net growth of 7 new research groups.

Formal communication with the directors of the Royal Netherlands Academy of Arts and Sciences (KNAW) occurs twice yearly. In addition, the supervisory board of the affiliation of the Hubrecht Institute with UMC Utrecht, which consists of two board members of the KNAW and two board members of UMC Utrecht, meets at least twice a year and the directors of the Hubrecht Institute join these meetings as observers. Moreover, there is frequent informal contact, whenever needed, on issues such as the building activities, fundraising, biotech activities, animal rights etc.

2.3. Building activities

The affiliation with UMC Utrecht in 2008 and the consequent collaborations with UMC researchers has led to a need for additional space. Expansion of the institute is being achieved in three phases.
In 2010 the fish facility was expanded, using space in courtyard between the Hubrecht Institute and the Fungal Biodiversity Centre. In the future it will be used for microinjections, but temporarily it provides space to one or two research groups.
The second phase was an expansion of the rodent facility, finished in 2013 and doubling the size of the mouse house. This new space includes a multifunctional area that can be used as an extension of the fish facility or of the mouse facility, depending on what type of space is most needed. A frog-room was has been included in the plans.

The third phase is the expansion of the laboratory building, which is in full swing now and is scheduled to be finished in August 2015. This extension will provide a 60% increase in lab and office space, as well as an increase in the number of meeting rooms. Moreover, this expansion will provide a larger canteen with sufficient capacity to accommodate all occupants of the building complex and space in the lobby for outreach activities. The expansion will be connected to the current building at all levels by hallways to ensure that the Hubrecht will remain a single entity. Two additional floors will be rented to UMC Utrecht to house research groups interested in regenerative medicine, which will eventually lead to intensified interactions between the Hubrecht Institute and UMC Utrecht.

2.4. Strategy and policy

To maintain and improve the position of the Hubrecht Institute as a world leader in the field of developmental biology and stem cell research, the board employs the following strategy:

1. It operates according to an international recruitment strategy that is focused strictly on excellence. Group leaders have full scientific freedom and receive all the positive and negative consequences of such responsibility.
2. The Hubrecht Institute employs a tenure-track system for junior group leaders.
3. The institute is equipped with the most advanced equipment (microscopes, cell sorters, DNA sequencers) managed from a well-embedded facility support.
4. It stimulates active national and international grant recruitment (including donations) to increase the critical mass of the institute.
5. It enhances collaborations with the best national and international groups in the field. Collaborations with the UMC Utrecht, and between groups within the institute are also stimulated.

To enhance collaboration within the institute, an elaborate system of communication has been implemented. Various internal meetings serve to strengthen the internal cohesion between and within the individual research groups. Besides a single, monthly meeting with all group leaders, which serves as the main, formal communication forum with the academic staff, the institute has a monthly meeting during which one of the group leaders presents the future scientific goals. In addition, there are weekly lunch meetings, during which two postdocs or graduate students present their ongoing research. These are well attended and appreciated by all academic scientists (staff members, postdocs, graduate students and technicians) present. The director also has monthly meetings with post-docs and graduate students to inform them about developments at the institute, but more importantly for them, to provide feedback to him on how to further improve the Hubrecht Institute as a workplace.
Both research groups and the personnel committee also initiate monthly social events. The board of directors aims to celebrate professional and personnel highlights with the whole institute to improve community feeling. For example, once a year at the end of New Year's speech of the institute director, 5 of our employees are awarded the Embryo award. This award is given to PhD students, post-doctoral students, scientific staff or non-scientific staff, who demonstrated extraordinary commitment to the Hubrecht Institute.

The review committee was positively impressed to see so many collaborations between the research groups within the institute. Also the PhD students and postdocs asserted their appreciation of the collaborative atmosphere. The committee concluded that the new director is very successful in creating this open and collaborative atmosphere, something that should be safeguarded when moving to the new and larger environment.

2.5. Funding policy and earning capacity

In 2013 the annual budget of the Hubrecht Institute comprised of 20 M€, of which the KNAW provides 5.6 M€ lump sum. This budget has not been increased for over a period of more than 10 years. In fact it even decreased to some extent.
The affiliation with the UMC Utrecht, initiated in 2008 by former Hubrecht director Hans Clevers and the former chairman of the UMC Utrecht board, Geert Blijham, led to an investment of 40 M€ by the UMC Utrecht to be spent during the period 2008-2018. The UMC Utrecht contribution therefore increased the core budget by about 70%. This financial injection allowed the Hubrecht Institute to effectively grow by 10 more groups during the last 6 years.

In addition, the group leaders of the Hubrecht Institute have been very effective in recruiting external research funding totalling approximately 10 M€/year (earning capacity is about 50% of total budget). These funds include many prestigious European Research Council (ERC) awards: ERC starting grants (Ketting, Tijsterman, Berezikov, de Laat), ERC consolidator grants (Robin, van Rooij), and ERC advanced investigator grants (Clevers, van Oudenaarden) as well as 4 of

one of the most prestigious Dutch research awards, the NWO VICI award (Ketting, Cuppen, de Laat, van Oudenaarden).

