

HORIZON-MSCA-2021-DN-01



Project No. 101072632

Breaking the barrier

An integrated multidisciplinary approach to kill Gram-negative bacteria through existing antibiotics by making their outer membrane permeable

Deliverable 3.3

BREAKthrough Industry & Business Days

WP 3 – Training

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Lead participant	ABAC
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Version 1.0



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Revision History

Author(s)	Description	Date
Marco Cavallaro (accelCH)	Draft deliverable	22/10/2023
Jean-François Collet, Pauline Leverrier (UCLouvain)	Revision 1	28/10/2023
Margherita Sosio (Naicons), Antoni Torrens (ABAC)	Revision 2	30/10/2023
Jean-François Collet (UCLouvain)	Finalisation	30/10/2023



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Partner short names

ABAC	ABAC Therapeutics SL
accelCH	accelopment Schweiz AG
AUMC	Stichting VUMC
CNRS-IBS	Centre National de la Recherche Scientifique
ICIQ	Fundació Privada Institut Català d'Investigació Química
Naicons	Naicons Srl
Roche	Hoffmann-La Roche AG
Symeres	Symeres Netherlands B.V.
Syngulon	Syngulon
UCLouvain	Université Catholique de Louvain
UL FFA	Univerza v Ljubljani
UNEW	University of Newcastle upon Tyne
UNIMI	Università degli Studi di Milano
UQ	The University of Queensland
URV	Universitat Rovira i Virgili
VU	Stichting VU

Abbreviations

AP	Associated Partner(s)
D	Deliverable
DC	Doctoral Candidate
EC	European Commission
EU	European Union
HEU	Horizon Europe
M	Month
MS	Milestone
MSB	Management and Steering Board

1 Introduction

The BREAKthrough Days are workshop weeks with a special focus on broadening the Doctoral Candidates (DCs) skill set. They include scientific workshops as well as industry, business and transferrable skills workshops.

The present deliverable covers the BREAKthrough Industry & Business Days, which were held during the first annual meeting of the consortium from October 2 to 4, 2023, at the University of Milan, Italy.

The BREAKthrough Doctoral Candidates (DCs) had the opportunity to attend training sessions on business development (delivered by Syngulon), intellectual property (delivered by Roche Pharma) and visit our partner Naicons' laboratories for further scientific and technical training on natural products in drug discovery.



Figure 1: Group picture at the first Annual Meeting in Milan

2 Business development

The training was delivered by Guy Hélin, Co-founder and CEO of the Belgium-based company [Syngulon SA](#). It covered the following topics:

- Business development in the Biotech sector
- Intellectual Property & Freedom to Operate
- Science versus business model
- Business models in Pharma
- Business development for large pharma
- Business development start-up & SMEs in the Biotech sector
- Business development = just buying or selling?

It was notably emphasized that, although science is fundamental, a “business model does not start with the science, it starts with the customer. Without a customer there is no business model”¹.

The main takeaways for the DCs were that:

- Business development is important for any company either large or small
- There is no “one-size-fits-all” Business development organisation
- Building relationship takes time
- In Business development: never take no for an answer
- Every scientist (in a company) can play a role in Business development

The slides can be found in the Annex.

3 Intellectual property

The training was delivered remotely by Beat Rauber, Global Quality Manager Group Patents, Swiss and European Patent Attorney at F. Hoffmann-La Roche. It covered the following topics:

- An introduction to patents in life science
- Patent standards
- Novelty in patents
- Disclosure
- Patent categories
- Market exclusivity
- Patent “life cycle” from research to patent expiry
- Regulatory Data and Marketing Exclusivities
- Patent Protection Strategy
- Patent Cost

The slides can be found in the Annex.



Figure 2: Picture of Guy Hélin delivering the training on business development



Figure 3: Picture from the presentation

¹ Understanding the Business Development Opportunity in Biotechnology, Fit for Health 2.0, 2016

4 Natural products in drug discovery

The training titled “Natural products screening programs: from sample preparation to lead optimization” was delivered during a visit of the [Naicons Srl](#) laboratories in Milan, by Naicons co-founder Dr. Margherita Sosio. It covered the following topics:

- Drug discovery and development
- NP vs synthetic products
- Screening process
- Naicons strategies
- The future? The micro4all platform

Dr. Matteo Simone, Scientist at Naicons, introduced the DCs to [micro4all](#), an innovative platform built upon a large, diversified and proprietary strain library, the molecules those microbes produce and a database connecting different types of information on the molecules.



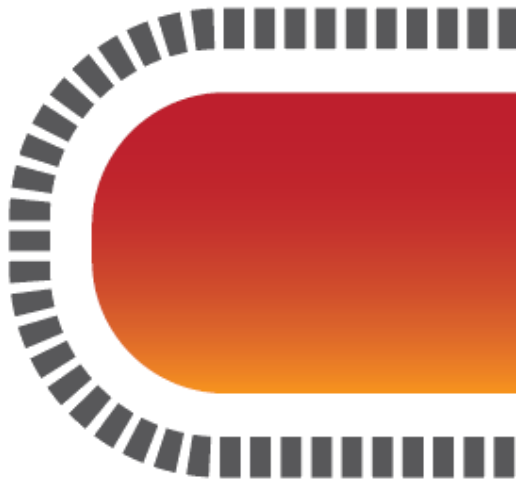
Figure 4: Pictures from the visit at Naicons Srl

5 Conclusion

We would like to express our gratitude to our dedicated trainers for their invaluable guidance and expertise throughout these training sessions. Their unwavering commitment has been instrumental in enhancing our DCs' skills and knowledge.

The next BREAKthrough Days will consist of scientific training sessions, to be held at the CNRS Institute for Structural Biology, in Grenoble, France, in April 2024.

6 Annex



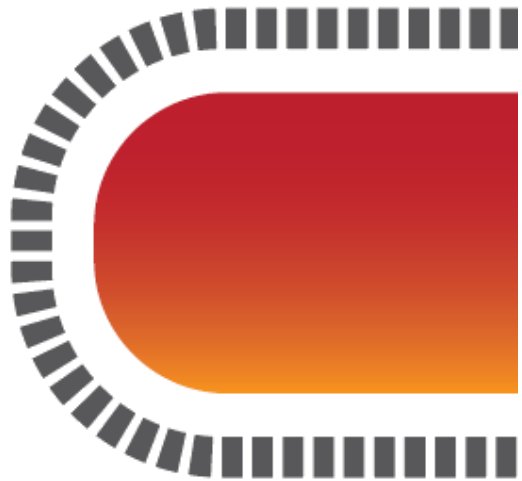
Business development

Guy Hélin, Co-founder & CEO Syngulon

1st Annual Meeting – October 4, 2023 - Milan



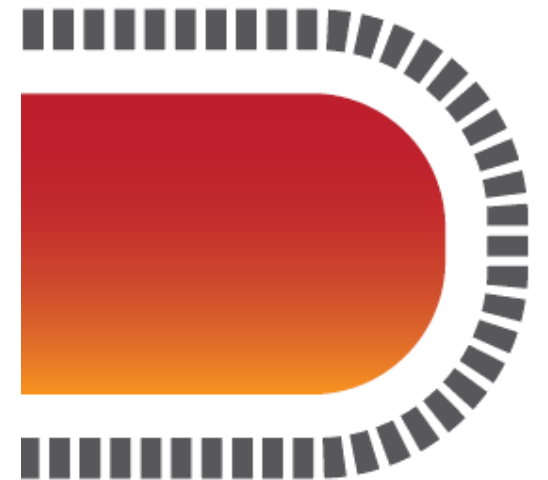
Funded by
the European Union



BREAKing through **with** **bacteriocins**

Alex Quintero, Guy Hélin & Philippe Gabant
Syngulon

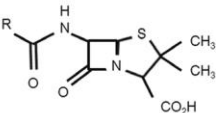
1st Annual Meeting, 02-04 October 2023, Milan



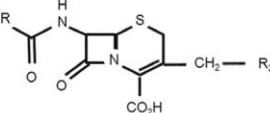
Funded by
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Antimicrobial compounds

