# Pharmaceuticals
# R&D Event

Boston, US
June 28, 2023

# *Agenda Pharmaceuticals R&D Event*

| Session | Start/EDT | Start/CEST | Content | Speaker |
|---|---|---|---|---|
| 1 | 08:00 am | 14:00 pm | Welcome | Oliver Maier |
| | 08:10 am | 14:10 pm | Transforming Bayer Pharma for Sustained Growth | Stefan Oelrich |
| | 08:25 am | 14:25 pm | Reshaping Innovation at Bayer Pharma | Christian Rommel |
| | 08:50 am | 14:50 pm | Making a Difference in Neurology & Rare Diseases<br>Leveraging a Unique Platform to Build a Presence in Immunology | Christian Rommel |
| | 08:55 am | 14:55 pm | Vividion Therapeutics: Removing the Boundaries of Druggability | Aleksandra Rizo |
| | 09:15 am | 15:15 pm | Q&A (15 min) | Stefan Oelrich, Christian Rommel, Aleksandra Rizo |
| | 09:30 am | 15:30 pm | Coffee Break | |
| 2 | 09:40 am | 15:40 pm | Driving Leadership in Focus Areas of Oncology | Dominik Ruettinger |
| | 10:00 am | 16:00 pm | Shaping new Treatment Paradigms in Cardiovascular Diseases | Maria Borentain |
| | 10:25 am | 16:25 pm | Q&A (15 min) | Dominik Ruettinger, Maria Borentain |
| | 10:40 am | 16:40 pm | BlueRock Therapeutics: Leading the way in PSC therapies | Seth Ettenberg |
| | 11:00 am | 17:00 pm | Asklepios BioPharmaceutical: Pioneering AAV-based Gene Therapies | R. Jude Samulski |
| | 11:20 am | 17:20 pm | Concluding Remarks | Christian Rommel |
| | 11:25 am | 17:25 pm | Coffee Break | |
| 3 | 11:35 am | 17:35 pm | Q&A and Closing Remarks (30 min) | All |
| | 12:05 pm | 18:05 pm | End of Event & Joint Lunch | |

# *Cautionary Statements Regarding Forward-Looking Information*

This presentation may contain forward-looking statements based on current assumptions and forecasts made by Bayer management.

Various known and unknown risks, uncertainties and other factors could lead to material differences between the actual future results, financial situation, development or performance of the company and the estimates given here. These factors include those discussed in Bayer's public reports which are available on the Bayer website at www.bayer.com.

The company assumes no liability whatsoever to update these forward-looking statements or to conform them to future events or developments.

# *Transforming Bayer Pharma for Sustained Growth*

Stefan Oelrich

# Key Messages Today

## 1

### *Revised innovation model*

Greater focus, streamlined portfolio, emphasis on precision medicine

## 2

### *Expanding US footprint*

Building US presence; Expanding both R&D and commercial footprint

## 3

### *Late-stage pipeline potential*

From two to up to four blockbusters with a combined peak sales potential of €12bn

# We Have Taken Actions to Increase Focus, Quality and Productivity of Our Innovation Model

*Focus*

**Portfolio too broad for company size**

› Focus areas driven by value, differentiation, feasibility and competencies

*Quality*

**Incremental innovation**

› Shift to breakthrough innovation leveraging scientific advances, platforms, precision medicine and AI

*Productivity*

**Complex operating model**

› Shift to value creation, asset-centric operating model, leaner governance with renewed leadership team

# Zeroing in on High Unmet Need With Great Value Potential

## Optimizing our R&D focus to 4 broad therapeutic areas

**Focus areas prioritized based on**

// Value & differentiation

// Feasibility & risk

// Bayer's strengths

**Oncology**

**Cardiovascular+[1]**

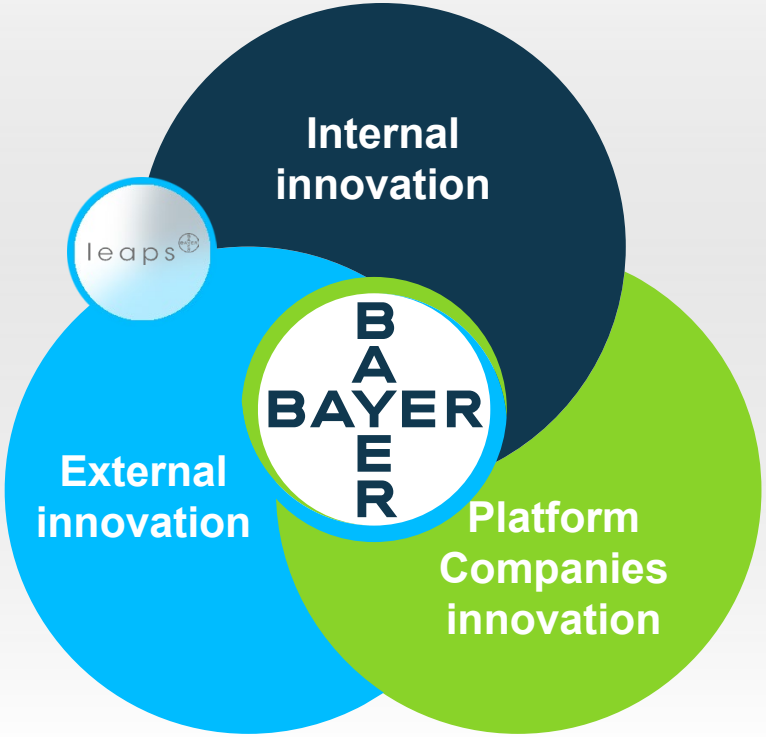
**Neurology & Rare Diseases**

**Immunology**

[1] including Precision Cardiovascular, Nephrology & Acute Care

# We Have Expanded Our Capabilities And Pipeline Through Strategic Acquisitions and Collaborations

## INNOVATION ENGINE




// Establishing Cell & Gene therapy platform through acquisition of BlueRock and AskBio

// Gaining access to cutting-edge chemoproteomics platform through acquisition of Vividion

// Collaborating with top academia, pharma partners and biotech companies

// LEAPS as a feeder of breakthrough technologies

**~ 100 deals** signed in the last 4 years

# Building US Footprint

## Research & Development

Increased presence at the world's most vibrant Pharma innovation hubs

// Increased R&D footprint in the US with the acquisition of BlueRock, AskBio and Vividion

// Established the Bayer Research and Innovation Center in Cambridge/Boston

## Commercial

Expanding US commercial footprint reflecting new products and pipeline assets with global rights

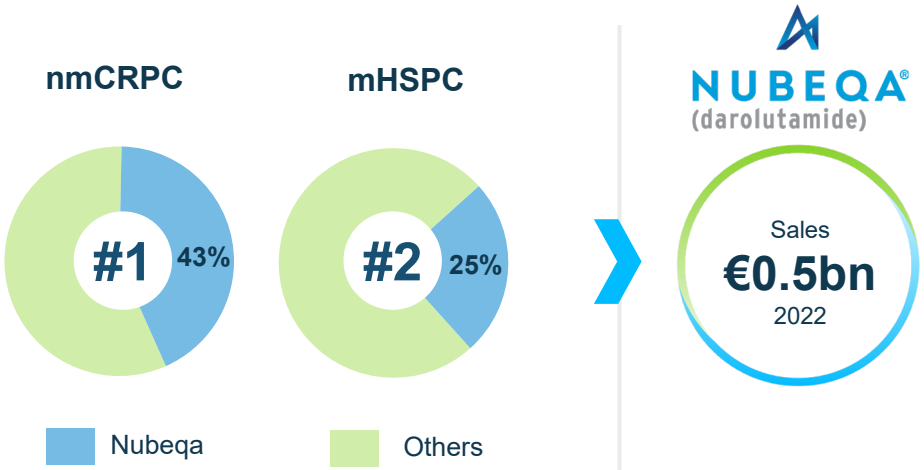
// Improved presence in oncology, in particular to support Nubeqa

// Ensuring Kerendia & Verquvo in cardio-renal have appropriate marketing and sales support

# Nubeqa Has The Potential to Become The New Standard of Care in Prostate Cancer Across Indications

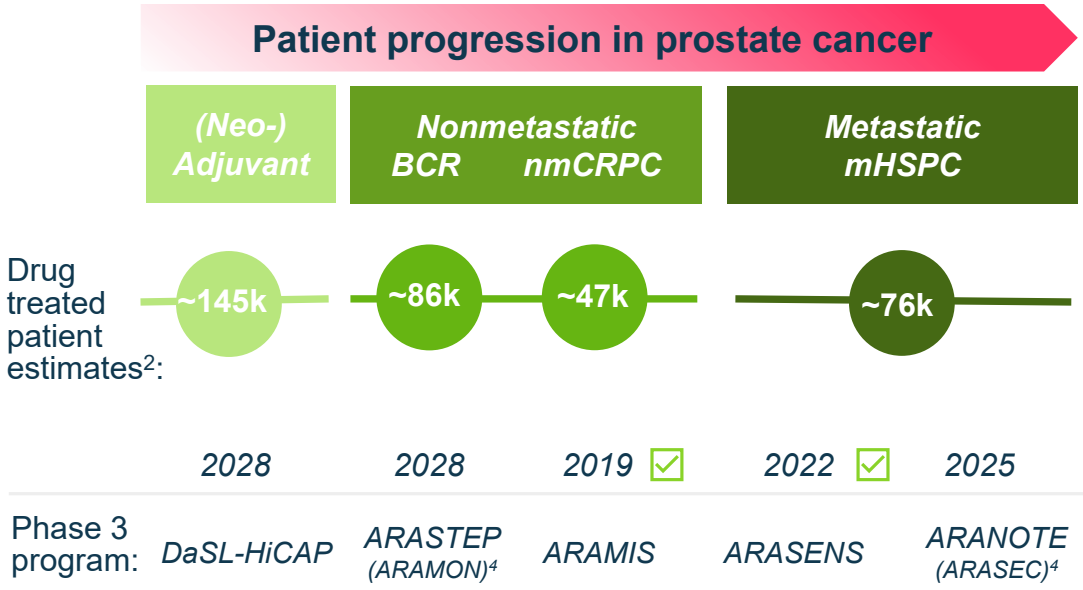
## Launch Performance

// US Market Share[1]




// Ex-US, additional approvals will drive further growth

## Expanding to earlier prostate cancer settings




// Committed to make Nubeqa available to a broad spectrum of prostate cancer patients

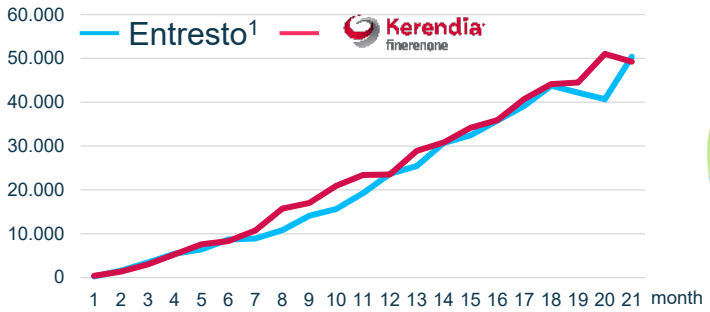
[1] Source: IQVIA January 2023 3-month rolling market share, adjusted to reflect nmCRPC and mHSPC only [2] 2030 Treated Estimates G7: US, EU5, J [3] Peak Sales Potential
[4] Not label generating; supports ARASTEP/ARANOTE submission

>€3bn Peak[3]

# Kerendia With Strong Launch Dynamics And The Option to Broaden The Use in CKD And to Expand into HF

## Launch Performance

**US launch performance** (monthly TRx)[2]



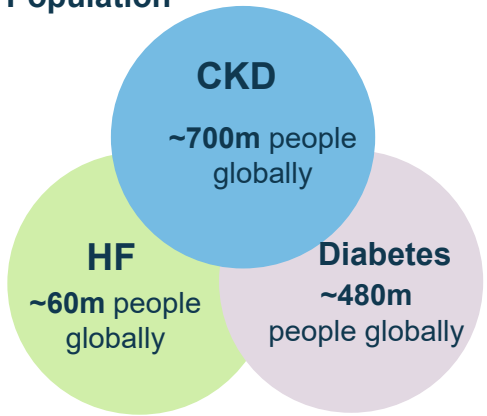

Kerendia finerenone

Sales
**€0.1bn**
2022

- // One of the strongest launch dynamics in CV despite initial COVID restrictions
- // Continued US market uptake with broad utility and relevance across GPs and specialists
- // China: NRDL Listing starting March 2023; granted Extended Indication in China in mid-May, including CV outcomes from FIGARO-DKD

## Expanding to additional indications

**Global Patient Population**[3]




// Growing recognition of strong interlink between CKD and HF

| *Chronic Kidney Disease* | | | *HF* |
|---|---|---|---|
| **T2D** | **T1D** | **Non-diabetic** | **HFmr/pEF** |
| *FIGARO-DKD* ☑ | *FINE-ONE* | *FIND-CKD* | *FINEARTS-HF* |
| *FIDELIO-DKD* ☑ | 2025 | 2026 | 2024 |

**>€3bn**
Peak[4]

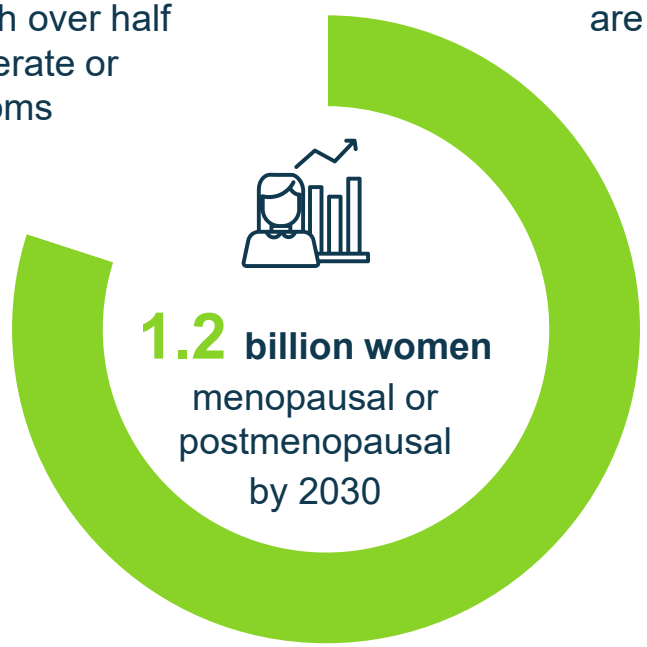
[1] Entresto developed and commercialized by Novartis [2] Source: IQVIA TRx April 2023 [3] Source: Vijay et al, 2021 [4] Peak Sales Potential

# Elinzanetant as Investigational Non-hormonal Treatment Option in The Menopause Market With Peak Sales Potential of >€1bn

## Market Characteristics

**80%** of women will experience vasomotor symptoms, with over half reporting moderate or severe symptoms

**~60%**[1] of women with menopausal syptoms are not treated



**1.2 billion women** menopausal or postmenopausal by 2030

## Elinzanetant

- First, non-hormonal, once-daily, oral neurokinin-1,3 receptor antagonist
- Differentiated, double mode of action
- Phase II indicated significant and rapid improvement in VMS and positive safety profile

## Current Status

- Four Phase III studies (OASIS-1 – OASIS-4)
- First Phase III data expected in H2 2023
- Potential launch: 2025

**>€1bn** Peak[2]

[1] Source: Market Research - IPSOS - Global VMS Women Segmentation [2] Peak Sales Potential

# Currently Un(der)treated Patients May Provide Asundexian a Strong Entry Point Into The Anticoagulation Market

## Market Characteristics

### Stroke prevention in AF

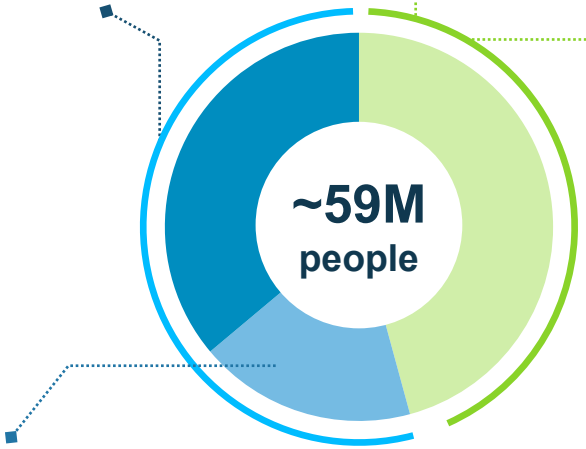
// **~32m diagnosed AF patients** in top 8 markets[1]

// **Standard of care:** DOACs (or VKA)

### Non-cardioembolic stroke

// **~27m diagnosed patients** in top 8 markets[1]

// **Standard of care:** Single/Dual APT




// Continuous high recurrence despite APT,and safety concerns with DAP

// Unmet need: higher efficacy without increase in bleeding vs. SOC

// **~1 in 3 patients in AF un(der)treated** due to (fear of) bleeding

// Unmet need: lower bleeding with otential for efficacy benefits over SOC

## Asundexian

// Innovative, once-daily, oral small molecule FXIa inhibitor

// Paradigm shift in thrombosis prevention, with the potential to uncouple efficacy from bleeding risk

// Broad Phase II study program PACIFIC confirmed consistent safety and near maximum FXIa inhibition

## Current Status

// Two Phase III studies (OCEANIC-AF and OCEANIC-STROKE)

// U.S. FDA Fast Track Designation granted for both indications

// Phase III data expected in H2 2025

**>€5bn**
Peak[2]

[1] Top 8 markets: US, CN, JP, EU5; [2] Peak Sales Potential

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# *Reshaping Innovation at Bayer Pharma*

Christian Rommel

# Key Messages Today

- We have reshaped our approach to innovation guided by value, differentiation, feasibility, and our competencies.
- We have streamlined our portfolio towards precision medicine, with a narrower therapeutic area focus but a wider range of modalities.
- We will leverage partnerships, data science, new trial designs, biomarker technologies, and improved governance to accelerate our drug development processes and move to a higher, more sustainable R&D productivity.
- We are already starting to see a step change in the quality and differentiation of our new molecular entities with the vast majority offering the potential to be first- or best-in-class.

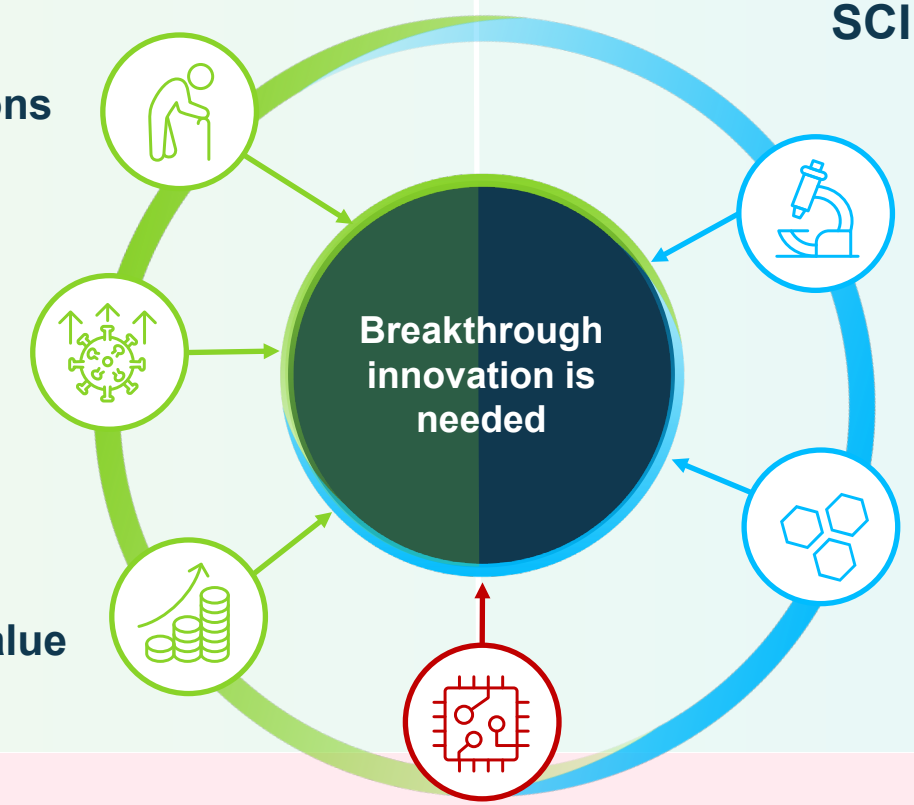
# Patients and Society Need and Demand Transformational Change

## HEALTH SYSTEMS UNDER PRESSURE

Ageing populations

Increasing burden of chronic diseases

Paying for value




## ERA OF GROUND-BREAKING SCIENTIFIC DISCOVERY

Scientific breakthroughs

Data Science-driven R&D

## REDEFINITION OF DISEASE

Precision treatments for homogeneous populations | Shifting to cure and prevention, holistic care beyond “the pill”

# The New Face of Bayer Pharma R&D

Building on 160 years of innovation, we've significantly transformed our organization and shaped our strategy

**New Bayer innovation strategy setting the path for scientific leadership and increased value for patients**

- Diversified modalities
- Refocused therapeutic areas
- Increased R&D footprint in the US

**Extended capabilities and pipeline through strategic acquisitions**

- BlueRock
- AskBio
- Vividion

**Fast-tracked our ambition through key R&D decisions**

- New R&D operating model
- Leaner, simpler governance
- Rigorous portfolio health check

## KEY FIGURES:

**€3.2bn** spend on R&D

**5,800 FTEs** at Bayer Pharma R&D *(including platform companies)*

**25 NMEs** and 45 projects in development

**€9bn** value increase of late-stage assets since 2021

**~100 deals** signed in the last 4 years

# Our People are Key for our Transformation and Future Success

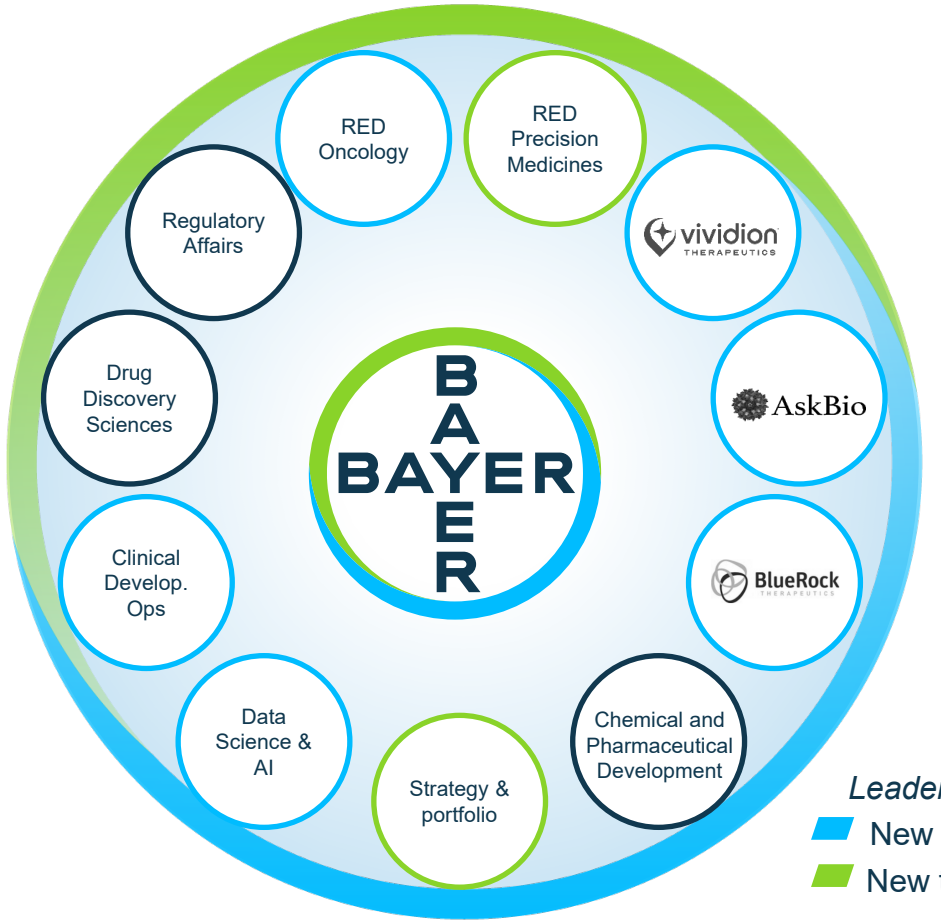
Revamped leadership in action to transform our organization and unleash the potential of our people

## UNLEASH R&D TALENT

// Attract, retain & engage diverse, innovative talents
// Systematic talent up/re-skill
// Foster open, bold, breakthrough innovation culture

## NEW WAYS OF WORKING & LEADING

// Simplification of processes & governance
// Increased agility and collaboration
// Shift to empowered, self organized teams, flow-to-work pools, etc.



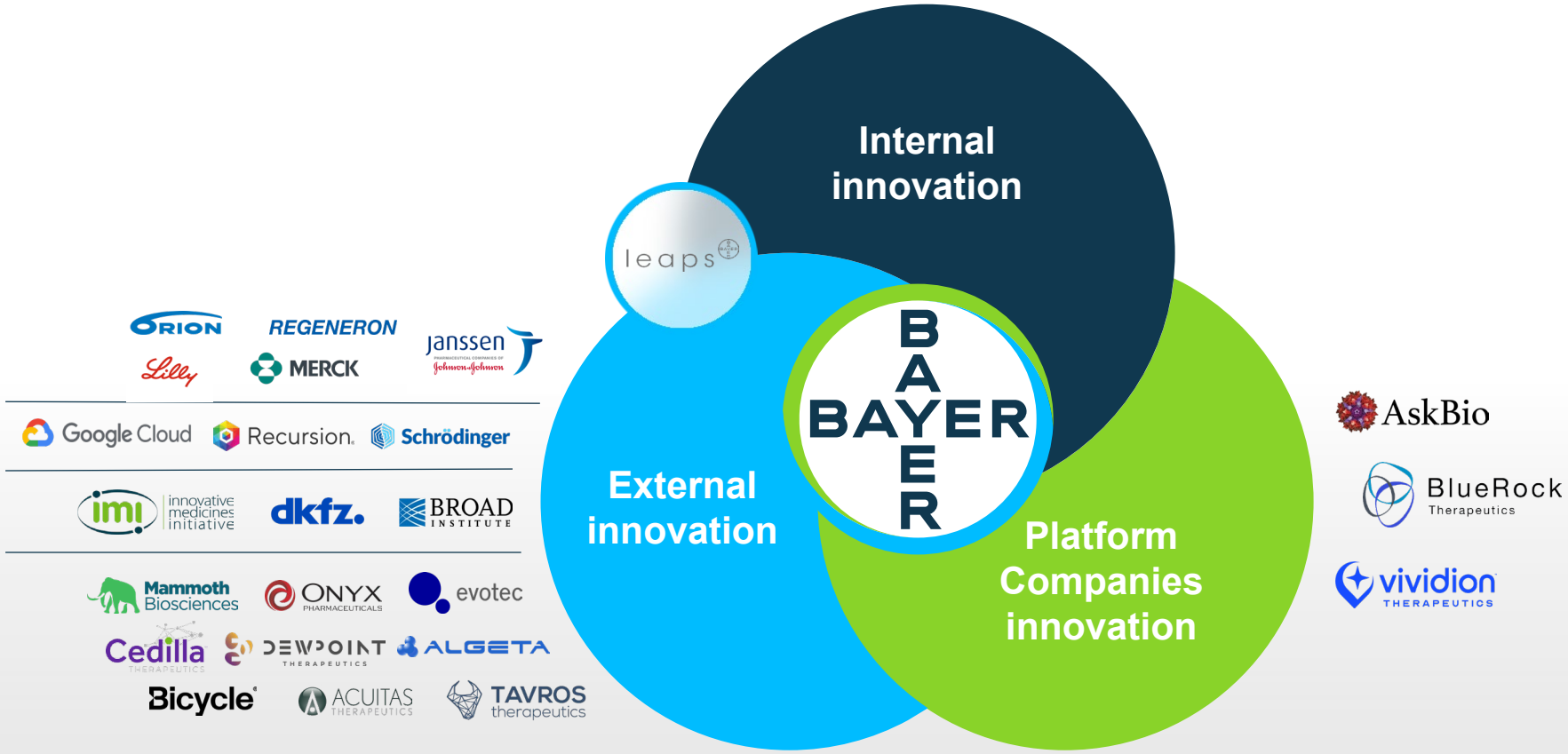

*Leadership across innovation functions*
New to Bayer
New to the role

## REVAMPED R&D LEADERSHIP

// **70% renewal** of R&D Leadership team
// **70% refreshment** in next leadership level
// **50:50 gender diversity** ratio including most senior levels
// **Expanded geographic presence**: US, China, Japan and Europe

# A Multi Faceted Innovation Engine to Unlock Value for Patients

Addressing need for breakthrough science with diverse research capabilities, technologies and talents



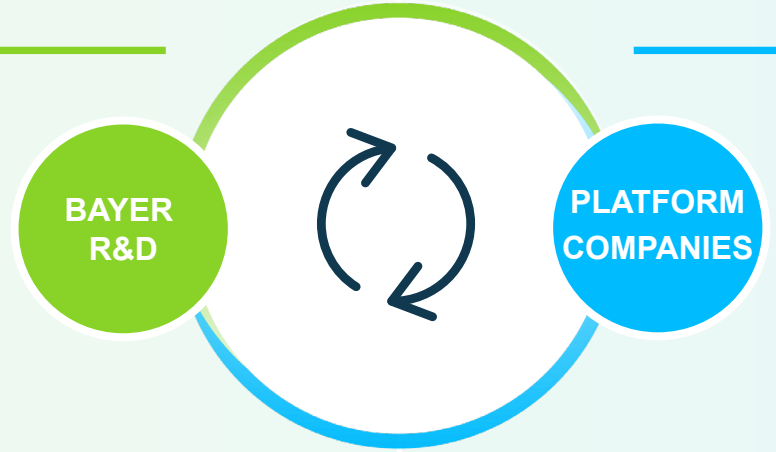
# Bolstering Science and Pipeline Through our Platform Companies

## Balancing organizational synergies and scientific independence

### BAYER R&D

Makes decision on

- Therapeutic and portfolio strategy
- Resource allocation
- Capability building




### PLATFORM COMPANIES

Independently lead

- Platform strategy
- Platform portfolio
- Technology and science

AskBio · BlueRock THERAPEUTICS · vividion THERAPEUTICS

### SYNERGIES

- Cross-company interaction and synergistic BD&L activities to accelerate technology development
- Building on respective scientific capabilities to expand early pipeline
- Leverage Bayer's expertise to accelerate pre-clinical and clinical development
- Ensure scalable and reliable product manufacturing

