VISION PAPER
SYSTEMS BIOLOGY

medicon valley alliance
Creating Opportunities

THE EUROPEAN UNION
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Interreg IV A
ÖRESUND – KATTEGAT – SKAGERRAK

invest in skåne
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The Medicon Valley Beacons is part of the collaboration project "Medicon Valley – a world-class life science cluster" between Medicon Valley Alliance and Invest in Skåne. It is partly funded by the EU Interreg IV Programme.

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① WHAT IS SYSTEMS **BIOLOGY?**

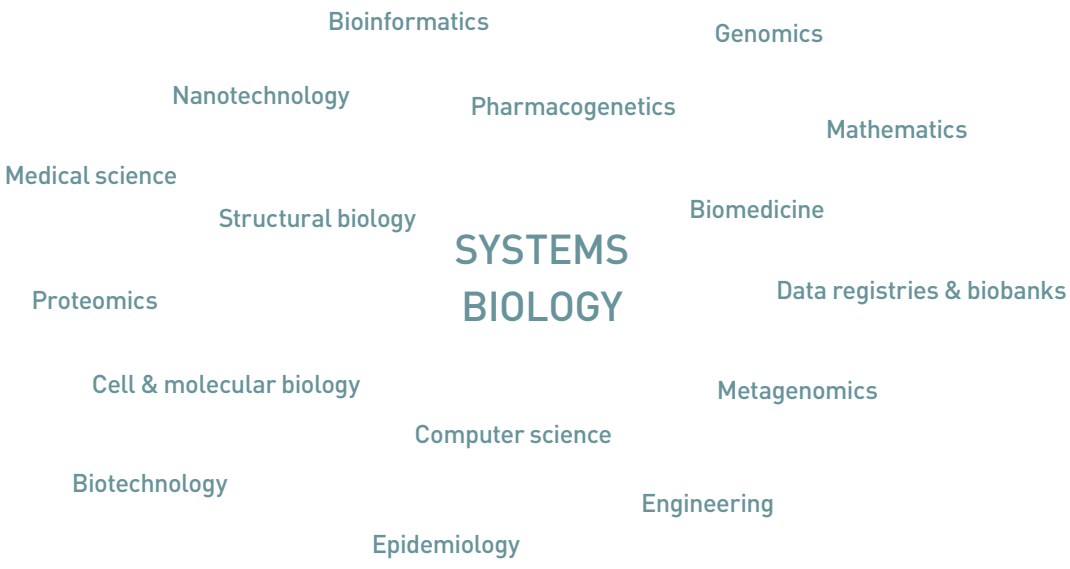
Systems biology is the study of how different components, such as molecules, genes or cells in a biological system interact, and how their interactions shape the function and behavior of the system. Systems biology is a holistic approach to biological and biomedical research, which enables researchers to uncover what is special about the individual and not what is general for all people.

By using computational models, systems biologists analyze the impact of different variables on biological systems. Variables could be genetic variations or the vast amounts of phenotypic data found in e.g. patient records and biobanks. By running correlations of such data, it becomes possible to reveal undiscovered disease trajectories.

Definition of systems biology

"Systems biology is a new field of biology that aims to develop a system-level understanding of biological systems. System-level understanding requires a set of principles and methodologies that links the behaviors of molecules to system characteristics and functions. Ultimately, cells, organisms, and human beings will be described and understood at the system-level grounded on a consistent framework of knowledge that is under-pinned by the basic principles of physics."
(Kitano 2001: 2)

Systems biology is a highly cross-disciplinary and potentially rather broad research field. "It requires collective efforts from multiple research areas, such as molecular biology, high-precision measurement, computer science, control theory and other scientific and engineering fields. Research needs to be carried out in four key areas: (1) genomics and other molecular biology research, (2) computational studies, such as simulation, bioinformatics, and software tools, (3) analysis of dynamics of the system, and (4) technologies for high precision, comprehensive meas-urements" (Kitano 2001:3).



Systems biology as a research fields is based on huge amounts of healthcare data, which is generated 24/7 as a result of the major technological breakthroughs over the past years, e.g. genome sequencing and the overall digitalization of society. "Significant progress in biotechnology has allowed the measurement of tens of thousands of "omic" data points across multiple levels (DNA, RNA protein, metabolomics) from a single tumor biopsy sample in a reasonable time frame for making clinical decisions. With this data in hand, the challenge from the bioinformatics and systems biology point of view is how does one convert data into information and knowledge that can improve the delivery of personalized therapy to the patient" (Ram et al., 2012: 147). Burill (2014) estimates that about 150 exabytes (150 billion gigabytes) of data was generated via healthcare applications in 2011, and the volume is expected to grow by 1 to 2 exabytes annually.

There is an increasing focus on "network medicine" as a research field. It "applies systems biology and network science methods to human disease. Networks can be used to visualize and analyze a broad range of biological processes, with nodes in the network representing a biological entity (e.g., gene, protein, disease) and edges representing the relationships between entities (e.g., physical interactions, transcriptional activation, correlations in gene expression levels)." (Silverman & Loscalzo 2012: 2).

Leroy Hood, founder of the Institute for Systems Biology in Seattle, WA, and pioneer within systems biology, has introduced the "P4 medicine" concept – predictive, preventive, personalized and participatory medicine. He believes that P4 will be the future in the healthcare system as the technological advances within systems biology become applicable in the clinic. It will entail new treatment methods and new drug discoveries. In addition, Leroy Hood predicts that in 15 years, we will be talking about the "welfare industry" as opposed to the "healthcare industry" and thus require a change in the business models of the industry.

