


Kick-off session: "Biotechnology
for a sustainable bioeconomy"



Title: Streamlined Streptomyces cell factories for industrial production of valuable natural products

Project acronym: MISSION

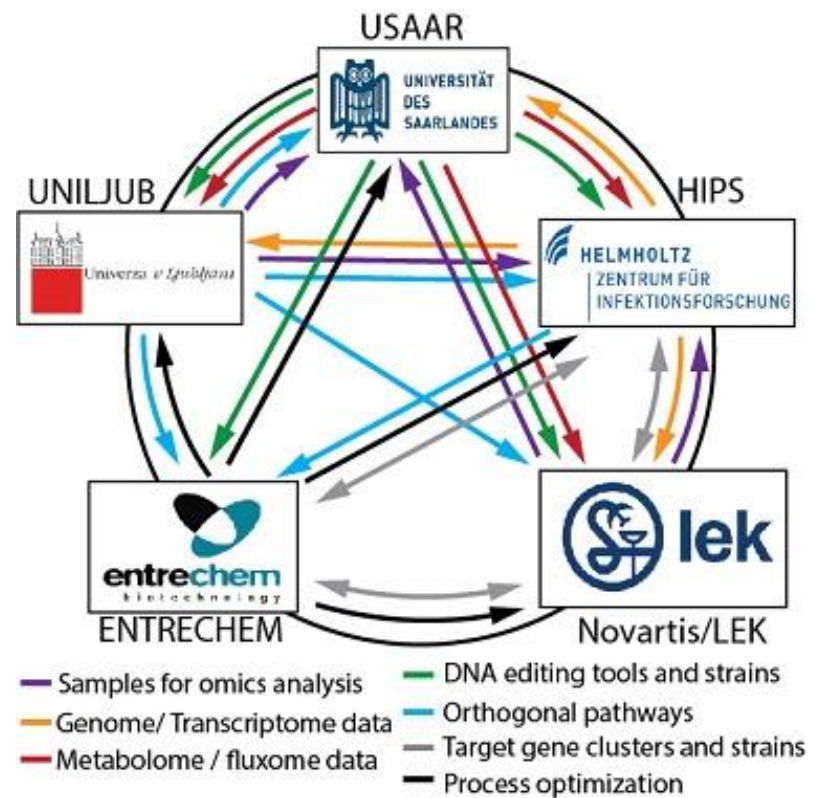
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- University of Saarland, Germany
- Helmholtz Institute of Pharmaceutical Research, Saarbrücken, Germany
- University of Ljubljana, Slovenia

