A summary of the 2nd NO-Age International symposium: 'Genomic instability in human brain'

Amund Hov[1], Ruben Gudmundsrud[1], Brian C. Gilmour[1], Hilde L. Nilsen[1,2], Jon Storm-Mathisen[1,3], Linda H. Bergersen[1,4,5], Evandro F. Fang[1,2]

[1]The Norwegian Centre on Healthy Ageing (NO-Age), Norway
[2]Department of Clinical Molecular Biology, University of Oslo and Akershus University Hospital, 1478 Lørenskog, Norway
[3]Amino Acid Transporters Lab, Division of Anatomy, Department of Molecular Medicine, Institute of Basic Medical Sciences (IMB) and Healthy Brain Ageing Centre (SERTA), University of Oslo, NO-0317, Oslo, Norway
[4]The Brain and Muscle Energy Group & Electron Microscopy Laboratory, Department of Oral Biology, University of Oslo, NO-0316, Oslo, Norway
[5]Center for Healthy Aging, Faculty of Health and Medical Sciences, University of Copenhagen, DK-2200, Copenhagen N, Denmark

[*]Correspondence: e.f.fang@medisin.uio.no

After the success of the 1st Norwegian Centre on Healthy Ageing (NO-Age) International symposium, we welcomed everyone to the 2nd NO-Age International symposium on the 12th June 2019 at the Akershus University Hospital (detailed programme). Here we give a summary of this one-day intensive scientific meeting, to which enthusiastic responses were received.

The agenda of the symposium focused on how genomic stability and repair mechanisms impact ageing and disease in the human brain, covering from the very recent breakthroughs of the roles of DNA repair in healthy brain ageing to the new mechanisms and potential therapeutics for Alzheimer's disease and Parkinson's disease. We had 15 speakers from all corners of the world contributing to a fully packed day of lectures and networking. Some 60 representatives from the scientific and medical community were present.

***NO-Age reception for the international speakers**. Back row (Left to right): Hilde L. Nilsen (organizer, UiO and the Akershus University Hospital), Jon Storm-Mathisen (organizer, UiO), Silje Torsetnes (NO-Age volunteer, UiO), Minoru Takata (guest, Kyoto University), Tinna Stevnsner (guest, Aarhus University), Vilhelm A. Bohr (guest, NIA and Copenhagen University), Hansang Cho (guest, University of North Carolina at Charlotte). First row (Left to right): Jian Xiao (guest, Wenzhou Medical University), Brian C. Gilmour (NO-Age editor), Armond Hov (NO-Age editor), Linda H. Bergersen (organizer and host, UiO and Copenhagen University), William McEwan (guest, University of Cambridge), Jinsan Zhang (guest, Wenzhou Medical University and Mayo Clinic), Evandro F. Fang (organizer, UiO and the Akershus University Hospital). On the way from the airport Peter McHugh (guest, University of Oxford). Photo: Ruben Gudmundsrud (NO-Age editor)*

