"When one is not enough: Addressing novel therapies for chronic metabolic diseases through public-private partnerships"

Philip Larsen, Global Head of Diabetes Research and Translational Medicine, Sanofi Germany; and chairman of Strategic Governance Group for IMI Metabolic Disorders (Innovative Medicines Initiative)

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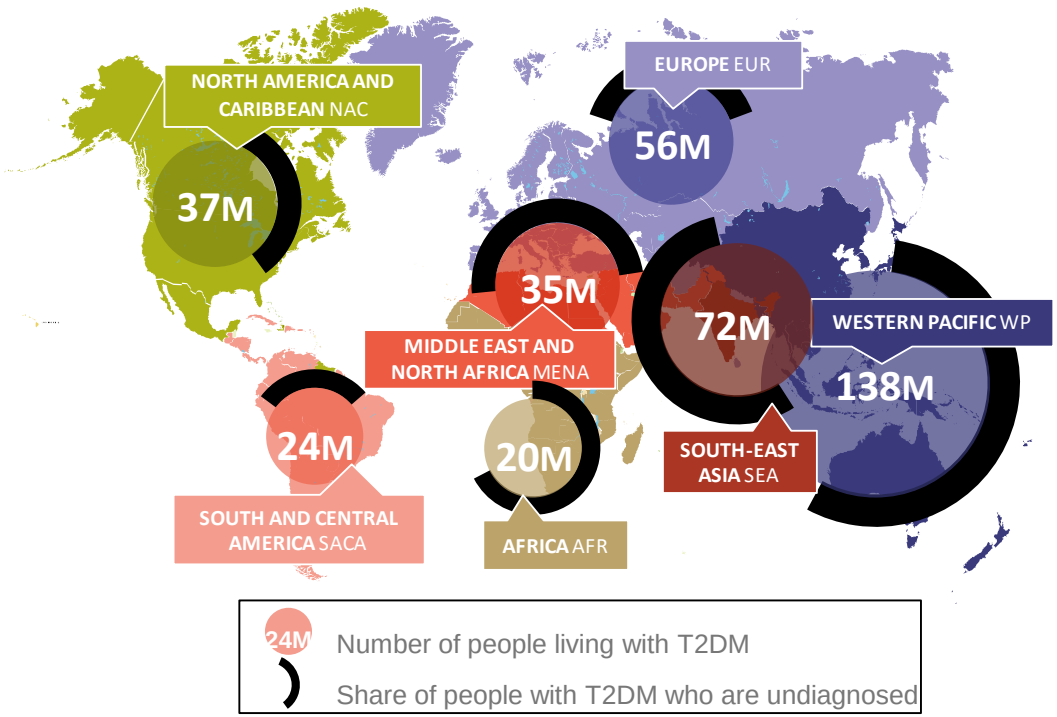
Diabetes: a worldwide epidemic, driven by affluence and ageing populations

380M people living with diabetes



Huge burden to society, with 550b$ spent globally on T2DM in 2012 (direct and indirect)

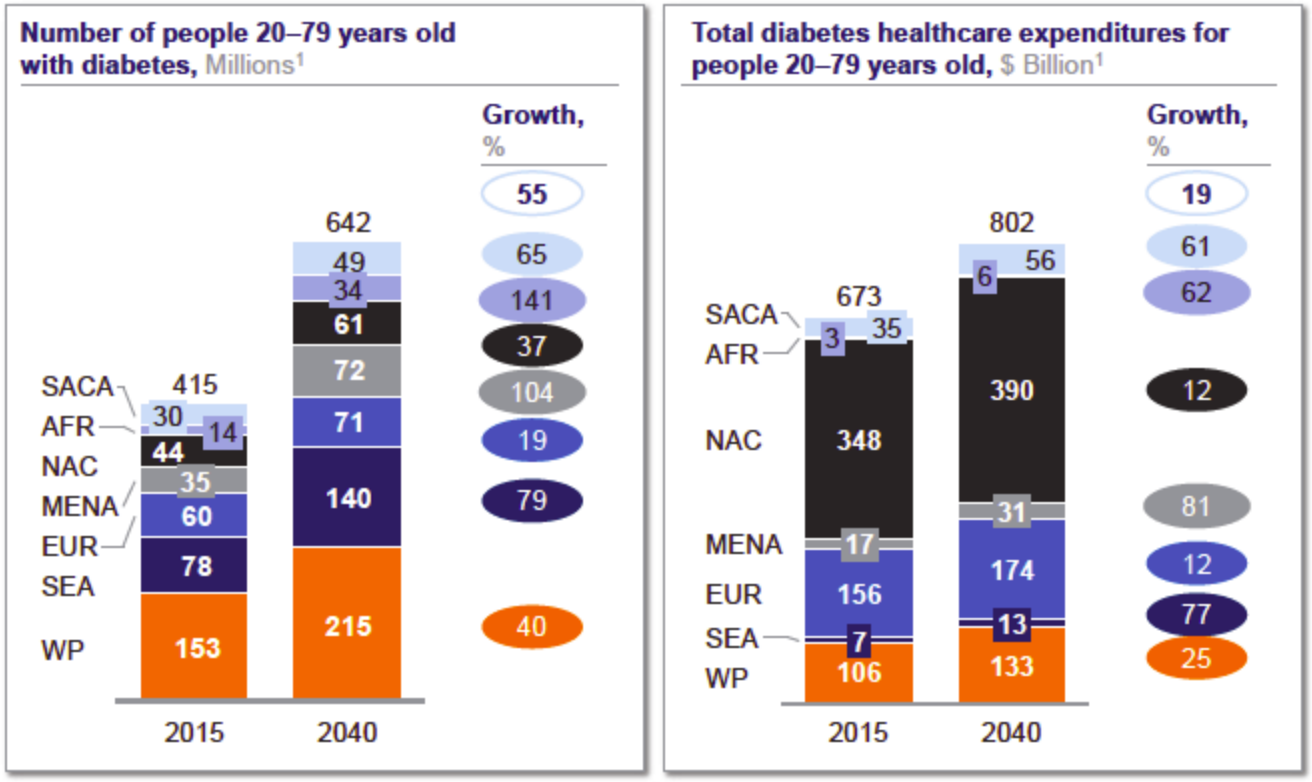
50% of diagnosed patients not treated, 50% of treated patients not controlled

Late stage complications increasing

- US prevalence & incidence of T2D complications up by 69% in 2010 vs. 2000

1. 2013 figures
Source: Sanofi

Diabetes will continue to affect all parts of the world



1 Figures may not sum, because of rounding. Regions: SACA: South and Central America; AFR: Africa; NAC: North America and Caribbean; MENA: Middle East and North Africa; EUR: Europe; SEA: Southeast Asia; WP: Western Pacific.
Source: *IDF Diabetes Atlas*, 7th edition, International Diabetes Federation, 2015

The simple view on Diabetes Disease manifestations

Obesity, lack of physical activity

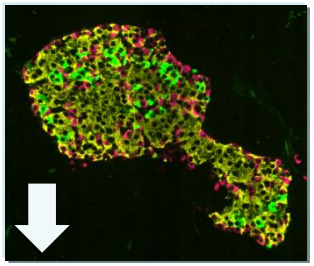
Reduced insulin sensitivity

Hyperinsulinaemia

β cell dysfunction

Progressive loss in β cell function & mass

T2DM



Breakdown of tolerance

Islet autoantibodies, epitope spreading

Progressive loss of β cells & dysfunction

Disease manifestation at ~ 70 % β cell loss

T1DM

β cell status diversity at disease manifestation

- 80 % of obese individuals do not develop hyperglycemia, impaired glucose tolerance..
- Genetic defects and environmental factors underlying disease manifestation

- High variance in onset & disease progression
- Genetic defects, diabetogenic triggers, exposure to antigen(s), dysfunctional immune tolerance drives disease manifestation

In the United States, life time risk of diabetes for people above 20 years of age is 40%, and patients live longer with their disease

Life-years spent with diabetes are increasing

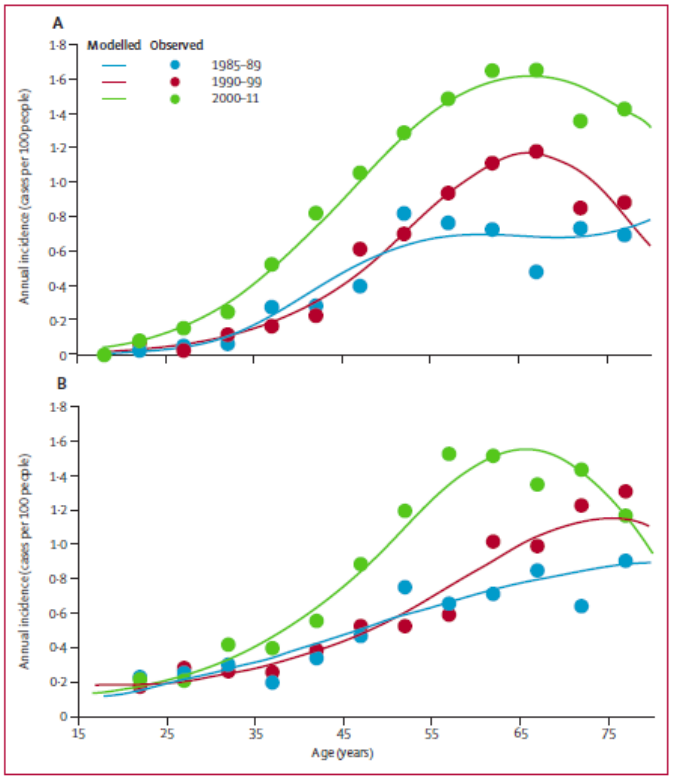


Figure 1: Incidence of diagnosed diabetes in the USA in men (A) and women (B), by age and decade: the National Health Interview Survey, 1985–2011

Life-years lost to diabetes are decreasing

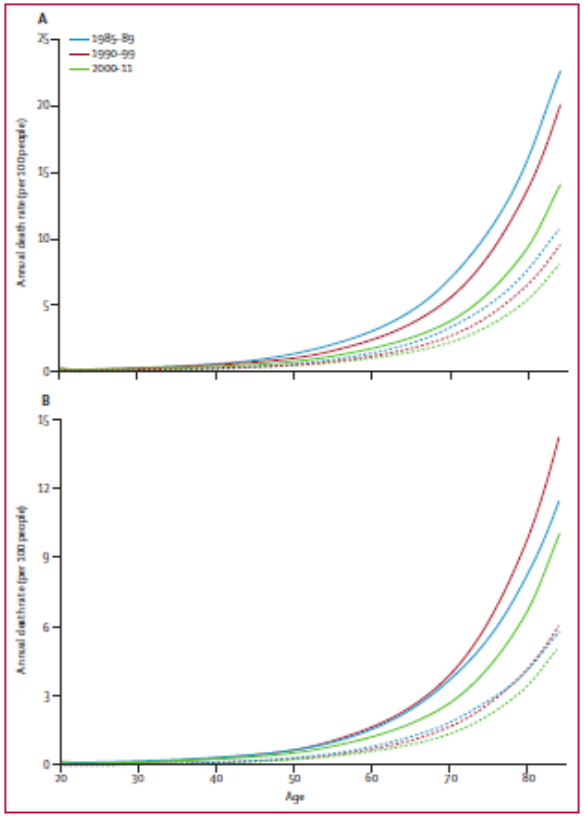


Figure 2: All-cause mortality in the USA in men (A) and women (B) with and without diagnosed diabetes, by age, decade, and sex: the National Health Interview Mortality Follow-up Survey, 1985–2011
Solid lines represent population with diagnosed diabetes; dashed lines represent population without diagnosed diabetes.

