Zurich University of Applied Sciences

TACKLING ANTIBIOTIC RESISTANCE BY TRANSCRIPTION REPRESSOR INHIBITORY COMPOUNDS[#, $]

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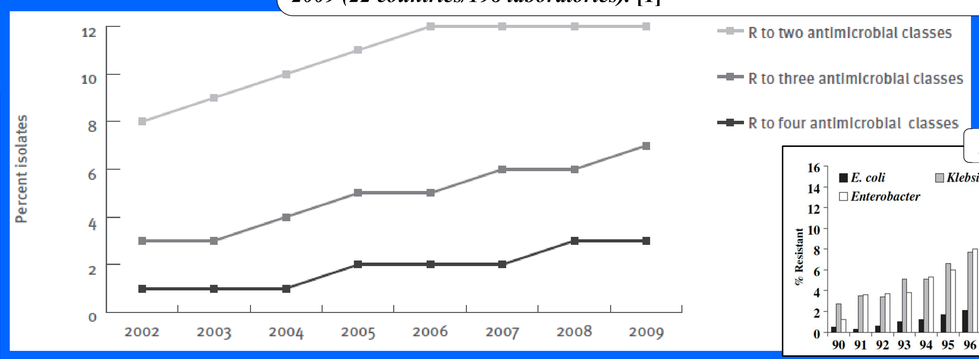
Increasing resistance

The past decades have seen a dramatic worldwide increase in human-pathogenic bacteria that are resistant to one or multiple antibiotics, as seen in the graphical and pictorial representations of several representative cases, which clearly show the issues of antibacterial resistances and the increasing occurrence.

More and more infections caused by resistant micro-organisms fail to respond to conventional treatment, and in some cases, even last resort "treasury" antibiotics.

In the hospital environment, increasing numbers of patients are infected by highly-resistant bacteria, for example methicillin-resistant *Staphylococcus aureus*.

***Combined resistance (R) of Escherichia coli to aminopenicilines, third-generation cephalosporins, fluoroquinolones and aminoglycosides. EARSS/EARS-Net 2002-2009 (22 countries/198 laboratories).* [1]**



***Resistance development.* [3]**

***Antibiotic resistance develops depending on its application history.* [2]**

Aminoglycosides

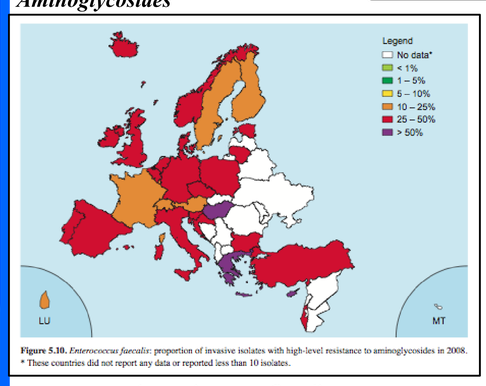


Figure 5.10. *Enterococcus faecalis*: proportion of invasive isolates with high-level resistance to aminoglycosides in 2008.
* These countries did not report any data or reported less than 10 isolates.

intensive use; first line

Vancomycine

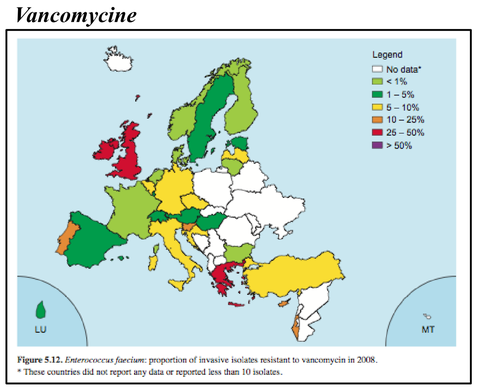
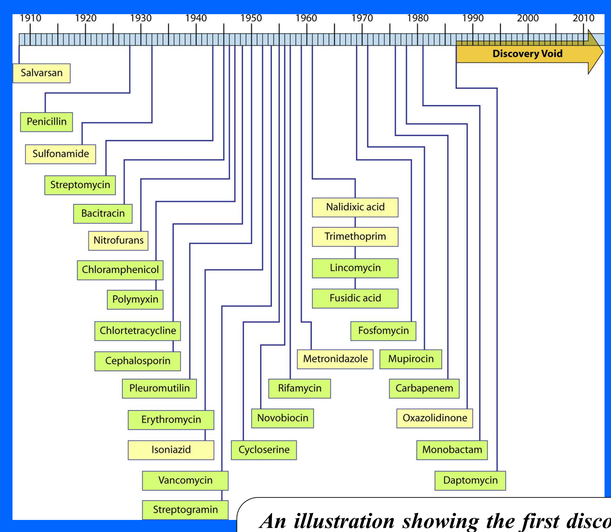


Figure 5.12. *Enterococcus faecium*: proportion of invasive isolates resistant to vancomycin in 2008.
* These countries did not report any data or reported less than 10 isolates.

treasury antibiotic, use in ICU as last option

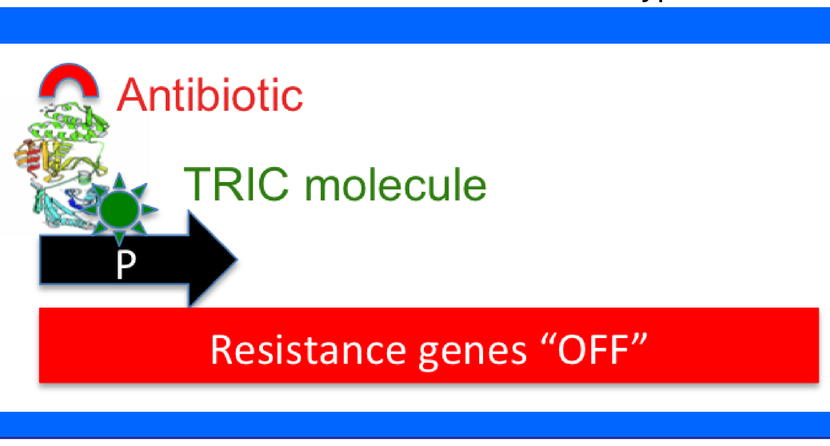
Discovery void



***An illustration showing the first discoveries of antibacterial classes, the "discovery void" since 1987 and the general decline in new antibacterials since 1960* [4]**

