AETIONOMY

COMPACT
COLLABORATION ON THE OPTIMISATION OF MACROMOLECULAR PHARMACEUTICAL ACCESS TO CELLULAR TARGETS

IMI1: LEARNING & EXPERIENCE

Tamas Letoha, MD, PhD
Pharmacoidea Ltd.

imi Innovative Medicines Initiative

efpia

Pharmacoidea Ltd.

The Company:	a biotech SME founded in 2006, Szeged, Hungary
CEO:	Tamas Letoha, MD, PhD
Mission:	bringing safe and innovative therapeutics against diseases with unmet medical needs
Team:	selected from forward thinking scientists interested to translate basic science results rapidly into innovative therapeutics, incorporating high added value by rational drug design and engineering
Expertise:	Bioinformatics, Drug Discovery and Delivery, Experimental Cellular Therapeutics, Functional Food Development

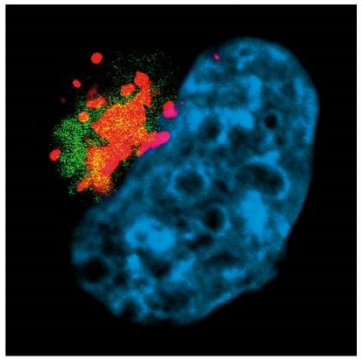
PHARMACOIDEA

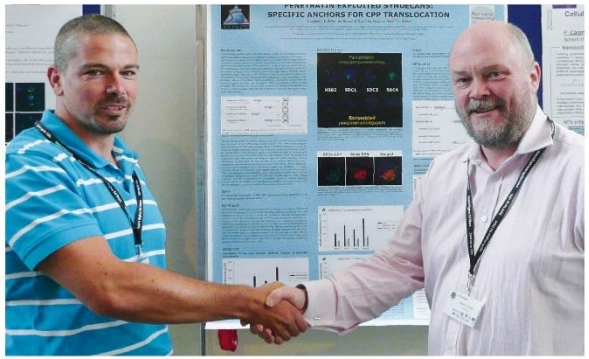
www.pharmacoidea.eu

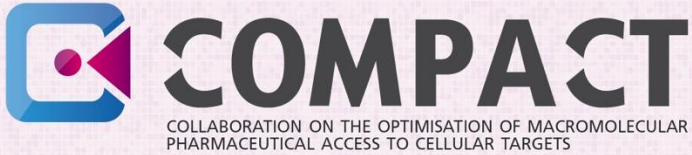
Novel Drug Delivery Technologies

Intracellular Targeting of Molecules (PCT/IB2007/052787):

- A novel approach for the delivery of membrane impermeable drugs
- New drug target against viral infections
- 2008. June, Cardiff, UK – Cellular Delivery of Therapeutic Macromolecules, Drug Discovery Today Award
- 2009. September, Montpellier, France 3th Conference of Intracellular Delivery of Therapeutic Molecules: From Bench to Bedside, Award of the French Innovation and Transfer Office
- 2012. Innovative Medicines Innitiative: Pharmacoldea is part of the COMPACT Consortium in the Call of „Drug Delivery"







A Public-Private Partnership to Develop Novel Delivery Systems for Biopharmaceuticals

Ekkehard Leberer (Sanofi)

Enrico Mastrobattista (Univ. Utrecht)

2012.11.01 – 2017.10.31

Goals

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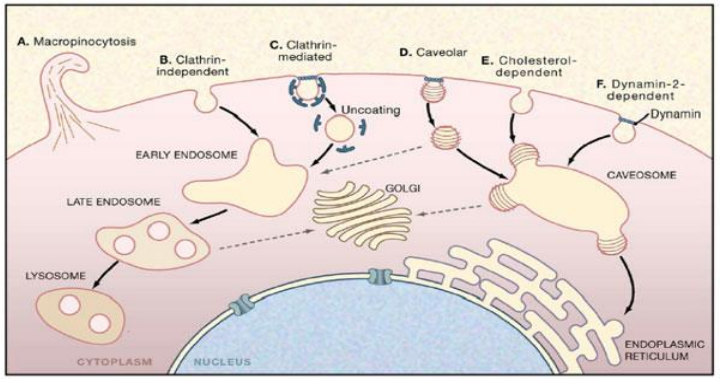
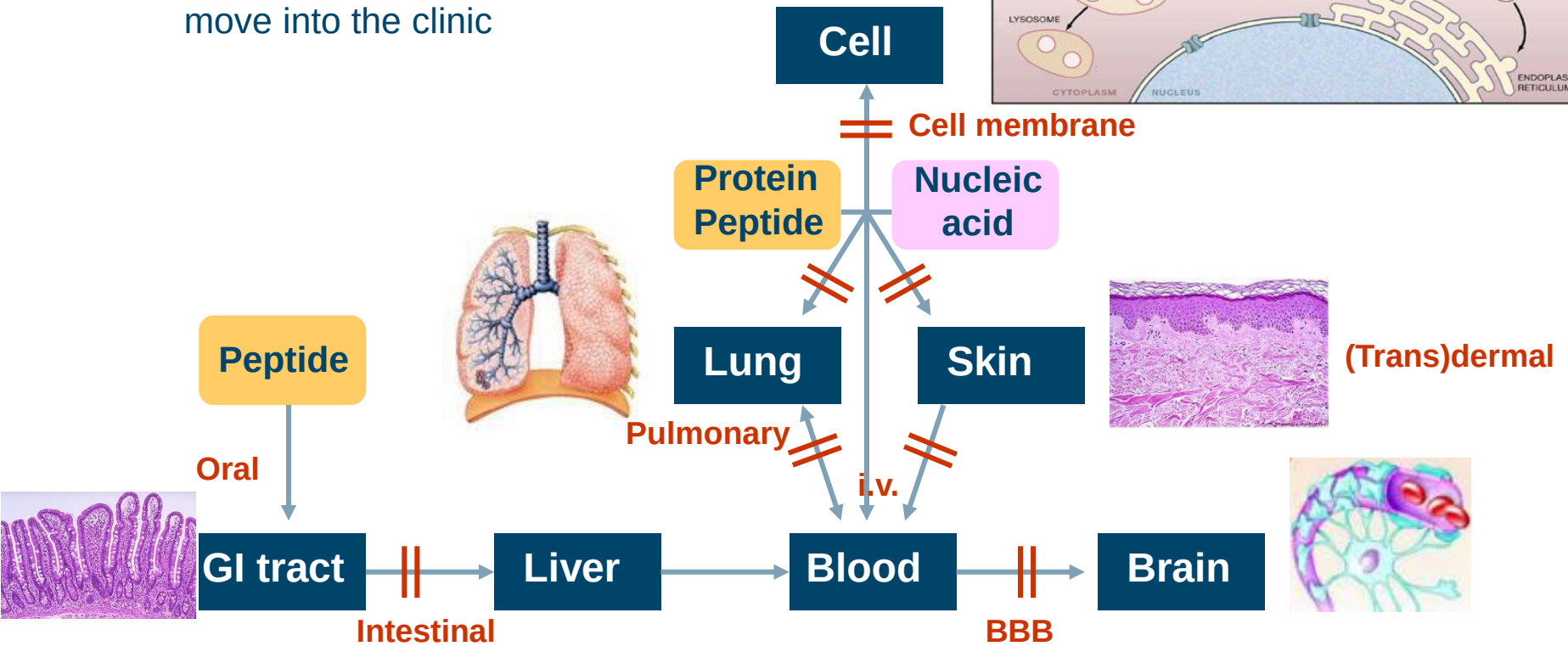
- Improve understanding of intracellular uptake and trafficking of biologics
- Develop nanocarriers to deliver biologics
  - To and across epithelial/endothelial barriers
    - Intestine; brain (BBB); lung; skin
  - Across cellular membranes into target cells
  - With drug like properties and the potential to move into the clinic

