Healthy longevity, precision medicine and next-generation therapeutics

The Future of Life Science at Engelsberg 2023

Published: April 2024
Publisher: Stockholm Science City Foundation
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Introduction

Life science is all about revealing the mysteries of life. Life science research aims to understand and explain various processes and phenomena related to living organisms, with the ultimate goal of increasing human knowledge, allowing people and animals to lead healthier lives, and improving the well-being of our planet. An important long-term goal is to support the healthy ageing and longevity of humans. This can be achieved at several different levels: basic research activities aim to map and understand the fundamentals of biology, the mechanisms of ageing and processes associated with disease; while applied research and development at academic institutions and businesses often involves finding new approaches and developing products to characterize and treat diseases.

"The intention of the report is to focus on key topics which highlight the status, immediate challenges and possibilities for the future."

To explore how different ongoing initiatives within life science increase both our health and life spans, Stockholm Science City Foundation hosted the symposium *The Future of Life Science: Healthy Longevity, Next-generation Therapeutics, and Precision Health*, at Engelsberg Ironworks on May 4-5, 2023.

This report aims to give an overview of some of the current, important advances within life science that were highlighted during the symposium. The intention of the report is not to cover all the topics discussed at the symposium, but rather to focus on key topics which highlight the status, immediate challenges and possibilities for the future. At the end of the document, there are reflections on the key drivers for investments in research and development within life science.

Engelsberg Ironworks

Background

During the last century, life expectancy has almost doubled globally[1] as result of both social and medical advances. At first, the decline in infectious diseases and deaths among children and the young accounted for a rapid increase in average lifespans. Cardiovascular disease and cancer, which mainly affect older people, subsequently became predominant factors limiting life expectancy, and the major focus for medical research. Today, death is often the result of a chronic disease, which develops over a long lifespan. Treatments of chronic diseases have successfully reduced mortality and hence more people with chronic diseases survive for longer.[2] This means that the lifespan increases but not always the 'healthspan', i.e. the years a person is healthy, not just alive.

Many recent advances within life science and healthcare have the potential to increase both healthspans and lifespans. This report briefly discusses three different parallel trajectories which were highlighted during the symposium:

- The shift towards precision medicine and the use of next-generation therapeutics.
- The promise of preventive actions.
- The rise of geroscience which applications aim to delay the processes of ageing.

Different interventions to increase health and/or decrease the burden of disease can be represented on a ladder with the most reactive action on the bottom and the most preventive action on the top (see Fig 1). Until recently, human medicine has mostly been focused on relieving symptoms and in some cases curing diseases, alongside basic preventive actions such as avoiding smoking and minimise exposure to harmful substances. With the accelerating rate of scientific discoveries and medical and technical development, we are now rapidly moving up the steps towards the ability to cure an increasing number of diseases - including those earlier defined as chronic - and to regenerate normal functions in genes, cells and tissue. To understand the individual risks of developing different diseases. Hence, lifestyle changes and preventive interventions can now be suggested at the personalized level.

"We are now rapidly moving up the steps towards the ability to cure an increasing number of diseases."

Recently, clinical studies have been set up to examine if ageing processes can be delayed or even reversed. The benefits and challenges of reaching the upper steps will be further discussed in this report.

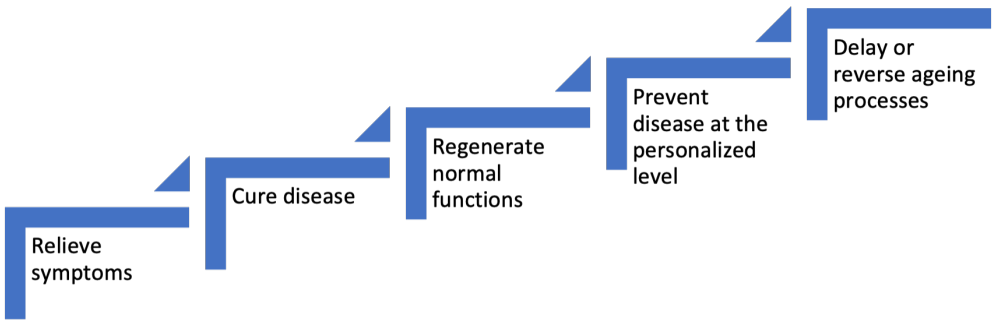

Figure 1: Ladder of interventions to increase health or decrease the burden of disease.

[1] *Data Page: Life expectancy at birth, part of the following publication: Saloni Dattani, Lucas Rodés-Guirao, Hannah Ritchie, Esteban Ortiz-Ospina and Max Roser (2023) - "Life Expectancy". Data adapted from Human Mortality Database, United Nations, Zijdeman et al., James C. Riley. Retrieved from https://ourworldindata.org/grapher/life-expectancy*

[2] *Eileen M. Crimmins (2015). Lifespan and Healthspan: Past, Present, and Promise. Gerontologist, 55(6), 901–911. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4861644/pdf/gnv130.pdf*

Systems biology, precision medicine and next-generation therapeutics

Status and promises for the future

During the last few decades, there has been an explosion in the amount of data describing biological systems. New technologies and experimental procedures have been developed enabling studies of more complex systems, which better explain the biological processes of living organisms. By combining studies of genes, proteins and other molecules, such as metabolites, in cells and tissues, new understanding of biology and the mechanisms of diseases is generated. This has given rise to the concept of systems biology - the study of biological systems whose behavior cannot be reduced to a linear sum of the functions of their parts.

