Innovation Day:

A market overview for researchers

Speakers:

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- *Amanda Silva Brun - CNRS, Université Paris Cité*

Hémicycle Simone Veil , November 14th, 2023

Life Sciences Leadership School

New medicines increase human life expectancy

- Life expectancy: + 45 years during the XX century

- The "collective curative medicine" :

- 8000 Molecules, Vaccines, Antibiotics, Anesthesia...

1860 :

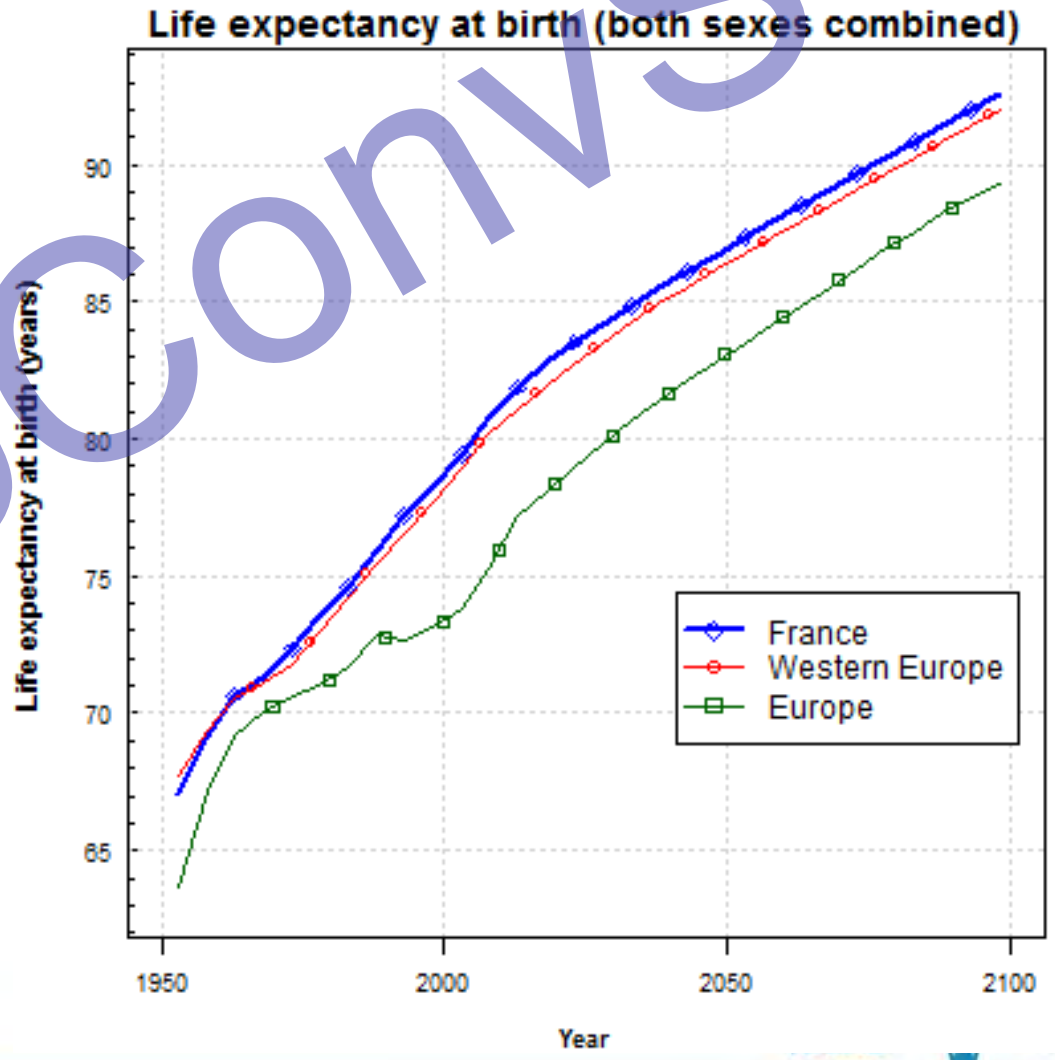
- 38 years for men,
- 41 years for women

1913 :

- 48 years for men,
- 52 years for women

2017 :

- 79.5 years for men
- 85 years for women



Source: United Nations, Department of Economic and Social Affairs, Population Division (2017). World Population Prospects: The 2017 Revision

People over 80 are more and more

- 2 billion people over 60 years old in 2050

	Persons aged 60 years or over (millions)				Percentage change	
	2000	2015	2030	2050	2000-2015	2015-2030
	607.1	900.9	1402.4	2092.0	48.4	55.7
	Persons aged 80 years or over (millions)				**Percentage change**	
	2000	2015	2030	2050	2000-2015	2015-2030
	71.0	125.3	201.8	434.4	76.5	61.1

New pathologies & needs linked to old age will appear

United Nations, Department of Economic and Social Affairs, Population Division (2015). *World Population Ageing 2015* (ST/ESA/SER.A/390).

New medical needs are emerging

- **Normal aging**
  - Sensory Changes
    - Hearing Loss
    - Visual Acuity
    - Vestibular Function
  - Muscle Strength & Fat Changes
  - Immuno-senescence
  - Urologic Changes

- **Somatic disease & multiple chronic conditions**
  - Cardiovascular Disease
  - Hypertension
  - Cancer
  - Osteoarthritis
  - Diabetes
  - Osteoporosis

- **Physical function**
  - Walking Speed (1.1 m/s for men and 0.8 m/s for women)
  - Mobility disabilities
  - Falls
  - Frailty

- **Psychological an cognitive**
  - Dementia
  - Cognitive aging
  - Depression

Health issues in 85 Years Old and Over Population Front Public Health. 2017 Dec 11;5:335 www.frontiersin.org

Key numbers for worldwide drug market

1. Revenue of the worldwide pharmaceutical market : $ 1,587 billion in 2022

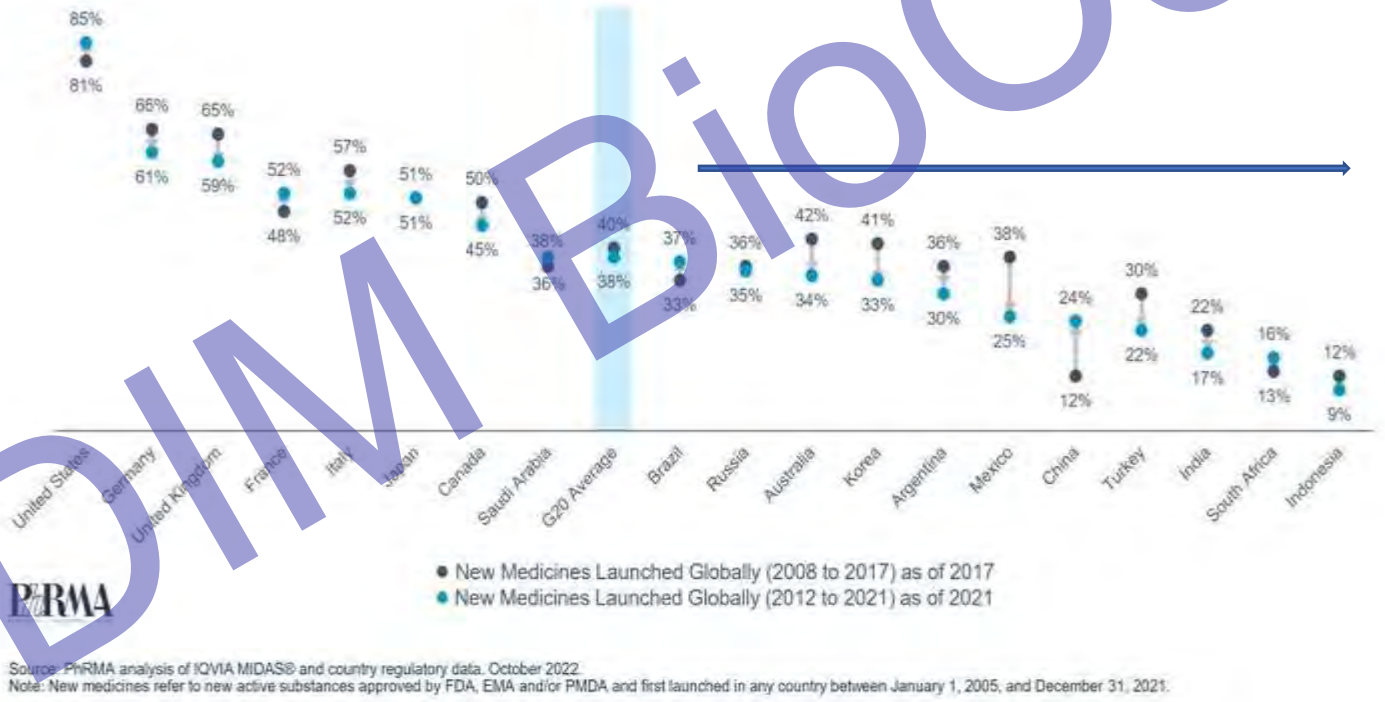
(Pharmaceuticals Global Market Report)

2. The North American region accounted for over half of the pharmaceutical market revenue worldwide.

3. Pharmaceutical research and development expenses: $ 244 billion in 2022

New medicines approved by the agencies are not worldwide accessible

- New medicines approved by the FDA, EMA or Japan's are not worldwide accessible
- % of available new drugs has declined in most G20 markets
- Huge need to secure conditions to attract new drugs in the right part



Source: PhRMA analysis of IQVIA MIDAS® and country regulatory data, October 2022.
Note: New medicines refer to new active substances approved by FDA, EMA and/or PMDA and first launched in any country between January 1, 2005, and December 31, 2021.

Why do we need to create start-ups in Life Sciences ?

Flexible and agile solution

- Create a culture of innovation in Life Sciences should be a top priority of every country
- It is the driver of higher value of health care for patients and non-patients
- Innovation belongs in all functions and levels of one health care organization
- “High or low tech” sectors search and develop better ways of delivering products and services
- Create a “big pharma” /large medtech from scratch is complex and long process

- *Create an attractive climate for new health care solutions is easily accessible*
- *Creation of Start-ups will be instrumental to improve the health care*

2022 in FDA: 24 out of 37 new drugs come from small to midsized companies

- 16 Small molecules
- 8 Biologics

Figure 4: Small-to-Midsized Bio/Pharmaceutical Companies: New Drug Approvals, 2022, by the FDA's Center for Drug Evaluation and Research

Agios Pharmaceuticals Pyrukynd (mitapivat) Small molecule	Guerbet Elucirem (gadopiclenol) Small molecule	MediWound Nexobrid (anacaulase-bcdb) Biologic	Revance Therapeutics Daxxify daxibotulinumtoixnA-lanm) Biologic
Alnylam Pharmaceuticals Amvuttra (vutrisiran) Small molecule	Idorsia Pharmaceuticals Quviviq (daridorexant) Small molecule	Mirati Therapeutics Krazati (adagrasib) Small molecule	Rigel Pharmaceuticals Rezlidhia (olutasidenib) Small molecule
Amply Pharmaceuticals Relyvrio (sodium phenylbutyrate/ taurursodiol) Small molecule	Immunocore Kimmtrak (tebentafusop-tebn) Biologic	Mycovia Pharmaceuticals Vivjoa (oteseconazole) Small molecule	Santen Pharmaceutical Omlontio (omidenepag isopropyl ophthalmic solution) Small molecule
Bioverativ Therapeutics Enjaymo (sutimlimab-jome) Biologic	Immunogen Elahere (mirvetuximab soravtansine-gynx) Biologic	Phathom Pharmaceuticals Voquezna (amoxicillin; clarithromycin; vonoprazan) Small molecule	Spectrum Pharmaceuticals Rolvedon (eflapegrastim) Biologic
CTI BioPharma Vonjo (pacritinib) Small molecule	Mallinckrodt Terlivaz (terlipressin) Small molecule	Polarean Xenoview (hyperpolarized Xe-129) Small molecule	Taiho Oncology* Lytgobi (futibatinib) Small molecule
Dermavant Sciences Vtama (tapinarof) Small molecule	Marinus Pharmaceuticals Ztalmy (ganaxolone) Small molecule	Provention Bio Tzield (teplizumab-mzwv) Biologic	TG Therapeutics Briumvi (ublituximab-xiiy) Biologic