- Novartis/LEK, Slovenia
- Entrechem, Spain

- Total project budget: 1.791.000 €
- Project start: 01 May 2018



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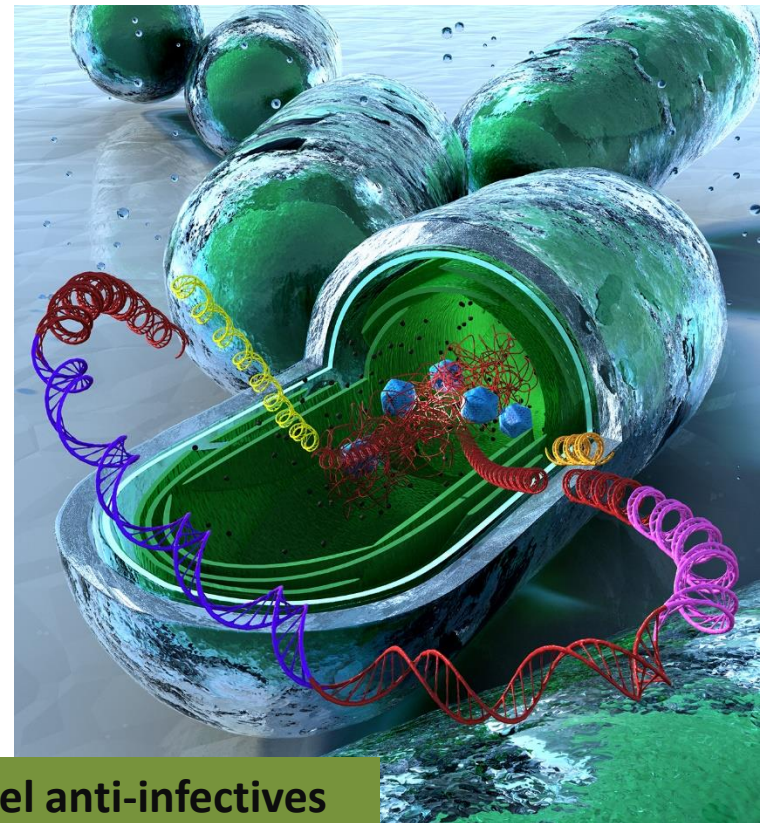
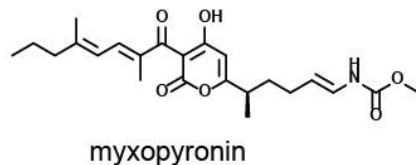
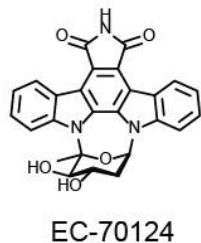
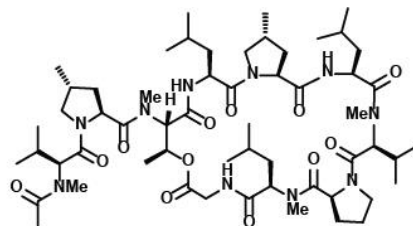
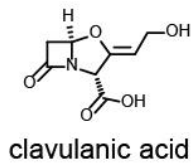
***Streptomyces*: Two-time Noble Prize winner!**



Streptomyces rimosus

Project Objectives:

- ✓ **Synthetic biology and metabolic engineering** to create a chassis strain of *S. rimosus* with superior growth and robustness, and tuneable metabolic activities
- ✓ “Plug-in” of secondary biosynthetic pathways to derive streamlined cell factories for **novel anti-infectives and anti cancer drugs**



**Novel anti-infectives
and anti-cancer drugs**

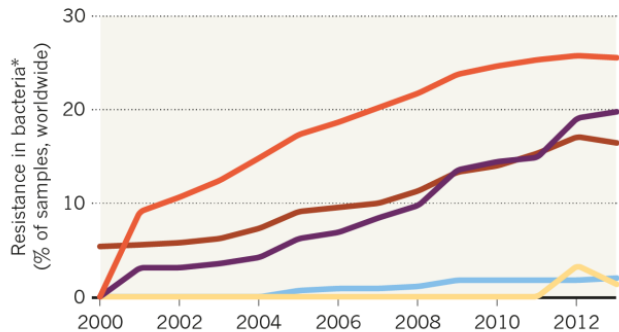
Project Topic Area: New compounds for medicine and pharma

Global resistance

THE SPREAD OF ANTIBIOTIC RESISTANCE

An increasing proportion of bacteria display resistance to common antibiotics.

— Fluoroquinolones — Cephalosporins (3rd gen) — Aminoglycosides
— Carbapenems — Polymyxins

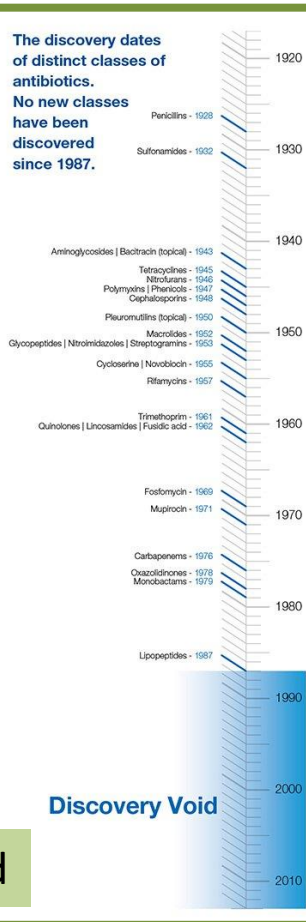


*Enterobacteriaceae, including *Escherichia coli*, *Klebsellia pneumoniae*, *Enterobacter* and *Salmonella*

