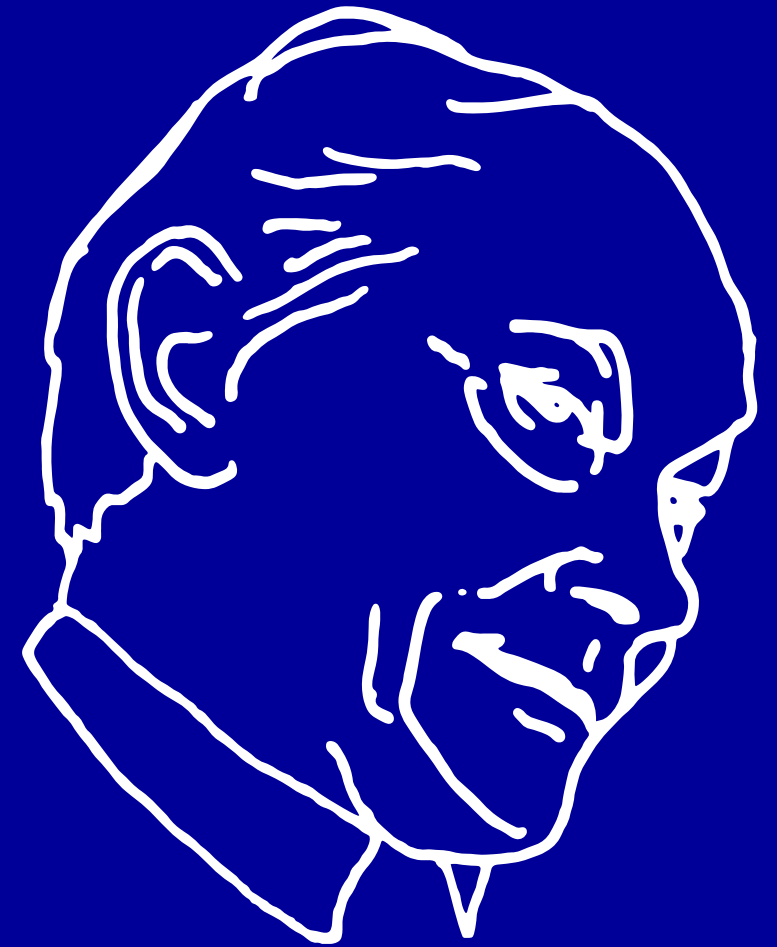


Welcome to Evotec

“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

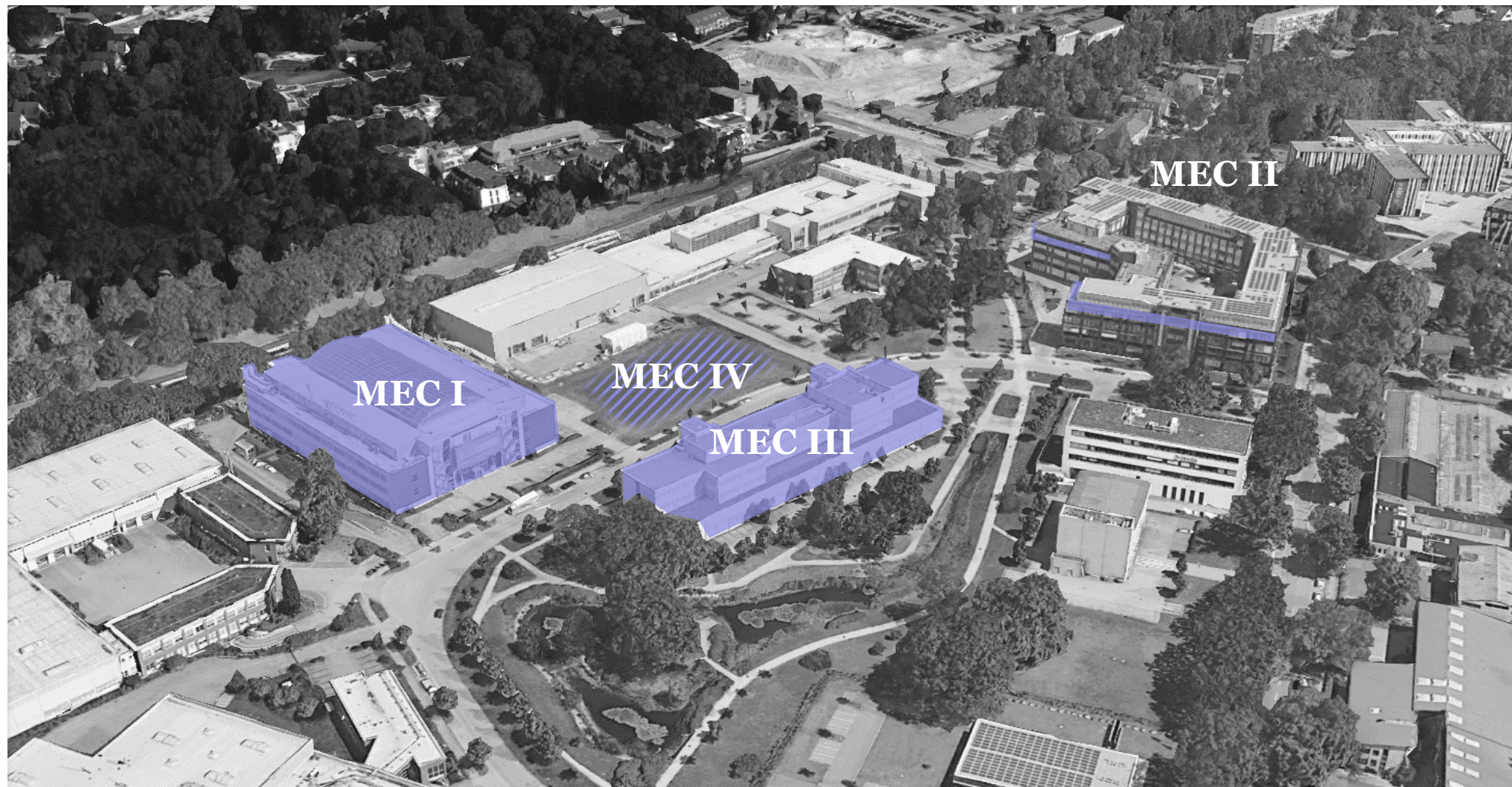
PanOmics

The Lighthouse of iPSCs



Our home base is growing further

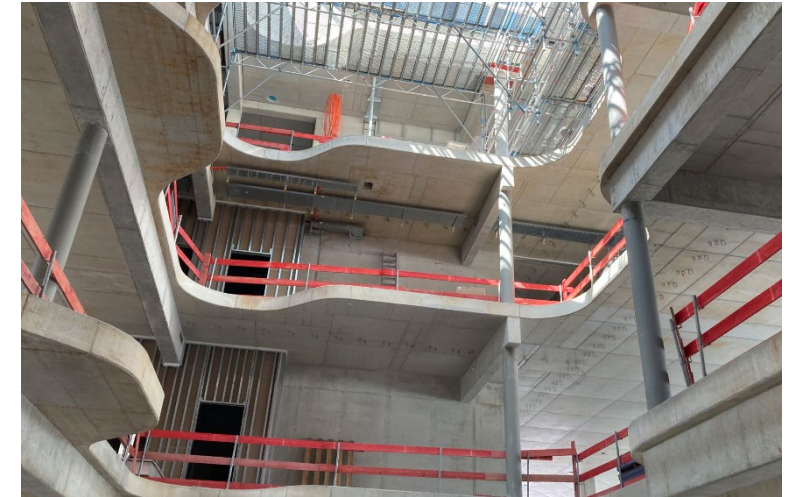
Footprint of Manfred Eigen Campus





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

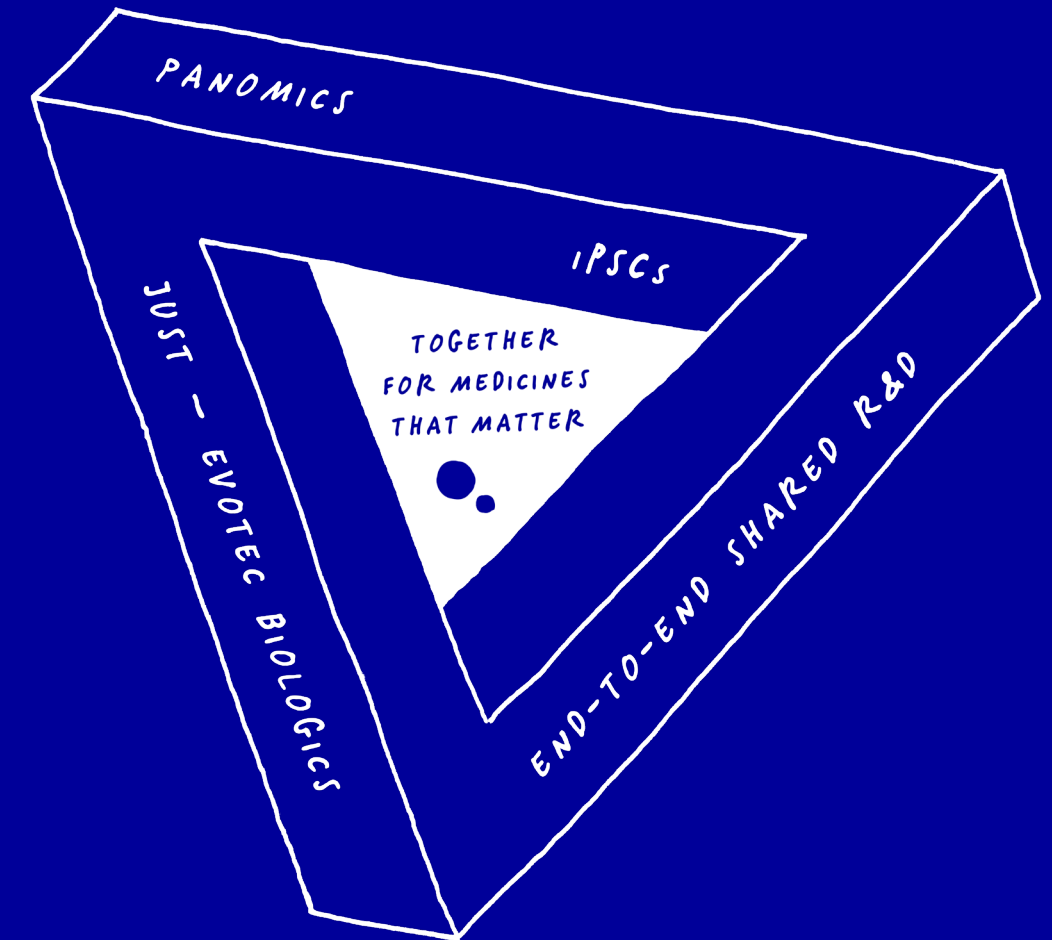


Markus Dangl

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 <ul style="list-style-type: none">• <i>Better disease understanding & diagnostics</i>• <i>Advanced disease modelling</i>• <i>A.I. use cases along the value chain</i>
11:00-11:15	<i>Coffee Break</i>
11:15-12:15	Impactful therapies <ul style="list-style-type: none">• <i>Integrated platform</i>• <i>Diabetes</i>• <i>Oncology</i>
12:15-13:30	<i>Lunch Break</i>
13:30-16:00	Round Tables



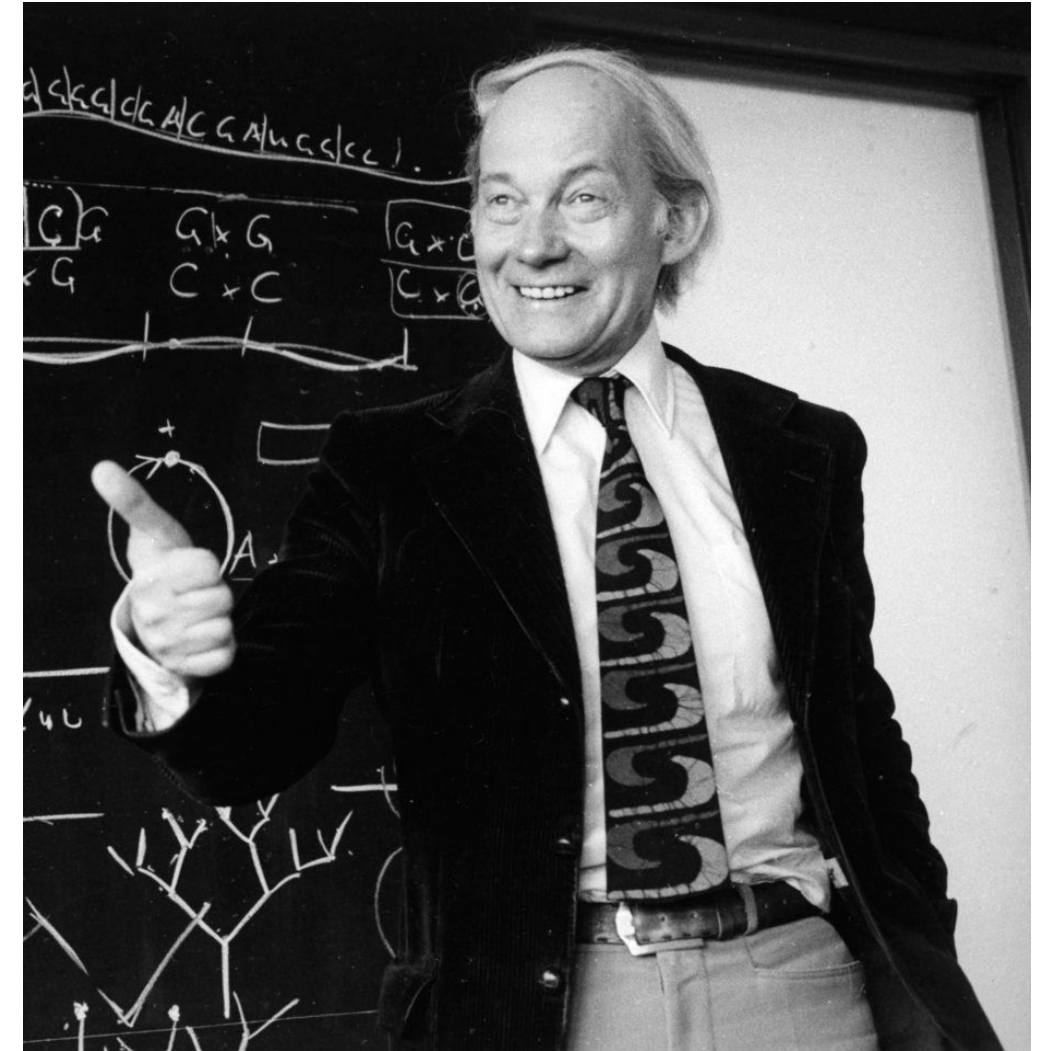
Creating the future will work #together

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

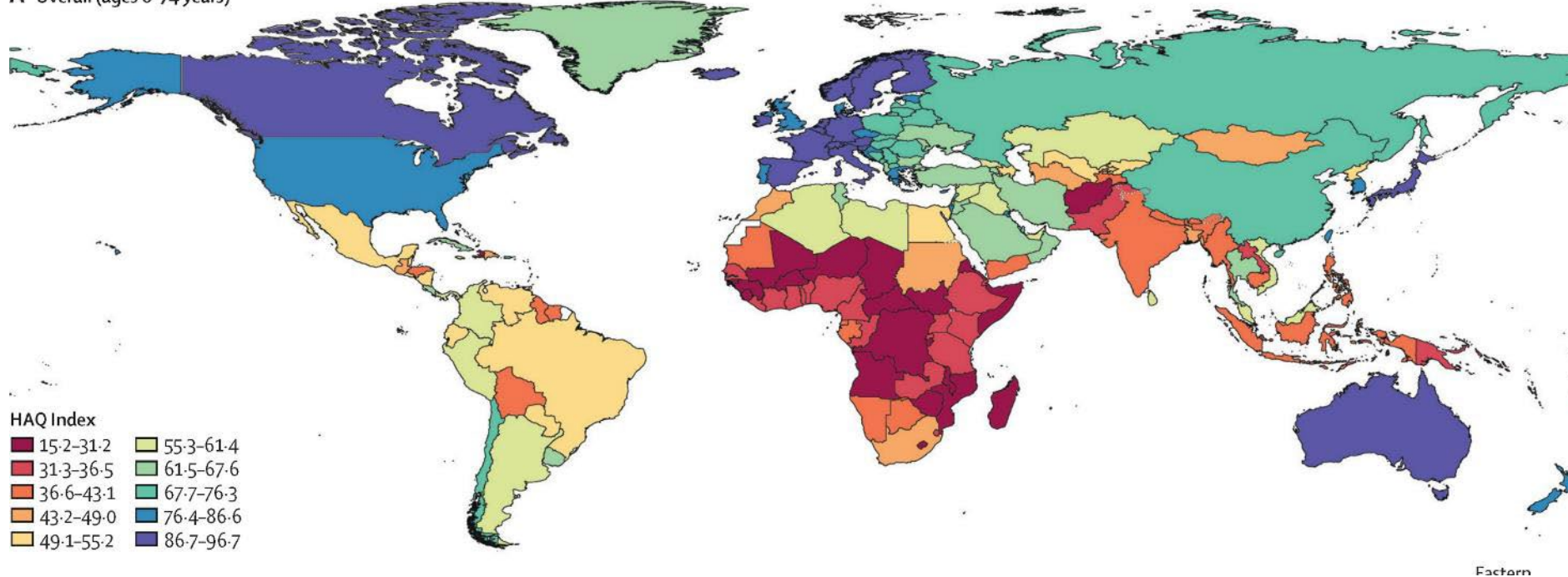
State-of-the-art services as core offering for partners



“Just the beginning” of best days in medicine

Health Access and Quality (HAQ) index analysis

A Overall (ages 0–74 years)



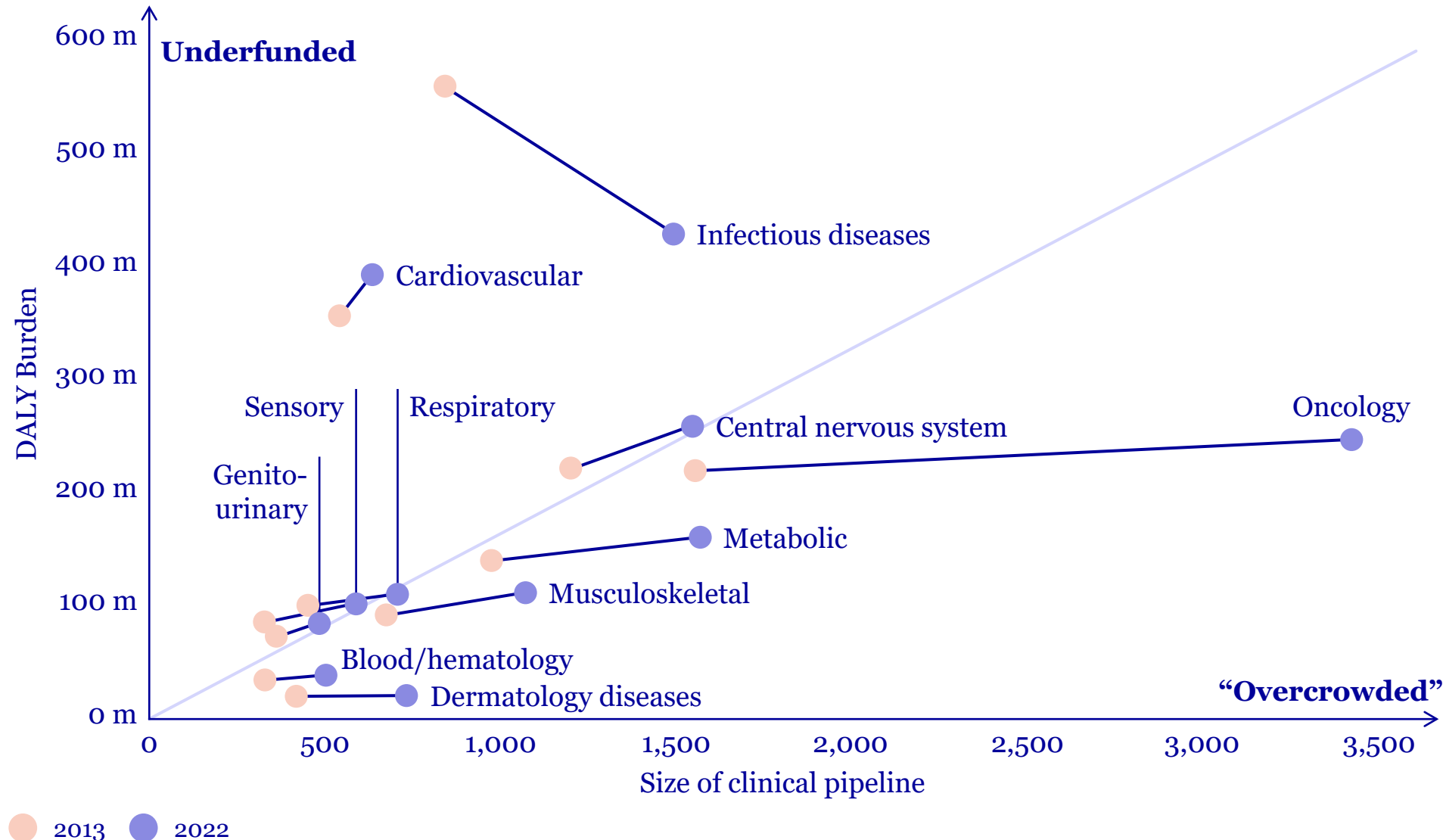
Access to innovative medicine remains a severe unmet need^{1,2}

- 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



Big innovation is happening, but next challenges around the corner

Case study: Obesity



Illustrative calculation

U.S. Obesity
Prevalence¹

140 million

Annual price of new
GLP-1 medication²

~15,000 USD



Estimated total annual
costs to health system²

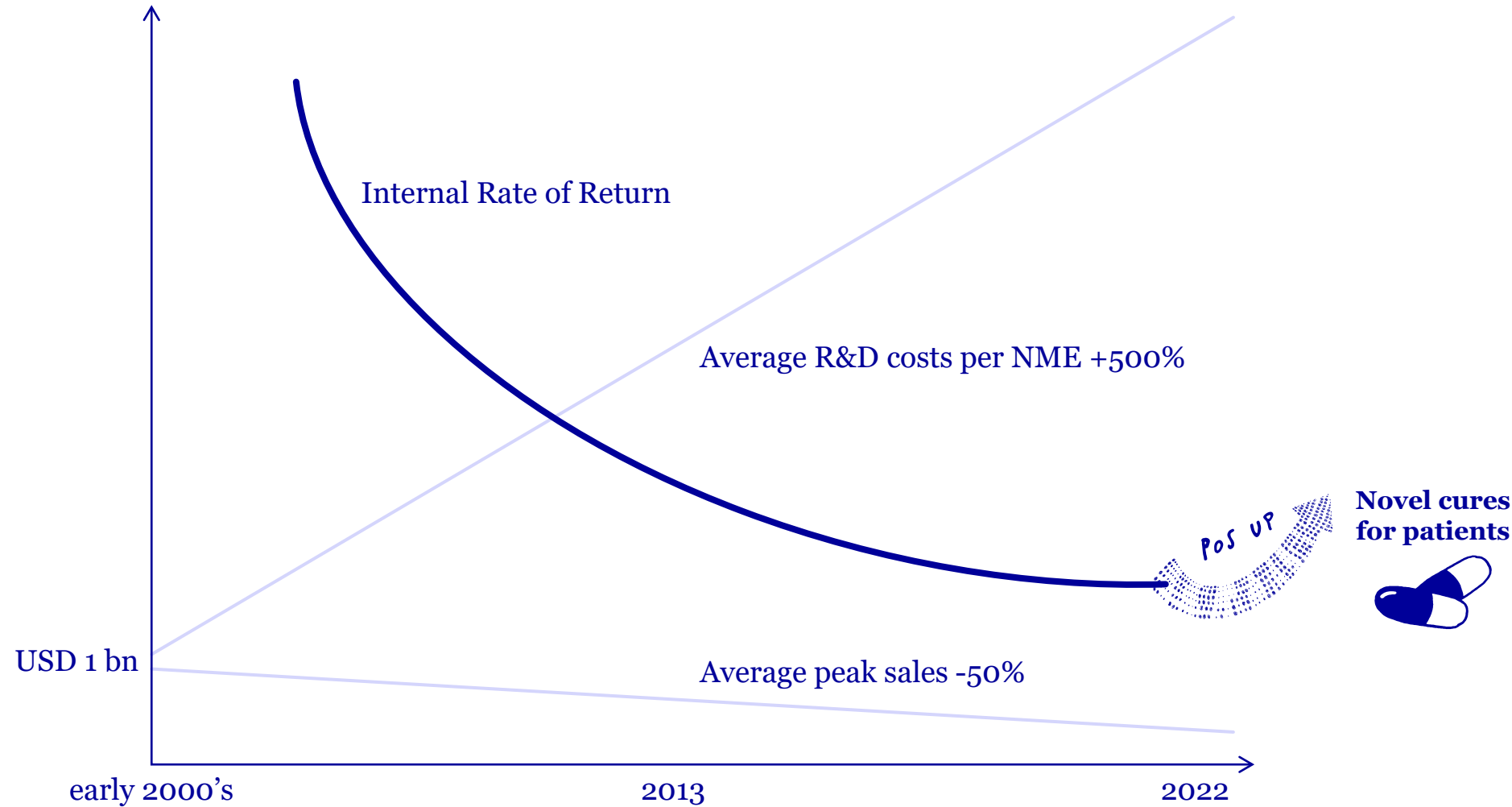
1.5-2 Trillion USD

~10% of entire
US economy



Reverting IRR¹ 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 IRR¹
- IRA² 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