Systems biology often focuses on complex interactions within an organism, tissue or cell. It includes both experimental approaches and mathematical modelling. Increased knowledge at the mechanistic and systemic levels has led to the development of precision medicine within healthcare, where the most suitable treatment can be given to a specific patient at the right time, based on individual factors including genes, environment and lifestyle of the patient. Systems biology, precision medicine and the data revolution in life science and healthcare have been topics of earlier symposia and are discussed in previous reports. [3,4]

Genome sequencing has enabled precision diagnostics based on different mutations and genetic profiles, and has led to new treatments which are more effective, often with fewer or less severe adverse effects. This has increased survival among several patient groups, including cancer patients and those with rare diseases.

Claudia Langenberg

"Changes in protein levels often reflect the consequences of a disease, which makes them good predictors."

Recently, the use of protein profiling has further increased the understanding of a large number of diseases. At the symposium, **Claudia Langenberg**, Director of the Precision Healthcare University Research Institute at Queen Mary University of London, UK, and Professor of Computational Medicine at the Berlin Institute of Health at Charité, described how her research group has used genomics in combination with profiling of proteins present in blood plasma to create a so-called proteo-genomic map of human health, describing the connections between different diseases and traits to the levels of different proteins in blood plasma and to gene variants. The map both confirmed already-known associations between gene expressions, protein levels and diseases but also revealed new associations. For example, previously unknown variations associated with neglected diseases were found. Changes in protein levels often reflect the consequences of a disease, which makes them good predictors of health and disease, and hence can be used as biomarkers. The profiling of proteins can also provide information which leads to improved understanding of disease pathways and mechanisms and may be used to find new targets for drugs. It has also been shown that changes in protein profiles in the blood may occur before any symptoms occur. Protein profiling can therefore be used in early detection with high accuracy.

[3] *Stockholm Science City Foundation. (2020). Report: The Future of Life Science – Health data and precision medicine.*
https://ssci.se/sites/default/files/Health%20Data%20and%20Precision%20medicine_0.pdf

[4] *Stockholm Science City Foundation. (2023). Report: The data revolution in life science and healthcare.*
https://ssci.se/sites/default/files/Data%20revolution%20in%20life%20science%20and%20healthcare.pdf

To summarize, the multi-omics approaches (i.e. combining profiling of different components such as genes, proteins or metabolites) increase the understanding of mechanisms taking place under normal conditions as well as in diseased states. They also enable early and more precise detection and diagnostics of specific diseases. Providing higher diagnostic accuracy and the possibility to stratify patients into specific groups increases the chances of selecting a treatment that works and diminishes the risks of using a less effective or futile treatment. This means that precision medicine may also reduce costs.

Eskil Degsell

Precision medicine is however not solely to be associated with advanced technologies that enable molecular analyses and targeted treatments. Differences in personal life such as family support and interactions with healthcare professionals often affect how certain diseases progress at the individual level. **Eskil Degsell**, patient and next-of-kin representative at Karolinska University Hospital, highlighted several studies which provide evidence for the importance of these "softer" factors. For example, markedly prolonged survival was recorded for patients with glioblastoma (brain tumors) who had family members able to provide a high level of care.[5] Another example shows that the median survival is six months longer for lung cancer patients who could report symptoms through a web application, enabling early detection of relapses.[6]

The progress of new precise diagnostics and increased understanding of disease mechanisms go hand in hand with the development of advanced therapeutics. Biological pharmaceuticals have taken an increasing share of the newly registered drugs during the last two decades.[7] Lately, the next generation of biological drugs, including cell- and gene therapies, have entered the market. So-called, Advanced Therapy Medicinal Products (ATMP) are being developed and released to market at an accelerating rate. ATMPs consist of genes, cells or tissues, and often aim to be curative treatments, where one or a few doses are expected to restore normal functions in the body.

"Markedly prolonged survival was recorded for patients with glioblastoma (brain tumors) who had family members able to provide a high level of care."

Karina Thorn

At the symposium, **Karina Thorn**, Corporate Vice President and head of RNA and Gene Therapies at Novo Nordisk, gave an overview of the global market status and development pipeline of cell-, RNA-, and gene therapies. To date, more than 70 treatments are on the market, while another 700 are in clinical trials and 1600 are in preclinical development. Altogether, more than 200 clinical indications are covered. Hence, in the coming decade, next-generation therapeutics will enable completely new ways to cure diseases. The healthcare systems, the health economics consideration as well as the market access system for new drugs will have to adapt to these changes.

"In the coming decade, next-generation therapeutics will enable completely new ways to cure diseases."

