evotec

DDup

DRUG DISCOVERY UPDATES #1

DIABETES
A MAJOR PANDEMIC

REGENERATIVE MEDICINE
HOPE FOR BETTER MEDICINES

CURE BETA
A SYSTEMATIC APPROACH TO BETA CELL FAILURE

CONTENT & CONTACT

FOR YOUR FUTURE DD PROJECT PLEASE CONTACT:

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Dr Werner Lanthaler, CEO

WELCOME TO DDUP!

DEAR DRUG DISCOVERY PARTNERS,

What is new? What can be done better? Where and how can we optimize our partnership with you? These were the questions that triggered the idea to launch this regular newsletter for our partners and friends.

We continually develop our technological skills, science based expertise and our capabilities in building and maintaining outstanding integrated drug discovery alliances. In addition, we strongly believe that high quality interactions and communication not only with our customers but also the scientific community are key drivers of successful drug development. We constantly strive to conduct drug discovery at the highest level and thereby provide the best services to you and your projects.

It's therefore a great pleasure for me to introduce to you the first edition of our brandnew newsletter "DDup", which means Drug Discovery update. DDup should give you the opportunity to get a better "look and feel" of what is going on at Evotec.

Creating a better visibility of what we do should trigger a discussion, should raise questions and ultimately it should make us work even better together with you.

DDup's intention is to give you 2-4 times a year the basis, for a better insight into Evotec's key technologies, our ideas on key therapeutic areas and potential ways of working together.

Our first main topic "Metabolic Diseases" is dedicated to the recently announced partnership with the Harvard University and the Howard Hughes Medical Institute (HHMI) in the field of Diabetes and our ideas on regenerative medicine. It is our clear goal to become the top-quality partner in this highly innovative area.

It is our vision to develop drugs, which don't just fight the symptoms, but tackle the roots of degenerative diseases which afflict a significant portion of the population all over the world. Having access to the brightest people in the field and leading technologies is a prerequisite to accelerate targets into products and achieve our goal to generate novel drugs that make a difference to patients. This is what we want to achieve together with Prof. Doug Melton and a collaborative partnership with the Harvard Stem Cell Institute (HSCI) and HHMI that is unique in its structure and scope.

In light of this collaboration with the HSCI it is a great honour for me that we could win Prof. Doug Melton, who will be a key strategic advisor for Evotec in the field of regenerative medicine, as the first DDup interview guest.

I hope you enjoy browsing through DDup and if you may have any further questions please don't hesitate to contact us.

Yours sincerely
for the management of Evotec
Werner Lanthaler

TO TACKLE THE ROOTS OF THE DISEASE

Douglas A. Melton is the Thomas Dudley Cabot Professor in the Natural Sciences at Harvard University, and an investigator at the Howard Hughes Medical Institute. Additionally, Dr. Melton serves as the co-director of the Harvard Stem Cell Institute and the co-chair of the Harvard University Department of Stem Cell and Regenerative Biology.

Dr. Melton serves on the Scientific Advisory Board of the Genetics Policy Institute, holds membership in the National Academy of the Sciences, and is a founding member of the International Society for Stem Cell Research. Melton's early work in the 1980s pioneered the technique of *in vitro* transcription. This later shifted to general developmental biology research in Xenopus, and eventually in the mid-1990s, became centered on the development of the pancreas.

His current research interests include pancreatic developmental biology and the directed differentiation of human embryonic stem cells, particularly in pertinence to type 1 diabetes, which afflicts both his children.

In 2007 and 2009, Melton was listed among Time Magazine's *100 Most influential People in The World.*

Excerpt of laudatio by Michael J Fox: *"In 50 years' time, Doug Melton's inclusion on this list will probably seem prescient. By then, wherever the field of stem-cell research may stand, we will surely have gained the clarity required to look back and recognize the scientific heroes who believed in its transformative potential—and refused to let its promise go unfulfilled. To anyone touched by illness or injury, a scientist who goes out in search of a cure always looks heroic, as Doug surely does."*

In August 2008, Melton's lab published successful *in vivo* reprogramming of adult mice exocrine pancreatic cells into insulin secreting cells which closely resembled endogenous islet beta cells of pancreas in terms of their size, shape, ultrastructure and essential marker genes. Unlike producing beta cells from conventional embryonic stem cells or recently developed induced pluripotent stem cell (iPS) technique, Melton's unique method involved direct cell reprogramming of adult cell type (exocrine cell) into other adult cell type (beta cell) without reversion to a pluripotent stem cell state. His team used a specific combination of three transcription factors, Ngn3 (or Neurog3), Pdx1 and Mafa for such direct cell reprogramming to yield cells capable of secreting insulin and remodelling local vasculature in pancreas to counteract hyperglycemia and diabetes.

5 MINUTES
WITH DOUG MELTON ON REGENERATIVE MEDICINE

CD: The topic of regenerative medicine has gained increasing attention and visibility over the past few years. To what extent and in which areas do you think will regenerative therapeutic approaches actually become clinical reality?

DM: I think we are just at the beginning of seeing new medicines and therapies that will come from stem cell science. An apt comparison may be with the time that it became possible to engineer and produce biologically active proteins such as insulin and antibodies. It took years from the ability to clone genes to get to the product, but in the end, the visionary leaders were right and new medicines came out of the science of molecular biology. Similarly, the fact that our bodies depend, to varying degrees, on stem cells for the continual renewal of our tissues and organs means that harnessing that biology will lead to new therapies and medicines. And by new medicines, I mean to include drugs discovered using stem cells as tool as well as the cells for transplantation.