However, by the end of 2018 the UMC contribution as well as the internal reserves of the Hubrecht Institute will be completely spent. The review committee expresses serious concerns about the funding, also given the fact that the space occupied by the Hubrecht institute will increase by 60% when the new building will become available. The committee had intense discussions regarding this financial threat, not only with the directors of the institute, but also with the dean and the chair of the scientific advisory board. (see also section 2.9)

2.6 Research training

Together with the UMC Utrecht and Utrecht University, the Hubrecht Institute played a major role in the creation of the Graduate Program CS&D (Cancer, Stem Cells, and Development) as part of the Graduate School of Life Sciences (GS-LS). The Hubrecht as a whole and individual Hubrecht group leaders actively participate in the CS&D school by yearly organizing multiple graduate courses, including the 'developmental biology' and 'zebrafish in development and disease' courses.

The Hubrecht Institute has hosted approximately 50 PhD students at any given time since 2008 and on average, 10 PhD students have defended their thesis each year. All PhD students at the Hubrecht Institute are enrolled in the Cancer, Stem Cells and Developmental Biology (CS&D) graduate school (until 2013 known as Cancer Genomics and Developmental Biology, CGDB). For each PhD student a PhD committee is installed, consisting of a professor who acts as the thesis supervisor, the direct supervisor (if distinct from the thesis supervisor) and two members, at least one of which is not employed at the Hubrecht Institute. The committee convenes with the PhD student once per year to discuss progress of the project and to check whether the theoretical requirements (in total 14 weeks of courses/seminars over the 4-year period) are met.

During the site visit the committee spoke with 5 PhD students and 5 postdocs. The committee was pleased to hear that this group unanimously described the Hubrecht Institute as an inspiring and stimulating environment to work in. Furthermore, all those present praised its open and collegial atmosphere, as well as the challenging and internationally oriented character of the research. Also the efforts of the new director to stimulate collaboration in-between group leaders was greatly appreciated.
However, the committee observed a striking imbalance between the opportunities for training and support to the PhD students as compared to those offered to postdocs. (see 4.7)

2.7 Scientific output

Both the scientific output of the Hubrecht Institute and its impact score are impressive, as is demonstrated by publication records of the individual group leader (the full list comprises over 100 pages) and by a stable normalized impact score of about 2.9 over the past 10 years. This means that in this respect the Hubrecht Institute is comparable to EMBL (3.0) and MIT (2.5). In addition, over the past five years there has been sharp increase in the number of intra-collaborative publications. In the top 10% most highly cited Hubrecht publications, at present nearly half are the result of intra-collaborative research.

The committee acknowledges that the scientific output of the Hubrecht Institute grants the institute an outstanding position in the field.

2.8 Visibility and integration

The Hubrecht Institute is well integrated in the UMC Utrecht and Utrecht University.
About half of the group leaders have formal professor appointments at the UMC Utrecht (van Rheenen, Clevers, Cuppen, de Laat, van Oudenaarden, Kops) and at Utrecht University (Geijsen, Korswagen, van Oudenaarden). Jeroen Bakkers is in the last formal stage to obtain a

professorship at the UMC Utrecht. Two group leaders have professor positions at Leiden University (de Koning, den Hertog). Therefore, the majority of the group leaders have professor positions in the Netherlands.
In addition, three of the most recent recruits (Catherine Robin, Eva van Rooij, Geert Kops) have part-time appointments at the UMC Utrecht. These dual appointments further stimulate collaborations and improve the exchange of knowledge, expertise and sharing of equipment.

The affiliation of the Hubrecht Institute with the UMC Utrecht, has led to new collaborations and strengthened existing partnerships. One striking example is the recently established Foundation Hubrecht Organoid Technology (HUB), which aims to use organoid technology, developed at the Hubrecht Institute, for translational and clinical applications. The organoid technology also formed the basis of a successful collaboration between the Hubrecht Institute and the UMC Utrecht in the field of cystic fibrosis. The Hubrecht Institute expects that this project leads to an improvement in the treatment of patients with cystic fibrosis.

At the national level, the Hubrecht Institute is active in several consortia. An example is the recently awarded NWO Gravity program (CancerGenomiCs.nl). Internationally, the Hubrecht Institute operates in many European and international projects. Recently, a close collaboration between the Hubrecht Institute and the Skolkovo Center for Stem Cell Research, the Whitehead Institute for Biomedical Research (Cambridge, MA, USA), and the UMC Groningen was initiated. The Hubrecht Institute will work with this international team to set up a new stem cell institute in Russia.

Next to the academic achievements, the Hubrecht Institute has applied for 12 patents since 2008. Several of these patents were licensed to the HUB. Another patent laid the foundation for a spin-off company, Cergentis BV that was founded in 2012.

The Hubrecht Institute is increasingly involved in public media (newspapers, popular magazines, TV) and other community engagement activities. Group leaders of the Hubrecht also are often invited speakers by national civil society organizations such as the Association foundations for rare diseases (VSOP), Cystic Fibroses foundation (NCFS), Dutch Cancer Society (KWF), and Dutch Heart Foundation (NHS).
The Hubrecht frequently hosts (inter)national visitors of the Utrecht Science Park (USP), participates in local events (Festival Der Beschaving), collaborates on talent workshops with Utrecht Life Sciences (ULS), is going to be involved in the U-talent program from the Junior College Utrecht for secondary schools to nurture talent, provides information for exhibitions in the University Museum Utrecht (‘Down to the bone’) and is engaged in lunch seminars at Studium Generale (Cuppen, ‘Pimp your mind’; Clevers ‘Playing with genes’, ‘Building with cells’).
In addition, the Hubrecht is represented in various fund raising events organized by the Foundation Friends of the Hubrecht Institute (service clubs, JFK gala).

