

# *Welcome to Evotec*

“Manfred Eigen Campus” in Hamburg





# Welcome to Hamburg!

Evotec SE Headquarter



## The roots

A red cube?

Site acquired from Eli Lilly in 2012

## The people

2012: 185 employees

2023: 760 employees

## The focus

CNS diseases

iPSCs

## The future

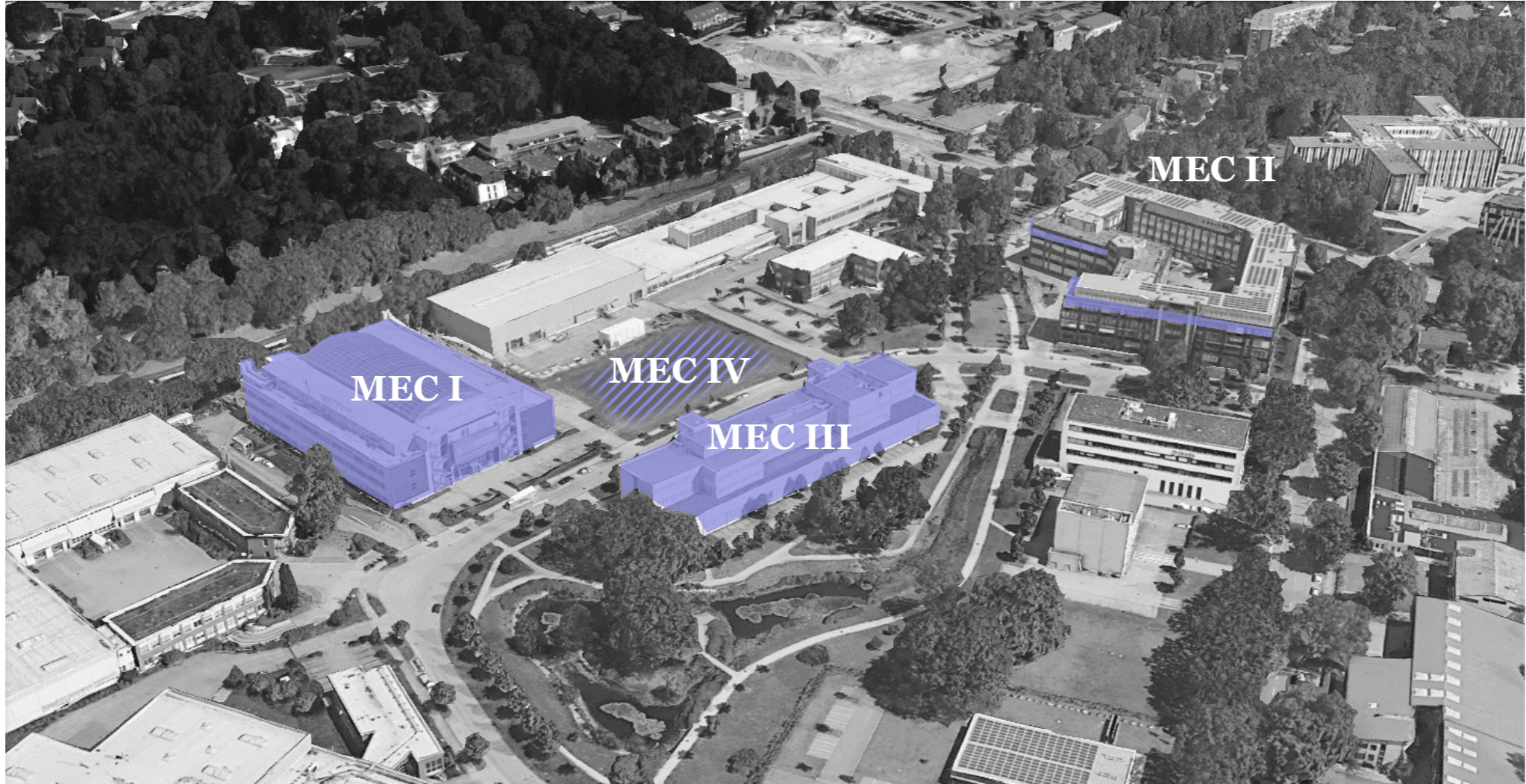
PanOmics

The Lighthouse of iPSCs



# Our home base is growing further

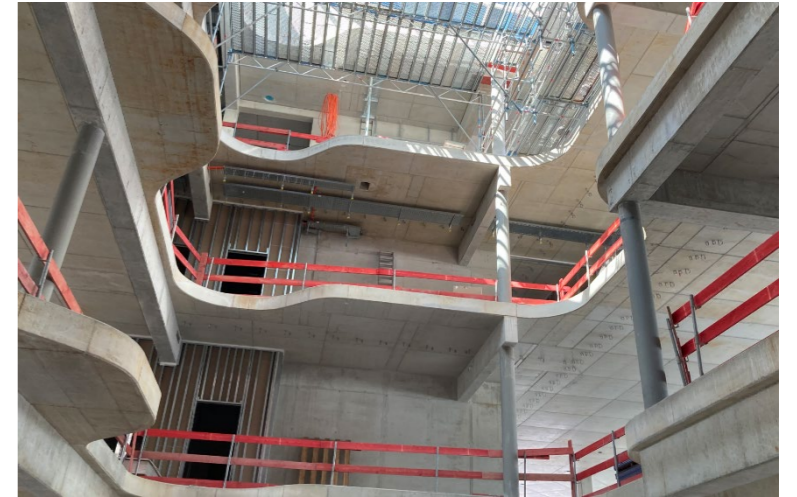
Footprint of Manfred Eigen Campus





# The iPSC Lighthouse, coming in 2025

Manfred Eigen Campus IV





# Global collaborative model for highest efficiency and precision

Platforms & technologies and network for higher probabilities of success (PoS)





## Your hosts today



**Claudia Karnbach**

EVP

Global Head of Strategic  
Partnerships and Alliances,  
Site Head Evotec SE Hamburg



**Werner Lanthaler**

CEO



**Cord Dohrmann**

CSO



**Bhushan Bonde**

Group Leader

*In silico* R&D



**Sandra Lubitz**

SVP

Stem Cell Biology



**Christiane Honisch**

SVP

Head of Diagnostics



**Olivier Radresa**

SVP

Head of Nephrology



**Andreas Scheel**

EVP

Head of Cell Therapy



**Christine Günther**

Entrepreneur in Residence &  
Medical Director Cell Therapy



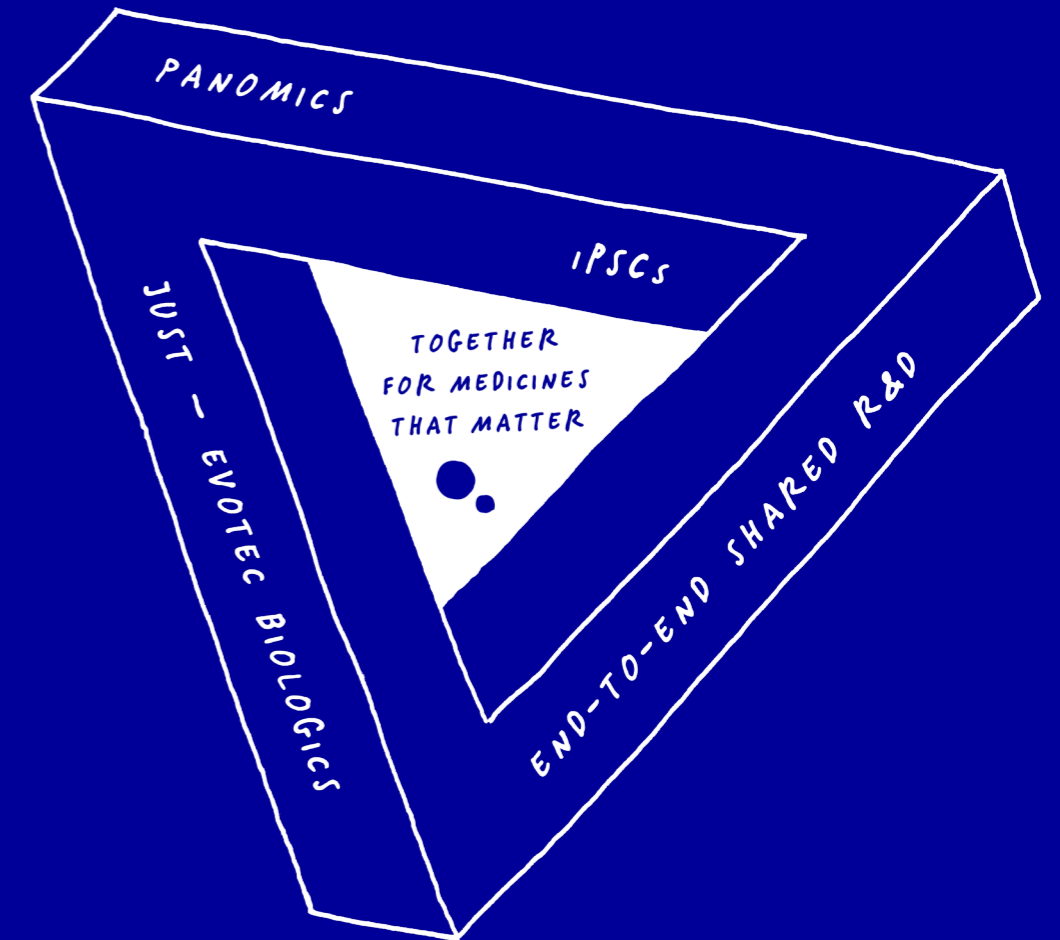
**Markus Dangl**

EVP

Head of Innovate Oncology

# *Shaping new Markets*

From disease understanding to pipeline building





# Agenda

- 9:00-9:30      **Shaping (new) markets**
- 9:30-11:00    **PanOmics – From patients for patients**
- *Better disease understanding & diagnostics*
  - *Advanced disease modelling*
  - *A.I. use cases along the value chain*
- 11:00-11:15    *Coffee Break*
- 11:15-12:15    **Impactful therapies**
- *Integrated platform*
  - *Diabetes*
  - *Oncology*
- 12:15-13:30    *Lunch Break*
- 13:30-16:00    **Round Tables**



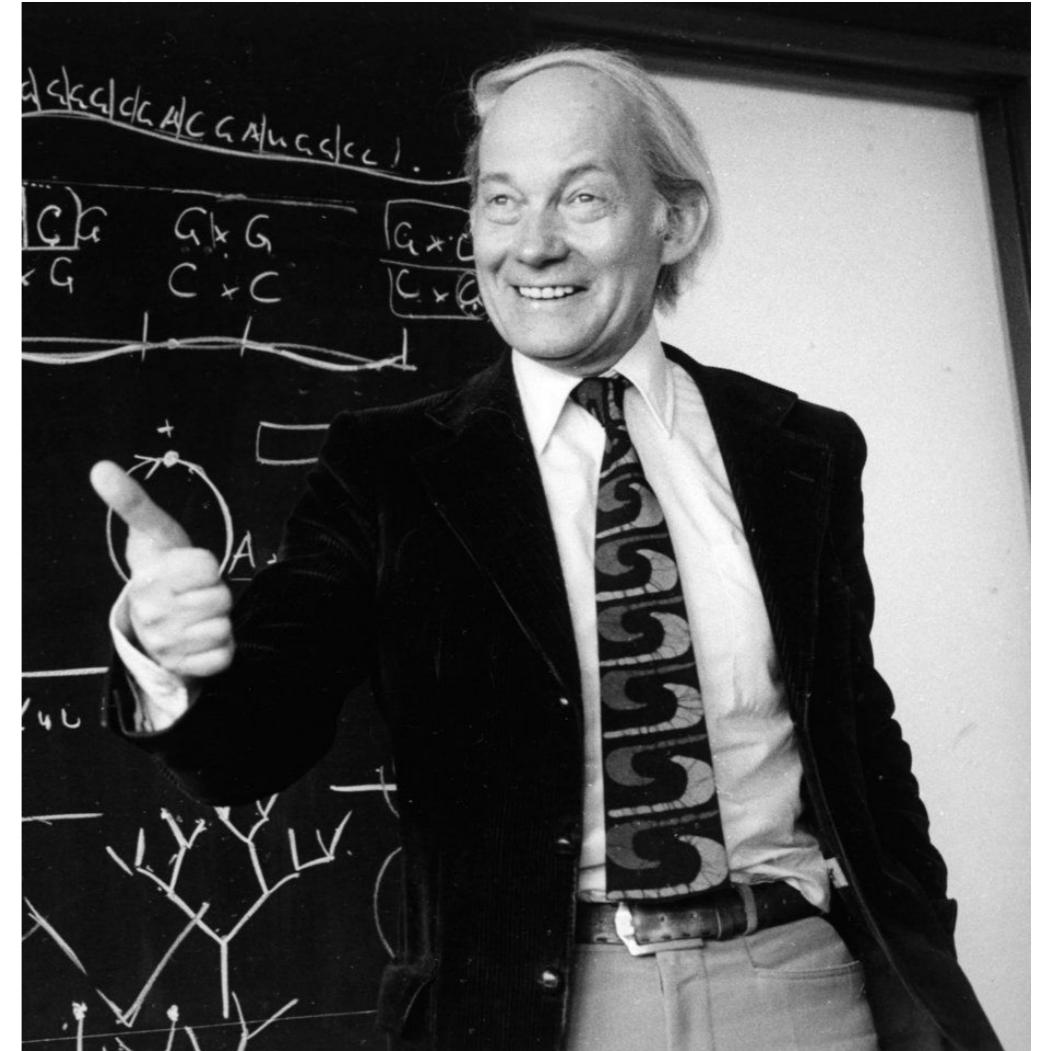


# Creating the future will work #together

Our contribution to the industry

*„The goal of Evolution is not one single human, it is mankind.“*

**Manfred Eigen** (1927–2019)  
Co-founder of Evotec, Nobel Prize 1967





# Accelerating medicines that matter

About us

## **4,000++ scientists empowering Partners**

Across all disciplines and disease areas from target to commercial manufacturing

## **Co-creating pipelines**

Leveraging our assets, targets or proprietary platforms for licensing, co-development or potential NewCo creation, frequently combining with Partners' programs, and ideas

***R&D Biotech that offers accelerated, high-value pipeline-building, services and solutions***

## **Performance - “Beyond FTEs”**

Collaborating with “end in mind”, result-driven partnership models

## **Track record - Highest quality, most capital-efficient execution**

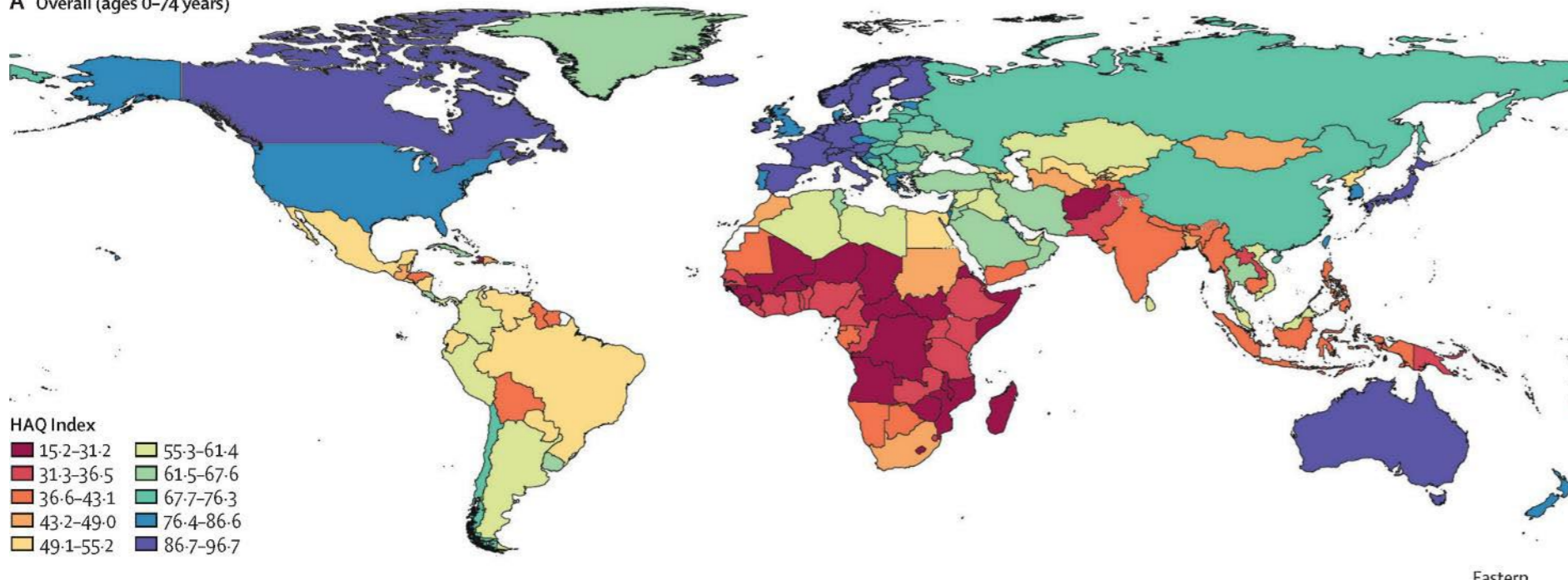
State-of-the-art services as core offering for partners



# “Just the beginning” of best days in medicine

## Health Access and Quality (HAQ) index analysis

A Overall (ages 0–74 years)



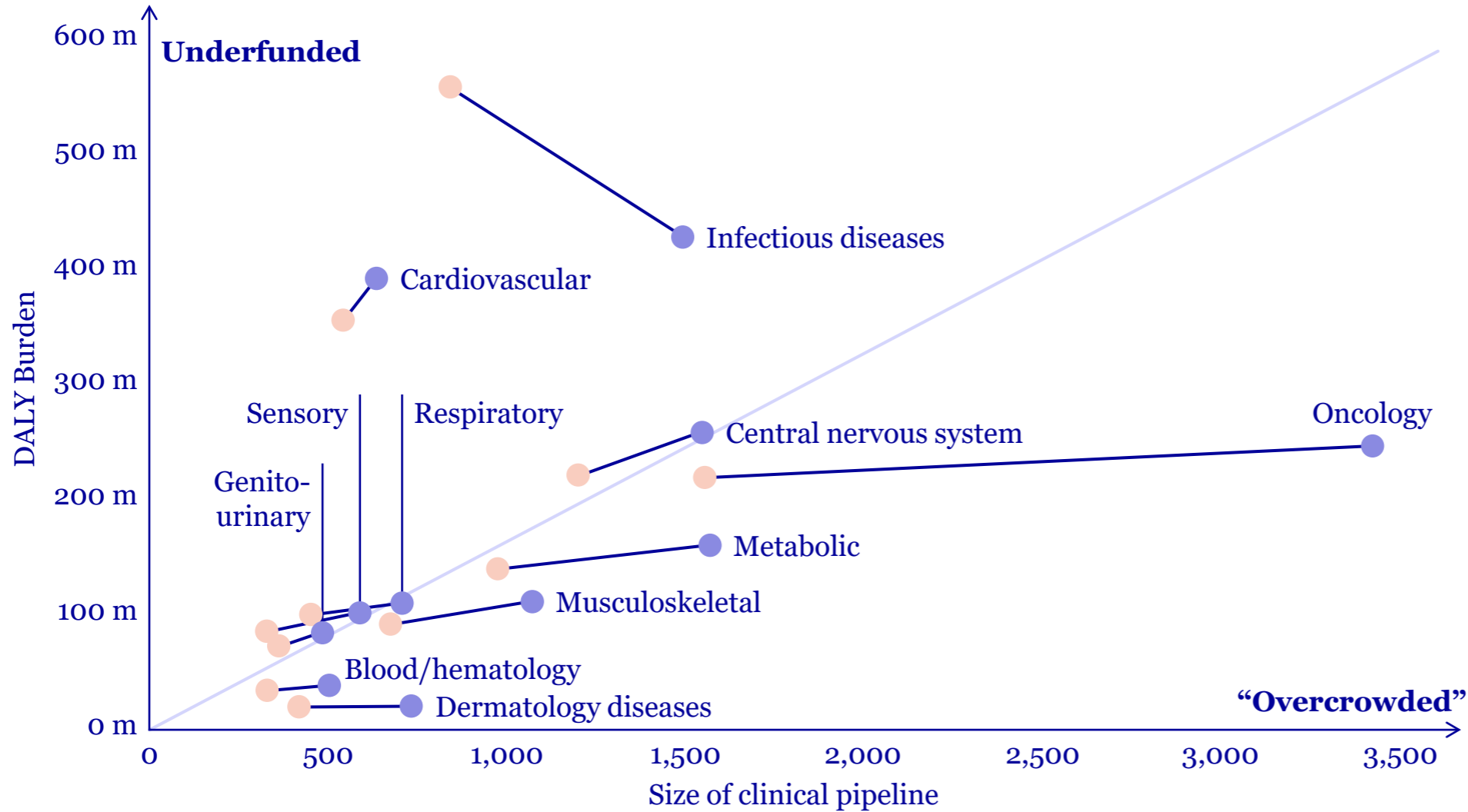
**Access to innovative medicine remains a severe unmet need<sup>1,2</sup>**

- High-burden diseases in higher-income countries represent **23% of global disease burden**
- High-burden diseases in low and middle-income countries (LMIC) represent **40% of global burden**



# Precise and effective drugs will find markets

Unmet need analysis – DALY Burden versus industry pipelines



- Demand for differentiation with innovation is expanding
- Revolving change between the industry's priorities and R&D investments

● 2013 ● 2022



# Big innovation is happening, but next challenges around the corner

Case study: Obesity



## Illustrative calculation

U.S. Obesity  
Prevalence<sup>1</sup>

140 million

Annual price of new  
GLP-1 medication<sup>2</sup>

~15,000 USD



Estimated total annual  
costs to health system<sup>2</sup>

1.5-2 Trillion USD

~10% of entire  
US economy

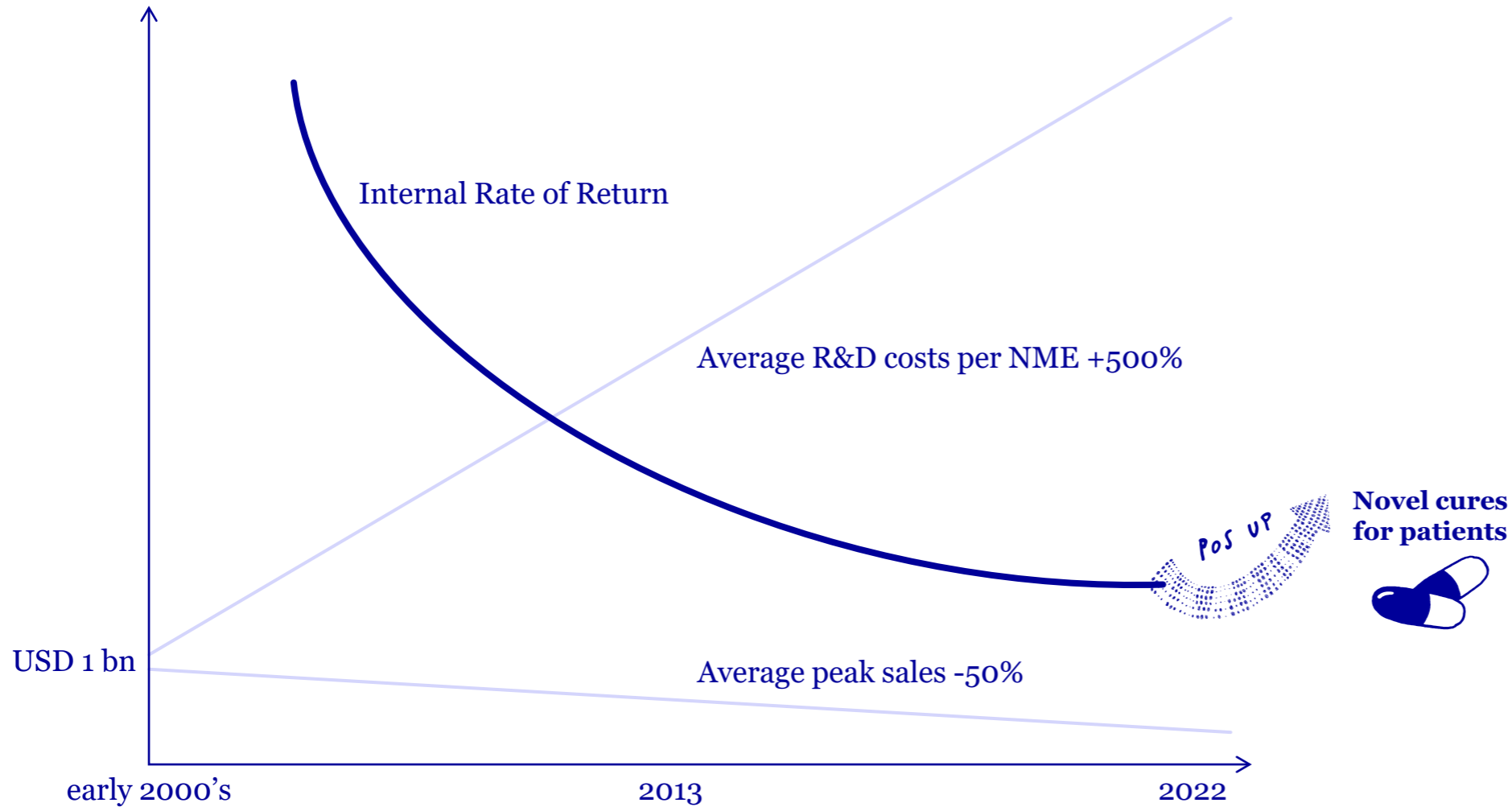
<sup>1</sup> Dan, Adrian G. "Surgery for Obesity ... a Family Journey!" *Bariatric Times*, 1 Jan. 2023, [bariatrictimes.com/surgery-for-obesity-family-journey/](http://bariatrictimes.com/surgery-for-obesity-family-journey/).

<sup>2</sup> Thompson, Derek. "The Weight-Loss-Drug Revolution Is a Miracle—and a Menace." *The Atlantic*, 27 Jan. 2023, [www.theatlantic.com/newsletters/archive/2023/01/the-weight-loss-drug-revolution-is-a-miracle-and-a-menace/672861/](https://www.theatlantic.com/newsletters/archive/2023/01/the-weight-loss-drug-revolution-is-a-miracle-and-a-menace/672861/).  
Source: Bloomberg Businessweek; SEMAFOR Flagship; team analysis



# Reverting IRR<sup>1</sup> by bringing Probabilities of Success (PoS) up

R&D productivity (illustrative)



## R&D productivity has not recovered, yet

- Higher spent with lower peak sales leads to deteriorating IRR<sup>1</sup>
- IRA<sup>2</sup> is “new” reality
- In 2023, average return of some pharma companies are set to improve (e.g. GLP-1 drugs)
- A.I./ML-driven technologies start to improve attrition rates
- Novel cures and higher PoS shape new markets and increase IRR



# Together for medicines that matter

Game changers within business to business / partnered R&D and pipeline building

## **Need for more precision**

*Most drugs still provide benefit in only 50% of patients*

## **Need for better disease understanding**

*More than 30% have a lifetime risk for cancer*

## **Need for better safety earlier**

*60% of all drugs still do not pass Phase I*

## **Need for wider access**

*Less than 20% of world's population have access to life changing biotherapeutics*

## **Better pipeline building**

*Right indication, right patients, right dose*

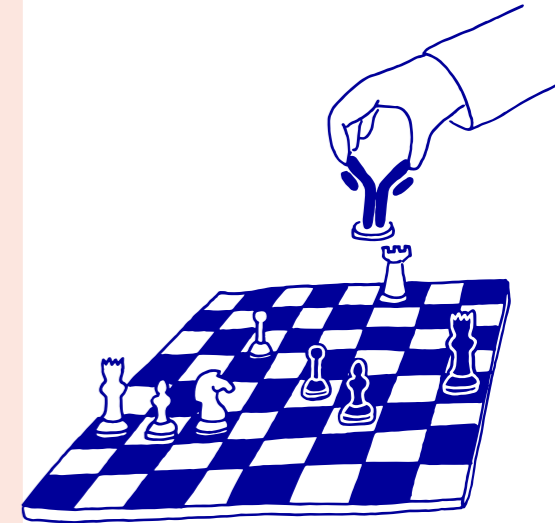
## **Technology convergence**

*A.I./ML coming together with drug discovery, development, safety prediction and molecular diagnostics*