The economic impact of data on the healthcare system is significant, which is positive for many healthcare systems around the world that are under severe economic pressure. In an analysis by the McKinsey Global Institutes, it is estimated that "applying big-data strategies to better inform decision making could generate up to $ 100 billion in value annually across the US healthcare system, by optimizing innovation, improving the efficiency of research and clinical trials, and by building new tools for physicians, consumers, insurers, and regulators to meet the promise of more individualized approaches." (Cattell et al., 2013:1).

Researchers are continuously developing tools to handle and analyze the large amounts of data. Thus, the future challenge lies in how to transform the huge amounts of data into information and knowledge on how the biological system works and how it affects diseases and how treatments of patients can be improved.

② WHY SYSTEMS BIOLOGY?

Systems biology will undoubtedly revolutionize medical research and clinical practices. By acquiring a better understanding of the biological network, it will provide new drug discoveries and new diagnostics, but also knowledge on how to use existing drugs in new combinations, which control and regulate the many parameters in the system, as well as providing novel treatment methods (Friboulet & Thomas 2005).

In a Nordic perspective, there are huge competitive advantages to be had by becoming an international research hub for systems biology. This is mainly due to the long tradition of collecting healthcare data coupled with each citizen's personal social security number, which have been in place for decades. In addition, data is available in numerous other registries, e.g. socioeconomic information, which makes the Nordic countries unique locations for conducting longevity studies to complement e.g. clinical studies and real world evidence for market access and post-marketing surveillance.

Medicon Valley has strong competences within e.g. the utilization of "omics" data. This was determined in a study conducted by Boston Consulting Group and its evaluation of various strongholds in the region. "Medicon Valleys is especially competitive in top-down systems biology (utilization of –omics data), which is most relevant for applications towards medicine. Combined with the world leading patient registries that are present in Medicon Valley, this provides a compelling opportunity to create a unique position." (Boston Consulting Group 2012: 59).

H-INDEX BENCHMARKING: SYSTEMS BIOLOGY

Research area	Average	Medicon Valley	Boston	Cambr. UK	Silicon Valley	Sthlm. Uppsala	Zurich	London	Berlin	Tokyo
Systems biology	33	30	63	42	44	21	26	29	24	22
Systems medicine	11	10	15	8	14	5	3	18	3	26
Computational biology	99	88	170	130	133	72	57	91	74	79
Bioinformatics	40	38	60	54	41	32	18	41	25	49
Proteomics	32	33	48	34	41	26	28	27	27	27
Metabolomics	30	31	38	32	24	20	27	48	22	28
Transcriptomics	76	62	125	84	102	59	49	70	56	73
Interactomics	37	28	86	48	48	18	26	28	28	25
Mathematics	51	54	72	45	62	39	42	51	44	50
Personalized medicine	18	19	32	12	26	16	9	21	12	16
Microbiology	115	122	171	102	138	96	84	121	94	110

> 0 % -20 to 0 % <-20 %

Colours indicate relative H-index of MV compared to average of leading life science clusters

Note: The search terms: Web of Science "Category terms" Scopus "keywords" and Scopus "unqualified terms". Generally, the analysis was restricted to articles published after 2000. In cases where the number of hits exceeded the limit for citation analysis, the analysis was further restricted to articles published after 2007, 2008 or 2009. Source: Web of science, Scopus.

Thus, with the strong academic environment, the Nordic health registries and the future demand for better healthcare solutions, it makes sense to strengthen the research field within systems biology in Medicon Valley. Many other regions have academic environments that are stronger than the ones in Medicon Valley and many regions have research centers with large financial means dedicated solely to systems biology research. Nevertheless, what the other regions lack is what gives Medicon Valley a unique competitive edge, namely the data registries and the populations' general willingness to share data. This gives researchers in this region a unique window of opportunity to strengthen Medicon Valley's position as a global leader within systems biology research. Creating a Medicon Valley Beacon within systems

biology will create a strong basis for the other MV Beacons. An indepth understanding of the biological network is fundamental for studying immunology and according to Friboulet & Thomas (2005: 2406) "autoimmune diseases will be understood and cured only through a systems biology approach". Systems biology is also closely related to structural biology, as it is important to know the structure of cells/proteins etc. on a molecular level if one is to fully understand the system-level interactions. Once the structure is known and understood, it is possible to understand the behavior, interaction and interdependency in the biological system.

Medicon Valley Beacons: collaborating regionally to compete globally

Medicon Valley Alliance (MVA) exists to make Medicon Valley an attractive destination for the best talent within life science. MVA launches and drives initiatives that put Medicon Valley firmly ahead in the global race for talent. The vision is to release the full potential of Medicon Valley by focusing on the entire life science cluster and spot synergies across borders, disciplines and the public-private divide.

For Medicon Valley to be a serious contender in the highly competitive global life science race, the cluster as a whole needs to strengthen its ability to attract a constant stream of talent and capital. The "Medicon Valley Beacons" was launched by MVA in early 2012 and aims to achieve this by showcasing the region's scientific strongholds and acting as regional landmarks on the global life science map.

The objective is to develop, expand and brand selected research environments that build on Swedish-Danish synergies between existing strongholds – in both the private and public sector – and which span the entire life science value chain from early research all the way to commercialization, in order to drive economic growth and job creation in the region.

Four Beacons – systems biology, structural biology, immune regulation and drug delivery – have been selected following an extensive evaluation of existing life science strongholds in the region based on analysis and input from regional stakeholders. Each Beacon is characterized by being highly cross-disciplinary, building on existing regional strongholds and addressing future demands and medical needs. The individual Beacons focus on areas where there is considerable potential for synergies in Medicon Valley for creating world-leading research environments.