Marsh and Helenius, Cell 124, 729-40





Scope of modalities

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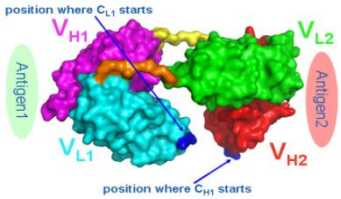
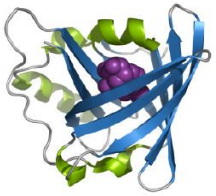
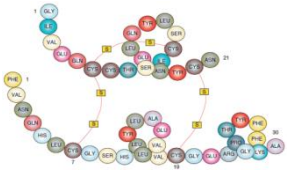
Proteins, peptides, oligonucleotides; size > 1 kDa



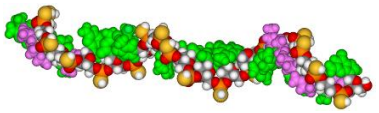
Antibodies
Antibody fragments



Scaffolds



Peptides



ASOs
siRNAs
miRNAs

Advantages

- Rational drug design instead of random high-throughput screening
- Opportunity ot access „non-druggable“ targets, e.g. transcription factors, protein-protein interaction
- Nucleic acid therapeutics
  - Tailored for their target sequences (ASOs, siRNAs, miRNAs)
  - Novel therapeutic modalities
    - anti-miRs, miR-mimics, long ncRNAs, mRNA replacement
  - miRNAs: Novel unexplored target space
    - Key regulators of cellular proliferation and differentiation
- Higher success rate than small molecule drugs

COMPACT strategy

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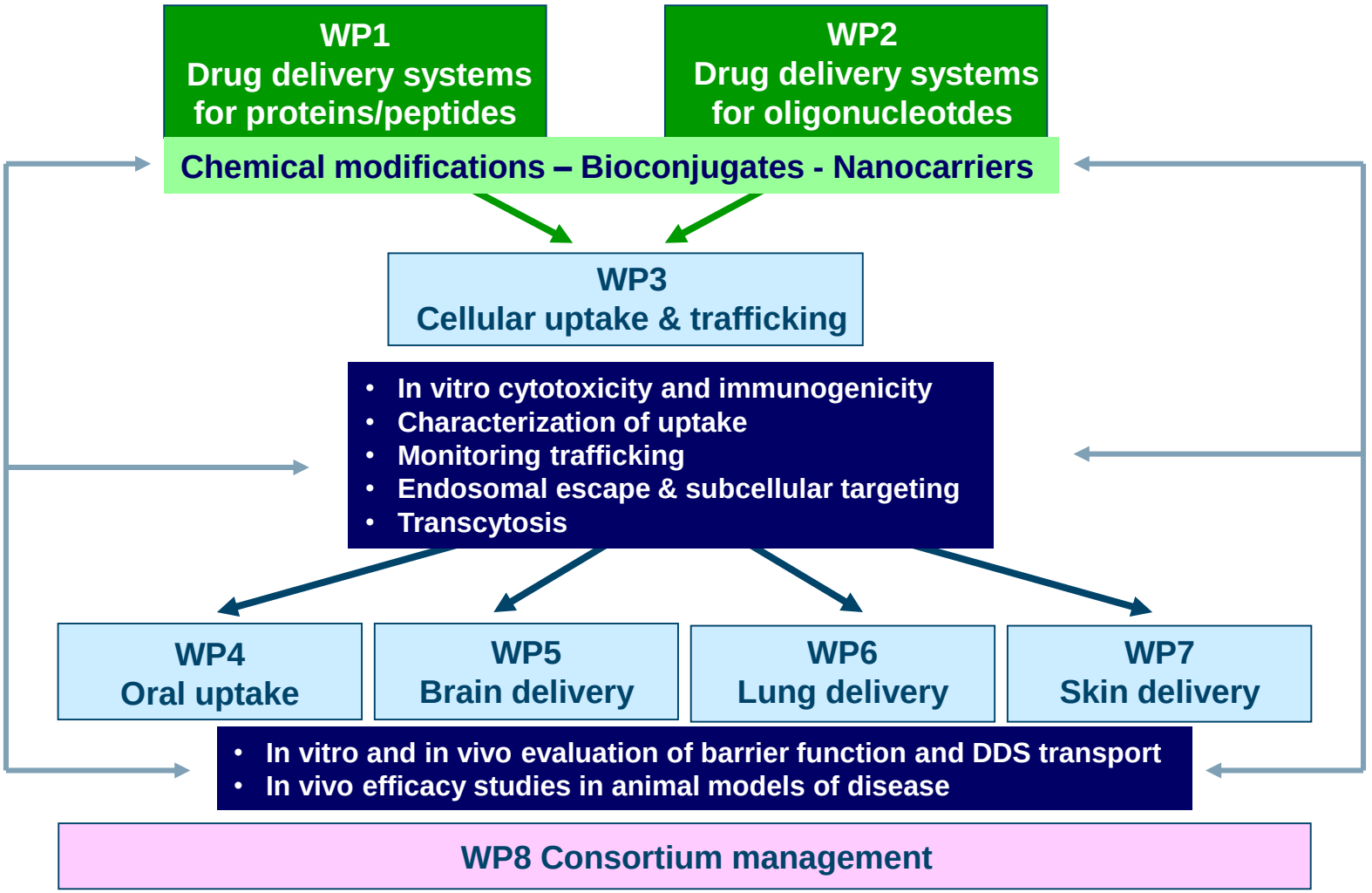
Work package matrix structure with iterative approach of nanocarrier generation and testing



