World leading translational

ALZHEIMER CENTER

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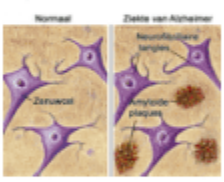
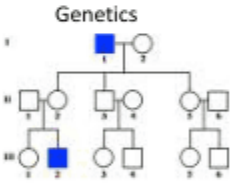
KAROLINSKA INSTITUTET, SWEDEN

Alzheimer disease research at Karolinska Institutet

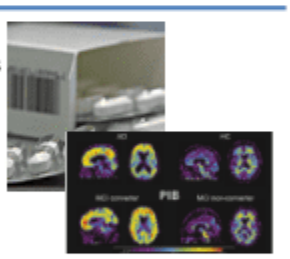
Experimental research



Genetics



Clinical research;
Diagn & therapeutics



Epidemiology;
Risk factors

SWEDISH brain POWER

Care &rehab
research

Background

Demography

Increase in prosperity and medical progresses gives expectation for a prolonged (average) length of life all over the world the coming decades. More and more, people dare to dream about an active life many years after retirement. But – increased length of life also implicates that an increased number of persons will be affected by age-related diseases, such as dementia. For example, in Sweden with an average length of life around 80 yrs, it has been calculated that every third inhabitant who survive their 65' birthday will develop a dementia disorder. The demographic evolution results in an increase of current figure of persons with dementia worldwide from 35.6 million to 115.4 million in 2050. Out of these, 2/3 will develop the most common form of dementia; Alzheimer disease.

Costs

The estimated cost for dementia care today on a global level is 600 billion dollars. In Sweden, the annual societal costs for care and caring of persons with dementia have been estimated to 50 billion SEK – which is more than the total defense costs. Should we fail to develop new drug treatment to prevent or at least halt the course of Alzheimer disease, the burden on the societal economy will be even harder. In this perspective, the monetary efforts put on research on dementia disorders are heavily underfinanced. In a comparison between the societal costs for dementia to other diseases, we have found that economic support for research on dementia disorders is only 1/15 of support for vascular disorders and 1/25 of cancer research.

Clinical research

The most important concrete result from research on Alzheimer disease so far is the development of drugs that to a smaller extent reduce the symptoms. In Alzheimer disease, the nerve cells producing the signal substance acetylcholine die, which impacts memory and cognition. Three out of the four drugs currently on the market functions via a more effective use of the acetylcholine. The fourth drug on the market counteracts the effect from glutamate, which is another signal substance. Patients with severe Alzheimer disease have too high levels of glutamate och are often improved by such treatment.

The research has also resulted in improved diagnostics. Today, the disease can be diagnosed at least 5 yrs earlier than 15 yrs ago. This means that disease halting drugs can be installed earlier and give the patients more "healthy" years. In addition, an earlier diagnosis give the patients and the relatives time to be better prepared before the changes of life situation that the disease eventually will bring.

Epidemiological research

We are learning more and more regarding risk factors. Beside the genetic factors, we know that many lifestyle related factors increase the risk for Alzheimer. In the "Kungsholmen project" (initiated by Prof Winblad in 1987), we followed the elderly population in this part of Stockholm for two-three decades and were able to show that factors like diabetes, high cholesterol, hypertonia, low physical activity, poor eating habits and low socializing activities are all increasing the risk to develop Alzheimer disease. Thus, we have here a window of opportunities to decrease the prevalence of Alzheimer through preventive efforts.

Basic laboratory research

The setbacks regarding disease modifying drug development forces us to re-think and put the question whether we have overestimated our insights in the most basic disease mechanisms. Perhaps we have been too focused on the beta-amyloid hypothesis as sole explanation. Our conviction is that if our society will have a chance to deal with the great challenge of Alzheimer, we have to intensify the basic research in this area. At our research unit in Huddinge, Stockholm, we have unique pre-requisites to contribute to both the understanding of the causes of the disease, as well as to the development of new treatment strategies. Our basic research is in the frontline worldwide, eg we were among the leading centers developing the beta-amyloid hypothesis.

Since many of our collaborators are clinically active physicians at the Karolinska University Hospital in Huddinge, we have possibilities to without delays transfer results from basic research into clinical trials after having achieved positive results from studies on cell lines and animals. The access to clinical expertise also helps us to exclude, in early stages, tracks/targets that for some reasons are not relevant for humans.

Future treatment strategies

With this said, there are many researchers not experiencing the same optimism as a few years ago regarding a close breakthrough in our attempts to conquer the disease. The last drug coming to the market was for >10 yrs ago. Several new clinical trials on promising candidates have been discontinued due to negative results or serious adverse events. The new substances being tested are still only on a pre-clinical stage.

To only affect the symptoms is under no circumstances an optimal strategy, since it that way the cell death is not influenced. A lot of research efforts have been aimed at finding new therapies halting or at least reducing the process leading to cell death. Typical for Alzheimer are the microscopic plaques in the brain. These plaques consist of the protein beta-amyloid, and the dominating hypothesis is that the nerve cells are intoxicated and damaged under some of the different phases leading to the development of plaques. Many of the tested therapies have dealt with attacking the beta-amyloid, either through decreasing the production, halting the aggregation or through increasing the clearance of amyloid. So far, the results from many of these clinical trials have been discouraging, either with no effect and/or severe side effects. Alternative strategies, such as trying to affect the tau protein fibrils, another typical distinctive feature for Alzheimer, have not yet resulted in any positive results in phase III clinical trials.

