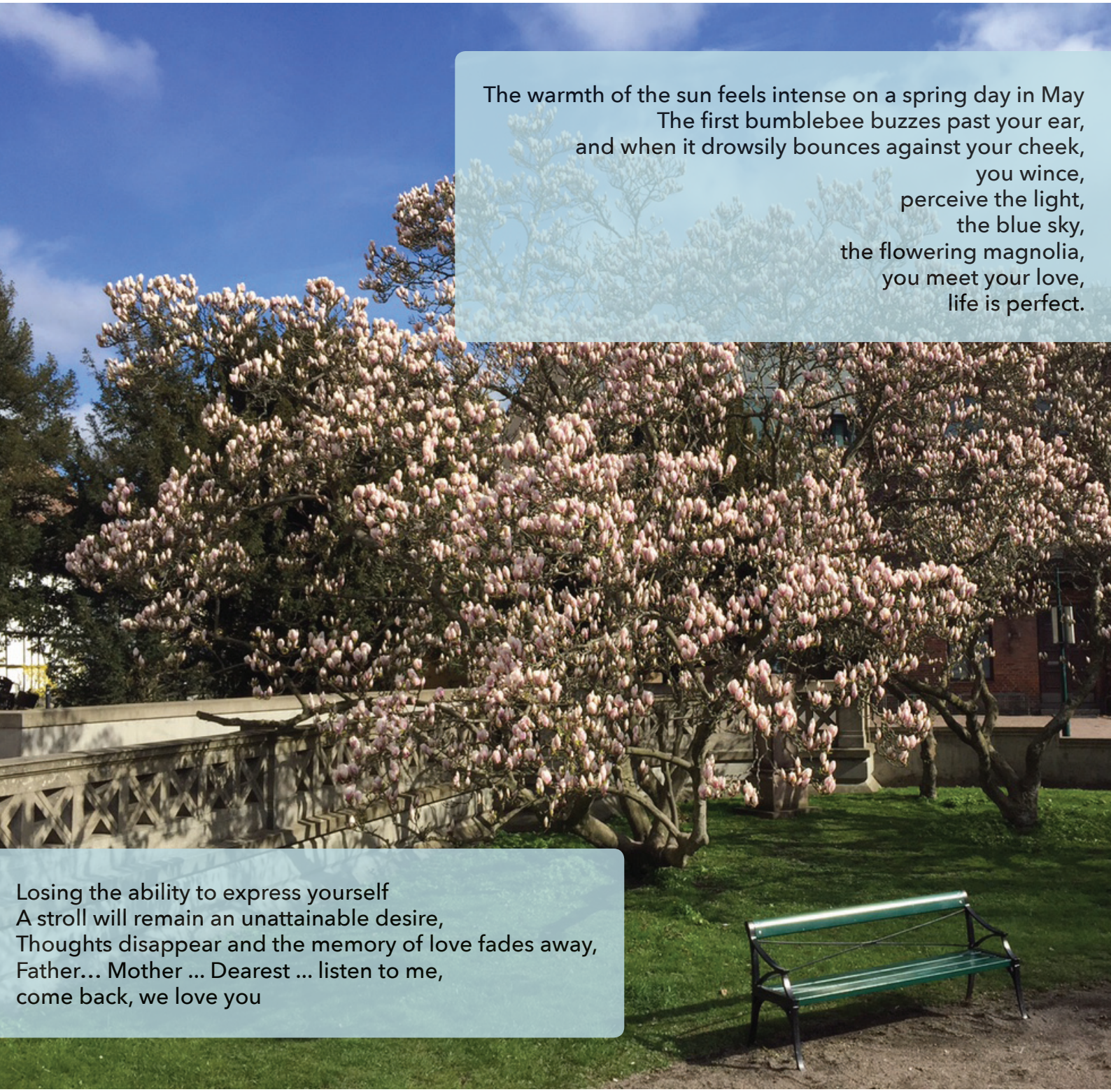
A HEALTHY AGING BRAIN PROMOTES SWEDISH GROWTH

a strategic innovation agenda

to combat diseases of the aging brain


The warmth of the sun feels intense on a spring day in May
The first bumblebee buzzes past your ear,
and when it drowsily bounces against your cheek,
you wince,
perceive the light,
the blue sky,
the flowering magnolia,
you meet your love,
life is perfect.
Losing the ability to express yourself
A stroll will remain an unattainable desire,
Thoughts disappear and the memory of love fades away,
Father… Mother … Dearest … listen to me,
come back, we love you

"In 20 years, Sweden will be leading the development of innovative treatments for diseases of the aging brain as a result of national and international partnerships between key players in academia, healthcare, industry, government and patient organizations"

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SUMMARY

Among children born today, half are expected to reach the age of 100 years, and thus are at risk of acquiring a disease of the aging brain such as Alzheimer's disease (AD), Parkinson's disease (PD) or stroke, against which few or no effective treatments are available. Globally, the societal cost for these diseases has increased by approximately 35% over the last 5 years and will exceed one trillion USD by 2018. From a societal perspective, discovering and developing treatments for these diseases is therefore one of our greatest challenges. Swedish research in the field of AD, PD and stroke is world leading. With a comprehensive strategy and long-term and sustainable financing, Sweden has a unique opportunity to develop products for diagnosis and treatment of the disease. Such products would reduce human suffering and minimize the cost to society, thereby increasing Swedish growth and competitiveness.

This document describes an innovation agenda to stimulate the process from discovery to development of treatments and products, with action plans through 2035. The agenda was developed jointly by representatives of academic research, health care, government agencies, companies in Sweden and the global pharmaceutical industry.

The strategy is based on creating an unbroken, optimized innovation chain (research-discovery – development – market) where each link and stakeholder in the chain is important for a successful outcome. Specifically, this will enable an increase in entrepreneurship that can ultimately pave the way for a new global industry based in Sweden.

"discovering and developing treatments for these diseases is one of our greatest challenges"

THE AGENDA'S ACTION PLAN

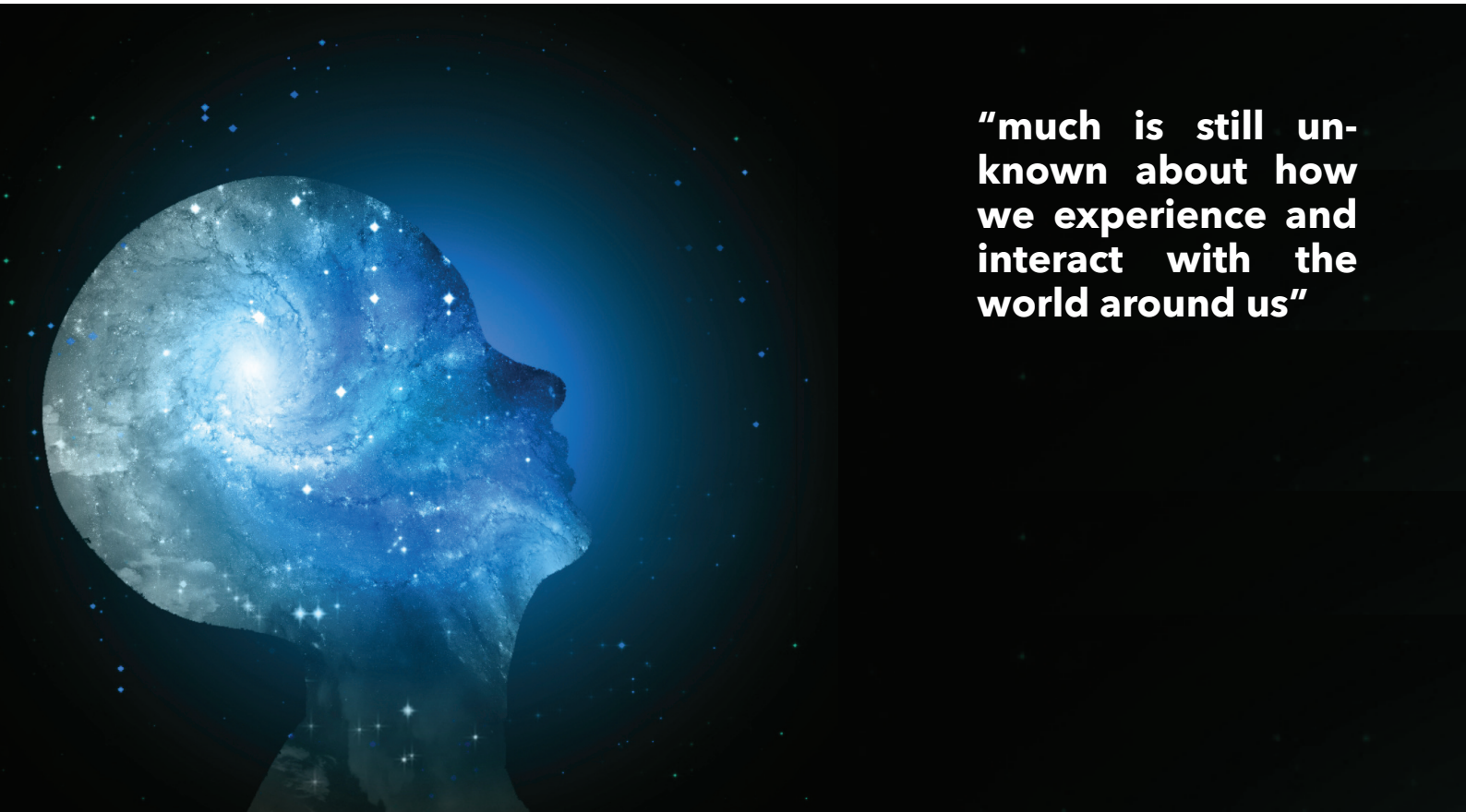
- **Develop innovation**
- **Optimize the process of innovation**
- **Increase the competence and attractiveness**
- **Create sustainable long-term funding**
- **Establish a national innovation network for collaboration**

>THE BRAIN
the last frontier

The brain - the most fascinating structure in the universe. This tissue, weighing little more than one kg and consisting mostly of fat, is composed of billions of neurons wired in a network of more than one million billion connections that create infinite patterns of activity. These patterns are expressed in our behavior, our thinking, our decisions, future strategies, relationships and interactions with others. The brain has a unique ability to be innovative and devise creative solutions to important, contemporary problems, irrespective of race, gender or age of its host. A healthy brain is a prerequisite for a humane society and for creative innovations in all sectors of society.