COMPACT is in line with major trends in pharma industry

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- **R&D expenditure shift towards external innovation**
  - Example Sanofi
    - Objective is ratio internal/external 50/50

    (Chris Viehbacher, CEO, Xconomy Jan. 17, 2012)

- **R&D portfolio continue to shift from „small molecules“ towards „biologics“**
  - Top ten drugs by sale
    - 2001: 1 biologics: Procrit
    - 2010: 3 biologics: Enbrel, Remicade, and Humira
    - 2012: 7 biologics: Humira, Enbrel, Remicade, Rituxan, Lantus, Herceptin, Avastin
      - Humira (AbbVie) was the 2nd best selling drug world wide with sales of 8.5 B $
      - Lantus (Sanofi) was the 8th best selling drug world wide with sales of 6.6 B $1

Ref.: Arrowsmith J., Nat. Rev. Drug Disc. 11, 17 – 18, 2012; www.fiercepharma.com/special-reports/15-best-selling-drugs-2012; ACS Chem. Neurosci. 4, 905-907, 2013

Funding and team

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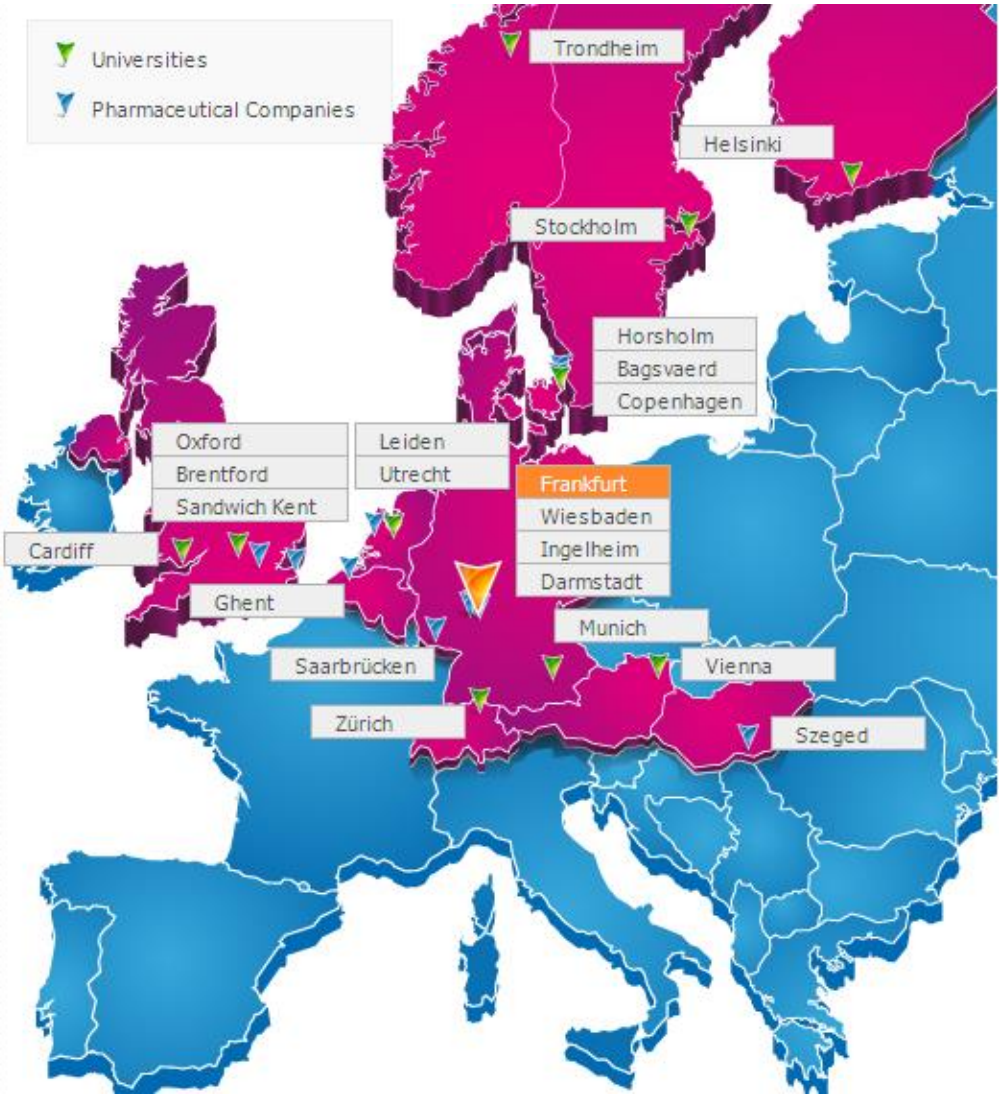

- Term Nov 2012 – Oct 2017
- Total budget: 30 M€
  - IMI funding: 13.5 M€ (incl. 25% in kind from acad./biotech)
  - EFPIA in kind contribution: 16.5 M€
- Team
  - Currently 132 scientists
    - 82 academia/biotech
      - 35 IMI funded:
        - 9 Post Docs
        - 19 PhD students
        - 7 technicians
    - 50 EFPIA
  - Plus administrative, legal and financial support staff
  - Distributed across 12 countries