[5] *Boele FW et al. (2022). The Added Value of Family Caregivers' Level of Mastery in Predicting Survival of Glioblastoma Patients: A Validation Study. Cancer Nurs. 45(5): 363-368.* https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8964825/

[6] *Denis F et al. (2017). Improving Survival in Patients Treated for a Lung Cancer Using Self-Evaluated Symptoms Reported Through a Web Application. Am J Clin Oncol. 40(5):464-469.* https://pubmed.ncbi.nlm.nih.gov/25811297/

[7] *de la Torre BG & Albericio F. (2023). The Pharmaceutical Industry in 2022: An Analysis of FDA Drug Approvals from the Perspective of Molecules. Molecules 28(3):1038.* https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9921400/

Challenges

What are the challenges related to precision medicine and the next-generation therapeutics? With the introduction of precision medicine, we are moving away from generalized treatment schemes towards much more individualized treatments using targeted and sometimes individually tailored drugs. This shift will challenge the way in which clinical trials are performed, the way healthcare is delivered, and how healthcare systems fund treatments.

One direct and immediate challenge is that research needs to be more tightly integrated into clinical practice. Even though research and clinical practice need to be more integrated, Claudia Langenberg stressed that we should be careful not to confuse the excitement in the lab at being able to do multi-omics and collect a billion data points, with health outcomes. While researchers often want as much data as possible, healthcare relies on simple, cost-effective methods, providing clear and actionable results. At present, multi-omics and protein profiling in blood samples are typically too expensive for regular use in healthcare, and the validation of protein profiles as biomarkers for use in clinical practice is still ongoing.

Effective implementation of precision medicine also requires data access and data sharing among hospitals. Legislation in Sweden has made the sharing of personal data such as genetic data challenging, and in November 2023 an official report including a review of the legislation and suggestions for changes was handed to the Swedish government. [8]

The more we learn about genes, proteins, metabolites or epigenetic modifications, the greater the potential for developing more precise diagnostic methods. As described above, these methods may be used to detect very early stages of diseases, and also to assign risk scores for the risks of developing different diseases. This is clearly a good thing, but it may raise ethical challenges. One is that for an increasing number of diseases, there are methods to accurately predict the risks of developing the disease but no treatments exist, which raises the question of when and if such predictive tools should be used.

A major challenge with novel cell and gene therapies is related to costs. Often the promise is that only one or a few treatments are potentially curative, but the cost per treatment is very high. The cost depends on several factors. **Firstly**, the production cost is much higher than for traditional pharmaceuticals since these pharmaceuticals are based on biological material that may be difficult and expensive to produce in large quantities. Cell therapies often require individualized treatments where biological material from the patient is used as the starting material and then modified in a laboratory before it is reintroduced into the patient. Hence, new types of infrastructure for the production of advanced therapeutics are often needed. **Secondly**, precision medicine implies that patient groups are stratified into smaller groups for which specific drugs or other interventions are developed. Hence, more variants of drugs must be produced and the development costs for each drug variant will be borne by fewer patients. **Thirdly**, the price a company can ask for a novel drug depends on the availability of alternative treatments and how the novel treatments compare to the existing ones.

"A major challenge with novel cell and gene therapies is related to costs."

How can the high cost of a novel treatment be justified and what are the consequences of introduction? In Sweden, the healthcare law states three core principles:[9]

1. **human dignity** - equal entitlement to dignity, everyone should have the same rights, regardless of their status in the community.
2. **need and solidarity** - those in the greatest need and most severe conditions take precedence in medical care.
3. **cost-effectiveness** - when a choice has to be made between different healthcare options, there should be a reasonable relationship between the costs and the effects, measured in terms of improved health and improved quality of life.

[8] *SOU 2023:76. Vidareanvändning av hälsodata för vård och klinisk forskning. Retrieved March 2024 from https://www.regeringen.se/rattsliga-dokument/statens-offentliga-utredningar/2023/11/sou-202376/*
[9] *Anell A, et al. (2012). Sweden: Health system review. Health Systems in Transition, 14(5):1-159 https://pubmed.ncbi.nlm.nih.gov/22894859/*


Lars Sandman

One has to remember that when resources are limited there is always an opportunity cost associated with a specific investment, and the cost-benefit of a treatment is often measured in cost per quality-adjusted life-year (QALY). The idea is to not only measure the number of extra years a treatment adds to a patient's life but also the quality of life during these years. To get the QALY for a specific treatment, the added life length (in years) is multiplied by the quality of life (where full health has the value 1 and death has the value 0). **Lars Sandman**, Professor of Healthcare Ethics and Director of the National Centre for Priorities in Health at Linköping University, pointed out that research has shown that in the Swedish healthcare system, the marginal cost of one QALY is approximately 200,000 SEK.[10] Hence, if resources in the system are limited and stable over time, the introduction of a novel treatment costing 200,000 SEK per QALY means that for each gained QALY, you will have to sacrifice one QALY somewhere else in the system. If a new treatment costs 1,000,000 SEK per QALY, five QALYs will be lost somewhere else. The health you win for some patients will be lost somewhere else, and most often you will not know where that health is lost. As Lars Sandman put it, when resources are limited and governed by yearly budgets you have to prioritize, and the prioritization will always include comparing and weighing different values against each other.

