Introduction to the Japanese Foundation for Rare Disease Research - JFRDR

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20260608

Agenda

- **Executive Summary**
- Biopharma Innovation – Brief History and Economics
- The Curious Case of Rare Disease Drugs – from Industry Driver to Global Drug Loss
- JFRDR
  - Value Proposition and Business Model
  - Funding Options

Our understanding of the world is based on **mathematical and mental models**, the quote below holds true for both

"All models are wrong, but some are useful"

George Box in Box and Draper, 1987: *Empirical Model-Building and Response Surfaces*

Successful biopharma innovation requires both: Innovation in **Science & Technology** and in the way innovation is **Organised** and **Funded**

Science & Technology

Major advances since the 1980's with technological capabilities outstripping biological understanding

e.g.: Penetrance and Expressivity in genetic diseases

Organisation & Funding

Only marginal change since the early 1980's with pressure for developing new models increasing of late

e.g.: Hundreds of drugs "stranded" in clinical trials due to commercial reasons

In this deck, the focus is put on the current and emerging models of the underlying economics of drug R&D and in particular on

- **The role of governments in shaping the innovation ecosystem**
- **The under-appreciated role of the cost of capital**
- **How the novel business model of JFRDR can help tackle the ultrarare disease challenge**

Executive Summary: There are **four main reasons why JFRDR is needed and should be funded by the government**

1. Social Contract

Rare Disease **patients** in Japan and elsewhere need drugs to **survive and live better lives**

2. Biomedical Innovation

The Japanese R&D ecosystem needs **public investment to re-establish long-lost competitiveness**, especially for **emerging modalities**

Here is an **opportunity for Japan** to duplicate the success of GHIT in an **emerging global collaboration to address another market failure: Ultrarare disease drug loss**

4. National Security

At a time when global supply chains and alliances are disrupted, **Japan needs a much larger degree of biopharma innovation and manufacturing capability (= lower dependence on US)** than available today

3. Business Model Innovation

JFRDR provides the Japanese policy makers with an opportunity to **test an alternative business model** for **financing, developing and reimbursing biopharma innovation**, focusing on drugs for which **market mechanisms fail**

Source: JFRDR

Will the JFRDR model work?
We will only find out if we try!

„Es ist nicht genug zu wissen, man muß auch anwenden; es ist nicht genug zu wollen, man muß auch tun."

“Knowing is not enough; we must apply. Willing is not enough; we must do.”

Source: Goethe: Wilhelm Meisters Wanderjahre

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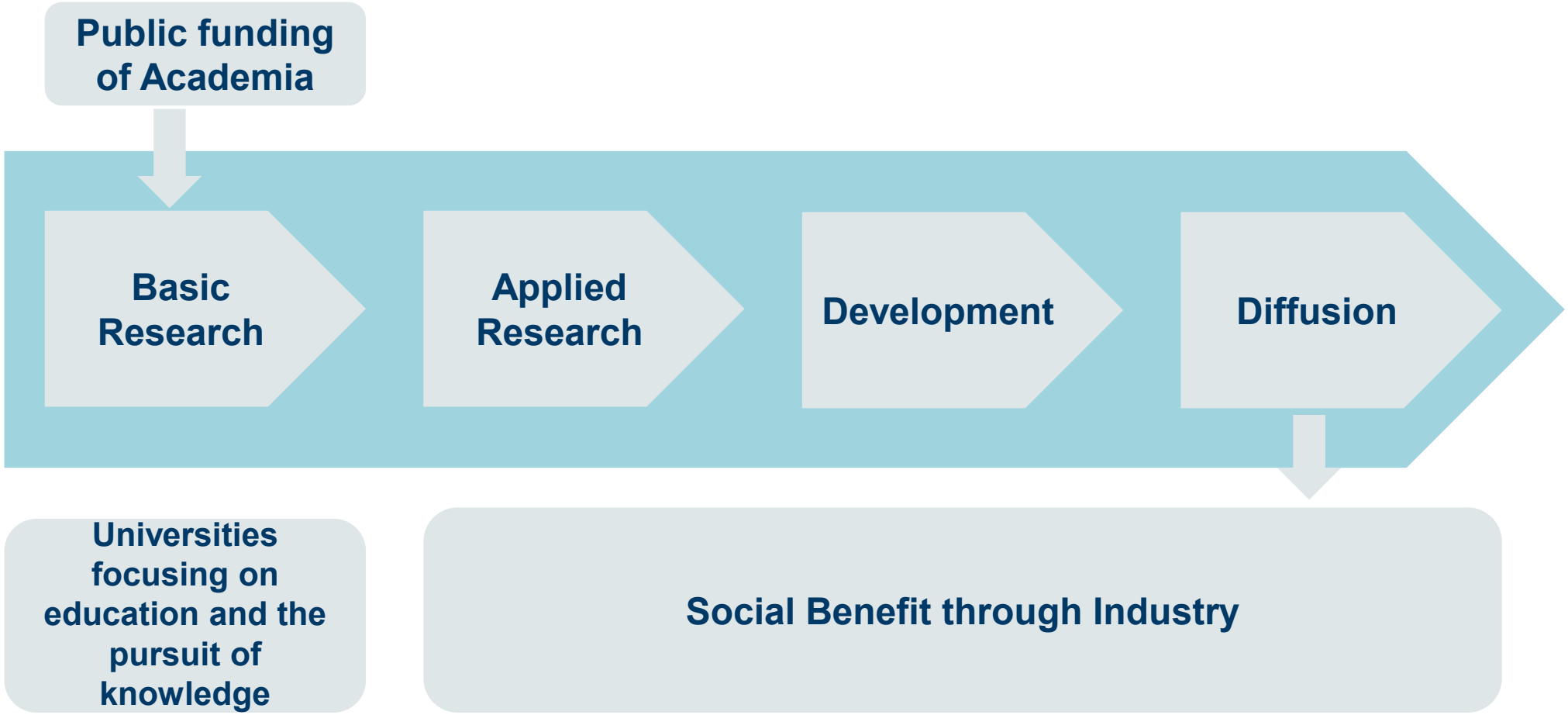
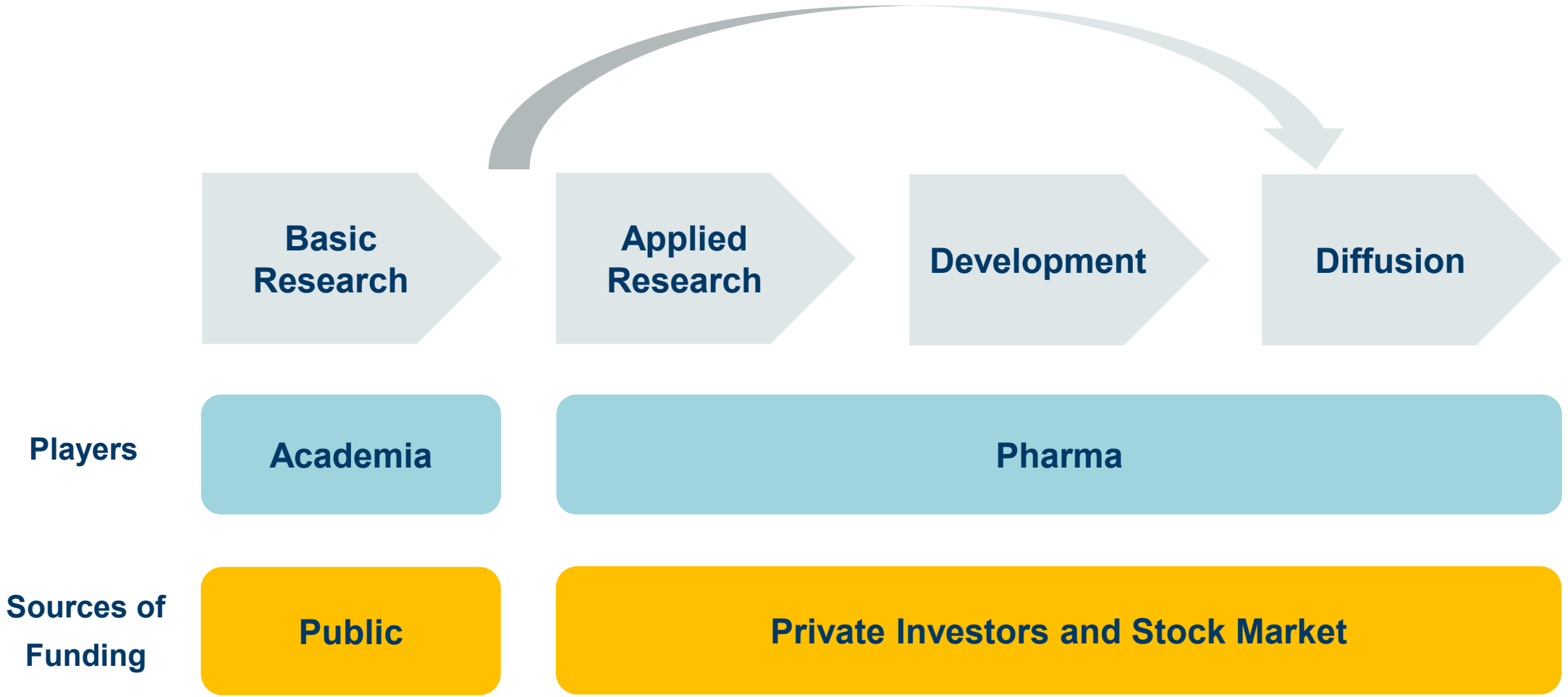
- A Potential Solution for Ultrarare Diseases: JFRDR

In the US, the post-WW II consensus on funding biomedical research was based on Vannevar Bush‘s report on „**Science – the Endless Frontier**[1]“, where **public science funding would ultimately lead to social benefit**



Source: 1) https://nsf-gov-resources.nsf.gov/2023-04/EndlessFrontier75th_w.pdf

In a highly simplified view on the division of tasks, publicly-funded **Academia** focused on **Basic Research** and **for-profit Pharma** took care of **translation, development and commercialisation**



Source: JFRDR

Around 1980, the dominant **Political Economy** of Western countries radically changed, leading to **major financial and antitrust deregulation,** as well as the new model of **VC-financed biotech and focused BigPharma**, all ultimately **fuelled by rapidly rising US price levels**

Main Reform Triggers

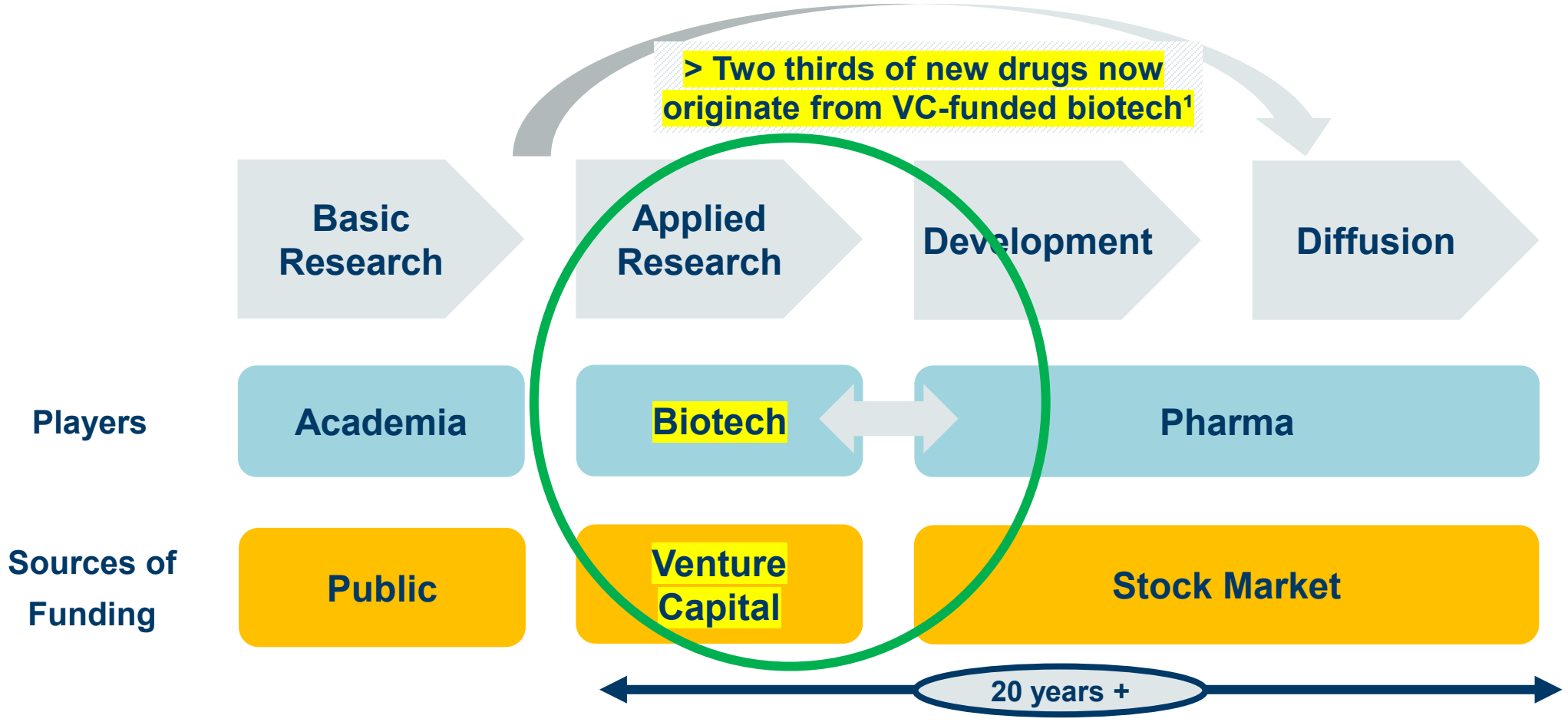
Bipartisan deregulation driven by political unhappiness with **slowing innovation at a time of reduced science funding**

- **Bayh Dole Act**
- **Diamond vs Chakrabarty**
- **Strengthening of Patent Courts**
- **Cut in top tax rate on capital gains from 49% to 28% in 1978**
- **Relaxation of the Prudent Man rule**
- **Orphan Drug Act 1983, Breakthrough Denomination 2012**
- **Lax NASDAQ listing requirements**
- A dozen more regulatory and legislative changes around 1980
- **(for the larger context, cf. Kurt Anderson's "Evil Geniuses")**

- **An explosion of innovation…**
- **…and of US price level for newly-launched drugs…**
- **…increasingly driven by the emergence of VC-funded biotech and focused Big Pharma**

Source: JFRDR

These policy changes in the US around **1980** aimed at removing some of the key barriers to innovation and drove the **emergence of the current US Biomedical Innovation System** in which **innovation looks like being driven by markets**



Source: 1) https://www.fiercebiotech.com/biotech/emerging-biopharma-companies-dominate-rd-pipeline-22-iqvia-finds

There is a **legitimate alternative view** of **funding** that is not so much talked about, a view in which the **vast majority of biomedical R&D funding** comes from **public sources - the financial contribution from VCs is crucial but limited**

Billions of US$ invested by **California, Massachussetts, New York, Texas**, Pennsylvania, North Carolina and other states in local ecosystems in the last twenty years

NIH, etc

Biopharma in US

Crucial entrepreneurial and managerial role in transforming academic seeds into products for patients

