Connecting Development and Late Life Health

Epigenetic mechanisms and beyond

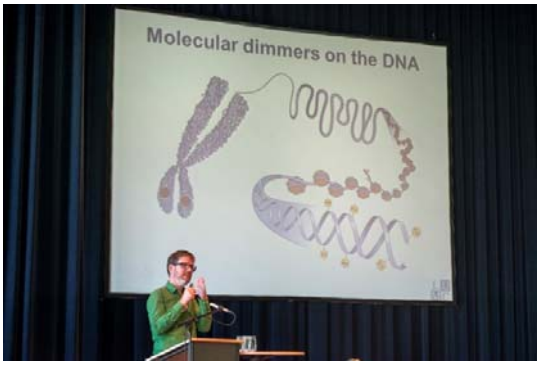
October 12-14, 2015, Meeting venue: Stadsgehoorzaal Leiden, Aalmarktzaal, Leiden, The Netherlands

Summary of three days interaction with IDEAL stakeholders

Session 1: Developmental exposure, phenotypic and clinical consequences

Program day 1 - Monday October 12, 2015

- **Prof. Eline Slagboom (LUMC, coordinator IDEAL consortium)** Introduction
- **Key note: prof. Mark Hanson, University of Southampton**: DOHaD and its relevance across the life course for global health
- **Anastasia Nyman, KI**: IVF: what are the consequences?
- **Urs Meyer, ETH Zürich**: Prenatal exposure to infection, early and late consequences in mice
- **Bas Heijmans, LUMC**: The prenatal epigenome and studies into long-term health
- **Ruth Müller, Munich Center for Technology in Society**: Experience, Exposure and the Epigenome. Mapping the Social and Ethical Aspects of Epigenetic Approaches to Public Health



Plenary discussion session 1:

Must we promote the general public to take a life-course perspective, that starting in early life development is essential for promoting healthy ageing? The answer of the audience in this matter was: "Yes". Clinicians always say: "Preventing is better than curring", and this holds up for healthy ageing. In order to deal with problems at late life we have to somehow intervene during development, maybe even before conception. The bottleneck in this is the question about how to stimulate this way of thinking for the general population. It means that the overall public opinion needs to be changed; we need to create some way of awareness for healthy ageing.

The general public has taken up the issues on e.g. security of their passwords, the bankers and resulting economic downturn and the climate change, and they get angry about it because it affects their daily life. But they seem to be kept down about their health or the future of their children. But if you ask them, they say: "Yes, we want to have healthy children". We have to make our policymakers understand the importance of the questions and of the information that is available, by getting engagement by the public.

Nevertheless, it is also the task of scientists to communicate better to the outside world. They need to explain in laymen's speech what the normal individual should do to commence healthy ageing at early age. But who is the target for 'healthy-ageing'? Is this targeted at the elderly or at the youngsters of the population? In other words, at which moment of life course do we start informing the public? Should this also be done at old-age, and not just for the next generation? Especially in lower social-economic classes it is very difficult to intervene at the right time, because they don't participate well. An solution would be to make science 'sexy', in order to permeate. As a tool we could think of utilizing 'popular TV' and 'target-specific' role models.

A similar extend of difficulties in informing the general public is encountered with Assisted Reproductive Technology (ART) and the long term effects on the offspring. We know that there are some late life effects, and that ART-children are born with a lower birth weight and preterm, and we know that this may have an effect later in life. Although ART has brought lots of happiness to parents that otherwise would not have gotten children, it is important to inform the users of the ART-technique about the possible negative effects later in life. The problem is that you can tell average Joe, that he has an increased risk of 5%, but he doesn't know what these 5% mean to him. This needs to be communicated better, with clear examples. The most mentioned advice by the audience, to accomplish this is that pro-activity of the scientists is demanded in this issue.

Program day 2 - Tuesday 13, 2015

Session 2: Clinical views and hopes

- **Key note: Prof. Sicco Scherjon, UMCG**: Introduction to the clinicians view and hopes
- **Christianne de Groot, VUMC**: Preeclampsia and late effects
- **Kaare Christensen, SDU**: It ain't necessarily so - twin studies chalenging DOHAD
- **Bas Zwaan, WUR**: Does the link between development and ageing make sense in the light of evolution?