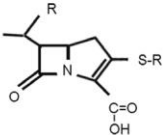
Antibiotics



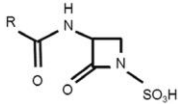
Penicillins



Cephalosporins

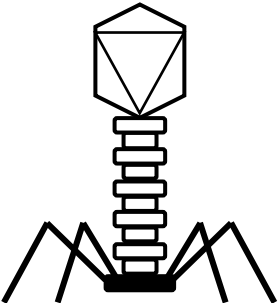


Carbapenems

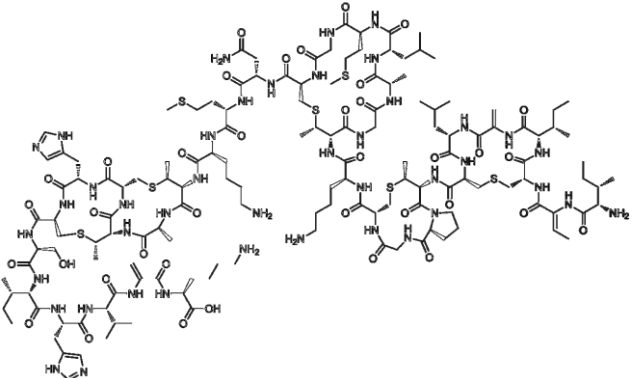


Monobactams

Phages

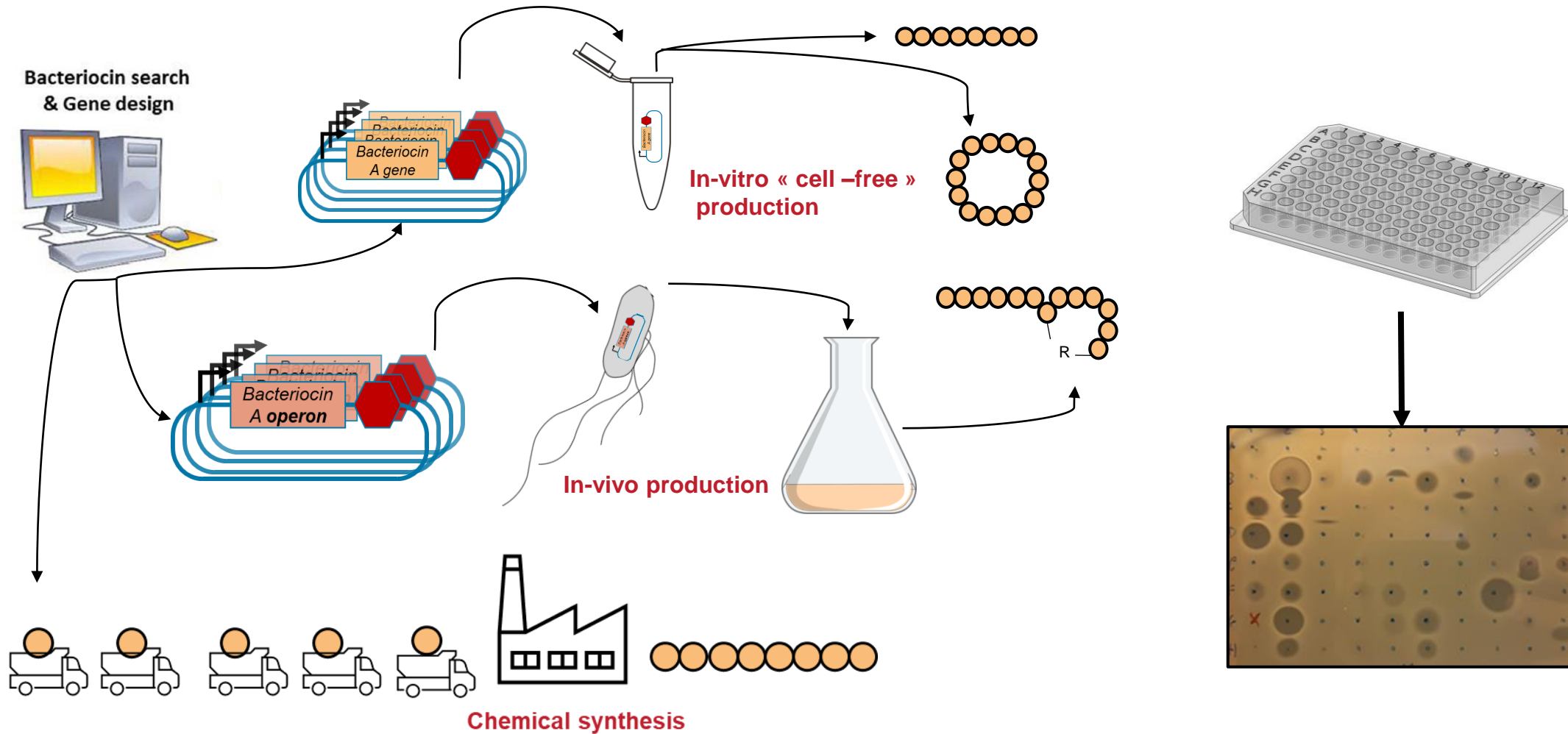


Bacteriocins



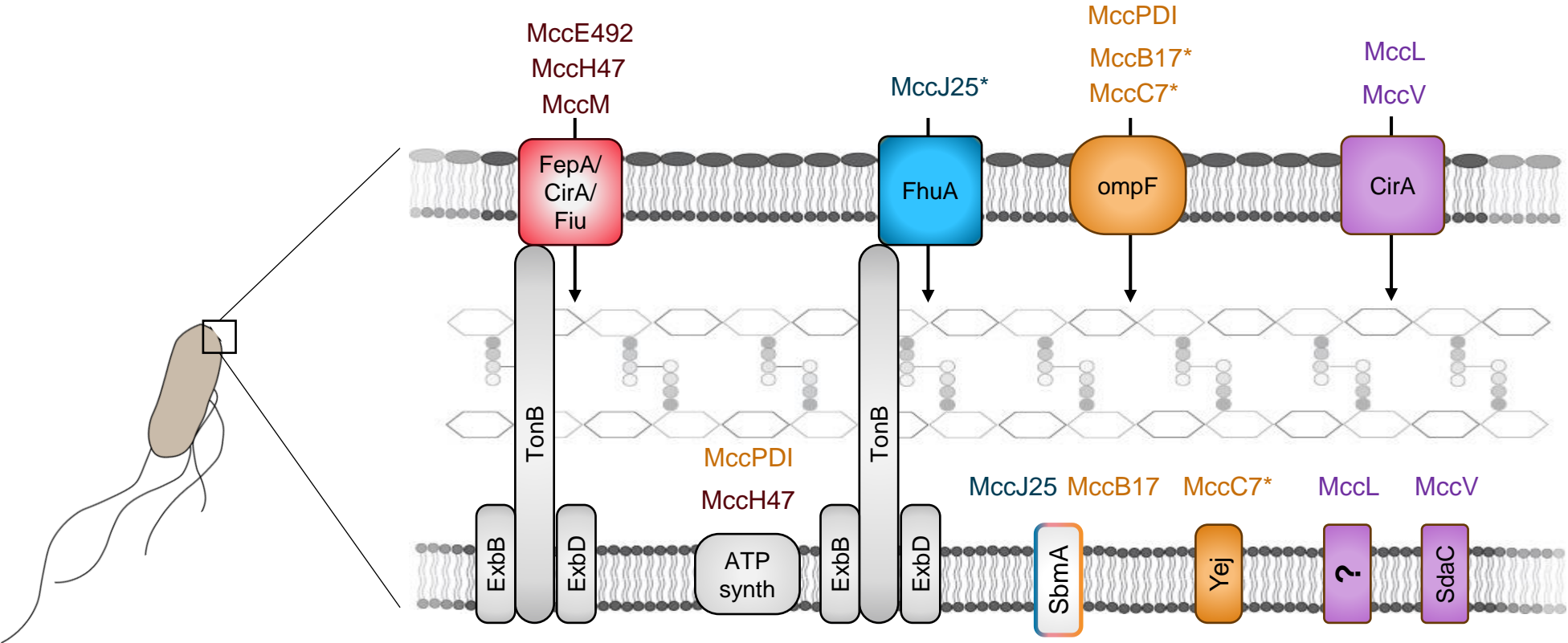
Nisin

Syngulon Paragen collection



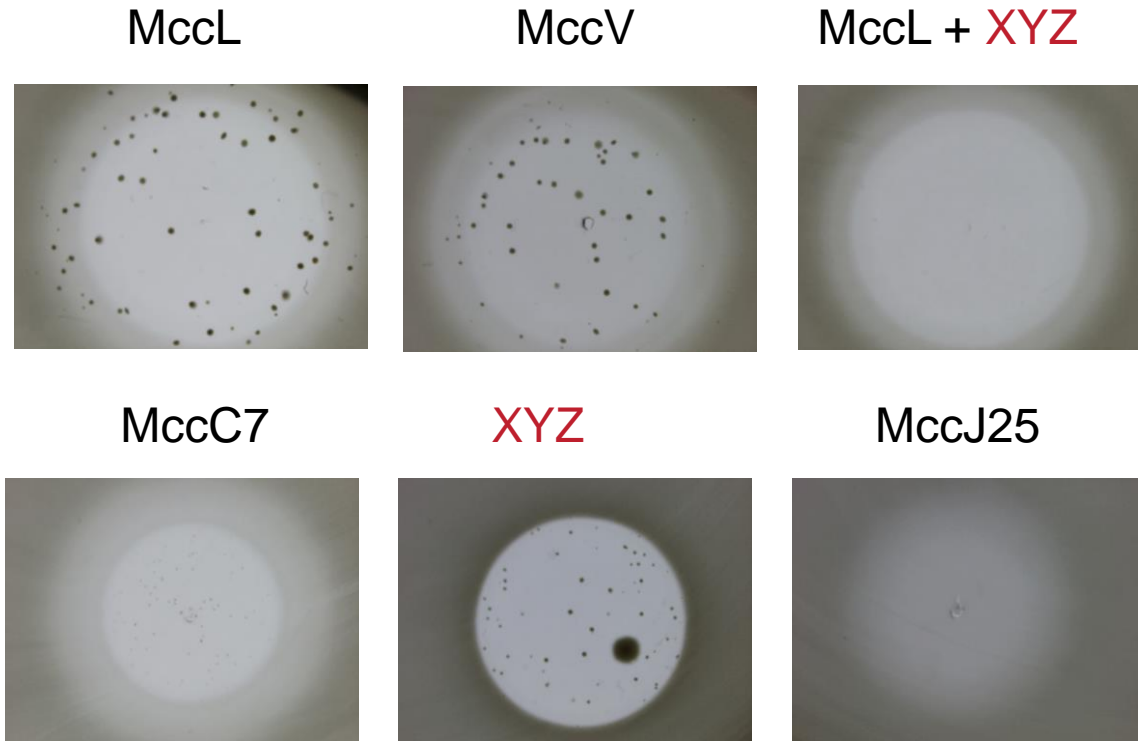
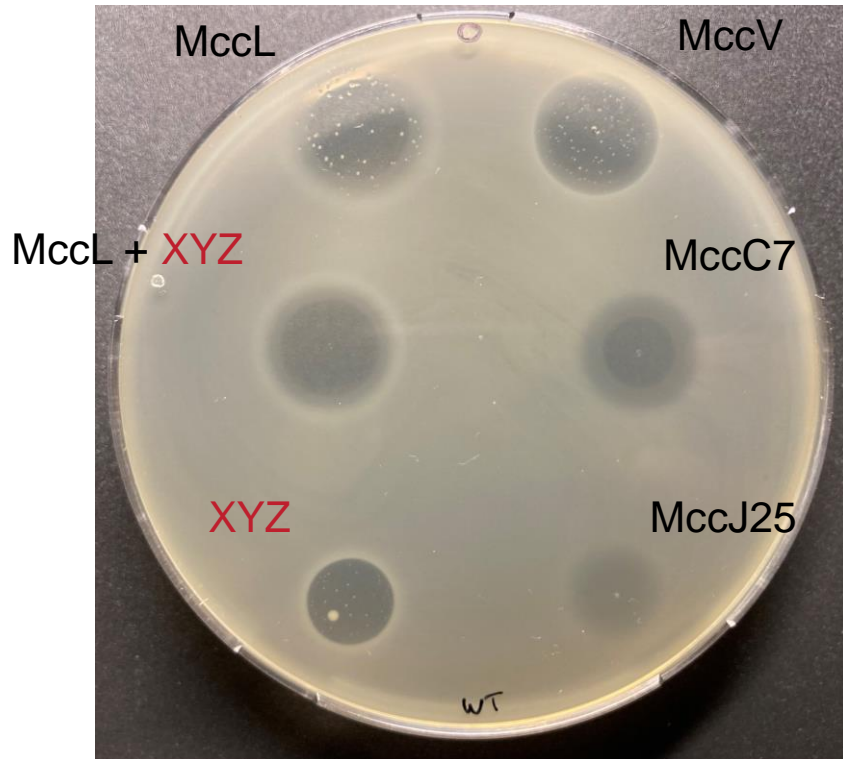
Modified from Gabant, P., & Borrero, J. (2019).

Bacteriocins “gates” in the Gram - envelope



Modified from Telhig *et al.*,(2020). Bacteriocins to thwart bacterial resistance in gram negative bacteria.

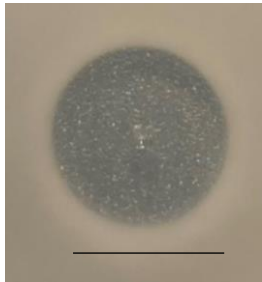
Bacteriocins in preventing AMR



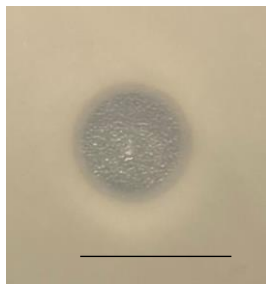
Identifying new gates for bacteriocins

XYZ sensitivity mutants

WT



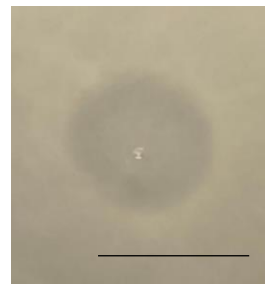
XYZ^R m₁



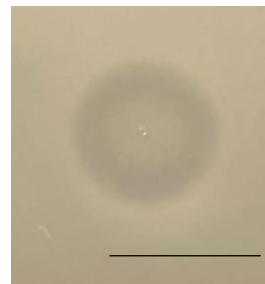
XYZ^R m₂



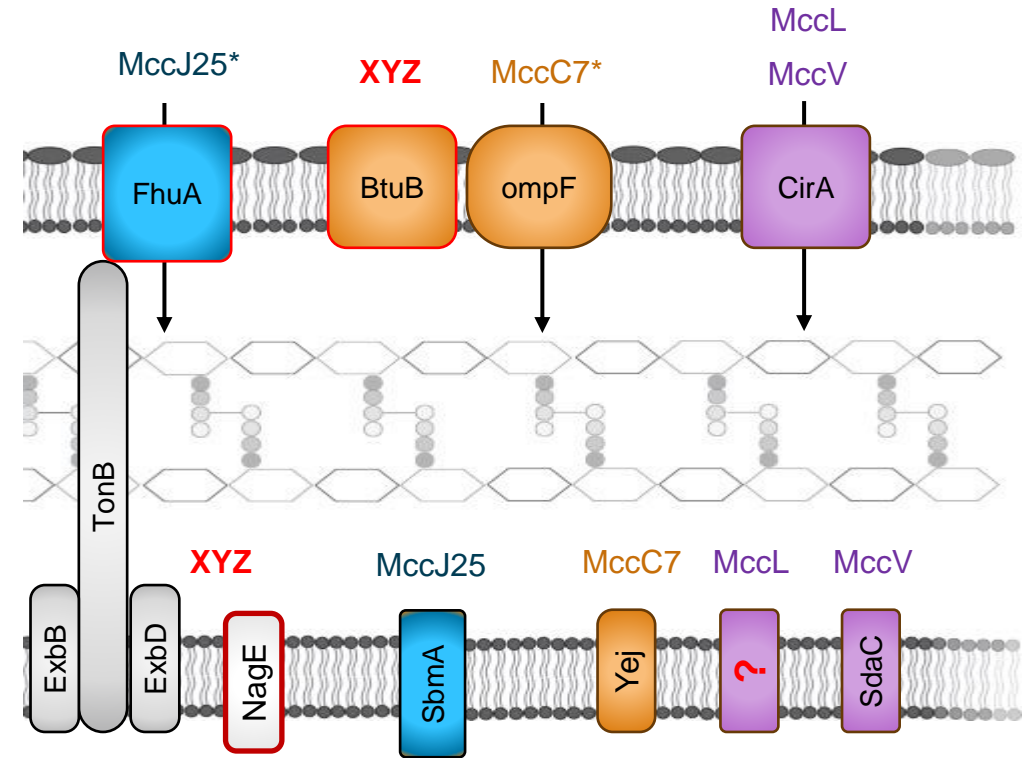
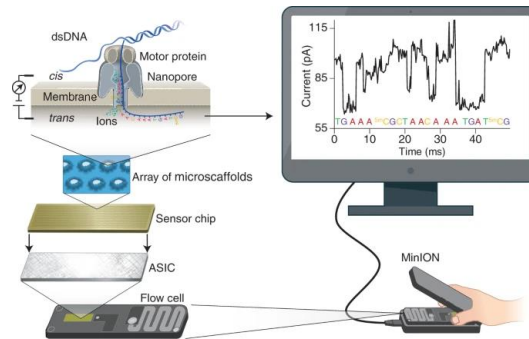
XYZ^R m₃

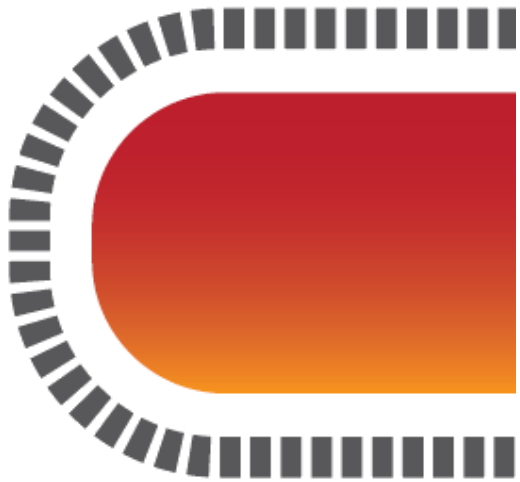


XYZ^R m₄



MinION nanopore sequencing





Business development

Guy Hélin, Co-founder & CEO Syngulon

1st Annual Meeting – October 4, 2023 - Milan



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Business development

Agenda

- Introduction
- Business development in the Biotech sector
- IP & FTO
- Science versus business model
- Business models in Pharma
- BD for large pharma
- BD start-up & SMEs in the Biotech sector
- BD = just buying or selling?
- The 3 others W
- Take home messages
- References

Introduction



Introduction

The One Health Triad



Introduction

What is business development?

Definition 1 (Google):

“Business development (BD) is the process that is used to identify, nurture and acquire **new clients and business opportunities** to drive growth and profitability.”

BUT: not really adapted to the Biotech!

Introduction

What is business development?

Definition 2 (Wikipedia):

“Business development entails tasks and processes to develop and implement growth opportunities within and between organizations. It is a subset of the fields of business, commerce and organizational theory. Business development is the creation of long-term value for an organization from customers, markets, and relationships. Business development can be taken to mean any activity by either a small or large organization, non-profit or for-profit enterprise which serves the purpose of ‘developing’ the business in some way.”

BETTER but still: not really adapted to the Biotech!

Business development in the Biotech sector

- For larger companies

What?

Why?

“B2B business development in pharma involves **developing partnerships with other companies in the industry to drive growth, improve efficiency, and bring new products to market.**” (Google answer)

- For start-up & SMEs (= for-profit companies)
 - BD is critical for implementation of the Business model
 - **BD is not only a matter of development and growth, but of survival?**



IP & FTO

- IP = Intellectual Property

To protect your product/technology

- FTO = Freedom to Operate

To bring your product/technology to the market

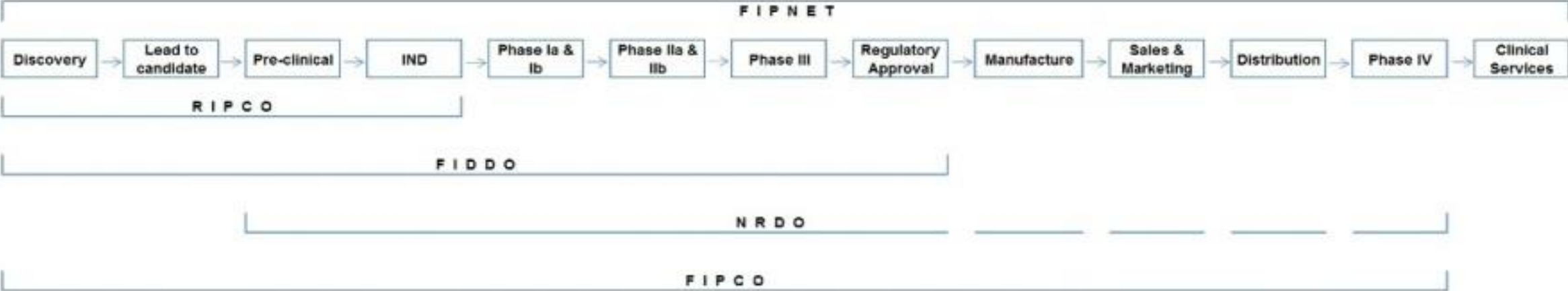
Science versus business model

- Science is fundamental
- BUT “business model does not start with the science, it starts with the customer. Without a customer there is no business model”²
- Customer \neq final user / consumer
- Customer = willing to pay for the product

Business models in Pharma

Common business models in the biotech sector

FIPNET companies control their product throughout the whole value chain, but contract for complementary assets at one or more points on the chain.



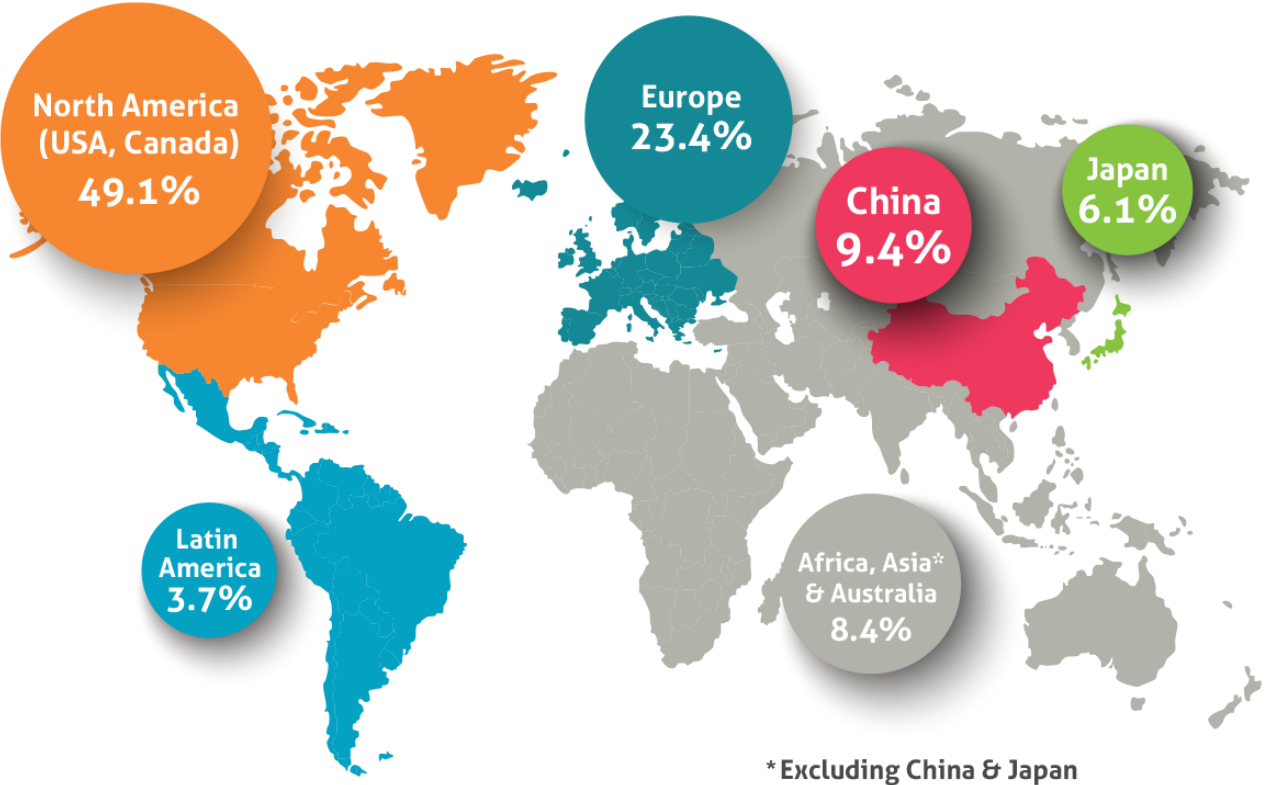
Legend - Typical Business Models

- RIPCO -** research intensive/royalty only pharmaceutical company
- FIDDO -** fully integrated drug discovery & development
- NRDO -** no research development only
- FIPCO -** fully integrated pharmaceutical company
- FIPNET -** fully integrated pharmaceutical network

Source: <https://bioengineeringcommunity.nature.com/posts/45149-ripco-fipco-nrdo-fipnet-vipco>

World Pharma market 2021

BREAKDOWN OF THE WORLD PHARMACEUTICAL MARKET – 2021 SALES



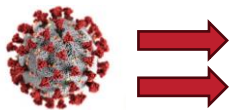
Note:
Europe includes Belarus, Turkey, Russia and Ukraine; percentages might not add up due to rounding

Source: IQVIA (MIDAS) Q4 2021 MAT, May 2022; data relate to the 2021 global retail and hospital pharmaceutical market (prescription only) at ex-factory prices.