Social Security

$50bn + pa for science and technology

World-leading Science

VC-funded biotech

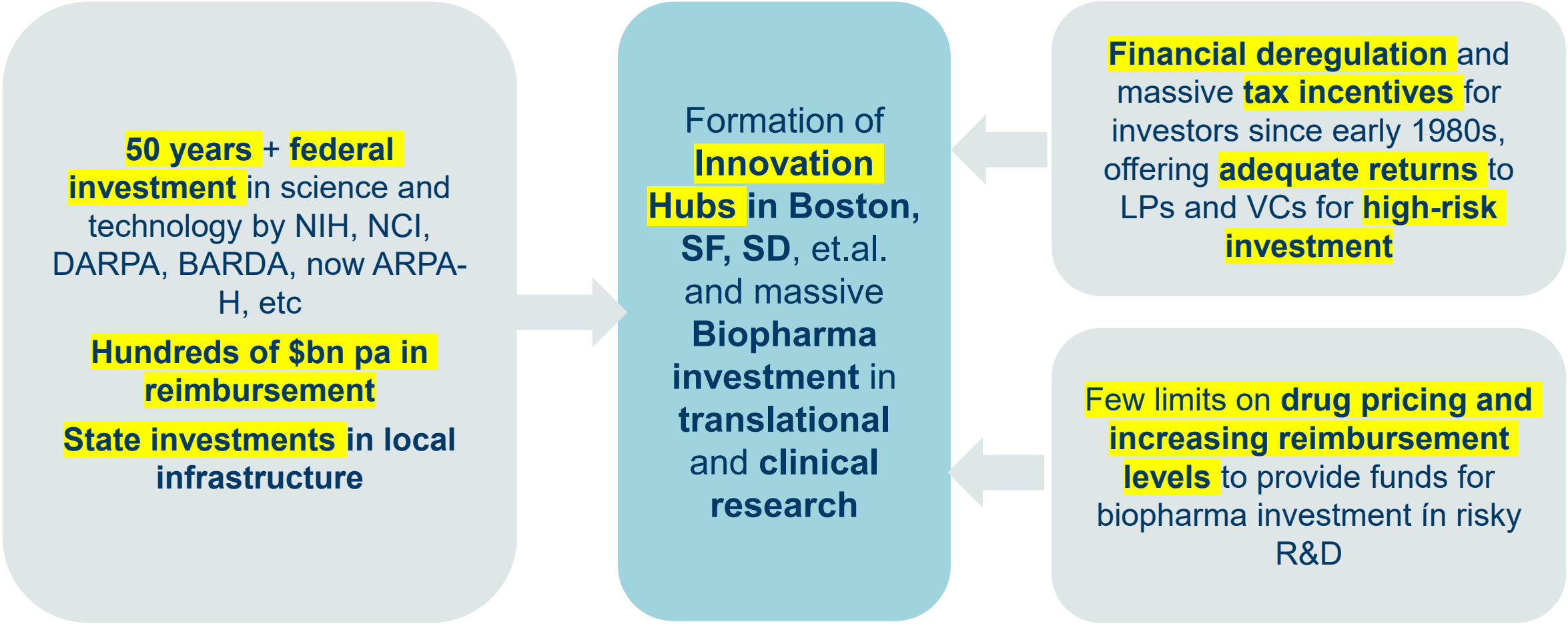
Varying between $10bn - $25bn pa

Hundreds of $bn pa in reimbursement

70% of global biopharma revenues

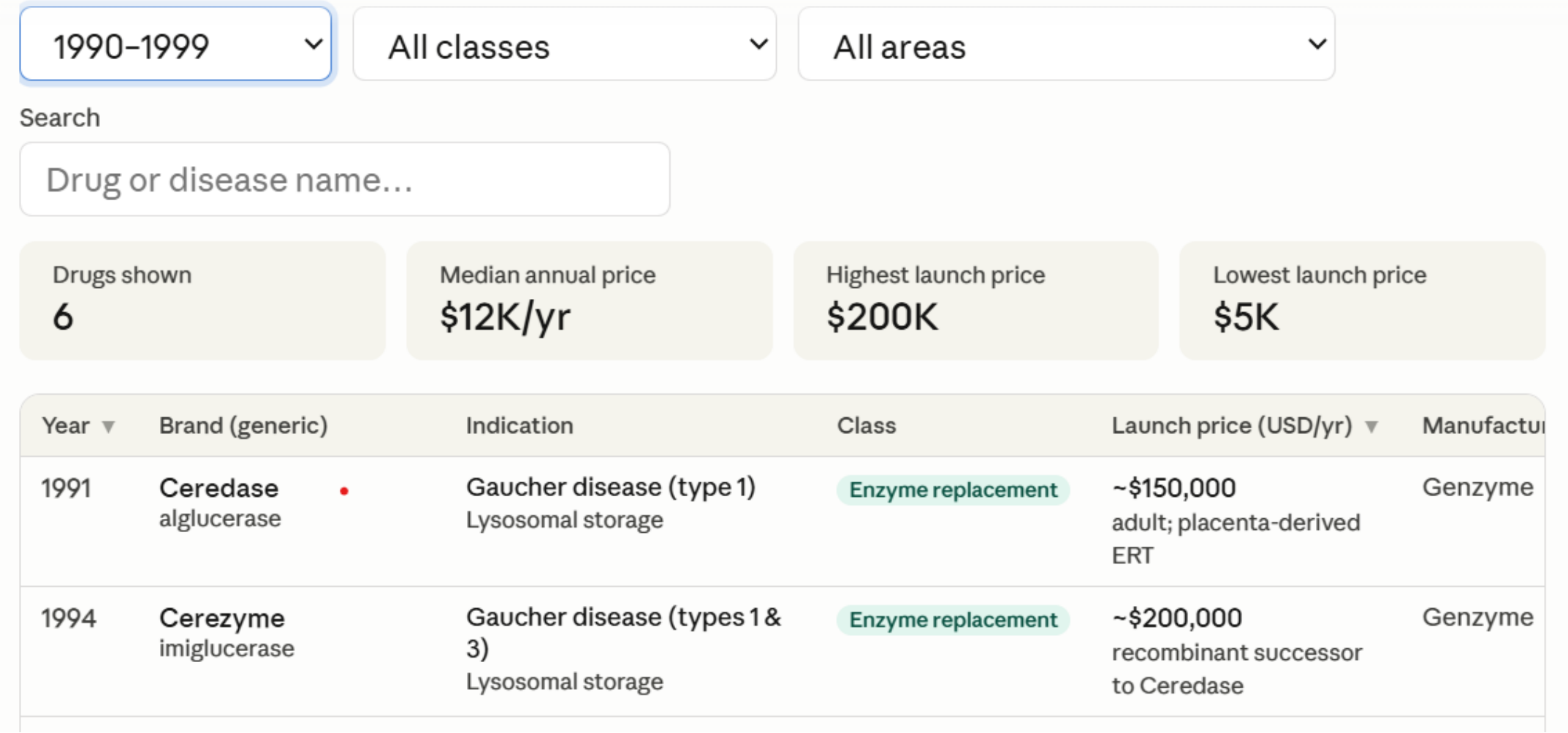
Source: JFRDR

Two reasons for success of the US biopharma innovation ecosystem: Public funding and financial deregulation – it is neither desirable nor effective to **copy single elements** of this policy mix at much smaller scale, so little wonder **Europe and Japan have been falling behind**



Source: JFRDR

For **orphan drugs**, median launch prices increased from **$12K pa** in the **1990s**…



Sources: Published WAC/list prices at or near US launch from academic literature, FDA approval records, press releases, ICER reports, and pharmaceutical trade media. All prices are annual list price (WAC) unless otherwise noted. One-time therapies show single-treatment price. Prices shown are at or near launch; many have since increased substantially – selection of 75 well-documented orphan drugs out of a total of 491 novel orphan drugs approvals between 1990 and 2022

…to $490K pa in the 2020's – (21x for Lenmeldy vs Ceredase!)

2020–present | All classes | All areas

Search

Drug or disease name…

Drugs shown	Median annual price	Highest launch price	Lowest launch price
20	$490K/yr	$4.3M	$3K

Year	Brand (generic)	Indication	Class	Launch price (USD/yr)	Manufactu
2020	Tecartus brexucabtagene autoleucel	Mantle cell lymphoma (r/r) Oncology	CAR-T	$373,000† one-time; 3rd CAR-T approved	Kite / Gilea
2020	Oxlumo lumasiran	Primary hyperoxaluria type 1 Metabolic	RNA therapy	~$470,000 RNAi; ultra-rare renal disorder	Alnylam
2023	Lyfgenia lovotibeglogene autotemcel	Sickle cell disease Haematology	Gene therapy	$3,100,000† one-time; lentiviral gene therapy	Bluebird b
2023	Casgevy exagamglogene autotemcel	Sickle cell disease / β-thalassaemia Haematology	Gene therapy	$2,200,000† first CRISPR-based therapy approved	Vertex / C Therapeu
2024	Lenmeldy atidarsagene autotemcel	Metachromatic leukodystrophy (MLD) Neurology	Gene therapy	$4,250,000† highest list price of any US drug at launch (2024)	Orchard Therapeu

Same source as previous page

Measured in **drug approvals** the model has been **spectacularly successful**, but success has come at the cost of **rapidly increasing prices levels in the US**

Analysis of around 100 injectable oncology drugs from 1990 to 2024

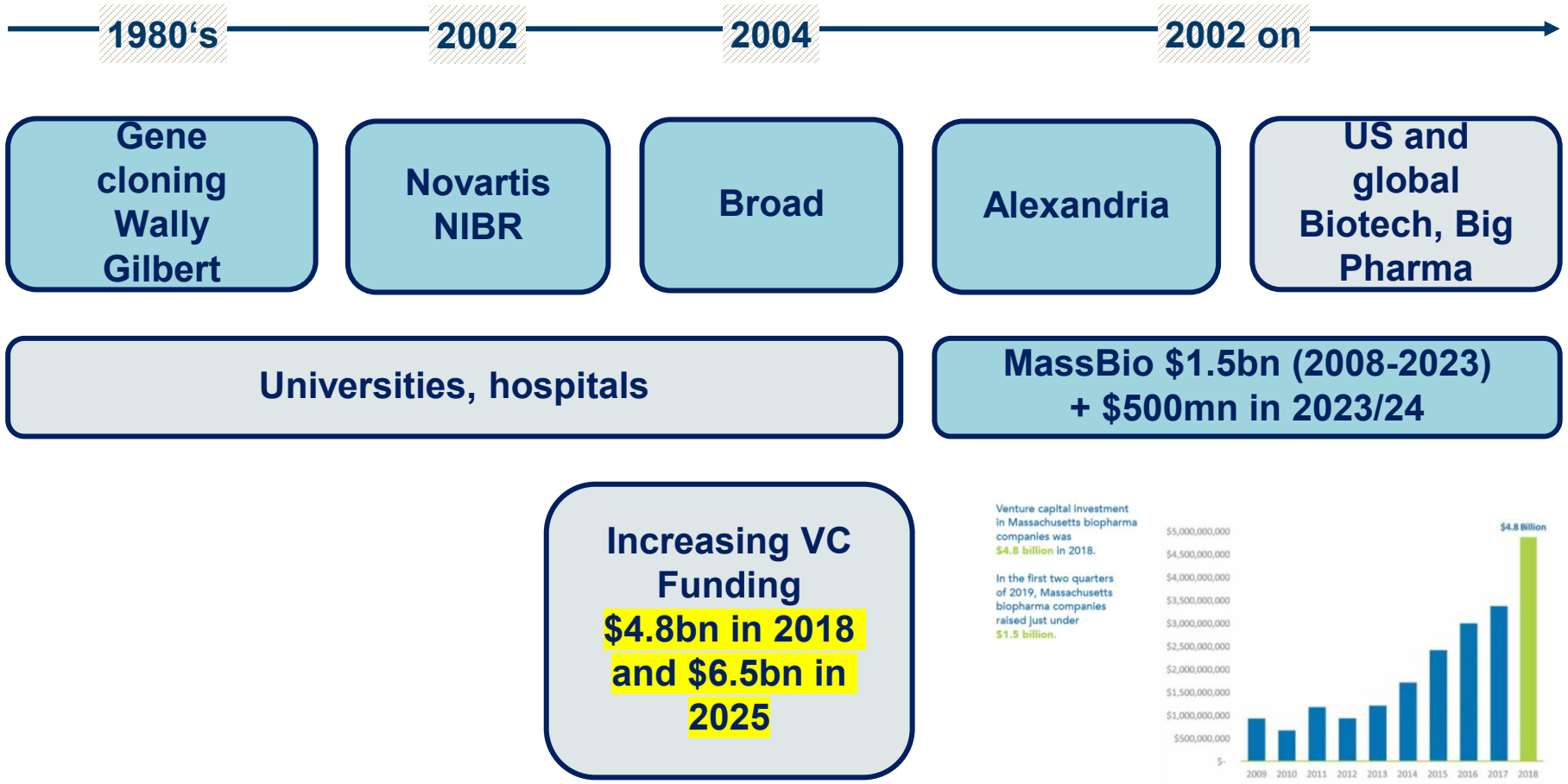
US gross annual treatment cost at launch

- Drugs like irinotecan launched at **~$5,300/month** in 1996 and rituximab at **~$3,500/month** in 1997
- By 2015, daratumumab launched at **~$17,500/month**
- Newer ADCs and bispecifics in the 2020s routinely start at **$20,000–$80,000/month**
- Dinutuximab (a paediatric neuroblastoma antibody approved in 2015) launched at **~$90,000/month** — among the highest in the dataset

As a result, the **US revenue share in global sales and profits** of most oncology drugs has increased from around **50% to >two thirds** in the **last 15 years**

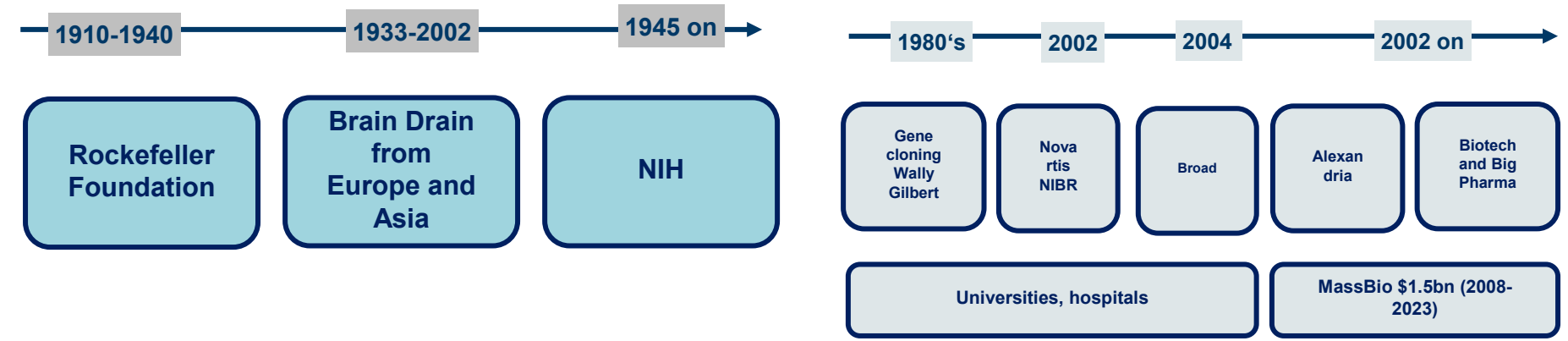
Sources: Monthly prices at FDA approval from MSK/Bach Center dataset (1965–2013); supplemented with ASP/WAC data from CMS, academic literature, ICER reports, and trade press for 2014–2024. All prices are nominal WAC (list price) at or near US launch — not inflation-adjusted and not net of rebates.

The emergence of the **Boston Biocluster dates back to the 1980s**, with the main impetus arguably due to **NIBR** and Real Estate Developer **Alexandria** in the early 2000‘s - other US hubs except SF were similarly positioned , but have been falling increasingly far behind



Source: JFRDR

But it was the **slow emergence of the US as a biology research powerhouse**[1] which ultimately laid the foundation for the **Boston innovation hub** – exhortations to „imitate Boston“ fail to grasp this reality



„Only in the fields of IT and biomedicine did the state (DARPA and NIH) invest at scale in the translation from scientific discovery to technological innovation“[2]

Source: JFRDR; 1) George Palade: Tides of Genius in: Pfenninger & Shubik: The Origins of Creativity, Oxford 2001
2) William H. Janeway: Doing Capitalism in the Innovation Economy, New York 2018

Why has the US become dominant in biopharma innovation? It looks like a **creative reinvention** of **Hamilton's arguments** aimed at protecting the **nascent US manufacturing industry in the 1790s**

Common Theme: Gvt needs to establish the basis of an ecosystem for industry to compete

- **Protective tariffs** on imports competing with domestic manufactures
- Bounties and premiums (**direct subsidies**) for domestic producers
- **Exemptions from duties** on raw material inputs needed by manufacturers
- **Improvements in transportation** to reduce internal trade costs
- **Inspection and quality standards** to build the reputation of American goods
- **Encouragement of immigration** of skilled artisans from Europe

Alexander Hamilton: Report on the Subject of Manufactures, 1791

1980s – 2020s

- **Global dominance** built on the foundations of long-term **public investment and financial deregulation**
- Coupled with measures to
  - **Contain unwelcome competition (China)** and
  - **Exercise pressure on foreign and US companies to invest in US..**
  - **..and on foreign governments to pay higher prices**

Source: JFRDR

However, after 45 years in operation, the **current US-dominated biopharma innovation model** is quickly **reaching its limits** at a time when **Science & Technology progress faster** than ever

Price levels are diverging more and more (**US = 2.5 to 3.4x Japan** for brand name drugs)[1], leading the US government to its aggressive policy of **MFN**

General Biopharma Trends

Established pharma companies are **rebalancing** their portfolios towards **lower average risk**

(e.g.: Recent termination of gene therapy programs by Pfizer and exit from cell therapies by Takeda, Sanofi and others)

VCs and other investors have become more cautious regarding CGT (e.g: Bluebird Bio) and are looking for less risky blockbuster opportunities (e.g.: obesity, cardio-renal and vaccines)

Sources: 1) RAND Corporation: Report on International Prescription Drug Price Comparisons, using 2022 data
2) https://www.fiercepharma.com/special-reports/most-expensive-drugs-us-2025

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What do we mean by **“Rare Disease”** Drugs?
The classic definition: “**Orphan**” Drugs, a driver of biopharma revenues since 1983

“Rare Disease” Drugs

- Drugs for diseases with **orphan status**, i.e. < 200,000 patients in the US and <50,000 patients in Japan
- Historically a **driver of the industry** growing from zero before 1983 to **>20% of biopharma revenues** in mid-2020’s