## **Better business models**

*Shared economy in R&D*

- *From fixed to variable costs*
- *More effective learning curves for all*





# The biopharma innovation toolbox has never been richer

Illustrative examples

Evolution of targeted  
**protein degradation**

**Multi-omics**  
gaining momentum

**mRNA vaccine**  
technology used

Discovery  
with **iPSCs**

First use of **CRISPR**  
nucleases in gene editing

First **gene therapy**  
trials launched

Completion of the  
**Human Genome Project**

**Cell therapy** evolving as  
new modality in many diseases

Establishing of  
**A.I. in medicine**

**Personalized  
medicine**

**Gene editing evolving  
as a modality**



AHEAD OF  
THE CURVE





# Let's talk about modality agnostic pipeline building

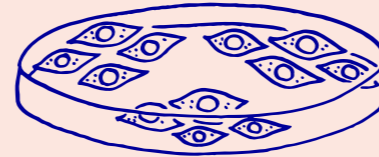
Our focus for today

## Our focus areas

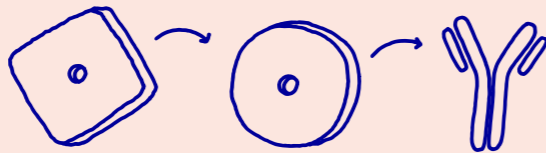
PanOmics<sup>1</sup>



iPSC cell therapy



Just – Evotec Biologics



End-to-End Shared R&D

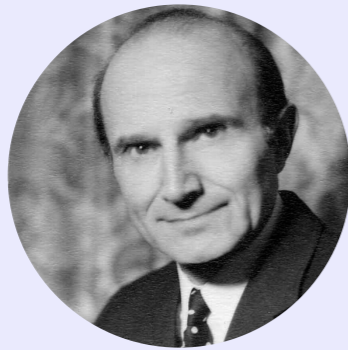




# We follow science, and open massive new opportunities

## Selected scientific giants

### From bone marrow transplants to induced pluripotent stem cells



George Mathé

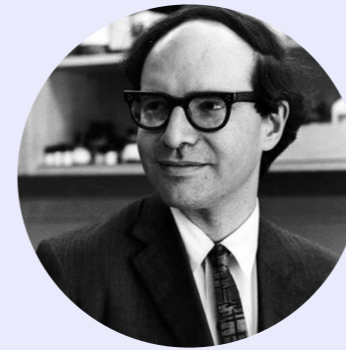


Shinya Yamanaka

### From DNA to RNA to Proteins – “PanOmics”



Leroy Hood



Walter Gilbert



Paul Berg



Frederick Sanger



Matthias Manns



Mark Wilkins

### From discovery of antibodies to biologics



Emil von Behring



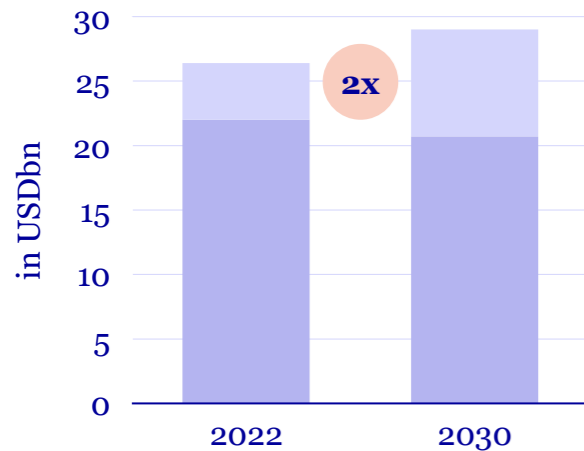
Brigitte Askonas



# New technologies leading to new opportunities

Shaping (new) markets

## End-to-End shared R&D

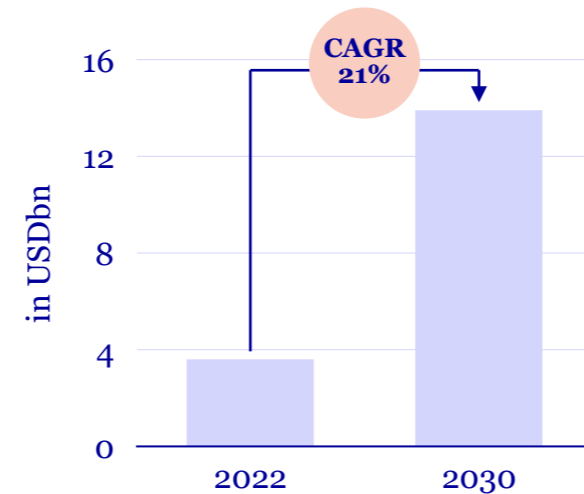


Outsourcing  
Large Pharma in-house

### Drivers

Deteriorating IRRs increase demand for outsourcing & higher efficiency

## PanOmics

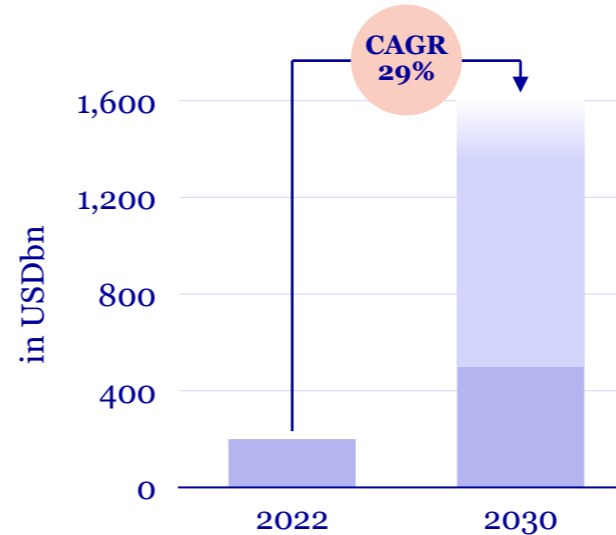


Multi Omics market

### Drivers

Precise medicines & diagnostics leading to patient specific treatments

## iPSC cell therapy

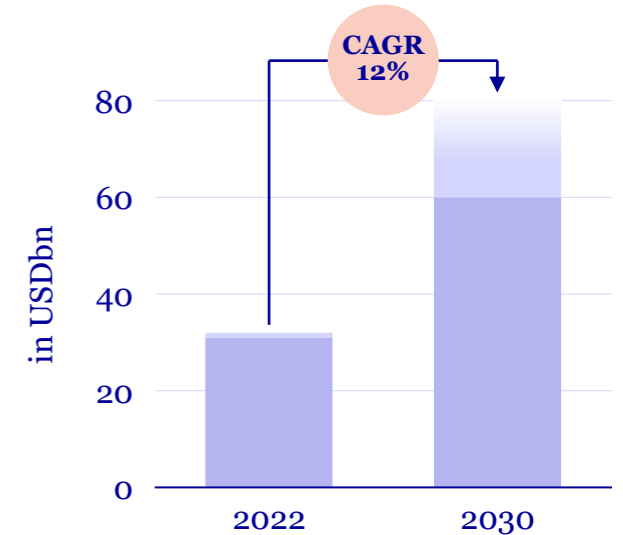


Replacing (donor) allogenic therapies  
iPSC cell therapy

### Drivers

From donor dependency to scalable off-the-shelf solutions

## Biologics



Continuous manufacturing  
Biologic discovery & manufacturing

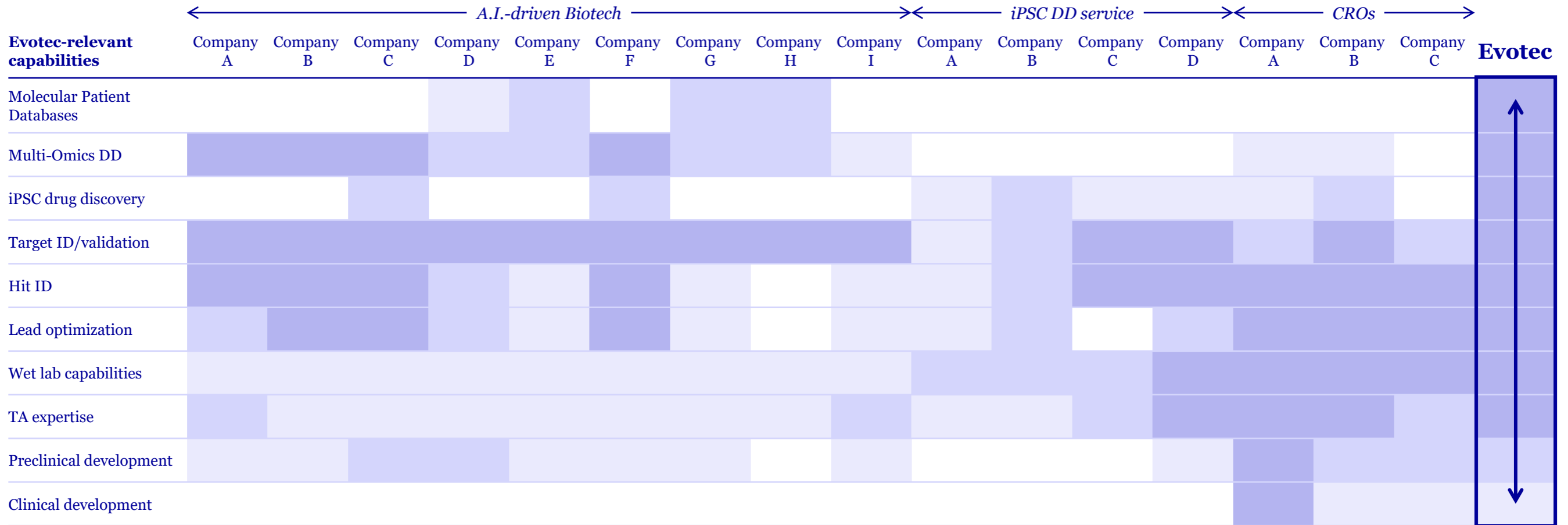
### Drivers

Regulatory changes (e.g. IRA) driving need to increase agility & flexibility



# Broadest set of value adding capabilities

Unique integrated offering



*Unique starting points with Molecular Patient Databases*

Level of offering ■ High ■ Medium ■ Low □ No offering

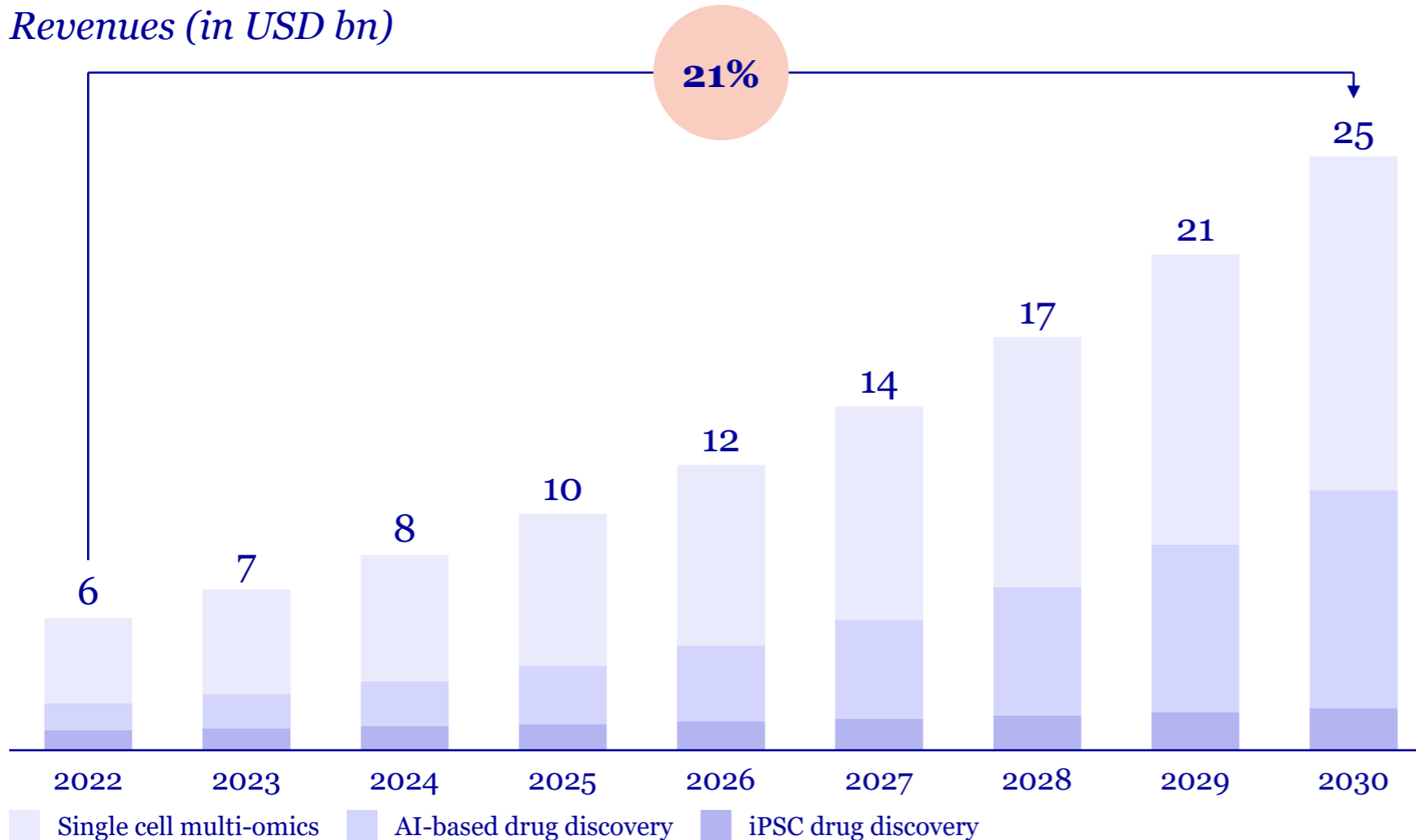


# PanOmics is a massive opportunity

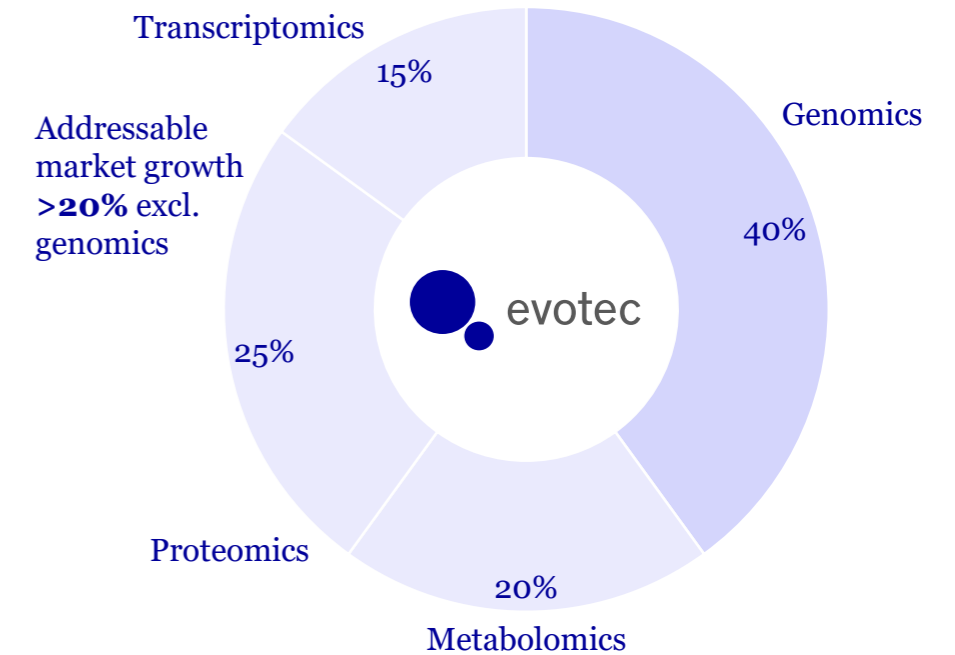
## Addressable market analysis

### Addressable market

Revenues (in USD bn)



### Market distribution and growth by application – 2030

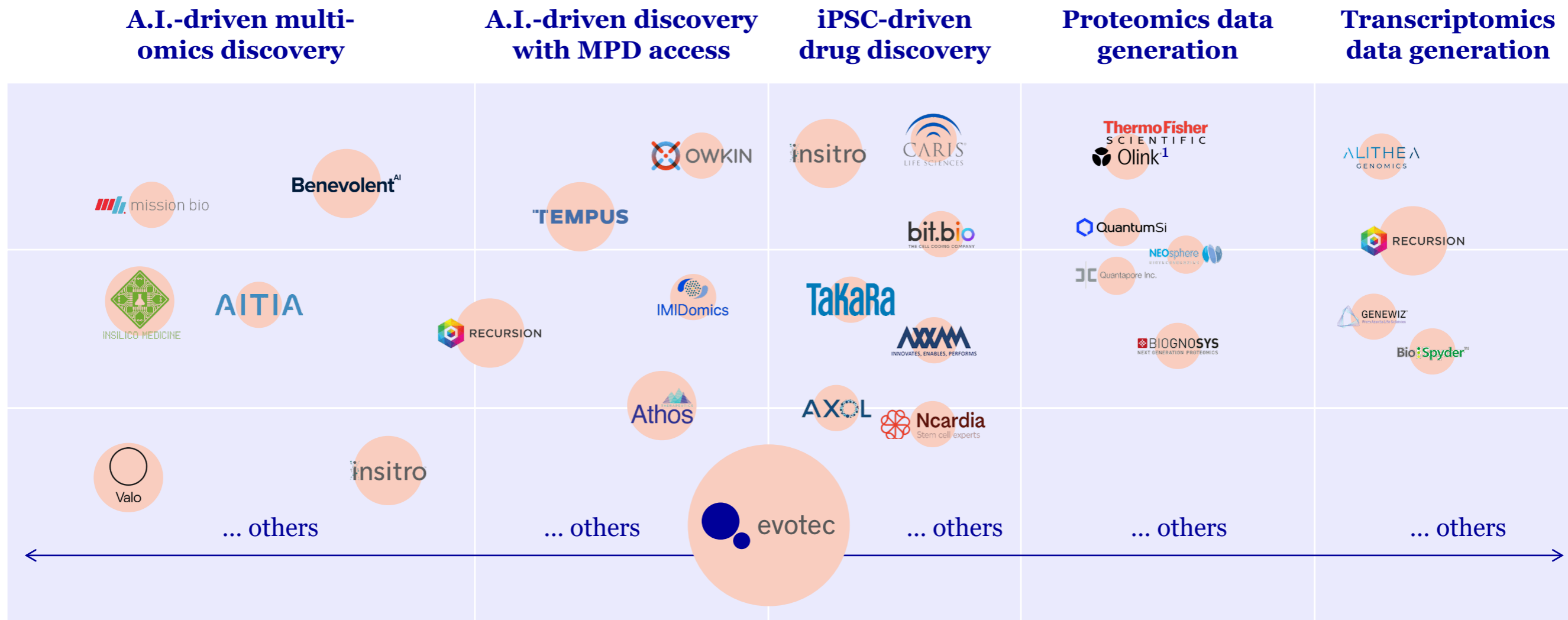


- **Genomics** will continue to grow
- **Proteomics** and **metabolomics** to outpace Genomics



# Fully integrated offering to secure data integrity

Simplified competitive landscape analysis



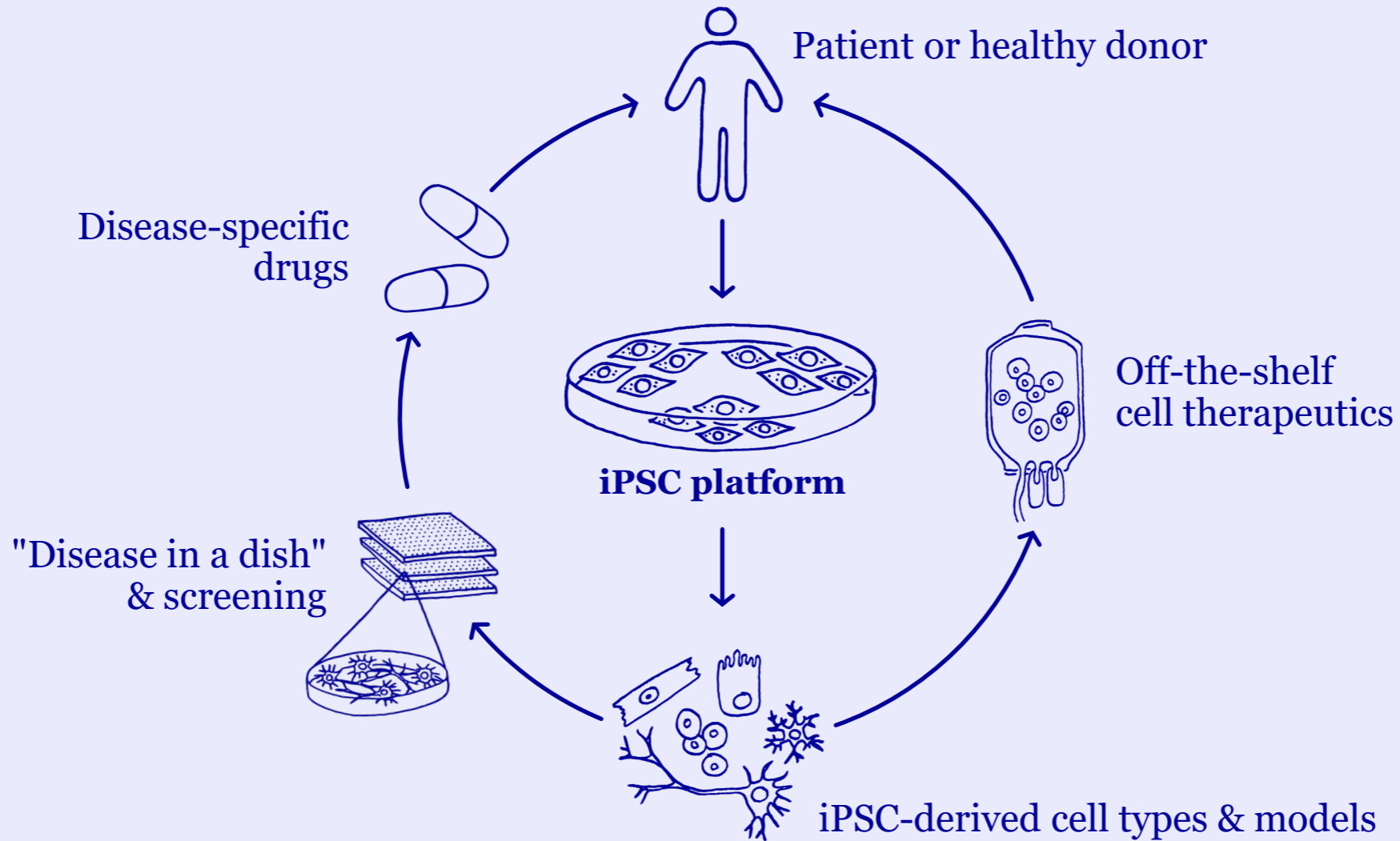


# From humans for humans

iPSC-based drug discovery and off-the-shelf cell therapy

**E.iPSC –**  
Human disease  
relevant modelling

**iPSC-based  
off-the-shelf  
therapeutics**



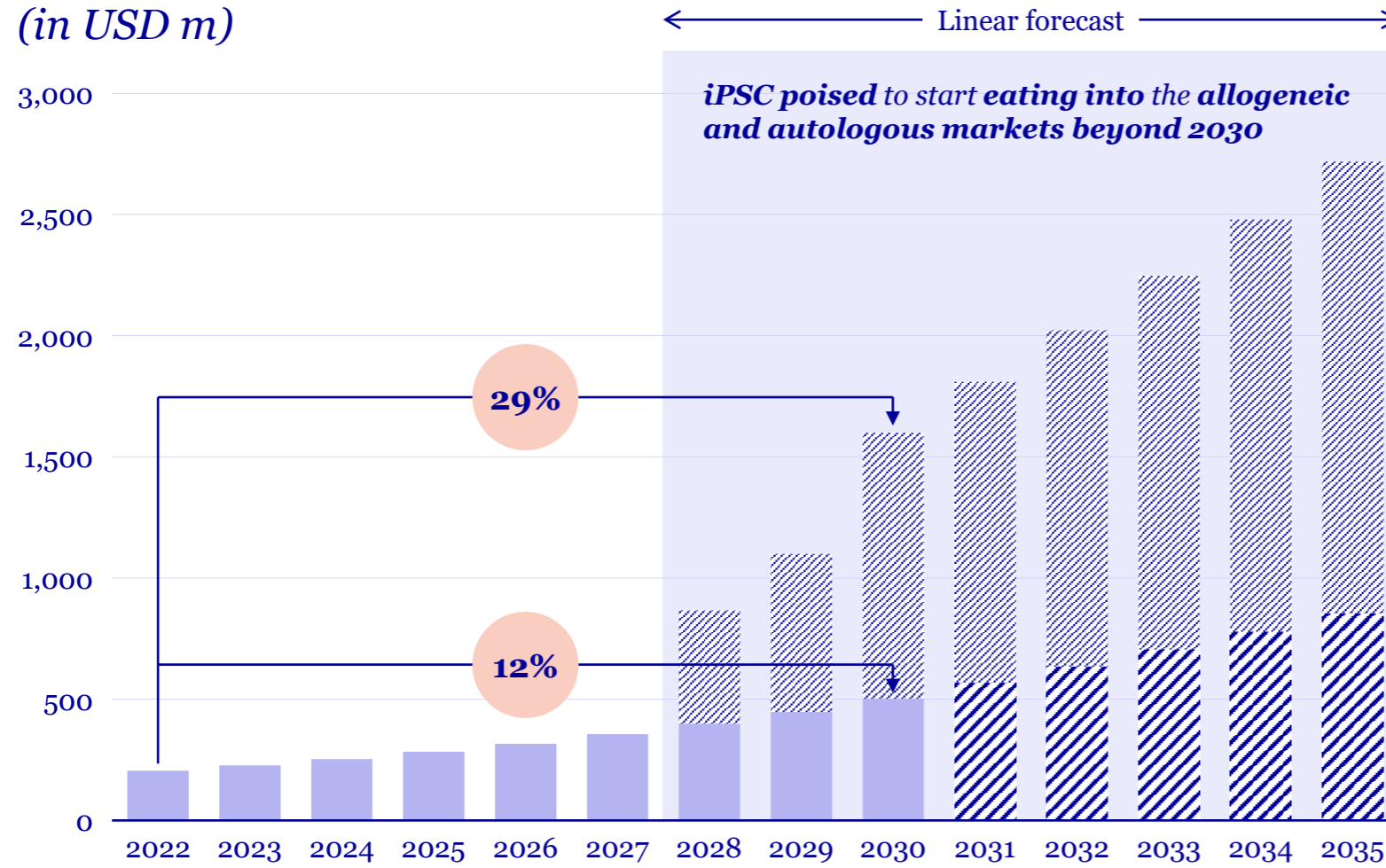


# iPSC market growth will be driven by clinical and commercial validation

## Addressable market analysis

### Addressable market

(in USD m)



### Heterogeneous mix of service and product players – no other integrated offering for partnered pipeline building







# Providing cost efficient access for biologics is our “North Star”

Limited access to biologics exists today in many patient segments



**70%**

higher prices for antibodies vs. small molecules in the US alone

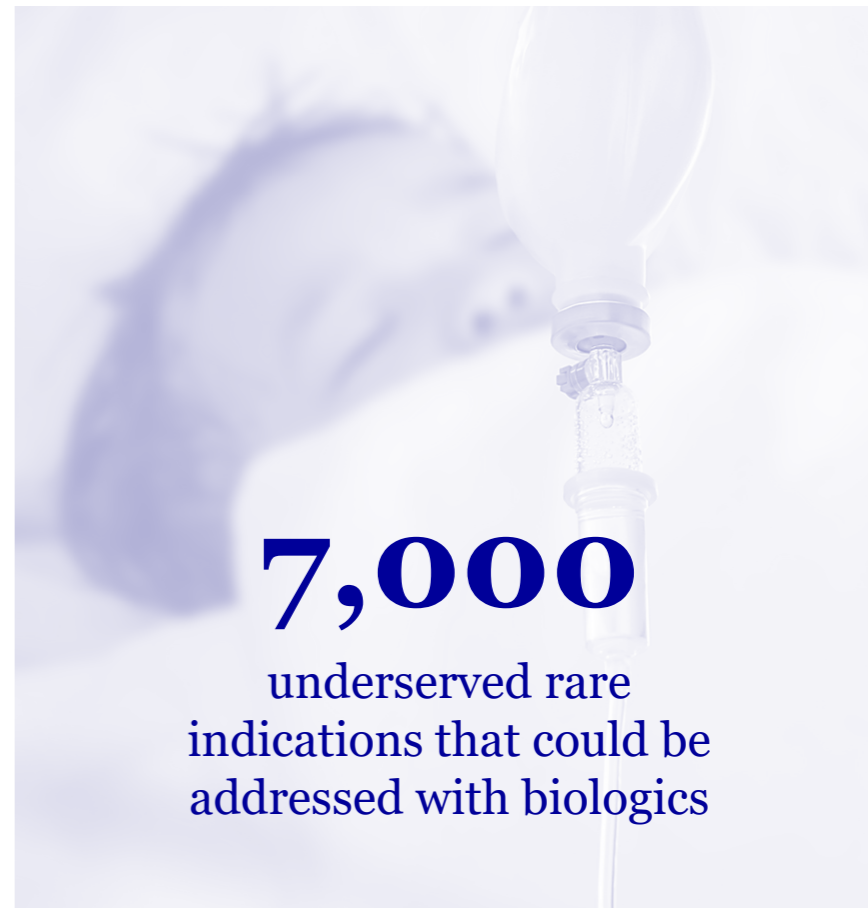
Underserved populations



**6 bn**

without access to biologics based on geography

Underserved regions<sup>1</sup>



**7,000**

underserved rare indications that could be addressed with biologics

Underserved indications

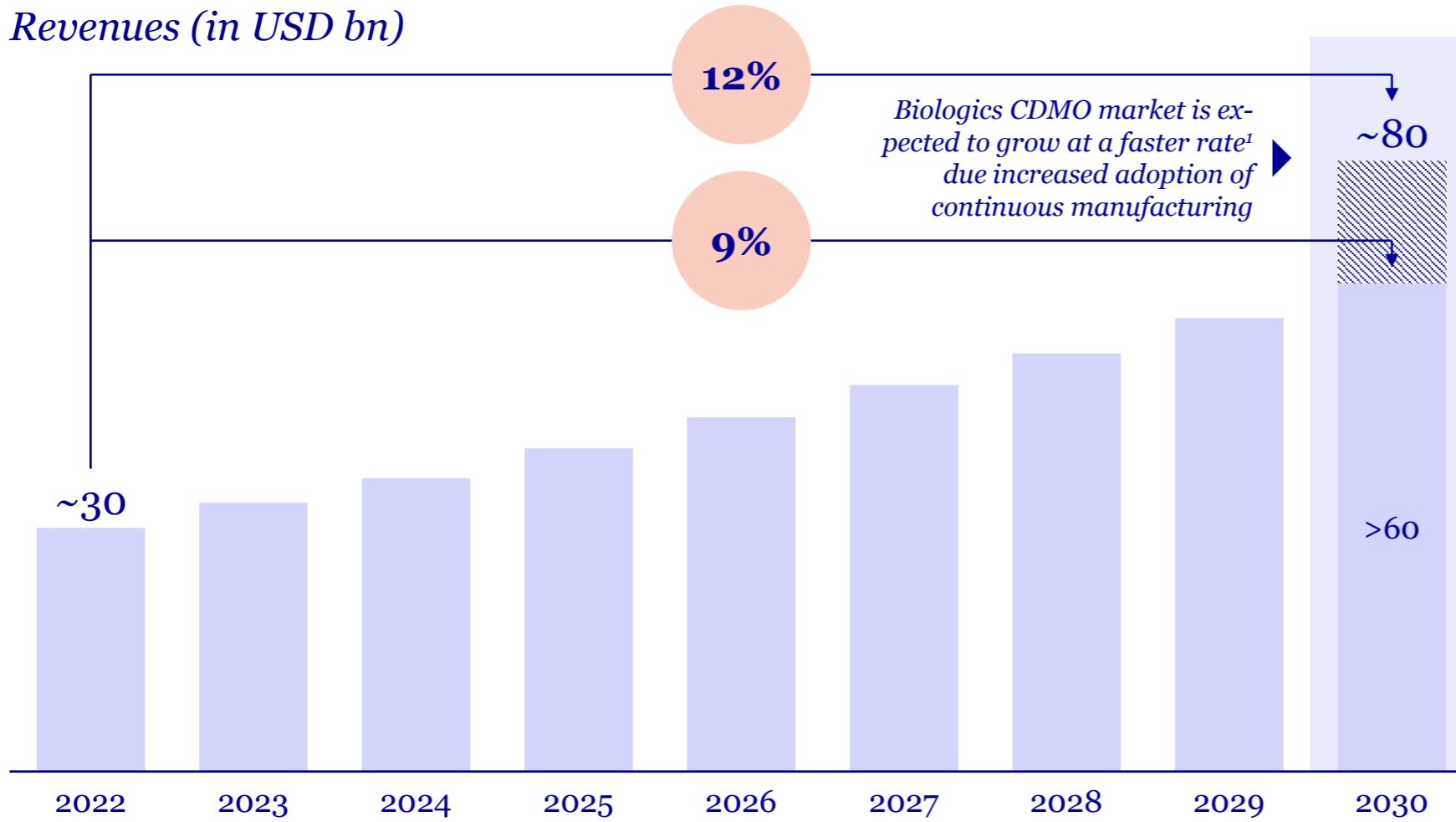


# Continuous manufacturing is the paradigm shift shaping the market

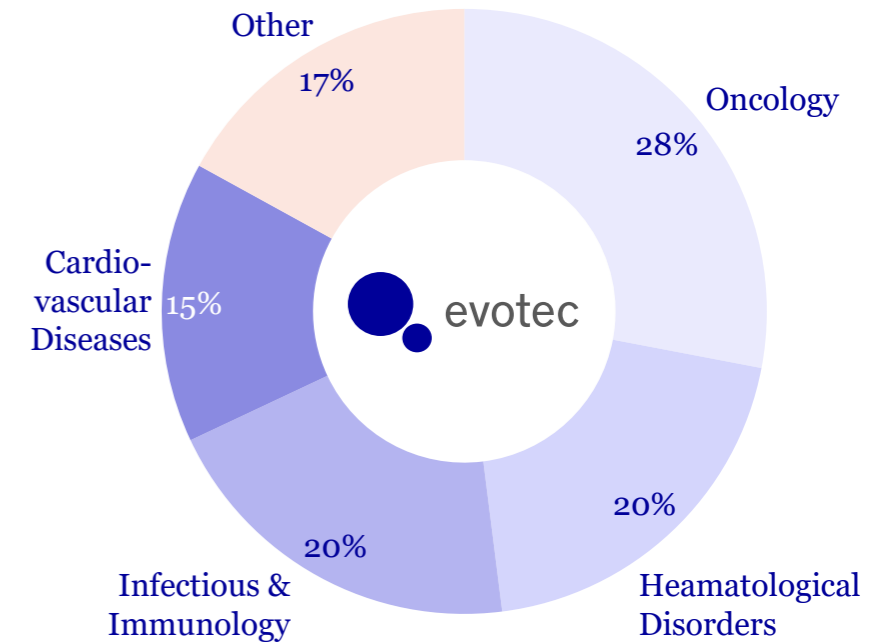
## Market size and growth

### Biologics discovery + manufacturing market

Revenues (in USD bn)



### Market shares by Therapeutic Areas 2022

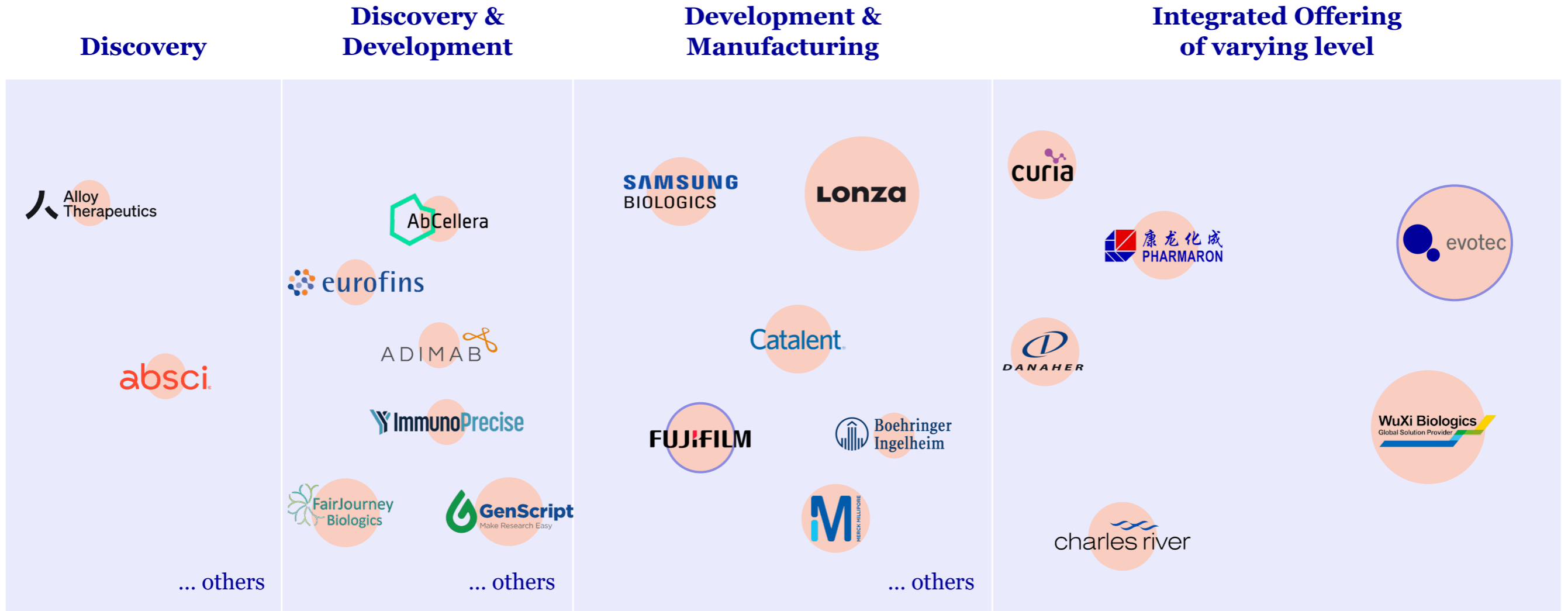


- **Oncology dominated** the market in the past
- **Hematological disorders** and **cardiovascular diseases** expected to **drive** the market growth in the next years