Unique opportunity to work with industry and academia

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- **7 EFPIA partners**

SANOFI, gsk, abbvie, Boehringer Ingelheim, Merck Serono Living science, transforming lives, novo nordisk®, Pfizer

- **14 Academic plus 2 Biotech partners**
  - Utrecht University Dept. Pharmaceutics
  - University of Copenhagen
  - Helmholtz Inst. for Pharmaceutical Research Saarland
  - Cardiff University
  - Stockholm University
  - Norwegian University of Science and Technology
  - University of Vienna
  - LMU Munich–Dept. of Pharmacy
  - University of Zurich
  - University of Ghent
  - PharmacoIdea Ltd. (Hungary)
  - BioneerPharma (Copenhagen)
  - Utrecht University Dpt.Infectious Diseases and Immunology
  - University of Helsinki
  - Leiden University
  - Oxford University

COMPACT expertise

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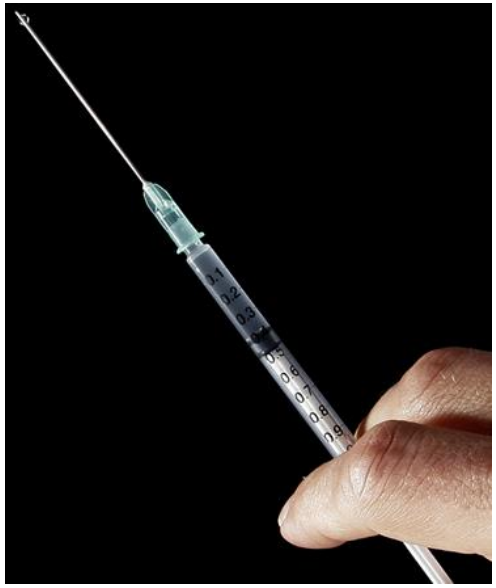
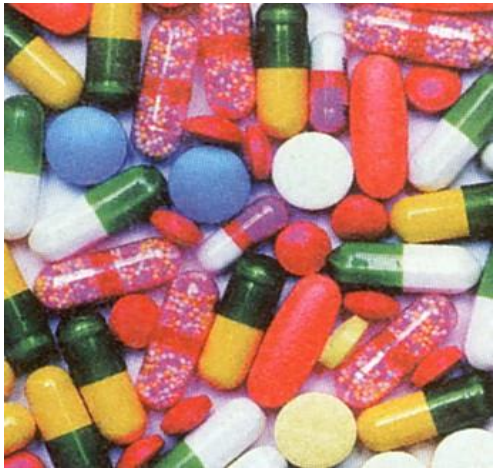
Acedemic/biotech partners

- Nanotechnology
- Biochemistry
- Molecular biology
- Cell biology
- Animal biology
- Imaging
  - *In vitro*
  - *In vivo*
- Biodistribution
- Cytotoxicity
- Immunology
- Data mining



Pharma partners

- Disease models and pharmacology
- PK
- Toxicology
- CMC
- Clinical research; Regulatory



Summary

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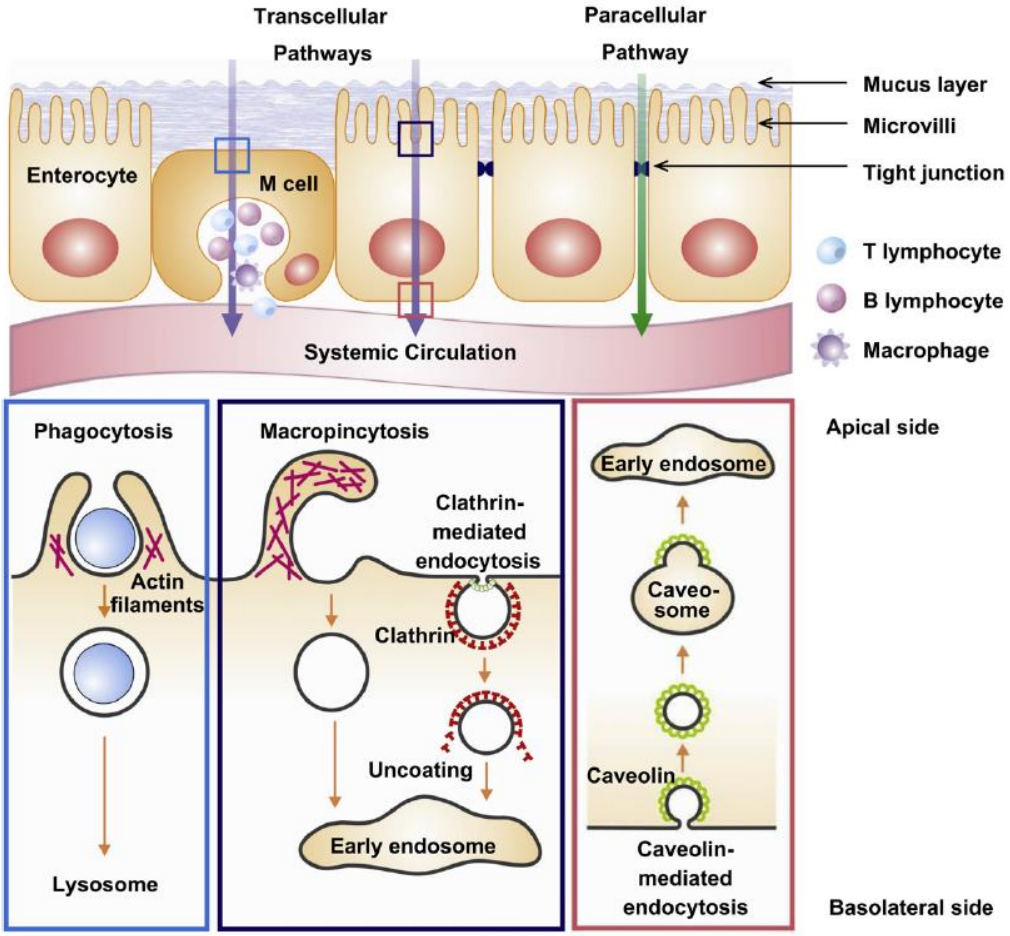