2.9 Challenges, ambitions and potential threats

When the new building will be ready for occupancy at the end of 2015, the institute intends to resume the recruitment of new group leaders (expected one junior group leader per year). The long-term goal is to integrate the stem cell and developmental biology groups together with more quantitative sciences (such as the physical and technical disciplines). New interdisciplinary group leaders are expected to work closely with the current group leaders. The current institute director has accumulated experience with interdisciplinary research during his time at MIT (2000-2012), where he has trained graduate students and post-docs with backgrounds in physics, biology, biophysics, engineering, computer science, and systems biology. Interdisciplinary groups or cross-disciplinary collaborations between groups can attack scientific problems that cannot be solved by groups of researchers with a uniform background.

A major threat to these ambitions however, is, as already detailed above, the insecurity regarding the financial future of the institute.

The long-term budget shows that by the end of 2018 both the UMC budget and the institute's general reserve will be completely spent.
The estimated costs for 2016 to run the institute including the new laboratory building are 13.5 M€, whereas the KNAW lump sum is only 5.6 M€.
The board of the Hubrecht Institute is currently discussing with the UMC Utrecht and the KNAW how to continue this collaboration after 2018. The board has expressed its hope that the UMC Utrecht will renew its agreement with the Hubrecht Institute and that the KNAW will increase the lump sum in the future. This would enable the institute to continue to expand its current research portfolio and to exploit opportunities provided by the new building, which is expected to be fully functional in September 2015.

To construct this new building a significant structural investment (35 M€) has been made by KNAW / UMC Utrecht and the Hubrecht Institute. With the new building the Hubrecht Institute will expand by 60%.

The review committee underscores that this expansion is essential for hosting current and new investigators, but stresses that it will be concurrently essential to raise the baseline funding that the institute receives. Such an increase will allow for the management of the new building and the newly recruited group leaders.
As already mentioned above, the committee is extremely concerned by the fact that the budget allotment from the KNAW has not been revised over the past 12 years. Another reason for concern is that the current arrangement with the UMC expires in 2018. This, together with the current expansion of the institute will lead to a significant deficit. These concerns have been extensively discussed with the board of the institute, the dean and the chair of the scientific advisory board. (see section 4.7)

3. THE INDIVIDUAL RESEARCH GROUPS

3.1. Group Bakkers

Jeroen Bakkers has been a group leader at the Hubrecht Institute since 2003 and since 2008 he has been a senior group leader. His research is focused on understanding mechanisms of cardiac development and disease using the zebrafish as a model system. His main research line is to identify genes and pathways that regulate the left-right axis and asymmetric organ development based on alterations in heart laterality (leftward position and directional heart looping). To this end his laboratory has performed several ENU-based forward genetic screens over a period of 2-3 years, resulting in the validation of 10 independent mutant zebrafish lines. These mutant lines fall into two different classes; Class I, affecting left-right axis formation and laterality of all organs: Class II, affecting heart looping without affecting laterality of other organs. Thus far his group has mapped and identified the underlying mutation in 5 of these mutant lines using classical mapping approaches and sequencing candidate genes in the genomic region. This strategy has proven very profitable, resulting in multiple publications, including Noël ES, et al in Nat. Commun last year, regarding Nodal-independent and tissue-intrinsic mechanisms controlling heart-looping chirality. He still has half of these important zebrafish mutant lines in which to map and clone the affected genes, indicating that this line of research is likely to be productive for several more years.
To identify novel genes that are expressed in a specific pattern in the zebrafish embryo (left-right asymmetry, heart field), the Bakkers group has collaborated with the Alexander van Oudenaarden group to develop a new technique that they have named RNA tomography (Junker et al. Cell 2014). This technique is based on sectioning of a whole embryo in thin (15 µm) slices within 3 different orientations and extracting and sequencing RNA from individual slices. This has been a very productive strategy and has yielded the identities of many fascinating genes whose pattern of expression suggests regulatory roles in left-right patterning and cardiac progenitor cell specification and differentiation. The in vivo assays and biologic systems that the Bakkers group has developed should prove very valuable in the evaluation of the mechanistic roles of these newly identified genes in development.

3.2. Group Clevers

Hans Clevers has made numerous contributions to stem cell biology. Among his many discoveries is the identification of Lgr5 gene as a marker for cycling stem cells in the intestine. Using knock-in mouse models, Hans Clevers has shown that Lgr5 identifies stem cells in multiple additional organs, including the stomach, hair follicles, kidney, liver and pancreas. The intestinal stem cells have been shown to be the precursors to cancer. LGRs are receptors for the R-spondin signals, all findings made by the Clevers lab.
More recently, the Clevers lab has developed culture technologies for expansion of single Lgr5 stem cells from various organs, stomach, liver, pancreas, and prostate into organoids. These organoid cultures grow in a stable manner, and can be transplanted to generate tissues in colon and liver. Stem cells can be expanded from biopsies from patients with hereditary disorders and repaired using CRISPR-mediated gene modification. Most future efforts of the lab will now be directed at exploiting the R-spondin/Lgr5-based organoid culture systems, aiming disease modelling for hereditary disorders of liver, gut, and lung. In addition, various cancers are grown into organoids and the consequences of chemotheraoy tested. Human organoids for regenerative medicine strategies, either using healthy donor organoids or by genetically modifying mutated genes using the CRISPR technology and gene is another highly promising activity.