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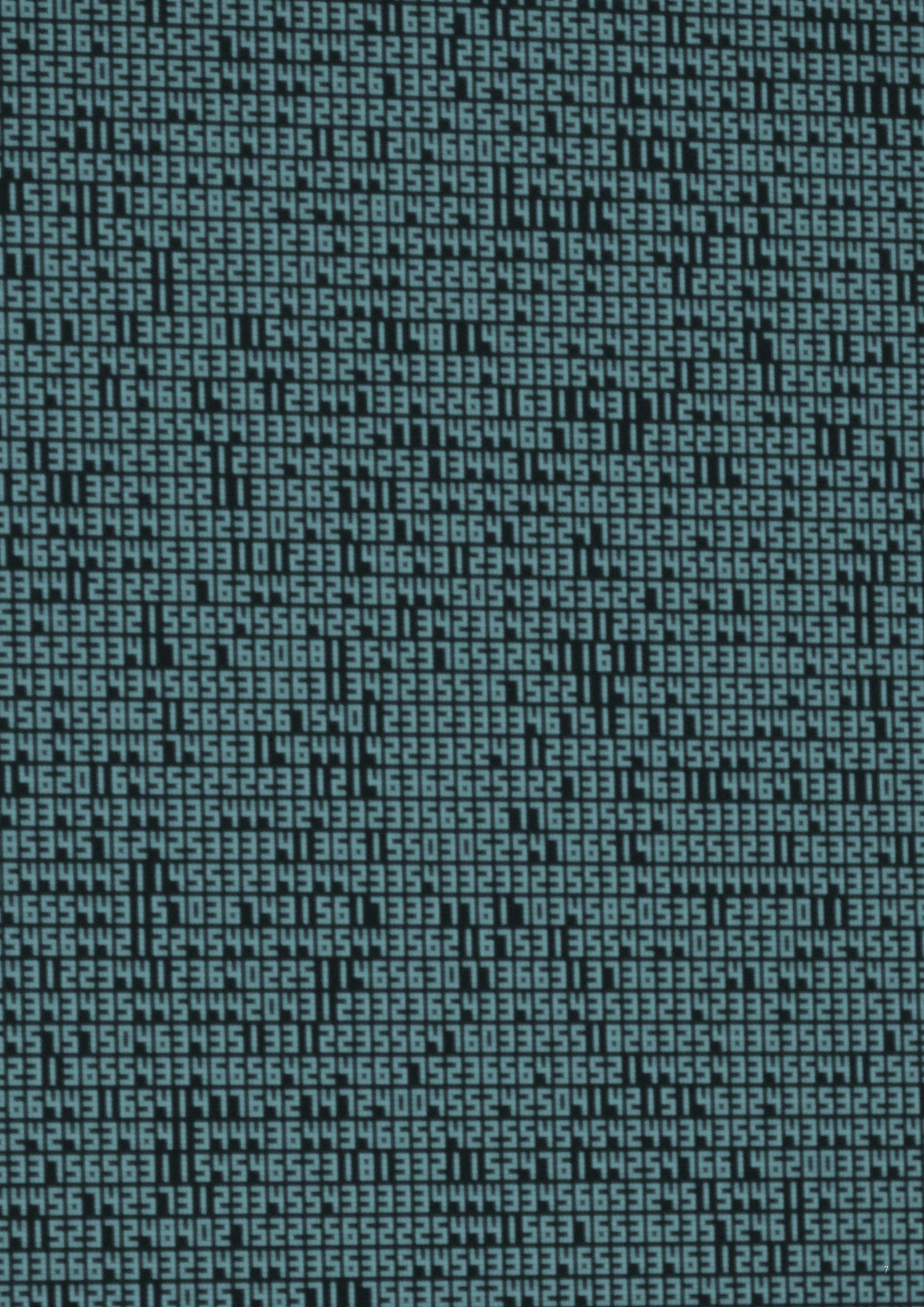
Photo: Ryoji Ikeda



③ VISION & CHALLENGES

There are obvious reasons for strengthening the research field of systems biology, and Medicon Valley has a unique opportunity to get a head start compared to the many competing regions if forces are joined now. Our unique position is based on a long research tradition within the field, as well as the extensively developed infrastructure with registries and bio banks, coupled with the civil registration system of all citizens.

Imagining the systems biology ecosystem in Medicon Valley in 2025

By 2025, Medicon Valley will have established its position as an important research hub for systems biology on a global scale. As systems biology and network medicine have grown as research disciplines in the past decade with groundbreaking discoveries to follow, Medicon Valley has managed to strengthen its position by profiting from the unique competitive advantage of the region, namely the data registries.

The high quality and quantity of the data registries have provided a significant competitive advantage within register-based research, which has supported the systems biology field. Denmark and Sweden have managed to set up measures that allow data to be pooled and thus create a larger critical mass, which is attractive for researchers in both the public and private sector. Thus, Medicon Valley has developed into the preferred life science cluster for performing register-based research and for finding talented young scientists with systems biology competences.

It has led to the development of revolutionizing tools that can process data in real-time to propose treatment strategies that are customized to the individual patient. It has also made it possible to predict disease trajectories quite precisely based on analysis of numerous parameters in the biological system. Further, the research within systems biology has been strengthened significantly since the inauguration of the Medicon Valley Center for Systems Biology, which gathered researchers within the field, and led to new discoveries and new solutions. This is mainly due to the development of new ways for collaborating between the public healthcare system, academia and the industry. This is because systems biology is highly cross-disciplinary and thus required unconventional modes of collaboration. Other life science clusters look towards Medicon Valley as a best-practice cluster with a well-functioning ecosystem and collaboration within the triple helix.

