Max-Planck’s Lead Discovery Center GmbH

LDC – a (Proven) Model for Bridging Academia to “Pharmaceutical Industry”
Structure

- Mission & Organization
- The Pipeline
- Case Studies & Business Model
  - GPR81 Antagonists
  - P2X7R Antagonists
- Summary & Outlook
Major Motivation – Increase the Rate of Cures!
Infectious Diseases, Cancer, Metabolic & Inflammatory Disorders, Alzheimer‘s, Parkinson‘s, etc.
Drug Discovery.....Against the Odds?
Model for NCE (New Chemical Entity) Development

- **Synthesis**
- **Examination & Screening**
- **Preclinical Test (Animals)**
- **Clinical Test (Humans)**
- **Product Surveillance**
- **Phase I**
- **Phase II**
- **Phase III**
- **Phase IV**

**Years**
- 12
- 11
- 10
- 9
- 8
- 7
- 6
- 5
- 4
- 3
- 2
- 1
- 0

**Substances**
- 10,000
- 20
- 10
- 5
- 2
- 1

**Source:** Pharmaceutical Research Manufacturers Association
Time to Rethink the Traditional Pharma Model

- Lack of €€€
- Lack of expertise
- Incentives?
- Risk aversion
- Lack of confidence
- Economical return (mid-term)
Push versus Pull

search for
THE BEST SOLUTION
to a very particular problem

TARGET
hit generation

HIT
lead generation

LEAD
lead optimization

CANDIDATE
preclinical development

DRUG
clinical trials
market introduction
~12 years

INDUSTRY & VC
Cardiovascular D
Metabolic D
Oncology
solid tumors
blood cancers
lymphoma
Immunology
Respiratory
Neuroscience
Antiinfectives...

KRAS

~12 years

ACADEMIA

PULL

search for
THE BEST SOLUTION
to a very particular problem
Push versus Pull

search for
THE BEST APPLICATION
of excellent science

PUSH LDC-oids

ACADEMIA

Cardiovascular D
Metabolic D
Oncology
Immunology
Respiratory
Neuroscience
Antiinfectives
...

KRAS

INDUSTRY & VC

TARGET
hit identification

HIT
hit generation

LEAD
lead generation

CANDIDATE
lead optimization

DRUG
preclinical development

~12 years

market introduction

blood cancers
lymphoma

solid tumors
Lead Discovery Center

Translating academic ideas into innovative drugs

- World Class Science
- High Quality Drug Discovery
- Flexible Partnering Structures
82 institutes
ca. 17,000 employees
>15,000 publications p.a.; 32 nobel laureates
~40 institutes with life science (biomedical) oriented research programs (BMS and CPTS)
>€1.7 Bn. annual research budget
central tech transfer unit:

- 3,900 inventions
- 2,300 contracts
- 135 spin-offs
LDC Twists the Traditional Pharma Model

**target hypothesis**
pathologic mechanism

**high quality**
drug discovery incubation

(Pre-)clinical development, regulatory work and drug marketing by Pharma

**Academia**
Target ID
Target validation
Year „0“

**Innovation and Medical Need**
“If I'd asked my customers what they wanted, they’d have said a faster horse”
    
Henry Ford

**Assay development**
**Screening**
**H2L**
**LO**

**Preclinical PoC**

**Development**

**Industry**
Year „~15“
& x billion €
Corporate Overview

Setup
- founded in 04-2008 by Max-Planck-Innovation
  - framework contract with Max-Planck-Society
    - Broad academic network, e.g. collaboration with Helmholtz

Company profile
- 74 employees, 85% of PhD-level from ex-Pharma/Biotech

Unique set-up
- A couple of established “DON’T’s”:
  1. ~20 active drug discovery projects (complementary to industry)
  2. broad range of indications (indication-agonistic)
  3. despite initial small molecule focus, open to other modalities
  4. early partnering with industry
Validated Business Model

2011
- CDK9 cancer program licensed to Bayer
  Deal volume 137.5 m€ + royalties; currently in Ph1b trials

2013
- Strategic Drug Discovery Alliance with Merck Serono
- Discovery Alliance with AstraZeneca
  Axl cancer program licensed to Qurient

2014
- Discovery Alliance with Daiichi Sankyo

2015
- Discovery Alliance with Roche
- Discovery Alliance with Infinity Pharmaceuticals
- Discovery Alliance with J&J Innovation
- CDK7 cancer program licensed to Qurient
- Extended Alliance with AstraZeneca (+3 yrs)
...continued!