Life expectancy for diabetes patients is improving but there is still room for improvement

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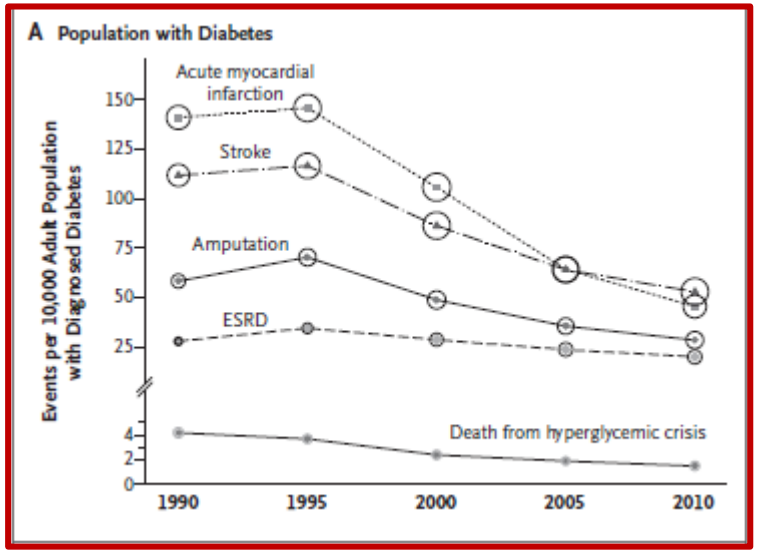
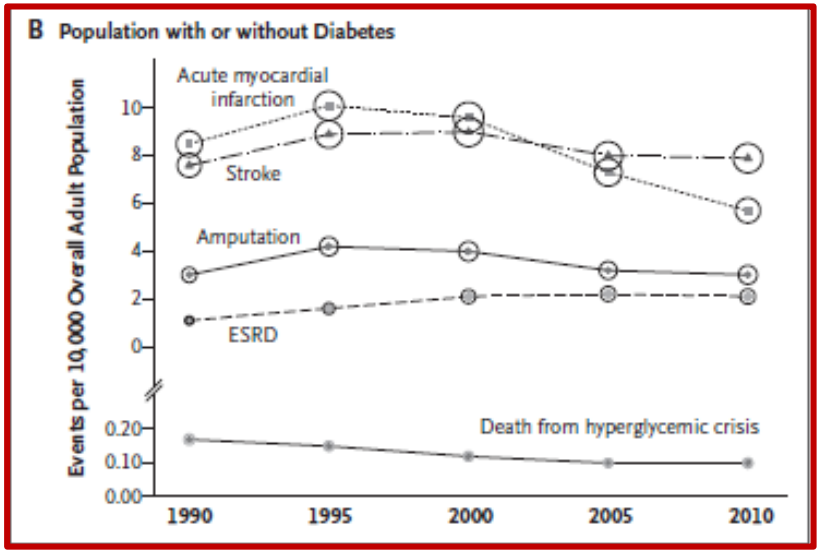
Gregg et al. 2014 Lancet Diabetes Endocrinology **2**:867-874

imi

Despite clear improvements of Diabetes Care there is still room for improvements





Circle size is proportional to the absolute number of cases

Gregg et al., 2014 NEJM **370**:1514-1523

Existing Diabetes Medications Address Glucose very well, but has little impact on Diabetes Related Co-morbidities

- Existing unmet needs in Diabetes Care
  - Renal disease
  - Non Alcoholic Steatohepatitis
  - Cardiovascular disease
  - Peripheral vascular disease
  - Obesity
  - Tackle root cause of disease(s)
  - Adherence to existing therapies

Lack of fundamental insights to the complex biology underlying these conditions block innovation opportunities in the field

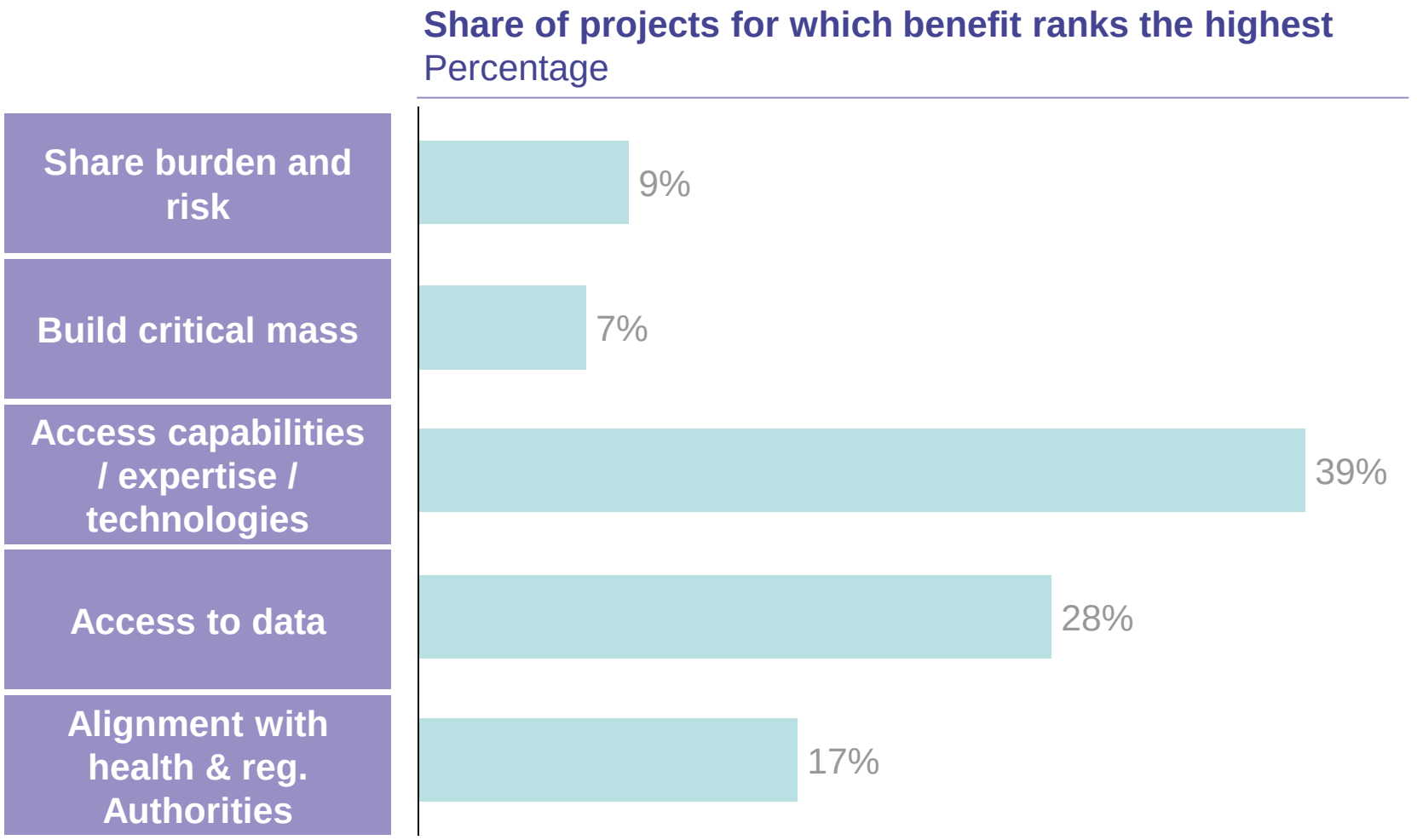
Can industry incentivize breakthrough research in specific fields of interests?