# We have a fully integrated offering

## Key competitor analysis



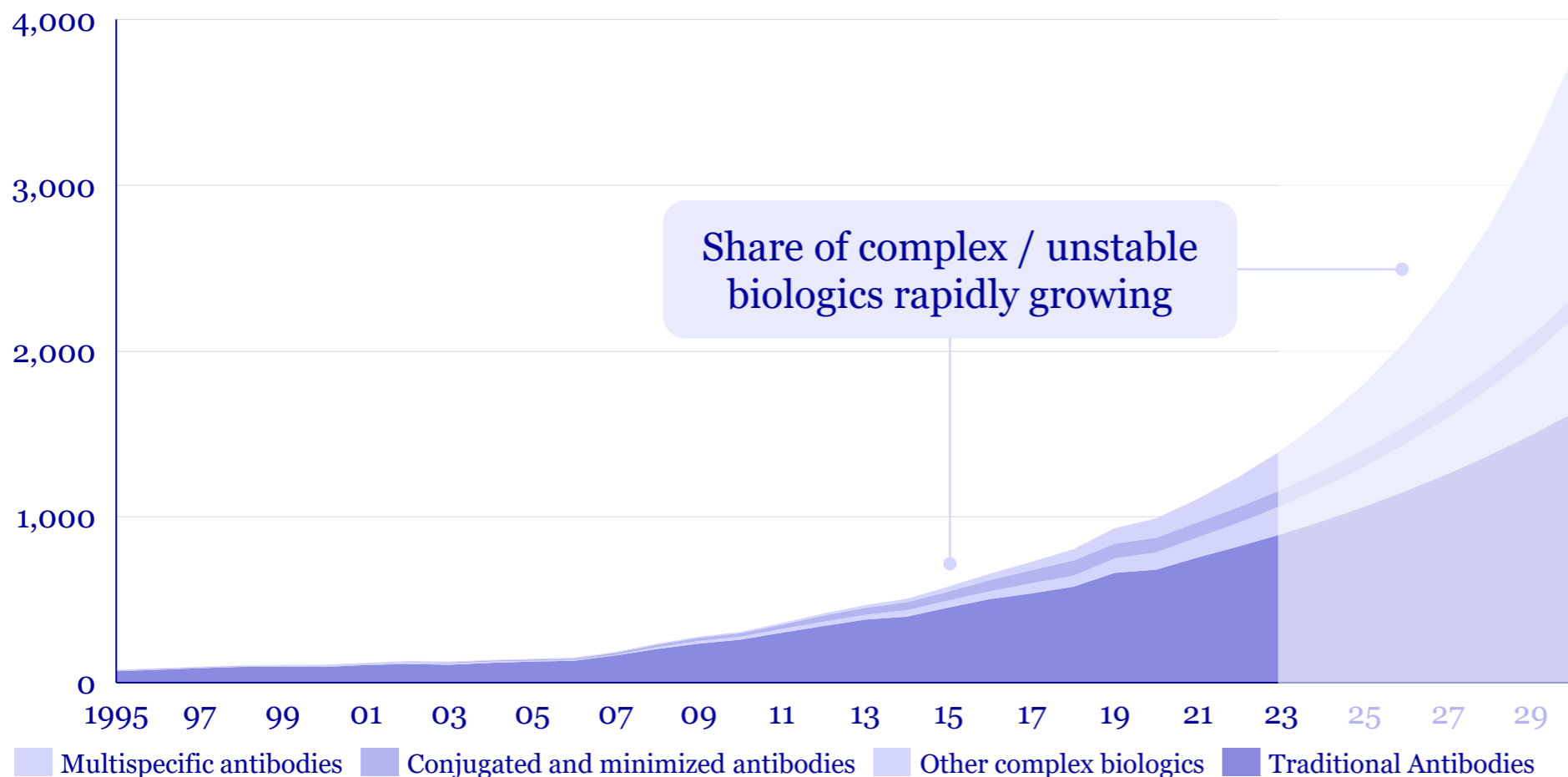


# Our continuous platform will even further excel with complex biologics

## Trends in global biologics pipelines

### Size of global pipeline by therapeutic modality

Number of products<sup>1</sup>, from Phase I to III



### Share of complex biologics in the pipeline

**Just**  
● EVOTEC BIOLOGICS

**>40%**

**Industry average**

**~30%**

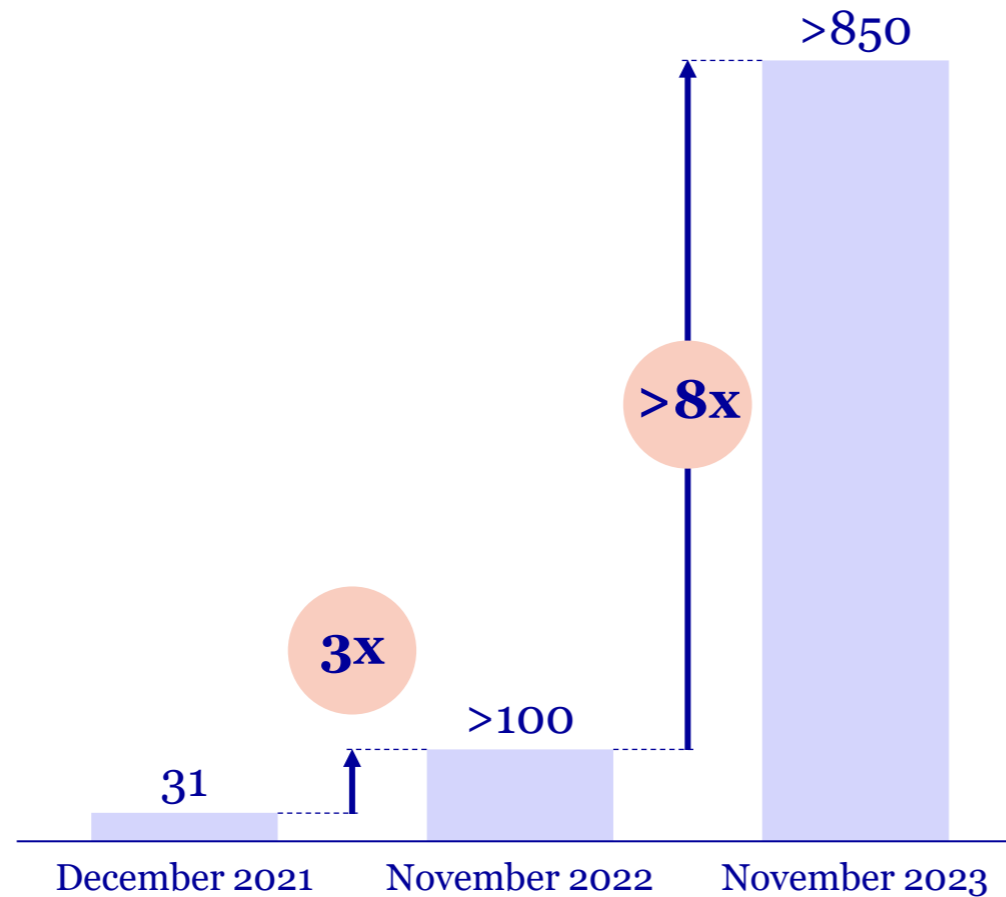


# Just – Evotec Biologics is building markets faster than expected

Key achievements 2021-2023

## Closed Sales

in € m



## Key progress

**SANDOZ**

Up to US\$ 640 m for development work plus massive upside



Anti-Plague mAb development programme initiated

Development programme for Orthopoxvirus mAb candidates

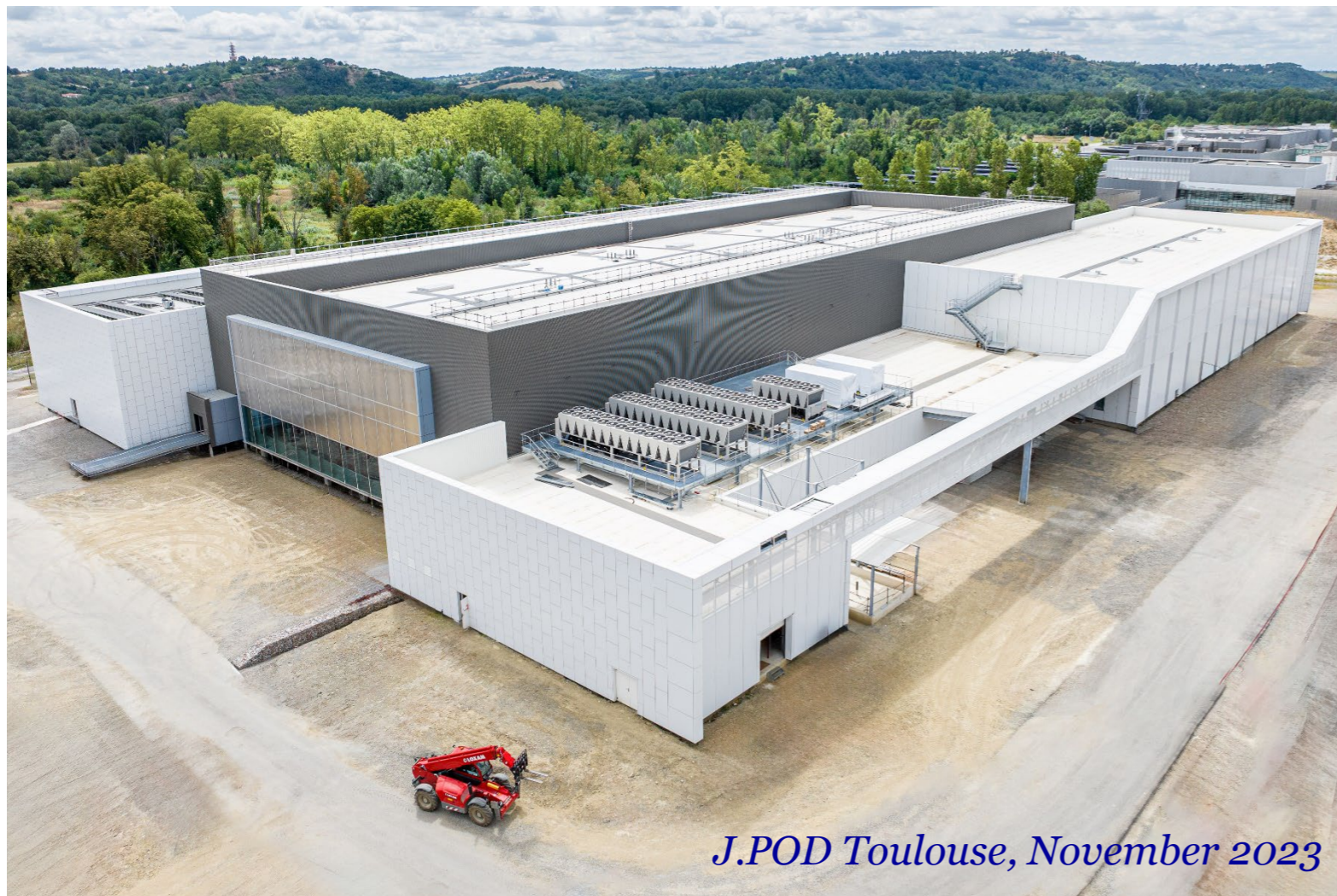


**First phase III trial** in H2 2024 for treatment of auto-immune glomerulonephritis



# Redmond is online – Toulouse ready to start in 2024

Progression on track



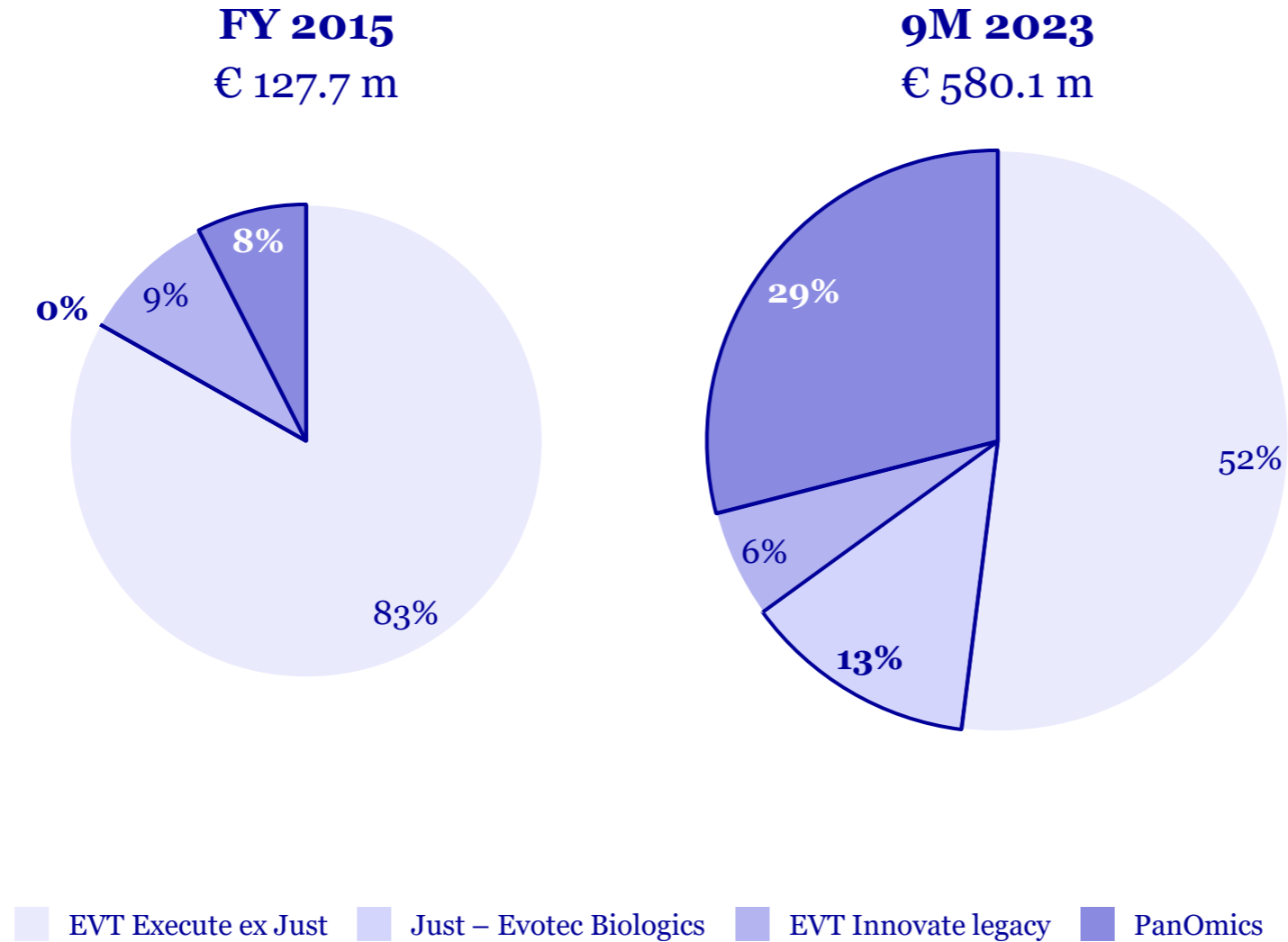
## J.POD – commercial biologics manufacturing site in Toulouse stepping up

- Ground-breaking for second biologics facility J.POD Toulouse in September 2022
- Building of shell and installation of PODs completed – on track for completion in H2 2024
- Ready to initiate FIH<sup>1</sup> programs
- Start of Business Development: Filling CLD/PD<sup>2</sup> labs in 2024 to have manufacturing process ready when cGMP suites are operational in 2025



# Paradigm-shifting platforms are key growth drivers

Revenue distribution 2015 versus 9M 2023



## Revenue CAGRs<sub>2015 - 9M 2023</sub> outpacing base business

- PanOmics ~50%
- € 76.5 m incremental contribution from Just – Evotec Biologics since 2019
- EVT Innovate ex PanOmics ~20%
- EVT Execute ex Just – Evotec Biologics ~20%

**On track to reach revenue aspiration 2025**

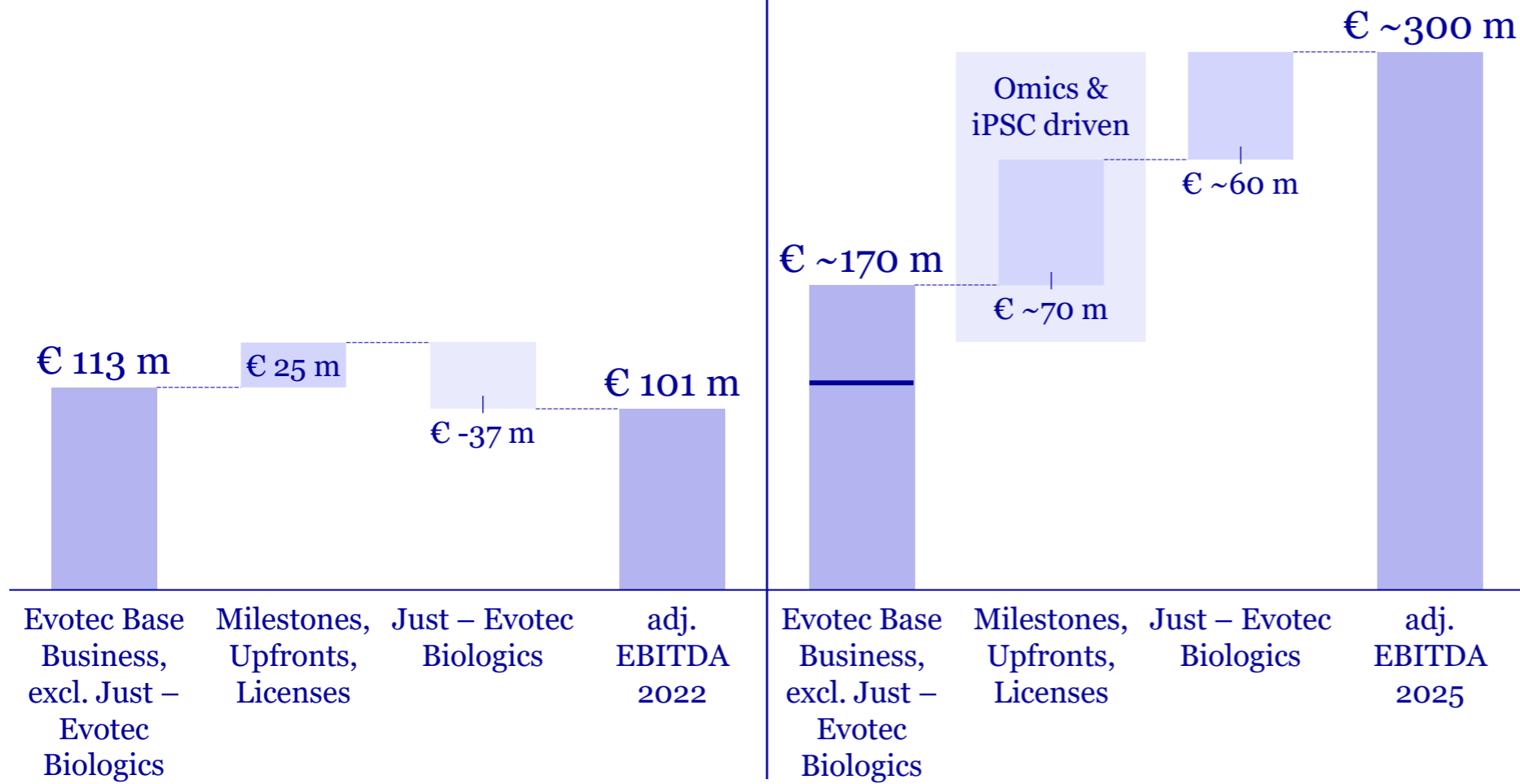


# ... and a key contributor to acceleration of milestones

Mid-term adj. EBITDA bridge

**2022**

**2025 aspiration**



## Well-balanced cascade

- Income from Milestones, Upfronts, Licenses expanding due to increasing breadth and depth of PanOmics-based pipeline
- Accelerated growth of Just – Evotec Biologics
- Base business adj. EBITDA CAGR of 15%
  - Robust top-line growth
  - Operating leverage
  - Efficiency Programmes (e.g. VPP)





# Action Plan 2025 on track

Action Plans in numbers



## Underlying external challenges

Financial crisis

MERS

Avian Influenza

Brexit COVID-19

War in  
Ukraine

Cyber-  
attack

Israel  
Gaza war



# Agenda

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# R&D productivity remains the grand challenge for big pharma

Record spending does not translate into R&D output – selected KPIs

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**\$ 138 bn**

*R&D Spending of  
“Top 15 Pharma” in 2022<sup>1</sup>*

**< 2%**

*Clinical pipeline  
growth<sup>2</sup>*

**~ 44%**

*Pharma companies with  
negative R&D productivity<sup>3</sup>*

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**\$ 6.16 bn**

*R&D expenditure per new drug<sup>4</sup>*



# Increasing the probability of success is key

Attrition rates have not improved – selected KPIs

**~95%**

*False discovery rate  
in the pre-clinic<sup>1</sup>*

**>93%**

*Clinical attrition up  
to market launch<sup>2</sup>*

**>32%**

*Post-market safety events  
of FDA-approved drugs<sup>3</sup>*

**0.78**

*Annual drug launches per “Big Pharma”<sup>4</sup>*

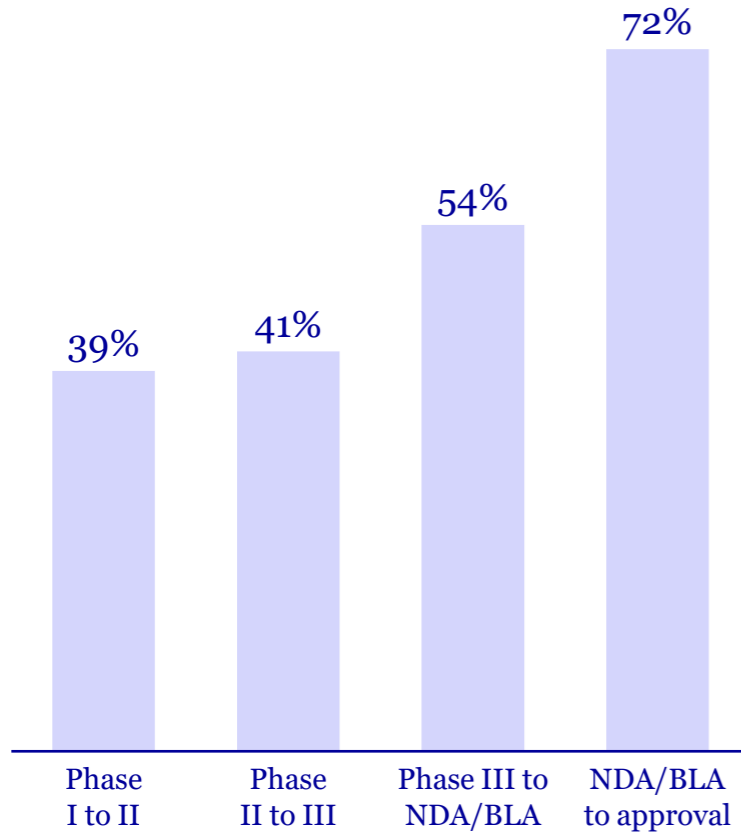


# Probability of success on the decline in most indications

Overall composite clinical success rate for all indications at 6% in 2022

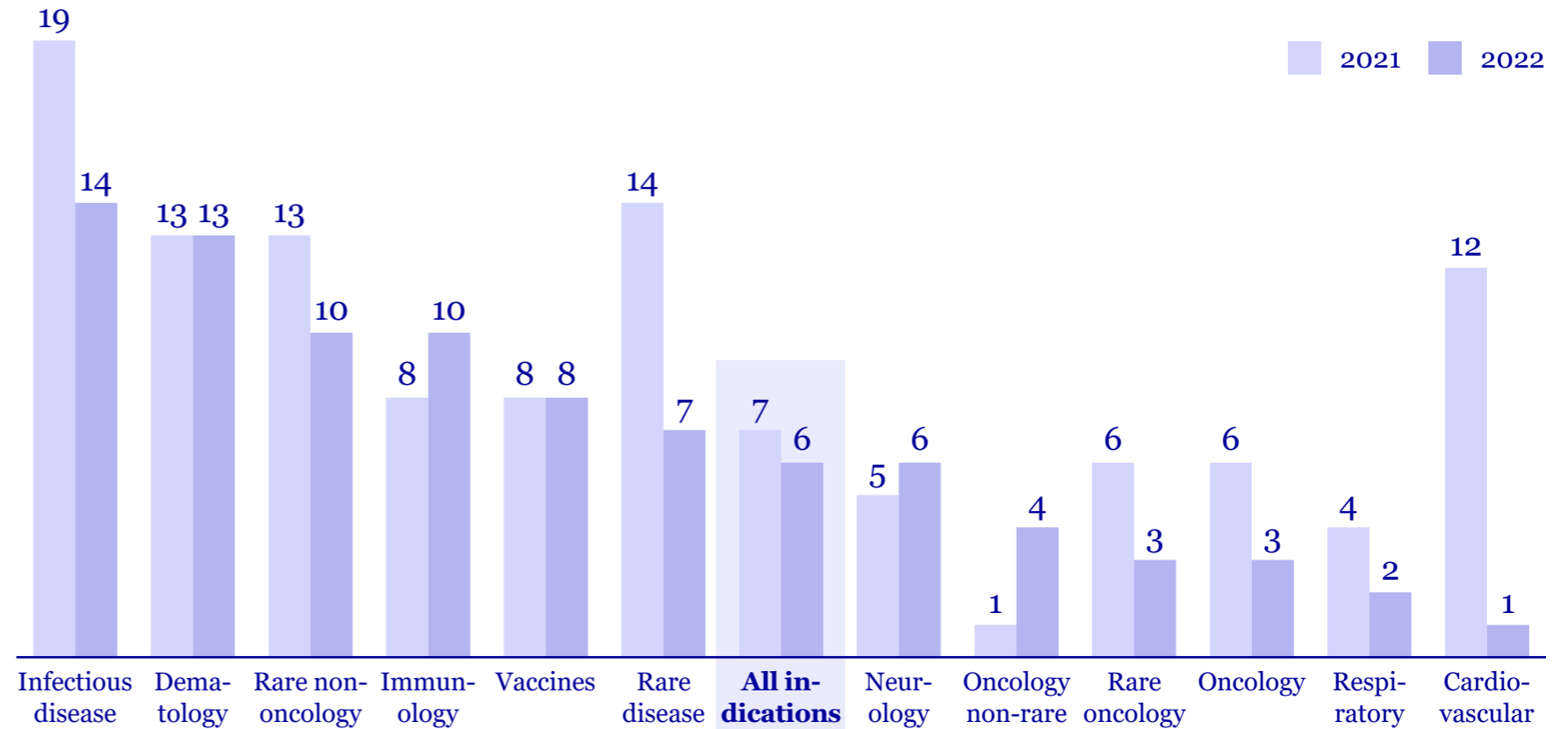
## Probability of success

success rate = number that advanced to next phase/total number advanced & suspended



## Overall clinical success rates

in %



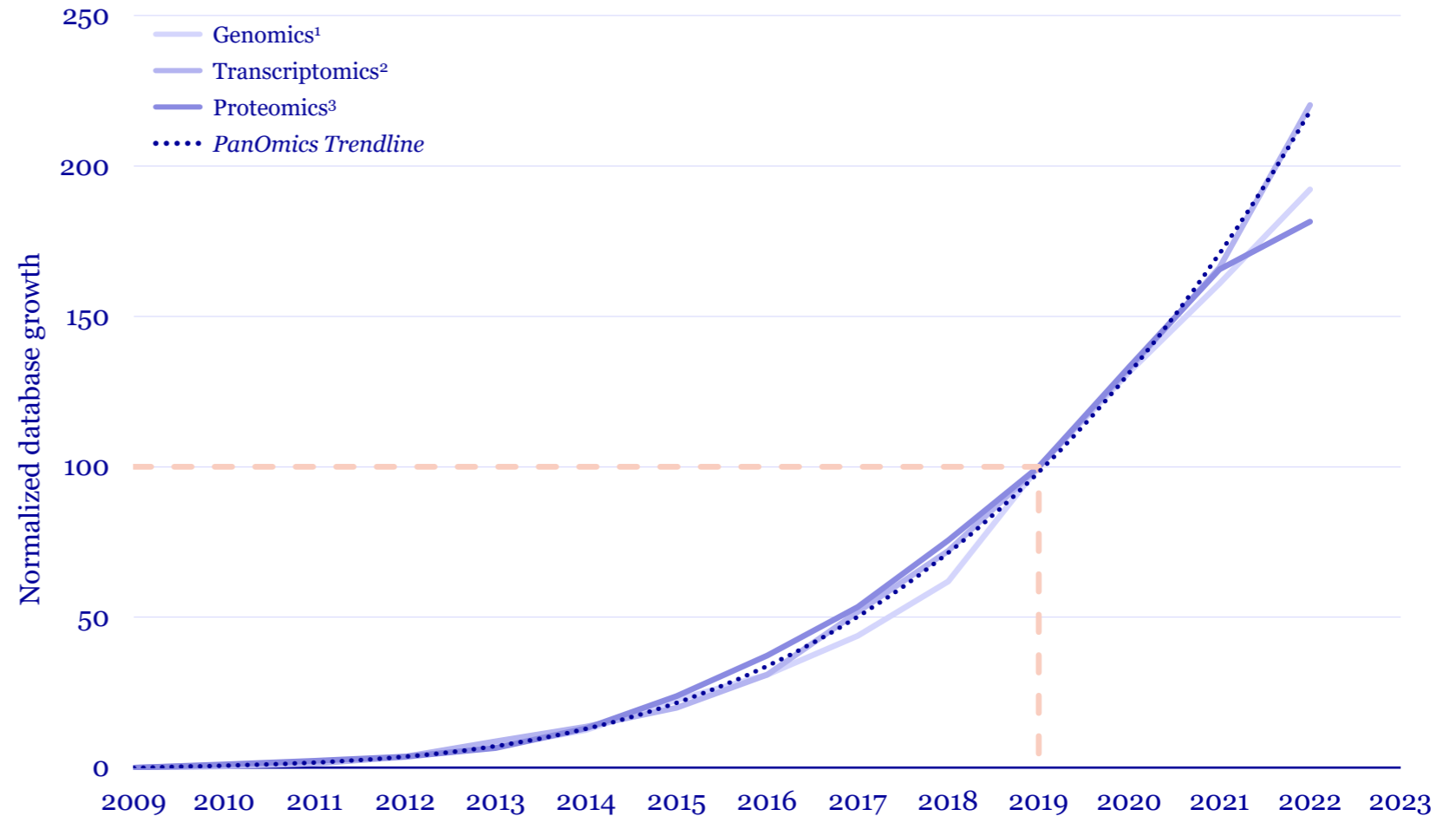


# Omics data is a key driver of the precision medicine megatrend

## Published Omics data

- *Published Omics data keeps accumulating at an exponential rate*
- *Between 2019 and 2022 as much Omics data was published as in the ten prior years combined (2009 to 2019)*
- *Unpublished Omics data generated by Biotech and Pharma is expected to exceed published Omics data*

## Exponential Omics data generation



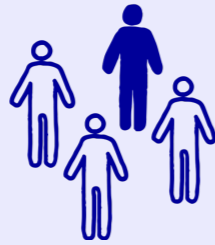


# A precision medicine platform is driven by PanOmics

Leading A.I./M.L. driven drug discovery & development platforms

## Molecular patient databases

Re-defining health and disease via molecular disease profiles



## Patient derived disease models & precision medicine approaches

Focus on disease relevance



## Patient stratification and biomarkers

Precision diagnostics and tracking of diseases



### PanOmics

*Data Generation*

- Genomics, **transcriptomics**, **proteomics**, metabolomics data at industrial scale
- High performance, industrial scale platforms

### PanHunter

*Interactive Omics Analysis*

- User friendly A.I./M.L. driven multi-omics analysis platform
- Exceeding industry standards in e.g. predicting drug safety

### E.iPSC

*Drug Discovery*

- One of the largest and most sophisticated iPSC platforms for drug discovery in the industry
- First IND in clinical development; large pipeline evolving



# R&D investments generate highly strategic partnerships with upside

~40% average annual revenue growth since 2015

Total R&D costs since 2010

**€ ~450 m**

About € 2.5 m invested per partnered project.

Break-even well before entrance in clinical trials.

Total number of pharma deals / partnered product opportunities



**>40**

~140 partnered product opportunities

Total revenues received

**€ >1 bn**

Total upfronts received

**€ >500 m**

Total MS upside

**€ >15 bn**

Average Royalties

**~8-10%**





# Using human derived disease models as real paradigm shift

## *Neurodegeneration* alliance with BMS

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### **Broadened and deepened strategic alliance in neurodegeneration**

- Extension and expansion for 8 more years
- Collaboration leverages Evotec's iPSC disease modelling capabilities in the field of neurodegenerative diseases
- \$ 50 m upfront payment
- Potential milestone and performance based payments of > 4 bn
  - Already \$ 40 m in payments received in 2023
- Tiered royalties of up to low double-digit percentage for each programme





# Largest deal in one of the most competitive fields in the industry

*Targeted protein degradation* alliance with BMS

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## Developing a pipeline of breakthrough therapies based on molecular glue degraders

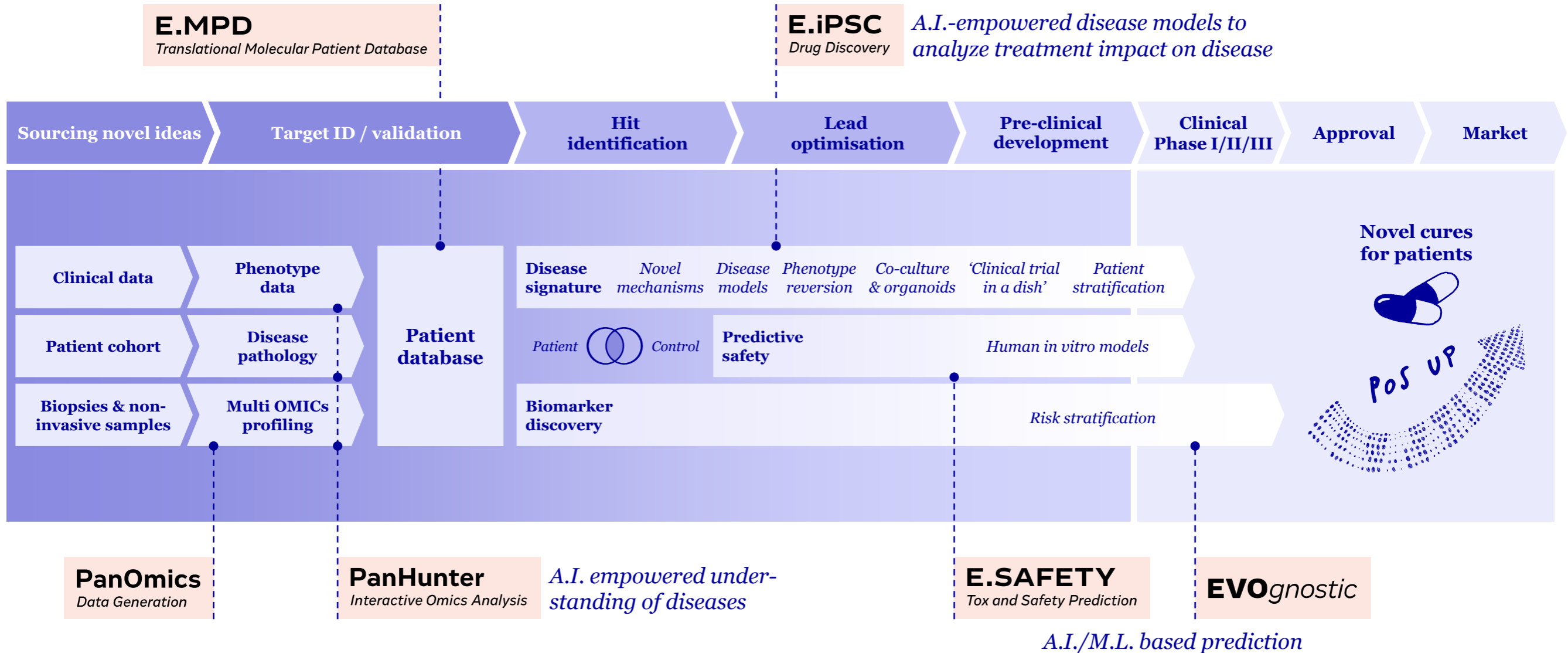
- 8-year extension and significant expansion of original agreement signed in 2018
- Collaboration leverages Evotec's PanOmics and PanHunter platforms including A.I./M.L. capabilities
- Upfront payment of \$ 200 m
- Performance payments of \$ 75 m announced in March 2023
- Additionally, tiered royalties for each program
- Total deal value of up to € 5 bn; milestone-based payments





# Industrialised PanOmics approach towards molecular disease insights

## Overview of PanOmics-driven drug discovery





***Pipeline building starts  
with better disease  
understanding – E.MPD***



# First in class discovery starts with patient data

Portfolio of Evotec Molecular Patient Databases (E.MPD)

## E.MPD Now

Therapeutic Area	Patients
<b>Chronic Kidney Diseases (CKD)</b>	<b>12,000</b>
<b>Immune Mediated Diseases</b>	<b>3,000</b>
<b>Metabolic disease (Liver)</b>	<b>2,000</b>
<b>Healthy Controls</b>	<b>1,500</b>




## Next steps

In progress	Patients
<b>Acute Kidney Injury (AKI)</b>	<b>950</b>
<b>Obesity</b>	<b>TBD</b>
<b>Immune, Oncology</b>	<b>TBD</b>
<b>Neuro</b>	<b>TBD</b>
<b>And many more ...</b>	



# Significant advantages of E.MPD over public domain datasets

Standard technology, data QC and rich data annotations to improve outcomes

		Public Domain	 <b>E.MPD</b> <small>TRANSLATIONAL MOLECULAR PATIENT DATABASE</small>
<b>Cohort planning/design</b>	Physician engagement		
	Prospective and longitudinal studies		
<b>Clinical data</b>	Sample ID linked to source data (e.g. hospital)		
	Sample tracking (batch effects!)		
	Medical records		
	Evotec QC of medical record data		
	Number of annotations (age, sex, medication, comorbidities, ...)	1-5	50-500
<b>Analysis data</b>	OMICS technology platform	several, no control	one, fully validated
	Availability of multi-omics data sets		
	Data acquisition (sensitivity, sequencing depth, ...)		
	Data comparability (combining cohorts)		



# Re-defining patients' health and disease

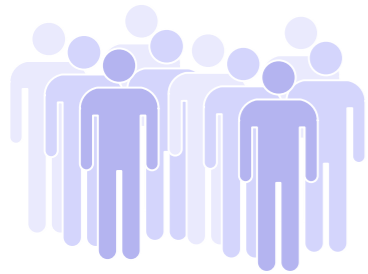
E.MPD, PanOmics and disruptive computational technologies increase disease insight



## E.MPD

TRANSLATIONAL MOLECULAR PATIENT DATABASE

### Patient cohorts



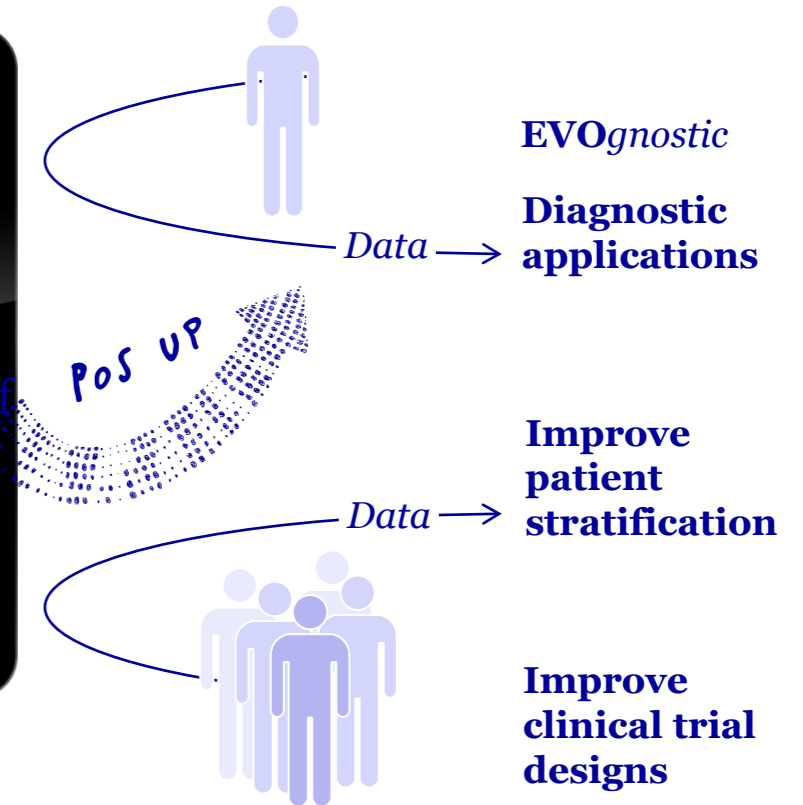
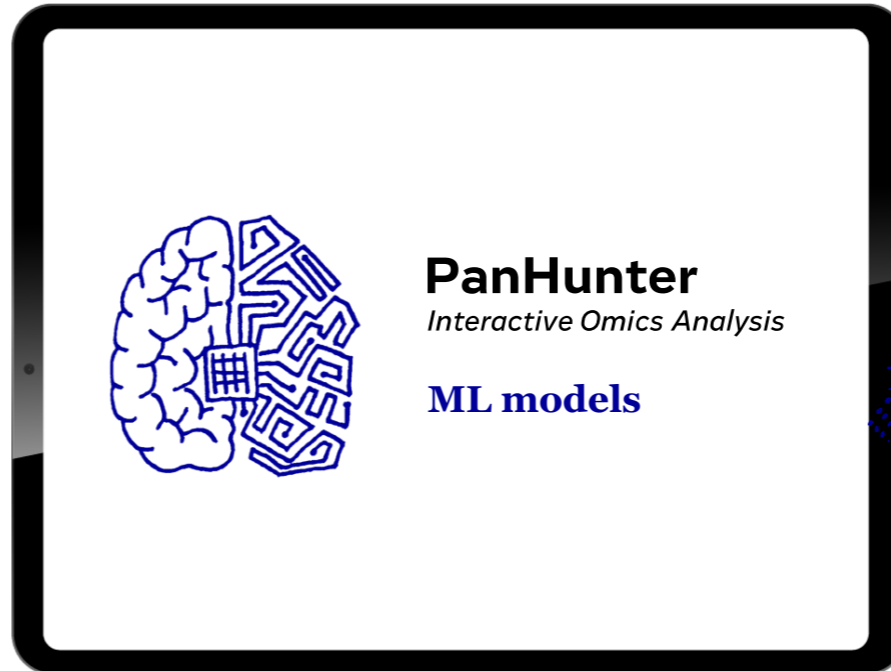
#### Clinical data

Comorbidities, Histology, Diagnosis, Organ function, Blood chemistry, BMI...