As systems biology has become a prestigious research field and a true Beacon for life science research in Medicon Valley, the local talent pool has grown immensely. Thus, some of the brightest young talents within computer science, math, bioinformatics, medicine and biology are educated in Medicon Valley. It has created a positive circle where world-leading researchers have located to Medicon Valley, which in turn has strengthened the research field even more.

Global R&D companies find it paramount to be present in the region as some of the world's most prominent systems biologists are located in Medicon Valley and local talents are abundant. In addition, the access to extensive data registries and biobanks makes Medicon Valley extremely attractive as a preferred location for placing R&D activities.

The groundbreaking new discoveries of how biological systems function are gradually applied to other related research fields, e.g. agriculture, food and industrial biotech, which are areas where Denmark and Sweden also excel. This only solidifies the strong position of the region in the global competition for attracting talent and investments.

Building a strong research community within systems biology in Medicon Valley is not an easy task and various steps must be taken. Initially, strengthening the network between the many stakeholders by bringing them together to exchange knowledge is a first step coupled with communications efforts to highlight the existing competences. At a later stage, activities must be further integrated. This can be done by creating a joint institute/center where academia meets industry in a pre-competitive setting that encourages open innovation.

Challenges

The vision outlined above is ambitious, but achievable. However, there are challenges, which need to be addressed:

- **Lack of relevant competences for analyzing data**
- **Data quantity and quality**
- **Usage of data for research and ensuring anonymity**
- **Legal barriers related to data protection**
- **Public opinion and acceptance of data utilization**

First, the biggest challenge is to improve the competence level. It is no longer a question of collecting data at a sufficiently high quality level, but the challenge lies in developing methods to analyze and interpret the data, which in turn can be put into good use and eventually benefit the patients. Thus, the overall competence level must be improved within the many disciplines that are connected to systems biology. In addition, there is also a need for a larger talent pool with the appropriate skills that can make sense of the huge amounts of data.

Another challenge is the data quantity and quality. In terms of data quantity, it will be ideal to pool the many data sources, registries, biobanks etc. into a central coordinating body/secretariat in order to create a critical mass. This is a tremendous job as there are issues concerning e.g. sample and storage methods, ownership of data/bio-material etc., which make coordination complicated. Another challenge is the reliability and quality of the data. The data stems from many different sources and is often entered into systems by many different people with different focus and different competences. Thus, it is a challenge to ensure that the data is compatible.

Lastly, there is a great challenge in ensuring that the available data can be used for research from legal and ethical perspectives. There is an ongoing public debate – both on the national and European level – concerning the use of data for research purposes and the risk of abuse and lack of anonymity. In order for systems biology to truly be a beacon in Medicon Valley, it is important that the unique data, which is present in the region, is made available for research purposes. Naturally, this should be made available with the appropriate approvals and guarantees for anonymity, but it is important to remove unnecessary barriers for coordination of data across Medicon Valley.

The last two challenges are addressed in a separate MVA project, the KADABRA project (for more information about the project, please see section 5.4.3). There are also national initiatives in Denmark and Sweden, as well as in the Nordic Council, which look into these matters.

④ NEXT STEPS

This paper has outlined the vision for what the systems biology ecosystem in Medicon Valley could be like in 2025. It also highlights some of the challenges towards realizing this vision. The next step will be to develop specific actions, which can be carried out in the short, medium and long term to fulfill this vision.

An important short-term step, which is imperative for driving this MV Beacon forward, is the provision of additional funds from key stakeholders. If we wish to make a difference and create significant results, it will require that stakeholders, who have a particular interest in specific Beacons, invest in a further development of the systems biology Beacon after the funding from the Interreg project expires in late 2014.

In order to strengthen the cohesiveness of the research community and create awareness of systems biology as a stronghold, MVA intends to establish reoccurring seminars and after-work network meetings. The aim is for stakeholders to meet on a regular basis around relevant scientific topics to enhance their competence level and to network with relevant stakeholders. It will offer opportunities to learn more about systems biology, exchange knowledge and widen the scope of the involved stakeholders.

⑤ APPENDIX – STAKEHOLDER MAPPING

The following is a non-exhaustive initial mapping of some of the major stakeholders in Medicon Valley, which are relevant to this initiative. The information is derived from the websites of universities, organizations and projects. Naturally, many more could be included in a stakeholder mapping within systems biology and other stake-holders outside the geographic area of Medicon Valley that are also of relevance. Those stakeholders should be included in a detailed mapping of the area along with a mapping of the core facilities and other relevant infrastructures in the region.

5.1

Universities in Medicon Valley

The following is a non-exhaustive initial listing of departments/groups within the field of structural biology at the universities in Medicon Valley that focus on life science. Obviously, many other scientific fields are relevant to structural biology, which should be included in a more extensive mapping at a later stage.