PUBLIC PRIVATE PARTNERSHIPS IN SUPPORT OF BIOPHARMACEUTICAL RESEARCH

Global Biopharmaceutical Public Private Partnership landscape

CPI	Critical Path Initiative
CDISC	Clinical Data Interchange Standards Consortium
DNDi	Drugs for Neglected Diseases initiative
AMP	Accelerating Medicines Partnership
IMI	Innovative Medicines Initiative

Drivers for value generation in PPPs
Internal Sanofi survey

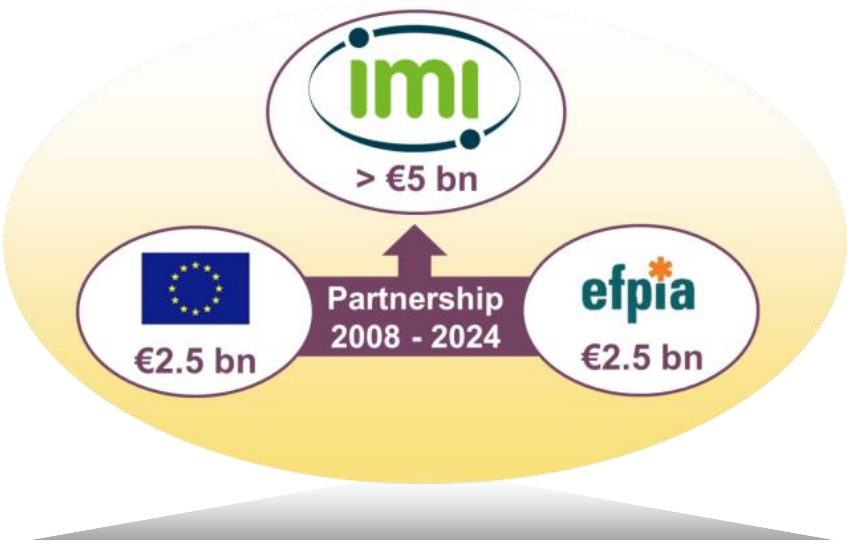


The Innovative Medicines Initiative (IMI) is the largest Public-Private Partnership (PPP) in the global healthcare sector

Architecture and principles

- Research topics developed **by EFPIA**
- Companies invest **with own FTE**
- Public partner‘s selection is **highly competitive**
- Projects are mainly in the non-competitive space but IP framework allows **expansion in competitive area**
- IMI organization serves as **neutral platform**
- **Consensus-driven joint leadership** by EFPIA and public leader

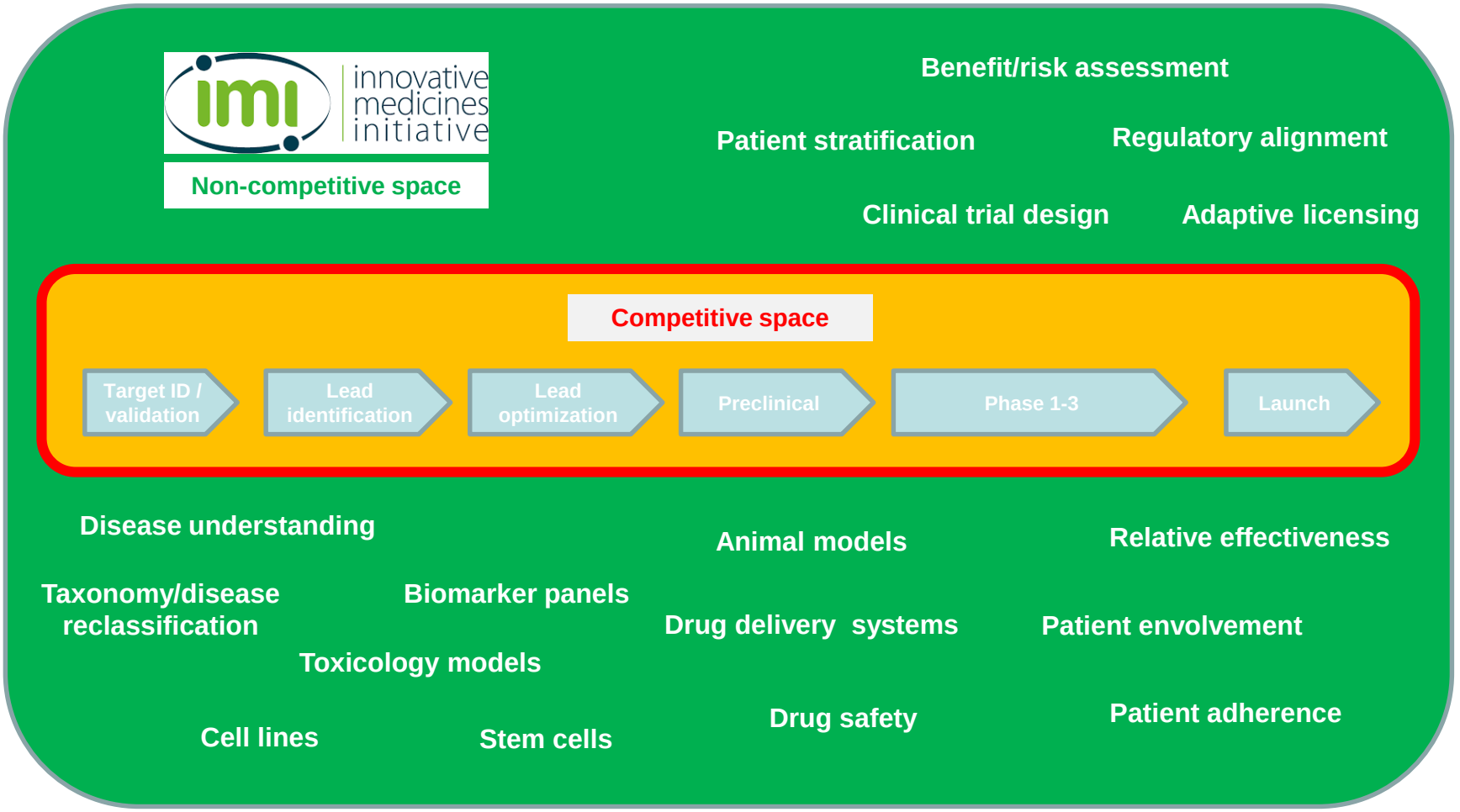
Partnership between EFPIA and the European Comission



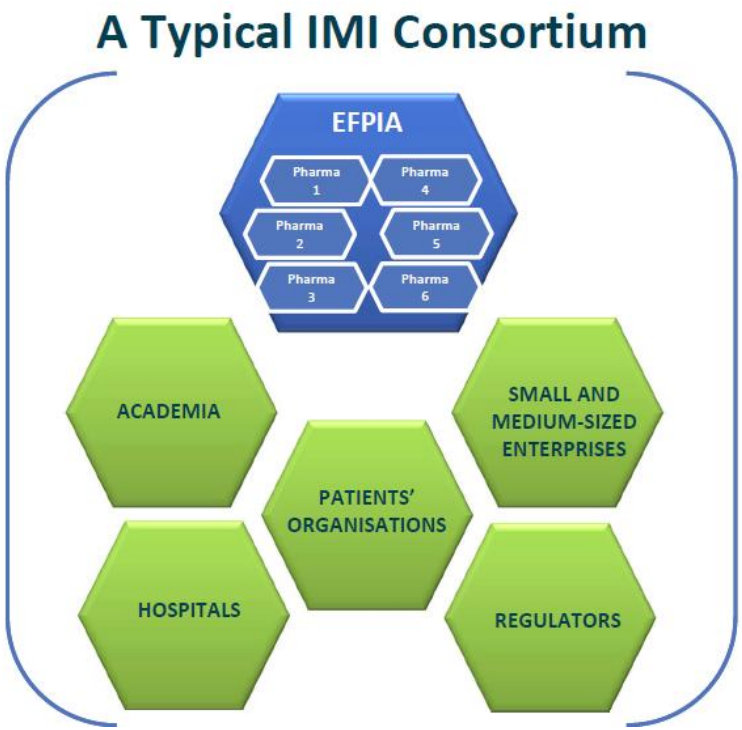
IMI 1		IMI 2
2008-2013[1]	+	2014-2024
€2bn		€3bn

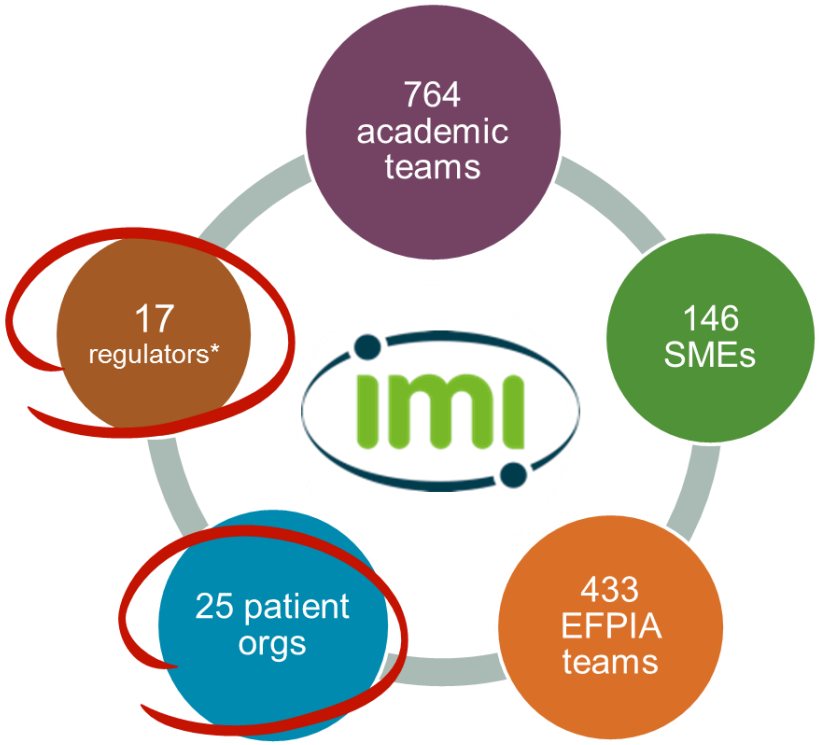
IMI projects are mainly in the non-competitive space

based on IMI 2 Strategic Research Agenda



IMI success involving the key stakeholders in pharma R&D





* e.g. EMA, FDA, national agencies, ECDC

IMI projects meet the objectives and have started to deliver

EFPIA expectations towards IMI scientific deliverables

- **Direct support for EFPIA pipelines**
  - access to innovative screening libraries
  - validated predictive biomarkers
  - validated disease models (in-vitro/in-vivo)
  - innovative drug delivery systems
  - patient stratification
- New safety testing paradigms
- Improved disease understandind and taxonomy
- Better clinical trials and new regulatory pathways
- Improved benefit-risk assessment methods and tools
- Anticipation and rapid reaction towards significant public health threats
- Publications with high citation impact

IMI projects are delivering, examples:

imidia
- First human beta cell validated by 4 pharma companies
- Validation platform for Biomarkers, Drug Targets and Functional Disease Models in place