#### PanOmics

Transcriptomics, Proteomics, Metabolomics, Exome Seq, SNPs...

### Physician Network





# Transformative outcomes leading to new alliances

3 Parallel value-chains to maximize "return on investment" for our partners

## PanOmics & E.MPD Discovery today

### Our Partners

- Shared vision on **PanOmics & Molecular Patient Databases**
- Shared vision on **clinical development**
- Shared vision on **value-creation for Patients** and stakeholders

### Internal R&D Pipeline

#### Internal Discovery

- Reach inflexion point
- Partnering
- Outlicensing

### EVOgnostic & Disease markers

#### Innovative new molecular diagnostics

Molecular markers of disease progression

### Partnered Discovery Pipeline

#### Top 5 Pharma partners

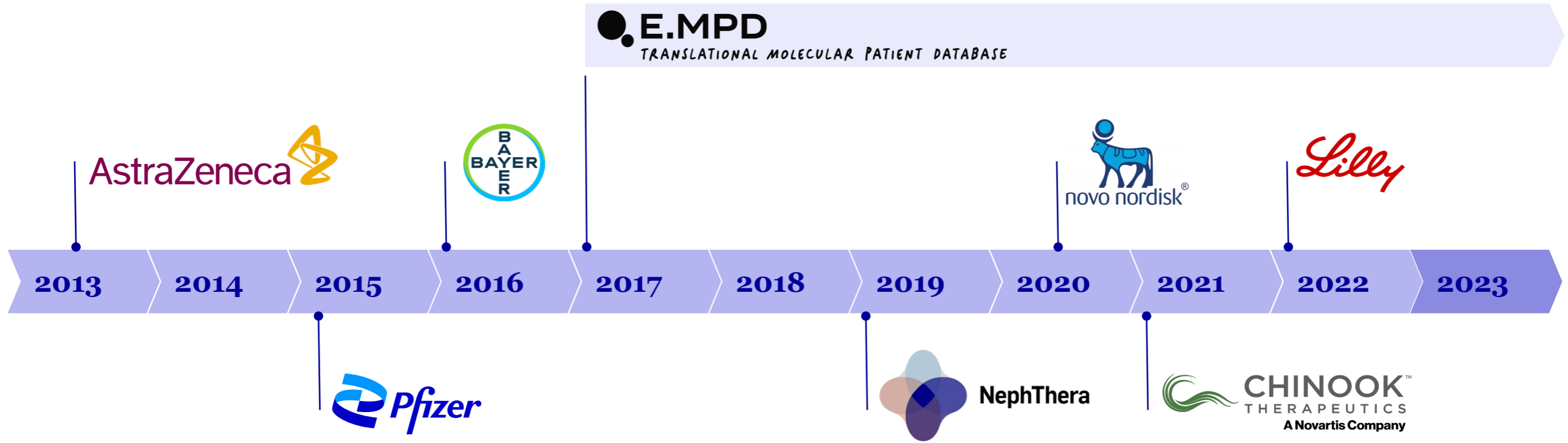
- Joint Discovery Pipeline
- Milestones incentives
- Royalties





# 7 partnering deals alone in Kidney Diseases

Value creation with limited investments



**Typical terms** • Upfront: € 1.5 – 6 m • Milestones: € 100 to 280 m • Royalties: 2 to 10%



# E.MPD expansion creates new opportunities

PanOmics-driven molecular disease understanding benefits **all key therapeutic areas**

## **E.MPD** TRANSLATIONAL MOLECULAR PATIENT DATABASE



Kidney diseases



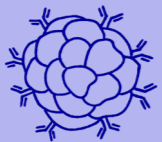
Liver  
disease



Inflammation



Fibrosis



Oncology



Neuro-  
inflammation



Infectious  
Diseases

- Unmet medical needs in Kidney diseases, acute & chronic
- Prospective longitudinal studies
- Pre-disease / early-stage disease cohorts

- Access to **Liver fibrosis** patient cohorts
- Access **Cardiovascular patient** cohorts
- Access to **Inflammatory & Autoimmune** diseases

- Access to **Oncology & Neuroinflammation** space
- Studies for effective treatment monitoring in **Tuberculosis**
- Cohort studies to understand **Acute Respiratory Distress Syndrome (ARDS)**



# Internal R&D pipeline for developments **TOGETHER** with partners

An innovative portfolio complementing current kidney diseases Standards of Care

## A portfolio with a clear value proposition ...

- Focus on biological mechanisms not targeted by standard-of-cares (eg SGLT2i, GLP/GIP agonists, MCR antagonists)
- Positioned for **Large indications** or **Rare diseases**
- **Opportunities for extension** in Cardiac, Liver, Pulmonary and Immune diseases

## ... grounded in high-quality science

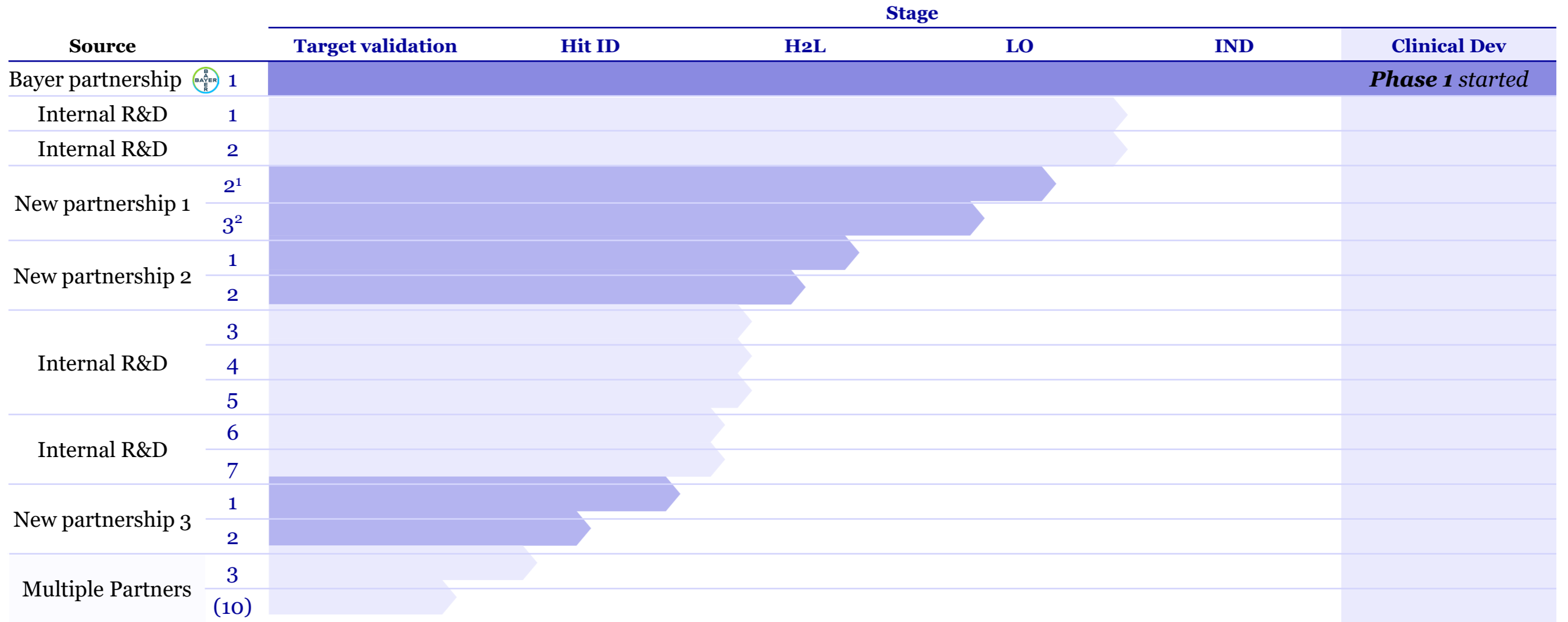
- Targets validated in Evotec's Molecular Patient Database (E.MPD) > **10k CKD patients**
- Progressed using most relevant Kidney assays
- **iPSC-derived** models including **3D organoids**
- Comprehensive panel of **in vivo models**

Potential indications	Target	Target ID	Target Validation	Hit ID	Hit to Lead	Lead Opt.	IND
DKD, Lung, fibrosis	Target 1	Small Molecule					
FSGS, AKI, AKI-to-CKD	Target 2	Small Molecule					
DKD, CVD, Metabolic	Target 3	Antisense Oligonucleotide (ASO) <sup>1</sup>					
DKD, CVD, Metabolic	Target 4	Small Molecule					
DKD, CVD, Liver fibrosis	Target 5	Small Molecule					
Early discovery E.MPD							



# Pipeline delivers first clinical candidates – more to come

> 25 active programs due to deliver MS payments in mid-to-short term





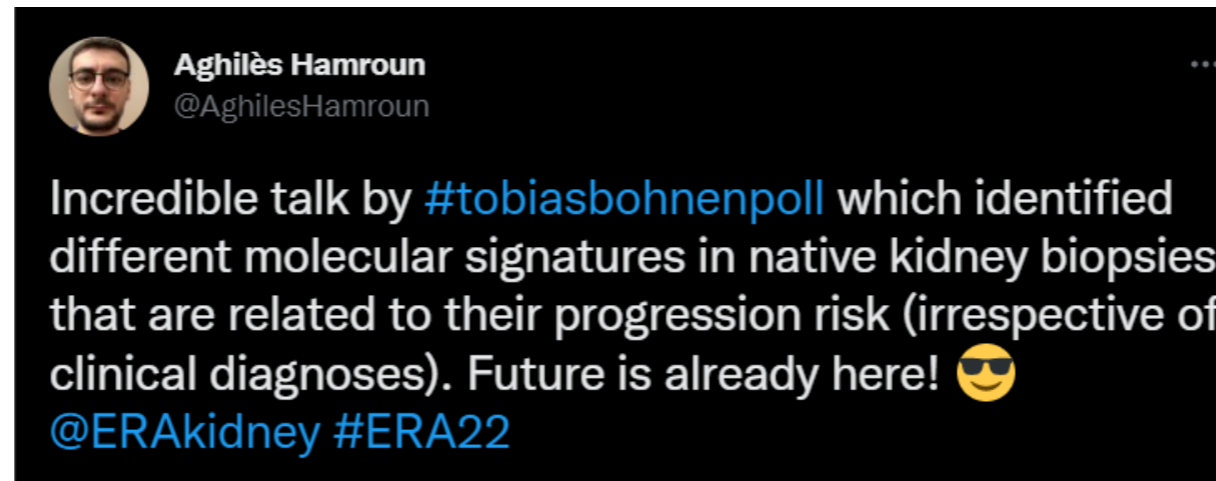
# PanOmics & E.MPD driven Discovery publicly recognized by peers

“The Future is Now”

---

## “A Systems Nephrology Framework for the Molecular Classification of Chronic Kidney Diseases”

- Oral presentation at the 59<sup>th</sup> ERA Congress in Paris (May 20, 2022)
- 5 more communications at the American Society for Nephrology (Nov 2023)





***Better pipeline building needs  
better patient stratification –  
EVOgnostics***



# Identification of disease markers leading to new alliances

The *EVOgnostic* value chain

## PanOmics & E.MPD Discovery now

## Our Partners

- Shared vision on **PanOmics & Molecular Patient Databases**
- Shared vision on **clinical development**
- Shared vision on **value-creation for Patients** and stakeholders

### Internal R&D Pipeline

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- Outlicensing

### *EVOgnostic* & Disease markers

#### Innovative new molecular diagnostics

Molecular markers of disease progression

### Partnered Discovery Pipeline

#### Top 5 Pharma partners

- Joint Discovery Pipeline
- Milestones incentives
- Royalties



# PanOmics driven diagnostics<sup>1</sup> from target identification to the clinic

Capabilities for accurate patient stratification driving personalised drug discovery

## Diagnostic Panels (EVOgnostic Disease Focus)

Partnered  
In-Vitro Diagnostics



Laboratory  
Development Test

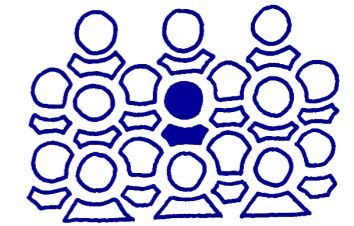


## Patient Stratification and Biomarker Discovery (EVOgnostic Tools)

Biomarker  
Discovery



From target ID to  
Clinical Trial  
Design



**EVOgnostic  
Products**

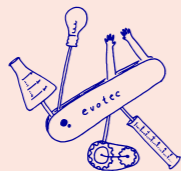
**Partnered development  
of IVD test kits, Licensing**

**Biomarker panels  
enabling LDT based  
testing, Licensing**

**Partnering/Service on  
data sharing and  
content inquiries**

**Biomarker discovery  
for early drug  
development**

**A.I./ML-driven patient  
stratification for better  
Drug Discovery**



**A comprehensive PanOmics driven diagnostic toolbox  
to successfully develop the right drug for the right patient at the right time**





# Understanding complex diseases requires better diagnostics

*Autoimmune diseases* with connective tissue involvement (CTD)

## Heterogeneous disease populations

with similar disease specific drivers and immune mechanisms

### Rheumatoid Arthritis

- A most common IMID (0.5% global prevalence)
- Inflammation of small and large joints

### Systemic Lupus Erythematosus (SLE)

- ~5 Mn people globally affected
- Inflammation of connective tissue

### Sjögren's syndrome

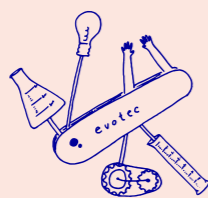
- 0.4-3 Mn people globally affected
- Affecting salivary and lacrimal glands

### ANCA Vasculitis

- 4.6–42.1 cases/100 000 individuals/year
- Inflammation of blood vessel walls

**EVOgnostic addressable unmet needs**

**Early and accurate diagnosis** to avoid organ involvement  
**Better treatment and disease progression monitoring**



**Applying a comprehensive panOmics driven diagnostic toolbox to complex disease populations to improve treatments**



# PanOmics driven diagnostics<sup>1</sup> to improve treatment selection

## Case Study 1\*: Understanding complex autoimmune diseases - Vasculitis

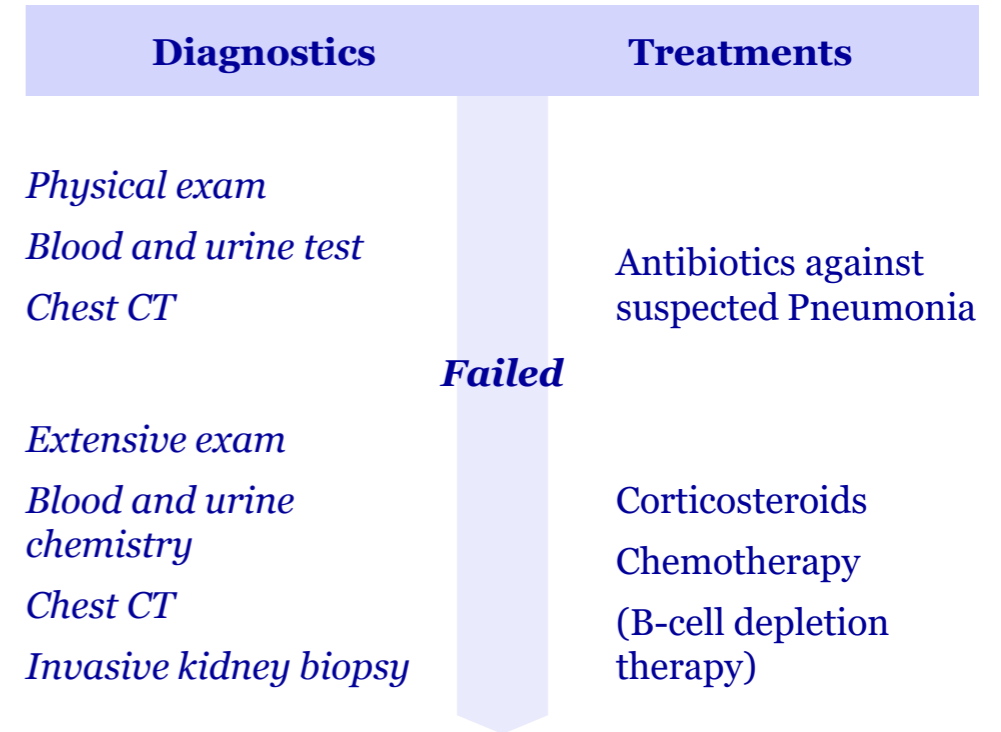


Harold Ramis (“Ghostbuster”), died from Vasculitis complications four years after diagnosis

### Vasculitis

- an autoimmune multi-systemic inflammatory vessel disease
- complex to diagnose and easily misdiagnosed
- risk of severe long-term implications

- Chest pain<sup>2</sup>, malaise and anorexia
- Elevated creatinine levels
- Suspected to have pneumonia
- Persisting symptoms for several weeks



\*The study cases described are fictitious for the purpose of illustration of the impact of disease on patients today.

<sup>1</sup> for reasearch use only

<sup>2</sup> [A case of ANCA associated vasculitis in a patient presenting with chest pain - PMC \(nih.gov\)](#)



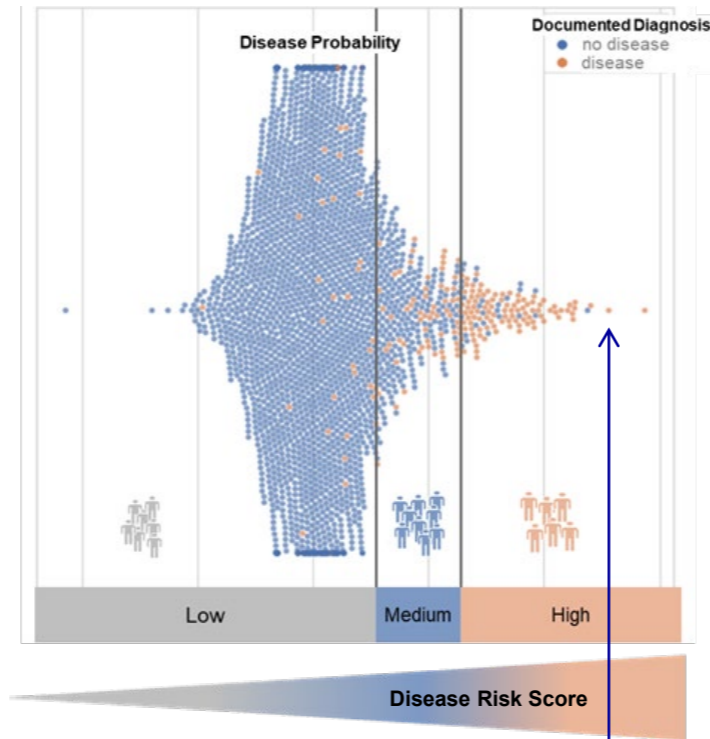
# PanOmics-driven diagnostics to improve treatment selection

PanOmics combined with ML to improve diagnosis and treatment

One blood sample per patient

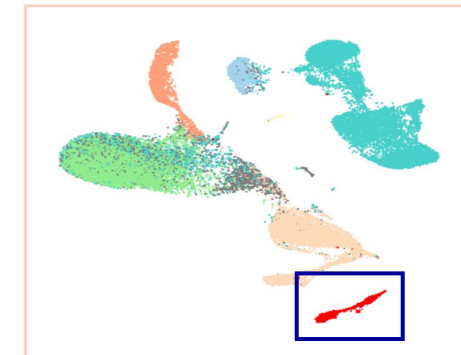
## EVOgnostic Kidney Health-to-disease map

Patient stratification based on machine learning of PanOmics results from 2000 patients

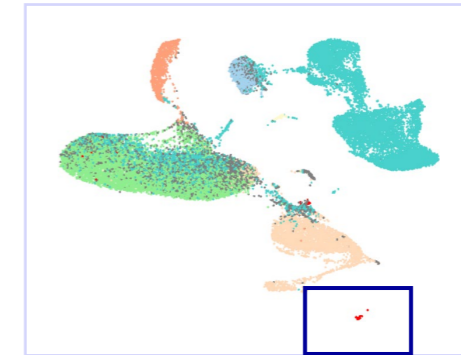


## High resolution of a blood sample down to individual blood cells

PanOmics at the single cell level



**At diagnosis:**  
B cells driving disease



**Under B-cell depletion therapy:**  
Depleted B cells under therapy

A single PanOmics test of a blood sample positions a patient on the map for probability of Vasculitis disease

and provides disease understanding at the molecular level for treatment monitoring



# PanOmics driven prognosis for better disease management

## Case study 2\*: Understanding complex autoimmune diseases – Systemic Lupus Erythematosus (SLE)

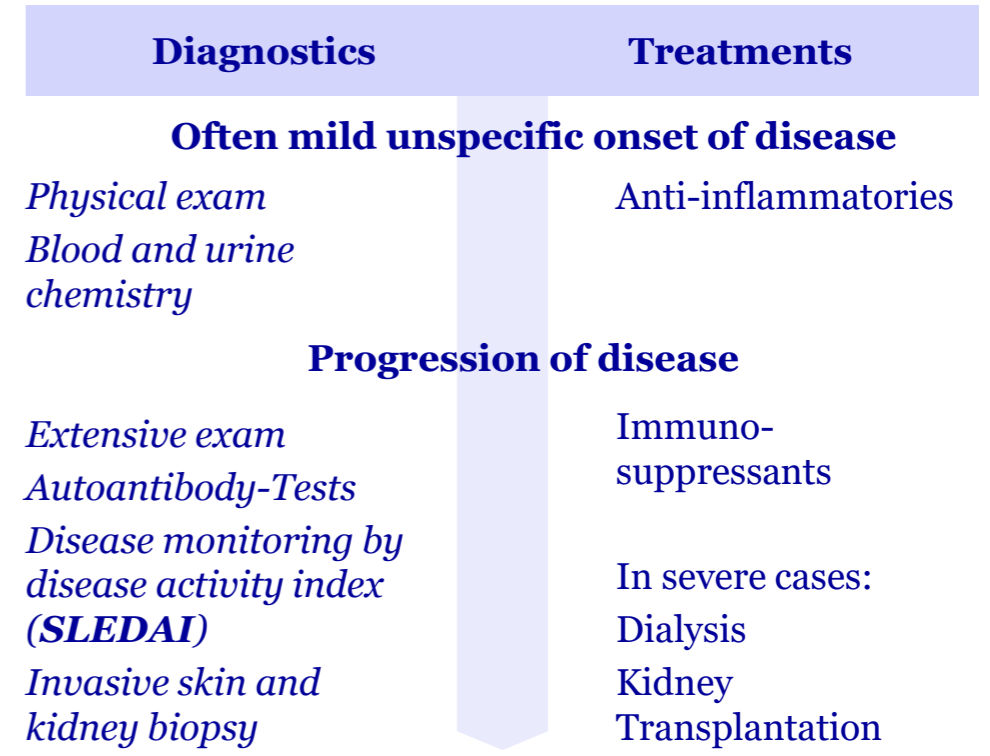


Selena Gomez, diagnosed with SLE, received kidney transplant in 2017

### Systemic Lupus Erythematosus (SLE)

- an autoimmune disease with multi-systemic manifestation
- easily misdiagnosed
- delayed diagnosis can lead to irreversible organ damage

- Unrelenting fatigue, weakened immunity
- Often multi-year journey before SLE diagnosis
- Potential of kidney inflammation and failure / Organ transplantation





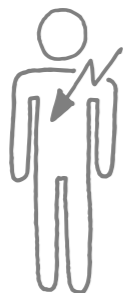
# PanOmics driven prognosis for better disease management

PanOmics combined with ML to monitor disease activity, improve prognosis and treatment

## SLE disease activity index (SLEDAI)

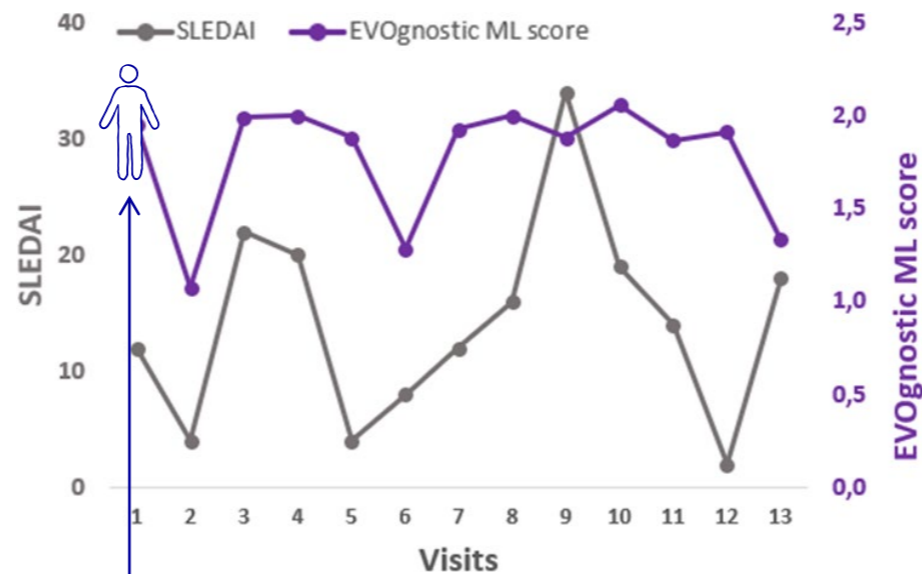
Today a weighted diagnostic metric of 24 components is used to measure disease activity

• Seizure	8
• Psychosis	8
• Organic Brain Syndrome	8
• Visual Disturbance	8
• Cranial Nerve Disorder	8
• Lupus Headache	8
• Cerebrovascular accident	8
• Arthritis	4
• Myositis	4
• Low Complement	2
• Increased anti-dsDNA	2
• Thrombocytopenia	1
• Leukopenia	1
• Alopecia	2
• Mucosal Ulcers	2
• New Rash	2
• Fever	1
• Pericarditis	2
• Pleuritis	2
• Vasculitis	8
• Urinary Casts	4
• Hematuria	4
• Proteinuria	4
• Pyuria	4



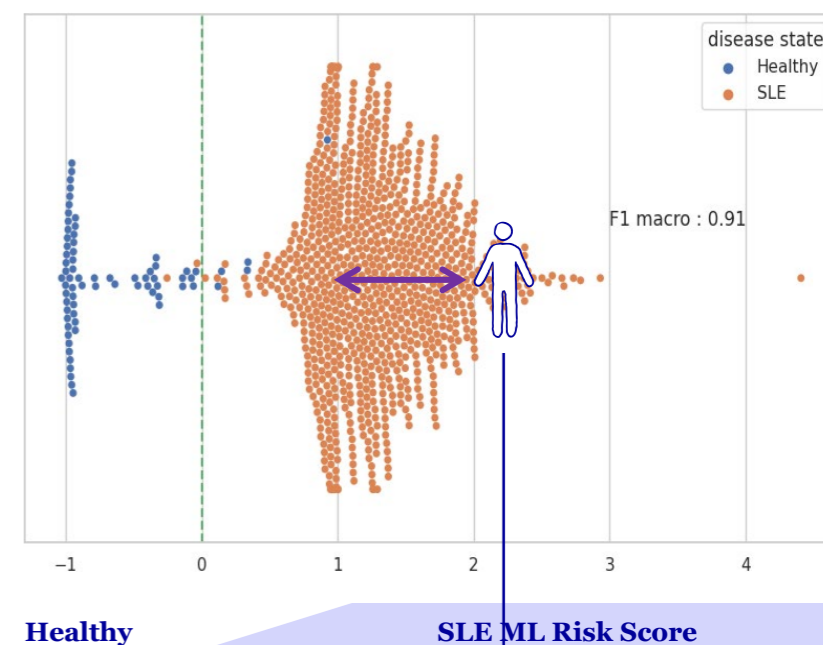
## EVOgnostic disease score reflects disease flares

SLE patient monitored over 13 visits.  
The patient had two flares (Visit 3-5 and 8-12).



## EVOgnostic SLE Health-to-Disease Map

Assessment of disease progression based on PanOmics results from one blood sample



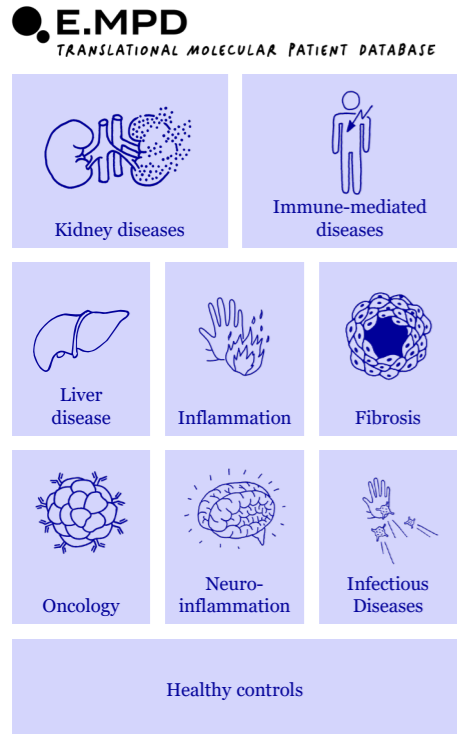
A single PanOmics test of a blood sample positions a patient on the map for prediction of disease progression in SLE



# Multiple opportunities ...just at the beginning

## Health-to-Disease Maps and biomarker discovery

### Patient cohorts



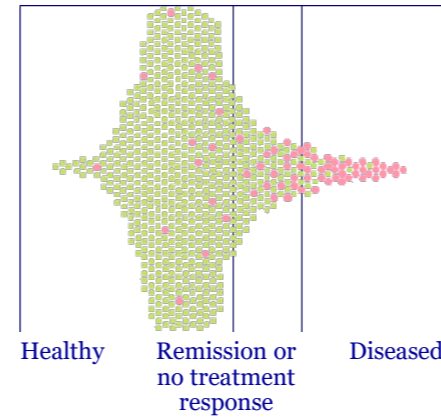
### Physician Network

### PanOmics and ML

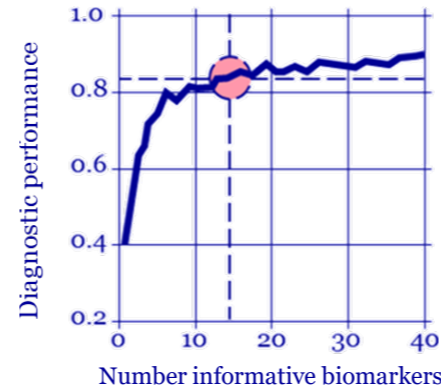


### Patient Stratification

#### Health-to-Disease Map



#### Biomarker Discovery



### Evotec Opportunities

**EVOgnostic - Evotec's panOmics driven diagnostics is a comprehensive toolbox to successfully develop the right drug for the right patient at the right time**

- A.I./ML driven accurate patient stratification for better drug discovery with **pharma partners**
- Biomarker panels enabling partnerships with the **diagnostic industry and clinical laboratories**
- Companion diagnostics driving precision medicine in complex diseases e.g. kidney, cardiovascular and autoimmune diseases with **pharma and diagnostic partners**



# ***Better pipeline building needs advanced disease modelling***



# A cure for Leah

Case study: Amyotrophic lateral sclerosis (ALS)

---



## Leah

- Amyotrophic lateral sclerosis (ALS)
- Age 30
- First symptoms at 25
- Diagnosed at 27, bound to wheelchair since age of 28
- Prognosis: 2-5 year life expectancy
- Formed not-for profit network 'Her ALS Story'<sup>1</sup>





# Ice Bucket Challenge in 2014 to raise awareness for ALS<sup>1</sup>

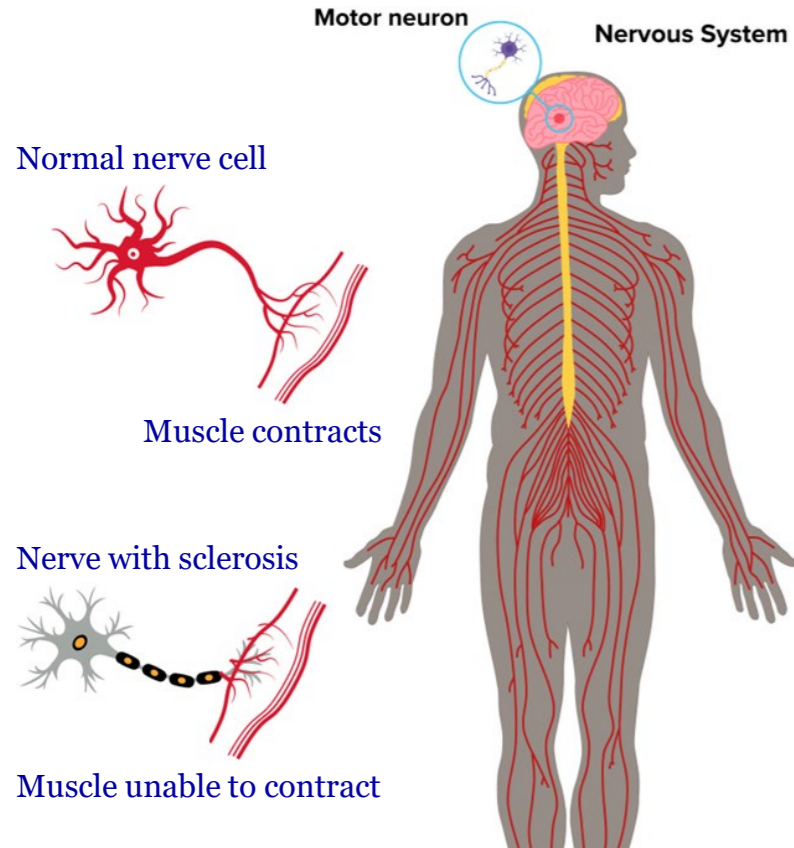
ALS, amyotrophic lateral sclerosis, also known as motor neuron disease or Lou Gehrig's disease