COMPACT has initiated to establish a technology platform to

- Generate novel nanocarrier-based drug delivery systems (DDS‘s) with model payloads
- Analyze their cellular uptake and trafficking
- Follow their delivery across epithelial and endothelial biological barriers, including the intestinal barrier
- Analyze their biodistribution and pharmacokinetic properties
- Analyze the pharmacology of model payloads

The Consortium

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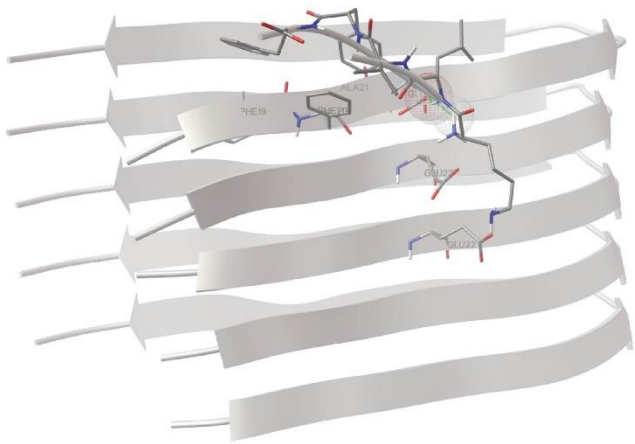
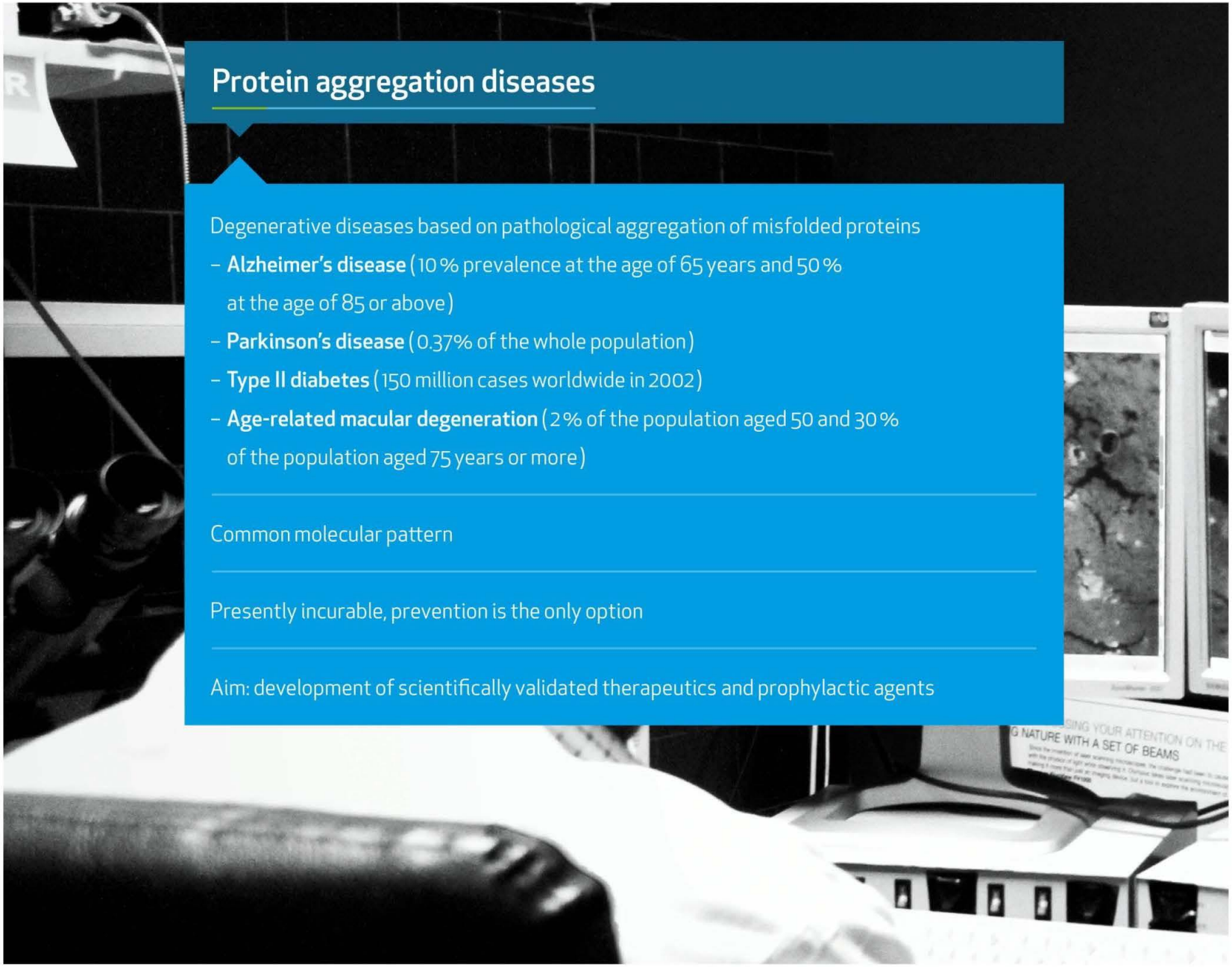
www.compact-research.org

Bioinformatics

Accelerating the rate of discovery & reducing expensive lab work

- High quality, cost effective curation, literature informatics solutions and annotation
- Comprehensive database of protein-protein and protein-small molecule interactions
- Highly complex data content
- Kinetic parameters, pharmacokinetics and pharmacodynamics values, dose response details
- Simple search window to search biomedical entities
- Author and journal based filters
- In silico screening, QSAR algorithms





Protein aggregation diseases

Degenerative diseases based on pathological aggregation of misfolded proteins

- **Alzheimer's disease** (10 % prevalence at the age of 65 years and 50 % at the age of 85 or above)
- **Parkinson's disease** (0.37% of the whole population)
- **Type II diabetes** (150 million cases worldwide in 2002)
- **Age-related macular degeneration** (2 % of the population aged 50 and 30 % of the population aged 75 years or more)

