BIH Lecture Series | Frontiers in Translational Medicine – Scientific and Structural Challenges

An Industry Perspective

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Outline

- Translational Medicine
- The dilemma in pharmaceutical R&D
- Biomarkers in clinical drug development
- Use of human biospecimen/Global Regulation on Data Protection (GRDP)
- Industry – Academia collaborations: opnMe.com

Translational Medicine – Scientific Frontiers …and some successes

Basic Research

Diseases

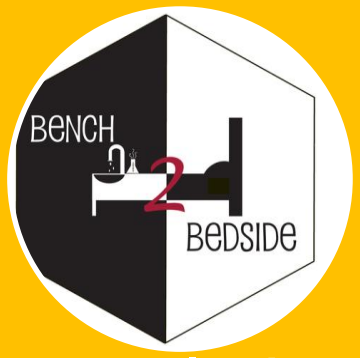
Genomics, Proteomics, …

Target discovery

Compound discovery

In vitro models

Animal studies



Translation

Biomarker

Mechanisms of Disease

Disease Positioning

Patient selection

Clinical Research

Clinical studies

Drug intervention

Patient outcome

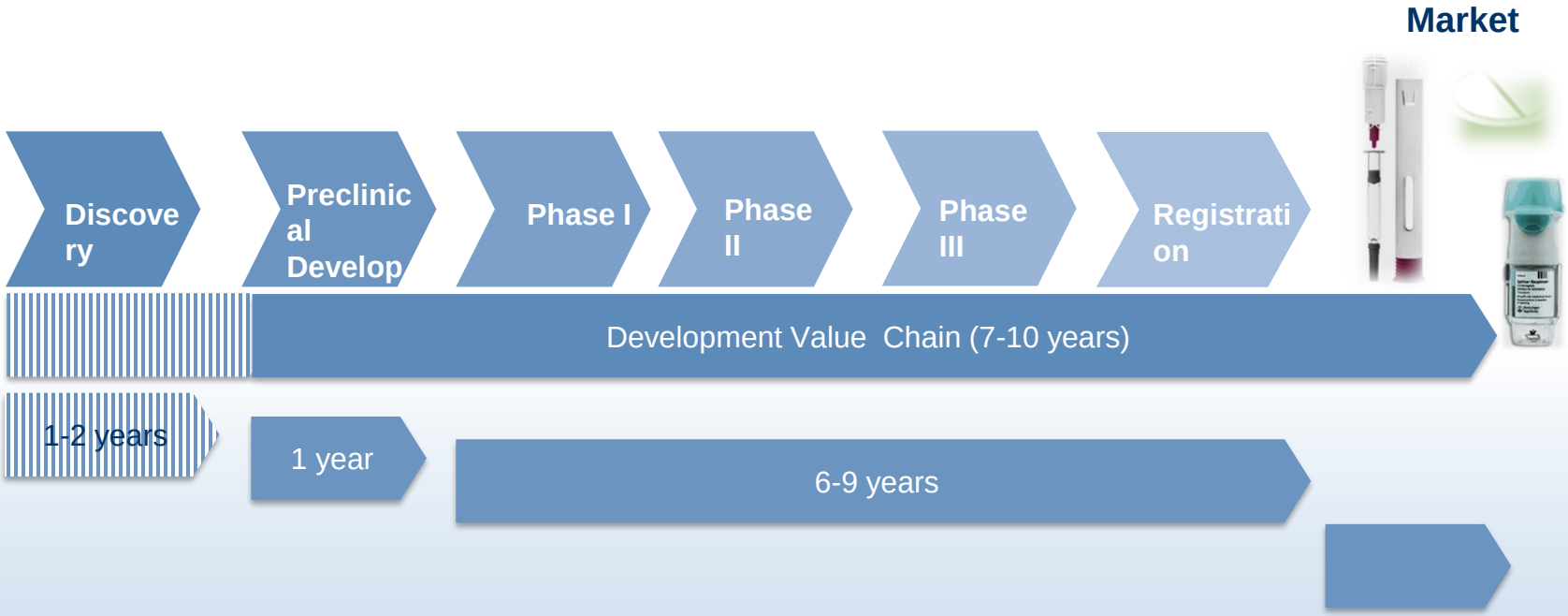
Translational Medicine & Drug Development

Translational Medicine:
Integrated application of
- clinical methods & technologies
- biomarkers
- modeling & simulation
- study designs

- Improve confidence in human drug concepts & candidates
- Understand the therapeutic index in humans
- Enhance cost-effective decision making in ***exploratory development (→ Proof of Clinical Principle-PoCP)***
- Increase ***confirmatory development*** success (→late stage)

Sustainable and competitive pipeline of innovative products in the best interest of the patients

The pharmaceutical R&D value chain



The pharmaceutical R&D dilemma

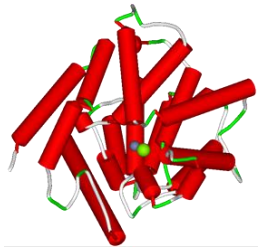
Lengthy Costly Low success

….The Issue with Translational Medicine

Two dominant questions in drug discovery & early clin. development:

1) Will hitting the target translate into therapeutic improvement?
2) Which patients will respond best (and how can we identify them)?

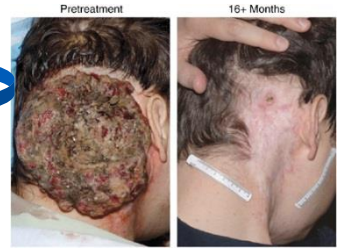
Molecular target



In vitro models

Animal Models

Clinical Efficacy



Two learnings:

1) Mice are not just furry plastic plates
2) Humans are no nude mice

development:
Essential along the entire value chain

PoCP*

Market

Discovery | Preclinical Develop | Phase I | Phase II | Phase III | Registration

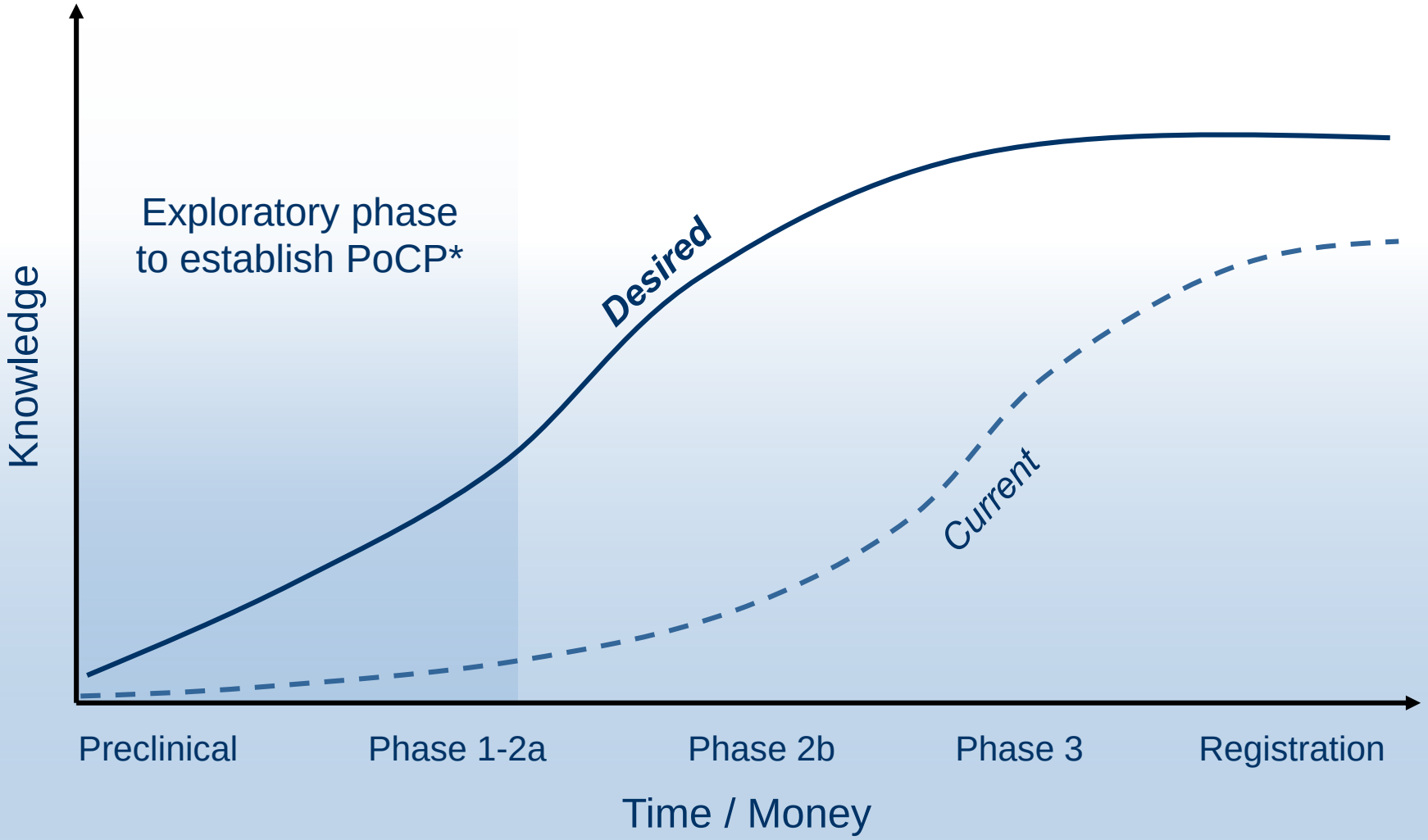
Development Value Chain (7-10 years)