©nature

Source: CDDEP ResistanceMap, based in part on data obtained under license from IMS MIDAS

Discovery void



www.statnews.com

A Nevada woman dies of a superbug resistant to every available antibiotic in the US

„The perfect storm“

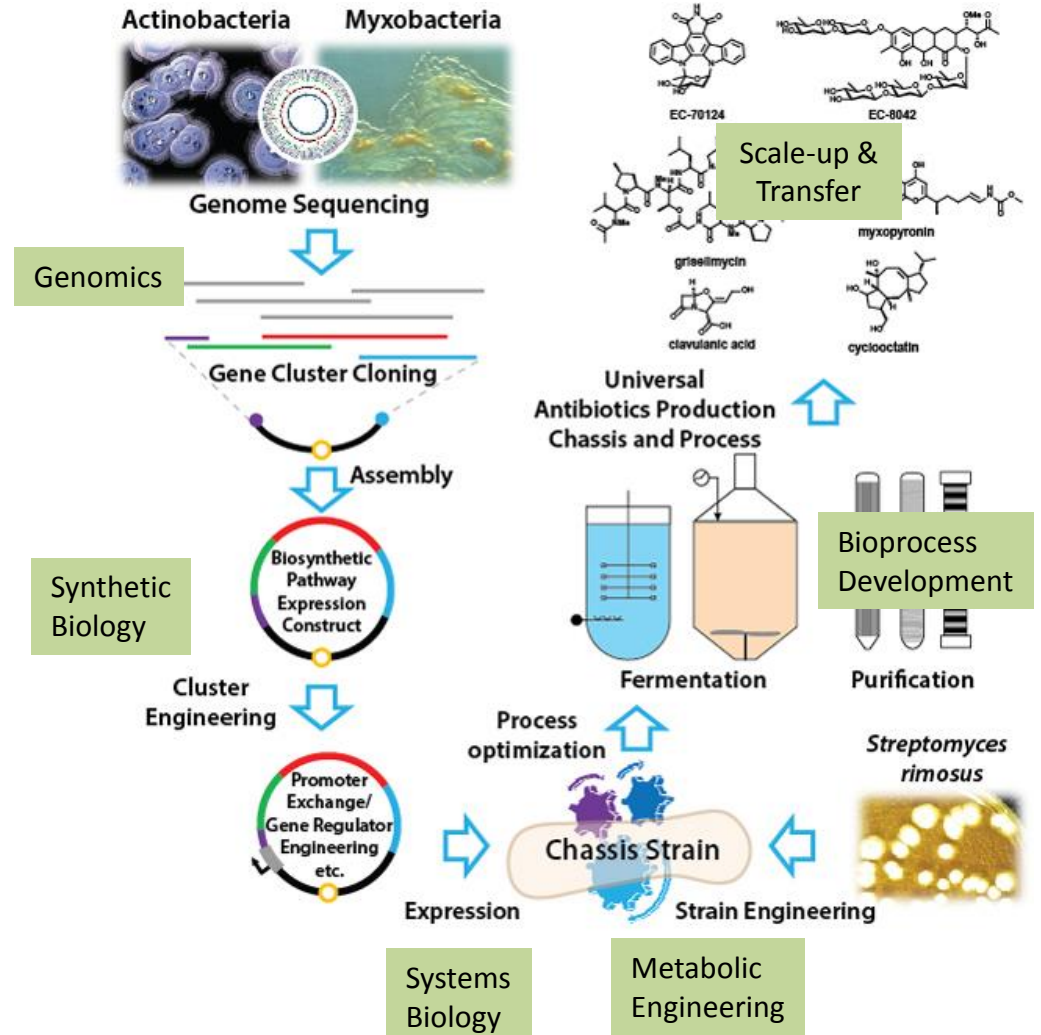
GLOBAL A failure to address the problem of antibiotic resistance could result in:



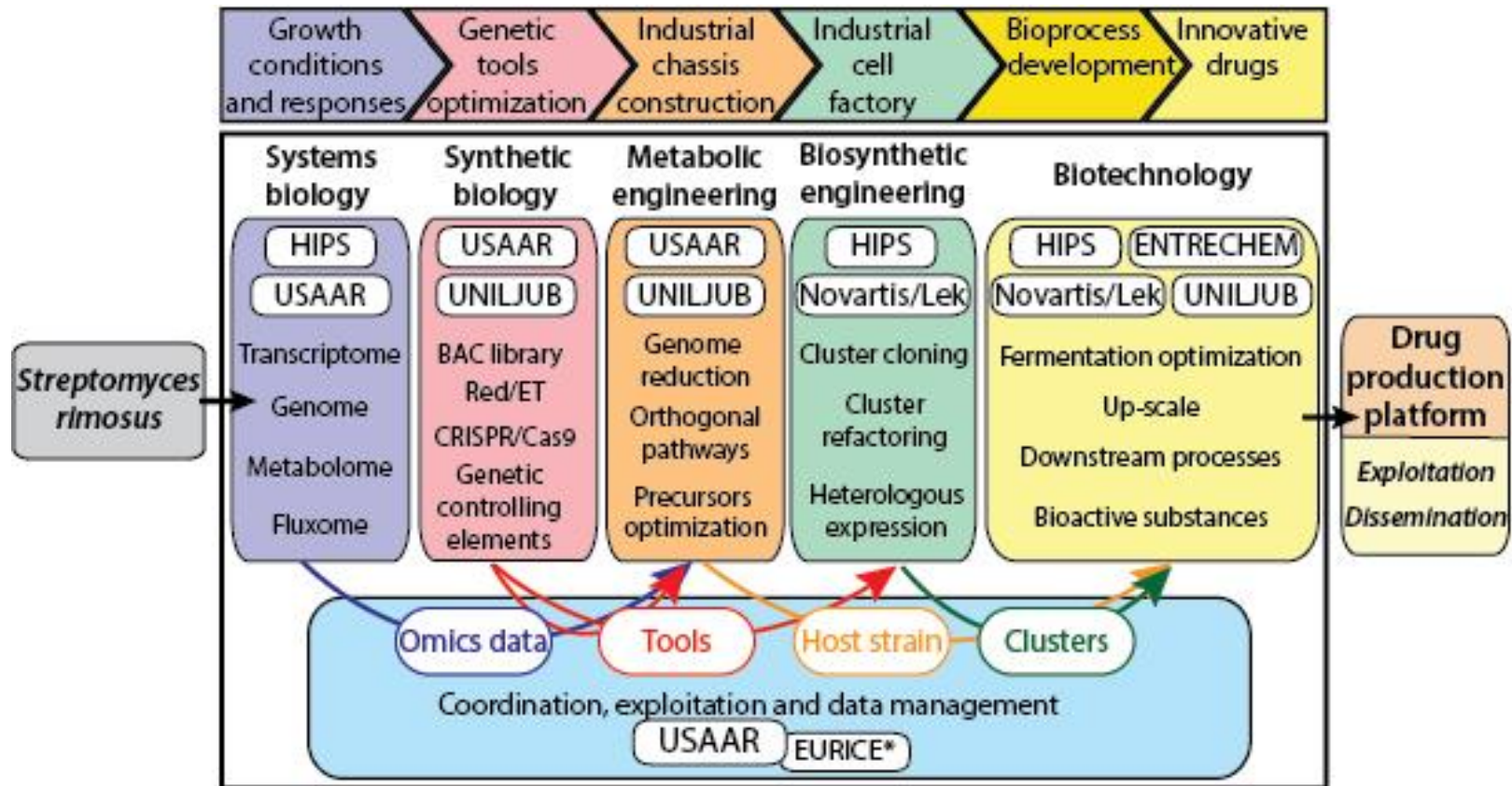
10m
deaths
by 2050

Costing
£66
trillion

Scientific Approach



- Scientific Approach and MISSION value chain:

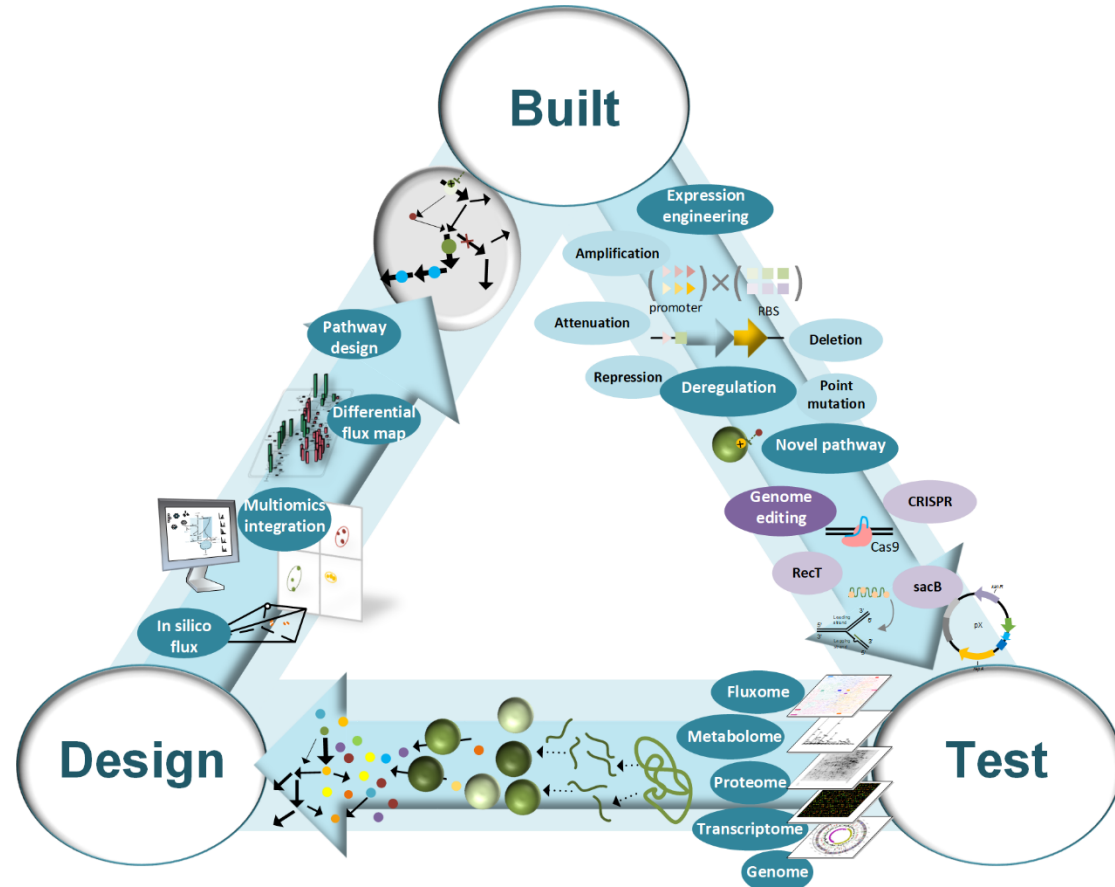


Objectives:

- ✓ Systems-wide profile of wild-type and industrial *S. rimosus*
- ✓ Analyze new strains created
- ✓ Integrate multi-omics data to understand cellular function and identify targets for metabolic engineering.
- ✓ GEM as premium knowledge and database.

Deliverables:

- ✓ Multi-omics data sets of initial and new strains
- ✓ Target identification for strain engineering
- ✓ Systems biology model