The model of opportunity costs outlined above is of course an oversimplification of the reality of social economy. Firstly, one treatment may, for example, prevent the onset of not only the primary disease but also secondary diseases which may be costly for society over a longer timescale. Secondly, the model does not include societal costs related to the inability to work or costs related to informal caregivers such as family and relatives.


Jakob Tellgren

Even if novel and presumably curative therapies, such as gene and cell therapies, are associated with a very high upfront payment, they may be cheaper in the long run than using existing treatments continually for 20 or 30 years to lessen symptoms and/or the progression rate of disease. However, the money to pay up-front for the curative treatment needs to be taken from somewhere in the system. As **Jakob Tellgren**, Vice President and Head of MSD operations in the Nordic and Baltic region, pointed out during the symposium, the market access system (i.e. the system for approvals, recommendations, subsidies and payment of new drugs) is not yet set up for these new treatments. It needs to be updated to be fit for purpose and it could be beneficial if new models are negotiated between the governments, payers and industry.

Relating to the market access system is also the question of whether the claimed long-term effects of cell and gene therapies can be trusted, and how the risks of lower than predicted efficacy could be mitigated or shared between industry and healthcare systems. A solution may be for the healthcare systems and suppliers to work with health outcome bonds, where payments are based on outcomes. This would make it easier for the healthcare systems to invest in drugs, medical products and other interventions with high upfront costs that would decrease costs in the long run. In the next section, the use of outcome-based bonds for preventive actions is discussed further.

"The potential to cure patients by combining precise diagnostics coupled to novel effective treatments is certainly very attractive"."

Even though precision medicine presents many challenges to healthcare providers, industry, governments and the players of the market access systems, there is no reason to believe that its development will decline. The potential to cure patients by combining precise diagnostics with patient stratification and novel targeted treatments is certainly very attractive. Precision medicine includes both cost-driving and cost-saving mechanisms, and the transformation will require investments at different levels, including new infrastructure and reorganizations of healthcare systems.

[10] *Siverskog J & Henriksson M. (2019).Estimating the marginal cost of a life year in Sweden's public healthcare sector. Eur J Health Econ. 20(5):751-762. https://pubmed.ncbi.nlm.nih.gov/30796552/*

The promises and challenges of prevention

Preventing illness is the best way to decrease the burden of diseases. Prevention will increase the quality of life for individuals and their relatives, increase the average lifespan, and arguably reduce the burden of disease on the economy. A large number of diseases are related to lifestyle. For diseases with genetic components, the progression of disease is most often an interplay between genes, environment and lifestyle. Prevention can mean several similar but distinct things related to health. It is about preventing diseases from occurring in a healthy individual in the first place, preventing relapses or preventing the worsening of disease progression in a person with a disease.

Studies have shown the power of preventive measures in reducing the number of deaths from health disorders, such as heart and coronary diseases, thereby contributing to longer life expectancy. For example, coronary heart disease mortality has decreased by 70% during the last 40 years. One study showed that prevention accounts for 48% of this decrease, while the contribution from medical treatment is 42%.[11] Prevention in this case means both lifestyle changes such as reducing smoking, but also interventions to lower blood pressure and treat pre-diabetes throughout a population. Other areas where prevention has been shown to be effective are decreased incidents of lung cancer due to fewer people smoking, and lower incidents of secondary diseases among diabetics due to better control of blood glucose levels and blood pressure.[12,13] Even though preventive actions are often powerful, in the EU approximately only 3% of the healthcare budget is allocated to prevention.[14] Why are the investments in prevention low? In general, there seem to be several factors affecting the lack of willingness to promote and invest in preventive actions. These factors may be ethical, political or related to medical evidence.

"There seem to be several factors affecting the lack of willingness to promote and invest in preventive actions."

As discussed in the previous section, in Sweden the healthcare law states that the most severe conditions should be given priority in healthcare. When the resources in the healthcare systems are limited and set by yearly budgets, it is difficult to justify a large share of the money being invested in prevention. Also, as Lars Sandman pointed out, in most situations we seem to value and prioritize now rather than then. If you have a person with a manageable (even if not severe) disease in front of you, you will probably prioritize that person over someone who might become ill (possibly with a very severe disease) at a later date.