1-2 years | 1 year | 6-9 years

- **Biomarker teams** established at Lead Optimization start
- **PK/PD analyses**
- **Translational biomarkers** studies in animals
- First-in-man studies in HV, **safety & tolerability**
  - **Biomarker exploration & hypothesis testing** in man
    - PoCP studies in **specified patient populations**
    - M&S to inform dosing and population specifics
    - Development of **CDx**
      - Banking of human biospecimens
      - Exploration of additional indications
- **Therapy optimizati**
- **New indications**
- New combinations
- Post approval committments

*PoCP = Proof of Clinical Principle, i.e. ‚first sign of efficacy'

In other words:
Shift the Development Knowledge Curve…



*PoCP = Proof of Clinical Principle, i.e. ‚first sign of efficacy'

Biomarkers

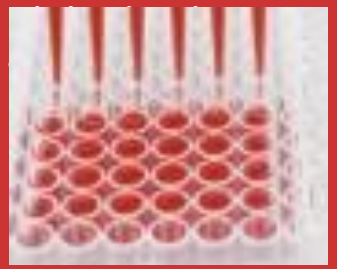
Biomarker definition:

A characteristic that is objectively **measured and evaluated as an indication** of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention

Biomarker classification by ‚nature‘

‚Classic‘ Biomarkers

- Soluble biomarkers (e.g. plasma, serum, urine, etc.)
- Blood cell analysis
- Tissue analysis

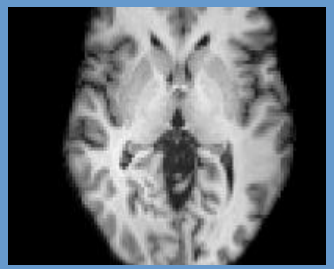


Genomic Biomarkers

- DNA-Sequencing
- DNA-Methylation
- RNA-Expression
- Micro RNA analysis

Imaging Biomarkers

- Magnetic Resonance
- Computer Tomography
- Nuclear medicine modalities
- Ultrasound



Biomarkers in clinical drug development

1. **Understand your drug as early as possible during clinical development:**
   - Does a sufficient amount of drug reach the target for the desired period of time?
   - Does the drug bind to the target?
   - **Does drug binding elicit a pharm cal effect expected considering the underlying mode of actio**
   - **Does the drug alter disease p gy?**

Pharmaco-dynamic

Risankizumab

2. **Assess and monitor drug safety:**
   - Does the drug (have the potential to) elicit a toxic response before its benefits become clinically evident?

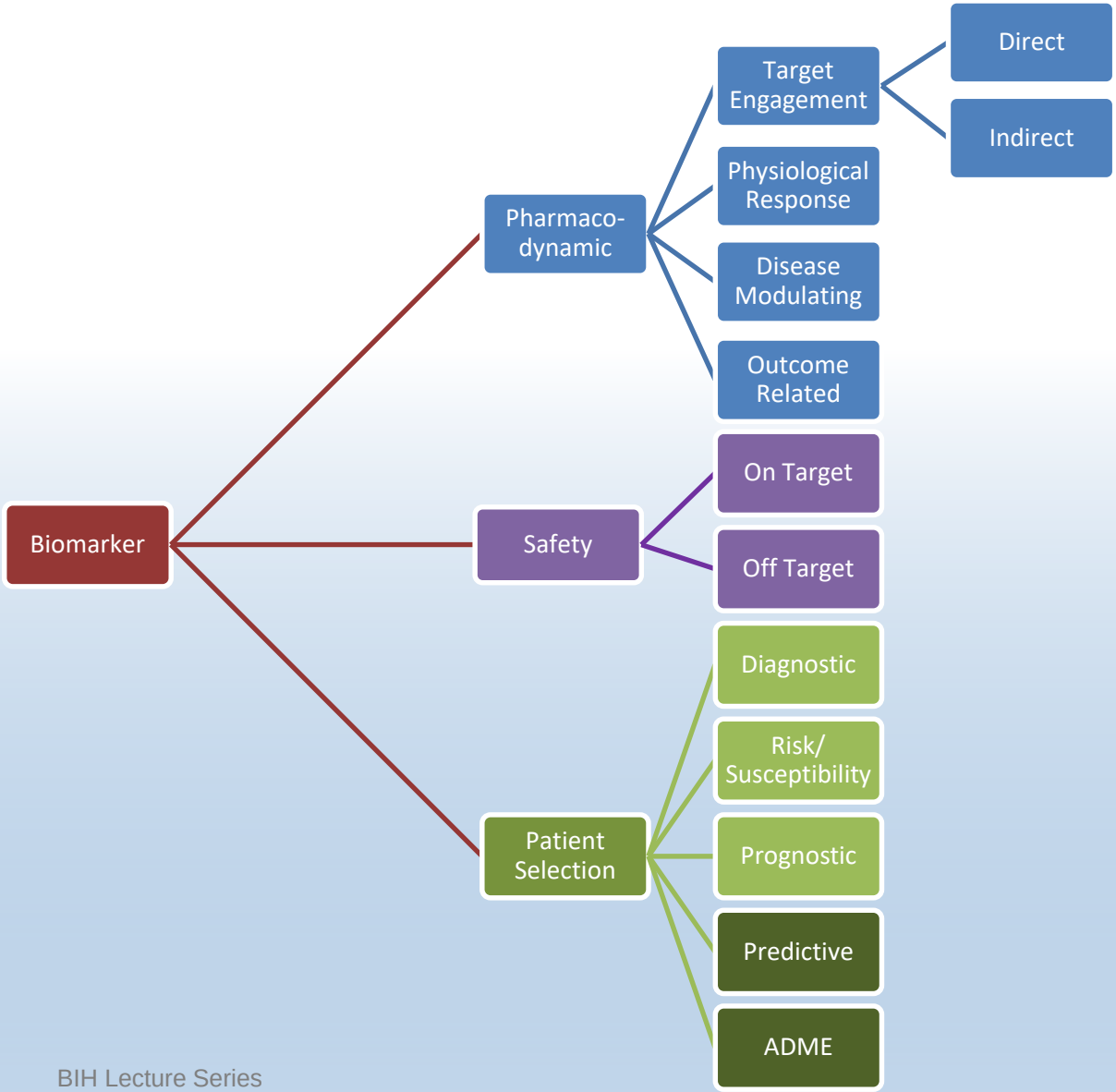
Safety

3. **Find the right patients:**
   - Support diagnosis
   - **Include the right patients into t trials**
   - Selection of right patients for in efficacy and/or safety (CDx)

Patient Selection

Spesolimab

Biomarker Categories (in the BI language)



“Three Pillars of Survival“

Can the flow of medicines be improved? Fundamental pharmacokinetic and pharmacological principles toward improving Phase II survival

Drug Discovery Today • Volume 17, Numbers 9/10 • May 2012

Paul Morgan[1], Piet H. Van Der Graaf[1,2], piet.van.der.graaf@pfizer.com, John Arrowsmith[3], Doug E. Feltner[4], Kira S. Drummond[5], Craig D. Wegner[6] and Steve D.A. Street[7]

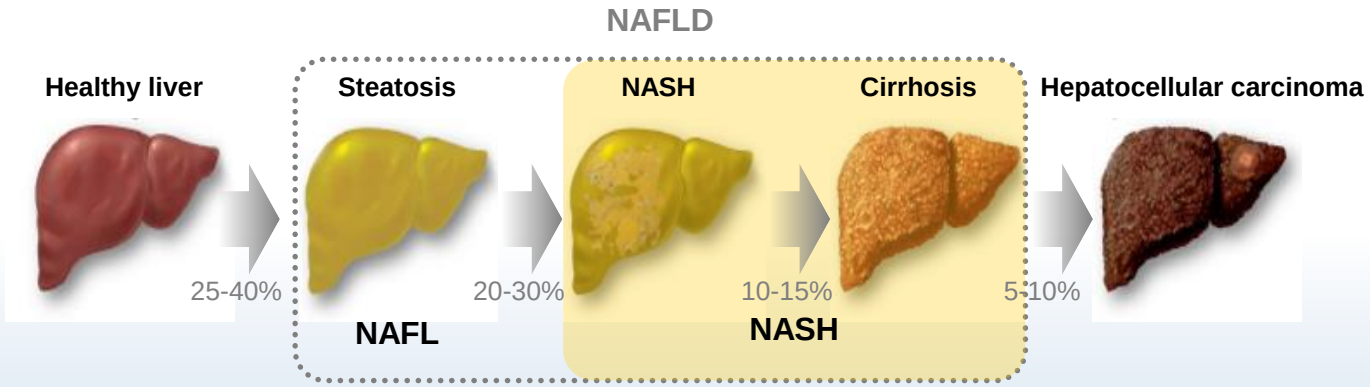
Three Pillars of Survival:

- Exposure at the site of action over a desired period of time
- Binding to the pharmacological target
- Expression of functional pharmacological activity

An integrated understanding of the above fundamental pharmacokinetic and pharmacodynamic principles determine the likelihood of drug candidate survival in Phase II trials and improve the chance of progression to Phase III.