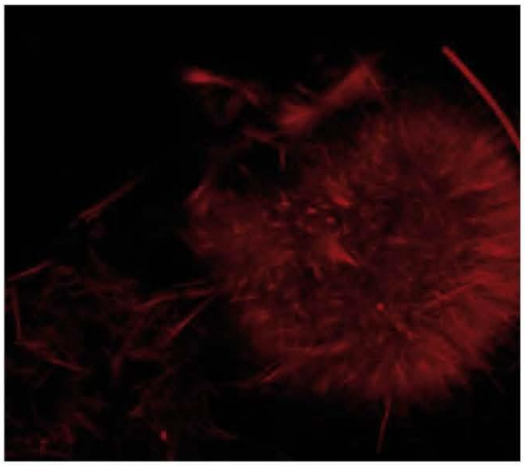
Common molecular pattern

Presently incurable, prevention is the only option

Aim: development of scientifically validated therapeutics and prophylactic agents

Protein aggregates (plaques)

β-amyloid (Alzheimer)
α-synuclein (Parkinson)
amylin (Type II Diabetes)
drusen (AMD)

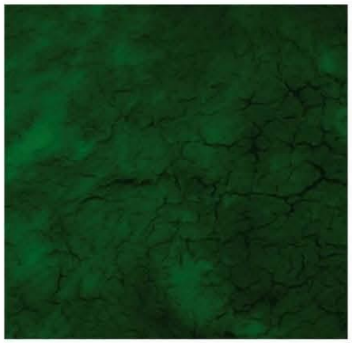


Plaque Busters

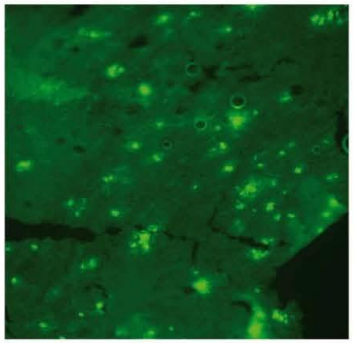
High-throughput bioassays + transgenic animal models (APPswe)
+ in silico modeling and docking algorithms + structure-activity relationships

A molecular library of new chemical entities

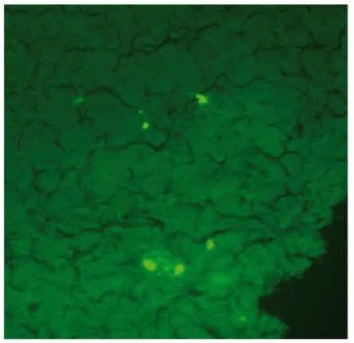
like thorough molecular lancets, plaque busters can specifically recognize and eliminate pathological protein aggregates/plaques (see figure below)



Normal brain



Alzheimer's brain



Alzheimer's brain
+ Plaque Busters

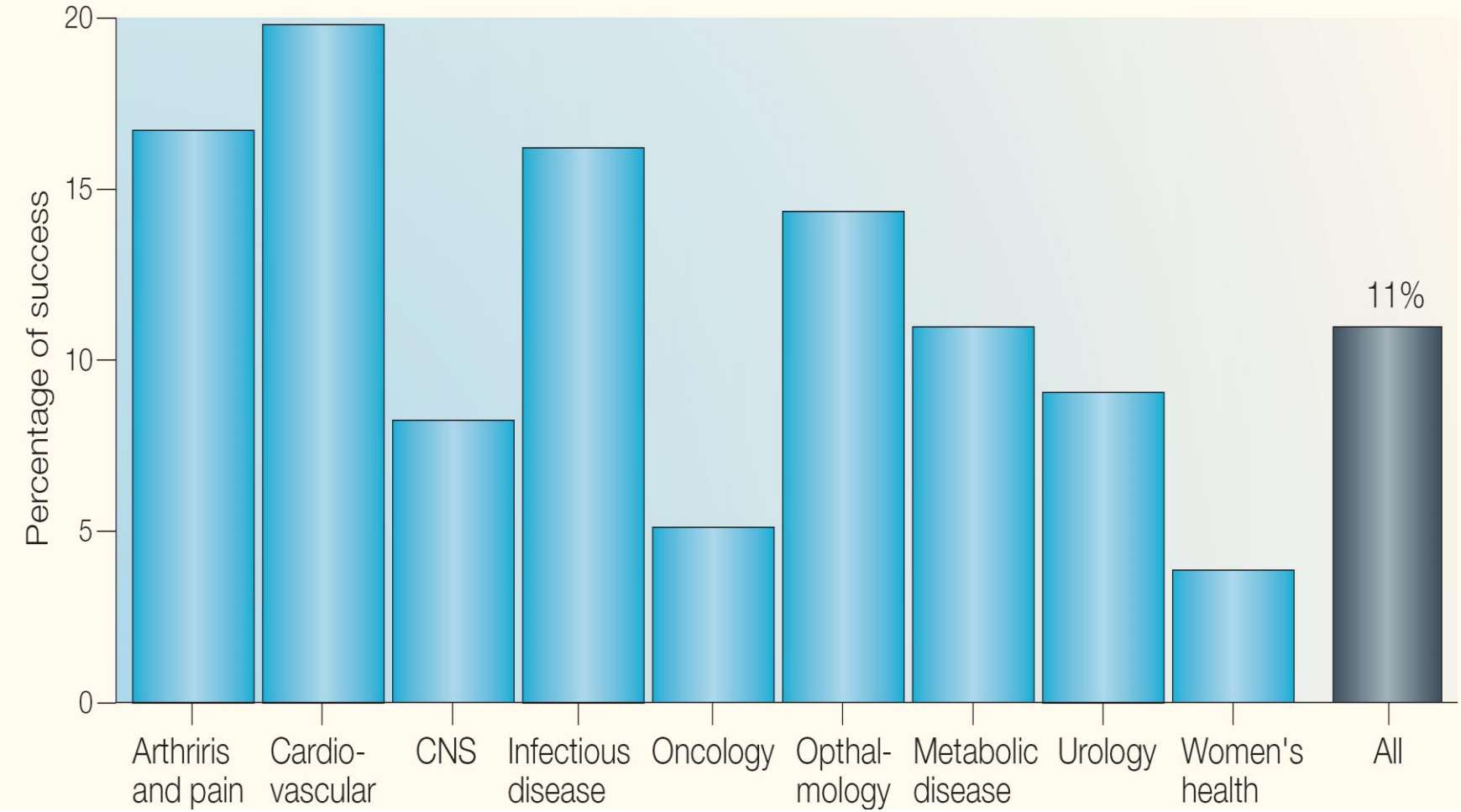
Overview on Concept and Goals

AETIONOMY

Prof. Martin Hofmann-Apitius
(Fraunhofer SCAI)