# Our Science & Portfolio Strategy Evolution

## *TARGETS*

Classical, well characterized drug targets › “Undruggable”, new drug targets

## *INDICATIONS*

Mainly large indications › Value driven from large to rare

## *TECHNOLOGIES*

Small molecules › Mix of innovative, diverse modalities

## *PATIENT POPULATION*

Broad › Precise

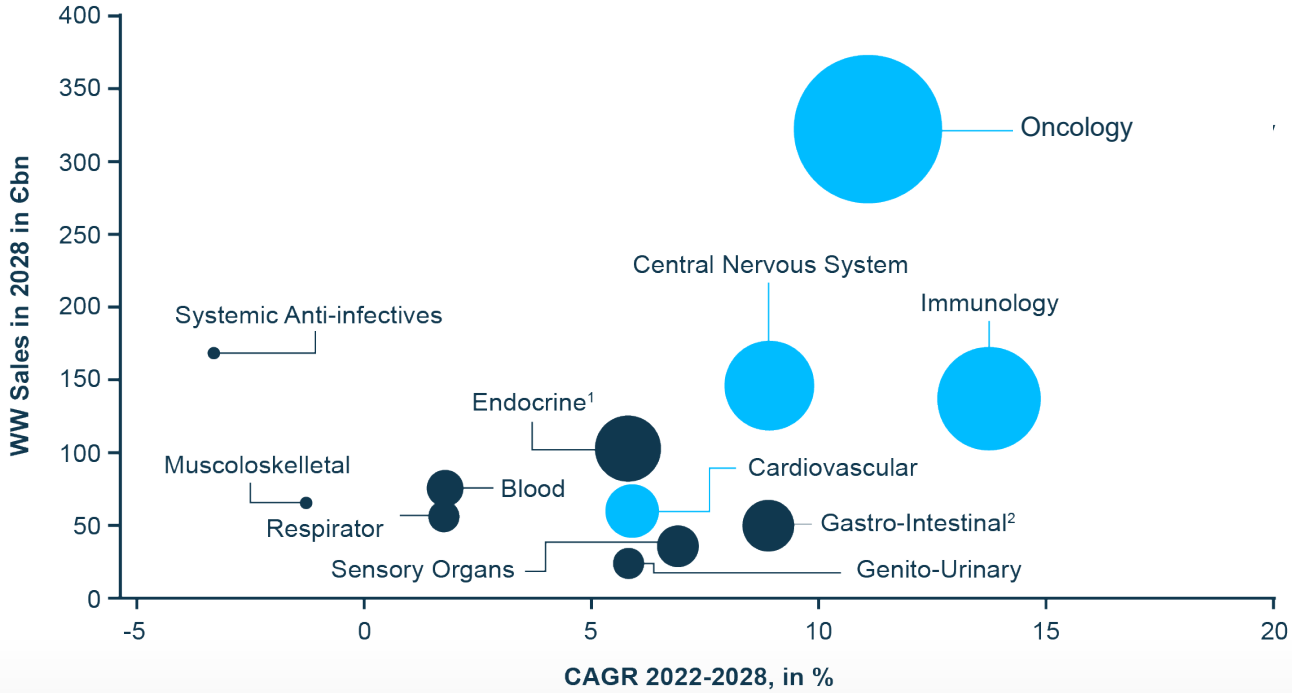
## *INNOVATION*

Mostly internal › Diversified R&D ecosystem

## *FOCUS*

Follow the science › Driven by science & highest unmet needs

# Innovation and Growth Potential as a Key Focus to Increase Value




= Focus areas

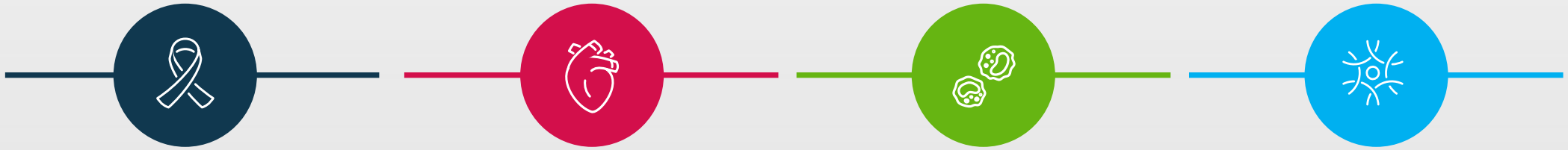
Bubble size represents absolute change in scales between 2022-2028, in case of a positive CAGR

Source: Evaluate Pharma; incl. OTC sales; May 8, 2023; [1] Endorine includes Obesity; [2] gastro-Intestinal includes OTC

# Refined Focus Areas with Highest Impact and Value Potential

Clear strategic mandates guiding decision making and resource allocation

| Oncology | Cardiovascular+ | Neurology & Rare Diseases | Immunology |
|---|---|---|---|
| **Become a Top Oncology Company** | **Remain Top player, shift to precision medicine** | **Advance a competitive Cell & Gene therapy pipeline** | **Build expertise and portfolio** |
| Drive leadership in focus areas, accelerate growth through competitive early-stage pipeline | Enhance our leadership in precision cardiovascular, nephrology and acute care | Drive and de-risk platform with focus on first-in-market potential | Advance our pipeline to build a presence and support other focus areas |

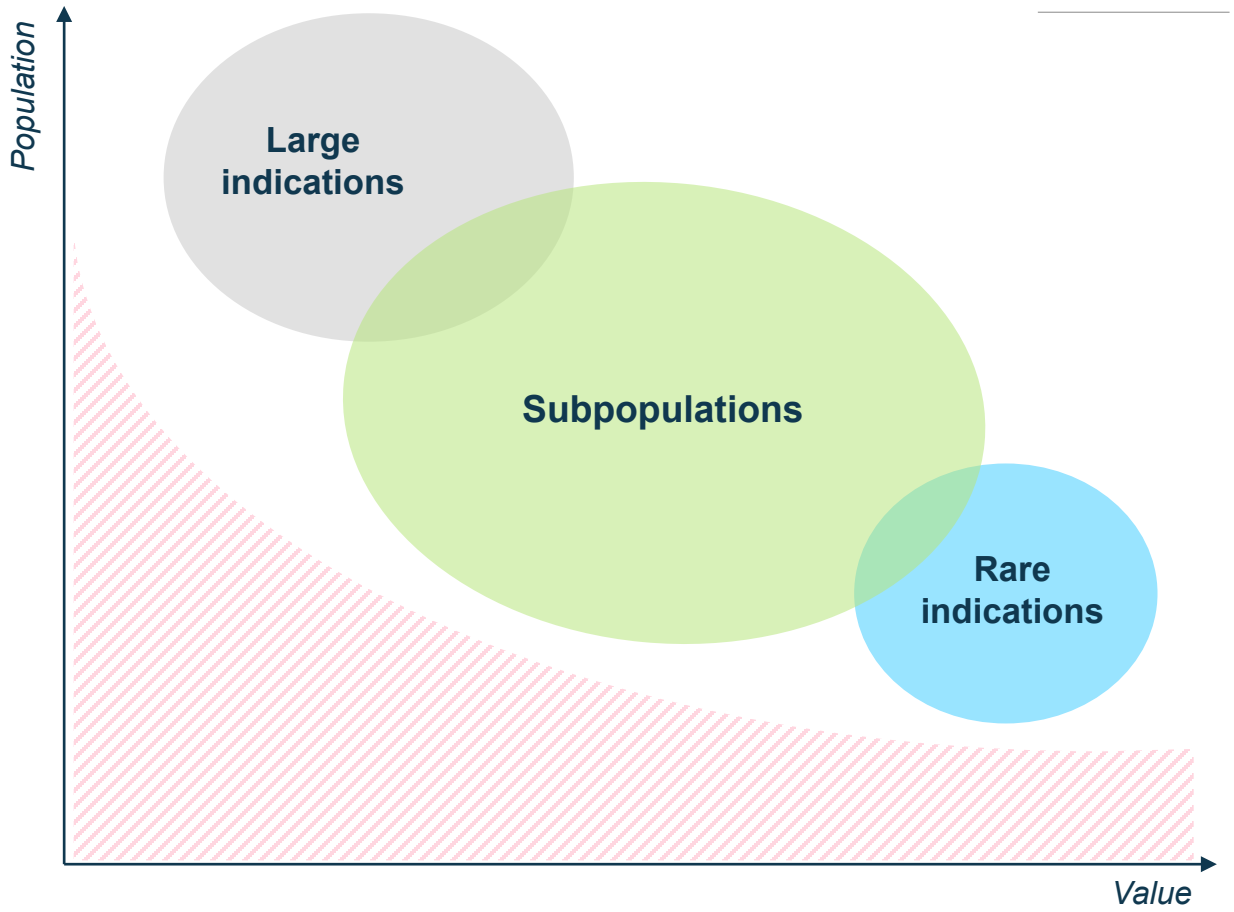


# Targeting the Sweet Spot of Precision Medicine Across our Focus Areas

## Through disease understanding and value potential assessment

- Address individual patients' needs to **achieve improved and sustainable health by delivering transformative medicines**: the right treatment, to the right patient, at the right time
- **Optimized outcomes** by focusing on highest unmet needs, value potential, differentiation and risk mitigation
- Open for disruption in large indications

*Illustrative*



# A Diverse and Innovative Modality Toolkit to Deliver our Ambition

## Delivering innovative and competitive medicines in our focus therapeutic areas

| | | | Oncology | Cardiovascular+ | Neurology & Rare Diseases | Immunology |
|---|---|---|---|---|---|---|
| **Small Molecules** | Small Molecules (SMOL)<br>RNA targeting<br>Protein degraders<br>Peptides<br>Conjugates | Bayer | ● | ● | | ● |
| **Protein Therapeutics** | Antibody Conjugates<br>Multispecific antibodies<br>Monoclonal antibodies | Bayer | ● | ● | | ● |
| **Radiotherapy** | Targeted Radiotherapy<br>Antibody \| SMOL \| peptide | Bayer | ● | | | |
| **Chemoproteomics** | Covalent binders<br>Heterobifunctional degraders<br>Molecular glues | vividion THERAPEUTICS | ● | ● | | ● |
| **Cell Therapy** | Pluripotent Stem Cells (PSCs) | BlueRock THERAPEUTICS | | ● | ● | ● |
| **Genetic Medicine** | Adeno-Associated Virus (AAV) based gene therapy | AskBio | ● | ● | ● | |
| | CRISPR-based gene editing | Mammoth Biosciences | | | | |
| | Non-viral gene delivery | ACUITAS THERAPEUTICS | | | | |

*Combined with Bayer in-house innovation capabilities*

● Bayer innovation capabilities ● Innovation capabilities added since 2019

# Reshaping R&D Execution Through Data Science and AI

Exploiting increasing convergence of biology and technology to continuously optimize our portfolio

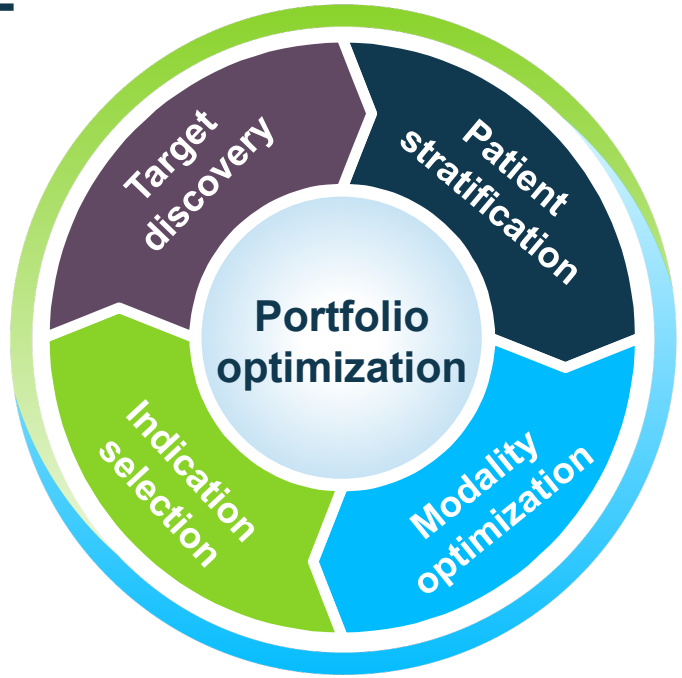
## PRIORITIES

// Dedicated **Data Science & AI organization** created in 2021

// Uncovering new biology harnessing the power of **multi-modal data**

// AI driven **compound optimization**

// **Automation** and **machine learning** accelerating clinical trials powered by **real world data**




## PARTNERSHIPS

Accelerating drug discovery with **Google Cloud**, applying machine learning for Quantum chemistry

**Schrodinger** collaboration to co-develop de novo design to accelerate drug discovery

Partnership with **Recursion** to strengthen digital drug discovery and advance new therapies

# Moving to Higher, Sustainable Level of R&D Productivity

## Supported by key levers

### INCREASE IN PTS

- // Moving toward precision medicine
- // Improved validation of targets and translation to patient - target disease link
- // Strategic investments in new biomarker approaches
- // Improved patient profiling and selection using advanced Data Science/AI approaches

### REDUCTION OF COSTS

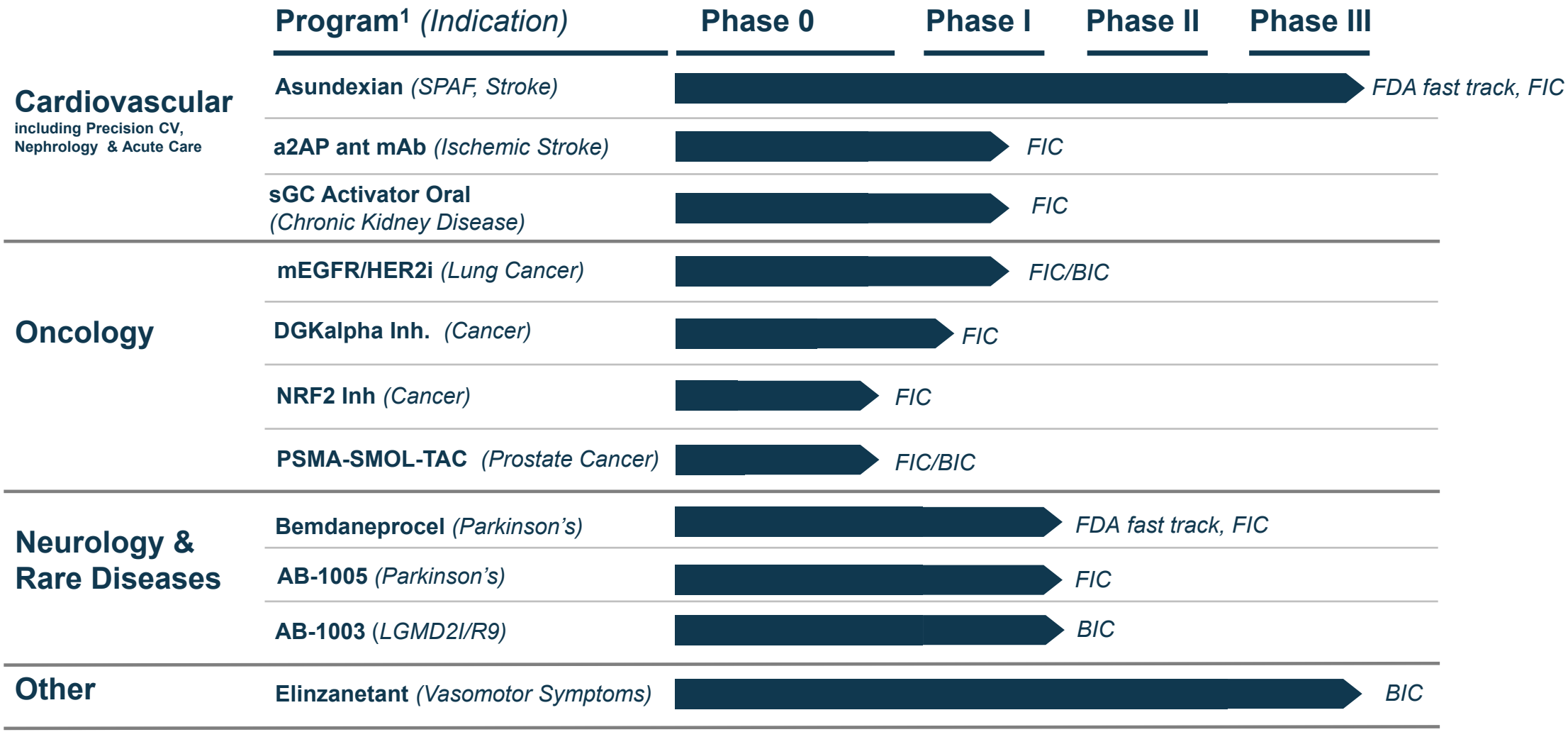
- // Digitization of clinical trials
- // Lean, innovative, adaptive clinical trial design in stratified population, as well as platform studies
- // Reduction of in-vivo/wet lab work by applying prediction tools
- // New ways of working leveraging organizational synergies

### DECREASE IN CYCLE TIMES

- // Improved governance and decision making (fail / accelerate fast)
- // Accelerate development from IND to launch through tailored development approaches
- // Unlock the potential of Real-World Data with AI and Machine learning. Automation and digitization enabling decentralized trails

# Pursuing Industry Leading Innovation Across all Focus Areas

Selected assets with innovation, differentiation and high value profile




[1] Selected assets out of 40+ development projects

# A Focused R&D Strategy to Deliver an Innovative, Differentiated and Sustainable Pipeline

## OUR FOCUS

**4 core Therapeutic Areas**

- Oncology
- Cardiovascular+
- Neurology & Rare Diseases
- Immunology

**6 modalities**

Small molecules, Protein Therapeutics, Radiotherapy, Chemoproteomics, Cell Therapy, Genetic medicine

**3 platform companies**

AskBio, BlueRock, Vividion

## OUR PRIORITIES

### Science & Portfolio

// Launch elinzanetant and asundexian
// Progress and accelerate high-value assets
// Focused investments in BD&L
// Maximize impact from platform companies
// Unlock full potential of precision medicine

### Productivity

// Excellence in execution to generate more value and improve capital efficiency in R&D
// Shift to asset-centric operating model
// Increase agility and dynamic resource allocation
// Accelerate data science & AI across R&D value chain

# Key Messages Today

- We have reshaped our approach to innovation guided by value, differentiation, feasibility, and our competencies.
- We have streamlined our portfolio towards precision medicine, with a narrower therapeutic area focus but a wider range of modalities.
- We will leverage partnerships, data science, new trial designs, biomarker technologies, and improved governance to accelerate our drug development processes and move to a higher, more sustainable R&D productivity.
- We are already starting to see a step change in the quality and differentiation of our new molecular entities with the vast majority offering the potential to be first- or best-in-class.

# *Making a Difference in Neurology & Rare Diseases*

Christian Rommel

# Bayer in Neurology & Rare Diseases

## Opportunity to become leaders in transforming patient care

### MARKET ATTRACTIVENESS

**High unmet medical needs**

// Many underserved or previously intractable diseases with high unmet need

**Paradigm shift in patient treatments**

// Transition from symptomatic treatment to transformative therapies addressing disease root causes with long-lasting clinical benefit

**Attractive growth market**

// Exciting scientific breakthroughs in Neurology and rapid advances in new modalities including CGT

// ~7000 known rare disease, 80% of which are genetic in origin


### BAYER'S KEY STRENGTHS

**Enabled by our existing capabilities**

// State-of-the-art technology platforms for cell and gene therapy

// Bundling capabilities of strong in-house teams, platforms and partnerships in key technologies such as gene editing and lipid nanoparticles

// Bayer know-how and experience across the value chain

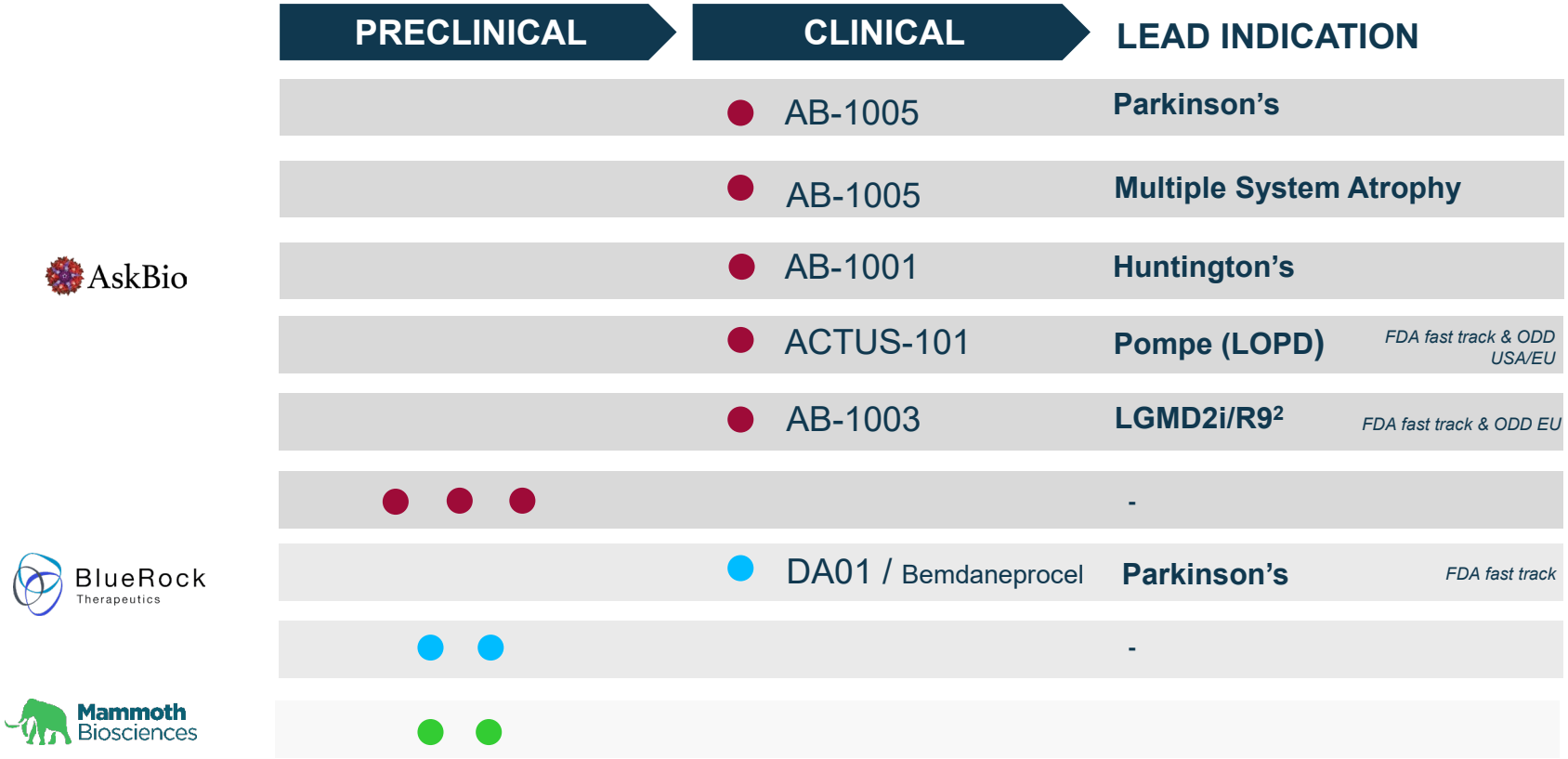
// Infrastructure and upscaling know-how

**Synergies with other therapeutic areas**

// Opportunity to address unmet needs at the intersection of cardiovascular and ophthalmology to leverage synergies

# Neurology and Rare Diseases Pipeline Overview

## Significant proportion of our cell & gene therapy pipeline to enable potential medical advances in NRD




### STRATEGIC PRIORITIES

**Further inclusion of BlueRock and AskBio** in Bayer's Innovation ecosystem, leveraging synergies while keeping them largely independent

Build a **competitive and differentiated portfolio** and de-risk assets and platform approach in clinical stage

Once derisked, identify **areas for scale and growth**

NRD Pipeline Overview - all platform companies' therapeutic areas ex-NRD not shown

# *Leveraging a Unique Platform to Build a Presence in Immunology*

Christian Rommel

# Bayer Entering Immunology

## Significant unmet medical need despite rapid scientific advances

### MARKET ATTRACTIVENESS

**High unmet medical needs**

// Many underserved diseases

// Globally increasing incidence & prevalence

**Robust research innovation**

// Advancing disease understanding, biomarker research to drive future precision therapies

**Potential for long-lasting remission**

// Novel precision targets empowered by new technology (incl. Machine Learning & AI) for better disease understanding

**Attractive growth market**

// Among top-growing pharma markets

// Efficient clinical trials and attractive PTS


### BAYER'S KEY STRENGTHS

**Enabled by our existing capabilities**

// Access to highly differentiated Vividion's chemoproteomics platform

// Highly differentiated small molecules library

// Covalent and non-covalent small molecules, direct functional modulators, degraders

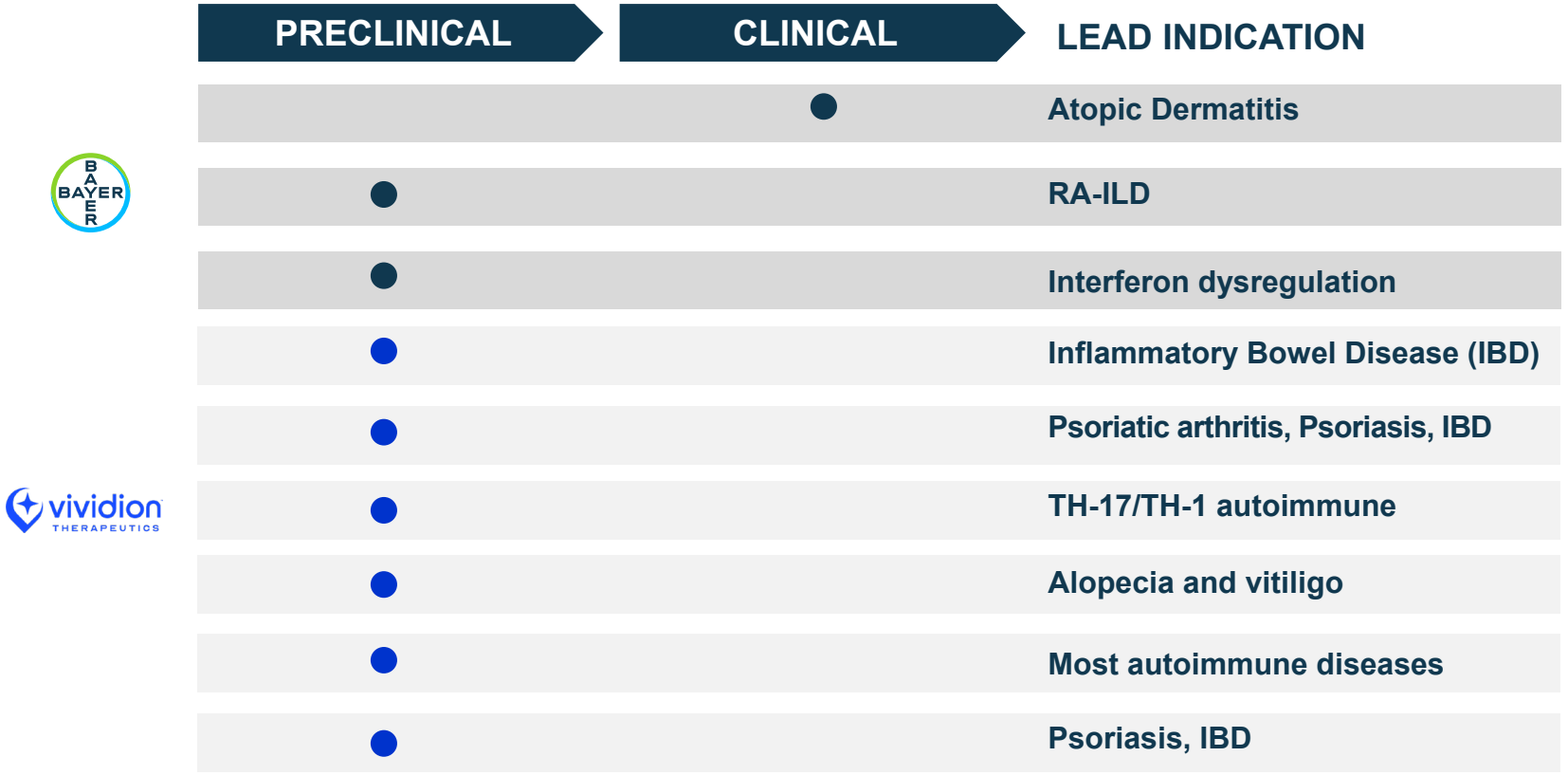
// Rapidly accelerating assets in preclinical and clinical development

**Synergies with other therapeutic areas**

// Relevant expertise enabling Bayer's other strategic focus areas

# Immunology Early Pipeline Overview

## Targeting central drivers of inflammation




### STRATEGIC PRIORITIES

Leverage existing capabilities to **fully enable Vividion platform** and realize synergies with Bayer R&D

**Develop strong foundation** and **accelerate data generation** to drive disease understanding

**Augment early-stage pipeline** through attractive external innovation once de-risked

# *Vividion Therapeutics: Removing the Boundaries of Druggability*

Aleksandra Rizo

# Key Messages Today

- While hundreds of proteins are known to be drivers of diseases, just ~10% can be drugged by current therapies
- Chemoproteomics technologies can be used to selectively target and bind to yet unaccessible proteins, thereby removing today's boundaries of druggability
- Vividion has a world leading industrial scale chemoproteomics platform based on a unique covalent custom build library that can identify potent and selective drugs in innovative and efficient way thereby unlocking the full potential of small molecule therapies
- Bayer's strength in small molecules enables significant synergies and ability to leverage Vividion's platform
- Vividion is advancing an attractive pipeline in Oncology and Immunology with first program to enter the clinic in 2023

# Company Overview

## SCIENTIFIC FOUNDERS

### BENJAMIN CRAVATT

**Professor and Co-Chair,**
Dept. of Molecular Medicine
The Scripps Research Institute
Member, Natl Academy of Sciences
2022 Wolf Prize in Chemistry

### PHIL BARAN

**Chair, Chemistry**
The Scripps Research Institute
McArthur Genius Award
Member, Natl. Academy of Sciences

### JIN-QUAN YU

**Professor, Chemistry**
The Scripps Research Institute
McArthur Genius Award

## COMPANY PROFILE

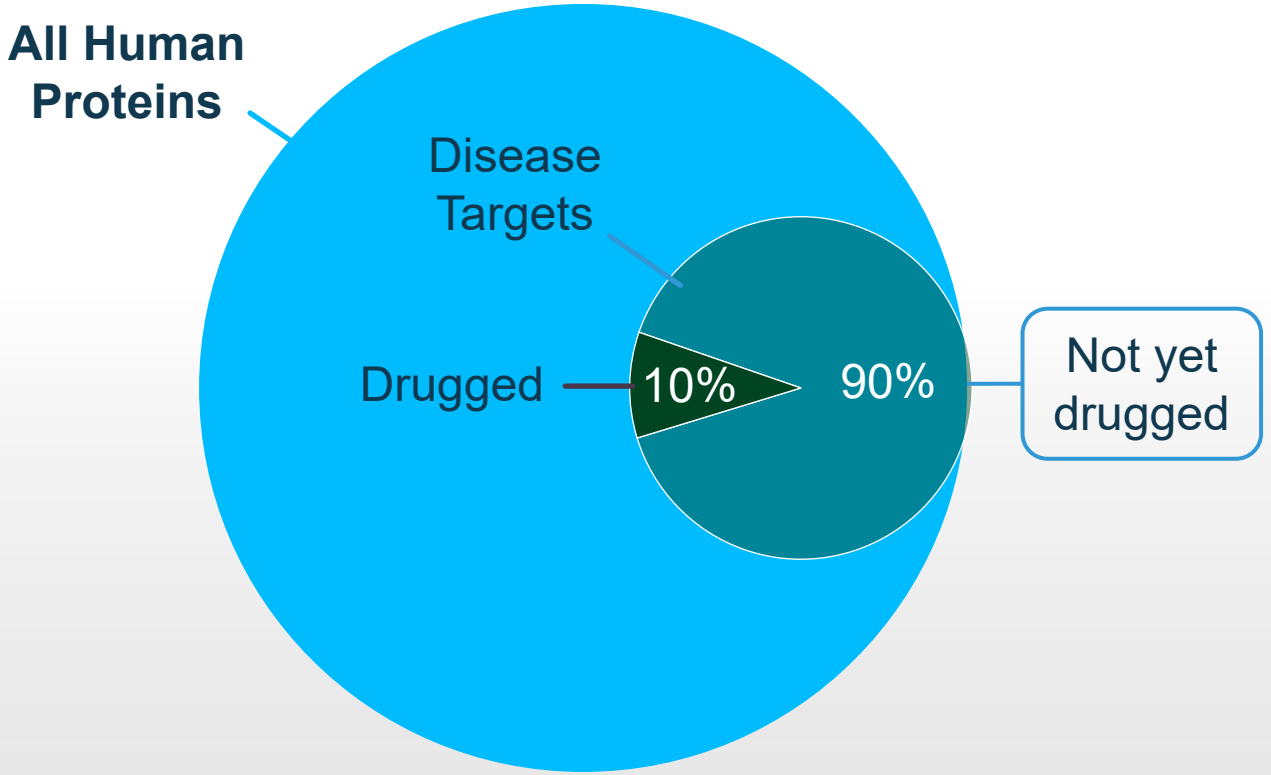
- **Small molecule drug discovery and development**
- **Operations initiated in 2017**
- **~200 employees**
- **8,000 m² of lab/office space in San Diego, CA**