Source: <https://www.efpia.eu/publications/data-center/the-pharma-industry-in-figures-economy/world-pharmaceutical-market>

The 20 largest pharma companies in the world

RANK	COMPANY	HEADQUARTERS	2022 REVENUES (\$USD)
1	Pfizer	United States	\$100,330,000,000.00
2	Merck & Co.	United States	\$59,283,000,000.00
3	AbbVie	United States	\$58,054,000,000.00
4	Janssen (Johnson & Johnson's pharmaceutical segment)	United States	\$52,563,000,000.00
5	Novartis	Switzerland	\$50,545,000,000.00
6	Roche Pharmaceuticals (division of Roche Group)	Switzerland	\$47,697,382,199.00
7	Bristol Myers Squibb	United States	\$46,159,000,000.00
8	Sanofi	France	\$45,293,039,800.00
9	AstraZeneca	United Kingdom	\$44,351,000,000.00
10	GSK	United Kingdom	\$36,882,899,400.00
11	Takeda Pharmaceutical	Japan	\$30,636,784,577.00
12	Eli Lilly	United States	\$28,541,400,000.00
13	Gilead Sciences	United States	\$27,281,000,000.00
14	Amgen	United States	\$26,323,000,000.00
15	Novo Nordisk	Denmark	\$24,998,446,020.00
16	Bayer (Pharmaceuticals Division)	Germany	\$20,280,056,800.00
17	Boehringer Ingelheim	Germany	\$19,487,900,000.00
18	Moderna	United States	\$19,263,000,000.00
19	BioNTech	Germany	\$18,234,986,040.00
20	Viatris	United States	\$16,218,100,000.00



Source: <https://www.drugdiscoverytrends.com/2023-pharma-50-largest-companies/>

BD for (large) pharma

<https://www.merck.com/company-overview/business-development-licensing/>

<https://www.pfizer.com/about/partners/research-and-business-development-partnerships>

<https://www.sanofi.com/en/partnering/meet-the-partnering-team>

<https://www.merckgroup.com/en/partnering/collaboration-in-healthcare.html>

<https://www.novartis.com/about/strategy>

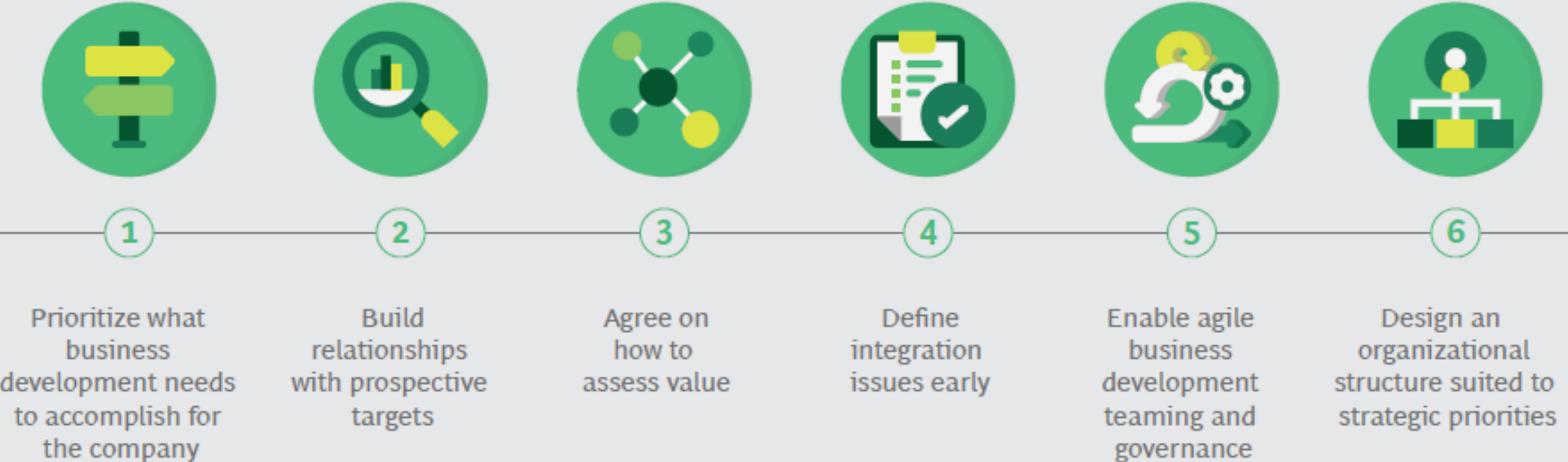
BD for (large) pharma

BD at large pharma (FIPCO/FIBCO) can be organized by

- Therapeutic area: e.g. oncology, dermatology
- Technology: emerging, digital, AI
- Geography: North America, Europe, Asia OR centralized
- Stage: early- versus late-stage R&D, R&D versus commercial

BD for (large) pharma

EXHIBIT 1 | Six Success Factors for Pharma Business Development



Source: BCG analysis.

Source: (1)

BD start-up & SMEs in the Biotech sector

- For start-up & SMEs (= for-profit companies)
 - BD is critical for implementation of the Business model
 - BD is not only a matter of development and growth, but of survival
 - Business models:
 1. Technology partnering
 2. Asset creation and out-licensing
 3. Product development and commercialization





Balancing & controlling microbial life on earth

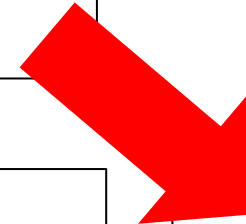
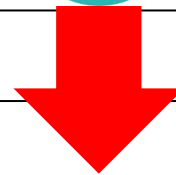
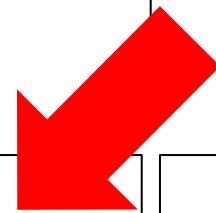
August 2023

Corporate Presentation





Syngulon's technologies solving 3 problems



Antibiotic-free Selection



Production in a fermentation process; key markets are biopharma and cosmetics but also enzymes;

1 (small) licensing deal with **Enzymicals** for diagnostic enzymes
1 signed licensing deal with **industrial biotech company**

Contamination



Bacteriocins target the bacteria having a negative effect on the production process; key markets are ethanol, cooling towers, feed, animal health;

R&D partnership with **TEREOS** to improve industrial fermentation / 1 large development and licensing deal with Chinese **EPPEN** for feed probiotics with bacteriocins

Antimicrobial Resistance



Human pharma applications of bacteriocins as alternative or complement to antibiotics in the context of AntiMicrobial Resistance AMR (e.g. MRSA) + microbiome modulation + cancer

NEWCO for human pharma



NDA





Our core technology

frontiers
in Bioengineering and Biotechnology

BRIEF RESEARCH REPORT
published: 06 September 2019
doi: 10.3389/fbioe.2019.00213



PARAGEN 1.0: A Standardized Synthetic Gene Library for Fast Cell-Free Bacteriocin Synthesis

Philippe Gabant* and Juan Borrero†

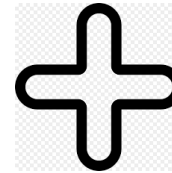
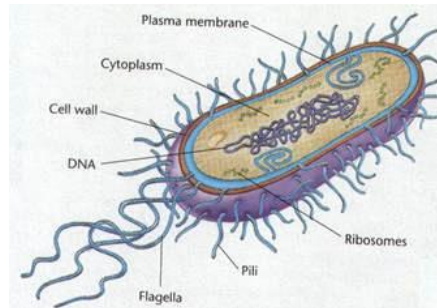
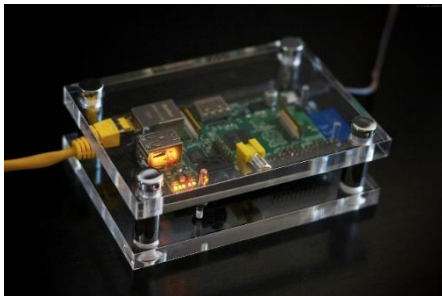
Syngulon, Seraing, Belgium

OPEN ACCESS

- PARAGEN: largest collection of bacteriocins
- 10 families of patent applications about:
 - use in fermentation processes
 - production of cocktails
 - engineering of new bacteriocins
 - inducing natural bacteriocins
 - control of bacteriocin half-life
 - « arming » of friends
 - specific use of bacteriocin
 - circular bacteriocin
- 3 co-owned with 1 university



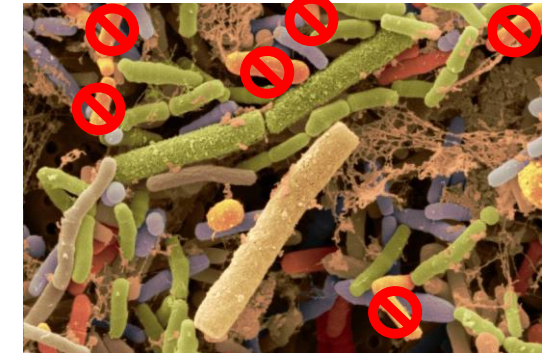
Synthetic biology



Bacteriocins



André Gratia



Scimat/Science Photo Library

2 fundamental differences with IT:

1. “Evolutionary” based chassis
2. Self coding and self replicative

- Discovered in 1925 by Belgian scientist: “**André Gratia** (1893–1950): Forgotten Pioneer of Research into Antimicrobial Agents”
- **Not toxic for humans and animals**
- Active against antibiotic-resistant bacteria (VRE, MRSA...)
- Availability of broad and **narrow spectrum** of activity
- Can be produced by *in vivo* / *in vitro* / chemical synthesis



The value we drive

Antibiotic-free Selection



- For production in a fermentation process
- “off the shelf” – NO customization
- **2 patent families with 8 issued patents**
- 1 signed (small) licensing deal with



- 1 signed licensing deal with industrial biotech company



- Ongoing evaluation with 1 large AH

Target sectors



Biopharma



Cosmetics



Enzymes

The needs we'll address



“avoid unnecessary risk of spread of antibiotic resistance”



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

“resistance to antibiotics should be avoided”



Cosmetic ingredient database (Cosing) – List of substances prohibited in cosmetic products

Regulators guidance for industry



Yield increase



The value we drive

Contamination



- Standardized analysis of contaminants by metagenomics
- Customization of bacteriocins cocktails
- 10 patent families with 10 issued patents
- + 1 patent family on yeast
- 1 R&D partnership with largest EU ethanol producer since 2017



- 1 (large) signed in 2019 exclusive licensing deal in feed with



Target sectors



Ethanol

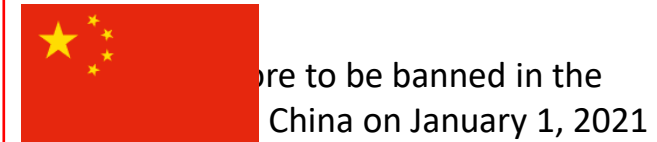
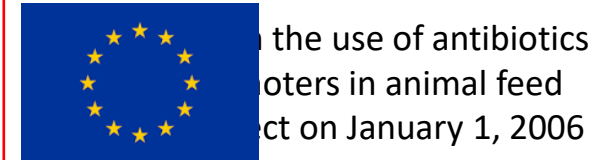


Feed & Food



Industrial needs

The needs we'll address



Ban of antibiotics in feed



Yield increase



The value we drive



Antimicrobial Resistance



- Proof of concept at lab scale with



- Narrow spectrum bacteriocins are ideal for:

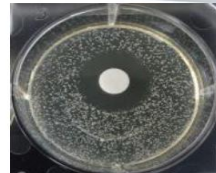
- killing antibiotic-resistant bacteria (VRE, MRSA...)
- balancing and controlling microbiomes

- 1 Patent family on specific use of bacteriocin

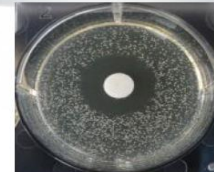
- NEWCO for human pharma



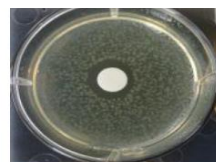
Target sectors



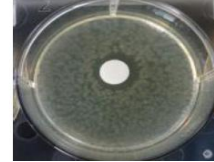
P. acnes ATCC 10390



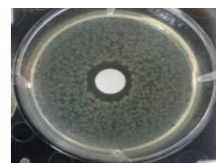
P. acnes ADO36



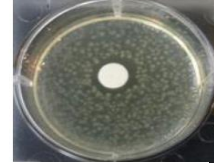
C. difficile DSMZ 1296



C. difficile 13.22



C. perfringens ATCC 13124



C. perfringens Clinical strain



Pharma

The needs we'll address



“New report calls for urgent action to avert antimicrobial resistance crisis”
29 April 2019



EUROPEAN MEDICINES AGENCY
SCIENCE · MEDICINES · HEALTH

The emerging and steady increase of microbes that are resistant to antimicrobial treatments has become a global public health concern that threatens the effective treatment of infectious diseases.



AMR action fund

The world is losing its most powerful tool in healthcare: antibiotics.

These infections can affect anyone, of any age, in any country. AMR is a universal issue that impacts us all – we are all at risk. The ground-breaking AMR Action Fund expects to invest more than US\$1 billion to bridge the funding gap and respond to the AMR threat.

July 2020

AMR crisis

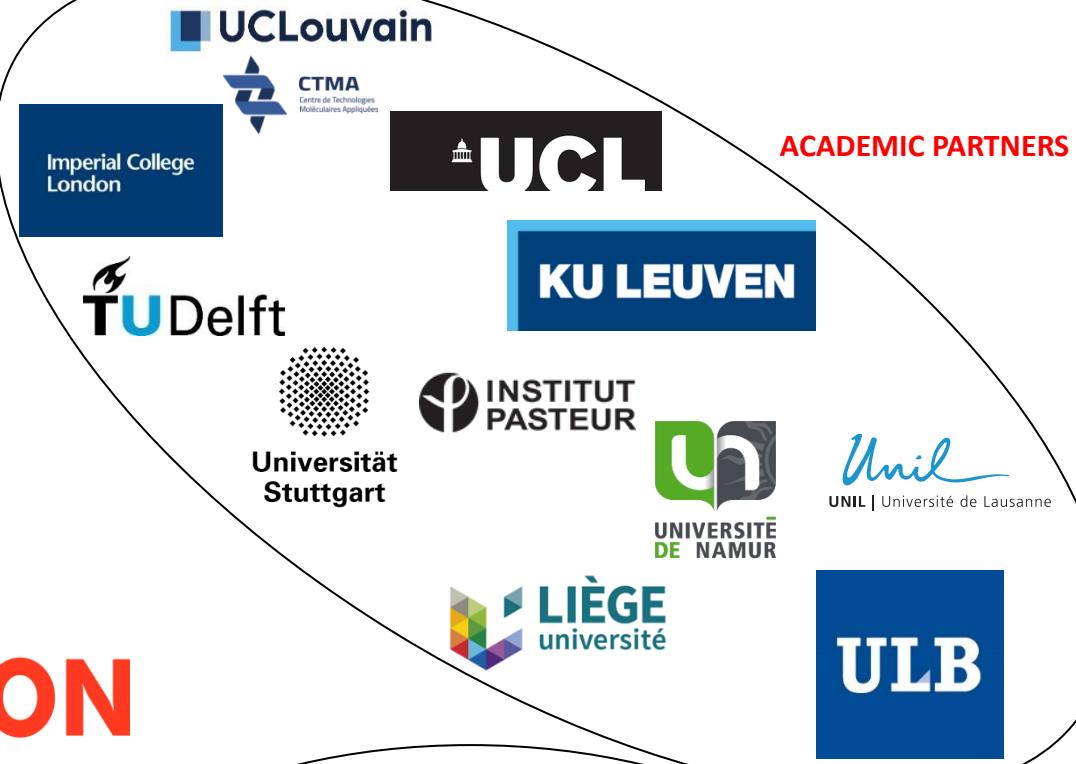


Our position in the Ecosystem

R&D FUNDING



ACADEMIC PARTNERS



Ethanol 1G



Animal Health

Ethanol 2G

Cosmetics

Biopharma

CUSTOMERS AND PROSPECTIVE LICENSEES



R&D PARTNERS



CLUSTERS AND TRADE ASSOCIATIONS

Our R&D: 21 projects since 2016



- 2. PARAGEN: Development of a collection of bacteriocins for their applications to avoid microbial contaminations in industrial fermenters based on metagenomic analysis
- 3. ALGOTECH: optimisation of microalgae bioproduction using synthetic biology
- 4. « Research project responsible » (RPR): Development of genetic technologies for the improvement of Gram-positive bacteria
- 5. BEL-SME: Production of recombinant enzymes to generate oligosaccharides from algal biomass
- 6. ComRaDes (Computation for Rational Design): Development of genetically optimized strains for the scale of industrial fermentation



Technologies



- 7. EVOL-MODEL: Development of evolution system to increase the number and properties of bacteriocins + modelling to measure their actions
- 8. STAPHCONTROL: "In company PhD training" on Staphylococcus aureus
- 12. ERAMIN BaCLEM: Bio-assisted Closed Loop recycling of E-mobility Metals from waste PCBs and Li-Ion Batteries
- 16. ELITHE: enzymes by synbio for production of new biobased elicitors
- 17. PROSECO: Proteases and serpins for the control of half-life of bacteriocins
- 20. BREAKthrough: Breaking the barrier - An integrated multidisciplinary approach to kill Gram-negative bacteria through existing antibiotics by making their outer membrane permeable

Antibiotic-free Selection



- 1. « Technical Support Study » (EST): scale up of fermentation technologies for the production of bacteriocins and recombinant products
- 15. ULB POC COHERENCE + exclusive in-licensing of 2 issued Patents: US Patent 10,696,997 + EP 316449381
- 21. PROACTIF: antibiotic-free selection for *Bacillus*

Contamination



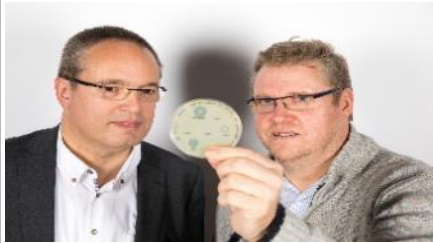
- 14. ULB POC Yeast + exclusive in-licensing 2020 Patent application

Antimicrobial Resistance



- 9. PhD Doctoral Training Programs (2) @Imperial College - Development of bacteriocins potential for human pathogen control including AMR and persistence + (1) @UCLondon - Bacteriocins against *Enterococcus faecalis*
- 10. « Research project responsible » (RPR): bacteriocins against infections by *Mycobacterium tuberculosis* and *Vibrio cholerae*
- 11. STOPPERSIST: « In company PhD training » on persistence
- 13. « Vaincre la Mucoviscidose » + « Association Grégory Lemarchal » (Cystic Fibrosis): *Pseudomonas aeruginosa*
- 18. SKINCURE: post-modified bacteriocins to fight skin pathogens
- 19. CRITIC: baCteRiocin against Intracellular sTaphylococcus InfeCtion

Team



Guy Hélin, Co-founder, CEO
Dr. Philippe Gabant, Co-Founder, CSO



- Dr. Mohamed El Bakkoury, CTO Yeast**
- Dr. Luz Perez, R&D Project Manager**
- Félix Jaumaux, PhD Student**
- Dr. Anandi Martin, Senior Project Manager - Infectious Disease**
- Loïc Mues, R&D Scientist**
- Dr. Kenny Petit, R&D project manager**
- Denis Dereinne, R&D Scientist**
- Dr Alex Quintero, R&D Project Manager**



Collaboration with:
Universidad Complutense Madrid (UCM)
Dr. Juan Borrero



Scientific Advisory Board

- Pr Joseph Martial (Chairman), ULg, Liège (BE)**
- Pr Bruno André, ULB, Brussels (BE)**
- Adj-Pr Mike Chandler, University of Georgetown (USA)**



- Pr Pascal Hols, UCL, Louvain-la-Neuve (BE)**
- Pr Didier Mazel, Institut Pasteur, Paris (FR)**
- Pr Laurence Van Melderen, ULB, Charleroi (BE)**
- Pr Ruddy Wattiez, UMons, Mons (BE)**



- IN MEMORIAM**
- Dr Régis Sodoyer, ex-Sanofi Pasteur, Lyon (FR)**



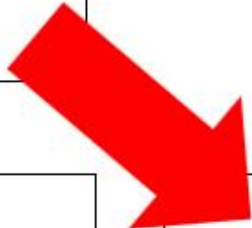
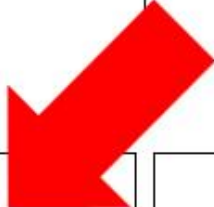
R&D Partners



BD start-up & SMEs in the Biotech sector



Technologies



Antibiotic-free Selection



Technology licensing

Contamination



Bacteriocins target the bacteria having a negative effect

Asset creation and out-licensing

Antimicrobial Resistance



Product development (and commercialization?)