Cancer program licensed to Merck
- currently in Ph1 trials
Start of LDC Biologics
Option/License Agreement with Boehringer Ingelheim
on Schizophrenia program

Tumor metabolism program license to Sotio, incl. LO
Series A funding of Rewind Therapeutics, Leuven/Belgium (€15.2 m€)
Cancer Drug License & collaboration (RaND)
Collaboration & License Deal (CMT1A) with Grünenthal
License granted to Quench Bio, a biotech company funded by the venture firms Atlas Venture and Arix Bioscience
2nd financing round – UGI Sense AG
Research collaboration with Apeiron Biologics, Vienna/Austria

Watch out for a Dortmund-based oncology spin-off…
& an Early Stage Fund…
Summary - Commercialization from 2011 to 2018

- 16 drug candidate deals
- 11 licenses +/- sponsored collaboration --- 1 discontinued
- 2 option/license deal – 1 option turned down
- 1 sponsored co-development program
- 1 asset transfer
- 50% attrition rate
LDC’s Business Model: Share Fair – Fair Share

- LDC operates on a pure cost coverage basis
- back-loaded licensing deals with pharma or biotech
- de-risking innovative target approaches
- any licensing returns are shared with the academic PI
Advanced & Active Portfolio Projects

**Target**
- **Target ID**
- **Target Validation**

**Assay Development**
- **Hit**
- **Screening**
- **Hit-to-lead conversion**

**Lead**
- **Lead-to-candidate conversion**

**Candidate**
- **PD**
- **P1**

**Indication**
- extr. Cyclophilins
- autoimmune, COPD, PAH
- sepsis, autoimmune
- CV, etc.
- psychiatric stress disorders
- obesity
- type 2 diabetes
- cancer, autoimmune
- cancers, autoimmune
- cancer
- heart failure
- obesity, fibrosis
- Alzheimer’s, etc.
- lung cancer
- antibacterial
- K-Ras dependent cancers

**Partner**
- LDC GmbH 02

**Secured funding**
- open for partnering
- encumbered
- partnered project

**Pivotal MS**
Early Stage Portfolio Projects

Partner

- ASPA
- WWC1/2
- Ephrin B2
- Kras/PDEδ stab.
- Pdx1
- KinSub
- Gcn2
- MiWaKa
- AMT
- TTLL, CCP inhibitors
- ER stress-inhibitors
- Stomial3
- PDDementia
- HtrA1
- sFRP1
- NTNU1
- Ire1

Indication
- obesity, T2DM
- cognition
- chronic kidney disease
- cancer
- diabetes
- cancer
- cancer

Calcification, CKD
- Parkinson, mitochondrial disease
- neurodegeneration, cancer
- various, e.g. CFTR
- pain
- Parkinson’s
- AMD (inflammation)
- cancer
- osteoporosis
- A1ATD
Biologix - Early Stage Portfolio Projects

**Partner**
- anti-IL-11
- anti-KLK8
- anti-FGFR4
- anti-GDF15

**Indication**
- cancer
- Alzheimer's
- LVH
- Cachexia, IO
Stalled Projects – Funding Needed

**Target**
- CDK12/13
- Draxin
- Sirt7
- RhoGEF12
- Plexin-B1/Sema4D
- Notch
- Beclin-1/Autophagy ind.

**Hit**

**Lead**

**Candidate**

**Indication**
- cancer
- osteoporosis
- cancer, metab. syndrome
- heart failure, fibrosis
- osteoporosis, MS
- cancer (T-ALL)
- antiviral, neurodegeneration
- antibacterials
- AML
- Parkinson’s
- neuroblastoma
- cancer

**DegS**

**AML1/ETO**

**LRRK2 - GTPase**

**Lin28B**

**STS - Steroid Sulfatase**

- MS, epilepsy, CMT
- leukemia, lymphoma
- cancer

**AK2**

**14-3-3/FC-A**

**NP-derived enzyme inhibitor**

- secured funding
- open for partnering
- encumbered
- partnered project
- Pivotal MS

LDC GmbH 02-2019
GPR81 Antagonists

Academic Partner:
S. Offermanns Lab, Max Planck Institute for Heart & Lung Research, Bad Nauheim/Germany
Rationale for the Development of GPR81 Antagonists as Anti-Obesity Drugs

Wild-type (WT) or GPR81-deficient mice (KO) were fed with a high-fat diet (HFD) or normal chow (NC). The gain in body weight was expressed as percentage of initial body weight (n=6-10 per group). Shown are mean values ±SEM.