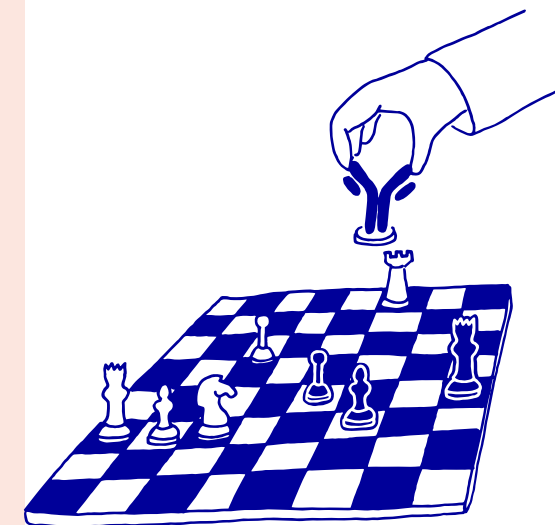
Technology convergence

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

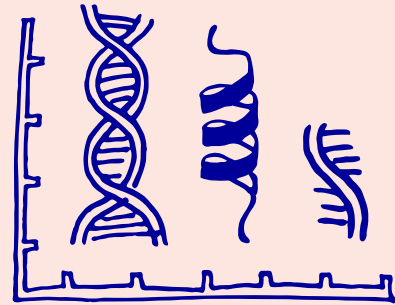


Let's talk about modality agnostic pipeline building

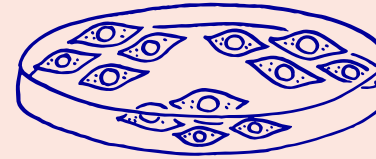
Our focus for today

Our focus areas

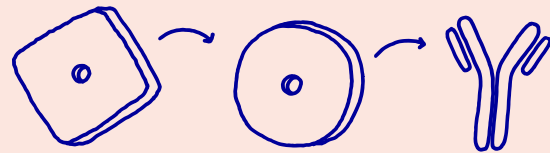
PanOmics¹



iPSC cell therapy



Just – Evotec Biologics



End-to-End Shared R&D

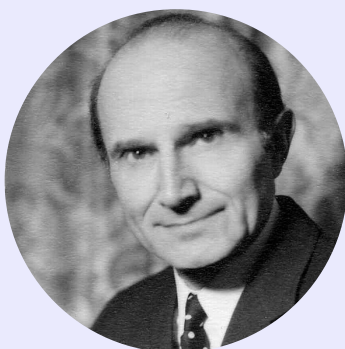




We follow science, and open massive new opportunities

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



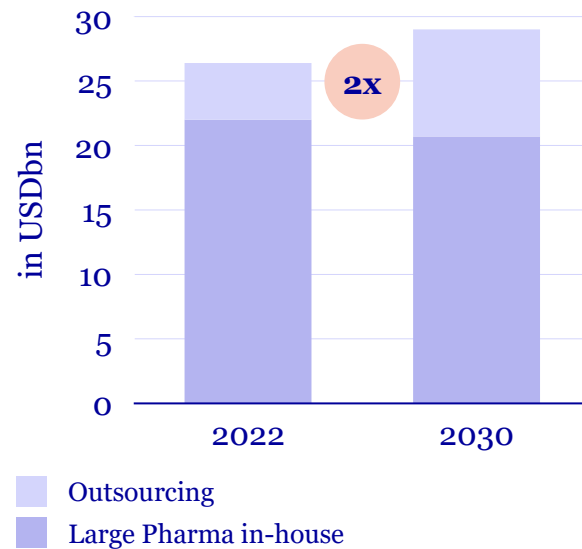
Brigitte Askonas



New technologies leading to new opportunities

Shaping (new) markets

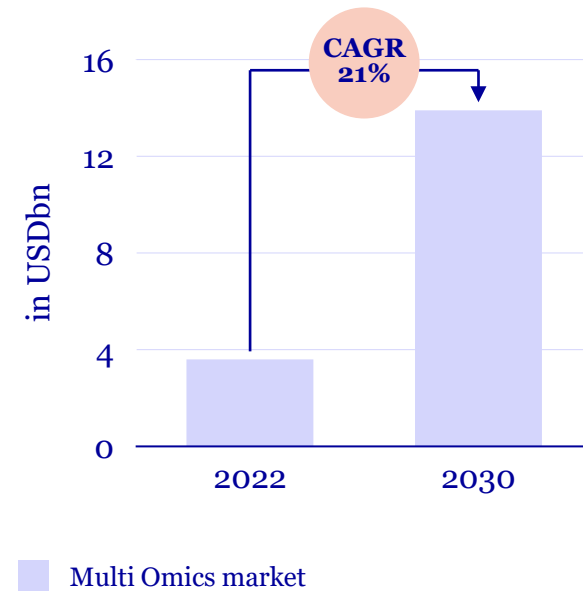
End-to-End shared R&D



Drivers

Deteriorating IRRs increase demand for outsourcing & higher efficiency

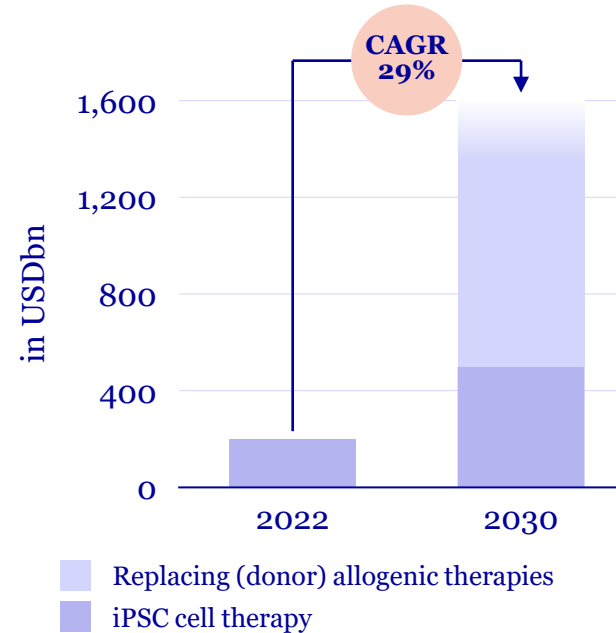
PanOmics



Drivers

Precise medicines & diagnostics leading to patient specific treatments

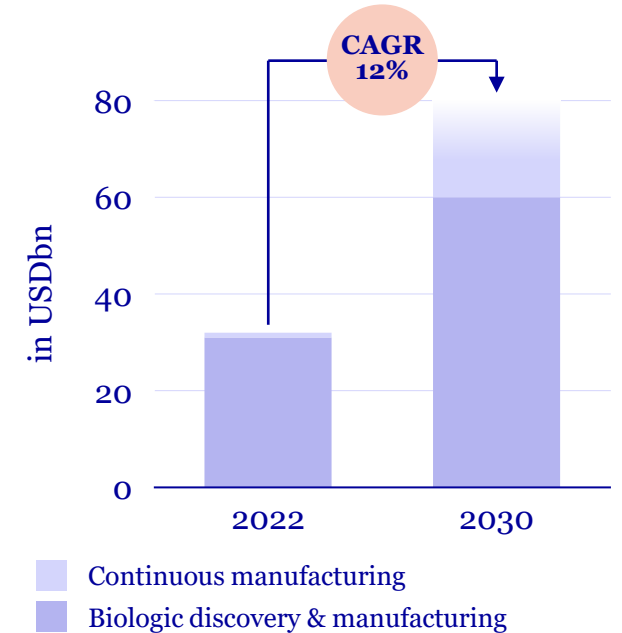
iPSC cell therapy



Drivers

From donor dependency to scalable off-the-shelf solutions

Biologics



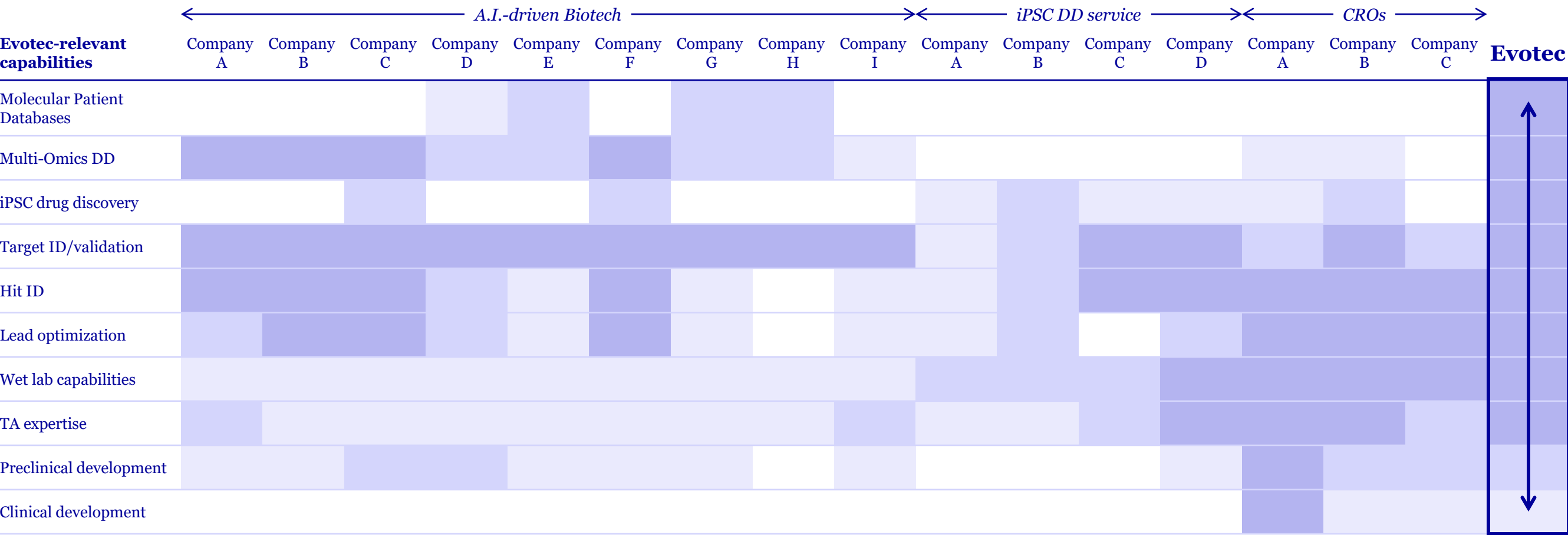
Drivers

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

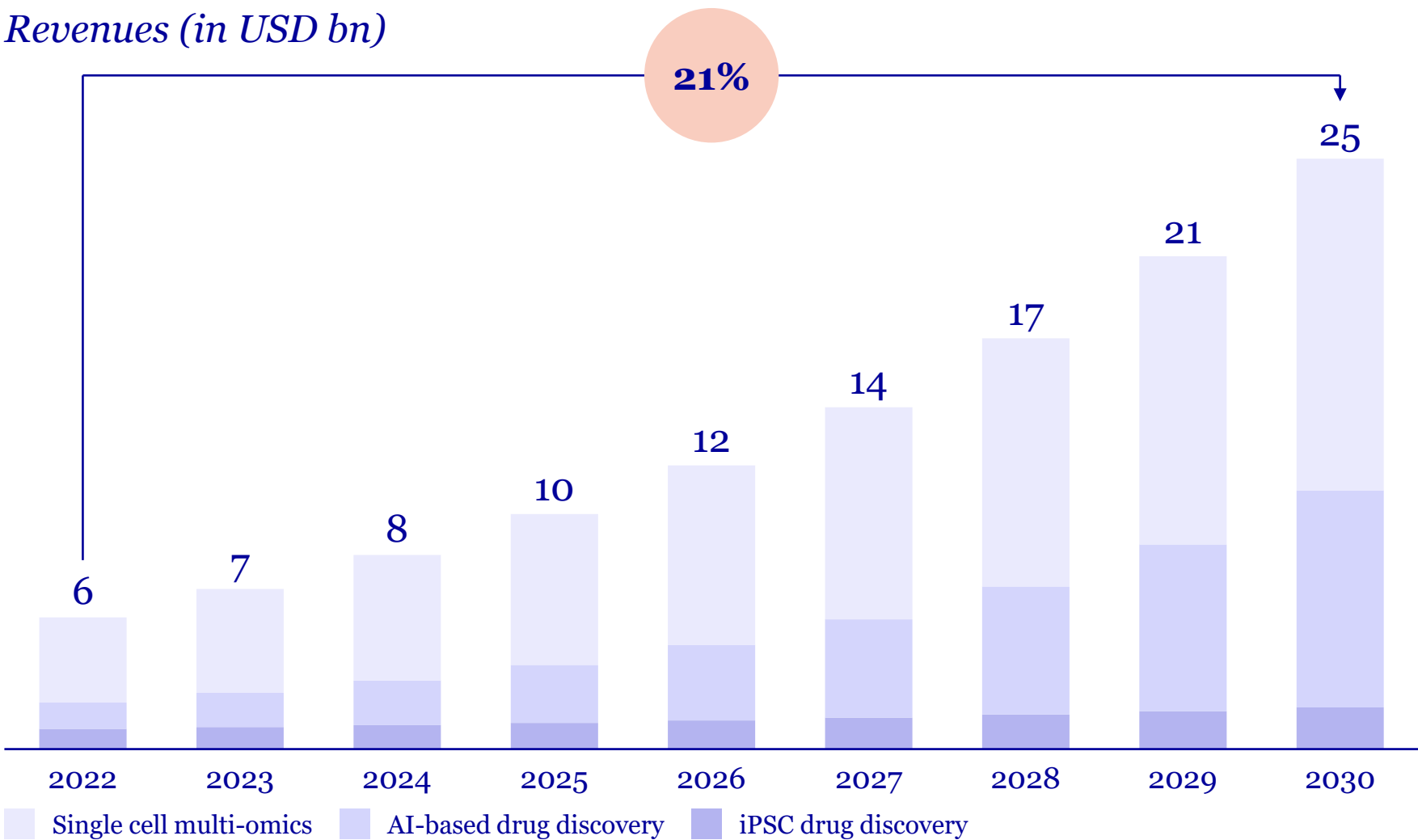


PanOmics is a massive opportunity

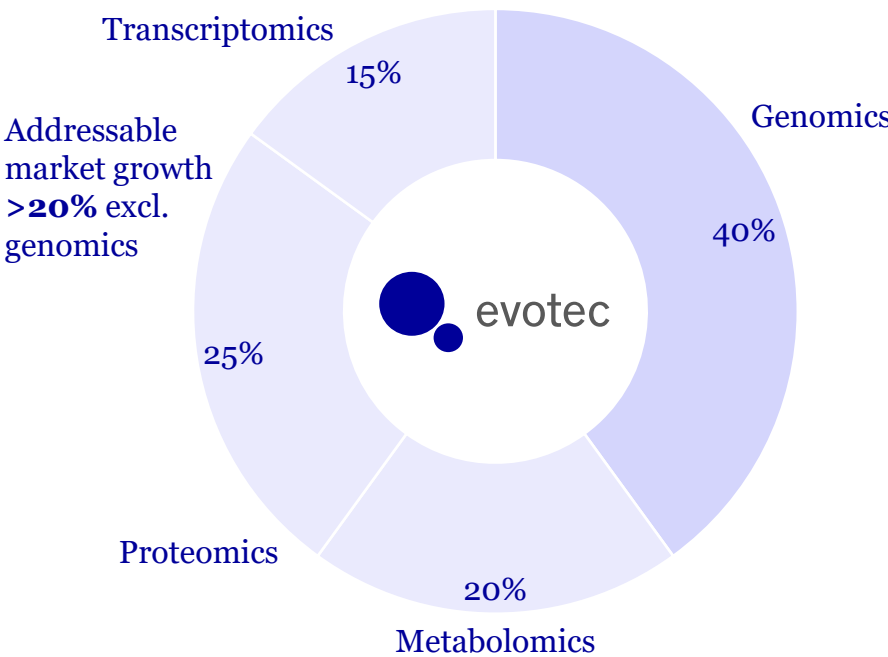
Addressable market analysis

Addressable market

Revenues (in USD bn)



Market distribution and growth by application – 2030

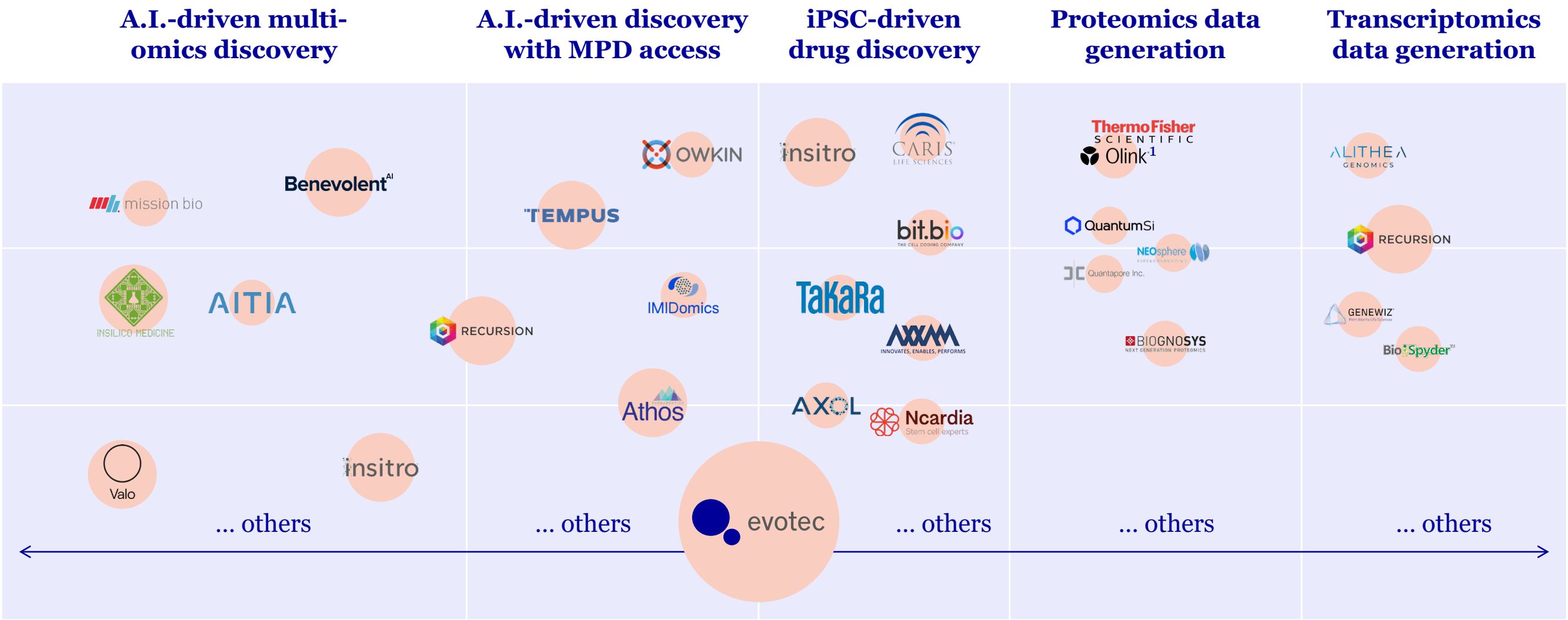


- **Genomics** will continue to grow
- **Proteomics** and **metabolomics** to outpace Genomics



Fully integrated offering to secure data integrity

Simplified competitive landscape analysis



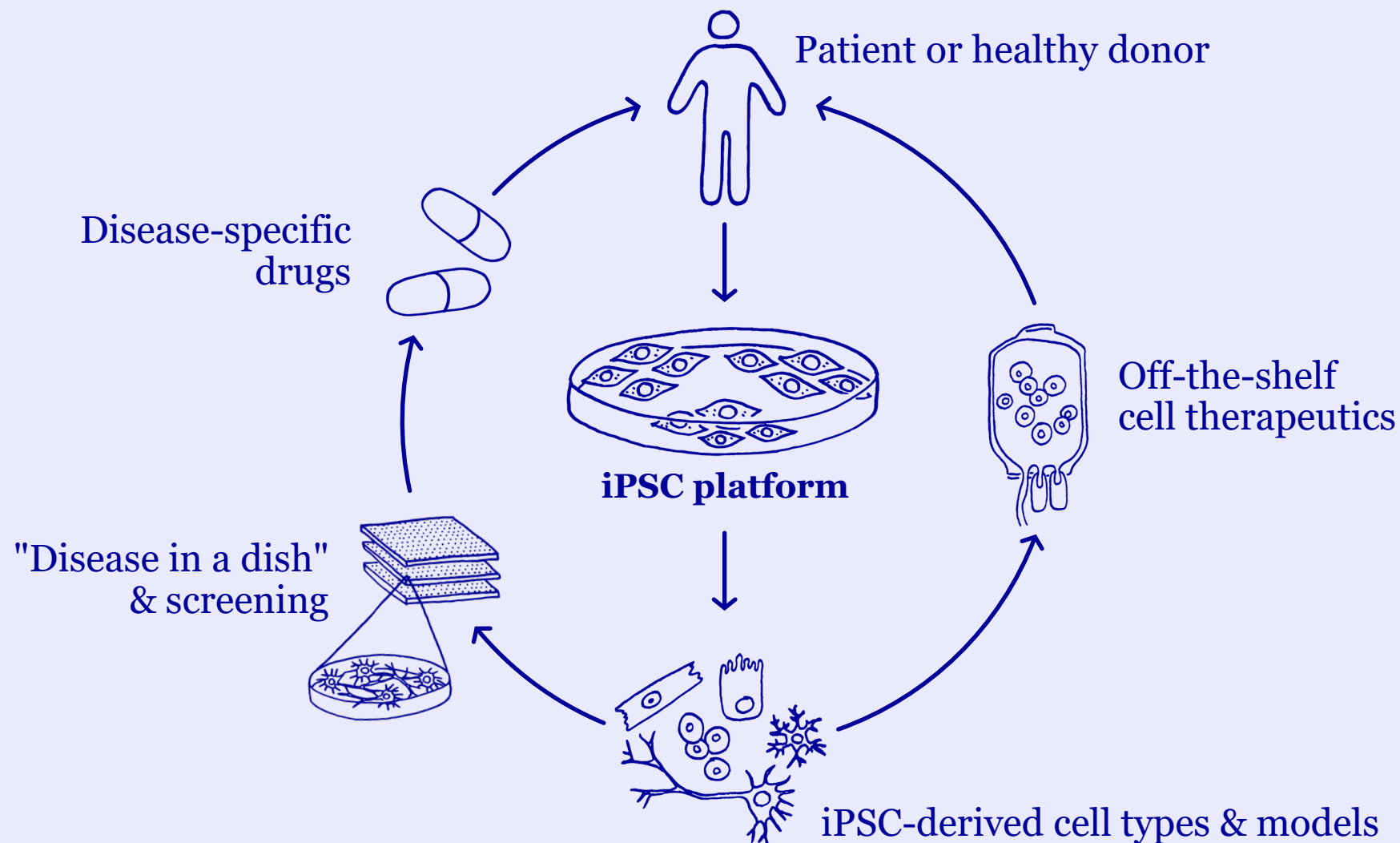


From humans for humans

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

E.iPSC –
Human disease
relevant modelling

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

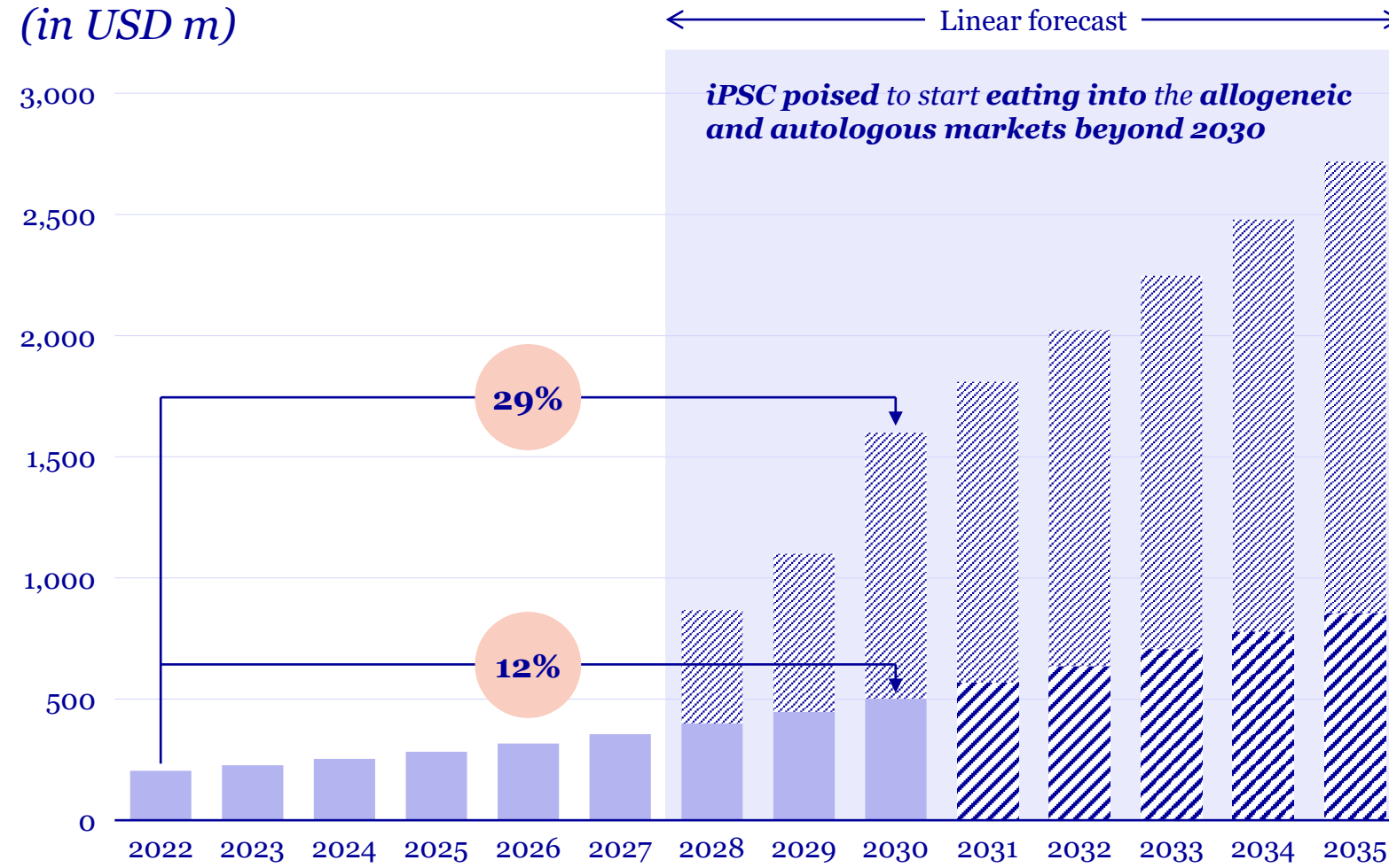




iPSC market growth will be driven by clinical and commercial validation

Addressable market analysis

Addressable market (in USD m)



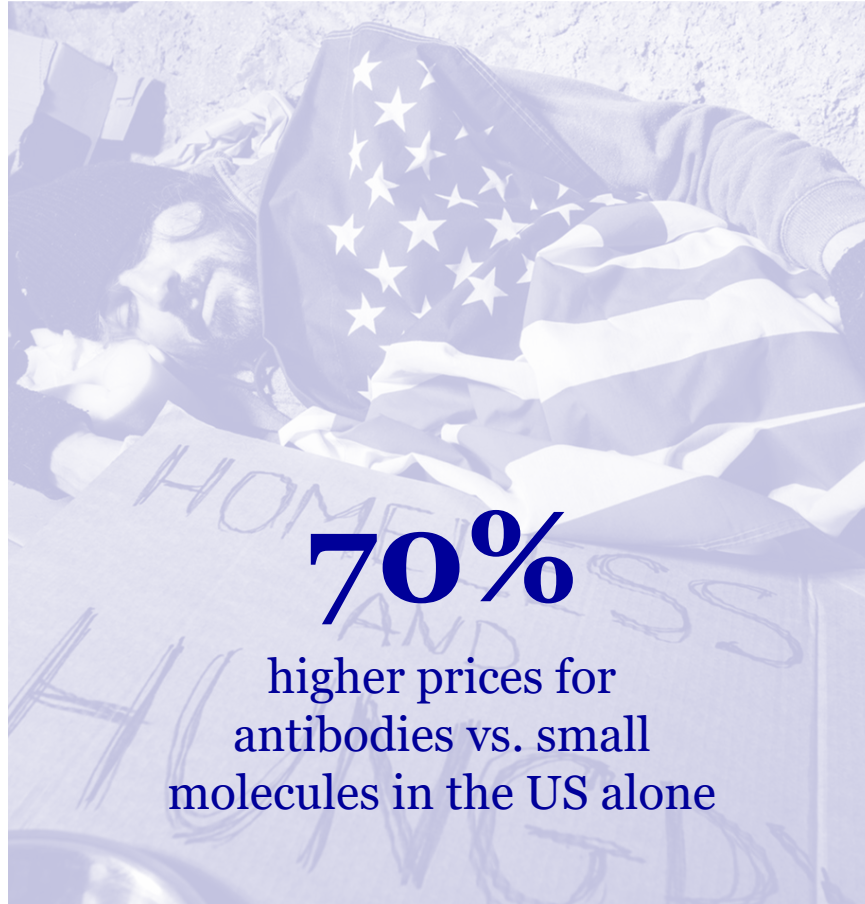
Heterogeneous mix of service and product players – no other integrated offering for partnered pipeline building





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

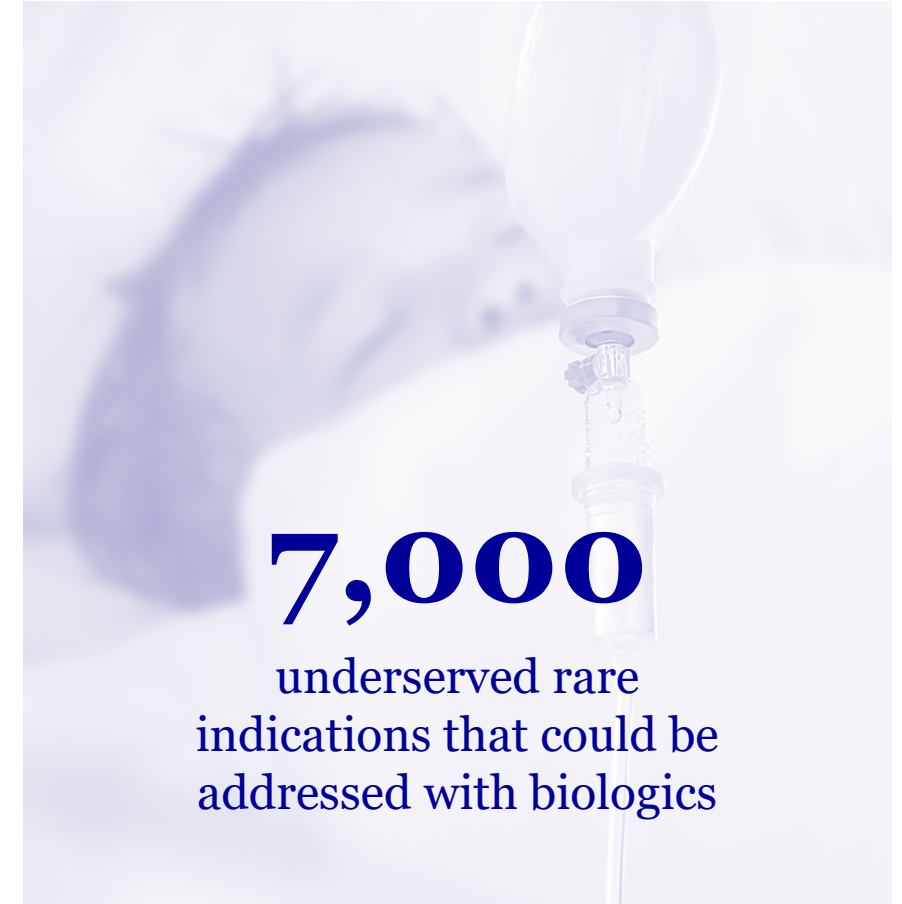
Underserved
populations



6 bn

without access to biologics
based on geography

Underserved
regions¹



7,000

underserved rare
indications that could be
addressed with biologics

Underserved
indications

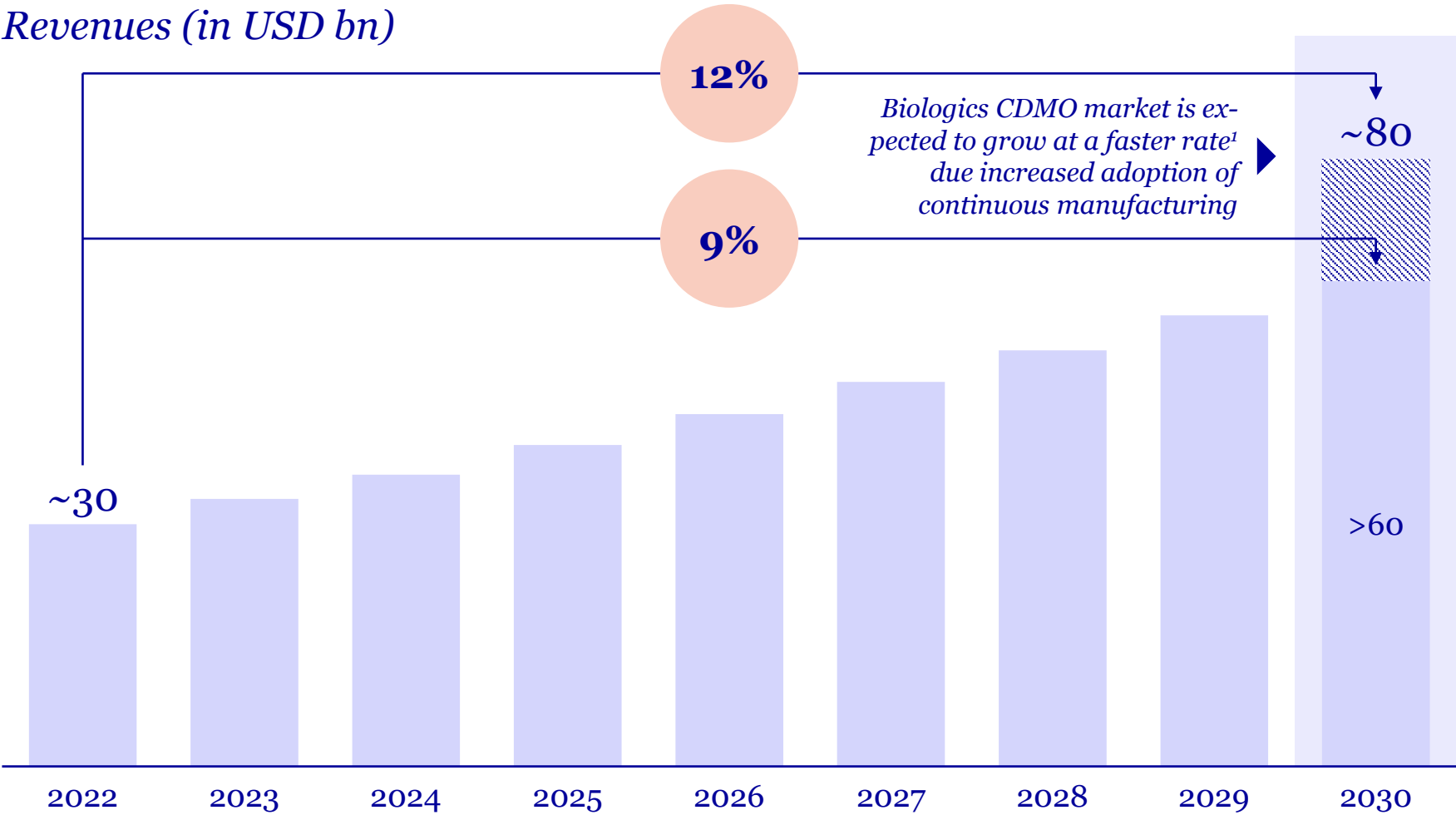


Continuous manufacturing is the paradigm shift shaping the market

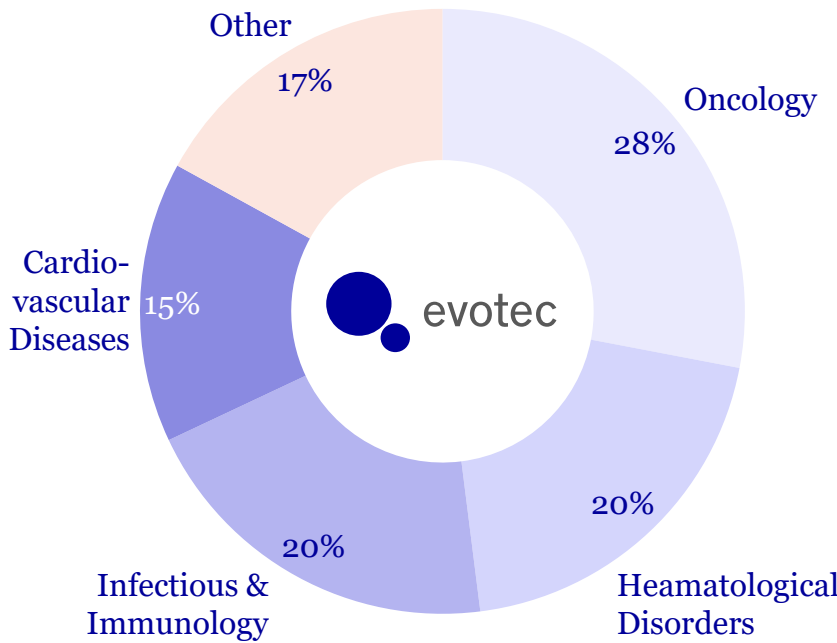
Market size and growth

Biologics discovery + manufacturing market

Revenues (in USD bn)