5.1.1 Lund University

Computational Biology & Biological Physics Group:
CBBP pursues a very broad spectrum of research activities. In particular, the group builds models of macromolecules and living systems, and investigates biological processes by applying machine learning and statistical techniques.
http://cbbp.thep.lu.se/

Computational and systems biology,
Dept. of laboratory medicine:
The lab is interested in exploring, and applying, computational methods to study human cancer, with a particular focus on malignancies of the blood. Current activities range from theoretical mathematical/statistical projects to large-scale genomics projects and clinical studies. The group works in the interface between computational biology and hematology. The activities are markedly multi-disciplinary and bring together a diverse group of individuals with different scientific backgrounds.
www.cbio.se

CREATE Health:
The mission of CREATE Health is to create an integrative approach to solve complex clinical problems, by developing new techniques and instruments for medical applications – from bedside to bench and back again. The mission is being achieved by bringing together, both physically and logistically, investigators from diverse fields, such as technology development within bioinformatics, nanotechnology, proteomics and transcriptomics as well as clinical oncology, cancer genetics and tumor cell biology, in order to create a unique environment to address the new challenges. The vision of CREATE Health is to create a substantial social impact for the patient, through the direct application of research for the selection of an optimal, individually-based, cancer treatment and to develop novel diagnostics and therapeutics, based on identified markers and molecular signatures as well as potential targets, the latter through the participation of the pharmaceutical industry. The focus of CREATE Health is to address these problems by integrating cuttingedge technologies with clinical needs.
www.createhealth.lth.se

Lund University Diabetes Centre (LUDC):
LUDC is active in several different areas of diabetes research. The aim is to identify the genetic factors responsible for the development of diabetes, how they interact with the environment and then to integrate this knowledge with identifying the pathophysiology in pancreatic islet cells and insulin target tissue. Diabetes research at LUDC can be subdivided into three parts; discovery, validation and translation. The aim of the discovery is to identify genetic and non-genetic factors responsible for the development of diabetes and its complications. And in the validation phase to describe how they interact with the environment and cause impairment of insulin secretion and action, which is characteristic of the disease. Ultimately, this knowledge will be translated into the clinic as improved personalized medicine and the development of novel therapies.
www.ludc.med.lu.se.

5.1.2 Malmö University

Computer Science:

The research in Computer Science includes the development and analysis of concepts, methods and tools that aim to make the programming and use of computers easier, more efficient, and more reliable. The Faculty of Technology and Society is also engaged in building a new research area called Computer Models and Computation.

http://bit.ly/1sEOZVr

5.1.3 Technical University of Denmark

DTU Systems Biology:

Research at DTU Systems Biology covers the fields of cellular, molecular and structural biology, bioinformatics, computational biology, industrial biotechnology, biomedicine and health. Systems Biology addresses both the overall properties of a biological system and uses scientific approaches to understand specific mechanisms.

http://bit.ly/1sKWfOF

Integrative Systems Biology, Center for Biological Sequence Analysis:

The Integrative Systems Biology Group is at the leading edge of these developments, focusing mainly on understanding how intracellular networks of genes, proteins, metabolites and other small molecules regulate cellular behavior and how perturbations to these regulatory systems may lead to disease for the individual. The research strategies typically rely on the integration of massive amounts of experimental data. Pathways and protein complexes are key levels of analysis helping to understand how genetic changes in many different molecular components lead to the same or similar phenotypes. The group also works on combining molecular level systems biology data with medical informatics data from the healthcare sector, such as for example electronic patient records and biobank questionnaires. The aim is to combine and stratify patients not only from their genotypes, but also phenotypically based on the clinical descriptions in the medical records which describe disease development in detail. The groups have specific focus on treatment related disease correlations and other comorbidities.

http://bit.ly/1vpV4Gd

5.1.4 University of Copenhagen

Department of disease systems biology, Center for Protein Research:

In the Department of Disease Systems Biology, we analyze a wide range of data related to biology and medicine. In particular we create data integration techniques that in terms of scope go beyond conventional combinations of data and that connect more levels of disparate data types. At present, it is quite common to combine data on genetic variation linked to specific indication areas, with molecular level systems biology analyses of the genes and proteins found to be associated with a particular phenotype. It is also common to combine statistical, epidemiological approaches applied to information in public registries and biobanks. In some cases systems analyses of genes that link to the statistical trends are then discovered. We go beyond this situation and perform, for example, integrative text mining analysis of large corpora of Danish electronic patient records from exactly the same individuals that we have molecular level information for – and in this manner approach the problem of patient stratification from widely different angles.

http://www.cpr.ku.dk/research/dsb/

Biotech Research and Innovation Center (BRIC):

BRIC is a center of excellence for biomedical research. The scientists in the center focus on understanding the molecular mechanisms leading to various diseases, including cancer, CNS-related diseases and metabolic diseases. Disease-oriented basic research is the main focus of the research at BRIC. Our overall aim is to contribute to a basic understanding of how and why disease occurs, to discover new disease-related genes, and to identify new diagnostic markers, which are essential to provide more efficient treatment.

http://www.bric.ku.dk/

Section for Computational and RNA Biology, Dept. of Biology:

The research in the Section of Bioinformatics – biological research using computers – spans the DNA, RNA and protein worlds. It covers the methodological spectrum from wet-lab molecular biology to advanced computational model building and statistical inference. The section is organized into three overall research areas: (1) Bioinformatics Centre; (2) Experimental RNA Biology; and (3) Population Genetics and Statistics.

http://www1.bio.ku.dk/binf/

Computational biology, Dept. of computer science:
Computational biology is concerned with the ''development and application of data-analytical and theoretical methods, mathematical modelling and computational simulation techniques to the study of biological, behavioral, and social systems.'' Bioinformatics and Computational Biology are interdisciplinary fields that apply techniques of computer science, applied mathematics, statistics, and biochemistry to solve biological problems. Following the definitions of the National Institute of Health (USA), bioinformatics is ''research, development, or application of computational tools and approaches for expanding the use of biological, medical, behavioral or health data, including those to acquire, store, organize, archive, analyze, or visualize such data.''
http://bit.ly/1wxLVZ9

Human-Centered Computing,
Dept. of computer science:
The Human-Centered Computing (HCC) section is concerned with the theory and practice of how people engage with computing. Currently our focus is on computer supported collaborative work (CSCW), health informatics, human computer interaction (HCI), information retrieval, and systems development.
http://www.diku.dk/english/.