Non-alcoholic steatohepatitis (NASH): A liver disease of high unmet medical need

Progression of fatty liver disease



39 mio
NASH patients

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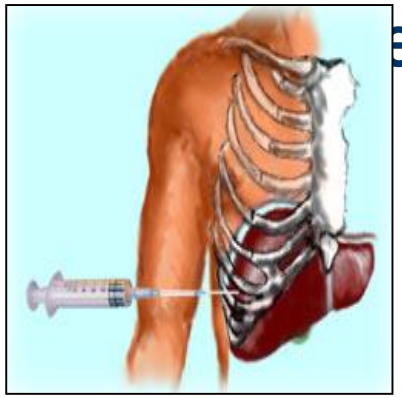
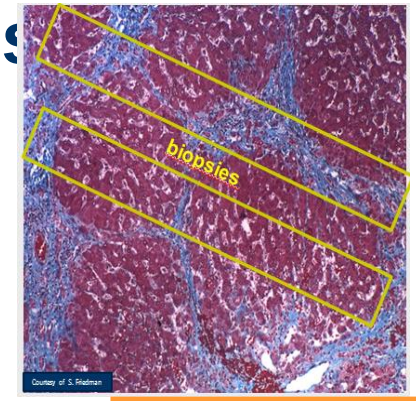
- NASH grading by liver biopsies has several limitations
- Which patients are fast progressors?

Biomarkers for NASH and Liver Fibrosis: Liver Biopsy – Grading / Staging & Need for

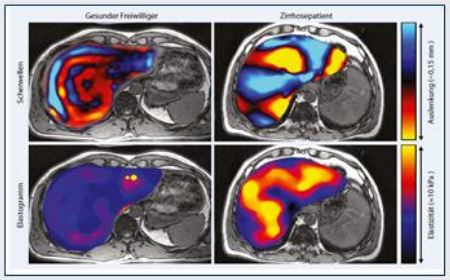


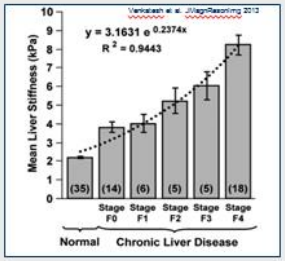


- Biopsy still gold standard for diagnosis and grading of NASH/fibrosis
- Lesions unevenly distributed
- Only a small region assessed
- Sampling errors lead to misdiagnosis/misgradings

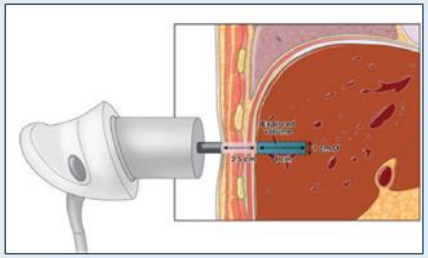
Investment in alternative imaging modalities & soluble biomarkers to establish link to clinical NASH grading

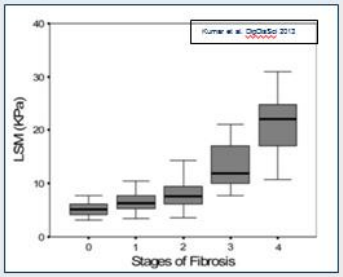
Magnetic Resonance Elastography (MRE)





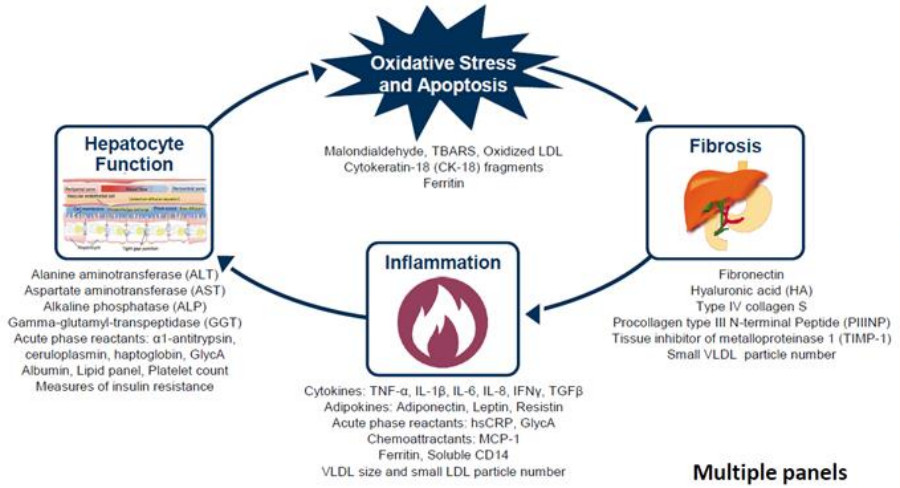
Transient Elastography (TE)





- MRE provides quantitative assessment of fibrosis in entire liver, but method not readily available
- TE has potential for patient selection method in clinical trials

Specialized Biomarkers



1. Adapted from Fitzpatrick et al., Noninvasive biomarkers in NAFLD World, *J Gastroenterol* 2014;20(31):10851-10863.
2. Armutcu et al., Adv in Clin Chem 2013;61:67-125.

Imaging to support therapeutic concepts in IO

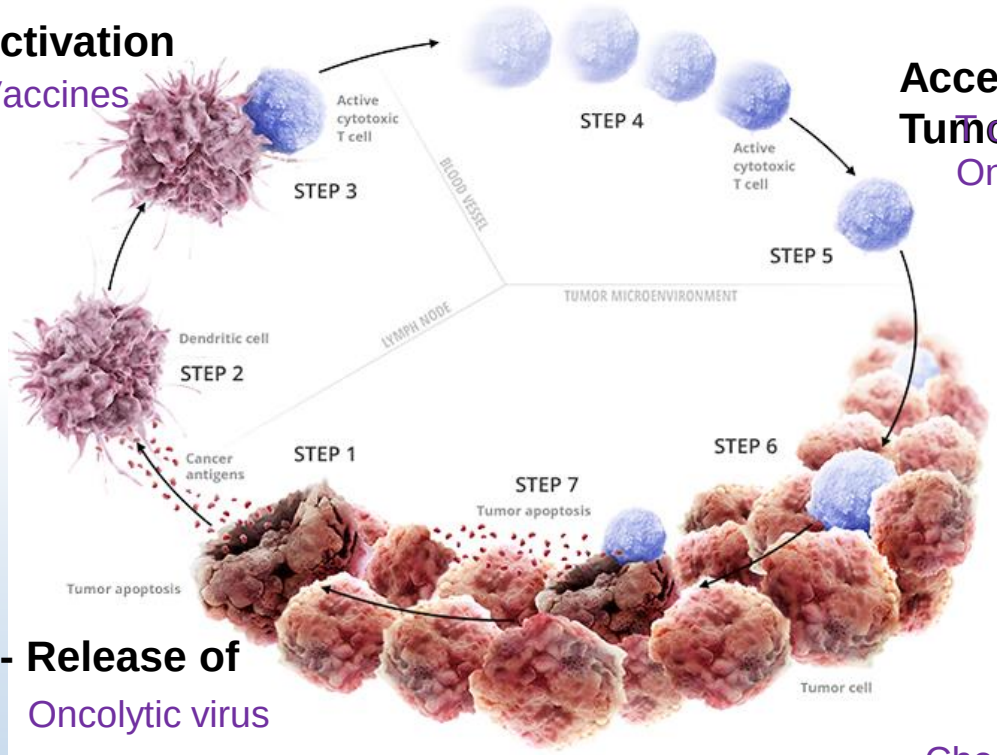
Priming and Activation

Cancer Vaccines

Imaging T-cell activation

Antigen Presentation

Cancer Vaccines



Accessing the Tumor

T cell Engagers

Oncolytic virus

DCE-MRI

Imaging of TIL presence

TME Modulators

Tumor Cell Death - Release of Antigens

Oncolytic virus

Tumor cell metabolism & texture (FDG PET/CT)