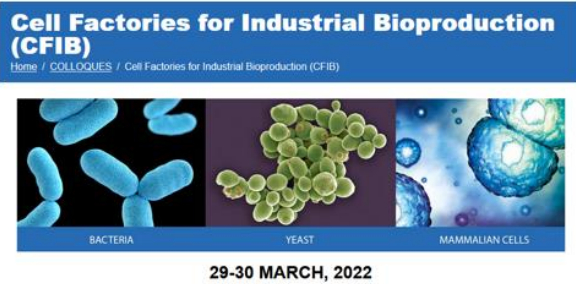


BD = just buying or selling?

- For large pharma = BUYING
- For SME = SELLING



BD = just buying or selling?



Taking a license on CRISPR/Cas9: a testimony

March 29, 2022

Guy Hélin
Co-founder & CEO
ghelin@syngulon.com



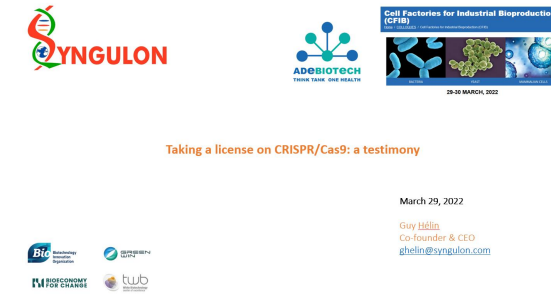


Taking CRISPR license in 2018: our journey

2017: full agreement on termsheet for **non-exclusive license with sublicensing as part of Joint Licensing provision in September**

2018: full agreement on license agreement in July ... subject to Board approval

2018: license agreement signed in September with Press Release in October



CRISPR-Cas9 Intellectual Property Licensing Knowledge Centre News Our Team Contact Us



Dublin, Ireland, and Seraing, Belgium, October 16, 2018:

ERS Genomics Limited and Syngulon, a synthetic biology startup developing original genetic technologies using bacteriocins, announced today a non-exclusive license agreement which provides Syngulon with worldwide access to ERS' CRISPR-Cas9 genome editing intellectual property for use in combination with Syngulon Patent Rights. ERS Genomics holds rights to the foundational CRISPR-Cas9 patent portfolio from Dr. Emmanuelle Charpentier, an inventor of the breakthrough gene-editing technology.

"Genome editing has many applications beyond drug discovery and development and making the CRISPR-Cas9 patents available to synthetic biology startups such as Syngulon is a growing and important part of our business. We are thus very pleased to include them in our expanding portfolio of licensees," said Eric Rhodes, CEO of ERS Genomics.

"By combining modern genetics with synthetic biology, Syngulon is developing its collection of bacteriocins a.k.a. anti-microbial peptides to fight contaminants in different industrial applications. Syngulon outlicenses its patented technologies on a non-exclusive basis and will be able to sublicense ERS' CRISPR-Cas9 patents as part of a Joint Licensing agreement thus enabling its licensees to benefit from the use of CRISPR-Cas9 genome editing in implementing Syngulon's technologies using bacteriocins," commented Dr Philippe Gabant, Co-founder & CSO of Syngulon.

Dr. Emmanuelle Charpentier's research unveiled the key components and mechanisms of the CRISPR-Cas9 system, leading to the landmark publication with Jennifer Doudna, (Jinek et al., 2012), which laid the foundation for the use of CRISPR-Cas9 as a highly versatile and precise genome editing tool.

Financial details of the agreement were not disclosed.

PRESS RELEASE

ERS Genomics and Syngulon Sign License Agreement on CRISPR-Cas9 Genome Editing Patents for Industrial Applications

DUBLIN, Ireland, and SERAING, Belgium, October 16, 2018 - ERS Genomics Ltd and Syngulon, a synthetic biology startup developing original genetic technologies using bacteriocins, announced today a non-exclusive license agreement which provides Syngulon with worldwide access to ERS' CRISPR-Cas9 genome editing intellectual property for use in combination with Syngulon Patent Rights. ERS Genomics holds rights to the foundational CRISPR-Cas9 patent portfolio from Dr. Emmanuelle Charpentier, an inventor of the breakthrough gene-editing technology.

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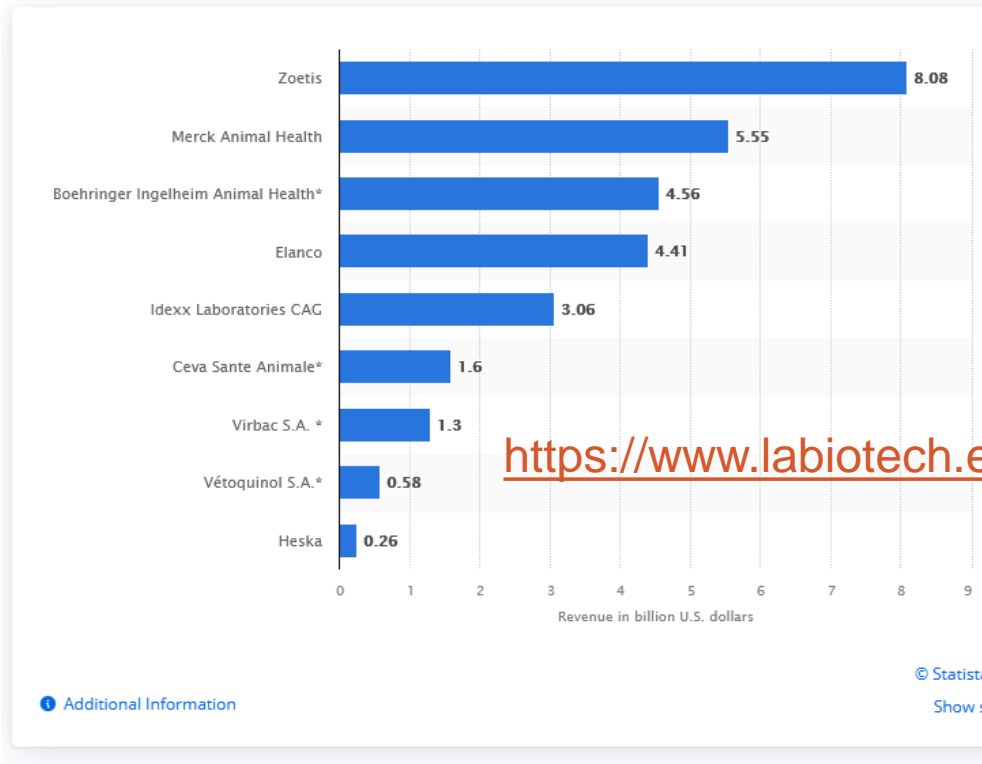


The 3 other W



The 3 other W

Leading animal health companies in 2022, based on rev
(in billion U.S. dollars)



Top 20 Global Beauty Companies: Annual Beauty Sales

1. L'Oréal \$37 billion
2. Unilever \$25 billion
3. The Estée Lauder Companies \$17.7 billion
4. Procter & Gamble \$14.4 billion
5. Shiseido \$9 billion
6. Bath & Body Works \$7.9 billion
7. Johnson & Johnson \$7.7 billion
8. LVMH \$7.5 billion
9. Natura & Co \$7.1 billion
10. Beiersdorf \$7 billion
11. Coty \$5.3 billion
12. Kao \$5 billion
13. LG \$4.8 billion
14. Amorepacific \$4.4 billion
15. Henkel \$4 billion
16. Colgate-Palmolive \$3.5 billion
17. Chanel \$3.4 billion
18. Mary Kay \$2.8 billion
19. Revlon \$2.1 billion
20. Kose \$2 billion (9-mo. FY)

<https://www.labiotech.eu/best-biotech/industrial-biotechnology-companies-europe/>



The One Health Triad



The 3 other W: Who?

- BD at large pharma (FIPCO/FIBCO)
+ R&D therapeutic area

Scientists



The "Not-Invented-Here Syndrome"

- Senior management at start-up & SMEs

The 3 other W: Where/When?

- At global partnering conferences



The 3 other W: Where/When?

- At targeted partnering conferences



The One Health Triad



The 3 other W: Where/When?

- At NON-partnering conferences



WORLD VACCINE CONGRESS | WASHINGTON
3-6 April 2023 | Walter E. Convention Center | Washington DC



THE MOST IM



8TH BIOPRODUCTION CONGRESS
5-6 October 2023 - Lyon

ACCELERATING BIOPHARMA DEVELOPMENT FOR PATIENTS

The 3 other W: Where/When?

- At scientific meetings/conferences

Event on: October | 09-10 | 2023

5th International Conference on
**Applied Microbiology and
Beneficial Microbes**

Theme : Advanced Innovations in Microbiology and Research on
Beneficial Microbes

Hyatt Place London Heathrow Airport, London, UK



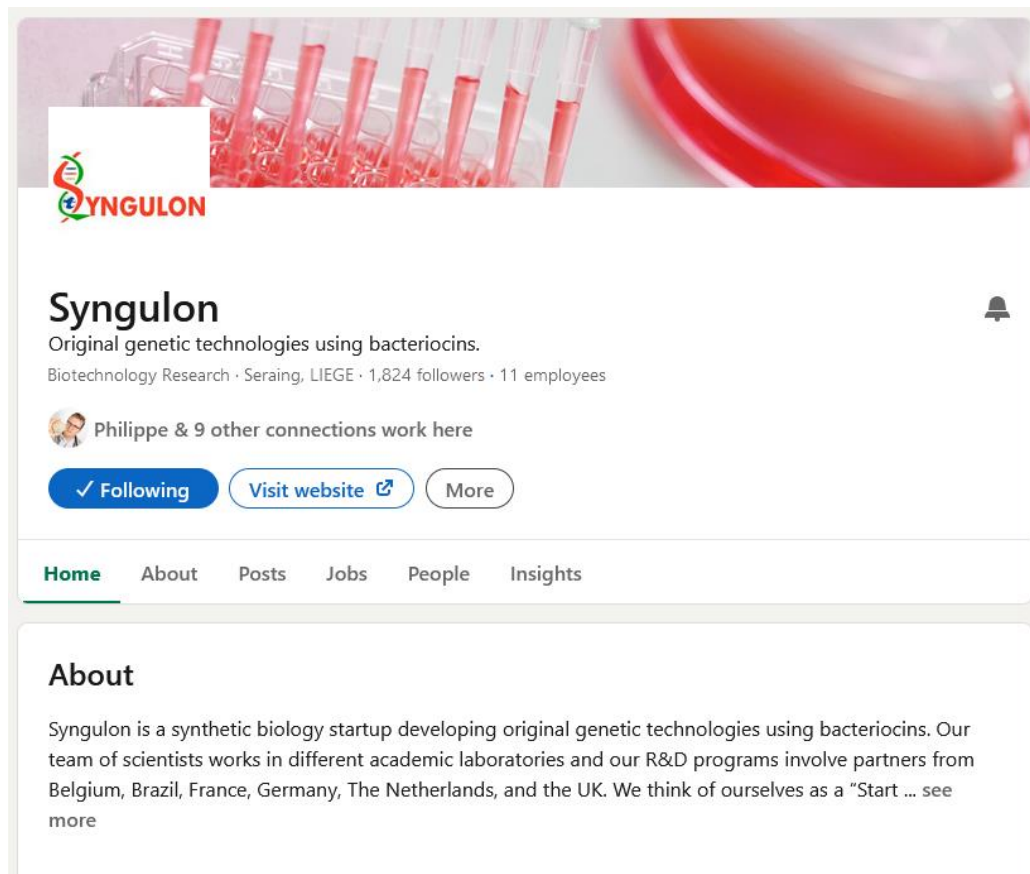
**Bacteriocin
International
Conference**

June 19-21, 2023
Lille, France



The 3 other W: Where/When?

- Online / social media



The One Health Triad



Follow Us On



Take home messages

- BD is important for any company either large or small
- There is no “one-size-fits-all” BD organization
- Building relationship takes time
- In BD (and in life?): never take no for an answer
- Every scientist (in a company) can play a role in BD



The One Health Triad



Some references

1. Building effective business development in Pharma, BCG - Boston Consulting Group, 2021
2. Understanding the Business Development Opportunity in Biotechnology, Fit for Health 2.0, 2016
3. Everything You Need to Know About Biotech Business Models, LABIOTECH, 2020 – updated 2023
4. RIPCO, FIPCO, NRDO, FIPNET, VIPCO, Nature, 2019

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Patents in Life Science

BREAKthrough 1st Annual Meeting; October 4, 2023, Milan

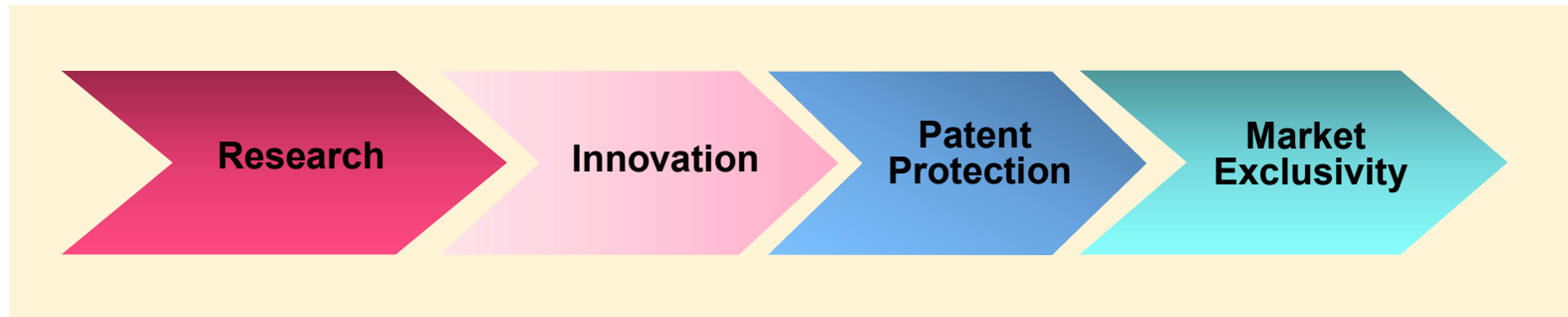
Beat Rauber

Global Quality Manager Group Patents, Swiss and European Patent Attorney
F.Hoffmann-La Roche AG



Introduction

- Originator pharmaceutical companies aim at creating, producing and marketing **innovative solutions** of high quality for **unmet medical** needs
- Innovation is converted into **patents** that can lawfully provide protection against copycat versions of third parties (market exclusivity).



What is a Patent?