“Orphans’ growth advantage looks set to slip to just 1% by the end of the decade, potentially marking the end of an extraordinary run”

Worldwide Orphan Drug Sales & Share of Prescription Drug Market (2020-30)

Source: Evaluate Pharma: Orphan Drug 2025 Orphan Drug Report

Source: JFRDR

What do we mean by **"Rare Disease"** Drugs?
Today we are focusing on "Ultrarare Disease Drugs" as defined below

"Rare Disease" Drugs

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"Ultrarare Disease" Drugs

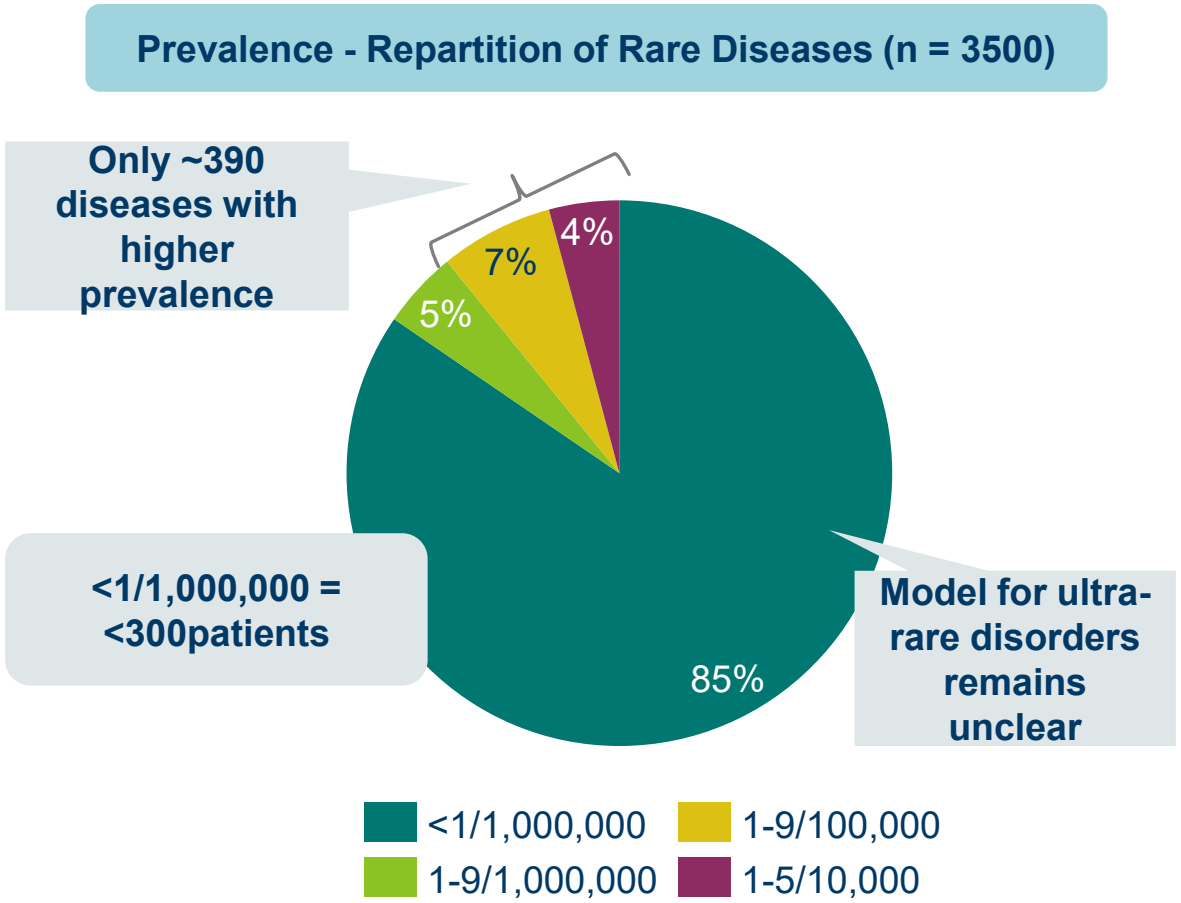
- Drugs for diseases deemed **too rare to be financially viable** in the **biopharma R&D and regulatory model**
- Differing definitions of **US incidence** some-where between **low teens to up to 1,000 patients** or **required price per patient >$500K**

"Nano-rare Disease" Therapeutics

- **N=1/n=few**
- Today mostly **antisense nucleotids** for **individual patients** or a small number of patients; (gene editing expected)
- Require **IND in US** but **no FDA approval**, in **EU** only **IRB approval**
- Essentially **hospital products** following a **different pathway**

Source: JFRDR

Only about **400 rare diseases** have sufficient patient numbers to be **commercially viable**, most of these are now being addressed on the market or in clinical pipelines



- Many diseases **unknown incidence** and **prevalence**
- **N=1 is a subset** of the total, e.g.: >150 mutations causing PKU
- Often, **more patients than expected are identified** once a treatment is available
- On the other hand, **penetrance** and **expressivity** are variable and there are limitations for treatment, e.g.: Prior exposure to AAVs

Source: Wakap et al, European Journal of Human Genetics volume 28, pages165–173 (2020), DOI: 10.1038/s41431-019-0508-0

Note to the Reader

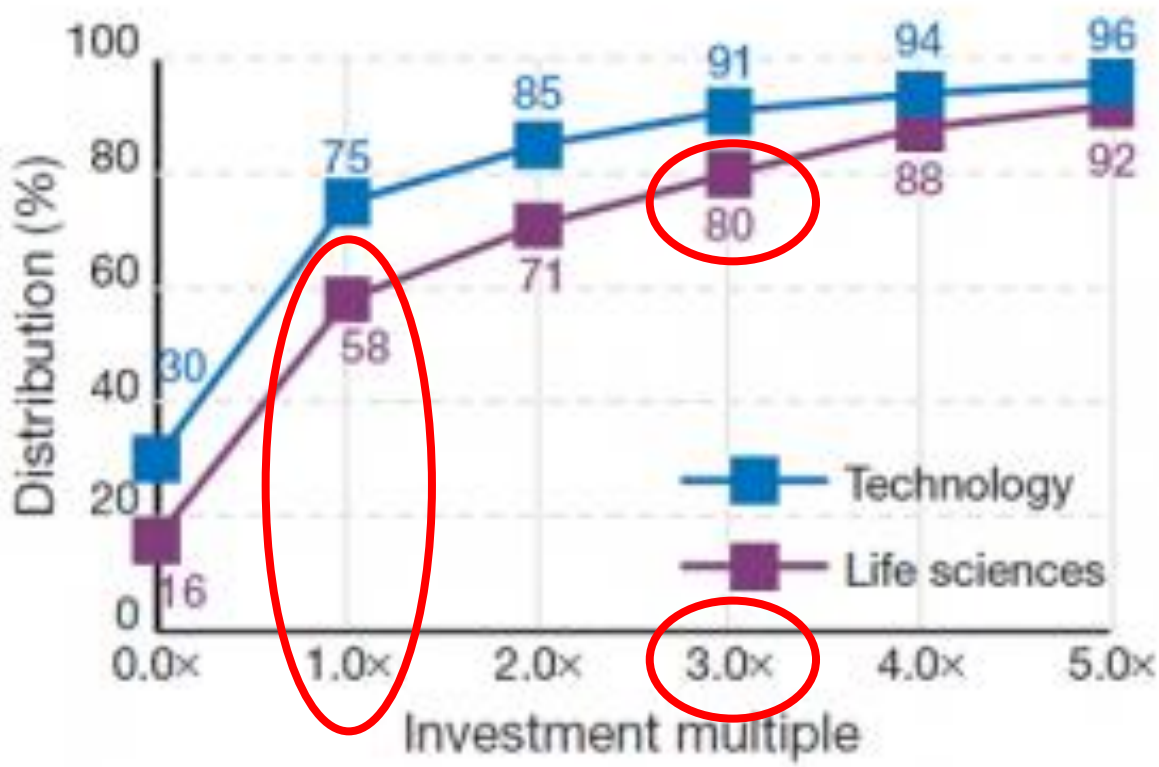
- This chapter focuses on the **economics of the Venture Capital model** at a **systems level**
- Thus, the "**multiples required**" to entice investors to invest their money into a VC fund are calculated based on the **overall returns of all VC funds;** in other words, a few **successful projects, companies and funds** need to pay for the multiple **losses** incurred by all **other projects, companies and funds**
- To drive home the main point, namely the **importance of the cost of capital, the model is based on highly simplified assumptions**
  - A fund invests in **ten companies** with **one project each at IND; after ten years one of these projects will have been approved and the company owning it is acquired by a pharmaceutical company**
  - **The fund** will have spent roughly **25% of its total investment in the successful company,** the others having failed along the way
- In reality**,** VC funds usually invest only in specific – often later/less risky - stages of drug and/or company development and usually do so in **a consortium** with other investors to manage risk
  - In this way, **exit multiples** are generated for funds from **drugs that ultimately fail,** but these multiples are **other investors' losses**
- All calculations in the presentation take into account only development cost and focus on the role of **cost of capital**
- **CMC, commercialisation** and all related costs will only be reintroduced at the end for a **like-for-like comparison with the VC-funded Biopharma model**

Source: JFRDR

The **economics of VC-funded Biotechs**
Expected and actual returns of VC funds in tech and the life sciences

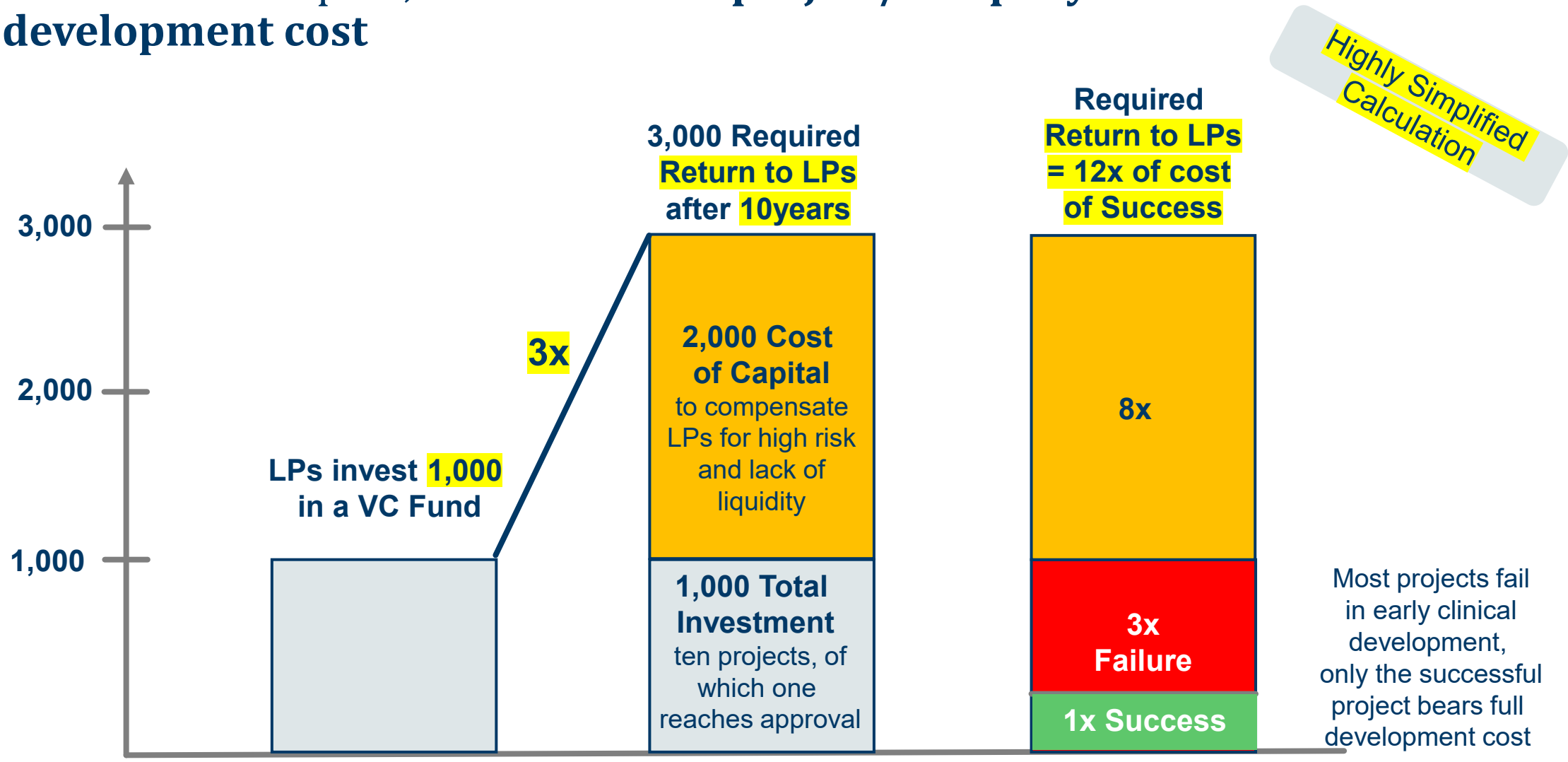
- As a Life Sciences investor, you stand a **58% chance** of losing part of your principal
- In combination with the **lack of liquidity,** this translates to average expectation of **investment multiples of 3x over ten years,** corresponding to a 13% compound interest pa – only **20% of funds** in the sample have delivered on this promise
- Some investors expect **5x,** corresponding to 17% compound interest pa

Actual Fund Returns



Source: Booth et al: https://lifescivc.com/2011/07/life-sciences-the-rodney-dangerfield-of-venture-capital;
A similar distribution of returns can be found in https://www.baybridgebio.com/blog/biotech-power-law

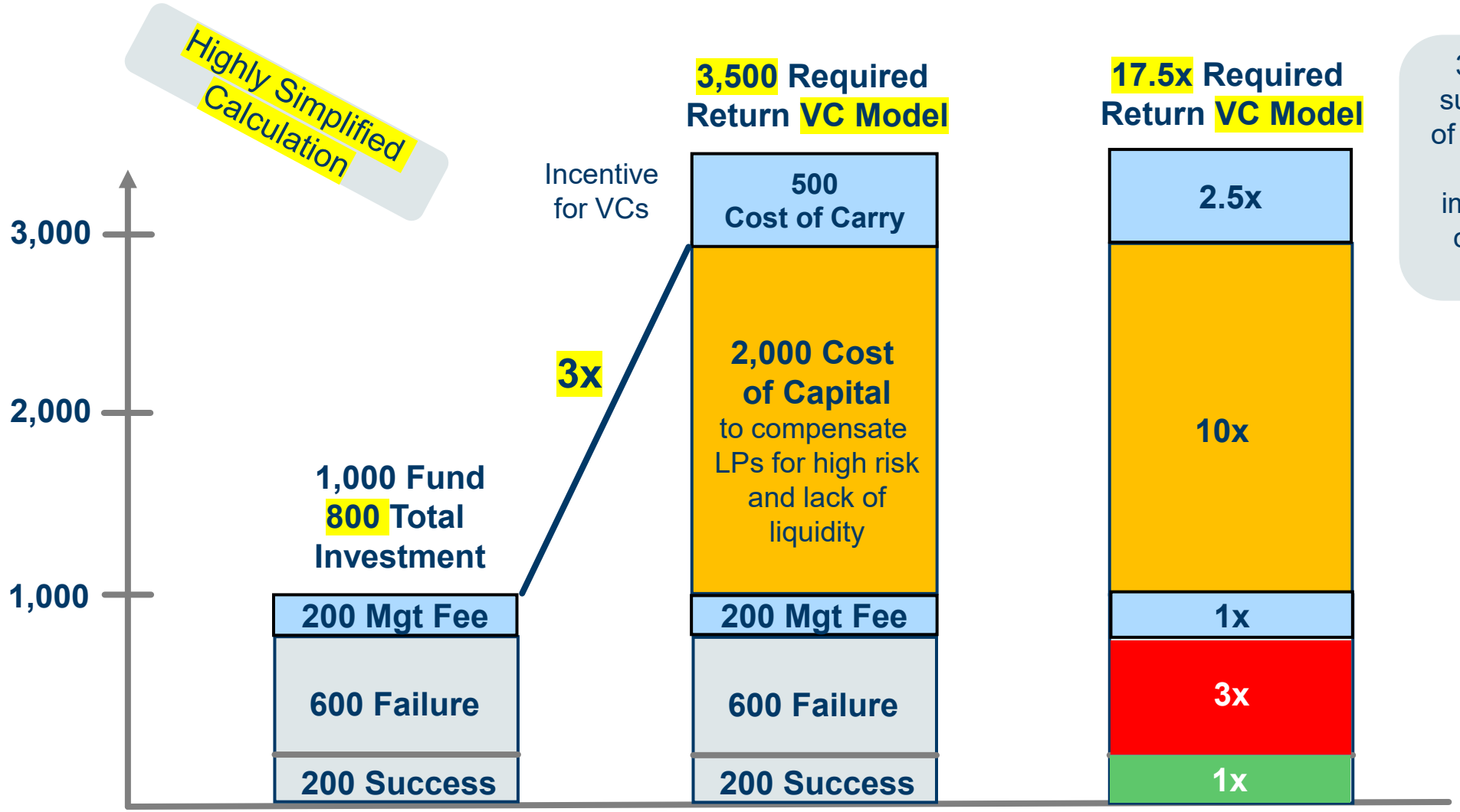
At first sight, with a systems-wide **economically-reasonable** expectation of **3x return** on invested capital, **one successful project/company** needs to **return 12x** of its **development cost**