Adapted from Chen and Mellman, Immunity 2013

Checkpoint Inhibitors

T cell Engagers

Oncolytic virus

Biodistribution studies to support novel drug formats

FDG: Fluor-Deoxy-Glucose

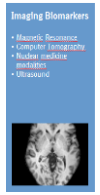
PET: Positron Emission Tomography

DCE-MRI: Dynamic contrast enhanced MRI

TIL: Tumor-infiltrating Lymphocyte

TME: Tumor micro-environment

Nuclear imaging to assess T-cell infiltration and activation



Assess changes in T-cell numbers and T-cell activation

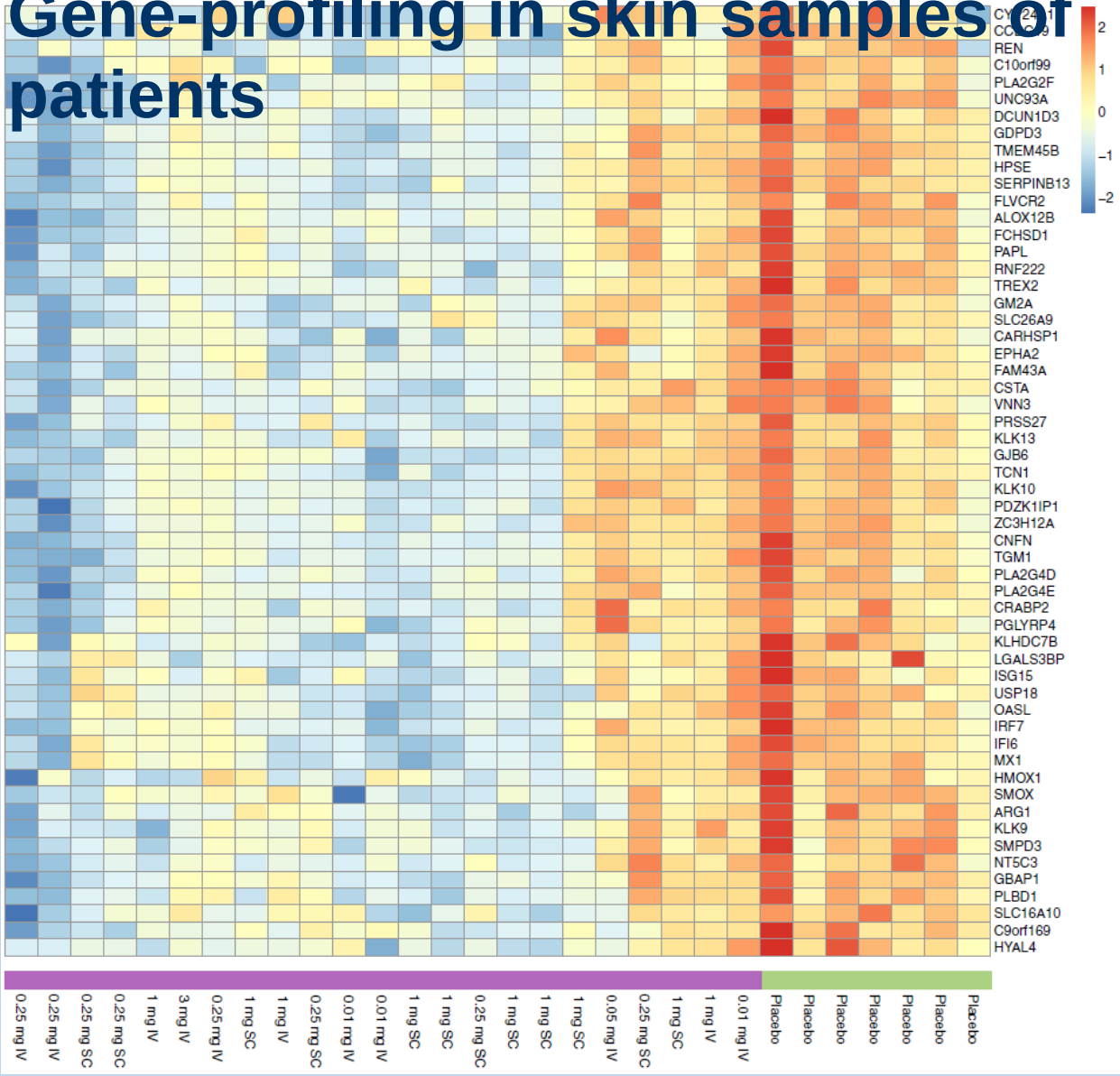
			Status
In clinical use Exploratory	[^{18}F]AraG PET*/CT	Activated T cells	• IP: CellSight Technologies Inc. • PhI/II development on-going
FIH 2017	[^{89}Zr] anti-CD8 PET*/CT	CD8^{+} T cells	• IP: ImaginAb

- Explore feasibility of imaging approaches for IO treatment paradigms
- Explore time points best suited for imaging assessment after start of treatment
- Define relevance of observed changes for pharmacodynamic effects, assess predictive value

PET: Positron Emmission Tomography

Genomic Biomarker example in psoriasis:

Gene-profiling in skin samples of patients



Risankizumab:
mAb IL-23 inhibitor

Modulations of

- IL-23 / IL-17 axis
- Epidermal development
- Keratinocyte differentiation
- Epidermal cell differentiation
- Keratinization

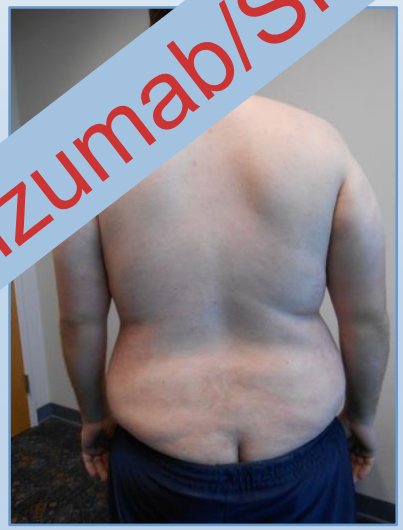
Krueger et al., JACI 2015

IL-23 blockade: A new therapeutic option fo psoriasis patients

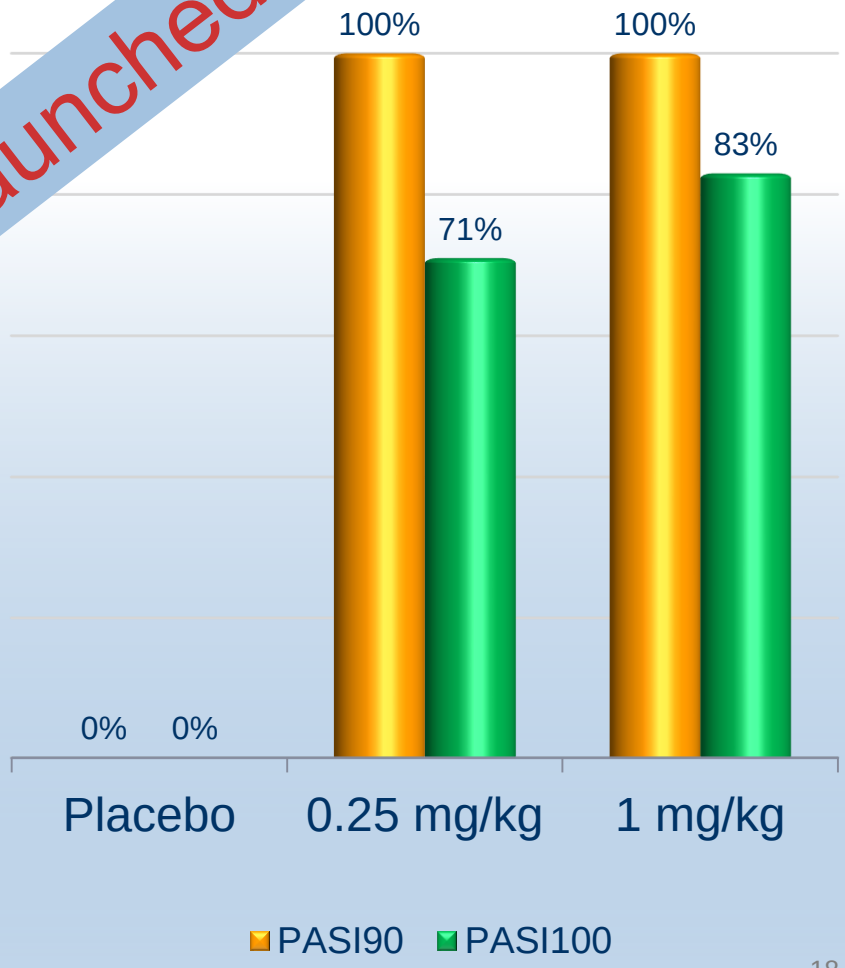
Risankizumab (anti-IL-23 Ab)

Pretreatment

Single dos
at 24 w



How many patie an „almost clear“ (PASI90)
or „clear“ (kin in the 3 dose cohorts?



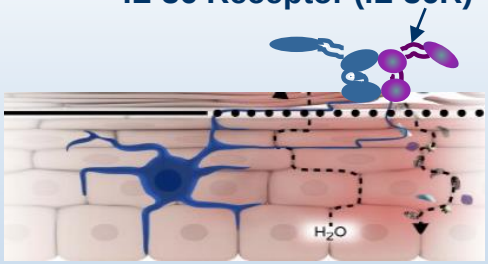
Risankizumab/Skyrizi® launched in April 2019

IL-36 receptor regulates the inflammatory response in skin and intestine

Skin

IL-36 ligands

IL-36 Receptor (IL-36R)



Barrier Damage

Inflammation

T cell

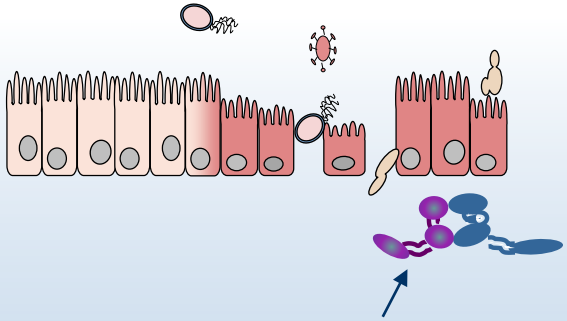
Neutrophil

Macrophage

Fibroblast

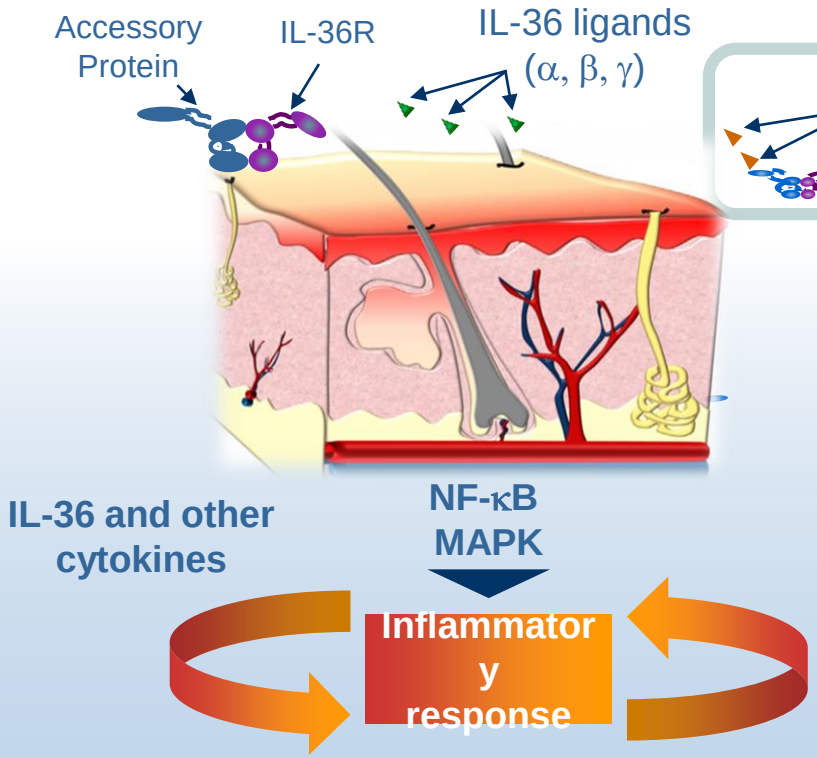
Aberrant Tissue Remodeling & Fibrosis

Intestine



IL-36 Receptor (IL-36R)