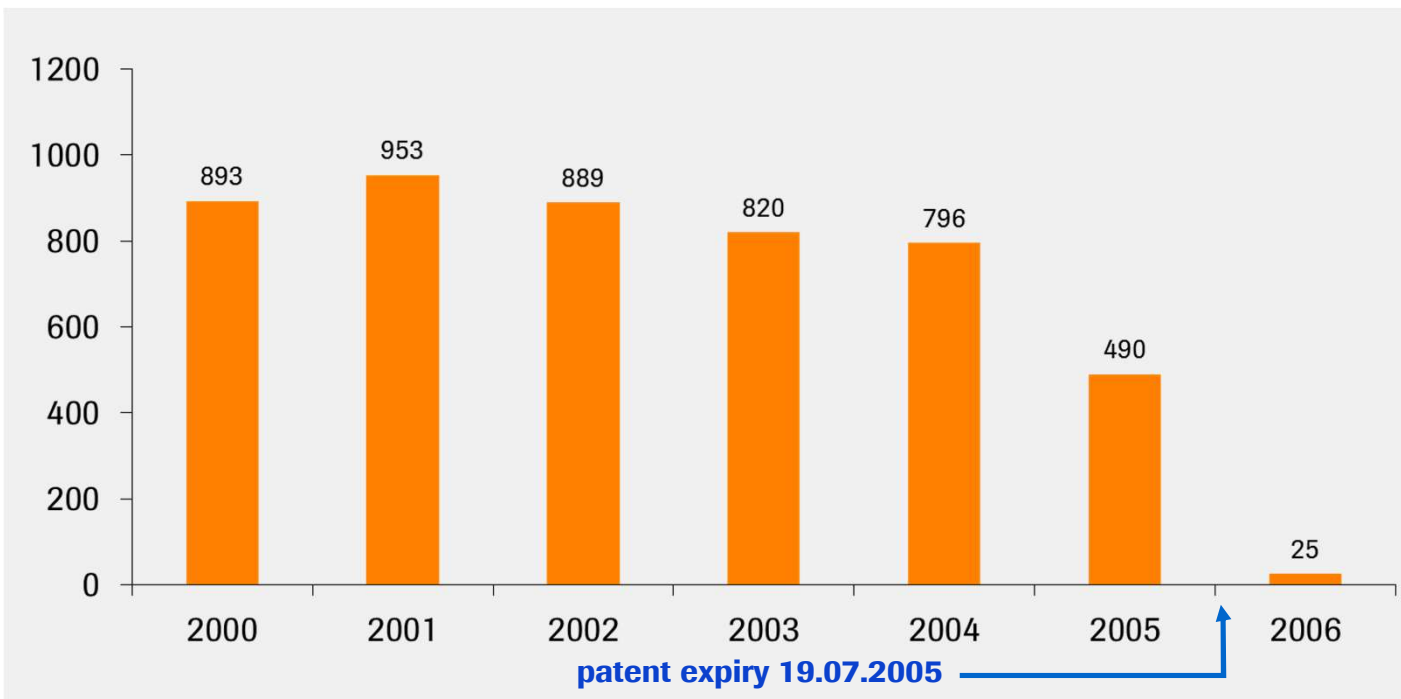
What you must know about patents!

- **Exclusive rights** as an **incentive to innovate** and **in return for publication** of the invention.
- **Right to exclude** others from making, using, offering for sale, or selling the invention in a **specific country for 20 years** (may be extended for up to 5 years).
- But no **affirmative right** to use or exploit the invention.



Why Patents are so important

Sales of ROCEPHIN in USA in Mio CHF



Patent Standards

What is required for obtaining a patent?

A patentable invention has to satisfy:

- Novelty
- Inventive step
- Industrial Application, Utility

The description must:

- Sufficiently disclose the invention

The claims have to be:

- Clear and supported by the description



Novelty

No protection for what is already known!

- An objective element
- Is invention identical with what is already known (state of the art)?
- Not difficult to assess
- To be considered at filing stage!



Inventive Step

No patents for obvious improvements!

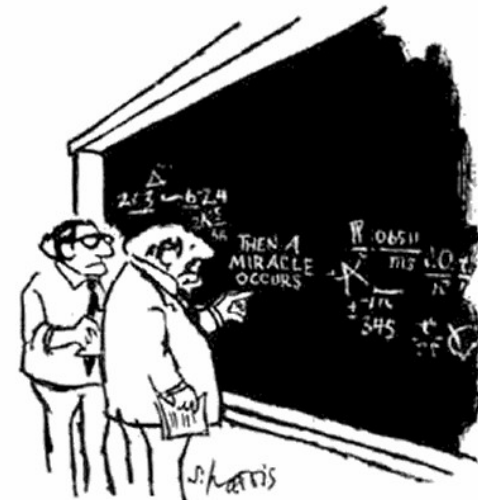
- A subjective element
- Is the invention obvious in the eyes of an average skilled person in the art?
- Difficult to assess
- May be substantiated later
- Not decisive at filing stage!



Disclosure

Detailed enough to reproduce

- Protection of public interest
- Complete description of invention
- Detailed enough to enable a skilled person to reproduce
- Best practical embodiment must be disclosed!



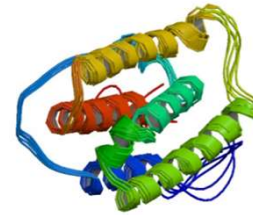
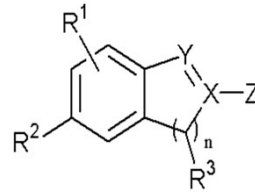
"I THINK YOU SHOULD BE MORE EXPLICIT
HERE IN STEP TWO."

Patent Categories

What can be patented?

Products

New chemical or biochemical entities

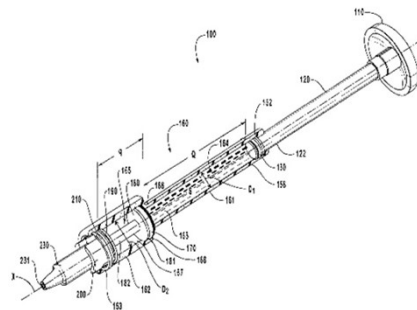


Product Modifications

Salts, Polymorphs, Crystalline Modifications, Pharmaceutical Compositions, Galenical Formulations, Intermediates

Objects

New Devices, Research tools



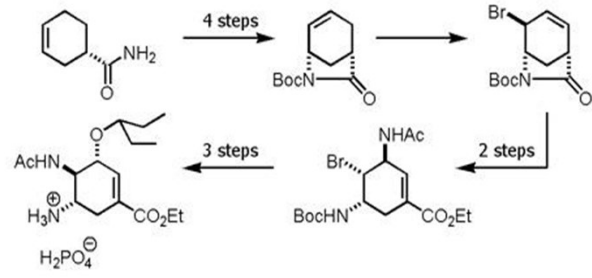
Sr. No.	Ingredients	Qty. (%w/w)
1.	Mometasone Furoate anhydrous	0.050
2.	Benzalkonium Chloride As Benzalkonium chloride solution 10%/w/v	0.01%/w/w 0.1%/w/w
3.	Anhydrous citric acid	0.195
4.	Glycerol	2.0
5.	Dispersible cellulose	2.0
6.	Polysorbate 80	0.01
7.	Sodium Citrate	0.277
8.	Water for injection	q.s.

Patent Categories

What can be patented?

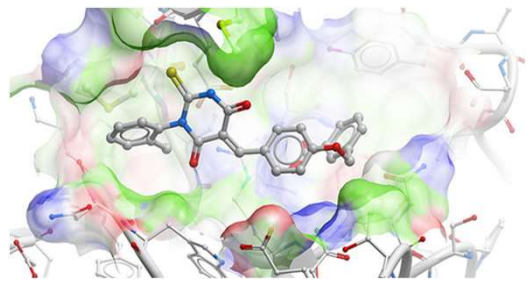
Processes

New synthetic approaches



Uses

New Therapies, dosage regimes, New Dosage Regime



Market Exclusivity

Primary and secondary patent rights

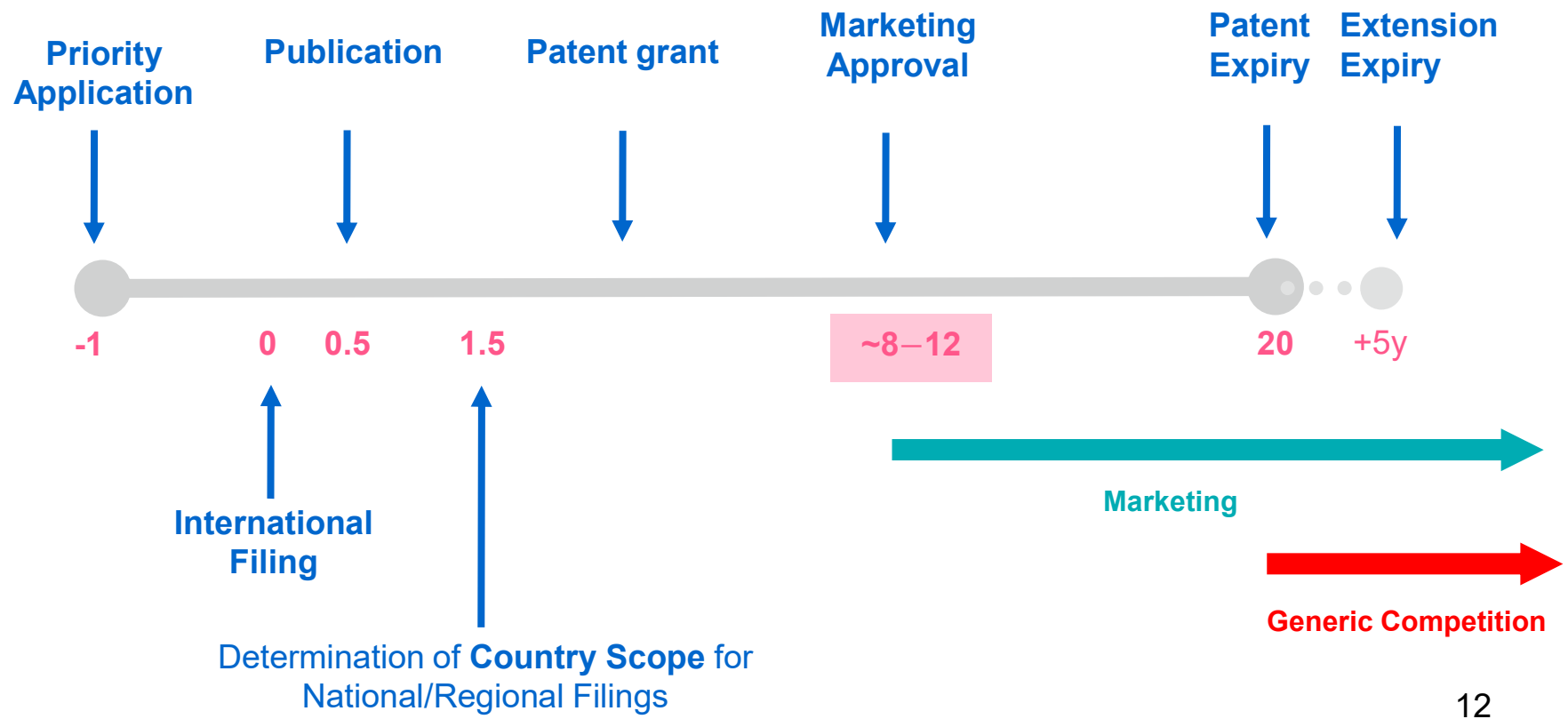
Patents directed to **Compounds**

- Provide **Market Exclusivity** for pharmaceutical products
- Protection for the **Pharmaceutically Active Ingredient**

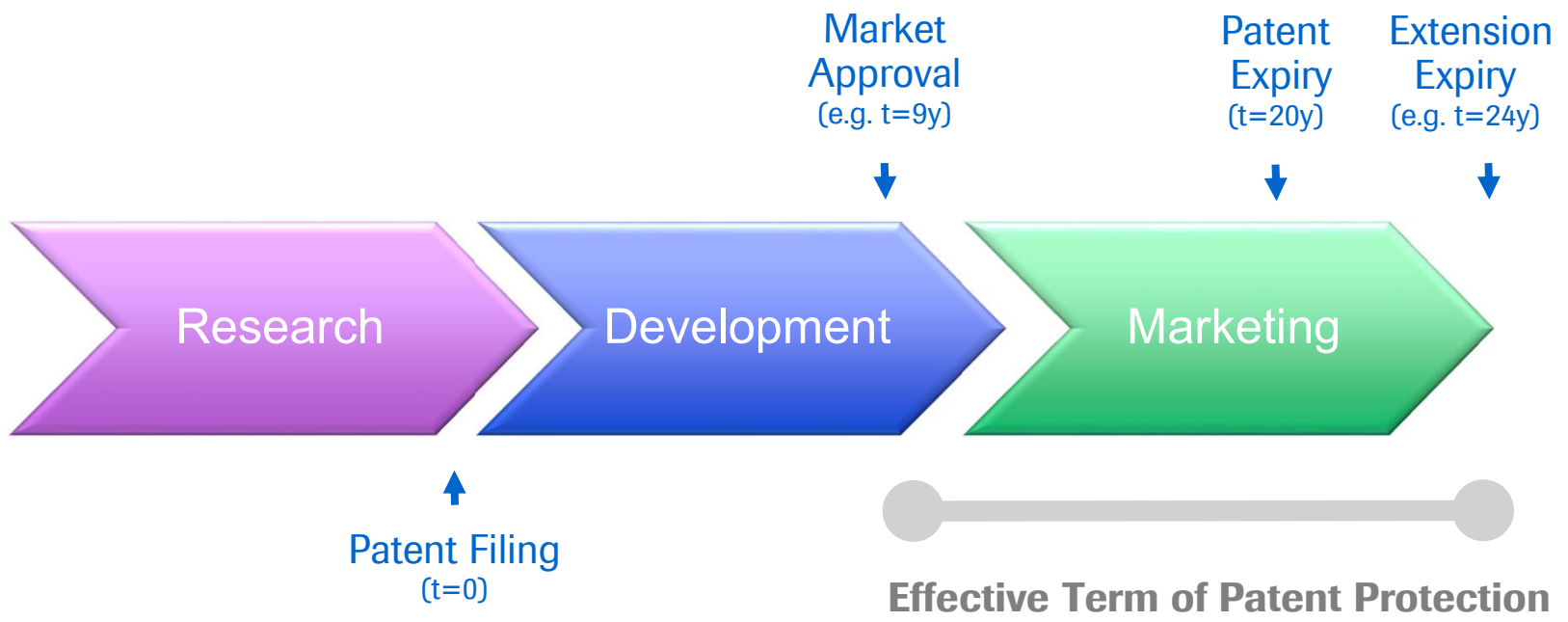
Patents directed to **Other Aspects**

- **No guarantee of market exclusivity** but may contribute
- Provide **protection for a specific aspect only**, such as for formulations, processes, uses for new therapies or indications, administration schemes, research tools etc..

Patent CV for a molecule which matures to a market product



From Research to Patent Expiry





Extension Regimes to compensate for Regulatory Delays

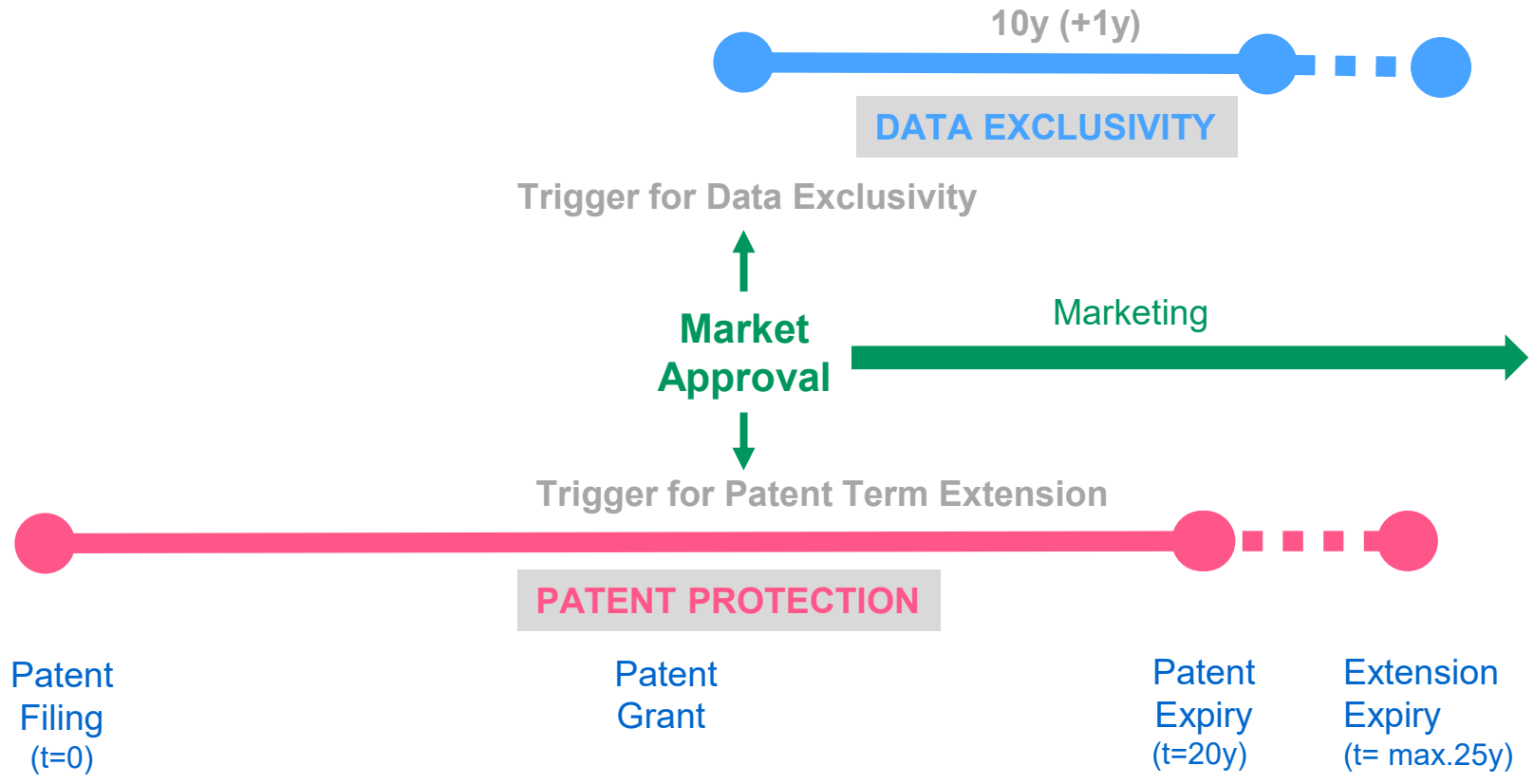
- **Europe:**
 - Supplementary Protection Certificates (SPC) Available in Europe for EU member states incl. CH/LI, IS, NO. (EEC Council Regulation 469/09)
 - Provides for a 15 year market exclusivity from market approval with a cap of 5 years from basic 20 years patent expiry.
- **US:**
 - More complex as effective patent term is determined on patent office delays (PTA) and regulatory delays (PTE). PTE regime provides for a 14 year market exclusivity from market approval with a cap of 5 years from basic 20 years patent expiry.
- **Other extension regimes:**
 - Australia, Canada, Israel, Japan, South Korea, Russia, Singapore, Taiwan also provide extension regimes of up to 5 years from basic 20 years patent expiry.
- **No extension regimes:**
 - South American countries like Brazil or Asian countries like China or India do not have meaningful extension regimes. Patents expire after 20 years.