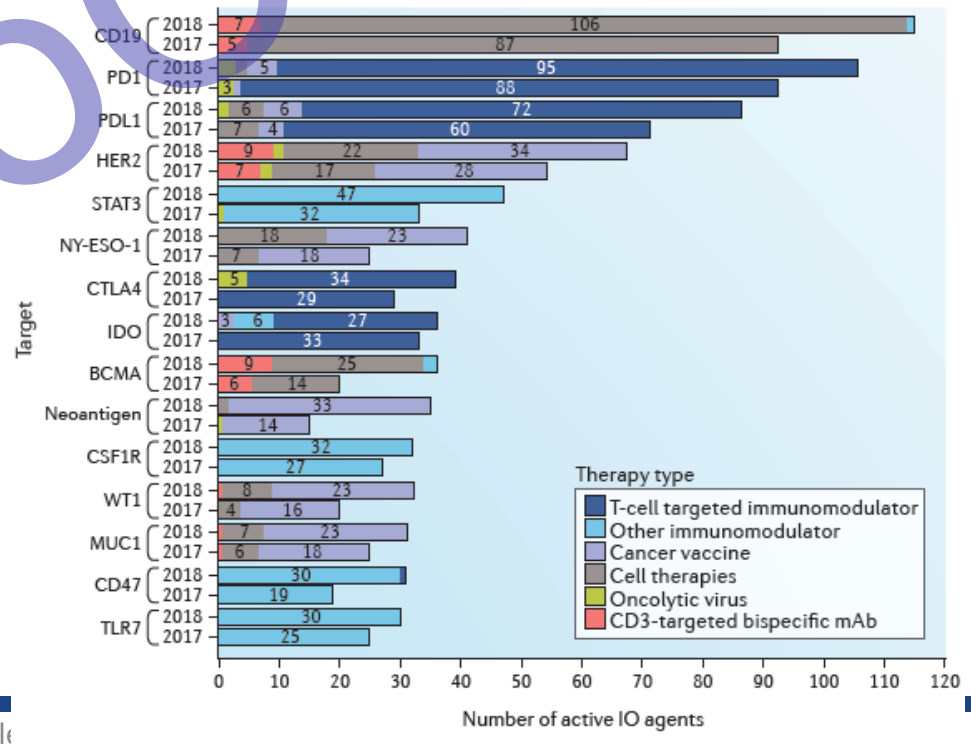
*Taiho Oncology is a subsidiary of Taiho Pharmaceutical Co., Ltd. which is part of Otsuka Holdings Co.

Source: Center for Drug Evaluation and Research, US Food and Drug Administration and Company Information

CIPREVO
Cancer & Innovation

Knowing your project's competitors very well

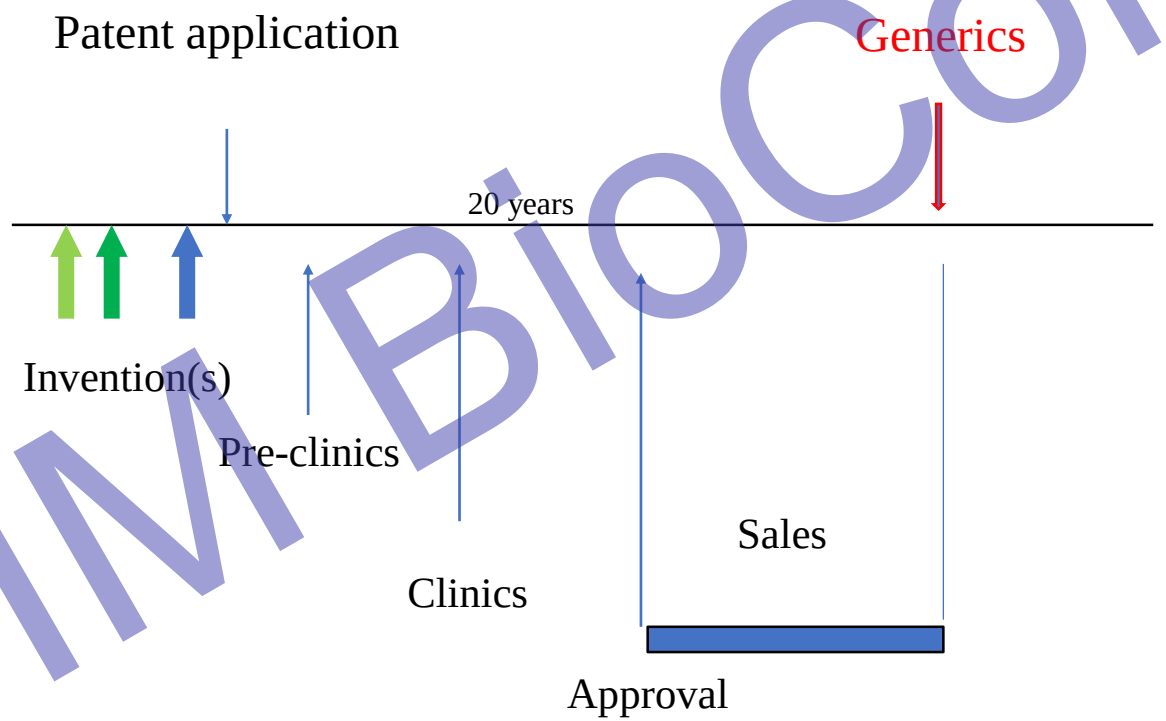
- Who is racing ahead and with some means?
- 3,394 agents in Immuno-Oncology
- What are my chances if I start today?
- What is the added value of my project?
- What is my differentiation?
- What is my benchmark?
- "First-in class"
- "Best in class"
- "Fast follower"



NATURE REVIEWS | DRUG DISCOVERY VOLUME 17 | NOVEMBER 2018 | 783

Key point: When will you reach the market?

Strict execution of the retroplanning to preserve the value of the project
Maximise the sales before generics arrival



How to enter in the market ? Target Product Profile

TPP or The Specifications

Desired object versus present object

Balance with the present object

Difficult exercise

Continuous exercise

TPP subject to internal changes

TPP subject to external changes

TPP subject to trade secrets

Iterative exercise

www.fda.gov/media/72566/download

Example of TPP

- Indications and Usage
- Dosage and Administration •
- Dosage Forms and Strengths •
- Contraindications •
- Warnings and Precautions •
- Adverse Reactions •
- Drug Interactions •
- Use in Specific Populations •
- Drug Abuse and Dependence •
- Overdosage •
- Description •
- Clinical Pharmacology •
- Nonclinical Toxicology •
- Clinical Studies • References •
- How Supplied/Storage and Handling •
- Patient Counseling Information

Product class:						
Product name:	*To be completed once product approaches phase 2b*					
Date of TPP endorsement						
Dates of TPP revisions						
	Desired		**Minimally acceptable**		***"Insert Product Name"* profile** (Completed as product approaches phase 2b)	
	Target	**Rationale**	**Target**	**Rationale**	**Target**	**Rationale**
Indication						
Expected efficacy						
Target population(s)						
Route of administration						
Formulation & presentation						
Dosage schedule						
Safety profile						
Co-administration						
Shelf-life & storage						
Manufacturability						
Price						
Product registration and WHO prequalification						

Take home message

- Yes, we're going, but let's take a very careful look around using the TPP tool every day.
- Questions
- Contact: gregoire.prevost@lslead.com

Life Sciences Leadership School

Back up slides

Why should we consider 4P Medicine?

- **Predictive**
  - Each individual (or group of individuals) has a different risk of developing a disease independently of the weight of environmental factors. These risks must be finely characterized.
- **Preventive**
  - Active risk prevention must be developed.
- **Personalized**
  - Take into account individual risks. Targeted approaches.
- **Participatory**
  - Participation of patients and/or patient groups is essential for effective prevention and treatment

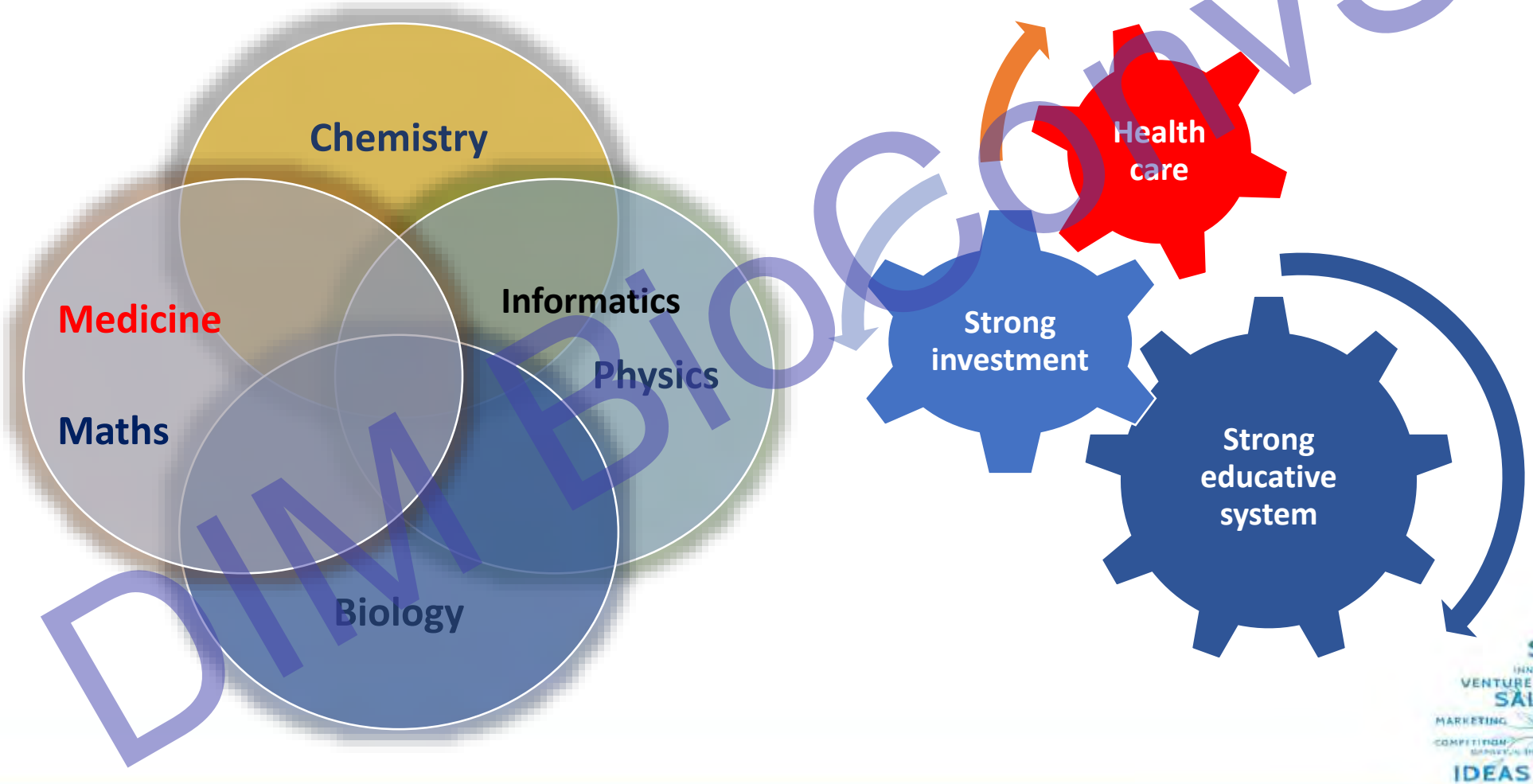
For and With the Patient

Become a health actor with Patient University

- At the Université de la Sorbonne, from 2010, the first French training program in therapeutic education open to patients
- Patients become patient experts in their pathology and active players in the healthcare system.
- Our patient experts are in great demand
- Diploma of health democracy to train user representatives
- Diploma for the coordination of care paths in cancerology