Sarah Neville

Sarah Neville, Global Health Editor for the Financial Times, has in her professional work studied not only the National Health Service (NHS) in the UK but also other healthcare systems globally. Sarah highlights that moving from reactive healthcare upstream towards prevention is a huge challenge for politicians. Voters' interests most often favor keeping their local hospitals – even those that have been shown to provide healthcare of

[11] *Ahmadi, M., & Lanphear, B. (2022). The impact of clinical and population strategies on coronary heart disease mortality: an assessment of Rose's big idea. BMC public health, 22(1), 14. https://pubmed.ncbi.nlm.nih.gov/34991551/*

[12] *Nathan DM; DCCT/EDIC Research Group. (2014) The diabetes control and complications trial/epidemiology of diabetes interventions and complications study at 30 years: overview. Diabetes Care. 37(1):9-16. https://pubmed.ncbi.nlm.nih.gov/24356592/*

[13] *King P, Peacock I, Donnelly R. (1999). The UK prospective diabetes study (UKPDS): clinical and therapeutic implications for type 2 diabetes. Br J Clin Pharmacol. 48(5):643-8. https://pubmed.ncbi.nlm.nih.gov/10594464/*

[14] *Nurse, Joanna et al. (2014). WHO Report: The case for investing in public health. https://www.researchgate.net/publication/277189955_The_case_for_investing_in_public_health*

questionable quality – and maintaining the number of available hospital beds. Sarah pointed out that the NHS has faced tremendous challenges in moving money from hospital settings towards primary care and further upstream.

In a similar way to market access systems not being set up for advanced curative treatments, healthcare reimbursement systems in most countries and the associated business models for industry do not encourage preventive healthcare policies. Under current models for financing healthcare in most of the world today, prevention is rarely commercially viable. Incentives for governments to work more actively on prevention should be strong, but the focus on 1) activities rather than value, 2) keeping to annual budgets and 3) prioritizing patients with the most severe conditions, make it difficult for healthcare systems to allocate resources to prevention which will probably pay back in 10-15 years.

"Politicians may be reluctant to introduce interventions that interfere too much with how people choose to live their lives."

However, the preventive actions may not be handled by healthcare systems alone. Many preventive interventions and incentives, such as high taxes on tobacco, usage restrictions and communication campaigns, target other parts of society and often involve political decisions. Sarah argues that governments should look at health from a wider perspective. Social factors such as education, housing and employment are extremely important determinants of health. It may however be difficult to know which spending gives which results. In addition, politicians may be reluctant to introduce interventions that interfere too much with how people choose to live their lives.

Adil Mardinglou

As mentioned in the previous section on precision medicine, multi-omics technologies have now started to move us into the era of precision prevention, making it possible to assess personal risk scores for certain diseases that may lead to specific lifestyle recommendations. This opens up some interesting questions. One is whether healthcare should start to offer such risk assessments to healthy individuals. At the current development status of the methods, this is not justified from a cost as well as evidence/robustness perspective. **Adil Mardinglou** is Professor of Computational Biology at KTH Royal Institute of Technology, and Professor of Systems Biology at King's College London. At the symposium, he discussed the possibilities that multi-omics analyses provide regarding early risk prediction. Adil is also co-founder of a company that offers these analyses together with lifestyle recommendations as a wellness service to individuals who pay privately for the service. Adil agrees that the healthcare systems should only offer validated, robust and cost-effective services. But using private out-of-pocket business model allows Adil and his collaborators to validate the methods further and to develop business models that would in the future also work for healthcare systems.

Related to the possibility of measuring risk scores is the question of personal responsibility for one's health. Lars Sandman (Linköping University) mentioned that in Sweden there is a shift in attitudes towards a higher degree of individual responsibility. It may be argued that healthcare should not prioritize people who have unhealthy behaviors. There have been some reasonable arguments against the viewpoint, for example that the cause of diseases is often multifactorial and it may be hard to associate a disease with a specific behavior. However, when risk factors become measurable at the individual level and it becomes possible to map which behaviors might be unhealthy for a *specific* person, that argument may be weakened.

The use of economic bonds based on outcomes may make it more attractive to invest in preventive actions. An interesting example is how Region Stockholm in a pilot study has used an outcome-based bond model developed by the Swedish company Health Integrator.[15] In this pilot,

[15] *Health Integrator. (2023). Report: HEALTH INTEGRATOR - PREVENTION OF TYPE 2 DIABETES, 24-month report. Retrieved from: https://www.healthintegrator.se/_files/ugd/a01ac1_624d40538400498a8c449307dfe40a14.pdf*

925 individuals with pre-diabetes (defined as long-term blood glucose levels, HbA1c, levels of 42-47 mmol/mol, indicating a high risk of developing type 2 diabetes) were identified and included in a program where they were offered different types of support for physical training, diet and other lifestyle-related factors. The cost of 30 million SEK for the support program, administration etc. was financed upfront by private money from an insurance company. Two years later, the outcomes were measured and the healthcare system (Region Stockholm) paid the investor (the insurance company) a sum based on specific outcome indicators. The results showed that after two years, 54% of the participants had lowered their long-term blood glucose level to a value below the level indicative of pre-diabetes, and 85% of the participants felt that the health program had been a contributing factor to improved quality of life. Only 7.5% of participants developed an HbA1c indicative of type 2 diabetes over 2 years, compared to an average of 23% if no lifestyle intervention is used. Since the average extra costs for the healthcare system per person with type 2 diabetes is known, the cost-benefit analysis is straightforward, and it is possible to calculate the savings for healthcare systems when preventive interventions for individuals with pre-diabetes are used. Allocating private money to finance prevention upfront and letting the healthcare systems pay back once the cost savings are evident would solve the problem of limited yearly resources and diminish thew risk of sacrificing health when introducing preventive interventions or new expensive treatments.