Market shares by Therapeutic Areas 2022

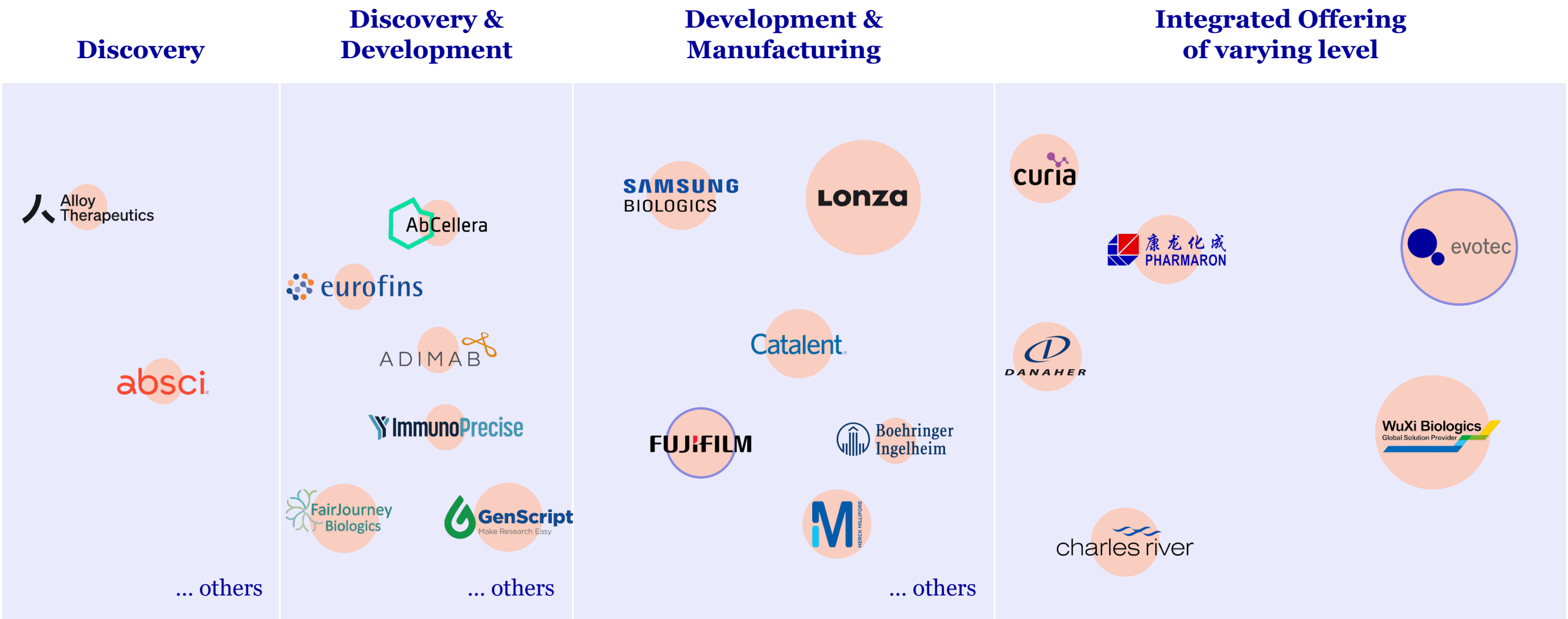


- **Oncology dominated** the market in the past
- **Hematological disorders** and **cardio-vascular diseases** expected to **drive** the market growth in the **next years**



We have a fully integrated offering

Key competitor analysis

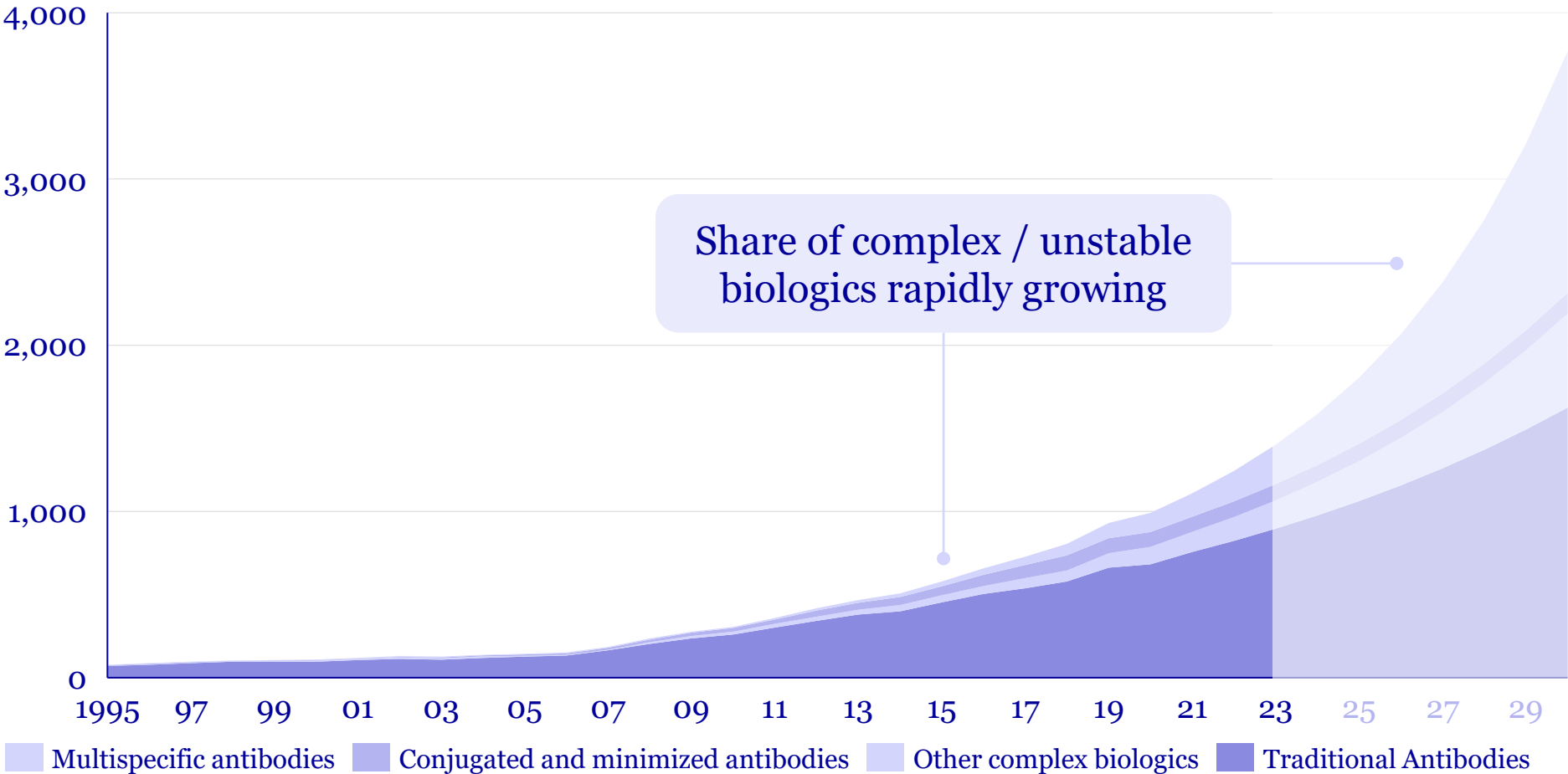




Our continuous platform will even further excel with complex biologics

Trends in global biologics pipelines

Size of global pipeline by therapeutic modality
Number of products¹, from Phase I to III



Share of complex biologics in the pipeline

Just
● EVOTEC BIOLOGICS

>40%

Industry average

~30%

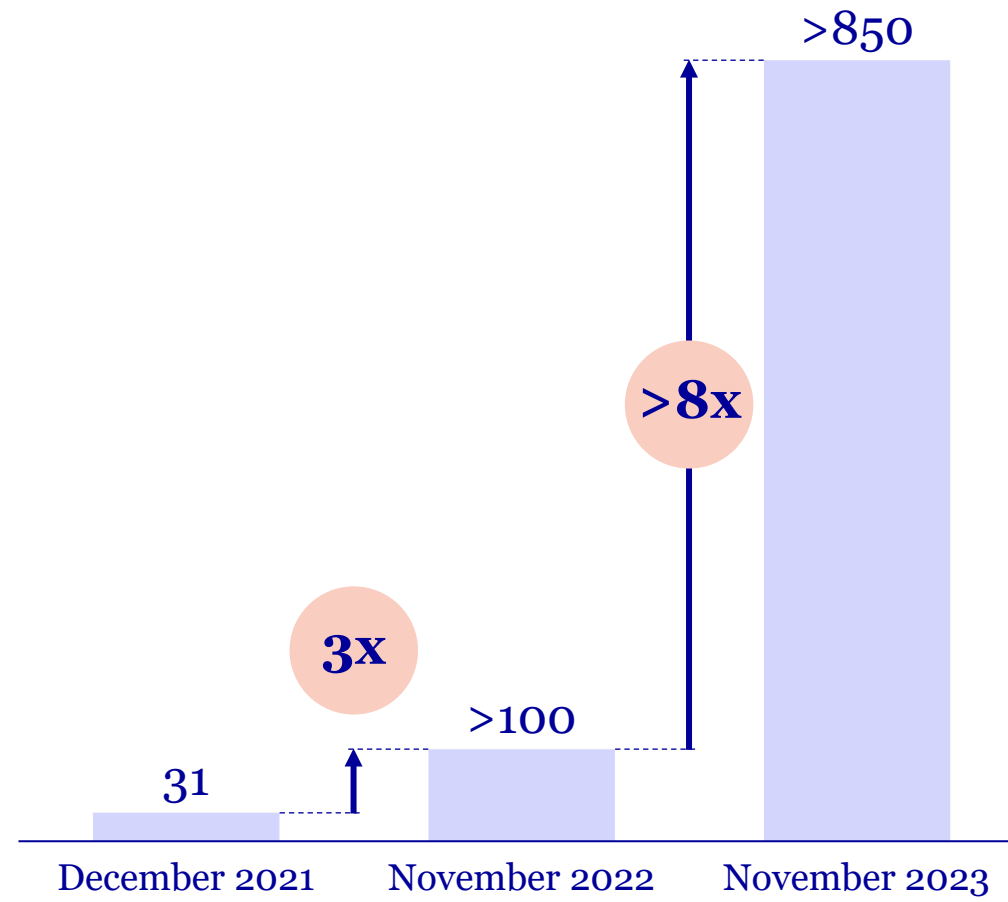


Just – Evotec Biologics is building markets faster than expected

Key achievements 2021-2023

Closed Sales

in € m



Key progress

SANDOZ

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



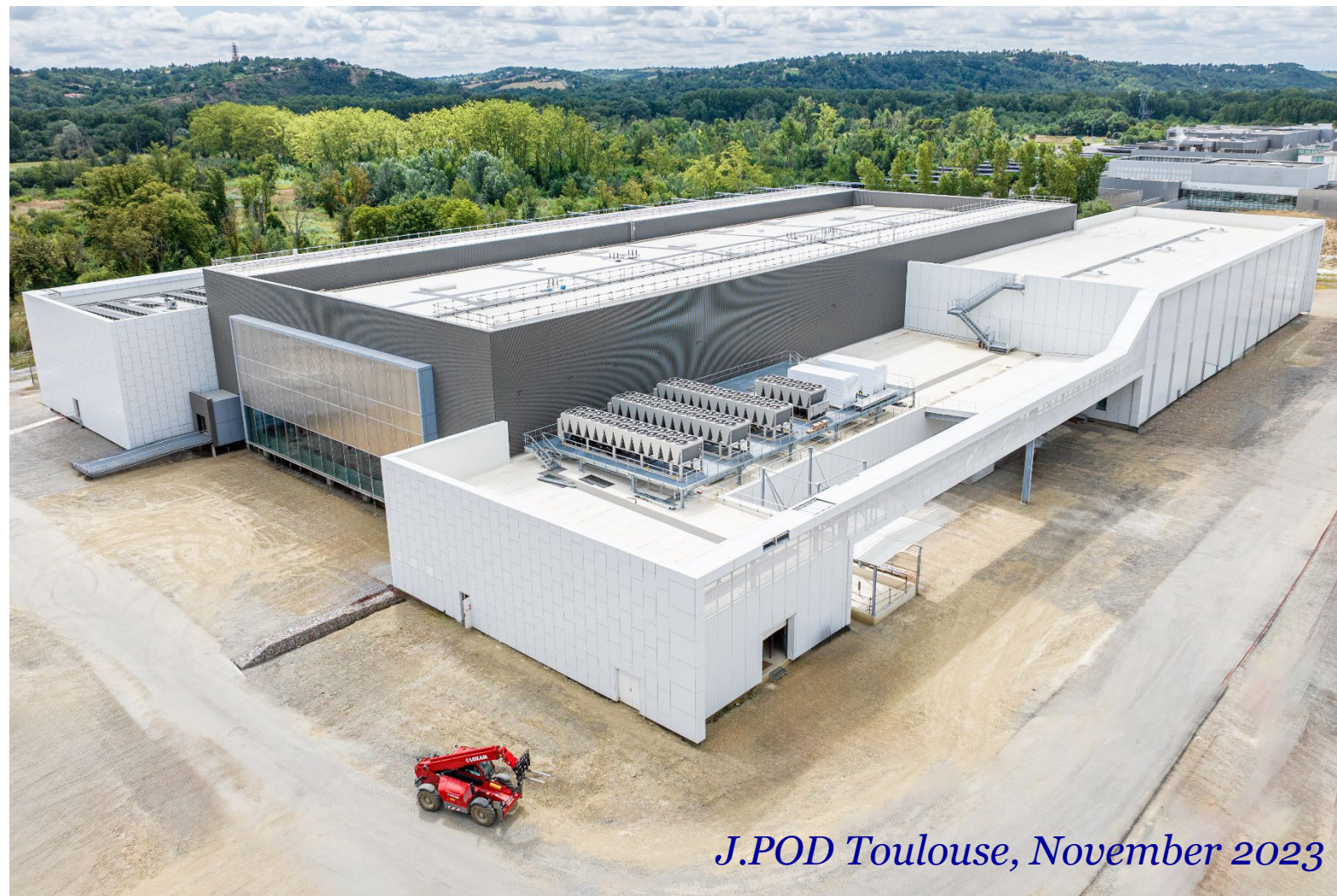
Anti-Plague mAb development programme initiated

Development programme for Orthopoxvirus mAb candidates



Redmond is online – Toulouse ready to start in 2024

Progression on track



J.POD Toulouse, November 2023

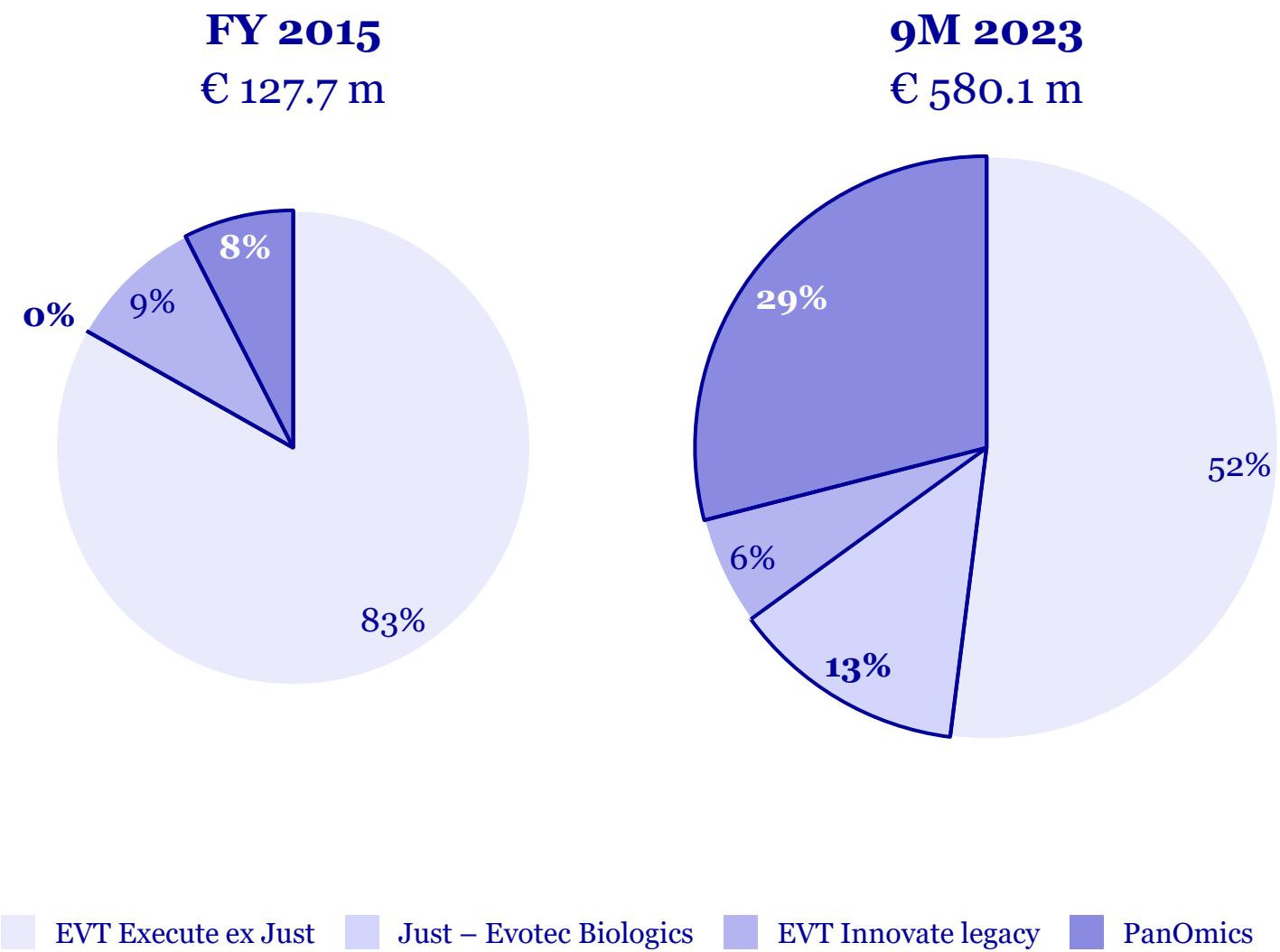
J.POD – commercial biologics manufacturing site in Toulouse stepping up

- 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 FIH¹ programs
- Start of Business Development: Filling CLD/PD² 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_{2015 - 9M 2023}
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%

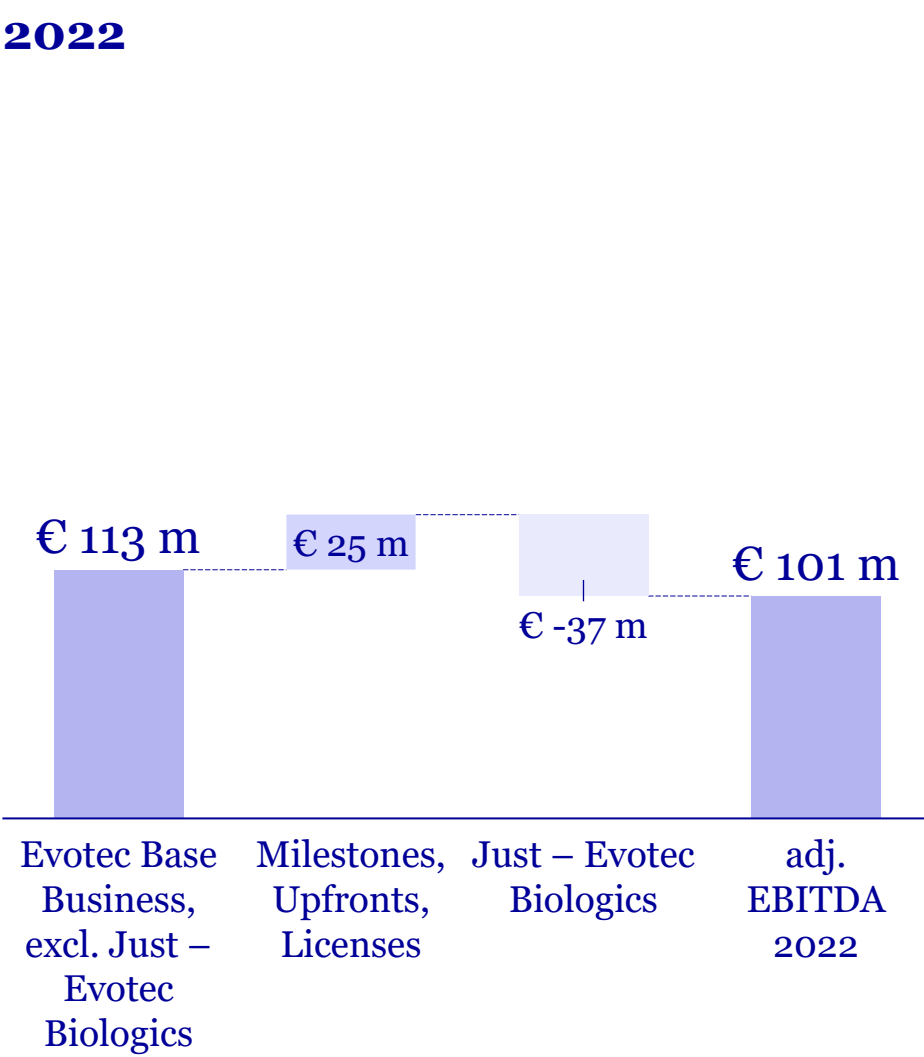
**On track to reach
revenue aspiration
2025**



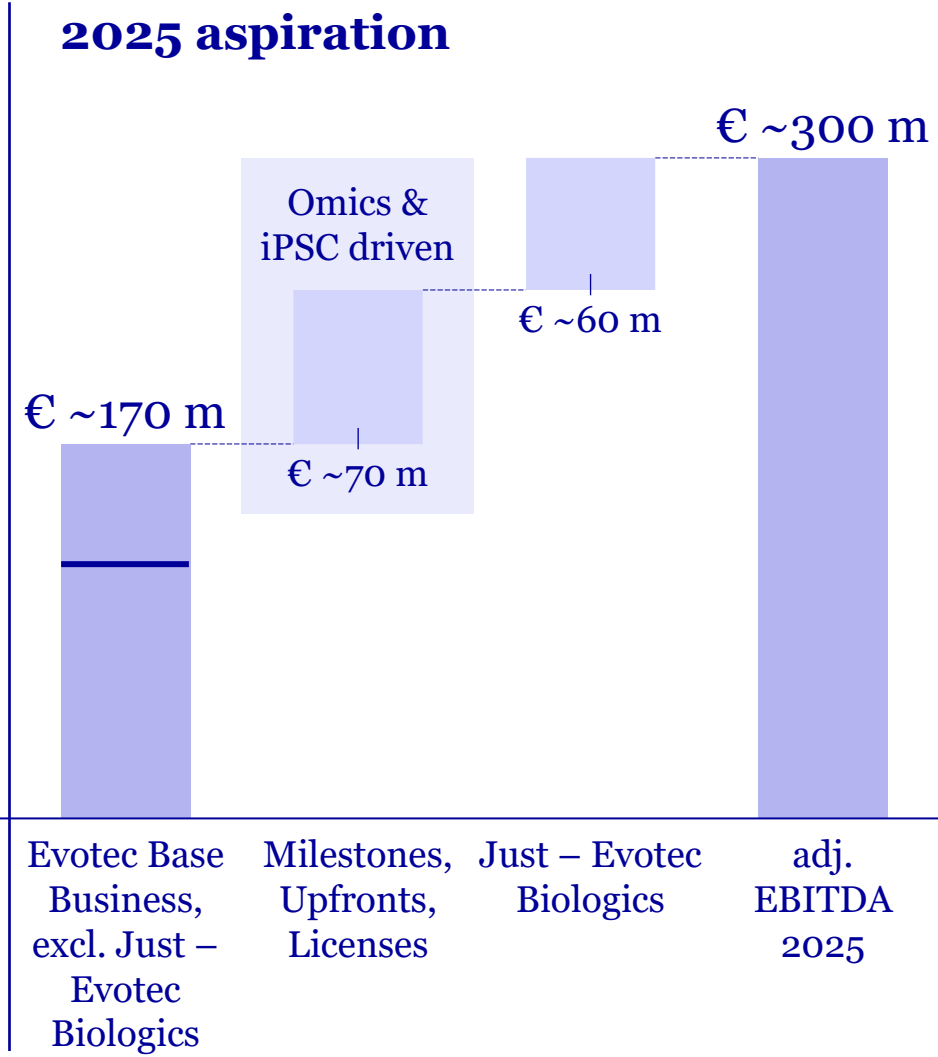
... and a key contributor to acceleration of milestones

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
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Agenda

9:00-9:30	Shaping (new) markets
9:30-11:00	PanOmics – From patients for patients <ul style="list-style-type: none">• <i>Better disease understanding & diagnostics</i>• <i>Advanced disease modelling</i>• <i>A.I. use cases along the value chain</i>
11:00-11:15	<i>Coffee Break</i>
11:15-12:15	Impactful therapies <ul style="list-style-type: none">• <i>Integrated platform</i>• <i>Diabetes</i>• <i>Oncology</i>
12:15-13:30	<i>Lunch Break</i>
13:30-16:00	Round Tables



R&D productivity remains the grand challenge for big pharma

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

\$ 138 bn

*R&D Spending of
“Top 15 Pharma” in 2022¹*

<2%

*Clinical pipeline
growth²*

~44%

*Pharma companies with
negative R&D productivity³*

\$ 6.16 bn

R&D expenditure per new drug⁴



Increasing the probability of success is key

Attrition rates have not improved – selected KPIs

~95%

*False discovery rate
in the pre-clinic¹*

>93%

*Clinical attrition up
to market launch²*

>32%

*Post-market safety events
of FDA-approved drugs³*

0.78

Annual drug launches per “Big Pharma”⁴

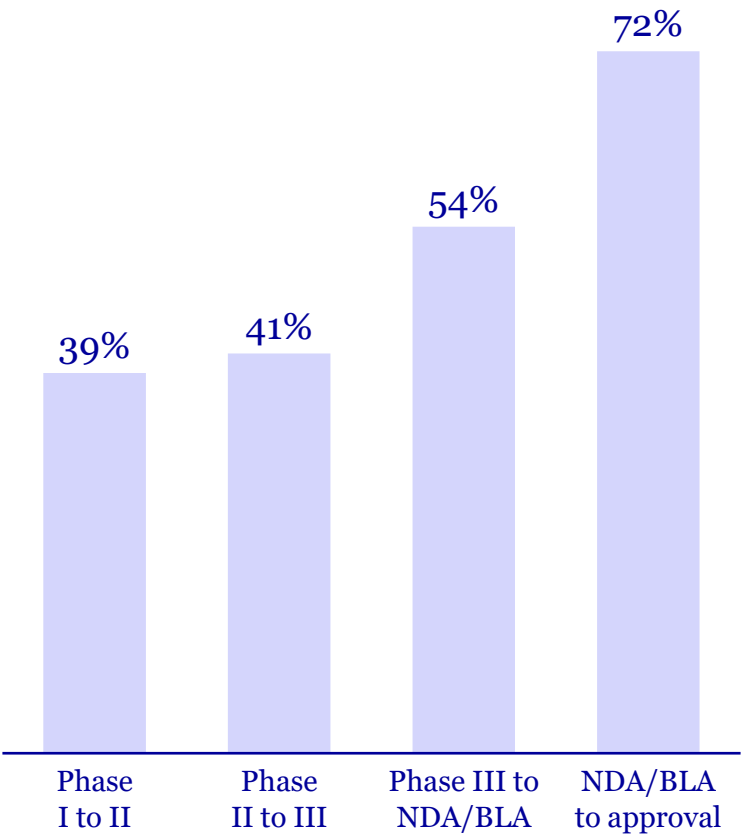


Probability of success on the decline in most indications

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

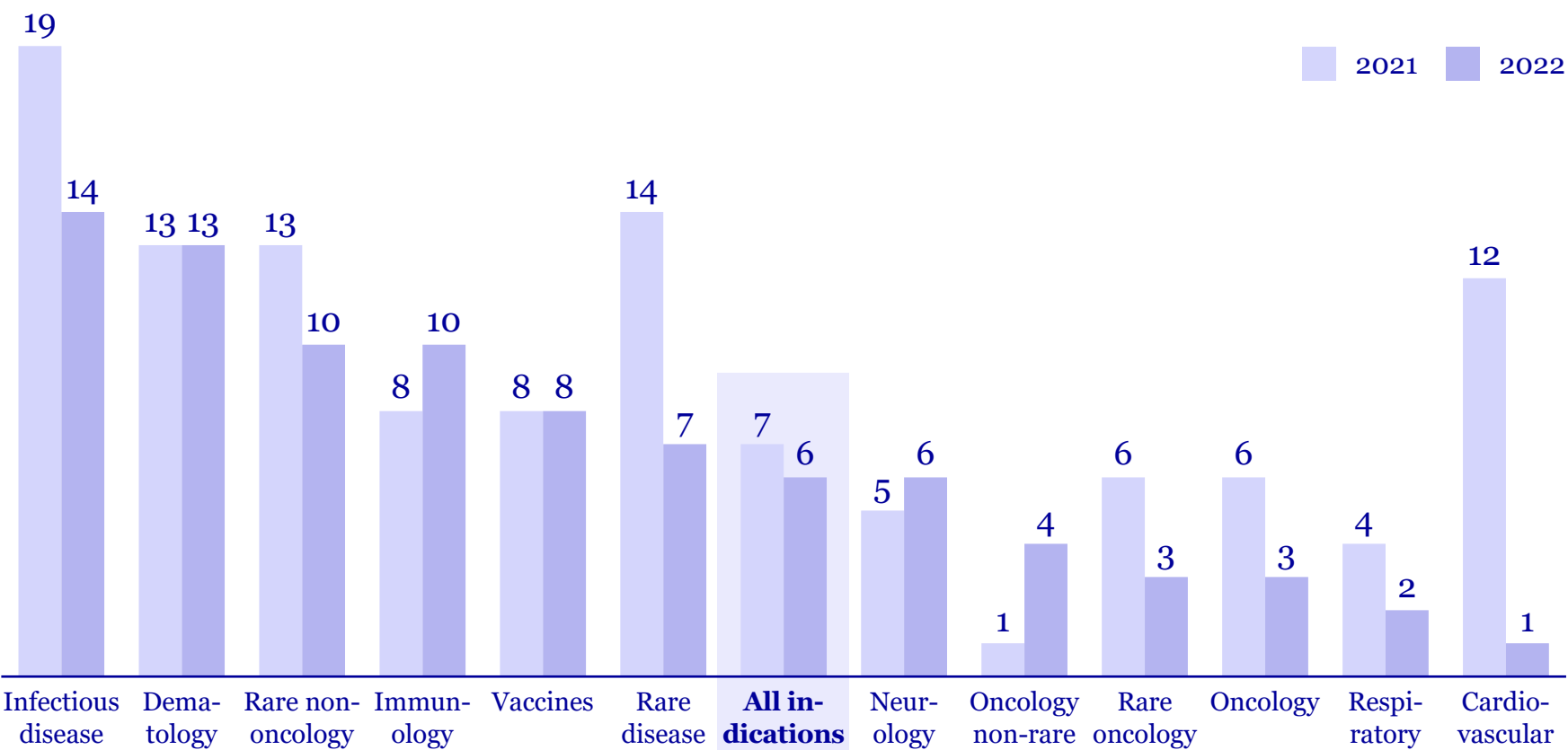
Probability of success

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



Overall clinical success rates

in %



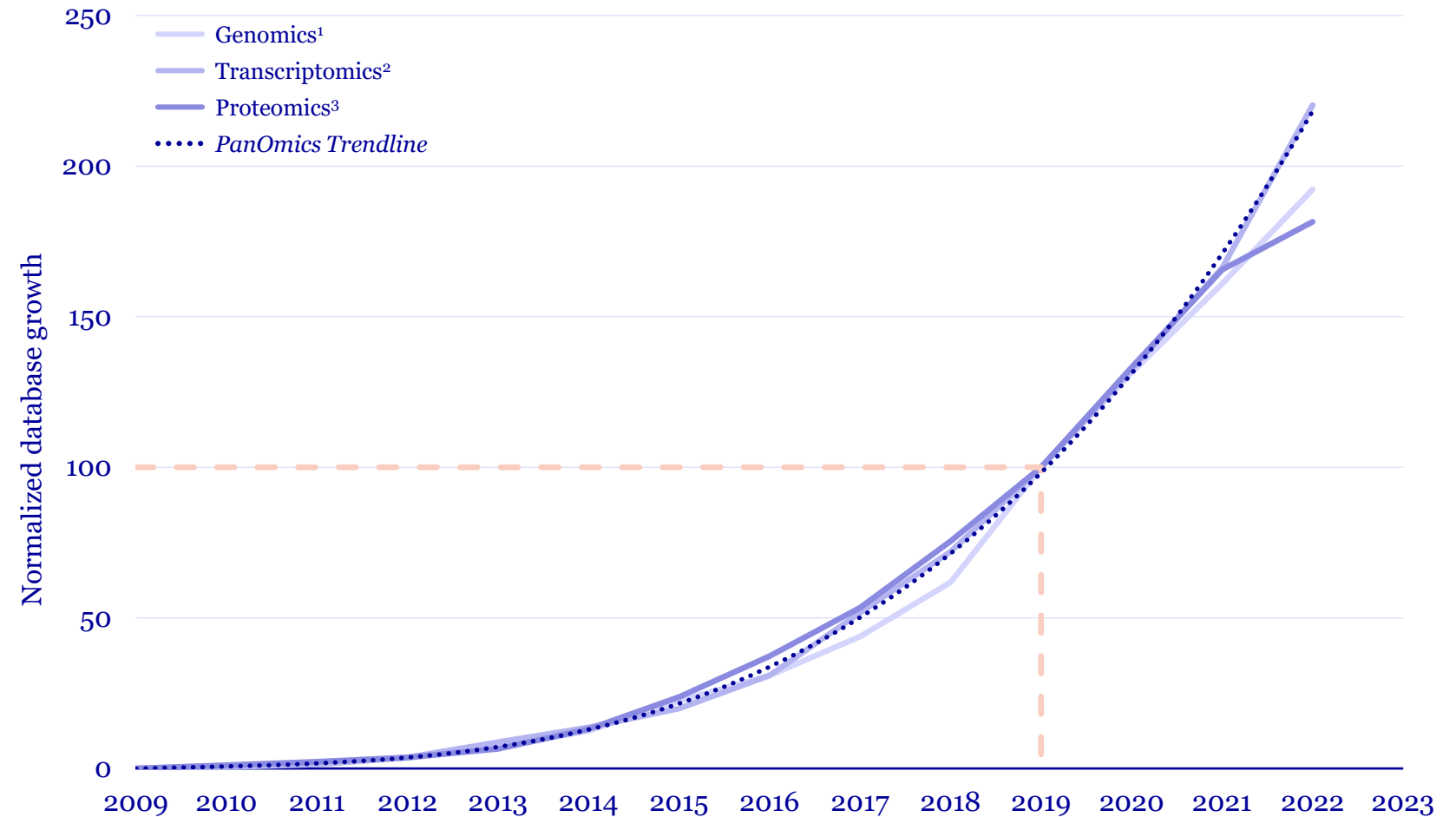


Omics data is a key driver of the precision medicine megatrend

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



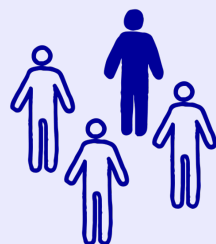


A precision medicine platform is driven by PanOmics

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

AstraZeneca

Bristol Myers Squibb™

Johnson & Johnson

Pfizer

Takeda

BAYER

Boehringer
Ingelheim

CHINOOK
THERAPEUTICS
A Novartis Company

Janssen

Lilly

novo nordisk®

sanofi

>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

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

Developing a pipeline of breakthrough therapies based on molecular glue degraders