# Bayer-Vividion Synergies


- Bayer acquired Vividion in August 2021
- Vividion's unique chemoproteomics platform fits well with Bayer's historical strength and expertise in small molecules
- Acquisition places Bayer and Vividion in a strong position to unlock undruggable targets and generate first-in-class novel drug candidates for the benefit of patients
- Through Bayer's "Arm's Length" operating model, Vividion operates autonomously and with full accountability to develop and advance its portfolio and technologies
- As a result of this structure, Vividion can maintain its entrepreneurial culture of a startup while accessing Bayer's global resources and strengths to accelerate transformation and advance new scientific breakthroughs

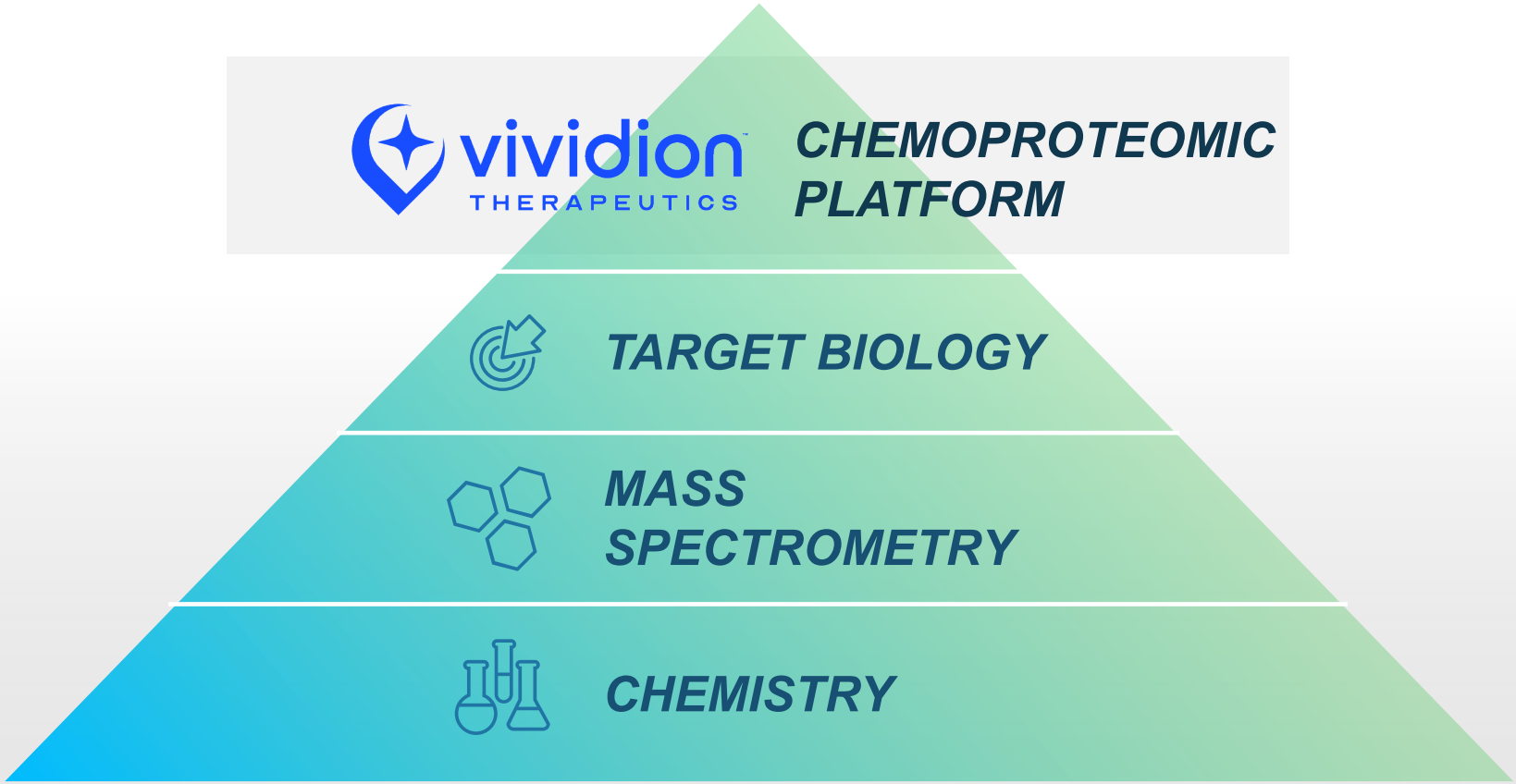
# Limitations of Conventional Small Molecule Drug Discovery

- 100s of human proteins are known to cause disease
- Only ~10% of these disease-causing proteins/targets are drugged by current therapies[1]
- Despite advances in genomics, structural biology, and high-throughput screening, most disease relevant targets are inaccessible to conventional chemistry – perceived as pocketless or undruggable



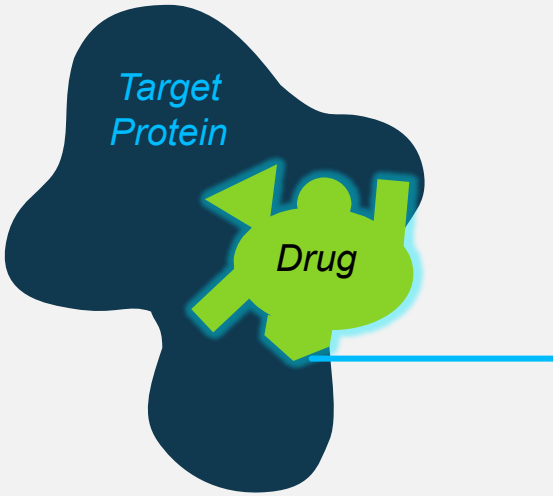

[1] Source: Oprea et al.,Nature Reviews Drug Discovery, 17: 317-332, 2018.

# Potential to Transform Small Molecule Drug Discovery



# Vividion's "Covalent First" Platform Expands Druggable Space

## REVERSIBLE DRUG



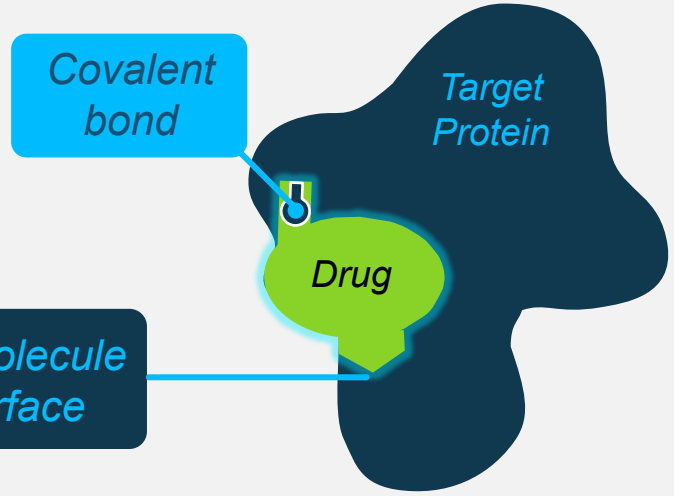

**Drug-like potency and selectivity requires:**

- // Large contact surface between drug and protein
- // Multiple specific types (polar) of interactions
- // **Deep pockets**

Drugs for targets **within druggable classes**
(e.g., enzymes, receptors)

*Protein-small molecule interaction surface*

## VIVIDION "COVALENT FIRST" DRUG




**Drug-like potency and selectivity requires:**

- // Small contact surface and minimal polar interactions that guide covalent bond formation
- // Reactive amino acid (cysteine)
- // **Shallow pockets**

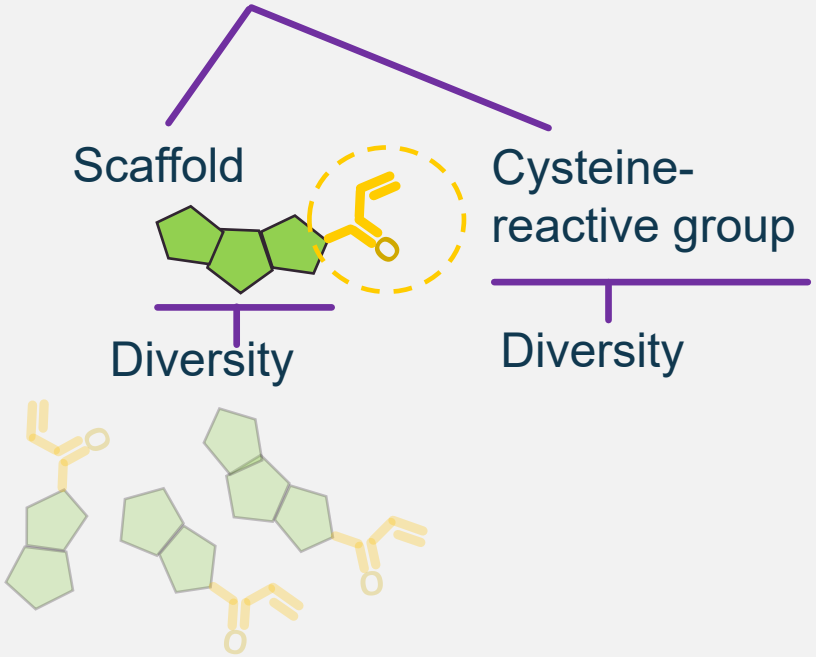
Allows for druggability **of all/any disease relevant targets**
(e.g., enzymes, receptors, transcription factors, ubiquitin ligases)

# Foundations of the Vividion Platform

## 1. THE CHEMISTRY

### Unique Covalent Small Molecule Library

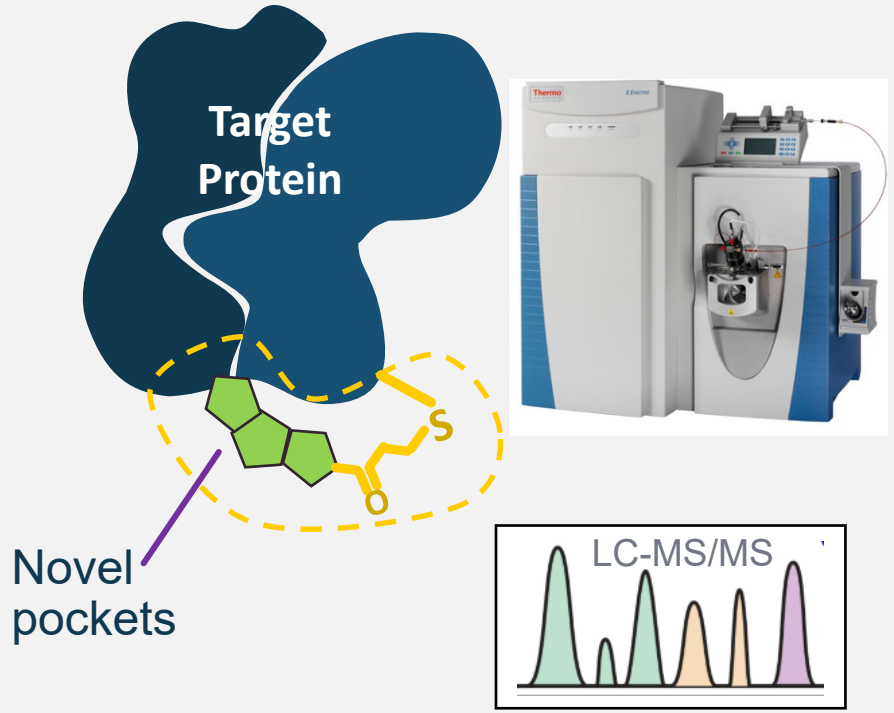
VVD compounds are comprised of 2 distinct structural elements:




## 2. THE PLATFORM (ASSAY)

### Proteome-wide Footprinting of Small Molecule-Target Interactions in Native Systems

CELLS / LYSATES / TISSUE



# The Innovation and Efficiency of the Vividion Drug Discovery Platform

## VIVIDION "COVALENT FIRST" CHEMOPROTEOMICS APPROACH

Public Databases

Human Genetics

Structural Biology

Literature

Propose and Evaluate
**Many Targets**

ATG16L1, IRF5, PKCO, MyD88, IRF8, IFIH1, USP30, PRMT5, DTL, KRAS, HTT, A20, YAP1, GBA, SMRCA2, CRBN, STAT3, HUWE1

Prioritize Targets

Relative Interest Level

1. Evaluate Sites
2. Select Proteome
3. Build Targeted Screening Method
4. Execute Screen
5. Evaluate results

Actionable Hits

## CONVENTIONAL SMALL MOLECULE DISCOVERY APPROACH

Public Databases

Human Genetics

Structural Biology

Literature

*Filtered for druggable classes*

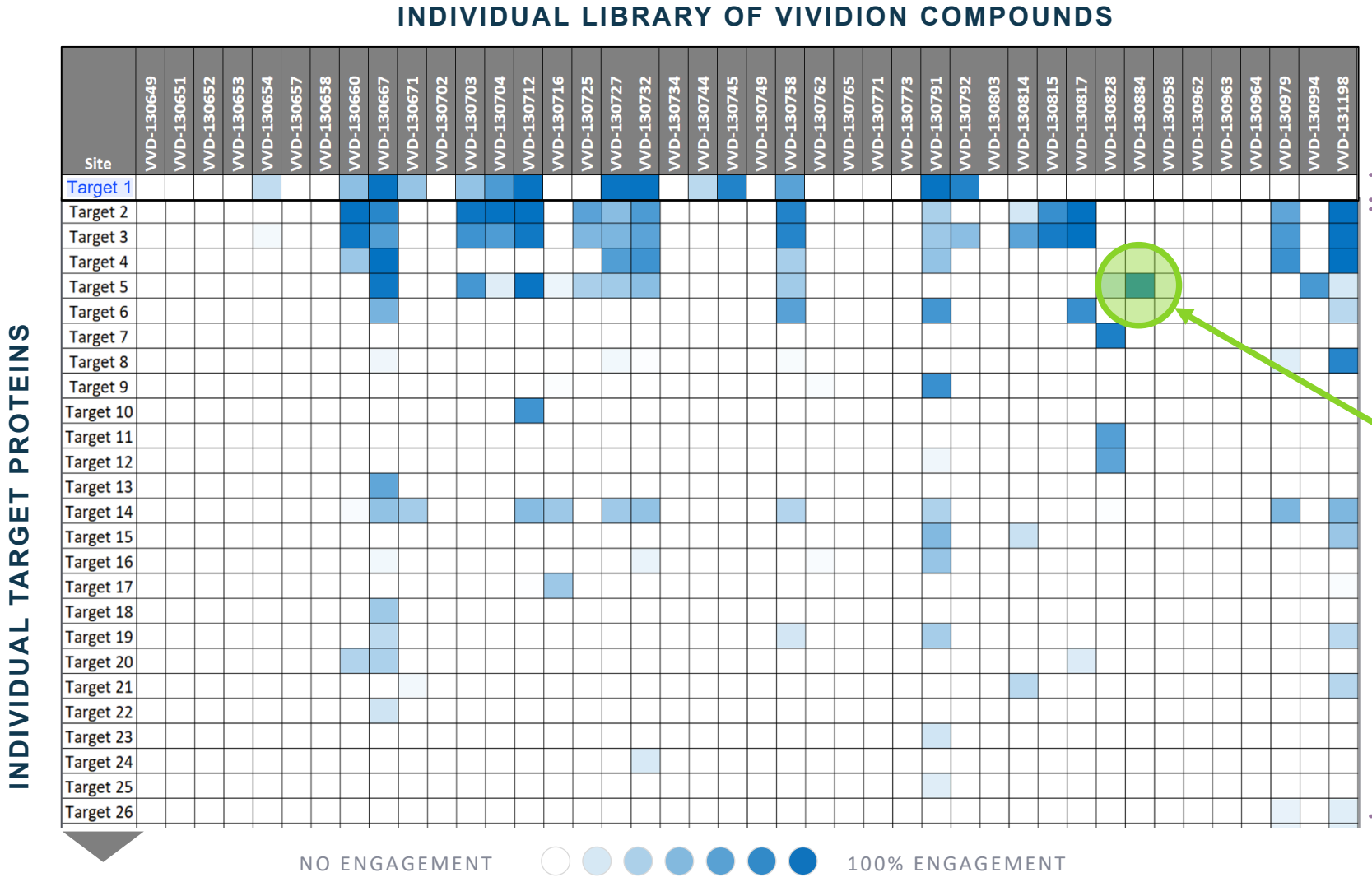
**Target**

Functional Assay Development

**HTS Screen**

**Hits against a target**

# Industrial Scale Chemoproteomics Platform Accelerates Discovery of Novel Shallow Pockets



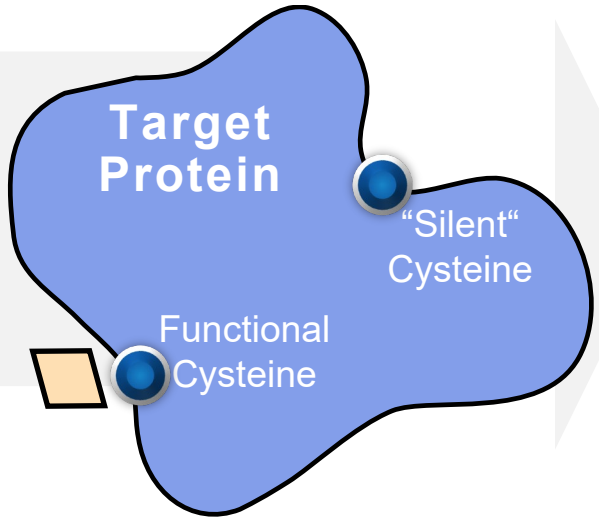

Most screening assays only capable of tracking one target at a time, usually in unnatural settings

**Vividion technology** simultaneously tracks small molecule interactions against 1000s of targets in natural settings to discover **potent and selective compounds at the same time**

# Range of Approaches to Modulate Undruggable Targets

First-in-class and/or Best-in-class Small Molecule Therapeutics

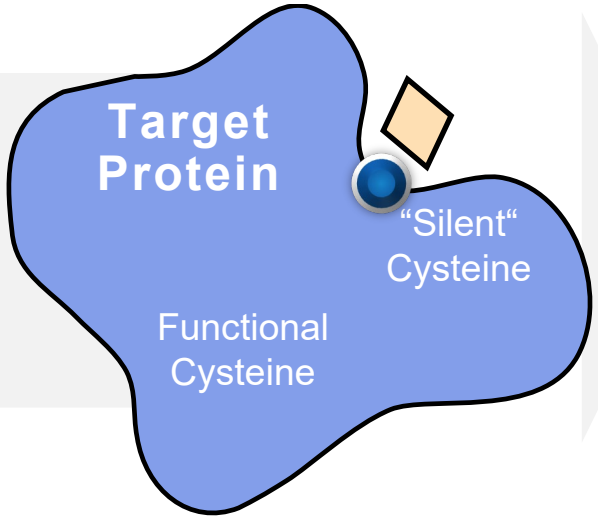
**TARGETING FUNCTIONAL SITES**




**DIRECT FUNCTIONAL MODULATORS (DFMs)**

// Allosteric Inhibitors
// Allosteric Activators
// Protein-protein Interaction (PPI) Inhibitors

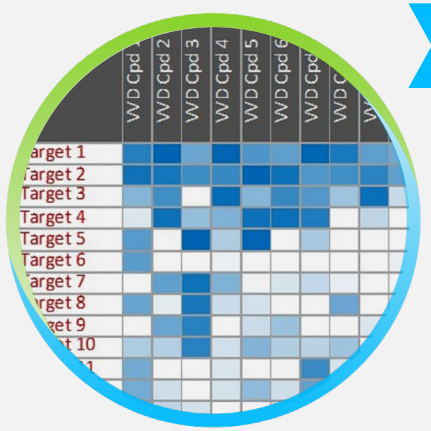
**TARGETING NON-FUNCTIONAL SITES ("SILENT LIGANDS")**



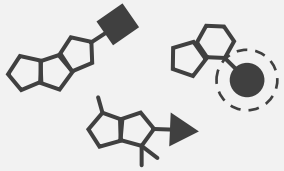

**PROTEIN DEGRADERS**

// Functionalize silent binders to enable targeted protein degradation

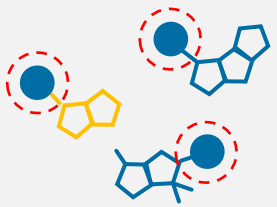
# Continuous Library Expansion Allows for Pipeline Growth and Durable Competitive Advantage



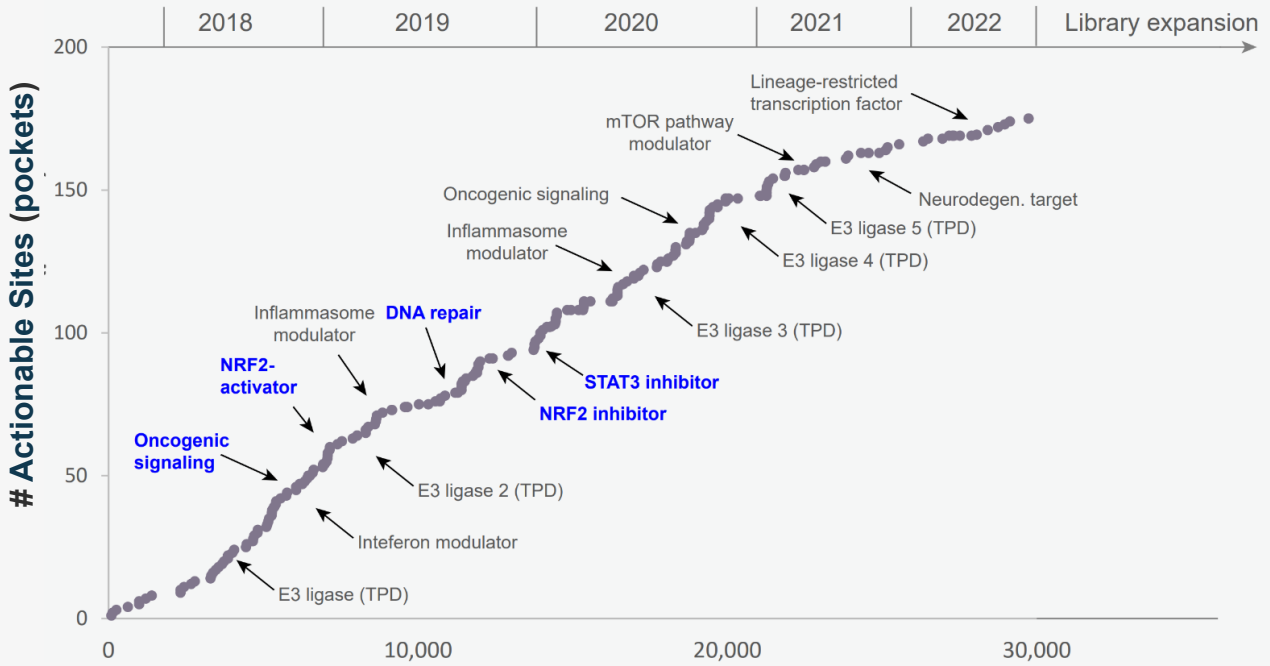

**Vividion unique covalent chemistry library**



**Screening & iterative learning**

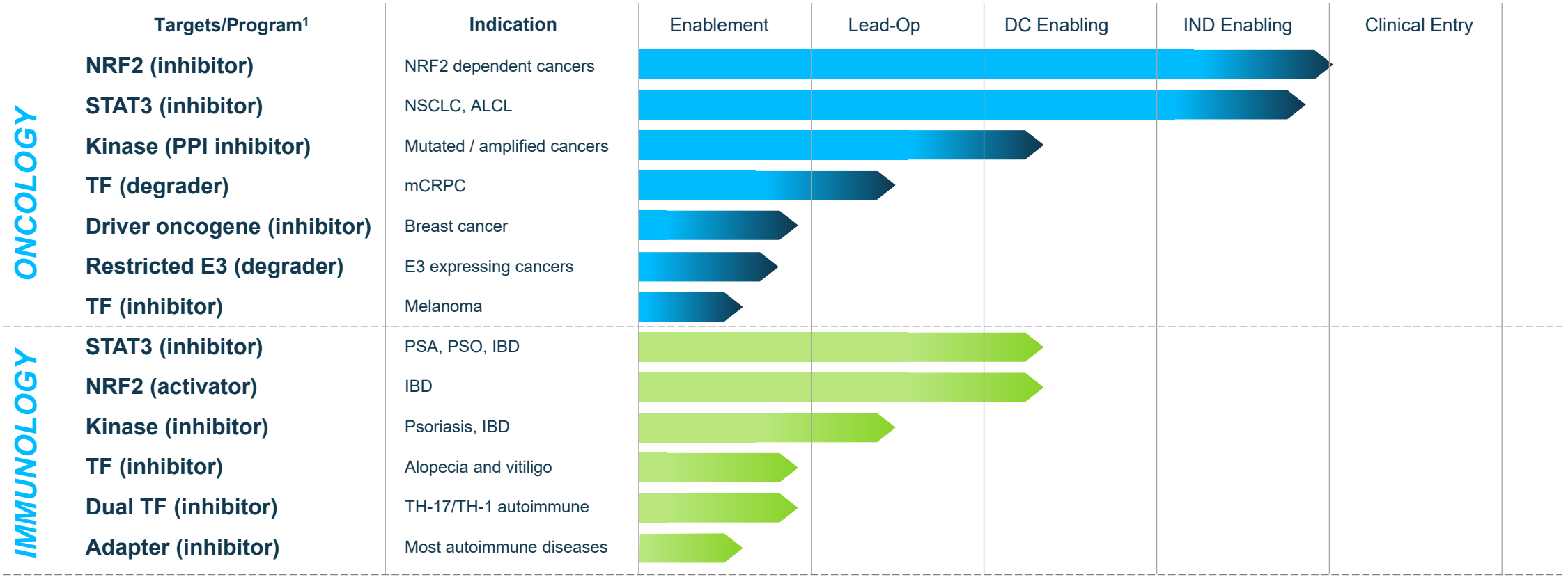


**Proteome educated library innovation**



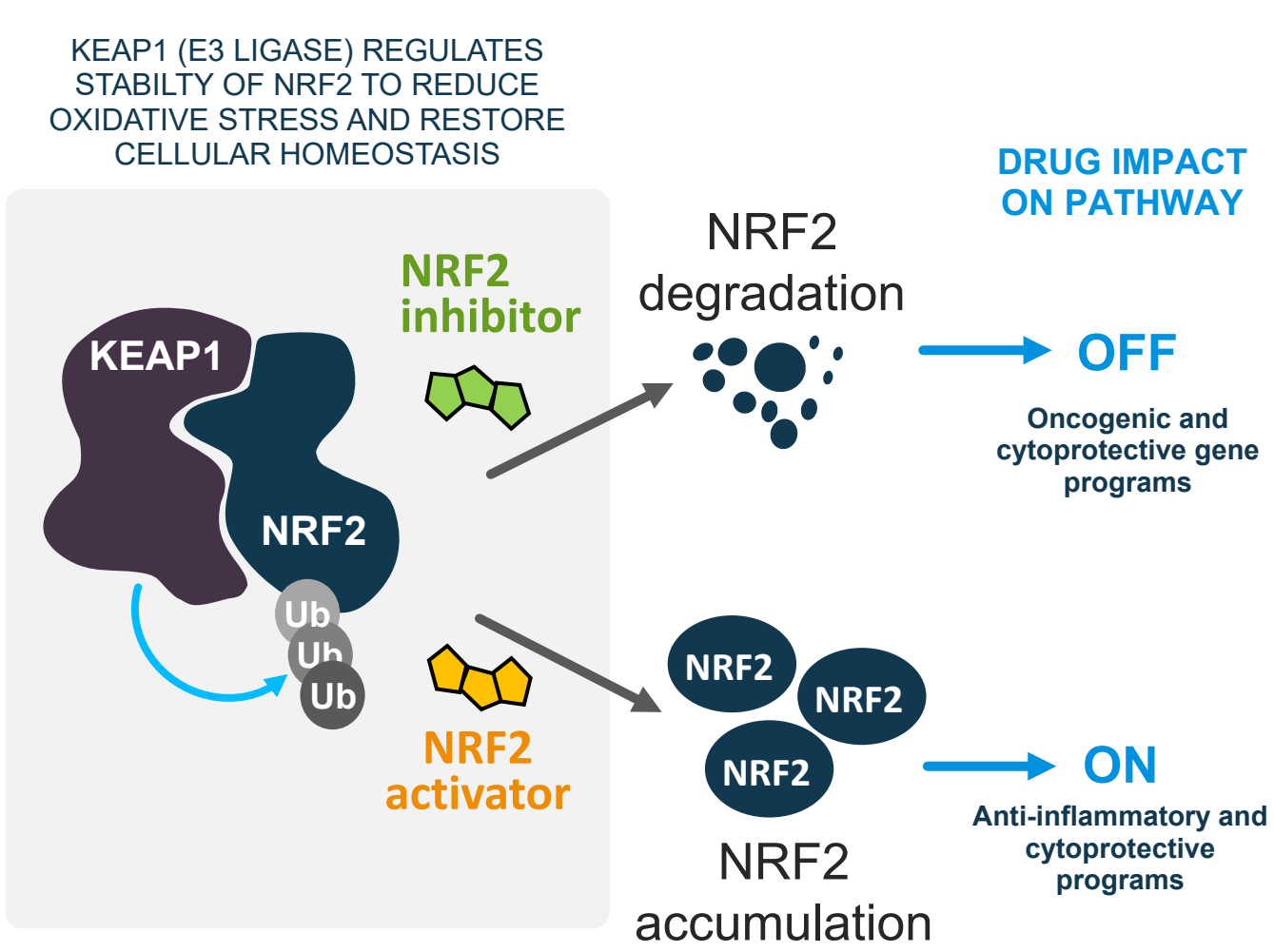
# Unique Pipeline of First or Best in Class Programs

## Pipeline Progress as of 2Q2023




[1] Multiple Roche-partnered programs in different stages of development; milestone payments can be expected per agreement

# Targeting Traditionally Undruggable Transcription Factor NRF2 Enables Two Distinct MOAs to Address Oncology and Immunology Diseases




## ONCOLOGY: NRF2 inhibitor

- // Increase KEAP1-directed proteasomal degradation of NRF2
- // Constitutive activation of NRF2 function enriched in multiple solid tumors (lung sq/ad, esophageal sq/ad, head & neck, bladder cancer)
- // Potential to broaden the patient population further (pan-cancer approach) in combination with SOC chemotherapy

**Upcoming milestone:** VVD-037 expected to enter the clinic by end of 2023

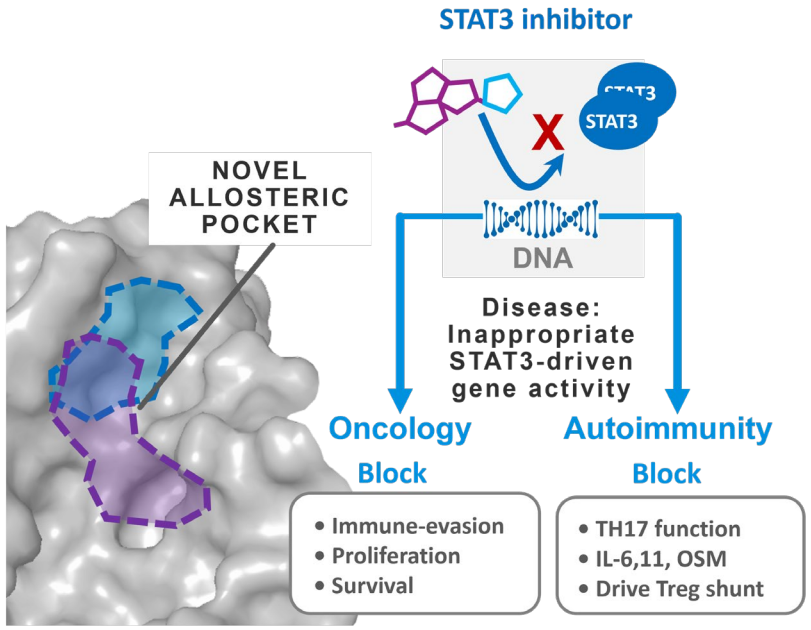
## IMMUNOLOGY: NRF2 activator

- // Decrease KEAP1-directed proteasomal degradation and drive NRF2 accumulation
- // Initial indication IBD where pre-clinical evidence demonstrates impact on all three pathological domain levels (cytoprotective/tissue preservation, leukocyte trafficking and inflammatory mediator production)
- // Potential for other inflammatory diseases where oxidative damage, insufficient stress resistance and chronic inflammation contribute to the underlying pathophysiology (e.g., COPD, NASH)