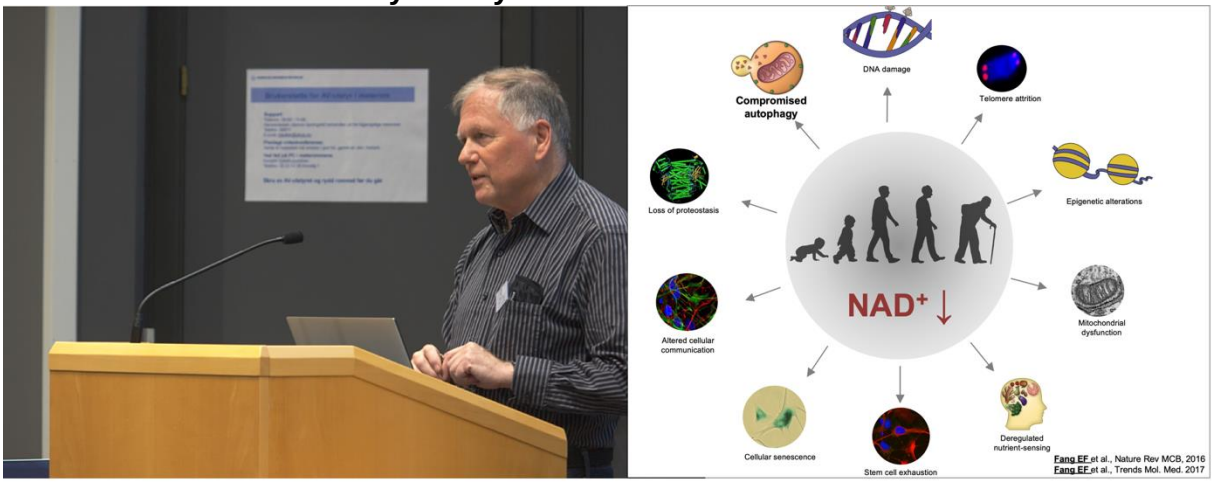
1. Healthy brain ageing and Society

As the proportion of the elderly increases worldwide, Alzheimer's and other diseases of the ageing brain are set to become the next leading health problem, both in terms of social and economic impact. According to the 2018 dementia report, there were 50 million individuals worldwide with dementia, with the number expected to increase to 82 million by 2030, doubling the already staggering financial cost of 1 trillion US dollars.

Anne Rita Øksengård from Norwegian Health Association delivers an informative and inspiring Opening Speech on the socio-economic pressure of dementia. Photo: Amund Hov (NO-Age editor)

Luckily people are taking notice. We had the good fortune to have representatives from the Norwegian Health Association (Nasjonalforeningen for folkehelsen), a non-governmental organization (NGO) dedicated to promoting healthy ageing, with a focus on dementia and cardiovascular disease. As an NGO, the Norwegian Health Association relies heavily on *"crowd funding"* to support research, as opposed to the traditional system of government grants. Crowd funding allows the Norwegian Health Association to bridge between the public and academic spheres of disease, and to showcase this they presented a video they have produced to spread awareness of dementia. We highly encourage you to have a look before continuing with this summary.

2. Common themes from keynote by Dr. Vilhelm A. Bohr



The Keynote speaker Dr. Vilhelm Bohr presents latest understandings on NAD^+ reduction in ageing, as well as its linkages to the hallmarks of ageing. Left Photo: Amund Hov (NO-Age editor). Right model: Evandro F. Fang

The publication of the Hallmarks of Ageing (*Cell*, 2013) helped to organise the early chaos of ageing research, setting in motion the creation of the current, multi-disciplinary field that NO-Age is a part of. The importance of the paper is clear in the number of citations it has acquired since its publication, as well as its use by several of our speakers (as if it were an anti-ageing mantra).

Previously, and still even today, it was assumed that the processes controlling ageing were natural, pre-determined, and uncontrollable. The suggested hallmarks of ageing helped to combat this opinion, while also doing wonders to summarise the different processes involved. To many in the field of ageing, understanding these processes offers the hope of eventually treating, repairing, and reversing the ageing process, leading to longer, healthier lives.

However, this does not mean that we have ageing all figured out. It is still unclear the degree to which each category contributes to different ageing-related diseases. It is also likely that there is significant overlap between different ageing processes and that a treatment for one may do little for the others: if so, then the correct combinations will need to be found before real progress can be made. With this in mind, Bohr urged the ageing research community to come together and collaborate to a larger degree and to build on each other's expertise.

3. A long (and expensive) string of failures

To date more than *250* clinical trials have launched and failed in *treating* those with Alzheimer's and other age-related neurodegenerative diseases, a group of diseases with the progressive loss of structure or function of neurons, let alone in curing them. While a few medications have been shown to relieve some symptoms, this often requires early diagnosis and can come with a range of side effects.

To understand how so many of these therapies fail, it is useful to know a bit about how this kind of research is typically carried out. The bodies and organs of different animals differ significantly, the structure and function of the brain especially. Observing a human disease in a different animal often requires artificially mimicking the disease in the animal of interest. This modified animal is then referred to as a *model* for the disease.