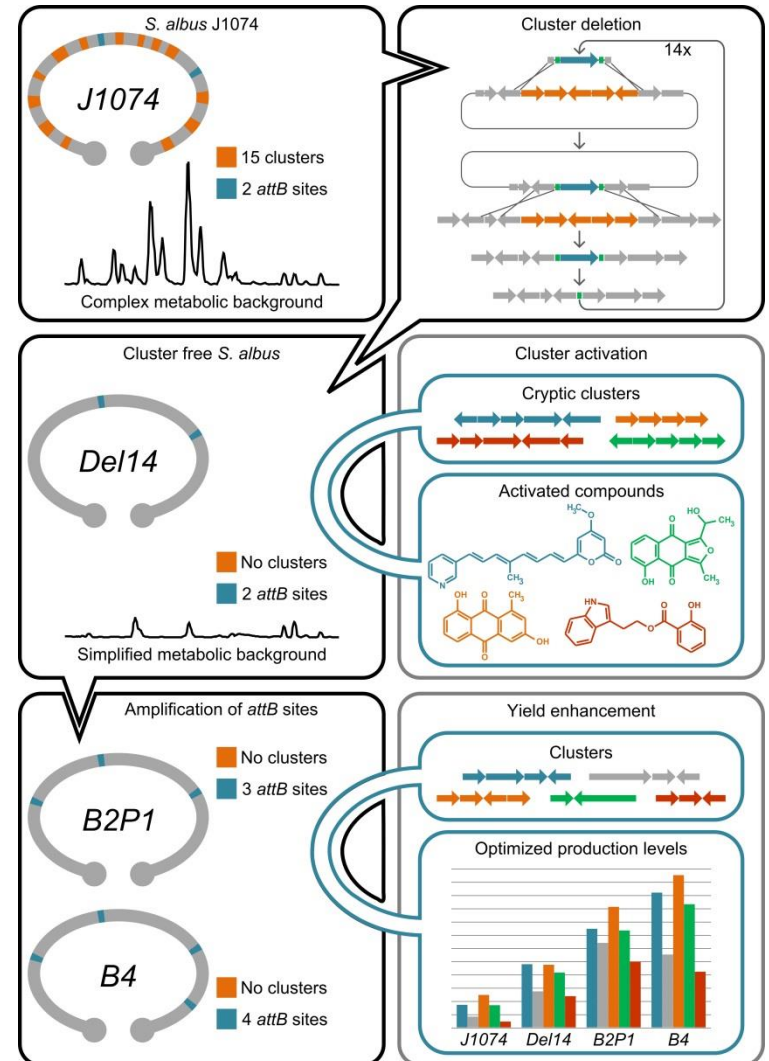
Becker and Wittmann (2018) Curr. Opin. Microbiol. In press

Objectives:

- ✓ To provide a standard operating procedure for streamlined genome engineering of an industrial *S. rimosus* strain.
- ✓ To generate the *S. rimosus* chassis strain for optimized heterologous production of bioactive natural products.
- ✓ To reconstruct and verify synthetic promoters, RBSs and terminators in an industrial *S. rimosus* strain.

Deliverables:

- ✓ Technology platform for the efficient genome engineering of *S. rimosus*
- ✓ First-generation *S. rimosus* chassis strain
- ✓ Final collection of improved *S. rimosus* chassis strains and their genome sequences