**Upcoming milestone:** Potential IND by end 2024

# STAT3 is Traditionally Undruggable Transcription Factor That Plays Key Roles in Multiple Oncology & Immunology Diseases

## STAT3




**Utilizing same mechanism/inhibitor in two different disease areas offers potential to address multiple patient populations**

## ONCOLOGY

// Prevents STAT3 DNA binding and blocks downstream gene transcription

// Addresses primary checkpoint therapy resistance mechanism in genetically defined patient population (LKB1 mutant lung adenocarcinoma)

// Additional opportunity in T-cell lymphomas where STAT3 GOF mutation and/or high-pSTAT3 levels supports STAT3 dependence

**Upcoming milestone:** VVD-850 potential IND by end of 2023

## IMMUNOLOGY

// Blockade of STAT3 DNA binding prevents both IL-6 cytokine family and IL-23 signaling for inhibition of TH17 cell function with novel potential to simultaneously increase Treg frequency

// Central role in multiple pathogenic cytokine signaling pathways hence potential to treat wide spectrum of human autoimmune diseases

// Initial entry in psoriasis & psoriatic arthritis followed by IBD

**Upcoming milestone:** Potential IND by end of 2024

# Key Messages Today

- While hundreds of proteins are known to be drivers of diseases, just ~10% can be drugged by current therapies
- Chemoproteomics technologies can be used to selectively target and bind to yet unaccessible proteins, thereby removing today's boundaries of druggability
- Vividion has a world leading industrial scale chemoproteomics platform based on a unique covalent custom build library that can identify potent and selective drugs in innovative and efficient way thereby unlocking the full potential of small molecule therapies
- Bayer's strength in small molecules enables significant synergies and ability to leverage Vividion's platform
- Vividion is advancing an attractive pipeline in Oncology and Immunology with first program to enter the clinic in 2023

# *Driving Leadership in Focus Areas of Oncology*

Dominik Ruettinger

# Key Messages Today

- Our Oncology R&D strategy is based on precision drug development which enables fast identification of the most promising targets and commercially viable programs
- We focus on expanding the druggable target pool, developing "kinder medicines", and addressing resistance
- We are rapidly building an early pipeline in precision molecular oncology and next gen immuno-oncology
- Targeted radiotherapies (TRT) provide another highly attractive opportunity in oncology - we have a wealth of expertise and experience

# Oncology will Remain a Major Segment of the Pharma Market and we have a Strong Foundation to Build on

## Oncology opportunity

### MARKET ATTRACTIVENESS

**High unmet need**

// Growing health burden, with cancer being the second leading cause of death at present

// 30M new cases annually expected by 2040

**One of the largest and fastest growing segments**

// 2021-28 CAGR of 12%, expected to reach >€300bn by 2028

**Disruptive innovation in Oncology**

// Access to “undruggable” targets, new biomarker approaches & diagnostic tools create numerous opportunities for new precision therapeutics


### BAYER'S KEY STRENGTHS

**Scientific and clinical expertise**

// SMOL chemistry and peptide therapeutics

// Vividion as leaders in chemoproteomics

// Targeted Radiotherapy (TRT)

// GI, GU (notably prostate) and other high unmet need cancers

**Commercial capabilities**

// Successfully launched several assets

Nexavar (sorafenib) tablets · Stivarga (regorafenib) tablets · Xofigo radium Ra 223 dichloride · Aliqopa (copanlisib) · VITRAKVI (larotrectinib) · NUBEQA (darolutamide)

**6**

Approved medicines

**€1.8bn**

2022 Oncology Revenue

Source: EvaluatePharma (July 2022), Pharmaprojects (Oct 2021); IQVIA Pharma Deals (January 2021); McKinsey analysis

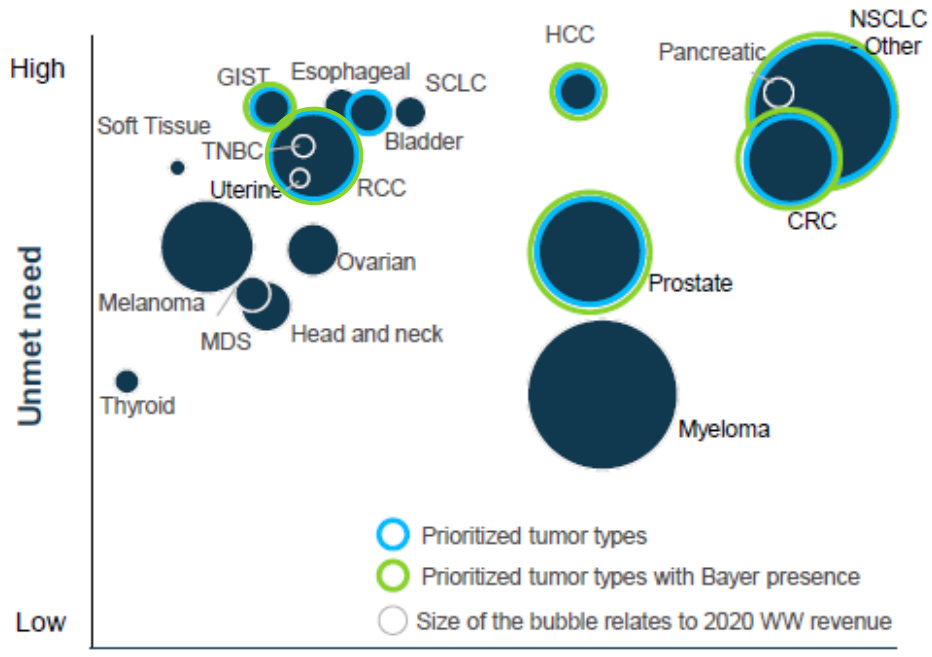
# Focus Where External Opportunity Meets Internal Strength

**SCIENTIFIC FOCUS:** PRECISION DRUG DEVELOPMENT

- Targeted Radionuclide Therapies (TRT)
- Precision Molecular Oncology (PMO)
- Next Generation Immuno-Oncology (IO)

- **Genitourinary (GU)** Prostate, Bladder, Renal cancers
- **Gastrointestinal (GI)** Colorectal, Liver, Gastric cancers
- **Lung Cancer** (NSCLC)
- **Other Tumors** with high unmet need

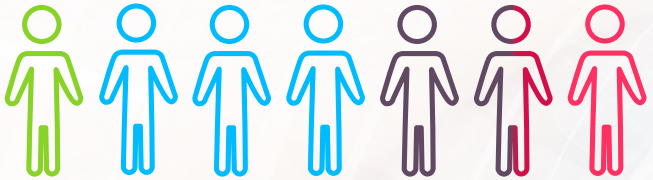
**(PROJECTED) UNMET NEED**



# A Rapidly Expanding, Changing Patient Population

## Patients are younger, diagnosed earlier, increasingly treatment resistant

**TODAY**



**FUTURE**

**OUR FOCUS**

- // High impact and kinder medicines
- // Higher selectivity for target
- // Expanding the pool of "druggable" targets
- // Modalities/Targets working regardless of mutational status, pre-treatments e.g., TRT
- // Disease-centric drug development

= Early onset cancer patient (<50 years old)

= Early diagnosed patient

= GI, GU, and lung Cancers (predicted increase annual incidence > 20% )

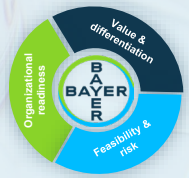
= Cancer patient (cured)

Source: Nat Rev Clin Onc 2022;19:656 Nat Med 2023;29:1113 Cancer Research UK, https://www.cancerresearchuk.org/health-professional/cancer-statistics/worldwide-cancer/incidence, accessed June 2023

# We aim to Meet the Needs of Cancer Patients with Precision Drug Development

Identifying high impact and commercially viable programs earlier

## Precision Drug Development




**Right Target** — **Biology** + **Defined patient** + **Measurable impact**

&

**Fit for purpose modality**

Leverage Bayer strengths in small molecules, biologics and TRT

vividion THERAPEUTICS

**Driven by value & differentiation**

Considering elements such as FIC/BIC, pricing power, unmet need & competitive intensity

**Increase productivity & success rate of delivering Precision Medicines that patients need**

# Oncology – Pipeline Update[1] (as of Jun 16, 2023)

## Rapidly building a balanced portfolio with 3 new clinical entries in 2023

| Candidate medication | Indication | Modality | Compound Origin | Phase 0[2] | Phase I | Phase II | Phase III |
|---|---|---|---|---|---|---|---|
| **Darolutamide** (AR Inhibitor) | **Prostate Cancer** (mHSPC) *(ARANOTE)* | Small Molecule | Orion | | | | |
| | **Adjuvant Prostate Cancer** *(DASL-HiCaP)*[3] | Small Molecule | Orion | | | | |
| | **Prostate Cancer with Biochemical Recurrence after Curative Radiotherapy** *(ARASTEP)* | Small Molecule | Orion | | | | |
| **Copanlisib** (PI3K Inhibitor) | **Non-Hodgkin Lymphoma** (CHRONOS-4) | Small Molecule | Bayer | | | | |
| **Regorafenib** (combi Nivolumab) (BAY 734506) | **Solid tumors** (recurrent or metastatic) | Small Molecule | Bayer | | | | |
| **mEGFR/HER2 Inhibitor** *(BAY 2927088)* | **Advanced Non-small Cell Lung Cancer with EGFR Mutation and/or HER2 Mutation** | Small Molecule | Bayer/Broad Institute | | | | |
| **DGKzeta Inhibitor** *(BAY 2965501)* | **Advanced solid tumors** | Small Molecule | Bayer/DKFZ | | | | |
| **CCR8 Ab** *(BAY 3375968)* | **Advanced solid tumors** | Protein Therapeutics | Bayer | | | | |
| **Elimusertib** (ATR Inhibitor) *(BAY 1895344)* | **Advanced solid tumors, Non-Hodgkin's Lymphoma, Mantle Cell Lymphoma** | Small Molecule | Bayer | | | | |
| **AhR Inhibitor** *(BAY 2416964)* | **Advanced solid tumors** | Small Molecule | Bayer/DKFZ | | | | |
| **DGKalpha Inh** *(BAY 2862789)* | **Cancer** | Small Molecule | Bayer/DKFZ | | | | |
| **PSMA TAC** *(BAY 3546828)* | **Advanced Prostate Cancer** | Radiotherapy | Lantheus (prev. Progenics) | | | | |
| **PSMA SMOL TAC** *(BAY 3563254)* | **Advanced Prostate Cancer** | Radiotherapy | Noria Therapeutics/PSMA Therapeutics | | | | |
| **VVD NRF2 Inh** *(BAY 3605349)* | **Cancer** | Small Molecule | Vividion | | | | |
| **VVD STAT3 Inh** *(BAY 3630914)* | **Cancer** | Small Molecule | Vividion | | | | |

Focus today

Protein Therapeutics | Cell Therapy | Contrast Agent | Genetic Medicine | Radiotherapy | Small Molecule

[1] Bayer and partner sponsored + 3rd party label enabling studies with first patient first visit [2] Pre-clinical selected assets on path to IND [3] Co-operative group trial led by Australian and New Zealand Urogenital and Prostate Cancer Trials Group (ANZUP)

# mEGFR/HER2i *(BAY 2927088):* Targeting Underserved NSCLC Mutations

Covalent and potent molecule with high selectivity for mutants over wild-type EGF receptor

PHASE I

## UNMET NEED

// Exon 20 insertion (ex20ins) mutations in EGFR and HER2 in NSCLC are associated with poor patient prognosis and resistance to first- and second-generation TKIs

// New therapies are also needed to overcome secondary resistance mutations (eg EGFR C797X) to TKI therapy as well as toxicity from wtEGFRi

// Limited efficacy and tolerability of recently approved treatments for EGFR exon20ins

## PROFILE & MODE OF ACTION

// Oral, reversible, potent TKI targeting EGFR and HER2 driver mutations, including ex20ins and EGFR C797X acquired resistance mutations

// High selectivity for mutant forms vs. wild-type EGFR

## ADDRESSABLE PATIENT POPULATION

| Indication | Patients |
|---|---|
| Advanced Non-small Cell Lung Cancer with EGFR mutations or HER2 mutations 1L and 2L | 1L - ~20K patients<br>2L ~9K patients<br>US, EU5 & Japan |

## ASSET POTENTIAL

| Indication | Asset Potential |
|---|---|
| Advanced Non-small Cell Lung Cancer with EGFR mutations or HER2 mutation | ●●○ |

●○○ <€500m ●●○ €500m–€1bn ●●● >€1bn

## CURRENT STATUS + NEXT MILESTONES

FPFV October 2021, ongoing expansion cohorts to complete in 2023

# mEGFR/HER2i *(BAY 2927088)*: Key Preclinical Data

Indicates potential for high clinical activity with reduced EGFR-mediated toxicities

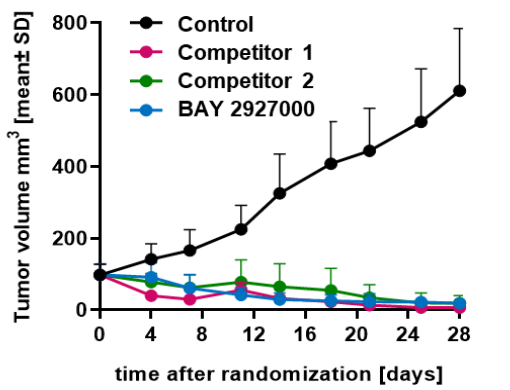
PHASE I

## PRECLINICAL DATA

// Strong activity and selectivity for mutants vs. wild-type EGFR

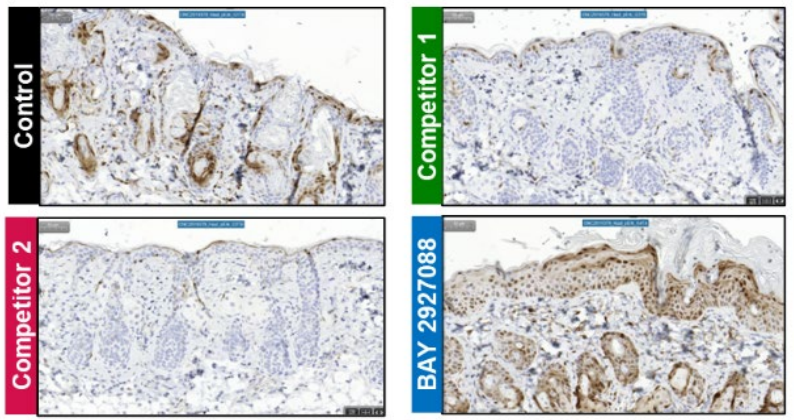
// Ongoing FiH trial in patients with advanced NSCLC harboring specific EGFR or HER2 mutations

**High potency in EGFRex20ins tumor models**




EGFRex20ins model - LXFE 2478ASVins

**Wild-type EGFR signaling in murine skin is preserved**




Brown staining: active wtEGFR signaling (pERK1/2)
3 hours after application compounds

// BAY 2927088 is highly potent in EGFR/HER2 exon20ins and EGFR C797S in vitro and in vivo

// BAY 2927088 is less potent on EGFR wild-type: Treatment at efficacious dose does not affect wild-type EGFR activity in murine skin – in contrast to competitors

# DGKa/z (*BAY 2965501 / BAY 2862789*): Inhibiting Diacylglycerol Kinases to Overcome Immunosuppression

## Highly selective DGK inhibitor for cancer immunotherapy with first-in-class potential

PHASE I

### UNMET NEED

// Most cancer patients do not derive clinical long-term benefit from immune checkpoint inhibitors (ICIs) due to primary or acquired resistance.

// Multi-indication asset for immune sensitive tumors and potential to address immune checkpoint inhibitors resistance

### PROFILE & MODE OF ACTION

// Modality: SMOL

// DGK inhibition can overcome an immuno-suppressive tumor environment with a differentiated mode of action: enhancement of suboptimal T cell priming against low-affinity tumor antigens and (re-) activation of silenced T-cells

// The inhibition of DGKz and DGKa with 2 highly selective NMEs represents a First in Class and Best in Class multi-indication potential in immuno-oncology with monotherapy and combination options

### ADDRESSABLE PATIENT POPULATION

| Indication | Patients |
|---|---|
| Advanced Non-small Cell Lung Cancer, PD-1 Relapsed/Refractory | ~120k patients US, EU5 & Japan |

### ASSET POTENTIAL

| Indication | Asset Potential |
|---|---|
| NSCLC, PD-1 R/R | ●●● |

●○○ <€500m ●●○ €500m–€1bn ●●● >€1bn

### CURRENT STATUS + NEXT MILESTONES

FPFV November 2022 (DGKz). Anticipated completion of dose escalation mid of 2024
FPFV expected Q3 2023 (DGKa). Anticipated completion of dose escalation H2 2024

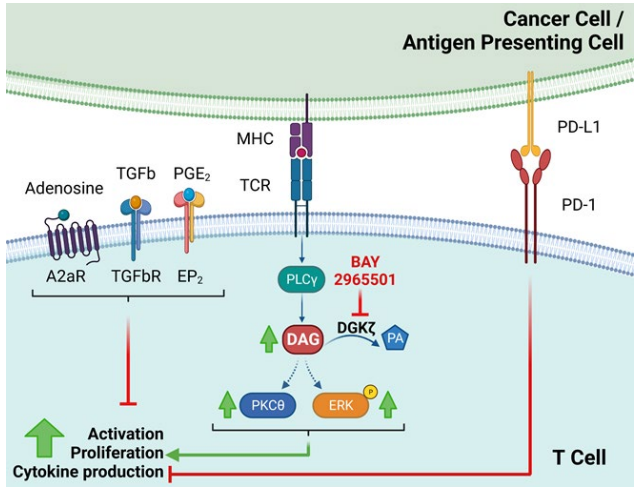
# DGKz (*BAY 2965501*): Key Preclinical Data

Highly selective DGK inhibitor for cancer immunotherapy with first-in-class potential

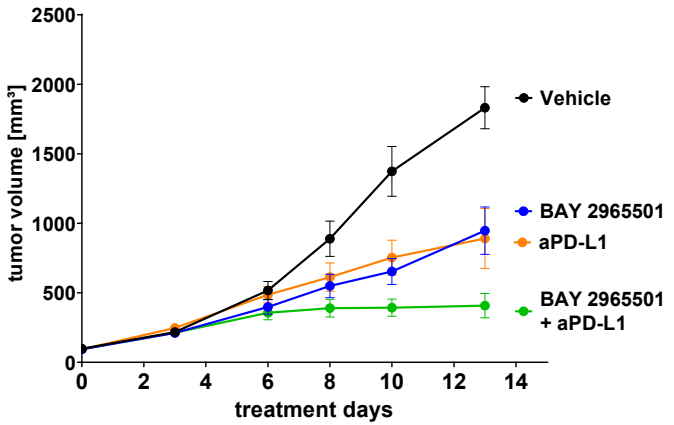
PHASE I

## PRECLINICAL DATA

### DGKZ ACTS AS AN INTRACELLULAR IMMUNE CHECKPOINT




### ANTI-TUMOR ACTIVITY COMPLEMENTARY TO ANTI PD-L1 ANTIBODY




### DGK INHIBITION INCREASES T-CELL ACTIVATION

// via enhancement of suboptimal T-cell priming against low-affinity tumor antigens

// via (re-) activation of exhausted T-cells regardless of suppressive ligands in tumor microenvironment (e.g. PD-L1, TGFβ, PGE2)

Source: Offringa, Kirchhoff et al., AACR 2023

# CCR8 *(BAY 3375968)*: Reactivating the Immune Response Against Tumors

Depleting suppressive Tregs through CCR8 may overcome checkpoint inhibition resistance

PHASE I

## UNMET NEED

// Most cancer patients do not derive clinical long-term benefit from immune checkpoint inhibitors (ICIs) due to primary or acquired resistance.

// Regulatory T cells (Tregs) are one of the key resistance mechanisms hampering the efficacy of ICIs across many tumor types.

## MODE OF ACTION

// Our CCR8 (chemokine receptor 8) antibody is designed to deplete tumor-resident, activated regulatory T cells resulting in a (re-) activation of the anti-tumor immune response.

// BAY 3375968 is expected to demonstrate a better efficacy and side effect profile than other non-CCR8 Treg-targeting agents due to specific depletion of tumor-infiltrating CCR8+ Tregs without impacting effector cells and peripheral Tregs.

## ADDRESSABLE PATIENT POPULATION

| Indication | Patients |
|---|---|
| Advanced solid tumors in combination with ICI<br>- NSCLC,TNBC, Melanoma, HNSCC | >200K patients<br>US, EU5 & Japan |

## ASSET POTENTIAL

| Indication | Asset Potential |
|---|---|
| Advanced solid tumors in combination with ICI<br>- NSCLC,TNBC, Melanoma, HNSCC | ●○○ <€500m ●●○ €500m–€1bn ●●● >€1bn |

## CURRENT STATUS + NEXT MILESTONES

FPFV October 2022. Anticipated completion of dose escalation H2 2024

# CCR8 Antibody *(BAY 3375968)*: Key Preclinical Data

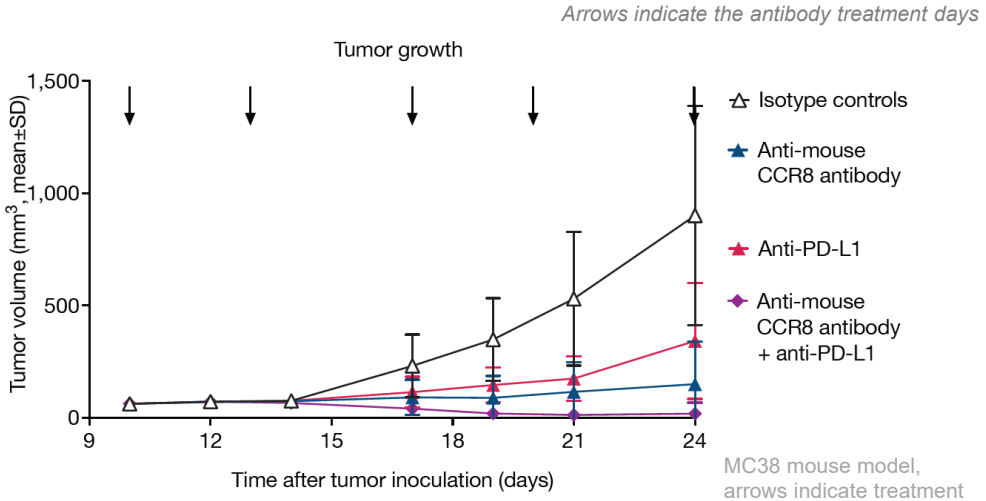
Depleting suppressive Tregs through CCR8 may overcome checkpoint inhibition resistance

PHASE I

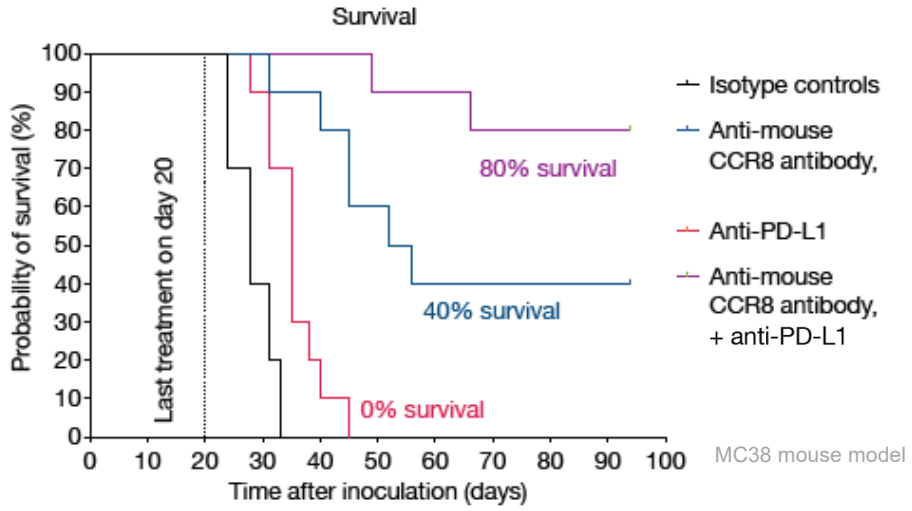
## PRECLINICAL DATA

// An anti-mouse CCR8 surrogate antibody (Ab) showed strong in *vivo* response in monotherapy which was further improved by combination with a checkpoint inhibitor anti-PD-L1 agent

**_In vivo_ tumor growth inhibition by CCR8 Ab and in combination with anti-PD-L1**




**_In vivo_ survival by CCR8 Ab and in combination with anti-PD-L1**



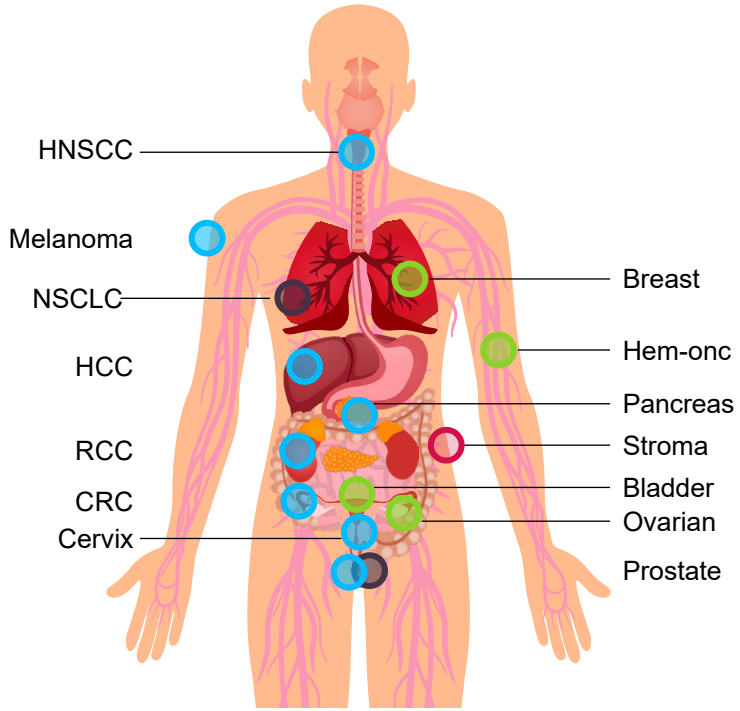
# Targeted Radiotherapies (TRT) Offers a Specific Mode of Action which Addresses Treatment Resistance in Areas of High Unmet Need

## SPECIFIC MOA OF TRT CAN UNLOCK A BROAD OPPORTUNITY SPACE

DNA double-strand breaks
=> no treatment resistance

Cross-fire effect to
maximize tumor cell killing

Combination potential
with targeted therapies
(e.g. ICIs/DDRi's)




Address tumor types that are not druggable by ADCs

Potential to target stromal cells in tumor microenvironment

Potential to overcome mechanisms of resistance

Target "cold" tumors where IO does not work or sensitize these

**MARKET EXPECTED TO GROW TO $20BN BY 2030**

Source: Nuclear Medicine Report & Directory 2021 and 2022 (Part 1, 2, 3) - MEDraysintell; TRT Market Sizing for Compass

# We have the Right Expertise, Tools & Manufacturing Capabilities in Place to Produce Best-in-Class TRT Precision Medicines

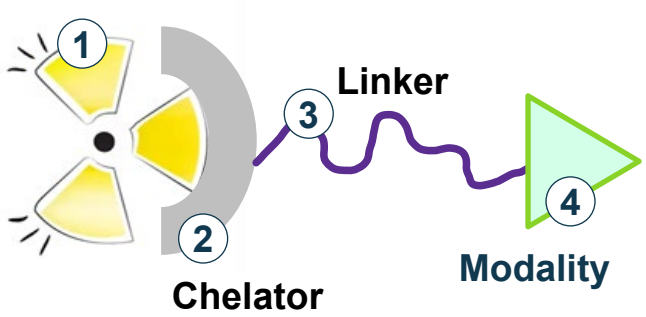
*Strong scientific experience & expertise as well as commercial capability*

*Through multiple iterations, we now have the toolkit to produce best-in-class medicines augmented through smart deals: Ratio & Bicycle*

*Differentiated & fit for purpose assets for high value patient populations of high unmet need*


Xofigo
($^{223}RaCl_2$)

// Launched in 2013 for mCRPC
// Several Lifecycle management activities ongoing




Highly differentiated mechanism of action achieved by synergistic design of components

**7**
**Pre-clinical programs**

**2**
**P0 & P1 programs**

Rapid expansion of programs expected through internal discovery and external deals

# Key Messages Today

- Our Oncology R&D strategy is based on precision drug development which enables fast identification of the most promising targets and commercially viable programs
- We focus on expanding the druggable target pool, developing "kinder medicines", and addressing resistance
- We are rapidly building an early pipeline in precision molecular oncology and next gen immuno-oncology
- Targeted radiotherapies (TRT) provide another highly attractive opportunity in oncology - we have a wealth of expertise and experience

# *Shaping new Treatment Paradigms in Cardiovascular Diseases*

Maria Borentain

# Key Messages Today

- CV diseases represent a significant health burden and #1 leading cause of death with still high unmet medical need
- Our focus within cardiovascular include selected areas within nephrology and acute care
- Our R&D approach is based on three value pools with an increasing focus in precision medicine: targeting rare indications, subpopulations, and disruption in large indications
- Building on our strong heritage and expertise we will continue to develop innovative therapies to address the needs of patients with cardiovascular diseases

# Bayer to Continue Leadership Position in CV

## MARKET ATTRACTIVENESS

### High unmet medical needs

// Leading cause of death
// Increasing disease burden and rising comorbidities
// Huge impact on healthcare systems and workforce

### Emerging trends

// Novel drug modalities offer new opportunities
// Advanced tools like multi-omics enable precision medicine
// Digital solutions enable early diagnosis and targeted treatment

### Attractive growth market

// Worldwide market value of €65bn (2022) continuing to grow at a steady pace
// Pharma industry underinvests in CV R&D in relation to disease burden
// Huge opportunity in precision CV due to scientific progress


## BAYER'S KEY STRENGTHS

### Record of success

// Industry leader in cardiovascular
// Expertise along the entire value chain
// Established global commercial footprint

### Exciting recent and near-term launches

// Late-stage pipeline asset asundexian: Innovative, once-daily, oral small molecule FXIa inhibitor
// Successful launch of Kerendia with LCM potential

### Strategic focus on precision CV

// Expertise available to address and internalize scientific progress
// External collaborations & platform companies further enhance our transition into precision CV

# CV: A Success Story set to Continue

Recent successes fuel our ambition for the future to help even more patients in need

## Bayer has a strong R&D and commercial record in CV

- Adempas riociguat
- Xarelto rivaroxaban tablets
- Verquvo (vericiguat) tablets
- Aspirin Cardio
- Adalat

Xarelto rivaroxaban tablets

**€4.5bn**
2022

Aspirin Cardio

**€0.8bn**
2022

## *CV expected to drive future sales of Bayer Pharma*

**Verquvo (vericiguat) tablets**

Worsening HFrEF & Stable HFrEF

Peak[1] ~€0.5bn

**Kerendia finerenone**

T2D CKD, HFpEF & ndCKD

Peak[1] >€3bn

**Asundexian[2]**
(investigational FXIa inh.)

SPAF, stroke

Peak[1] >€5bn

// Bayer among the **top leaders** in CV

// We aspire to build on our R&D successes and **strengthen our CV leadership**

[1] Peak = Peak Sales Potential; [2] Late-stage pipeline asset

# We Focus on Three Value Pools to Build on our Leadership in CV

Gradual shift from large indications to high value subpopulations and rare indications

**PATIENT FOCUS**

*Addressing the highest unmet medical need for patients with rare diseases*

*Catering to subpopulations of larger indications with high unmet medical need*

*Opportunistic focus on real disruption in large indications with highest standard of care*