3.3. Group Creyghton

Menno Creyghton is a tenure track group leader since 2011 who came from the Jaenisch lab where he did his postdoc. Amongst other work he identified K27 acetylation as an important

epigenetic mark for enhancers. Since joining the Hubrecht Institute he has focused on large scale identification of enhancer networks in the human brain, and has what seems a nice paper on this topic in press in Cell Reports. The proposal in this publication that there are co-regulated enhancer networks is interesting, however testing this in more mechanistic ways in the human brain appears challenging. Some of the single cell technologies (of van Oudenaarden's and especially Kind's) may help with this quest. On the other hand Menno Creyghton can now productively engage with European (or world) networks of neuroscientists to apply his type of analysis to specific patient cohorts, though this engagement apparently has yet to take place.

3.4. Group Cuppen

Edwin Cuppen is a tenured group leader since 2006 and since 2009 a 50% group leader spending the other 50% of his time as Professor of Human Genetics at the UMC Utrecht. He is an international leader in genomics of different organisms (mostly rat but also zebrafish) and human genetics and cancer, and has wide-ranging international collaborations. His productivity over the reporting period is excellent to outstanding, with senior author publications in Nature, Nature Genetics, and Cell Reports. He also is an asset to the Institute because of his connections with the UMC Utrecht and he seems to be in charge of organizing the sequencing and genomics efforts throughout Utrecht, which is invaluable.

3.5. Group De Koning

The De Koning group focuses on the differentiation of human pancreatic cells towards insulin producing beta cells to use them for the therapy of diabetes patients. In parallel to his senior group at the Hubrecht Institute, Eelco de Koning holds an appointment at the Medical School of the University of Leiden, where he runs a human pancreatic tissue bank with the goal to expend beta-cells under GMP conditions. At the Hubrecht Institute he is currently using 3D organoid technology to identify, characterize and expand human progenitors with the goal to differentiate them effectively into insulin producing beta-cells. He combines this with single cell technology including RNA-Seq to identify individual subpopulation within the beta cell lineage tree.
Eelco de Koning provides the Hubrecht Institute with an important direct clinical angle in the field of diabetes. His work is innovative at the clinical and fundamental research side and he takes advantage of the technologies developed at the Hubrecht Institute in an efficient manner. His work provides an alternative approach to the strategies using human ES cell differentiation worked on by others and thus provides him with an interesting niche and if successful with a unique angle to develop innovative treatment options for diabetic patients.

3.6. Group De Laat

The De Laat group is studying the complex transcriptional landscape of the mammalian genome. This group was the first to adapt a novel technology called chromosome conformation capture (3C) to explore DNA topology in cells of higher organisms. This group of methods became instrumental to show the direct contact of distant enhancers with its cognate gene promoters. During the last years the group has consequently further developed these technologies to address specific questions including 4C, 5C, HiC and others. Based on the development of these techniques and ideas to commercialize them, Wouter de Laat co-founded the biotech company Cergentis in 2012. In the future the group will further develop and optimize the various 3C technologies for uncovering novel principles of DNA folding and gene regulation as well as make them even more applicable for clinical diagnostics.

3.7. Group Den Hertog

Jeroen den Hertog is an established investigator at the Hubrecht Institute, having served as a Group leader since 1997 and Deputy Director for Research since 2008. Den Hertog is also a Professor of Molecular Development Zoology, Leiden University. Scientifically, he is an internationally recognized leader in protein-tyrosine phosphatase research. His long term focus is on the role of protein tyrosine phophatases (PTPs) in development, using the zebrafish as an animal model system. One current focus is on the study of mechanisms through which mutations of PTPN11/SHP2 lead to the human diseases Noonan's and Leopard's syndrome. Recent accomplishments include showing heart displacement defects induced by these mutations in a collaboration with J Bakkers (Development, 2014). He has also identified new substrates of Shp2, including PZR and FER (PLOS ONE, 2014). Another focus has been on the role of the Pten genes in hematopoietic stem cells. He has shown that Pten dependency distinguishes between two different classes of HSCs and the functional consequences of these different types of HSCs is a focus of his ongoing research. His work on Pten using the zebrafish is novel and interesting and opens up a new research area in the mechanisms through which this important tumor suppressor influences normal development and carcinogenesis. He has been very generous in sharing the unique resources he has generated with the scientific community.
In addition to his work on phosphatases, Jeroen den Hertog is engaged in a collaboration with the medicinal chemistry department at Utrecht University to identify novel bioactive small molecules derived from fungi, again capitalizing on the zebrafish system. This work has become increasingly productive over the past two years, with the identification of a new compound with antibiotic activity against methicillin-resistant Staphylococcus aureus and new compounds that inhibit the phosphatase activity of shp2.