VC = Venture Capital; LP = Limited Partner, i.e. investors in the VC fund

Source: JFRDR

But VCs do not work for free - multiples of "cost of success" **with VC compensation** (2% pa plus 20% >1x carry) rise to **17.5x;** for the **successful project/company** this implies an **annual cost of capital of above 30%**



30x of cost of success in case of required return to LPs of 5x, implying annual cost of capital >40%

Source: JFRDR

Two **random plausibility checks** with real life cases confirm the order of magnitude of the above analysis

Zolgensma
(onasemnogene abeparvovec-xioi)

- Sma-type 1 targeting gene therapy
- Developed by **Avexis**, total **accumulated deficit** as per March 2018 = **$581.7mn**
- Acquired by **Novartis i**n April 2018 for $8.7bn gross (minus $586.6mn cash holdings) = $8.1bn net
- $8.1bn net exit value : $600mn total investment = **~13.5x**

Yescarta
(axicabagene ciloleucel)

- CD-19 targeting autologous CAR-T therapy for DLBCL et al
- Developed by **Kitepharma**, total **accumulated deficit** as per Sept 2017 - estimated **~$690mn**
- Acquired by **Gilead** in August 2017 for $11.9bn gross (minus ~$625mn cash holdings) = $11,25bn net
- $11.25bn net exit value : $690mn total investment = **~16x**

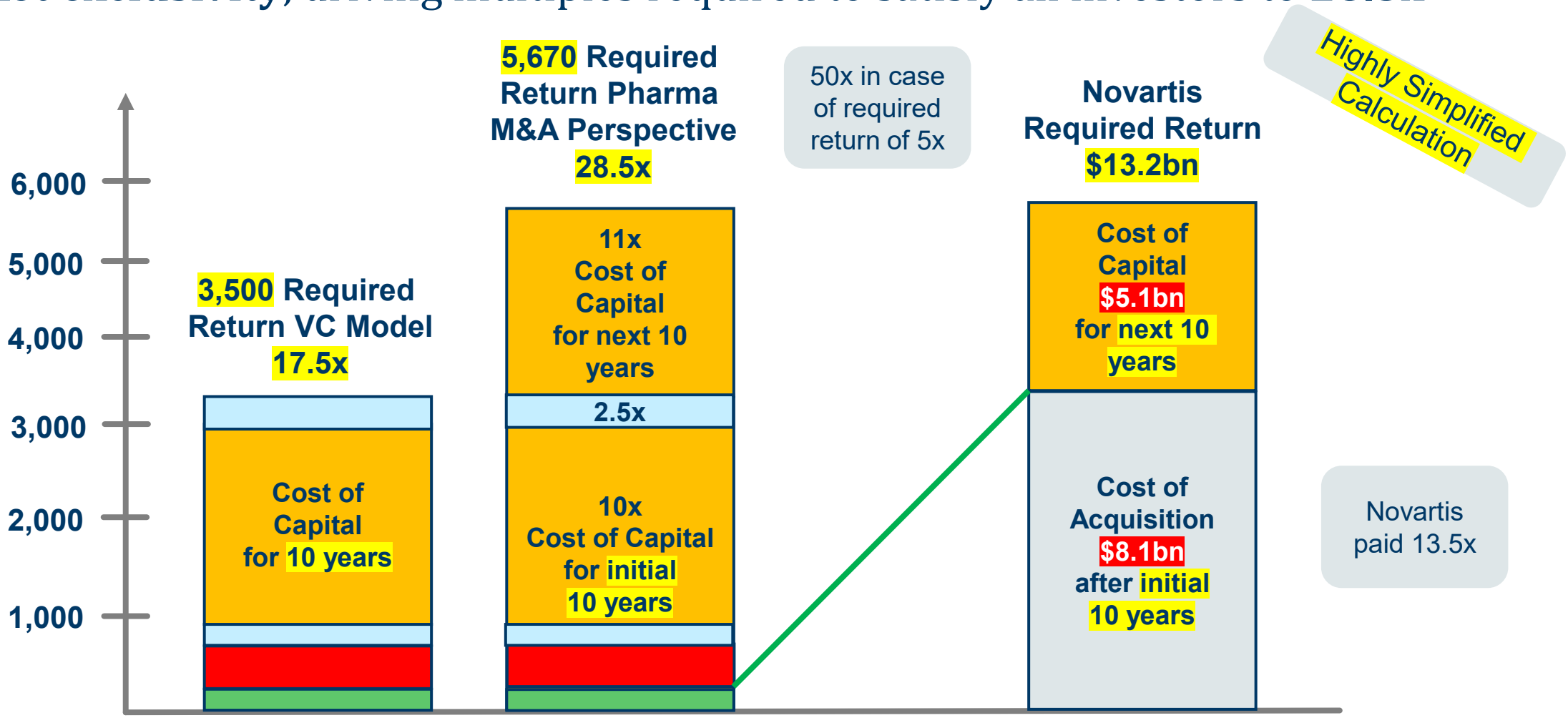
Sources: for Avexis - https://www.sec.gov/Archives/edgar/data/1652923/000155837018004054/avxs-20180331x10q.htm

For Kite - https://www.bamsec.com/filing/151058017000003?cik=1510580

https://www.sec.gov/Archives/edgar/data/1510580/000156459015001985/kite-10k_20141231.htm#Item_7_Management_Discussion

https://www.sec.gov/Archives/edgar/data/1510580/000119312517161774/d384838dex991.htm

But this is not the end of the story; once it has **acquired an approved drug, pharma** needs to recoup **its own cost of capital of 10% pa** for this transaction during **market exclusivity**, driving multiples required to satisfy all investors to **28.5x**



Note: This analysis assumes an acquisition (M&A); the cost of capital could be lower in case of a licensing deal made up of upfront, milestone and royalty payments

Source: JFRDR

So the Novartis acquisition of Avexis/Zolgensma does not look like a good investment – they paid less than the **right price, but there are not enough patients in the US to recoup the cost of capital**

Novartis paid $8.1bn for Avexis

Total required return for Novartis $13.2bn

Price per patient in US $2.1mn

Need 6,300 patients over ten years

(more if considering COGS)

US incidence of SMA1 is less than 350

(two competing drugs)

- **To make a reasonable return, Novartis needs to find many more patients in other countries at significantly lower prices:** Life cycle management has limited upside (intrathecal injection for kids >2y)
- **$5mn would have been an economically reasonable clearing price**
- **This drug would no longer be developed by VC-funded Biotech today**
- **The development of next generation SMA1 gene therapy is funded by the Brazilian gvt in Brazil**

Sources: 1) Verhaart et al. Orphanet Journal of Rare Diseases (2017) 12:124 DOI 10.1186/s13023-017-0671-8
2) https://database.earth/population/united-states-of-america/births

Zolgensma and the difficult story of economics vs morals & politics

It's not the company that is "too greedy" or the price that is "too high", it's the wrong business model!

Zolgensma Pricing Rationales According to LLM Claude

Perspective	Price Estimate	Rationale
Internal advisor	$5 million	Maximum extractable value
Novartis (framing)	~$2.1M	"50% below 10-year Spinraza cost"
ICER (health economists)	$310K–$900K	Cost per QALY gained
Academic pricing model	~€1.7M	R&D costs + investor return

The Anchoring Game Novartis Played

This is where it gets strategically interesting. In the months before launch, Novartis CEO Vas Narasimhan tossed out a range of price anchors from $1.5 million to $5 million. Just before the big reveal, he told reporters the price would be "well shy of $5 million" — **so when $2.1 million landed, it felt like a discount**. Critics called this deliberate **psychological anchoring**.

Source: Claude prompt: "Speculation before launch what the right price of Zolgensma should be

Drug Loss is a global challenge and it is **getting worse –** the current biopharma business model based on high cost of capital is the main culprit that needs to be addressed

Most visible and politically sensitive

Less severe than in Japan but increasing numbers

Hundreds of drugs stopped in clinical development due to commercial reasons

Many drugs not affordable for local healthcare systems

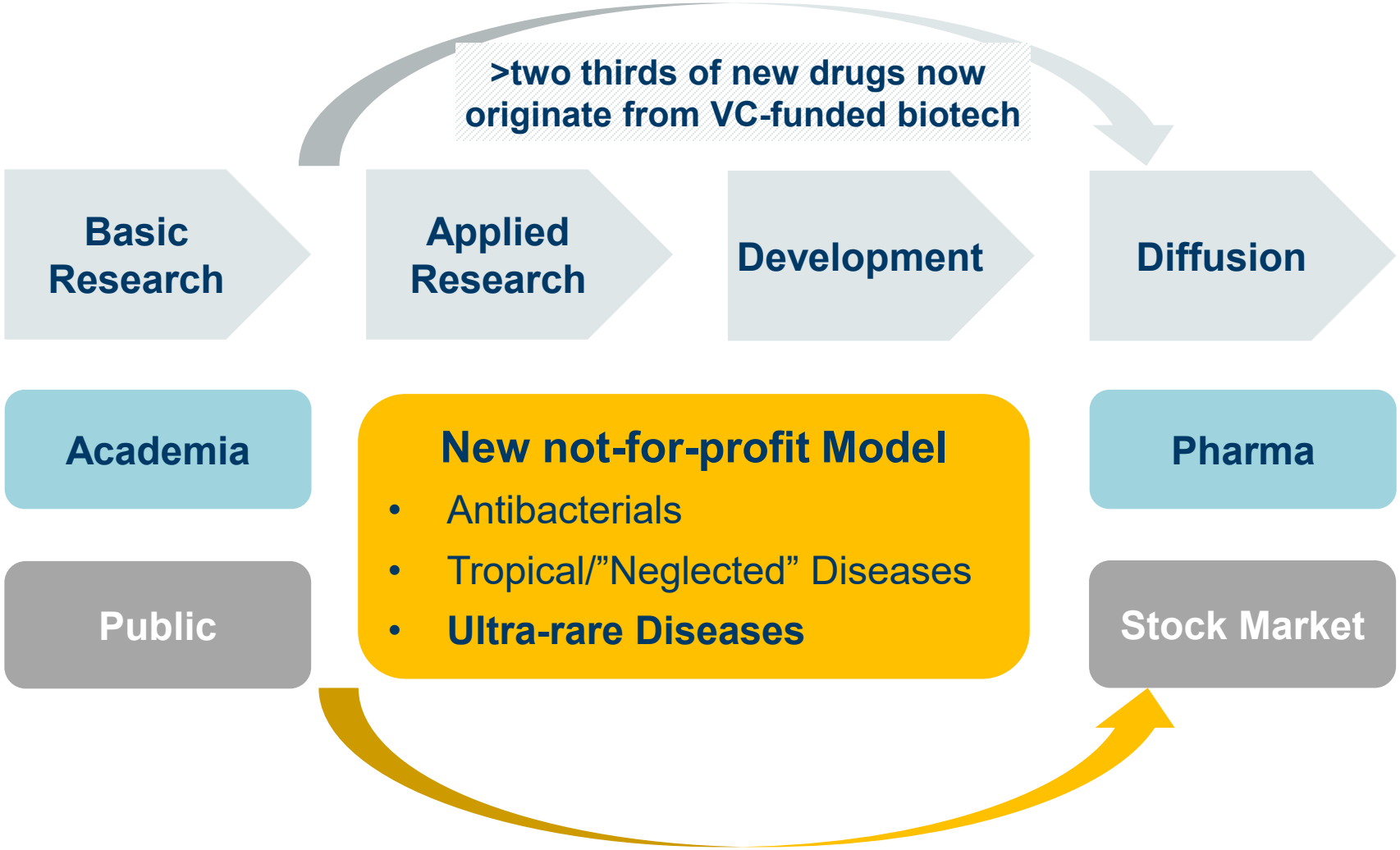
Challenges to be tackled

1. **Failure rates** are high – AI will help but not solve this issue
2. **Regulatory complexity** – too burdensome, too expensive , too long – needs to be adapted
3. **CMC** is too expensive – correct, limited economies of scale
4. Biopharma **valuations** are low/IPO window is closed since 2022, first signs of re-opening

The main challenge is the current VC-funded biotech business model with its high cost of capital and it is beginning to be addressed across the globe

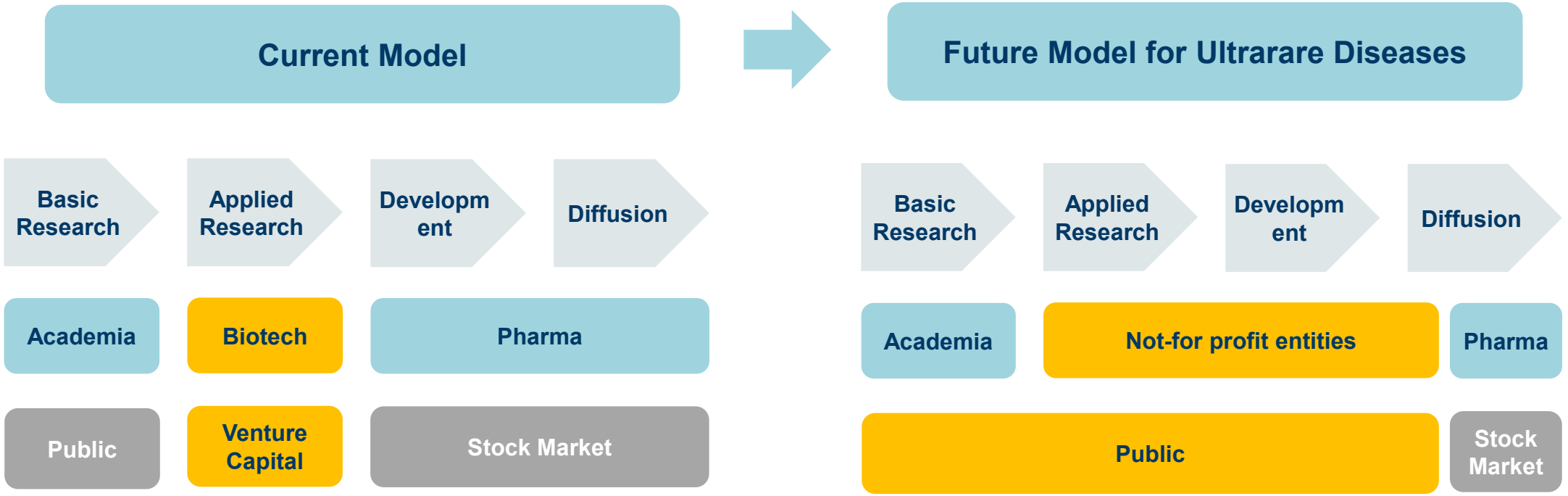
Source: JFRDR

We **need a new model** to tackle these **market failures** and given timelines, risk and cost of capital, **it cannot be a for-profit model**



Source: JFRDR

Future innovation for thousands of ultrarare diseases will require a **different "business model"** which operates **in parallel** with the current model