Achievements in the field of regenerative medicine have certainly not kept pace with expectations raised from scientific advances made in particular in the stem cell field. However, it is important to point out that regeneration is part of our daily lives. Most human tissues and organs regenerate constantly, albeit to varying degrees. Without continuous regeneration we would quickly succumb to a multitude of insults and injuries which we have to endure on a daily basis.

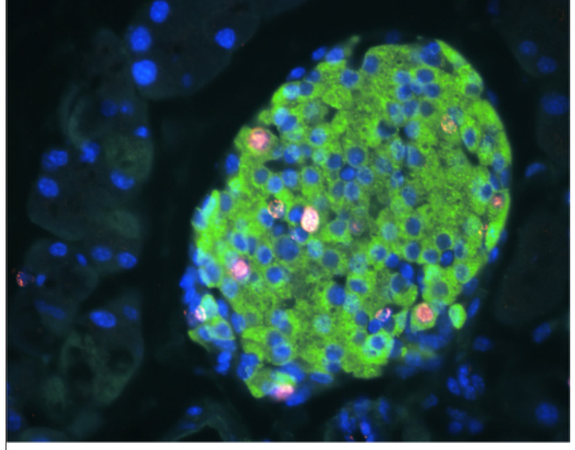
> "Achievements in the field of regenerative medicine have certainly not kept pace with expectations."

It is also important to remember that regenerative medicine has been in medical practice for quite some time. There are a number of treatments in routine medical practice that are based on regenerative drug products. Stem cells from umbilical cord blood that have been used for years to regenerate the blood and immune system of some patients with leukemia and other diseases. Another example is Erythropoietin, one of the most successful biotech drugs on the market, which stimulates the formation/regeneration of red blood cells and exemplifies how endogenous regenerative mechanisms that act on stem cells can be exploited as highly effective drugs.

In light of these facts it is reasonable to assume that the future of regenerative medicine is very promising and that there will be more drug products exploiting regenerative mechanisms and principles.

CD: You just mentioned the use of umbilical cord stem cells as well as Erythropoietin as examples of regenerative medicine. It is probably fair to say that people usually associate cell therapeutic approaches with regenerative medicine. What do you believe is the more promising approach in regenerative medicine: Cell based or pharmacological therapies?

DM: This is a difficult question to answer as it generally very much depends on characteristics of the



Replicating beta cells in islet of Langerhans in adult mouse pancreas; nuclei of dividing cells stained for replication marker Ki67; Insulin green, Ki67 red, DNA/nuclei blue

individual disease. Despite the fact that stem cell based therapies are already successfully applied in certain indications, so far there is very limited success with stem cell based therapies in most other indications where they have been tried including heart failure, spinal cord injuries, and diabetes.
In many ways diabetes is a disease well suited for a stem cell based therapy because the replacement of a single cell type, insulin-producing beta cells, can provide an enormous benefit to the patient. Furthermore, in order for beta cells to fulfill their function they do not need to be an integral part of the pancreas, where they usually reside, but can be delivered to other more accessible organs such as the liver. Still, there are a number of challenges that need to be addressed in order to develop a stem cell based therapy for diabetes or any other disease:

First of all, the generation of fully functional mature cell types from stem cells has not yet been achieved for most of the body's more than 200 cell types. Secondly, differentiation protocols have to be highly efficient and robust, approaching the goal of 100% of the cells differentiating to preclude tumor formation from undifferentiated transplanted cells. Thirdly, stem cell transplants have to be patient compatible to avoid immune rejection. Thus, although conceptually the development of stem cell based therapies is straight forward there are considerable challenges associated with the industrial scale needed for most of the required steps.

> "The future of regenerative medicine is very promising."

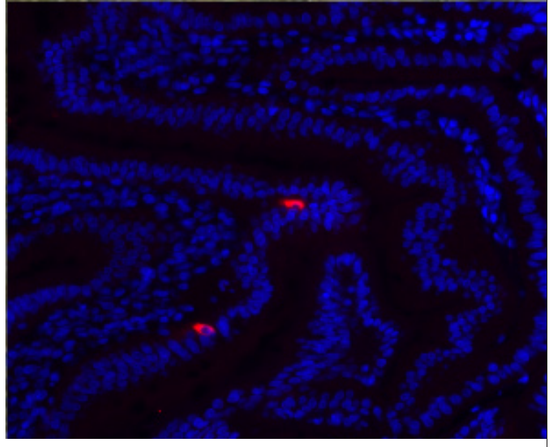
In contrast to the development of stem cell based therapies, which seem relatively straight forward on a conceptual level, the development of pharmacological treatments that target the regeneration of endogenous cells and tissues may seem more difficult or complex. However, there are natural

> "There are natural physiological mechanisms that stimulate the replication or neogenesis of certain cells whenever needed."

physiological mechanisms that constantly monitor the need for regeneration and stimulate the replication or neogenesis of certain cells whenever needed. These mechanisms are excellent targets for pharmaceuticals. Today's major challenge is to identify the mechanisms and then select and exploit the most suitable drug targets.

CD: What are the most promising mechanisms and how might they be identified?

DM: There probably are three or four major mechanisms that are suitable for pharmacological intervention: protection, replication, neogenesis and possibly transdifferentiation. Strictly speaking protection may not be a regenerative process but nevertheless it is an important mechanism to mention in this context as it can contribute



GIP producing endocrine K-cells in rat intestine;
GIP producing K-cells in red, nuclei/DNA in blue

to the maintenance of a tissue or organ by tipping the scale of degenerative and regenerative processes in favor of regeneration.