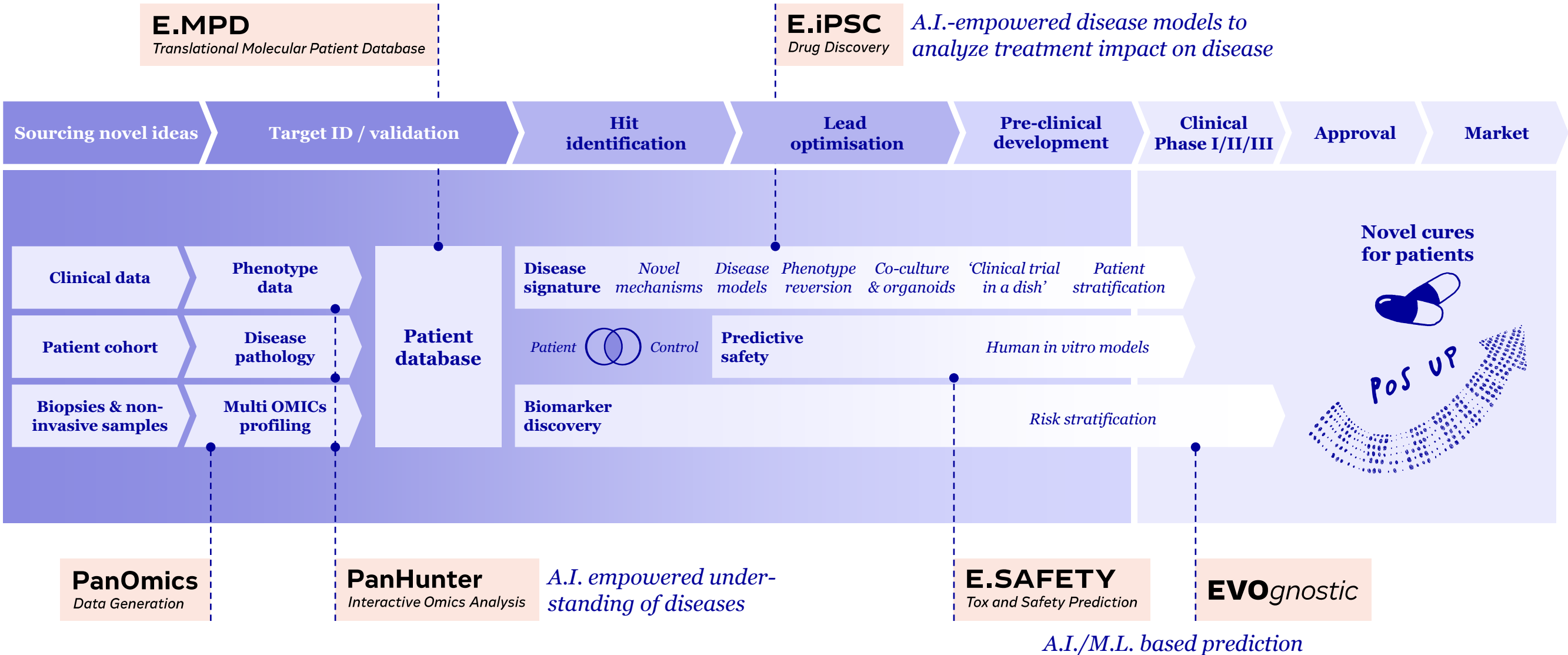
- 8-year extension and significant expansion of original agreement signed in 2018
- Collaboration leverages Evotec's PanOmics and PanHunter platforms including A.I./M.L. capabilities
- Upfront payment of \$ 200 m
- Performance payments of \$ 75 m announced in March 2023
- Additionally, tiered royalties 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***

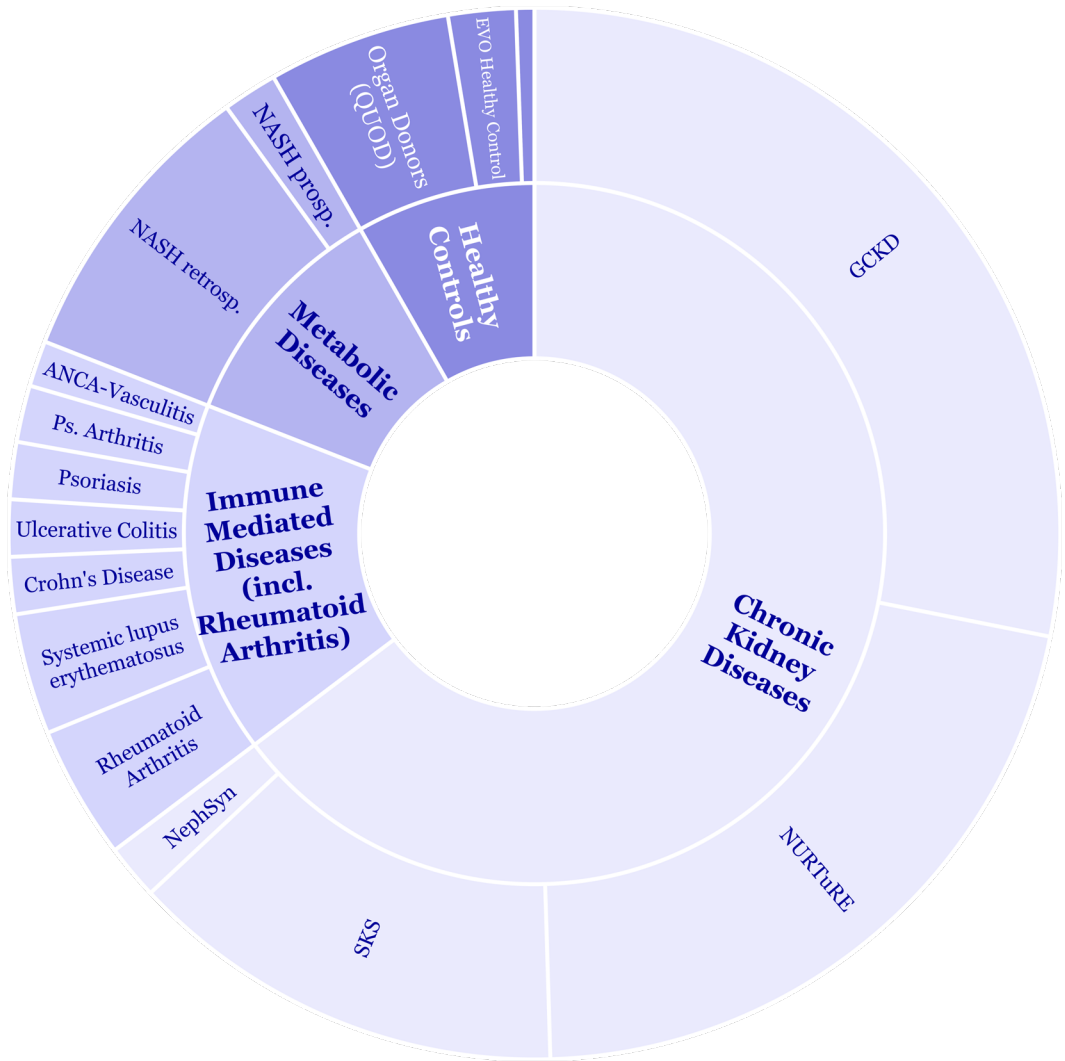


First in class discovery starts with patient data

Portfolio of Evotec Molecular Patient Databases (E.MPD)

E.MPD Now

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






















Next steps

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



Significant advantages of E.MPD over public domain datasets

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

		Public Domain	 E.MPD <small>TRANSLATIONAL MOLECULAR PATIENT DATABASE</small>
Cohort planning/design	Physician engagement		
	Prospective and longitudinal studies		
Clinical data	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
Analysis data	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

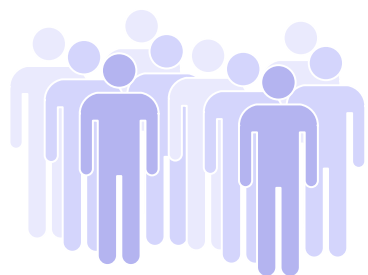
E.MPD, PanOmics and disruptive computational technologies increase disease insight



E.MPD

TRANSLATIONAL MOLECULAR PATIENT DATABASE

Patient cohorts



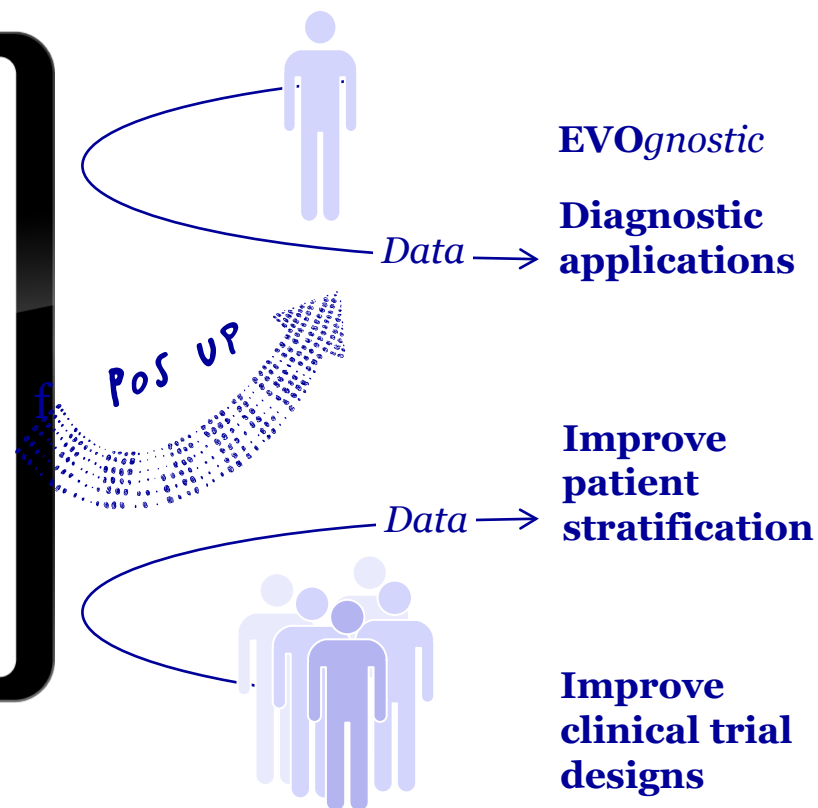
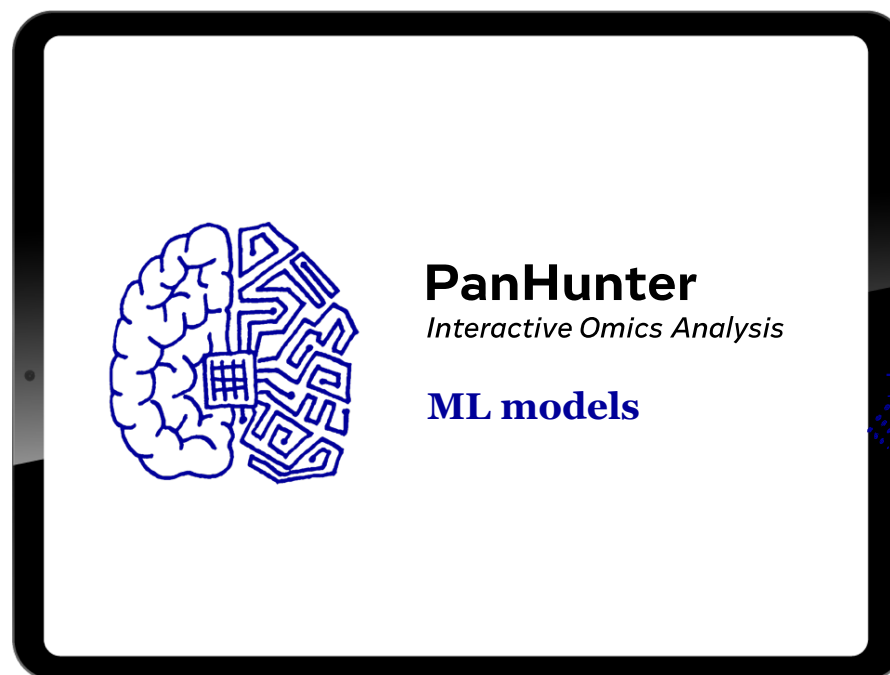
Physician Network

Clinical data

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

PanOmics

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





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

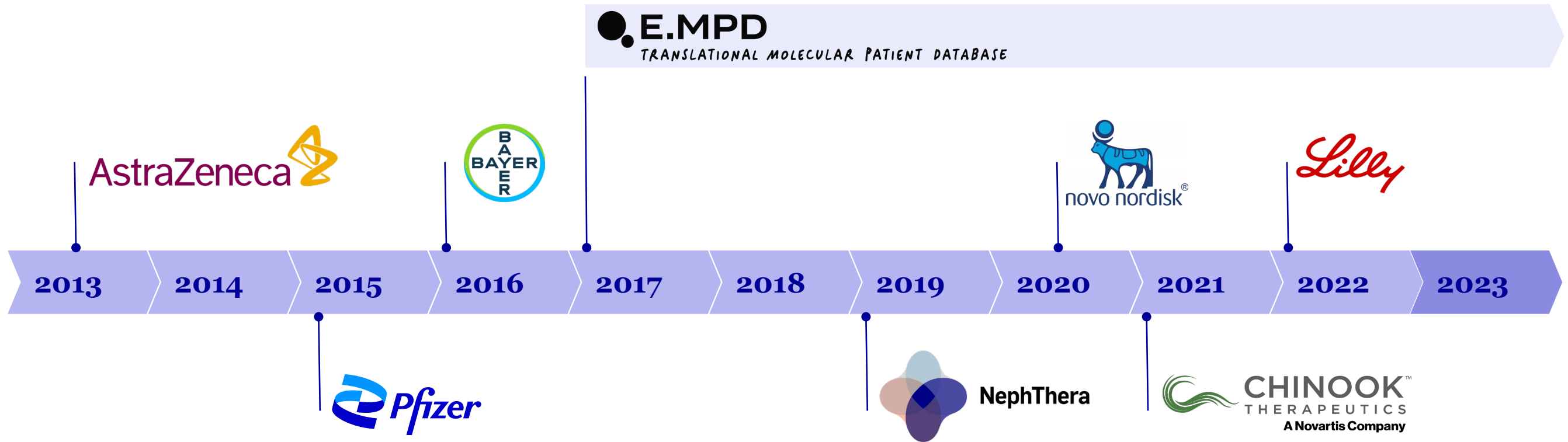
Top 5 Pharma partners

- 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



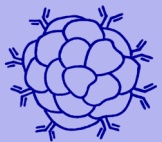
Liver
disease



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

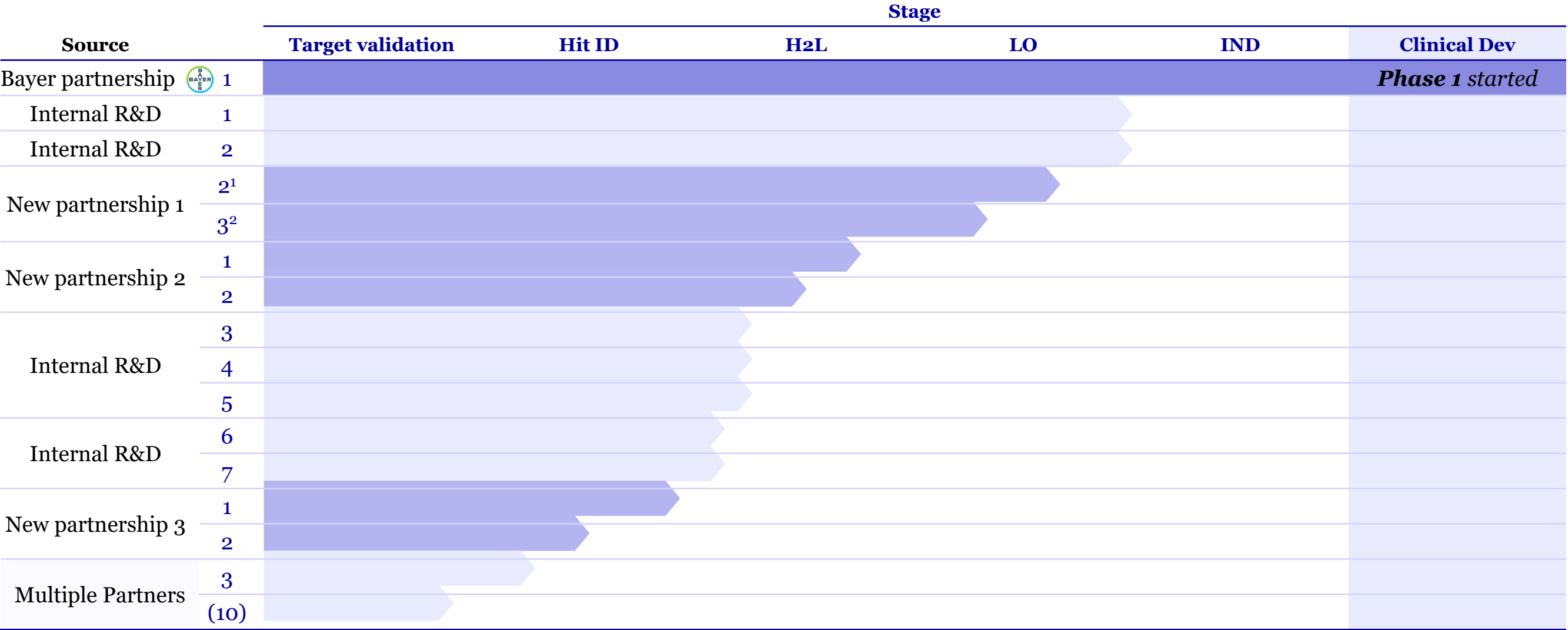
- Targets validated in Evotec's Molecular Patient Database (E.MPD) > **10k CKD patients**
- Progressed using most relevant Kidney assays
- **iPSC-derived** models including **3D organoids**
- Comprehensive panel of **in vivo models**

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) ¹					
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



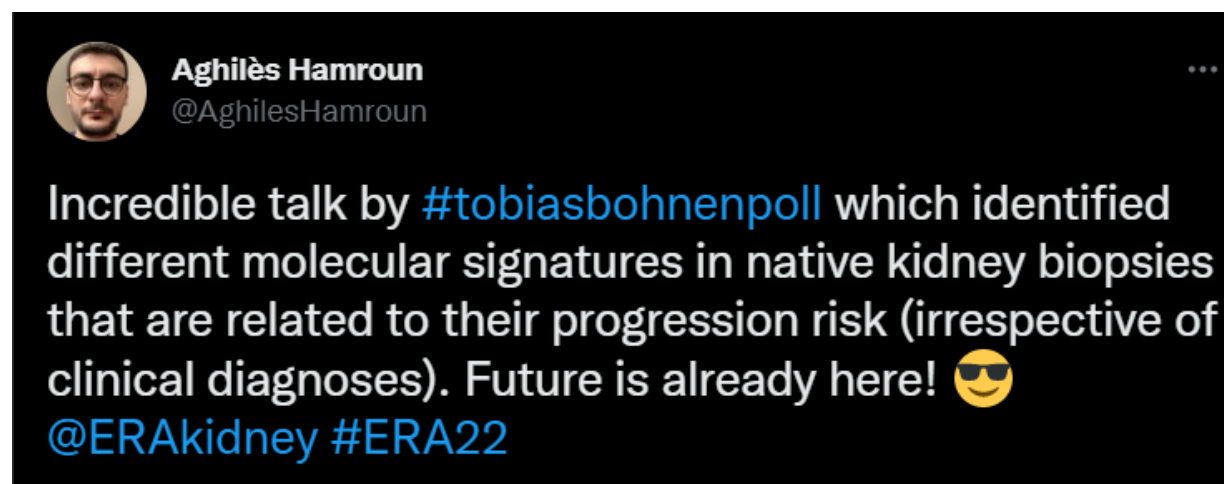


PanOmics & E.MPD driven Discovery publicly recognized by peers

"The Future is Now"

"A Systems Nephrology Framework for the Molecular Classification of Chronic Kidney Diseases"

- Oral presentation at the 59th 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

Internal Discovery

- Reach inflexion point
- Partnering
- Outlicensing

EVOgnostic & Disease markers

Innovative new molecular diagnostics

Molecular markers of disease progression

Partnered Discovery Pipeline

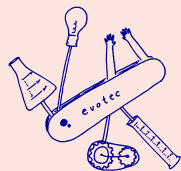
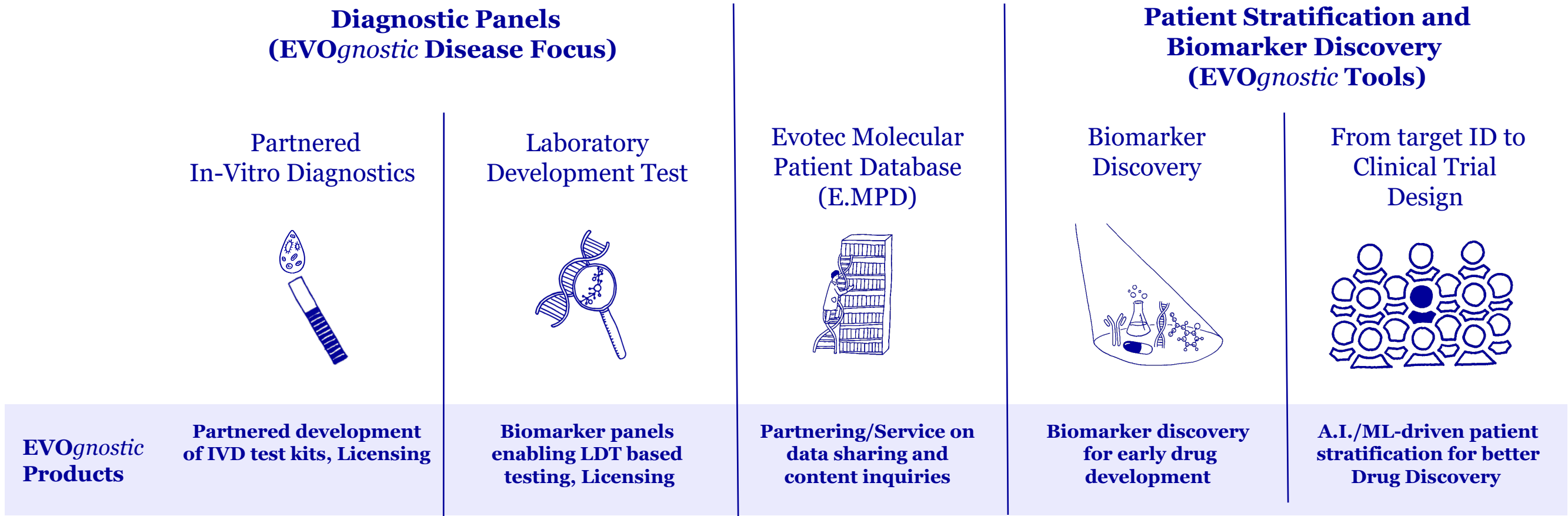
Top 5 Pharma partners

- Joint Discovery Pipeline
- Milestones incentives
- Royalties



PanOmics driven diagnostics¹ from target identification to the clinic

Capabilities for accurate patient stratification driving personalised 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

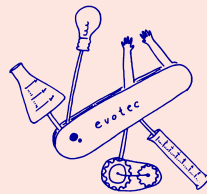
- **0.4-3 Mn people globally affected**
- **Affecting salivary and lacrimal glands**

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 diagnostics¹ 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 pain², malaise and anorexia
- Elevated creatinine levels
- Suspected to have pneumonia
- Persisting symptoms for several weeks

Diagnostics		Treatments
Physical exam Blood and urine test Chest CT	Failed	Antibiotics against suspected Pneumonia
Extensive exam Blood and urine chemistry Chest CT Invasive kidney biopsy		Corticosteroids Chemotherapy (B-cell depletion therapy)

*The study cases described are fictitious for the purpose of illustration of the impact of disease on patients today.
1 for reasearch use only
2 [A case of ANCA associated vasculitis in a patient presenting with chest pain - PMC \(nih.gov\)](#)



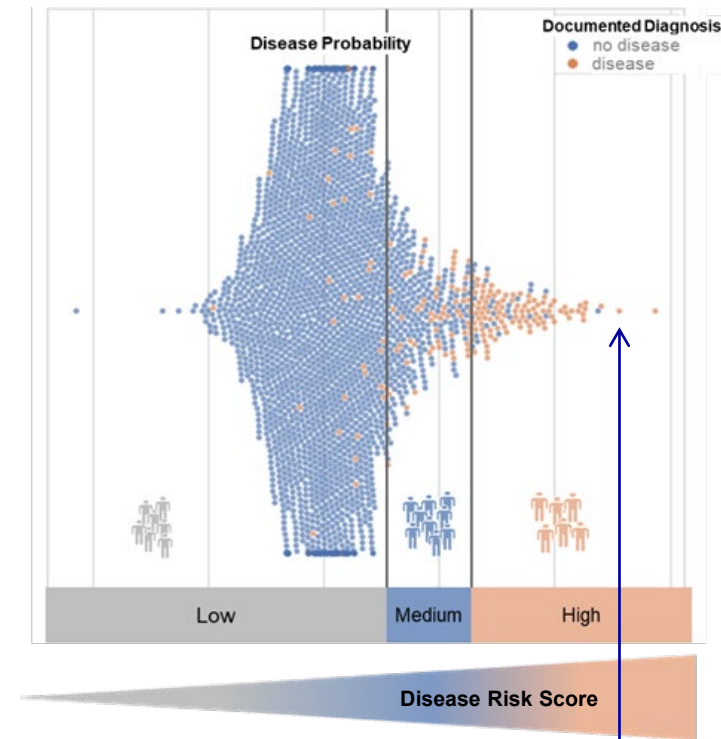
PanOmics-driven diagnostics to improve treatment selection

PanOmics combined with ML to improve diagnosis and treatment

One blood sample
per patient

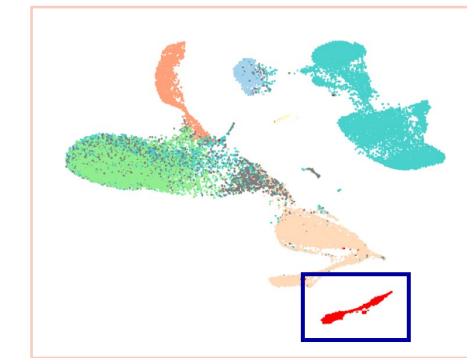
EVOgnostic Kidney Health-to-disease map

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

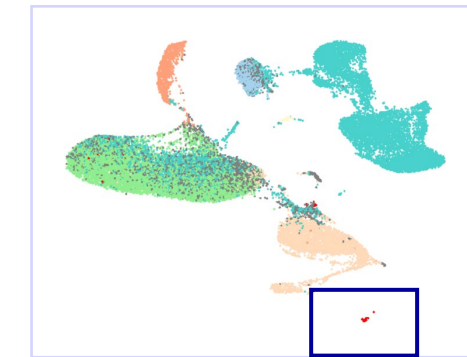


High resolution of a blood sample down to individual blood cells

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

Diagnostics	Treatments
Often mild unspecific onset of disease	
Physical exam Blood and urine chemistry	Anti-inflammatories
Progression of disease	
Extensive exam Autoantibody-Tests Disease monitoring by disease activity index (SLEDAI) Invasive skin and kidney biopsy	Immuno-suppressants In severe cases: Dialysis Kidney Transplantation

• The study cases described are fictitious for the purpose of illustration of the impact of disease on patients today
• SLEDAI – Systemic lupus erythematosus disease activity index – global disease score tool that evaluates the lupus erythematosus disease activity based on a series of clinical and laboratory variables
[A case of ANCA associated vasculitis in a patient presenting with chest pain - PMC \(nih.gov\)](#)



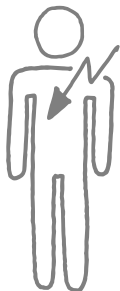
PanOmics driven prognosis for better disease management

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

SLE disease activity index (SLEDAI)

