

VISION PAPER
DRUG
DELIVERY



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① WHAT IS DRUG DELIVERY?

Drug delivery can be defined as a formulation or device that optimizes the therapeutic effect, safety, and/or compliance of an active pharmaceutical ingredient. Technologies include drug preparation, administration routes, targeting, metabolism and toxicity.

Thus, drug delivery is the process or method by which drugs are administered to patients so that the drugs reach the diseased area. For drugs to be effective, they need to arrive where they are required in the body and in the correct dosage. Ensuring that drugs mainly target a diseased area is also highly desirable as it reduces the side effects, which may occur when drugs influence other parts of the body.

Drug delivery R&D focuses on developing new ways of getting drugs absorbed into the body, new ways of ensuring targeted delivery (i.e. that the drug is mainly active in the target area of the body), and new ways of ensuring sustained release (i.e. that the drug is released over a period of time in a controlled manner).

The overall aim of any drug delivery system is to improve its efficacy, safety and compliance regarding the medicinal product. This can be achieved by implementing various drug delivery technologies that enable improved bioavailability, targeted delivery, or an alternative route of administration etc. A drug delivery system should not exert a pharmacological effect in the absence of the API.

Though the primary goal of drug delivery technologies is to ensure better treatment, the technologies can also be implemented in other parts of the medicinal sector. The targeted delivery of drugs used in cancer treatment can be used to develop diagnostic tools for cancer and vice versa. The technology used in diagnostics might be similar to technologies used in drug delivery and to distinguish the two it is essential to investigate the purpose of the technology.

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② WHY DRUG DELIVERY?

Optimizing drug delivery plays a central role in drug development. Many promising drug candidates are discarded, because there is no known method of directing them to the diseased area of the body. The blood-brain barrier is, for instance, notoriously difficult to penetrate, making it difficult to treat brain tumors or diseases such as epilepsy and Alzheimer's.

The shift towards treating patients with macromolecular biopharmaceuticals, such as protein-based and nucleic-acid-based drugs, is also intensifying the demand for developing new innovative drug delivery systems – not least because biopharmaceuticals are key to personalizing medicine. Biopharmaceuticals are difficult to deliver orally because they are vulnerable to enzymatic degradation in the gastrointestinal tract and their large molecular size makes them difficult to absorb. Thus, the success of bringing new biopharmaceuticals to the market and tailoring treatment to the individual patient is therefore closely linked to the development of drug delivery systems.

There are two main factors that are the keys to why drug delivery has been chosen as a Medicon Valley Beacon: 1) the future demand for drug delivery systems in the global bio pharma industry (as mentioned above) and 2) the strongholds available in Medicon Valley within drug delivery. The creation of a Drug Delivery Beacon has the potential to create a truly innovative world-class hub within the field, by bringing together Medicon Valley's strong research activities in this field, which have been dispersed until now.

The drug delivery research environment in Medicon Valley should be able to compete in the global race to attract and maintain world-class expertise within translational research of drug delivery methods and technologies.

The vision is to setup a Center for Drug Delivery Research to foster disruptive innovations by combining biology, medicinal chemistry, pharmaceutical sciences, nanotechnology, mathematical modelling, material sciences, and design.

The region holds many scientific strongholds within drug delivery at the universities, and the skills base in the companies in Medicon Valley has many complementarities. The local pharmaceutical companies have a long tradition of pioneering drug delivery technologies. The strongholds present in Medicon Valley reflect to a large extent what is required to build an international and attractive region for drug delivery.

Drug delivery is one of the most cross-disciplinary areas of research that exists, which is why it often involves a large number of different stakeholders. It comprises all areas of the pharmaceutical sciences, chemistry, (bio) material sciences, cell and organ biology, molecular biology, and applied mathematical modelling. In addition, advanced analytical and imaging methods have frequently emerged due to the need for developing new methods caused by novel drug delivery systems.

Throughout the industry, there is a general consensus that the industry demand for drug delivery is increasing significantly, especially due to the increase in novel therapies (e.g. gene therapy).