Mechanisms that drive the de novo formation of a specialized cell type such as replication or neogenesis are particularly attractive in cases where protective mechanisms on their own cannot restore function because the degeneration of a certain cell type or tissue has progressed too far. The major challenge for these kinds of mechanisms is to stimulate and trigger them in a cell type or tissue specific manner to avoid possible hyperplasia in other tissues. However, as the human body coordinates replication and neogenesis continuously in many different organs depending on physiological cues, conceptually there is no reason to assume that this is not possible as long as the responsible pathways and targets can be identified.
Finally, transdifferentiation could be viewed as a variation of neogenesis although in this case a cell type is not differentiated from a stem cell but rather from another mature cell type. The importance of transdifferentiation as a regenerative mechanism is currently hard to judge. Still, the fact that it is possible to turn one mature cell type into another is intriguing, may be of great therapeutic value and should be explored rigorously. To identify the relevant pathways that govern these mechanisms in individual cell types will require a better understanding of how the body controls and coordinates the size of organs and tissues under normal conditions. An improved understanding of these processes and mechanism oriented screening approaches should lead to the relevant molecular pathways and thus generate potential pharmaceutical intervention points.

> "Expectations may have been set too high, largely because the subject of stem cell biology was injected into the political arena."

> "Replication or neogenesis are particularly attractive in cases where protective mechanisms on their own cannot restore function."

CD: You indicated that progress in the field has not kept pace with expectations. Why do you think this is?

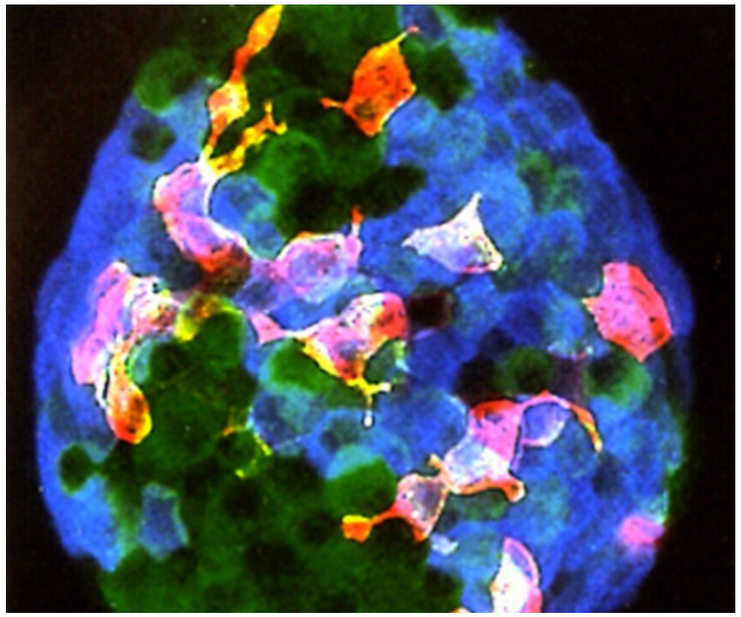
DM: Expectations may have been set too high, largely because the subject of stem cell biology was injected into the political arena. In my view, we'd be much farther along if more emphasis had been given to basic research on the principles and mechanisms of organ formation and regeneration. More research efforts on understanding the relevant mechanisms and pathways will be the key for future advances in the development of stem cell based therapies as well as the identification of targets for pharmacological intervention.

Another reason may be that we are using suboptimal *in vitro* and *in vivo* models and have limited experience regarding the relevance and predictive power of these models. An important goal should be to define and characterize current models in more detail and find ways to generate improved and possibly standardized models, preferably using human cells and tools that allow a more efficient and systematic validation of candidate targets and compounds. Investing into the development of improved tools and models as well as mechanism based screening approaches will be important for further advances in the field of regenerative medicine. Degenerative diseases such as diabetes, represent an enormous public health challenge but only limited advances that address this challenge have been made in recent years. Nonetheless, it has become increasingly obvious that efforts to develop drugs that target mechanisms that are potentially disease modifying will be well rewarded. Thus, the paradigm of regenerative medicine will be a central theme in finding treatments that slow or reverse disease progression for the foreseeable future.

> "Efforts to develop drugs that target mechanisms that are potentially disease modifying will be well rewarded."

CD: Thank you for your time.

Dr. Cord Dohrmann (CD), CSO of Evotec, is a developmental biologist by training and has been actively pursuing the discovery and development of beta cell regeneration drugs for more than ten years.