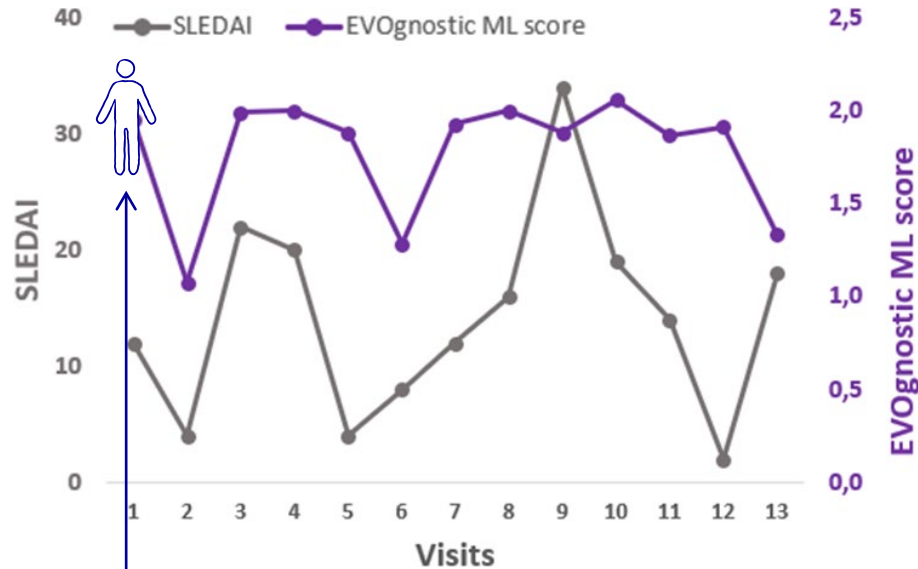
Today a weighted diagnostic metric of 24 components is used to measure disease activity

<ul style="list-style-type: none">• Seizure• Psychosis• Organic Brain Syndrome• Visual Disturbance• Cranial Nerve Disorder• Lupus Headache• Cerebrovascular accident	<ul style="list-style-type: none">8888888
<ul style="list-style-type: none">• Arthritis	<ul style="list-style-type: none">4
<ul style="list-style-type: none">• Myositis	<ul style="list-style-type: none">4
<ul style="list-style-type: none">• Low Complement• Increased anti-dsDNA• Thrombocytopenia• Leukopenia	<ul style="list-style-type: none">2211
<ul style="list-style-type: none">• Alopecia• Mucosal Ulcers• New Rash• Fever• Pericarditis• Pleuritis• Vasculitis• Urinary Casts• Hematuria• Proteinuria• Pyuria	<ul style="list-style-type: none">22212284444



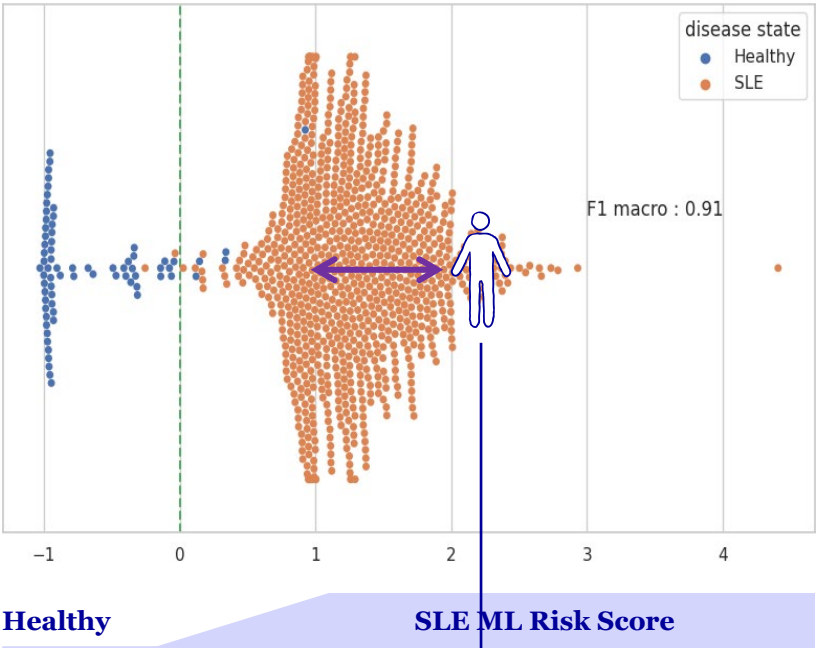
EVOgnostic disease score reflects disease flares

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



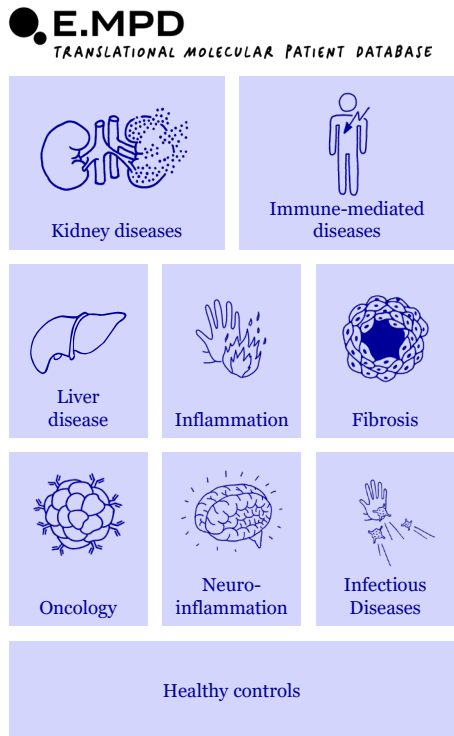
A single PanOmics test of a blood sample positions a patient on the map for prediction of disease progression in SLE



Multiple opportunities ...just at the beginning

Health-to-Disease Maps and biomarker discovery

Patient cohorts



Physician Network

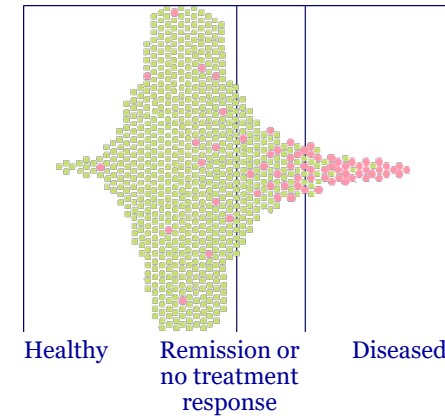
PanOmics and ML



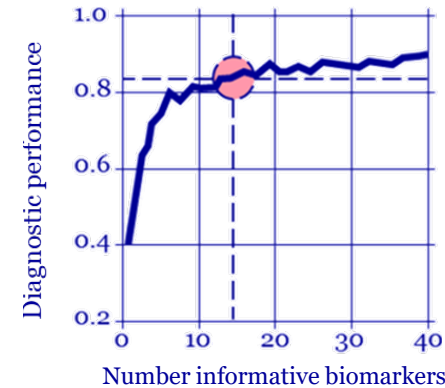
Machine Learning (ML)

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)



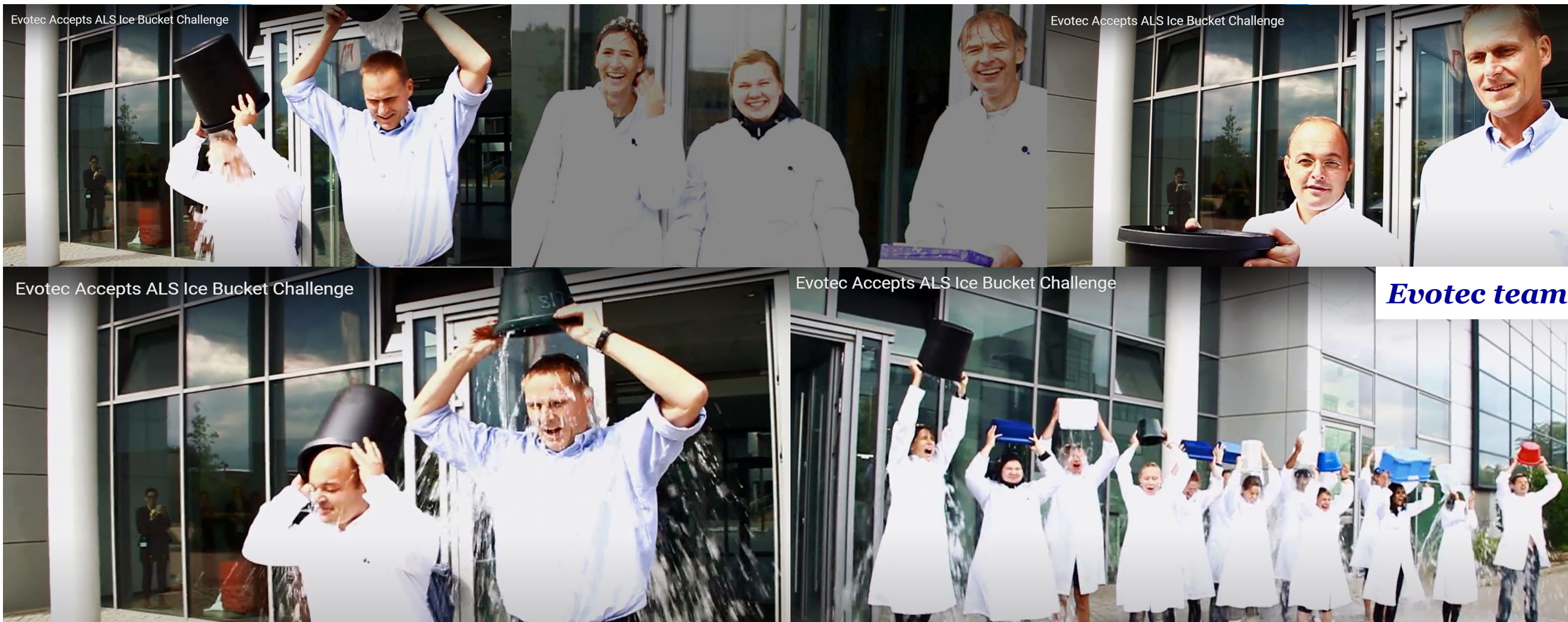
Leah

- 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'¹



Ice Bucket Challenge in 2014 to raise awareness for ALS¹

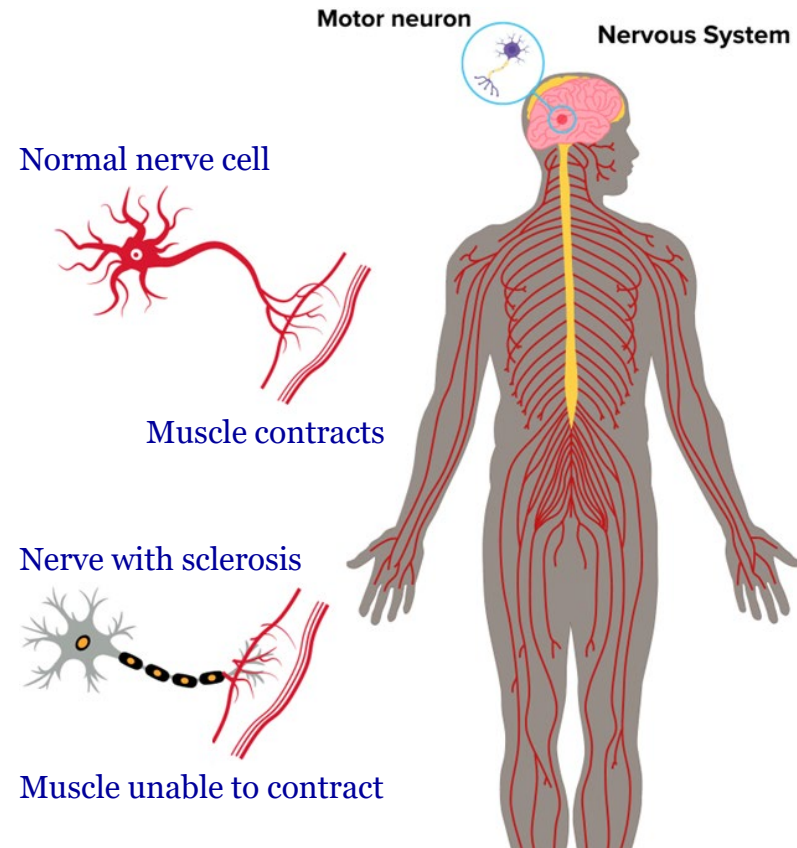
ALS, amyotrophic lateral sclerosis, also known as motor neuron disease or Lou Gehrig's disease





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 onset¹
 - ~75k² diagnosed prevalent patients worldwide (2022), expected to increase to ~80k (by 2030)
 - Limited treatment options
 - No known cure to stop or reverse ALS

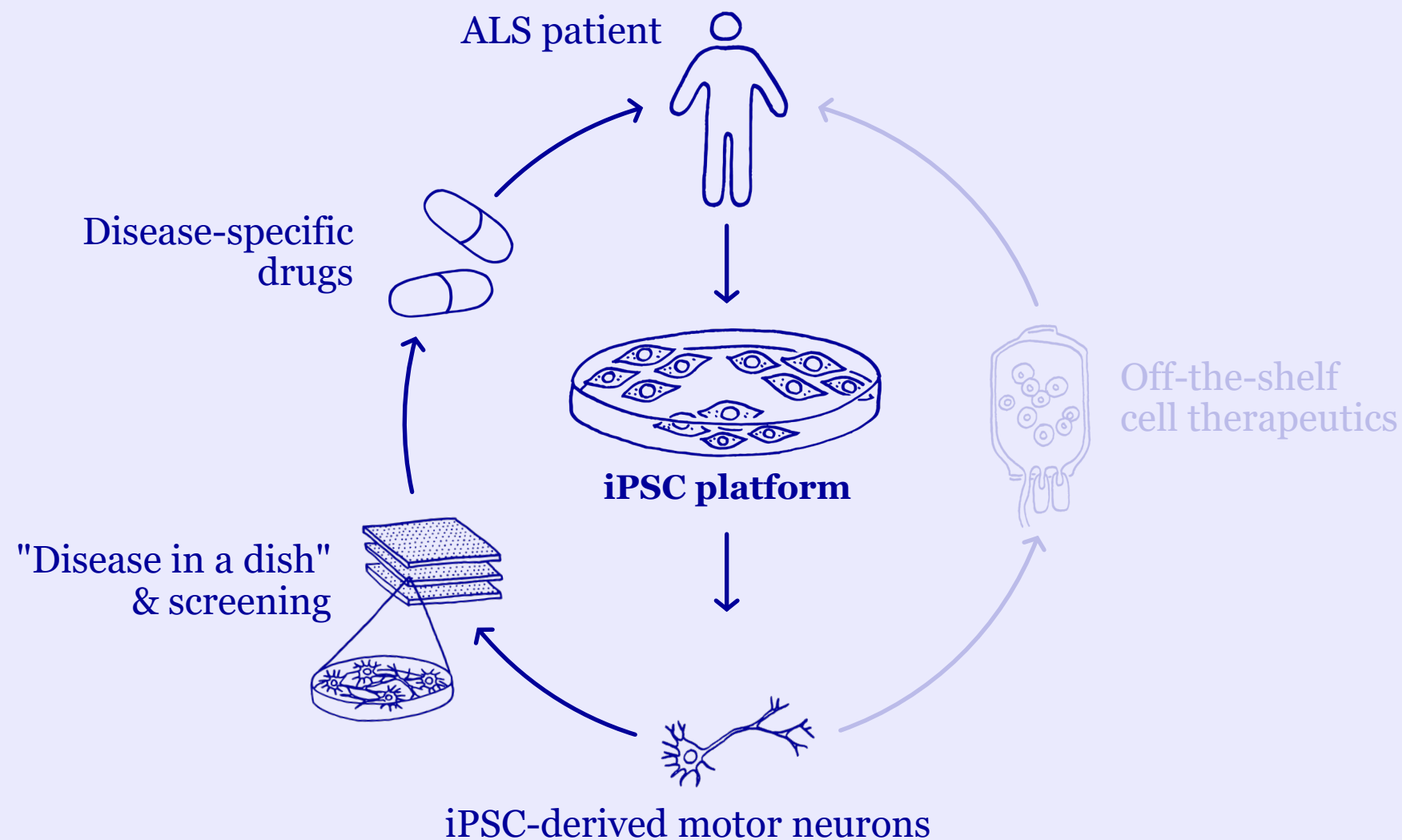
*High failure rates in ALS clinical trials due to overreliance on non-physiological ALS mouse models.
→ strong need for better representation of disease with human cellular models for improved clinical translatability.*



From humans for humans

iPSC-based drug discovery

E.iPSC –
Human disease
relevant modelling





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



evotec

NEWS RELEASE

12 September 2013

'RESEARCH NEVER STOPS'

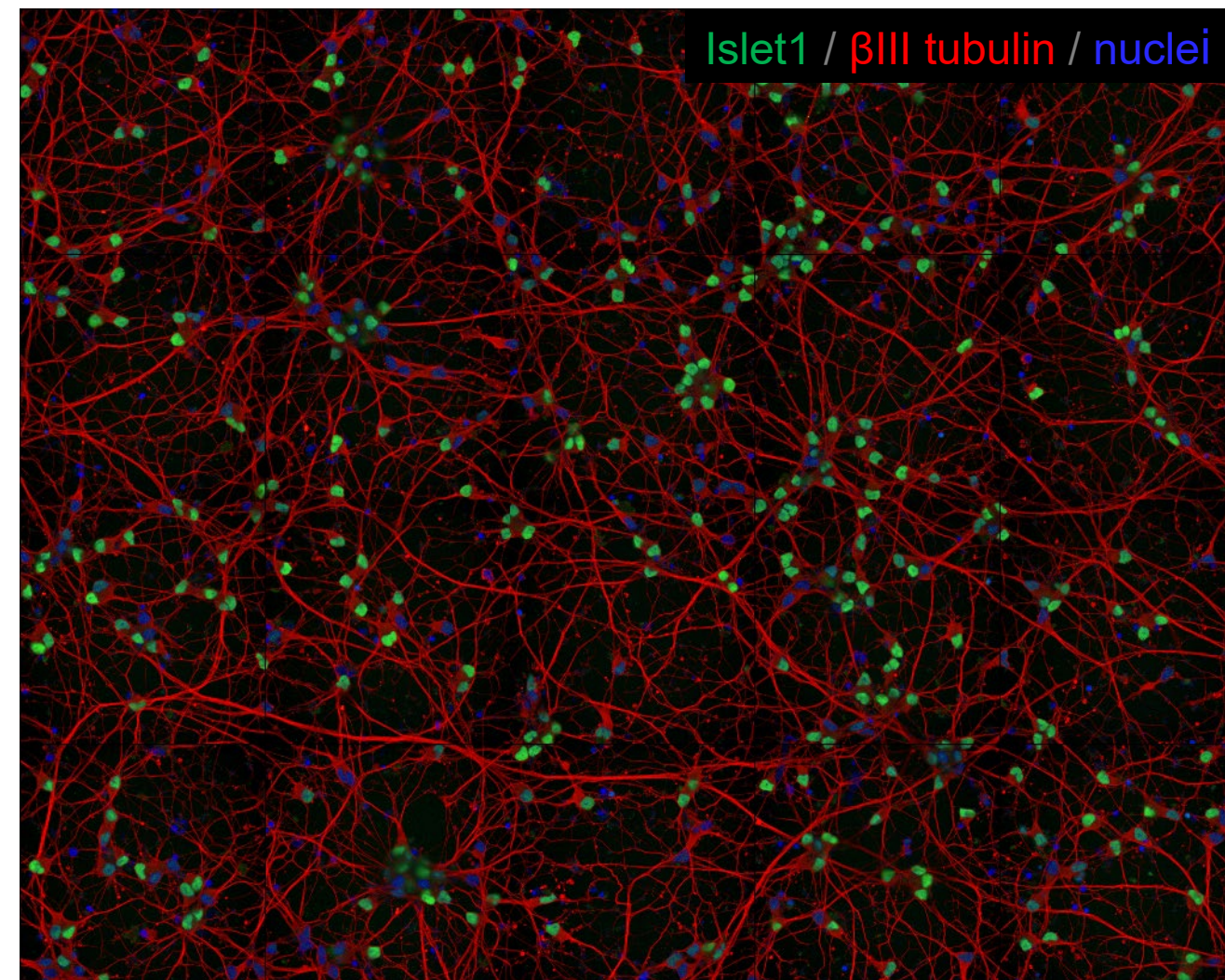
info@evotec.com | www.evotec.com

**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)

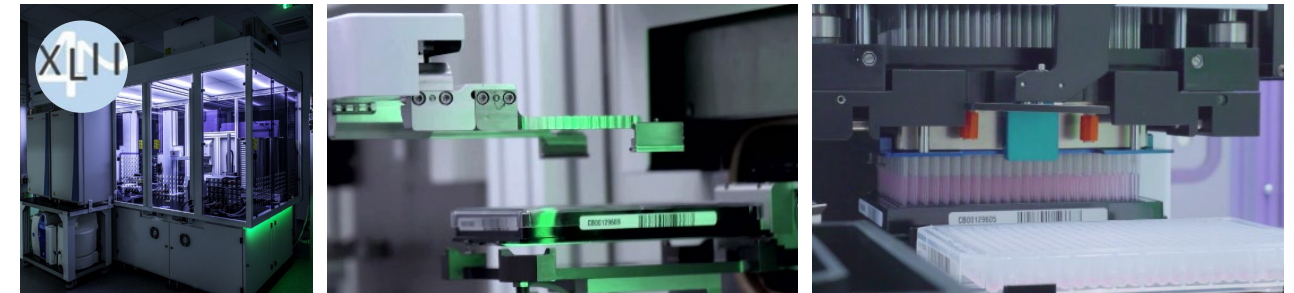


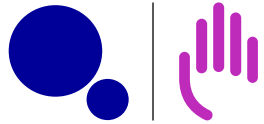
Automated workflows

- Sterile long-term culture
- High throughput drug screening

> 20 drug discovery programs

1st IND in clinical development since 2021

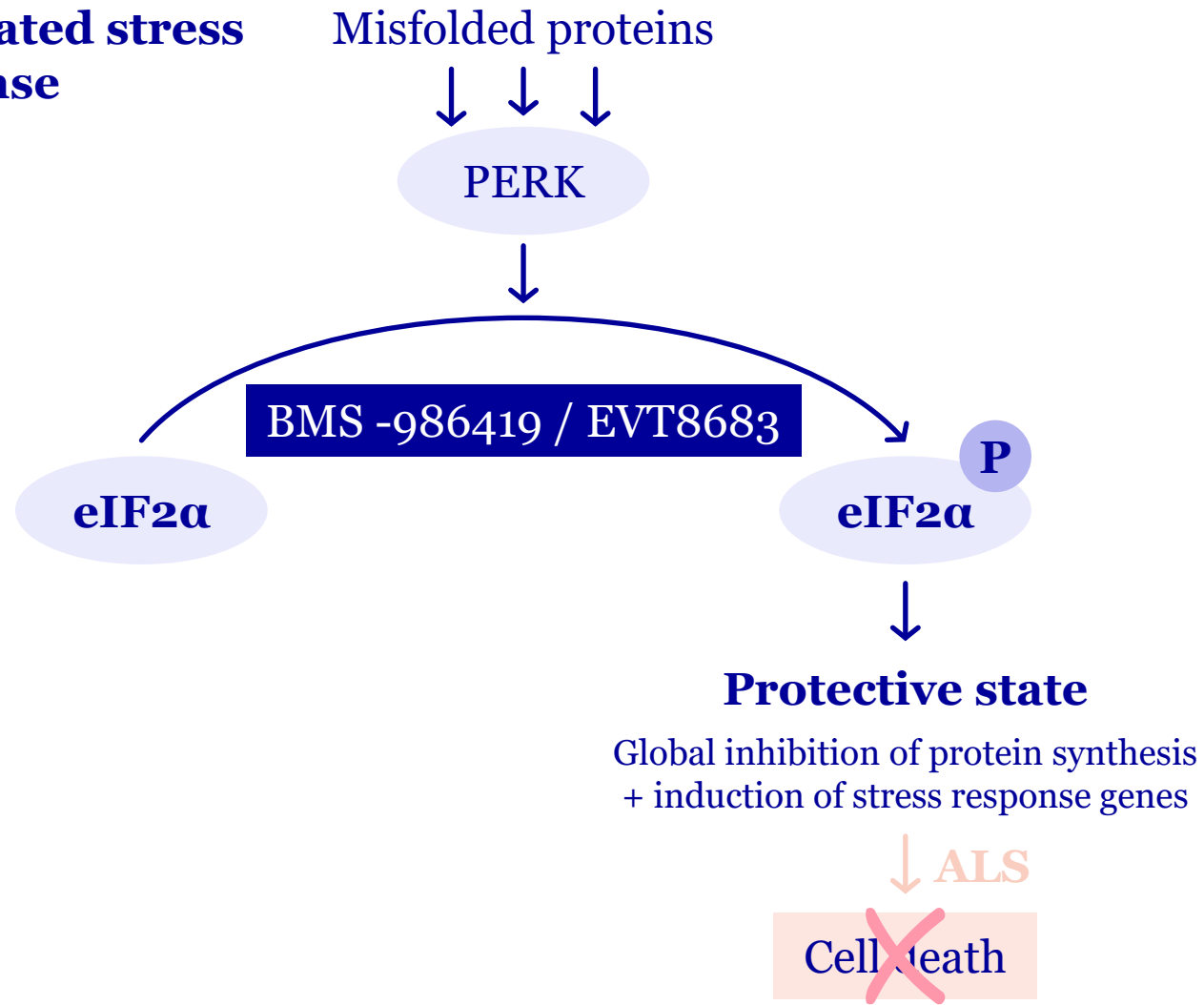




BMS-986419* restores normal Integrated Stress Response (ISR) function

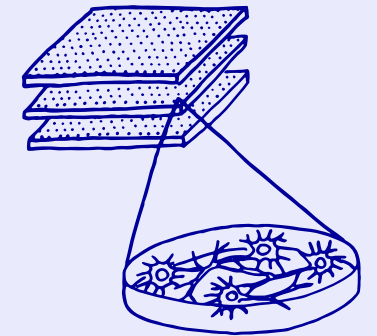
Chronic activation of ISR in ALS disease can lead to cell death

Integrated stress response

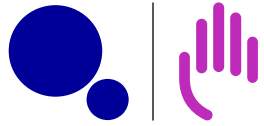


- The eIF2 complex is an ISR¹ “master regulator” that becomes dysfunctional in chronic disease: chronic stimulation of ISR leads to cell death

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



- Phenotypic screening in iPSC-derived motor neurons identified ISR¹ 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 conditions¹

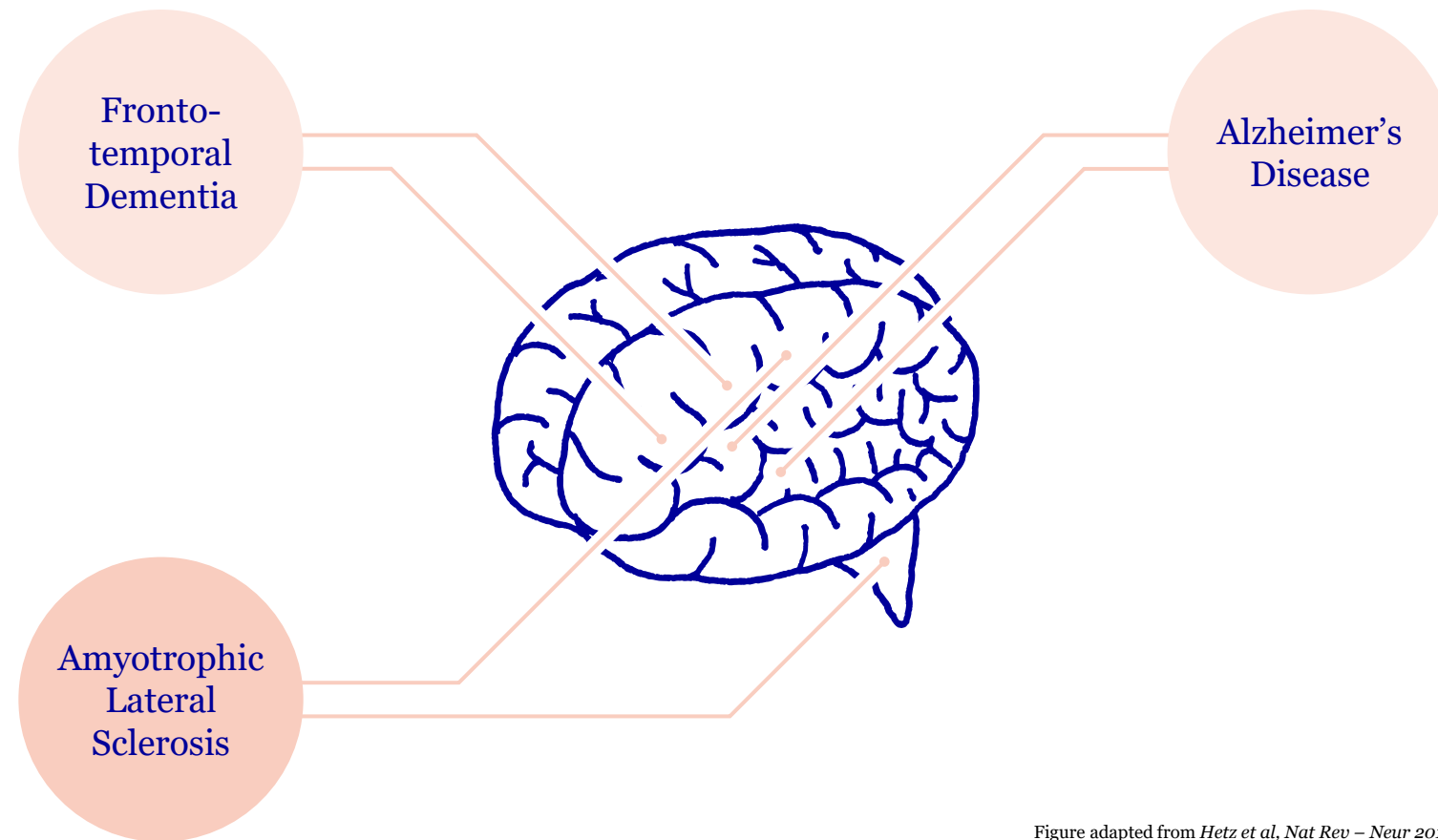


Figure adapted from Hetz et al, Nat Rev – Neur 2017

BMS-986419 / EVT8683

- Safe and well-tolerated in Phase I clinical study in healthy volunteers²
- 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	
Partnered	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	 Boehringer Ingelheim
Internal R&D	Psychiatric disease	Neurons, astrocytes, microglia, co-cultures	SCZ, MDD, ...	Next Collaboration opportunities	
	Eye diseases	Photoreceptors, retinal organoids	Diabetic retinopathy, glaucoma, ...		
	Kidney diseases	Podocytes PTECs Kidney organoids Ureteric bud organoid ¹ Immuno-Kidney organoids ¹	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 ¹	Chron's, IPF ² , ... AIDs ³		