The forecast moreover shows that the medical/pharmaceutical sciences will move from a reductionist analysis of the effects of drugs to a more holistic analytical approach, spurred by topics such as poly-pharmacology and poly-pharmacy, which again emphasizes the importance of drug delivery.

It is expected that successful drug delivery research can lead to considerable savings overall, and the figures mentioned are in the double-digit percentages of total health care cost in any Western country alone.

Not surprisingly, this is driven by the need for cost savings on personalized medicines where drug delivery is to play a crucial role.

However, due to the cross-disciplinary feature of the field, a beacon within drug delivery is not created by individual organizations alone, but requires a combined effort, commitment and a common vision from both public and private organizations and is created by improved and increased collaboration among all relevant stakeholders.

The stronghold analysis also shows that a number of cultural assets present in Medicon Valley such as a high level of trust and a low power-distance, support innovation created in cross-disciplinary and cross-organizational environments.

The drug delivery area is developed as part of the “Medicon Valley Beacons”-project. The Medicon Valley Beacon within drug delivery aims to unite relevant key stakeholders in Medicon Valley to create a world-class research and business environment within drug delivery that will ensure the region’s future attractiveness.

Creating such a Beacon shall help to create regional excellence as well as regional identity that will differentiate Medicon Valley from competing regions and thereby make it easier for companies to attract the best scientists, experts and partners within drug delivery.

In recent years, MVA has facilitated the process towards developing a Drug Delivery Beacon in close collaboration with key stakeholders. The process has been supervised and guided by a steering group¹ that decided to engage Boston Consulting Group and an independent consultant to investigate the potential of the area in more depth and clarify the work further during 2012.

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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 aim 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 4-5 research environments that build on Swedish-Danish synergies between existing strongholds – in both the private and public

sectors – 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 – structural biology, immune regulation, systems biology 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.

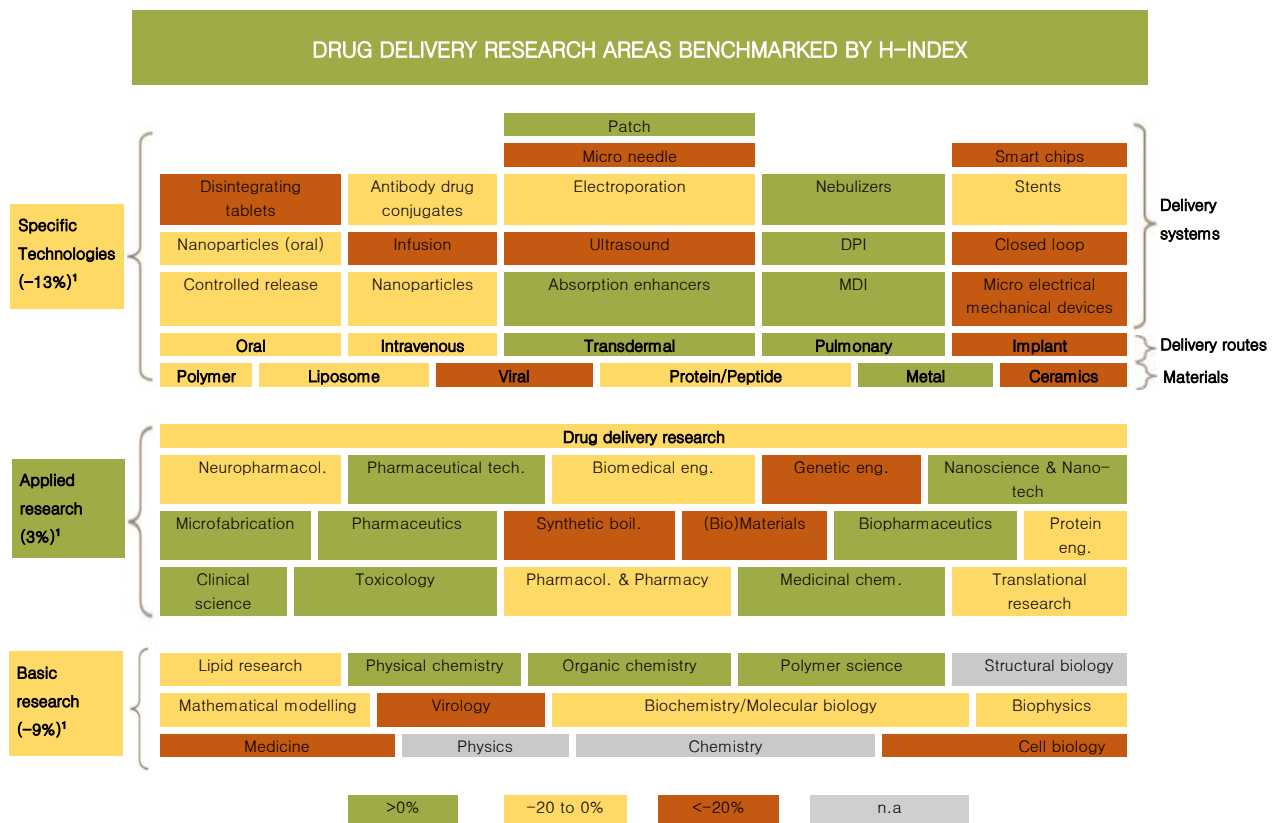
The individual Beacons focus on areas where there is considerable potential for synergies in Medicon Valley for creating world-leading research environments.