Ahmed et al., Cell Metab. (2010)
H2L, medchem, next generation compounds

GPR81 HTS (GPR81 chAMPion assay) in antagonist mode (~430k Compounds)

IC50s in GPR81 chAMPion assay (antagonist mode)

26 hits

Focus on 3 hit classes (classes A, P, AT/Pa)

GPR81 GloSensor cAMP assay, GPR81 HTRF assay, GPR81 GTPγS binding, lipolysis assays

SAR & SPR

H2L, medchem, next generation compounds

Optimized hits

PK/MTD, efficacy

ADMET assays

Current status, close to lead nomination

Assay Cascade
Current frontrunner LDC9917 meets *in vitro* TCP requirements

### LDC9917
- **IC$_{50}$ = 3 nM (GPR81-Ca)**
- Full effect: 122%
- MS-I data acceptable
- Permeable; no efflux
- Plasma stable
- No tox alerts
- 1.000-fold hERG margin
- Solubility acceptable
- CEREP: 2 off-targets to consider

### LDC3803 (screening hit)
- **IC$_{50}$ = 1.4 µM (GPR81-Ca)**
- MS-I data bad
- Solubility bad
ERK Signaling

chAMPion cells: GPR81 transfected vs mock cells

- Inhibition of lactate-stimulated ERK phosphorylation

Confirmation of MoA in T47D cancer cell lines (vs. L6 adipocytes have high basal pERK levels)
Lipolysis – Isolated Mouse Adipocytes

- solvent
- iso
- iso+lactate
- iso+lactate+209917 (0.3 µM)
- iso+lactate+209917 (1 µM)
- iso+lactate+209917 (3 µM)
- iso+lactate+209488 (0.3 µM)
- iso+lactate+209488 (1 µM)
- iso+lactate+209488 (3 µM)
- iso+pia
- 209917 (1 µM)
- 209917 (3 µM)
- 209488 (1 µM)
- 209488 (3 µM)

increase in FFA (mM) shown are values subtracted from solvent

iso, 10nM isoproterenol
10µM PIA
Target rationale:
- Binding of lactate activates the GPR81 receptor = inhibition of lipolysis in adipocytes
- Development of antagonists for the treatment of obesity

Status:
- Identification and validation of hit class
- >300 compounds synthesized in H2L
- Lactate competitive antagonists
- Profiling assays: cellular chAMPion (Ca\(^{2+}\)) and lipolysis assay, pERK assay
- Rigorous ADMET profiling → no sign of class-wide toxicity issue
- CEREP profiling (limited No. of off-targets)

Next steps:
- Evaluate effect in WT vs. GPR81 KO adipocytes
- Short term in vivo experiments in mice after PK/tox
A Potent Brain-Permeable P2X7 Antagonist for the Treatment of Neuroinflammatory Disorders

Wholly owned subsidiary of LDC
Background – P2X7R & AFC-5128

P2X7 Receptor
- ATP-gated-ion channel
- essential for the maturation and release of pro-inflammatory cytokines, including IL-1β

AFC-5128/P2X7R - Mechanism of action of antagonist
- Inhibition of the inflammatory response
- Inhibition of pore formation
- CNS penetrant
- Single digit nM
- Composition of matter (IP)

Potential role in neuroinflammation, pain and neurodegenerative diseases
# AFC-5128 Profile