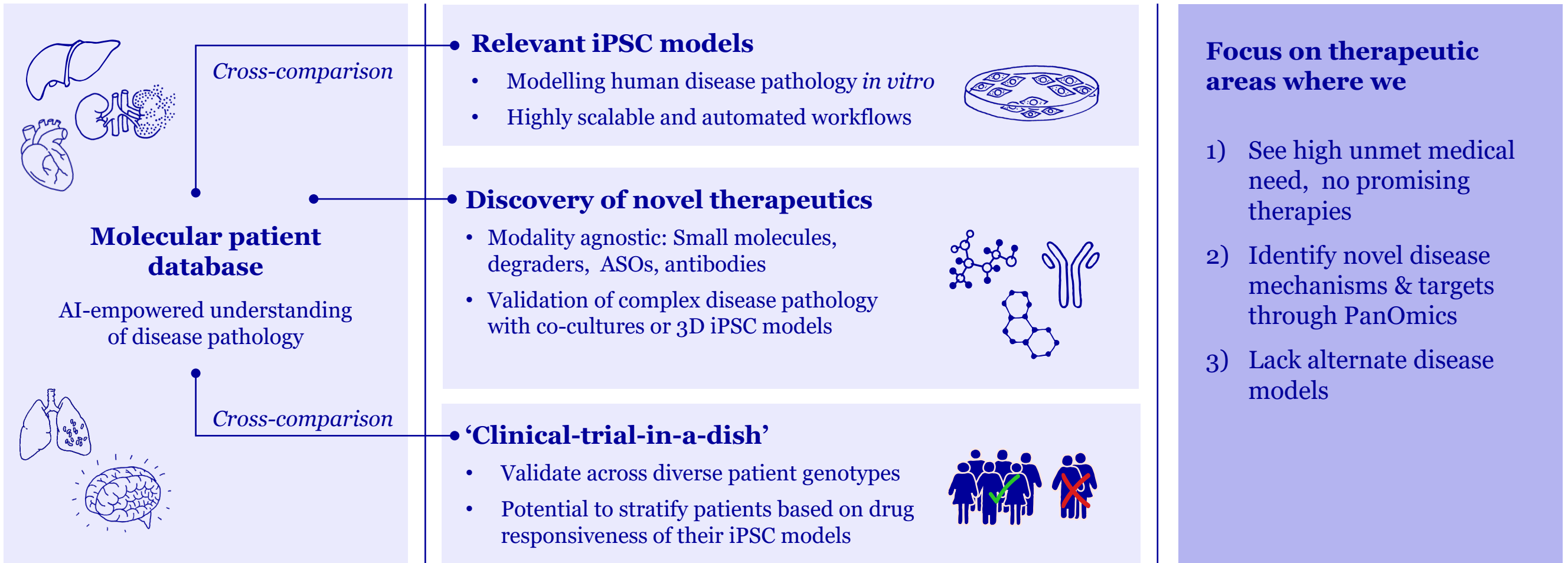
From humans, for even more humans

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



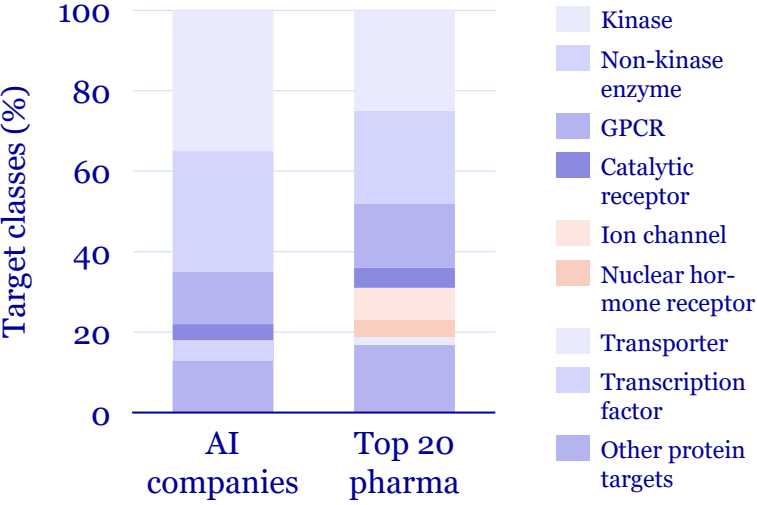
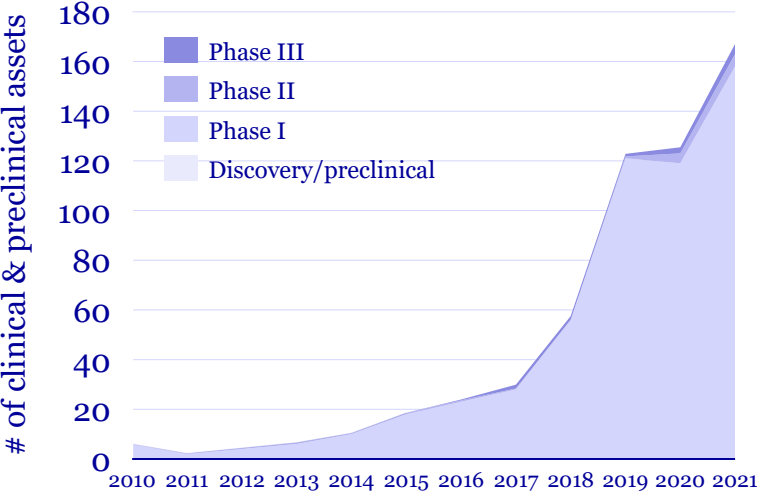
High recognition in scientific community

- 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)

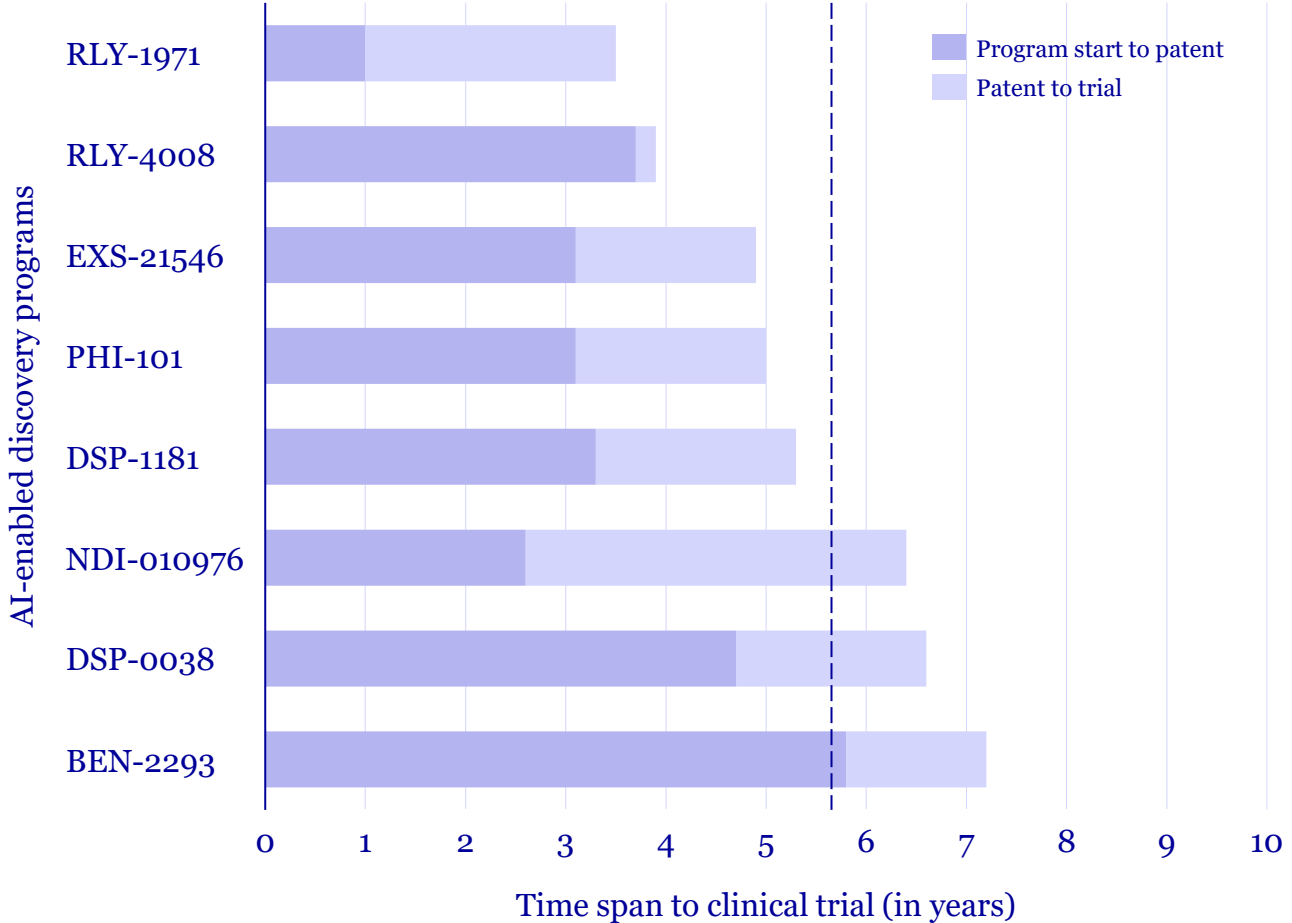


Reduction of time to clinical trials observable, but early days

Outcomes, not only speed matters



Potential to reduce time from bench to clinical trial





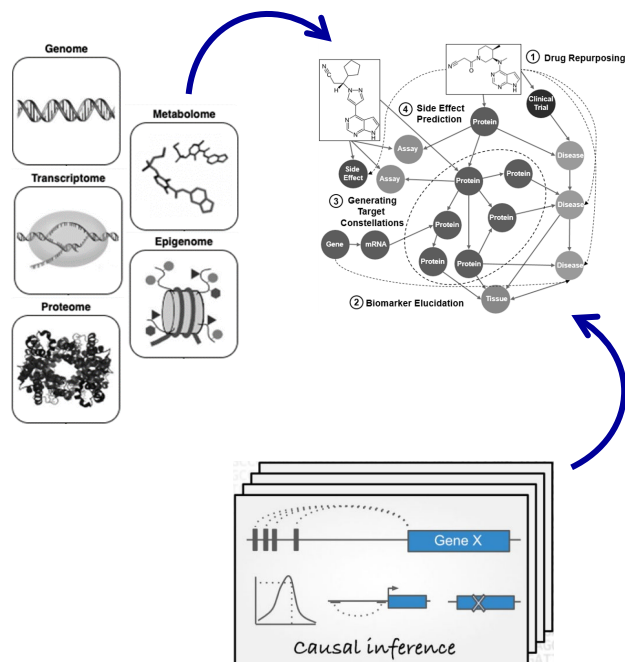
Integrated A.I./M.L. throughout the drug discovery value chain

Examples of applications

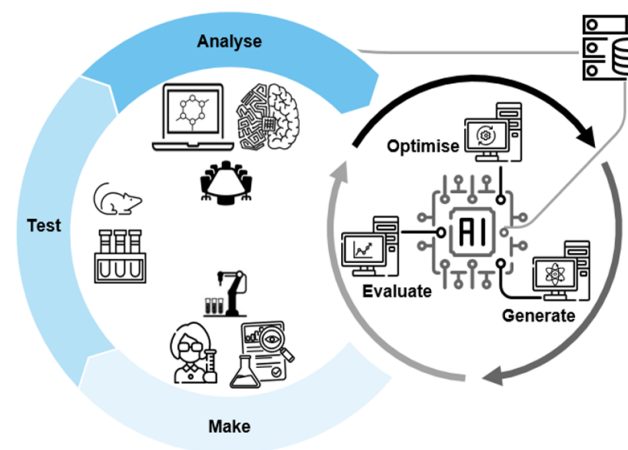


PanOmics data analytics and compound profiling along the full value chain

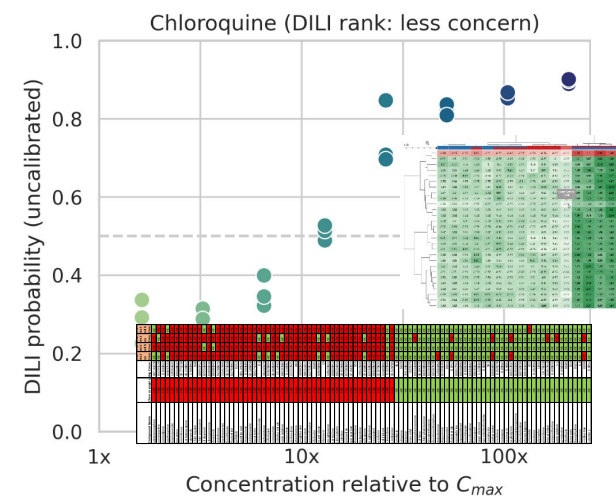
1. Target ID / Validation



2. Hit and Lead Optimisation



3. Safety prediction

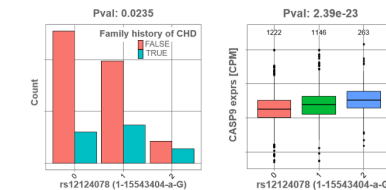


70 → 87% prediction accuracy improvement over current gold standard HCI based DILI platform¹

4. Patient selection



Patient stratification



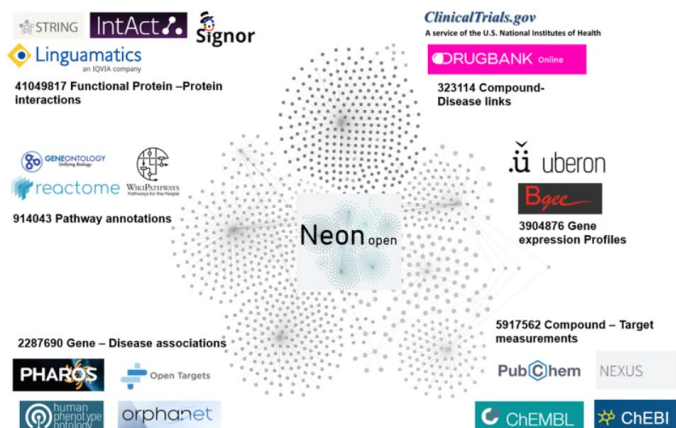
(Automatized bivariate analysis of clinical & genotyping data for a selected cohort of interest)



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

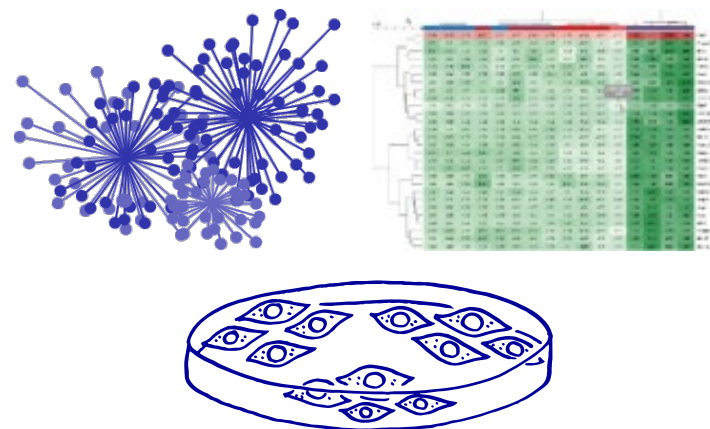
Selection, identification and validation to a ranked compound hitlist using automatic workflows

Target Identification



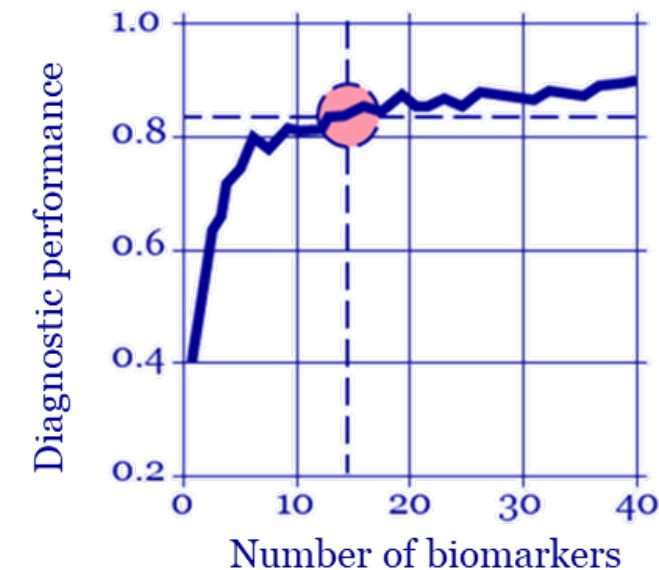
Potential novel target for disease modulation

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

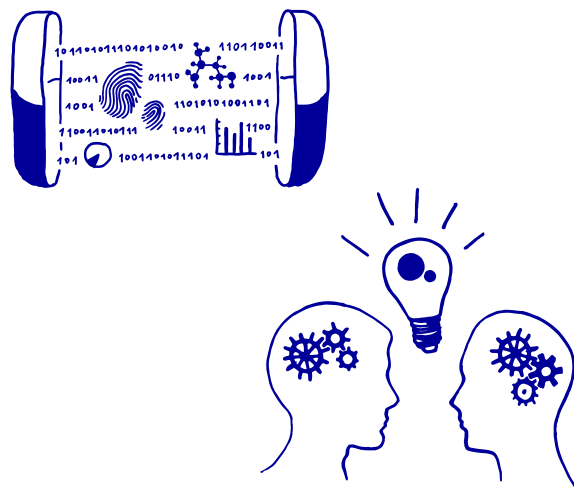
Small Molecule Generative Design

Starting from Series of Target X inhibitors

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

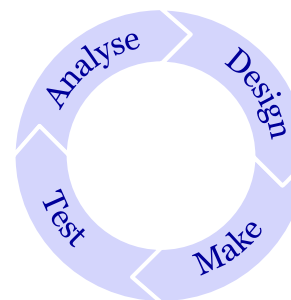
A.I. Generative Design

- Reinforcement Learning
- Synthesizability assessment

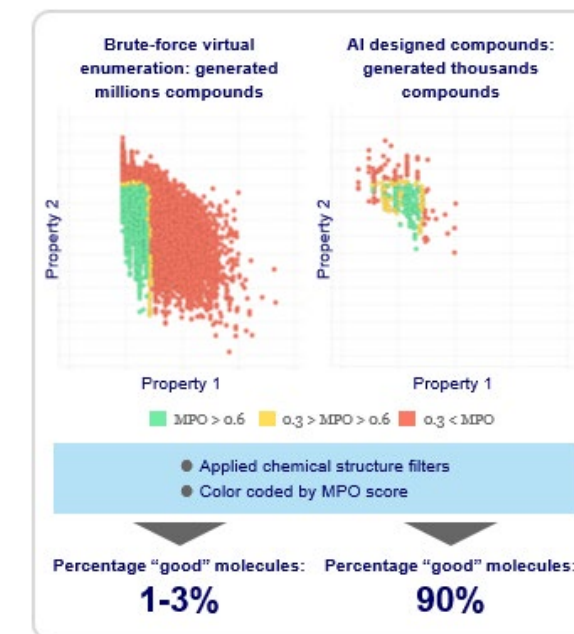


Novel compound series identified

- 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

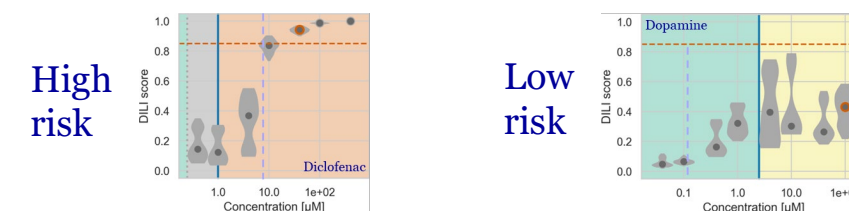


Proprietary safety database

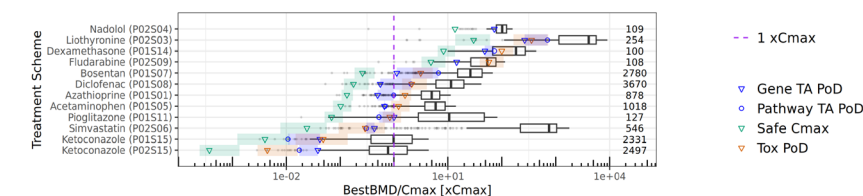


Safety liability modelling

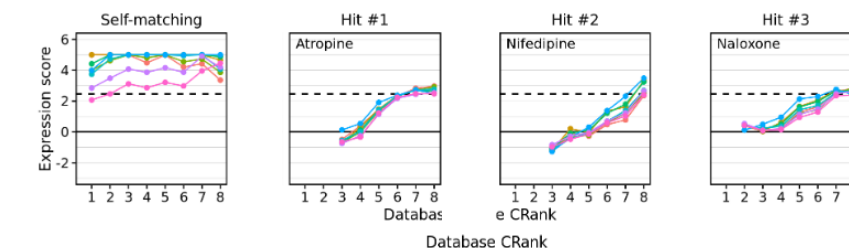
AI/ML predictions of safety liability risk



Mechanism of action & PoD safe dose prediction



Compound matching to safety database



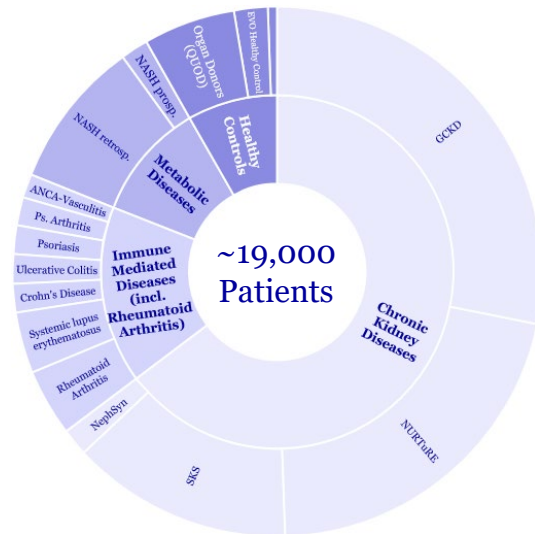
Superior prediction versus traditional approaches; DILI prediction shown to increase from 70% to 87%



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

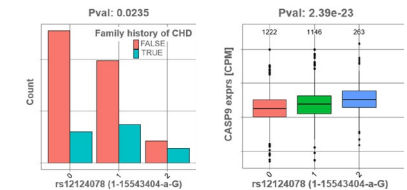
Validation

- 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



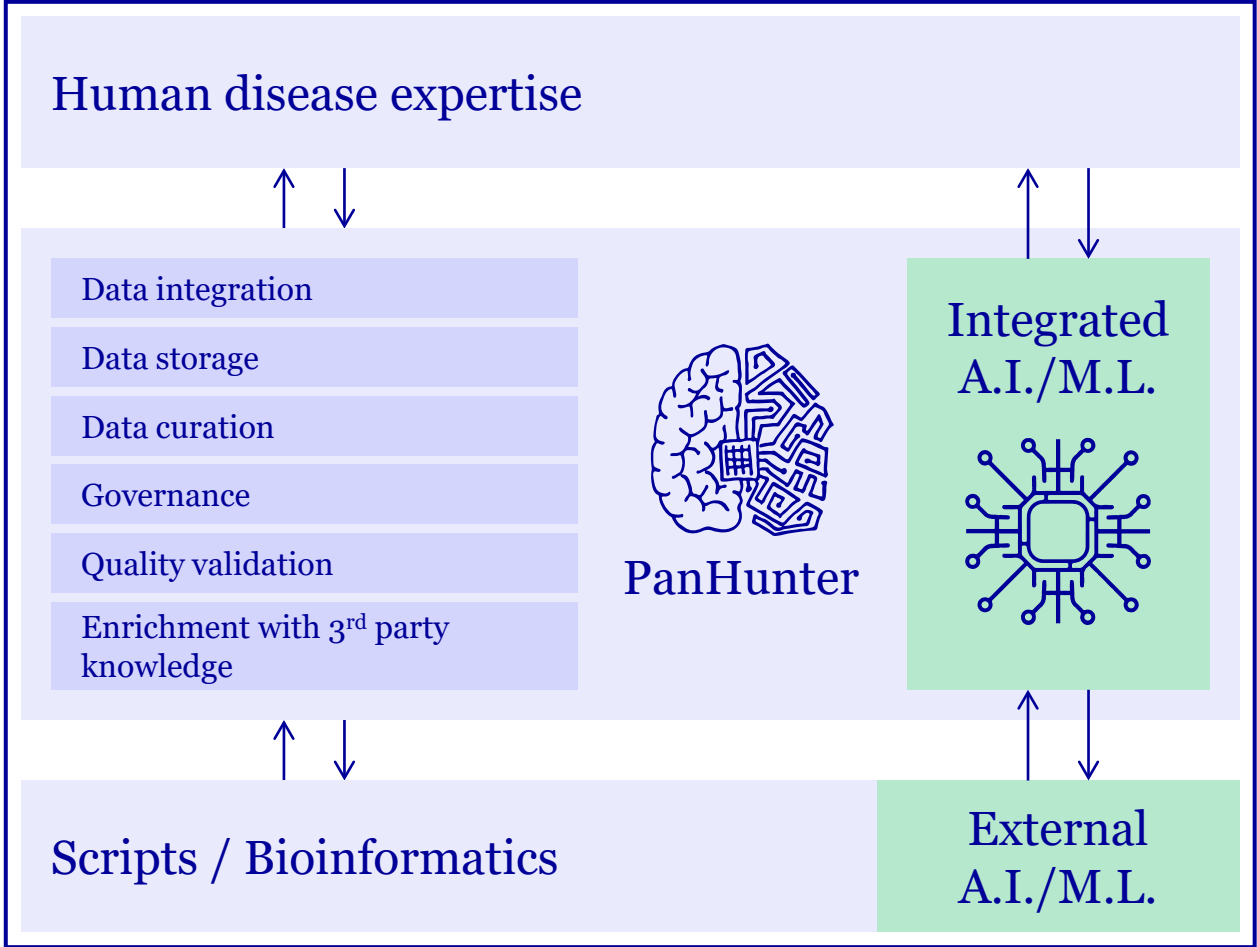
PanHunter is the platform to manage high dimensional data

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

PanOmics continuum

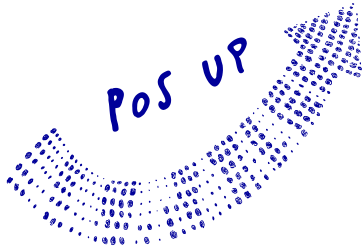
Genomics		
Whole genome	Whole exome	
Transcriptomics		
ScreenSeq	Bulk	TempoSeq
SingleCell	Spatial Single Cell	
Proteomics		
ScreenPep	Olink	Shallow
Metabolomics		
Clinical data		
Patient information	Medication	
Compound information		
Structural features	Assay data	
Meta data		
Experimental setup	Pharmacology	

Value generation



Actionable output

A.I. supported Target ID
Drug Screening result visualization and interpretation
Automated reporting
Disease understanding
Model validation
Safety prediction





Agenda

9:00-9:30	Shaping (new) markets
9:30-11:00	PanOmics – From patients for patients <ul style="list-style-type: none">• <i>Better disease understanding & diagnostics</i>• <i>Advanced disease modelling</i>• <i>A.I. use cases along the value chain</i>
11:00-11:15	<i>Coffee Break</i>
11:15-12:15	Impactful therapies <ul style="list-style-type: none">• <i>Integrated platform</i>• <i>Diabetes</i>• <i>Oncology</i>
12:15-13:30	<i>Lunch Break</i>
13:30-16:00	Round Tables



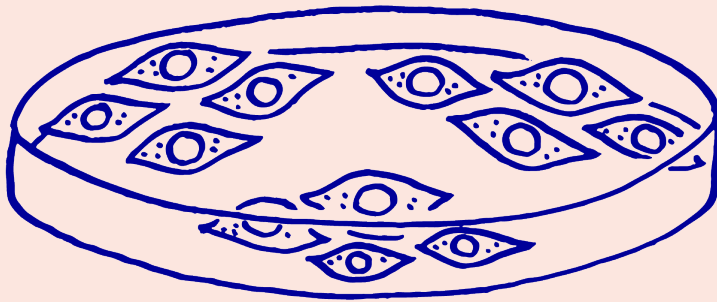
Agenda

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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 **TIL¹** therapy, 25% of heavily pre-treated, terminally ill melanoma patients are still alive >8 year^{2,3,4}

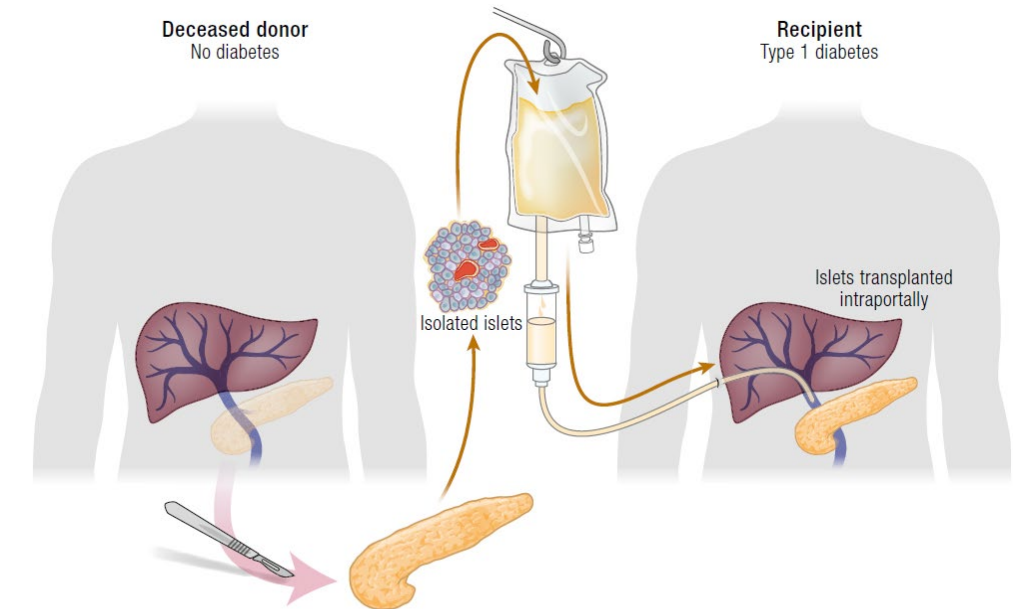
2012

2022



Emily Whitehead was 1st pediatric patient to receive **CAR T cell therapy** in 2012 to treat ALL⁵. She celebrated 10 years of being cancer-free in May 2022⁶.