Sections of Systems Biology Research,
Dept. of Biomedical Sciences:
The research focuses on the mechanisms and effects of regular and acute physical activity and inactivity on integrative whole body physiology and patho-physiology with a particular focus on muscle, adipose and heart tissue in healthy and individuals with metabolic life style diseases.
http://bit.ly/1rs3yVz

Dept. of Cellular and Molecular Biology:
The focus of the department is the functional cell, its genetic components and molecular cellular mechanisms in a medical context. With a firm foundation in the basic function of the normal and differentiating cell, an understanding of the molecular, cellular and genetic mechanisms behind disease and aging is sought. The aim of the department is to exploit new discoveries and mechanistic insight as guide-lines for translational medicine in terms of novel principles for the treatment and diagnosis of disease in an internationally competitive, inspiring, productive scientific environment exploiting state of the art (and beyond) methodology.
http://icmm.ku.dk/english/research/

Systems Pharmacology,
Dept. of Drug Design and Pharmacology:
The focus is on the interaction between drugs and biological systems in animals and humans, from the cell- and tissue level to organ systems and the whole body. The research is aimed at characterizing potential new drug targets and predicting the effect as well as the body's uptake, distribution and excretion of drug candidates. The research is translational, extending from basic science to therapeutic applications. It encompasses the use and development of experimental models for human diseases, as well as pharmacological studies in animals and humans. An important objective is to bridge the gap between laboratory and clinic.
http://bit.ly/ZXCSqq

Molecular and Cellular Pharmacology,
Dept. of Drug Design and Pharmacology:
The focus is on a range of biological systems, particularly those that regulate brain function, as well as elements and processes implicated in many neurological disorders. The research is aimed at developing novel drug design strategies to treat disorders such as epilepsy and stroke. The research includes in vitro and in vivo pharmacological studies to better understand cognitive functions and treat conditions such as pain and depression.
http://bit.ly/1z6FuBL

The Dynamical Systems Interdisciplinary Network:
Mathematical Modeling and Statistical Methodology for the Social, Health and Natural Sciences. The project network encompasses visual cognition, neuronal signaling and networks, renal and cardiovascular physiology, metabolomics, molecular dynamics and econometrics. By combining ideas from the many fields where an understanding of dynamical systems are essential, and by combining comprehensiveness with indepth expertise, we will create an internationally unique research center, where pioneering methodology can be developed thanks to cross-disciplinary collaboration.
http://dsin.ku.dk/

5.2

Industry in Medicon Valley

Information about different treatments takes place at the registration and approval of drugs based on a very controlled clinical trial set-up with strictly defined inclusion and exclusion criteria. The usage of the drugs when they come on the market may in many cases be very different from such a controlled setting. In recent years, the biotech and pharmaceutical industry has therefore focused more and more on real world evidence of the effects and safety of their drugs. This surveillance is not only done to control the drug safety and discover any unwanted side effects early, but also to discover unexpected positive side effects and drug interactions, for comparative cost-effectiveness, comparative clinical effectiveness, biomarker discovery, etc.

Apart from the pharmaceutical and biotech companies in the region, there are other types of commercial opportunities which are linked to systems biology research. These are primarily within IT-solutions for data handling, data mining, data capture, etc.

5.3

Infrastructure in Medicon Valley

In both Sweden and Denmark the infrastructure for systems biology is very well developed. Data registries are extensive both when it comes to health care data and social and economic information. Biobanks are organized at different levels nationally, regionally, and locally at hospitals, but interconnected when it comes to the data registries with details about the biological samples. What makes the infrastructure unique is the civil registration system. Each citizen is from the day of birth, or immigration to the country, equipped with a personal identification code number. This means that the different registries with data about the citizens can be cross-linked to each other, and important associations between lifestyle or environmental factors and disease can be discovered.

5.3.1 Registries

Denmark and Sweden have national registries which cover a time span of more than 50 years back both with health care and socioeconomic data. The information about childcare institutions, education, jobs, family, address, etc. is handled by "Statistiska Centralbyrån" in Sweden and "Danmarks Statistik" in Denmark. Information about healthcare-related things, such as vaccinations, diagnosis, all pathology samples, any drug prescription, any lab test done in the country, etc. are handled by "Socialstyrelsen" in Sweden and "Statens Serum Institut" in Denmark.

A more recent set-up is the national clinical quality registries in each country. Within different disease areas a growing number of extensive data bases are developed to determine best practice based on real-life evidence and a systems biology approach. The build-up of data is based both on data capture, and specific reporting by health care professionals. The data quality is optimized by allowing more and more of the reporting being done as part of the treatment routine.

5.3.2 Biobanks

The Nordic countries have been pioneers in the development of registry-based biobanks. In this project, scientists within the Nordic region will be sharing information and infrastructure through a common biobank registry in order to enhance knowledge about the causes of colorectal cancer.

A biobank is a systematized collection of biological material samples with associated databases used for research and in other applications. In this project, a large, interdisciplinary network of Nordic experts will collaborate on finding the best ways to identify the causes of colorectal cancer. The infrastructure of the Nordic countries is similar enough that biobank-based research can be implemented not only nationally, but at a large-scale Nordic level as well.