<table>
<thead>
<tr>
<th>Affectis AG - P2X7R antagonist AFC-5128 profile</th>
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</thead>
<tbody>
<tr>
<td><strong>Pharmacology and Safety</strong></td>
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<tr>
<td>- <em>In vitro</em> profiling (binding and cellular activity) $IC_{50}$ (nM):</td>
</tr>
<tr>
<td>- Human 3 nM</td>
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<td>- Mouse 280 nM</td>
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<tr>
<td>- Rat 500 nM</td>
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<tr>
<td>- Highly selective over P2X2, P2X3 and P2X4 up to 1 µM / 100µM</td>
</tr>
<tr>
<td>- Excellent <em>in vivo</em> CNS permeability in rat and mouse</td>
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<tr>
<td>(Brain / Plasma after p.o admin = 1/1)</td>
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<tr>
<td>- No significant formation of reactive metabolites</td>
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<tr>
<td>- <em>In vivo</em> toxicology (mouse and rat MTD) defined</td>
</tr>
<tr>
<td>- <em>In vivo</em> pharmacokinetic profiles (ms, rat) for p.o and i.p administration</td>
</tr>
<tr>
<td><strong>Efficacy</strong></td>
</tr>
<tr>
<td>- Positive efficacy data from animal models of epilepsy (rat/ms), neuropathic pain (rat) and multiple sclerosis (mouse) after oral / i.p. administration</td>
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Therapeutic Indications

- Multiple Sclerosis
- Neuropathic Pain
- Epilepsy
AFC-5128 blocks P2X7 and thereby prevents IL-1β processing
AFC-5128 reduced disease severity in a MOG-induced mouse EAE model when given orally in a prophylactic regimen.
AFC-5128 prevented demyelination in a MOG-induced mouse EAE model when given orally in a prophylactic regimen.

Spinal cord inflammatory infiltrates and demyelination (H&E & FluoroMyelin staining)
Efficacy mouse EAE (SJL Relapsing/Remitting MS Model)

Clinical Efficacy
(SJL mice immunised with PLP_{139-151}/CFA)

- Vehicle (n=16)
- Methylprednisolone i.p. QD 5 mg/kg (n=15)
- AFC-5128 p.o. BID 125 mg/kg (n=21)
- AFC-5128 p.o. BID 250 mg/kg (n=21)
- AFC-5128 p.o. BID 500 mg/kg (n=21:16)*

Relapse Onset
(SJL mice immunised with PLP_{139-151}/CFA)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Relapsing animals</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vehicle</td>
<td>8/16</td>
<td>50</td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>6/15</td>
<td>40</td>
</tr>
<tr>
<td>AFC-5128 125 mg/kg</td>
<td>8/21</td>
<td>38</td>
</tr>
<tr>
<td>AFC-5128 250 mg/kg</td>
<td>8/21</td>
<td>38</td>
</tr>
<tr>
<td>AFC-5128 500 mg/kg</td>
<td>1/16</td>
<td>6*</td>
</tr>
</tbody>
</table>

*A Fisher’s exact two-tailed test, p=0.0038

AFC-5128 reduced disease severity and relapse onset
Therapeutic Indications

Multiple Sclerosis

Neuropathic Pain

Epilepsy
Anti-Epileptogenic Effects of AFC-5128 in a Rat PTZ Kindling Model

Compounds administered i.p. 45 min before PTZ:

- Tanshinone II A SO₃Na (TIIAS, 30 mg/kg) and Brilliant Blue G (BBG, 50 mg/kg), both with 20% PEG-400

AFC-5128 (AFC, 30 mg/kg) with vehicle (DMA/β-CD).

AFC-5128 showed marked anti-epileptogenic effects in a rat PTZ kindling model. The protective effect lasted even after discontinuation of drug dosing.
Conclusion

**Key points:**
- Brain-penetrant
- Orally available
- Close to candidate level
- Working with world-class experts

**IP situation:**
- Patents granted in major worldwide markets

**Business opportunity:**
- Looking for Licensing Partner
Why Does Translation Work at LDC?

- Sourcing innovative ideas from & through academia
- Trust relationship LDC/academics
- Incentive structure beyond just publications
- Industry standards @ LDC
- Projects do not compete with pharma projects
- Critical funding for early stage drug discovery projects provided
- Only 50% attrition!
- and…

Innovation and Medical Need

„If I’d asked my customers what they wanted, they’d have said a faster horse“

Henry Ford

Concept: M. Stein-Gerlach

Location TZDO

High Quality
Collaborative Drug Discovery

…and many more