Regulatory Data and Marketing Exclusivities

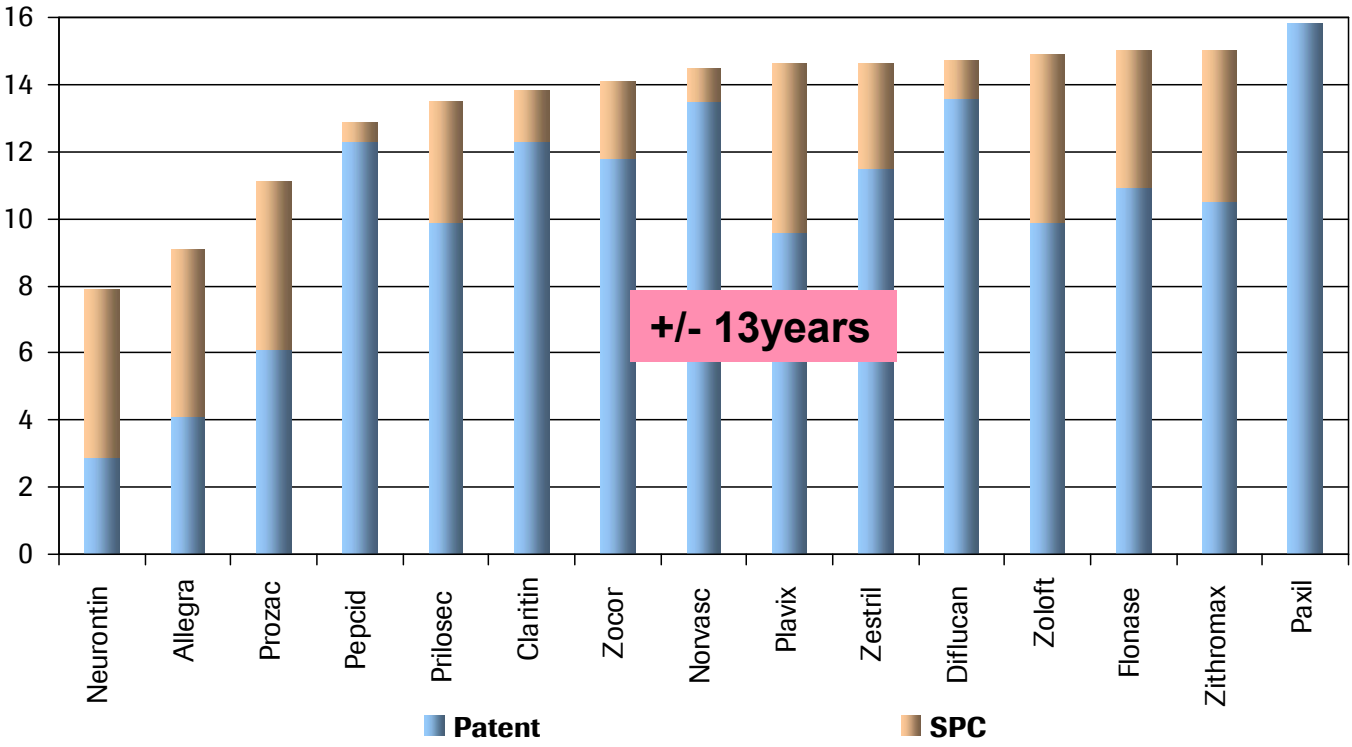


- **Data Protection:**
 - **Europe:** Protection of regulatory data for 10 years (8+2+1). (+1) for a market authorization of a further indication. (EC Regulation EC 726/2004).
 - Period after which a generic/biosimilar product can be approved based on innovator's data in an abbreviated filing procedure.
 - Data Exclusivity does not prevent a competitor from generating its own regulatory data and getting regulatory approval on this data.
 - **USA:** 5 years for new chemical entities. 3 years plus in case of new clinical investigation. 12 years for biologics (BLA exclusivity)
- **Orphan Drug Exclusivity**
 - **Europe:** Provides 10 years market exclusivity for a medicament for rare diseases (prevalence of not more than 5 in 10000; EC Regulation 141/2000).
 - **USA:** 7 year Orphan Drug Exclusivity
- **Pediatric Exclusivity**
 - **Europe:** 6 month pediatric extension based on an SPC and an agreed PIP (pediatric investigation plan. (EEC Regulation 1901/2006
 - **USA:** 6 month pediatric exclusivity on top of patent and regulatory exclusivities.

Patent Protection vs. Regulatory Data Protection



Effective Patent Term in the Europe (UK)



Patent Protection Strategy

- The goal is **Market Exclusivity** for pharmaceutical products.
- The focus is on the **Protection of the Pharmaceutically Active Ingredient.**
- Patent protection for **further Innovative Developments** is important.

Related products (e.g. prodrugs, salts, polymorphs)

New pharmaceutical formulations

New routes of administration

New dosing schemes

New medical uses and indications

New manufacturing processes



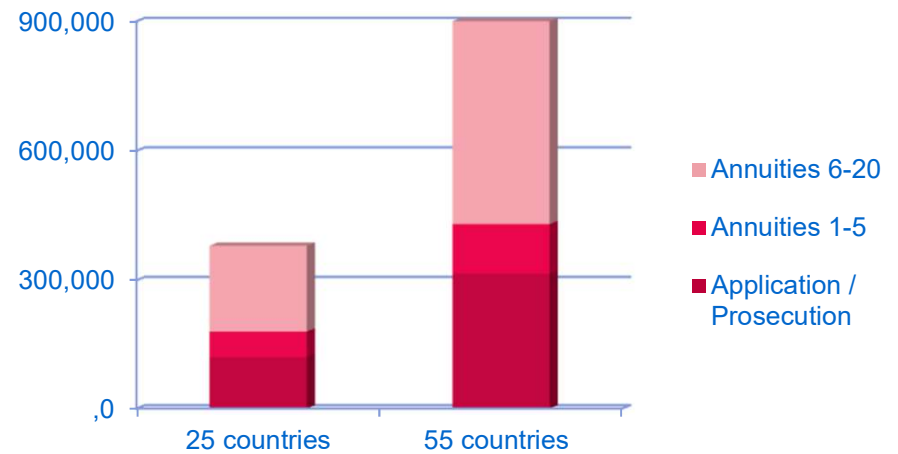
Patent Protection Strategy

- File with a sense of urgency with the required minimum of information
- Set up claims with a reasonable broad scope
- Try to obtain granted patents at the latest before commercialization
- Do not disclose information that may jeopardize later patenting
- File in all important markets



Patent Cost

- Cost for priority and international filing relatively low
- First substantial cost block comes with the national filings and the local patent prosecution via local law firms (translation cost)
- Cost block raising over the years ist the annual cost for maintenance. Cost substantially increases from the 5th year onwards
- **Annual Patent Portfolio Management is an imperative task!**





Many thanks for your attention!



Beat Rauber
beat.rauber@roche.com



NP screening programs: from sample preparation to lead optimization

Oct 4, 2023

*Margherita Sosio
Naicons Srl, Milan*

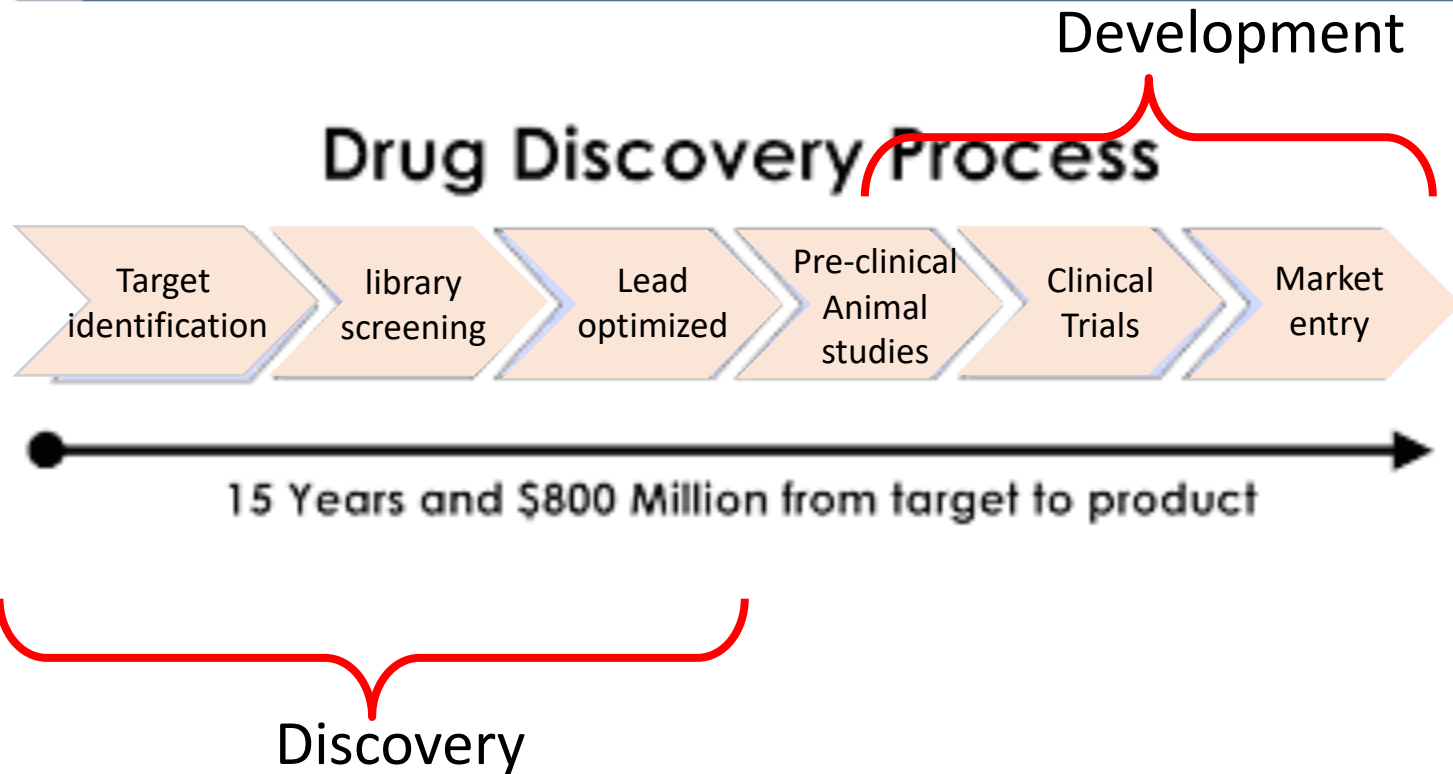




1. drug discovery and development
2. NP vs synthetic products
3. Screening process
4. Naicons strategies
5. the future? The micro4all platform