The Medicon Valley Beacons are 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.

3 REGIONAL STRONGHOLDS

In 2012, Boston Consulting Group (BCG) mapped and evaluated the regional strongholds which are relevant for drug delivery research, as described in their separate report (BCG – Medicon Valley Drug Delivery Initiative, October 2012). To map the area, BCG applied the “stacks concept”, as illustrated below. It benchmarks scientific performance by using the H-index, which combines both scientific productivity and impact in one measure. Each research area of relevance to drug delivery research was benchmarked against the top global life science

regions within drug delivery, namely Silicon Valley (US), Cambridge (US), London (UK), Cambridge (UK), Tokyo (JAP), Zurich (CH), Heidelberg (GER) and New York (US). Since the benchmark only includes absolute top-level regions, even average performance is considered as strong. The report concluded that Medicon Valley’s performance is strong both within basic and applied research. The region has its strength within specific technologies like protein/peptides, polymer-based, oral, intravenous, and pulmonary drug delivery.



Colours indicate relative H-index of MV compared to average of leading life science clusters
 1. Average of relative H-indices weighted by number of publications. Note: Data includes articles published within selected research/technological areas since 2000. Sources: Web of Science, Scopus.

In addition to the bibliometric study, qualitative dialogue with key stakeholders showed that Medicon Valley is indeed an attractive region for drug delivery research.

The major universities in Medicon Valley have wide areas of expertise and substantial activity in the field of drug delivery and related research fields.

There is, of course, an overlap but also a complementarity and particular strength at each institution. To exemplify, a few key competence areas of each university partner are outlined below:

- University of Copenhagen is highly competent in the formulation of protein drugs, oral drug delivery, nano-medicine, bioimaging, medicinal chemistry, dosage form analysis and development of preclinical disease models.
- The Technical University of Denmark has strengths in biomedical engineering, synthesis, nanomedicine, nano- and micro-technology and has a strong function for supporting innovation.
- Lund University has comprehensive fundamental sciences for physico-chemical characterization, surface and colloidal chemistry, mathematical modelling of advanced drug formulations, delivery to target cells/organs, as well as pharmacology and pharmacokinetics.
- Malmö University has activities related to electrochemical analysis, sensors, molecular imprinting, analysis of barrier properties, physicochemical characterization of mucus and lipid based formulations.



The region has a long tradition in drug research and development, which has been driven by a high representation of pharmaceutical, biomedical and biotech companies in the region. Most of these companies were originally founded by university researchers and thus have a strong history of close collaboration with local universities. The companies are generally rooted in local society in spite of an increasingly globalized and competitive international market.

The success of companies like AstraZeneca, Novo Nordisk and Lundbeck has impacted the university curriculum in the region substantially, where research in medicinal chemistry and small molecule drugs for decades was a central part of the companies' research programs and in the educational system of the universities. However, the interest in small molecule drugs has declined rapidly and the drug research focus has changed towards biologics, which has intensified formulation and drug delivery research.