Prof. Duncan McHale
(UCB Pharma)

The Challenge



Reasons for Failure

- **Wrong target**
- **Lack of pharmacological effect in the target organ at achievable dose**
- **Lack of sufficient effect from single mechanism**
- **Disease heterogeneity**
- **Phenotypic classification**

Current Classification

- Refined version of 200 year old classification
- Based on phenotypic features of disease
- Does not necessarily reflect underlying disease mechanisms
- Where classification has become more mechanistic then new effective therapies have been developed
- Oncology is a good example

"I'm pretty sure you've got what this guy had."

What About Alzheimer's & Parkinson's?

- Archetypal phenotypic diseases
- Multiple rare families with different causative genes
- For PD there are environmental mimics
- Differing disease courses
- No disease modification therapies
- If we do not start early with the right treatment it will be too late
- If we do not have confidence in the biological rational for treatment then companies will not continue to invest
- Multiple failures in anti amyloid approaches
- There is a lot of data available in the literature and in databases we can access

AETIONOMY Project Vision

- To lay the ground for new approaches in translational research in AD and PD by paving the way for model-driven research in these indication areas.

- To establish the AETIONOMY approach as a “blueprint” for disease-specific data-, information-, knowledge- and model-integration.

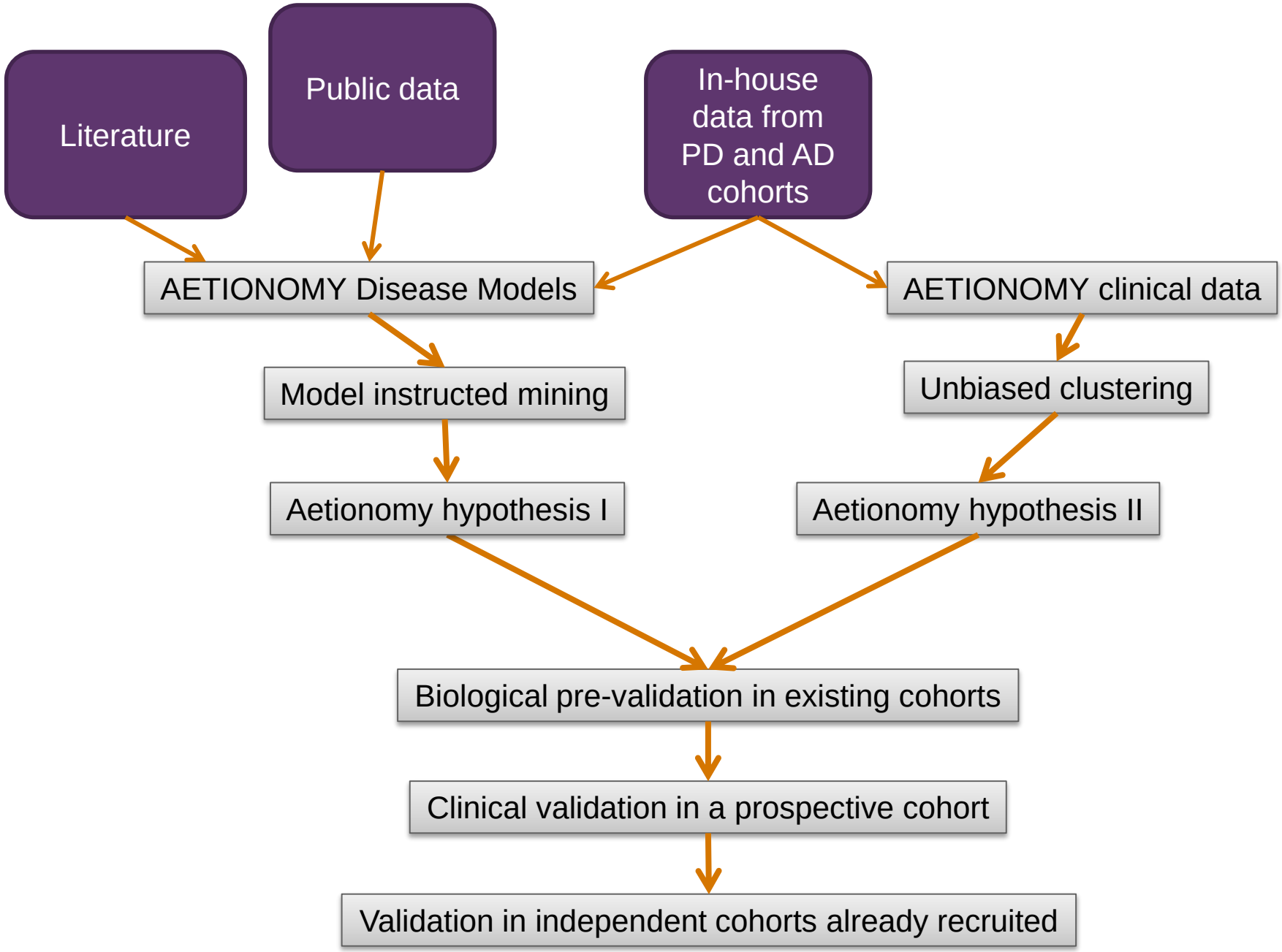
- To model disease in a way that allows for the generation of testable hypotheses on possible mechanisms underlying PD and AD.

Key Figures

- We have 5 years to demonstrate that our concept is valid
- We have a total budget of 17.8 Mio € to support the work
- In AETIONOMY, quite heterogeneous expertise comes together to address a scientific challenge that has not been solved so far by hundreds of researchers with hundreds of millions of € or $
- The expertise is distributed over 9 academic, 4 industry and 2 SME partners. 2 partners representing patient interest groups. These 17 partners will collaborate over 5 years to achieve the major goal of AETIONOMY: the development of a taxonomy of disease based on disease mechanisms and the validation of this taxonomy in the course of clinical studies.