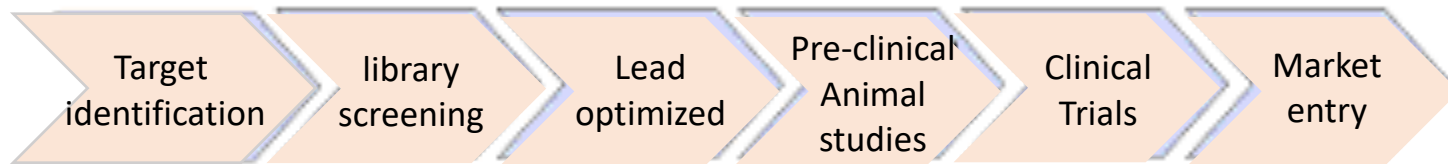
R&D of new drugs





R&D of new drugs

Drug Discovery Process



15 Years and \$800 Million from target to product

3–6 years

1–2 years

5–8 years

Cost per program

2–5 M\$

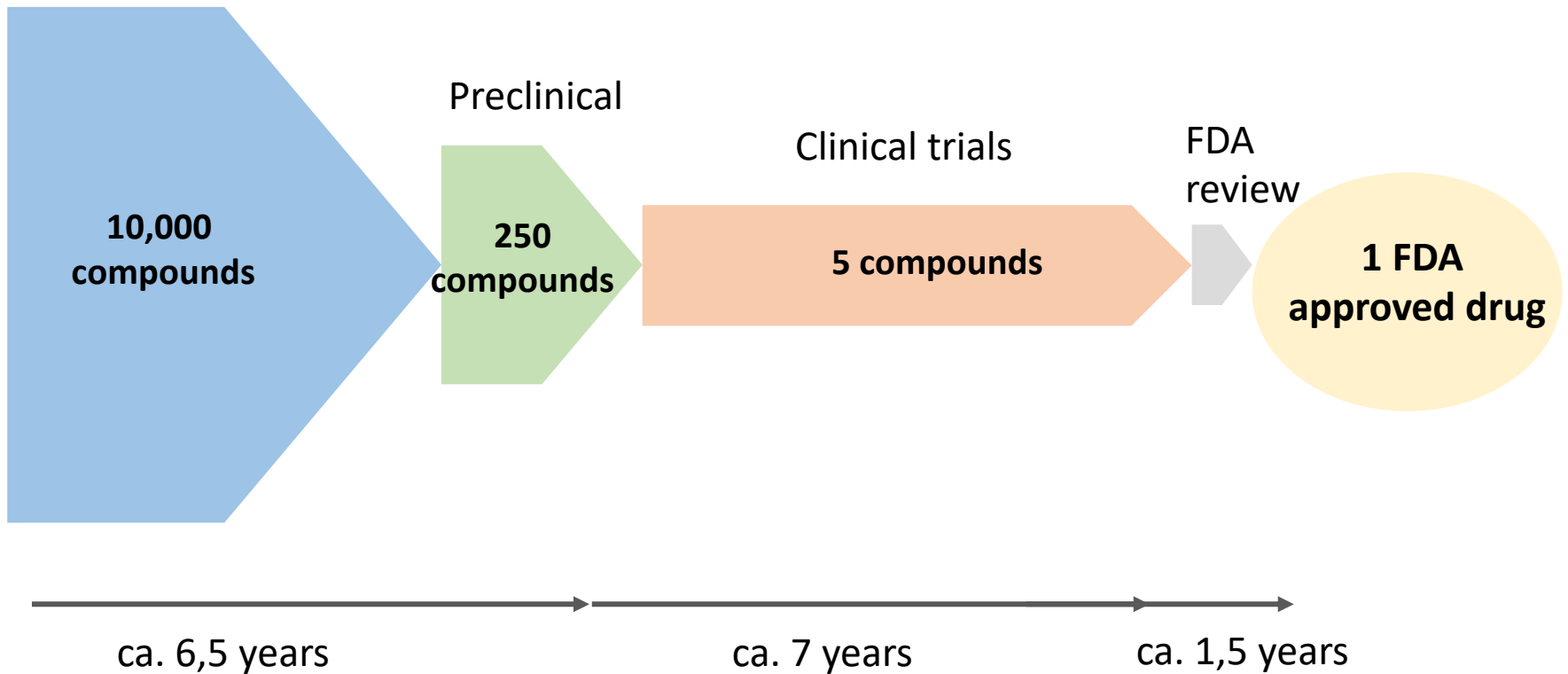
2–3 M\$

60–300 M\$



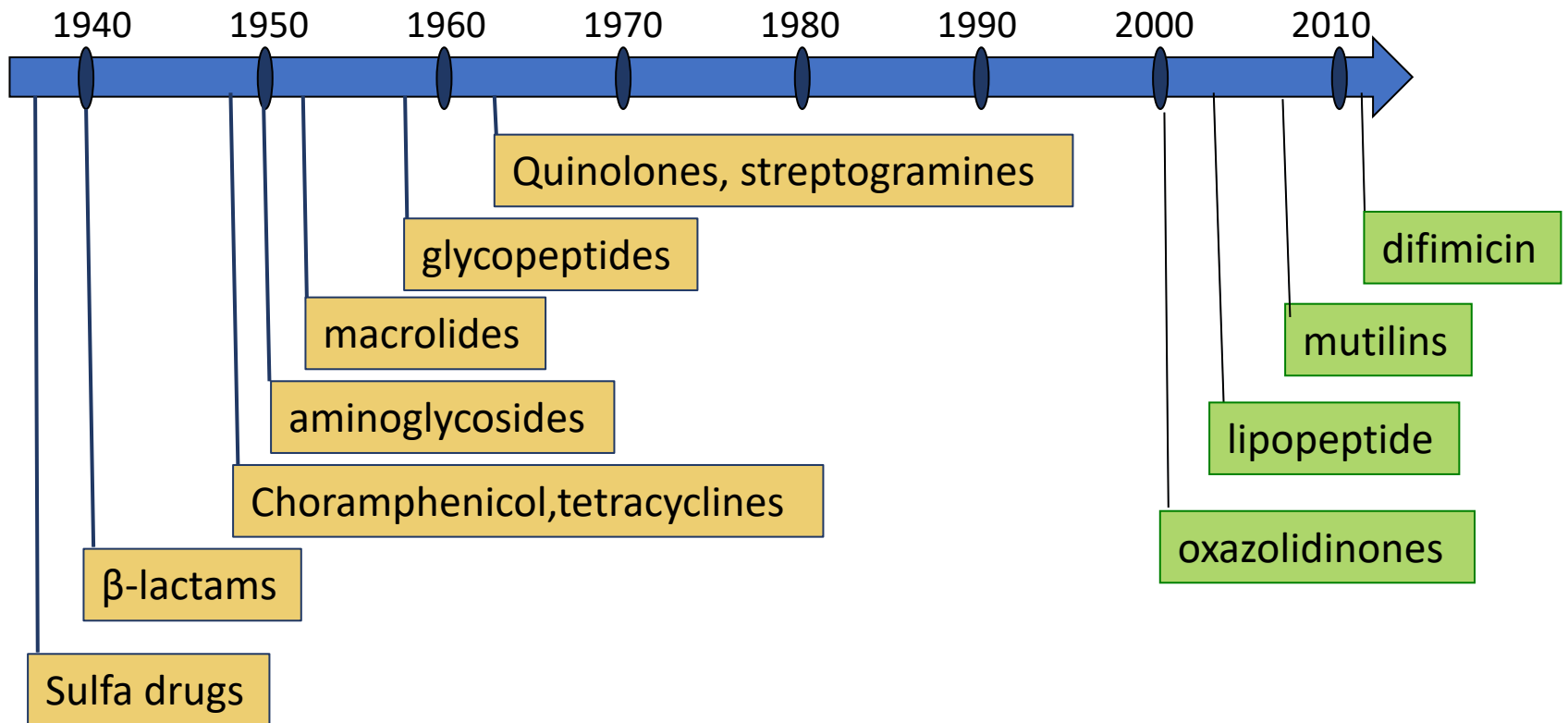
Drug discovery & development timeline

Drug discovery





→ Golden Era ← ← Innovation gap →





the need for new antibiotics

- infectious diseases represent the first cause of mortality in the developing **world** and the fourth cause in the developed world
- changes in human population (ageing, immunosuppression, invasive procedures) provide new niches for opportunistic pathogens
- the use (and abuse) of antibiotics has led to the emergence of resistant strains
- **resistant** strains emerged soon after antibiotics entered clinical use
- multiple drug-**resistant** strains are now quite common



how were antibiotics discovered?

- most marketed antibiotics are naturally produced by soil-inhabiting microorganisms
- their discovery occurred through screening of *randomly* isolated microbes
- since the 1950s, most big pharma companies were involved in screening microorganisms for new antibiotics and other drug leads
- tens of millions of microbes have probably been screened, mostly for new antibiotics
- most antibiotics are still produced today by *fermentation*
- many antibiotics for human use were marketed at a time of minimal *regulatory requirements*



why this decline?

- A. decreased productivity of the industry
- B. regulatory issues
- C. market choices
- D. high bar for antibacterial developmental candidates
- E. outdated/inappropriate technologies



regulatory issues

- existing antibiotics work very well, except of [^]R strains
- frequency of [^]R strains greatly varies from site to site
- diagnostics not yet routinely employed
- non-inferiority clinical trials versus comparator antibiotic



Strategies by big pharmas

- preference for chronic and life-style drugs
- medical need is within niche market
- limited life-time of antibiotics

internal competition

- focus on blockbusters: one pill fits all



Decline in NP research

- Introduction of HTS against defined targets
- hype for Combinatorial Chemistry, random chemical libraries
- Advance in molecular biology, cellular biology and genomics which increased the number of molecular targets
- decreased emphasis in key areas, particularly infectious disease
- rediscovery of known compounds (labour-intensive process)



Challenges in NP research

chemical libraries provide a quick route to screening (compress the hit to lead process)

but limited extent of chemical space

importance of chemical diversity

NP research challenges

increase chances to find novel compounds

reduce the hit to lead time and effort

explore different approaches

manipulation of NPs

combinatorial chemistry of NP scaffolds

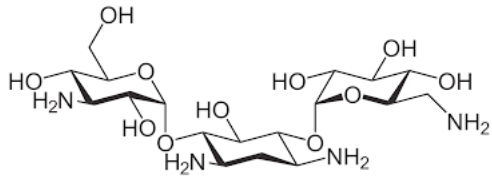
combinatorial biosynthesis



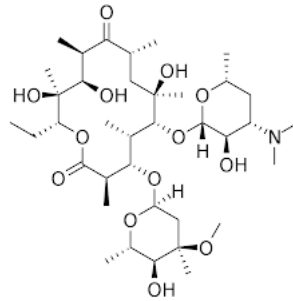
Success of NP research

NPs have provided many of the older drugs

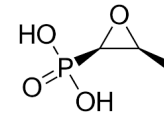
Still, it has been estimated that over 50% of drugs approved in 1981-2020 are NP, NP-derived or NP-inspired compounds (Newman et al. J. Nat. Prod. 2020)



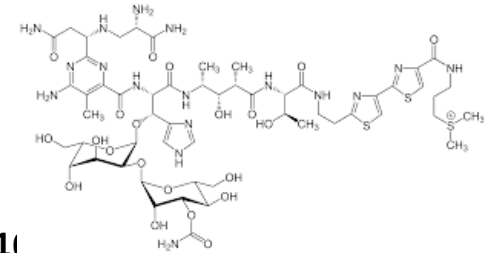
kanamycin, M_r 379



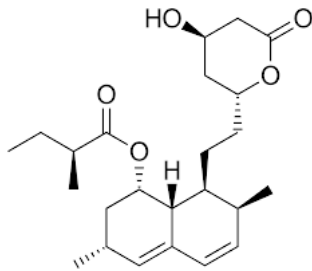
erythromycin, M_r 720



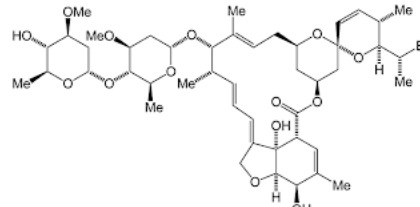
phosphomycin, M_r 100



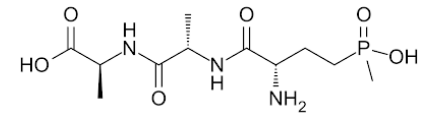
bleomycin, M_r 1415



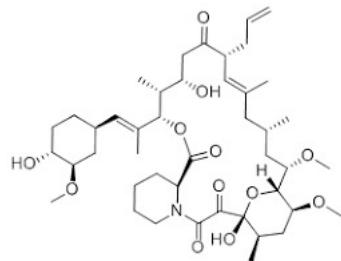
lovastatin, M_r 403



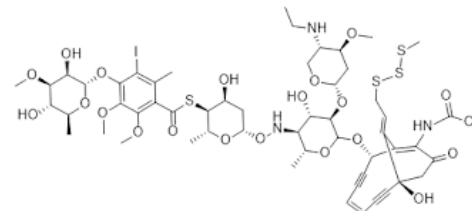
avermectin, M_r 873



bialaphos, M_r 323



FK506, M_r 802

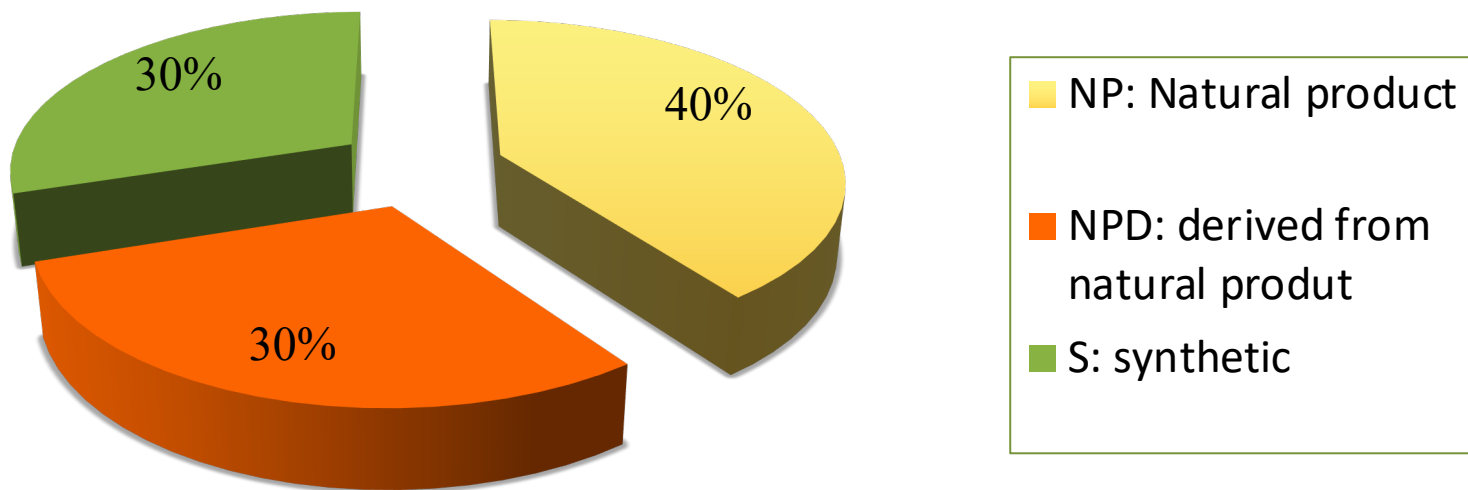


calicheamycin, M_r 1071



why natural products?

Antibiotics: natural product vs synthetic product



Natural Products as Sources of New Drugs over the Nearly Four Decades from 01/1981 to 09/2019 (Newman D.J., *J. Nat. Prod.* 2020)



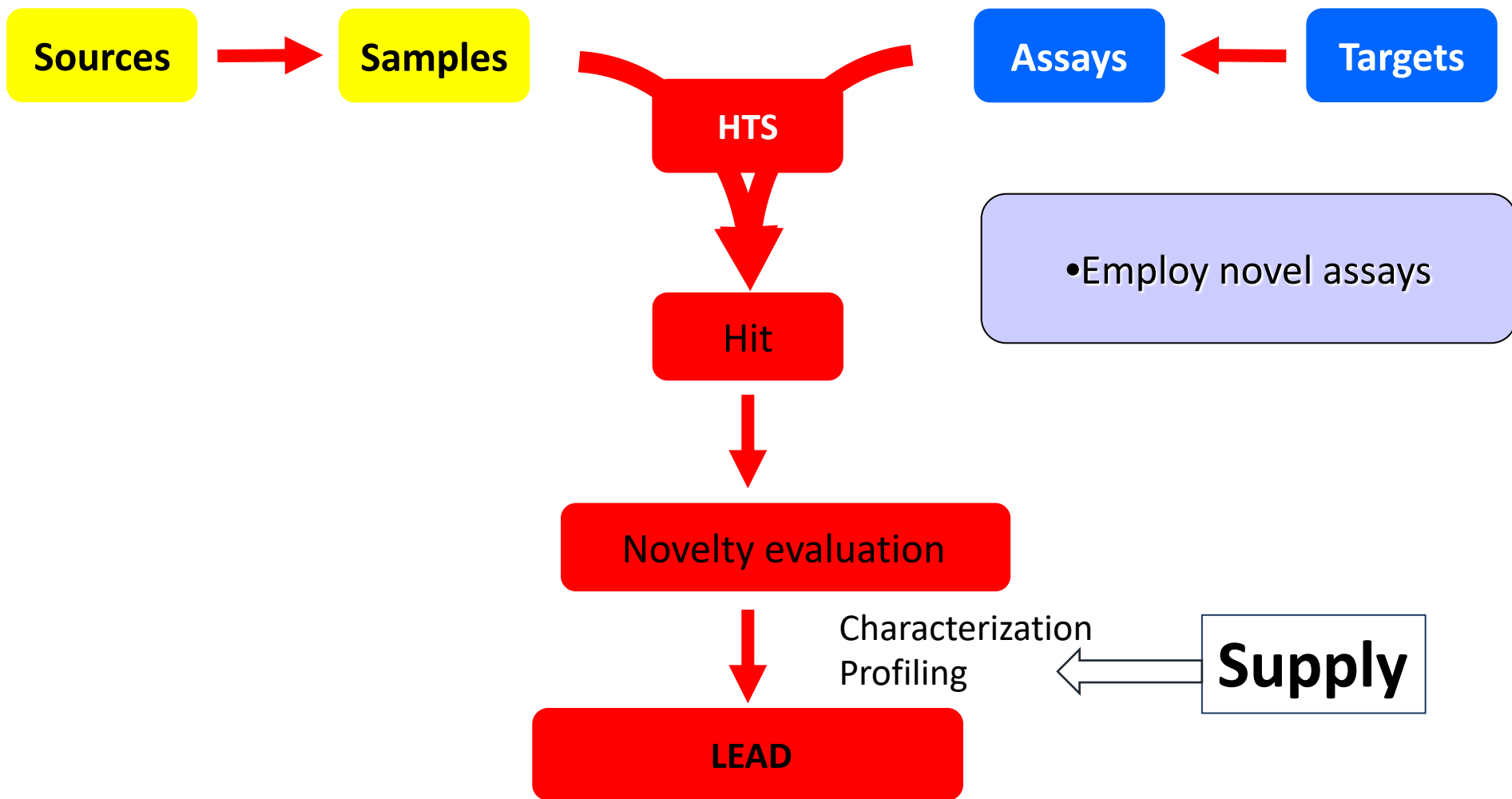
screening microbial products

Key elements:

- (1) a library of microbial strains that produce a diverse and biologically relevant set of compounds;
- (2) appropriate tests to detect compounds of potential value;
- (3) samples derived from the strains;
- (4) instrumentation and data capture tools adequate to the size of the screening program;
- (5) identification of the molecules responsible for the activity and recognition of known compounds;
- (6) additional tests to profile the molecules;
- (7) ability to supply increasing amounts of active compounds.



Element of a screening process





Targets for Antibiotics

A good target is

- essential to the viability of the target cell(s)
- present and well-conserved in the desired group of pathogens, where it plays the same role
- absent or significantly different in the organisms that should not be affected by the drug (i.e. humans, animals)
- likely to be vulnerable in multi-resistant pathogens

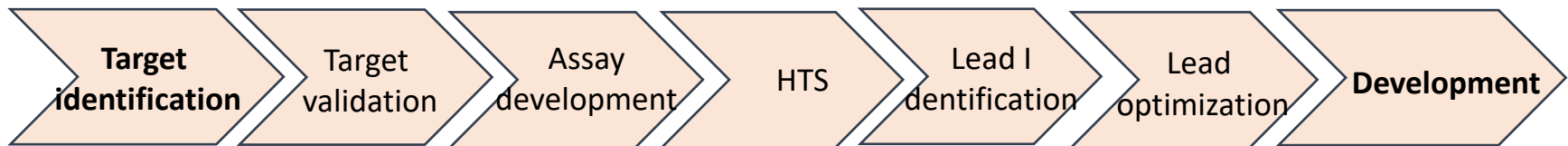


Assay Requisites and Performance

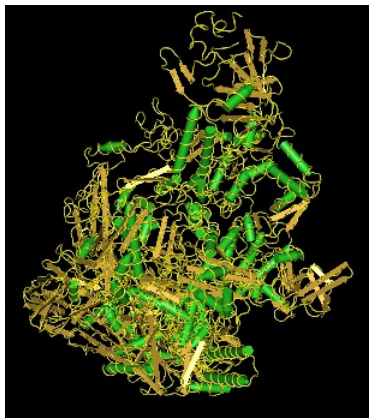
- specificity for the desired target
- sensitivity for detecting bioactive substances present in low concentration
- executable in a miniaturized format
- amenable to automation (liquid dispensing and data acquisition)
- robust (acceptable signal to noise ratio)
- insensitive to components in fermentation extracts (extract preparation)