The brain is complex, and although knowledge of the brain has increased rapidly in recent decades, much is still unknown about how we experience and interact with the world around us. It is therefore a major challenge to combat diseases of the aging brain, against which very few treatments are available. Sweden, being a world leading force in the area of brain research, is in a favorable position for meeting this challenge. This agenda describes how future cross-border joint ventures among academia, healthcare, government and business, can lead to development of new treatments for diseases of the aging brain.

The agenda's vision of "a healthy aging brain increases Swedish growth" means that support for the agenda's action plan will enable the development of entrepreneurship and new treatments and products in Sweden. This ultimately reduces the number of individuals affected by diseases of the aging brain, which reduces societal costs, and thus contributes to increased Swedish growth and competitiveness.



"much is still unknown about how we experience and interact with the world around us"

>THE CHALLENGE

Diseases of the aging brain have a severe impact on the affected individuals, their caregivers, and society at large. In 2010 the total societal cost for diseases of the aging brain, Alzheimer's disease (AD), Parkinson's disease (PD) and stroke were estimated, in Sweden alone, at approximately 80 billion SEK annually, more than the cost for cancer and heart/vascular disease. Medical advances in general have contributed significantly to the increase in life expectancy, a trend that is expected to continue. According to calculations from Statistics Sweden, the proportion of people over 65 will increase by 30% by 2050. Moreover, it is estimated that 50% of the children born today will reach their 100th birthday. However, there are no treatments that can halt the progression of AD and PD, nor are there therapies that can restore brain function in stroke survivors. Hence, in a future where life expectancy increases, more and more people will be affected by AD, PD and stroke, ensuing large human and societal burdens.

An incomplete understanding of the many complex mechanisms behind age-related neurological diseases has made it difficult to find new effective approaches to treatment. For this reason, many major international pharmaceutical companies have abandoned or drastically reduced their research and drug development for brain diseases. This includes AstraZeneca in Sweden.

Evidently, one of the greatest societal challenges today is to find new treatments that can prevent, cure or alleviate the consequences of diseases of the aging brain. It is necessary, therefore, to bring together powerful national and international efforts that can link into, and strengthen, the innovation process - from research, processing of discoveries into innovations, product development and marketing. This will include development of small molecule drugs, biologics, drug delivery systems, diagnostic instruments, neurotechnology, as well as innovative combinations of these approaches.

> THE AGENDA ACCEPTS THE CHALLENGE

This strategic innovation agenda describes the roadmap for how academia, government and industry can jointly combat diseases of the aging brain through a comprehensive innovation strategy to stimulate the innovation process. The agenda therefore formulates a medium-term strategy (1-10 years) aimed at increasing both the innovations stemming from research discoveries and entrepreneurship in this area. The strategy includes the creation of networks with a focus on innovation and increased collaboration between the stakeholders based on existing expertise and resources. Furthermore, a long-term strategy (10-20 years) for increased development and commercialization of innovations is also included. The goal of the agenda is to identify areas and suggest measures to create a seamless and optimized innovation process, from discovery to treatment of the patient, and the commercialization of innovations.

Seminal research and entrepreneurship are prerequisites for a vibrant and dynamic innovation landscape. The scientific excellence of Swedish brain researchers is recognized worldwide, with pioneering discoveries in AD, PD and stroke (left box below), which provide the basic conditions for achieving the objectives of the agenda. The long-term funding of high-quality research and focus on entrepreneurship must be maintained in order to continue to create innovations. Improved funding of brain research will also train new generations of brain researchers for careers in academia, industry and healthcare. This is further strengthened by safeguarding skills of the scientists made redundant by AstraZeneca's closure of research and development in diseases of the nervous system.

Today, Swedish researchers/entrepreneurs and small businesses are developing innovative therapies against AD, PD and stroke, based on research discoveries at our universities and companies (right box below). Additionally, several international companies are co-developing diagnostic instruments with Swedish researchers based on Swedish findings. There is thus considerable scope for greater entrepreneurship within the research community. In Sweden, the absence of players willing to finance the first parts of the innovation chain with seed capital is a problem. This limits the flow of new ideas that can be refined into innovations and reduces the number of new companies in Sweden that can create jobs and growth in the Swedish economy. To accomplish this growth, it is necessary to develop a comprehensive national innovation strategy with national coordination. This is particularly important in the transition from early research to commercial development where ideas are likely to be lost and innovators may leave the country.

SWEDISH DISCOVERIES OF SIGNIFICANCE FOR THE DEVELOPMENT OF FUTURE INNOVATION

- *Genetic mutation linked to Alzheimer's Disease*
- *First findings about the spread of misfolded proteins in the brain*
- *The brain's ability to repair and reshape after stroke*
- *The role of dopamine in PD (Nobel Prize 2000)*
- *First dopamine agonist, bromocriptine, in clinical practice*
- *The first animal models for PD*
- *New ligands (detection molecules) for PET*
- *New biomarkers for AD and PD*
- *New antibodies for amyloid (AD) and alpha synuclein (PD)*

SWEDISH PIONEERING DRUGS TARGETING BRAIN DISEASE

- *L-DOPA: A drug whose positive effect against PD was discovered by Arvid Carlsson, Sweden's recent Nobel Prize winner. L-DOPA is still the most prescribed drug for PD.*
- *Zimelidine: The First SSRI (selective serotonin reuptake inhibitor) drug in the market. It was discovered by scientists at Astra AB, and laid the foundation for the development of new drugs for depression such as Prozac.*
- *Lidocaine: is an anesthetic and drug for atrial fibrillation, discovered by chemists at Astra AB. It is listed by the WHO in "the most essential medications needed in health care".*
- *Pridopidine: Developed by Carlsson Research AB for Huntington's Disease and now in late stage clinical development by Teva Pharmaceuticals.*

THE INNOVATION PROCESS

The innovation process supports the entire innovation chain, from development of discoveries to the development and marketing of internationally successful products and services (Figure 1).

Innovations related to AD, PD and stroke are created in different areas of specialization that can be divided into prevention, diagnosis, alleviation/ cure and performance improvement (rehabilitation). The area of "prevention" includes treatments or measures that prevent disease progression. "Diagnosis" includes the production of various investigative methods and tools (e.g. biomarker kits or brain imaging) to allow diagnosis of a disease as early and accurately as possible, and also to monitor disease progression and functional improvements after different treatments. "Relief/cure" includes the production of various types of products to facilitate healing or relief of symptoms and effects of disease (e.g. drugs or implantable electrodes for electrical stimulation) or different types of aids that compensate for the effects of the disease (e.g. the shake-free spoon for patients with PD). The "improvement of function" area covers various products (e.g. drugs or robotic technology) to improve brain function after injury or disease and also how to assess what rehabilitation strategies are effective.

The innovation process begins with a discovery that is the result of intuition or exploratory research that can create value through patenting and formation of a new company. Through experimental or clinical validation the impact of the discovery on the disease can be assessed (which eventually could increase its value). To foster the development of a discovery through innovation, it is necessary to create opportunities, resources, and incentives. Most importantly resources and companies to finance innovation are needed. Furthermore, a positive attitude among stakeholders is essential for progress to be made. The innovation will be evaluated through clinical trials and assessments of health economics, usefulness in healthcare (thresholds for use), and feasibility of implementation. The innovation process must therefore be carried out in collaboration with various constellations of stakeholders: academia, health care, industry, patient organizations and authorities. Here, the development of innovative financial and markets are crucial for success.

For diseases of the aging brain, enabling an uninterrupted and optimized process of innovation will yield the best result from the effort and capital invested. This is particularly important because of the following: (1) Due to the slow progression of AD and PD and heterogeneous disability and recovery in stroke, development is time consuming, costly and high risk. This is why the industry demands strong validation of the disease-relevance of new discoveries. In order not to lose valuable innovations, increased resources and improved infrastructure are needed for the validation of findings. In addition, seed funding and long-term and sustainable financing are needed for the development of small companies. (2) Development of new diagnostic tools that are needed to detect PD and AD in the early stages and to monitor the effectiveness of disease treatment. (3) Innovative clinical trial protocols and methods required for a robust assessment of innovations. (4) The Swedish health care system needs to simplify regulations and procedures, if the introduction to the market of Swedish neurotechnological innovations is to be successful at the global level.

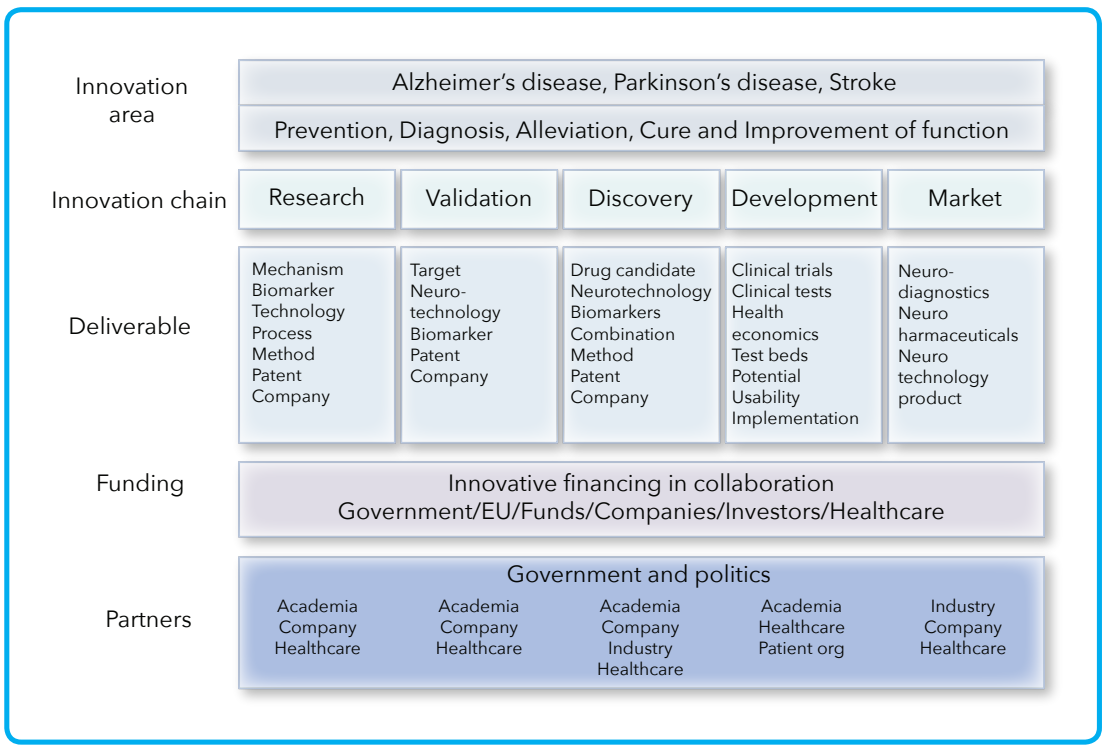


FIGURE 1
The innovation process – from discovery to market for diseases of the aging brain with a focus on prevention, diagnosis, alleviation, cure and improvement of brain function

TECHNOLOGIES & INFRASTRUCTURE at the forefront

Brain function is the result of complex electrical and chemical communication among billions of cells throughout the brain, and through input from our senses: hearing, vision, smell, taste, balance and touch. These sensory paths provide various possibilities to access the brain for treatment, such as behavioral therapy, robotics, electrical, magnetic- or optical stimulation, in addition to treatments based on drugs an biologics or various combinations of all of these treatments. Swedish research is strong in these areas with regard to AD, PD and stroke and utilizes technologies at the absolute forefront of research, for the development of innovative therapies.