Substantial public and private funding has in the past decade been financing research in drug delivery technology, e.g. in the areas of nano- and biotechnology, protein engineering and device technology.

The long tradition in the pharmaceutical area and the last 30 years of heavy investment in the biotechnology industry has created a research and innovation environment, which in combination with the substantial new investments in drug delivery research by companies and government in the past decade, provides unique opportunities. With the appropriate strategic focus, the region can turn drug delivery R&D into a general stronghold on an international level.

A list of specific areas within drug delivery where the region has strongholds is listed below. These areas form the foundation for the regional research strongholds that the Medicon Valley Beacon can be built upon.

Nano- and micro-technology:

Nano-science has in recent decades become a highly important part of biomedical and biotechnology research. The Technical University of Denmark, University of Copenhagen and Lund University all have substantial nano-science research and education programs that underline the importance of this field. The Technical University of Denmark runs one of the largest university clean room facilities in northern Europe, and multiple spin-out companies have resulted from university research that is focused in the biomedical technology area. Likewise, nanotechnology is increasingly becoming part of drug delivery research and biotechnology, and this has also resulted in several spin-outs from the universities. The research in nano-science in the region is on a high international level but cannot yet be considered as being within the top 5 regions in the world. However, there is huge potential for improving the position of this research field by increasing the integration between industrial and academic research.

Formulation and delivery of proteins and peptides (protein engineering):

Due to the presence of many companies in the region who are focused on the delivery of proteins and peptides, e.g. Novo Nordisk, Zealand Pharma and more recently Lundbeck, there has been a natural driving force at the universities to conduct research in the protein formulation and engineering areas. In particular, due to the size and investments made by Novo Nordisk, the research funding in this area is substantial. Competences within protein engineering and protein formulation are strongly developed and the Novo Nordisk Foundation Center for Protein Research is the largest protein research center in Europe. The Technical University of Denmark further adds to the region's protein expertise within the production area, and the Novo Nordisk Foundation Center for Biosustainability will focus on the sustainable production of biological materials in the coming years. This center also involves partners at Lund University. There is a long history of research in freeze-drying technology and protein and peptide formulation for various administration pathways. This experience includes various dosage forms that have been developed, e.g. conventional parenteral dosage forms including depot formulations and in-situ gel formulations, transdermal dosage forms, patches, intranasal dosage forms and solid dosage forms for oral administration.

(Bio)material sciences research:

There is a very long research tradition in material sciences at the universities in the region, which has been driven by a unique infrastructure in material characterization. MaxLab provides a unique facility for frontline research and before the last reactor was closed, Risø was also a very important research facility. Together with a general state-of-the-art infrastructure at the universities, these facilities provided the foundation for excellent research in material sciences. Particularly important research fields in this regard have been several of the physical chemistry groups at Lund University and physics groups at the University of Copenhagen. In addition, there are a few strong groups within biomaterial chemistry research, which is going to be an important factor in developing this area in the coming years. The tradition within material research in the region is a great opportunity in drug delivery research through the acquired competences to design and characterize advanced biomaterials.

Medical devices for drug delivery:

For years, companies in Medicon Valley have pioneered in developing innovative medical devices, and the industry possessed highly qualified manufacturing, assembling and QA competences. Novo Nordisk, AstraZeneca, Coloplast etc. have a strong product portfolio within medical devices. Of particular importance for supporting this stronghold is the highly developed skills and abilities to take the end-users perspective into consideration when designing devices. The research in nano- and micro-technology in the region furthermore adds value as a technology supplier to the medical device area. Several university spin-outs have success in this area.

Enhancing bioavailability of poorly soluble compounds:

Since the beginning of the 1990s, a research group has existed at the Faculty of Pharmaceutical Sciences focusing on drug delivery technologies to improve the bioavailability of poorly soluble compounds with particular focus on solid dispersions and lipid based formulations. Consequently, numerous PhD students and graduate students have been doing their thesis within in this area and thus provide a strong contribution to this field of expertise.