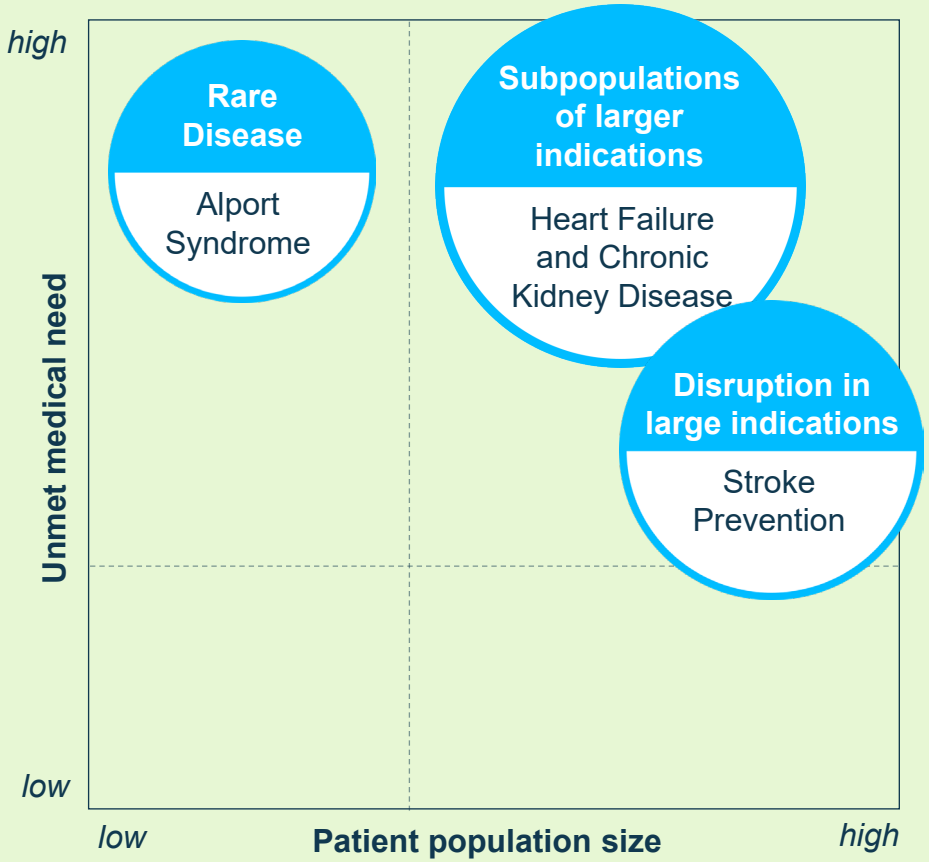
**DISEASE AREAS**

***Cardiovascular***

***Nephrology***

***Acute Care***

**SELECTED INDICATIONS (INDICATIVE)**



# Cardiovascular+ – Pipeline Update [1] (as of Jun 16, 2023)

| Candidate medication | Indication | Modality | Compound Origin | Phase 0[2] | Phase I | Phase II | Phase III |
|---|---|---|---|---|---|---|---|
| **Finerenone** (MR Antagonist) | **Heart Failure** (HFmr/pEF) (FINEARTS-HF) | | Bayer | | | | |
| | **Non-diabetic CKD** (FIND-CKD) | | | | | | |
| **Vericiguat** (sGC Stimulator) | **Heart Failure** (HFrEF) (VICTOR[3]) | | Bayer | | | | |
| **Asundexian** (FXIa Inhibitor) (BAY 2433334) | **Stroke Prevention in Atrial Fibrillation** (OCEANIC-AF) | | Bayer | | | | |
| | **2º Stroke Prevention** (OCEANIC-STROKE) | | | | | | |
| | **Major Adverse Cardiac Events Prevention** (PACIFIC-AMI) | | | | | | |
| **Congestive Heart Failure rAAV Gene Therapy** *(AB-1002 aka NAN-101)* | **Congestive Heart Failure** | | AskBio | | | | |
| **sGC Activator Oral** *(BAY 3283142)* | **Chronic Kidney Disease** (CKD) | | Bayer | | | | |
| **Anti-a2AP** (BAY 3018250) | **Acute Ischemic Stroke; Pulmonary Embolism** | | Bayer | | | | |
| **sGC Activator Inhale** (BAY 1211163) | **Acute Respiratory Distress Syndrome** | | Bayer | | | | |
| **SEMA 3a** (BAY 3401016) | **Alport Syndrome** | | Bayer/Evotec | | | | |
| **Anti-coagulant** (BAY 3389934) | **Anti-coagulation** | | Bayer | | | | |

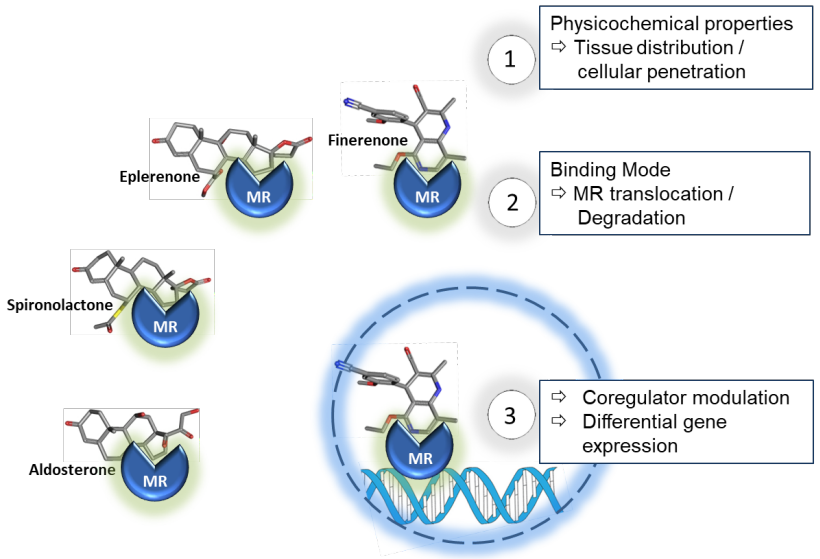
**Protein Therapeutics** **Cell Therapy** **Contrast Agent** **Genetic Medicine** **Radiotherapy** **Small Molecule** **Focus today**

Cardiovascular +: Including Precision Cardiovascular, Nephrology & Acute Care

[1] Bayer and partner sponsored + 3rd party label enabling studies with first patient first visit [2] Pre-clinical selected assets on path to IND [3] Conducted by Merck & Co

# Finerenone is a Potent, Highly Selective Non-Steroidal MRA with Differentiated Profile

## DIFFERENT BINDING MODES BETWEEN THE STEROIDAL MRAs AND THE NONSTEROIDAL FINERENONE[1]




// Finerenone and steroidal mineralocorticoid receptor antagonists differ in their molecular receptor binding mode resulting in distinct effects on gene expression

## PRECLINICAL DATA: RECEPTOR PROFILE, DRUG METABOLISM AND TISSUE DISTRIBUTION OF FINERENONE[2]

| | Spironolactone | Eplerenone | Finerenone |
|---|---|---|---|
| **MRA Class** | Steroidal | Steroidal | Non-steroidal |
| **Potency** | High | Low | High |
| **Selectivity** | Low | Medium | High |
| **Metabolites** | Multiple, active | No active | No active |
| **Tissue distribution[3]** | Kidney>>heart (>6-fold) | Kidney>heart (~3-fold) | Balanced (1:1) |

// No sexual side effects including gynecomastia

// Balanced kidney safety

// Low incidence of hyperkalaemia-related adverse events with clinical impact and permanent treatment discontinuation[4]

Source: [1]Kolkhof P, Nowack C, Eitner F. Curr Opin Nephrol Hypertens. 2015;24:417-424. [2]Modified from: Kolkhof B, Borden SA. Mol Cell Endocrinol. 2012;350:310-317. [3] Determined in rodents. [4] Agarwal R, Filippatos G, Pitt B, Anker SD, Rossing P, Joseph A, Kolkhof P, Nowack C, Gebel M, Ruilope LM, Bakris GL; FIDELIO-DKD and FIGARO-DKD investigators. Cardiovascular and kidney outcomes with finerenone in patients with type 2 diabetes and chronic kidney disease: the FIDELITY pooled analysis. Eur Heart J. 2022 Feb 10; 43(6):474-484. doi: 10.1093/eurheartj/ehab777. Erratum in: Eur Heart J. 2022 May 21;43(20):1989.

# Large Integrated Program to Investigate Finerenone as a Foundational Treatment for Chronic Kidney Disease (CKD)

Strong launch dynamics and the option to broaden the use in CKD

PHASE III

## STUDY DATA

### Finerenone effective in reducing cardiovascular and renal events in patients with T2D and CKD

### Key results of the FIDELITY pooled analysis[1]:

**Composite CV Outcome**

**HR = 0.86**
(95% CI 0.78-0.95), *p*=0.0018
NNT 46[2]
Relative risk reduction compared to placebo

**-14%**

**Composite Kidney Outcome**

**HR = 0.77**
(95% CI 0.67-0.88), *p*=0.0002
NNT 59[2]
Relative risk reduction compared to placebo

**-23%**

## ONGOING PHASE III STUDIES

### Potential to Broaden the Use of Finerenone in CKD

**Non-diabetic CKD** — FIND-CKD

- FIND-CKD: randomized, double-blind, placebo-controlled, parallel-group, multicenter phase III trial in CKD patients without diabetes
- Phase III data expected in 2026

**CKD in Type 1 Diabetes** — FINE-ONE

- FINE-ONE: randomized, double blind, placebo-controlled, parallel-group, multicenter phase III trial in CKD patients with type 1 diabetes (T1D)
- Phase III data expected in 2025

Source: Agarwal, R. et al., data presented at ESC 2021
[1] including > 13,000 randomized pts; [2]at 36 months

# Potential to Expand the Indication of Finerenone in Heart Failure

## Phase 3 FINEARTS-HF with mildly reduced / preserved EF (HFmrEF/HFpEF ) is ongoing

PHASE III

### UNMET MEDICAL NEED

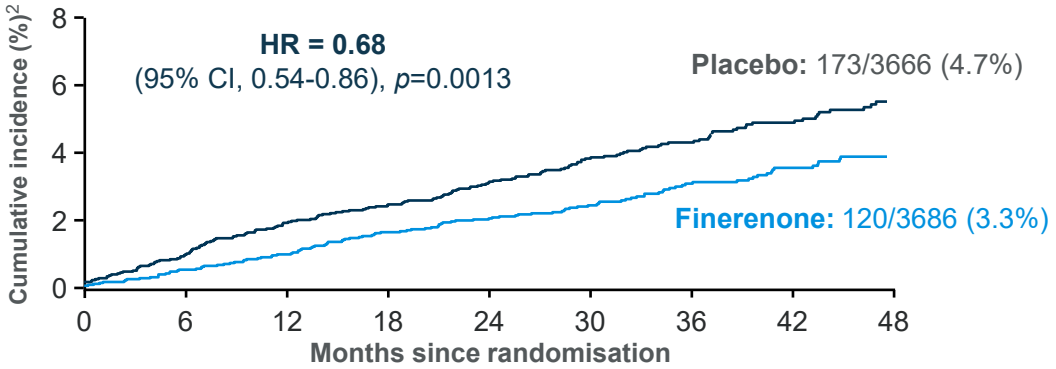
- HF is the fastest-growing global CV disease with approximately ~60m HF patients worldwide
- About 50% of HF patients have HF with LVEF ≥ 40%. They suffer from a high CV mortality rate (42% within 5y of diagnosis) despite SoC
- Renal dysfunction and HFmrEF/pEF frequently coexist, due to shared comorbidities and factors impacting macrovascular and microvascular circulation

### UPCOMING DEVELOPMENT MILESTONES

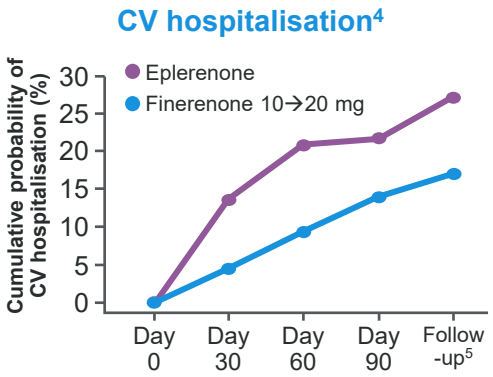
- Phase 3 data expected in 2024

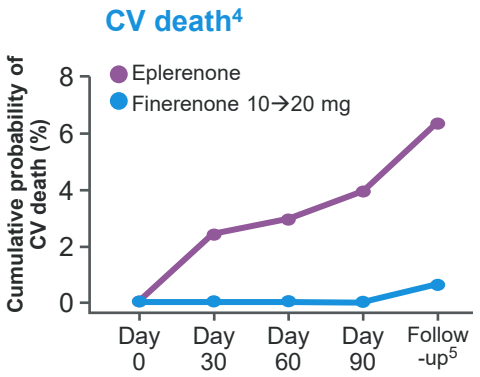
### Clinical data suggest benefit of finerenone in heart failure

**Phase 3 FIGARO-DKD: Reduced risk of HF-related death or first HHF[1]**




**Phase 2 ARTS-HF[3]: Reduced risk of CV hospitalization and CV death vs eplerenone**



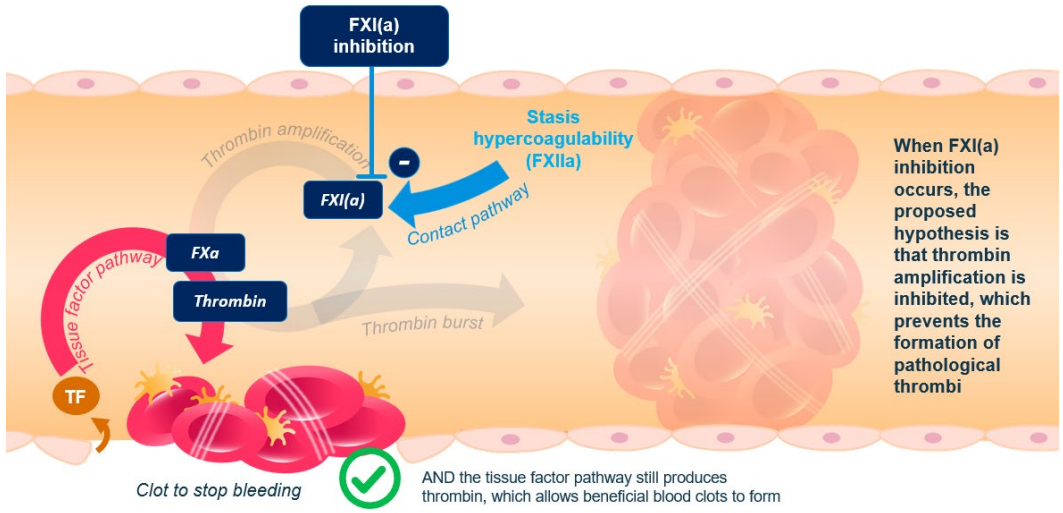




[1] First hospitalisation for HF defined as first event after randomisation; [2] Source: cumulative incidence calculated by Aalen–Johansen estimator using deaths due to other causes as competing risk. Filippatos G, *et al. Circulation* 2022;145:437–447
[3] Both phase 2a study ARTS and phase 2b study ARTS-HF were in HFrEF, [4] Source: Kolkhof P, et al. Handb Exp Pharmacol 2017;243:271–305; 2. Filippatos G, et al. Eur Heart J 2016;37:2105–2114; [5] 30-day period after cessation of study drug

# FXI(a) Inhibitors Are a Promising And Distinct New Class of Drugs For Thrombosis Prevention

Separating thrombosis protection from haemostasis via selective modulation of the coagulation system

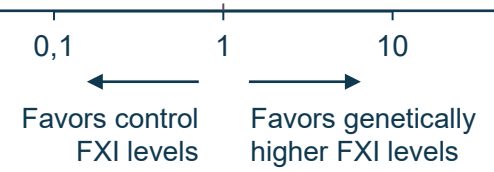
## Mode of Action[1-3]




// **Paradigm shift** in thrombosis prevention, with the potential to uncouple efficacy from bleeding risk

## Patients with genetically higher FXI levels show increased risk of ischemic stroke[4]

| Ischemic stroke subtype^x | Cases (N) | Controls (N) | OR 95% CI | *p*-value |
|---|---|---|---|---|
| Cardioembolism | 3,071 | 28,722 | | 0.0003 |
| Large artery atherosclerosis | 2,454 | 28,880 | | 0.02 |
| Small vessel occlusion | 2,736 | 27,588 | | 0.69 |
| Undetermined cause | 4,755 | 25,292 | | 0.0002 |




FXa, activated Factor X; FXI(a), activated Factor XI, FXII(a), activated Factor XII; TF, tissue factor.

Source: [1] Piccini JP et al. Lancet 2022;399:1383–1390. [2] Fredenburgh JC, Weitz JI. Hamostaseologie 2021;41:104–110. [3] Gailani D et al. J Thromb Haemost 2015;13:1383–1395. [4] Gill D et al. Stroke 2018;49:2761–2763

# Phase III Decision for Asundexian Strongly Backed by Results From PACIFIC Phase II Program

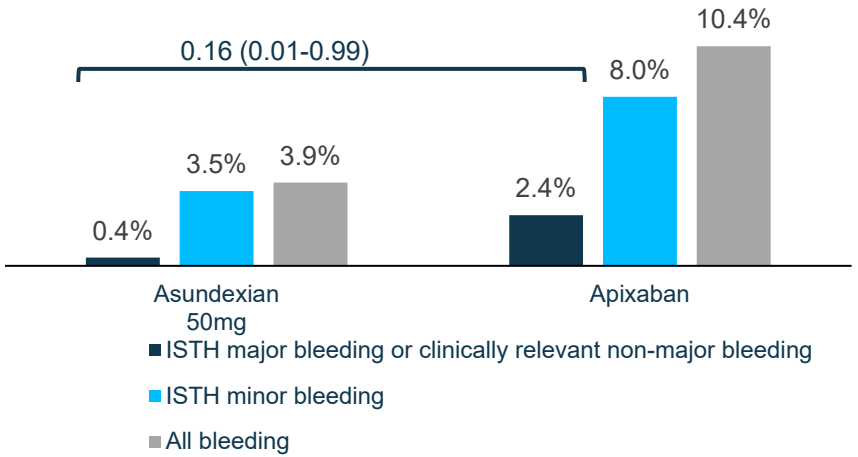
Innovative, once-daily, oral small molecule FXIa inhibitor

## Study Data: PACIFIC-AF

// **Bleeding**: Asundexian at near maximum FXIa inhibition showed lower rates of observed bleeding versus apixaban in PACIFIC-AF

// **Efficacy**: too few events to draw conclusion

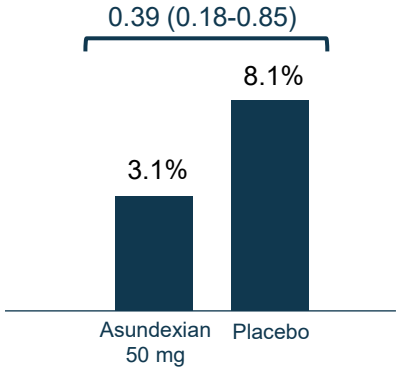
**Proportion of participants with bleeding event, % of patients[1]**




## Study Data: PACIFIC-STROKE

// **Bleeding:** no significant increase vs. Placebo on top of Antiplatelet/Dual Antiplatelet

**Recurrent stroke and TIA in patients with any extra-/intracranial atherosclerosis[2]**




**Broad Phase II study program PACIFIC confirmed consistent safety at near maximum FXIa inhibition[1]**

Source: [1] Piccini JP, Caso V, Connolly SJ, Fox KAA, Oldgren J, Jones WS, Gorog DA, Durdil V, Viethen T, Neumann C, Mundl H, Patel MR; PACIFIC-AF Investigators. Safety of the oral factor XIa inhibitor asundexian compared with apixaban in patients with atrial fibrillation (PACIFIC-AF): a multicentre, randomised, double-blind, double-dummy, dose-finding phase 2 study. Lancet. 2022 Apr 9;399(10333):1383-1390. doi: 10.1016/S0140-6736(22)00456-1. Epub 2022 Apr 3. PMID: 35385695. Data presented at ACC 2022 and ESC 2022. [2] Data presented at ESC in August-2022 in Barcelona, and ESOC May-2023 in Munich (data on file)

# OCEANIC Phase III Program

Study program well on track

## The OCEANIC program consists of two Phase III studies

### OCEANIC-AF

| Patients with atrial fibrillation | |
|---|---|
| **Active comparator-controlled trial (apixaban)** | |
| # of patients | **~18,000 patients** |
| Minimum treatment period | **9 months** |
| Primary efficacy endpoint: | **stroke or systemic embolism** |
| Primary safety endpoint: | **ISTH major bleeding** |
| First patient first visit: | **Q4 2022** |
| Data expected: | **H2 2025** |

### OCEANIC-STROKE

| Patients with non-cardioembolic ischemic stroke | |
|---|---|
| **Placebo-controlled trial** | |
| # of patients | **~9,300 patients** |
| Minimum treatment period | **3 months** |
| Primary efficacy endpoint: | **ischemic stroke** |
| Primary safety endpoint: | **ISTH major bleeding** |
| First patient first visit: | **Q1 2023** |
| Data expected: | **H2 2025** |

**Started in Dec 2022 (~27,000 patients, across 40 countries)**
**First topline data expected H2 / 2025**

# The NO/sGC/cGMP Pathway is a Key Modulator of Patho-Mechanisms in Cardiovascular and Renal Function

## Bayer has a strong 20+ year legacy in sGC

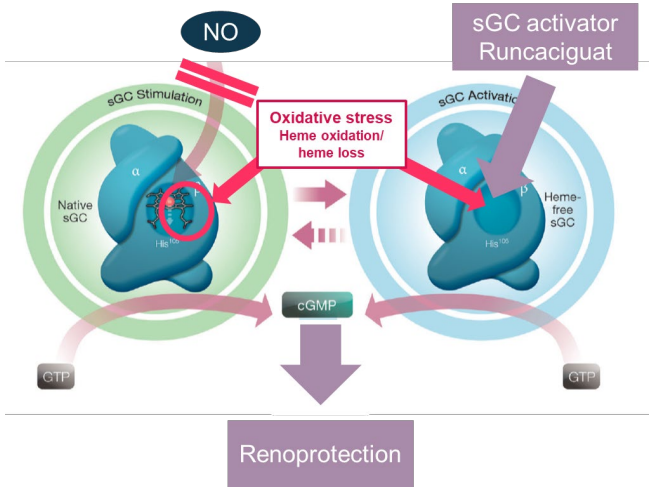
PHASE I

### UNMET NEED

// Impairment of the NO/sGC/cGMP signaling can cause cardiovascular, cardiopulmonary and cardiorenal diseases

// Oxidative stress is a hallmark of CKD/DKD and there is a need to reduce progression to end-stage renal disease (ESRD) and CV mortality

// Inactivation of sGC disrupts the local regulation of perfusion, resulting in ischemia, the main cause of end-organ damage in diabetes patients




### PROFILE & MODE OF ACTION

// Oxidative stress results in heme-oxygenation and heme-free sGC (soluble Guanylyl Cyclase)

// Oxidized/ heme free sGC limits the activity of Nitric Oxide (NO) and therefore impairs cGMP signaling

// Re-activation of sGC is expected to restore regulation of perfusion in affected organs

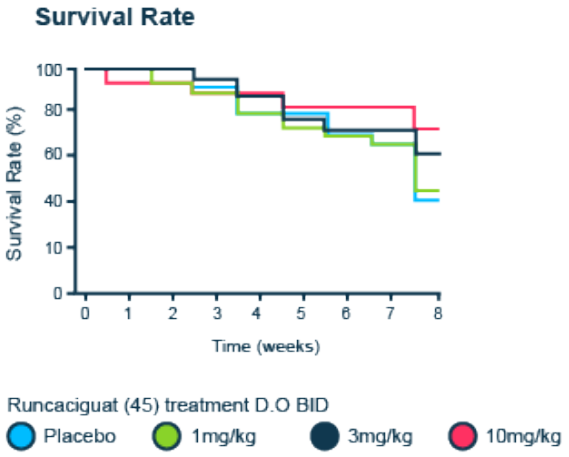
// sGC activators specifically

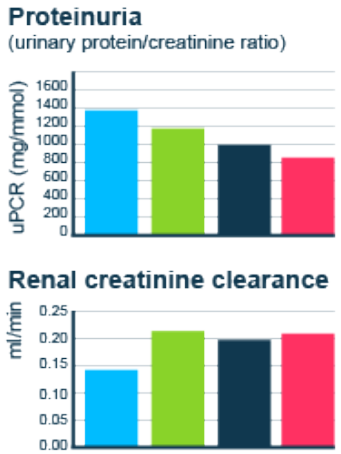
- // Binds and activates oxidized/ heme free sGC
- // Independent from and additive to endogenous NO

Source: Stasch & Hobbs, Handb Exptl Pharmacol 2009; Follmann et al., Angew. Chem. Int. Ed. 2013;52:9442-9462 Sandner, Biol Chem. 2018 Jun 27;399(7):679-690; Sandner et al., Handb Exptl Pharmacol 2021

# sGC Activator Front-Runner Runcaciguat Confirmed Strong UACR Reduction of the Drug Class

- In various experimental models, soluble guanylyl cyclase (sGC) activators[1]
  - Lowered blood pressure
  - Decreased proteinuria
  - Improved renal outcomes
- These sGC activators did so in a dose-dependent manner, in diabetic, as well non-diabetic, CKD models



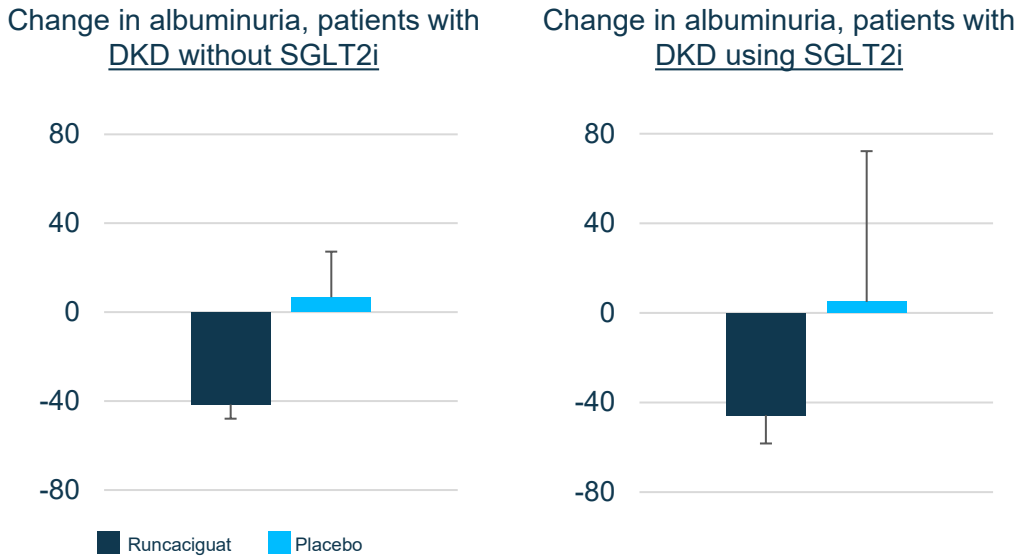




**Phase 2 CONCORD Study[2]:**

**Runcaciguat demonstrated beneficial effects in patients with CKD & advanced CVD**

- A reduction in UACR was observed in all strata and significant UACR reductions were seen in patients with diabetes on top of RAASi and on top of SGLT2 inhibitors
- The small reduction in SBP with runcaciguat suggests that improvement in UACR is not driven by changes in BP
- A small reduction in eGFR was observed with runcaciguat

**Runcaciguat was well tolerated**




Data show estimated mean percent change and 95% confidence interval (ANCOVA) for the PPS.

Source: [1] Hahn MG et al. J Med Chemistry 2021;64:5323–5344; [2]Ron T. Gansevoort et al. Oral presentation ERA 2023

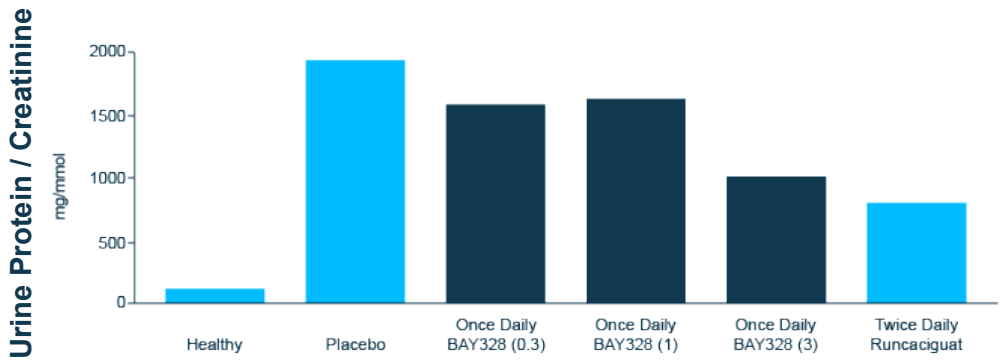
# sGC Activator Oral (BAY 3283142)

## Preclinical pharmacodynamic data confirm comparable profiles of BAY3283142 and runcaciguat in CKD

PHASE I

### PRECLINICAL DATA

BAY3283142 vs Runcaciguat preclinical comparison
Progressive CKD Rat Model (ZSF-1)




// Preclinical model shows BAY328 is highly effective in CKD prevention (decrease in proteinuria and glomerulopathy)

// BAY3283142 pharmacokinetics with favorable Peak/Trough profile allows for once daily dosing

### ADDRESSABLE PATIENT POPULATION

| Indication | Patients |
|---|---|
| Chronic Kidney Disease | CKD is a progressive condition that affects >10% of the general population worldwide, amounting to ~700 million individuals[1] |

### Asset Potential

| Indication | Asset Potential |
|---|---|
| Chronic Kidney Disease | ●●● |

●○○ <€500m ●●○ €500m–€1bn ●●● >€1bn

### Upcoming Development Milestones

Initiation of Phase 2 program

Source: [1] Vijay et al, 2021

# Anti-a2AP (BAY 3018250)

Timely vessel opening represents a high unmet medical need in acute ischemic stroke (AIS) and pulmonary embolism, areas without innovation for more than 2 decades

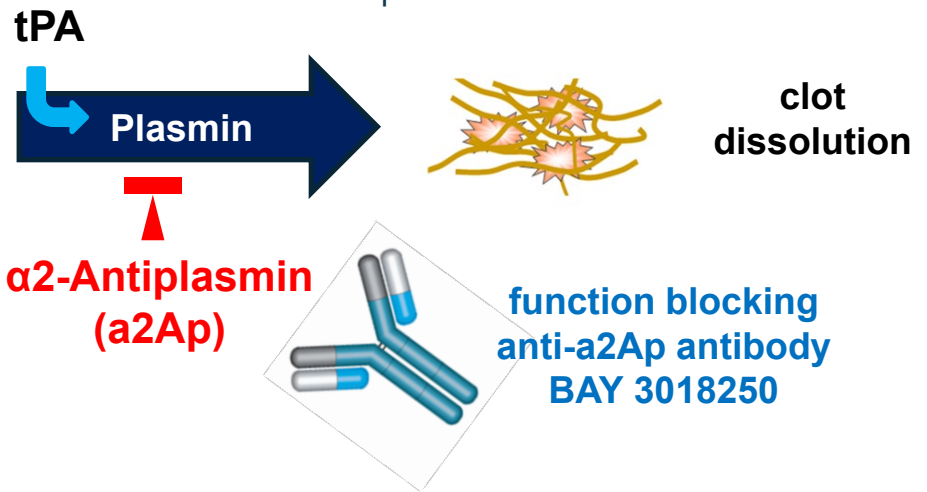
PHASE I

## UNMET NEED

- Current thrombolytic drugs have shown limited efficacy and notable hemorrhagic complication rates
- Surviving patients often experience significant sustained disability
- The clinical and economic burden of AIS is considered high and still rising
  - >2 million patients hospitalized with AIS in US, EU4 and JP
  - Average healthcare cost of stroke per person estimated at ~US$140k in US
- Incidence of PE is still rising and comes with high mortality as well as considerable economic burden
  - >500k patients hospitalized with AIS US, EU4 and JP, expected to increase to 700K by 2030
  - In EU and US deaths are expected to be around 600k by 2030. Average healthcare costs are US$12-20k in the US

## PROFILE & MODE OF ACTION

- Fibrinolysis
  - Active lysis of acute embolic or thrombotic clots without increasing risk of bleeding by blocking the endogenous Plasmin inhibitor a2Ap




Potential for significant differentiation vs SoC with a profile that allows use in a broad eligible population based on efficacy coupled with no increase in bleeding profile

# Anti-a2AP (BAY 3018250)

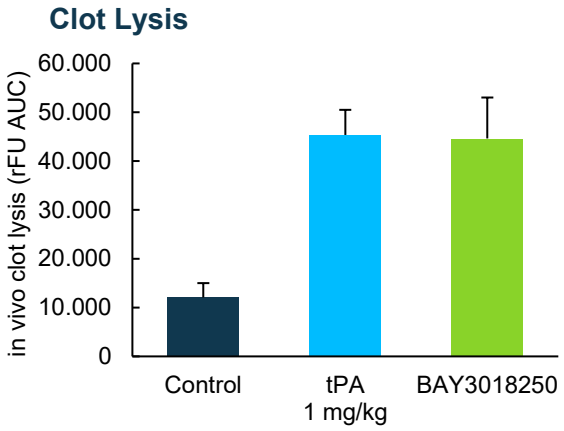
Potential to be the first in class, effective thrombolytic with no increase in bleeding risk and a wider treatment window

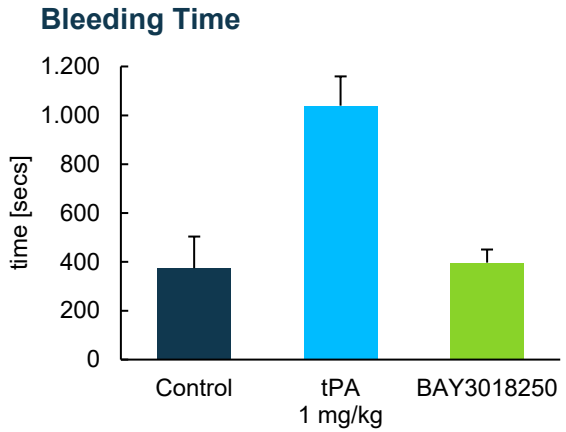
PHASE I

## PRECLINICAL DATA

In animal models, BAY 3018250 demonstrated to be an effective thrombolytic with no increased bleeding risk.