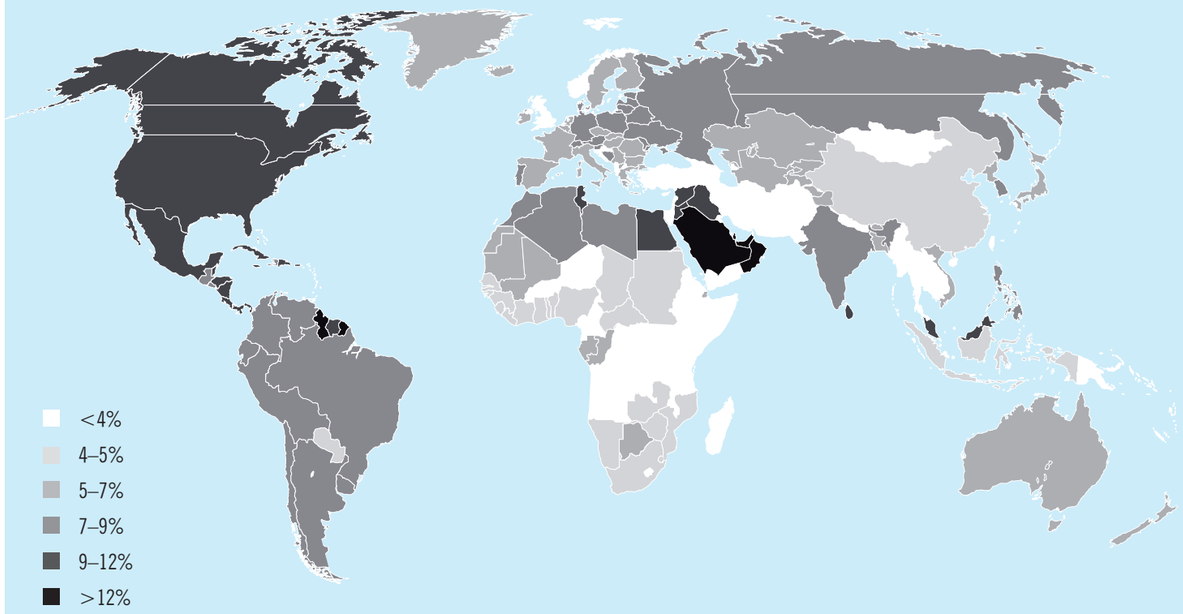


Rat Islet; Insuiln (blue), glucagon (green), pancreatic polypeptide (red), somatostatin (white)

The global antidiabetic market was $ 24 billion in 2008 with insulins and analogs at $ 12.5 billion and PPAR agonists at $5.8 billion. Actos and Lantus emerged as the top selling PPAR agonist and insulin analogue in 2008 with sales of $4.2 billion and $3.3 billion followed by newer insulin analogues. By 2019, Morningstar projects the worldwide diabetes market, excluding insulin, will grow to over $55 billion.

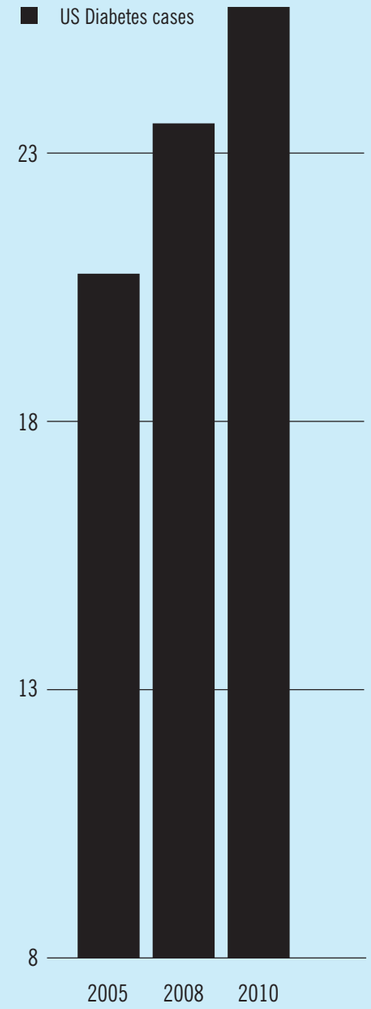
FACTS & FIGURES

GLOBAL BURDEN



US DIABETES CASES

Diabetes, the CDC says, costs $174 billion annually (2007), which include direct medical costs ($ 116 billion) and indirect costs ($ 58 billion, disability, work loss, premature mortality), compared with $ 132 billion in 2002. Diabetes/obesity is the fastest growing disease in the U.S., afflicting one in four Americans. It is estimated that if current trends continue, as many as 1 in 3 U.S. adults could have diabetes by 2050. Just in 2010, 1.9 million new cases were diagnosed in adult Americans.



AT A GLANCE

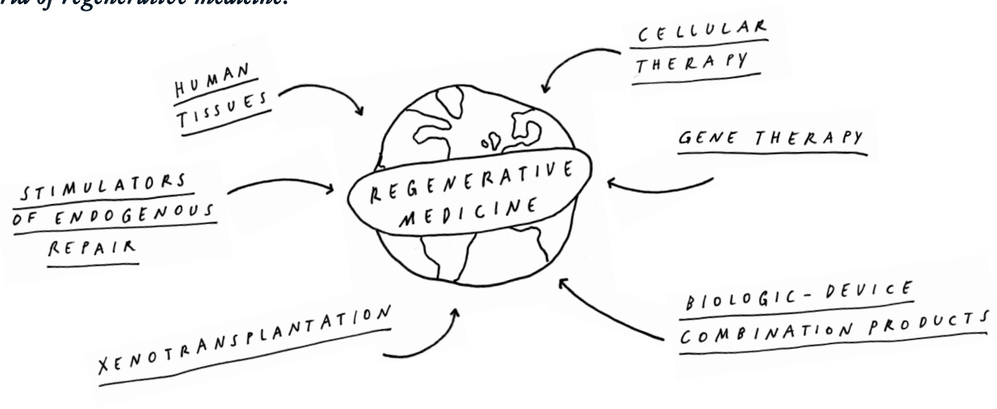
	2010	2030
Total world population (billions)	7.0	8.4
Adult population (20-79 years, billions)	4.3	5.6