3.8 Group Deschamps

Jacqueline Deschamps is an established senior researcher in the Hubrecht Institute. Over the past decade, Deschamps has studied how Hox and ParaHox (Cdx) genes are involved in axial patterning. Her interest also lies in the nature of upstream signals that regulate the expression of Cdx genes. Deschamps has made significant findings in the area of progenitor cell populations for embryonic trunk and posterior structure and how these cells expand during development.

3.9 Group Geijsen

Niels Geijsen is a tenured group leader since 2010 and previously held a faculty position at Harvard. His work focuses on signalling and transcriptional regulation of pluripotency states in human and in mouse. He had a very good collaborative paper with Wouter de Laat in Nature. The ongoing and proposed work on Dazl is interesting and creative. The work on ALS and on novel ESC manipulation strategies also sounds interesting.

3.10 Group Guardavaccaro

The Guardavaccaro group works on ubiquitin-mediated degradation of proteins a process involved in many decisions by cells. Daniele Guardavaccaro focuses on understanding how protein degradation and the ubiquitin-proteasome systems regulate cell growth and proliferation as well as cell migration and invasion. As a recent example of discoveries made by the Guardavaccaro lab, it was found that entry into mitotis is regulated by the phosphorylation-dependent degradation of two bHLH transcription factors: TFAP4 and DEC1. Here, the destruction of TFAP4 appears to be required for entry into mitosis during the cell cycle, and the degradation of DEC1 functions during the recovery during G2 DNA damage checkpoint.
In future work, Daniele Guardavaccaro proposes to examine the role of ubiquitin-mediated degradation in cell migration. It was argued that this aspect is less studied and that there was less competition compared to other areas of protein degradation. In other future research, it

is planned to employ an in vivo degradation assay to develop a high- throughput screen aimed at the identification of new degradation factors and pathways in the zebrafish as a model organism, using a novel reporter generated in the lab. This approach will involve an unbiased ENU-based forward genetic screen. Moreover, in a collaboration with the lab of Huib Ovaa at the NKI, modulators of ubiquitin-dependent proteolysis will be translated towards mechanism-based therapeutics.

3.11 Group Kind

Jop Kind has been recruited as a tenure track junior group leader only very recently, in 2014. He has started at Hubrecht Institute after a highly successful postdoc with Bas van Steensel at the Netherlands Cancer Institute in Amsterdam and a PhD and postdoc at the European Molecular Biology Laboratory in Heidelberg, Germany. He brings exciting and complementary single cell technology to the institute together with interesting questions on how nuclear architecture contributes to genome regulation.

3.12 Group Knipscheer

Puck Knipscheer is a new investigator at the Hubrecht Institute, having been recruited in 2011 into the position of Junior Group Leader. Knipscheer trained in DNA repair with Prof J. C. Walter at Harvard Medical School. During her postdoctoral fellowship, she co-developed a unique assay in Xenopus oocyte extracts to study the mechanisms of repair of DNA interstrand crosslinks (ICLs) under physiologic conditions in vitro.
In her own laboratory, she has used this assay to study whether the Fanconi anemia pathway plays a direct role facilitating nucleolytic incisions that actually resolve the ICLs. Using immunodepletions with antibodies against several different endonucleases her group also found that XPF-ERCC1 is of major importance for ICL repair and the unhooking incisions while MUS81-EME1 and FAN1 at most play a minor or redundant role. They also found that XPF-ERCC1 acts in close collaboration with an adapter protein SLX4/FANCP that is important for ICL localization. (Klein Douwel et al. Mol Cell, 2014). This high profile paper is particularly significant because it represents the first paper from Knipscheer's laboratory, and signifies her successful integration into the Hubrecht Institute as an independent investigator.
In addition to this research line, Knipscheer has initiated a new research line to investigate particularly stable G4 or G-quadruplex structure that forms in sequences containing 4 stretches of at least 3 guanines. G-quadruplexes have been implicated in several biological processes and could also cause problems during DNA replication, making this an important area for detailed mechanistic investigations.

3.13 Group Korswagen

Rik Korswagen is a senior investigator at the Hubrecht Institute, appointed first in 2000 and tenured in 2005. Korswagen is interested in Wnt signalling and development using C.elegans as a model system. His laboratory has made inroads into the mechanism of Wnt secretion and long range Wnt signaling. He identified subunits of the retromer complex, an intracellular trafficking complex that mediates transport from endosomes to the trans-Golgi network, as being required for Wnt signaling. Korswagen and co-workers have shown that recycling of the multipass transmembrane protein Wntless is dependent the retromer; in the absence of retromer function, Wntless is degraded in lysosomes. He collaborated with the Van Oudenaarden group in establishing that feedback control is important in regulating fine-tuned gene expression in the C. elegans Wnt pathway.

In future research, Rik Korswagen intends to investigate the mechanism and regulation of Wnt secretion in more detail using his collection of genes found to be required for Wnt signaling. He

will also try to come to an understanding of the cell biological aspects of Wnt transport in mammalian cells.