1. Accelerates clot dissolution on a PE model
2. Increased clot dissolution in a venous thromboembolism model
3. In vivo bleeding experiments do not indicate an increased risk of bleeding




## ADDRESSABLE PATIENT POPULATION

| Indication | Patients |
|---|---|
| Acute Ischemic Stroke;<br>Pulmonary Embolism | AIS: 500k (US, EU4, UK, JP)<br>PE: 250k (US, EU4 and JP) |

## Asset Potential

| Indication | Asset Potential |
|---|---|
| Acute Ischemic Stroke;<br>Pulmonary Embolism | ●●● |

●○○ <€500m ●●○ €500m–€1bn ●●● >€1bn

## Upcoming Development Milestones

// Decision to move to Phase 2 in H2 2023

# Sema3A mAB[1] for Alport patients

## Aiming to delay disease progression and onset of end-stage renal disease

PHASE I

### UNMET NEED

- Rare genetic kidney disease with progressive loss of filtration capacity, leading to end stage renal disease and dialysis early with the need for kidney transplant in 4th/5th decade
- Progressive hearing-loss (frequent)
- Variable vision impairment (less frequent)

### PROFILE & MODE OF ACTION

- Semaphorin-3A (Sema3A) is an extracellular guidance protein and a well-known regulator of the actin cytoskeleton
- Alterations of the actin cytoskeleton, particularly of podocytes, are a key pathophysiological feature of Alport Syndrome
- Sema3A is upregulated in injured human kidneys and implicated in the development and progression of acute and chronic kidney diseases
- Sema3A antibody blocks Sema3A activity

### ADDRESSABLE PATIENT POPULATION

| Indication | Patients (rare orphan disease) |
|---|---|
| Alport | 1 in 5,000 – 10,000 (globally) |

### Asset Potential

| Indication | Asset Potential |
|---|---|
| Alport | ●●○ |

●○○ <€500m ●●○ €500m–€1bn ●●● >€1bn

### Upcoming Development Milestones

- Start of Phase 1 with first dosing of healthy subjects in June 2023
- Study data expected in 2024

[1] Compound Origin: Bayer / Evotec

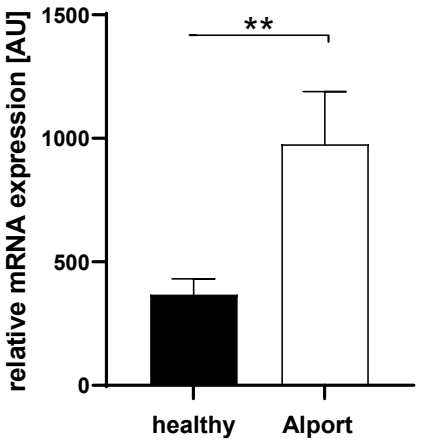
# Sema3A mAB[1] for Alport patients

First to market potential in Alport syndrome – a rare genetic disease

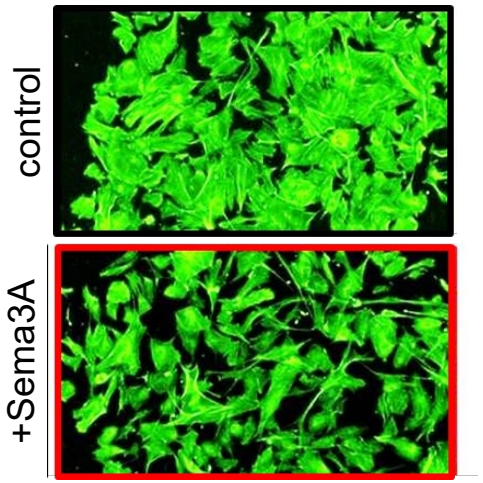
PHASE I

## PRECLINICAL DATA

### Evidence of Sema3A in kidney disease

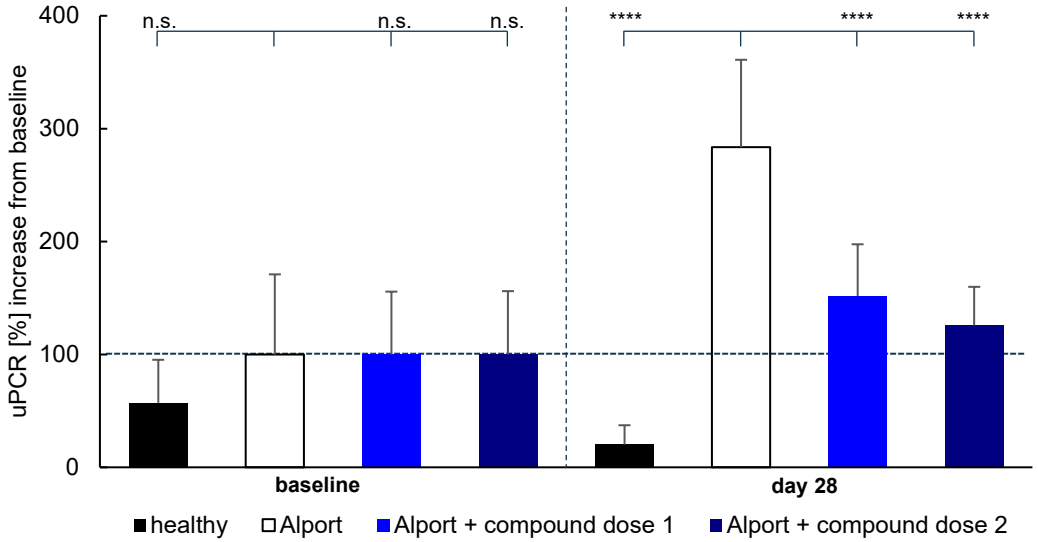



Sema3A is upregulated in injured mouse kidneys




Sema3A induces detrimental changes in primary human kidney cell morphology

### Therapeutic efficacy of Sema3A inhibition in Alport mouse model




Sema3A inhibition significantly reduced proteinuria progression in Alport mice

[1] Compound Origin: Bayer / Evotec

# Key Messages Today

- CV diseases represent a significant health burden and #1 leading cause of death with still high unmet medical need
- Our focus within cardiovascular include selected areas within nephrology and acute care
- Our R&D approach is based on three value pools with an increasing focus in precision medicine: targeting rare indications, subpopulations, and disruption in large indications
- Building on our strong heritage and expertise we will continue to develop innovative therapies to address the needs of patients with cardiovascular diseases

# *BlueRock Therapeutics: Leading the way in PSC Therapies*

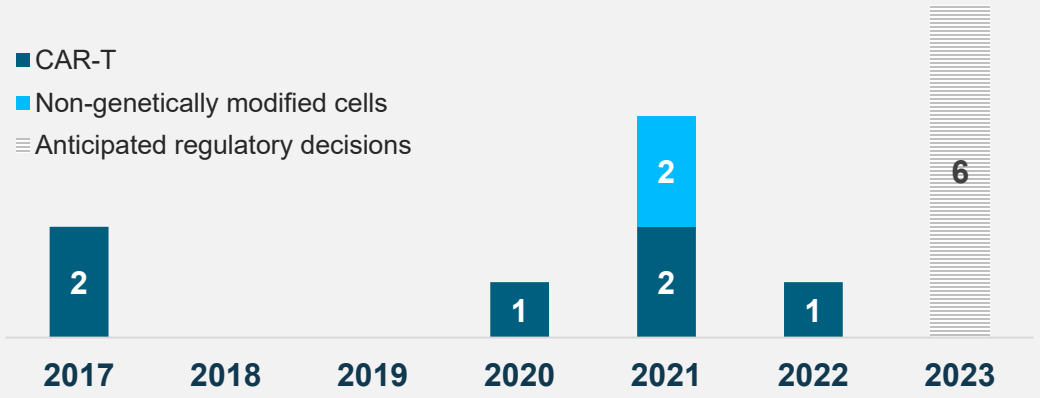
Seth Ettenberg

# Key Messages Today

- A new frontier of cellular medicine was launched with the commercialization of cell therapies for hematological cancers
- Pluripotent stem cell (PSC) derived therapies with the potential to broaden the impact of cellular medicine beyond cancer are the next frontier.
- BlueRock is one of the leaders of this next field, with end-to-end capabilities for delivering innovative PSC-based therapies
- Near-term OpCT-001 IND filing for the treatment of primary photoreceptor diseases (e.g., retinitis pigmentosa, cone/rod dystrophies)
- Advancing bemdaneprocel for Parkinson's Disease into phase 2 clinical development based on positive readout of our phase 1 study
- Bayer and BlueRock are working to change the future of medicines by replacing the cells that are lost to diseases

# The Cell Therapy Market Is Expected to Reach >USD25bn by 2026

## HISTORY OF FDA CELL THERAPY APPROVALS[1]




*FDA Approved Cellular and Gene Therapy Products*

- First cell therapy approved in 2017, majority of currently approved cell therapies still CAR-T based for hematological malignancies
- Cell therapies expected to remain one of the fastest growing therapeutic options in the pharmaceutical sector
- Key considerations for successful commercialization:
  - streamlining supply chain and administration logistics
  - patient and caregiver support
  - innovative payment solutions

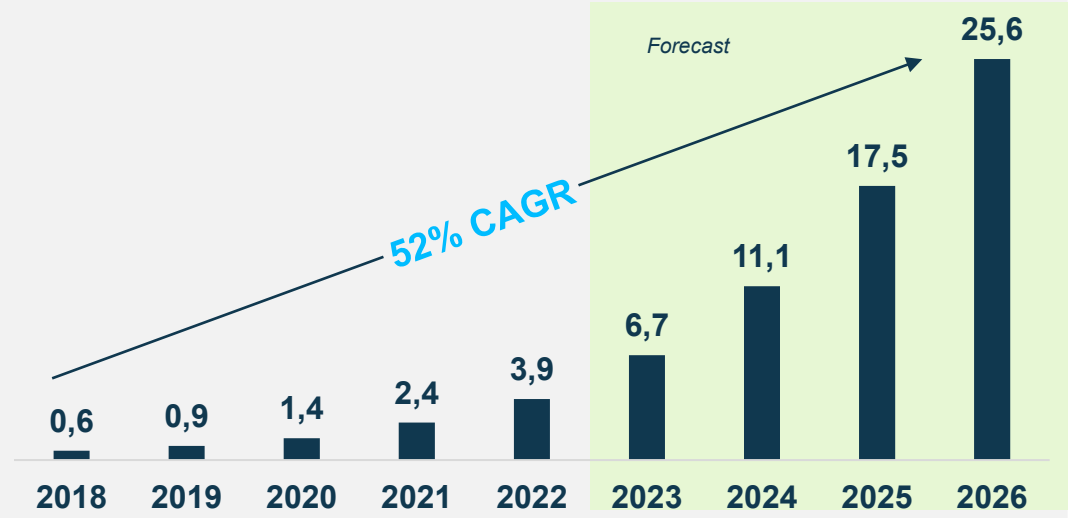
## NUMBER OF CELL THERAPIES IN CLINICAL DEVELOPMENT TODAY[2]

*Informa, June 2023*


*Only unapproved agents in clinical development included*

- ~640 cell therapies in clinical development across TAs
- Multiple ongoing phase 3 trials for approved CAR-T (e.g., label expansion)

## GLOBAL SALES OF CELL THERAPIES[3] (USDbn)




Cord Blood approvals not included in approved therapies
Sources: [1] FDA Approved Cellular and Gene Therapy Products [2] Pharma Intelligence, Informa [3] EvaluatePharma, Oct. 2022 for pipeline and sales/ forecast

# BlueRock Therapeutics is a Leader in PSC Biology, Bringing Therapies From Bench to the Clinic

**MISSION: To discover and develop new cell therapies that change the way disease is treated and improve patients' lives**

## Cell Replacement

**REPLACE** CELLS

**RESTORE** FUNCTION

**REVERSE** DISEASE

## Engineered Cells

**ENGINEER** CELLS

**DELIVER** PAYLOAD

**TREAT** RARE & COMMON

## FOUNDING SCIENCE

**Lorenz Studer, MD**
MSK Cancer Center

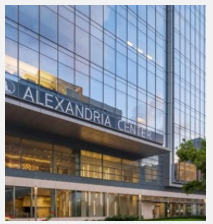
**Gordon Keller, PhD**
University Health Network

**Bruce Blazar, MD**
University of Minnesota

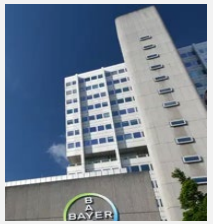
## FOUR SITES ACROSS USA, Canada and Germany

**Cambridge (HQ)**
// Immunology Research
// Clinical & Regulatory
// Pilot cGMP facility
// Genome Biology

**New York**
// Neurology Research
// Platform technology




**Toronto**
// Cardiac research
// Device and
// formulations
// Pilot cGMP facility



**Berlin**
// Support for clinical programs and coordination of regulatory processes in Europe

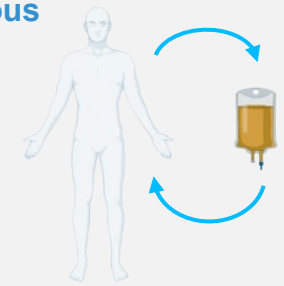
**Focus on four disease areas (Neurology, Cardiology, Immunology, Ophthalmology)**

# Within the Cell Therapy Space, Pluripotent Stem Cells Have the Broadest Therapeutic Potential

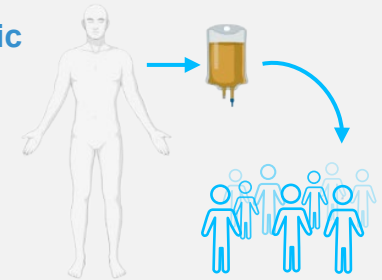
## AUTOLOGOUS VERSUS ALLOGENEIC CELL THERAPY

// Cell therapy is the administration of cells into a patient that are derived from the patient (autologous) or a healthy donor (allogeneic)

**Autologous**



**Allogeneic**



## SOURCES FOR CELL THERAPY

**Adult Harvestable Cells:**

// Harvested from adult donor
// Limited available quantities, difficulty in access and cell expansion
// Examples include:
  // Isolated T-cells for CAR-T therapy
  // MSCs
  // HSCs

**Pluripotent Stem Cells (PSC):**

// Can differentiate into any cell type in the body
// Allogeneic PSCs with unlimited potential for expansion and scalability

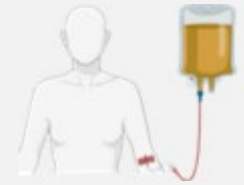
## ADMINISTRATION

// Final cell product can be administered in different ways, depending on the therapeutic approach and indication

**Systemic delivery**

Examples include:

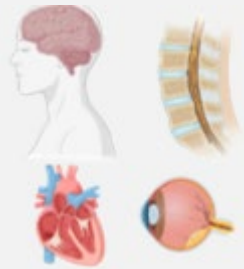
// Intravenous



**Direct delivery to target area:**

Examples include:

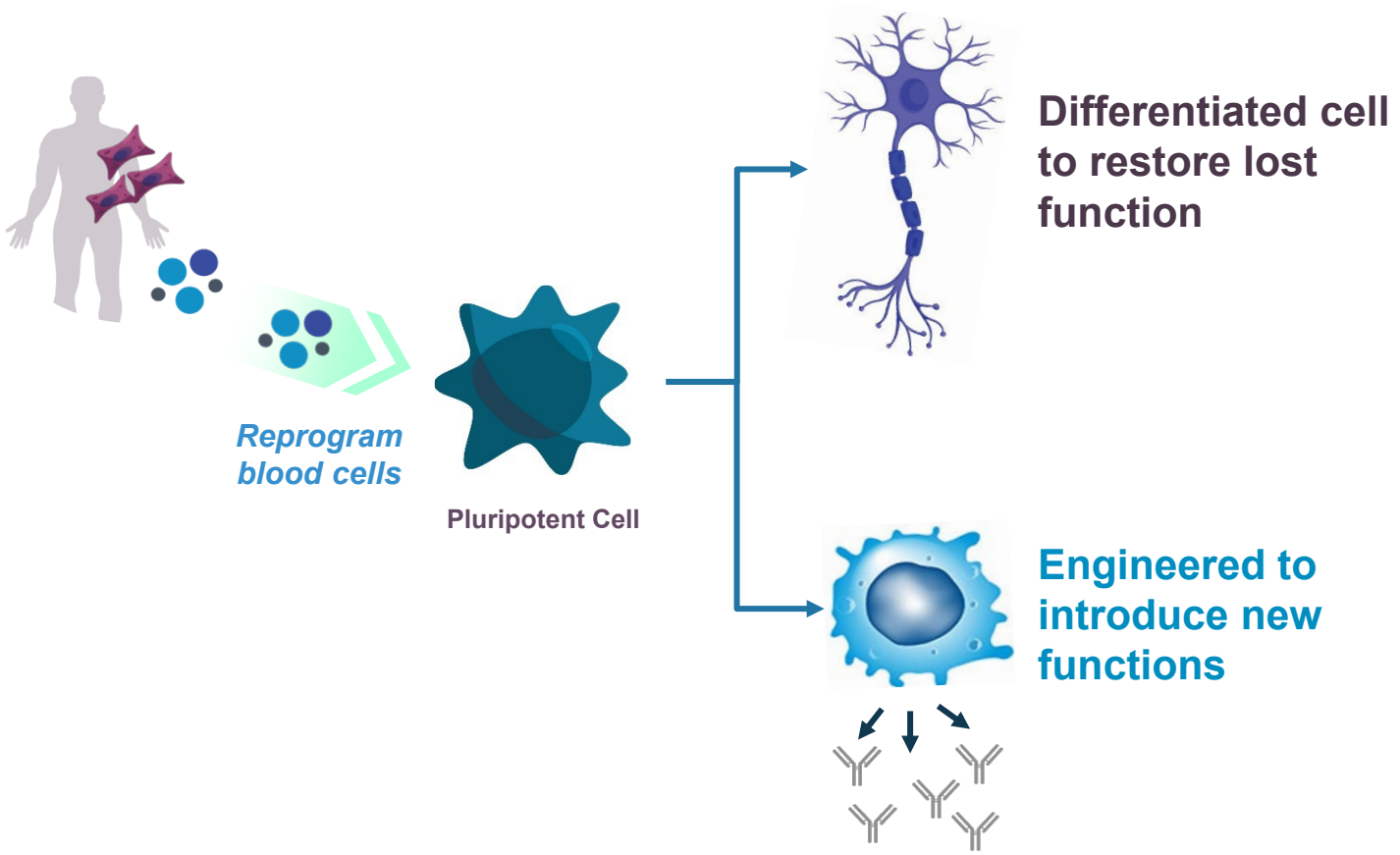
// Intracranial
// Spinal cord
// Heart
// Eye



Source: [1] El-Kadiry 2021. Frontiers in Medicine, p.2340.

# Pluripotent Stem Cells Have the Potential to Restore Lost Cellular Function and Introduce New Functions to Address Multiple Diseases

## THERAPEUTIC POTENTIAL OF PSCs




## EXAMPLES OF TARGET DISEASE AREAS

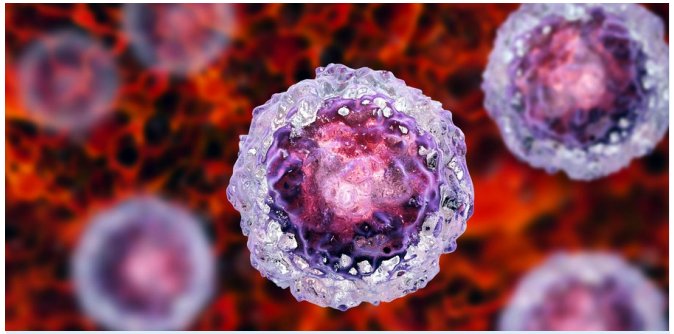
- // Parkinson's Disease
- // Heart Failure
- // Retinitis Pigmentosa
- // Geographic Atrophy (AMD)

- // Oncology
- // Alzheimer's Disease
- // Metabolic Diseases
- // Autoimmune Diseases

Source: El-Kadiry 2021. Frontiers in Medicine, p.2340.

# BlueRock Has End-to-end Capabilities in PSC Technology

## CORE FOUNDATIONAL REPROGRAMMING TECHNOLOGY



- Donor material **fully consented for commercial use**
- Proprietary, non-integrating, **high-efficiency reprogramming technology**; deep analytics
- Defined **cGMP-compliant** processes, including **master cell banking**

## EXPERTISE IN BRINGING CELL THERAPY TO THE CLINIC

- Thorough understanding and ability to **differentiate cells into specified medicines at scale, reproducibly**
- Demonstrated ability to bring **differentiated cells into clinical development**

## COMMERCIAL MANUFACTURING CAPABILITIES

- **Commercial scale production** of cryopreserved product
- Technology transfer **to commercial manufacturing** facility in Berkeley (Bayer)

# Ongoing Partnerships for Continued Advancement of PSC Therapies

## PARTNERSHIP GOALS

**Technologies to accelerate pipeline execution**

**Enabling technologies to bolster platform**

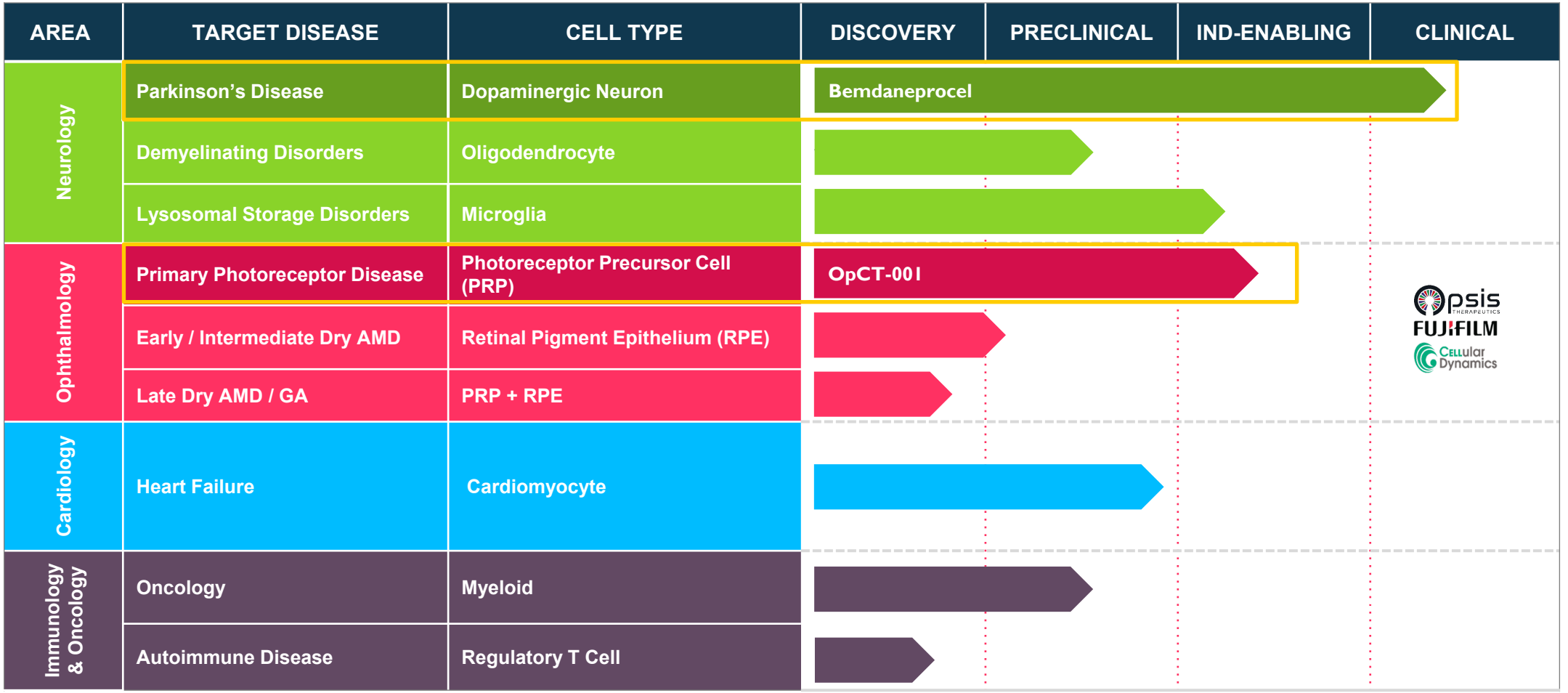
**Capabilities and programs to enhance pipeline**

## ONGOING PARTNERSHIPS

Ncardia
UHN
Memorial Sloan Kettering Cancer Center
iPS Academia Japan
SENTI BIO
EMERALD
BioCardia®
editas MEDICINE
rune labs
BE THE MATCH®
WARF Wisconsin Alumni Research Foundation
Opsis Therapeutics
FUJIFILM Cellular Dynamics

***Partnerships enables BlueRock to continually push the boundaries of PSC-based therapies***

# BlueRock's Pipeline Addresses Areas of High-Unmet Needs



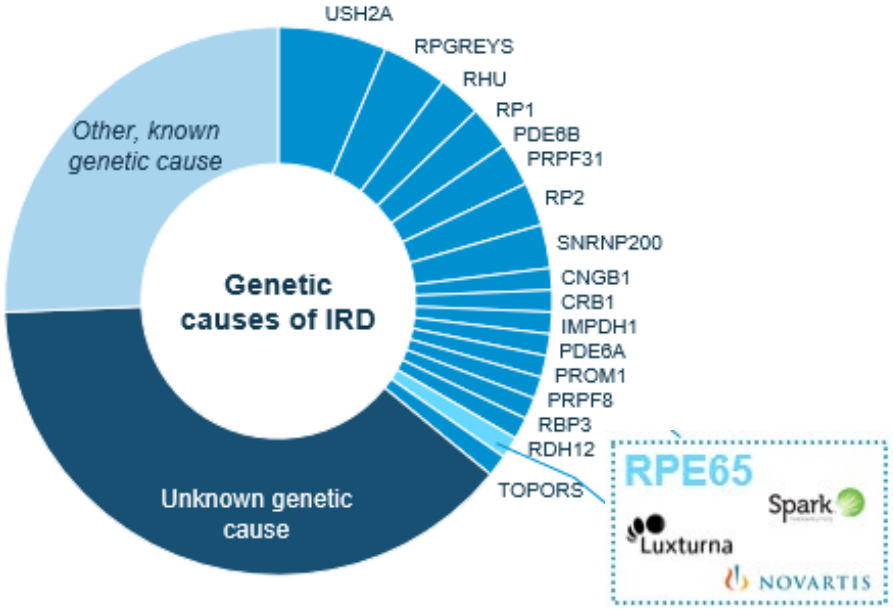

Focus today

# Primary Photoreceptor Disease is a Group of IRDs That Lead to Irreversible Vision Loss in Children and Adults

## Primary Photoreceptor Diseases (PPD) Background

- A group of inherited retinal disorders (IRDs) that specifically affect the function / structure of the photoreceptor cells (cone, rods) in the retina
- Includes Retinitis Pigmentosa, cone and cone-rod dystrophies; ~65% of all IRDs

### GENETIC CAUSES OF INHERITED RETINAL DISORDERS (IRDs)




[1] US, EU4 + UK
Source: Rattner, A. et. al. Annu. Rev. Genet. 2009, Kantar Health, 2020 and Luxturna PI [4] BR Analysis

## CURRENT TREATMENTS AND UNMET NEED

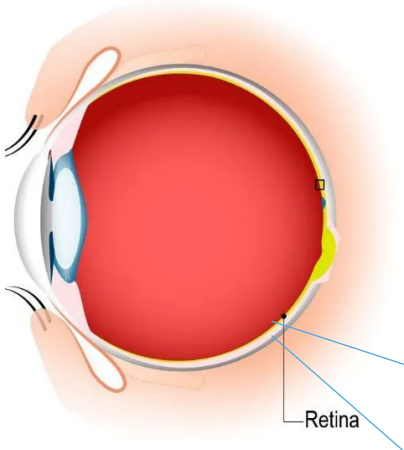
- Over 200k[1] patients are currently affected with primary photoreceptor disease
- There are no specific treatment options available, management is focused on supporting patients as vision loss progresses (guide dogs, visual aids)
- Most therapies in development only target specific genetic mutations

## CELL THERAPY APPROACH

- BlueRock's cell therapy can potentially treat an entire class of diseases
- OpCT-001 will be evaluated for patients with Retinitis Pigmentosa as well as cone and cone-rod dystrophies

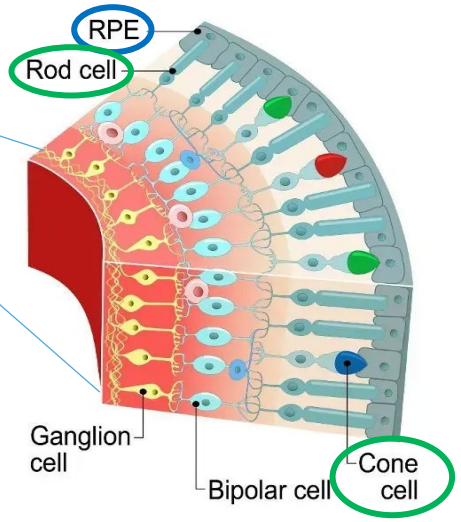
# BlueRock's Ophthalmology Ambition: Restoring Vision by Replacing Degenerated Tissue in the Retina with Functional Cells

## ANATOMY OF THE HUMAN EYE




### Retinal pigment epithelium (RPE)

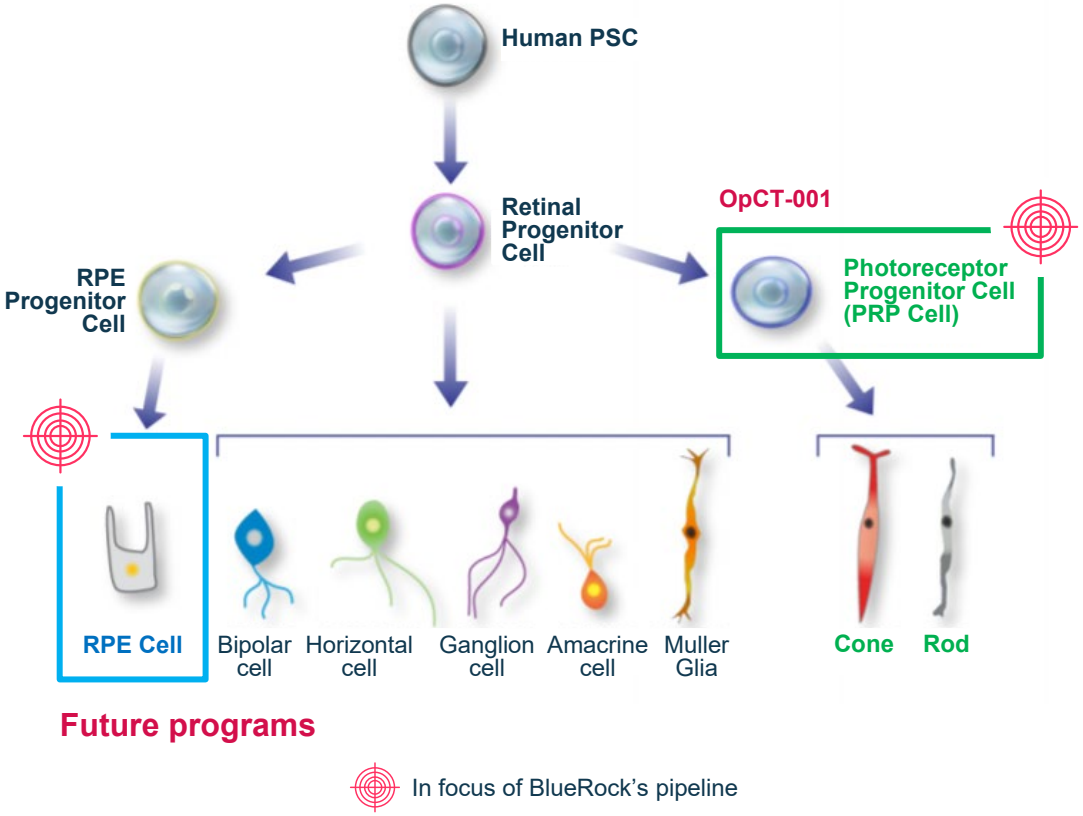
- Single layer of cells, essential for maintaining vision
- Changes in the RPE can impair visual function and lead to retinopathy (i.e., RP, AMD, SD)




### Photoreceptors in the retina

- Convert light into nerve signals
- **Rods**: responsible for vision at low light levels
- **Cones**: active at higher light levels, responsible for color vision

## PSC DERIVED RETINAL CELL DIFFERENTIATION

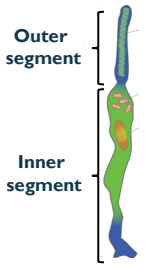



Source: Yang, et al., 2021. Frontiers in pharmacology, 12, p.727870.