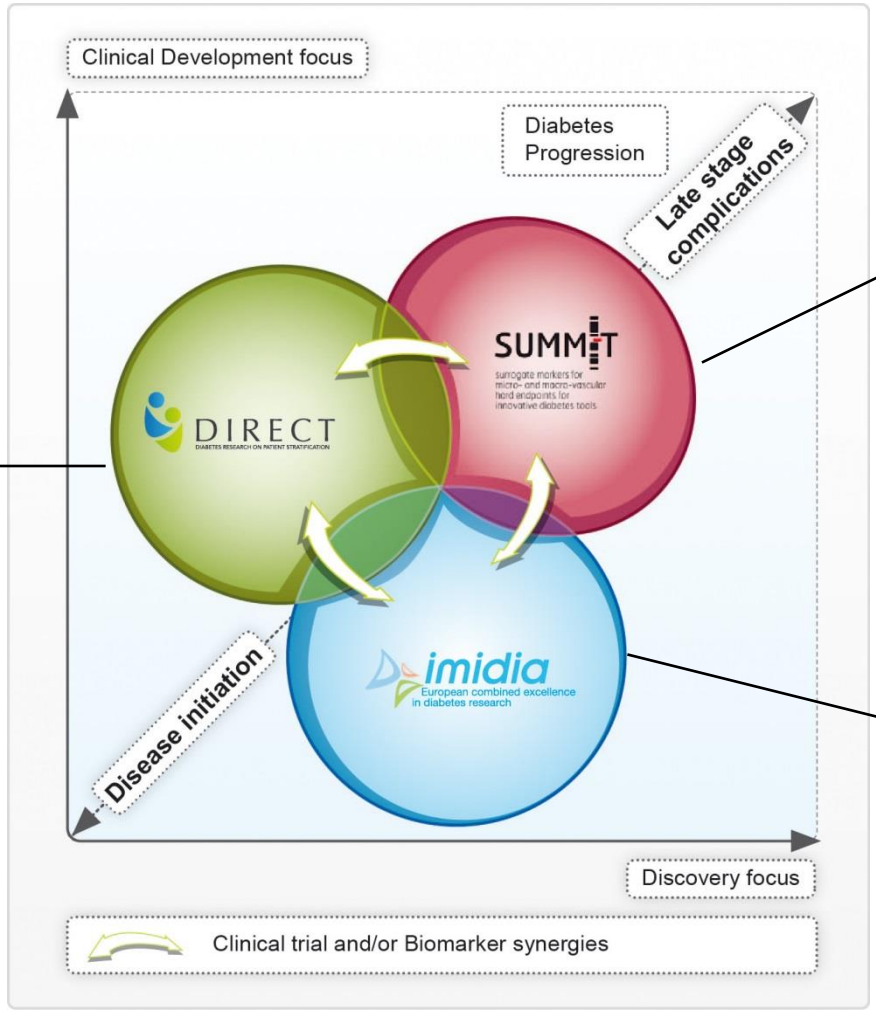
SUMMIT
- Biomarker panel of rapid chronic kidney disease progression in T2D avilable and published
- New knock-out mouse model for advanced atherosclerosis in T2D available

COMPACT
- Sanofi development compound (mouse version) within the project to test the Drug delivery across the BBB
- Fish sarcoplasmic proteins (FSP) as novel insulin carriers

EUROPEAN LEAD FACTORY
- 8 screens of Sanofi targets screened on innovative on Sanofi sites
- Chemical matters identified promising and under evaluation

PROTECT
- Implementation of benefit-risk methods in Sanofi to assess^medicines in restricted group and real-life context

IMI1 programs in Diabetes



Patient stratification

Models and biomarker candidates

Tools and models, Focus on ß-cell

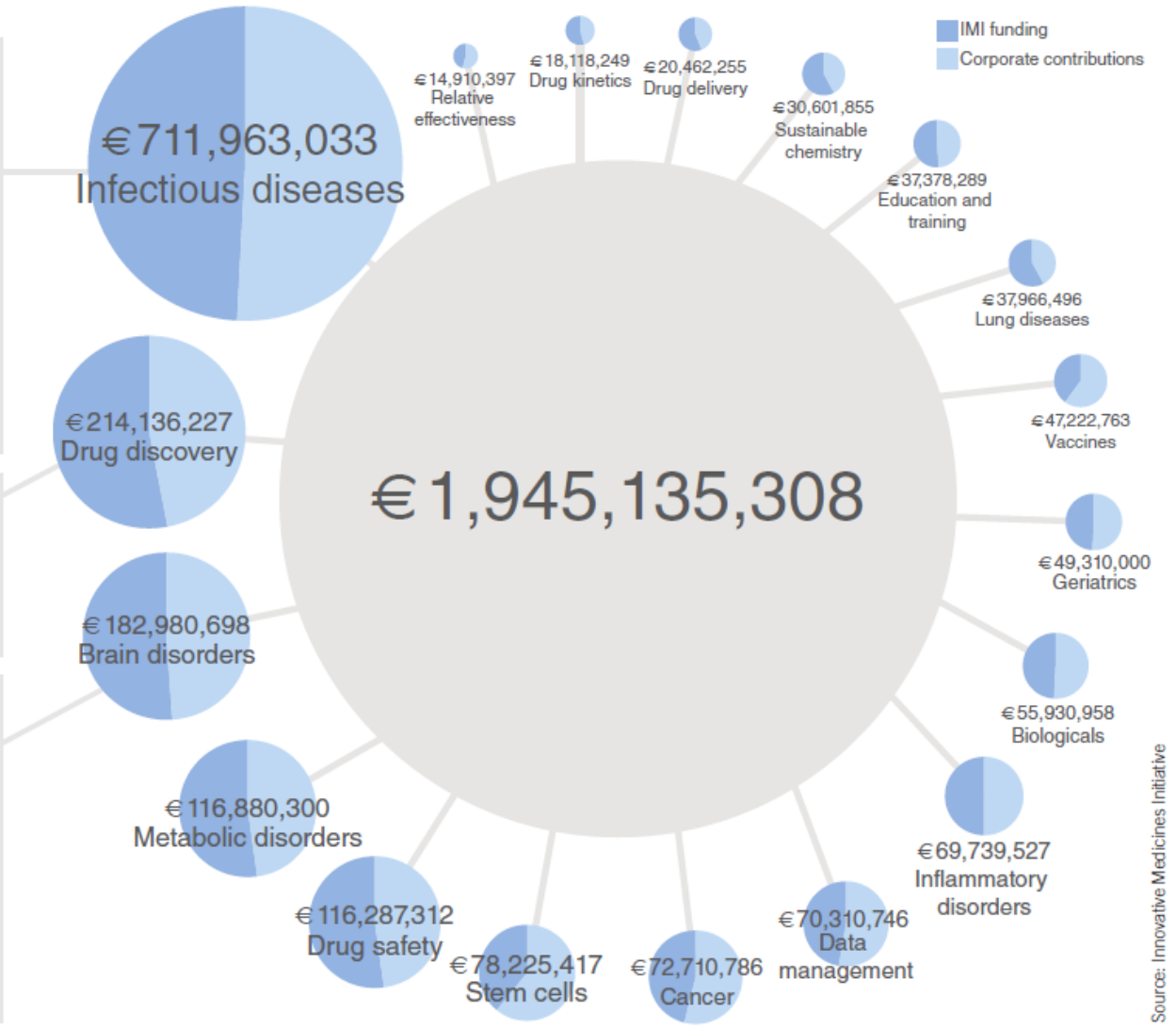
Total budget spent in IMI 1 on indication/topic

Partners

AiCuris	GSK
Animal Health	**Janssen**
Division of Sanofi	Johnson & Johnson
Astellas	**MedImmune**
AstraZeneca	Merck
AstraZeneca/	**Merck Sharp &**
MedImmune	**Dohme**
Basilea	Merial
Boehringer	**Novartis**
Ingelheim Animal	Pfizer
Health	**Rempex**
Cubist	Sanofi

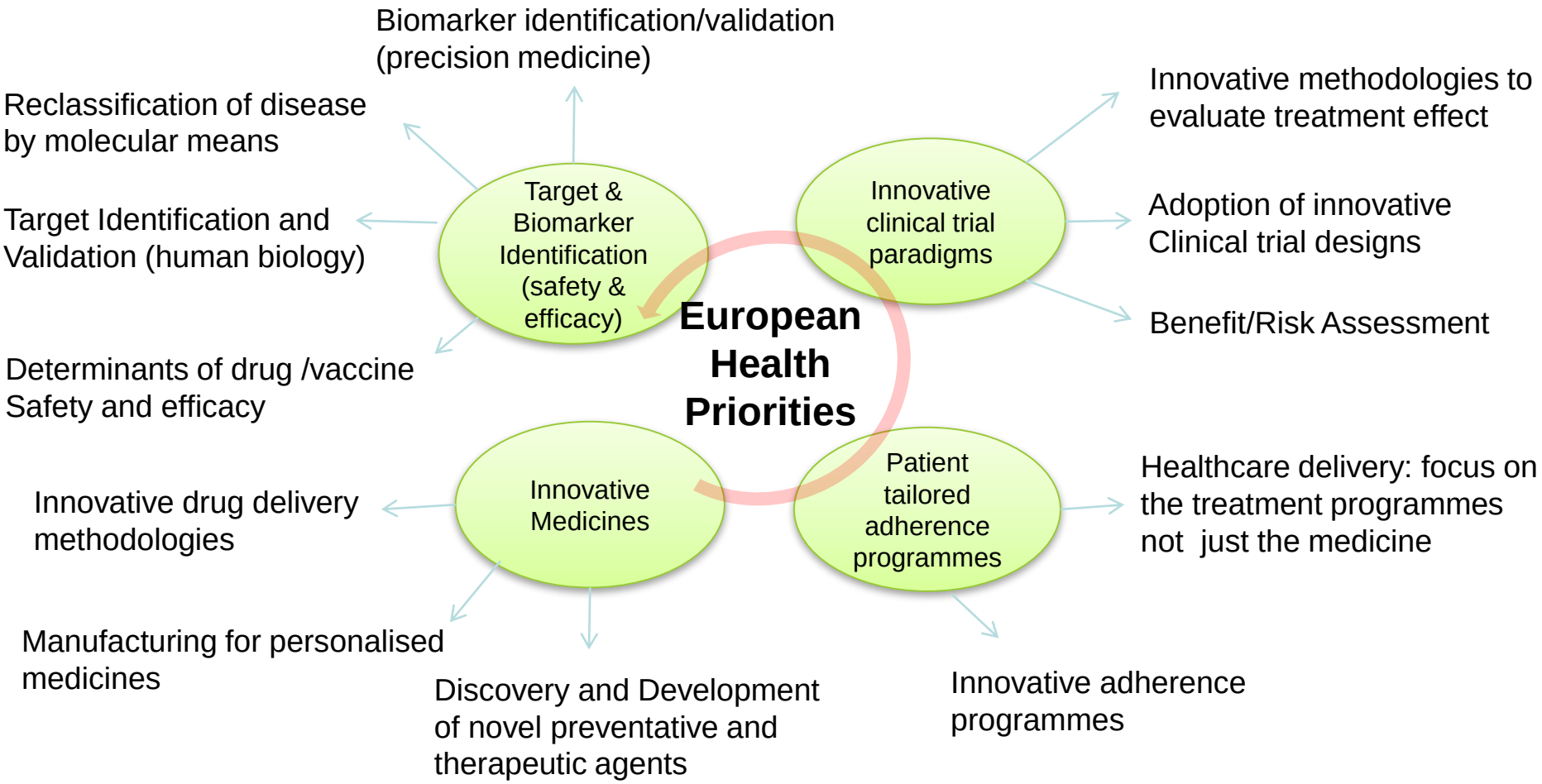
AstraZeneca	**Novartis**
Bayer	Pfizer
Janssen	**Sanofi**
Lundbeck	UCB
Merck	