INFRASTRUCTURE FOR DRUG DISCOVERY

Drug discovery and development for diseases of the brain is hampered when drug candidates produce unacceptable side effects, are toxic, do not reach the brain tissue (do not pass through the blood-brain barrier), or are not effective enough when they reach their target in the diseased brain. National infrastructures and methodology platforms for drug discovery such as SweTox and SciLifelab provide advanced methodology and professional support to researchers and companies in these aspects of development. The Alzecure Foundation is a unique research facility for drug development against AD, PD and related diseases, and may serve as a model for future collaborations between drug developers, academic research, national platforms and industry.

INNOVATIVE DRUGS

Swedish researchers have developed relevant animal models for AD, PD and stroke with widespread international application in drug discovery and development. Swedish companies and researchers have also successfully developed methods to validate drug candidates through both phenotypic behavioral screenings in experimental models and mathematical computer-based models. Furthermore, they have made world-leading discoveries on disease-modifying treatments for AD and PD based on innovative immunotherapy. National analytical instruments such as high field magnetic resonance scanners and magnetoencephalography instruments and, in the future, high energy particle accelerators such as the ESS (European Spallation Source) and MAX IV, will enable more detailed knowledge about protein and brain structure/function that can facilitate the development of drugs with improved properties.

BRAIN DIAGNOSTICS

Brain imaging techniques such as positron emission tomography (PET) magnetic resonance imaging (MRI), and biomarkers in cerebrospinal fluid (CSF) make it possible to monitor the effects of new treatments in the brain, as well as to improve diagnosis and monitor disease progression. New tools that streamline and improve brain imaging such as innovative software for image analysis and new approaches to the development of novel PET ligands (detection molecules) should be developed by Swedish companies and researchers in the future. Today, Sweden is the world leader in the development of diagnostic CSF biomarkers for AD and related dementias, and conditions are very favorable for the future development of improved diagnostic tools for PD and stroke.

GENE THERAPY

Approximately 50 clinical gene therapy trials for brain diseases have been performed globally, and these have demonstrated good safety profiles. Recent Swedish gene technology methods have made it possible to selectively modify genes on specific locations in human DNA, which will accelerate the clinical application of gene therapy. Several major pharmaceutical companies have products in their gene therapy development portfolio and Swedish researchers and companies are developing gene therapies for AD and PD.

TECHNOLOGIES & INFRASTRUCTURE
at the forefront

CELL-BASED THERAPY

Stem cell research in Sweden is world leading. For example, Swedish research has shown that it is possible to reprogram adult connective tissue cells into nerve cells. This approach may provide a starting point for the development of new personalized cell therapies for brain diseases. The first clinical transplantation trial of human embryonic stem cells in patients with PD is now being planned, with Swedish researchers in a leading role. Positive results can create innovations with great clinical potential. Treatment of the brain with molecules that do not pass the blood-brain barrier can be aided by implanting genetically modified encapsulated cells that produce and release active substances directly into the brain. Today, Swedish researchers are using this technology in clinical trials for AD.

NEUROTECHNOLOGY

Neurotechnology refers to medical devices and methods for the treatment of brain diseases and includes robotics, neuromodulation (electric and magnetic stimulation), and software (computer programs such as brain imaging analysis). Neurotechnology products can be expected to be of great importance for the development of therapeutics for diseases of the aging brain. Development of miniaturized electrode systems based on micro- and nanotechnologies, and brain-machine-interfaces are an area of strength in Swedish research where innovative electrodes for the treatment of AD, PD and stroke can be developed in the future. Developments in neurotechnology in Sweden will also produce robots, which can be tailored to individual needs for exercise and/or functional disability support. The aim is to produce robots that are user friendly, robust and cost-effective. Moreover, new opportunities for guided exercise and performance monitoring (kinematics) employing new communications technologies can be developed.

OPTOGENETICS

Optogenetics is a technology where genes that form light-sensitive proteins are introduced in neurons to manipulate the activity of specific groups of cells in specific brain regions. Optogenetic methods can enhance drug discovery and development and possible future applications to the modulation of brain function following illness.

IT & SOFTWARE

Sweden is a world leader in the development of advanced computer games and app-based applications for mobile phones and tablets. Clinical studies show that computer-based training programs can affect the disease progression of age-related brain diseases. Swedish software developers should have many opportunities to develop innovative solutions and commercial products in the field.

>VISION & SWOT

VISION - A HEALTHY AGING BRAIN INCREASES SWEDISH GROWTH

The goal of the agenda is that in 20 years Sweden will be leading the development of innovative treatments for disorders of the aging brain as a result of national and international partnerships between key players in academia, healthcare, industry, authorities and patient organizations.

TOWARDS RENEWAL AND GROWTH

To move towards the vision and reach the goals the following action plan is proposed:

1. Develop innovation
2. Optimize the process of innovation
3. Increase the competence and attractiveness
4. Create sustainable long-term funding
5. Establish a national innovation network for collaboration

STRENGTHS, WEAKNESSES, OPPORTUNITIES AND THREATS

The agenda analysis shows that in the area of diseases of the aging brain, the following is relevant:

strengths

- Sweden has a long tradition of excellent world-leading basic and clinical brain research
- Swedish clinical trials, with the participation of all categories of personnel, is known worldwide for its high quality
- Sweden has established major patient databases, quality registries and biobanks
- Sweden has a strong research infrastructure and access to advanced equipment
- Sweden has strong national platforms to support drug discovery and development
- Increasingly, scientists file patents for their novel research findings
- The research results can be refined into innovations and lead to the formation of companies
- Sweden has established national and regional innovation systems

VISION & SWOT

weaknesses

- Detailed knowledge about the development and the underlying mechanisms of brain diseases is still inadequate
- Discoveries developed into innovations are few and the development of new drugs has not been successful
- Risk is considered particularly high in the area of brain diseases which means few players are willing to invest early in the process
- The industrial sector in the pharmaceutical and medical technology development is weak
- The market in Sweden for medical technology is small
- Sweden does not currently have any major pharmaceutical players in brain diseases
- The understanding of the innovation process, and interagency drug discovery in academia is still low
- The clinical outcome measures are often crude
- The integration of databases, biobanks and quality registries is poor at the national level
- There are not enough Swedish networks that focus on innovations

opportunities

- There are few approved treatments for disease of the aging brain and a great medical need, so the commercial potential of products in the field is very large
- With its strong experimental and clinical disease-relevant research (translational research) Sweden has a unique opportunity to become a leader in the development of innovations
- There is a greater understanding among the actors in academia, government and the business community of the importance of translational brain research for the creation of innovations
- A passionate and enthusiastic research community leads efforts in the innovation process
- Growth in the research community is strong
- Competence already exists in Sweden following AstraZeneca's closure of brain R&D in Södertälje
- A multidisciplinary network with a focus on innovation can easily be established
- Grant awarding EU institutions have recognized the importance of innovations in the area

threats

- The slow progression of the diseases makes therapeutic development costly
- The financing of innovative companies and small and medium-sized companies (SMEs) in Sweden is poor
- Neuropharmacological research has low priority in both academia and industry
- Dismantling of large pharmaceutical companies involved in research in Sweden may result in the loss of skills and diminished interest in brain research
- It is difficult to have medical devices accepted as treatments in the Swedish health care system
- Reward systems for medical innovation from academia, healthcare and government funders are inadequate

CURRENTS STATUS

The aging brain disorders - AD, PD, and stroke - have many common risk factors, the disease symptoms partly overlap (e.g. dementia symptoms) and certain pathological changes in the brain are similar. Therefore, the agenda takes a common perspective and approach for these diseases.

DEMENTIA

Every four seconds someone in the world is diagnosed with dementia, characterized by memory impairment in combination with other cognitive impairments (disturbance of thinking). In Sweden about 150,000 people have dementia, and at least as many have mild cognitive impairment. Approximately 500,000 people are close relatives of a person with dementia. The need to find treatments against dementia is therefore enormous. Dementia has been highlighted as a public health priority by the G8 countries and WHO. The most common form of dementia is AD, which constitutes about 65-70% of all dementias. Approximately 20-25% of dementia cases result from changes in blood vessels (vascular dementia) that can cause stroke. In the remaining cases, dementia is associated with other neurological diseases such as PD.