IL-36 R Ab BI 655130/Spesolimab – New Therapeutic Concept for Skin Inflammation



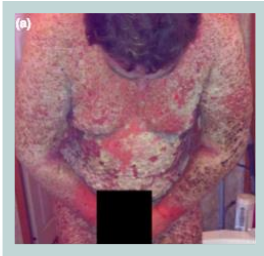
Spesolimab will:

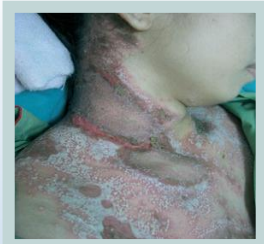
- Suppress IL-36R activation reducing epithelial cell/fibroblast/immune cell mediated inflammation
- Interrupt inflammatory response that amplifies pathogenic cytokine production

Generalized Pustular Psoriasis (GPP)

Disease Characteristics:

- **Orphan disease, very rare** type of psoriasis, which covers usually entire body
- Repeated, intermittent **acute flares with pustules** and erythema and scaling
- Systemic effects such as high fever, neutrophilia, elevated CRP
- **Life threatening and may lead to increased mortality**
- **Human genetic link: most severely affected GPP patients carry a LoF mutations in natural IL-36 RA**



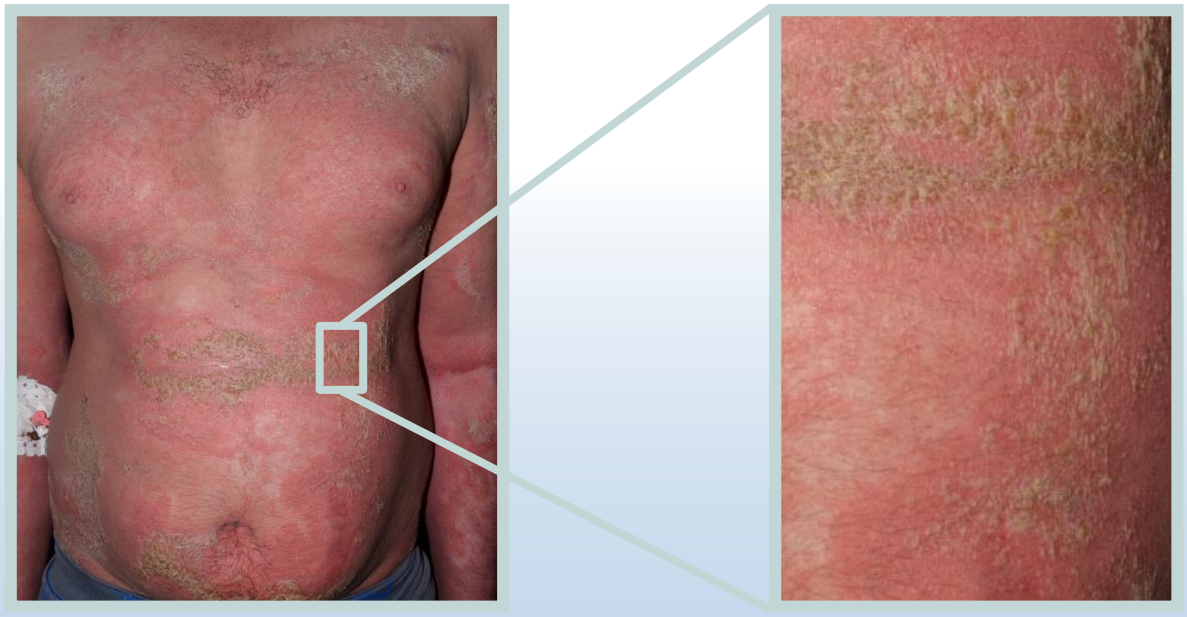


➔ **High unmet medical need**

- **No approved treatments in US/EU**
- **No acute flare treatment clinical trials** conducted to date

Severity of disease in patient with GPP before treatment

Baseline (before treatment)

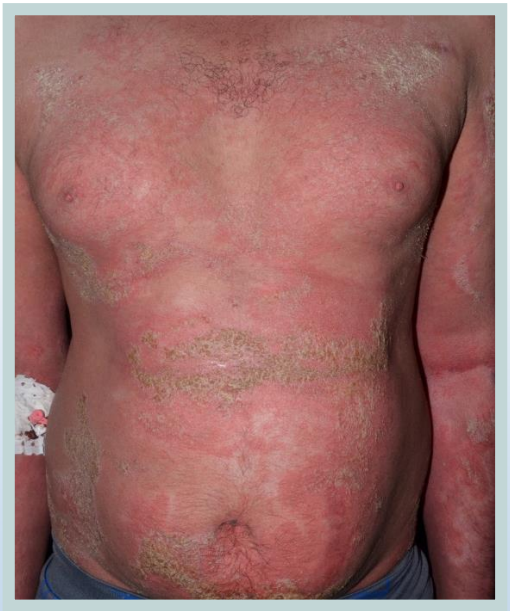


Total GPPGA score before treatment

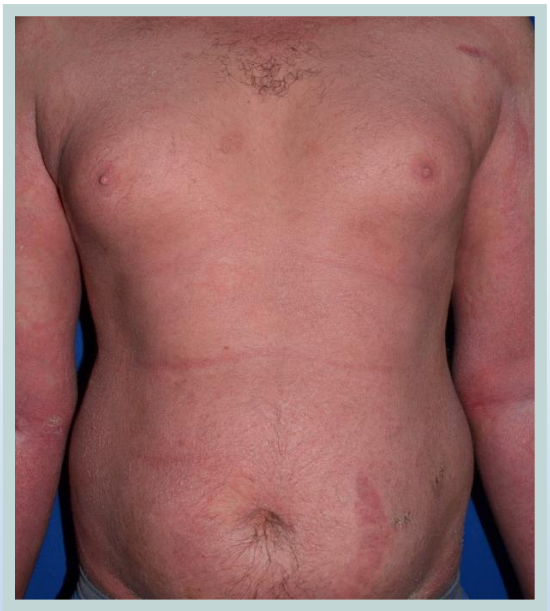
Clear (0)	Almost clear (1)	Mild disease (2)	Moderate disease (3)	Severe disease (4)

Response to treatment in patient with GPP after 1 week

Baseline (before treatment)



Week 1 post-treatment

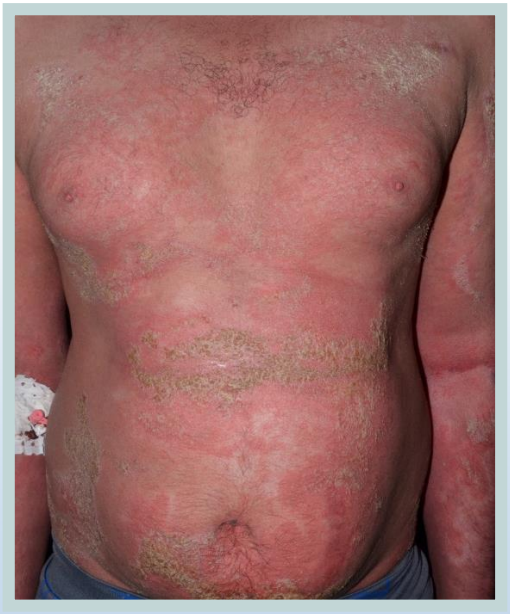


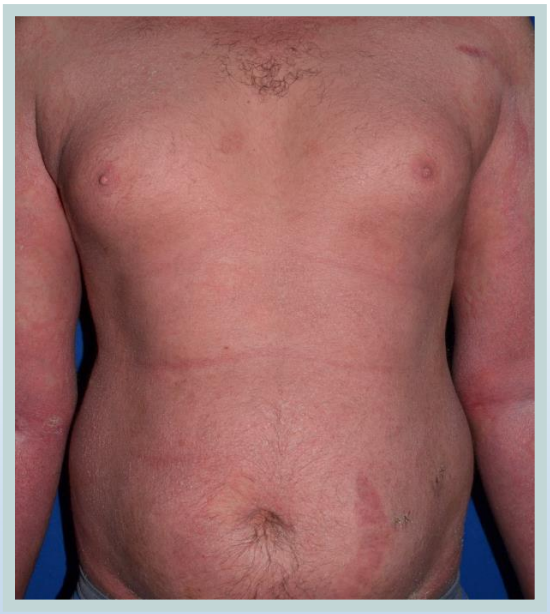
Total GPPGA score after 1 week

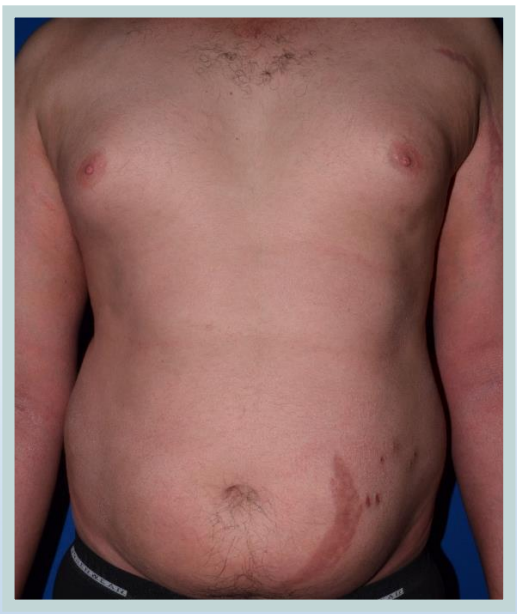
Clear (0)	Almost clear (1)	Mild disease (2)	Moderate disease (3)	Severe disease (4)