Short description of the division "Karolinska Institutet Alzheimer Disease Research Center" (KI-ADRC)

The main aim with our research is to understand the molecular and genetic mechanisms behind the disease and identify target molecules for diagnosis and drug treatment. Some examples of ongoing research areas:

- Beta-amyloid, gamma secretase and tau as potential target for treatment
- Genetic changes (mutations) leading to neurodegenerative diseases
- Cell death mechanisms and mitochondrial function in Alzheimer disease
- Cell and animal models for Alzheimer disease
- Studies on underlying mechanisms behind well established knowledge on risk factors for Alzheimer disease
- Diagnosis, prevention and pharmacological treatment of memory problems.

We have a long tradition of pharmacological research. Many of our researchers have contributed to the development of currently available symptom-reducing drugs. Currently, we are running unique studies trying to modify the disease process in patients with early Alzheimer through immunotherapy (ie vaccination). In addition, we are also performing epidemiological research in order to map genetic and environmental risk factors.

We have collaborated with a Japanese drug company (2000-2012) in order to find new treatment targets for Alzheimer. Within this collaboration, we have identified seven potential candidates for drug treatment and the company will now continue the development of these in order to go into clinical trials. The projects that have been part of this collaboration have been evaluated by international experts at three occasions and been judged as of extremely high quality.

From KI-ADRC, we are also leading and coordinating the national research network Swedish Brain Power, including the Swedish expertise on neurodegenerative disorders. The aim here is through increased national collaboration speed up the development of more sensitive diagnostics and early treatment for these types of diseases. The Swedish Brain Power network holds approx 30 research groups all over Sweden. From KI-ADRC, we are also leading and coordinating the European Alzheimer's Disease Consortium (EADC) comprising >60 clinical research centers all over Europe with the aim of eg increasing international research collaboration.

Thanks to our translational approach with strong basic research in close collaboration with the clinic, we are a greatly demanded partner by companies for clinical trials, especially in early phases of drug development. Our collaborators are also often requested internationally as experts for evaluations national efforts and research applications.

Our proposal: Establishment of a world leading Karolinska Institutet Alzheimer Center

The research on Alzheimer disease at Karolinska Institutet in Huddinge/Stockholm is currently performed within a number of divisions. We would like to unite these divisions under a joint umbrella; Karolinska Institutet Alzheimer Center. This would further strengthen and visualize our already now leading research on Alzheimer.

Our aim is to look for funding for an ambitious effort, focusing on basic and clinical research, ie translational research, on Alzheimer disease through establishing a strong, internationally leading Alzheimer center at Karolinska Institutet with a main research focus on increasing our understanding of the processes on molecular, cellular and genetic level leading to the abnormal cell death, and to based on these new insights, identify biological target molecules for diagnosis and treatment.

This effort would cost roughly 6 MSEK/yr during 5 yrs (more detailed budget at the end of this document).

Our wish is to have a possibility to broaden and deepen our research, but above all, to be able to test some more spectacular hypothesis. A pre-requisite for this is a more long term financially secured situation. As researcher, we are depending on quick delivery of results in order to make grant suppliers willing to continue their support. When it comes to this type of "high-risk research", where totally new approaches are tested, even more solid results are demanded in order to convince grant suppliers, authorities and industrial partners to continued support.

A great part of this effort would be as position support, both for basic and clinical research. Creative and competent researchers are the main important resource in order to reach good research, and as many other countries currently are increasing their efforts in this area, the competition is increasing. We would like to give the creative and competent researchers possibilities to devote their time to research, instead of spending a great deal of time to applications on new grants to survive. By offering long term employments (5 yrs) on good conditions, we would be able to make strategic recruitments. We also hope to be able to find senior researchers who are experts in complementary areas to be able to strengthen our knowledge in the current technical development of the research environment.

The great winners from such an effort are of course all patients given a chance to a better old age, not only in Sweden but all over the world. For Sweden, there is another potential bonus. The historically strong Swedish drug industry was to a great extent built upon the discoveries done in academia. Today, almost all drug companies have moved abroad. A strong medical basic research is the most efficient way to protect what is left, and as a dream scenario re-gain some of the lost land.

Budget

Tentative budget (in SEK*) for 4 positions as senior researchers

Item	Salary/month	Incl Soc costs (51,09%)	Total salary/yr
Senior researcher	50 000	75 545	906 540
x 4 positions			**3 626 160**
Strategic equipment			800 000
Running costs			450 000
Subtotal			**4 876 160**
Indirect administrative university costs (21,80%)			1 063 003
GRAND TOTAL			**5 939 163**

*100 SEK is approx 14.90 USD

Stockholm September 24, 2013

Bengt Winblad

Bengt Winblad
Professor