DIABETES AND IGT (20-79 YEARS)

	2010	2030
Diabetes		
Global prevelance (%)	6.6	7.8
Number of people with diabetes (millions)	285	438
IGT		
Global prevelance (%)	7.9	8.4
Number of people with IGT (millions)	344	472

EVOTEC — HARVARD RESEARCH COLLABORATION

This is how the FDA views the world of regenerative medicine:



Evotec establishes Research Collaboration with Harvard University and the Howard Hughes Medical Institute in Diabetes Research

In February 2011 Harvard University, the Howard Hughes Medical Institute (HHMI) and Evotec announced a strategic alliance aimed at discovering and developing new treatments in the field of diabetes. The initial goal of the alliance is to pursue a systematic and comprehensive approach towards the identification and development of physiological mechanisms and targets that regulate beta cell replication.

Harvard, HHMI and Evotec bring together extensive expertise and know-how in beta cell biology and diabetes along with an unparalleled set of tools to exploit beta cell related mechanisms and targets. This unique collaboration will be fueled by substantial contributions and resources from Harvard and HHMI as well as Evotec's firm commitment to deliver on their common goal to develop orally available small molecule therapies that trigger or support beta cell replication.

Therapies that trigger/support beta cell replication are expected to enhance or even restore the body's ability to produce sufficient insulin to maintain optimal glycemic control and thereby reduce and prevent the development of diabetic complications. Leveraging key insights about beta cell replication and forming co-development alliances with pharmaceutical companies at the appropriate point in the development chain are the core strategic drivers of the alliance.

Prof. Doug Melton becomes key strategic advisor for Evotec in the field of regenerative medicine and will contribute his experience and expertise in the field of beta cell regeneration, as well as his far reaching academic and industrial network.

HARVARD ASSETS — EVOTEC ASSETS

The recently established collaboration by Harvard and Evotec was based on the vision to combine academic and industrial excellence and expertise in the field of diabetes and in particular beta cell regeneration.

Doug Melton's laboratory is world leading in stem cell and beta cell biology with extensive experience in conducting screens designed to identify key mechanisms involved in beta cell development, function and regeneration. Evotec has extensive experience in conducting screens and selecting high potential drug targets and their development regardless of treatment modality – small molecules, peptides and biologicals.

Combining assets and experience from both institutions establishes one of the largest and most experienced teams of scientists dedicated to the identification of novel approaches targeting beta cells that can become drugs that make a significant difference to patients.

ASSETS CONTRIBUTED BY HARVARD INCLUDE:

- Small molecule inhibitors that specifically stimulate beta cell replication
- Beta cell replication assay suitable for HCS
- Candidate targets list that have been linked to beta cell replication

ASSETS CONTRIBUTED BY EVOTEC INCLUDE:

- Comprehensive bioinformatics capabilities for the assessment and *in silico* validation of beta cell targets
- Comprehensive suite of *in vitro* and *in vivo* models to assess beta cell related mechanisms
- Comprehensive small molecule drug discovery and development capabilities
- Extensive experience and expertise in selecting high value diabetes drug targets for further development
- *In vitro* and *in vivo* assays and models for the selection and validation of beta cell drugs
- Additional tools and assays for the identification of further target candidates
- Extensive experience and expertise in stem cell and beta cell biology

Together we intend to conduct an all-inclusive search for target candidates that have the potential to improve beta cell mass and function. The product pipeline currently includes small molecules with *in vitro* and *in vivo* activity and long lists of target candidates. Additional screens have been designed and will be conducted to identify additional target candidates that can be fed into our proven target selection cascade. The goal is to conduct a highly systematic and exhaustive search for beta cell targets and feed the most attractive candidates into rigorous selection process to select the most promising for further development.

evotec

EVOTEC EXPERTISE

IN THE FIELD OF METABOLIC DISEASES

Through the acquisition of DeveloGen, now Evotec Göttingen, Evotec has access to over 10 years metabolic disease experience in target identification/validation, *in vitro* and *in vivo* pharmacology as regulatory affairs and clinical development up to Phase III. The primary focus was put on the identification of novel mechanisms and targets that have the potential to become disease modifying, preventing or even reverting disease progression.

In diabetes Evotec has put together a unique pipeline of potentially first-in-class products targeting key underlying causes of type 1 and 2 diabetes. All of these three products have been partnered with top pharmaceutical companies highly experienced in the respective fields:

- DiaPep277 (Phase III): An HSP60 derived peptide drug that acts an immunomodulator targeting the autoimmune-mediated destruction of insulin-producing beta cells.
- EVT070 (preclinical): A novel class of insulin targeting insulin resistance a primary cause of type 2 diabetes and obesity. Orally available small molecule inhibitors improve blood glucose levels and lipid profiles without causing weight gain.
- EVT770 (preclinical): A beta cell regeneration factor targeting the loss of beta cells in type 1 and 2 diabetes. Biopharmaceutical stimulating beta cell proliferation and neogenesis to increase beta cell mass and function.

What sets Evotec apart from most other companies in the field is that EVT070 and EVT770 have been identified and selected by Evotec through unique screening approaches that delivered a pipeline of novel targets with great potential in metabolic diseases.

Finally, Evotec conducts all work from target identification/validation, hit and lead identification/optimization supported by structure guided drug design and ADMET profiling in house. Subsequent formal preclinical development as well as clinical development and regulatory affairs is managed by in house experts with extensive expertise and experience.