# OpCT-001 – Cell Therapy for PRP Cell Replacement

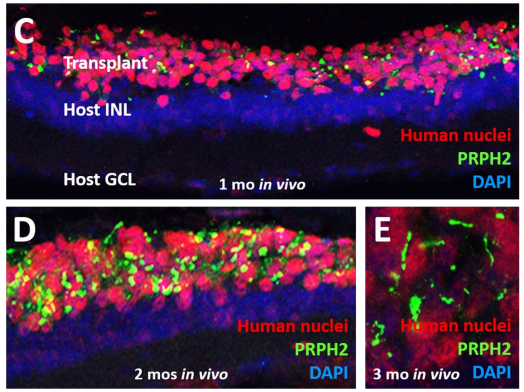
## OpCT-001 cells engraft and display characteristics of functional photoreceptors

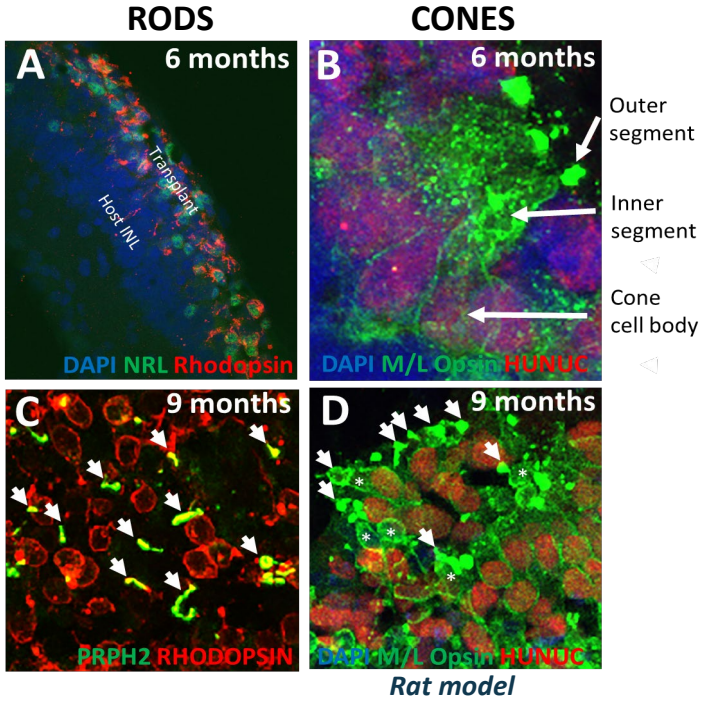
*In addition to phenotypic maturation, transplanted photoreceptors begin to show physical maturation including the formation of inner and outer segments and the trafficking of rhodopsin to outer segments*




- *Opsin protein expression*
- *Inner and outer segment formation*
- *Rods traffic rhodopsin to outer segments*
- *Outer segments are stable long-term*

**Outer Segment Formation**




***Rat model***

## ADDRESSABLE PATIENT POPULATION

| Indication | Patients |
|---|---|
| Primary Photoreceptor Disease | US, EU4/UK, ~200k |

## ASSET POTENTIAL

| Indication | Asset Potential |
|---|---|
| Primary photoreceptor disease | ●●● |

●○○ <€500m ●●○ €500m–€1bn ●●● >€1bn

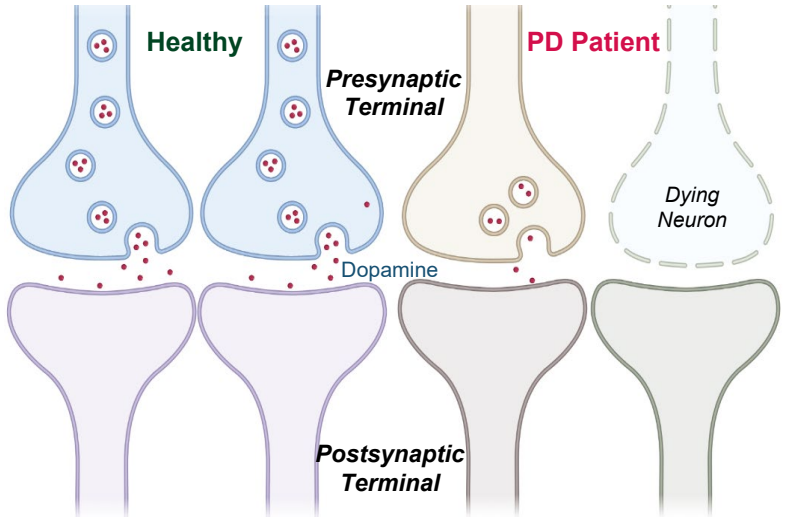
## STATUS AND UPCOMING DEVELOPMENT MILESTONES

IND submission in the next 12 months

# Parkinson's Disease is a Progressive, Neurodegenerative Condition Defined by Dopaminergic Neuron Loss and Motor Impairment

## PD Motor Symptoms Caused by Loss of DA Neurons

- Healthy dopamine neurons (DA) in the brain make the neurotransmitter dopamine critical for several brain functions, including movement
- Loss of DA cells results in less dopamine and leads to Parkinson's Disease




## Current Treatments and Unmet Need

- PD is the second most common neurodegenerative disorder in the US
- Limited treatment options available as patients progress
- Medications, effective at early stages, become less and less effective with disease progression
- Significant unmet need for longer-lasting therapies that will alter the disease trajectory

- **Bemdaneprocel is being developed as a one-time cell therapy that will provide dopaminergic neurons** to the brain to **restore lost dopaminergic function**
- The goal is to **alter disease progression and reverse symptoms** over time, so patients remain independent and live a life that is **not defined by their diagnosis**

Source: Song 2016. Frontiers in aging neuroscience, 8, p.65.; Kalia 2015. The Lancet. 386(9996), 896-912.; Bridi 2018. Frontiers in neuroscience, 12, p.80.

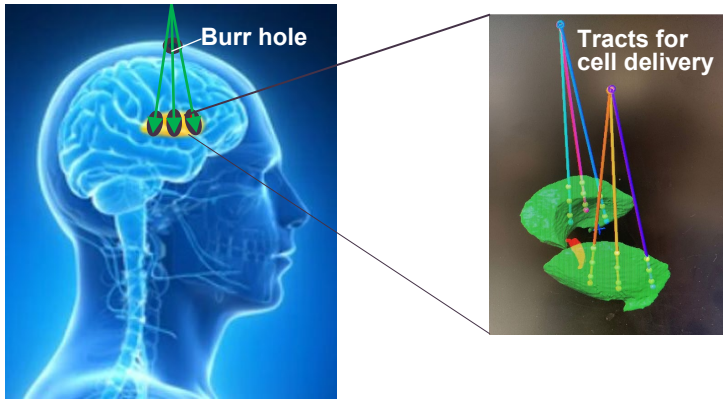
# All Patients from Phase 1 Trial have Completed 1-Year Follow-up

Memorial Sloan Kettering Cancer Center · UHN · BlueRock Therapeutics · Weill Cornell Medicine · UCI University of California, Irvine

## *Phase I Study Summary*

| | |
|---|---|
| **Trial Design** | • Multi-center, open label, Phase I trial assessing bemdaneprocel authentic cell therapy for Parkinson's Disease |
| **Enrollment Criteria** | • Subjects with PD (male/female)<br>• Patients diagnosed ≥3 and ≤15 years ago<br>• Responsive to L-dopa, but inadequate relief of motor symptoms |
| **Objectives** | • Safety, tolerability, PET-imaging for cell survival at years 1 & 2<br>• Preliminary efficacy (motor, non-motor) at years 1 & 2 |
| **Dosing** | • Two cohorts - low and high doses<br>• Immunosuppression for 12 months following transplantation |

## Bemdaneprocel Surgical Procedure




### *Surgery Overview*

// Single burr hole per hemisphere with three tracts for cell delivery

// Bemdaneprocel custom procedure minimizes needle passes and burr holes to decrease surgical risk and optimize coverage

Sources: ct.gov NCT04802733

# Bemdaneprocel is the First PSC-derived Dopaminergic Cell Therapy with Positive Data in PD

## TOPLINE PHASE 1 RESULTS

- The study met the primary endpoint; bemdaneprocel was well tolerated with no major safety issues by all twelve patients in both the low and high dose cohorts through one year
- Feasibility of transplantation, and evidence of transplanted cell survival and engraftment in both cohorts was demonstrated through one year.
- Detailed phase 1 trial data from primary and secondary endpoints will be presented at the 2023 International Congress of Parkinson's Disease and Movement Disorders (MDS) taking place in Copenhagen from Aug. 27 – 31, 2023

**Phase 1 Study Endpoints**

**Primary Endpoint:**

- Safety and tolerability at 1-year post-transplant

**Secondary Endpoints *(1- and 2-year post transplant):***

- Evidence of cell survival – F-DOPA PET
- Changes in motor function – Changes in MDS-UPDRS III
- Changes in waking hours in "OFF" state
- Continued safety and tolerability

## ADDRESSABLE PATIENT POPULATION

| Indication | Patients |
|---|---|
| Parkinson's Disease | US ~1 million |

## ASSET POTENTIAL

| Indication | Asset Potential |
|---|---|
| Parkinson's Disease | ●●● |

●○○ <€500m ●●○ €500m–€1bn ●●● >€1bn

## STATUS AND UPCOMING DEVELOPMENT MILESTONES

Q3 2023 planned presentation of Phase 1 data in a medical meeting
Phase 2 clinical study expected to begin enrolling patients in H1 2024

# BlueRock is a Leader in the Development of PSC-derived Therapies

## 2023 & Beyond

### PARKINSON'S DISEASE

// Report Ph1 results of bemdaneprocel

// Initiate bemdaneprocel Ph 2 study

// Advance follow-on PD program (DA02)

### OPHTHALMOLOGY

// IND filing for OpCT-001

// Initiate FIH study

### HEART FAILURE

// Demonstration of PoC in large animal models

// IND filing for cardiomyocytes

# *Asklepios BioPharmaceutical: Pioneering AAV-based Gene Therapies*

R. Jude Samulski

# Key Messages Today

// *Highly attractive market*:
Gene therapy market expected to grow significantly until the end of the decade

// *Pioneer in AAV-based gene therapy:*
Unparalleled pipeline, talent and manufacturing capabilities

// *Robust therapeutic pipeline:*
Balanced portfolio addressing monogenic and pathway disorders

// *Scalable platform for continued growth and innovation:*
Building a platform enables to extend the field of application of the technology to multiple diseases

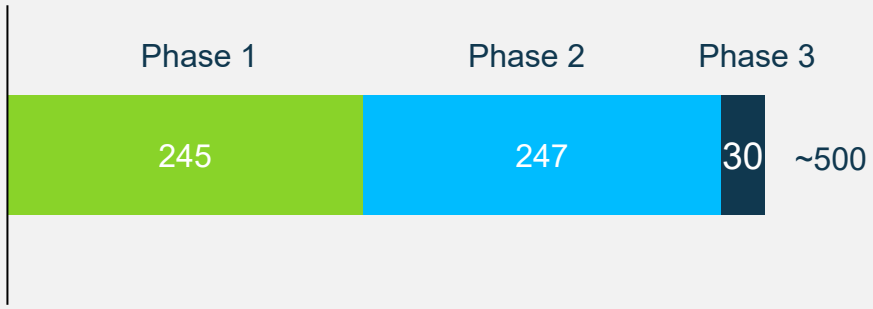
# FDA January 21, 2019

We anticipate that by 2020 we will be receiving more than 200 INDs per year, building upon our total of more than 800 active cell-based or directly administered gene therapy INDs currently on file with the FDA.
And by 2025, we predict that the FDA will be approving 10 to 20 cell and gene therapy products a year based on an assessment of the current pipeline and the clinical success rates of these products [....]
We're working to expand our review group dedicated to the evaluation of these applications to keep pace with the rapid expansion in new product development. Our eventual goal is to add about 50 additional clinical reviewers to the group charged with overseeing the clinical investigation, development, and review of these products

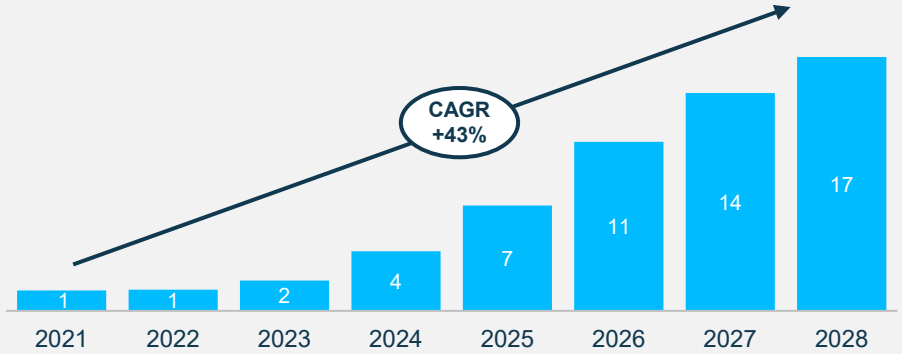
In the case of gene therapy, it's similarly a product innovation that has marked an inflection point in the development of these therapies, and a surge in new product activity. In this case, it was the advent of safe and effective vectors for the delivery of gene therapy products, such as the adoption of adeno-associated virus (AAV) vectors.

# The Gene Therapy Market is Expected to Reach €17bn in 2028

## Gene therapies in clinical development today[1]




## Gene Therapy sales [2021-2028; €bn][2]




// Majority of approved gene therapies are based on AAV vector technology

// First AAV gene therapy approval in 2017; number of gene therapy approvals is expected to increase significantly until 2030, resulting in strong anticipated sales growth

// Shaping of access models, policies and payer environment are crucial to sustainable success

Source: [1] ASGCT Q1/2023 report; [2] Evaluate Pharma Feb 2023 , Fx rate based on central financial 1.01US$ = 1€

# AskBio is a Pioneer in AAV-based Gene Therapy with Unparalleled Pipeline, Talent and Manufacturing Capabilities

- Founded in 2001 by R. Jude Samulski, Sheila Mikhael and Xiao Xiao who pioneered the AAV gene therapy field
- Dedicated to developing life-saving medicines that can potentially cure genetic diseases
  - ~7,000 rare diseases are known to date; ~80% of rare diseases are genetic in origin

## FIRST

to clone AAV for therapeutic purposes

to deliver AAV intrathecally

to treat DMD and Pompe patients

to deliver AAV to the brain

**PILLAR I**

### TECHNOLOGY

Renowned toolbox (capsids, regulatory elements, gene editing)

**PILLAR II**

### MANUFACTURING

Distinguished manufacturing capabilities (cell line/infrastructure)

**PILLAR III**

### CLINICAL DEVELOPMENT

Strong translational expertise, combined with academic network

**TRANSLATE INTO**

### PROMISING THERAPEUTIC PIPELINE

# AskBio Built Industry Leading Manufacturing Facilities and Technologies, which are Crucial to Bring Gene Therapies to Patients

## Gene therapy manufacturing overview

**Viralgen Clinical – GMP Manufacturing**
**San Sebastian, Spain**

**Viralgen Commercial – Production Capacity**
**San Sebastian, Spain**

### Pro10™ Cell Line

Serum free

Scaled up to 2,000 liters

Yields of 10^17

### Stable Packaged Cell Line

Increases yields

Pharmaceutical grade

### Inducible Promoters

Increases productivity

Turns off genes during mfg

### Novel manufacturing technologies at every stage

Improved yields

Higher throughput

In-house control

Unmatched batch purity

Reliable consistency

**TAAV – no-end DNA (neDNA)[1]**
**San Sebastian, Spain / Hampton UK**

### Plasmid Alternative

TAAV[2]

Shorter cycle time

Fewer bacterial contaminants

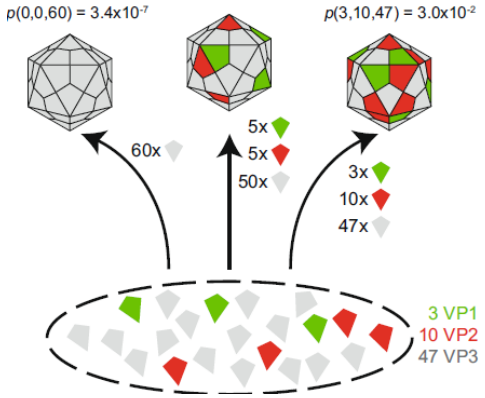
Lower cost

**RTP HQ – Additional production capacity**
**Durham, NC**

[1] neDNA is made using technology licensed from Touchlight IP Ltd; [2] Technology licensed from Touchlight IP Ltd

# AskBio Industry Leading Platforms

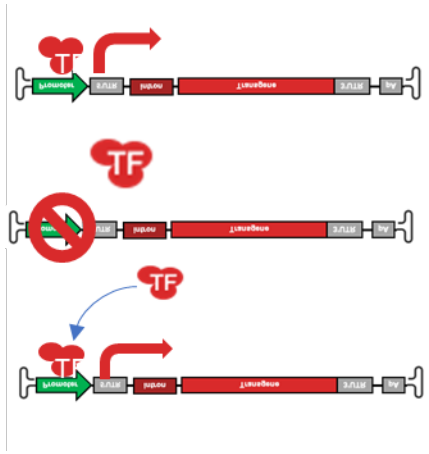
## AAV CAPSIDS




// Tissue-specific targeting

// Engineered chimeric capsids

## PROMOTERS & REGULATION




// Precise cell targeting

// On/off expression control

## GENE EDITING TOOLS


// Enhanced gene editing technology

## CELL LINES & MANUFACTURING

// Scaled, integrated manufacturing (Pro10™ cell line and plasmid alternative)

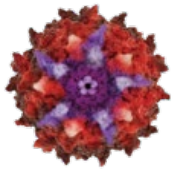
# AskBio's Technology and Pipeline is a Key Innovation Engine for Bayer's CVD, Neurology and Rare Disease Ambition

| Platform | | Asset[1] | Pre-clinical | Phase I | Status | Next Phase |
|---|---|---|---|---|---|---|
| Gene therapy platform (AAV[1]) AskBio | CNS | **Parkinson's** (AB-1005) | | | Positive Ph1 topline data | Phase 2 |
| | | **MSA** (AB-1005) | | | New Ph1 entry Q1/2023 | Pivotal |
| | | **Huntington's** (AB-1001-101) | | | New Ph1 entry Q1/2023 | Pivotal |
| | | **fAD** (CYP46A1 ± APPsα or PSEN) | | | Discovery | |
| | CV | **Congestive Heart Failure** (AB-1002) | | | First efficacy hints from Ph1 | Phase 2 |
| | | **Danon disease** (Lamp2B) | | | Discovery | |
| | Mono-genic | **Pompe (LOPD)** (ACTUS-101) | | | First data on relevance of target | |
| | | **LGMD2i/R9** (AB-1003) | | | New Ph1 entry Q1/2023 | Pivotal |
| | | **Hemophilia A** (Factor VIII.QQ) | | | Discovery | |
| | | **DMD** (µUtrophin) | | | Discovery | |

[1] Excludes partnered programs

# Balanced Portfolio Addressing Monogenic and Pathway Disorders

**MONOGENIC DISORDERS**



AskBio
MAKING HISTORY

**PATHWAY DISORDERS**

## MONOGENIC DISORDERS

- Mutation occurs in the DNA sequence of a single gene.
- Most monogenic disorders are rare diseases such as Pompe disease, Huntington's disease, hemophilia and cystic fibrosis.
- Historically the first to be targeted by gene therapy
- Smaller patient populations

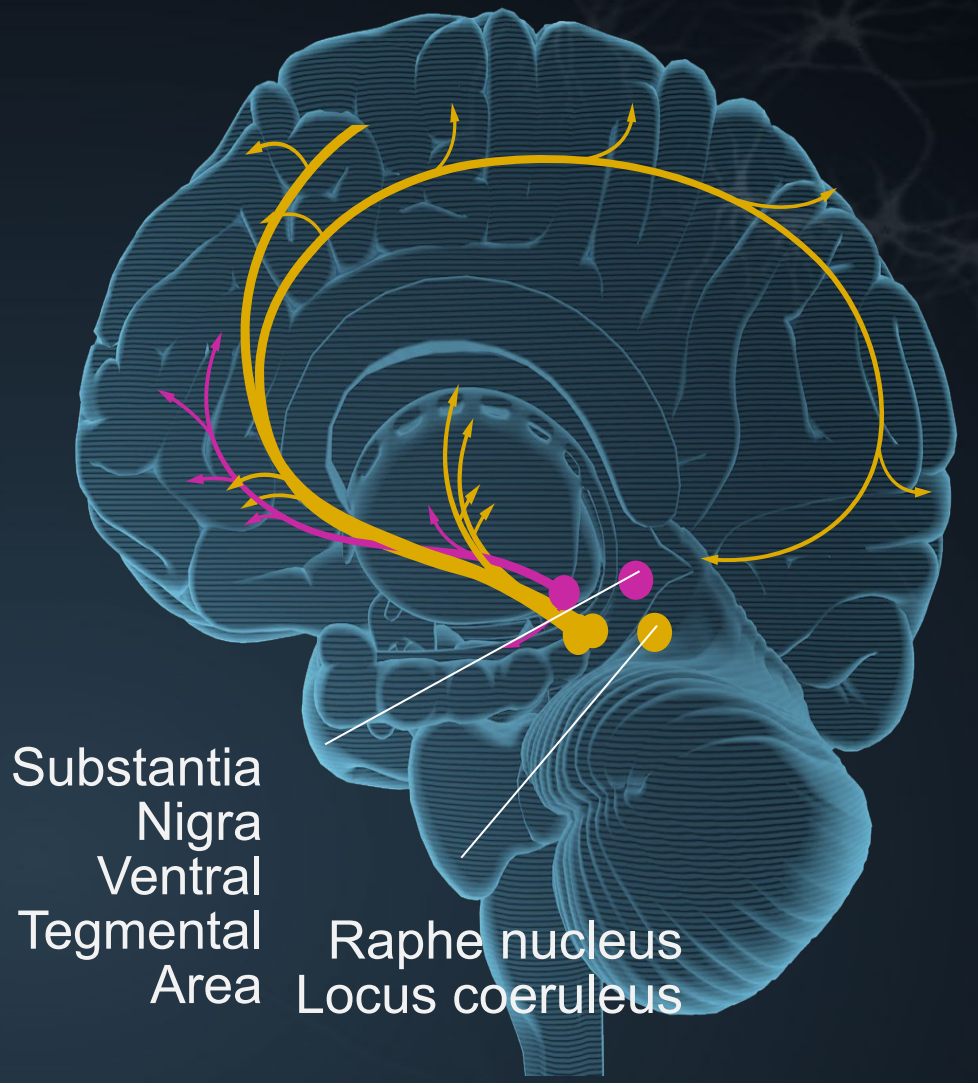
## PATHWAY DISORDERS

- Caused by mutations in several genes and can be compounded by environmental factors such as smoking or diet
- Common examples include heart disease, cancer and type 2 diabetes
- Require more complex therapeutic approaches than monogenic disease-targeting therapies, which are mainly gene addition (or augmentative) gene therapies
- Larger patient populations

# Midbrain Infusion of AAV2-AADC

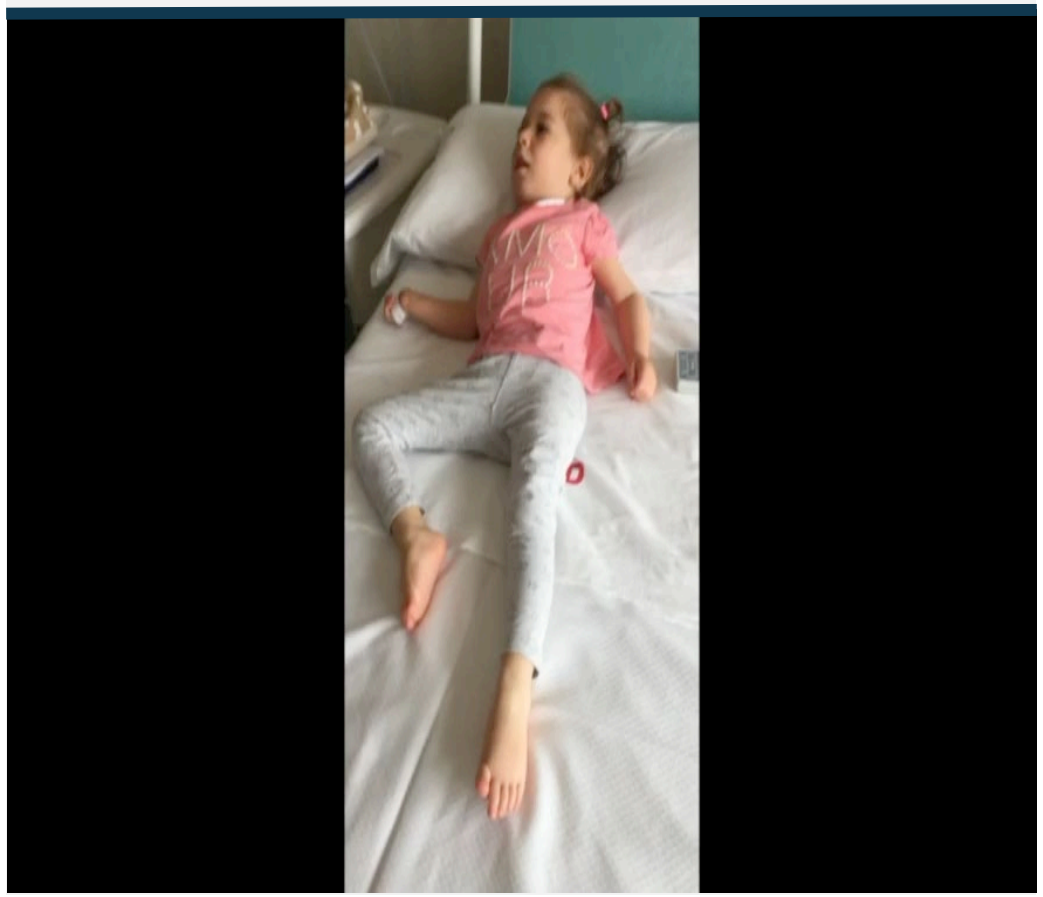
- Dopamine Pathways
- Serotonin Pathways

- Dopaminergic neurons in the midbrain (SNc, VTA) project to multiple brain regions
- Goal of gene delivery = restore dopamine synthesis in midbrain dopaminergic neurons



# AAV2-AADC: 5 Children Subsequently Learned to Walk Independently

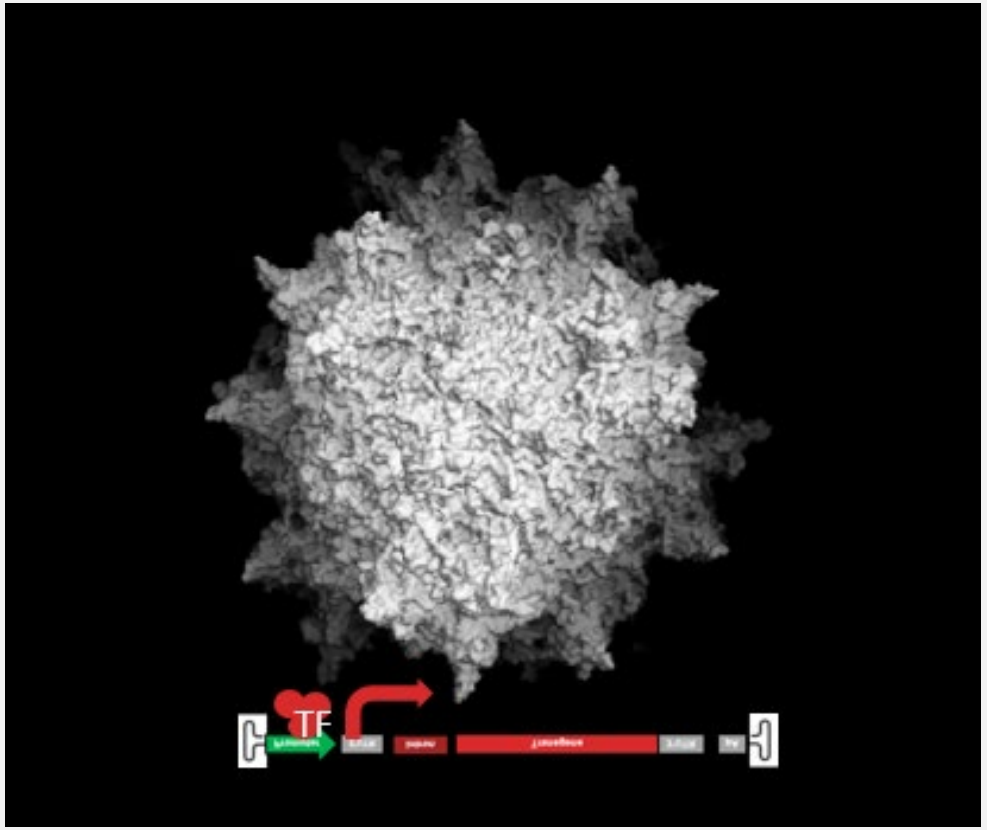
**SUBJECT 10 (BASELINE) - AGE 4.5 YEARS**



**3 YEARS POST-GT - AGE 7.5 YEARS**

# Building a Therapeutic Platform Enables to Extend the Field of Application of the Technology to Multiple Diseases

## VALIDATION IN SINGLE GENE DEFECT




## EXPANSION TO LARGER MARKET SIZES WITH SAME TECHNOLOGY

# Parkinson's Disease Gene Therapy (AB-1005)

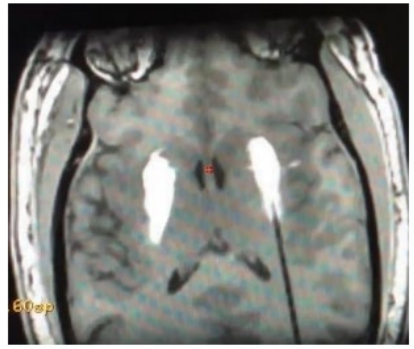
MONOGENIC DISORDERS — AskBio MAKING HISTORY — PATHWAY DISORDERS