Abbott	**Eli Lilly**
AbbVie	Esteve
AC Immune	**GRT**
Amgen	GlaxoSmithKline
Astellas	**HLU**
AstraZeneca	IDRS
Biogen Idec	**Janssen**
Boehringer	Lundbeck
Ingelheim	**Merck**
Eisai	



Source: Innovative Medicines Initiative

IMI2 Strategic Research Agenda: A flexible broad framework for 10 years



Drive change in delivery of medical practice

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Following IMI 1, partnership was renewed and reinforced through to 2024 with IMI 2

Key changes in IMI 2 vs IMI 1

Focus of following page

Strategy	• Definition of **seven strategic axis** where EFPIA companies determine strategy and portfolio (**Strategic Governing Group** (SGG) concept)
Scope	• Extension from “Drug Development” to “**Delivering Healthcare solutions**” • Focus on the “**last mile**” : Engage authorities on **access and delivery** (HTA, pricing, outcomes…)
Participation	• Extension to **tech providers** e.g. Siemens, General Electric, Google, IBM
Budget	• **Increase of overall budget** to 3bn€ from 2 bn€ in IMI 1
Global focus	• 500 Mio€ in-kind **contribution from non-EU regions** (EFPIA and partners contribution)

IMI 2 strategic approach - Strategic Governing Groups (SGG)
Strategic decision making within the disease areas

1. Strategic approach for selected disease areas

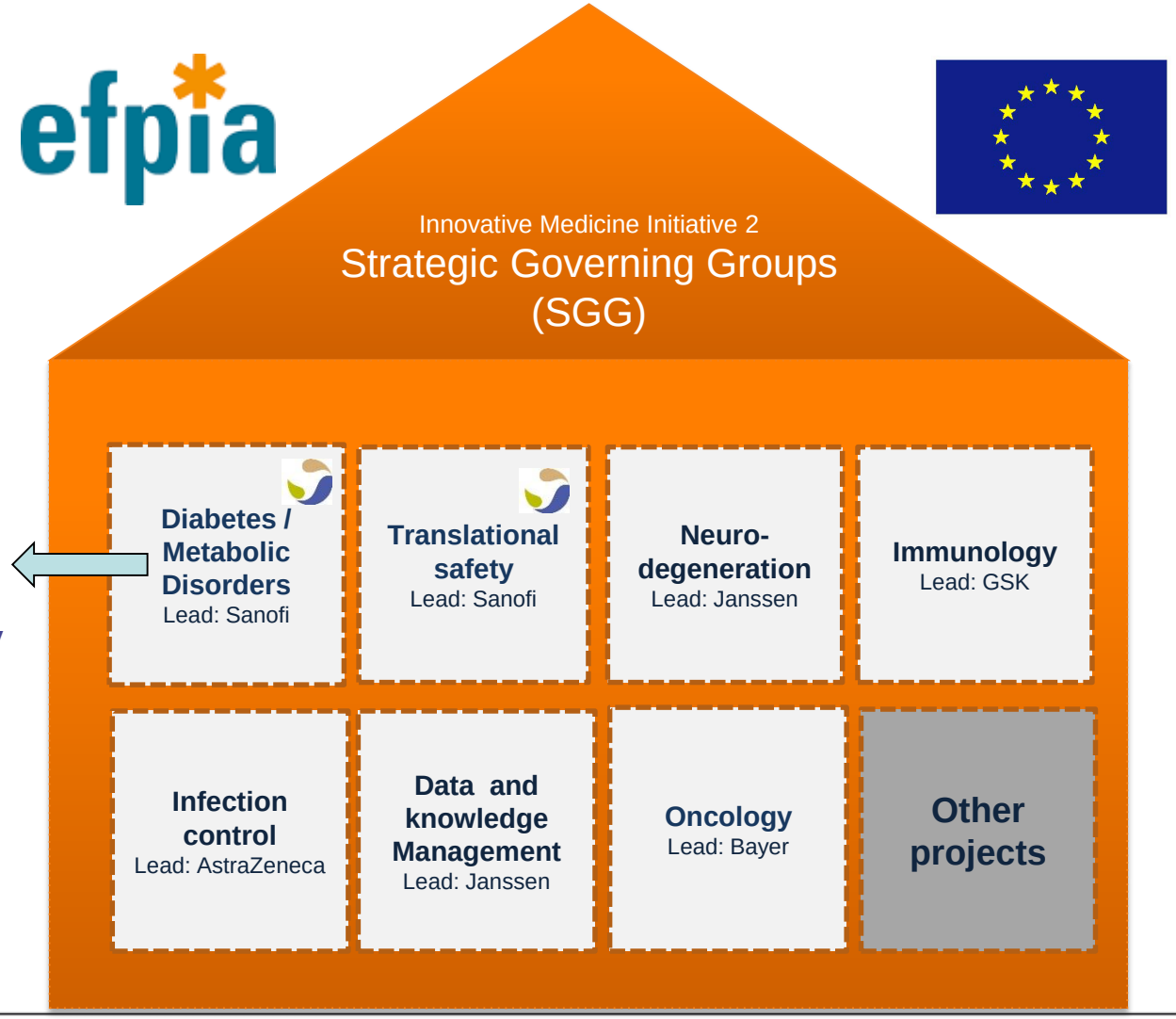
2. Understand and react to strategic gaps

3. Harvest synergies across projects and other PPPs

4. Drive extension of projects towards application

5. Companies are represented by senior expert leaders

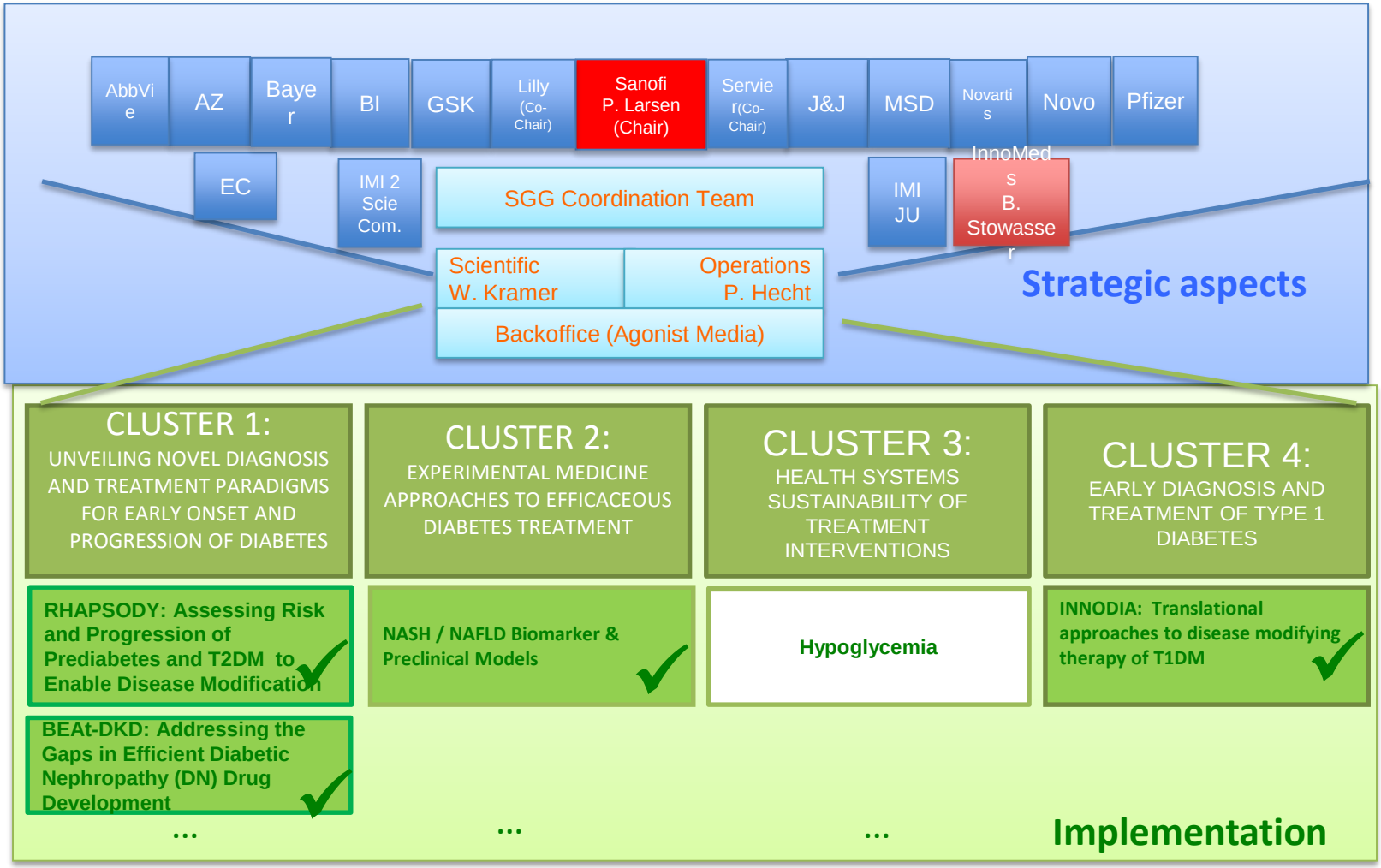
IMI 2 Strategic Governing Groups (SGG) established to date