"approximately 500 000 are close relatives of a person with dementia"

CURRENTS STATUS

ALZHEIMER'S DISEASE

In Sweden, every year, more than 25,000 individuals are diagnosed with AD. In AD, neuronal degeneration in the cerebrum lead to symptoms of dementia and death is usually within 10 years from diagnosis of the disease. AD is insidious, and can begin to develop 20-30 years before a dementia diagnosis. It is therefore important to study this disease from a lifetime perspective. Groundbreaking Swedish AD research has contributed to improved understanding of the disease process and to the discovery and development of methods for early diagnosis. Innovative treatments have been recently tested in the clinic.

prevention

Swedish studies have shown that in addition to advanced age and genetic factors, the risk of onset is affected by vascular factors, lifestyle and other environmental factors. High blood pressure, obesity and diabetes present in middle age increase the risk of AD in later life. Examples of protective factors are physical, mental and social activity and a balanced diet. Psychosocial factors are also important, and low level of education, depression, stress and loneliness can increase the risk. AD is therefore a multifactorial disease. Genetic background, biological and environmental factors interact throughout life simultaneously with the multiple biological processes that are involved in disease development. This knowledge has increased opportunities to influence the risk and prevent or delay dementia onset by interventions directed at risk factors. Swedish researchers have developed the first risk indicator for dementia that is now available in a mobile app version. It can be used to predict the risk of dementia later in life based on risk factors in midlife. Swedish researchers play a leading role in the ongoing EU project HATICE (Healthy Aging Through Internet Counselling), which aims to develop an internet-based platform for simultaneous multi-domain action for several risk factors.

treatment

The development of drugs for AD is directed partly toward alleviating disease symptoms (symptomatic treatment) and partly to stopping the disease process (disease modifying treatment). As the disease progresses, brain levels of the neurotransmitter acetylcholine are reduced. Three of the four drugs currently on the market against AD relieve disease symptoms by preventing the breakdown of acetylcholine, but they do not stop the development of the disease. Other systems of neurotransmitters may also be targets for drugs to alleviate symptoms of the disease, as well as drug therapy in combination with e.g. magnetic stimulation of the brain. The mechanisms leading to AD and premature death of neurons are complex and not fully understood. Specific genetic factors can cause illness but this is very rare (<0.1% of all cases) and most of those affected have sporadic AD. In AD, the most characteristic pathological changes in the brain are accumulations of amyloid protein in amyloid plaques or tau protein in neurofibrillary tangles together with inflammation. To date, therefore, experimental drugs have been directed to those mechanisms.

Despite intensive research, however, no new drugs have reached the market. Over 200 clinical trials have yielded negative results. Alzheimer's research is strong in Sweden, but animal models that reflect the complexity of Alzheimer's pathology are lacking and results from animal models have been difficult to translate into clinical treatments. Drug discovery and development is primarily directed towards preventing the accumulation of amyloid protein or tau tangles, where antibody therapy (immunotherapy) has recently been shown to be successful. Swedish researchers and companies in this area (BioArctic Neuroscience AB) have developed an innovative therapy that is now being tested clinically. Other pharmaceutical studies use the approach of preventing cell death, for example by supplying growth factors directly to the brain.

early diagnosis

Experience from many clinical studies has demonstrated that diagnostic markers are essential for effective clinical trials. These include new technologies and also new brain imaging techniques that enable measurement of structural and functional changes in the brain as well as biomarkers in the cerebrospinal fluid (CSF). Methods such as measuring amyloid proteins, will have great significance in the detection of early stage AD, which in turn would make it possible to intervene even earlier with countermeasures to halt or slow disease progression. The ability to quickly distinguish AD from other causes of dementia is a prerequisite for developing successful treatments. Researchers in Sweden are pioneers in the development of PET methods and in the development of biomarkers in CSF. In this area there are many opportunities for Sweden to develop valuable innovations for early detection and diagnosis of disease.

Swedish researchers and hospitals are famous worldwide for well documented and well executed clinical trials for AD. In Sweden there is a well characterized AD patient population and quality registries such as the Swedish Dementia Registry (SweDem). Success is based on strong cooperation among trial managers, health professionals, patients and the community. The direct interaction between pharmaceutical companies and leading international researchers in Sweden is a very important factor for the global pharmaceutical industry to consider in choosing to invest in clinical studies in Swedish hospitals. Well-documented biobanks also provide researchers with important materials for the development of relevant biomarkers.

CURRENTS STATUS

PARKINSON'S DISEASE

Parkinson's disease (PD) affects about 1% of the population in the 50-60 year age group. The disease is characterized by typical movement difficulties, tremor and muscle stiffness. These motor symptoms are due to a loss of specific brain cells that produce the neurotransmitter dopamine. The brain's ability to compensate for this loss of function explains why parkinsonian motor symptoms become manifest only after more than 60% of the dopamine-containing cells are lost. The disease also affects other neurotransmitters in the brain, and this is believed to cause depression, sleep disorders and decreased concentration, which often occur in PD. During the course of the disease, cognition is also affected, and severe dementia is experienced by a significant percentage of Parkinson's patients. In 90% of cases, the causes of PD are unknown, while in about 10% of familial cases, the disease is caused by mutations in a number of genes. One theory ascribes the development of PD to the spread and accumulation of misfolded proteins (especially alpha synuclein) in the brain. The intracellular accumulation of proteins that cannot be degraded would cause cell death through complex mechanisms.

Currently there is no cure for PD, however, symptoms may be treated with both drugs and neurostimulation (neuromodulation). Today, all patients are treated with L-DOPA, a substance that is converted into dopamine in the brain, thus providing a pharmacological dopamine replacement therapy. The scientific basis and experimental evidence for L-DOPA as a treatment was developed in Sweden by Professor Arvid Carlsson, who was awarded the Nobel Prize in 2000 for his discovery. L-DOPA is very effective on the typical movement difficulties of PD, but the response to this treatment changes during the course of the disease. After a few years most patients develop involuntary movements (dyskinesias). Swedish researchers and companies (Sensidose AB) have devised effective methods to reduce these complications. Bromocriptine, the first dopamine agonist in clinical use was also developed through Swedish research in neuropharmacology. The dopaminergic therapy, however, has only a partial effect on the non-motor symptoms of PD, such as sleep, depression and cognition. The development of methods to control the non-motor symptomatology of PD remains a significant challenge.

In order to develop curative treatments for PD, extensive additional basic research is required to better understand the disease etiology. Successful translational research is ongoing on several fronts, and new treatments to prevent or mitigate the consequences of the disease will probably be developed within 10 years. New strategies have been developed with the aim of either reducing the loss of dopamine-producing cells, elevating the levels of dopamine in the brain, reducing the spread of misfolded proteins, and/or mitigating non-motor symptoms. For example, Swedish researchers and companies have developed an antibody treatment for misfolded proteins designed to prevent the progression of PD. Another example (which has already reached clinical trial), is the substance PDGF-BB. This substance can potentially protect nerve cells in PD and was developed in Sweden by a collaboration between academic researchers and companies (NeuroNova AB). In addition, basic researchers in Sweden discovered several new molecular targets for drugs slowing disease progression (e.g. Nurr-1 receptor, sigma-1 receptor), which are currently being developed into innovations. In order to raise the levels of dopamine in the brain, non-pharmacological strategies based on stem cells or gene therapy are also being developed in Sweden. Stem cell technologies produce cells that resemble the patient's own dopamine neurons. Clinical transplantation studies with dopamine stem cells are now in the planning phase. Gene therapy transfers genes to the patient's own cells in the affected brain areas. With new Swedish technology developed by academic researchers and companies (Genepod AB), gene therapy can now be used to give the patient's own cells the ability to produce dopamine virtually anywhere in the brain. Moreover, both academic groups and companies are pursuing several research projects aimed at developing drugs that increase plasticity and drugs that can alleviate neuropsychiatric symptoms in Parkinson's patients. Additional drugs aim to prevent the development of treatment complications, especially dyskinesias caused by L-DOPA. Several Swedish companies are currently developing new treatments for PD (Integrative Research Laboratories-IRL AB, DanPet AB, Tedroff Neuro Care AB, Limulus AB, Neuronano AB). Electrical stimulation (deep brain stimulation, DBS) of certain nerve pathways in the brain relieves the motor symptoms of PD, and innovative Swedish research has also contributed to the development of new electrode materials and stimulation methods, which in the future can be developed into innovative treatments.

Today, PD is detected only when the majority of the dopaminergic cells are gone, therefore new biomarkers for early diagnosis are essential for a clinical application of treatments that aim at halting the disease. Extensive research is now underway in Sweden to identify predictive biomarkers for PD.

Swedish experimental and patient-oriented clinical research in PD is in the forefront, providing excellent conditions for important discoveries to be created that can be refined into innovations and new treatments. The Swedish Healthcare System provides very good opportunities to conduct clinical treatment studies extending over a long period of time. Furthermore biobanks, patient registries, and national and international research networks facilitate such studies.

CURRENTS STATUS

STROKE

A stroke occurs when blood flow to the brain is interrupted, e.g. by a blood clot, or by hemorrhage caused by rupture of a brain blood vessel. This leads to brain damage and loss of brain functions such as movement, speech and cognition, and is often accompanied by fatigue and depression. Globally, one person in six will suffer a stroke in their lifetime. In Sweden, stroke is the disease responsible for the most days spent in hospital for adults. It is the 3rd leading cause of death and the leading cause of disability in adults in Sweden, affecting about 120,000 people. The average age in Sweden for a stroke patient is about 73 years. Approximately 20% of those who suffer strokes in Sweden are under 65 and with future increases in retirement age, more and more working age people will suffer a stroke.

prevention

Risk factors for stroke encompass aging, hereditary, medical and social factors. Treatment of hypertension, diabetes, atrial fibrillation and cardiovascular disease prevents stroke, while lifestyle factors such as poor diet, lack of exercise and smoking increase the risk. Innovative methods for communicating information about risk factors to the general public can further reduce the incidence of stroke in the future.

recanalisation

Blood flow to the brain in stroke can be improved by removing the blood clot by pharmacological treatment (thrombolysis) or by mechanical removal (thrombectomy). The faster blood flow can be restored, preferably within one hour after onset, the greater the chance of reducing the spread of brain damage. Because of the rapid progression of injury, only about 13% of stroke patients in Sweden (and less than 1% of patients in the third world) are treated with thrombolytics. Innovations that provide early diagnosis of stroke will increase the number of stroke patients treated with thrombolytics. Swedish researchers and companies are already involved in this development (Medfield Diagnostics AB).

brain protection

There is evidence that reducing fever can diminish brain damage in stroke victims. Clinical trials are ongoing where Swedish researchers and companies (Quickcool AB, BrainCool AB) are developing new technologies that lower the temperature of the brain after a stroke. Swedish research has a long tradition in brain protection and research and development is currently underway in both academia and business (NeuroVive AB) with a focus on preventing secondary brain damage/reperfusion injury. However, so far, more than 100 clinical stroke studies with brain-protective substances have been carried out globally without success. Therefore, the pharmaceutical industry is currently less inclined to develop brain protective drugs for the acute treatment of stroke.

rehabilitation

Rehabilitation of a stroke patient, through exercise or compensatory measures, is an effective therapy for helping the stroke victim regain as much of lost brain function as possible. Our brains are plastic, i.e. the neuronal connections in the brain are remodeled for example during learning. During rehabilitation after stroke, brain plasticity is important for improvement of brain function when intact brain areas are remodeled and take over lost brain functions. Brain plasticity can be stimulated with low voltage electrical stimulation (transcranial direct-current stimulation, TDCS) or magnetic stimulation (transcranial magnetic stimulation, TMS). It is possible to start such treatments several months after the stroke, meaning that a majority of stroke patients can be candidates for various plasticity-stimulation treatments. With mirrors, tactile stimulation or virtual reality computer programs, the plasticity of the brain can be stimulated so the brain can decipher, for example, how to move partially paralyzed limbs. It is clearly proven that exercise improves motor function, but it is unclear how the frequency, intensity and format of the exercise affects recovery. Exercise that is pleasurable leads to an activation of the reward system of the brain and enhances the impact of the exercise. Computer games for training memory and motor function work according to this principle. Robotic technologies have been developed to activate and control functions of the brain, as well as for different types of training and for the evaluation of rehabilitation. Swedish researchers and companies (BioServo Technologies, Qualisys AB) are involved in these types of developments. Development of innovations based on small molecules or cell therapies that stimulate brain plasticity are ongoing in Sweden. It is a logistical challenge to evaluate recovery-stimulation treatments for stroke and it requires cooperation between different departments in the health care system. In Sweden, clinical stroke trials are known for their high quality. However, those who suffer strokes are a heterogeneous group, in terms of which areas of the brain are damaged, the extent of brain damage, and the profile of malfunctions. It is therefore important to develop better methods to identify relevant patient groups using innovative diagnostic tools and tests. Large and well-organized regional biobanks and quality registries, such as the "Riks-Stroke" and SITS (Safe Implementation of Treatments in Stroke) are valuable assets in this effort.