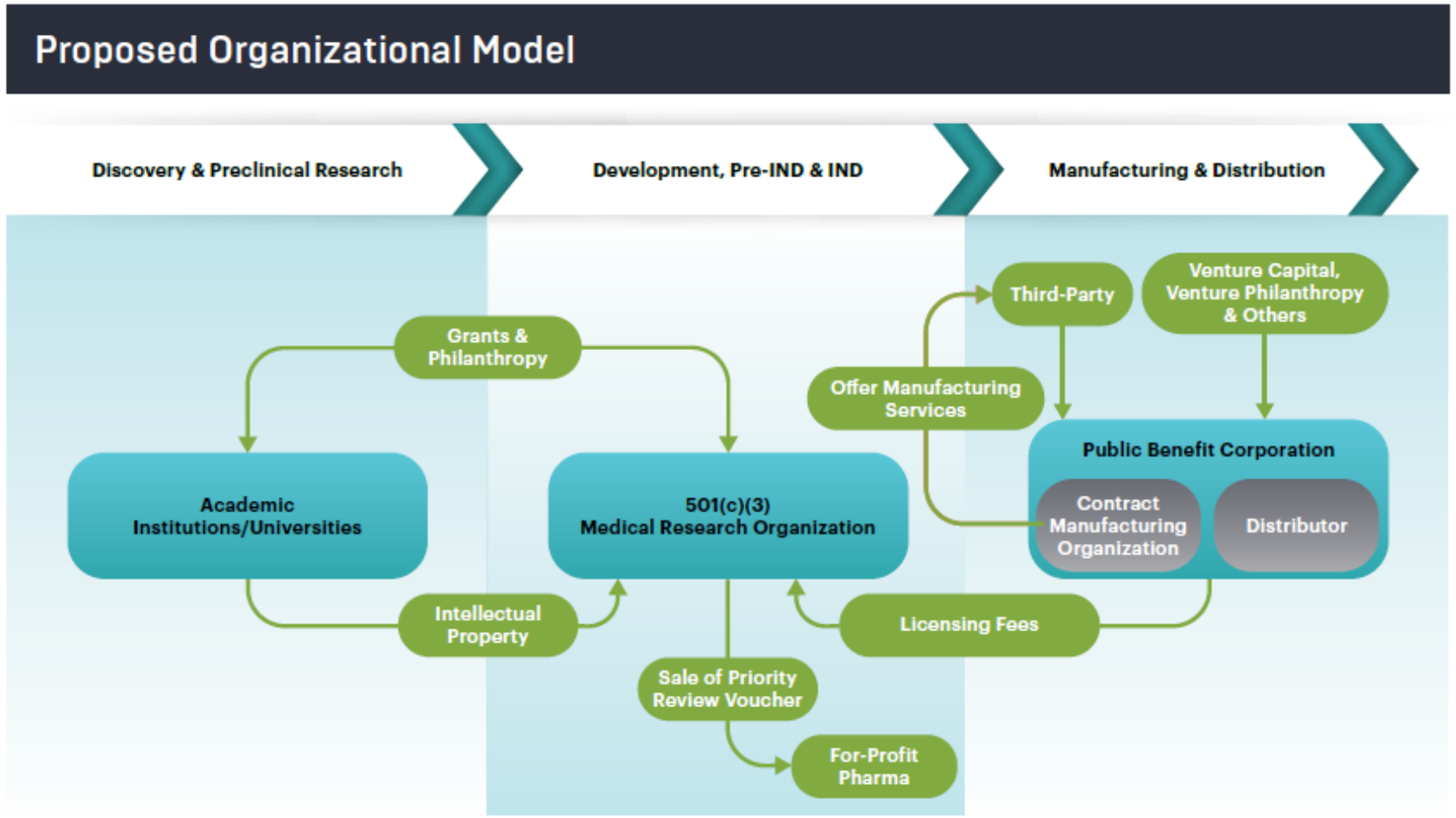


One way to look at this is to **extend the public financing** of Basic Science **without a direct economic return expectation** to the **clinical development of ultrarare diseases** to tackle **market failure**

Source: JFRDR

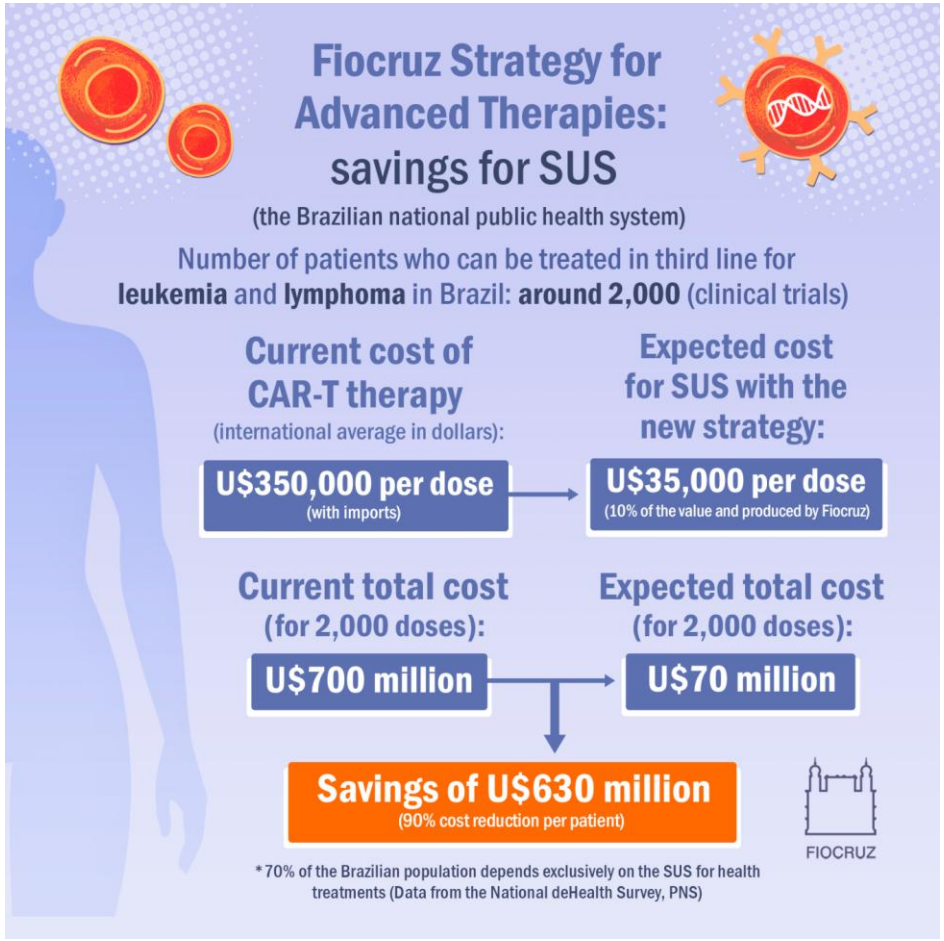
A proposed **mixed organizational model for CGT**: A non-profit conducts grant-funded R&D; an MRO further develops and translates the product through clinical trials and a public benefit corporation would manufacture and distribute the product on a financially self-sustaining basis

Not-for-profit approach advocated by Jennifer Doudna's Innovative Genomics Institute



Source: Innovative Genomics Institute: https://innovativegenomics.org/making-genetic-therapies-affordable-and-accessible/

A number of **novel business models** for **autologous CAR-Ts** provide further evidence for our economic analysis (**CHOP, Hospital Clínic Barcelona, Caring Cross** et. al.), suggesting **cost of capital** of up to **90%** per patient



- "**Caring Cross** is an **Australian non-profit** dedicated to accelerating the development of advanced medicines and **ensuring access to cures for all patients, everywhere"**
- **"Caring Cross** will provide technology, materials, and training to **Bio-Manguinhos/Fiocruz (part of the Brazilian Ministry of Health)** for the manufacture of CAR-T cell therapies and lentiviral vectors aimed for clinical development and approval"

Source: https://fiocruz.br/en/noticia/2024/03/fiocruz-and-caring-cross-announce-agreement-car-t-therapy-brazil-and-latin-america

Emerging models in action: **Two long-established basic research players in Europe,** moving forward into clinical research and commercialisation (where no alternatives exist

Telethon Italia

- Established in **1990**
- Funded by donations from the public and based on extensive national TV campaigns involving celebrities and patients
- Currently raise ~€50mn pa
- **Total financing since 1990 €741mn**
- Grant funding agency with in-house research labs (>600 researchers)
- Three approvals, full clinical pip[eline
- Now MA holder for Strimvelis after drug was withdrawn from market by Orchard Tx
- FDA recently approved Waskyra for Wiskott-Aldrich syndrome; US rights licensed to OTXL

AFM Téléthon and Généthon

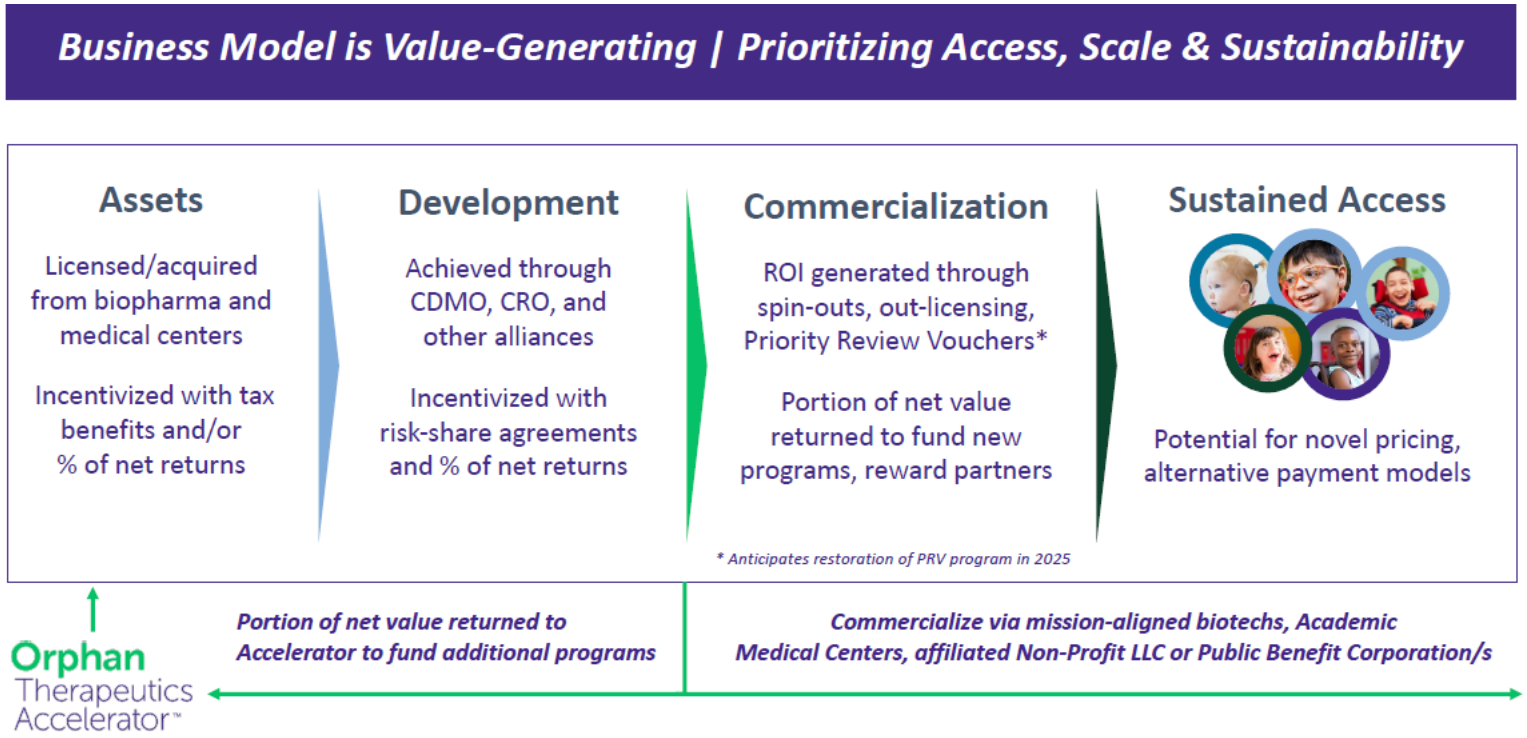
- Established **1958** and **1990** respectively
- Funded by donations from the public and based on extensive national TV campaigns involving celebrities and patients
- 2024 Telethon raised €96,553,593
- Initial focus on muscular dystrophy, now much broader
- **SMA1 project originated at Généthon, was then licensed to Avexis and later acquired by Novartis**

Sources: https:https://www.fondazionetelethon.it/en/: https://www.genethon.com/who-are-we/our-history/: https://www.afm-telethon.fr/en/our-history; Genethoin press release March 13, 2018

Emerging models in action: It is the mission of **OTXL** to "**Create a viable path** forward to bring promising treatments for **ultra-rare diseases** to patients"

OTXL – Orphan Therapeutics Accelerator

- Established **2024**
- Start-up funding provided by **Chiesi** and **Bial**
- Not-for profit model, funding still unclear, targets are patient organisations, charity, Venture Philanthropy
- Will initially focus on >100 candidates stuck in US clinical development due to lack of commercial viability



Source: https://www.orphantxl.com/about-us

Emerging models in action: **Gene therapy pioneer Jim Wilson** is working with governments to reduce development cost and make gene therapies available to patients in mi-income countries with innovative business models

Gemma Bio/Rare Tx

- Launched Oct 1, 2024 by **Jim Wilson,** a pioneer of **AAV-based gene therapy**
- Partnered with CRO **Franklin Biolabs**, specialised in gene therapy
- Partly VC-funded, partly government-funded
- **Public benefit model, i**.e. with responsibility to all stakeholders, not just shareholders
  - Aiming for **financial sustainability, not profit maximisation**
- **Tech transfer deals for** gene therapy platform **with Brazil**
- Brazilian government finances development of six gene therapies at pre-negotiated prices
- **And Abu Dhabi**

Sources: https://www.gemmabiotx.com/;
https://www.bizjournals.com/philadelphia/news/2025/07/07/gemma-bio-jim-wilson-abu-dhabi-gene-therapy.html?b=1751908897^22562564
https://www.prnewswire.com/news-releases/gemmabio-announces-100-million-agreement-with-brazils-leading-health-research-institute-302270296.html

Emerging models in action – various **subdivisions of NIH** are collaborating on a **commercially infeasible gene therapy** for an ultrarare disease, largely without support from external commercial partners (CROs)

- On May 8, 2026, the FDA cleared an Investigational New Drug (IND) application for MMA-101, an adeno-associated virus (AAV)-based gene therapy candidate for patients **with methylmalonyl-CoA mutase (MMUT) methylmalonic acidemia (MMA)**, a rare pediatric metabolic disease with **no approved treatment**
- Sponsored by the **National Human Genome Research Institute (NHGRI)** in collaboration with **NCATS** and **several NIH partners**, the program represents a unique effort to revive and **develop a rare disease therapy after commercial development was discontinued**
- In 2023, **Selecta Biosciences discontinued** its MMA gene therapy program because of **commercial constraints** and withdrew its IND application. The company **donated manufactured drug product, key reagents and regulatory documentation to NIH**
- "In 2017, **our team partnered with Selecta** to co-develop a gene therapy candidate for MMA, working together from early preclinical development through regulatory approvals and into patient screening," said Charles Venditti, M.D., Ph.D., chief of the Metabolic Medicine Branch at NHGRI and **principal investigator of the MMA-101 clinical trial**

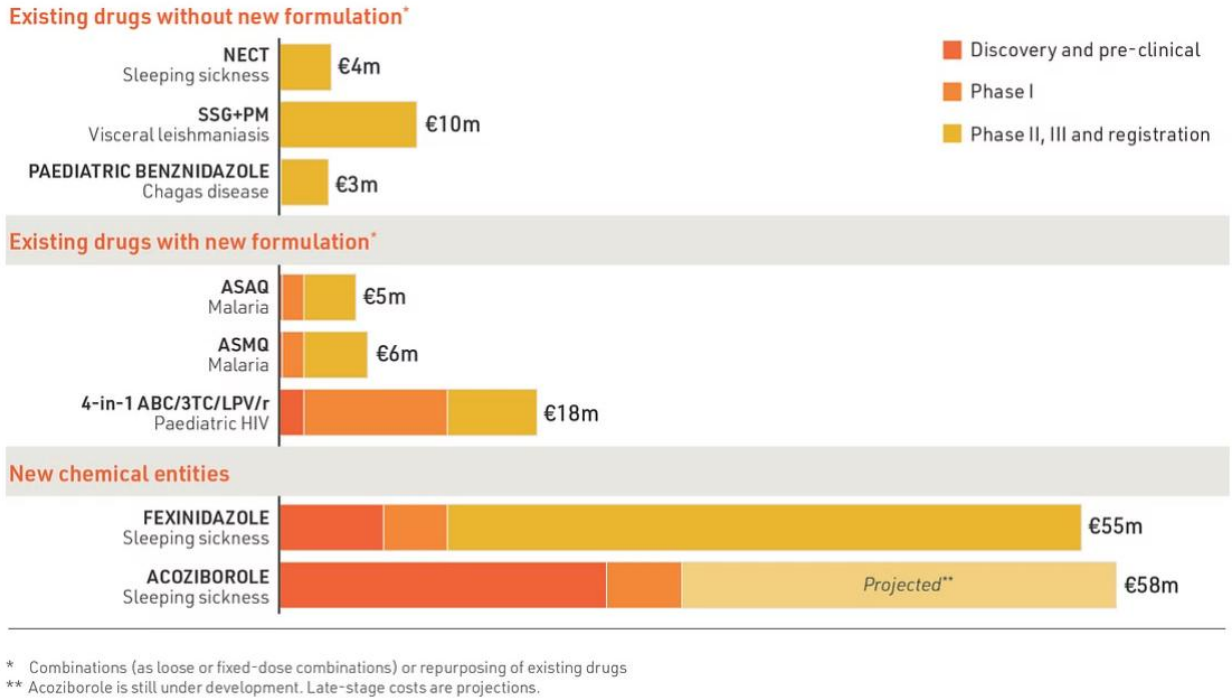
Sources: FDA Clears IND for Gene Therapy Candidate to Treat Rare Metabolic Disorder | National Center for Advancing Translational Sciences
New Path for a Gene Therapy Trial at NIH for a Rare Metabolic Disease | National Center for Advancing Translational Sciences

Emerging models in action: "**DNDi** acts as a conductor of a 'virtual orchestra' of over 200 partners around the world to develop treatments for patients – not profits"