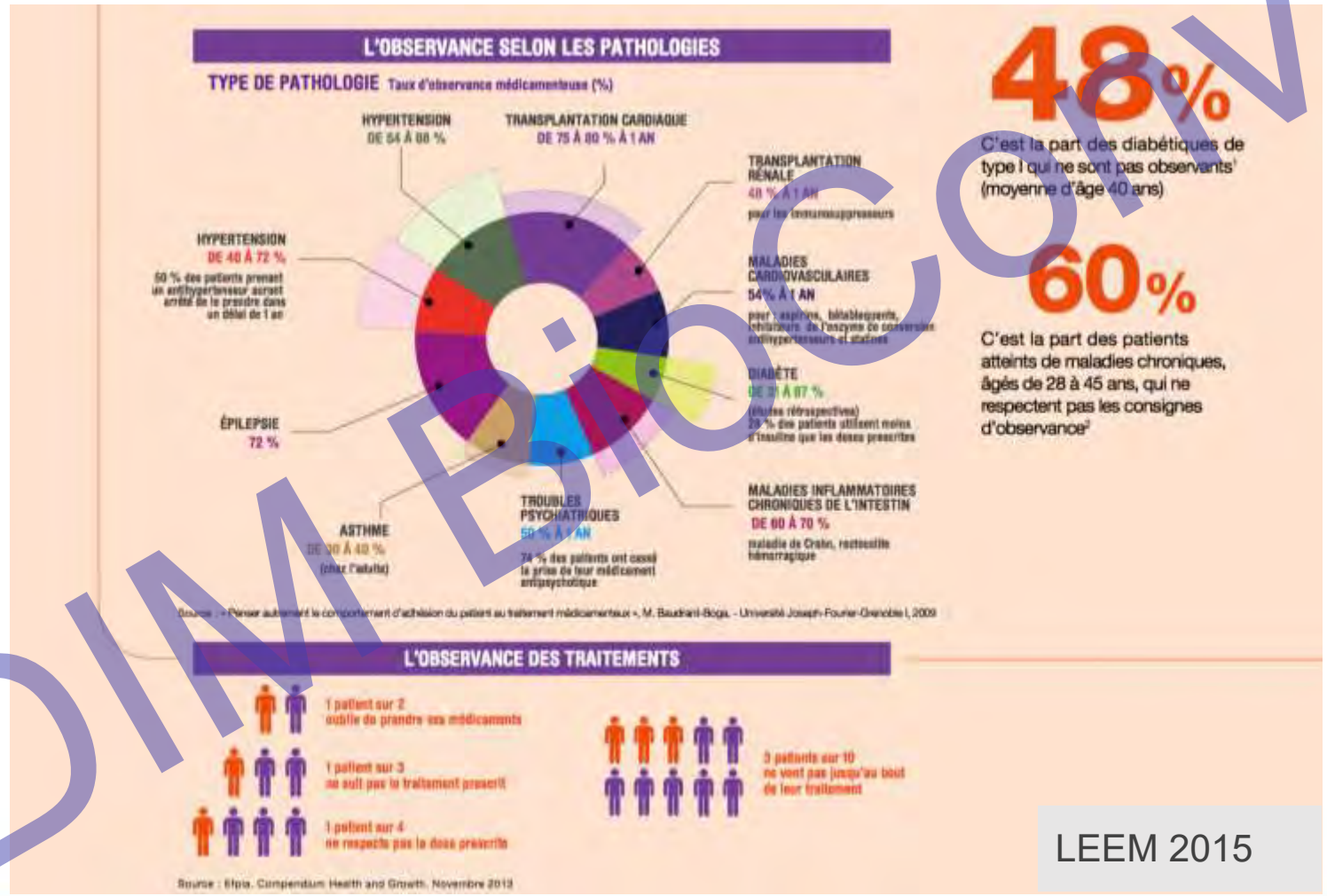
Strong and diversified basic research

Luck only smiles on well-prepared minds (Louis Pasteur)



Take home message: Medicine 4P

The adherence to drug treatment is very low



48%

C'est la part des diabétiques de type I qui ne sont pas observants[1] (moyenne d'âge 40 ans)

60%

C'est la part des patients atteints de maladies chroniques, âgés de 28 à 45 ans, qui ne respectent pas les consignes d'observance[2]

LEEM 2015

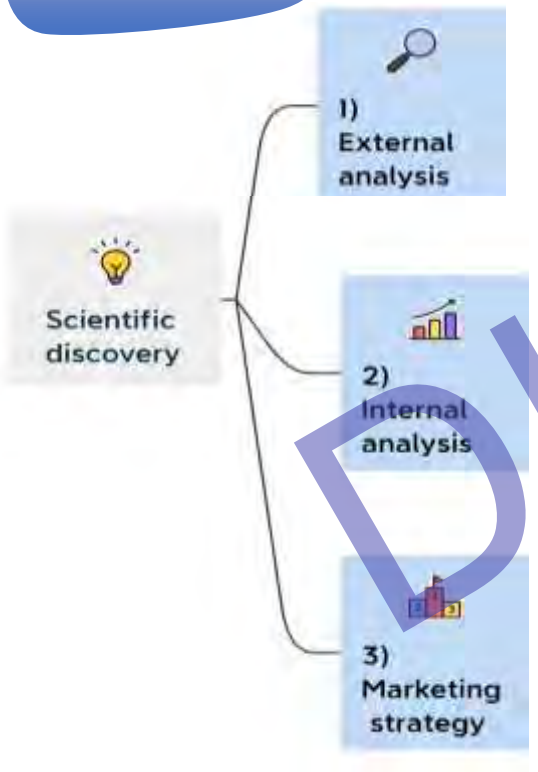
A focus on extracellular vesicle biotherapy market

Challenge

Translate a scientific discovery in product / service in the market?

Approach

A tentative roadmap



A focus on extracellular vesicle biotherapy market

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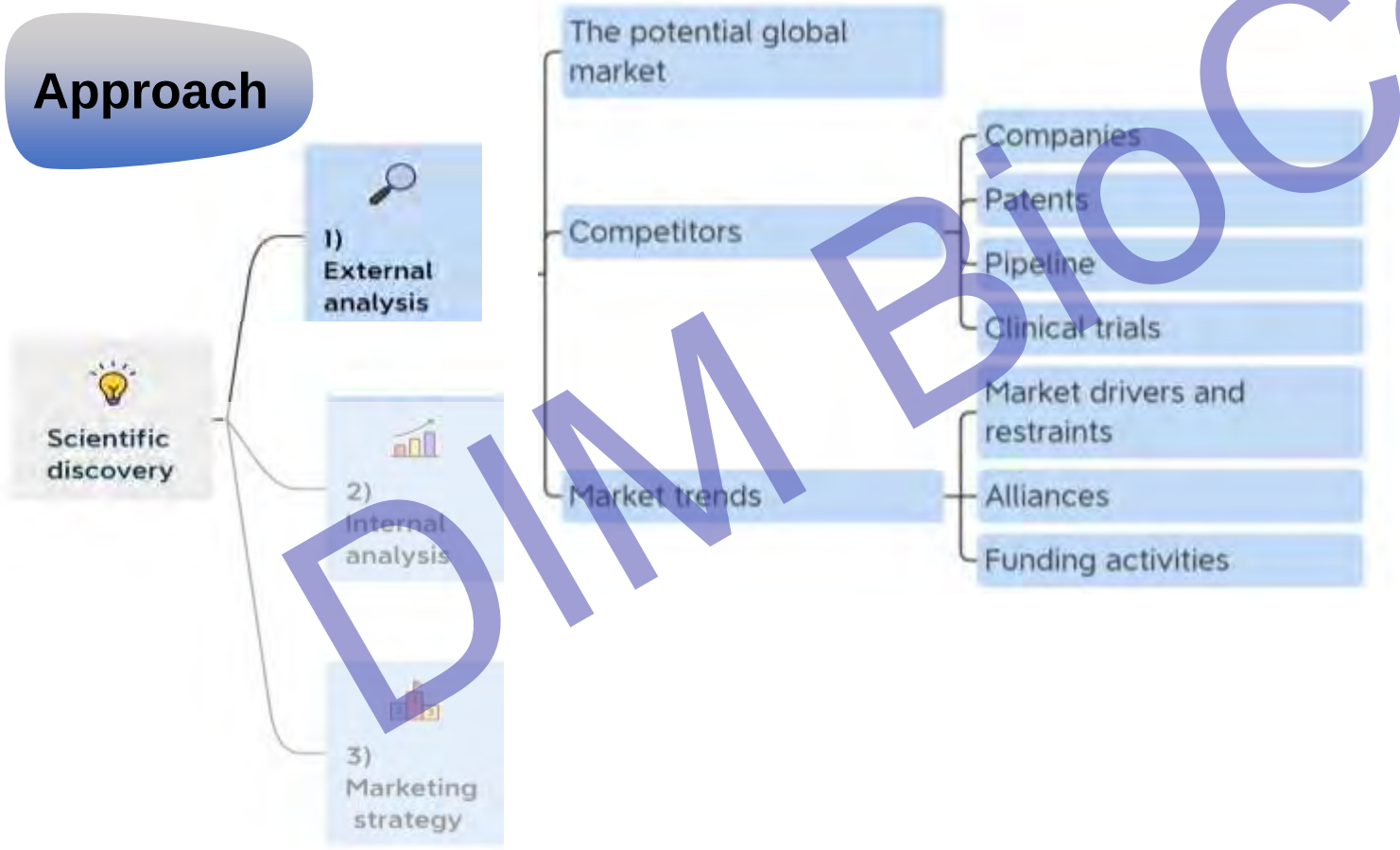