The project will enable researchers to create a common Nordic database of standardized information. A Nordic study population will be identified, and researchers will analyze samples from the biobank and compare them with the national cancer registers and material from questionnaires in order to try to zero in on the factors, environmental as well as genetic, that lead to colorectal cancer.

The Nordic initiative Nordic Biobank Network is a collaborative network between national biobanking infrastructures in the Nordic countries. Participants include BBMRI.se in Sweden, BBMRI.fi in Finland, BBMRI.no in Norway, Biobank Denmark, as well as researchers from Iceland, Faroe Islands and BBMRI.ee in Estonia – all working to achieve common results and strengthen research. The network also wishes to contribute Nordic expertise to developing the European biobank cooperation under BBMRI.ERIC.
http://bit.ly/1xNnPuv

5.3.3 MAX IV Laboratory

MAX IV Laboratory is a national laboratory operated jointly by the Swedish Research Council and Lund University. MAX IV Laboratory is a synchrotron radiation facility producing x-rays of high intensity. The facility currently consists of three storage rings: MAX I, MAX II and MAX III. The construction of the next generation, MAX IV, is ongoing and will be open to users in the summer of 2016. MAX IV will be the brightest synchrotron X-ray source in the world.

The MAX IV will consist of two storage rings: (1) a smaller ring with a circumference of 96 meters and electron energy of 1,500 MeV and (2) a bigger ring with a circumference of 538 meters and electron energy of 3,000 MeV. The electrons will be accelerated in a linac accelerator (250 meters long, maximum 3,400 MeV). What makes MAX IV different from the current storage rings is that MAX IV will be injected at full energy meaning that the rings can be filled with electrons continuously and thus be at a constant maximum 24/7.

The budget for MAX IV of approx. EUR 330 million excludes the construction of beamlines, which must be financed individually and the future operational costs. The MAX IV can hold up to 26 beamlines.

Synchrotrons generate intense beams of X-rays from an electron storage ring. Synchrotron X-ray crystallography is a mainstay method in structural biology for atomic structure determination. Developments in sources and instrumentation have reduced the size of crystals required to micrometers. Synchrotron X-rays are also increasingly used for techniques such as small angle X-ray scattering (SAXS) that yield low-resolution structures of macromolecules in solution.

More information:
www.maxlab.lu.se

5.3.4 European Spallation Source (ESS)

The ESS in close vicinity to the MAX IV in Lund will be a facility for research using neutron scattering techniques, and it will be the world's most powerful source of neutrons for science. The facility is a partnership between 17 European countries. The total budget for the construction of the facility is estimated at EUR 1.8 billion of which 50 % will be financed by Sweden, Denmark and Norway. The remaining 50 % is financed by other European countries and negotiations are ongoing. The current plan is to break ground during 2014 and to have the first neutrons and the first instruments installed by the end of the decade, with construction continuing until the facility is at full power and a suite of 22 instruments is installed. The construction of the facility is expected to be completed by the year 2025.

The ESS will provide precise structural and dynamic information of molecular structures and their functionalities in hard, soft and biological materials. The facility can be used for a wide range of disciplines such as physics, material sciences, biology, chemistry, pharmacology, nanotechnology and also disciplines such as geology and archeology/cultural heritage studies.

Neutron beams can be generated either by fission in nuclear reactors or in a process known as spallation. In the latter, charged particles such as protons from an accelerator collide with a target at high speed and generate neutrons. Neutrons can be used to study bio-molecular structures in much the same way as X-rays, whereas they are much more sensitive to hydrogen, an element that plays a key role in many biological processes, but is almost invisible by X-rays. The neutrons also do not cause the same kind of damage to the sample as X-rays do, making neutron and synchrotron sources highly complementary for structural biology studies.

There are 22 instruments in the ESS baseline, and the facility will be constructed with room for more. Currently, three instruments (Broad-Band High Flux SANS; Macromolecular Diffractometer; and Multi-Purpose Imaging) have been approved to commence towards construction, 16 more instruments are currently under consideration, and more proposals are expected in the next few years. In the initial planning phase, a "reference instrument suite" was drafted in which 22 instruments were suggested. Of those 22 instruments, at least 5-7 of the instruments are highly relevant for use in life science and will be able to investigate e.g. protein domain motions, protein complexes, protein-protein interactions, biological membranes, membrane dynamics, enzyme mechanisms, etc.

The ESS data management and software center will be located at the Niels Bohr Institute at the University of Copenhagen. It is expected that the data management center will employ approx. 60 people. Data management will be of great importance for these types of experiments, as they generate large amounts of data that has to be analyzed (this is also the case at synchrotrons). Advanced techniques and data management methods must therefore be applied to deduce information about the structure of the specific sample. The center will collect, store

and analyze the large amounts of data derived from the experiments at the ESS facility in Lund. In addition, the ESS-DMSC should drive activities such as the simulation of experiments, the development of hypotheses, visualization and analysis of data and develop analysis tools to facilitate the use of the ESS.

More information:
www.europeanspallationsource.se
www.ess-dmsc.eu

5.4

Related initiatives

A number of initiatives have been funded, primarily by the public sector, in order to ensure that the region reaps the full benefit of heavy investments in infrastructure. The short descriptions below are from the projects' own communication materials and websites.