# ALS is a fatal neurodegenerative disease with high unmet medical need

Causes the brain to lose connection with the muscles



## Amyotrophic lateral sclerosis (ALS)

- Rapidly progressing disease caused by death of motor neurons
- Motor neurons control voluntary muscle movement and breathing
  - Survival is typically only 2-5 years from symptom onset<sup>1</sup>
  - ~75k<sup>2</sup> diagnosed prevalent patients worldwide (2022), expected to increase to ~80k (by 2030)
  - Limited treatment options
  - No known cure to stop or reverse ALS

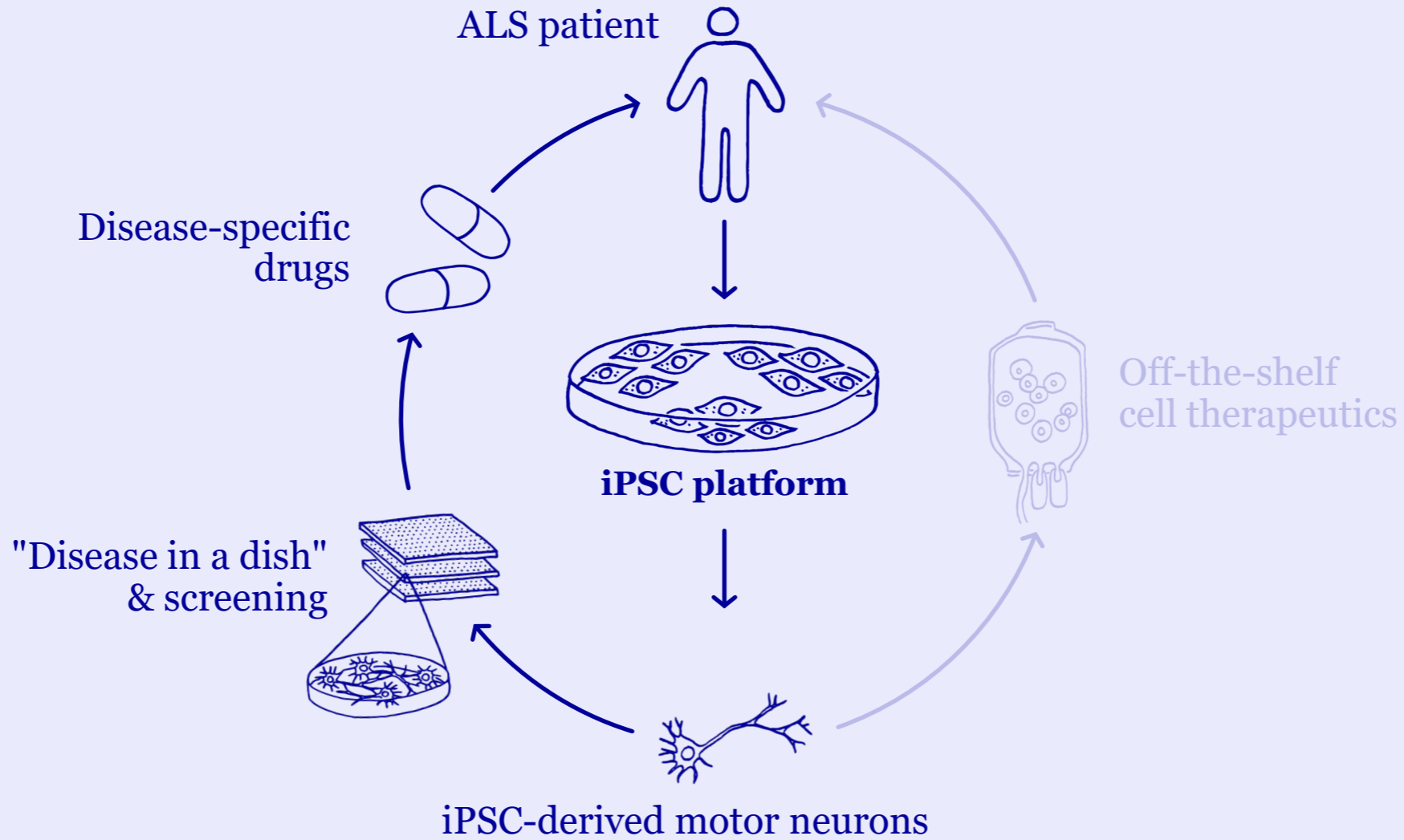
*High failure rates in ALS clinical trials due to overreliance on non-physiological ALS mouse models.  
→ strong need for better representation of disease with human cellular models for improved clinical translatability.*



# From humans for humans

## iPSC-based drug discovery

**E.iPSC –**  
Human disease  
relevant modelling



**iPSC-based  
off-the-shelf  
therapeutics**



HSCI HARVARD STEM CELL INSTITUTE

# Our first iPSC program dedicated to discovery of new ALS treatments

Established protocol for ALS patient derived iPSC motor neurons in collaboration with HSCI



## NEWS RELEASE

12 September 2013

'RESEARCH NEVER STOPS'

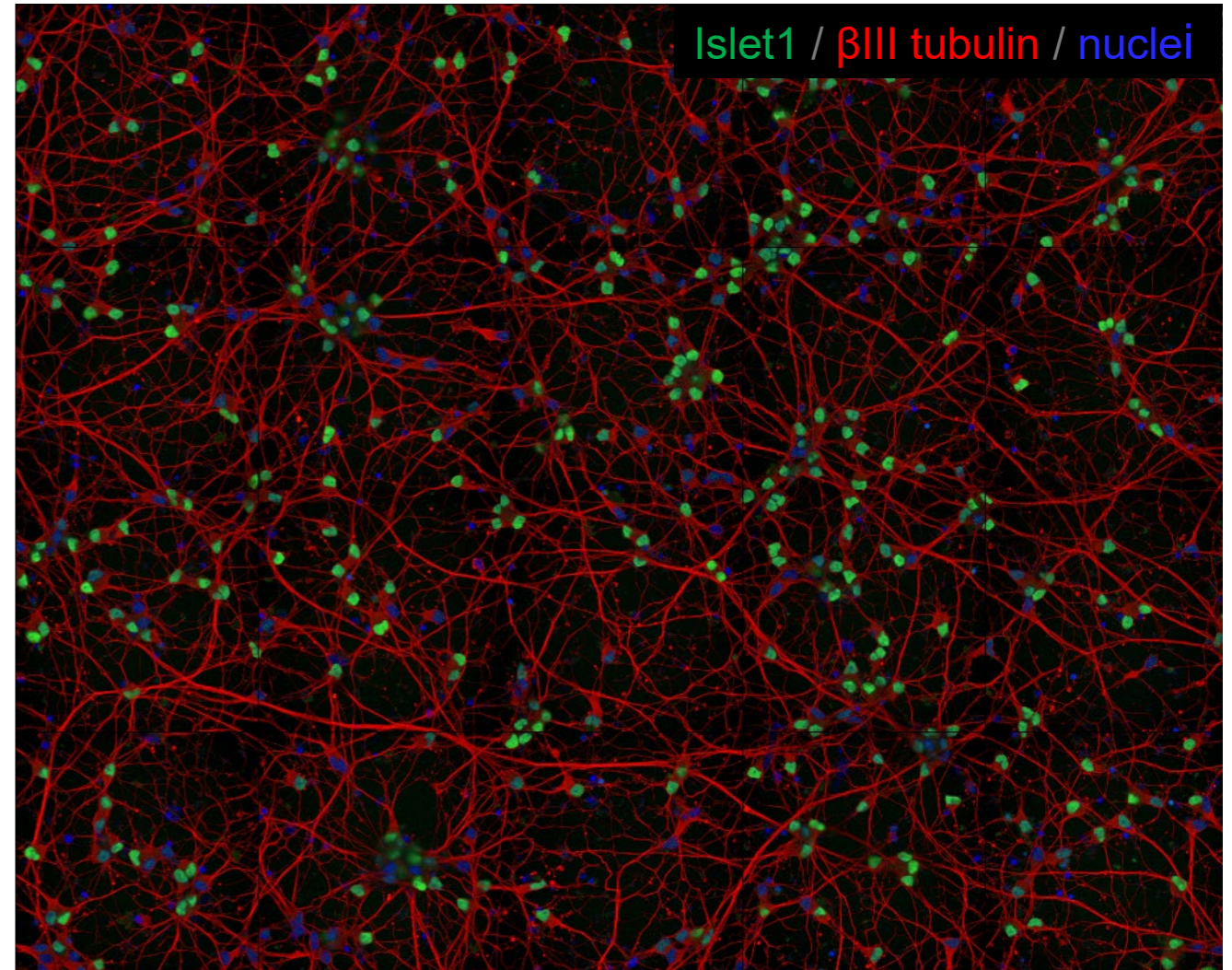
info@evotec.com | www.evotec.com

**Evotec and Harvard Stem Cell Institute form CureMN collaboration to advance ALS research**

Prof. Kevin Eggan



Prof. Lee Rubin





# Taking iPSC to an industrial level for large scale drug discovery

Highly scalable and automated laboratory workflows

## Industry scale

- High quality iPSC and iPSC-derived cells
- Optimized protocols in 2D & 3D
- Strict QC
- Upscaling for high throughput (high reproducibility)

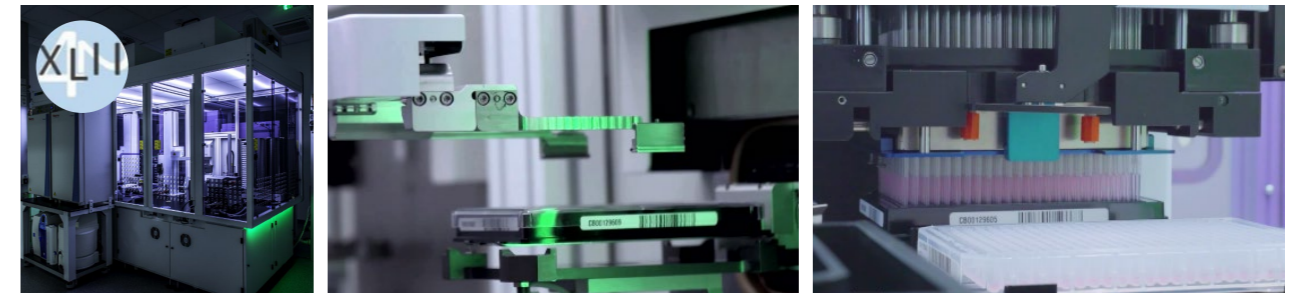


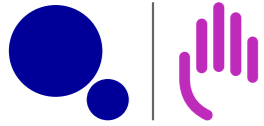
## Automated workflows

- Sterile long-term culture
- High throughput drug screening

> 20 drug discovery programs

*1<sup>st</sup> IND in clinical development since 2021*

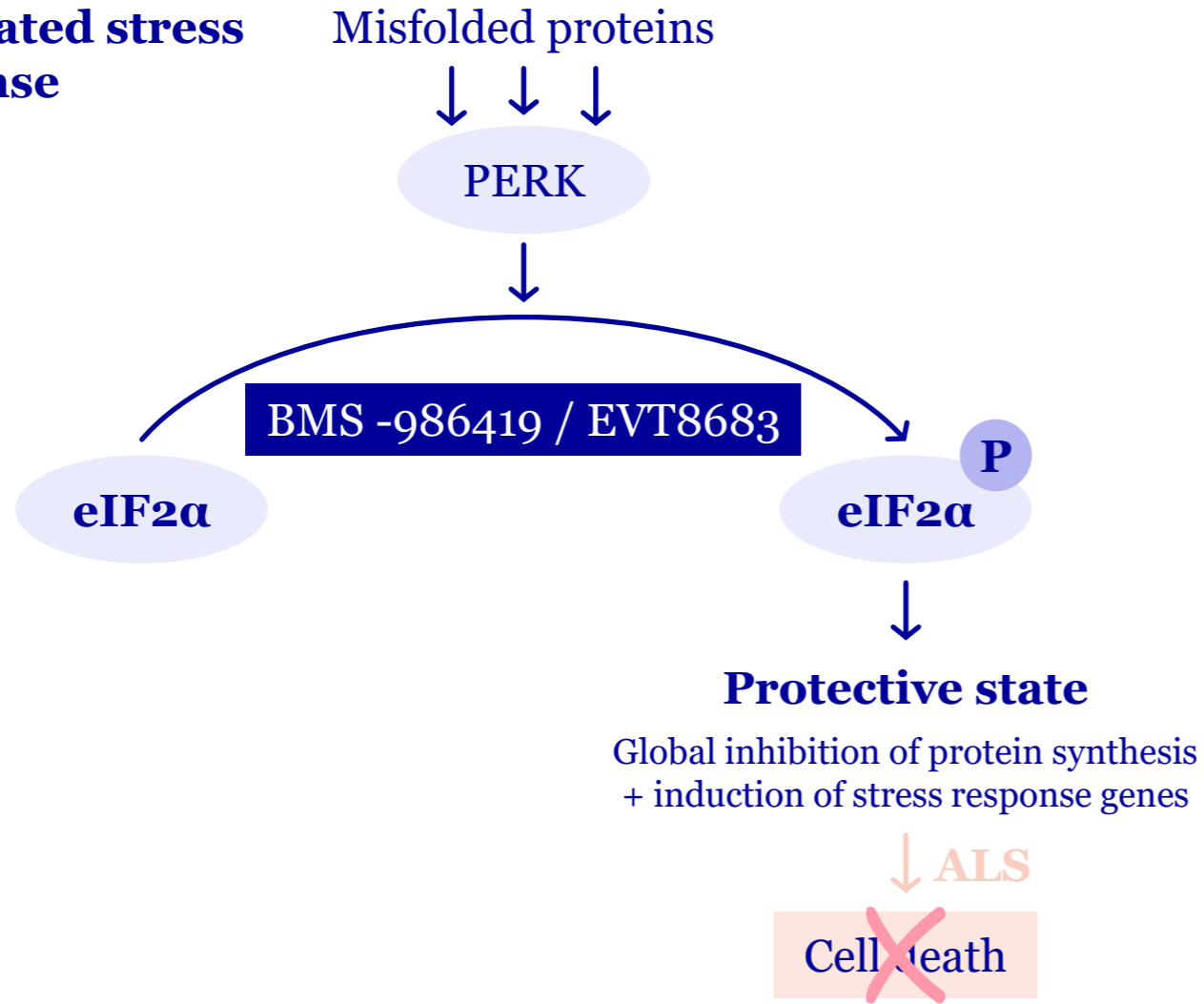




# BMS-986419\* restores normal Integrated Stress Response (ISR) function

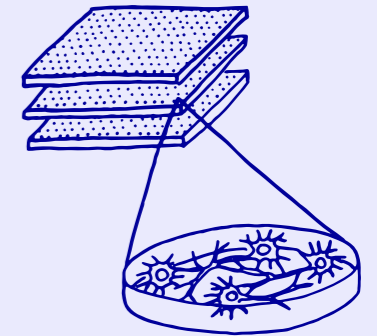
Chronic activation of ISR in ALS disease can lead to cell death

## Integrated stress response



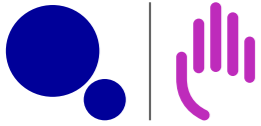
- The eIF2 complex is an ISR<sup>1</sup> “master regulator” that becomes dysfunctional in chronic disease: chronic stimulation of ISR leads to cell death

- We established *in vitro* model with iPSC-derived motor neurons recapitulating chronic stress



- Phenotypic screening in iPSC-derived motor neurons identified ISR<sup>1</sup> modulator

- **BMS-986419 / EVT8683** binds to a subunit in the eIF2 complex (eIF2B) restoring normal protein clearance and cellular homeostasis



# Potential across a range of neurodegenerative conditions

eIF2B activator (BMS-986419 / EVT8683) is moving into a Phase II trial in ALS

## Misfolded protein accumulation & evidence of ISR activation present in multiple neurological conditions<sup>1</sup>

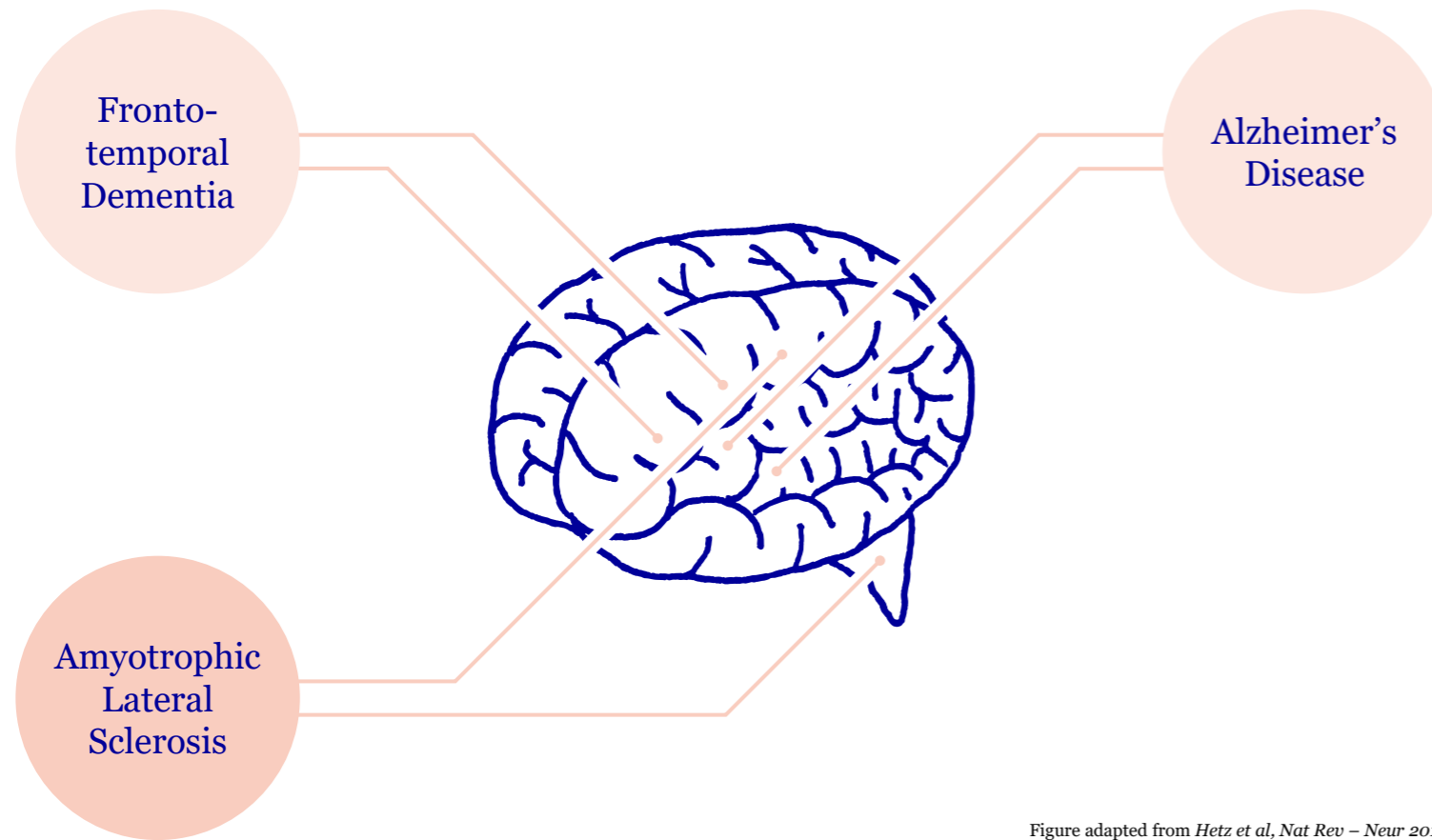


Figure adapted from Hetz et al, Nat Rev – Neur 2017

## BMS-986419 / EVT8683

- Safe and well-tolerated in Phase I clinical study in healthy volunteers<sup>2</sup>
- Potential opportunity as monotherapy or combinations
- **Phase II study in ALS initiating in 2024**



# A growing portfolio of iPSC models to tackle more diseases

Ongoing collaborations and opportunities leveraging our PanOmics drug discovery platform



*“Our unique combination of disease & platform expertise provides the basis for our success.”*

	Therapeutic area	iPSC model	Indication	Partner & status
<b>Partnered</b>	Neurodegeneration & inflammation	Neurons, astrocytes, microglia, co-cultures	AD, PD, ALS, ...	Partnered in 2016, >20 projects at different stages, first IND in clinic since 2021
	Eye diseases	RPE	AMD	Partnered in 2022, Hit validation stage
<b>Internal R&amp;D</b>	Psychiatric disease	Neurons, astrocytes, microglia, co-cultures	SCZ, MDD, ...	<b>Next Collaboration opportunities</b>
	Eye diseases	Photoreceptors, retinal organoids	Diabetic retinopathy, glaucoma, ...	
	Kidney diseases	Podocytes PTECs Kidney organoids Ureteric bud organoid <sup>1</sup> Immuno-Kidney organoids <sup>1</sup>	DKD, AKI, CKD, ADPKD, TOX/Safety, ...	
	Metabolic diseases	Hepatocytes Liver organoids	NASH/MASH/TOX/Safety, ...	
	Cardiovascular disease	Cardiomyocytes Cardiac microtissues	Dilated cardiomyopathy, TOX/Safety, ...	
	Inflammation & Immunology	Macrophages Tregs <sup>1</sup>	Chron's, IPF <sup>2</sup> , ... AIDs <sup>3</sup>	



<sup>1</sup> Planned for 2024

<sup>2</sup> Potential TAs: fibrotic diseases impacting liver, lung (IPF), kidney, heart, intestine (IBD), skin

<sup>3</sup> AID = autoimmune disease; Potential TAs: Rheumatology (RA, lupus), Gastroenterology (IBD, UC, CD, NASH), Dermatology (AD, psoriasis), Pulmonology (IPF, ILD, COPD), Nephrology (CKD, SLE)





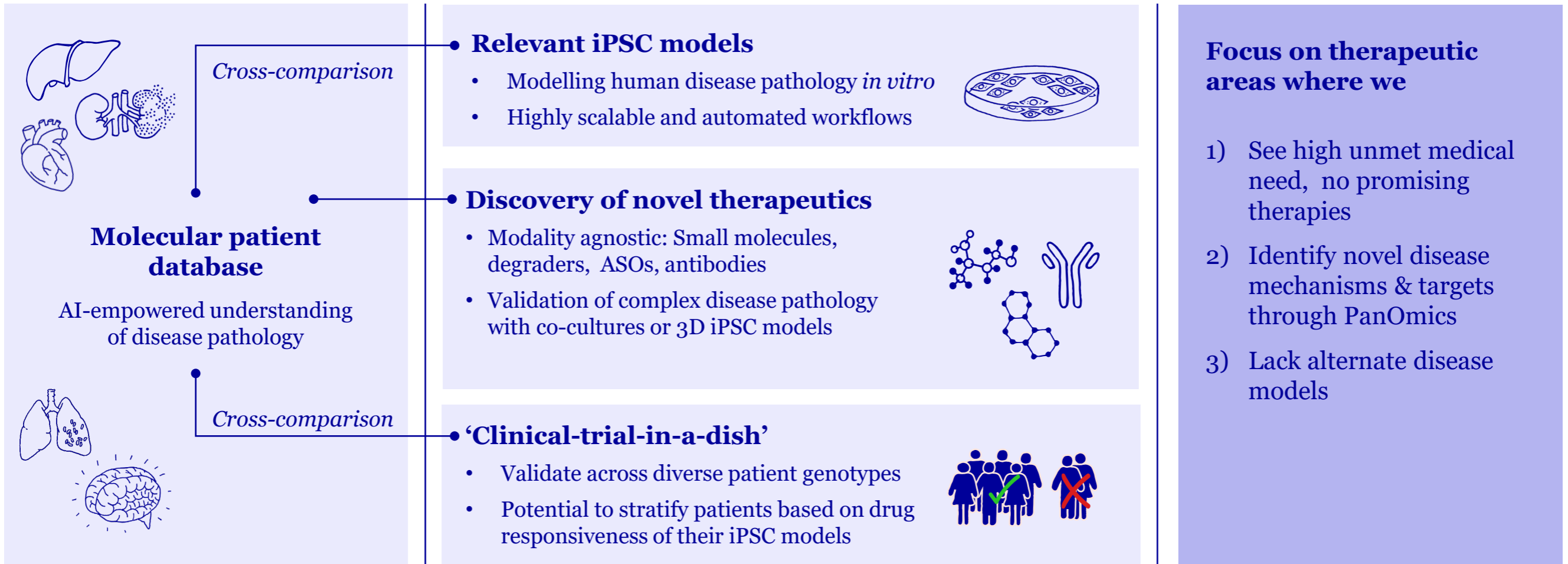
# From humans, for even more humans

More and more disease models to come

## Unravelling complex disease - E.MPD -

## Exploring disease biology at scale - E.iPSC -

## Fueling diverse program pipelines





# *Efficient pipeline building accelerating with A.I.*



# Strong influence of A.I. on the Pharma/Biotech Industry

Overview of anticipated benefits

## Linear

### **Precision:**

A.I. enables fine-tuning of compound properties for specific applications

### **Scalability:**

Automated processes can handle large-scale production efficiently

### **Cost Reduction:**

Fewer resources are required for R&D and manufacturing

### **Speed:**

A.I. accelerates antibody development, reducing time-to-market

Status today



## Non-linear

### **Increase of non-linear “Eureka” events:**

A.I. enables enabled findings outside of accessible human logic





# Sharing our peer-reviewed cutting-edge research work

Examples of research in the field of A.I./M.L. and High-Performance Compute for Drug Discovery



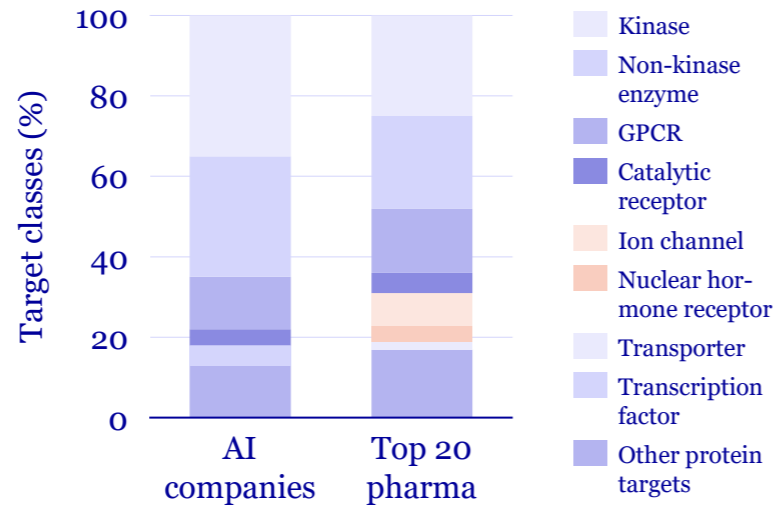
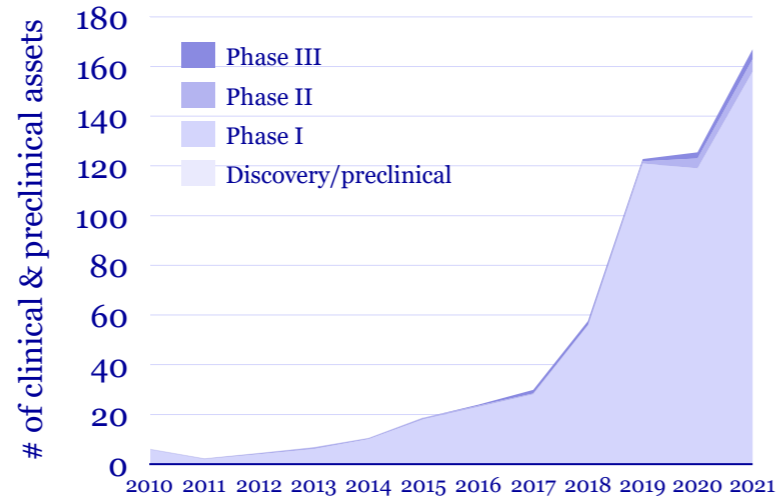
## High recognition in scientific community

- Two peer-reviewed books produced by Evotec teams on A.I./M.L. algorithm and HPC for A.I./M.L., Quantum Computing application to Drug Discovery and Development
- **A.I. in Drug Discovery** book copies sold/ accessed **115,000** times (till Oct2023- Published in 2021)
- **HPC for Drug Discovery and Biomedicine** copies sold/accessed **7,950** times (till Oct 2023-Published in Sept 2023)

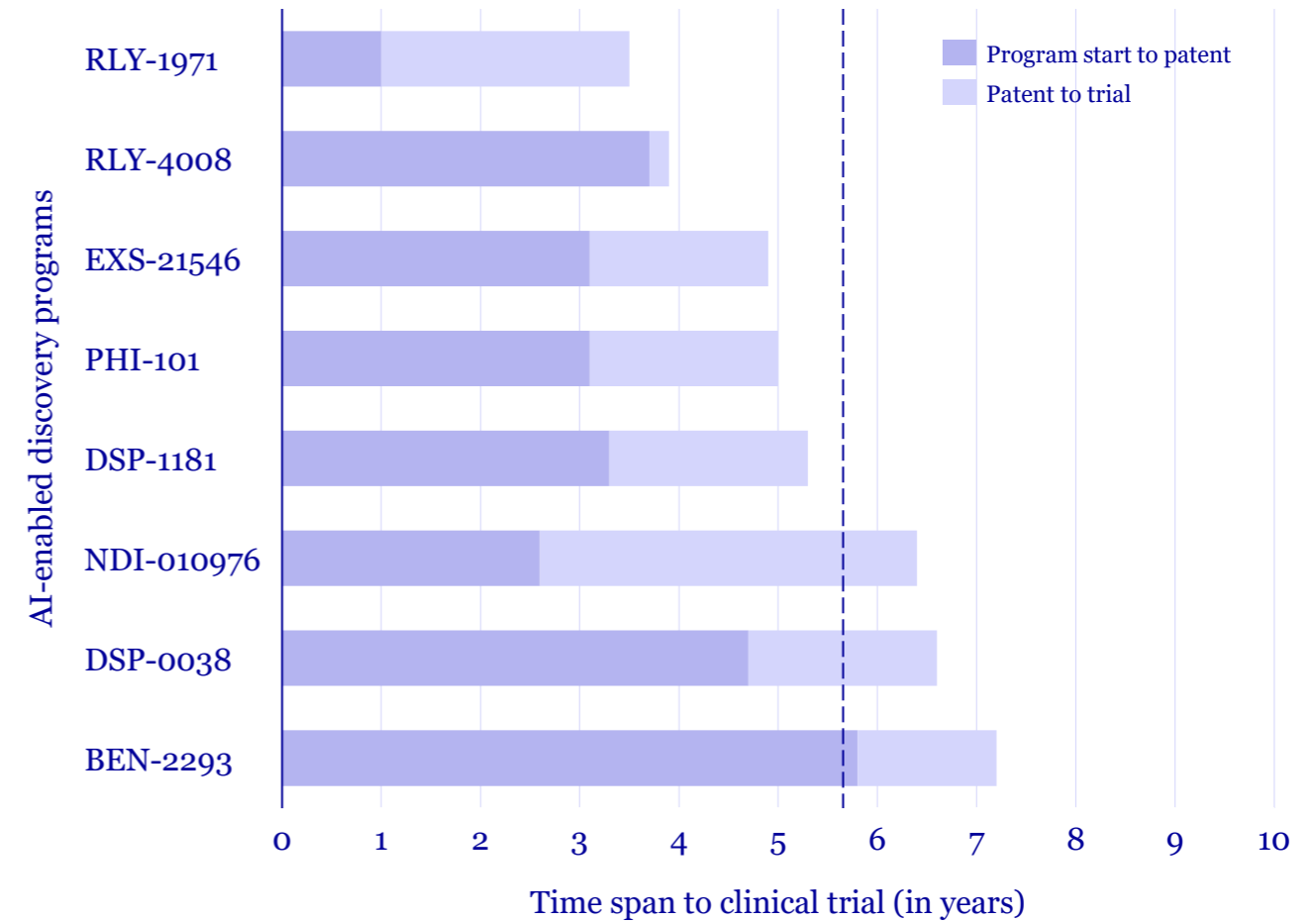


# Reduction of time to clinical trials observable, but early days

Outcomes, not only speed matters



## Potential to reduce time from bench to clinical trial





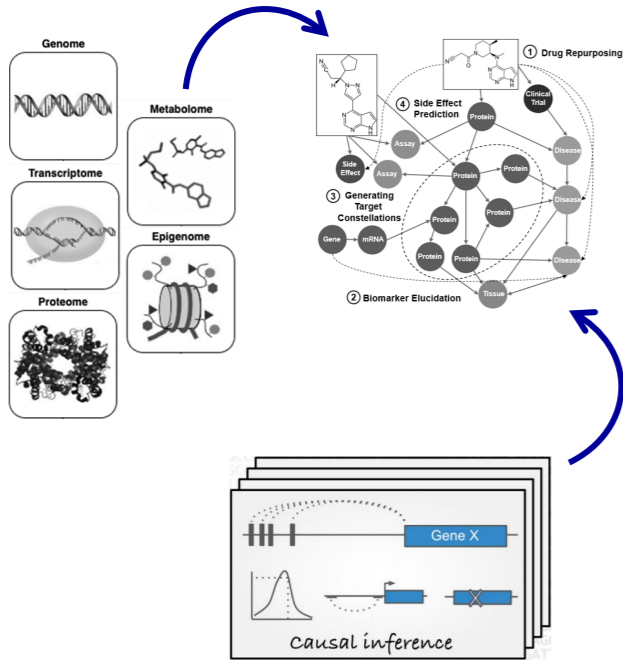
# Integrated A.I./M.L. throughout the drug discovery value chain

Examples of applications

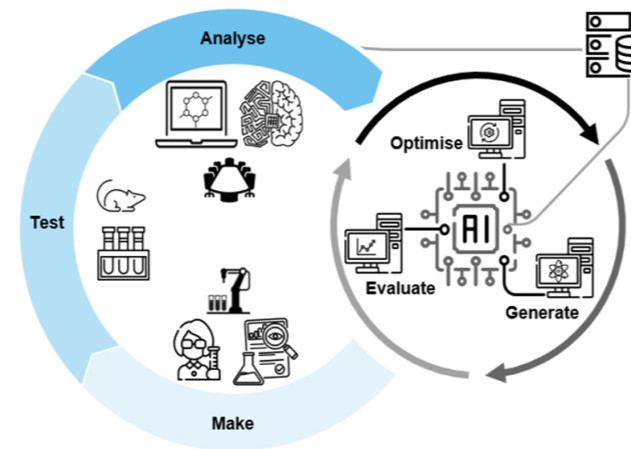


 PanOmics data analytics and compound profiling along the full value chain

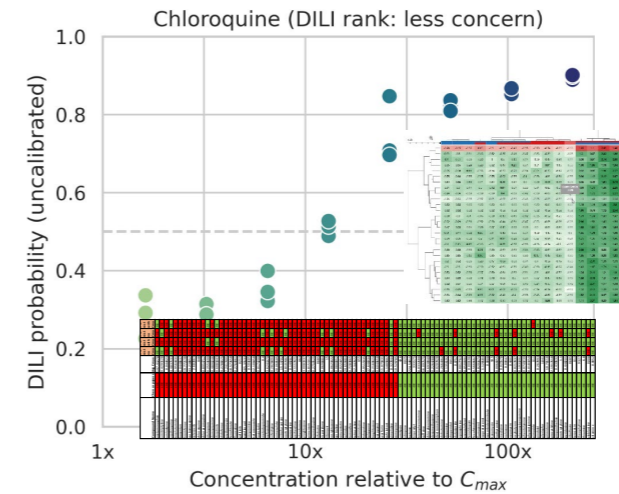
## 1. Target ID / Validation



## 2. Hit and Lead Optimisation



## 3. Safety prediction

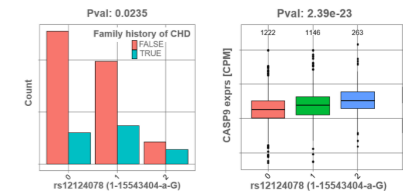


70 → 87% prediction accuracy improvement over current gold standard HCI based DILI platform<sup>1</sup>