The potential global market

Source: https://www.statista.com/

Advanced drug delivery systems

Regenerative medicine

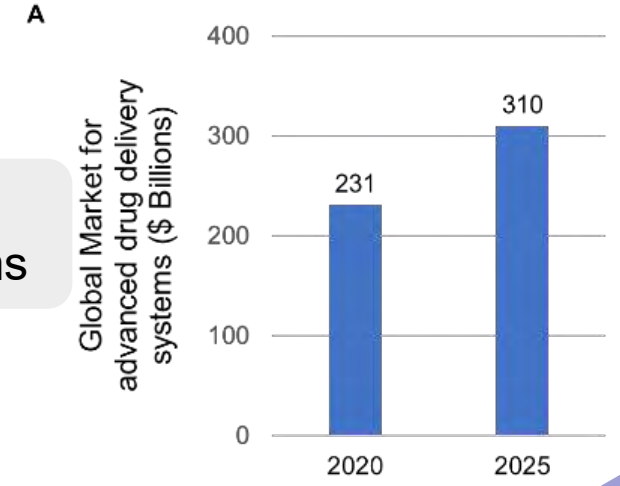
Anti-tumor therapy

Orphan indications

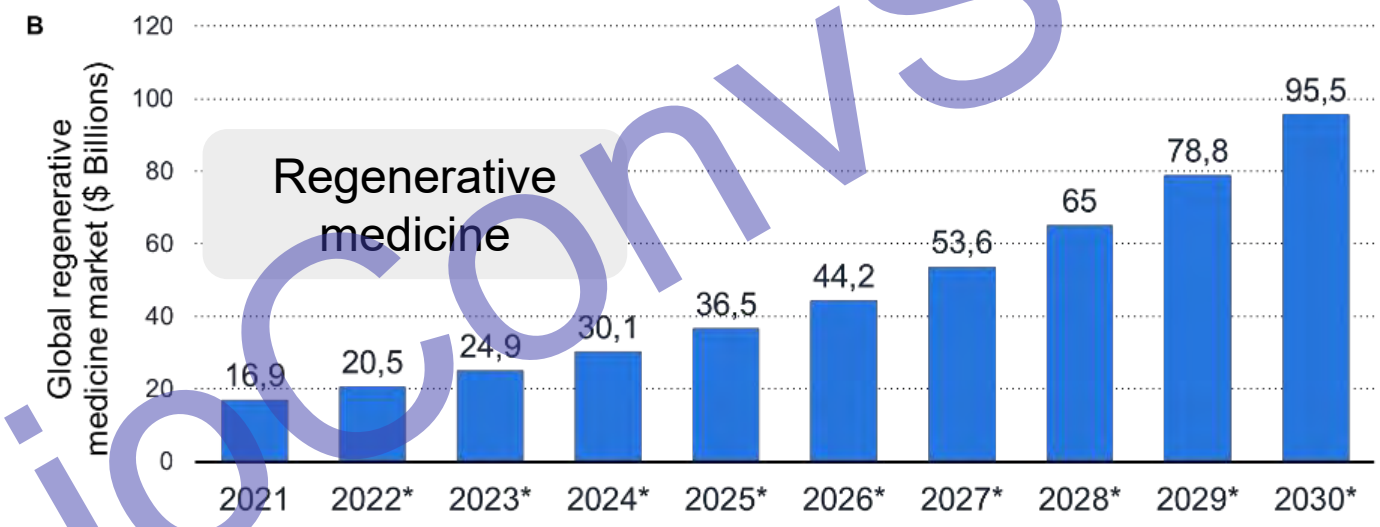
The potential global market

Source: https://www.statista.com/

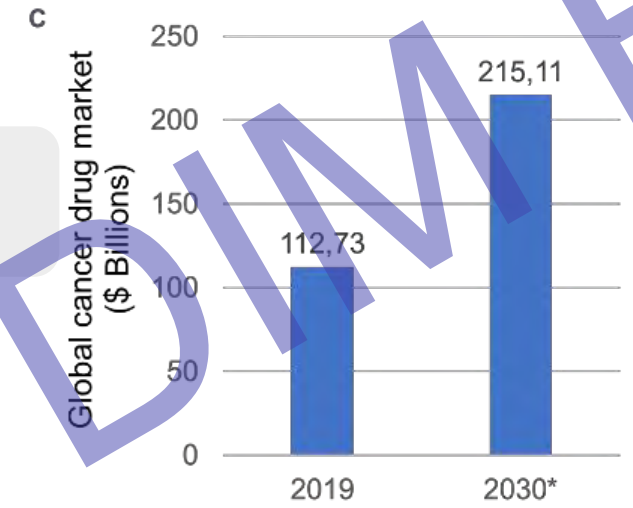
Advanced drug delivery systems



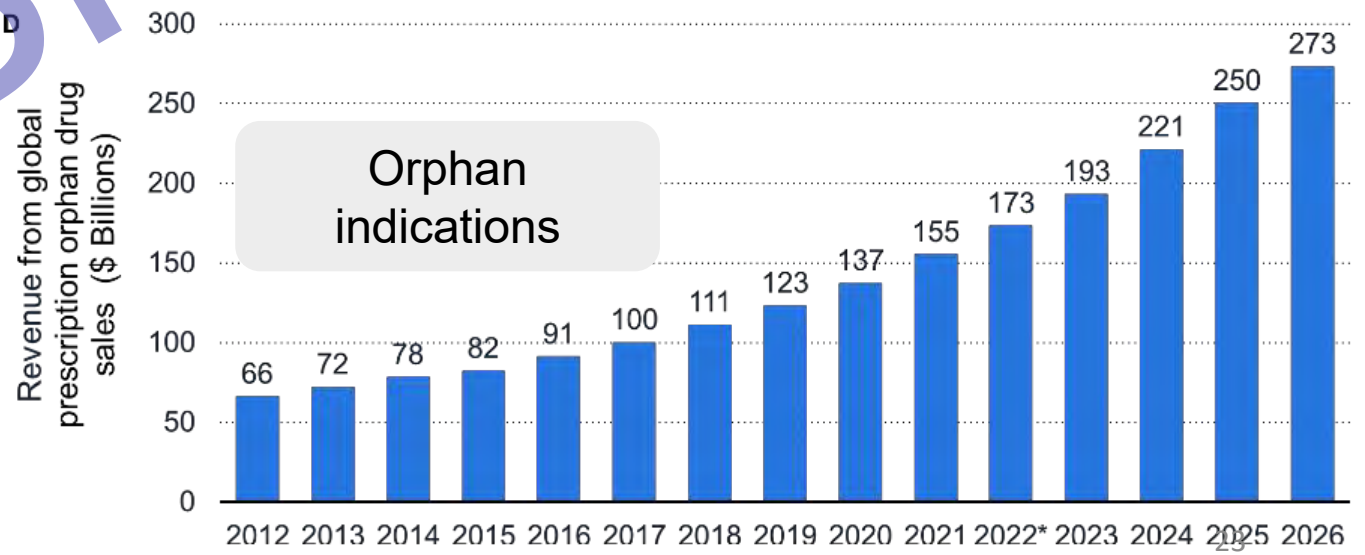
Regenerative medicine



Anti-tumor therapy



Orphan indications

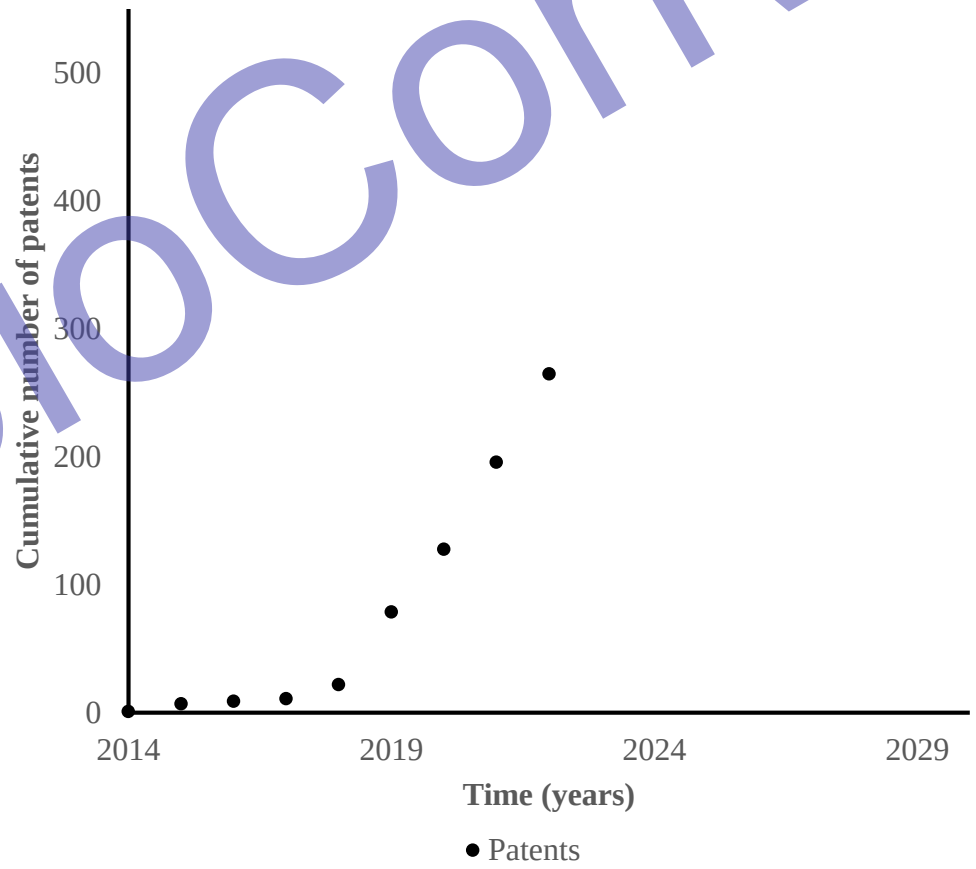


- Companies

COMPANY	COUNTRY	YEAR	STAGE	FOCUS
Aegle Therapeutics	USA	2013	Clinical	Dystrophic epidermolysis bullosa, burns and chronic pressure ulcers, etc.
Anjarium Biosciences	Swiss	2017	Not disclosed	Non-viral gene-therapy technology
Aruna Biomedical	USA	2005	Regulatory dossier preparation	Neurodegenerative diseases
Capricor Therapeutics, Inc.	USA	2005	Preclinical	EVs for vaccine development, protein delivery, and Duchenne muscular dystrophy
Carmine Therapeutics	USA	2019	Preclinical	Gene therapy based on red blood cell EVs for a broad spectrum of diseases.
Ciloa	France	2011	Preclinical	Recombinant EVs for vaccines, immunotherapies, etc.
Codiak BioSciences	USA	2015	Clinical	Cancer therapy via a technology platform for EV engineering
Direct Biologics	USA	2017	Clinical	Regenerative medicine and COVID
EV Therapeutics	USA	Not disclosed	Preclinical	Novel therapies to induce an anti-tumor imuune response in advanced stage metatastic colorectal cancers.
Everzom	France	2019	Preclinical	EV manufacturing service
Evox Therapeutics	UK	2016	Preclinical	Mainly rare disease therapy via engineered EVs
ExoCoBio	Korea	2017	Preclinical	Cosmeceuticals and biopharmaceuticals for skin and tissue regeneration
Exogenus Therapeutics	Portugal	2015	Preclinical	Treatment of chronic wounds mainly
Exopharm	Australia	2013	Clinical	Regenerative medicine via EVs for the therapy of arthritis, neurodegeneration, etc.
Kimera Labs	USA	2012	Clinical	Orthopedic, cosmetic and regenerative medicine
MDimune	Korea	2015	Preclinical	Oncology
Organicell	USA		Clinical	Covid 19, chronic obstructive pulmonary disease and osteoarthritis
ReNeuron	UK	1997	Preclinical	Drug delivery for oncology and others
RION	USA	2017	Clinical 1/2	Regenerative medicine
Stemcell Medicine	Israel	2010	Clinical 1/2a	Neurological disorders such as multiple sclerosis, pain, and neuromuscular injuries.
Unicyte AG	Switzerland	2015	Preclinical	Regenerative medicine
Vivazone Therapeutics	Australia	Not disclosed	Not disclosed	Peripheral arterial diseases

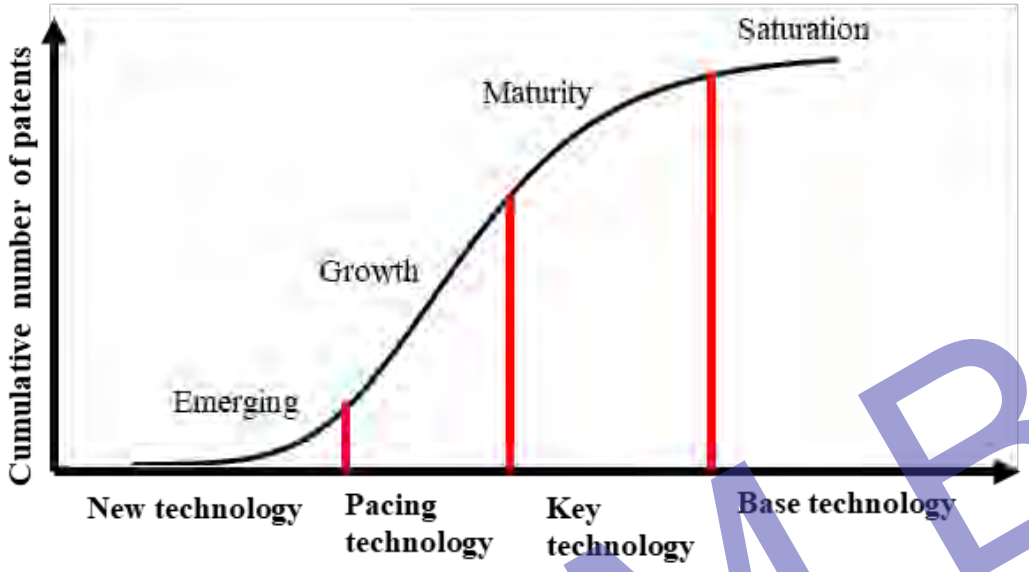
- Patents

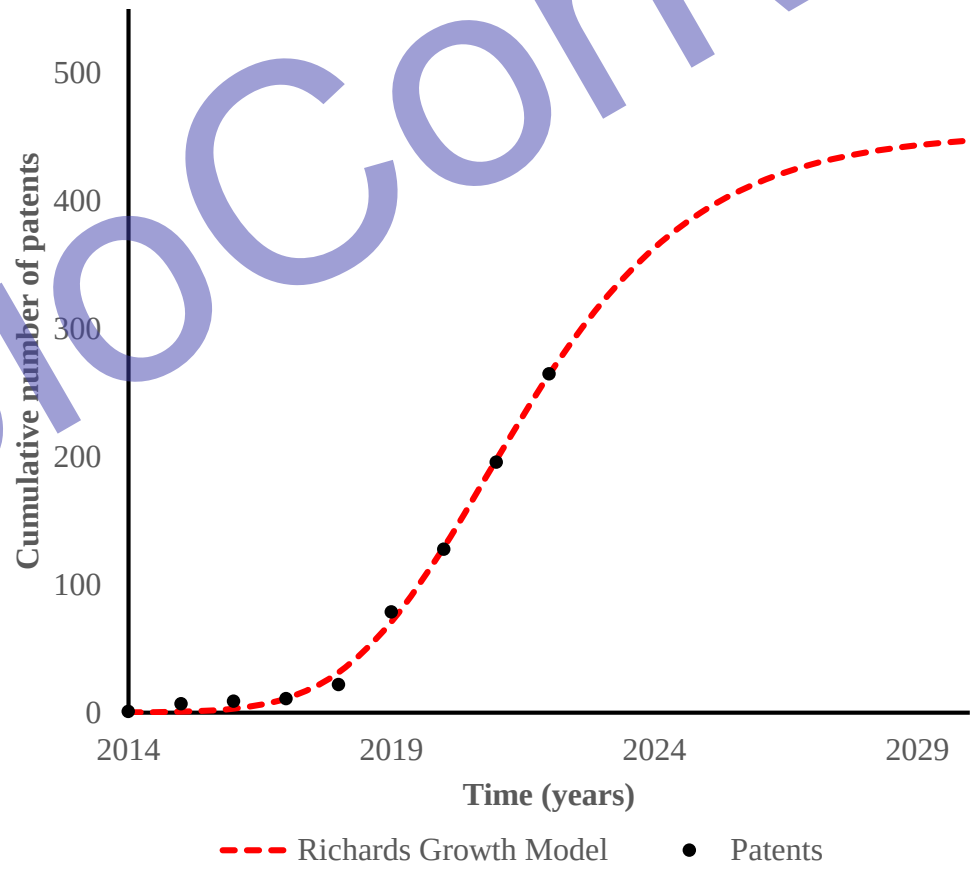
Source: https://worldwide.espacenet.com/