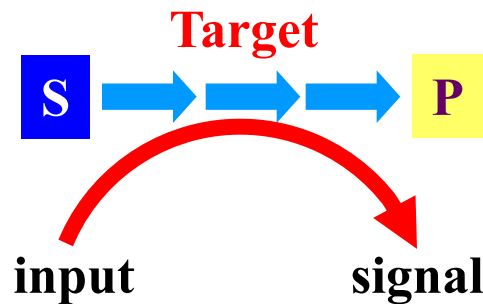
From target to assay



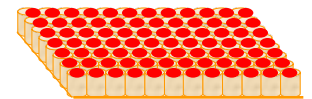
- primary assays
- secondary assays



validated target



assay concept



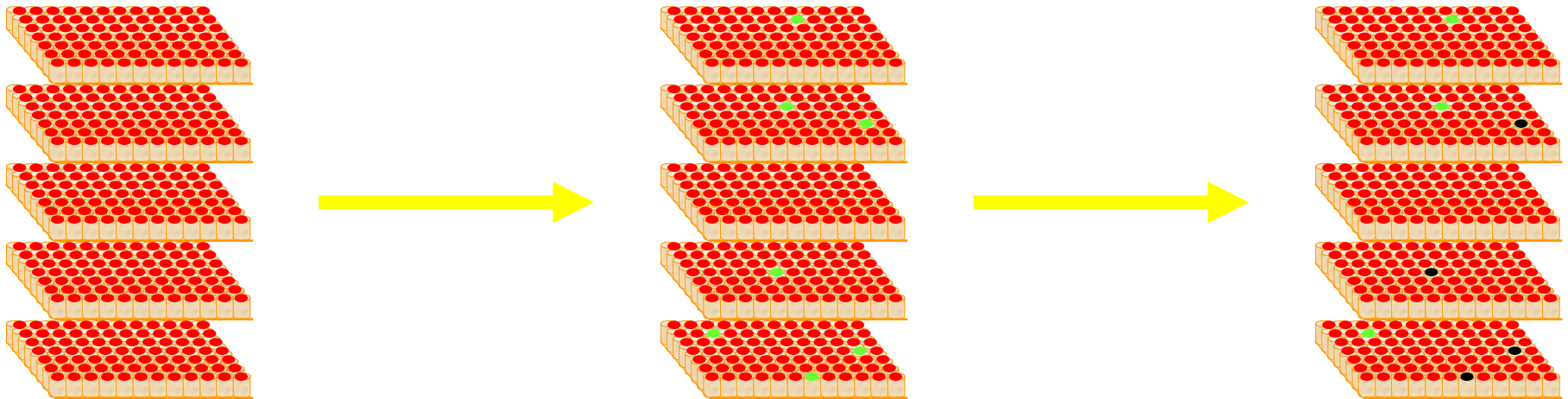
miniaturized assay





Screening is NOT a single test

Complex screening algorithm



Secondary screening tests
control for detection system
control for selectivity
control for interferences
additional properties





the screening flow

~120,000 extracts

S. aureus growth inhibition

Y

~3000 extracts

bacterial RNAP inhibition

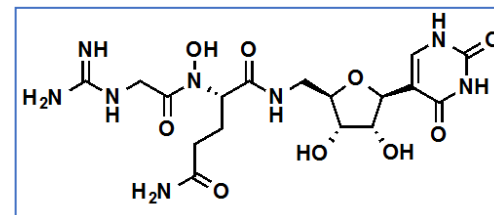
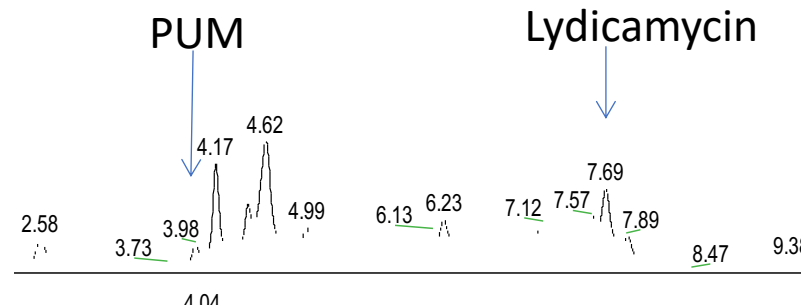
Y

SP6 RNAP inhibition

N

known compound dereplication

two extracts from two *Streptomyces* strains



PUM

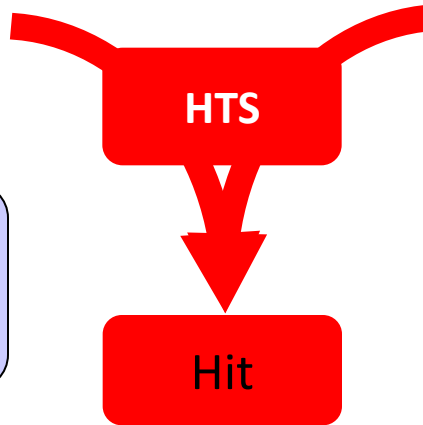


Element of a screening process

Sources



Samples



Assays



Targets

- Increase the number of strains

- Utilize novel approaches to strains

novel strains

metagenomic libraries

genome mining



Producer strains

over 40,000 microbial metabolites have been described
most of the metabolites are produced by either
filamentous fungi or filamentous actinomycetes

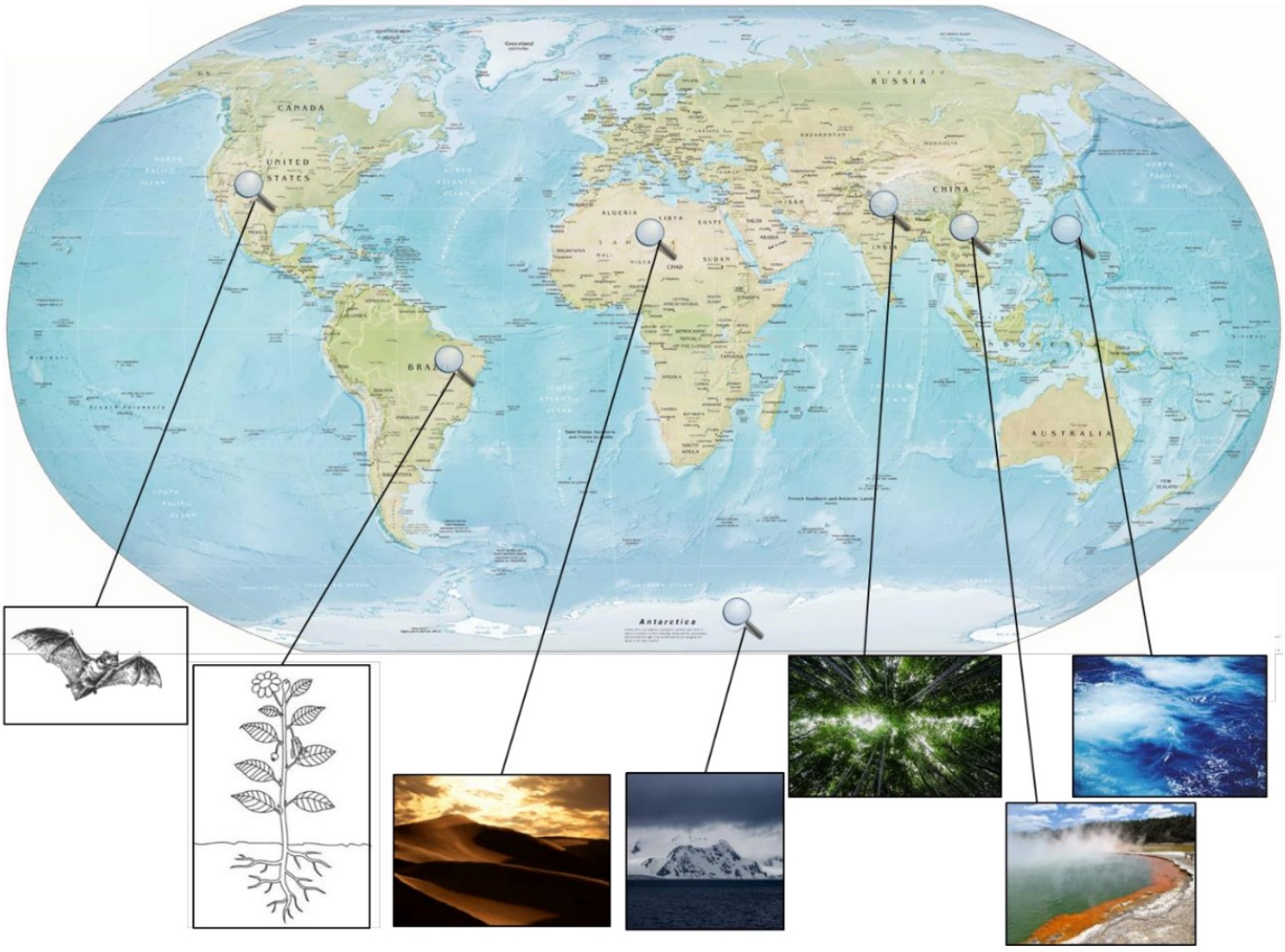
genomic studies have confirmed that the ability to produce
secondary metabolites is not uniformly distributed within the
bacteria



questions in NP discovery

Novel approaches:

- New Habitats
- Novel strains
- Genome mining
- New assays
- Genetic manipulation



Exploring New Habitats



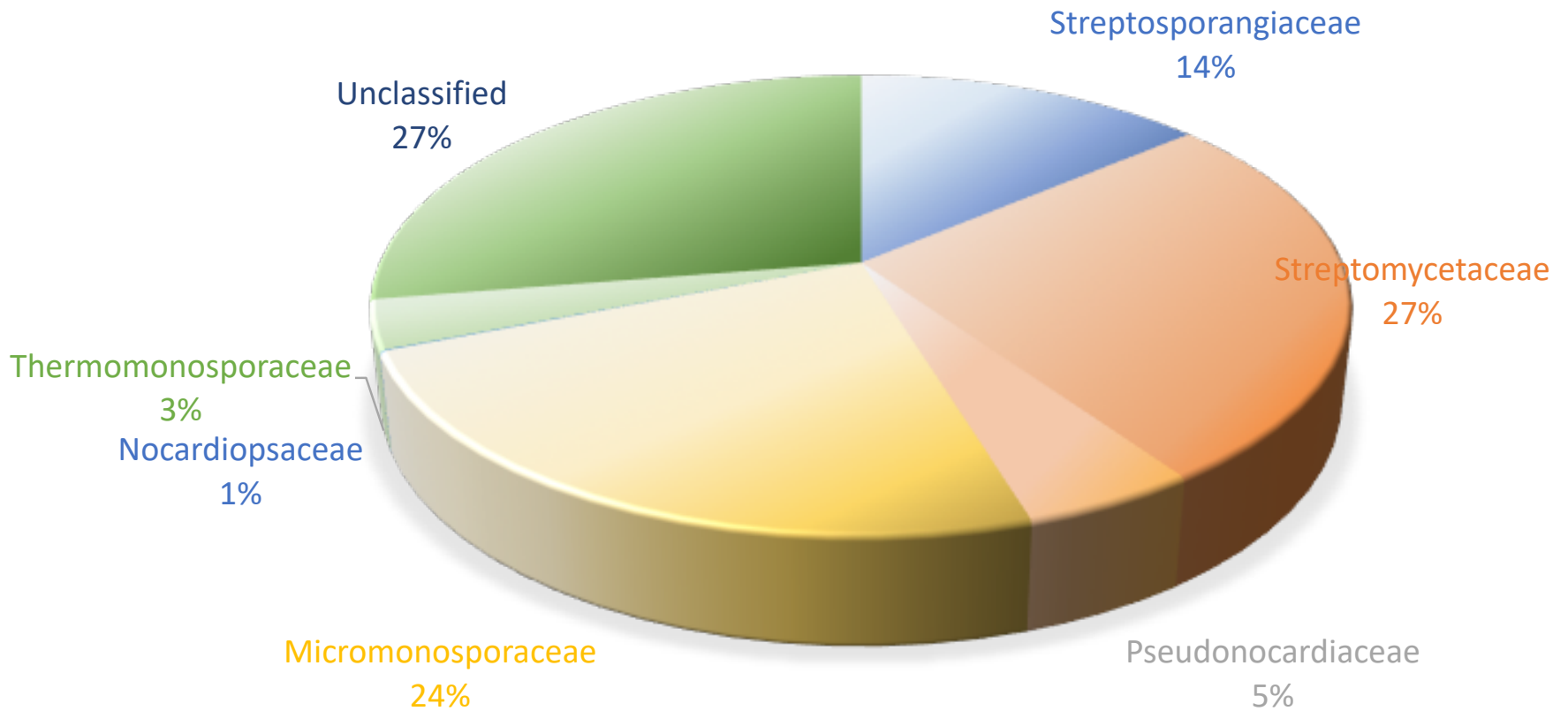
questions in NP discovery

Novel approaches:

- New Habitats
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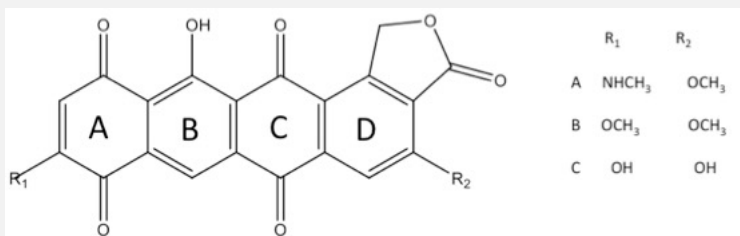
NAICONS strain library



>44 K strains, mainly actinomycetes

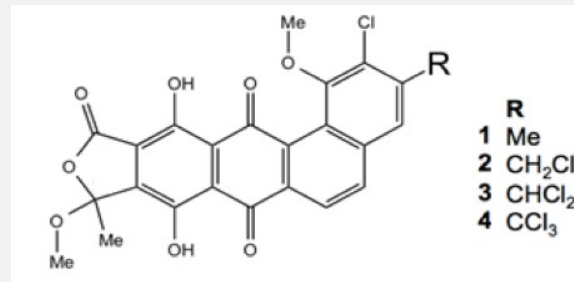


Paramagnetoquinone



- new tetracene member
- NMR-silent
- Broad spectrum activity
- *pmq*, biosynthetic cluster identified
(lorio, et al (2016). *J Nat Prod.*)

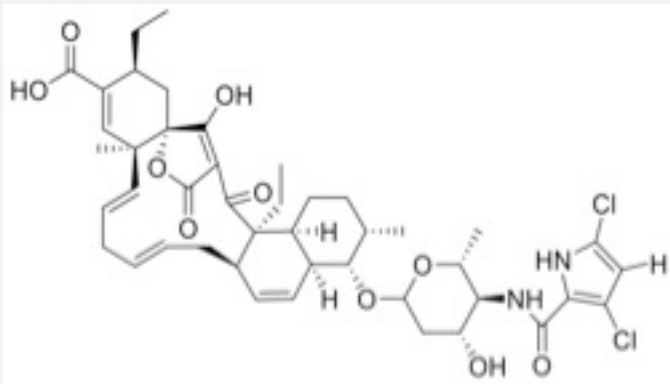
Allocyclinone



- new members of the angucycline class
- Cpd4, aromatic trichloromethylene substitution
- direct relation between number of Cl and Ab activity

Cruz JC, et al (2016). J Antibiot (Tokyo)

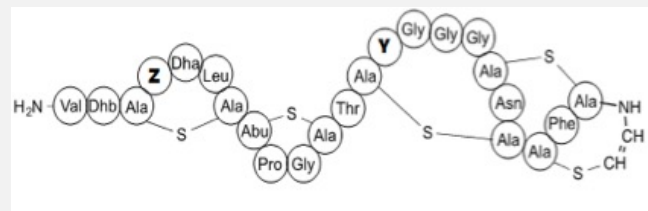
NAI-414



- Novel macrolactone
- Unique trichloropyrrole moiety
- Antimicrobial and antitumor activity

Mazzetti C, et al (2012) J Nat Prod. 75(6):1044-50.

NAI-108



- NAI-107, previously reported only from *Microbispora*
- New Congener, NAI-108
- NAI-108, consistent improvement in Ab activity

Cruz J et al (2015) J Nat Prod. 78(11):2642-7



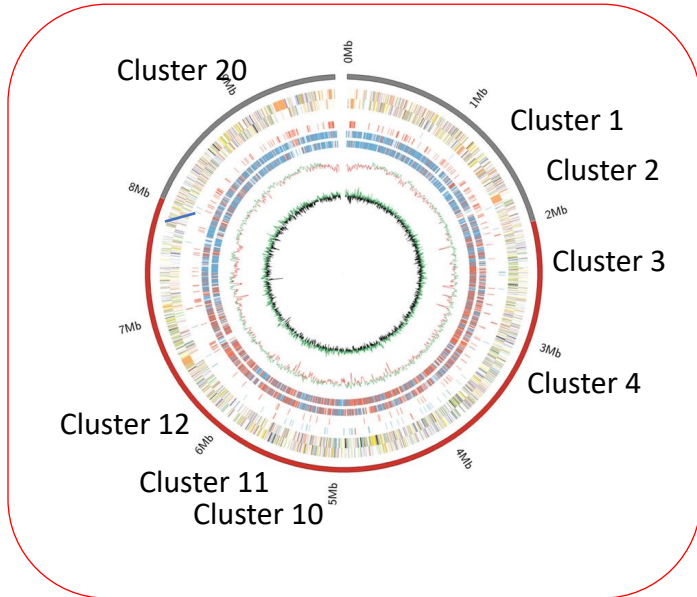
Novel approaches:

- Novel habitat
- Novel strains
- Genome mining
- New assays
- Genetic manipulation



Genome-based NP discovery

Challenges to Conventional Discovery of Natural Products



One strain, many clusters;
one cluster: one family of
compounds



Mining and engineering natural product biosynthetic pathways

Ability to alter NP structures through the genetic modification of their biosynthetic machinery

Combinatorial biosynthesis



“non natural” NP



changes in natural product research

- a deeper understanding of microbial diversity
- recognition of the genetic potential to produce bioactive molecules
- advances in MS for structure elucidation/databases and increasing use of metabolomics-inspired methods
- access to whole genome sequences
- improved tools to generate NP analogs



conclusions



- NP research can provide an important contribution to drug discovery
- biology can complement chemistry in expanding diversity of NPs
- realistic approaches should be pursued (novel tools and approaches are now available)
- Interplay of disciplines for the exploitation of the untapped natural product reservoir.





Core assets