## DISEASE & UNMET MEDICAL NEED

- Parkinson's Disease is the most common movement disorder caused by the progressive neurodegeneration of dopaminergic neurons
- Limited symptomatic treatment options available
  - Dopaminergic medications, effective at early stages, become less and less effective with disease progression
  - Deep brain stimulation (DBS) carries the risk of infections, stroke, seizures, is costly and typically requires follow-up maintenance surgeries
- No approved treatments to slow or change the course of disease progression

## OUR APPROACH

- The AB-1005 vector expresses a neurotrophic factor (GDNF) essential for the development and survival of dopaminergic neurons
- AB-1005 aims to slow, stop or reverse disease progression by restoring function and providing neuroprotection to susceptible dopaminergic neurons
- Restored dopaminergic tone potentially results in the improvement of motor control including restored ability to perform activities of daily living. Possible improvements on the non-motor symptoms of PD and the function of neuronal networks are being assessed.
- **Surgical Delivery:** One-time bilateral delivery of AB-1005 via minimally invasive, MRI-monitored neurosurgery



# Parkinson's Disease Gene Therapy (AB-1005)

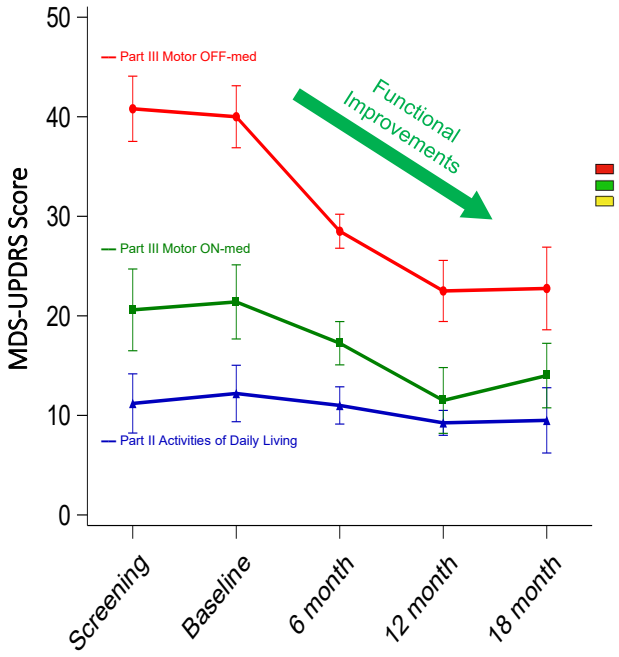
MONOGENIC DISORDERS — AskBio MAKING HISTORY — PATHWAY DISORDERS

## Turning back the clock on Parkinson's disease

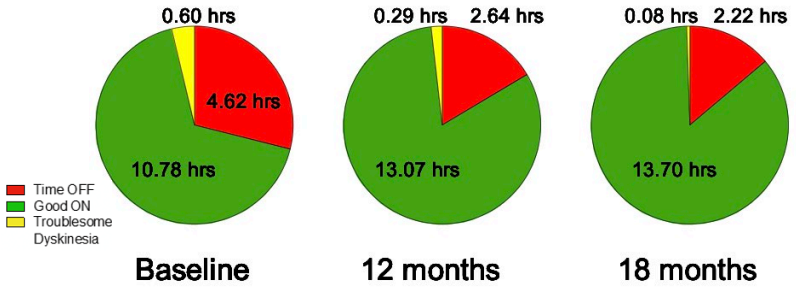
PHASE Ib

### CLINICAL DATA

Neurologist rated improvements in motor performance




Patient-reported recovery of motor performance




- 18-month clinical data **shows marked motor improvement compared to natural history**
- **Functional effects are progressive, similar to NHP studies**: Ongoing improvements reported beyond 6 months, unlike brief improvement in other CGTs or placebo effects
- **Clinically meaningful improvements consistent with anticipated MoA** – neuron regrowth and progressive restoration of dopamine function

### ADDRESSABLE PATIENT POPULATION

| Indication | Patients |
|---|---|
| Parkinson's Disease | US ~1 million |

### ASSET POTENTIAL

| Indication | Asset Potential |
|---|---|
| Parkinson's Disease | ●●● |

●○○ <€500m ●●○ €500m–€1bn ●●● >€1bn

### UPCOMING DEVELOPMENT MILESTONES

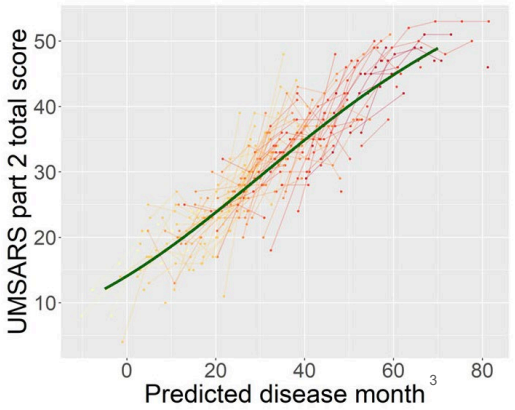
Initiation of randomized, double-blinded, sham-surgery controlled Phase 2 RESTORE-PD study

# Multiple System Atrophy (MSA) Gene Therapy

MONOGENIC DISORDERS — AskBio MAKING HISTORY — PATHWAY DISORDERS

## AB-1005 (AAV2-GDNF) already well tolerated in Parkinson´s Disease patients[1]

### DISEASE & UNMET MEDICAL NEED




**MSA** is a **fast-progressing** disease with **symptoms similar to Parkinson's**

- a-synuclein aggregation in the brain
- Glial dysfunction and loss of neurotrophic factors (GDNF)
- Neuroinflammation

**Onset:** Mid-life

**Prognosis:** Death ~8-10 years after diagnosis

**Epidemiology (US & EU):** Prevalence ~35K, incidence ~4.5K per year

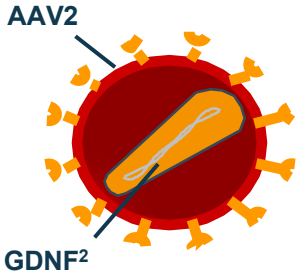
**Unmet medical need:** No disease-modifying therapy

**SoC:** Symptom management

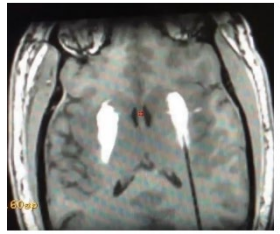
**Clinical competition:** Several clinical programs addressing α-synuclein

### OUR APPROACH

**Mode of action:** Restore and maintain brain cell function by expression of GDNF in the basal ganglia




**Surgical Delivery:** One-time bilateral delivery via MRI-monitored neurosurgery



### Why GDNF for MSA:

- 76% loss of GDNF in MSA post-mortem tissue[4]
- Degeneration of the dopaminergic neurons causes parkinsonian features in MSA
- Improve "sick-but-not-dead" neurons by GDNF restoration to
  - Enhance dopamine production
  - Increase neurite density
  - Reduce α-synuclein accumulation
  - Attenuate neuroinflammation

[1] Product has been applied in Phase 1 and Phase 1b studies for Parkinson's disease already; [2] Glial cell line-derived neurotrophic factor; [3] Source: Kühnel et al 2022, [4] Source: Goldstein et al 2019

# Multiple System Atrophy (MSA) Gene Therapy

MONOGENIC DISORDERS — AskBio MAKING HISTORY — PATHWAY DISORDERS

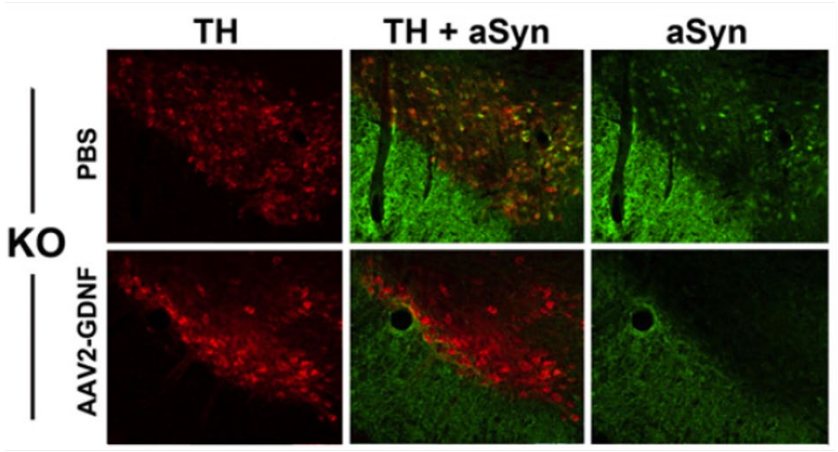
## MSA is an adult-onset, spontaneously occurring rare neurodegenerative disease

PHASE I

### PRECLINICAL DATA

// MSA is pathologically defined by glial cytoplasmic inclusions (GCIs) containing α-synuclein

// AAV2-GDNF delivery in a GM1 knock-out transgenic mouse attenuated the accumulation of α-synuclein in the substantia nigra.[1]




Source: Figure modified from Hadazcek et al 2015

### ADDRESSABLE PATIENT POPULATION

| Indication | Patients |
|---|---|
| Multiple system atrophy | US/EU ~ 35k |

### ASSET POTENTIAL

| Indication | Asset Potential |
|---|---|
| Multiple system atrophy | ●●○ |

●○○ <€500m ●●○ €500m–€1bn ●●● >€1bn

### UPCOMING DEVELOPMENT MILESTONES

Recruitment & dosing of Phase 1 RESTORE-MSA study

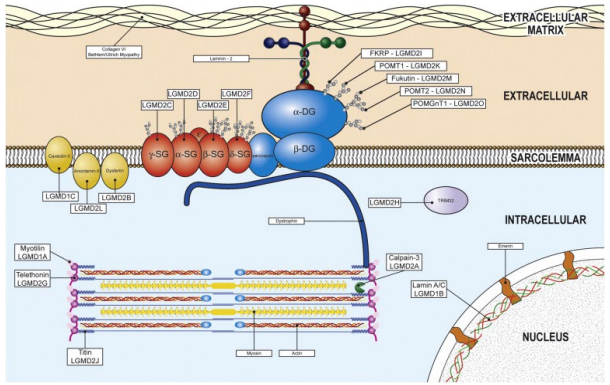
# Limb-girdle Muscular Dystrophy 2I/R9 Gene Therapy

MONOGENIC DISORDERS — AskBio MAKING HISTORY — PATHWAY DISORDERS

## AB-1003: Mitigate the Molecular Pathobiology and Improve Functions

### DISEASE & UNMET MEDICAL NEED

- Limb-girdle muscular dystrophy 2I/R9 (LGMD2I/R9) is a monogenic, rare disease.
- Autosomal recessive muscular dystrophy is caused by mutations in the gene for fukutin-related protein (FKRP), needed for glycosylation of α-dystroglycan (α-DG).
- LGMD2I/R9 patients are prone to cardiac fibrosis, respiratory complications, and dysphagia that may lead to early death.
- The management of LGMD2I/R9 is supportive. No disease-modifying treatments are approved.




### OUR APPROACH

- Single-time systemic administration of AB-1003 contains a normal FKRP gene and uses an AAV9 capsid and the Syn-100 promoter.
  - Self-complementary AAV technology to target and express FKRP protein, predominantly in skeletal muscle, diaphragm and cardiomyocytes.
  - Syn-100 muscle-specific promoter enables relatively low doses
- Non-clinical safety and bioactivity data from two different disease mouse models demonstrated FKRP expression in target tissues and functional improvements

# Limb-girdle Muscular Dystrophy 2I/R9 Gene Therapy

MONOGENIC DISORDERS — AskBio MAKING HISTORY — PATHWAY DISORDERS

## Innovative Clinical Trial Design to Support Accelerated Development and Regulatory Approval

PHASE I/II

### PRECLINICAL DATA

// Robust Bioactivity in Preclinical Dose Range Finding Study

| Evaluation | Low dose | High dose |
|---|---|---|
| Muscle strength | >75% of wild-type | >90% of wild-type |
| Exercise distance | >75% of wild-type | >90% of wild-type |
| Mean Serum CK levels | Comparable to wild-type | Comparable to wild-type |

// Part I of a Phase 1/2 study has started in Q1 2023:

- // Double-blind, randomized, placebo-controlled design (N=10) to establish safety, tolerability, and preliminary efficacy
- // Part I will build the foundation for the registrational Part II of the clinical study.

### ADDRESSABLE PATIENT POPULATION

| Indication | Patients |
|---|---|
| Limb-Girdle (LGMD2I/R9) | ~7k worldwide |

### ASSET POTENTIAL

| Indication | Asset Potential |
|---|---|
| Limb-Girdle (LGMD2i) | ●●○ |

●○○ <€500m ●●○ €500m–€1bn ●●● >€1bn

### UPCOMING DEVELOPMENT MILESTONES

- Dosing the First Subject
- Completion of Part I Enrollment

# Congestive Heart Failure Gene Therapy

MONOGENIC DISORDERS — AskBio MAKING HISTORY — PATHWAY DISORDERS

## AB-1002 (AAV2i.8.I-1c): improves intracellular calcium cycling, decreases fibrosis and reverses remodeling

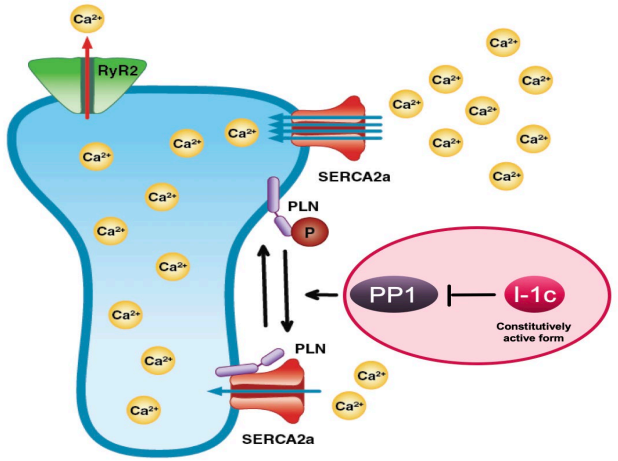
### DISEASE & UNMET MEDICAL NEED

// HF is a high prevalent disease, especially in the Western world

// For HFrEF well established guidelines are in place for treatment of those in earlier stages of the disease.

// In patients with end stage heart failure, mortality is 50% at 5 years, and limited therapeutic options are available.

// No disease modifying treatment available for any stages of CHF




### OUR APPROACH

// AB-1002 targets a subset of advanced HFrEF patients (NYHA III) who have non-ischemic etiology.

// Abnormal calcium cycling secondary to a decrease in the Sarcoplasmic reticulum calcium ATPase (SERCA2a) and an increase in protein phosphatase 1 activity in heart failure.

// AB-1002 uses gene therapy to deliver a critical protein: a constitutively active form of inhibitor 1 of c which when expressed improves intracellular calcium cycling, decreases fibrosis and reverses remodeling.

// These cellular/molecular effects improve the overall function of the failing heart and the functional status of the patient.

# Congestive Heart Failure Gene Therapy

MONOGENIC DISORDERS — AskBio MAKING HISTORY — PATHWAY DISORDERS

## AB-100 (AAV2i.8.I-1c): Preliminary results suggest clinically meaningful improvements

PHASE I

### CLINICAL DATA

// Eight subjects with non-ischemic congestive heart failure (CHF) treated; 7 of the 8 subjects completed primary follow up (12 months)

// No product- or delivery-related serious adverse events at either tested dose

// Study participants in both cohorts exhibit directionally favorable efficacy results as evidenced by

1. New York Heart Association (NYHA) class reduction
2. Left Ventricular Ejection Fraction (LVEF) increase
3. Peak oxygen consumption (VO2 max) improvement
4. Quality of life assessment improvement.

### ADDRESSABLE PATIENT POPULATION

| Indication | Patients |
|---|---|
| Chronic Heart Failure | US/EU5 ~ 1.6 million |

### ASSET POTENTIAL

| Indication | Asset Potential |
|---|---|
| Chronic Heart Failure | ●●● |

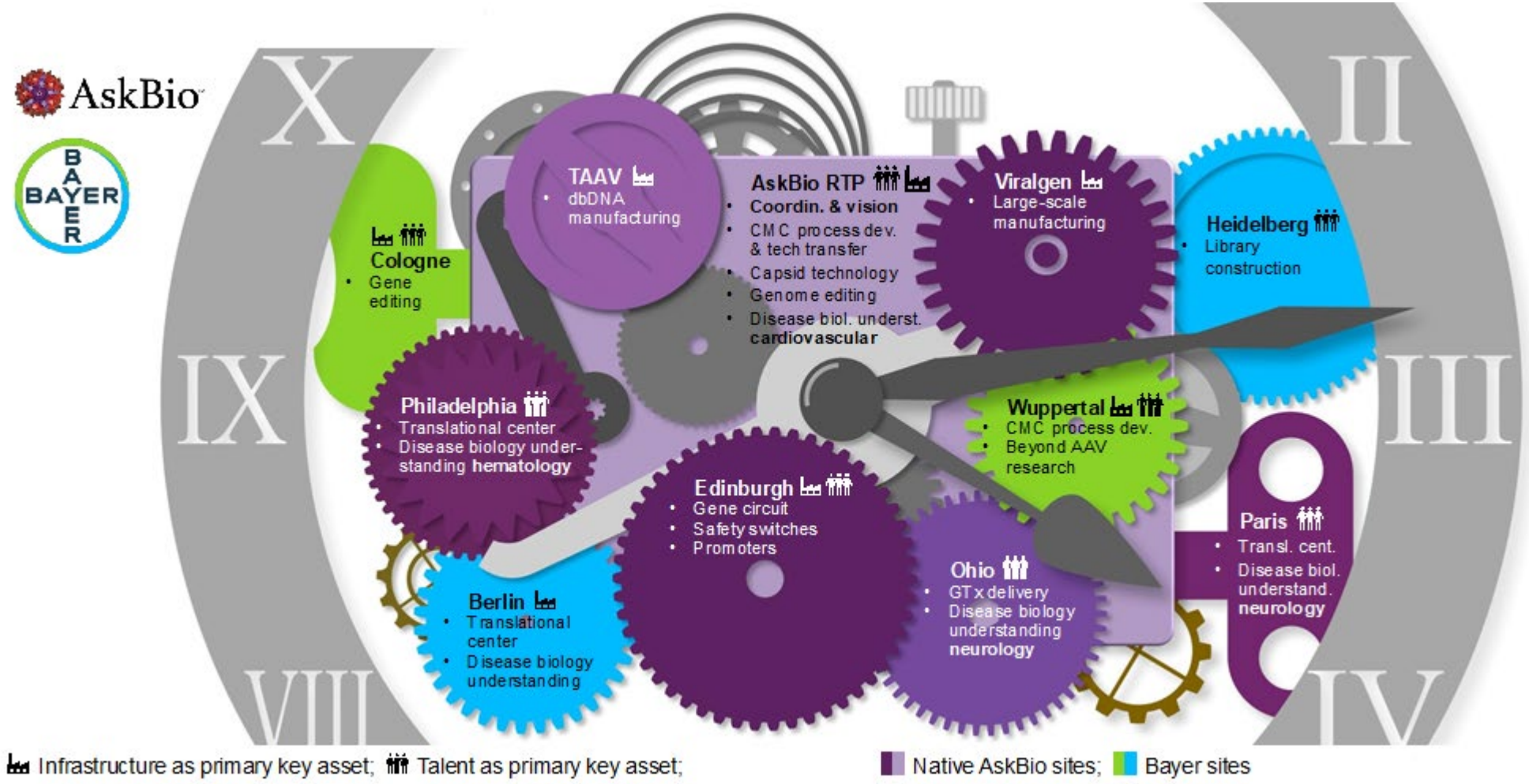
●○○ <€500m ●●○ €500m–€1bn ●●● >€1bn

### UPCOMING DEVELOPMENT MILESTONES

- Completion of Cohort 1 Expansion of Phase 1 with 3 additional subjects
- Initiation of GenePPhit: *A phase II, adaptive, randomized, double-blind, placebo controlled, multicenter trial*

# The Individual AskBio Sites Contribute Their Respective Competency Strongholds to the End-to-End Development Platform

## AskBio competence distribution



# Key Messages Today

// *Highly attractive market*:
Gene therapy market expected to grow significantly until the end of the decade

// *Pioneer in AAV-based gene therapy:*
Unparalleled pipeline, talent and manufacturing capabilities

// *Robust therapeutic pipeline:*
Balanced portfolio addressing monogenic and pathway disorders

// *Scalable platform for continued growth and innovation:*
Building a platform enables to extend the field of application of the technology to multiple diseases

# *Concluding Remarks*

Christian Rommel

# Key Takeaways

## 1

### *Seize the opportunity for more impact*

Building on our long legacy and learnings, world-class expertise and differentiating modalities and platforms, we have an opportunity to **increase the scale of our impact** for patients and for Bayer.

## 2

### *Clear focus on value & differentiation*

Through rigorous assessment and prioritization, we now have a sharper focus on the areas of **greatest unmet need and highest potential** where we can make a difference by targeting the sweet spot of precision medicine.

## 3

### *Execute Innovation strategy*

Our R&D strategy is already up and running – we have a clear strategic focus, the platforms, the strategic partners, the modalities and the capabilities to deliver at pace – **we are positioned to succeed.**

## 4

### *Ready to move to the next phase of our history*

We are building a **truly differentiated high-value pipeline**, delivering patient impact, and delivering on our bold Pharma ambition. Following a thorough portfolio pruning, the vast majority of our (pre)clinical NME's have the potential to be first- or best-in-class, today.

# Pharmaceuticals
# R&D Event

Boston, US
June 28, 2023

# Appendix: Pharmaceuticals – Pipeline Overview[1] (as of June 16, 2023)

## Phase 0[2]

- **DGKalpha Inh** *(BAY 2862789)*
- **PSMA TAC** *(BAY 3546828)*
- **PSMA SMOL TAC** *(BAY 3563254)*
- **VVD NRF2 Inh** *(BAY 3605349)*
- **VVD STAT3 Inh** *(BAY 3630914)*
- **Anti-coagulant** *(BAY 3389934)*
- **Next Generation Liver MRI** *(BAY 3393081)*

## Phase I

- **Elimusertib** (ATR Inhibitor) *(BAY 1895344)*
- **AhR Inhibitor** *(BAY 2416964)*
- **mEGFR/HER2 Inhibitor** *(BAY 2927088)*
- **DGKzeta Inhibitor** *(BAY 2965501)*
- **CCR8 Ab** *(BAY 3375968)*
- **Congestive Heart Failure rAAV Gene Therapy** *(AB-1002 aka NAN-101)*
- **sGC Activator Oral** *(BAY 3283142)*
- **Anti-a2AP** *(BAY 3018250)*
- **sGC Activator Inhale** *(BAY 1211163)*
- **SEMA 3a** *(BAY 3401016)*
- **Bemdaneprocel** (Parkinson's Disease Cell Therapy) *(BRT-DA01)*
- **Parkinson's Disease rAAV Gene Therapy** *(AB-1005 aka AAV2-GDNF-PD)*
- **Multiple System Atrophy rAAV Gene Therapy** *(AB-1005 aka AAV2-GDNF-MSA)*
- **Pompe Disease rAAV Gene Therapy** *(ACTUS-101)*
- **Huntington's Disease rAAV Gene Therapy** *(AB-1001 aka BV-101)*
- **LGMD2I/R9 rAAV Gene Therapy** *(AB-1003 aka LION-101)*
- **GPR84 Antagonist** *(BAY 3178275)*

## Phase II

- **Regorafenib** (combi Nivolumab) *(BAY 734506)*
  // Solid tumors (recurrent or metastatic)
- **Asundexian (FXIa Inhibitor)** *(BAY 2433334)*
  // Major Adverse Cardiac Events Prevention (PACIFIC-AMI)
- **Zabedosertib** (IRAK4 Inh.) *(BAY 1834845)*
  // Atopic Dermatitis (DAMASK)
- **Gadoquatrane** (High Relaxivity Contrast Agent) *(BAY 1747846)*
  // Magnetic Resonance Imaging (HRCA-PAT)
- **Runcaciguat** (sGC Activator) *(BAY 1101042)*
  // Non-prolif. Diabetic Retinopathy (NPDR) (NEON-NPDR)

## Phase III

- **Copanlisib** (PI3K Inhibitor)
  // Non-Hodgkin Lymphoma (CHRONOS-4)
- **Darolutamide** (AR Inhibitor)
  // Prostate Cancer (mHSPC) (ARANOTE)
  // Adjuvant Prostate Cancer (DASL-HiCaP)
  // Prostate Cancer with Biochemical Recurrence after Curative Radiotherapy (ARASTEP)
- **Finerenone** (MR Antagonist)
  // Heart Failure (HFmr/pEF) (FINEARTS-HF)
  // Non-diabetic CKD (FIND-CKD)
- **Vericiguat** (sGC Stimulator)
  // Heart Failure (HFrEF) (VICTOR[3])
- **Asundexian** (FXIa Inhibitor)
  // Stroke Prevention in Atrial Fibrillation (OCEANIC-AF)
  // 2º Stroke Prevention (OCEANIC-STROKE)
- **Elinzanetant** (Neurokinin-1,3 Rec Antagonist)
  // Vasomotor Symptoms (OASIS)
- **Aflibercept 8mg** (VEGF Inhibitor)
  // Retinal Vein Occlusion (QUASAR)

## Submissions

- **Aflibercept 8mg** (VEGF-Inhibitor)
  // EU, JP, US[4]: Diabetic Macular Edema (DME)
  // EU, JP, US[4], CN: Neovasc. Age-rel. Macular Degen. (nAMD)

Oncology
Cardiovascular+[5]
Neurology & Rare Diseases
Immunology
Others

New molecular entity
Life cycle management

Protein Therapeutics
Cell Therapy
Contrast Agent
Genetic Medicine
Radiotherapy
Small Molecule

[1] Bayer and partner sponsored + 3rd party label enabling studies with first patient first visit [2] Pre-clinical selected assets on path to IND [3] Conducted by Merck & Co [4] US submission made by Regeneron [5] Including Precision Cardiovascular, Nephrology & Acute Care

# Appendix: Abbreviations (1/4)

| | |
|---|---|
| AAV | Adeno-associated virus |
| Ab | Antibody |
| ADC | Antibody-drug conjugate |
| AF | Atrial fibrillation |
| AI | Artificial intelligence |
| AIS | Acute ischemic stroke |
| ALCL | Anaplastic large cell lymphoma |
| AMD | Age-related macular degeneration |
| APT | Antiplatelet therapy |
| AR | Androgen receptor |
| BCR | Biochemical relapse |
| BD&L | Business Development & Licensing |
| BIC | Best in class |
| bn | billion |
| BP | Blood pressure |
| CAGR | Compound Annual Growth Rate |
| CAR-T | Chimeric antigen receptor modified T cells |
| cGMP | Current good manufacturing practice |
| CGT | Cell and gene therapy |
| CHF | Congestive heart failure |
| CI | Confidence interval |
| CKD | Chronic Kidney Disease |
| CMC | Chemistry, manufacturing and controls |
| COPD | Chronic Obstructive Pulmonary Disorder |
| CRC | Colorectal cancer |
| CV | Cardiovascular |
| DA | Dopamine |
| DAPT | Dual Antiplatelet Therapy |
| DBS | Deep brain stimulation |
| DC | Development Candidate |
| DDRi | DNA damage repair inhibitors |
| DFMs | Direct Functional Modulators |
| DGK | Diacylglycerol Kinases |
| DKD | Diabetic Kidney Disease |
| DMD | Duchenne Muscular Dystrophy |
| DNA | Deoxyribonucleic acid |

# Appendix: Abbreviations (2/4)

| | |
|---|---|
| DOACs | Direct oral anticoagulants |
| eGFR | estimated glomerular filtration rate |
| EGFR | Epidermal Growth Factor Receptor |
| ESRD | End-stage renal disease |
| EU5 | France, Germany, Italy, Spain, United Kingdom |
| fAD | familial Altzheimer's disease |
| FDA | U.S. Food and drug administration |
| FIC | First in class |
| FIH | First-in-Human |
| FKRP | Fukutin-related protein |
| FPFV | First Patient First Visit |
| FTE | Full Time Equivalent |
| GA | Geographic Atrophy |
| GCIs | Glial cytoplasmic inclusions |
| GDNF | Glial cell line-derived neurotrophic factor |
| GI | Gastrointestinal |
| GM1 | GM1 gangliosidoses |
| GOF | Gain of function |
| GP | General practitioner |
| GU | Genitourinary |
| HCC | Hepatocellular Carcinoma |
| HER2 | Human epidermal growth factor receptor 2 |
| HF | Heart failure |
| HFF | Hospitalization heart failure |
| HFmrEF | Heart failure with midrange ejection fraction |
| HFpEF | Heart failure with preserved ejection fraction |
| HFrEF | Heart Failure with reduced Ejection Fraction |
| HNSCC | Head and neck squamous cell carcinoma |
| HR | Hazard ratio |
| HSCs | Hematopoietic stem cells |
| HTS | High throughput screening |
| IBD | Inflammatory Bowel Disease |
| ICIs | Immune checkpoint inhibitors |
| IND | Investigational New Drug |
| Inh | Inhibitor |
| IO | Immuno-Oncology |

# Appendix: Abbreviations (3/4)

| | |
|---|---|
| IRDs | Inherited retinal disorders |
| ISTH | International Society on Thrombosis and Hemostasis |
| LCM | Life Cycle Management |
| LC-MS/MS | Liquid chromatography tandem mass spectrometry |
| LGMD2i/R9 | Limb-Girdle Muscular Dystrophy |
| LOPD | Late onset Pompe Disease |
| LVEF | Left Ventricular Ejection Fraction |
| m | million |
| mCRPC | Metastatic castration resistant prostate cancer |
| MDS | Movement Disorders |
| mHSPC | Metastatic hormone sensitive prostate cancer |
| MOAs | Mode of action |
| MRA | Mineralocorticoid Receptor Antagonist |
| MSA | Multiple System Atrophy |
| MSCs | Mesenchymal stem cells |
| NASH | Non-alcoholic steatohepatitis |
| ndCKD | Non-diabetic chronic kidney disease |
| NHP | Nonhuman primate |
| nmCRPC | non-metastatic castration resistant prostate cancer |
| NME | New Molecular Entity |
| NNT | Number needed to treat |
| NO | Nitric Oxide |
| NRD | Neurology and Rare Diseases |
| NRLD | National Reimbursement Drug List |
| NSCLC | Non small cell lung cancer |
| NYHA | New York Heart Association |
| ODD | Orphan drug designation |
| OSM | Oncostatin M |
| OTC | Over-the-counter |
| PD | Parkinson’s Disease |
| PD-L1 | Programmed Cell Death Ligand 1 |
| PPD | Primary Photoreceptor Diseases |
| PPI | Protein-protein Interaction |
| PRP | Photoreceptor Precursor Cell |

# Appendix: Abbreviations (4/4)

| | |
|---|---|
| PSA | Psoriatic arthritis |
| PSC | Pluripotent Stem Cells |
| PSO | Psoriasis |
| PTS | Probability of Technical Success |
| RA-ILD | Rheumatoid arthritis associated interstitial lung disease |
| RCC | Renal cell carcinoma |
| R&D | Research & Development |
| RED | Research & Early Development |
| RNA | Ribonucleic acid |
| ROS1 | C-ros oncogene 1) |
| RP | Retinitis Pigmentosa |
| RPE | Retinal pigment epithelium |
| RTP HQ | Research Triangle Park Headquarter |
| SD | Stargardt's disease |
| sGC | Soluble guanylate cyclase |
| SGLT2i | Sodium-glucose Cotransporter-2 inhibitors |
| SMOL | Small Molecule |
| SOC | Standard of Care |
| SPAF | Stroke Prevention In Atrial Fibrillation |
| sq/ad | squamous/adenocarcinoma |
| T1D | Type 1 diabetes |
| T2D | Type 2 diabetes |
| TA | Therapeutic areas |
| TF | Transcription Factor |
| TH | T helper |
| TKI | Tyrosine kinase inhibitor |
| TNBC | Triple Negative Breast Cancer |
| TRT | Targeted radiotherapy |
| TRx | Total prescriptions |
| UACR | Urine Albumin Creatinine Ratio |
| Ub | Ubiquitin |
| VKA | Vitamin K Antagonists |
| VMS | Vasomotor symptoms |
| VTA | Ventral tegmental area |
| VVD | Vividion |
| WW | Worldwide |