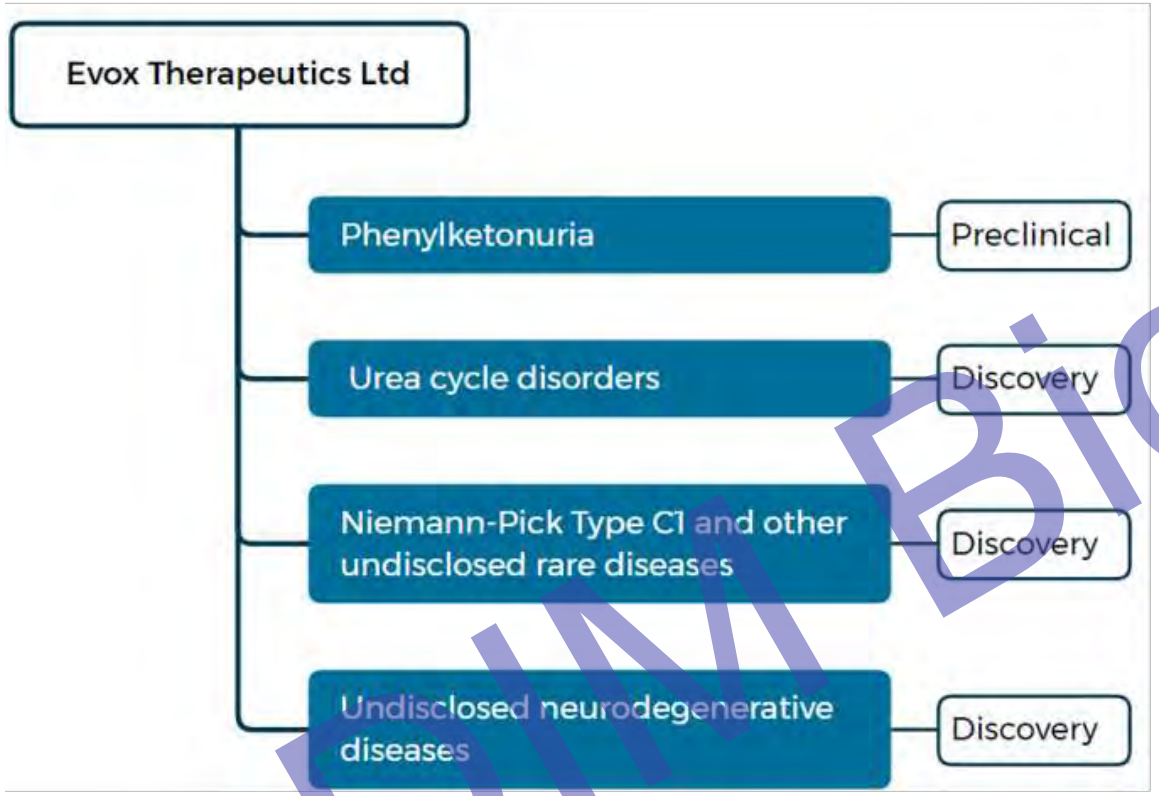
- Patents

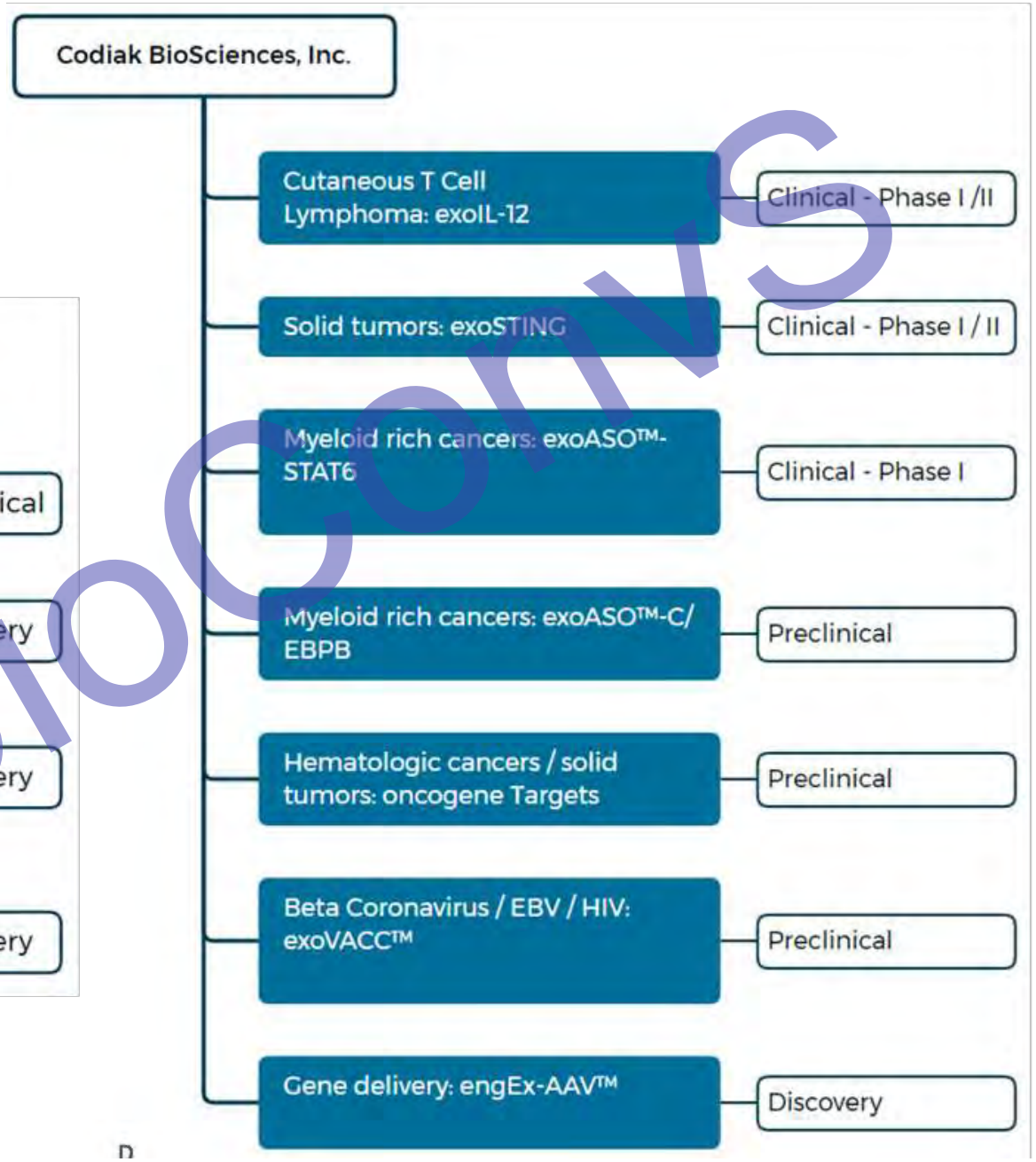
Richards model theoretical curve: we are still in a growth phase





- Pipeline





Clinical trials

Reference source: https://clinicaltrials.gov/

Reference	Therapeutic indication	EV-based product	Sponsor	Phase/ Country	Year /status
NCT04173650	Dystrophic epidermolysis bullosa	AGLE 102 bone marrow stromal cell EVs	Aegle Therapeutics	Phase 1| 2 USA	2023 / Not yet recruiting
NCT05078385	Burn wounds	AGLE 102 bone marrow stromal cell EVs	Aegle Therapeutics	Phase 1| 2 USA	2022 / Not yet recruiting
NCT04493242	Acute respiratory distress syndrome in patients with severe COVID-19	ExoFlo bone marrow derived extracellular vesicles	Direct Biologics, LLC	Phase 2 USA	**2020 / completed**
NCT05176366	Medically refractory ulcerative colitis	ExoFlo bone marrow derived extracellular vesicles	Direct Biologics, LLC	Phase 1 USA	2022 / Recruiting
NCT05130983	Refractory Crohn's disease	ExoFlo bone marrow derived extracellular vesicles	Direct Biologics, LLC	Phase 1 USA	2021 / Recruiting
NCT04592484	Advanced/metastatic, recurrent, injectable solid tumors	CDK-002 (exoSTING) HEK EVs engineered by loading with STING agonists	Codiak	Phase 1|Phase 2 USA	**2020 / Completed**
NCT05156229	Cutaneous T-Cell Lymphoma	CDK-003 (exoIL-12) HEK EVs engineered to display fully active IL-12 on their surface	Codiak	Phase 1|Phase 2 UK	2021 / Terminated
NCT05375604	Advanced hepatocellular carcinoma and patients with liver metastases from either primary gastric cancer or colorectal cancer	CDK-004 (exoASO-STAT6) HEK EVs engineered for surface-displaying an antisense oligonucleotide (ASO) targeting the STAT6 transcription factor	Codiak	Phase 1 USA	2022 / Recruiting

- Funding activities

– Alliances

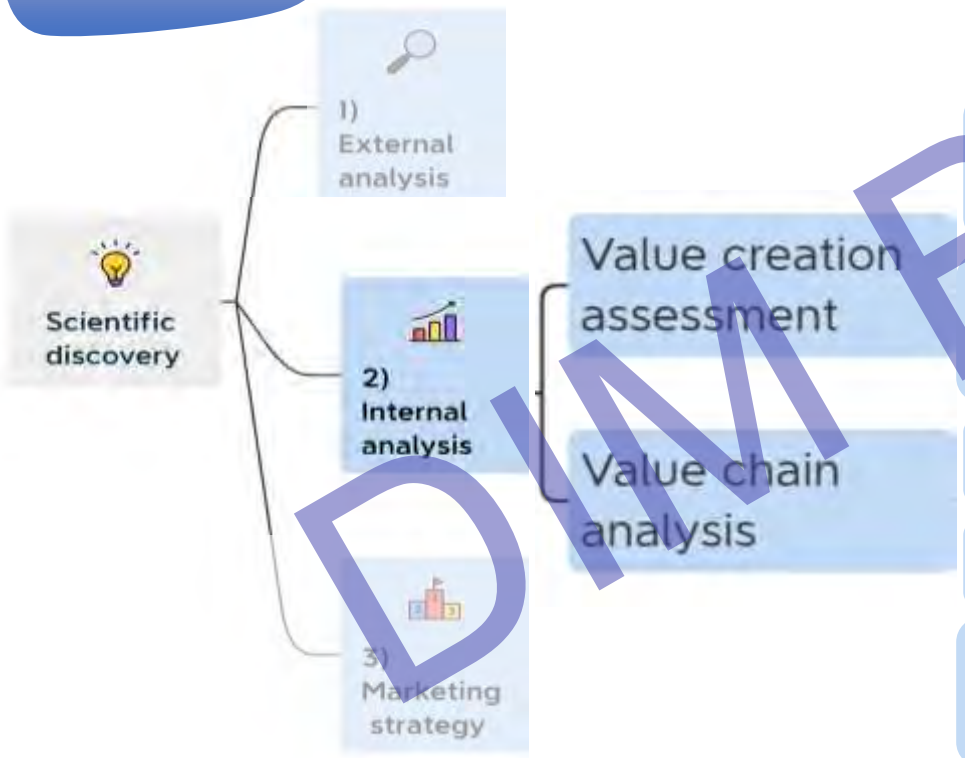
Partnerships, alliances and acquisitions			
	Date	Agreement	Deal
Evox Therapeutics and Takeda Pharmaceutical	2020	Research collaboration and license agreement	Partnership with Takeda for a multi-target collaboration to develop up to five novel protein replacement and mRNA therapies. Evox is eligible to benefit from about $882M from Takeda as well as tiered royalties on future net sales of each product.
Carmine Therapeutics and Takeda Pharmaceutical	2020	Research collaboration	Agreement with Takeda Pharmaceutical to develop red blood cell EV-based therapies for 2 rare diseases. Carmine is eligible to benefit from $900M in total milestone payments plus tiered royalties.
Codiak BioSciences and Lonza	2021	Acquisition and collaboration	Lonza negotiated access to the worldwide, exclusive and sub-licensable rights of Codiak's EV manufacturing technology. Codiak is eligible to receive about $65M of in kind manufacturing services to be dedicated to Codiak's clinical-stage programs
Evox Therapeutics and Eli Lilly	2020	Research collaboration and license agreement	Deal with Eli Lilly to develop targeted EVs for oligonucleotide delivery across the blood-brain barrier. Evox is eligible to receive approximately $1.2Bn in development, regulatory and commercial milestones as well as tiered royalties on future net sales.
ReNeuron and undisclosed partner	2020	Research agreement	Deal related to the delivery of an undisclosed pharma's gene-silencing technology via ReNeuron's EVs obtained by human neural stem cells

A focus on extracellular vesicle biotherapy market

Challenge

Translate a scientific discovery in product / service in the market?

Approach



At which extent the value of the product / service can be superior to its cost?

How to create value for patients, buyers, payers, regulators and investors?

Which is the process to generate this value?

Which are the critical steps?