"A crucial question is how much money preventative actions could save for the healthcare system and society."

A crucial question is how much money preventative actions could save for the healthcare system and society. A majority of the healthcare budgets are allocated to patients with chronic conditions, and it is for example estimated that 28% of all cancers in Sweden could be avoided with healthy lifestyles.[16] Intuitively, preventing disease should be an important way to save resources. However, the prevalence of a vast number of different diseases increases in old age. Even if one or two diseases were effectively prevented, people would most probably with time develop another disease.

For large savings, several major diseases would have to be prevented in parallel. There are certain habits, including physical activity, a balanced diet, avoiding smoking and excess alcohol consumption, and fostering meaningful social relations, that have been shown to lower the risk of developing several different diseases. A concept that has gained much attention during the last decade is to prevent age-related diseases by slowing the processes of ageing in general, which will be described in the next section.

[16] *Fridhammar A, Hofmarcher T, Persson S. (2020) Cancer I Sverige – Hur mycket beror på påverkbara riskfaktorer. IHE Rapport 2020:9, IHE: Lund. Retrieved from: https://static-files.cancerfonden.se/IHE%20rapport%202020_9_.pdf*

The rise of geroscience


Sara Hägg

It is well known that age is a major risk factor for a large number of diseases such as cardiovascular diseases, most chronic diseases and cancer. Might it be possible to slow ageing processes in controlled ways and thereby decrease the risks of developing a range of diseases? At the symposium, **Sara Hägg**, Associate Professor in Molecular Epidemiology at the Department of Medical Epidemiology and Biostatistics at Karolinska Institutet, described some of the fundamentals of the gradual molecular and functional decline in the body which takes place as we age. Molecular and cellular ageing can be detected early in life; organ and functional ageing is often detected during adulthood; and the whole organism ageing, which leads to pathological processes, appears predominantly late in life.

"Might it be possible to slow ageing processes in controlled ways and thereby decrease the risks of developing a range of diseases?."

Age-associated deterioration is the primary risk factor for major human pathologies, including cancer, diabetes, cardiovascular disorders, and neurodegenerative diseases.[17]

In 2013, nine tentative hallmarks of ageing were presented in a publication by Carlos López-Otín et al.[3] These hallmarks represent common denominators of ageing: **genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion,** and **altered intercellular communication**. This compilation has paved the way for an increased interest and activity in the field of geroscience, which seeks to understand the genetic, molecular, and cellular mechanisms that make ageing a driver for different pathological conditions. Investigators in the field aim to map the interplay between the fundamental processes of ageing and diseases and co-morbidities. Hence, they seek to discover similarities and differences among age-related diseases and find common, disease-related, ageing mechanisms that may be delayed, or even reversed, with interventions.[18]

Sara Hägg explained how ageing is associated with epigenetic alterations, and how epigenetic tags may be used as general biomarkers for ageing. The epigenome can be seen as tags in the DNA molecules that make it easier to identify different sections in the DNA and regulate their activities (i.e. the frequecy of how the genes in the sections are transcribed to RNA and translated to proteins). These epigenetic tags change during life. Hence, the epigenome is nowadays used as a marker of biological age – the epigenetic clock. This clock can (at the population level) be used to predict mortality and predict risks of developing diseases. It has also been shown that the epigenetic clock is associated with environmental and lifestyle factors. It is noteworthy that these are associations, but little is still known about the causalities. It is also important to note that the association of the epigenetic clock with ageing processes is valid on population levels but not on the individual level. This means that the relevance of using the epigenetic clock as a marker of the ageing process on the individual level is still weak.

[17] *López-Otín C et al. (2013). The hallmarks of aging. Cell. 153(6):1194-217. https://pubmed.ncbi.nlm.nih.gov/23746838/*

[18] *National Institute of Aging. Geroscience: The intersection of basic aging biology, chronic disease, and health https://www.nia.nih.gov/research/dab/geroscience-intersection-basic-aging-biology-chronic-disease-and-health*

Peter Ottsjö

Peter Ottsjö, science journalist and author of the book "Forever Young – My and Humanity's Dream of Immortality", described how, during the last decade, it has become more common to argue that ageing should be approached as a disease, and that more resources should be invested in research which aims to prevent ageing. There has been increasing activity in the field and in 2023 a review article updating the hallmarks of ageing was published.[19] The article suggested adding three additional hallmarks: disabled macroautophagy, chronic inflammation, and dysbiosis. The recent research summarized in the review further shows that there is a large degree of complex interplay between the different hallmarks and that some of the mechanisms and processes in the body that are beneficial at a young age become detrimental at an older age.