Plenary discussion session 2

"Awareness of programming effects leads to improvements in clinical care politics." This statement is broadly supported by both researchers and clinicians. Additionally, it was stated to look also at trans-generational (programming) effects. In this context, it was mentioned what epigenetics could bring to the clinic. In other words, how would knowledge of this field of expertise improve clinical care politics?

Maybe of greater importance than to answer this question is to know where our focus should be on concerning epigenetics. Should we, for example, focus on epigenetic changes as a result of pollution, or as a result of overweight? Nontheless, as researcher and clinicians we should create awareness among the general population to be able to implement the answers that epigenetics will give us to improve our health.

While the environment is temporal, the effects may be intra- (early postnatal life exposure), inter- (maternal and paternal) and trans-generational. Translation of this research to the a individual is not always possible and moreover, there is a difference between group/societal and the individual level. This is also because science only focusses on whole populations. Exampling: What does "morbidity risk" mean for short term health improvement? Moreover, some interventions were proven to NOT have an effect on health or reproduction. Small changes only work for individuals; we need large shifts for the population to see an effect (e.g. GOTO-study). We thus have to optimize the way we must interpret these results. Furthermore, we have to take it, as a society, more seriously.

The second statement: ***"Using pregnancy, and even "failed" pregnancy as a tool for identification of disease in later life is a baised selection"***, is acknowledged as being true. The overall tendency is that the selection is done to late in time to recognise women with problems later in life. At the same time, the clinicians point toward the problem that these patients are not recognized as such earlier in time and, therefore, difficult to include a t a different point in time.

But how do we pick out the women (and children) at risk? Before pregnancy? The solution should be to invest more in life-style education. Nevertheless, it is questioned by the audience whether this is what the general public wants. We, researchers and clinicians, have to create awareness among the public, but how well will this work in practice? Everybody knows that being too heavy is bad, nevertheless more and more people are getting overweight.

Regarding the third statement: ***"Why so few health scars late in life for twins, despite severe growth restriction in the third trimester"***, it is stated that researcher sometimes just have to be amazed by the extreme robustness of the measurements and not only be focused on the small differences.

Maybe, the use of birth weight as a proxy for growth-defects isn't the right one. At least it is questionable. Maybe Information on the mother should be incorporated as well to create a better overview on whether we can explain why there is a discordant birth weight. Because, If there is no assignable cause for abnormal birth-weight, than you have a problem. This will probably have late life consequences.


Session 3: Effects of Prenatal and Nutritional Exposures

- **David Gems, UCL**: Evolution of sexually dimorphic longevity in humans
- **Wilma Steegenga, WUR**: Reversible and irreversible diet-induced effects in the liver of aging mice
- **Karen Lillycrop, University of Southampton**: The effect of diet and generation on the ageing phenotype
- **Denis Duboule, EPFL**: Mechanisms Underlying the Organization of Epigenetic Set-Points at Hox Genes Loci
- **Key note: Prof. George Davey Smith, University of Bristol**: Life course Epidemiology and epigenetic mediators

Plenary discussion session 3

"The conventional wisdom that the underlying ageing process is "normal" and not pathological is not supported by science." The process of ageing as being something normal and natural and not something pathological is something that is taught to medical students. But from a biological perspective it is impossible to understand what this "normal and natural" process is. So Instead of being natural, it should be seen as a complex disease syndrome. Nonetheless, we should be careful with using terms as natural and normal in terms of ageing and disease.

But if ageing is a disease and not a natural process, at what age does this disease start? Already at the two cell stage, or later in the process? It is very difficult to answer this question, since do not really understand the biological process of ageing. There is not a single starting point in this aetiology, as with for example infection. There are many small processes happening that contribute to the pathology of ageing.

"Healthy diets can significantly improve vitality in old age. Any time is a good time to start with a healthy diet." Recent data showed that even exposed individuals, that were on a fat-diet for a long time, significantly improved their health parameters at older age. So the main message was: "you're never too old to start living healthy". Nevertheless, although the majority of the health parameters show plasticity at older age, some of them are of irreversible nature. So it is important to understand that waiting until older age also brings risk for irreversible damage.

"The impact of unhealthy lifestyles increases every generation." No discussion

"Epigenetic memory can be easily erased by gene activation, raising the question of causality" Denis Deboule elaborates on a lot of things, except on the statement.