## 4. Patient selection



Patient stratification



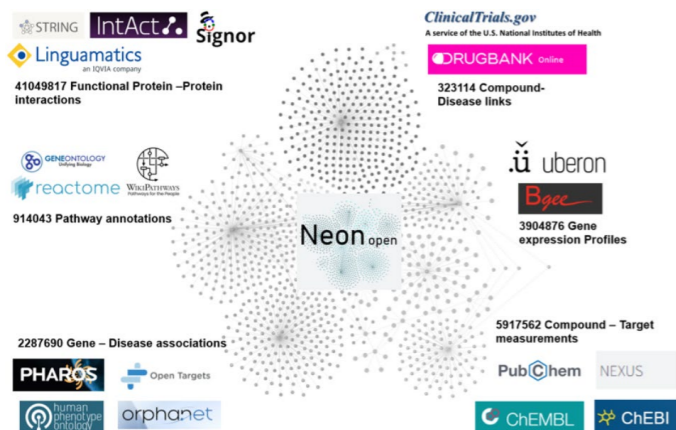
(Automated bivariate analysis of clinical & genotyping data for a selected cohort of interest)



# 1. Target ID / Validation with A.I. enabled data mining

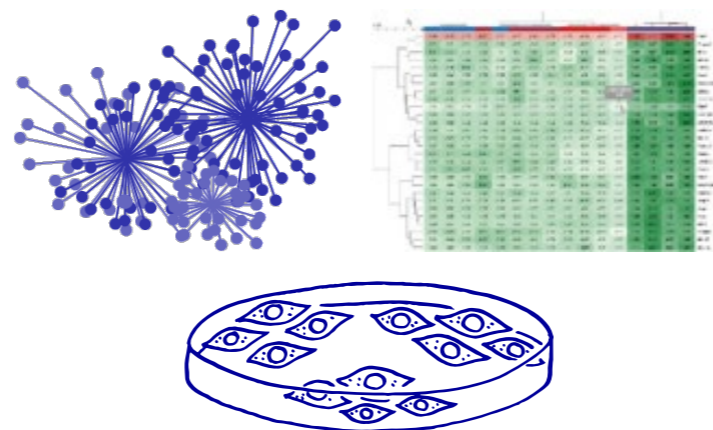
Selection, identification and validation to a ranked compound hitlist using automatic workflows

## Target Identification



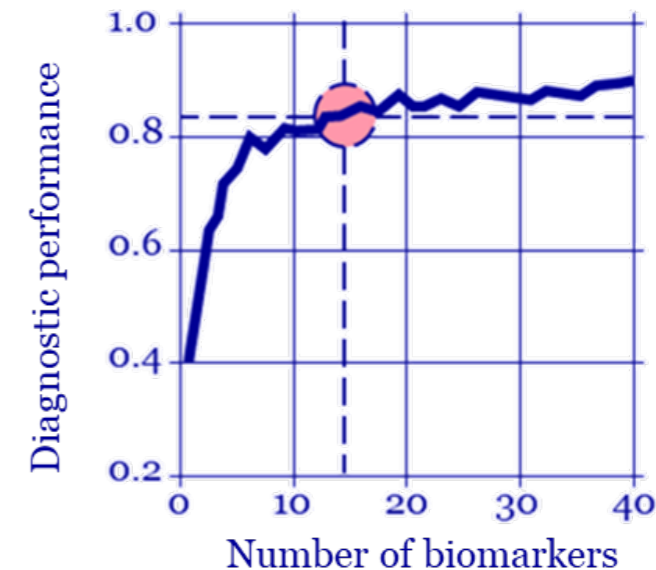
Potential novel target for disease modulation

## Target Validation



Selecting Target/screening

## Assay Development



Project timeline: 16-20 weeks

- New Target validation
- Aids in identification of new modalities
- Rapid mining of multi-omics datasets



## 2. Generative A.I. driven Drug Design – reinforcement learning

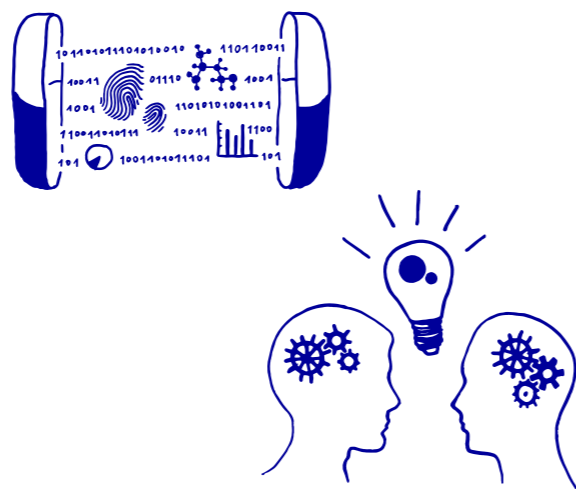
### Small Molecule Generative Design

#### Starting from Series of Target X inhibitors

- Compounds not potent enough
- Compounds not in the druggable (Physicochem) space
- Several ADMET issues

#### A.I. Generative Design

- Reinforcement Learning
- Synthesizability assessment

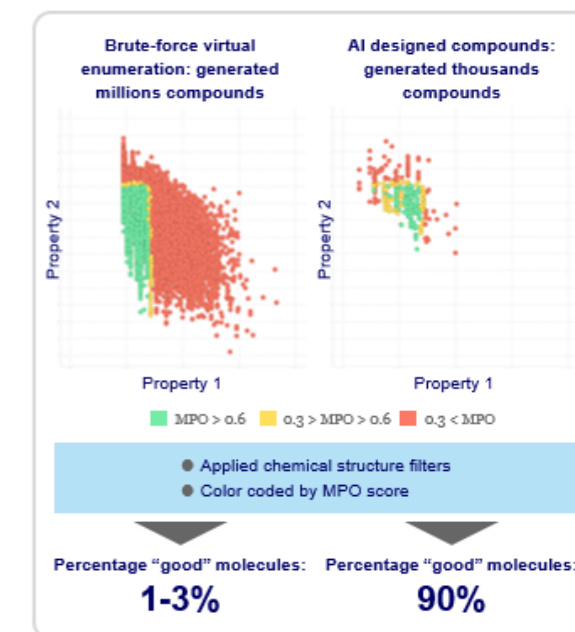


#### Novel compound series identified

- Identified **novel series** of Target X inhibitors
- **Increased** potency and bioavailability
- Improved overall **ADMET** properties



#### Impact on Drug Discovery



- Increased probability of Success to 90%
- Time reduced to 70% (average)

**Project timeline: 12 weeks**





# 3. Future of Safety Prediction is A.I. and Omics-driven

## High-throughput omics towards benefit-risk prediction: safety prediction example

### Relevant cellular models

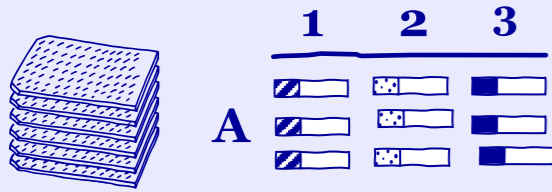


### Proprietary safety database



### Safety liability modelling

#### High-throughput omics



#### Organotypic (human) models



- Improving sensitivity and specificity of safety prediction
- Understanding mechanisms of toxicity

Known toxic compounds

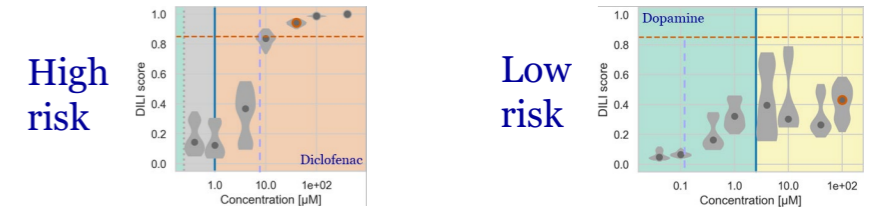
FDA DILI assigned drugs

Reference drugs with adverse organ toxicity

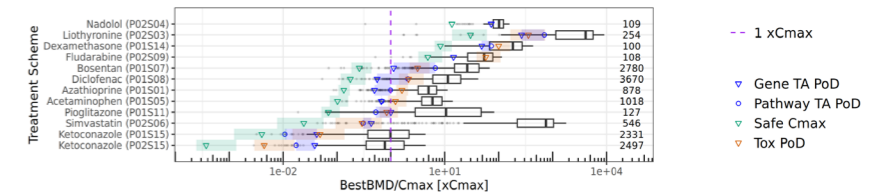
Marketed drugs

Mechanistic compounds & drug properties

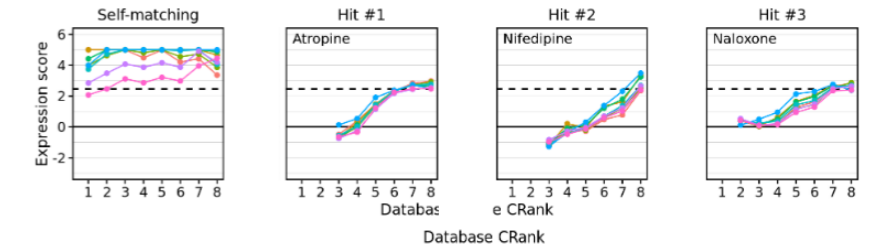
#### AI/ML predictions of safety liability risk



#### Mechanism of action & PoD safe dose prediction



#### Compound matching to safety database



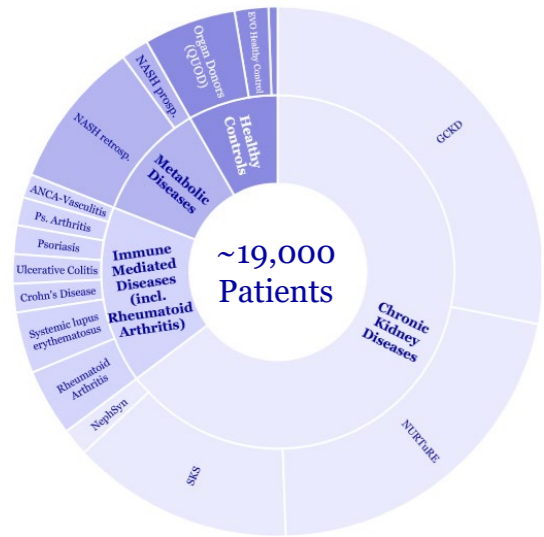
**Superior prediction** versus traditional approaches; DILI prediction shown to increase from 70% to 87%



# 4 Generative A.I. driven Patient selection

## Patient Cohorts

**E.MPD**  
TRANSLATIONAL MOLECULAR PATIENT DATABASE



Healthy controls

Physician Network

## A.I./M.L. based Model

- Use of 'omics' (Transcriptomics, sc/snRNA-Seq, Proteomics, Metabolomics, Exome Seq, SNPs) data
- Expert curated clinical/ Phenotypic (Comorbidities, Histology, Diagnosis, Organ function, Blood, Pathology) data
- A.I. model (bidirectional LSTM) training

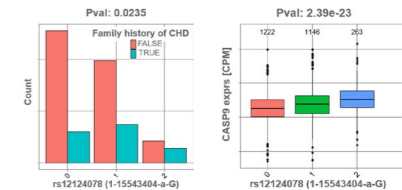
## Validation

- Validate the model (domain experts)
- Review the score and prediction
- Identify cohort-based patient selection

## Impact on Drug Discovery



Patient stratification



(Automatized bivariate analysis of clinical & genotyping data for a selected cohort of interest)

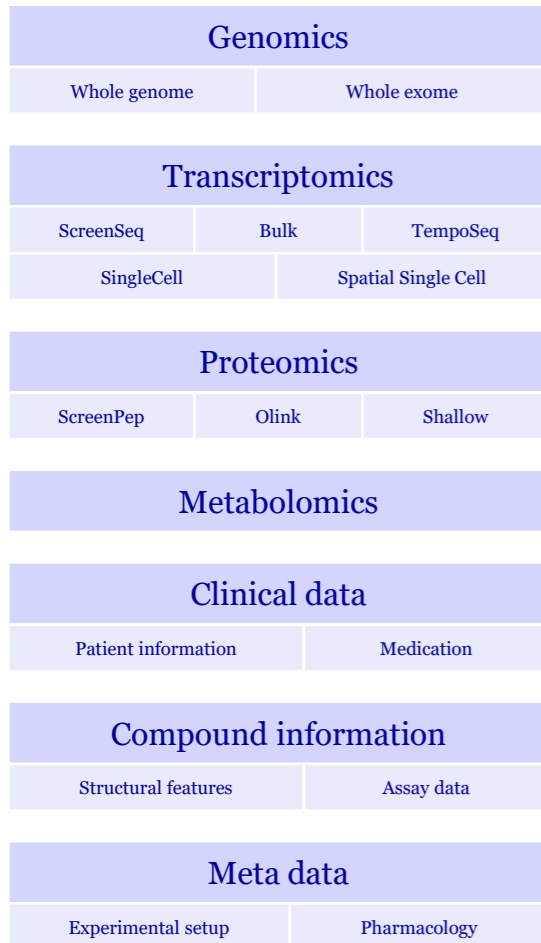
- Identification/Selection of Right Patient population
- Enable reduction in size, scope, duration and cost optimisation



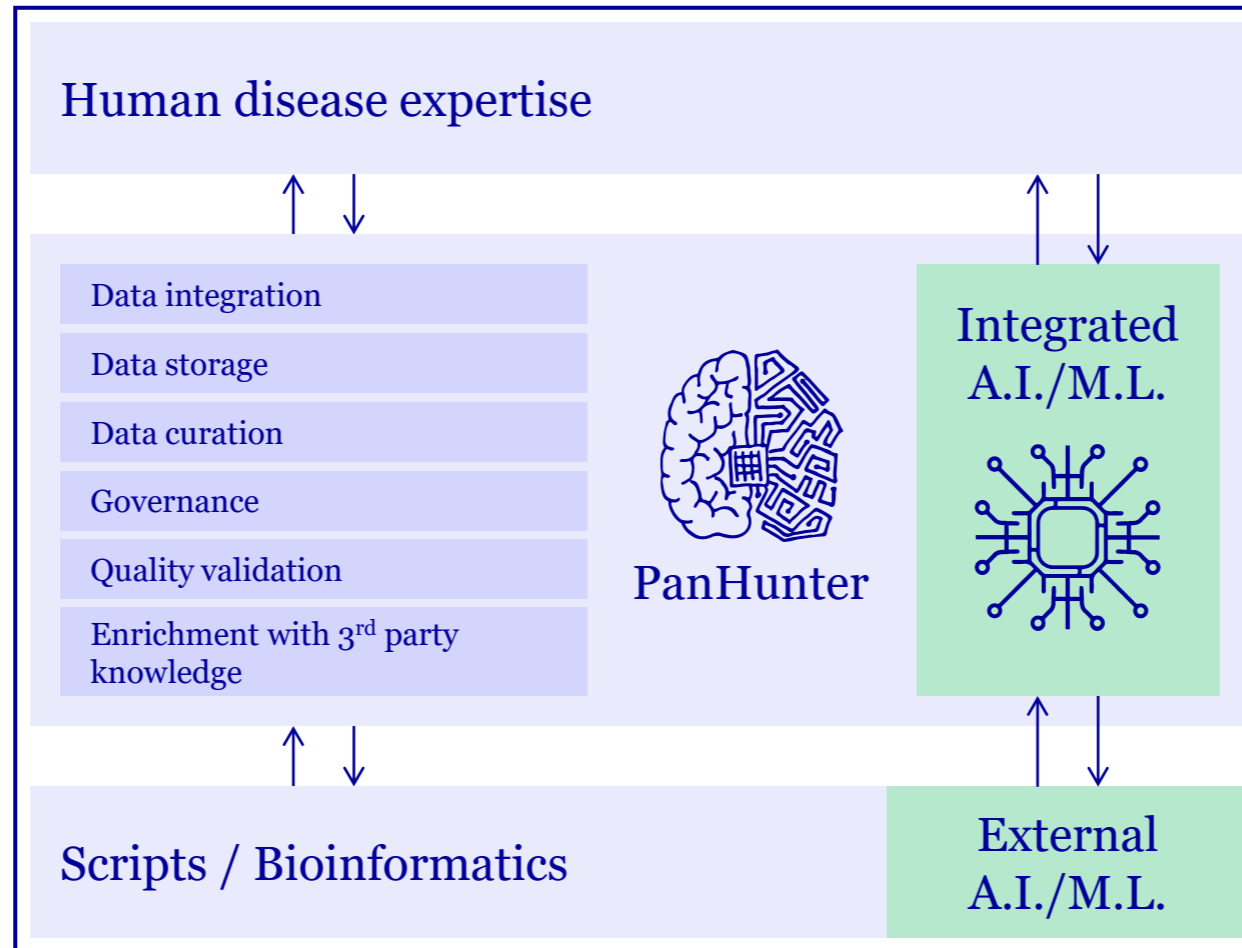
# PanHunter is the platform to manage high dimensional data

PanHunter: Full-scale A.I. driven analysis platform

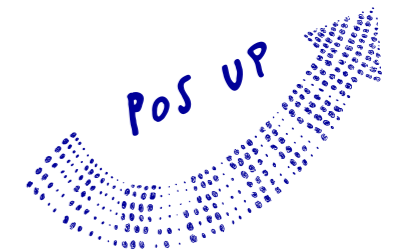
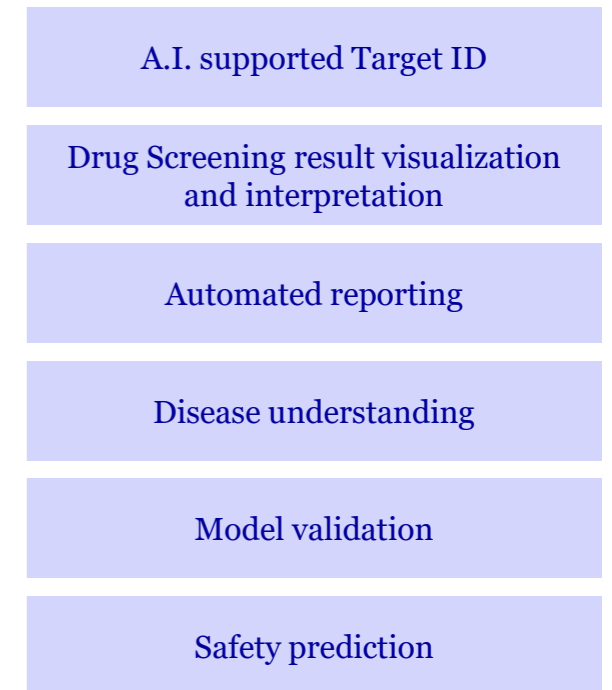
## PanOmics continuum



## Value generation



## Actionable output





# Agenda

- 9:00-9:30 Shaping (new) markets
- 9:30-11:00 PanOmics – From patients for patients
- *Better disease understanding & diagnostics*
  - *Advanced disease modelling*
  - *A.I. use cases along the value chain*
- 11:00-11:15 *Coffee Break*
- 11:15-12:15 Impactful therapies
- *Integrated platform*
  - *Diabetes*
  - *Oncology*
- 12:15-13:30 *Lunch Break*
- 13:30-16:00 Round Tables



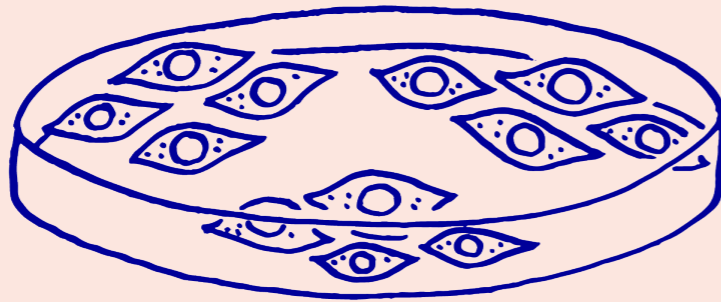
# Agenda

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# Introduction to cell therapy

## Background



## Cell therapy

is a treatment in which *viable cells (autologous, allogeneic, iPSC-derived)*, are injected, grafted or implanted *into a patient* in order to improve or cure a disease.

## Induced pluripotent stem cells

(iPSCs) are a type of stem cell that can be generated directly from a somatic cell. *iPSC technology* was pioneered by Shinya Yamanaka's lab. He was awarded the 2012 Nobel prize for the discovery that mature cells can be reprogrammed to become pluripotent.

## Immune cell treatments for cancer patients

### 1. Solid tumours

### 2. Blood cancers

Prior treatment

After 2 weeks



After a single treatment of autologous **TIL<sup>1</sup>** therapy, 25% of heavily pre-treated, terminally ill melanoma patients are still alive >8 year<sup>2,3,4</sup>

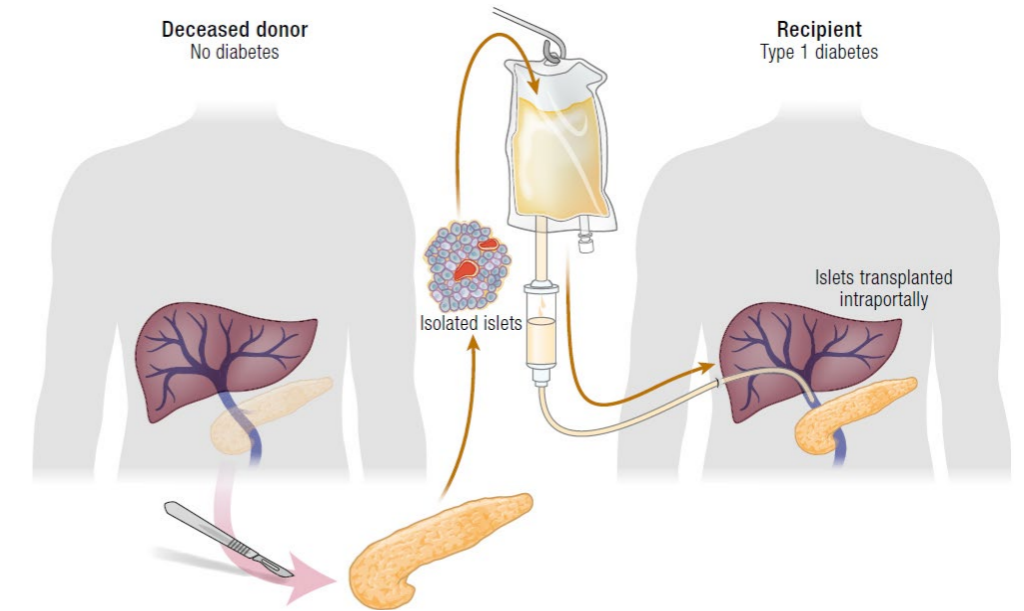
2012

2022



Emily Whitehead was 1<sup>st</sup> pediatric patient to receive **CAR T cell therapy** in 2012 to treat ALL<sup>5</sup>. She celebrated 10 years of being cancer-free in May 2022<sup>6</sup>.

## For diabetic patients: Beta cell replacement therapy



75% of type-1-diabetics are insulin-independent two years after cadaveric human islet transplantation



# Increasing market access for cell therapies

## Pipeline of cell & gene therapies 2023

	Therapy	Type	Indication	Status
Approved	<b>Hemgenix</b> (uniQure and CSL Behring)	Gene Therapy	Hemophilia B	Approved (February 2023)
	<b>Omisirge</b> (Gamida Cell)	Cell Therapy	Reduce time to neutrophil recovery and infection in patients with hematologic malignancies	Approved (April 2023)
	<b>Vyjuvek</b> (Krystal Biotech)	Gene Therapy	Dystrophic epidermolysis bullosa	Approved (May 2023)
	<b>Elevidys</b> (Sarepta Therapeutics)	Gene Therapy	Duchenne muscular dystrophy	Approved (June 2023)
	<b>Lantidra</b> (CellTrans)	Cell Therapy	Type 1 Diabetes	Approved (June 2023)
	<b>Roctavian</b> (BioMarin Pharmaceuticals)	Gene Therapy	Hemophilia A	Approved (June 2023)
BLA/MAA Accepted	<b>CTX001</b> (Vertex Pharmaceuticals & CRISPR Therapeutics)	Gene Editing Therapy	Sickle cell disease, β-thalassemia	EU decision expected in the fall of 2023 FDA decision set on sickle cell disease for December 8, 2023 FDA decision for β-thalassemia expected March 2024
	<b>Lifileucel</b> (Iovance)	Cell Therapy	Metastatic melanoma	FDA decision set for November 25, 2023
	<b>NurOwn</b> (BrainStorm Therapeutics Inc.)	Cell Therapy	Amyotrophic lateral sclerosis (ALS)	FDA decision set for December 8, 2023
	<b>Lovo-cel</b> (Bluebird bio)	Gene Therapy	Sickle cell disease	FDA decision set for December 20, 2023
BLA/MAA Submitted	<b>HPC Cord Blood</b> (StemCyte)	Cell Therapy	Unrelated Donor hematopoietic progenitor cell transplantation	BLA Pending

Anticipated 2024 decisions			
<b>Afami-cell</b> (Adaptimmune)	<b>CT-053</b> (CARsgen Therapeutics)	<b>Fidanacogene Elaparvovec</b> (Pfizer)	<b>Libmeldy</b> (Orchard Therapeutics)
<b>Tab cel</b> (Atara Biotherapeutics)	<b>Upstaza</b> (PTC Therapeutics)	<b>Vyjuvek</b> (Krystal Biotech)	<b>Elevidys</b> (Sarepta Therapeutics)

Sector Snapshot

Alliance for Regenerative Medicine 2

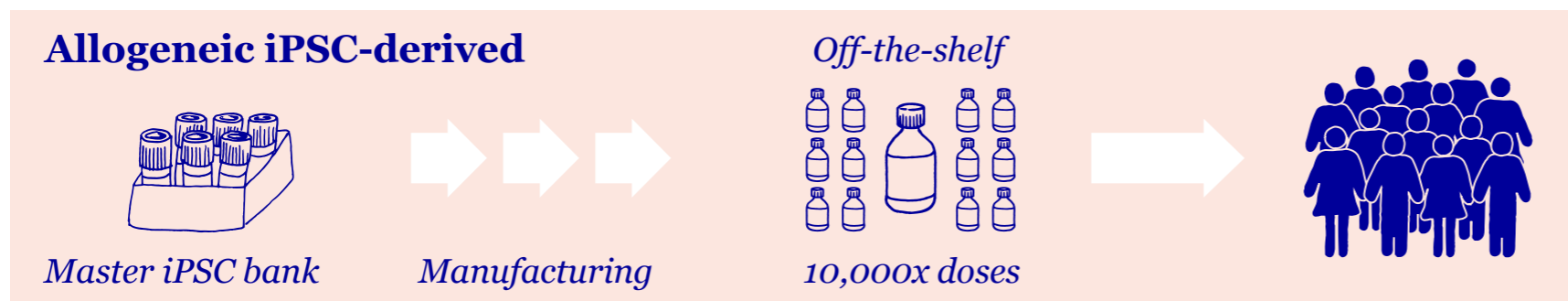
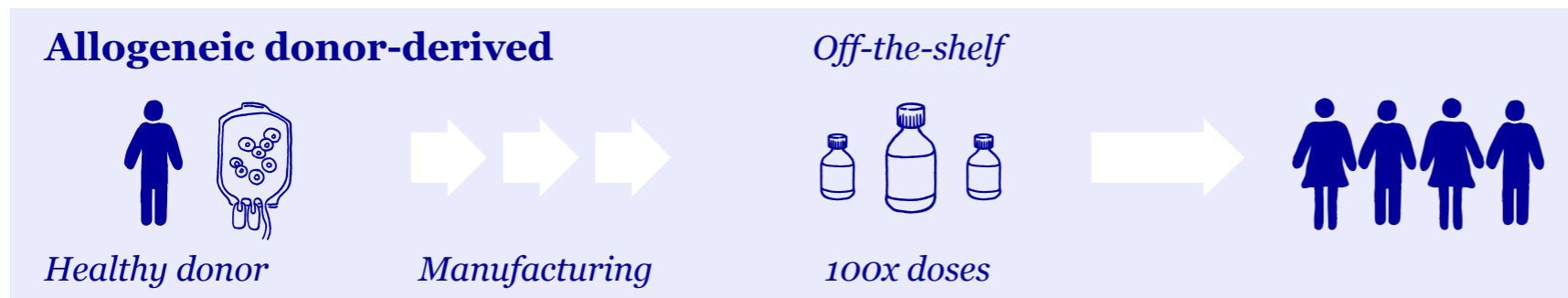
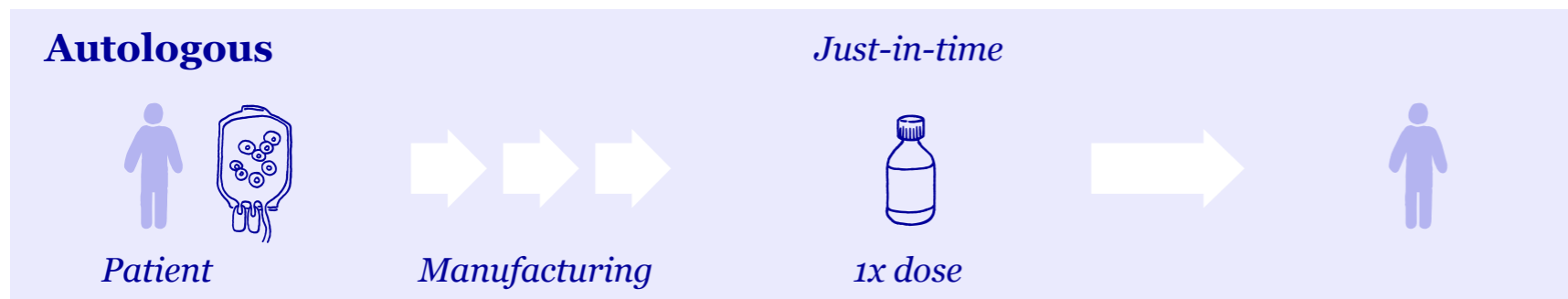
- **Nr of cell and gene therapies with market approval is increasing**
  - 80% autologous with limited pat reach
  - (Hem)Oncology, inherited genetic diseases
- **Next generation moving to off-the-shelf & larger indications approaching market**
  - Cardiovascular, Metabolics & Neurology
- **iPSC-based therapies early in development but entering clinical space**
  - no significant safety issues
  - Next-gen with gene-editing ready to go





# Revolutionising access to cell therapies

Advantage of “off-the-shelf” versus autologous/donor-based approach



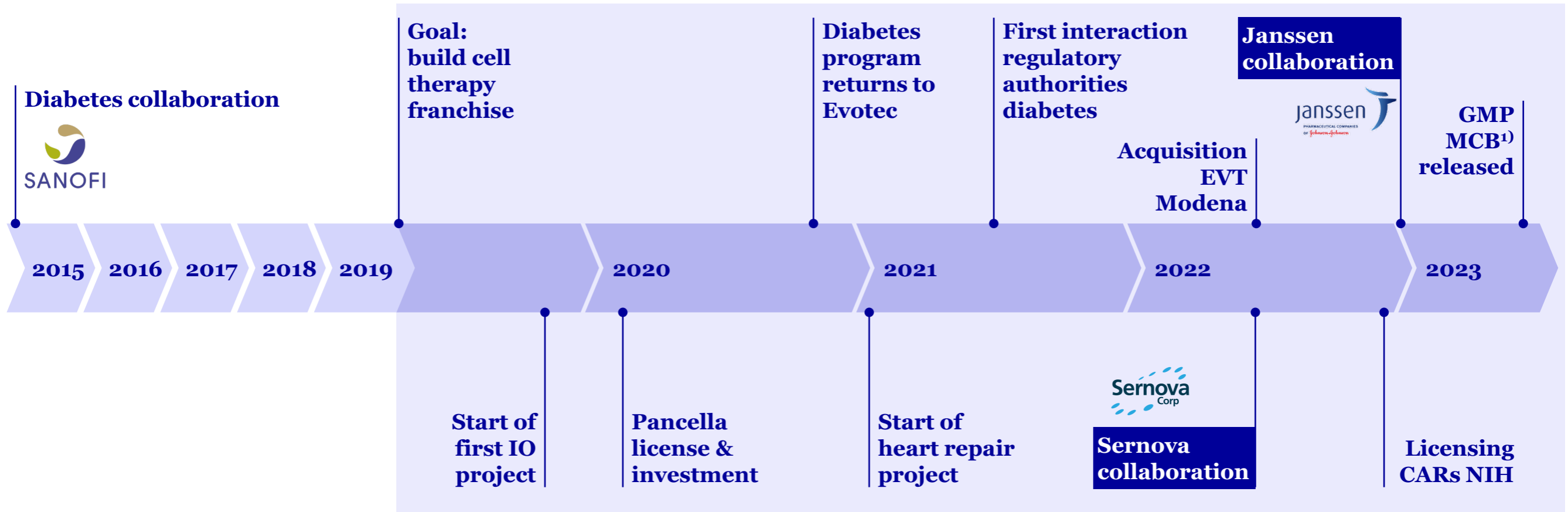
## iPSC-based off-the-shelf therapeutics

- **Reduced complexity:** Patient is not part of manufacturing process
- **Unlimited** starting material
- **Clonal** & high-fidelity gene editing
- **Consistent quality** of final product
- **On demand** product available to patients
- **Versatile:** Single platform suitable to manufacture multiple cell types & diseases



# Significant platform and project portfolio built over 4-year period

Strategic internal efforts from 2019 up to now



Single iPSC cell therapy project





Strategic focus on iPSC-based cell therapeutics



# A portfolio of off the shelf iPSC-based cell therapy programs

Evotec's internal and partnership project portfolio

	Field	Program/ Project	Disease area	Protocol	Pre-clinical research	Pre-clinical development	IND / Phase I	iPSC-derived cell types	
<b>Partnered</b>	<b>Cancer immuno-therapy</b>	 $\gamma\delta$ iT	Oncology	Undisclosed				iNK	Natural killer cells
	<b>Metabolic disease</b>	 E.iBeta (Device)	Diabetes					iT	$\alpha\beta$ and $\gamma\delta$ T cells
<b>Partnering opportunities</b>	<b>Cancer immuno-therapy</b>	iNK	Oncology					iMAC	Macrophages
		iMAC	Oncology					iBeta	Pancreatic islets
		$\alpha\beta$ iT	Oncology					iCM	Cardiomyocytes
	<b>I&amp;I<sup>1</sup></b>	iNK, $\alpha\beta$ iT	Fibrosis, SLE <sup>2)</sup>					iRPE	Retinal pigment epithelium cells
	<b>Metabolic disease</b>	E.iBeta (Engineered)	Diabetes					iPR	Photoreceptors
	<b>Other</b>	iCM	Heart failure						
		iRPE, iPR	Ophthalmology						
		...							