For which ones can we overperform competitors? => Comparative advantage

A focus on extracellular vesicle biotherapy market

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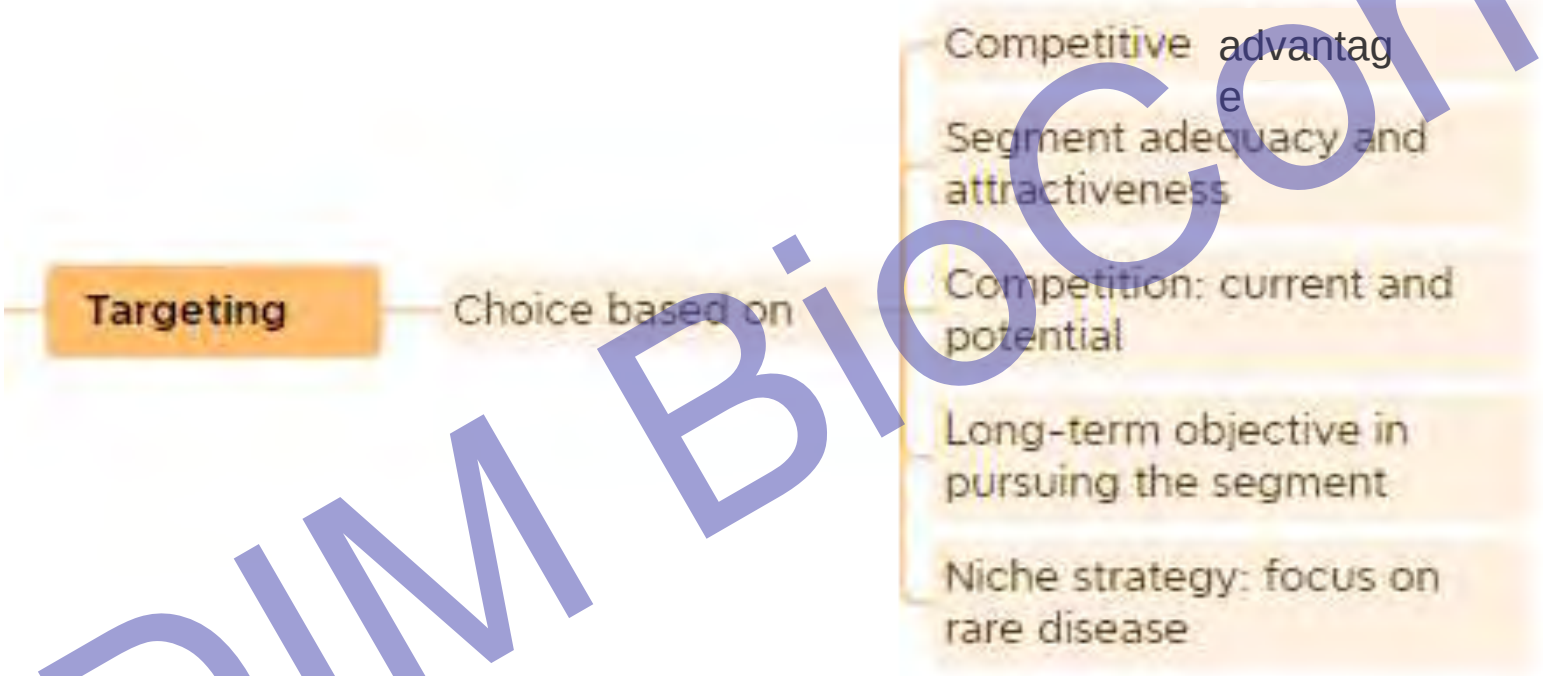
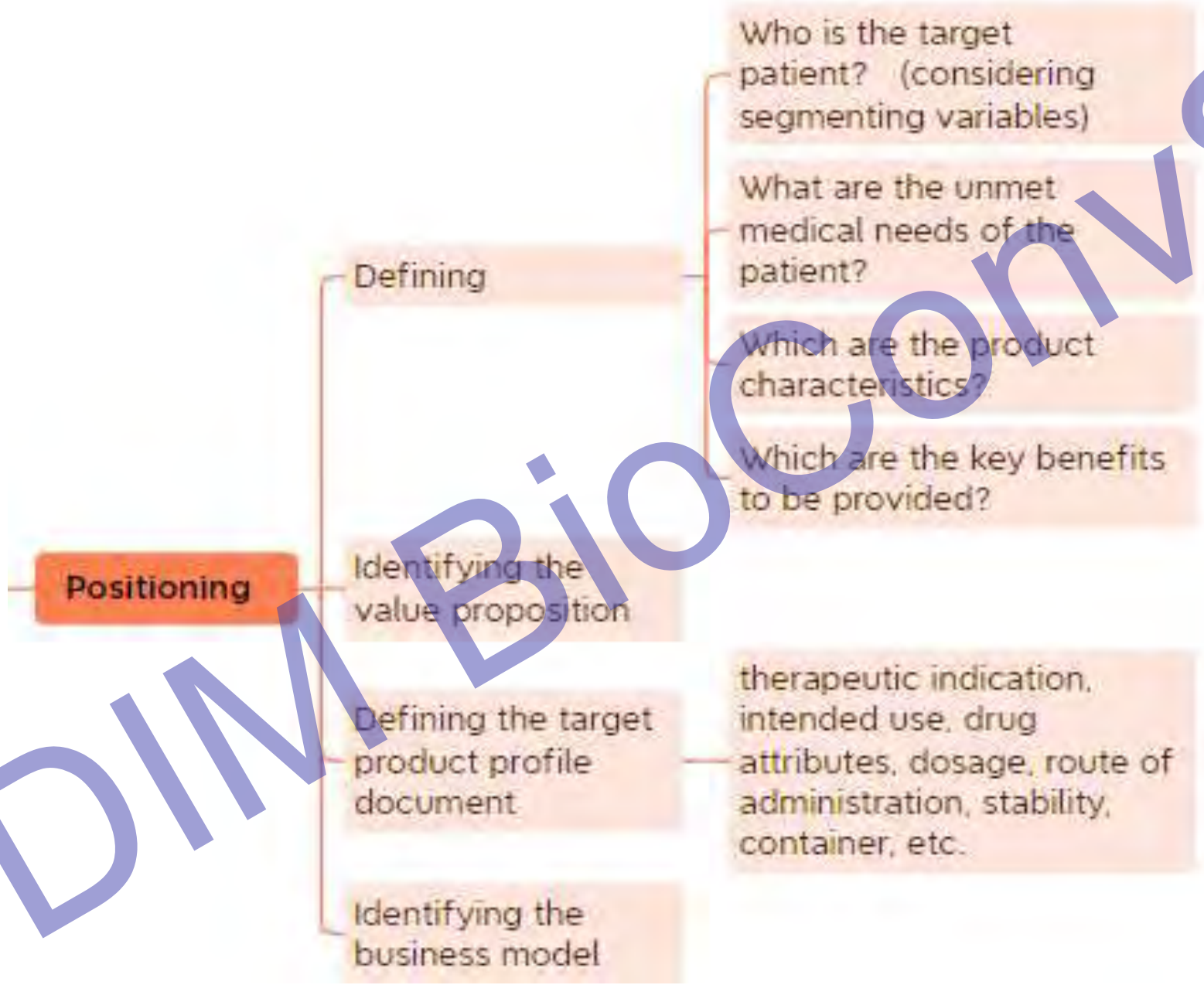




We thank you
With a souvenir:
our market tracker tool

External analysis → Internal analysis → Segmenting, targeting, positioning

Criteria	Relevant information	Sources
External analysis		
Which and how big is the market? Which other possible markets?		
How is the marketing growing?		
(In)direct competitors: which ones? When and where were they launched?		
Patents: what is protected? In which countries? Which status?		
Which are their pipelines? Which focus and advancement?		
Which are the clinical programs? Which is their design? In which countries? Which		
Which are the market drivers and restraints?		
Which are the alliances and funding activities? Which players? Where and		
Internal analysis		
Which are the main tasks for the most value-adding activities? How can they be		
Which is the competitive advantage?		
How to create value by increasing the willingness to pay and/or decreasing the		
How much is expected to be the willing to pay for the product?		
How to create value for patients, buyers, payers, regulators and investors?		
Segmenting, Targeting and Positioning		
Which possible therapeutic indications?		
Which options about patient demography: pediatric, adult and/or geriatric patients,		
Which relevant factors in the medical history of the patient?		
Which geographical localisation?		

Back-up Slides

Codiak bankruptcy: a business case
What happened?

CODIAK

Our Science Manufacturing Pipeline & Programs About Us

Codiak BioSciences to Pursue Asset Sale through Voluntary Chapter 11 Process

MARCH 27, 2023 AT 7:01 AM EDT

Download PDF

CAMBRIDGE, Mass., March 27, 2023 (GLOBE NEWSWIRE) -- Codiak BioSciences, Inc. (NASDAQ: CDAK), a clinical-stage biopharmaceutical company pioneering the development of exosome-based therapeutics as a new class of medicines, today announced that the Company has voluntarily filed for protection under Chapter 11 of the U.S. Bankruptcy Code in the United States Bankruptcy Court for the District of Delaware and will seek to pursue a sale process for its assets which is intended to maximize the value of the Company.

Codiak bankruptcy: a business case
What happened?

Pioneer advantages

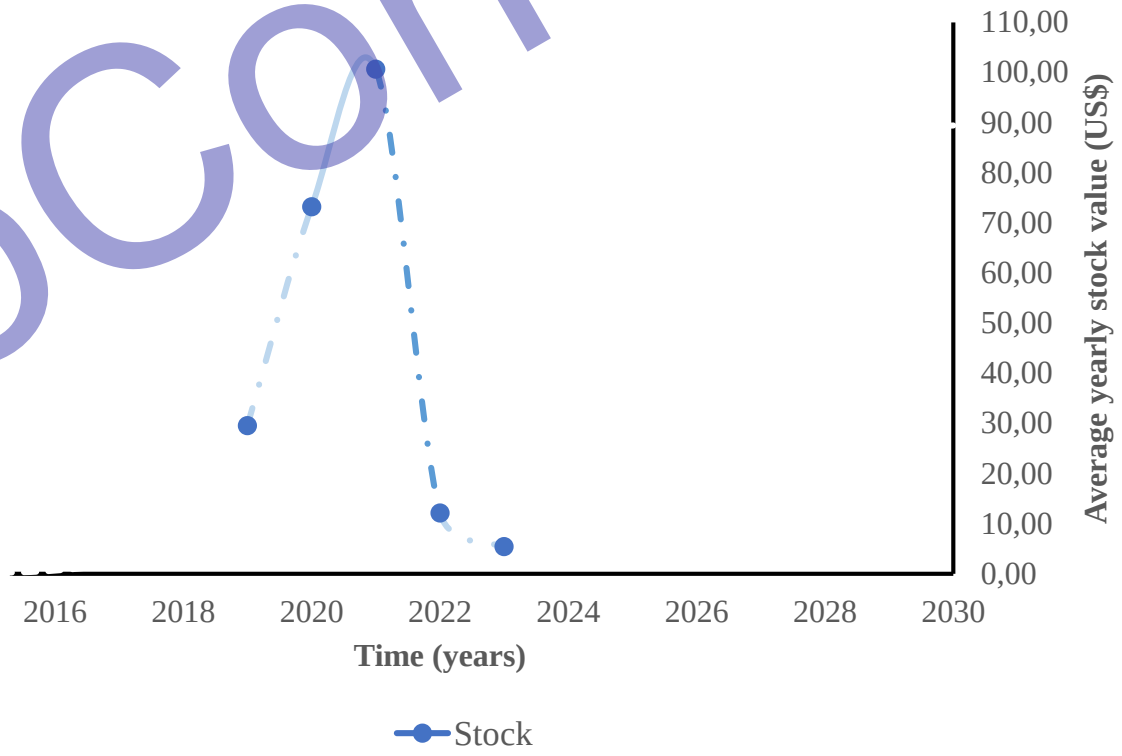
Technological leadership
Pre-emption of scarce assets (i.e. patents)

Pioneer disadvantages

Research and development expenses
Uncertainty of investor expectations
Uncertainty of regulation
Immature supply chain

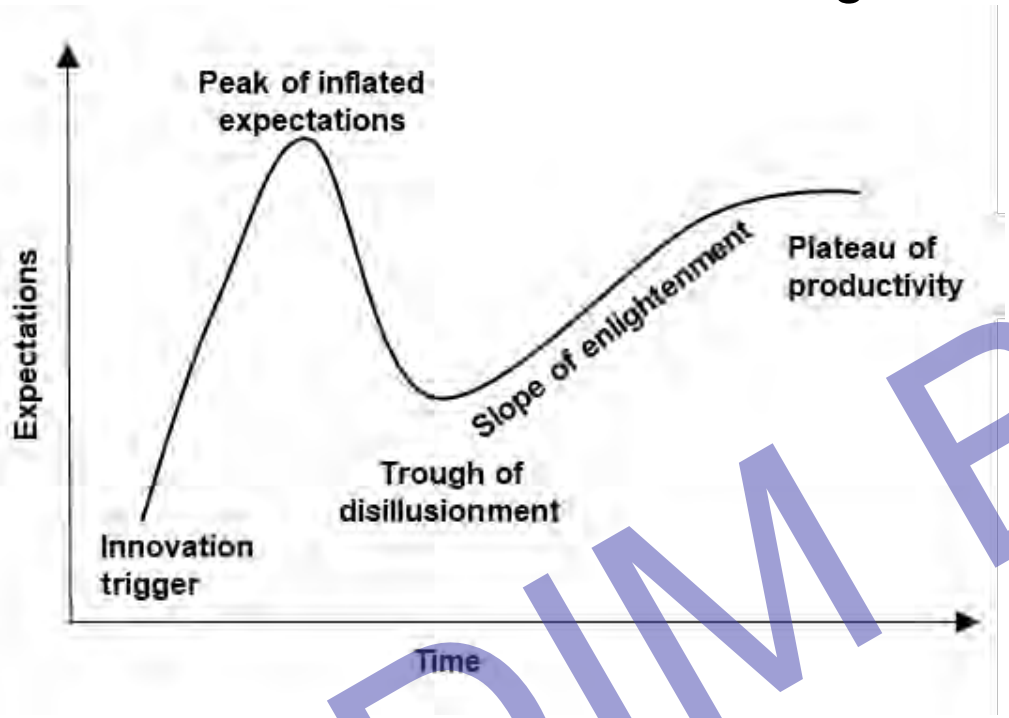
Codiak bankruptcy: a business case
What happened?