Tremendous knowledge has been gained during the last decades, but it is clear that a lot of research still needs to be done before the mysteries of ageing are revealed. Also, learning from the experience in precision medicine, there may be large individual variations in the biology of ageing. Hence, intervening with the mechanisms of ageing is not as straightforward as it may have looked when the hallmarks of ageing were first presented eleven years ago. Nevertheless, different so-called gerotherapeutic drugs have been shown to modulate fundamental molecular, cellular and/or genetic mechanisms of ageing in animal models.

"There are several critical challenges associated with clinical studies of gerotherapeutic drugs."

There has to be a clear path for approval and market access for companies to be interested in funding the development of gerotherapeutic drugs, and this is one area where the field struggles. There are several critical challenges associated with clinical studies of gerotherapeutic drugs. Clinical trials are usually centered on a disease-specific diagnosis, while geroscience trials aim to target the mechanisms of ageing and thereby delay or prevent the onset or delay the progression of multiple age-related diseases. It is not feasible to have time to death as an endpoint of the clinical trial and to run studies for 20 years or more. This points to the importance of finding biomarkers that measure relevant mechanisms of changes in body functions during the study - so called surrogate outcomes. Also, specifying intermediate goals that can be reached within reasonable timespans will be critical.[20]

The gerotherapeutic drugs tested in animal models and advised for clinical trials are usually drugs already on the market for a specific indication but which may also affect ageing mechanisms. One example of a clinical study that has received approval by the FDA (Food and Drug Association) is the TAME (Targeting Ageing with Metformin) study. Metformin is a drug that was approved by the FDA in 1994 to treat type 2 diabetes. It is used off-label for managing gestational diabetes, pre-diabetes and addressing weight gain issues caused by antipsychotic medication.[21] Research has also supported that metformin is associated with several age-related dysfunctions and diseases - potential positive effects include anti-ageing, anticancer, and neuroprotective effects.[22]

Rather than to study the effects of metformin on each separate condition, the TAME study is designed to measure time to a new occurrence of another disease among patients who already have one or several diseases (including cardiovascular events, cancer, dementia, and mortality). The intention is to measure incident multimorbidity during six years in individuals aged 65-79 years.

[19] *López-Otín C et al. (2023). Hallmarks of aging: An expanding universe. Cell. 186(2):243-278. https://pubmed.ncbi.nlm.nih.gov/36599349/*

[20] *Rolland, Y et al. (2023). Challenges in developing Geroscience trials. Nat Commun 14, 5038. https://doi.org/10.1038/s41467-023-39786-7*

[21] *Corcoran C, Jacobs TF. (2023) Metformin. In: StatPearls (Internet). Treasure Island (FL): StatPearls Publishing. Retrieved from: https://www.ncbi.nlm.nih.gov/books/NBK518983/*

[22] *Barzilai N et al. (2016). Metformin as a Tool to Target Aging. Cell Metab. 14;23(6):1060-1065. https://pubmed.ncbi.nlm.nih.gov/27304507/*

"Multimorbidity" means suffering from two or more of the supposedly independent "diseases of ageing" at once. The trial would measure the time it took people (on metformin or placebo) to be newly diagnosed with a second "disease of ageing". The analysis would be based on the delay in developing each additional diagnosed disease (or death), throughout the trial.[23] The TAME study will be the first clinical trial to target ageing per se, as measured by the potential drug-induced delay in multimorbidity of age-related diseases. The study is still, in April 2024, awaiting the final funding before it can start. A reason for the lack of interest in funding the trial is that Metmorfin is a cheap generic drug. Hence, there is no means to get a return on the investment and no interest from companies.

"As results from clinical trials start to be generated in the coming years and increasing investments in the geroscience research help demystify ageing processes and reveal new potentially druggable mechanisms, it will become clearer how feasible the geroscience approach is to prevent age-related diseases."

Delaying the ageing process is tempting and may have the potential to delay the onset of many diseases, and the pro-longevity community is growing at a rapid pace. The field has gained attention from tech-billionaires and several large investments have been made in different longevity start-ups. So far, what has reached the market is mostly different food supplements and nutrients claiming to enhance cognitive functions and health. During the last year, the field has also been increasingly highlighted in Swedish and international news media.

As results from clinical trials start to be generated in the coming years and increasing investments in the geroscience research help demystify ageing processes and reveal new potentially druggable mechanisms, it will become clearer how feasible the geroscience approach is to prevent age-related diseases.

What drives research and businesses within life science

What are the factors driving research and businesses within life science in certain directions? What determines the kind of research that is performed at universities, institutes and companies and which clinical operations are gaining ground? By following the discussions at symposia like Future of Life Science and other arenas relevant to the life science and healthcare sectors, a few factors stand out as important. The following summary is in no way comprehensive but rather a reflection of what has occurred to the mind of the author of this report. Still, if somebody wants to shift how the life science and healthcare fields are developing, it is important to understand what governs the development.

Technical ability

Technological proceedings and breakthroughs enable new measurements and generate possibilities for new research. Technologies developed in one field are often also modified to be applicable in other fields. The recent development of data handling and analysis (including AI/ML) is instrumental in the recent and ongoing development of life science and healthcare.