Future approaches will continue to focus on potentially disease modifying mechanisms in the fields of diabetes, obesity, metabolic syndrome and associated comorbidities such as diabetic complications and heart failure.

In the field of diabetes, Evotec is conducting additional screens designed to identify mechanisms and targets that will increase beta cell mass and function. A particular focus will be placed on beta cell regenerative approaches based on orally available small molecules.

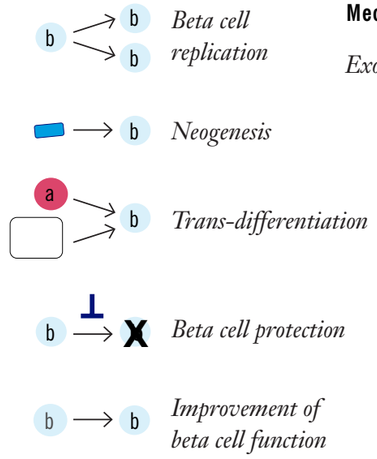
In the fields of obesity/metabolic syndrome, Evotec has identified a pipeline of highly innovative small molecule target candidates which are in various stages of validation. In addition Evotec is currently in the process of designing and conducting screens to identify mechanisms and targets increasing energy dissipation in peripheral tissues – a highly promising approach for the treatment of obesity.

In the field of diabetic complications, Evotec is currently focusing on chronic kidney disease. Here we are designing screens and assays geared for the identification of mechanisms and targets that protect and/or regenerate key cell types affected during disease progression.

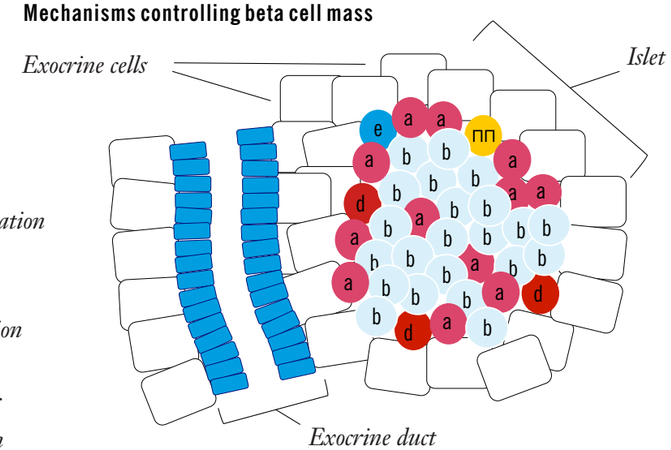
Dr. Dohrmann has spent over 20 years in biomedical research at leading academic institutions and in the biotech industry. He started his academic career in 1983 studying Biology at Tübingen University in Germany and conducting research as a DAAD scholar at Duke University, Durham, USA. Dr. Dohrmann completed his MA thesis at the Max-Planck Institute in Tübingen and subsequently enrolled at the Harvard Medical School in Boston, USA, where he received his Ph.D. in Cell and Developmental Biology in 1996.

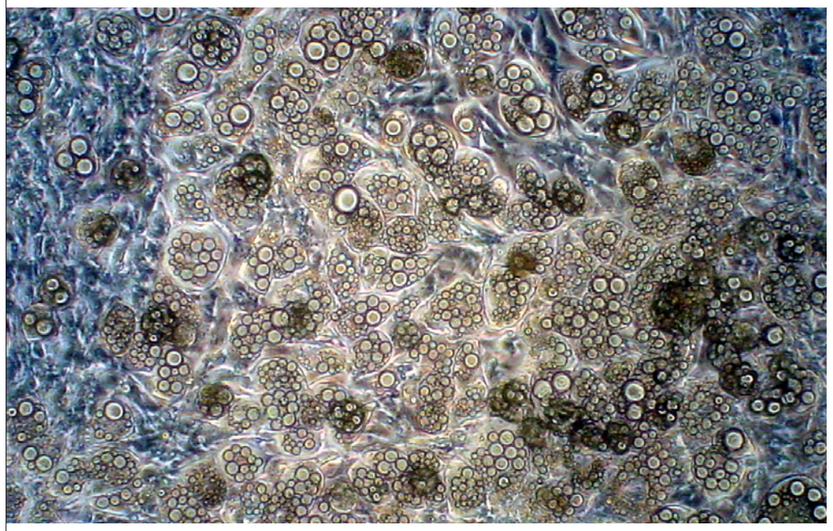
Dr. Dohrmann continued his career as a Shiseido research fellow at the Massachusetts General Hospital in Boston before joining DeveloGen in 1999. He served the company in various management positions including CEO, leading DeveloGen from a start-up to an internationally recognised metabolic disease company with strategic alliances based on highly innovative preclinical and clinical products for the treatment of diabetes and related disorders. Dr. Dohrmann has been advising the European Commission, the Max-Planck-Institute as well as venture capital firms and authored and co-authored a number of publications and patents.

As Chief Scientific Officer at Evotec he is responsible for scientific excellence in research and development including establishing academic collaborations, directing incubator research, initiating drug discovery alliances, and building highly competitive drug discovery platforms. It is his vision to build world-leading research teams in core disease areas who are focused on generating highly innovative drug discovery and development projects which have the potential to deliver therapies that significantly improve the life of patients.