A complicating factor: the stock market

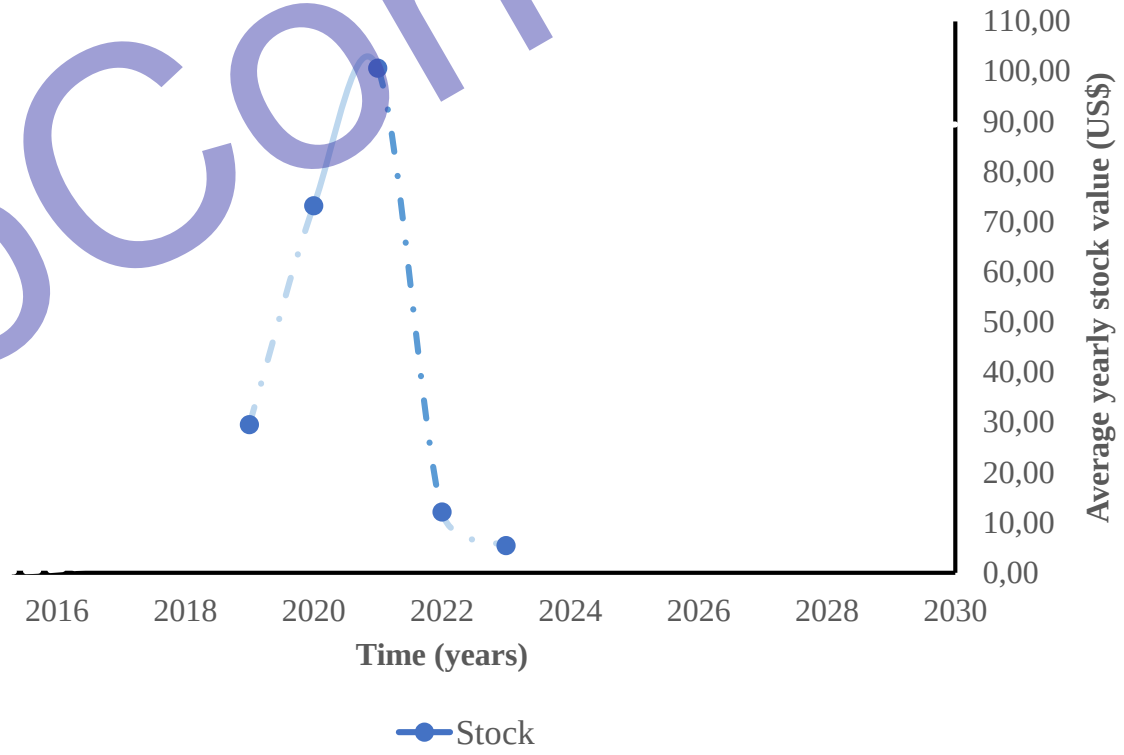


Codiak bankruptcy: a business case
What happened?

To much expectations:
this is usual for new technologies



Gartner Hype Cycle



Codiak bankruptcy: a business case
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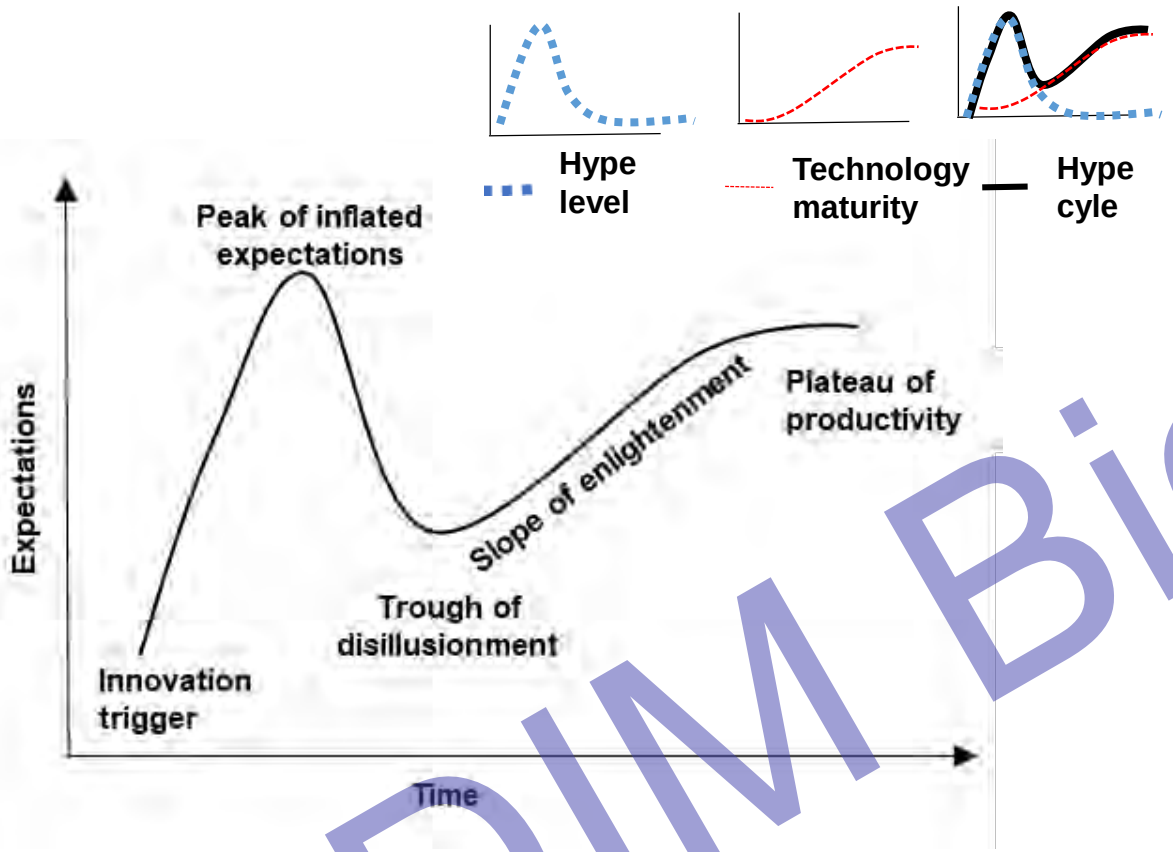
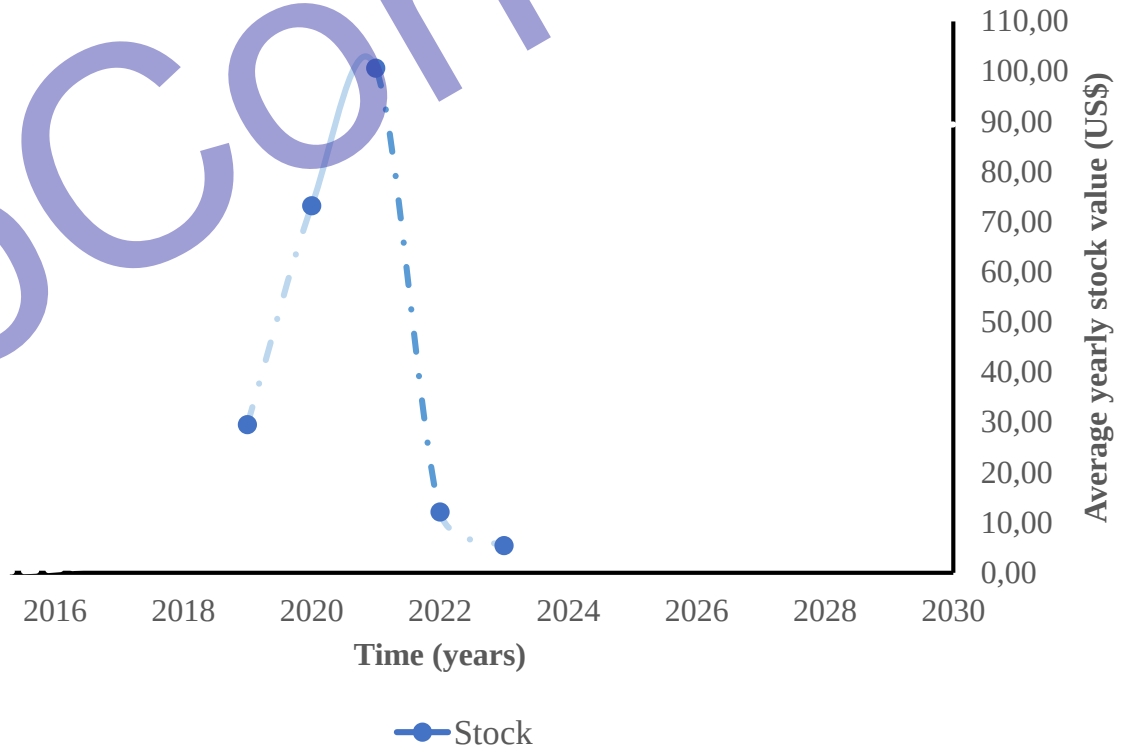
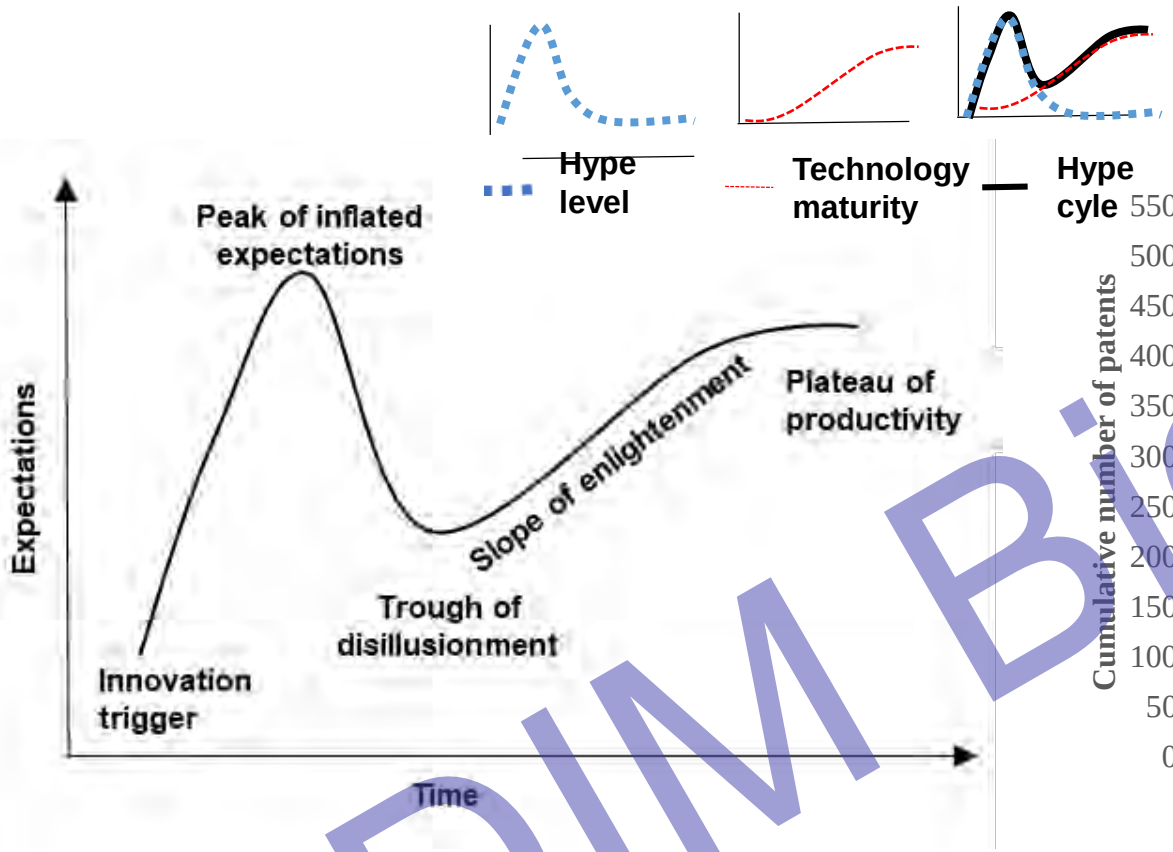