„Tackle all phases of diabetes and its complications, including prevention and early interception.“

Current set-up of the SGG Diabetes/Metabolic disorders

Strategic Governing Group
Diabetes / Metabolic Disorders



Pipeline of strategically aligned projects in diabetes

Strategic Governing Group
Diabetes / Metabolic Disorders

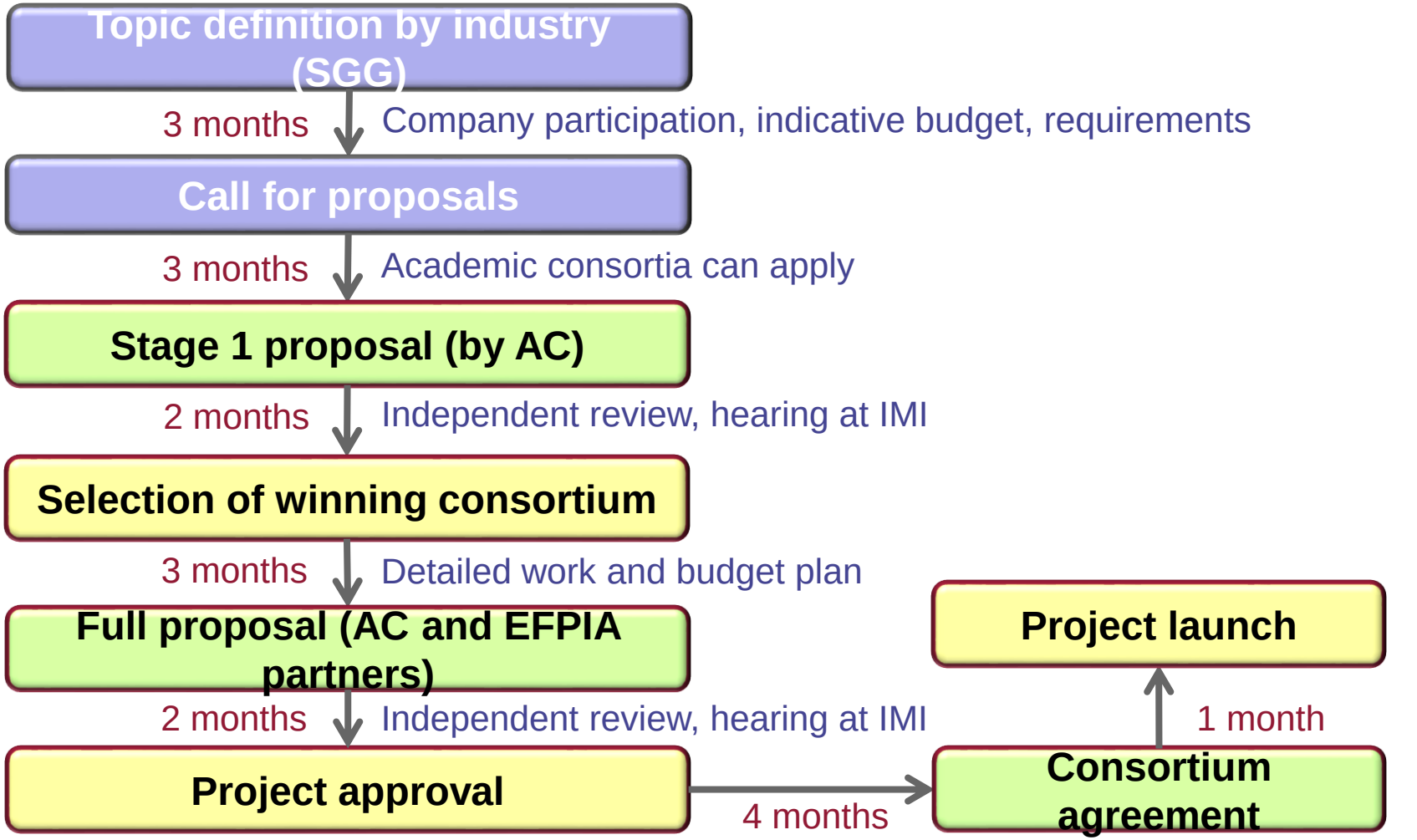
Title	Focus	Status	Budget (Mio)	Leader , Co-Leader Participating / Companies	# of Public Partners
INNODIA	Translational approaches to disease modifying therapy of **type 1 diabetes**	Project Started: 1 Nov 2015	35,26	Sanofi, **JDRF**, GSK, Lilly, Novo, Hemsley	27
RHAPSODY	Translational progression of Biomarkers to asses the **risk and progression of pre-diabetes and type 2 diabetes (T2D**) to enable disease modification	Project Started: 1 April 2016	14,5	Servier ,**Sanofi**, JnJ, Novo	22
BEAt-DKD	Identification and validation of candidate biomarkers and/or biomarker panels for enhanced understanding of key driver pathways that accelerate progression of **Diabetic kidney disease** in type 1 and type 2 diabetes patients	Full Project Proposal approved – start Q3/Q4 2016	28,55	AbbVie, **Sanofi**, Bayer, Lilly, MSD, JDRF	24
NASH / NAFLD	Predictive Biomarkers **for NAFLD (Non Alcoholic Fatty Liver Disease) and NASH (Non Alcoholic SteatoHepatitis**) for diagnosis staging and disease tracking	Application of academic partners currently ongoing - start Q2 / Q3 2017	31,64	MSD, **Pfizer**, BI, Lilly, Novo, Novartis, Sanofi, Somalogic, Ellegaard	tbd
Hypoglycemia	Understanding hypoglycaemia: underlying mechanisms, and addressing clinical determinants and consequences for diabetes patients by utilizing big data	Call topic in preparation for launch in Q3 2016	Est 20 – 25	Novo, Lilly, Sanofi, JDRF Abbott, Medtronics,	tbd

A few simple questions asked by IMI2 SGG

- What makes people develop type-2 diabetes?
- How to run a clinical trial in type-1 diabetes?
- In patients with diabetes, who is likely to develop diabetic kidney disease?
- How can NASH be diagnosed without a biopsy?

We don‘t know but should try to find out.

How an IMI2 project is set up



Ongoing and initiated IMI2 projects

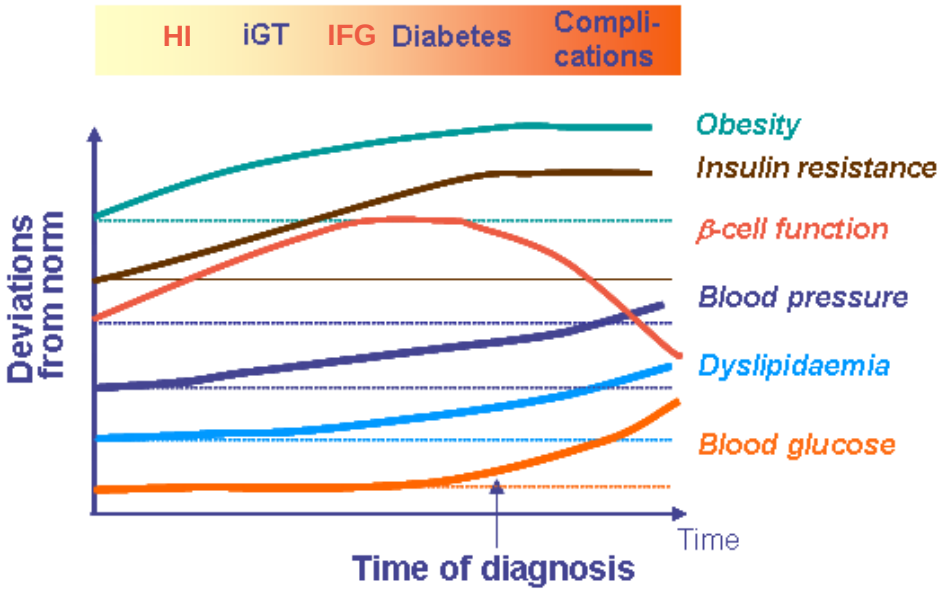
RHAPSODY
for precision therapy and prevention of diabetes