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

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

Sector Snapshot

Alliance for Regenerative Medicine

2

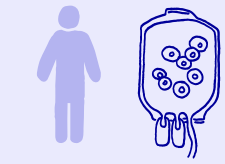
- **Nr of cell and gene therapies with market approval is increasing**
 - 80% autologous with limited pat reach
 - (Hem)Oncology, inherited genetic diseases
- **Next generation moving to off-the-shelf & larger indications approaching market**
 - Cardiovascular, Metabolics & Neurology
- **iPSC-based therapies 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

Autologous



Patient



Manufacturing

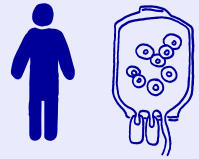
Just-in-time



1x dose



Allogeneic donor-derived



Healthy donor

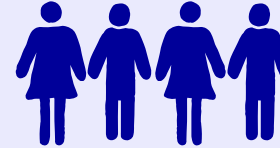


Manufacturing

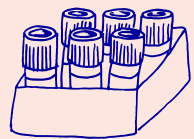
Off-the-shelf



100x doses



Allogeneic iPSC-derived



Master iPSC bank

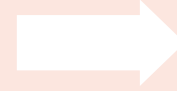


Manufacturing

Off-the-shelf



10,000x doses



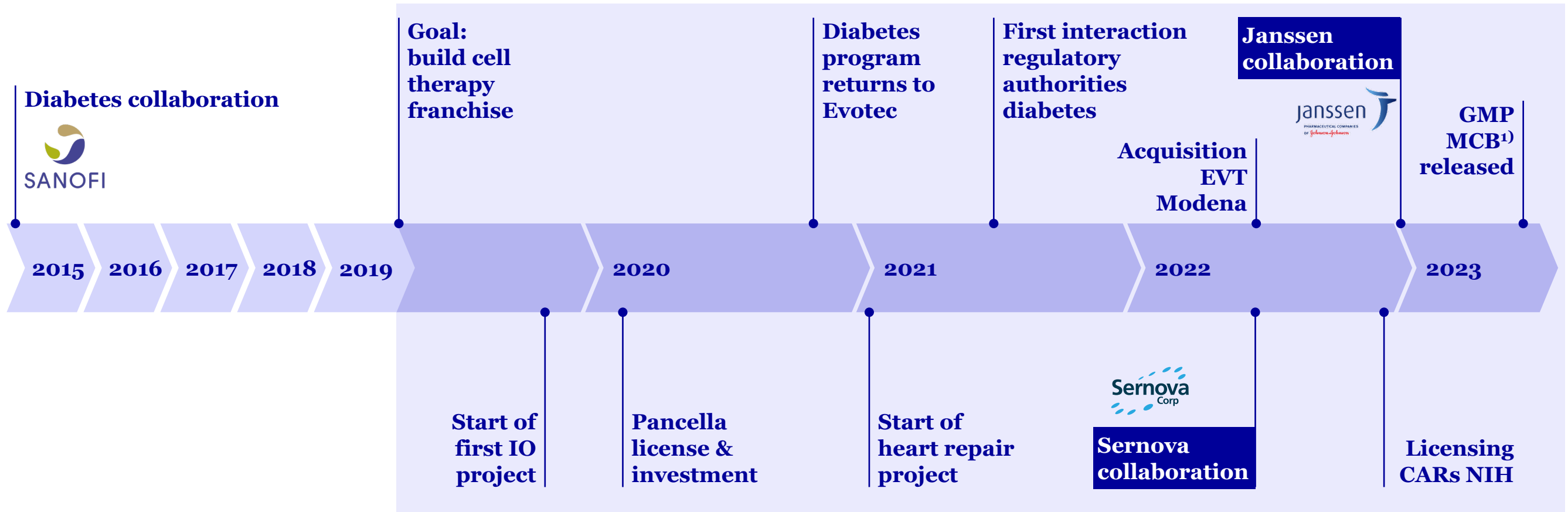
iPSC-based off-the-shelf therapeutics

- **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	
Partnered	Cancer immuno-therapy		$\gamma\delta$ iT	Oncology	Undisclosed				iNK	Natural killer cells
	Metabolic disease		E.iBeta (Device)	Diabetes					iT	$\alpha\beta$ and $\gamma\delta$ T cells
Partnering opportunities	Cancer immuno-therapy		iNK	Oncology					iMAC	Macrophages
			iMAC	Oncology					iBeta	Pancreatic islets
			$\alpha\beta$ iT	Oncology					iCM	Cardiomyocytes
	I&I ¹		iNK, $\alpha\beta$ iT	Fibrosis, SLE ²⁾					iRPE	Retinal pigment epithelium cells
	Metabolic disease		E.iBeta (Engineered)	Diabetes					iPR	Photoreceptors
	Other		iCM	Heart failure						
			iRPE, iPR	Ophthalmology						
			...							

► Each cell type can deliver multiple differentiated products

1 Inflammation and Immunology disease area
2 Systemic Lupus Erythematosus



Integrated platform for iPSC-based therapeutics

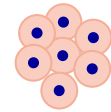


Truly “off-the-shelf”, fully scalable cell therapy products

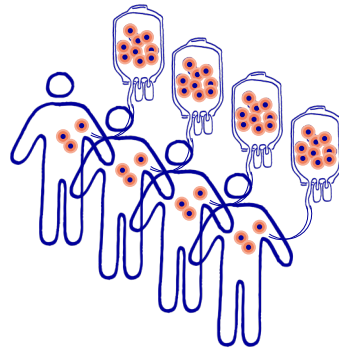
A process to overcome a major hurdle in cell therapy

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

- Fully characterized



GMP Master iPSC line

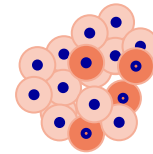


Patients

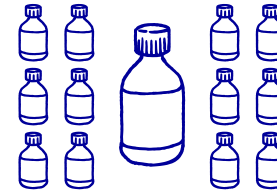
Precise
Gene editing



- Morphology/ Viability
- Confirmation of genetic modification



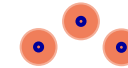
Gene edited iPSC pool



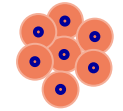
Off-the shelf cell therapy product

- Extensive QC
- Cryo-storage
- Clinical batch release

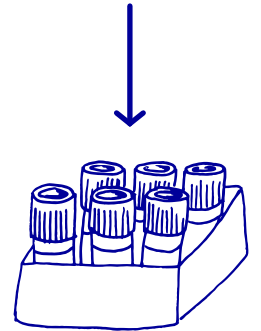
Single cell
clonal selection



Large scale GMP
Manufacturing



Engineered clonal iPSC pre-banks

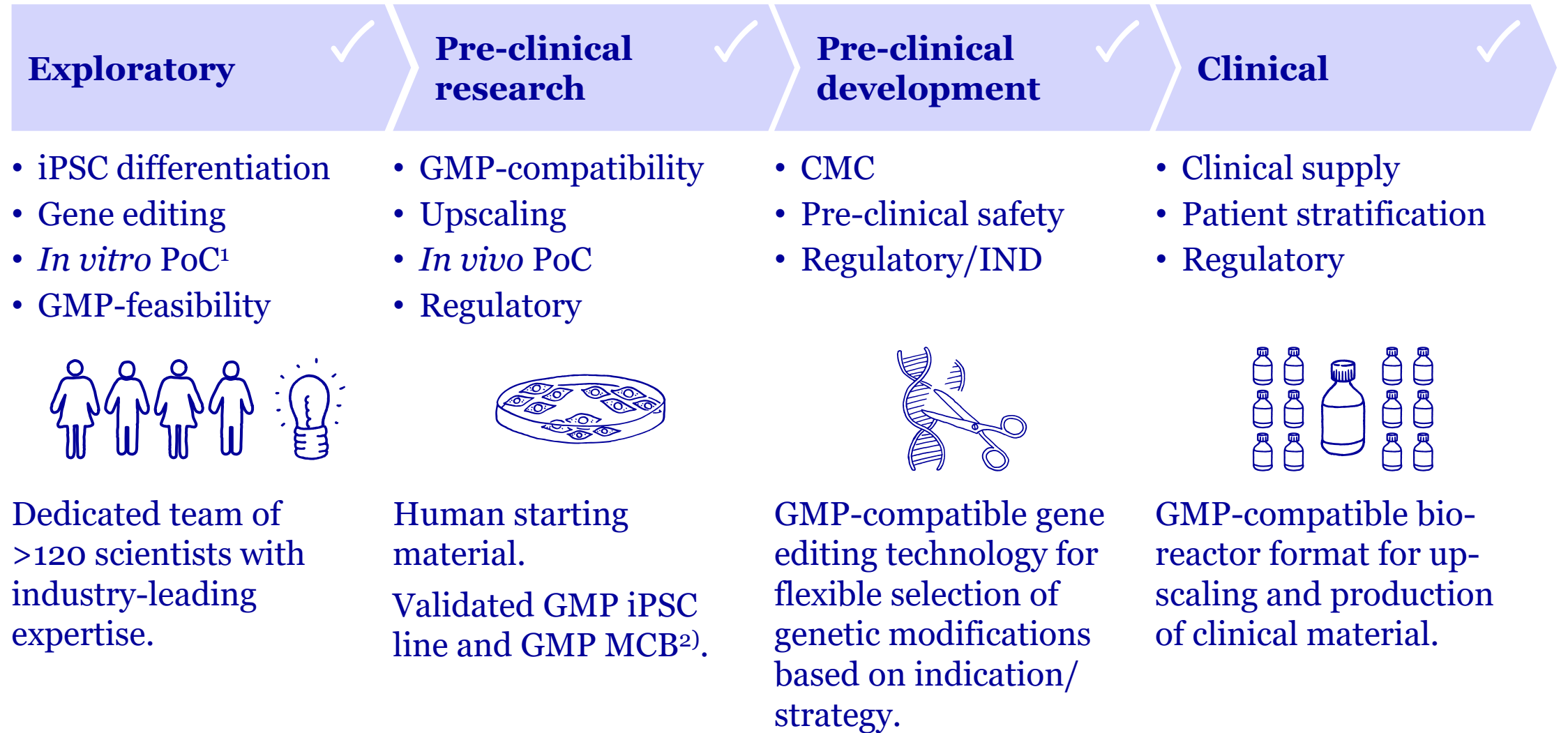


Engineered Master iPSC bank



Integrated platform for iPSC-based therapeutics is becoming reality

From iPSCs to patients

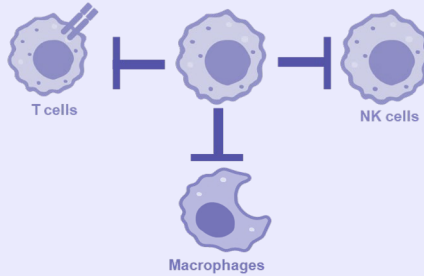




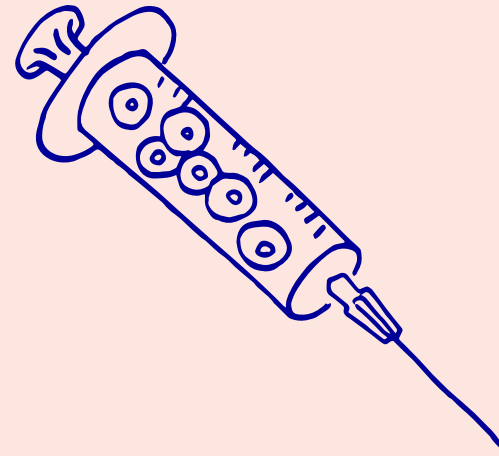
Multiplex gene editing to create highly efficacious and safe therapies

The power of gene edited iPSC cell therapies

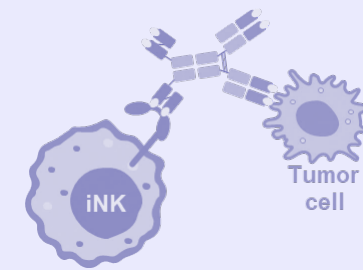
Immune-tolerance to prevent allo-rejection



Gene-edited, iPSC-derived cell therapies



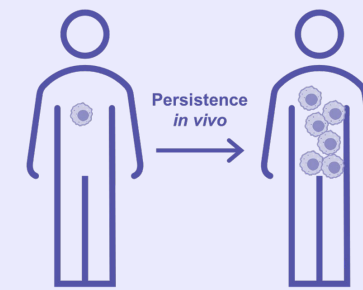
Tumor targeting via CARs and TCRs



Safety switches/tags



Increase cell persistence and overcome hostile tumour environment



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



evotec

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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



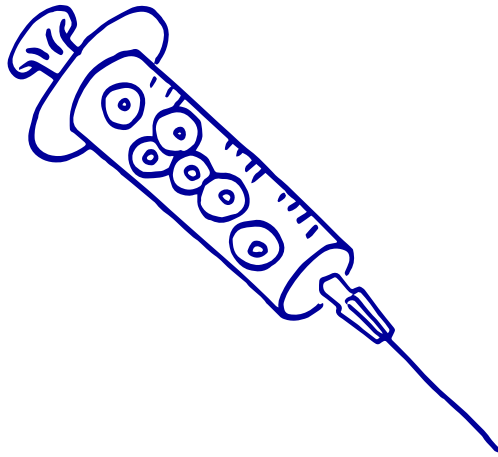
- Founded in 2009 as spin-off of the University of Modena and Reggio Emilia
- Scientific founder Prof. Massimo Dominici is one of the pioneers in clinical cell therapy
- State-of-the art GMP manufacturing facility (5 clean rooms, 1,200 m²) with room for significant expansion, ~ 25 FTEs
- cGMP facility 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*



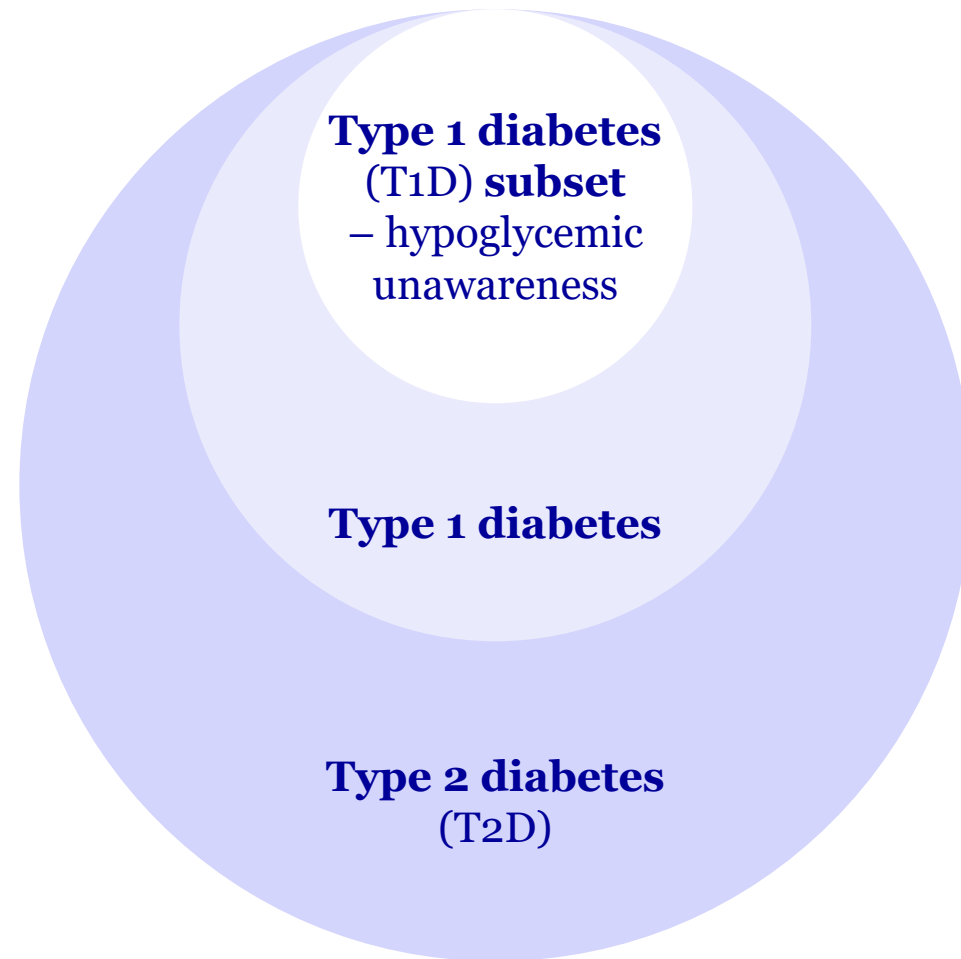
Pipeline building with iPSC-based cell therapy in Diabetes



Diabetes program with broad therapeutic scope

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

Size¹ 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 life-style: 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

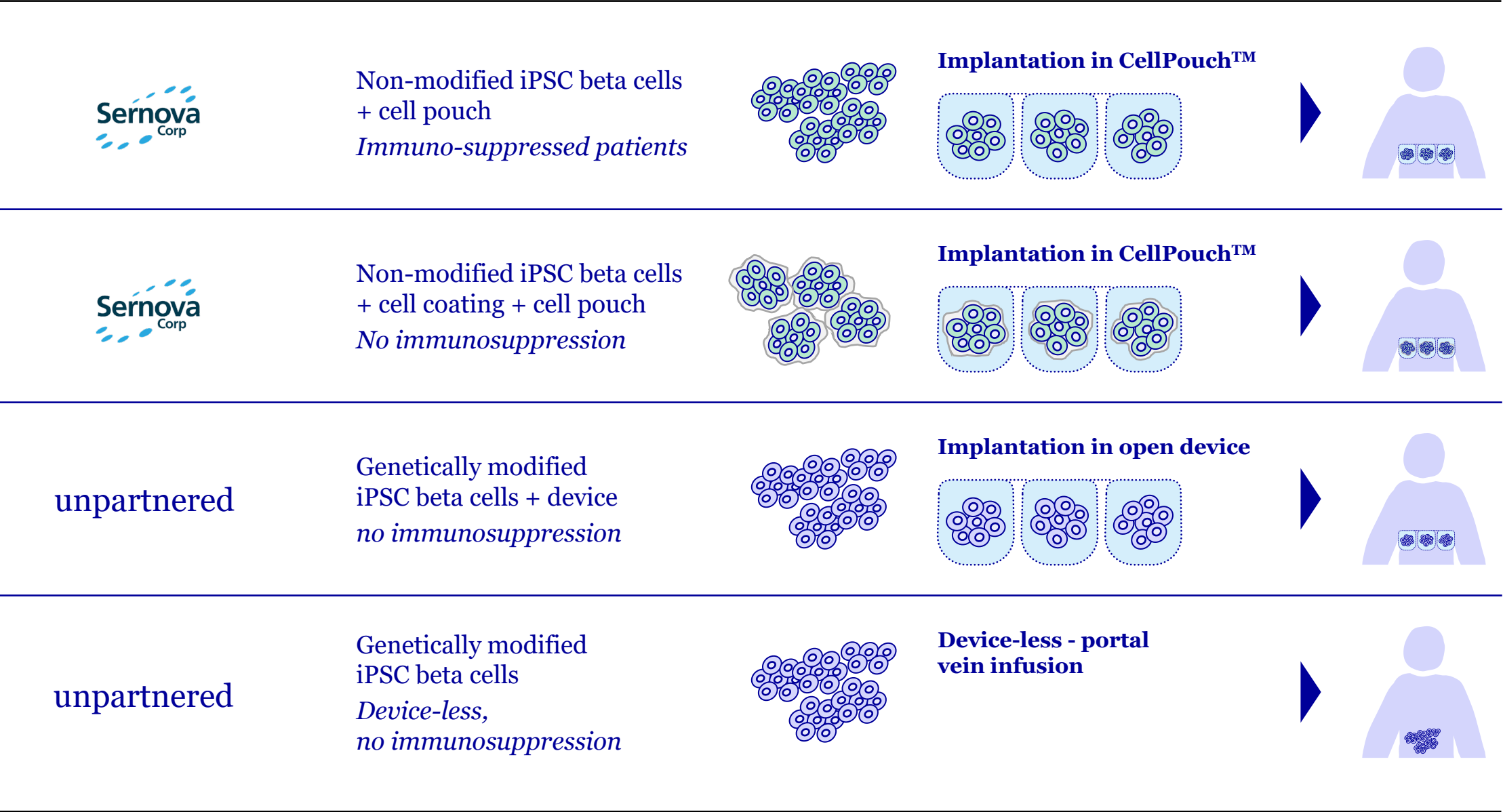
Next steps

- **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

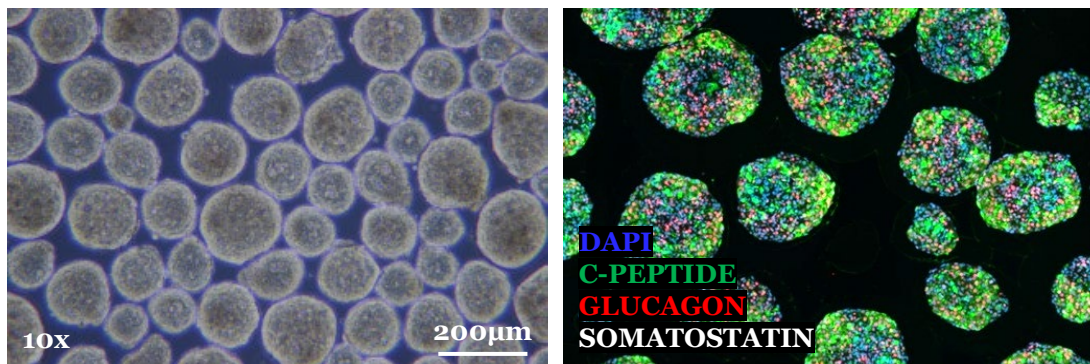




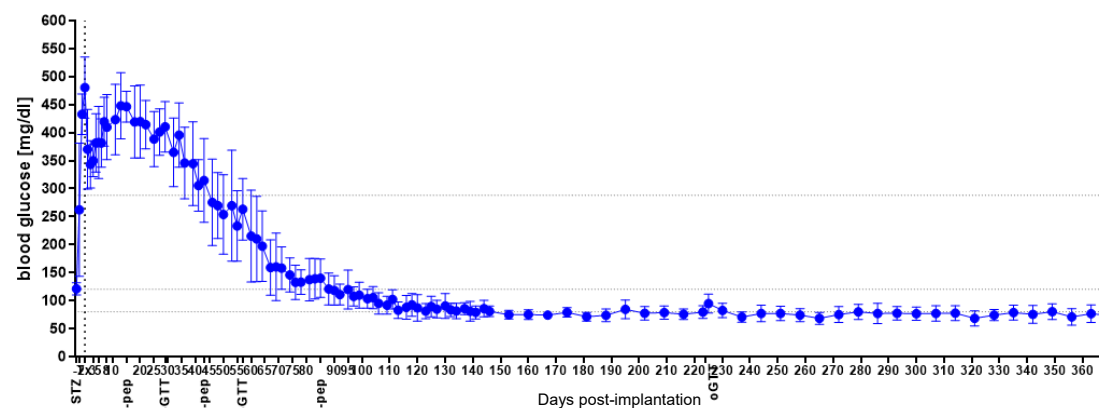
iPSC-derived islets for the treatment of Type 1 diabetes

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 PEI¹ (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

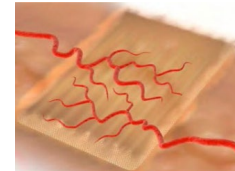
- **iPSC-based islet-like clusters mimicking human islet cells**
- Long-term function in rodent models of diabetes demonstrated
- Scalable 3D manufacturing procedure & manufacturing infrastructure
- Drug development expertise and cGMP manufacturing infrastructure



#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."...

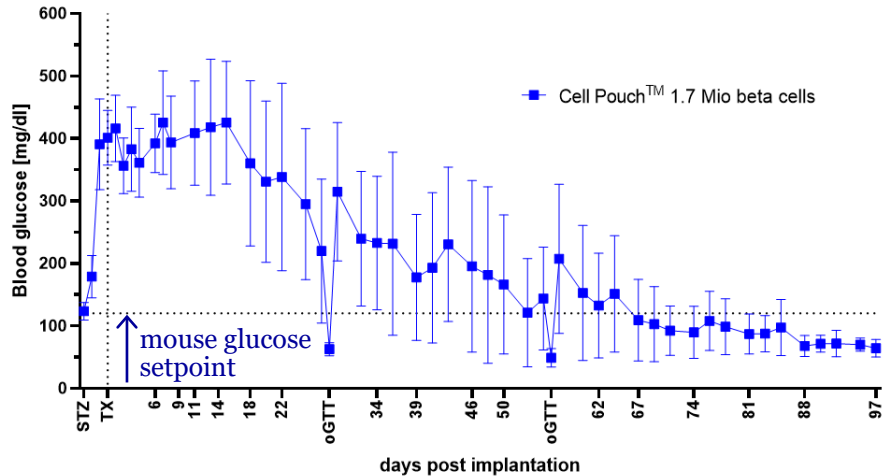
Sernova 2023, Cell Pouch with cadaveric human islets



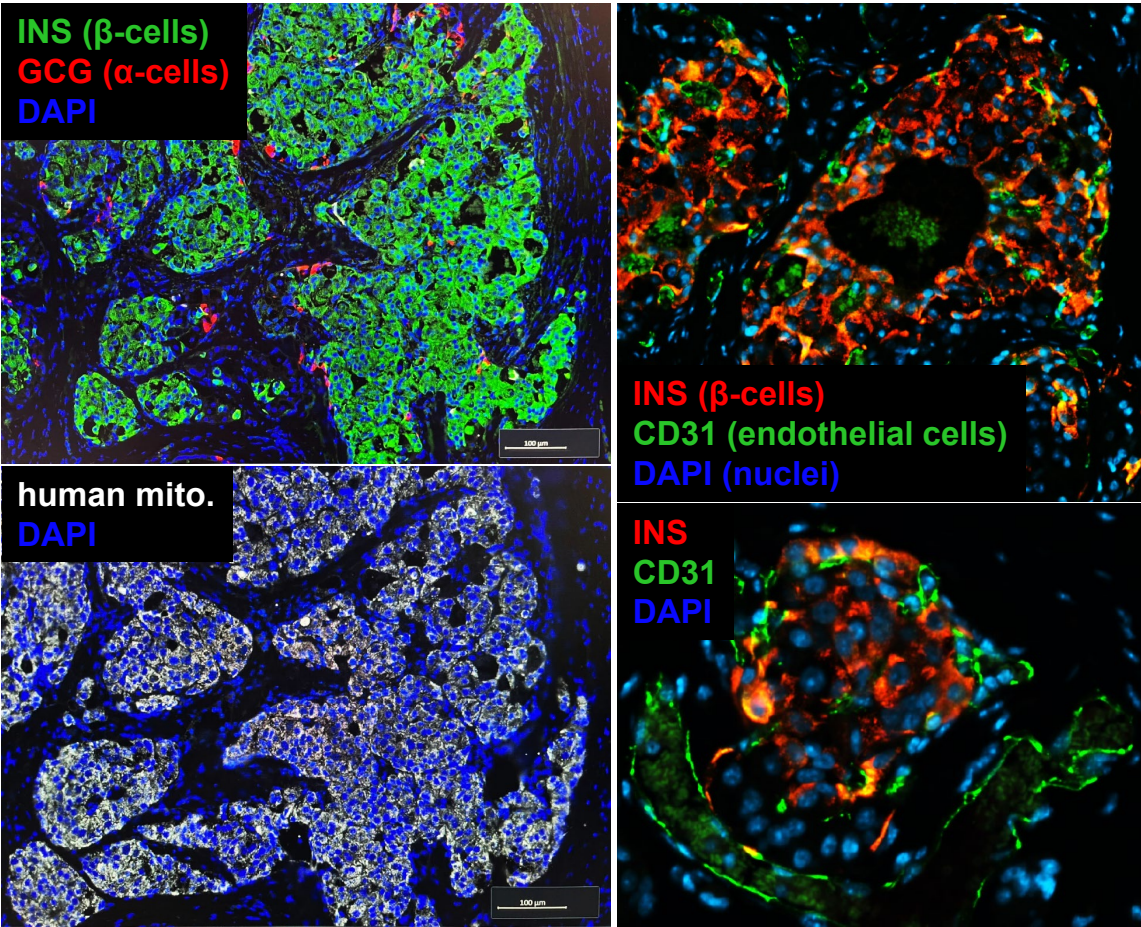
Excellent anti-diabetic activity of Evotec ILCs¹ in the Cell Pouch™

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

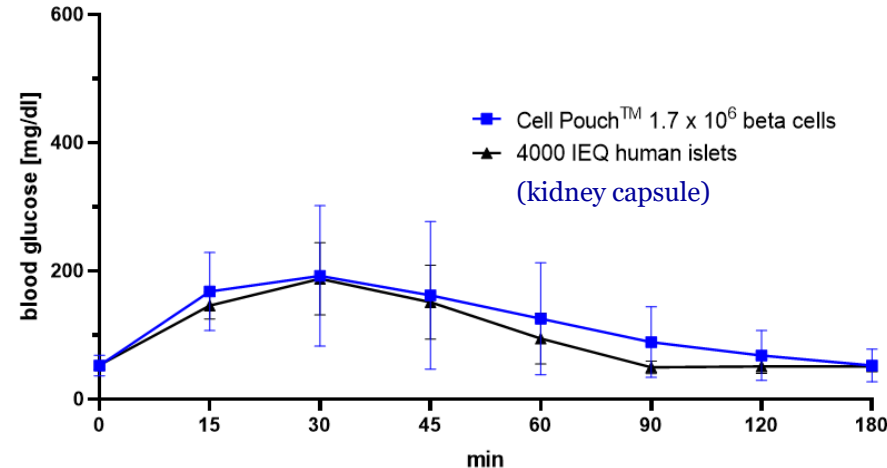
Efficient normalization of random fed glucose



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



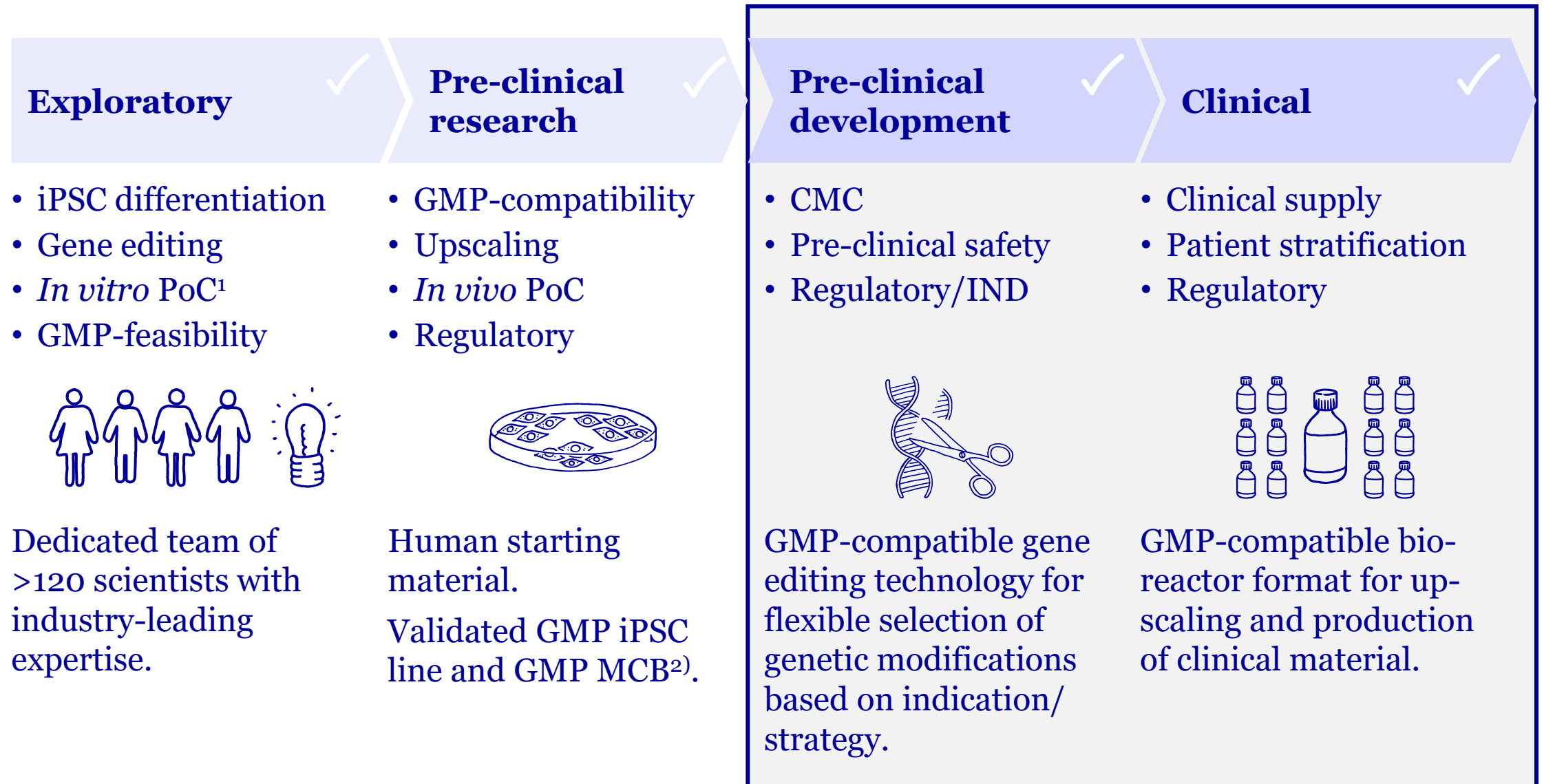
Efficient glucose clearance and no hypoglycemias in oGTT² (8 week timepoint)