DNDi – Drugs for Neglected Diseases Initiative

- **Not-for-profit** initiative to develop drugs for neglected diseases
- Set up in 1999
- Funded by **Médecins sans Frontières**, Institut Pasteur and government institutions of half a dozen developing countries
- **In 2024, €57mn raised for grants**
- Total raised in 20 years: **€880mn** – 62% public/38% private, ~15% from Gates Foundation
- Supported by in-kind contributions from commercial players a long the value chain

DNDi R&D real life expenses at cost



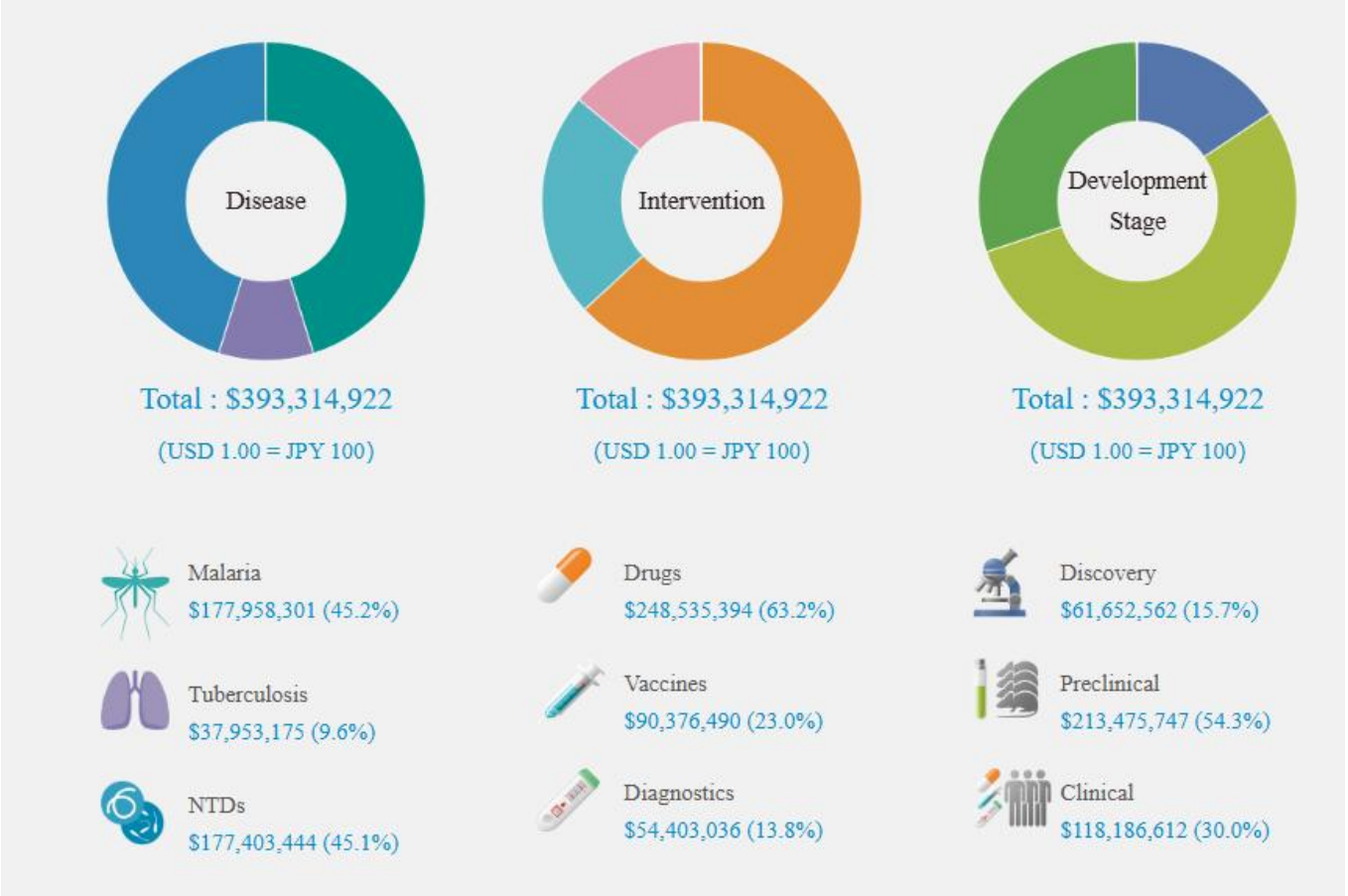
plus in-kind contributions by industrial partners

Source: https://dndi.org/about/who-we-are; https://dndi.org/wp-content/uploads/2025/06/DNDi-FinancialReport-2024.pdf

Emerging models in action: **GHIT** was set up in 2013 to "**leverage Japanese innovation** and leadership to fight against neglected infectious diseases through investing in **research** and **development**, and promoting **global partnerships**"

GHIT – Global Health Innovative Technology Fund

- Registered in **2013** as a general incorporated association in Japan
- Funded by the **Japanese government**, the Gates Foundation, the Wellcome Trust and **half a dozen Japanese pharmaceutical companies**
- Have allocated **$393mn since 2013**
- **First approval** for schistosomiasis treatment in **2024**



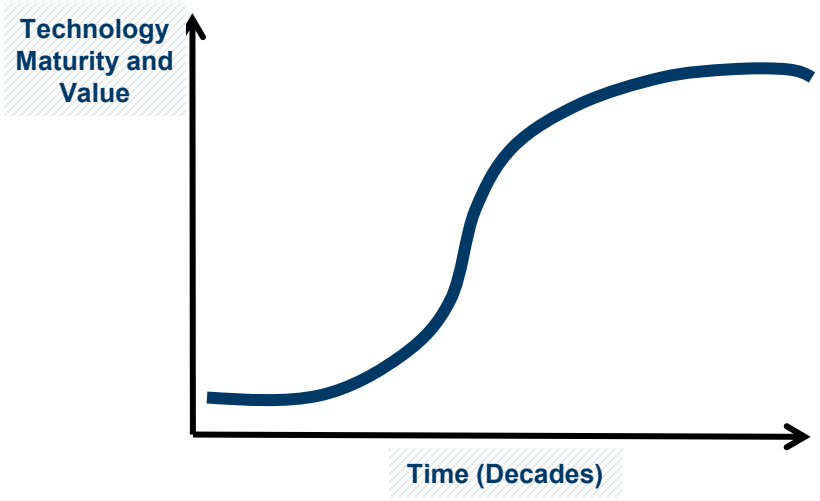
Sources: https://www.ghitfund.org/; https://www.ghitfund.org/investment/overview/en

Agenda

- Executive Summary
- Biopharma Innovation – Brief History and Current State
- The Curious Case of Rare Disease Drugs – from Industry Driver to Global Drug Loss
- **A Potential Solution for Ultrarare Diseases: JFRDR**
  - **Value Proposition and Business Model**
  - Funding Options

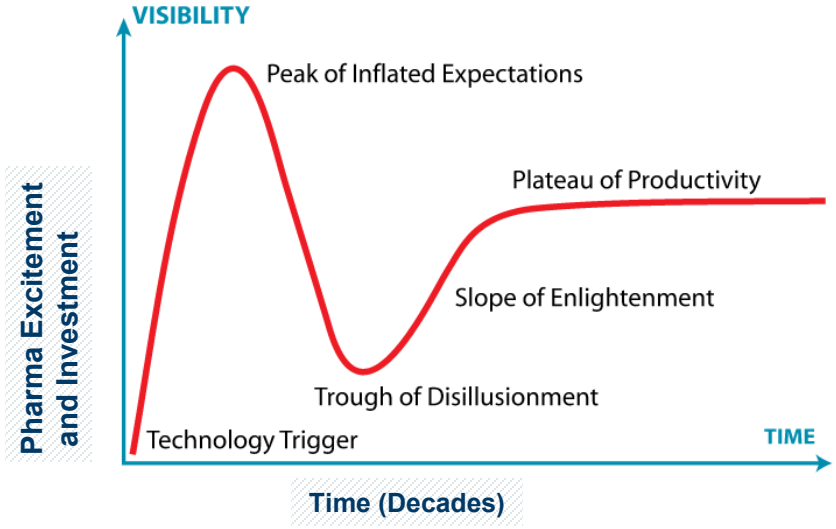
Science mapping - How do you forecast the **development of emerging technologies** in the bio-medical field?

S-Curve



The S-curve maps progress of science and technology

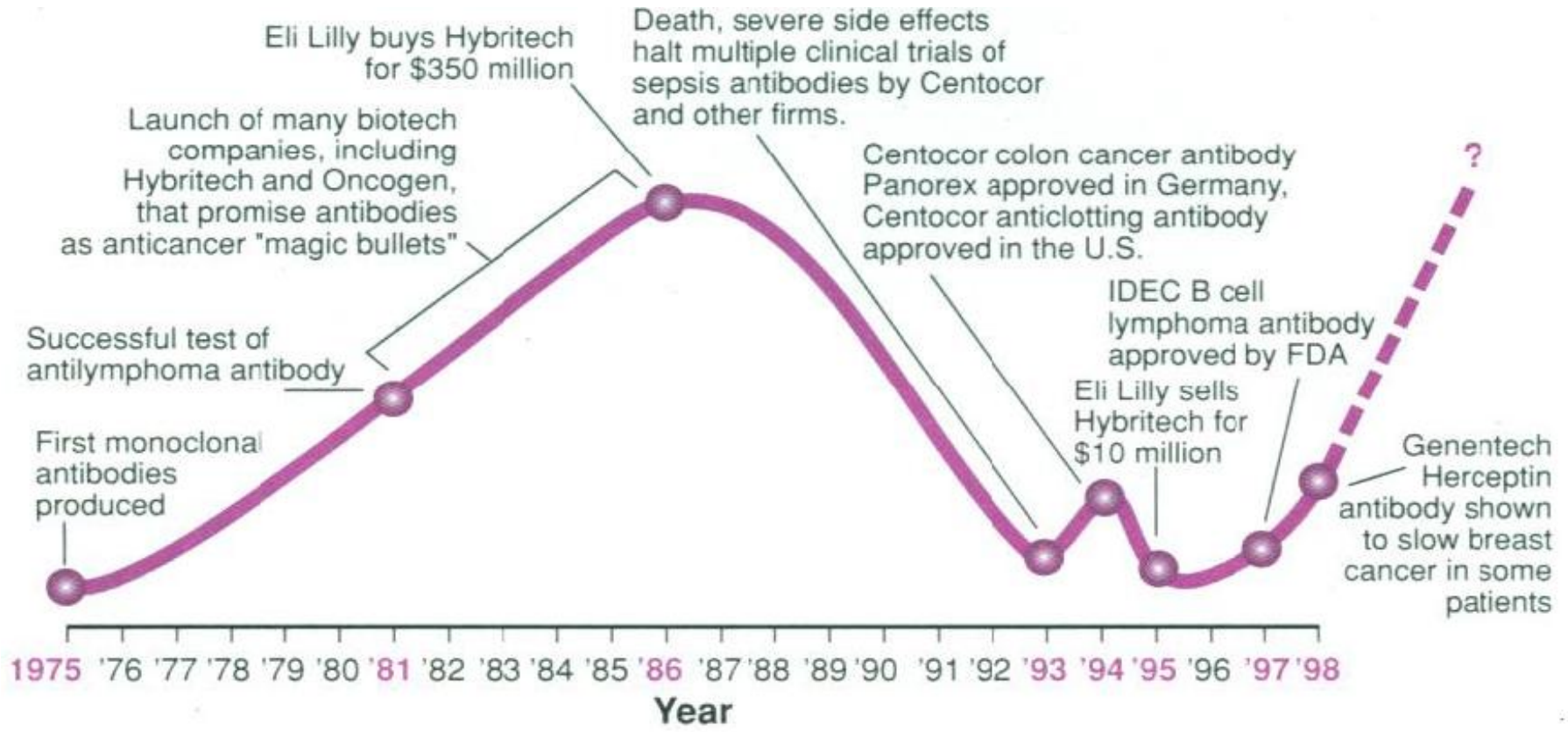
Hype Cycle



The Hype cycle maps industry and investor sentiment

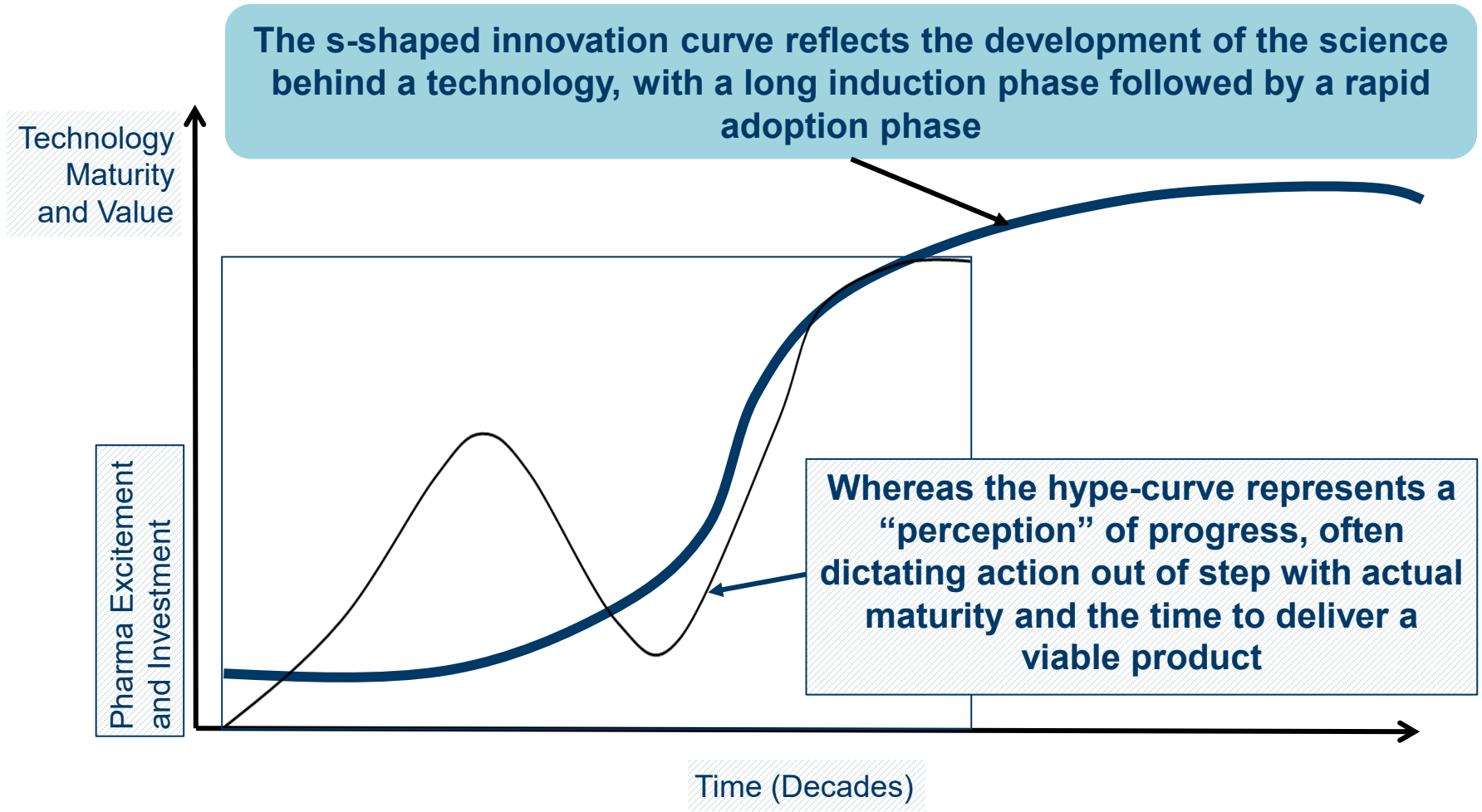
Source: JFRDR

The **hype cycle** was developed to characterise **IT technology cycles**; in 1998, it was first applied to Biopharma, more specifically **monoclonal antibodies**



Source: Antibodies stage a comeback in cancer treatment, Steven Dickman, Science, 1998

To anticipate the participation of Venture Capital and Big Pharma in an emerging technology, one must understand the relationship between the hype cycle and the S-shaped innovation curve

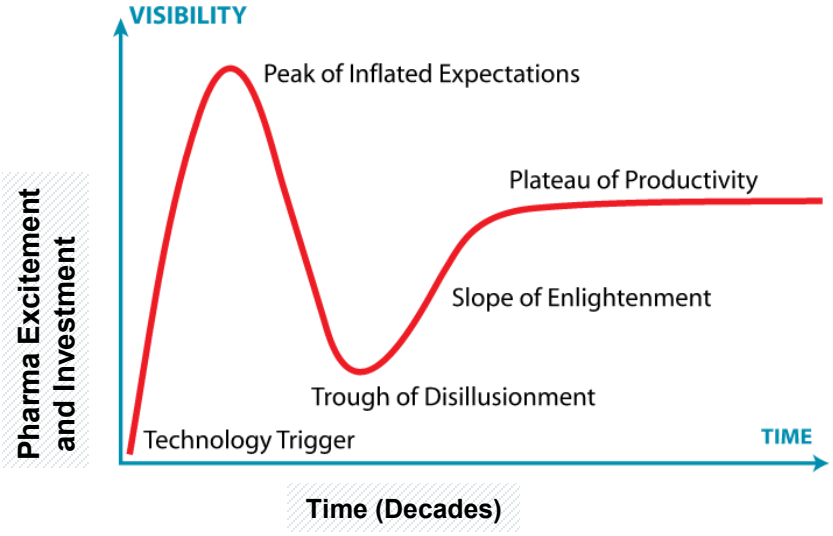


Source: JFRDR

The **VC model is driven by "exits"** that follow the **hype cycle** and its **impact** is **limited** in Europe and Japan