INNODIA

BEAt-DKD

imi nafld

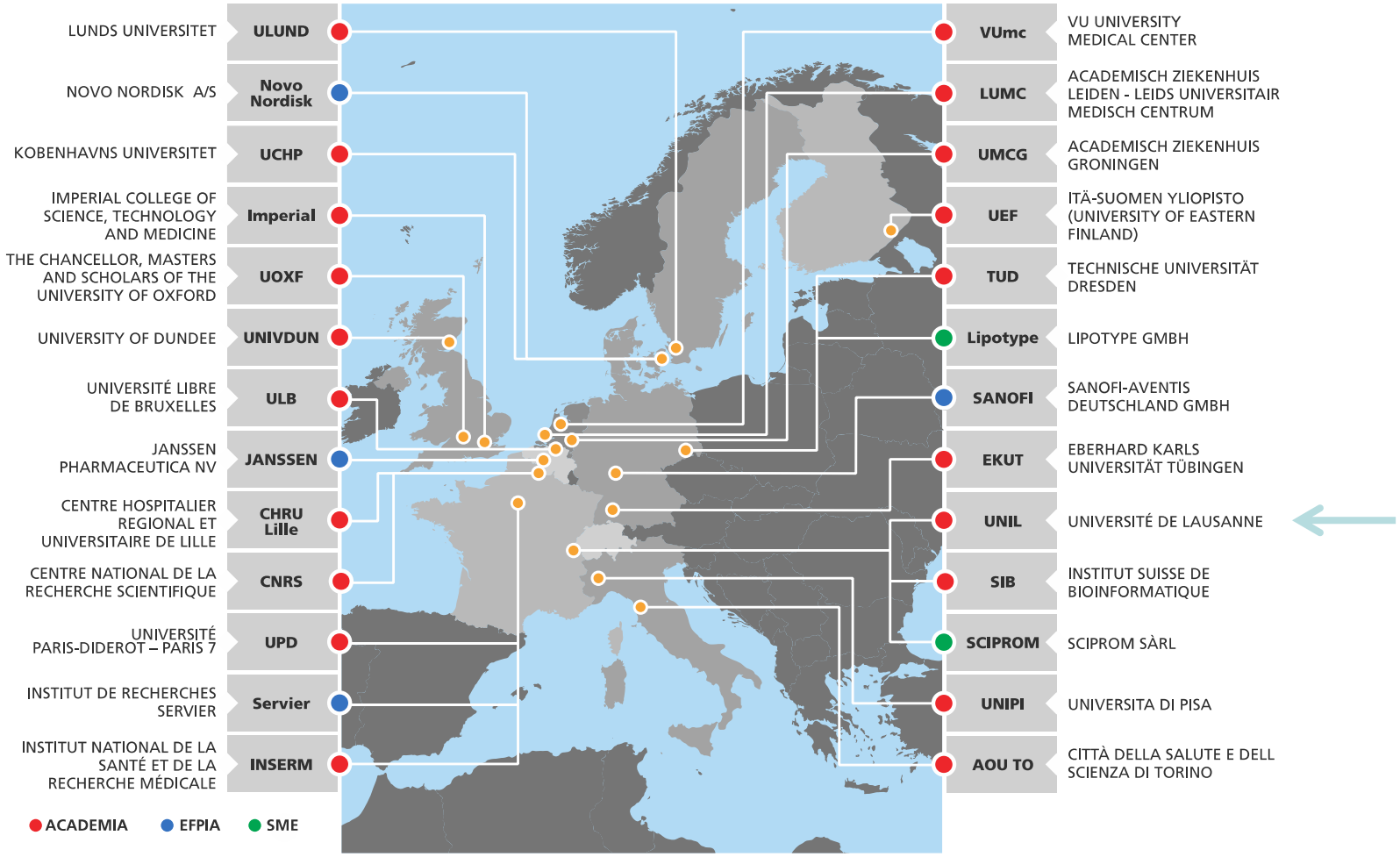
IMI2 RHAPSODY: problem statement



- T2D as a heterogeneous disease
- Factors leading to insulin resistance or beta-cell failure not understood on molecular level
- No robust circulating markers for insulin resistance and islet dysfunction

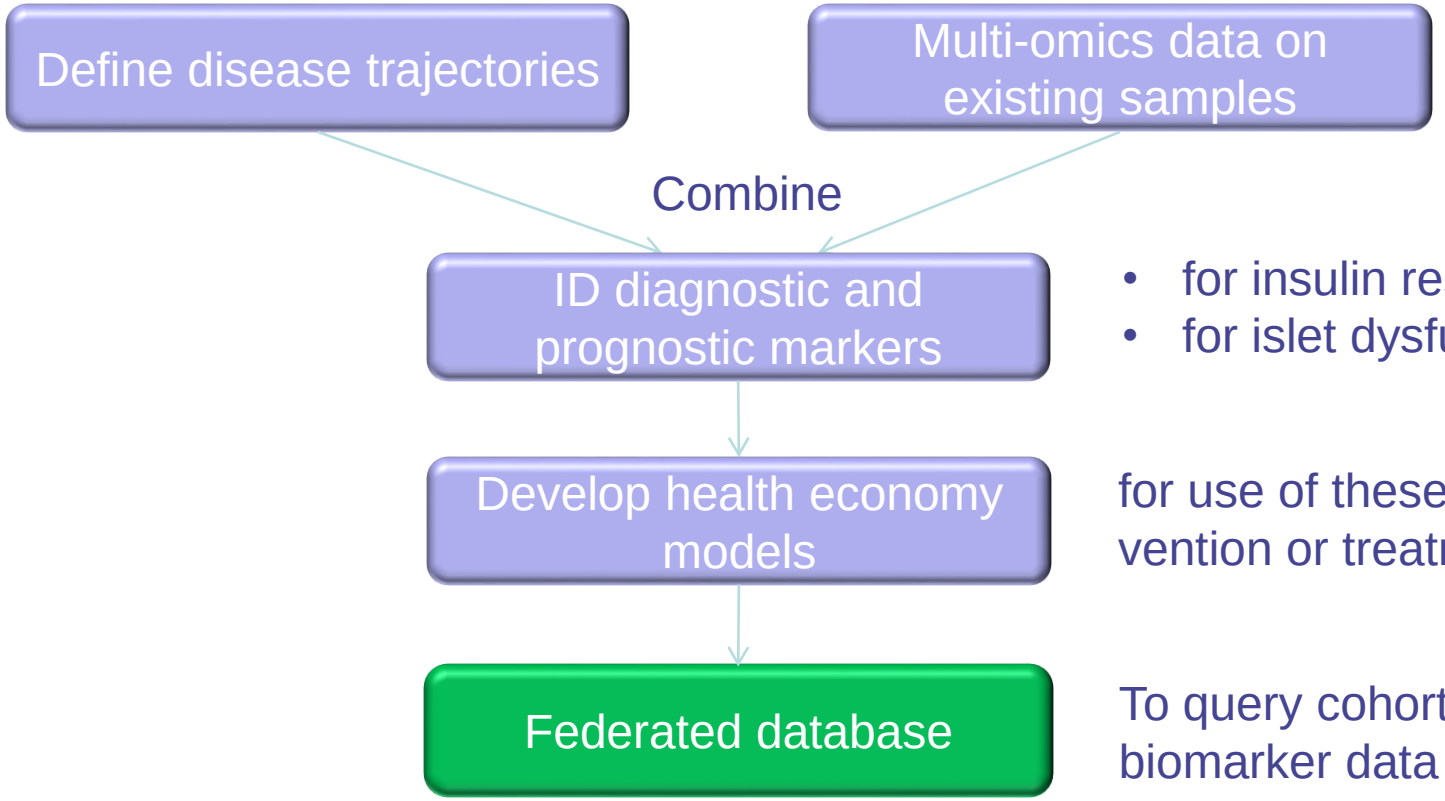
- **Goal: define a molecular taxonomy of T2D to support patient segmentation and clinical trial design for novel strategies to prevent and treat diabetes**

RHAPSODY consortium partners



RHAPSODY for precision therapy and prevention of diabetes

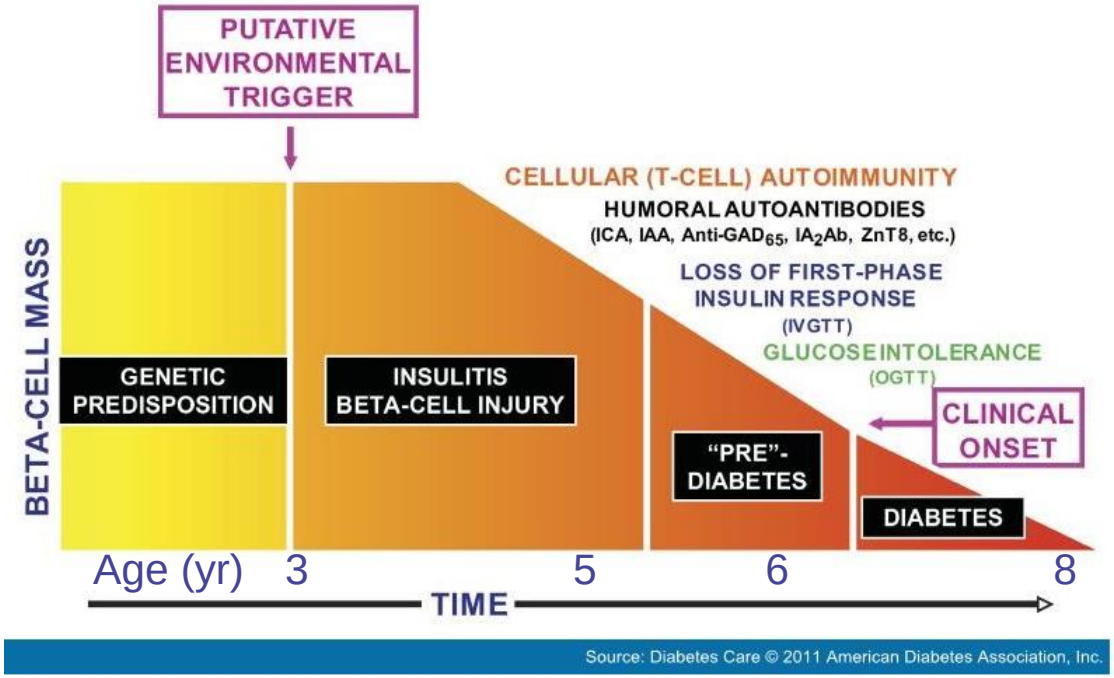
- Total budget 14.6 M€, Sanofi 1.6 M€ (in-kind), 4 years from April 2016
- Specific objectives



What makes RHAPSODY unique?

1. Composed of academic and pharma partners with long-standing expertise and relationships build in IMI-1 projects (IMIDIA, SUMMIT, DIRECT).
2. Interface to DIRECT as a unique opportunity for biomarker replication
3. Strong empasis on two components of T2D: islet biology and insulin resistance
4. Covers additional aspects not addressed elswhere:
   health economic and **regulatory paths** to move biomarkers forward
5. Establishment of a federated database as a ‘role model’ not only to link cohort data but also databases of other IMI projects.

INNODIA: Problem statement



- What is triggering beta-cell autoimmunity?
- When should treatment commence?
- Which patients should be treated?
- How to determine functional beta-cell mass?

- Goal: develop an EU infrastructure recruiting and analysing a cohort of newly-diagnosed T1D patients and family members, generating a bioresource to improve T1D clinical trial design.