A discovery void has occurred due to several reasons:
- **Financial aspect (chronic diseases are more lucrative).**
- **Resistance (high risk of short period of efficacy after market approval; resistance development already observed in clinical trial).**
- **Novel antibiotics are kept as treasury drugs (low market share).**

Researchers at the ZHAW and the FHNW are collaborating with the biopharmaceutical company BioVersys AG in order to tackle antibiotic resistance. They have identified the need for certain types of small organic molecules, called Transcription Repressor Inhibitory Compounds (TRICs).

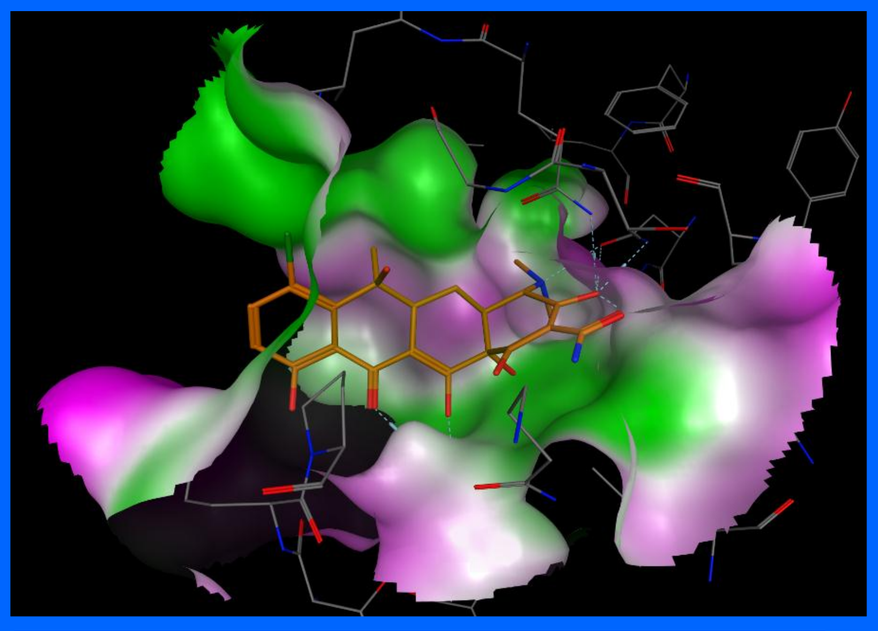


The TRICs are designed and synthesized by the organic and medicinal chemists at the ZHAW before they get tested at BioVersys AG for their biological activity and at the FHNW for their binding characteristics. In contrast to a wide range of traditional antibiotics for which bacteria have developed resistance, the TRICs do not interfere with the bacterial metabolism but work on the bacteria's genetic level. These TRICs switch off the bacterial defence program and the original antibiotic can kill the bacteria again.

The formulation of those small organic TRICs could be a combination with conventional antibiotics in one pill. Bacterial resistance, although being a complex and flexible mechanism, follows a general principle, which is genetically encoded. Resistance genes are clustered and regulated by global transcriptional regulators, which either recognize the antibiotic or its derivatives or act as stress sensors. Based on structural information of the transcription factors, the project partners develop compounds, which specifically inhibit global transcriptional regulators of bacterial resistance genes.

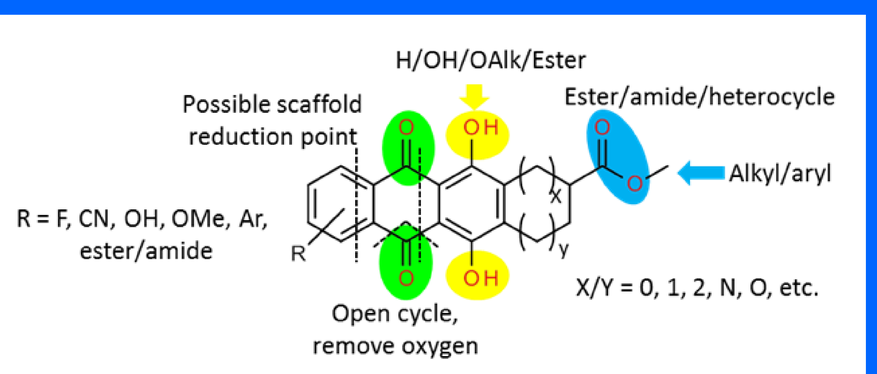
Rational structure-based drug design

Crystal structures of Tetracycline repressor protein (TetR) with bound ligands, such as 7-chlorotetracyline (as shown here) allow for detailed docking and computational studies within a rational design approach towards novel transcription repressor inhibitory compounds.



***Crystal structure of the active site of Tet repressor with bound 7-chlorotetracycline* [5]**

Medicinal chemistry approach



The complexity of the initial active scaffold (as shown here) has been transformed to an alternative structure to allow more modifications while remaining in the active site to increase potency as much as possible while having the freedom to manipulate the structure to include components that will affect the PK, PD and ADME profiles to produce a small molecule API.

Advantages of this approach:

- **disable the possibility for further development of antibiotic resistances.**
- **allows effective use of conventional, previously approved antibiotics.**

References

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