Over-reliance on transgenic mouse models may explain some of the difficulties in producing a lasting treatment. In the case of Alzheimer's, most therapies target a single protein: amyloid, which in Alzheimer's tends to clump around neurons, leading to their eventual death. The *models* these drugs are based on are artificially made to produce excess amyloid. If the accumulation of amyloid is instead a symptom, rather than a cause, of Alzheimer's then this could explain the high rate of failures.

The difficulty with finding a treatment for Alzheimer's is mirrored in other brain diseases, and the progressive failures of different treatments has pushed researchers to take a closer look at different areas, many related to the hallmarks of ageing

4. Role of genomic stability and DNA repair in disease and brain ageing

Vilhelm Bohr laid out the agenda for the first session by sketching out relations he and his collaborators have established between genomic instability and mitochondrial function. In collaboration with Evandro Fang, some of these findings were recently published in Nature Neuroscience, and we have already written an article on the possible role mitochondrial dysfunction may play in driving the progression of Alzheimer's and related diseases. Central in these topics is the molecule nicotinamide adenine dinucleotide (NAD^+) which is, among other things, used in the repair of DNA damage and the production of energy for the body. For reasons currently unknown, the level of available NAD^+ declines substantially with age, starting as early as the entry to adulthood.

Breakages are a common form of DNA damage repaired with the help of NAD^+ and can consist of anything from breaks caused by radiation and unwanted chemicals to the formation of cross-links: strong bonds that stop DNA from being separated for replication and protein production.

Peter McHugh and Minoru Takata presented work with a couple of proteins capable of repairing some DNA breaks. They also showed videos of how these proteins quickly move to the site of damage after irradiation. But could these DNA repair proteins have other functions? Continuing to look at DNA repair proteins, Magnar Bjørås presented on a family of proteins called NEIL (1, 2 & 3) that deal especially with oxidative DNA damage. Normally such proteins can help to prevent cancer, but somehow the rate of cancer remained unchanged when the function of all NEIL proteins was removed.

This led the group to search for alternative functions, eventually finding that mice without NEIL proteins showed improved learning and reduced anxiety. This, as well as the lack of effect on the rate of cancer formation, led them to believe that NEIL modulates the epigenome: switching genes on or off to different degrees in response to the outside world.

Arne Klungland took the podium to inform us that, while the epigenome is all well and good, the epitranscriptome is where the real cellular magic can be found. Transcripts from DNA can be modified over 150 ways before finally serving as a blueprint to produce proteins. It has only recently been established how some of these modifications can be regulated dynamically.

5. Exploring alternative clinical approaches for the ageing brain

Tinna Stevnsner presented in the session on genomic instability but was more interested on what she could find outside the cell. She and her team have looked at the brains of unusually healthy Danish centenarians (individuals over 100 years of age) to try to identify any factor that might have helped them retain their brain health.

They are currently crunching the numbers for several factors, such as: DNA repair capacity, NAD^+ balance, and mitochondrial function. Interestingly, increased mitochondrial activity was linked to lower cognitive function (in men), perhaps suggesting that working harder does not necessarily mean better function in the long term, and maybe that working smarter is indeed the better option.

The balance of NAD^+ in relation to mitochondrial fitness is also a research interest of Evandro F. Fang, who works with NAD^+ supplementation in multiple animal models in the hope of translating the findings into human therapies. Currently, the lab has experience using human cell cultures, roundworm (*C. elegans*) and fruit flies in the lab. Fang suggests that compromised mitophagy is a separate hallmark of ageing, in addition to the observed decline in mitochondrial function, and has used this cross-species approach to strengthen the hypothesis. For a previous discussion on how mitophagy relates to genomic instability see our previous post on the NO-Age website.

Hansang Cho has taken human cell cultures to a new dimension, literally. By embedding human cells in a carefully-designed, microfluidic environment he has been able to replicate known behaviours between neurons and supporting cells: effectively creating a 3D brain on a chip. To showcase the use of this system, he presented how it can be used to study how microglia are recruited to sites of amyloid aggregation in Alzheimer's disease, and showed a video captured using the system. Microglia form the basis of the brain's immune system but can do more harm than good if inflammation is not kept under control.