3.14 Group Rabouille

The Rabouille group attempts to understand the molecular mechanisms of the secretory pathway, mostly in Drosophila but recently also in mammalian cells. The group has uncovered how a large hydrophilic protein, Sec16 operates in the biogenesis of the endoplasmic reticulum exit sites. Catherine Rabouille and co-workers have performed a RNAi screen to identify Sec16 receptor candidates. In more recent work, the group has studied how stress granules (RNA-protein complexes) arise after nutrient deprivation. This is a mechanism of protein translation being stalled, to allow the cell to recover from stress.
Catherine Rabouille will expand her research line of stress granules, aiming to understand nutrient stress cell response also in mammalian cells and tumors. In other future work, the molecular factors that drive Sec body formation will be examined, including post-translational modifications of factors. It is also intended to understand phase transition driven by amino-acid starvation in cells.
It was also foreseen to generate mouse strains with mutations in the stress granule pathway.

3.15 Group Robin

The group of Catherine Robin studies the development of emerging hematopoietic stem cells (HSCs) in the mouse embryo. Robin has worked on hematopoiesis since the beginning of her career and made several significant contributions to the understanding of how the first HSCs are generated by the hemogenic endothelium. During her postdoctoral work with Elaine Dzierzak and subsequently as a junior group leader in Rotterdam, she contributed several seminal papers to the field, which includes the finding that the placenta is a hematopoietic organ during embryogenesis (Robin et al., Cell Stem Cell, 2009) and provided first imaging data on emerging HSCs from the aortic endothelium in vivo (Boisset et al., Nature, 2010). Catherine Robin joined the Hubrecht Institute in 2013 with an ERC consolidator grant awarded the same year. The current and future focus of her work remains on the molecular and cellular mechanisms of HSCs emergence and expansion in the embryo. In addition, the group is studying the microenvironmental niches and tries to identify HSC ancestors. To do that, top of the art technologies such as CEL-Seq and TOMO-Seq are used in collaboration with colleagues at the institute.

3.16 Group Van Oudenaarden

Alexander van Oudenaarden is director and senior group leader at Hubrecht Institute since 2012, having been a tenured Professor of Biology and of Physics at MIT previously. He is a world leader in quantitative and particularly in single cell biology. His arrival at Hubrecht Institute has already had a very substantial, exciting, and positive impact both at the director and group leader level. In particular the spirit and benefit of openness and a flat and collaborative structure is very apparent, and in a very short period of time has already resulted in high impact collaborative publications with different teams (eg Bakkers, Korswagen).

3.17. Group Van Rheenen

The group of Jacco Van Rheenen uses innovative intravital imaging approaches to study stem cells in normal tissues and cancer stem cells in disease and metastasis. He is now a tenured group leader after a successful period as a junior group at the Hubrecht. He continuously develops intravital imaging using “imaging windows” and applied this technique to answer

important biological questions including a study demonstrating the behavior of intestinal stem cells at the single cell level (Ritsma et al., 2014, Nature). In addition, his laboratory has addressed novel cellular mechanism driving tumor and metastasis formation including liver and breast cancer metastasis (Ritsma et al., 2012, Science TM; Kedrin et al., 2008 Nature Methods). His future work will use these imaging techniques in combination with molecular methods to study and manipulate Cancer Stem Cells and study the mechanisms of metastasis and therapy resistance.

3.18. Group Van Rooij

Eva van Rooij is an established investigator who was recruited in 2013 as a junior group leader and associate professor at the Hubrecht Institute and the University Medical Center Utrecht. She trained in molecular cardiology with Dr. Eric Olson. co-founded miRagen Therapeutics. She was very productive and published extensively during her tenure in industry. Since accepting a position at the Hubrecht Institute in 2013, she has competed successfully for several large grants and she has quickly built a group studying distinct research lines related to molecular mechanisms of cardiac disease and strategies for its treatment.
Her first research line is to explore opportunities to stimulate or boost the repair mechanisms that are endogenously present in the heart, with the ultimate aim to enhance cardiac regeneration after an ischemic insult. Her focus is on three main strategies: i) enhancing cardiomyocyte survival, ii) improving the recruitment and homing of stem cells and iii) improving the efficiency of stem cell mediated repair of the damaged tissue. These are very important studies given the prevalence and severity of myocardial infarction as a clinical problem.
Her group at the Hubrecht Institute recently published its first paper regarding systemic delivery of a mimic that can serve to therapeutically increase the level of a microRNA to block pulmonary fibrosis (Montgomery et al. 2014 EMBO Mol Med). This is an encouraging development and indicates that her laboratory is already functioning at a high level.
In a collaboration with the Clevers lab, Van Rooij and her group will also explore the involvement of Wnt signaling in heart injury. The Wnt target genes Lgr5, Lgr6, TNFRSF19 and Olmf4 (which mark specific stem cells in intestine, stomach and skin) are not expressed in the adult homeostatic heart. However, data from Dr van Rooij's group indicates that ischemic injury in the heart activates Wnt signaling and the transcription of target genes, like Lgr5 and Olfm4. Her group is now performing lineage tracing experiments to explore whether WNT signaling leads to a new cardiac population of progenitors that is induced upon heart injury.