Response to treatment in patient with GPP after 4 weeks

Baseline (before treatment)	Week 1 post-treatment	Week 4 post-treatment



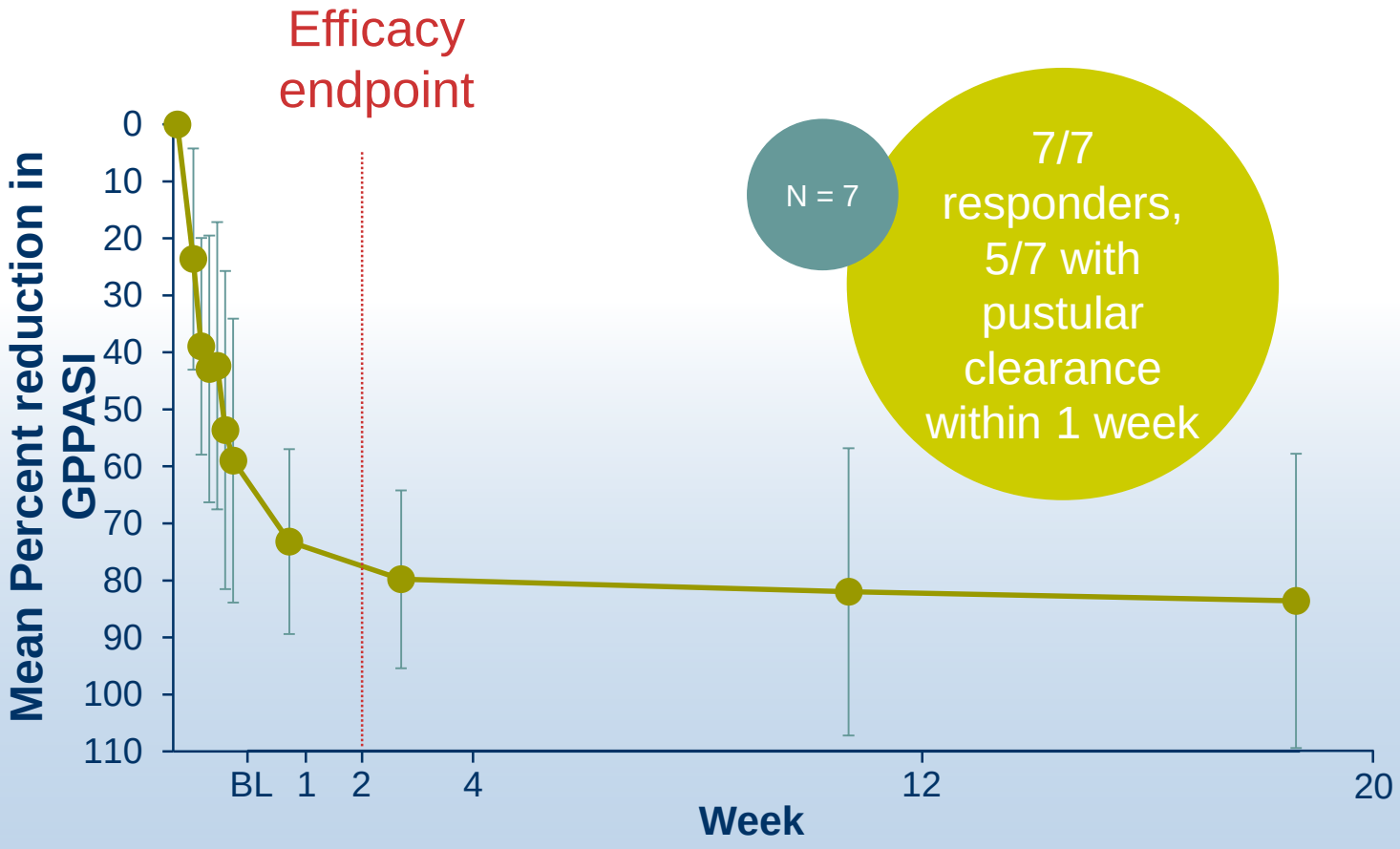




Total GPPGA score at Week 4

Clear (0)	Almost clear (1)	Mild disease (2)	Moderate disease (3)	Severe disease (4)

Efficacy of BI 655130 in Ph2 clinical trial measure in GPPASI*

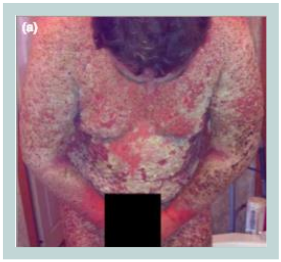


GPPASI* = GPP Activity Score Index

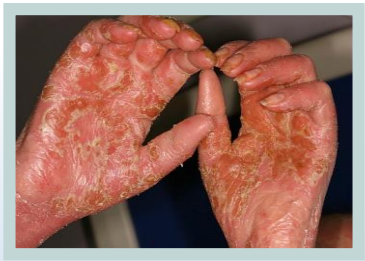
Spesolimab: First in class potential for various diseases

Spesolimab: First in Class potential

- Generalized Pustular Psoriasis

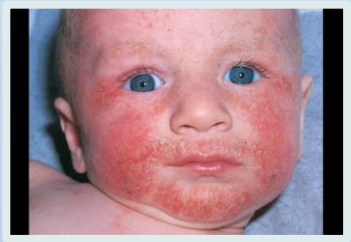


- Palmoplantar Pustulosis



- IBD (Crohn's disease, ulcerative colitis)

- Atopic Dermatitis



Summary und Outlook

Biomarkers are important for clinical drug development:

- Decision criteria, particularly in early clinical drug development
- Acceleration of clinical drug development (e.g. as surrogate endpoints)
- Selection of the “right” patient population
- Supportive in the assessment of an appropriate dose
- Differentiation from competitor drugs
- Assessment of additional indications
- …

Outlook:

- **Biomarkers play an increasingly central role in Precision Medicine concepts**

Translational Medicine – Structural Frontiers

Basic Research

Diseases

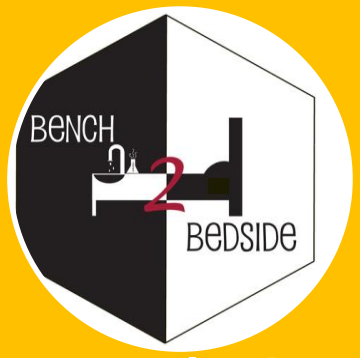
Genomics, Proteomics, …

Target discovery

Compound discovery

In vitro models

Animal studies



Translation

Biomarker

Mechanisms of Disease

Disease Positioning

Patient selection

Clinical Research

Clinical studies

Drug intervention

Patient outcome

Translational Medicine – Structural Frontiers … and solutions

- GDPR – Global Data Protection Regulation
- Access to and use of Human Biospecimens
- Pharma – academia collaborations: Open Innovation at BI
- …

Data Protection

Art. 1 GDPR Subject-matter and objectives

This Regulation lays down rules relating to the **protection of natural persons** with regard to the processing of personal data and rules relating to the **free movement of personal data**.

The dilemma:

- The pharmaceutical industry generates and processes health data
- Health data are considered as a **special category of personal data**
  - ➢ stringent data protection is required
  - ➢ the processing of health data is prohibited by default, exceptions

Data Protection

- **Art. 9 GDPR Processing of special categories of personal data**

1. […] the processing of genetic data, biometric data for the purpose of uniquely identifying a natural person, data concerning health […] **shall be prohibited**.

- 2. **Paragraph 1 <u>shall not apply if</u> one of the following applies:**
  - processing is necessary for the purposes of […] **medical diagnosis**, the **provision of health** or social care or treatment or the management of health or social care systems […]
  - processing is necessary for reasons of public interest in the area of **public health**, such as protecting against serious cross-border threats to health or **ensuring high standards of quality and safety of health care and of medicinal products or medical devices** […]

Access to human biospecimen and associated data is indispensable for drug development

- Address questions from authorities w/o starting a new clinical trial
- Analyze new scientific hypotheses/ verify scientific hypotheses
- Explain responder subgroups in clinical trials→ high sample number, cross trial
- Discover & validate new drug targets or biomarkers
- Identify rare efficacy or safety markers → high sample number, cross trial
- Confirm biomarker results in statistically significant & unselected cohorts
- Support companion diagnostics programs and assay development
- Enable collaborations: Banked samples & data may open doors

Biobanking at BI

Compliant and **comprehensive** sample and data collection, storage and long-term

BI maintains a biobank to support the development of innovative medicines.

BI's biobanking activities were first implemented in 2009 by setting up its DNA bank.

Afterwards, BI has expanded its biobanking strategy and infrastructure, also accommodating all other kinds of human biospecimen on a global level.

The **BI in-house DNA banking facility** has a dimension of 17,4m x 3,6m x 5m and a storage capacity of 5.5 Mio tubes (~500.000 donors).

For **other sample species** 4 biobanking locations are available at our biobanking service partner. Scalable according to demand.

Boehringer Ingelheim

Corporate Policy: Responsible Use of Human Biospecimens & Associated Data

Human biospecimens are materials taken from the human body, such as tissue, cells, blood, and other body fluids. The use of such human biospecimens and associated data has become increasingly important in research and drug development, especially for the understanding of complex, multi-factorial diseases. Such human biospecimen-based research is crucial to the development of new drugs and diagnostic products for the improvement of detection, prevention, diagnosis, intervention, treatment and cures of diseases.