- Fewer **financial resources** available for high-risk investments (e.g.: Pension Funds)
- **Low valuations** across the R&D value chain
- Fewer **exit options** (e.g.: **IPO**) and low **exit values,** ultimately influenced by **low reimbursement**
- Major difficulties of VC funds to report **increasing paper valuations** before exit to their investors
- Few entrepreneurs **experienced in managing investors**

Hype Cycle



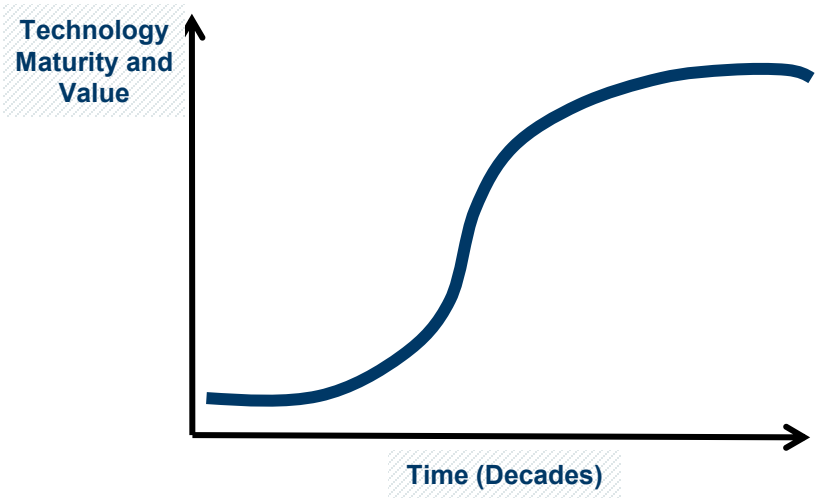
Key parameters
Start-ups, funding, deals, patents, clinical trials…

Source: JFRDR

Hence the need for **alternative business models,** guided less by financial exits than **scientific maturity**

- e.g.: **Publicly-funded**, **professionally managed**, **non-profit** biotechs
- **DARPA model**: attract highly qualified professionals from academia and industry
- Give them **ambitious objectives to achieve** in a few years
- Pay **decent salaries** and celebrate success, but **no value upside**
- **License at cost+ to local pharma in return for "reasonable" pricing guarantee**

S-Curve



Key parameters
Publications, research funding, key KoLs and topics, Gordon conferences…

Source: JFRDR

Due to the low number of patients in any one country, addressing the ultrarare disease challenge requires **new not-for-profit business models** and **global collaboration**

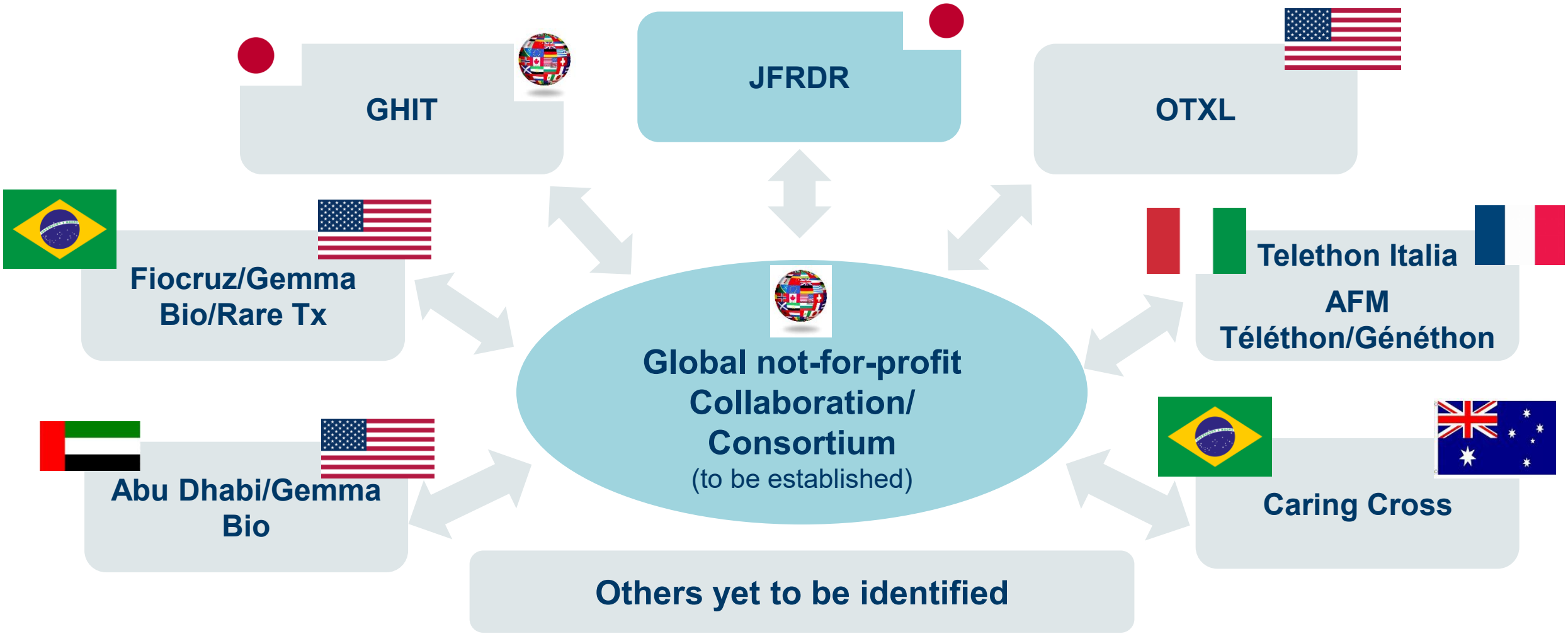
Not-for-profit Business Models

- Basic and translational research funded by governments
- **Clinical research, manufacturing and distribution** to patients delivered by **professionally managed not-for-profit** organisations
- Funded by **donations from the public, patient organisations**, corporate donations and **governments**

Global Collaboration

- Joint **registries**, **natural history studies**, **biomarker development** and **clinical studies**
- **Shared materials** and **services**: Oligos, vectors, LNPs, CDMOs, CROs…
- **Joint approaches** to **manufacturing**
- Shared models for ensuring **patient organisation & engagement,** as well as **patient access**

The Vision: JFRDR aims to be the **key Japanese player** in a **global collaboration** tackling **drug R&D** for **economically infeasible ultra-rare diseases**



Source: JFRDR

JFRDR follows such an **alternative non-profit business model**; its basic value proposition is to successfully **develop ultra-rare disease drugs thought to be commercially non-viable** and help making them accessible to **Japanese patients** via established commercial entities at "**reasonable prices**"

Basic Philosophy: Be complementary with market players, do not compete

Initial focus on Foreign approved drugs

Drugs in clinical trials outside Japan

Translational R&D projects in Japanese academia

- **License IP** from foreign license holders and TTOs
- **No/low upfronts**, but royalties in case of commercial success
- **Sufficient funding** for translational projects up to approval

- **Support development** through **grants, coaching, mentoring and project management** in close collaboration with patients, KOLs, hospitals, service providers (CROs, etc), PMDA and MHLW
- All ideally at **cost-plus**
- **Partner globally**

- **License out de-risked** assets to best qualified established players for distribution at "**reasonable prices**"
- **Limited royalty** terms in case of commercial success

Source: JFRDR

To achieve its objectives, JFRDR will implement a **new operating model in Japan** which is tied into **an emerging global ecosystem** tackling the **development** of **economically infeasible ultrarare disease drugs**

- Key to JFRDR's success will be
  1. A **professional management approach** to all activities, led by a small team of **seasoned executives** supported by top notch national and **global advisors** for project selection and KOL coaching
  2. The use of **low-cost capital** and **at cost-plus services** leading to drugs that can be commercialised at relatively **low reimbursement cost to the public healthcare system**
- **New models** for tackling **ultra-rare disease drug development** – many of them **not-for-profit** - are being set up in other geographies and **Japan** needs to establish an **organisation** that can **efficiently represent its interests** in the **emerging global network of similar-minded organisations**
- Together with these **peer organisations** in the US, Europe and elsewhere, **JFRDR** will strive to **adapt** the **not-for profit models** of **global virtual collaboration** for the development of **drugs** for **neglected and tropical diseases** (cf DNDi and GHIT) to the **specific requirements of ultra-rare diseases**

Source: JFRDR

JFRDR aims to finalise initial **fund-raising by the end of 2026** and to **start operations** in **early 2027**

Initial Founders and Funding

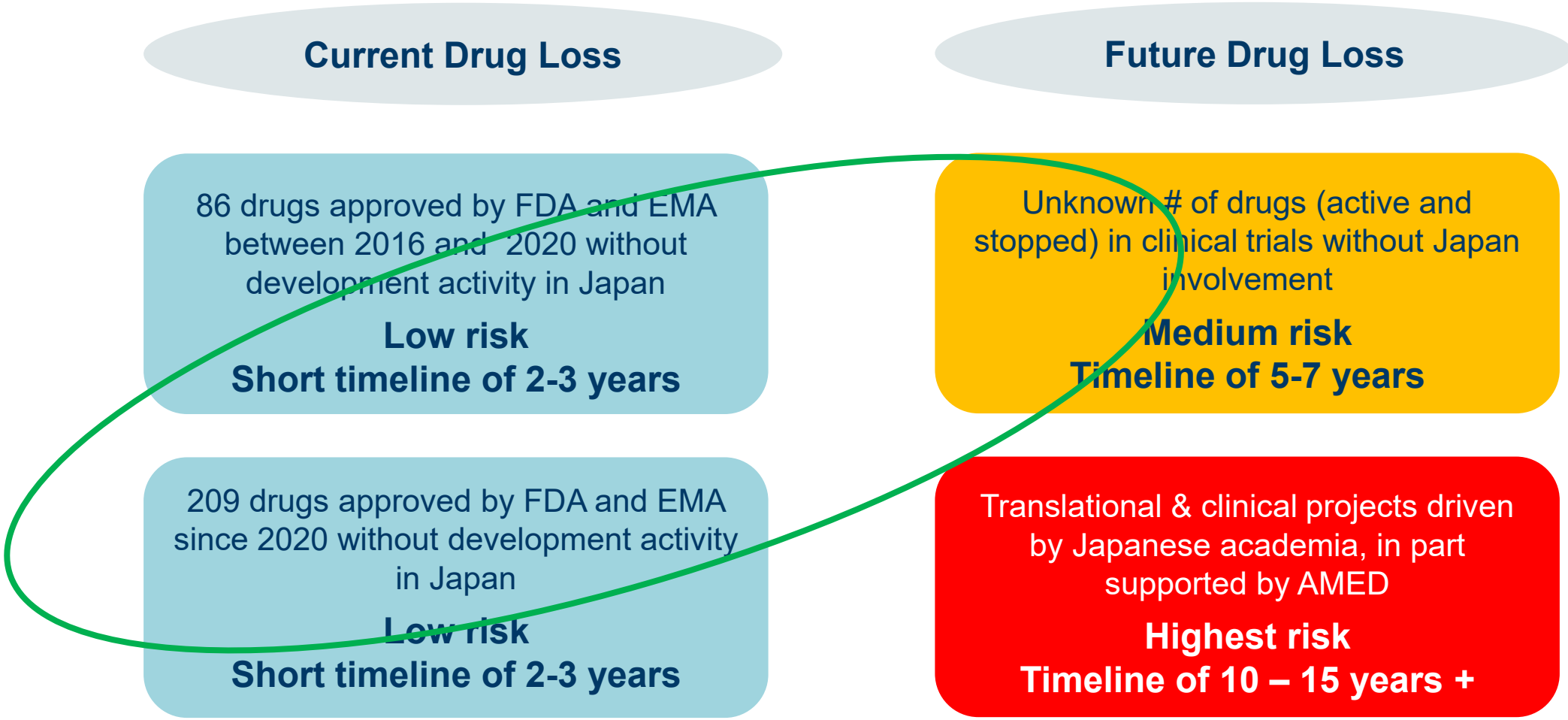
- **Hiroshi Mizushima**, Research Scientist and currently President, Mizushima Institute of Medical Information
- **Norikazu Eiki**, Former Chairman, Bayer Yakuhin
- **Rob Koremans**, CEO, Recordati SpA
- **Christian Elze**, Strategy consultant and advisor to companies, academia and governments
- Start-up funding provided by **Recordati SpA**

On-going Activities

- **JFRDR** is incorporated as a "**General Incorporated Association**", to be transformed into "Public Interest Incorporated Foundation - Koueki Shadan Hojin " at a later stage
- **CEO** with **hands-on rare disease experience** has been hired: **Hiroshi Kowaki** (ex-Alnylam, Amylyx et al)
- **Prioritising drug loss projects** and **preparing operations**
- **Fund-raising**

Source: JFRDR

JFRDR proposes to initially focus on **current drug loss projects** with the lowest **risk profiles** and **shortest timelines** to reach Japanese patients; in addition, the plan is to validate the business model by funding a number of **ex-Japan clinical development candidates**



Source: JFRDR

Filtering for “orphan drug status”, “no development in Japan” and “<1,000 patients estimated in Japan”, we arrive at a **current ultrarare disease drug loss of 50 drugs**

Current Drug Loss

1. 86 drugs approved by FDA and EMA by 2020
   Low risk
   Short timeline of 2-3 years
2. 209 drugs approved by FDA and EMA since 2020
   Low risk
   Short timeline of 2-3 years

5 Tiers		Candidates
1	86 drugs approved by FDA and EMA from 2016 to 2020	1 — 10 drugs
2	28 drugs approved by FDA and EMA from Jan 2021 to Mar 2023	2 — 5 drugs
3	113 drugs approved by FDA and EMA from Apr 2023 to Sep 2025	3 — 18 drugs
4	45 drugs approved by FDA and EMA from Oct 2025 to Mar 2026	4 — 7 drugs
5	23 gene therapy drugs approved by 4th Mar 2026	5 — 10 drugs

FILTERs

Source: JFRDR

In the first five years, JFRDR aims to deliver **5-6 PMDA approvals**

- JFRDR are currently **prioritizing** these **50 ultrarare disease drug loss projects** to identify the **first fifteen projects to start funding in years 1-5**
- The filters being used consist of **"likely impact on clinical practice in Japan", solidity of approval data reviewed by FDA and/or EMA" and "likely feasibility of obtaining IP rights for Japan"**
- For the **prioritized projects,** JFRDR will estimate **project-specific cost** to bring them to **PMDA approval stage** based on FDA approval documentation and with input from NCPN, AMED and CROs
- In addition, to **validate JFRDR's business model**, JFRDR plans to select and fund inclusion of a few Japanese patients (to be determined with PMDA) of **twelve ultrarare disease candidates** currently in clinical development outside Japan to generate a **first approval** in year 5
- The current budget estimate is based on **average cost per project** and amounts to **$60mn for the first five years**

Source: JFRDR

JFRDR are conscious of the fact that there remain **many unknowns** that are **difficult to model** at this stage; it will be one of JFRDR's roles to **catalyse** relevant players in the ecosystem to **provide answers over time**

1. Will JFRDR be able to generate **revenues from donations** (corporate and the public)?
    - JFRDR will invest in public relations and hopes to increasingly generate such revenues, both due to government funding as a signal and professional public relations
    - How successful this will be remains unclear at this stage
2. Which **funding model** will the government adopt?
    - Fully funded out of budget - or bond-funded, coverage with or without bond yield?
    - Initial full coverage with financial self-sufficiency of JFRDR over time?
3. How willing will **service providers** in the Japanese ecosystem be to operate at **cost-plus?**
4. How flexible will PMDA be in terms of **regulatory requirements** affecting cost of development
    - (E.g.: GMP-like vs full GMP, three PPQ runs vs one or two, clean room level 3 vs 4, etc)
5. How will MHLW adjust calculation of **reimbursement levels** to account for specific costs related to ultrarare diseases?
    - (E.g.: diagnosing patients, training hospital staff, patient registries, cost of travel and lodging for patients and families, etc)

Source: JFRDR

So who benefits from JFRDR? **Mainly Japanese stakeholders**, but also patients and their families outside Japan

Patients and their Families
Increased and faster access to therapeutics, in part delivering disease modification and/or cure

Academia
Capability building, increased scope for publications and treatment for patients