Conclusions and Recommendations

4.1 Overall assessment of the scientific standing of the Institute

The international review committee regards the Hubrecht Institute of outstanding scientific quality. When Hans Clevers accepted the position of president of the Royal Academy of Arts and Science in 2012, he succeeded in recruiting Alexander den Oudenaarden as his successor as institute director of the Hubrecht institute. The committee considers this choice an excellent one. Although Van Oudenaarden has been institute director of the institute for only two years, his influence already is clearly visible. All those interviewed by the committee referred to the many collaborations he initiated and stimulated, and to the open atmosphere surrounding the academic work within the institute. In addition, 14 new group leaders have been appointed during the past six years, which contributes to the maintenance of a dynamic academic environment. The groups consist of relatively young people (the average age is 30 years old), and are international in orientation (employees represent over 40 nationalities).

In the opinion of the committee, the quality of science done at the Hubrecht Institute is equal to that of the best research institutions in the world. In comparison to institutions such as the EMBL in Germany, or Stanford in the US, or the Welcome Trust laboratories in the UK, the Hubrecht Institute is performing at least at the same level in terms of scientific innovation and research output.

4.2 The scientific program, productivity and its quality

The institute director stimulates more interdisciplinary work in order to be able to attack scientific problems that cannot be solved by groups of researchers with a uniform background. The committee welcomes this initiative and fully supports it.
At the same time, the committee noticed that the Hubrecht Institute is getting increasingly involved in disease-oriented science, including cystic fibrosis, diabetes and cancer. The committee views this direction as an important and commendable development. However, the committee strongly suggests that the Hubrecht Institute should strive to maintain the strong basic science program for which the institute is famous. New cutting edge technological developments and expansion of multi-disciplinary approaches, which strongly focus on basic science, will remain the basis for future advances in clinical diagnostics and therapeutics.

4.3 The educational program and its quality

The Hubrecht institute is well integrated and actively participates in the graduate school system of Utrecht University. PhD students were very happy with the current system that seems to operate very well and stimulates collaborations with other parts of the university.

With respect to the coaching of junior investigators, the committee learned about a “buddy” system. The intention is that a senior investigator meets regularly with the junior, to provide guidance on funding opportunities, writing papers and mentoring. While this is commendable, the committee came to understand that the system is rather passive, as it depends on the junior faculty member actively seeking advice, rather than on the senior faculty member taking the initiative. The system would benefit from more structured regular meetings of junior group leaders with their buddy.

The committee also observed a striking imbalance between the opportunities for training and support to the PhD’s as compared to those offered to postdocs. It recommends to correct this imbalance and to support and structure current and ad hoc initiatives taken by the post docs. This includes assistance in writing grants, career development, and institutional policies on attending international conferences.

4.4 Relevance and societal impact

The recently established Foundation Hubrecht Organoid Technology (HUB) aims to use organoid technology for translational and clinical applications. It also formed the basis of a successful collaboration between the Hubrecht Institute and the UMC Utrecht in the field of cystic fibrosis. The committee was pleased to learn that the Cystic Fibroses Foundation (NCFS) considers the HUB a valuable instrument in helping improve the treatment of patients with cystic fibrosis, also by providing them with a broader platform to create awareness for this disease.

The committee also highly values the intensifying connections between the Hubrecht Institute and national civil society organizations such as the Association foundations for rare diseases (VSOP), Cystic Fibroses foundation (NCFS), Dutch Cancer Society (KWF), and Dutch Heart Foundation (NHS). These connections may help shortening the time lag that traditionally exists between the fundamental, interdisciplinary research as it is carried out at institutes like the Hubrecht Institute and the translational and/or clinical research as it is carried out at for example the UMC Utrecht. The committee encourages the shortening of this time span – yet strongly discourages the Hubrecht Institute from diverting away from its present and successful direction, which is to perform basic and fundamental research in developmental biology and stem cell research.

4.5. Infrastructure and Management

The committee has noticed inequalities in the funding capacities between the individual research groups. Some groups simply are more successful than others when it comes to fundraising. At the same time, the committee acknowledges that funding agencies like NWO have diminished budgets for basic research, while the Vernieuwingsimpuls (the system of Veni, Vidi, and Vici grants) is only available to researchers within a limited time span, and success rates in general are dropping. Competition is getting more severe.
Although the committee is in no position to judge NWO's general funding policies, it is deeply worried about the diminishing budgets for basic research in the Netherlands in general. It also recommends that the successful UMC affiliation with the Hubrecht Institute, which at present expires in 2018, should be renewed. At the same time, the KNAW should adjust its annual contribution significantly, in order to guarantee a healthy financial situation for the Hubrecht Institute. The current limited core funding available for the Hubrecht Institute is regarded as insufficient, and a major threat, also in view of the on-going expansion of the institute.

The new building will allow for new groups to enter and to expand the research programme of the Hubrecht Institute. However, it also might lead to a decrease in the intensity with which many groups now collaborate. The board of directors should remain alert and continue to stimulate inter-group collaborations, even when these groups have moved to the new building.

Groups that perform technologically innovative research have difficulties in finding relevant information on technology transfer procedures. The committee thinks this is poorly organized at the moment. The committee recommends the establishment of a technology transfer office with expertise in this area within the Hubrecht Institute.

The committee perceived that the current Scientific Advisory Committee makes limited contributions to the institute. The main role of the SAC is restricted to giving advice on for tenure appointments.