New Approaches in Translational Research

- AETIONOMY brings together scientists who do not necessarily work together at a routine basis
- Collaboration in such a multi-disciplinary team requires a culture of listening and mutual respect
- AETIONOMY tries to take a new approach towards AD and PD. We are not going to continue with “what we did anyway”, but rather will “walk the talk” and fill the new paradigm underlying our concept with life
- AETIONOMY has the potential to turn into a lighthouse project for future AD and PD research. Already now, before it even started, the project has substantial visibility (e.g. G8 summit). We need to work closely together in order to deliver to the promise.


Literature
Public data
In-house data from PD and AD cohorts
AETIONOMY Disease Models
AETIONOMY clinical data
Model instructed mining
Unbiased clustering
Aetionomy hypothesis I
Aetionomy hypothesis II
Biological pre-validation in existing cohorts
Clinical validation in a prospective cohort
Validation in independent cohorts already recruited

Expected Impact On The R&D Process

Increased homogeneity of disease will:

- Decrease trial sizes
- Improve benefit risk profiles of drugs
- Increase speed to patients

Improved understanding of the disease

- Ensures patients can access the right treatments for them regardless of phenotypic presentation
- Increased confidence in target

Reduce drug discovery costs by impacting attrition

The Consortium

www.aetionomy.eu

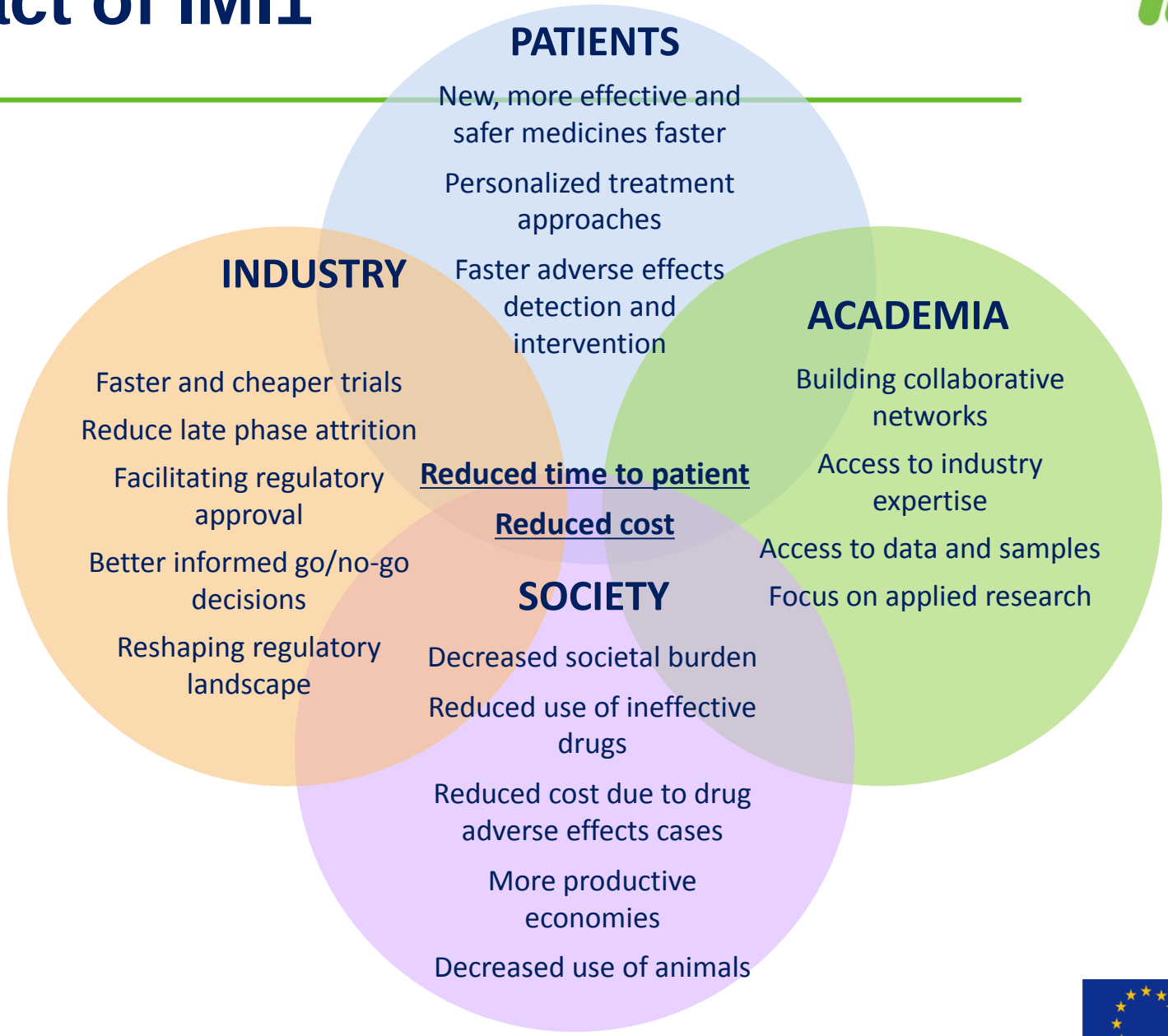
Partnership in IMI1

"Non-competitive" collaborative research for EFPIA companies

Open collaboration in public-private consortia (data sharing, wide dissemination of results)

Competitive calls to select partners of EFPIA companies (IMI beneficiaries)

Impact of IMI1



How will your results improve R&D productivity?

How will your project impact patients?

How will the project outcomes improve healthcare?

What Does IMI Expect From You?

Success!

To achieve success

Communicate & Collaborate!

Pharmacoidea's recent achievements

- Hungarian ambassador of Enterprise Europe Network (2012)
- Finalist at the European Venture Summit (2013)
- Role Model of Young Entrepreneurs Award (2013)
- Young InNOvators Network for SustainaBLE Ideas in the Agro-Food Sector (NO-BLE Ideas 2014): Best Noble Idea