Markers of this elevated, microglial immune response are thought to be present in cerebrospinal fluid (CSF) even before the patients start experiencing symptoms. Tormod Fladby pointed to this as a potential indicator of patients who could go on to develop disease.

Cerebrospinal fluid provides a way to export waste produced in the brain. The fluid is produced in brain compartments, picking up the soluble molecules in-between neurons before finally draining across the blood brain barrier to the spine. Unfortunately, the extraction procedure is rather invasive and requires puncturing a needle into the lower back. You may know this as a spinal tap; at least if you are into heavy metal.

Another condition which stands to learn from CSF is delirium: acute confusion following a seemingly unrelated illness. Delirium is an under-appreciated condition and occurs frequently with the elderly where it is largely seen as clinically *"normal"*. However, episodes of delirium are strongly associated with dementia, so further understanding of delirium could provide a window into shared mechanisms. Much remains to be studied about this condition; you can imagine trying to perform a spinal tap on a confused and uncooperative patient. Leiv Otto Watne has avoided this issue by analysing CSF samples from hip fracture patients, where the procedure is already routinely performed. Initial analysis points to a break down in the integrity of the blood brain barrier, which is critical to brain health.

All drug trails targeting the production and processing of amyloid in Alzheimer's have so far failed. For this reason, the lab of Jens Pahnke is looking at neurodegenerative diseases as a failure to export waste. Using mice models they were able to replicate human symptoms of Alzheimer's disease simply by knocking out certain transporters of cellular waste. According to their calculations, a small decrease or increase in the transport of beta amyloid can have a significant effect on the aggregation of plaques in the brain.

To expedite the discovery of potential therapies, he and colleagues are searching traditional herbal remedies for possible therapeutic candidates. Currently under clinical trials is a candidate derived from St. John’s Wort, long used to treat depression and other mental ailments. Working as a clinician he has personally seen changes in patients suffering from frontotemporal degeneration, a condition with sudden changes in behaviour and cognition, all very exciting.

In stark contrast to natural herbal remedies lies the almost science-fiction-like technology “Trim-Away”. First discovered as an anti-viral protein within cells, the active component of "Trim-Away", Trim21, acts as a last line of defence, destroying antibody-coated microbes, such as viruses. As Trim21 is targeted to anything that can be coated in antibodies, it immediately had great appeal for development as a tool to selectively degrade targeted protein. This line of discovery led Will McEwan to develop "Trim-Away", adding it to the roster of knockdown techniques already in use (i.e., CRISPR/Cas9, RNAi, etc.). He cleverly proposed that should people have problems with their cells, they need only "trim away" the offending protein. With regards to Alzheimer’s disease, Trim21 may be exploited to trim away tau tangles inside neurons, if an efficient way to pass the required antibodies across the blood brain barrier is found.

Finally, NO-Age organiser Linda H. Bergersen reminded us of an important fact we should all know; *physical activity benefits the body in many ways*. In fact, to date, no medical intervention is likely to be more effective for the diseases of ageing than an active and social lifestyle, as mentioned in our first meeting.

Other benefits of physical activity include reduced blood pressure, stronger bones, the prevention of breast and colon cancer, better sleep and, therefore, better chances of resisting the perils of dementia and cardiovascular disease. Proper sleep in particular has been highlighted for its importance in reducing all-cause mortality, possibly as it is the period in which most of the clearance of waste from the brain takes place.

We would like to thank our sponsors for making this event possible, namely Aladdin, Dojindo Molecular Technologies, Biotechne, Sigma-Aldrich and BioNordika.

A good ending for the 2nd NO-Age symposium: a group photo recording the smiling faces. *The talks could have easily filled days and covered a range of interesting topics and ideas. Despite the busy schedule, the speakers commendably kept to their allotted time. For speakers' bibliographies, affiliations, and abstracts, see detailed program. Photo: Amund Hov (NO-Age editor)*