► Each cell type can deliver multiple differentiated products



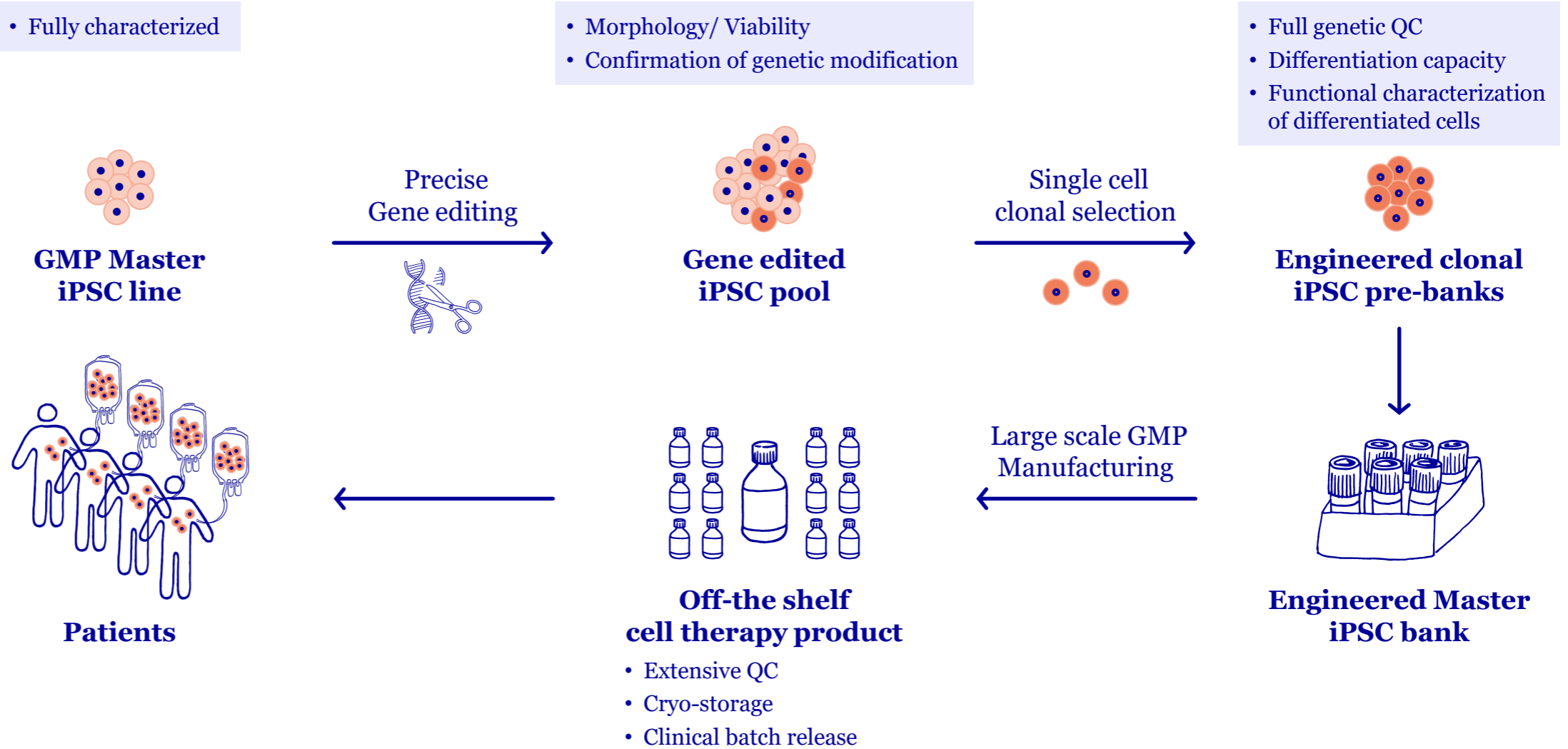
# *Integrated platform for iPSC-based therapeutics*



# Truly “off-the-shelf”, fully scalable cell therapy products

A process to overcome a major hurdle in cell therapy

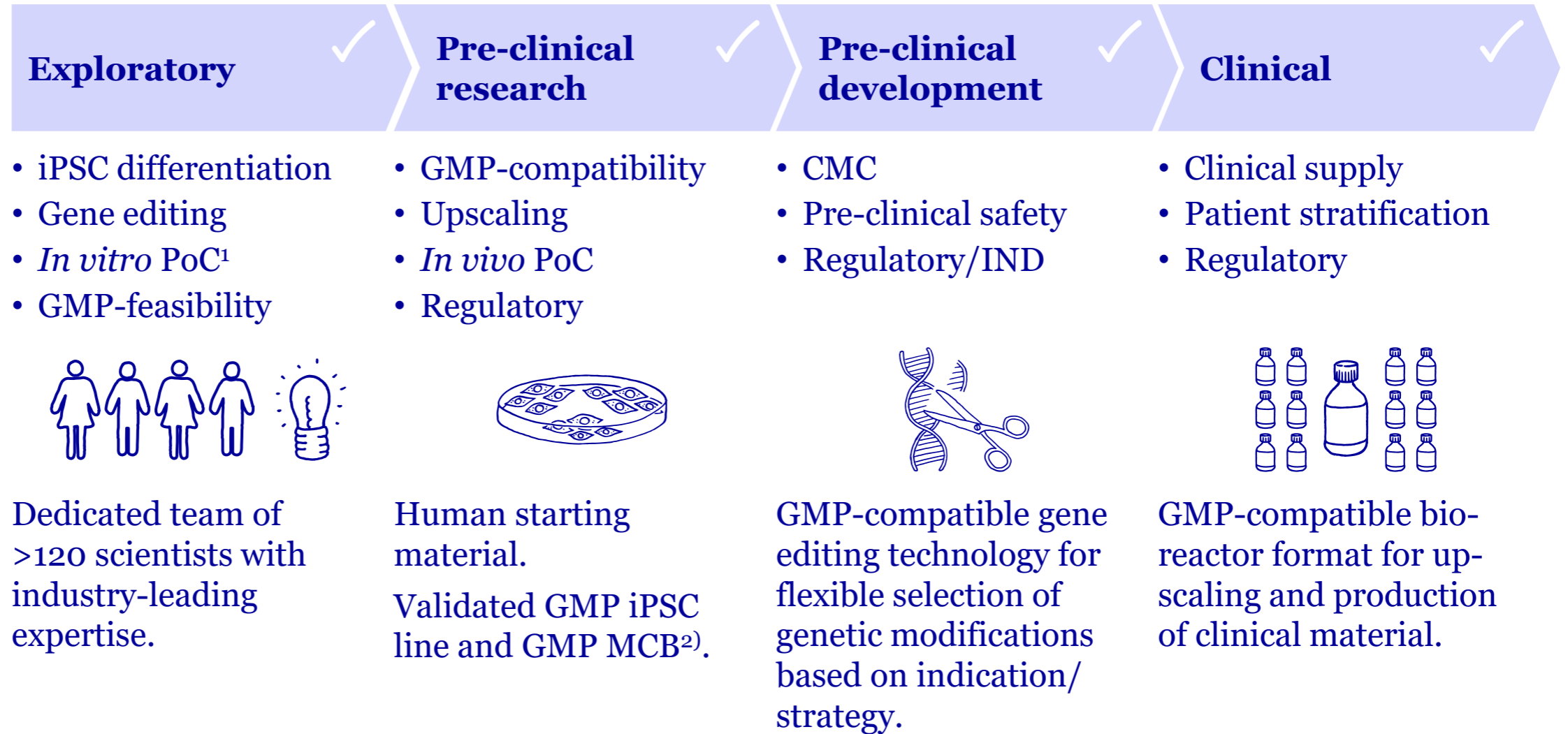
**Developing industrialized GMP manufacturing processes that are fully scalable to serve the market with up to tens of thousands of doses**





# Integrated platform for iPSC-based therapeutics is becoming reality

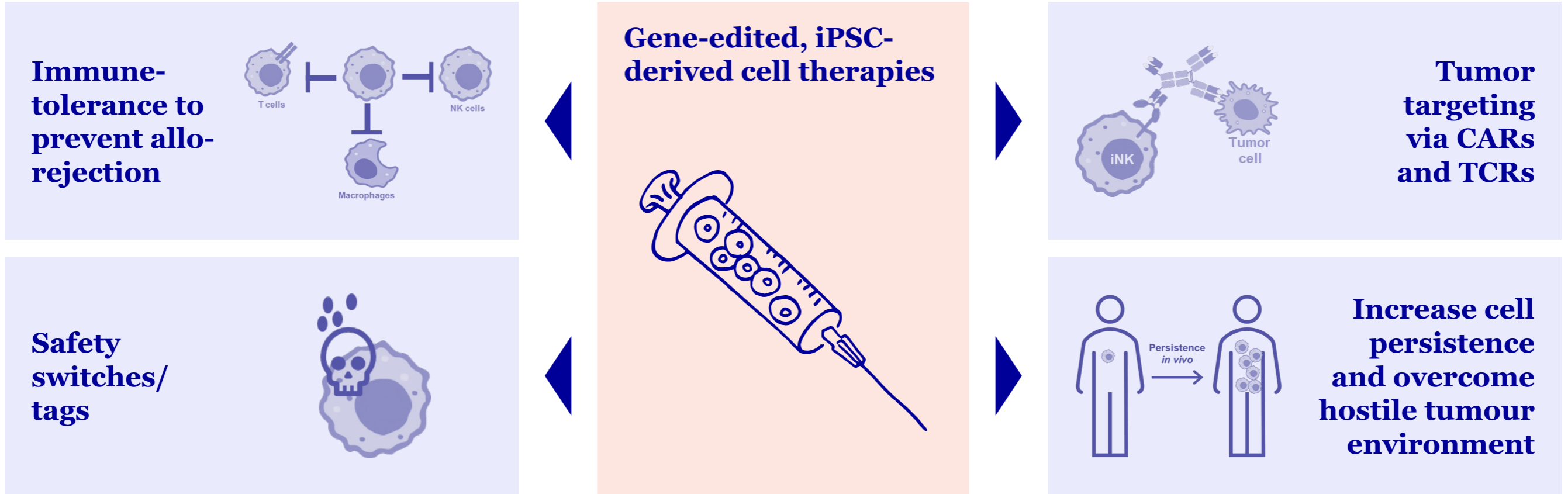
From iPSCs to patients





# Multiplex gene editing to create highly efficacious and safe therapies

The power of gene edited iPSC cell therapies



*Gene editing technologies to develop cell therapies that are custom made for a given disease indication and patient population increasing the likelihood of success*



# Centre of excellence for cell therapeutics manufacturing

Evotec Modena



#RESEARCHNEVERSTOPS

NEWS RELEASE, 30 MAY 2022

## EVOTEC ADDS CELL THERAPY MANUFACTURING FACILITY WITH ACQUISITION OF RIGENERAND

▶ EVOTEC'S EVOCELLS PLATFORM INTEGRATES INNOVATIVE OFF-THE-SHELF IPSC CELL THERAPY DISCOVERY WITH DEVELOPMENT AND MANUFACTURING



- Founded in 2009 as spin-off of the University of Modena and Reggio Emilia
- Scientific founder Prof. Massimo Dominici is one of the pioneers in clinical cell therapy
- State-of-the art GMP manufacturing facility (5 clean rooms, 1,200 m<sup>2</sup>) with room for significant expansion, ~ 25 FTEs
- cGMP facility accredited by Italian Authority for the manufacturing of clinical stage cell therapies
- Experienced to manufacture complex cell therapies including pre-GMP optimization steps
- Experience with CAR-T, MSCs, dendritic cells and exosomes
- Tech transfer for manufacturing of iPSC-based therapeutics on-going

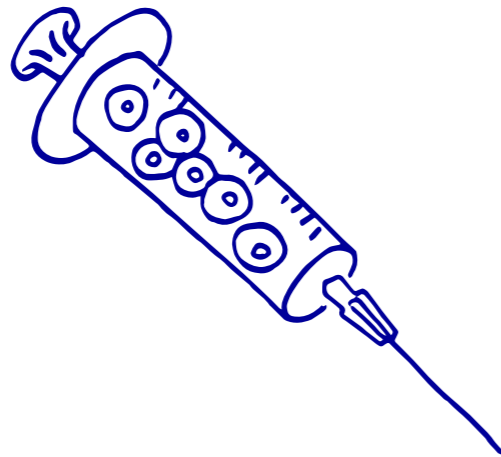




# A powerhouse for iPSC cell therapy research & development

Selected KPIs

**Translation from science into clinical application**



**>120**

*Scientists dedicated to cell therapy*

**>15**

*iPSC-derived cell types*

**>200**

*Cell production runs per year for Development material*

**>10**

*Cell therapy projects*



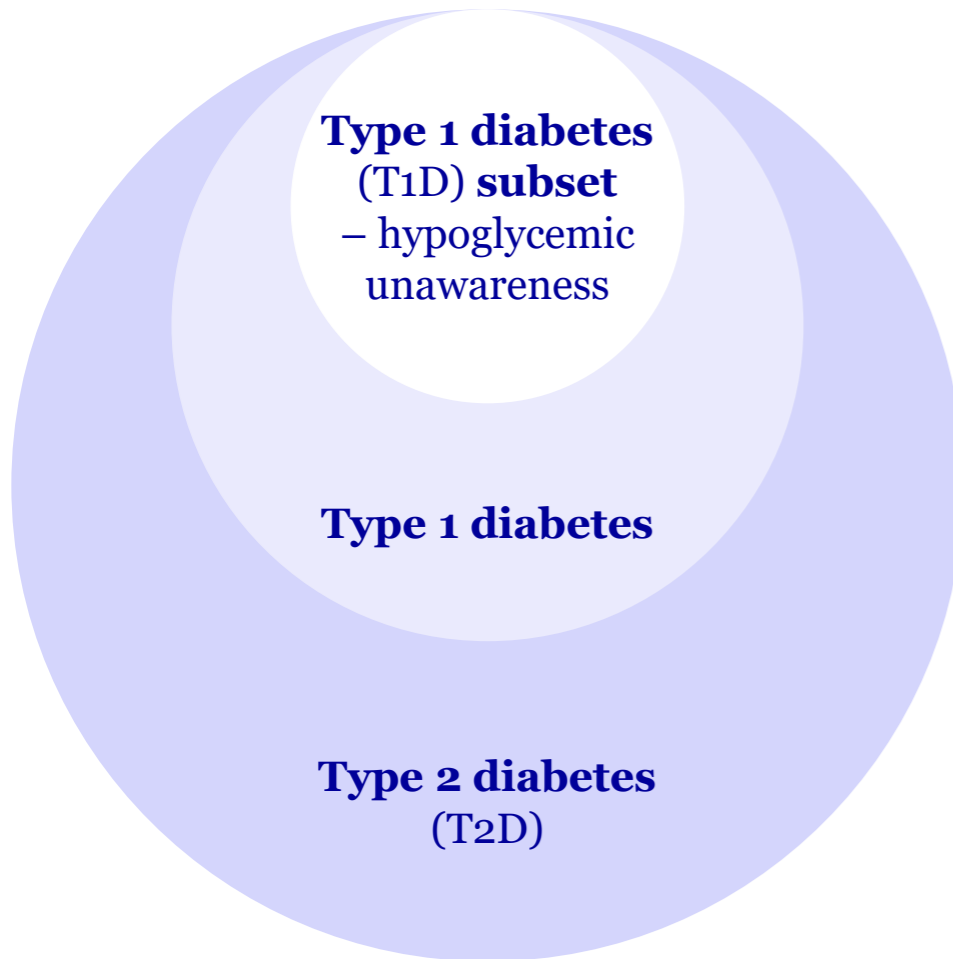
# *Pipeline building with iPSC-based cell therapy in Diabetes*



# Diabetes program with broad therapeutic scope

Targeting high-risk patients first to expand to large patient populations

## Size<sup>1</sup> of potential patient population



### Type 1 diabetes

- Standard of Care: intensified insulin treatment
- Gold standard islet transplantation
  - Limited availability and mostly restricted to **high-risk pts** with hypoglycemic episodes
  - Immunosuppression required

### Type 2 diabetes

- Standard of Care: change of lifestyle: weight loss, physical activity
- Oral drugs: metformin, GLP1-agonists, DPP4-inh., SGLTZ-2 inh.
- Insulin

Our goal is to provide a curative approach by **islet replacement therapy** with positive impact on long-term complications and quality of life

### Next steps

- **Gene edited beta cells** with cloaking technology to avoid immune rejection and need for immunosuppression
- This would widen the scope of the therapy for use in a much **broader T1D population**
- This approach would also offer the opportunity to potentially expand into **T2D** as well, which is a significantly larger market

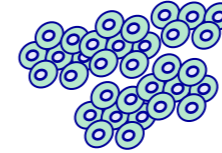


# Multiple product generations will enable true leadership

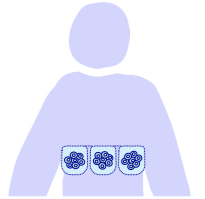
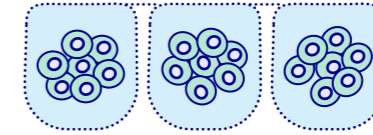
Opportunity for multi-project partnership with Pharma



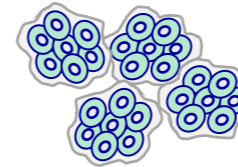
Non-modified iPSC beta cells  
+ cell pouch  
*Immuno-suppressed patients*



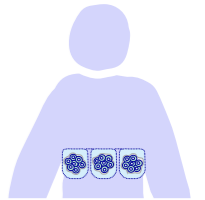
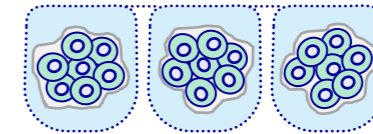
**Implantation in CellPouch™**



Non-modified iPSC beta cells  
+ cell coating + cell pouch  
*No immunosuppression*

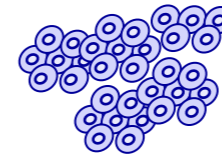


**Implantation in CellPouch™**

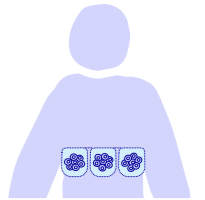
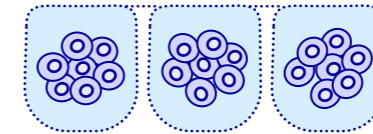


unpartnered

Genetically modified  
iPSC beta cells + device  
*no immunosuppression*

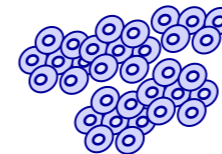


**Implantation in open device**

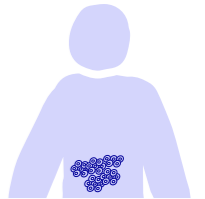


unpartnered

Genetically modified  
iPSC beta cells  
*Device-less,  
no immunosuppression*



**Device-less - portal  
vein infusion**

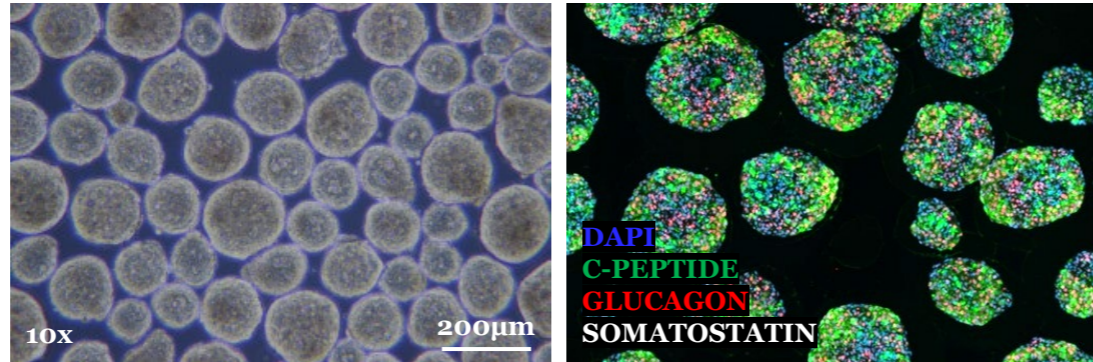




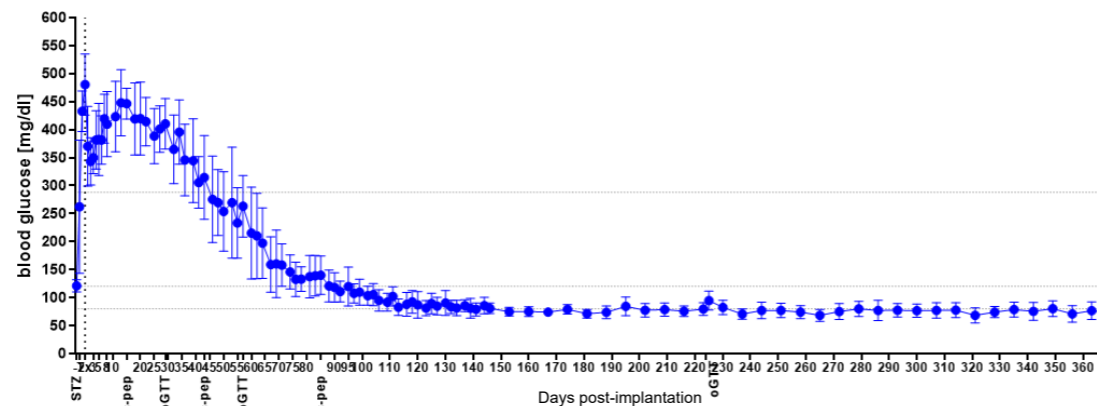
# iPSC-derived islets for the treatment of Type 1 diabetes

Evotec achievements and current focus

## iPSC-derived islet like clusters



## Random-fed blood glucose in diabetic mice implanted with 1.5M GMP iPSC-derived beta cells (kidney capsule)



- Scalable, GMP-compatible and IP-protected manufacturing procedure for iPSC-derived islet like clusters, with optimized beta cell fraction
- Manufacturing involves a cryopreservation step, and is currently implemented at Evotec's GMP manufacturing site
- QC strategy for product release in place
- Manufacturing and QC strategy endorsed by PEI<sup>1</sup> (German regulatory authorities)
- Long-term *in vivo* efficacy in translatable animal model
- Manufacturing of tox batch for pre-clinical GLP safety study as next step



# On the path to a first clinical candidate

Utilises Sernova's clinically validated Cell Pouch device

## Cell Pouch System

- Implantable medical device
- Provides vascularized environment for cells
- Long term survival
- Scalable, retrievable
- Positive Phase I/II clinical data with primary human islets on safety & efficacy
- Pts reach insulin-independence



## EVT3101

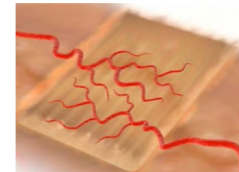
- **iPSC-based islet-like clusters mimicking human islet cells**
- Long-term function in rodent models demonstrated
- Scalable 3D manufacturing procedure & manufacturing infrastructure
- Drug development expertise and cGMP manufacturing infrastructure



#RESEARCHNEVERSTOPS

NEWS RELEASE, 17 MAY 2022

**EVOTEC AND SERNOVA ANNOUNCE EXCLUSIVE STRATEGIC PARTNERSHIP FOR IPSC-BASED BETA CELL REPLACEMENT THERAPY TO ADVANCE A "FUNCTIONAL CURE" FOR DIABETES**



Proprietary Cell Pouch is placed deep under the skin, allowing for vascularization & creating a natural environment for long-term function of therapeutic cells



Therapeutic cells are transplanted directly into the vascularized tissue chambers of the proprietary Cell Pouch and start to produce insulin after maturation

Patient's voice:

*"...After having T1D for 47 years with approximately 21,535 injections of various cow/pig, synthetic insulins, 34,310 finger sticks, 1,460 urine tests, 15 years on the pump, carbohydrate counting, blood tests, low blood sugar reactions, and doctors...doctors and more doctors' visits, I have now been free of the need for injectable insulin for 15 months."...*

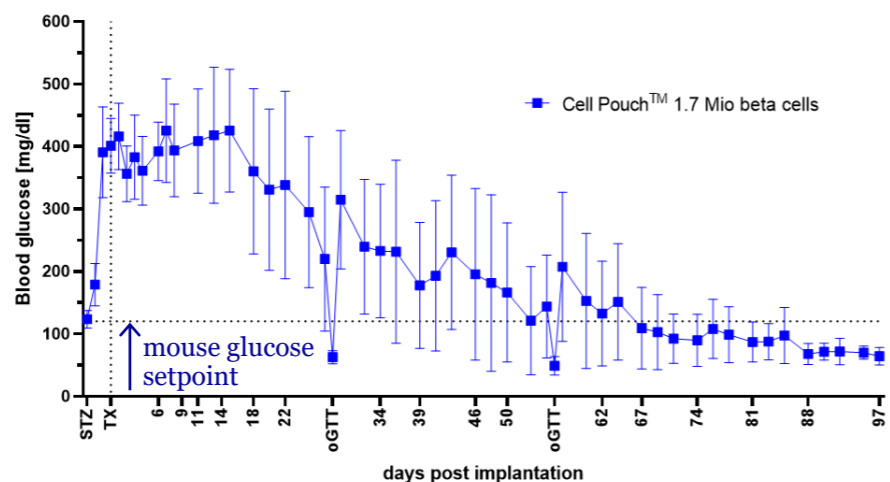
Sernova 2023, Cell Pouch with cadaveric human islets



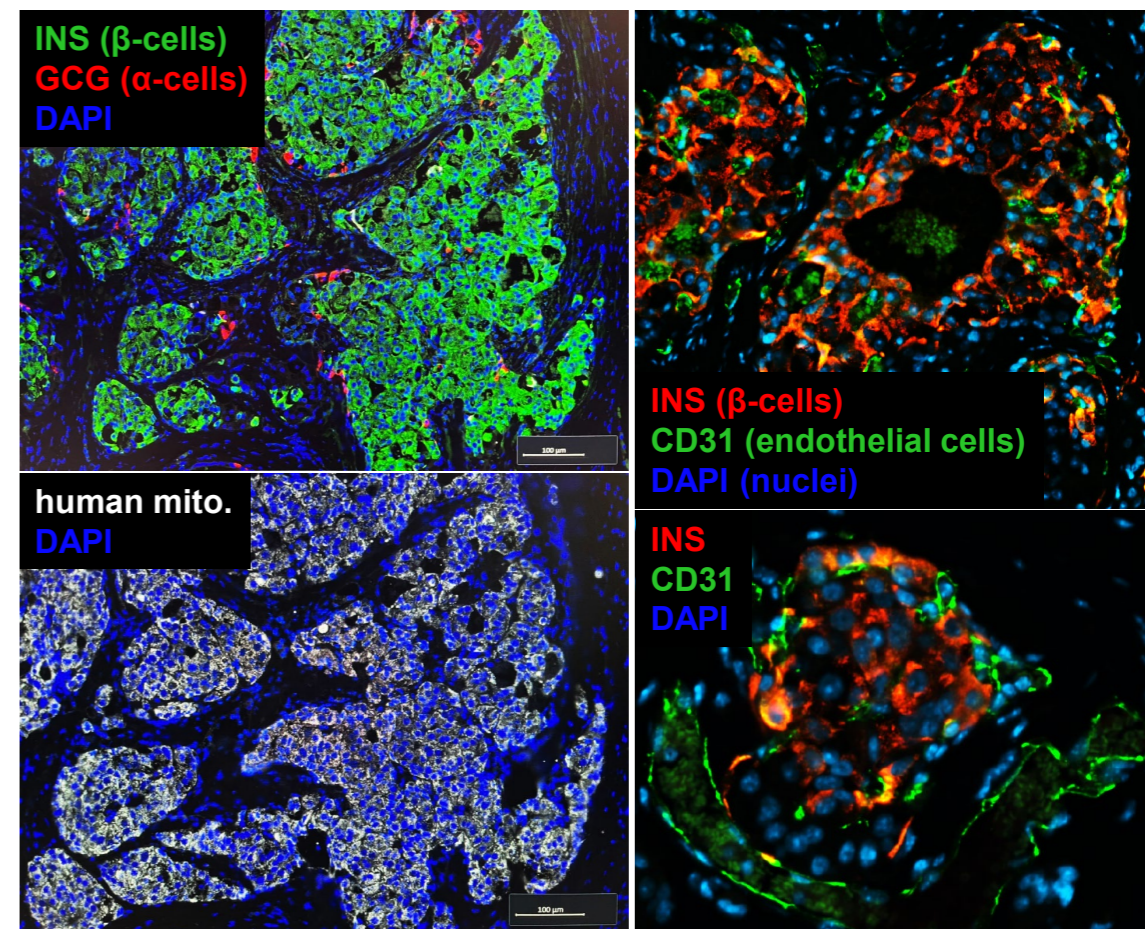
# Excellent anti-diabetic activity of Evotec ILCs<sup>1</sup> in the Cell Pouch™

Human islet-like potency; full tissue integration and blood supply for beta cells in mouse diabetes model

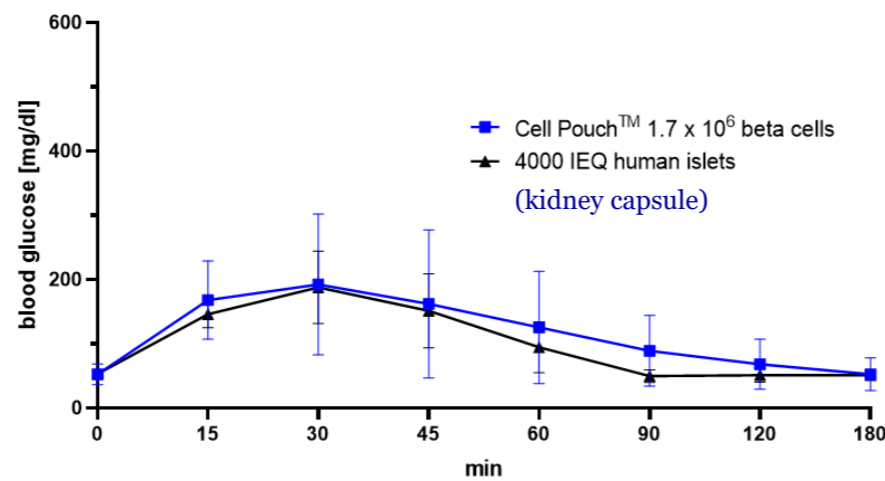
**Efficient normalization of random fed glucose**



**Excellent survival and tissue integration of islet cells, and optimal supply with blood vessels in the Cell Pouch**



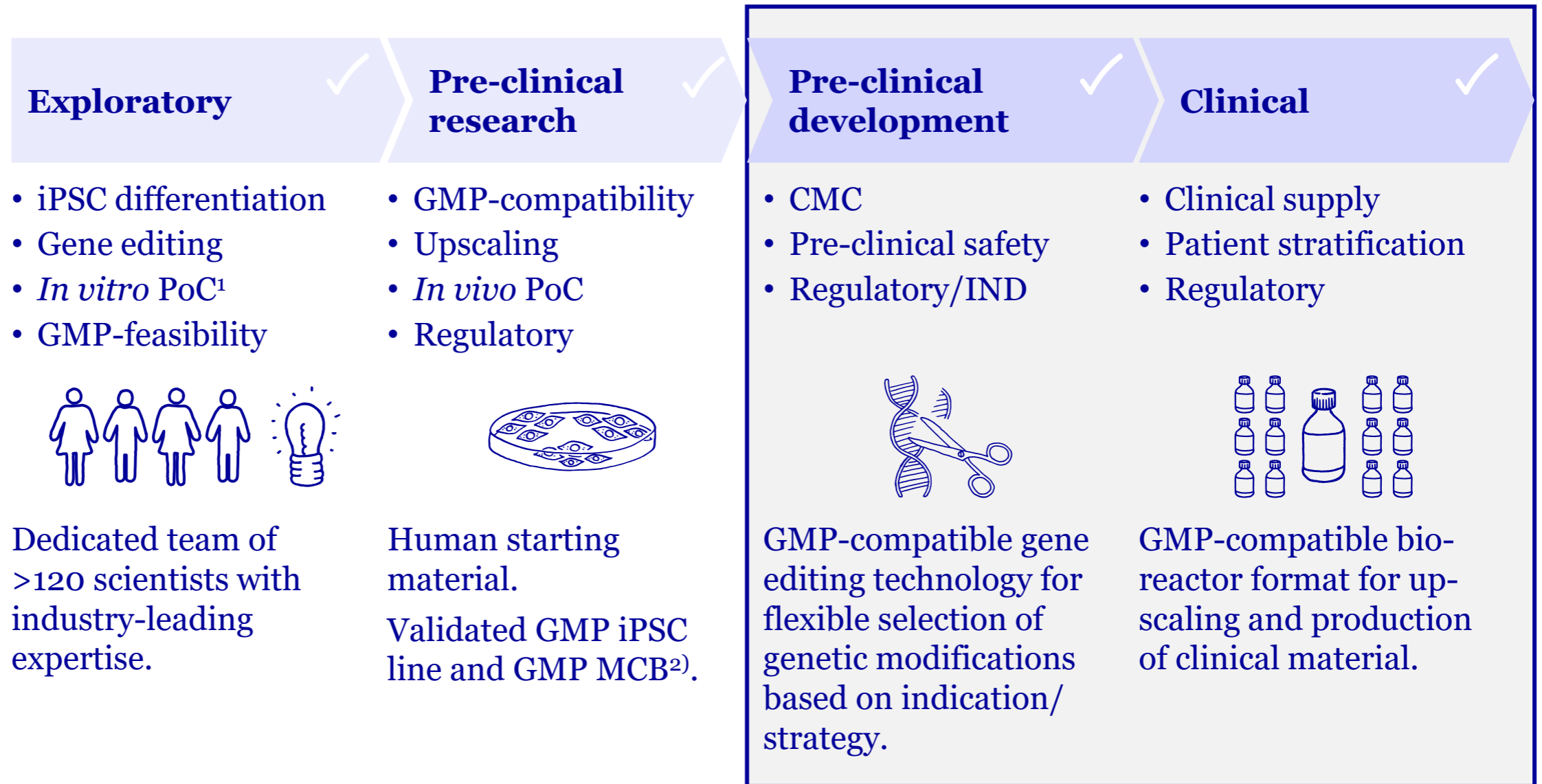
**Efficient glucose clearance and no hypoglycemias in oGTT<sup>2</sup> (8 week timepoint)**





# Translation into clinical development

From iPSCs to patients







# Gene-editing is the next step to increase efficacy & safety

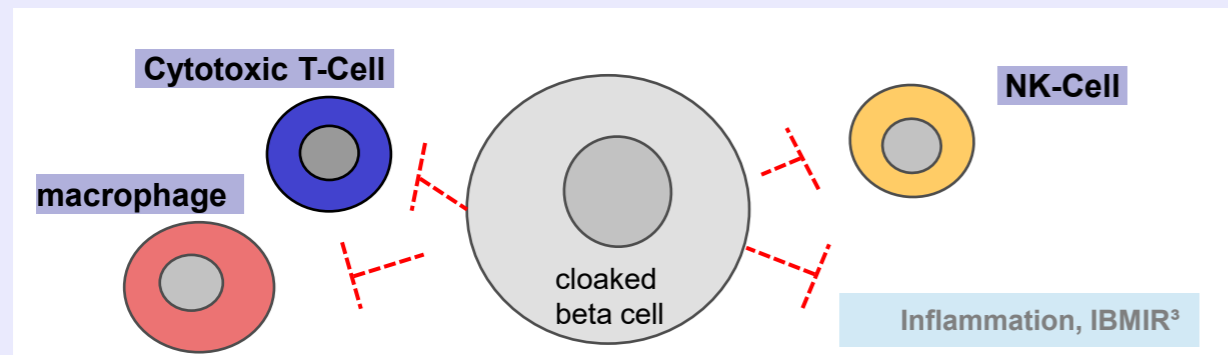
Introducing cloaking (immune-shielding) and FailSafe (drug-inducible kill-switch)

Nobel-prize awarded technology (2020 J.Doudna, E.Charpentier)

Combining two gene editing concepts to render its allogeneic “off-the-shelf” cell therapy products most durable and safe:

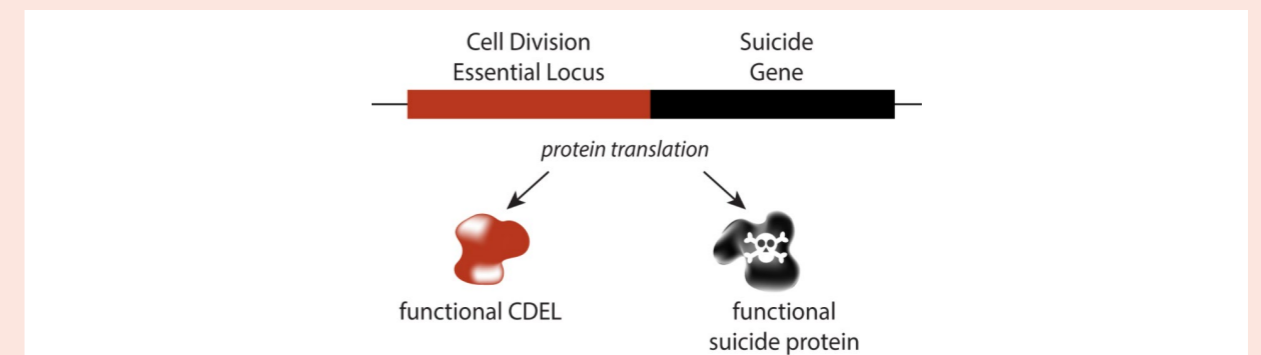
## Cloaking enables long-term persistence without immunosuppression

- Evading immune destruction of allogeneic “off-the-shelf” cell therapy
- Avoiding immunosuppressive drugs with significant long-term risks<sup>1</sup>
- Gene editing in iPSCs to block known pathways of allograft rejection (“cloaking”) is a promising alternative
- Evotec is currently evaluating two cloaking strategies: the in-house developed “EvoCloaking” and the in-licensed “iACT”<sup>2</sup>



## FailSafe is a safeguard against tumorigenicity for selective elimination of undesired proliferating cells

- Device-less and immune-evasive implantation of cell therapeutics with additional safety switch to selectively eliminate dividing graft cells
- Evotec has a license for the use of panCELLa’s drug-inducible “FailSafe®” technology<sup>4</sup>
- Proliferating cells get sensitive to a death-inducing drug while non-dividing graft cells are left unaffected
- Physical and transcriptional link between cell division and suicide genes strongly reduces chances of kill-switch elimination or silencing



1) Ruiz and Kirk 2015; doi: 10.1016/B978-1-4557-0268-8.00097-X

2) Harding, J., Vintersten-Nagy, K. et al. (2019). Induction of long-term allogeneic cell acceptance and formation of immune privileged tissue in immunocompetent hosts. bioRxiv. <https://doi.org/10.1101/716571>

3) Instant Blood Mediated Inflammatory Reaction

4) Liang Q, Monetti C, Shutova MV, Neely EJ, Hacibekiroglu S, Yang H, Kim C, Zhang P, Li C, Nagy K, Mileikovsky M, Gyongy I, Sung HK, Nagy A. Linking a cell-division gene and a suicide gene to define and improve cell therapy safety. Nature. 2018 Nov;563(7733):701-704



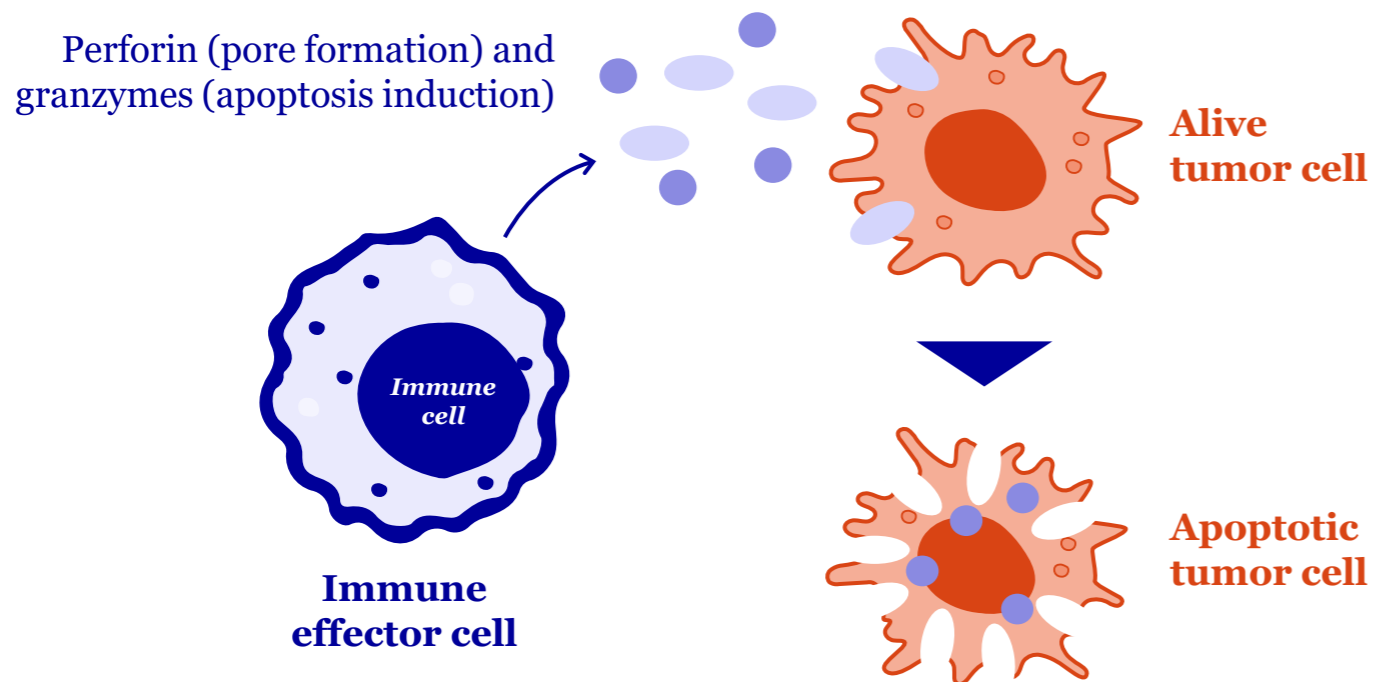
# *Pipeline building with iPSC based cells in Oncology and I&I*



# Immune cells can be serial killers – which is good

Why cell therapies are highly efficacious in the clinic – if they work

## Mode of action



- Immune cells can “recharge” their toxic payload to kill multiple tumor cells
- They can proliferate in the patients multiplying the administered dose
- They can persist for years including “memory function” against the tumor
- They can be genetically manipulated for increased efficacy and safety

## Cell therapy status quo

Currently marketed products

**Breyanzi**  
(lisocabtagene maraleucel) Suspension for IV infusion

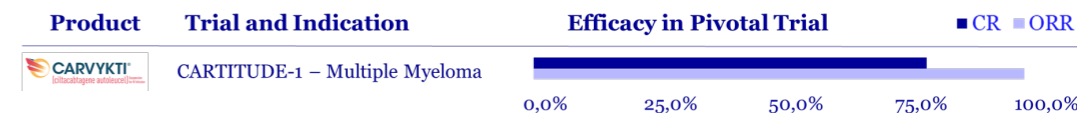
**TECARTUS**  
(brexucabtagene autoleucel) Suspension for IV infusion

**YESCARTA**  
(axicabtagene ciloleucel) Suspension for IV infusion

**Abecma**  
(idecabtagene vicleucel) Suspension for IV infusion

**CARVYKI**  
(ciltacabtagene autoleucel) Suspension for IV infusion

**KYMRIAH**  
(tisagenlecleucel) Suspension for IV infusion



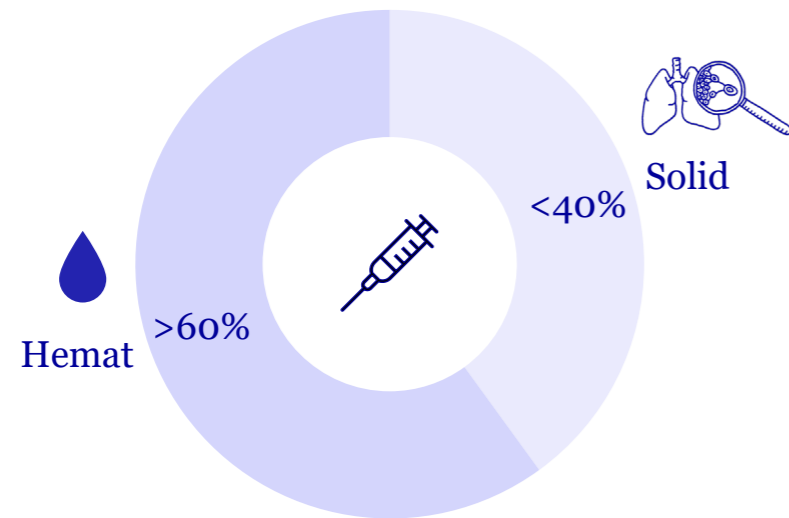
Autologous CAR T cell therapies available on the market primarily focus on the treatment of hematological cancers<sup>1</sup>



# Unlocking the full potential of cell therapies in oncology

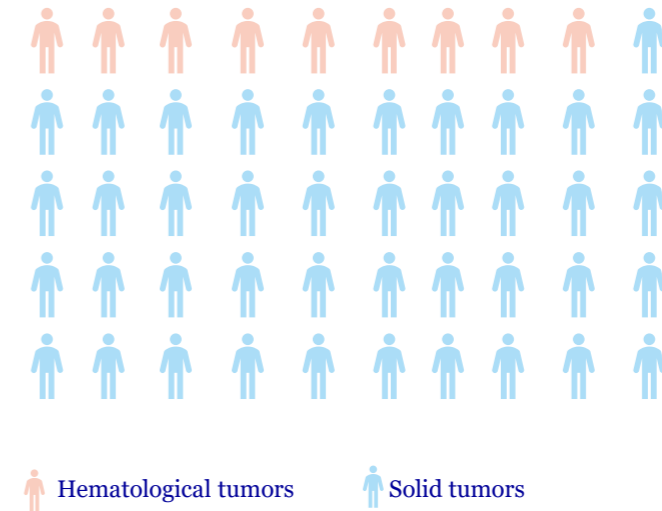
High unmet medical need in solid tumour indications

## Cell therapy late-stage pipeline



>60% of current late-stage pipeline focused on hematological cancers<sup>1</sup>

## Cancer incidence



~90% of new case of cancer are attributable to solid tumors<sup>2</sup>

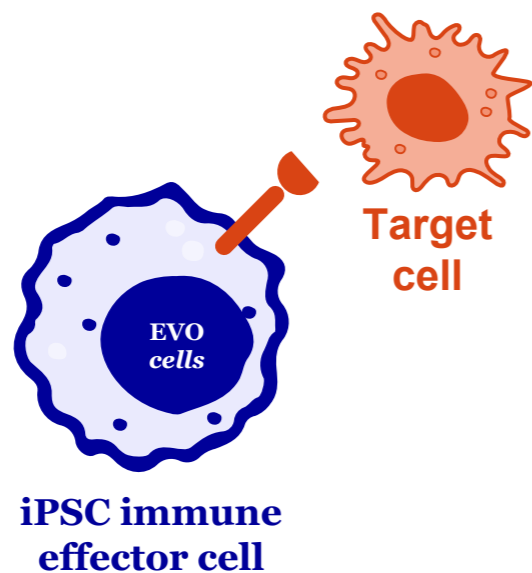
*Current cell therapies are highly efficacious mainly in liquid tumor indications; we believe that innovative and differentiated approaches are needed to translate this into solid tumors, too*



# EVOcells oncology and I&I: an iPSC-based immune effector cell platform

## Summary of platform components

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Fully leveraging all elements of the iPSC-based cell therapy platform combined with in-depth disease area and asset development expertise

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A broad range of iPSC-derived cell types to overcome the main hurdles of currently available cell therapies for cancer treatment

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Flexible selection of targeting moieties depending on strategy and disease indication/patient population

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Genetic modifications of immune effector cells to tackle the shortcomings of current approaches and further boost the clinical efficacy

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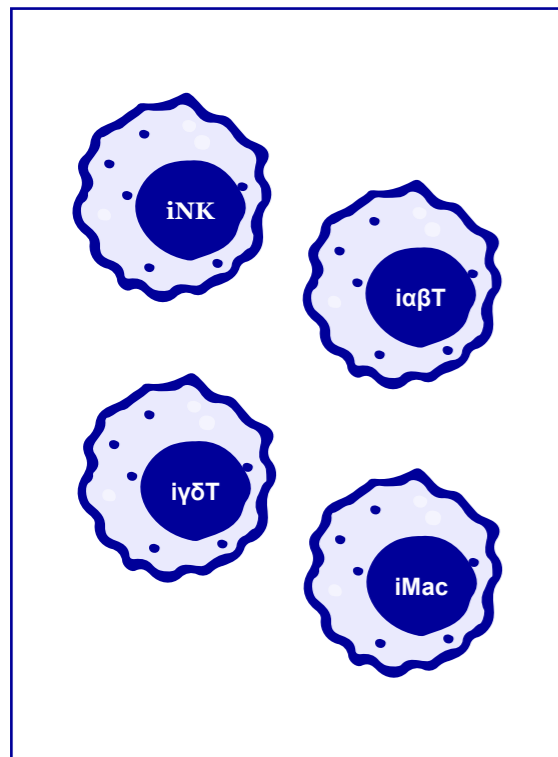
Early oncology product candidate pipeline in place including “lighthouse” projects; branching out into innovative treatments for auto-immune diseases



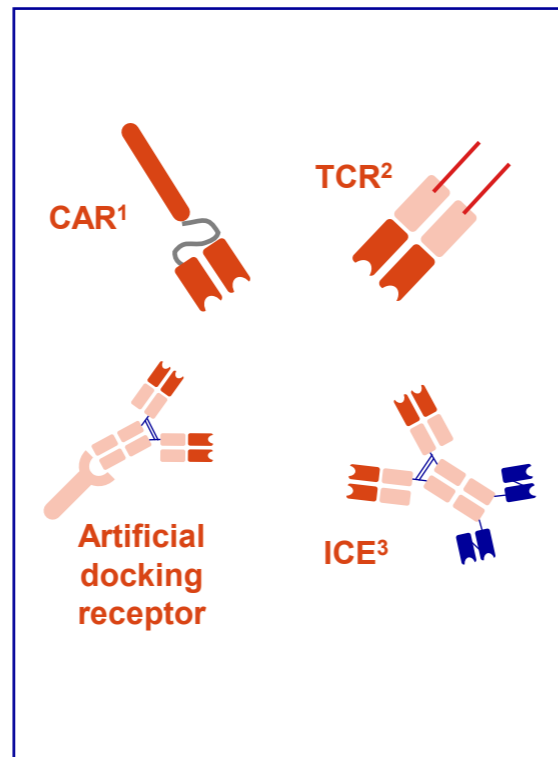
# A toolbox to generate a universe of cell therapy product candidates

Evotec's technologies for iPSC-derived immune cell therapy

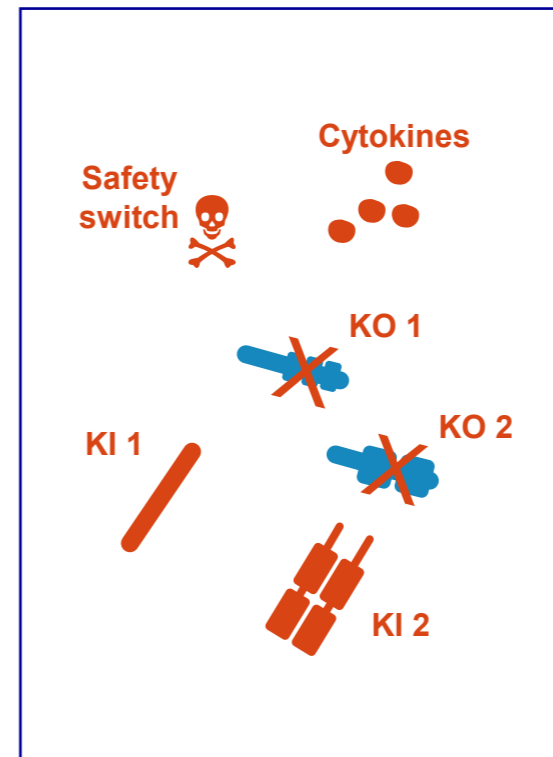
## Immune cell type



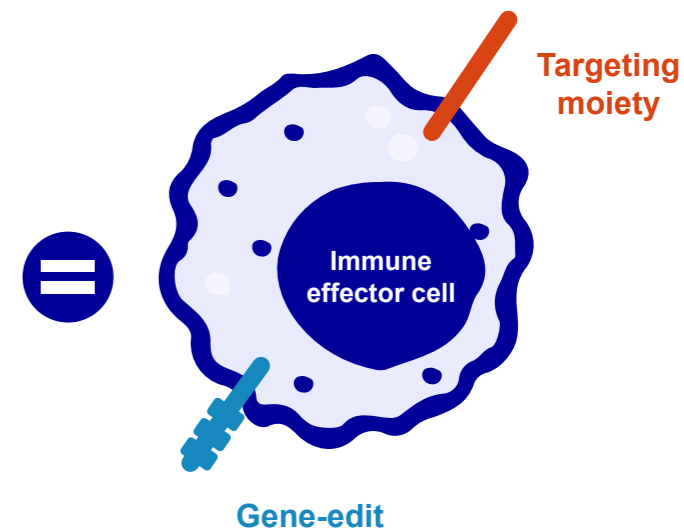
## Tumor targeting



## Gene-edits



## Cell products




*Combining iPSC-derived immune effector cells with different targeting modalities and gene-edits allows to generate an innovative and differentiated product candidate portfolio*



# The broadest iPSC-based immune effector cell portfolio in industry

Evotec's off-the shelf cell therapy programs

	Field	Program/ Project	Disease area	Protocol	Pre-clinical research	Pre-clinical development	IND / Phase I	iPSC-derived cell types	
<b>Partnered</b>	<b>Cancer immuno- therapy</b>	 $\gamma\delta$ iT	Oncology	Undisclosed				iNK	Natural killer cells
		iNK	Oncology					$\alpha\beta$ iT	$\alpha\beta$ and $\gamma\delta$ T cells
<b>Partnering oppor- tunities</b>	<b>Cancer immuno- therapy</b>	iMAC	Oncology					$\gamma\delta$ iT	$\gamma\delta$ T cells
		$\alpha\beta$ iT	Oncology					iMAC	Macrophages
	<b>I&amp;I<sup>1</sup></b>	iNK	Fibrosis						
		$\alpha\beta$ iT	SLE <sup>2</sup>						
		iMAC	Fibrosis						

► Each cell type can deliver multiple differentiated products

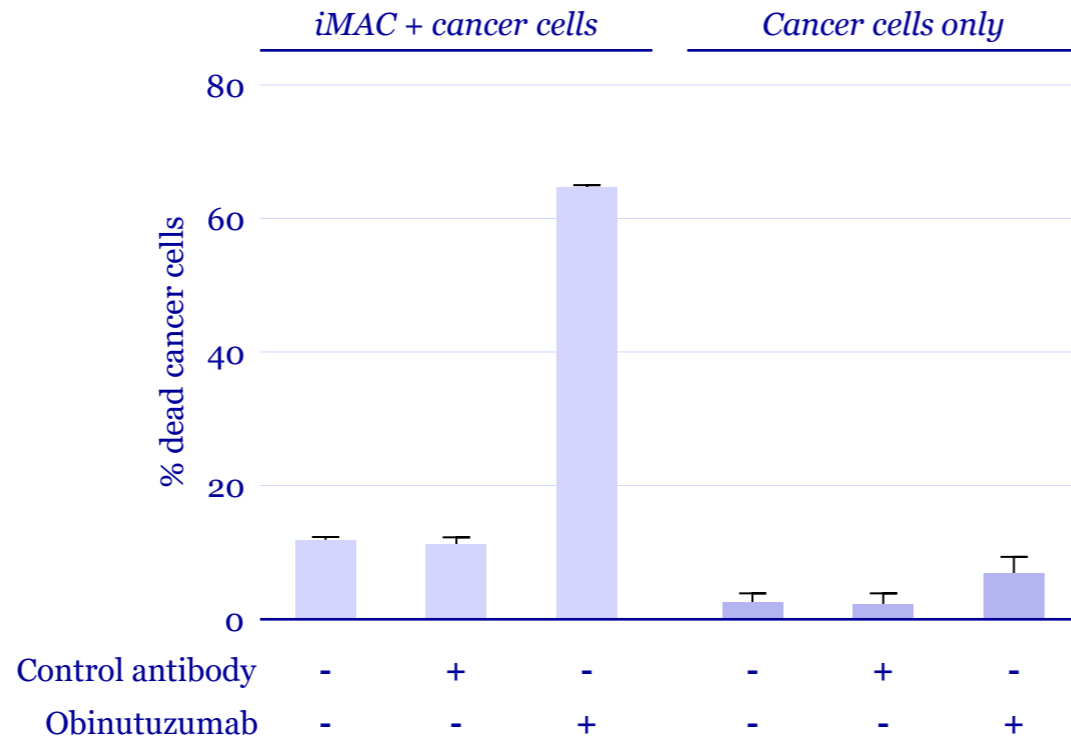
*Leveraging technologies and know-how across multiple product candidates and disease areas reduces development costs and timelines*



# A novel mode of action to eliminate patient-derived tumor cells

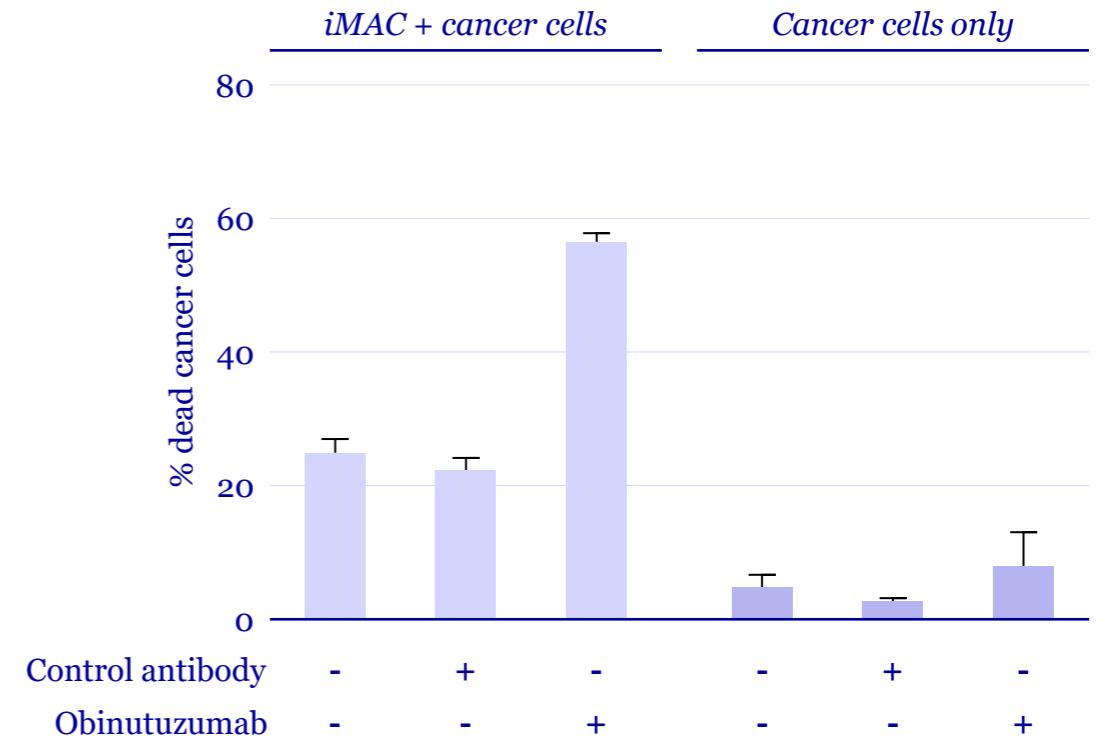
iPSC-based macrophages kill hard to treat primary cancer cells

## Tumor cells of patient #1



## Tumor cells of patient #2

E:T = 10:1



*iPSC-derived macrophages can kill tumor cells directly and also phagocytose cancer cells to activate the endogenous immune system potentially leading to increased clinical efficacy*

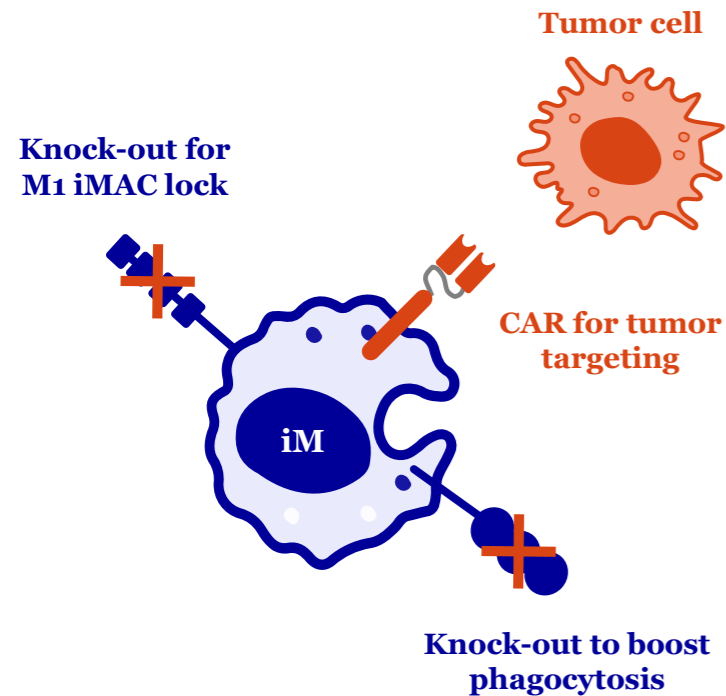




# Developing an efficacious cell therapy dedicated to solid tumors

iPSC-based, gene-edited macrophages to overcome the limitations of current cell therapy approaches

## Evotec's iMAC cell product candidates



## Limitations of autologous T and NK cell therapies

Poor infiltration into solid tumors

Hostile TME<sup>1</sup>, low immune cell infiltration

Highly susceptible to suppressive signals

Tumor escape due to single target approaches

Limited patient material, massive costs and complex logistics

## Potential solutions provided by iPSC-based macrophages

Natural ability to infiltrate and traffic into solid tumors

M1 iMACs are able to survive & reprogram the TME

Genetic engineering to overcome the main suppressive signal

Phagocytose and presentation of multiple tumor antigens to immune cells

iPSC-based macrophages with the ability to increase dose/re-dose patients

*Genetically optimized, iPSC-derived macrophages have the potential to overcome the obstacles of current cell therapies and can form the basis for a pipeline of highly efficacious solid cancer treatments*



# Agenda

- 9:00-9:30 Shaping (new) markets
- 9:30-11:00 PanOmics – From patients for patients
- *Better disease understanding & diagnostics*
  - *Advanced disease modelling*
  - *A.I. use cases along the value chain*
- 11:00-11:15 *Coffee Break*
- 11:15-12:15 Impactful therapies
- *Integrated platform*
  - *Diabetes*
  - *Oncology*
- 12:15-13:30 *Lunch Break*
- 13:30-16:00 Round Tables



## Breakout Sessions

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**Two sessions of 60 minutes Q&A in two groups**

*13:30-14:30h / 14:45h-15:45h*

**TEAM *PanOmics*: Cord, Christiane, Olivier, Sandra, Bhushan**

*MEC I*

**TEAM *Impactful Therapies*: Werner, Andreas, Christine, Markus**

*MEC III*

**Closing Remarks**

*MEC I at ~16:00h*

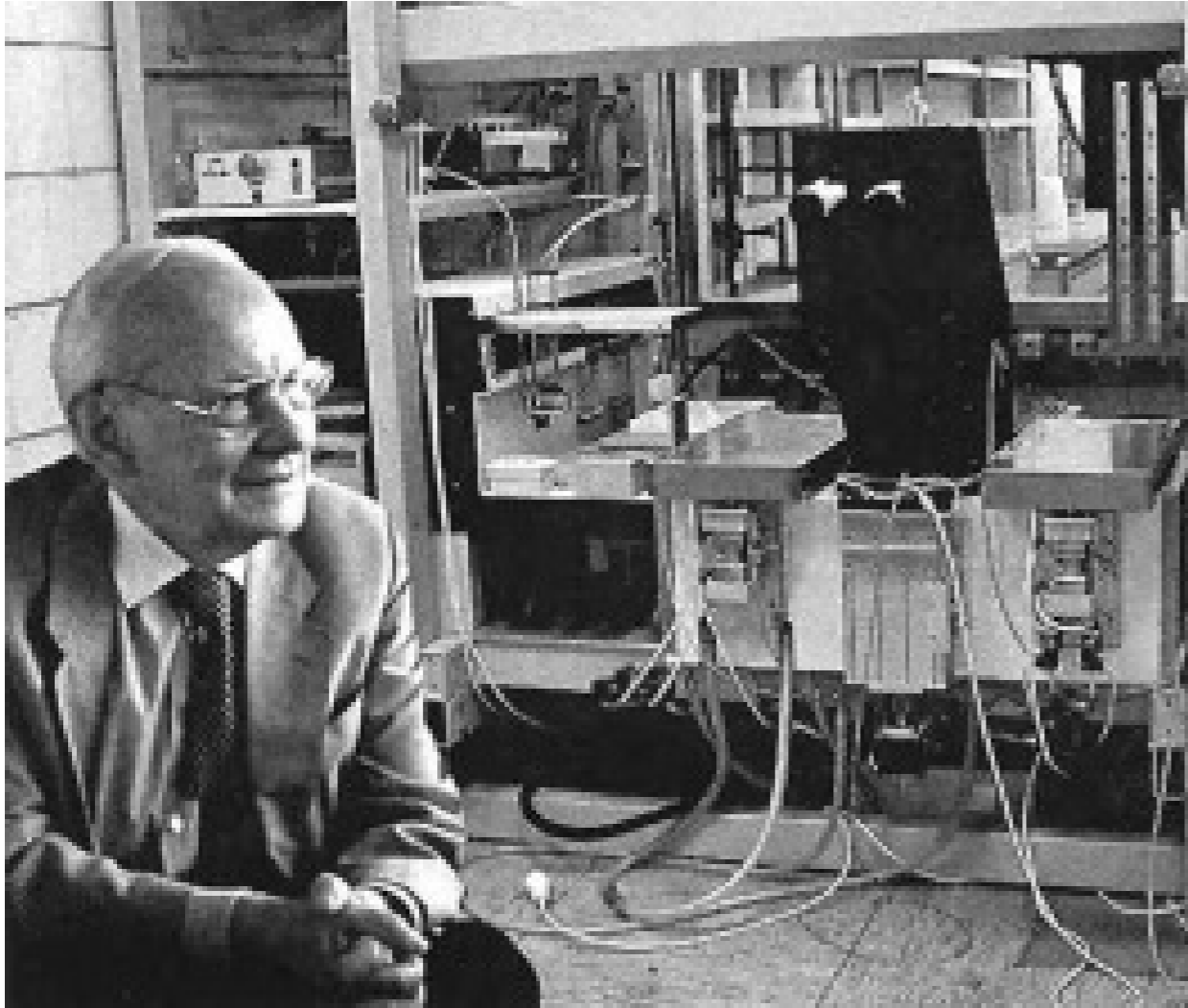
*#researchneverstops*

...and shapes new markets!





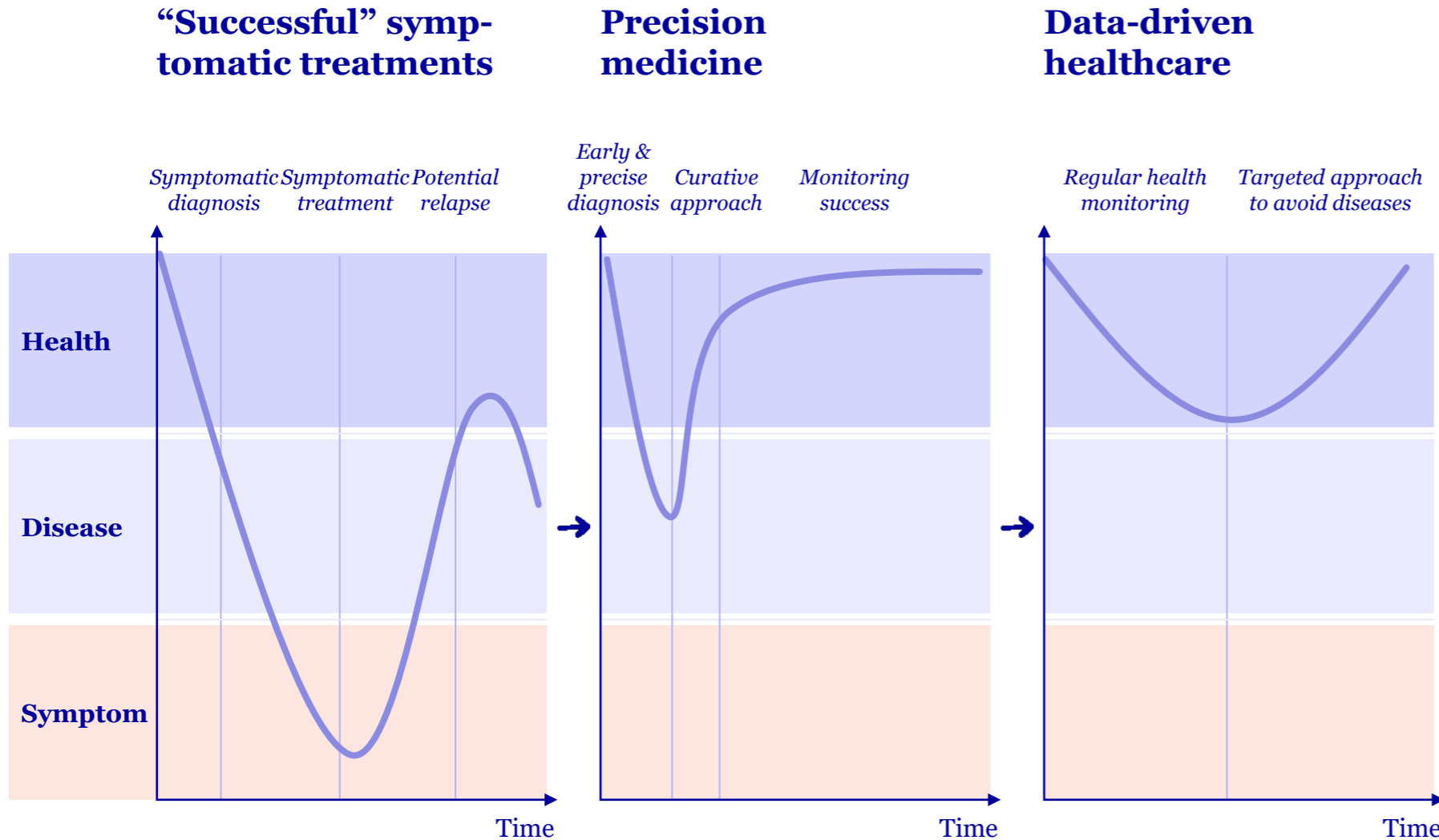
**The initial idea is more modern today than ever before!**





# Shaping new markets means doing things differently

From symptomatic towards data-driven, preventive treatments



## Our all-in efforts towards medicines that matter

- Industrialised PanOmics towards molecular disease understanding – enabled by PanOmics data generation “*without compromise*”
- “*From humans for humans*” discovery approach with iPSCs
- A.I.-powered PanOmics to enhance probability of success (POS) – in safety prediction and beyond
- A.I. and continuous manufacturing to break biologics access paradigm
- State-of-the art, A.I.-powered R&D value chain – proven at scale, by biotech and (big) pharma



# Looking forward to seeing you in Toulouse ...

## Capital Markets Day 2024



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+49 151 19405058 (m)

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