Mechanisms controlling beta cell mass





Mouse 3T3-L1 Adipocytes

TECHNOLOGY OVERVIEW

What we can deliver

FOR REGENERATIVE MEDICINE AND BEYOND – FULLY INTEGRATED HIGH CONTENT (HC) SCREENING PLATFORM

Conventional target identification efforts in many degenerative diseases have so far failed to deliver novel and highly relevant targets. Thus here is a need for new approaches that can deliver novel targets that are based on functional screens addressing key disease phenotypes.

Chemical genomics approaches have demonstrated much promise in delivering highly innovative compounds and potential targets with exciting activities in disease relevant models. To harness the full potential of this paradigm, Evotec has assembled what is probably the world's leading infrastructure to conduct HC screening embodying primary and stem cell based assays as systems to test candidate compounds and target candidates.

A crucial component of this technology platform is Evotec's highly experienced proteomics and mass spectrometry group that has been highly successful in profiling compounds within cellular contexts to elucidate their underlying mechanism of action and determine potential targets.

1.WORLD LEADING HIGH CONTENT SCREENING PLATFORM (OPERA™)

- Team of 10 scientists dedicated to HCS screening
- Proven track record – conducted >10 screens and medicinal chemistry programs
- Numerous cell types including primary cells and stem cells
- Various read-outs including protein translocation, marker expression, morphological parameters including differentiation, primary toxicity analysis
- Customized scripts for phenotype recognition
- Data analysis / storage

2. STEM CELL EXPERTISE

- Designed, developed and conducted stem cell based assays for medium and high throughput screening
- Received regulatory approval to use human embryonic stem cell lines for certain neurodegenerative diseases

3. HIGH END PROTEOMICS/ MASS SPECTROMETRY PLATFORM

- Cellular target profiling – Proteome-wide profiling of compound-target interactions within a relevant cellular environment.
- Qualitative and quantitative determination compound-target interactions
- Kinaffinity® – Kinome-wide selectivity profiling of kinase inhibitors
- Phosphoscout® – Proteome-wide profiling of phosphorylation patterns

SPECIFICALLY ON METABOLIC DISEASES

TARGET IDENTIFICATION THROUGH MECHANISM-BASED SCREENS

- Energy dissipation
- Insulin sensitivity
- Beta cell regeneration

TARGET VALIDATION AND COMPOUND PROFILING IN RELEVANT *IN VITRO* AND *IN VIVO* MODELS

- *In vitro* models for energy flow
  - — Glucose and triglyceride uptake
  - — Rate of triglyceride/glycogen synthesis
  - — Lipid/glycogen accumulation
  - — Lipolysis
  - — Respiration
- *In vitro* models insulin sensitivity and beta cell mass and function
  - — Insulin sensitivity
  - — Insulin secretion
  - — Beta cell proliferation
  - — Beta cell apoptosis

- *In vivo* models include
  - — Genetic rodent models (fa/fa- and ZDF-rats, db/db-, ob/ob-mice)
  - — Diet induced obesity (DIO; various diets)
  - — Non-obese diabetic mice (NOD)
  - — Akita mice
  - — Glucose clamp studies in mice
  - — Beta cell regeneration models (STZ/Alloxan induced diabetes in rats and mice)
  - — Diabetic complications (retinopathy/nephropathy)

COMPREHENSIVE SET OF METABOLIC READOUTS

Standard analysis

- Body weight, blood glucose
- Food intake and water consumption
- Body composition analysis
- Glucose & insulin tolerance test
- Clinical blood chemistry
- Pancreatic insulin content
- Metabolic cages

Specific / Custom analysis

- Locomotor activity
- Body core temperatur
- Hyperinsulinemic euglycemic clamp
- Non-target & target specific readouts
- Beta cell mass by morphometry
- Indication specific readouts (e. g. diabetic complications)

DR MATTHIAS AUSTEN

SHORT SUMMARY OF SCIENTIFIC CAREER

Dr Matthias Austen received his PhD in molecular biology from the medical school in Hannover, Germany, focusing on oncogenic transcription factors in cancer cells. He conducted his postdoctoral studies at the Whitehead Institute for Biomedical Research/MIT studying early patterning events in the developing zebrafish brain. In 2001, Matthias joined DeveloGen as a research scientist using zebrafish embryos to identify genes regulating the formation of insulin producing beta cells.

He then became head of the beta cell regeneration research group at DeveloGen and managed and coordinated a project focused on the development of a first-in-class type 2 diabetes insulin sensitizer drug. Both projects led to significant collaborations with MedImmune/Astrazeneca and Boehringer Ingelheim, respectively. Since August 2010, Matthias is VP Metabolic Research of Evotec and responsible for all research at Evotec Göttingen including metabolic disease and regenerative medicine.

1. One key field of Evotec is metabolic diseases, especially diabetes. What is so special about Evotec's scientific approach?

The standard of care in the diabetes field is already at a fairly high level with a number of highly effective treatment options on the market. However, current treatment options are targeting primarily symptoms rather than the underlying causes such as the autoimmunity directed against the beta cells in type 1 diabetes, insulin resistance in type 2 diabetes, and beta cell failure in type 1 and 2 diabetes. We decided to focus our attention on mechanisms that directly address the progression of diabetes and thereby develop drug candidates that have the potential to become disease modifying first-in-class therapies.

For more than ten years we have kept a tight focus on diabetes, obesity, the metabolic syndrome as well as associated complications and have put much emphasis on understanding disease related mechanisms and pathways. Based on this experience, our own target identification efforts as well as publicly available information we are constantly searching for new insights which could be entry points for pharmacological interventions. In contrast to many other companies, we are completely open as far as therapeutic principles are concerned and have successfully developed peptides, small molecules but also biologicals in the field. The primary drivers are to develop an understanding of the cellular and molecular mechanisms and, based on this, to select targets of highest biological relevance.