5.4.1 Strategisk Alliance for Register og Sundhedsdata (STARS)

The Danish Ministry of Health established the strategic alliance for registers and healthcare data (STARS) in September 2013. Representatives from academia, patient organizations, industry and healthcare providers are gathered in a new forum with the intention of kick-starting health research and make recommendations on how Denmark can best use the information in national disease registries and the national biobank to develop new and improved treatments for the benefit of patients. The STARS alliance consists of 17 central stakeholders within healthcare and research.
http://bit.ly/1qZNVEZ

5.4.2 Biobanking and Biomolecular Resources Research Infrastructure (BBMRI)

The Biobanking and Molecular Resource Infrastructure of Sweden (BBMRI.se) is the largest investment that the Swedish Research Council has made so far within the area of medical infrastructure. As biobanking is about optimizing the collection, storage and analysis of samples for medical research, BBMRI.se strives to build a national infrastructure of biobank samples from patients and healthy volunteers. This will generate new possibilities for discovering diseases at an early stage and determining the best treatment. In 2010, BBMRI.se became a national infrastructure after an agreement between The Swedish Research Council and Karolinska Institutet. BBMRI.se, hosted by Karolinska Institutet, collaborates with all medical universities in Sweden.
http://www.bbmri.se/

5.4.3 Epidemiology for health (EpiHealth, Lund University)

The country of Sweden has possibly the longest history of population-based data collection in the world. There-fore, it should come as no surprise to see that Sweden is the birthplace of an ambitious project called "Epidemiology for health" (EpiHealth). As its name suggests, EpiHealth aims to improve understanding and etiology of both chronic and infectious disease processes via state-of-the-art epidemiologic research. Two of the oldest universities in Sweden, Uppsala and Lund, have agreed to join forces to achieve this aim, with a steering committee of 11 members from both Lund and Uppsala driving the project forwards.

Epidemiology, however, is not just a tool used by other disciplines but is also a science in its own right; therefore EpiHealth does not intend to be just another data collection agency. EpiHealth will also provide a base to develop and teach the very latest in epidemiologic methodologies and techniques to advance the discipline further.

With this in mind, there are three major focus areas for EpiHealth:

- **Basic Science epidemiology:**
  To research the etiology of chronic and infectious diseases via further development of biomarkers and gene-level interactions.
- **Applied and Clinical Epidemiology:**
  To develop monitoring systems for the cost-effectiveness of healthcare delivery and prevention programs.
- **Epidemiologic Infrastructure:**
  The research and development of state-of-the-art epidemiological infra-structures (for example, registries, biobanks and technology platforms).

These will build upon already existing national epidemiologic infrastructures, such as national health quality registers, population-based cohorts and biobanks. EpiHealth will also develop new national and international research data registers and biobanks creating an "easy access" infrastructure for research both in Sweden and abroad.

EpiHealth is not just a pipedream; funding for the next five years, to the tune of SEK 52 million was granted from The Swedish Research Council ("Vetenskapsrådet") in late 2009, thanks mostly to the efforts of the EpiHealth "ad hoc" committee leader Prof Peter Nilsson and his team. Work to turn the EpiHealth concept into reality has started with the sourcing of a suitable infrastructure for EpiHealth in Southern Sweden, creating a fully functional website (www.med.lu.se/epihealth) and establishing a committee to formally run EpiHealth.

5.4.4 NordForsk / NORIA-net on Registries (Nordic Council) (2011-2013)

NordForsk has initiated the "NORIA-net on Registries" with the aim to increase the use of the unique data registries and biobanks in and between the Nordic countries, and thereby strengthen Nordic cooperation on registry-based research. The project period was 2011-2013.

NORIA-net is a coordination activity for the national and Nordic research funding agencies and policy makers. The NORIA-net should map and identify where there is added value in cooperating at the Nordic level and give strategic advice to NordForsk on how to strengthen Nordic research by increased the joint use of registries.

The report "A reinforced Nordic collaboration on registers and databases: challenges from six perspectives" will serve as important background material for the NORIA-net group. Activities within the NORIA-net has the aim to increase the coordination and accessibility of registries to the different research communities, map national work plans, as well as to investigate potential limitations (legal, ethical, political etc.) which impede cooperation and propose ways to overcome these. Coordination activities targeting statistical authorities, data inspection boards and ethical committees are foreseen.

The NORIA-net aims to arrange a high-level workshop in the spring of 2013 focusing on how to make Nordic register data available and possible to use by a broader research audience. The outcome of the workshop will be used by the NORIA-net to formulate recommendations on how to strengthen Nordic registry-based research.

For more information:
http://bit.ly/1qZ0vmf

5.4.5 KADABRA

In order to strengthen Medicon Valley's position in the global competition for talent and capital, the region needs to make full use of its competitive advantages. One such advantage is the comprehensive Swedish and Danish health data registries that can be pooled and the possibility to link data between the registries by using the unique social security numbers that exist in the two countries.

The KADABRA (KArtlägning av DAtakällor och register inom BRöstcancerområdet samt barriärer vid Användning) project will thus investigate how to combine Danish and Swedish data sources and health registries. It will map available data sources within breast cancer including barriers to access and coordinate these data sources. The project will result in a set of concrete proposals on how to coordinate and provide access to data. It will also suggest actions to overcome these barriers. The project focuses on breast cancer in order to reduce the complexity of the project and to build on regional strongholds. However, the idea is that the findings would be applicable on other therapeutic areas at a later stage.

The project period runs from November 2013-October 2014 and is cofinanced by the EU Interreg Program, Region Skåne and the Capital Region of Denmark.

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MEDICON VALLEY
BEACONS

The Medicon Valley Beacons is an initiative to create a handful of world-class research environments, known as Beacons, in the Danish-Swedish life science cluster, Medicon Valley.
The Medicon Valley Beacons cover the following areas: Immune regulation – Structural biology – Systems biology – Drug delivery – Independent living