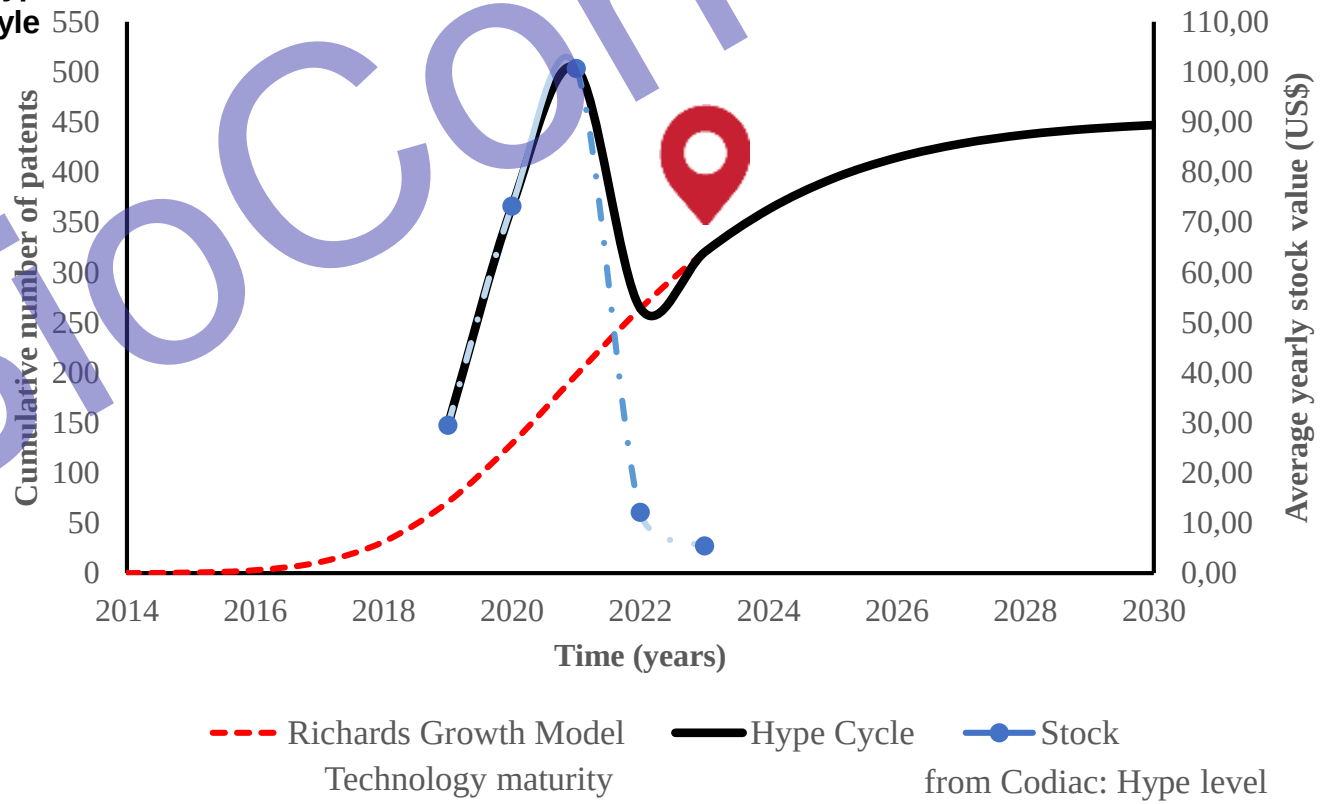
Gartner Hype Cycle is a combination of 2 curves



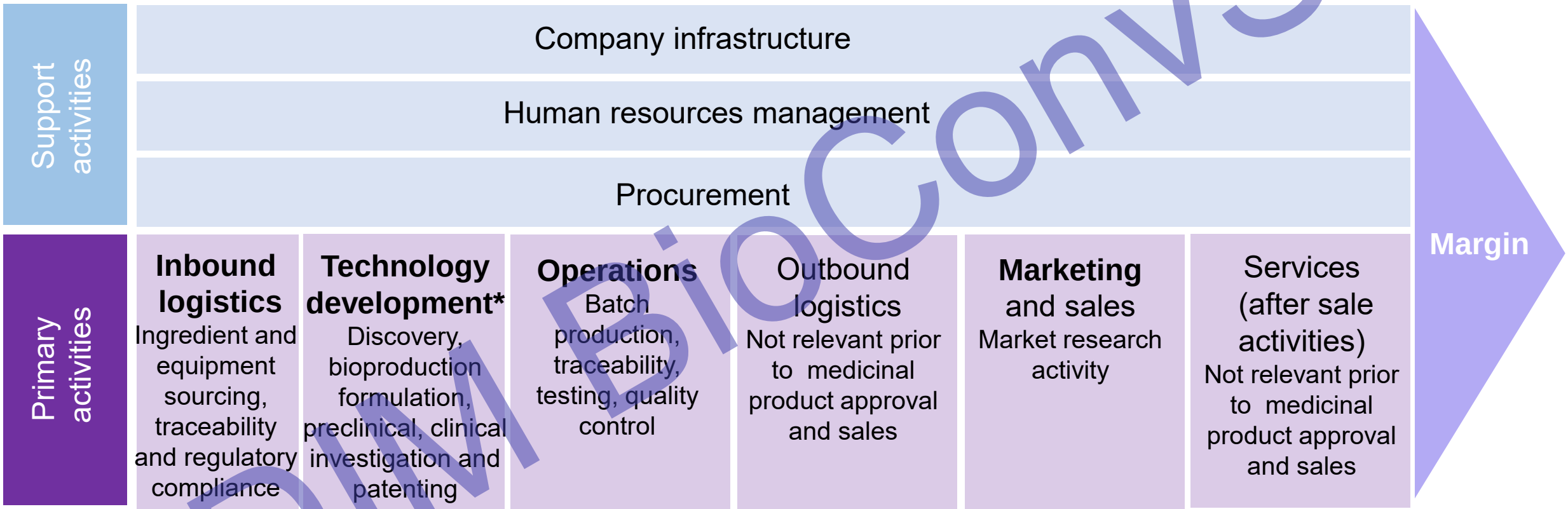
Codiak bankruptcy: a business case
What happened?



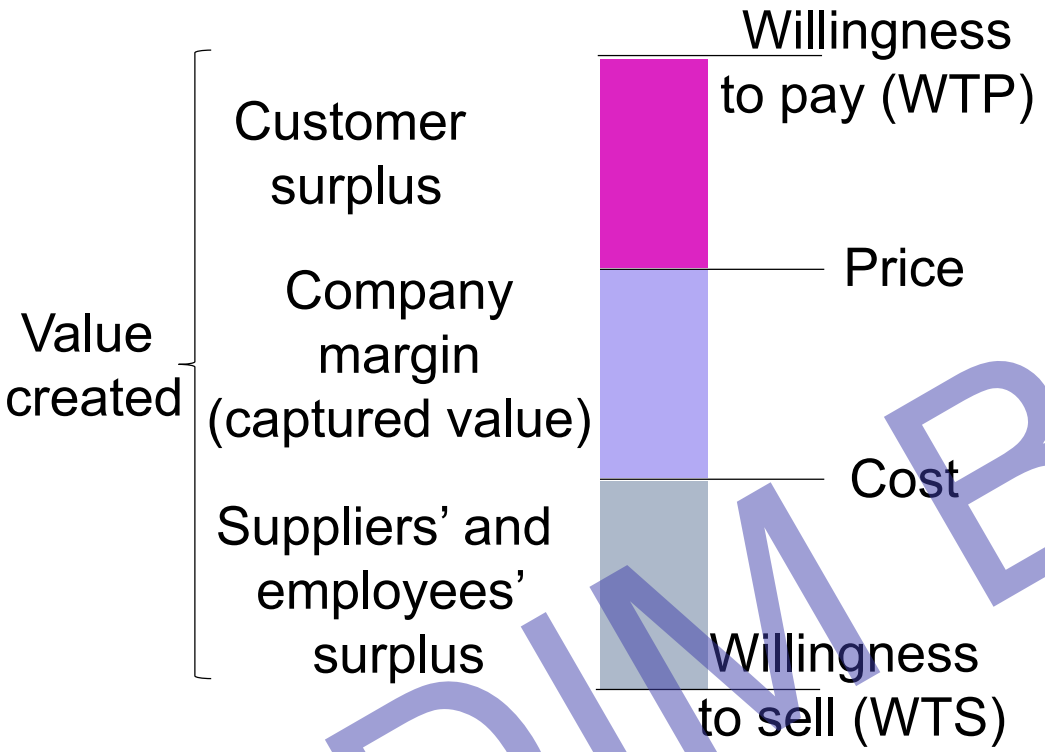
Our proposed Gartner Hype Cycle model: Towards a slope of enlightment



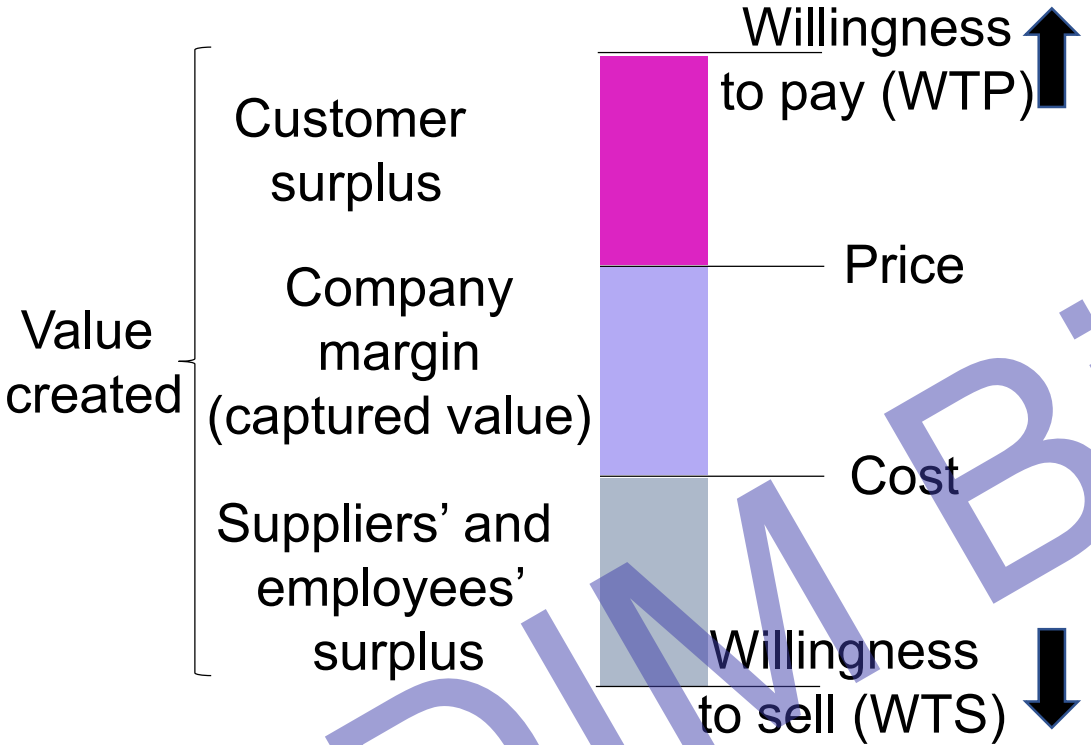
Porter’s value chain model



Value stick model



Value stick model



Expected enablers

-Therapy efficacy and safety relying on Codiak's technologies;
- Advantages compared to alternative treatments;
- The clinical indications to be approved by regulatory authorities;
- The timing of market introduction of competitive products;
- The obtention of adequate reimbursement from third-party payors

- High productivity (high-yield and scalable bioprocesses)