INNODIA: Consortium partners

Project Leader	Deputy Project Leader	Deputy Coordinator	Coordinator	Consortium Manager
Sanofi, Werner Kramer	JDRF, Dick Insel	University Cambridge, David Dunger	KU Leuven, Chantal Mathieu	Sanofi S&I, Thorsten Strube

EFPIA (n=4) /Associated partners (n=2)

Sanofi, GSK, Novo, Lilly,

JDRF, Helmsley Charitable Trust

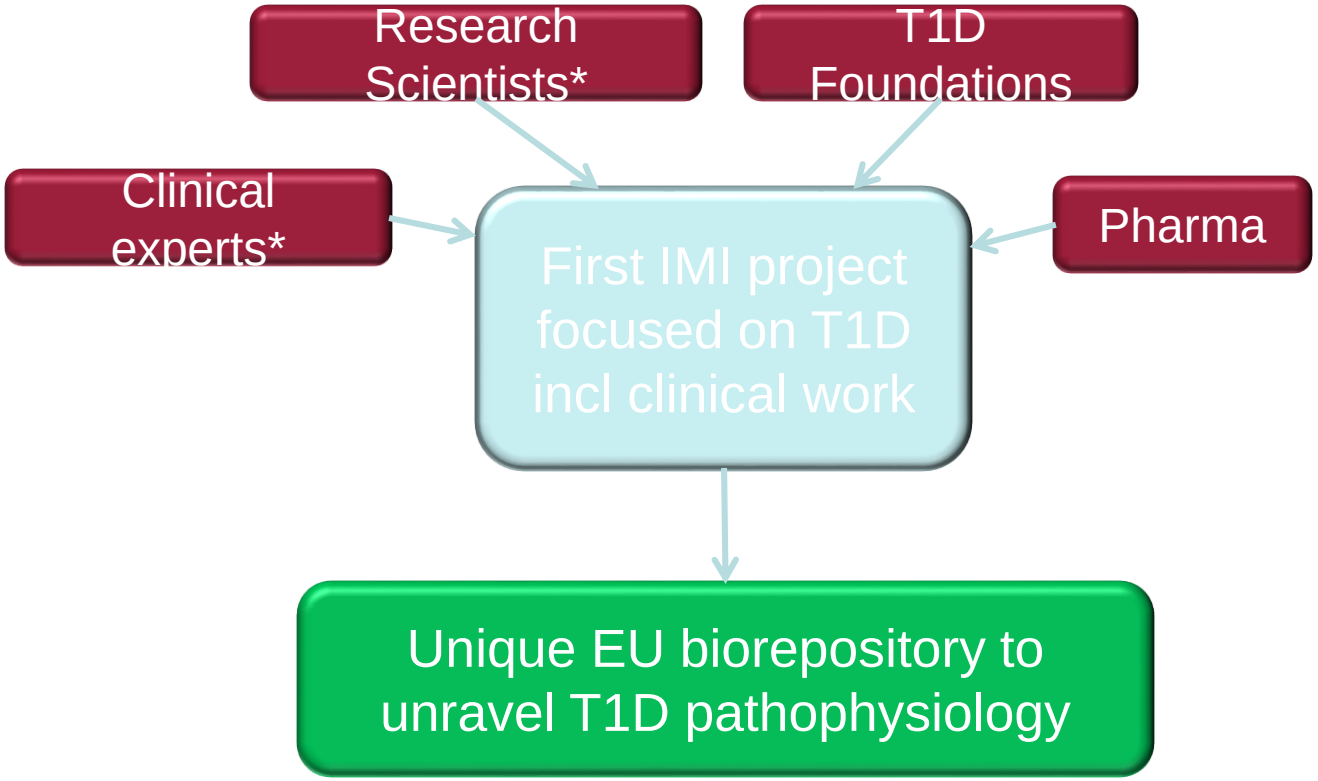
Key public/academic partners (n= 27)

KU Leuven, University of Cambridge, Université Libre de Bruxelles, INSERM, King's College London, Université de Lausanne, Università degli Studi di Siena, Helmholtz Zentrum München, Helsingin Yliopisto, Medical Research Council UK, Herlev University Hospital, SARL Endocells

INNODIA: An innovative approach towards understanding and arresting Type 1 diabetes

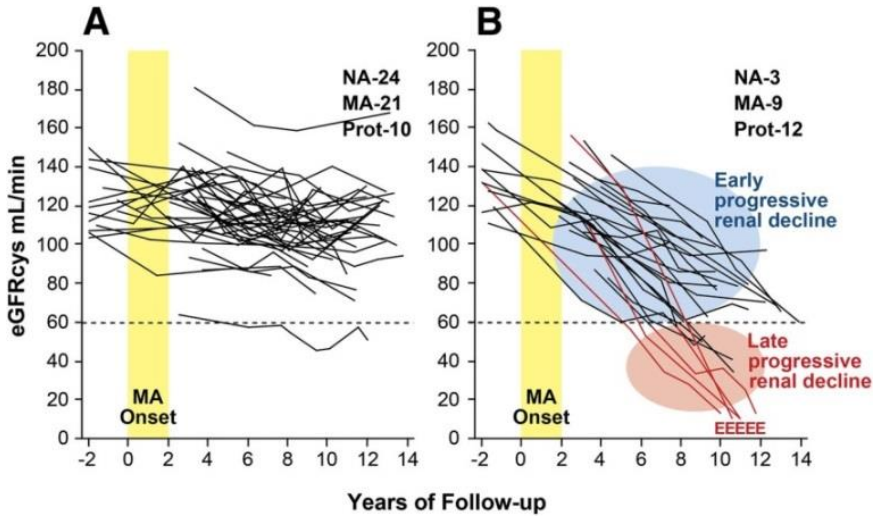
- Total budget 35.3 M€, Sanofi 8.4 M€ over 7 years
- Specific objectives:
  - **Recruit up to 5,000 newly diagnosed and at risk T1D subjects.**
  - **Establish collaborative network to address the knowledge gap in β-cell autoimmunity**
  - **Develop and apply novel methodologies in bio-resource and 'omics' technologies.**
  - **Establish unique integrated database assimilating historical data, with clinical and experimental data.**
  - **Conceive innovative clinical trial designs using novel validated biomarkers leading to shorter and focused intervention studies**

INNODIA: What is unique?



*Islet biologists and immunologists in one team!

Problem statement



- Diabetes primary cause of kidney failure
- Lack of biomarkers to predict disease progression and monitor drug response
- Standard of care has remained unchanged for >10 years: RAAS blockade

- Goal: Identify and validate biomarkers of DKD progression and treatment response, provide a systems medicine view of the pathogenesis of DKD

A Krolewski, Diab Care 2015

BEAT-DKD consortium partners

7 Pharma companies + JDRF

23 Academic Institutions

1 SME

Lead: Abbvie (D. Andress)
Co-Lead: Sanofi (A. Kannt)

Coordinator: U. Lund (M. Gomez)
Vice-Coordinators:
UMC Groningen (D. de Zeeuw)
U. Helsinki (H. Holthöfer)

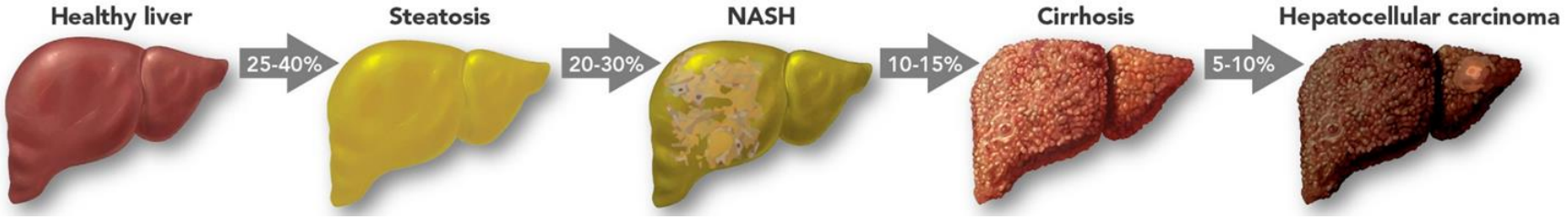
Project Management: U. Lund (J. Postma), Sanofi (B. Jablonka), Abbvie (R. Ebersbac

- Project was approved by the European Commission in June 2016
- Consortium agreement to be negotiated by September 2016

BEAt-DKD: Biomarker Enterprise to Attack Diabetic Kidney Disease

- Budget: 30 M€, Sanofi 2.8 M€, five years from September 2016
- Specific objectives:
  - Integrate data and samples from existing observational and intervention cohorts of diabetes patients with various degrees of DKD
  - Extend existing prospective (longitudinal) cohorts by N>500
  - Identify, validate and qualify novel circulating, urinary or imaging BMs to predict disease progression
  - Identify predictor biomarkers of safety outcomes (e.g. cardiovascular) in DKD patients
  - Identify Mechanisms and Pathways that can be targeted to treat DKD
  - Develop renal imaging technology, validate against reference measurements (biopsy)

IMI2 NASH: problem statement



Fat deposition in liver

Fat plus inflammation, scarring

Scar tissue replaces liver cells

- Prevalence sharply increasing in parallel with obesity and T2D
- „Silent“ disease, biopsy needed to confirm diagnosis

- **Goal: establish and validate non-invasive markers for classifying and evaluating subjects with NAFLD, and to predict rate of disease progression**

- 8 pharma companies, indicative budget 30 M€, call topic published April 20, 2016

Does it pay off? IMI1 has started to deliver…

Journal of Diabetes Research

Animal Models of Diabetic Macrovascular Complications: Key Players in the Development of New Therapeutic Approaches

http://www.kidney-international.org

Biomarkers of rapid chronic kidney disease progression in type 2 diabetes

Diabetes, Obesity and Metabolism 18: 6–15, 2016.

Pancreatic β-cell imaging in humans: fiction or option?

Biomaterials 75 (2016) 1–12

Multivalent glibenclamide to generate islet specific imaging probes

Heilkron [a], [d],

The Journal of Clinical Investigation

Technical advance

Development of a conditionally immortalized human pancreatic β cell line

Raphaël Scharfmann,[1] Severine Pechberty,[1,2] Yasmine Hazhouz,[2,3] Manon von Bülow,[4] Emilie Bricout-Neveu,[2,3] Maud Grenier-Godard,[1,2] Fanny Guez,[1] Latif Rachdi,[1] Matthias Lohmann,[4] Paul Czernichow,[2] and Philippe Ravassard[3]

Does it pay off?

Ongoing IMI projects are meeting their pre-defined KPI

- **The majority of the projects provide the expected outcomes**
- **IMI has delivered on several KPIs that will strengthen innovation at Sanofi**
- **IMI also delivers intangible benefits**
  - Jump starting in new research areas
  - Establishing academic networks
  - Identify and assess potential collaborators
  - Talent Development

Selected KPI from ongoing IMI projects with Sanofi participation (Status Q2/2016)

- Biomarkers/Panels of biomarkers (8)
- New disease targets (5)
- Pre-Leads (2)
- New disease models (5)
- New patient stratifications (3)
- New regulatory guidelines (6)
- New clinical trial infrastructures (4)

- **Not trimmed to efficiency, but allow access to xx M€ projects by contributing x M€, primarily in-kind**

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THANK YOU