As an innovation- and research-driven pharmaceutical company, Boehringer Ingelheim (BI) makes use of human biospecimens and associated data in current research and drug development programs. BI collects human biospecimens in clinical trials and acquires them from third parties for the purpose of future research. Their responsible use will support more efficient and faster development of new, innovative therapies.

BI is committed to the responsible use of human biospecimens and associated data and will apply high ethical, legal, quality, privacy and data protection standards to all acquisition, collection, storage and analysis procedures undertaken. Compliance with applicable legal, regulatory and internal provisions is a BI company goal.

Purpose and Scope

Human biospecimens and associated data are routinely used for research purposes in drug development programs. They are acquired from third parties or collected for specified, timely restricted analysis in the framework of BI-sponsored clinical trials. Moreover, human biospecimens are also a crucial resource for future, in many cases not yet predictable, medical research purposes. The latter requires compliant collection and long-term storage of biospecimens in a so-called biobank.

BI recognizes long-term access to human biospecimens and associated data as a vital prerequisite for future medical innovation. BI has adopted an integrated human biospecimen and biobanking framework to ensure responsible, compliant and secure collection, long-term storage and access procedures to human biospecimens and associated data.

With this policy BI commits to the responsible use of both human biospecimens and associated data in research and drug development including strict quality and data protection standards and a responsible biospecimen and data custodianship.

Biobanking

Banked human biospecimens and associated data represent an invaluable resource for current and future research on health and disease. BI is grateful to the voluntary donation of samples and actively encourages their collection during clinical trials.

As part of the biobanking process, human biospecimens and associated data for unspecified future research use will be collected, processed, stored, analysed and finally destroyed strictly according to an Informed Consent (IC) reviewed by an independent ethical committee or institutional review board. A quality management system (QMS) certifies compliance with relevant human subject and privacy regulations, including EU and German data protection regulations, international and national jurisdictions, ethical principles and other relevant regulations and guidelines.

Appropriate safeguards are inplace to protect the donors' identity and privacy. Human biospecimens and associated data are always coded and BI has no access to any information that may reveal the donor's identity. Both human biospecimen and associated data are stored in a secured, access-controlled environment. Also their analysis is controlled and regulated by Standard Operating Procedures (SOPs).

Acquisition from third parties

BI research and drug development also requires the acquisition of human biospecimens from third parties, including commercial providers. For any such acquisition BI complies with relevant human subject and data protection regulations, international and national jurisdictions, ethical principles and other relevant regulations and guidelines, including EU and German data protection regulations.

Oversight, Transparency & Dialogue

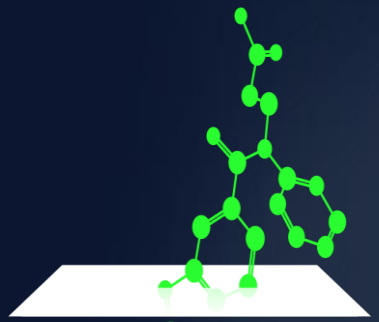
A Human Biospecimen Science & Ethics Advisory Board has been established. The board comprises medical/scientific, quality, legal, data protection and also external ethics expertise. It provides guidance regarding patient-centric, responsible and scientifically sound use of human biospecimens and associated data at BI. In addition, the BI Human Biospecimen Compliance Officer oversees the human biospecimen and biobanking framework on a daily basis.

Human biomedical research is a dynamic field. BI continues to monitor the international public discourse and constantly reviews its practices and procedures together with external experts and authorities.

BI is aware of the public dialogue about the responsible use of human biospecimens and associated data and committed towards transparency and high ethical, legal, quality, privacy and data protection standards.

Hubertus von Baumbach Joachim Hasenmaier Allan Hildebrand Simone Menne Andreas Neumann Michel Pairet

[Corporate Policy: Responsible Use of Human Biospecimens & Associated Data]



opnMe.com

The BI open Innovation portal

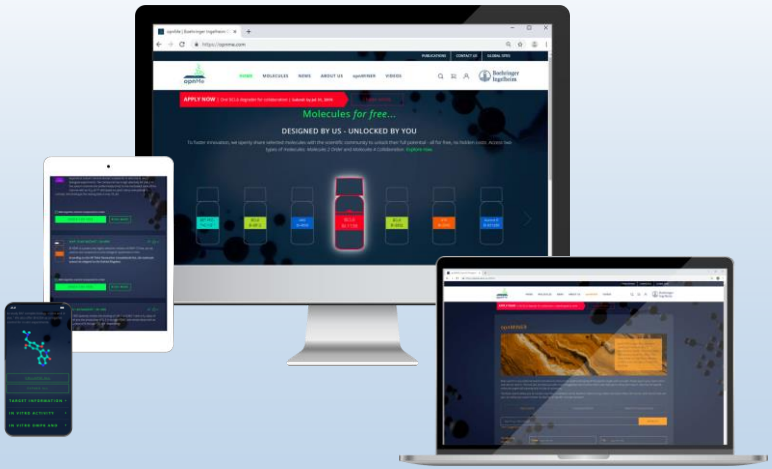
Boehringer Ingelheim

“They did not know it was impossible so they did it”

— Mark Twain

opnMe.com - Boehringer Ingelheim's open innovation portal

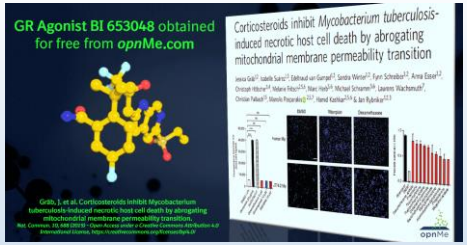
Door Opener for Academic Innovators



- **opnMe.com** gives scientists free access to selected, well-characterized pre-clinical tool compounds from Boehringer Ingelheim.
- **Molecules to Order (M2O)** are provided free-of-charge without the need to enter into intellectual property discussions.
- **Molecules for Collaboration (M4C)** invites scientists to submit research proposals to use our unique tools
and to find new indications for unmet medical needs.

opnMe.com - Boehringer Ingelheim's open innovation portal

Door Opener for Academic Innovators



> 1,100 biologists registered from >40 countries

- Modalities covered: NCEs incl. PROTACs® from the Dundee university, AAV, and Ab

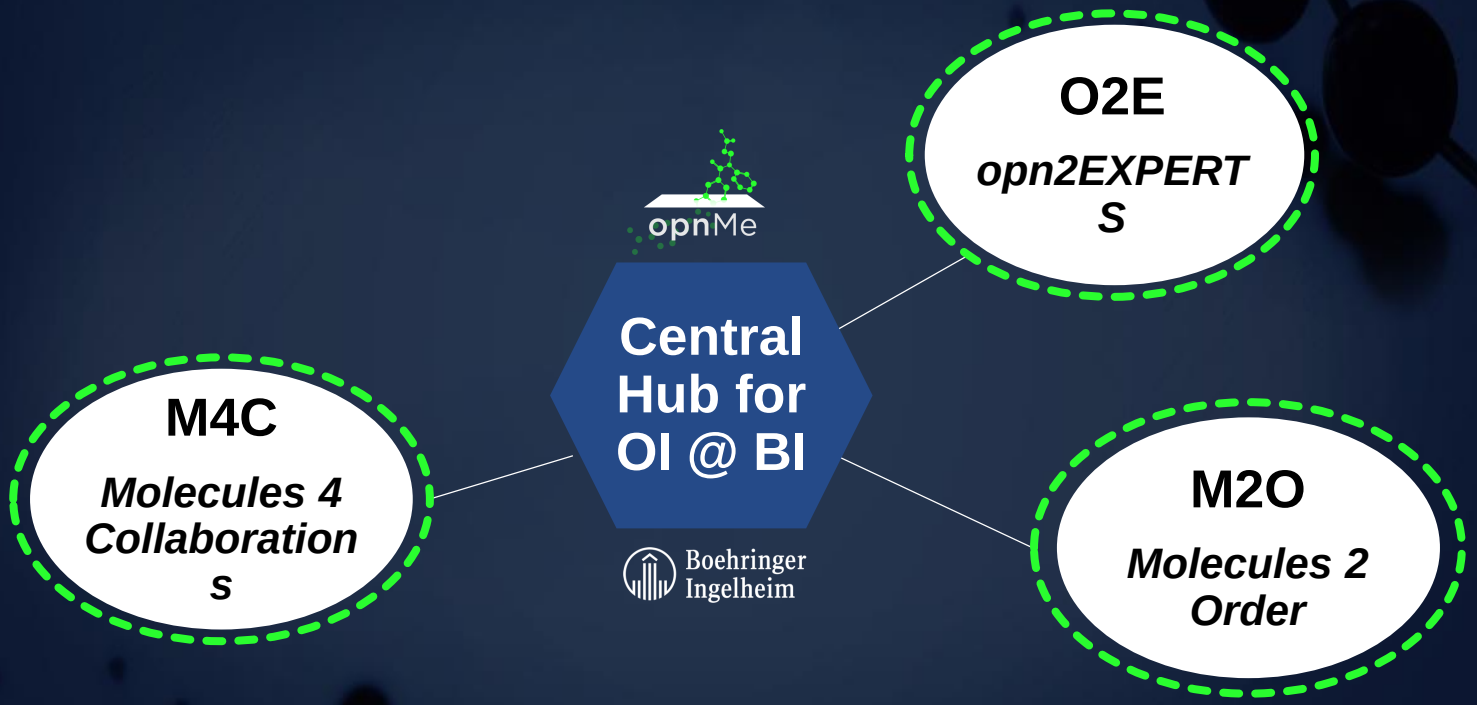
M2O: tools compounds available for free and without strings attached