The innovation landscape in the area of stroke is thus multifaceted. Especially in the field of rehabilitation, Swedish researchers and companies can be expected to generate innovations based on robotics, computer-based training programs, electrical, pharmacological or cellular stimulation of brain plasticity and reward systems.

CURRENTS STATUS

THE PERSPECTIVE OF THE PHARMACEUTICAL INDUSTRY

Until the 1990´s the global pharmaceutical industry developed many effective and highly successful drugs for brain diseases and the profits were reinvested into research and development in order to find the next generation of CNS drugs. There were great expectations placed on these efforts, not least in light of the new knowledge derived from modern molecular biology, the potential of automation in drug screening and of analytical methods as well as the rapidly evolving information technology. Unfortunately, very few novel CNS drugs were developed as a result of these efforts. As a consequence, over the last 5-10 years there has been a clear trend towards decreased investments by the industry in the development of new therapies to combat brain diseases. In fact, several global pharmaceutical companies completely ceased discovery and development of drugs for diseases of the brain, or drastically reduced their research and development (R&D) efforts in the area. Global companies have instead come to rely on in-licensing of drugs in the late stage of development. The decreased involvement of the industry in brain research is predicted to decrease the availability of new medicines against brain diseases for at least a decade. Since the global pharmaceutical industry is one major source of funding for new innovations, a reduced interest by the industry in CNS risks having a negative impact on the development of innovations in academia. In the long term, this can negatively impact on the establishment of new small and mid-sized companies.

There are three partly interconnected reasons why the industry has left the therapeutic area of brain disease: (1) high risk of failure (2) patent expiries (3) portfolio management.

(1) The successful medicines developed during the period 1970-2010 were based on scientific discoveries made during 1950-1990 and the companies successfully launched many new drugs that were all directed towards the same disease mechanisms. Today, this strategy is challenged by the realization that brain disease mechanisms are insufficiently understood, hence the risk of failure is high for CNS R&D. Insufficient knowledge about disease mechanisms has numerous implications: for example it can result in investments in invalid drug targets, or reduce the possibility of developing diagnostic markers (which in turn are critical for the selection of relevant patient groups for clinical trials). Furthermore, the translation of animal experimental data has prompted investments in targets that had little relevance to larger patient groups. Thus, drug companies have had great difficulty in addressing medical needs in brain diseases where the underlying disease mechanisms were less well understood.

(2) In general, CNS drugs take longer to develop compared to many other disease areas, which also results in higher costs. Since failures often occur late in the value-chain, the cost of failure also tends to become very high. There is a risk that these aspects of CNS R&D will impact on the investment appetite for several years into the future.

(3) A change in research area strategy is also a reason for the exodus by the pharma companies from the CNS area. The successful basic science research in other areas such as cancer, inflammation and metabolic diseases – which is the result of many years of massive investments in academic research over a long time - has resulted in increased understanding of these diseases and numerous new drug targets have been identified for pharmacological intervention. As a result, knowledge and tools for precision medicine in these diseases have become available. As a consequence, this results in many companies changing their portfolio priorities, and we have seen a shift in strategic focus from CNS to other areas.

There are however signs that the industry will start to reinvest in diseases of the brain as soon as the right conditions emerge. This requires, however, a better understanding of CNS diseases and an uncovering of novel disease mechanisms that can guide drug development both in early and in late phases.

Although many companies have left the CNS area, there still are important players left and new ones have emerged that now sponsor important clinical trials in AD and PD as well as stroke.

It is unlikely that a major pharmaceutical company will emerge in Sweden in the near future, but smaller companies will be created and will grow within a positive environment for research that supports innovations. In fact, ongoing research in Sweden has resulted in novel concepts and new principles for treating CNS disease including new biomarkers that will be tested in the future. There are good reasons to have a positive outlook on brain diseases where research has made great progress in translating findings from animal experimentation to human clinical studies.

In the future it may be necessary, however, to finance the early part of the innovation process, primarily or partly, from public as well as private sources. In addition, new collaboration models between academia and industry are emerging that focus on non-competitive areas of R&D (e.g. “open innovation” and “precompetitive” alliances) or through close collaborations between academia and small companies.

In the future, Swedish innovators/entrepreneurs as well as innovation companies will also compete globally for resources including funding from major pharma companies . In a historic perspective the Swedish research community has done well in this competition due to its excellence in brain research. In order to ensure continued success, a massive investment into basic and clinical research on brain function and mechanisms of brain disease is needed in the future. A long-term perspective on brain research is required and resources need to be directed to the most innovative groups displaying scientific excellence. This applies to both basic-preclinical and clinical research in this area. Only with a good basic understanding of brain disease mechanisms can the industry be expected to prioritize CNS over other areas.

In order to translate important discoveries into new therapies or medical devices, stimulation of entrepreneurship in the academic community is essential. There also needs to be an increased willingness to invest in applied science. Innovations should stem from discoveries that are of a sufficiently high quality, so that major pharmaceutical companies will regard the risk of further investments to be acceptable.

CURRENTS STATUS

DEVELOPMENT OF NEUROTECHNOLOGY

Neurotechnology is the fastest growing area within the medical device industry and this has recently also included the participation of global pharmaceutical companies. Neurotechnology encompasses robotics and neuromodulation, the latter including technology products that affect brain activity and function, e.g. various forms of implantable electrode devices. Within the health robotics area products are developed that facilitate nursing care and enhance independence for people with disabilities, which is a natural component in the future of healthcare. Recent years have seen a dramatic development of robotic technology and artificial intelligence. Research shows, for example, that it is possible for the paralyzed patient to use his/her brain activity to control artificial arms and hands. Several new products are in early clinical trials that enhance a patient's own ability to perform everyday tasks, for example by supporting hand movements or walking movements, or to allow intensive training of reduced functions. Sweden has considerable expertise in basic neuroscience, cutting-edge technology and businesses that are involved in the development of neurotechnological innovation for the treatment and diagnosis of AD, PD and stroke.

The problems neurotechnological innovations face (besides those mentioned above for drugs) are of an administrative and regulatory nature such as difficulty in obtaining reimbursement and the differences in regulatory approval in different countries. Harmonization of future national guidelines for the approval of neurotechnology in healthcare is necessary for successful development and commercialization of neurotechnological innovations.

SMALL & MEDIUM SIZED ENTERPRISES AT THE CENTER

Innovative small and medium sized enterprises (SMEs) have a significant role in promoting growth and increasing employment in the life sciences sector. As evident in this agenda there are many Swedish SMEs currently developing innovative projects in the fields covered by this agenda. Many of these companies also have significant potential in international markets if they are successful. Financing is crucial for businesses to start, grow and develop to full capitalization of the company. Financial support for exploring market conditions and moving forward from an idea to a first concept validation are of paramount importance, especially in the discovery of new therapeutics for diseases of the aging brain where development costs and time required exceed those in other therapeutic areas. Diagnosis of the disease, recruitment of patients for studies and monitoring disease progression are particularly challenging in drug discovery and development for AD, PD, and stroke. Identification of patients who can be included in clinical studies with the help of stringent inclusion/exclusion criteria, in order to select those that are most likely to respond to treatment, constitutes a specific challenge in the development of treatment for heterogeneous diseases such as AD, PD and stroke. This results in higher demand on accurate diagnostic tools and biomarkers (both biochemical and brain imaging). Development of biomarkers should be developed in parallel with the development of the therapies. This is also the phase where costs increase significantly and it is therefore hard for small companies to support the full cost. In order to increase investment in clinical development, which requires long and costly clinical trials, it is essential that early feasibility studies of innovative therapies and technologies are performed in small Phase 0/I studies. By generating early data on humans, such as with a mechanistic biomarker that provides early indication of efficacy, or shows that the drug reaches its target in the body, we can build confidence in the project and reduce the likelihood of costly failures in the later phase.

The action plan in this agenda creates the conditions that enable various forms of cooperation between SMEs, research institutes, universities, and health care. By linking stakeholders from different technologies, disciplines and areas of expertise it creates the conditions for strong networks and well-functioning national partnerships, a condition for continuing the strong innovativeness of Swedish SMEs. With support for this proposed action plan, Swedish life science research will be in a much better position to initiate cooperation in order to develop new pharmaceuticals, biomarkers and neurotechnology products for a global market. Support for the agenda enables continued growth and development of independent Swedish SMEs in the life science sector.

HEALTH ECONOMIC ASPECTS

Given the very substantial costs of brain disease to society and the expected increase in individuals affected, a health economic perspective should be integrated in the agenda action plan.

Economics is the science of how finite resources are managed, and health economics is the application to the healthcare area and more broadly to all sectors of society that are involved in the care of individuals with brain disease, at risk of illness or with a suspected illness. Health economic studies, together with discussions on the equal right to care and autonomy, are integral parts of the decision process in the health care system. Diseases of the brain will have major consequences not only for affected individuals and their environment, but also for society as a whole, since they are often long-lasting, life-long, progressive, disabling and difficult to treat. Health and social care also involves county councils, large municipalities and family members. In a time of economic hardship for healthcare and social welfare stakeholders, it is important to analyze the costs and assess the cost-effectiveness of new treatments.