Translation into clinical development

From iPSCs to patients





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

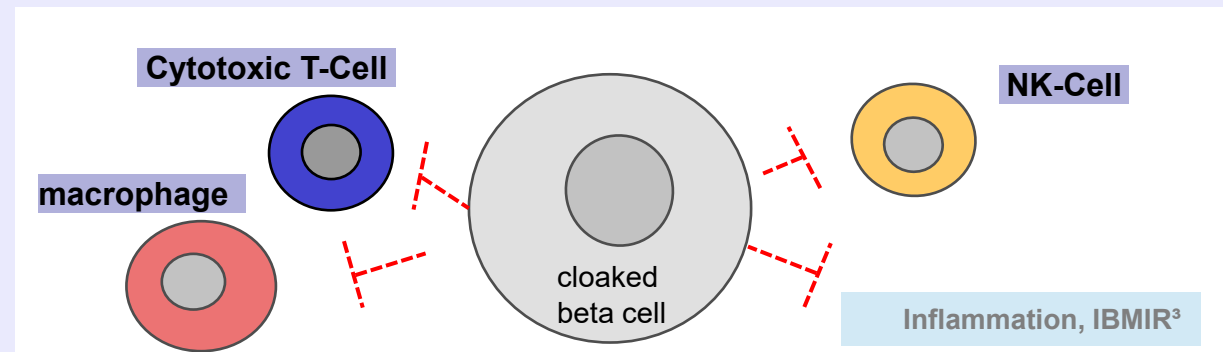
Introducing cloaking (immune-shielding) and FailSafe (drug-inducible kill-switch)

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:

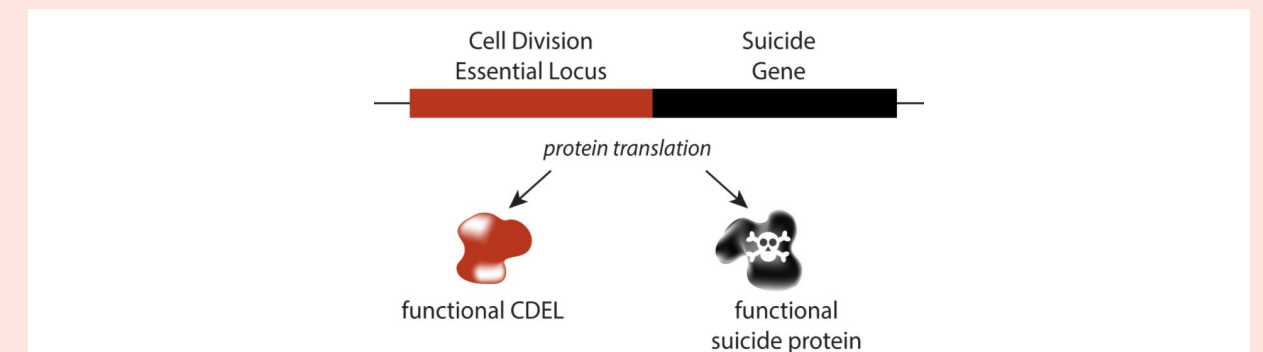
Cloaking enables long-term persistence without immunosuppression

- Evading immune destruction of allogeneic “off-the-shelf” cell therapy
- Avoiding immunosuppressive drugs with significant long-term risks ¹
- 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”²



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®” technology⁴
- 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





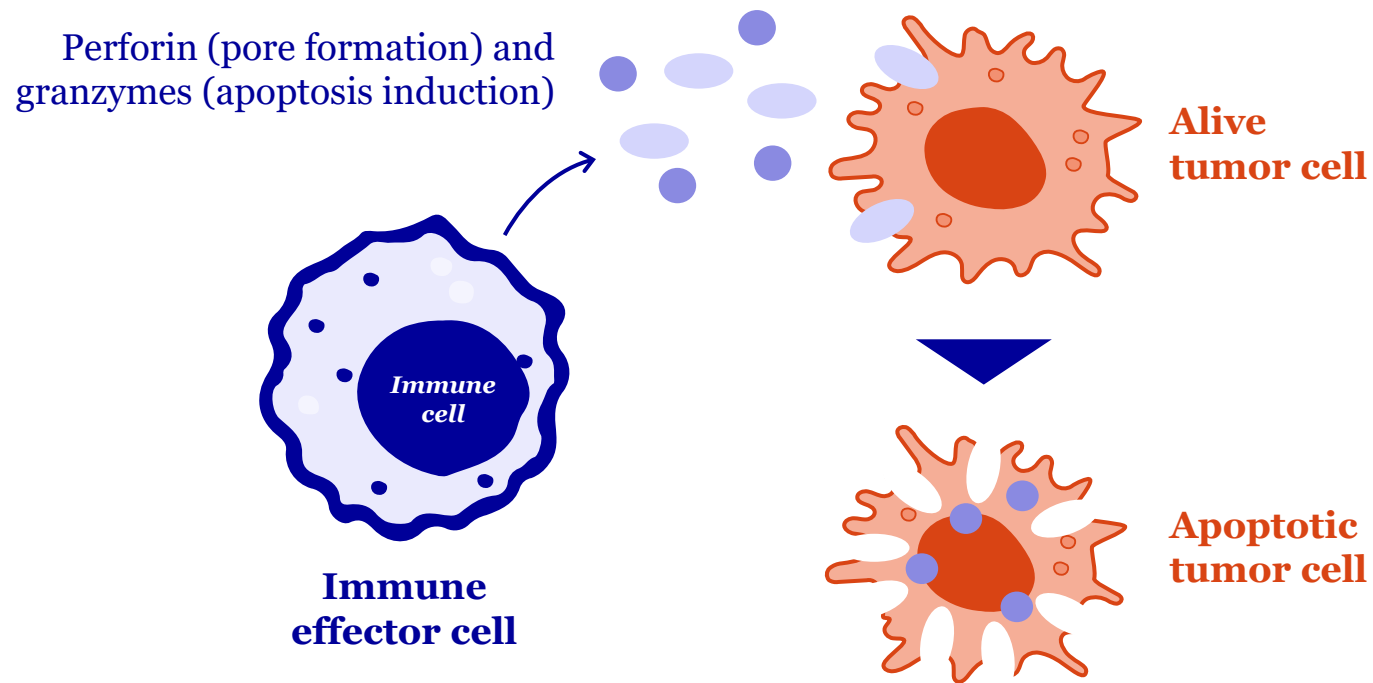
Pipeline building with iPSC based cells in Oncology and I&I



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

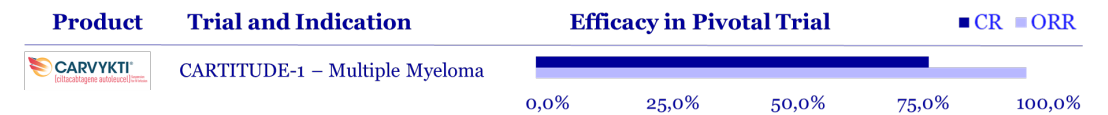
TECARTUS
(brexucabtagene autoleucel) Suspension for IV infusion

YESCARTA
(axicabtagene ciloleucel) Suspension for IV infusion

Abecma
(idecabtagene vicleucel) Suspension for IV infusion

CARVYKTI
(ciltacabtagene autoleucel) Suspension for IV infusion

KYMRIAH
(tisagenlecleucel) Suspension for IV infusion



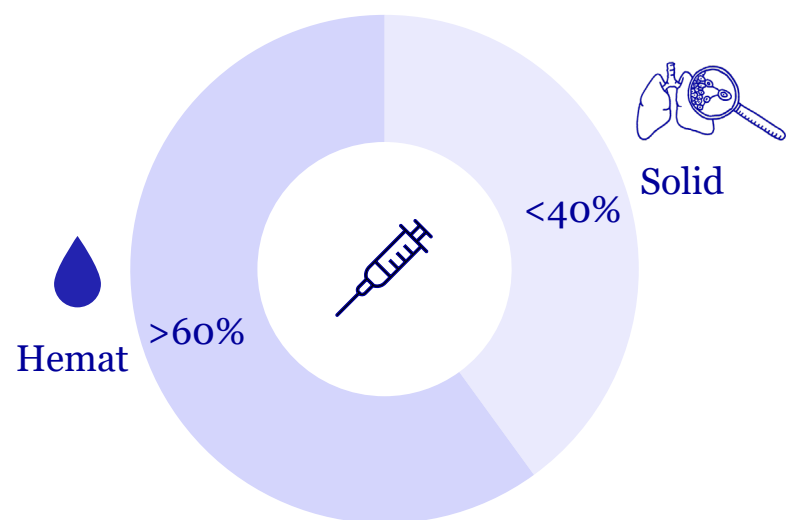
Autologous CAR T cell therapies available on the market primarily focus on the treatment of hematological cancers¹



Unlocking the full potential of cell therapies in oncology

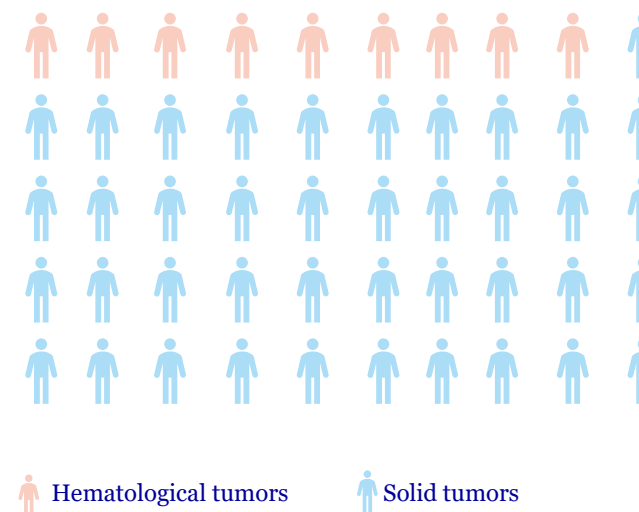
High unmet medical need in solid tumour indications

Cell therapy late-stage pipeline



>60% of current late-stage pipeline focused on hematological cancers¹

Cancer incidence



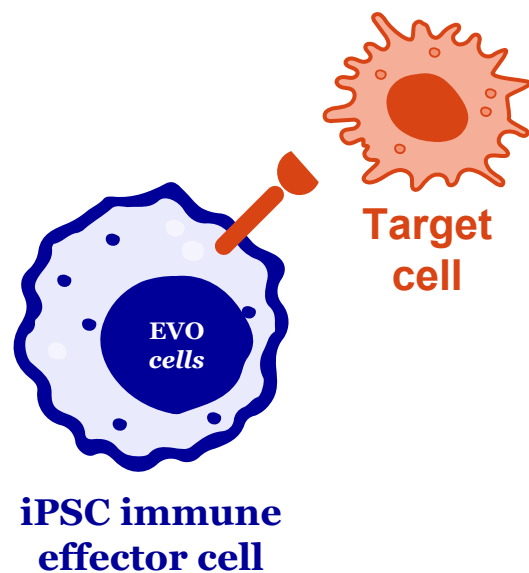
~90% of new case of cancer are attributable to solid tumors²

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



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

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

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

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

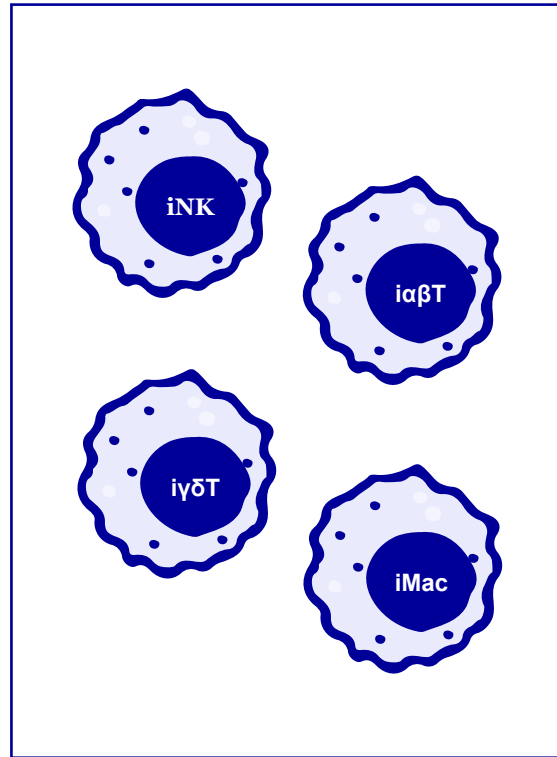
Early oncology product candidate pipeline in place including “lighthouse” projects; branching out into innovative treatments for auto-immune diseases



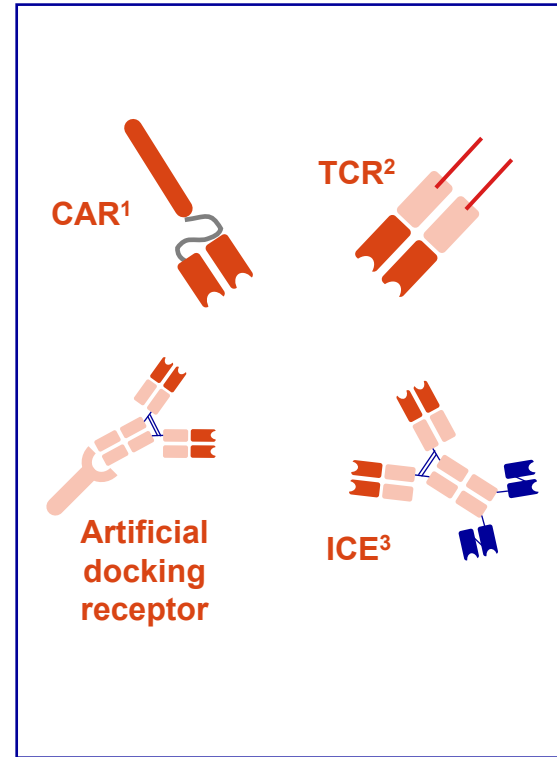
A toolbox to generate a universe of cell therapy product candidates

Evotec's technologies for iPSC-derived immune cell therapy

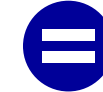
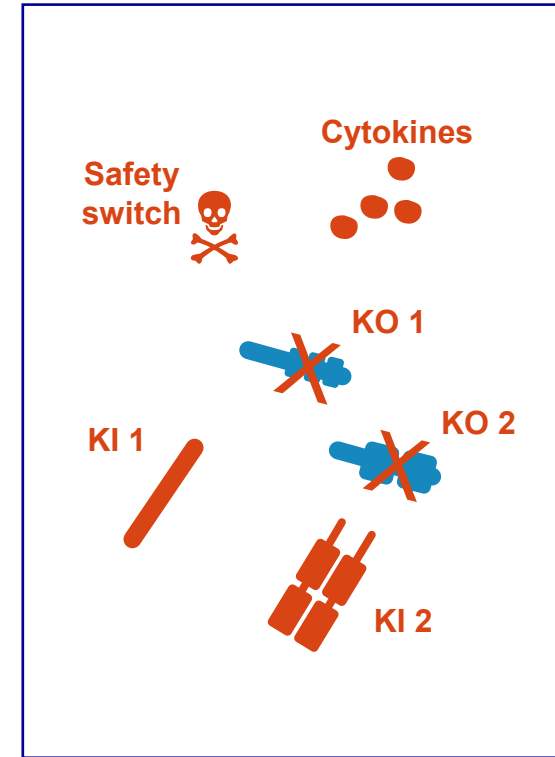
Immune cell type



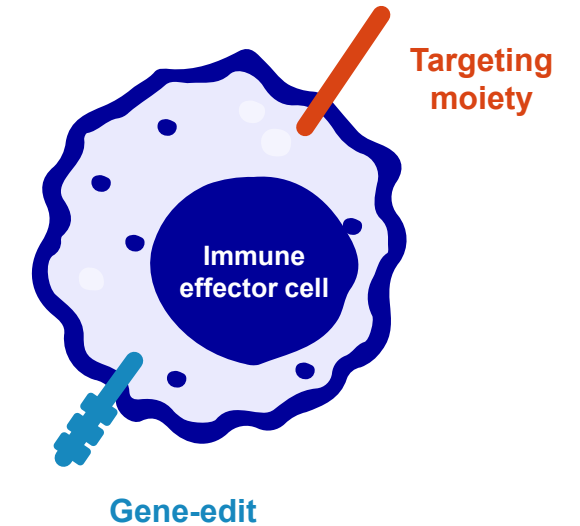
Tumor targeting



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	
Partnered	Cancer immuno- therapy	$\gamma\delta$ iT	Oncology	Undisclosed				iNK	Natural killer cells
		iNK	Oncology					$\alpha\beta$ iT	$\alpha\beta$ and $\gamma\delta$ T cells
Partnering opportunities	Cancer immuno- therapy	iMAC	Oncology					$\gamma\delta$ iT	$\gamma\delta$ T cells
		$\alpha\beta$ iT	Oncology					iMAC	Macrophages
		iNK	Fibrosis						
	I&I ¹	$\alpha\beta$ iT	SLE ²						
		iMAC	Fibrosis						

► Each cell type can deliver multiple differentiated products

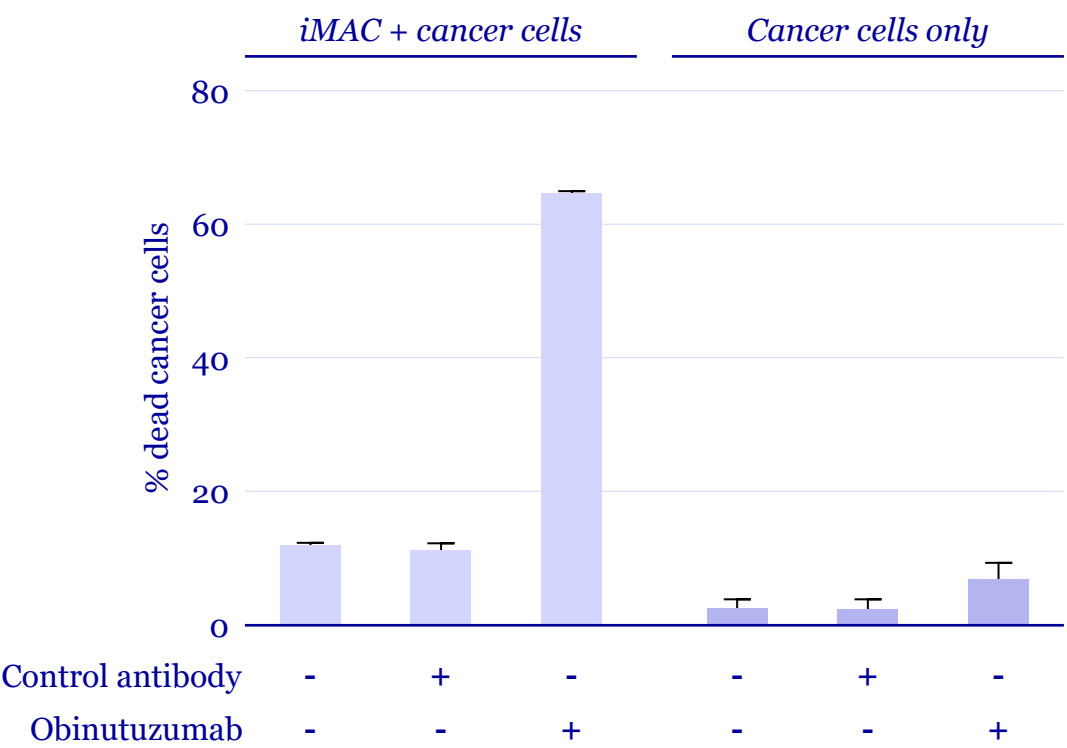
Leveraging technologies and know-how across multiple product candidates and disease areas reduces development costs and timelines



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

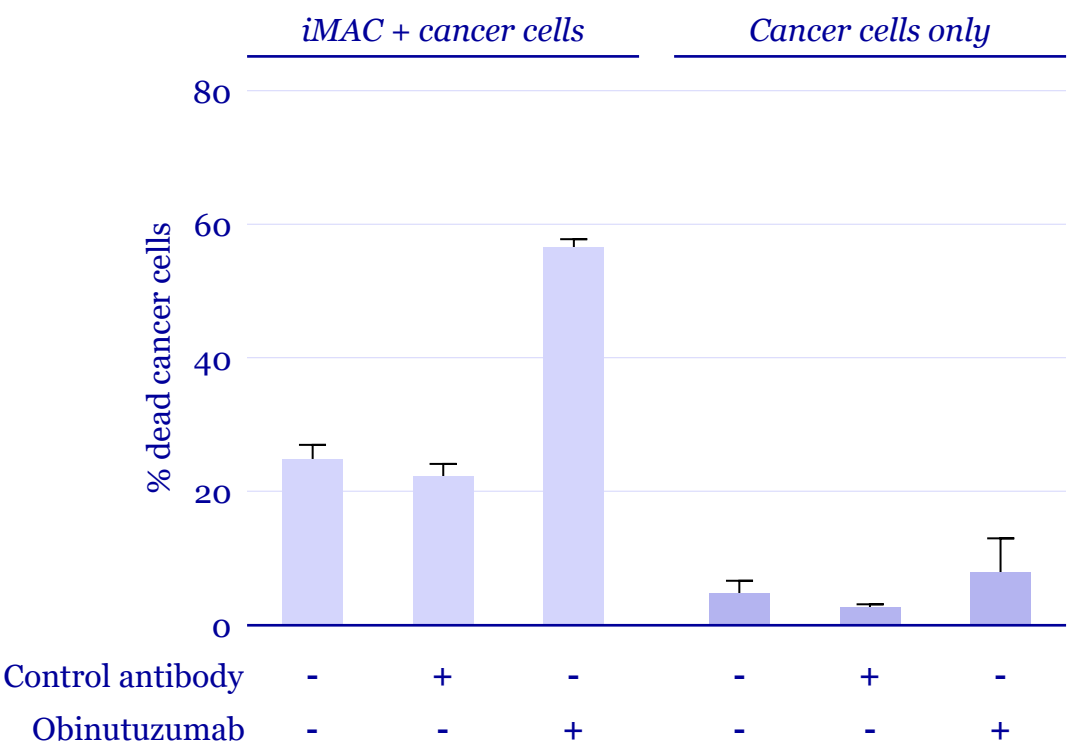
iPSC-based macrophages kill hard to treat primary cancer cells

Tumor cells of patient #1



Tumor cells of patient #2

E:T = 10:1



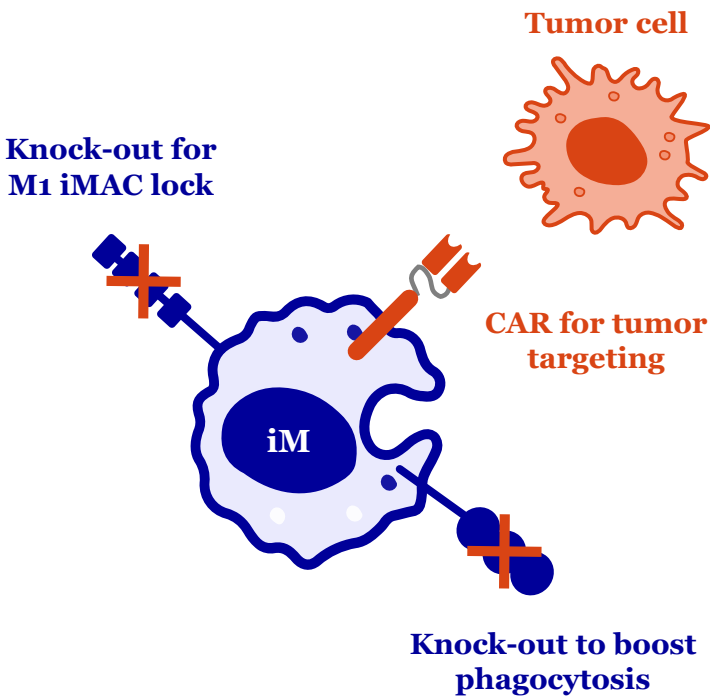
iPSC-derived macrophages can kill tumor cells directly and also phagocytose cancer cells to activate the endogenous immune system potentially leading to increased clinical efficacy



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 TME¹, 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 <ul style="list-style-type: none">• <i>Better disease understanding & diagnostics</i>• <i>Advanced disease modelling</i>• <i>A.I. use cases along the value chain</i>
11:00-11:15	<i>Coffee Break</i>
11:15-12:15	Impactful therapies <ul style="list-style-type: none">• <i>Integrated platform</i>• <i>Diabetes</i>• <i>Oncology</i>
12:15-13:30	<i>Lunch Break</i>
13:30-16:00	Round Tables



Breakout Sessions

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

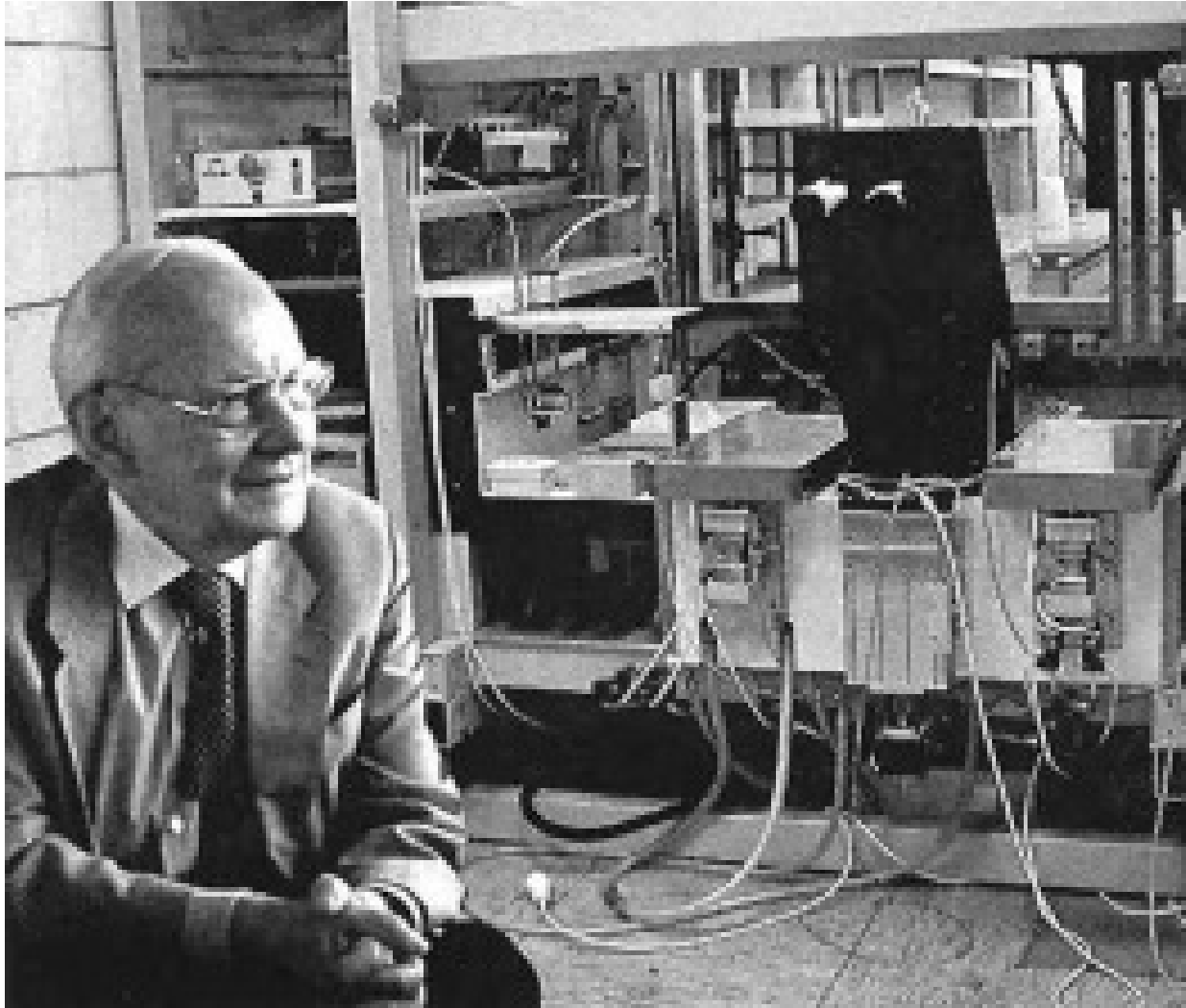
#researchneverstops

...and shapes new markets!





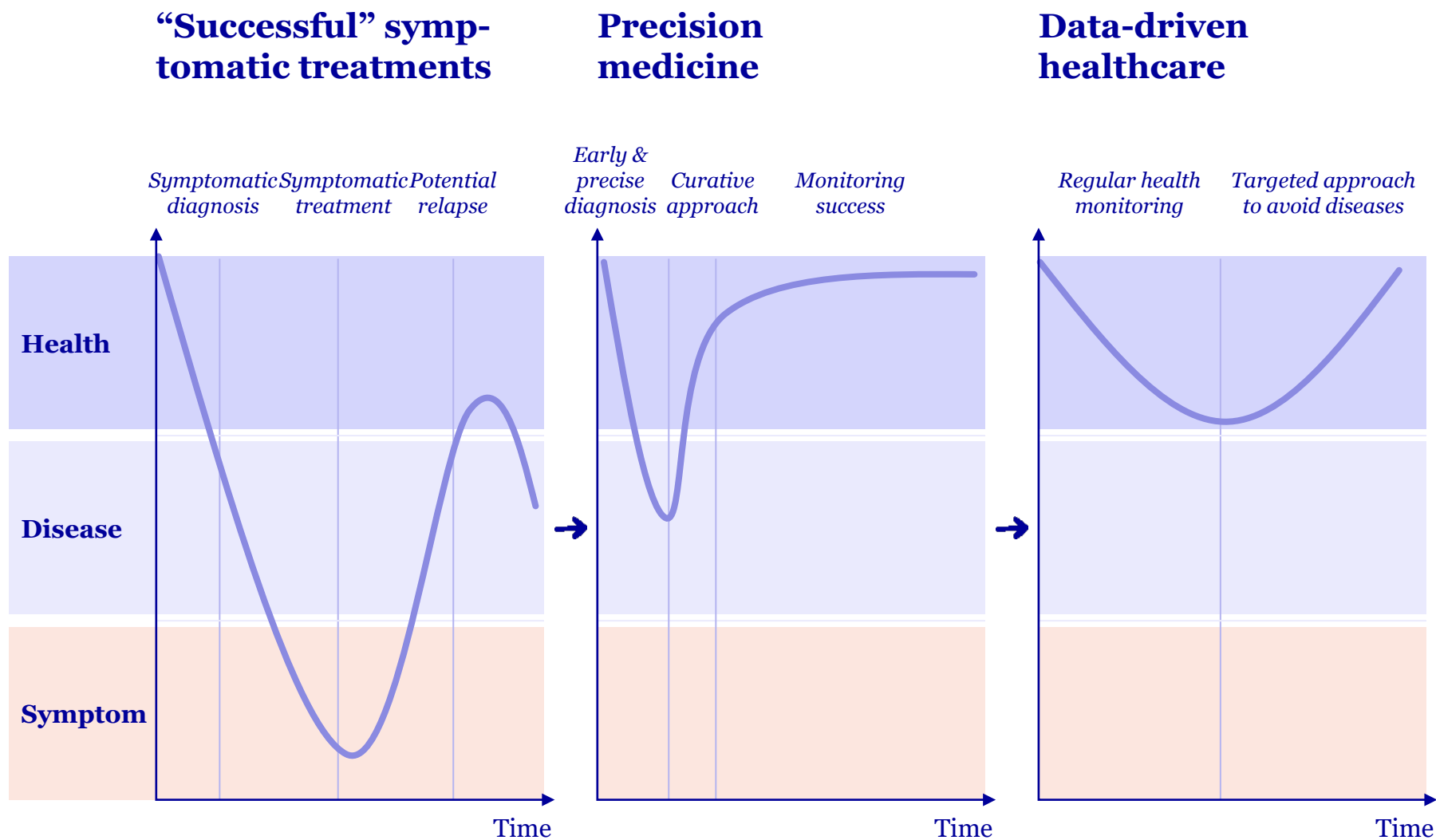
The initial idea is more modern today than ever before!





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



Next CMD 10 October 2024

Your contact:

Volker Braun, SVP Head of Global Investor Relations & ESG
volker.braun@evotec.com
+49 151 19405058 (m)