2. How can you contribute to finding new drugs in this highly interesting field of regenerative medicine?

At Evotec we have assembled a team of scientists that is not only very strong in preclinical drug discovery from a technological and capabilities point of view but in addition we have a strong background in developmental biology, genetics and pathway analysis. This is not only exemplified by Prof. Peter Gruss (President of the Max-Planck Society) and Prof. Herbert Jäckle (Vice President of the Max-Planck Society), both world renowned developmental geneticists who have contributed valuable concepts and projects, but also key employees who have studied in leading laboratories in the US and Europe and now contribute this background to our projects.

Starting from there we have accumulated more than a decade of experience in beta cell biology and several years of pharmacology in beta cell regeneration and protection. This includes establishing and running a range of *in vitro* as well as *in vivo* models. Combining this expertise with the excellent assay development, HTS and HCS screening as well as medicinal chemistry capabilities at Evotec enables us to efficiently develop novel therapeutic options for beta cell regeneration in diabetes. We can also leverage this expertise into adjacent fields of regenerative medicine.

3. In which project(s) are you currently involved?

Currently I spend a significant amount of my time managing the Evotec efforts related to the insulin sensitizer type 2 diabetes program partnered with Boehringer Ingelheim. A second major work area for me is beta cell regeneration, where I am involved in overseeing the MedImmune/Astrazeneca partnership covering therapeutic proteins for beta cell regeneration and especially in steering of the HSCI/HHMI collaboration. Finally, I am supporting my colleagues to establish additional regenerative medicine projects at Evotec in highly exciting fields such as chronic kidney disease.

4. How will your collaboration with the HSCI/HHMI look like?

Our collaboration with HSCI/HHMI represents really a new model of collaboration between industry and academia. We will pool our resources in the field of beta cell regeneration and then collaborate in our discovery and development efforts with each party contributing their special expertise, technologies, and capabilities. The goal is to build the strongest team in the industry in the field of beta cell regeneration and together pursue a systematic and very comprehensive approach based on top class science and technology.

The focus of the collaboration will be the discovery of innovative drugs that target beta cell regeneration via various mechanisms. This will include screens using primary beta cells for novel small molecule targets. These screens have already yielded several compound classes with associated candidate targets that are able to selectively induce the replication of primary beta cells. Taking advantage of Evotec's leading high content screening (HCS) capabilities, the Opera™ platform, these screens can be significantly expanded. If necessary, hits can then be followed up via Kinaxo's powerful target deconvolution technology which has recently been acquired by Evotec.

Finally, the HSCI/HHMI has already carried out extensive expression profiling in isolated beta cells from a range of rodent *in vivo* models in which beta cells are undergoing rapid expansion. These efforts have yielded a significant number of candidate genes whose expression is correlated with beta cell replication. The combined team consisting of HSCI/HHMI and Evotec researchers will select the most promising candidate targets from these genes, take them through the validation process and then initiate drug development where appropriate. Together with HSCI/HHMI we are approaching the identification of new beta cell regeneration approaches from multiple angles to maximize our chances of success as the field of beta cell regeneration will gain in importance in the years to come.

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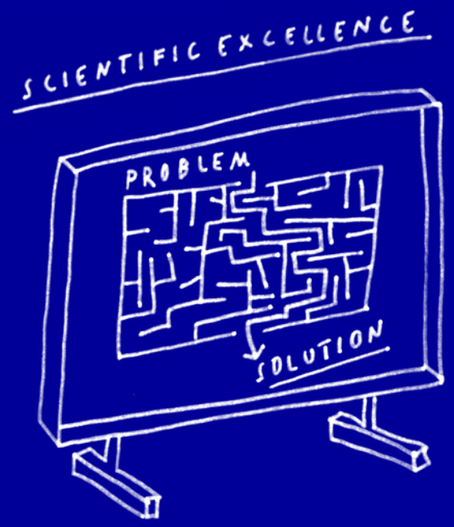

1) INTEGRATED SERVICES

- Target-to-IND integrated platform
- Hit identification
- Medicinal chemistry
- Structural biology and computational chemistry
- *In vitro* and *in vivo* biology
- ADMET

2) ASSAY DEVELOPMENT AND SCREENING

- Assay development
- High throughput screening
- High content screening (2.A)
- NMR and label-free screening
- Secondary screening and profiling
- Screening library (2.B)
- Ion Channel drug discovery (2.C)
- GPCR drug discovery (2.D)

3) FRAGMENT-BASED DRUG DISCOVERY

- Proprietary high throughput fragment screening platform
- Biochemical, NMR and SPR screening technologies
- Fragment library
- Structural biology
- Computational chemistry
- Fragment optimisation

4) MEDICINAL CHEMISTRY AND EARLY DEVELOPMENT

- Medicinal chemistry
- Computational chemistry (4.A)
- Structural biology (4.B)
- Compound library synthesis (4.C)
- Chemistry and early development support (4.D)

5) ADMET AND ZEBRAFISH SCREENING

- *In silico* and *in vitro* ADMET
- Zebrafish screening (5.A)
- Safety pharmacology

DD*up* *PREVIEW*

#2
GET OUT OF PAIN

#3
FIGHTING CANCER

FOR YOUR FUTURE DD PROJECT PLEASE CONTACT:

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