ACTION PLAN

1. DEVELOP INNOVATION

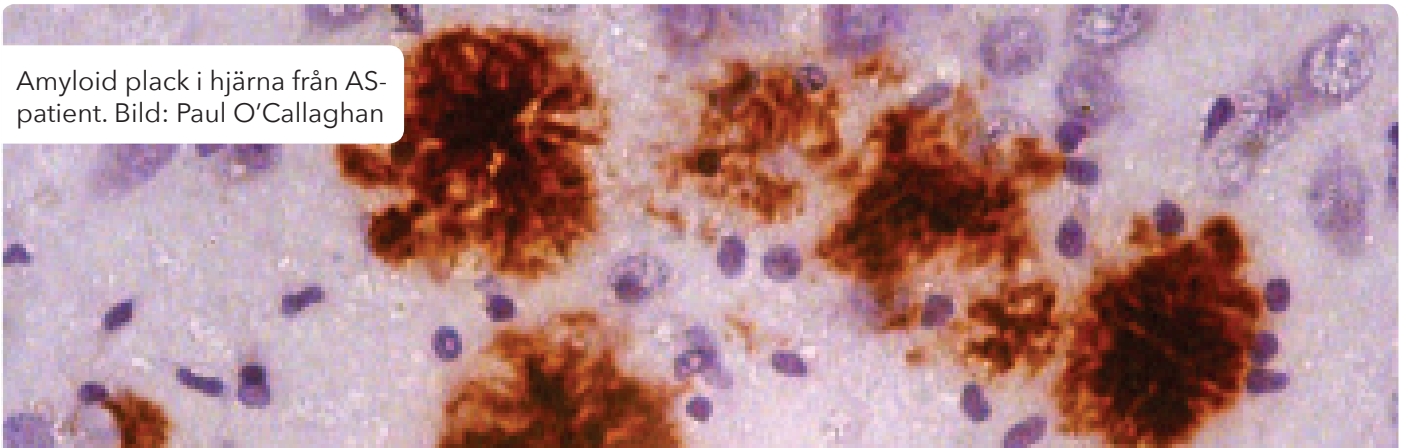
Knowledge of how the brain functions is the basis for developing ground-breaking innovations and treatments for brain diseases. About 80% of the current knowledge of the human brain comes from discoveries made during the last 20 years. The future potential is staggering. This has attracted the attention of governmental bodies in the US and the EU who have allocated large funds (over 10 years) to enable basic research on brain function, specifically, The Brain Research through Advancing Innovative Neuroscience Technologies (BRAIN) Initiative ($200 million/year) and The Human Brain Project (€50 million/ year). Similar efforts should be made by research funding agencies and organizations in Sweden. For Swedish innovation in disorders of the aging brain to continue, increased project funding from government and private donors is required for both interdisciplinary basic research on brain function and experimental and patient-oriented clinical research. Currently, far less than 1% of the societal costs for these diseases are allocated to research. As part of this effort, neuropharmacology should be re-established as a distinct academic discipline with dedicated services. This will raise the scientific profile, ensure the level of knowledge within medical/biological programs, and enable creative interactions with business and industry. Similarly, neurotechnology, especially robotics (including simulation-based neurorobotics), should be recognized as a new area of research. Today, there are several related activities, such as Robotdalen, Västerås; The Center for Medical Technology and Healthcare, Stockholm; Certec, Lund; the Swedish Strategic Research Area (SRA) and the Swedish e-Science Research Center, Stockholm. Another area of neurotechnology with high commercial potential is implantable electronic devices where Swedish researchers are in the forefront. However, there is no national structure or strategy leading these efforts.

A large part of outstanding Swedish research on age-related brain diseases is concentrated in Strategic Research Areas (SRAs) including Multi-Park and Stratneuro, the Linnaeus environments BAGADILICO, Neuronano Research Centre, Berzelius Centres, Stockholm Brain Institute and Uppsala Neuro Diagnostic Centre, as well as the Swedish Brain Power network. These networks are important catalysts of excellent research, and should be strongly supported in the future. Increased collaboration between networks and with the existing national methodology platforms is desirable in order to achieve synergy.

the agenda proposes

- ***Increased long-term funding for research on brain diseases from federal, state and private funders***
- ***Increased cooperation between Swedish researchers and interdisciplinary research groups in the field of diseases of the aging brain***
- ***Neuropharmacology and neuroscience technology to be established as academic areas***

"the goal is to increase the number of disease-relevant Swedish discoveries that can be developed into innovations"



Amyloid plack i hjärna från AS-patient. Bild: Paul O'Callaghan

2. OPTIMIZE THE PROCESS OF INNOVATION

The process of increasing the number of innovations to combat diseases of the aging brain is no better than its weakest link, so every step must be optimized and resources secured so that development will lead to products and commercialization. These include the initiation and processing of discoveries into innovations, such as the development of new diagnostic and medical technological instruments, drugs and therapies and improvement of clinical trial protocols and evaluation methods.

A: Encourage entrepreneurship - "from idea to implementation"

Sweden has very broad and solid expertise in the discovery and development of pharmaceuticals and therapeutics. An important driving force in the development of new innovations is that the appropriate conditions and resources are available for entrepreneurs to realize their ideas. Despite the growing medical need for treatment of brain disorders, we see little interest from the larger industry, venture capitalists and business angels to invest in new, and especially early, pharmaceutical projects in the field of brain diseases. Significant funding for basic research comes from research councils, charities and foundations and is awarded to researchers at universities. However, targeted resources for drug and therapeutic development are limited for both researchers and entrepreneurs who aim to pursue product development and start a new company. The same applies to businesses that are already established.

In order to create future growth with new creative ideas that are developed into innovations and new businesses it is of paramount importance that financing of early activities is prioritized and directed to the area of diseases of the aging brain. In addition, toxicological, pharmacokinetic, pharmaceutical and safety studies are costly but necessary for drug discovery and development. To boost innovative translational research, incentives should be given to the development of improved experimental models and clinical study protocols.

Several experimental models used to date have often been insufficiently predictive, resulting in poor translation of laboratory results to clinical studies. Moreover, a new trend in translational research is to perform multi-center preclinical drug testing studies with rigorous protocols similar those in clinical phase III studies.

"the goal is that creation of innovations in the area will increase and that corporate financing for early development is ensured"

the agenda proposes

- ***Targeted funding for drug and therapy discovery and development***
- ***Specific funding, "seed money" for start-up projects of new products (concept testing)***
- ***Specific funding for development of new products in the late preclinical phase***
- ***Specific funding for the preparation and initiation of clinical trials - a phase where costs increase significantly***
- ***Specific funding solutions that facilitate and improve preclinical to clinical translation***

ACTION PLAN

B: development of biomarkers

In order to monitor disease progression and the effectiveness of treatment, primarily neurological and neuropsychological examinations are currently used. These are often insufficiently sensitive to detect the disease before it has reached advanced stages. A development of new diagnostic methods and biomarkers is instrumental to both early interventions and reliable assessments of treatment effects. The development will apply to clinically validated biochemical biomarkers, brain imaging techniques, and other technologies allowing for sophisticated performance analyses (for example, multi-channel EEG) These instruments are essential for early diagnosis of disease, and thus to deliver better efficacy of disease-modifying treatments. In addition to assessing treatment effects, these tools will increase the understanding of disease mechanisms in clinical studies.

In order to develop successful treatments, it is important to both map the neurodegenerative diseases of different phenotypes (variants) and to identify the appropriate target for future treatments. Similarly, it is important to identify target groups of stroke patients with residual brain function using advanced brain imaging technology or robotics. Sweden's renowned population studies, patient registries, quality registries and established biobanks are important resources for research into disease and for the development and evaluation of new diagnostic instruments. This requires, however, national coordination for effective use. A prerequisite for clinically validated biomarkers for prediction, monitoring disease progression and treatment is that it be based on well characterized and accurately diagnosed patients and healthy controls that are followed over time with repeated examinations using standardized formats.

the agenda proposes

- ***Supporting the development of biomarkers and diagnostic methods that enable more stringent inclusion / exclusion criteria in clinical trials***
- ***Support for national coordination, management and secure operation of biobanks and patient databases***
- ***Support for longitudinal studies (up to 20 years) to follow patients with repeated clinical examinations and sampling of blood and CSF and imaging of the brain***

"the goal is to develop biomarkers for early disease diagnosis, prognosis and assessment of disease treatment"

ACTION PLAN

C: develop clinical infrastructure and clinical trials

By developing, validating and implementing more quantitative, objective and sensitive evaluation instruments/methods in clinical studies, the number of study patients is minimized, costs are better managed, studies provide more clear-cut results, and relevant performance measures are obtained. The risk of failed Phase III studies will also be reduced. In order to implement new biomarkers and enable the national Swedish research networks for AD, PD and stroke to conduct multi-center clinical studies within the country at a high quality, testing protocols, analytical methods and data processing must be standardized. Through continued and increased involvement in international networks such as the Innovative Medicine Initiative - European Prevention of Alzheimer's Dementia (IMI EPAD) for AD, Parkinson's Progression Markers Initiative (PPMI) for PD, synergy can be achieved through shared use of standardized procedures and data management. Patient associations should also be involved in the agenda action plan to enable awareness of ongoing studies and to support finding suitable patients for the studies.

"the goal is to improve protocols and to standardize objective methods for biomarker analysis used in clinical trials and for better assessment of the effectiveness of therapies, thus attracting the global pharmaceutical industry to conduct clinical trials in Sweden"

the agenda proposes

- ***Support for the development of clinical trial protocols (stage 0, I, II and III) for relevant categories of patients to be included in the studies and to objectively evaluate disease mechanisms that affect the disease progress***
- ***Support for the implementation of Phase 0 studies, small clinical studies to provide information about the individual variation of novel biomarkers and statistical analyses***
- ***Support in order to validate new biomarkers and technologies with respect to sampling, sample treatment effects, analysis and data management***

D: evaluate health economic aspects

Health and social care of people with brain disorders is complex with many players and payers, such as municipalities, counties, state, insurance companies, private healthcare companies, patients and their families. Therefore, the costs and effects of various interventions can be described in terms of each payer's perspective or from a societal perspective. The concept of "cost effectiveness" is often used loosely, in the sense that the cheapest treatment is thought to be preferable and that a measure bringing cost reductions is "cost-effective". This is a misleading argument. There is always a societal (and individual) willingness to pay (WTP) for a treatment that is judged to be more advantageous than another. This means that for a new treatment, a decrease in cost does not have to be delivered in order for it to be cost-effective. The problem is partly to find endpoints that are relevant, that provide opportunities to compare different situations, and to determine the WTP. Health economists and authorities who make decisions about how much, for example, drug therapy, should be subsidized by society ("reimbursement"), would then have an instrument that allows for comparisons between different medical situations, such as QALYs (quality adjusted life years) or DALYs (disability-adjusted life years).