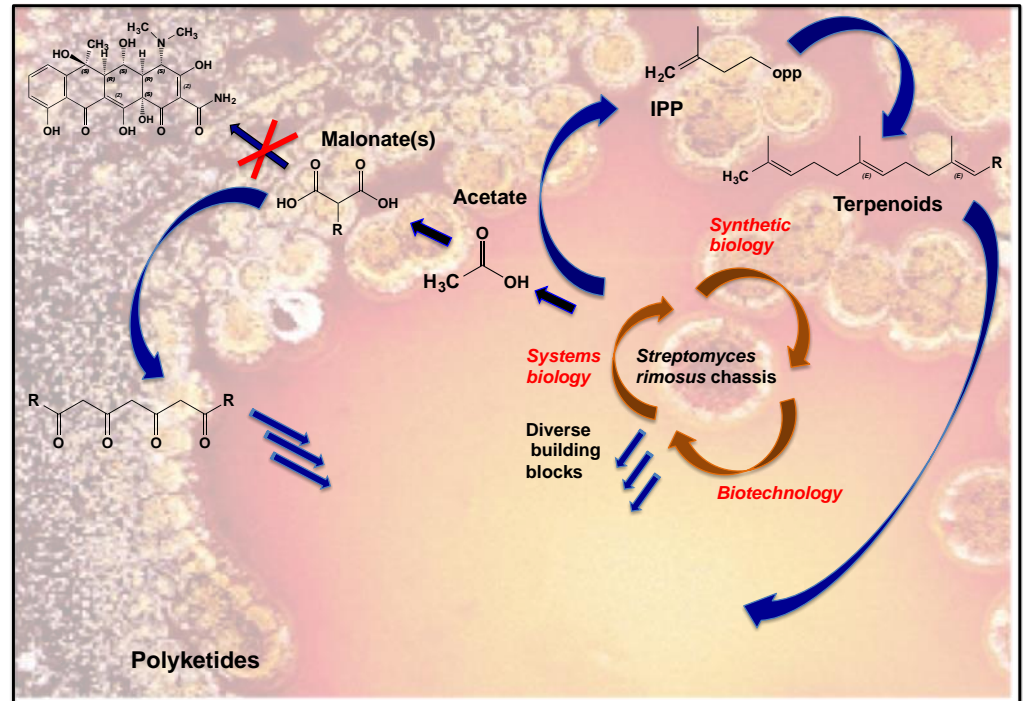


Objectives:

- ✓ Optimize building block, redox and energy supply.
- ✓ Implement novel precursor pathways to enhance the chemical space
- ✓ Implement orthogonal pathways to drive the production of e.g. polyketides, isoprenoids and other compounds (with WP2).

Deliverables:

- ✓ Bioinformatic data set on *S. rimosus* metabolic potential
- ✓ Cloned target genes (enzymes) or metabolic pathways
- ✓ Hosts carrying the new pathways



Objectives:

- ✓ Synthesize target gene clusters
- ✓ Re-engineer clusters
- ✓ Introduce clusters into suitable strains of *S. rimosus* and optimized versions (WP₃).
- ✓ Evaluate the productivity at lab scale.

Deliverables:

- ✓ Gene clusters encoding biosynthesis of target compounds
- ✓ Engineered gene clusters containing suitable promoters and regulatory elements located on replicative or integrative vectors
- ✓ Ready-to-use *S. rimosus* transformants

● Objectives:

- ✓ Re-adaptation of industrial media
- ✓ To scale down the process to lab-scale
- ✓ Strain testing at 5-L- and 20-L-fermenter scale.
- ✓ Down-stream processing.

● Deliverables:

- ✓ Re-optimized media and fermentation procedures at lab, 5-L and 20-L-fermenter scale
 - ✓ The best-performing strains tested and selected target compounds isolated
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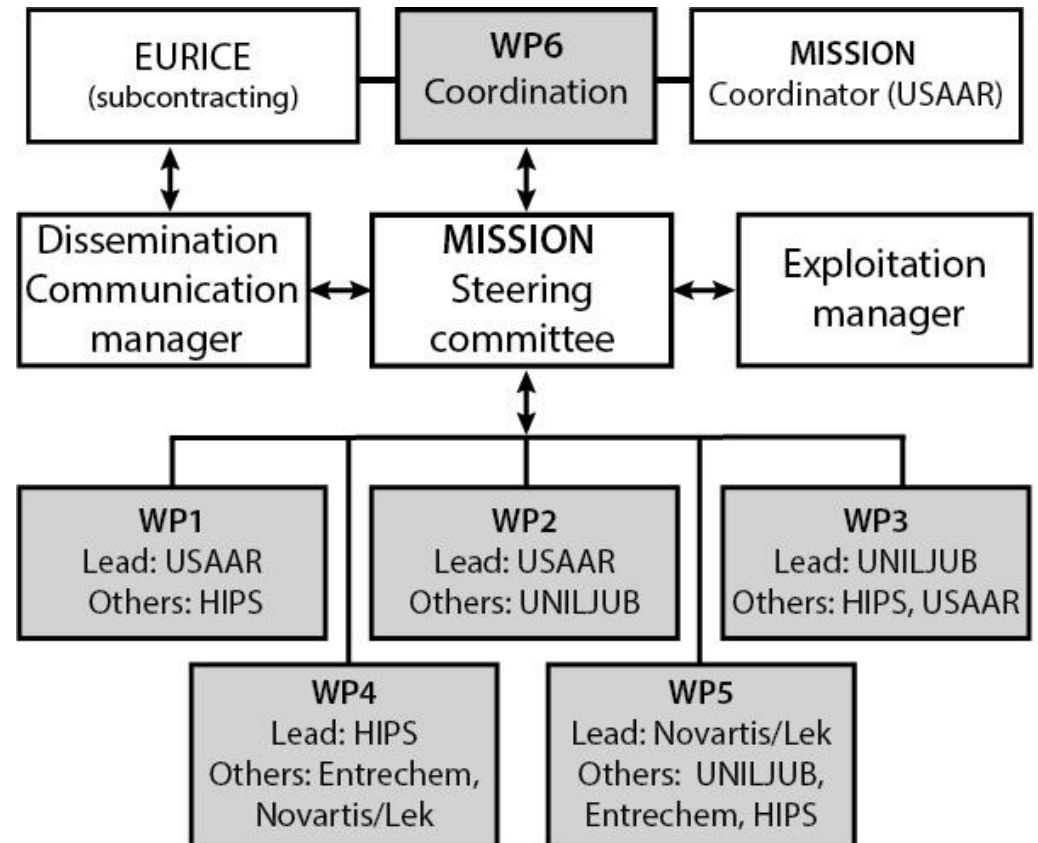
Project Plan WP6 – Coordination, exploitation and data management