- Delivered after only 5 clicks and 5 days to the labs
- >460 orders and >5,000 compounds shipped worldwide
- >10 articles cited opnMe including 2 Nature papers using BI tools

M4C: 5 challenges launched

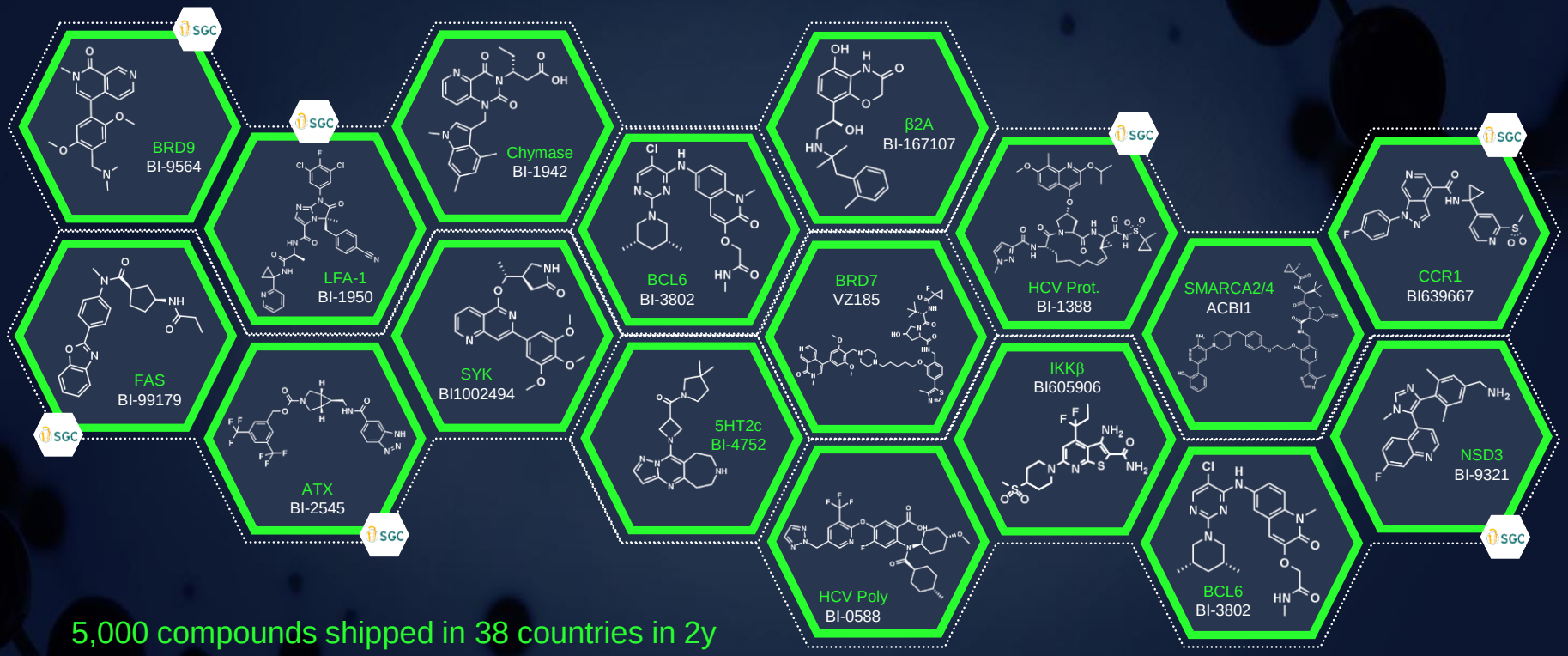
- >480 proposals received
- 16 collaborations running or in discussion
- 1 project already back into the early Research portfolio of BI

opnMe - an OI ecosystem to accelerate collaboratively innovation



opnMe.com is an efficient and reliable Open Innovation portal to foster new ideas

Selection of compounds available for free on *opnMe.com* to foster independent research



5,000 compounds shipped in 38 countries in 2y
48 tools available within a week with negative control
leading to >30 scientific papers

Compounds also shared on thesgc.org

Molecules for Collaboration - overview

- We believe that Boehringer Ingelheim's unprecedented, high quality molecules shared on opnMe have a great biology potential
- We invite novel proposals for disease research and proposals will be advanced together in collaboration with selected scientists
- Key milestone achieved: One molecule entered Boehringer Ingelheim's preclinical portfolio

	 GPR68	 SGLT6	 Complex 1 ROS	 AAV2-L1	 BCI6	 SOS1: KRAS
Proposals	37	17	215	81	140	116
Collaboration	6	2	3		1	
In Discussion			3	1	2	9

*Of the 7, 1 has started as a collaboration in July 2019

opn2EXPERTS – An additional chapter to opnMe.com

Background

- Crowdsourcing – Highly efficient to identify original solution to complex questions
- Crowdsourcing brings in 75% of the successful cases a solution from another field of expertise so it means that it is in general quite far from the original field of expertise

opn2Experts

- Versatile: Technologies, methodologies, assays, or other precisely formulated questions leading to a mutual benefit
- Allows colleagues to be very precise in their questions much more dedicated to their disease map
- Fast and flexible

Process

- opnMe team works with the BI biologists to prepare the question for publication
- Communication via social media (LinkedIn, Twitter), research platforms (Research Gate), direct mail (inospin), web-banners (Nature)

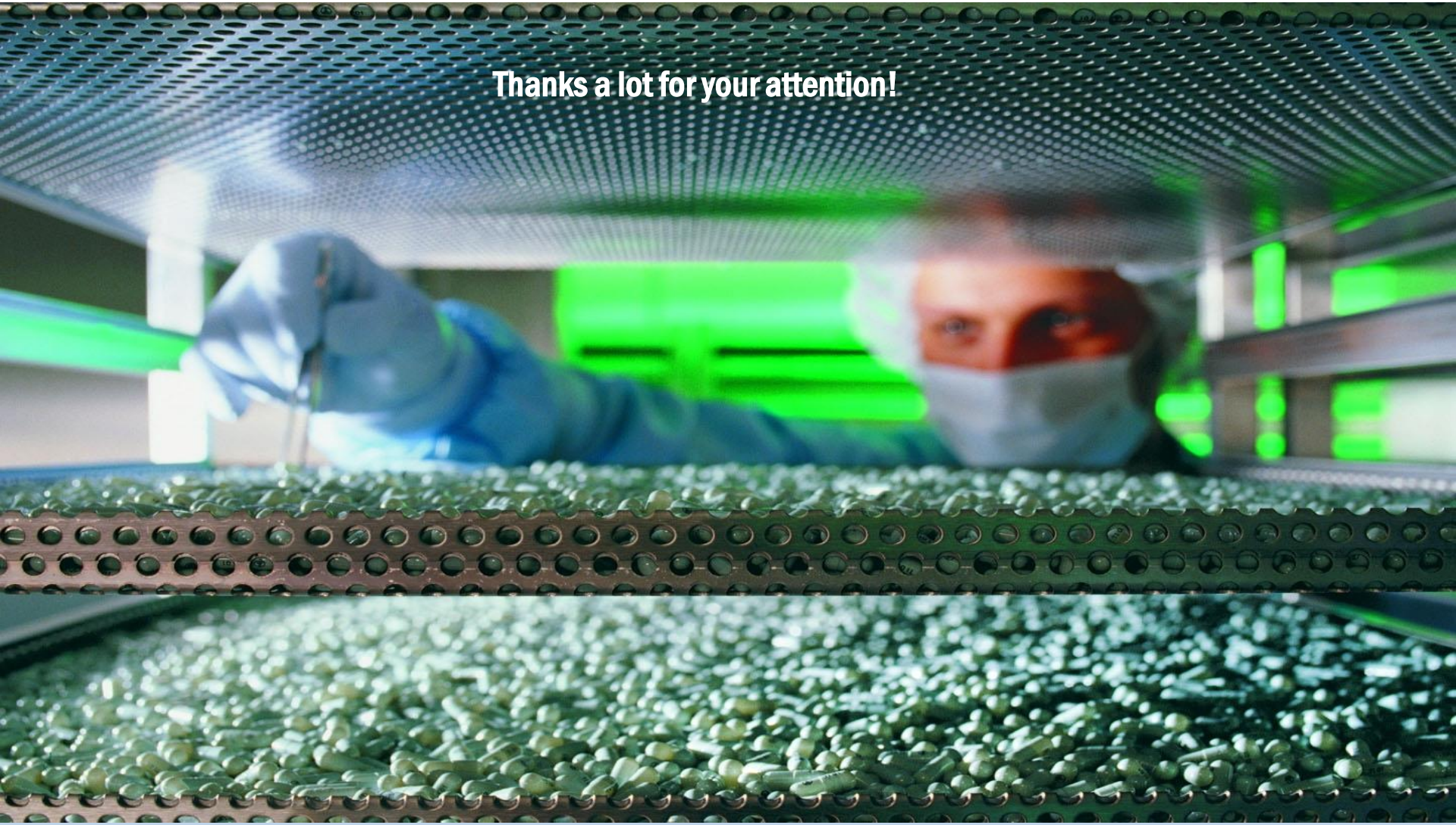
opn2EXPERTS is fast, flexible and dedicated to support innovation

Already 4 challenges online for Inflammation and CNS

Frontiers in Translational Medicine

- Scientific:
  - Lack of disease understanding
  - Lack of understanding of drug candidates
  - Limitations of biomarker applications

- Structural:
  - Data protection regulation
  - Access to and usage of human specimen
  - Disparate interests of industry versus academia


Thanks a lot for your attention!