"the goal is to develop a relevant and objective evaluation model for each disease area and to provide innovators with an adequate description of the economic benefits of innovation"

the agenda proposes

- ***Revise disease costs for AD, PD and stroke from a societal perspective, and review the distribution of resource consumption and costs among different societal actors***
- ***Perform a cost estimate associated with innovative treatments and diagnostic instruments***
- ***Describe a strategy of cost-effectiveness, analyzed from a societal perspective for innovations***

3. INCREASE COMPETENCE AND ATTRACTIVENESS

Creating innovation should be a natural part of research activity in academia and health care. However, this requires training of researchers and medical professionals in entrepreneurship and providing information to decision makers in government agencies.

National training activities should occur mainly at the local level, close to the researchers, in co-operation with small businesses (success stories) and industry.

To enable more individuals to be involved in innovation, its attractiveness must be increased. The current funding systems and criteria for employment in academia or health care do not reward innovation in the same way or to the same extent as they reward research activities.

A professional and dedicated medical staff is crucial for the success of clinical studies. It is therefore important that Swedish university hospitals build professional research platforms specialized for particular disease areas, and that the merit value and support for physicians participating in clinical studies and trials is raised. Collaboration and mobility between small companies, healthcare and academia should be encouraged at all levels.

Interaction between pharmaceutical companies, small companies and academia through joint training programs at doctoral/post-doctoral level and joint projects should be encouraged where projects are based on common goals. The plan should be designed so that participants can physically work at both the university and the company during the course of the project. Collaboration also allows people within the industry to have the opportunity to get academic qualifications through scientific publications and as supervisors. The possibility of bringing researchers from companies to academia should be improved and simplified.

"the goal is to create a group of highly trained, motivated innovators and entrepreneurs that drive the innovation process forward"

the agenda proposes

- ***Support for local training (doctoral/post-doctoral) in entrepreneurship and drug discovery and development in a collaboration between academia and business***
- ***Support for a national coordination of resources to increase exchange between the local educational initiatives***
- ***Support for increased cooperation and mobility between industry, academia and healthcare***
- ***Raise the qualification value of innovation activities and work experience from the pharmaceutical industry in impact evaluation and appointment of academic services***
- ***Special support for healthcare professionals participating in clinical trials of innovative therapies for diseases of the aging brain***

4. CREATE SUSTAINABLE LONG-TERM FUNDING

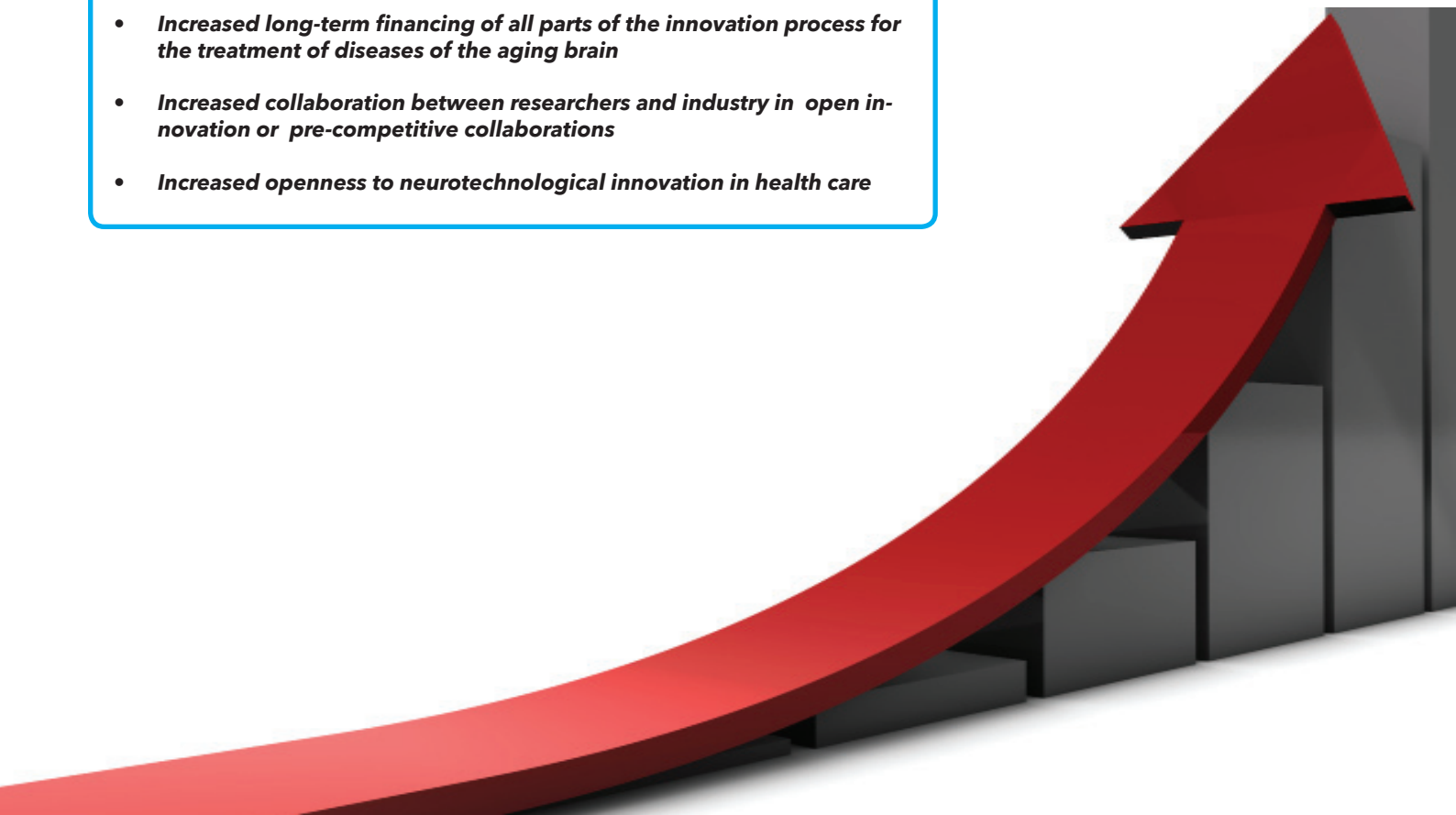
Long-term, sustainable financing for the various parts of the innovation process is a prerequisite for the successful development of new treatments for diseases of the aging brain. Meanwhile, it is clear that the current financial and working models are inadequate and must be improved and supplemented. Increased coordination and co-financing of innovation projects between government research funding agencies (Swedish Research Council, VINNOVA, Formas) should take place, as well as between governmental and private funds. Furthermore, new forms of cooperation, open innovation, pre-competitive collaborations, between companies and researchers should be considered.

Also, new kinds of cooperation between entrepreneurs/companies and the health care system must be developed, especially in the area of neurotechnology. Currently, such innovations are difficult to implement in health care, and there are informal and formal barriers together with a lack of national coordination. Decisions and responsibilities are often divided between political governance and hospital management. Therefore a climate of innovation should be created within the health care system, providing incentives for politicians as well as hospital management. Sweden needs a strong domestic market for neurotechnological innovation.

"the goal is to secure long-term and sustainable funding of the innovation process"

the agenda proposes

- ***Increased long-term financing of all parts of the innovation process for the treatment of diseases of the aging brain***
- ***Increased collaboration between researchers and industry in open innovation or pre-competitive collaborations***
- ***Increased openness to neurotechnological innovation in health care***



5. ESTABLISH A NATIONAL INNOVATION NETWORK FOR COLLABORATION

Sweden is ready to lead the development of innovative treatments for diseases of the aging brain. The participants writing this agenda, representing various stakeholders, have shown strong commitment and desire to form a "national innovation network for diseases of the aging brain" as a national Swedish arena for collaborations and training. Swedish researchers and entrepreneurs, national methodological platforms, small businesses, the pharmaceutical industry, health care, patient organizations, public agencies and private financiers should be invited to participate in the network activities.

The main task of the network is to organize annual partnership meetings for collaboration on the development of innovations and also for various training initiatives. The major challenges for creating innovations in the area require joint efforts and collaboration with corresponding international networks. Applications to the EC Horizon 2020/Eurostars, EIT Health or IMI will be supported, where the entire network or parts of it can be included as partners. The network will also become a national and international opinion leader. In order to fully implement the action plan of the agenda, an innovation program with a dedicated budget to evaluate, prioritize and finance innovation projects should be established and managed by the network.

"the goal is to join all the forces working in the innovation process in a national innovation network for diseases of the aging brain to implement the agenda's action plan"

the agenda proposes

- ***Support the formation of a national innovation network for diseases of the aging brain***
- ***Support for annual network meetings, training initiatives and awareness campaigns***
- ***Support for the formation of a national innovation program for diseases of the aging brain for full implementation the agenda's action plan***

THE FUTURE - PROPOSED GOALS

BY 2020:

- A national innovation network for the diseases of the aging brain is established that organizes annual joint partnership meetings, local educations programs to increase the attractiveness of the area and stimulate entrepreneurship
- There will be increased collaboration between academia, national methodological platforms, healthcare and corporate drug discovery and development
- There will be more innovation in preclinical discovery and development in research companies
- There will be funding from Horizon 2020 / Eurostars, EIT Health and IMI

BY 2025:

- There will be innovations developed in the field of biomarkers and neurotechnology
- There will be well-organized joint national quality registers and biobanking facilities to support all stakeholders in the innovation process that will become role models and the global standard
- Sweden will be an attractive venue for clinical trials with Swedish clinics as obvious partners

BY 2035:

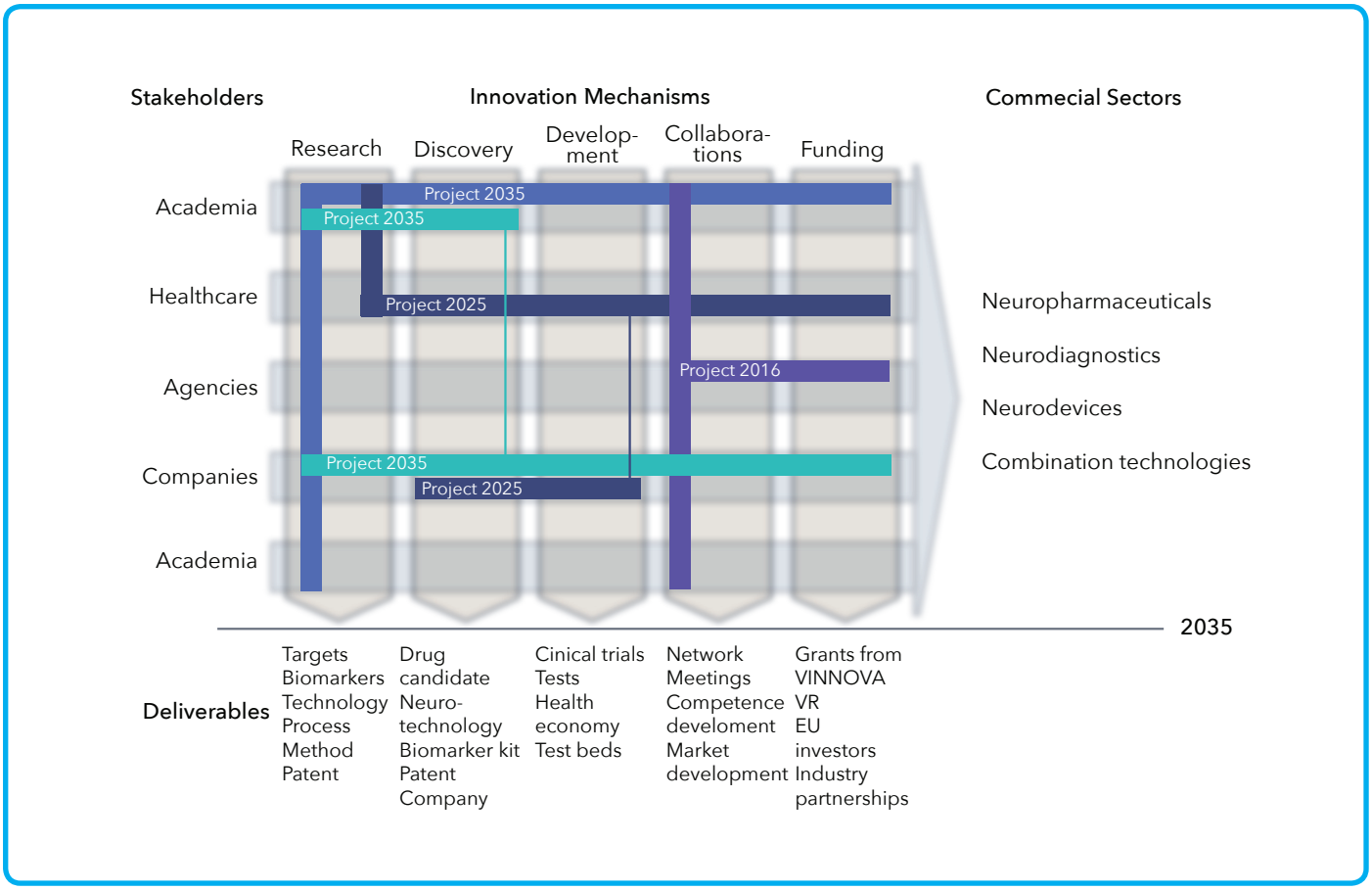
- There will be at least two Swedish SMEs transformed from a research company to a drug discovery and development business with future marketing and sales capabilities
- There will be at least one new treatment based on a Swedish innovation that cures or prevents the development of AD or PD, or that restores function and minimizes disability after stroke
- There will be diagnostic Instruments developed (laboratory-based biomarkers, brain imaging algorithms, in silico quantitative prediction models) and clinical evaluation instruments for the efficient evaluation of clinical products (computer based, medical)
- There will be neurotechnology products (computer games, robots, tools) on the market
- There will be an increased presence of international pharmaceutical companies in the field in Sweden

NEXT STEPS

In order to attain the goals proposed by the agenda and implement its action plan, a "national innovation network to combat diseases of the aging brain" will be established where success is based on cooperation between the stakeholders of the agenda (Figure 2). During the time the agenda was being compiled, several innovation projects have been initiated among various stakeholders and preparation of Horizon2020 applications has also been initiated. Four product areas have been identified where the network participants interact in defined projects to reach objectives in the agenda. Five innovation mechanisms are at the core of the action plan and these contribute to an optimized, coherent innovation chain that leads to new products and therapies and, ultimately, to increased Swedish competitiveness and growth.

FIGURE 2

A scheme of how the goals of the agenda will be reached and products created by joint cross-border projects among the stakeholders of the agenda



>THE AGENDA PROCESS

This agenda has been developed within the framework of the strategic areas of innovation, a joint venture between VINNOVA, the Swedish Energy Agency and Formas. The purpose of the initiative is to create conditions for Sweden's International Competitiveness and sustainable solutions to global societal challenges.

There is a need for a strategic agenda for age-related diseases of the brain because this area represents unique challenges for entrepreneurial and industrial development in Sweden. This agenda is therefore a collaborative effort compiled by national stakeholders from industry, academia, healthcare, government and other organizations. Three workshops/meetings in Lund and Stockholm as well as an editorial meeting in Gothenburg in 2015 have been instrumental for the writing of the agenda. The work during this period has also taken place in smaller local meetings, emails, telephone and Skype conferences and in various working groups and constellations, and with a steering committee with representatives from various areas and with national representation supporting the activities. Various reference groups/individuals have contributed their unique expertise during the work, including several representatives from global industries. We would like to thank all participants who contributed with their valuable time and expertise to establish a national strategy for the future, how to combat the disease of the aging brain.

"There is a need for a strategic agenda for age-related diseases of the brain because this area represents unique challenges for entrepreneurial and industrial development in Sweden"

Tadeusz Wieloch, Lund University, Coordinator & Editor
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Small & Medium Sized Enterprises: BioArctic NeuroScience AB (Johanna Fälting*, Gunilla Osswald), BioServo Technologies AB (Tomas Ward*), CBD Solutions AB (Samuel Svensson), DanPET AB (Dan Peters), Denator AB (Charlotte Emlind, Karl Sköld), GE Health Care (Helena Nordvarg) Integrative Research Laboratories Sweden - IRL AB (Peder Svensson*), KaroBIO AB (Marie Österlund), Limulus AB (Per Petersson), Red Glead Discovery AB (Johan Evenäs, Martina KvistReimer), SARomics Biostructure AB (Sten Sörensen), Quickcool AB (Lennart Sjölund)

Region Skåne: Ulf Malmqvist

Others: AlzeCure Foundation (Johan Lundqvist *), The Swedish Association of the Pharmaceutical Industry – LIF (Karolina Antonov), SweTox (Ian Cotgreave, Heike Helmold), SciLifeLab (Per Arvidsson), Astra Zeneca Biohub (Magnus Björsne)

Invited international company representatives: Jan Egebjerg, (Lundbeck A/S), Christer Köhler*, (LaCie AB); Bernd Sommer, (Boehringer Ingelheim Pharma), Gert Rode, (GE Health Care)

** editorial board*

> LINKING WITH OTHER AGENDAS

Several other strategic agendas and programs granted by VINNOVA have touched on points on this agenda, "combating diseases of the aging brain". A central theme that is consistently found in virtually all the agendas and programs puts the innovation process in a special area.

The Strategic Innovation Program (SIP) SWElife generally focuses on common diseases with several different actors along the value chain, such as health and social care, academia, small businesses, global industry, organizations and government agencies. The program has been expanded with another agenda "personalized medicine" where the focus has been on *individually tailored treatments*.

Medtech 4 Health is another SIP that would generally strengthen the process of innovation in *medical technology/devices*.

Agenda - An Aging Population - touches on a central theme of this agenda with respect to the *target audience*.

Agenda - image-based medical diagnostics - deals with another important field in this agenda - *imaging technologies* - for diagnosis and monitoring of disease progression.

Digitization and technology and service within health and social care and other actors in society affect agendas: **eHealth in the home, GAME, Digital Innovation & Growth, Health and Social Care in the Information Society, Strategic Agenda for service innovation in Sweden, Patient involvement in service innovation, Nanotechnology for sustainable social, additive manufacturing and 3D printing, Photonics - an enabling technology for Sweden**. These have fewer connections to this agenda, but there are interesting points in common. Gaming is an interesting development in the rehabilitation and training, but app development is also an emerging industry where monitoring of disease and other applications are rapidly developing. The strategic program - the Internet of Things and smart electronic systems - also have a slight connection to this agenda in regard to *digitization* and *technology development*.

>COMPANIES & ORGANIZATIONS supporting the agenda

Academia: University of Gothenburg (UGOT), Karolinska Institute (KI), Lund University (LU), Royal Institute of Technology (KTH), Uppsala University (UU), Umeå University (UMU)

Health care providers: Region Skåne, Västra Götalandsregionen, Stockholm County Council, Uppsala County council

Swedish pharmaceutical companies and associations: BioArctic Neuroscience AB, Bioservo Technologies, CBD Solutions AB, DanPet AB, Denator AB, Genepod AB, IRL – Integrative Research Laboratories Sweden AB, Karo Bio AB, Limulus AB, Medfield Diagnostics AB, NeuroVive Pharmaceutical AB, Read Glead Discovery AB, SARomics Biostructures AB, Tedroff Neuro Care AB, Qualisys AB, Quick Cool AB, Quixolabs AB, The Swedish Association of the Pharmaceutical Industry (LIF)

Research networks: BAGADILICO (Linnaeus environment for basal ganglia diseases LU), MultiPark (SRA at LU/UGOT), Neuronano Research Centre (Linnaeus environment, LU), SeRC (SRA within e-science at KTH, KI and SU, and LiU), the Stockholm Brain Institute, StratNeuro (SRA at KI/UMU), Swedish Brain Power (network of Swedish researchers in PD, AD and amyotrophic lateral sclerosis), SWEPAR-Net (network of Swedish university clinics and preclinical scientists that organizes clinical trials for PD at the national level), Uppsala Berzelii Techology Center of Neurodiagnostics (SRA at UU)

Other organizations: AlzeCure Foundation (non-profit research foundation), Central and regional ethics committees, Swedish center for toxicological sciences (SweTox), The Swedish Brain Foundation

Patient organizations: Alzheimer Sweden, The Swedish Parkinson Association, The Swedish Stroke Association