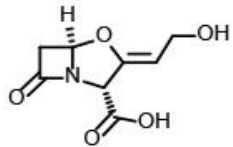
Objectives:

- ✓ To successfully organize and conduct project coordination activities, meetings, internal and external reporting, communication, data management, exploitation

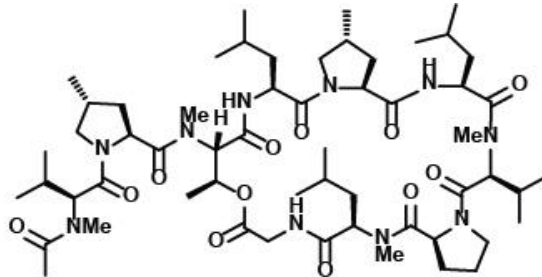
Deliverables:

- ✓ RTD reporting, financial reporting, publication, intellectual property
- ✓ Website
- ✓ Project presentation
- ✓ Project reports for progress report meetings (6-month basis)

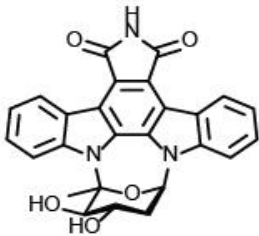




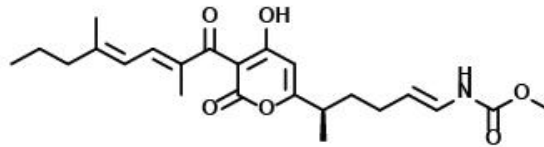
clavulanic acid



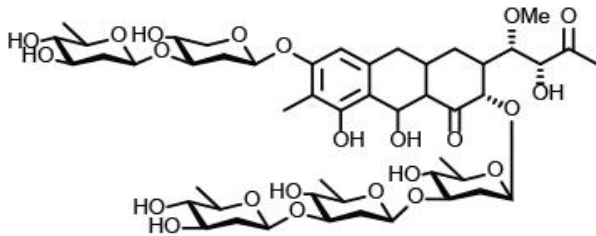
griselimycin



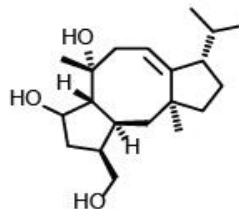
EC-70124



myxopyronin



EC-8042



cyclooctatin

- Widely exploitable microbial hosts for the production of industrial goods
- High value anti-infectives and anti-cancer drugs in sufficient amount and quality for further development

- What is proposed:

- ✓ Designing and creating novel streamlined *Streptomyces rimosus* cell factories

- What should be achieved:

- ✓ A ready-to-use bioactive small molecules production platform

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