Infrastructure strongholds

The region has had a large pharmaceutical, biomedical and biotechnology industry for decades. This has resulted in large public and private investments in university research in relevant areas and education within the necessary scientific disciplines.

Medicon Valley has three excellent universities within natural, life and technical sciences (Copenhagen University, Lund University and the Technical University of Denmark), all located within a very short distance (1 hour drive) of each other.

As a consequence, there is a huge general research potential in the area, which makes the environment very attractive for companies of all sizes.

The large public and private investments in Medicon Valley have occurred over a long period of time and this has resulted in university facilities and infrastructure that are comparable to universities like Harvard, MIT and Oxford University.

One of the key drivers for developing the infrastructure of excellent lab facilities and very specialized equipment is the fact that both Denmark and Sweden have very high salaries in general. This leads to high labor costs, which makes infrastructure that optimizes research output by saving time and thereby reducing labor cost a good investment.

Besides the generally good conditions and well-equipped laboratories that Medicon Valley universities offer, large investments in facility centers have been made, e.g. the Core facility for integrated microscopy at Copenhagen University, the Center for Electron Nanoscopy at DTU and the clean room facility DANCHIP at DTU.

Huge investments from private foundations in large centers have furthermore strengthened the research environment in Medicon Valley, e.g. within protein engineering. This area is of high importance in relation to establishing a focus on drug delivery in the region.

In the coming decade, the world's most brilliant x-ray synchrotron and the most powerful neutron source will be operational in Lund, i.e. the MAX IV Laboratory in 2016 and the European Spallation Source (ESS) in 2019 and the MAX IV. The facilities will be unique and provide the infrastructure for world-class biomaterial research in the drug delivery field and provide possibilities within drug formulation development that will be difficult to find elsewhere. As most modern drug delivery systems rely on nano-scale particles, access to these world-leading facilities will give Medicin Valley a significant competitive edge compared to other regions in the world.

The region hosts companies of all sizes and within multiple disciplines in connection with drug delivery research and development. The region is highly attractive for companies and investors in the drug delivery area due to the impressive infrastructure that the universities and public research facilities provide.

With the close proximity of the universities and companies in the region, it should be an ideal place for technology-driven research and development in the drug delivery area from an infrastructural point of view.

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④ VISION FOR DRUG DELIVERY

In order to reap the full benefit of the many strongholds that the region has within drug delivery, a vision for a Drug Delivery Beacon has been developed. It was developed at a full-day workshop held during the spring of 2012, which brought together scientists and leaders from academic institutions and representatives from industrial R&D in the region to discuss

and brainstorm on how to develop this area. Based on the input from the participants at the workshop and from the members of the steering group, a vision was developed in which the overall ambition is to create a center for drug delivery research in Medicon Valley in order to strengthen the research environment.

Vision statement

To be internationally recognized within a decade as one of the world's leading centers for drug delivery research in basic and translational drug delivery research, innovation, and education, where ground breaking technologies in drug transport, and tissue and cellular targeting are developed for the benefit of both patients and society.



The key words in the vision statement are defined as follows:

World's leading: measured by benchmarking the center's annual performance in the three dimensions mentioned above against the best drug delivery centers/groups in the world

Ground breaking: based on bibliometrics (e.g. the Leiden indicators for quality assessment of scientific publications)

Within a decade: 10 years from the opening of a center for drug delivery research

Internationally recognized: measured in three dimensions – academia, industry, and society:

Academia	Industry
<ul style="list-style-type: none"> Bibliometrics (citation-index, h-index, no. of downloads of PhD-theses, etc.) 	<ul style="list-style-type: none"> Number of companies involved
<ul style="list-style-type: none"> Ability to attract and retain talent, measured as number of non-Scandinavian post graduates that works at the center for more than three years 	<ul style="list-style-type: none"> Amount of private funding per year Number of strategic collaboration agreements signed
<ul style="list-style-type: none"> Number of patents granted 	<ul style="list-style-type: none"> Number of spin-outs founded Amount of venture capital attracted to spin-outs
<ul style="list-style-type: none"> Funding/grants obtained from outside sources, i.e. EU, NIH 	<p>Society</p>
<ul style="list-style-type: none"> Education delivered to international students 	<ul style="list-style-type: none"> Changes of therapeutic guidelines