[23] *Sens Research Foundation: A TAME Attempt to Slow Aging Part 5: Winning the Game with a Weak Hand (2023). Webpage: https://www.sens.org/tame-attempt-slow-aging-part-5-metformin-win-game-weak-hand/*

Curiosity
Curiosity and excitement are important drivers. Researchers are most often driven by the desire to learn more.

Payability
Costs related to health are paid for by public tax money, private insurance money and out-of-pocket money. The ratios of these sources of money vary in different countries and between people. In Sweden, the largest share of all the healthcare provided is financed by tax money (more than 80%).

As already mentioned, the most severe conditions are prioritized in Swedish healthcare, and this means that budgeting and investment decisions inevitably involve comparison of different options. Limited resources and balanced yearly budgets make long term investment difficult, for example in disease prevention. Reorganization of healthcare systems also requires resources - it is easier to fund new products that fit in the existing organizations and workflows, which means that disruptive technologies and therapies may not be favoured. Use of financial models like outcome-based bonds may change priorities in the future and facilitate investments in prevention and expensive "one-shot" treatments which will bring long term benefits.

Profitability
Profitability varies depending on perspective. An academic researcher relies on funding agencies, and the likelihood of receiving funding impacts the type of research that is carried out.

From the perspective of companies and investors, the important question is: how can I get the best return on investments and maximize profit within a reasonable timeframe? For pharma and medtech companies, the regulatory and market access systems in different countries are important when selecting development projects on which to focus.

From the perspective of taxpayers and politicians, it is important to understand where they will get the most "bang for their buck". We should not forget that an important factor is how to keep the taxpayers/voters onside.

Curability
The available knowledge at a given point in time regarding different disease mechanisms, the potential to target specific mechanisms, and the possibility of finding treatments with reasonable effort affect the priorities within research and development. This factor certainly functions in balance with the unmet needs for different treatments.

Possibilities within the limits of policies and regulations
Policies and regulations affecting research and healthcare are usually quite rigid and they take time to change. Hence, these set the framework for a lot of the activities even though certain research, development and innovation projects aim to challenge, and in the longer run change, current policies and regulations.

Sustainability
Climate change has highlighted the need for global measures on sustainability. The UN Sustainable Development Goals goals include not only environmental goals, but several others related to health, equality and economic growth. This influences research, development and all business and societal activities globally.

Appendix: Program for symposium

The Future of Life Science: Healthy longevity, precision medicine and next-generation therapeutics

May 4-5, 2023

Session 1: Introduction to healthy longevity - biological, medical, and societal perspectives.

- Ola Rosling – President & Co-Founder of Gapminder Foundation.
- Sara Hägg – Associate Professor in Molecular Epidemiology at the Department of Medical Epidemiology and Biostatistics, Karolinska Institutet.
- Peter Ottsjö – Peter Ottsjö – Author of the book Forever Young – My and Humanity's Dream of Immortality. Science and technology journalist at Ny Teknik.

Session 2. Next-generation therapeutics - regenerative medicine, gene and cell therapies.

- Karina Thorn – Corporate Vice President of RNA & Gene Therapies, Novo Nordisk.
- Anna Falk – Professor in Developmental Neurobiology, Lund University.
- Johan Rockberg – Professor, Division of Protein Technology, KTH Royal Institute of Technology.
- Maria Rankka – Executive Chairman, Cellcolabs. Co-founder ABC Labs.

Session 3. Precision medicine, precision health, and prevention.

- Claudia Langenberg – Director of the Precision Healthcare University Research Institute, Queen Mary University of London. Professor of Computational Medicine at the Berlin Institute of Health at Charité.
- Adil Mardinoglu – Professor, Division of Systems Biology, KTH Royal Institute of Technology, Professor of Systems Biology, King's College London.
- Samuel Philip Nobs – Senior Postdoctoral Fellow, Weizmann Institute of Science.
- Jakob Tellgren – Vice President and Head of Nordic and Baltic Region, MSD.

Session 4. Perspectives on the shift to precision medicine and preventive care.

- Sarah Neville – Global Health Editor, Financial Times.
- Lars Sandman – Professor in Health Ethics and Director at the National Centre for Priorities in Health, Linköping University.
- Eskil Degsell – Vice Chairman of Swedish Brain Tumor Association. Patient and Next of Kin Representative, Karolinska University Hospital.

Contact us!

Stockholm Science City works based on needs to strenghten Stockholm's competitivness within life science. We develop concepts, create relationships and spread knowledge.

Ylva Williams is the CEO at Stockholm Science City

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Sveavägen 166, 113 46 Stockholm

The financiers of the Foundation

Karolinska Institutet

KTH Vetenskap och Konst

Stockholm University

Stockholms stad

Region Stockholm

A report from the symposium *Healthy longevity, precision medicine and next-generation therapeutics*

Published: April 2024
Ansvarig utgivare: Stockholm Science City Foundation
Analysis and author: Andreas Namslauer

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