Program day 3 - Wednesday October 14, 2015

Session 4: Late effects: The role of the genome in age-related disease and lifespan regulation.

- **Key note: Prof. Eline Slagboom, LUMC**: Omics biomarker studies connect development , ageing and longevity
- **Ingrid Meulenbelt, LUMC**: The thyroid pathway in OA linking early and late life
- **Laurent Sachs, CNRS**: Stress sensitivity of limb development in *Xenopus tropicalis*
- **Key note: Prof. Silvère van der Maarel, LUMC:** Facioscapulohumeral muscular dystrophy: a metastable epiallele disease?


Plenary discussion session 4

"If we cannot classify those over 70 years, interventions promoting healthy ageing will essentially fail." Elaborating a little bit further on this statement it is pointed out that, up to today, there is no evidence based medicine for people above 70 years of age. So in the part of the population in which the problems/diseases appear most often, we do not have a proper classification of patients groups, hampering the treatment of this highly heterogeneous population. This due to the fact that the older we become, the more we differ from each other as a result of life.

It is brought up by the audience that we could learn from biographical life course analysis in which we take into account the way the elderly have lived and the things they encountered during life, to somehow correlate that with responsiveness to treatment. Nonetheless, there is already a lot of attention on quality of life aspects in treatment of the elderly, especially regarding the medical practical point of view. For example, there is a lot of collaboration, especially with nursing home doctors, about how the end stage of life could be organized. But there is more attention needed for what the elderly would actually want themselves.

A way to get a better view on what the population wants/needs, cohorts like the "1946 cohort" are needed to figure out what effects of development are on later life. These kinds of cohort studies will bring the connection between 'before' and 'after' treatment. An alternative is to perform intervention studies on the elderly, like in the GOTO-study, to make classifications regarding treatment options. This way we could actually try to treat people before they get ill.

But will we get an outcome of these studies; in other words will we be able to discriminate groups, keeping in mind the selection shadow, since this can be very heterogeneous in mechanisms. The principle of selection shadow puts forward that different mechanisms lead to similar phenotypes, so we must be cautious in our expectations. Heterogeneity of ageing can be the outcome of a complex biological system, and this could be a results of tiny differences in environment. Nonetheless, everything could be stochastic, but we are not able to tell at the moment. A problem in humans is that the genetic background is only measured by the genetic variation and not by quantitative molecular profiles after challenges.

“For elderly individuals only biomarkers detecting the dynamics of ageing will be useful, not developmental clock markers.” The effect of developmental clock markers have proven their purpose, but it was found that they level off as you are studying mortality at older ages. So wouldn’t it be better to use epigenetics as a marker for the higher environmental influences, instead of developmental or genetic influences? More practically, did the fundamental research as performed in work-package 1 (Ingrid and Laurent) brought us closer to such a biomarker or did it give us more biological mechanistic insight?

This question is answered with the statement that biomarkers are seen as the golden standard that you want to reach when it comes to applied research. But sometimes fundamental research is too much focused on 1 gene. Geneticists think that there is a master-gene regulating everything, but that is probably not the case. We know that we have to look at homeostasis of whole gene-networks but this than brings about the difficulty to identifying one single biomarker. Furthermore, for now we are looking into the pathological processes but not yet into the phenotypes. As soon as we have the right individuals selected we can try to find markers that classify these patients.

“Loss of epigenetic control due to environmental hazard determines irreversible pathology in elderly.” This statement is supported by the argument that there is an increasing number of events with life that need a certain amount of epigenetic plasticity to cope with these environmental stresses. With age these shifts in plasticity result in irreversible pathology. Maybe researchers should start with identifying (epigenetic) biomarkers to determine which individuals will develop disease later in life.

As an example, osteoarthritis is put forward. It is questioned by the audience when are these people tested to actually be at risk? People are currently sent home when they come in with joint complains, but we should actually treat them to prevent progression. Nonetheless, clinicians need to use common sense because they do not have biomarkers yet. They ask the researchers: how could we quickly help people with OA?

This shows the still existing gap between research and the clinic, since this is not yet possible. To close this gap in the future, we need to challenge ourselves to get stimulated, but not when there is damage. On one hand, you have the irreversible effects, and on the other hand it is also good to challenge the system to reverse. We should focus on how to stimulate reversible changes, not irreversible ones.