4.6 Overall scoring

The committee has based its findings on an evaluation by the director and the individual group leaders, the lectures of the group leaders, discussions with the group leaders and with the post docs and Ph.D. students.
The committee decided to score the institute as a whole according to the SEP protocol and make recommendations at the institutional level. Scoring and recommendations at the individual group

leader level were made available to the director of the Hubrecht Institute.

- *Quality*: international recognition and innovative potential. 5
- *Productivity:* scientific output. 5
- *Societal relevance:* societal quality and impact. 5
- *Vitality and feasibility:* flexibility, management and leadership. 5

4.7 Recommendations

Recommendation 1: The Hubrecht Institute is the flagship institute of the KNAW and should be funded at a level commensurate with its premier national and international standing.

Recommendation 2: The Hubrecht Institute should maintain its focus on basic research, particularly when connections with UMC Utrecht and other societal relevant parties intensify.

Recommendation 3: With regard to the “buddy system”, the committee recommends that the Hubrecht Institute implement a system of more structured regular meetings of junior group leaders with their buddy, and to provide more structural assistance to postdocs in career development.

Recommendation 4: Technology transfer is poorly organized at the moment. The committee recommends the establishment of a technology transfer office with expertise in this area within the Hubrecht Institute.

Recommendation 5: The committee recommends more involvement of the SAC in matters such as giving advice on future research directions of the institute and that the SAC has more regular meetings with the senior leaders of the institute.

Appendix 1

Program ***site visit Hubrecht Institute***

Sunday 9 November 2014		
	Committee members: arrival at hotel	Apollo Hotel Utrecht City Centre
19.00-21.30	Committee members: dinner	Oudaen, Oudegracht 99, Utrecht

Monday 10 November 2014		
08.30-08.45	Arrival and coffee/tea	Board room
08.45-09.15	Alexander van Oudenaarden - General introduction	Board room
	Presentations group leaders 10 minutes; Q&A/discussion 10 minutes	
09.15-09.35	Alexander van Oudenaarden - Quantitative biology of development & stem cells	Board room
09.35-09.55	Catherine Robin - Hematopoiesis and stem cells during embryonic development	Board room
09.55-10.15	Jacco van Rheenen - Cancer biophysics	Board room
10.15-10.30	Break	Board room
10.30-10.50	Eelco de Koning - Diabetes and islet neogenesis	Board room
10.50-11.10	Jacqueline Deschamps - Genetics of morphogenesis during axial elongation in the mouse embryo	Board room
11.10-11.30	Edwin Cuppen - Genome biology and medical genetics	Board room
11.30-11.50	Wouter de Laat - Biomedical genomics	Board room
11.50-13.05	Lunch / Opportunity for site visit team to evaluate	Board room
13.05-13.25	Rik Korswagen - Wnt signaling in development and disease	Board room
13.25-13.45	Puck Knipscheer - Molecular mechanisms and regulation of DNA repair	Board room
13.45-14.05	Daniele Guardavaccaro - Ubiquitin ligases and cancer	Board room
14.05-14.25	Jop Kind - Spatiotemporal regulation of genomic function	Board room
14.25-14.40	Break	Board room
14.40-15.20	Opportunity for site visit team to talk to junior group leaders and to visit the laboratories	Board room & institute
15.20-16.05	Opportunity for site visit team to talk to a number of PhD students and postdocs	Board room
16.05-16.15	Break	Board room
16.15-16.45	Opportunity for site visit tem to talk to Frank Miedema, dean and vice president executive board UMC Utrecht	Board room
16.45-17.15	Opportunity for the site visit team to talk to René Medema, chairman of the scientific advisory board & chairman board of directors Netherlands Cancer Institute (NKI)	Board room
17.15-18.00	Opportunity for site visit team to talk to representatives from societal relevant organizations (Jacquelien Noordhoek, Dutch Cystic Fibrosis Foundation (NCFS) & Mariëtte Driessens, Association Foundations for Rare and Genetic Diseases (VSOP)	Board room

	and Mariëtte Oosterwegel on outreach	
19.30-	Dinner	Den Draeck, Oudegracht 114, Utrecht

Tuesday 11 November 2014		
08.45-09.00	Arrival and coffee/tea	
	Continuation presentations group leaders	
09.00-09.20	Jeroen den Hertog - Protein-tyrosine phosphatases in development	Board room
09.20-09.40	Eva van Rooij - Molecular cardiology	Board room
09.40-10.00	Catherine Rabouille - Secretion regulation	Board room
10.00-10.20	Menno Creyghton - Neuro epigenetics	Board room
10.20-10.55	Break	Board room
10.55-11.15	Niels Geijsen - Stem cell modeling of human genetic disease	Board room
11.15-11.35	Jeroen Bakkers - Cardiac development and genetics	Board room
11.35-12.00	Alexander van Oudenaarden - Future perspectives	Board room
12.00-12.20	Hans Clevers - Lgr5 stem cells, Wnt signaling & cancer	Board room
12.20-13.00	Lunch	Board room
13.00-13.30	Meeting site visit team with directors	Board room
13.30-15.30	Preparation of draft report	Board room
15.30-16.00	Presentation of preliminary conclusions to directors and group leaders. Theo Mulder will be present too	Board room or auditorium
16.00-17.00	Drinks/informal meeting with Hubrecht employees	Canteen