Mission statement

- The scientific focus is to develop ground-breaking technologies that facilitate drug transport over biological barriers and enhance tissue and cellular targeting for treatment and diagnostic purposes.
- The center for drug delivery research is located in Medicon Valley and operates as a precompetitive and internationally open environment where scientists work in project teams converging many different disciplines based on the regional strongholds.
- The research is translational, leading to changes in clinical practices for benefit of the individual patient as well as society.
- Organizationally, the center for drug delivery research is integrated with the local universities and is committed to provide the best teaching environment for pre- and post-graduate students.
- University hospitals in the region are affiliated with the center and are committed to deliver strong clinical input to the research.
- The center for drug delivery research provides core facilities with access to state-of-the-art instrumentation for approved projects.
- The scientific ambition is to publish new insights in the top-ranked international journals but also to explore commercialization either through company spin-outs or external collaborations.

The vision and mission for a future center for drug delivery research is focused on an innovative organization and a unique structure. The aspiration is to make the center unique in the sense that:

- Long-term financial commitment to the research will attract the most talented scientists
- The center will cover all aspects of drug delivery research from basic research to the clinic
- Public-private partnerships combine basic research with translational research in a unique way
- Precompetitive research will take place in an open innovation environment
- A unique governance structure strengthens the universities' commitment to the center and a matrix organization will innovatively combine basic and translational research
- The center is a cross-border collaboration in order to fully utilize the region's potential
- The research facilities will be allocated in a flexible way based on interdisciplinary projects
- The flexible project organization will circumvent barriers between different research disciplines by providing a new platform for cross-fertilization

This vision for the Drug Delivery Beacon will use the regional strongholds in terms of available scientific expertise as well as experimental facilities. By creating a joint platform for closer collaboration, it will lead to a higher integration of drug delivery research in the region and a more efficient use of the existing and new infrastructure. This will lead to both a higher quality and quantity of research and innovation, opportunities to develop new drug delivery technologies and hopefully increase the number of spin-out companies.

The scientific environment anchored in the center outlined above, and supported by extensive network activities between the future center and its collaborators, will significantly improve the attractiveness of the region for international talents with a specific interest in the drug delivery research field. By creating a life science environment of high international class by focusing long-term resources on drug delivery technologies, the region will become a magnet for international talent.

⑤ CURRENT STATUS (Q4 2014)

The work that has been done in recent years has certainly highlighted the immense potential that this research area has in terms of solving future demands for innovative drug delivery systems. It has also highlighted the many strongholds that are present in Medicon Valley as well as the huge interest from key stakeholders to strengthen the research community by establishing a joint Medicon Valley Center for Drug Delivery Research.

The overall vision for the Drug Delivery Beacon is to establish a Medicon Valley Center for Drug Delivery Research. The key stakeholders in the region support this vision and have been contributing to the efforts of developing the Beacon in recent years.

The crucial issue in terms of reaching the goal of establishing a research center is to secure commitment for long-term funding. Long-term funding has not been secured yet, but MVA will continue to drive the agenda by highlighting the huge potential of drug delivery research in Medicon Valley and encourage closer collaboration.

In fact, progress has been made in terms of strengthening the drug delivery research community in Medicon Valley. The mere fact that a group of key stakeholders has been meeting on a regular basis in recent years has certainly strengthened personal relations and broadened the network across Øresund.

At the MVA annual event in November 2013, focus was on the Medicon Valley Beacons and how they can create value and business opportunities. A session at the event was dedicated to the Drug Delivery Beacon where the state of innovation in drug delivery was discussed and the huge potential of this research area was once again emphasized. The presentation and panel discussion related to Drug Delivery is available as videos on the MVA website (www.mva.org/drug-delivery-videos).

MVA will continue to spot opportunities for potential synergies, and continue to highlight regional strongholds which can already be branded internationally at this stage.





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