Founding Companies
Positive effect on reputation

Industry
De-risked product supply/local infrastructure, materials, equipment and capabilities in academia, hospitals and CROs, etc

Innovation Ecosystem
Capability building in academia and hospitals beyond iPSCs, CMC infrastructure for novel modalities, higher attractiveness for foreign researchers and investors, ultimately higher value added and tax base, lower biopharma imports & higher exports, lower drug prices

Patients and their Families worldwide
Increased number of products with patient access for ultrarare disease therapeutics

Source: JFRDR

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In Japan, **public funding** is the only **viable approach** for JFRDR to initiate operations; this may be supplemented at a later stage by private donations

Financial Investment	Private Donations	Public Funding

Not feasible by definition	• **The public**: Examples from Italy and France show this can be a viable model
	  • Public will need to be sensitized and educated over time
	• **Corporations**: GHIT example shows is can be a viable model
	  • Unlikely to take first-mover action, may follow gvt lead
		• Several **good rationales** exist for public funding
		  • Social contract, improvement in ecosystem, ned innovation model, national security
		• Funding can use a number of **different mechanisms** and ultimately comes down to a **political choice**

Source: JFRDR

A closer look at **potential funding models** for a non-profit organisation tackling market failure like JFRDR shows three basic mechanisms are available: Annual budget, dedicated bonds and government-backed loans

Government Funding out of General Budget

- Subject to annual budget appropriations
- Not adequate for long biomedical research timelines
- Needs to be financed by general bonds
- Full cost born by current tax payers

Government Funding via Dedicated Bond Issuance

- Requires long-term funding commitment by gvt
- Permits spreading cost of funding over decades
- Main cost born by future tax payers who benefit from funded activities

Government Funding via Long-term Loans

- Long established process in Japan (FILP)
- Borrowing cost similar to other alternatives ad spread to future tax payors
- Loans need to be repaid either by recipient or by government
- No limits on organisational set-up

- Significant limits on organisational set-up (as per Cabinet Office)

Source: JFRDR

In the US, a number of State governments have funded biomedical research via **dedicated bonds**, the best examples being the California Institute of Regenerative Medicine (CIRM) and the Cancer Prevention Research Institute of Texas (CPRIT)

CIRM First Funding Cycle
2004 - 2020

- Proposition 71, approved by voters in 2004
- State government issued $6bn in bonds
- **$3bn funded CIRM for these ten years**
- **$3bn funded interest payments over 30 years**
- Bonds are being repaid from year 10

CIRM Second Funding Cycle
2020 - 2030

- Proposition 14, approved by voters in 2020
- State government to issue $7.8bn in bonds over ten years
- **$5.5bn to fund CIRM for these ten years**
- **$2.3bn to fund interest payments over 40 years**
- Bonds are being repaid from year 10, annual repayment $260mn

Sources: https://www.cirm.ca.gov/about-cirm/history/; https://www.cprit.texas.gov/

Life Insurers (or other **financial institutions with large bond holdings**) could participate in government-guaranteed funding in a number of ways, that could lead to an **optimal funding model** compared to direct funding by government

How would it work?

- Life Insurer sells part of its bond holdings and extends ten year loan to JFRDR
- JFRDR pays annual bond yield to Life Insurer
- **MoF guarantees principal and pays back Life Insurer after ten years**

What are potential variations?

- Life Insurer could forego part or all of bond yield payments as a financial contribution to social contract
- Bonds could be repaid over a longer period of time

What is the upside of this approach?

- Life Insurer generates significant branding impact for its business
- Funding mechanism reflects long biomedical R&D timelines
- Financial burden is shifted to future tax payers
- No limits on organisational set-up (tbc)

Source: JFRDR

Example for gvt-backed loan: Could a life insurer like **Meiji Yasuda** contribute to funding JFRDR? Statements on website and in annual report suggest this could align with current vision and strategy

- "We feel the need to go **beyond creating conventional economic value** and simultaneously **create social value**. Meiji Yasuda will leverage the advantages of being a **mutual company** supported by policyholders who are "mutual members" and owners of the company in order to promote management that prioritizes both its policyholders' benefits and **contributions to society for the fut**ure"
- "A mutual company system, which is founded upon the **spirit of mutual aid**, is best suited as a life insurer tasked with providing functions to **supplement Japan's public social security systems** and perfectly dovetails with the needs of modern society as we transition to a more sustainable society"
- **Priority issues** (materiality) for Meiji Yasuda
  - **Prolong healthy life expectancy**
  - **Support sound development of children**

Sources: https://www.meijiyasuda.co.jp/english/ and https://www.meijiyasuda.co.jp/english/disclosure/annual-reports/backnumber/2024.html

Funding is also a **political choice**: The **preferred financing model** is **full funding by government**; alternatively, JFRDR could **gradually** become **self-financing**; however, this would entail **higher prices** and potentially more **limited patient access**

Preferred Approach
JFRDR generates no profit and is fully funded by government

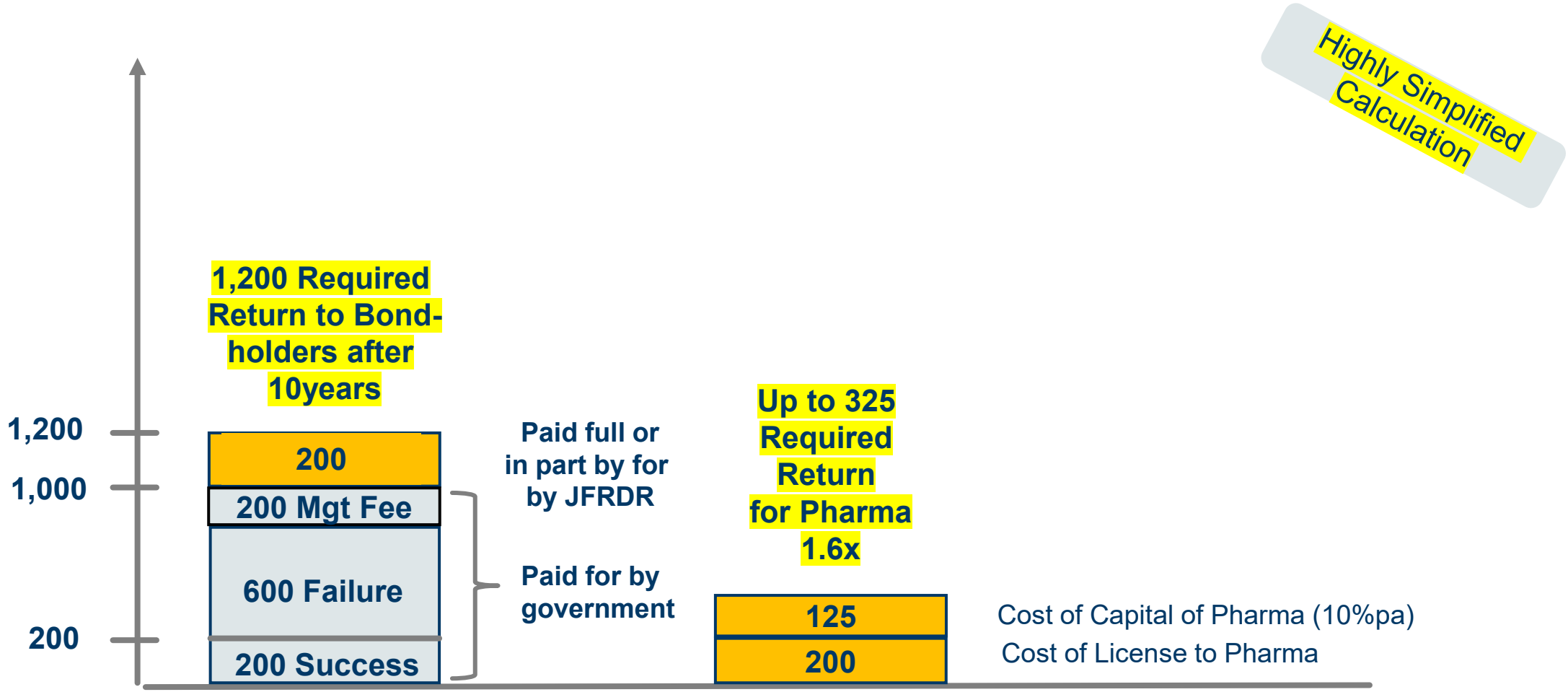
- Approach followed by **California for CIRM**
- Government pays for the **full cost of JFRDR throughout its lifetime** (Basic Science model) incl all or part of bond yield
- JFRDR is not sustainable on its own but contributes to the **sustainability of the healthcare system and the competitive-ness of the larger innovation ecosystem**
- **Prices of drugs** developed by JFRDR will be in the range of **20% - 25%** of what is required in the VC model – **best accessibility**

Alternative Approach
JFRDR is expected to become financially sustainable over time

- **FILP** approach
- Government would fully fund JFRDR for the first five to ten+ years to allow for the build-up of a mature portfolio
- The maturing portfolio will **gradually allow JFRDR to reach "steady state" in which all cost can be fully covered and it becomes financially sustainable**
- **Prices of drugs** developed by JFRDR will be in the range of **50%** of what is required in the VC model, **reducing savings** to the **healthcare system**

Source: JFRDR

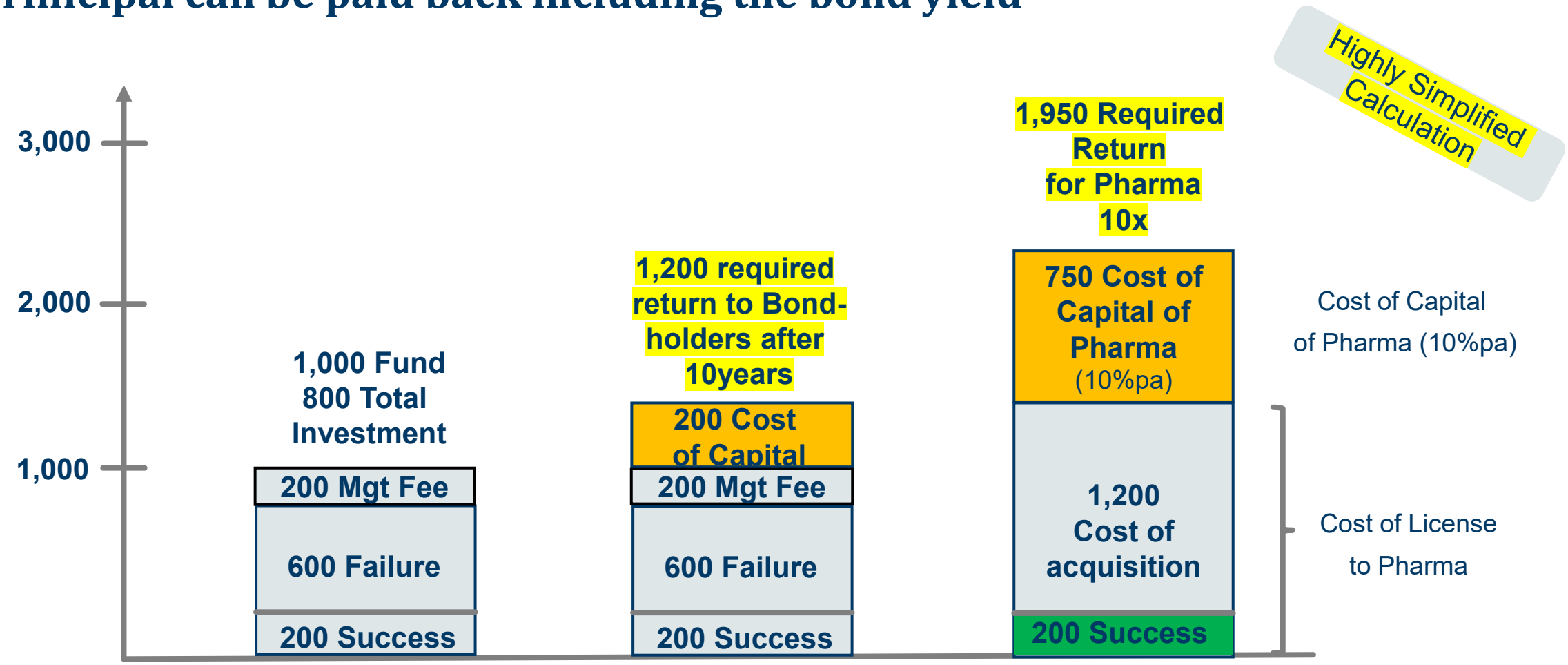
Preferred Approach: Assuming the **principal** and part of bond yield **is funded by government**, JFRDR could license the successful drug for 200 or less to pharma which would then need to generate sales of up to 325 over ten years to cover its cost of capital



Note: Current yield of ten year Japanese government bonds is closer to 2.5%

Source: JFRDR

Alternative Approach: In a **self-sustaining model**, there will be a management fee but no carry for management; if the drug is then licensed to Pharma for 1,200, bond **prinicipal can be paid back including the bond yield**

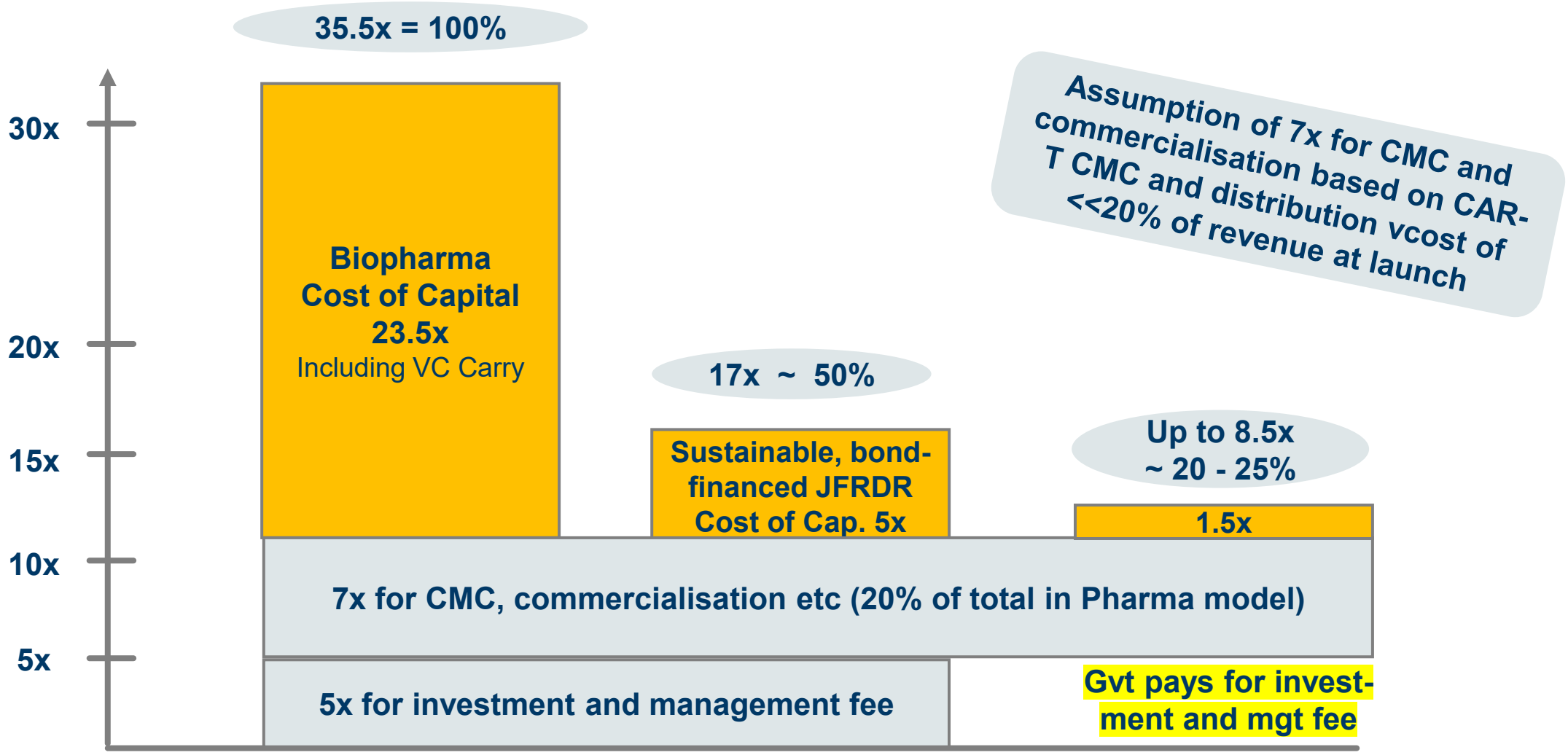


Note: This analysis assumes an acquisition (M&A); the cost of capital would be lower in case of a licensing deal made up of upfront, milestone and royalty payments

Source: JFRDR

Note: Current yield of ten year Japanese government bonds is closer to 2.5%

Finally, in a like-for-like comparison where **CMC and commercialisation cost** are equal and pharma distributes in all three scenarios based on an acquisition, **prices for JFRDR-developed drugs can be reduced to 20%** to **50%** compared with the VC model



Source: JFRDR