DNA topoisomerases as targets for antibacterial chemotherapy

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Unlocking Nature's Diversity

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Enzymes:
Gyrases - *E. coli, M. tuberculosis, S. aureus, Arabidopsis*, *Plasmodium*
Topo IV - *E. coli, S. aureus*
Topo VI – *Methanosarcina mazei*, *Arabidopsis*, *Plasmodium*
Other topo IIs (yeast, human)

Drugs & toxins:
Quinolones (e.g. ciprofloxacin)
aminocoumarins (e.g. novobiocin)
simocyclinones, naphthoquinones,
CcdB (toxin-antitoxin)
Microcin B17
Chemical libraries

Inspiralis

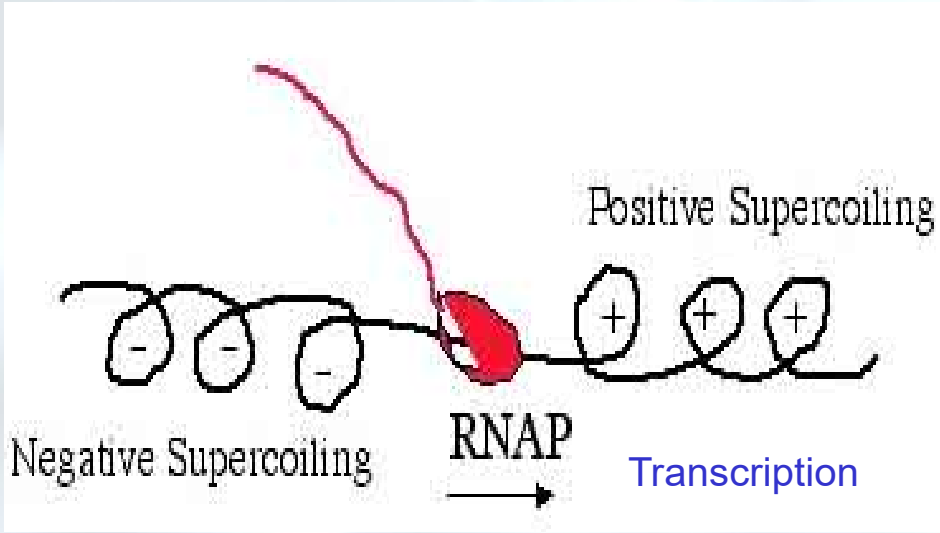
Tools:
X-ray crystallography, NMR, etc.
Enzymology, Molecular Biology, Genetics, HTS
Chemical Genetics

Natural products:
Novel plant toxins/
insect gut bacteria
Galleria

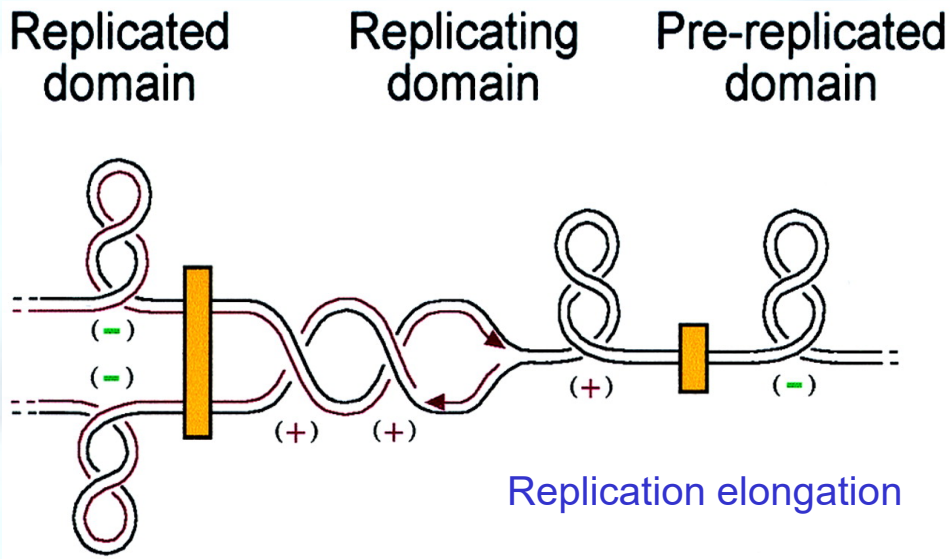
Outputs:
Fundamental knowledge on topoisomerase structure/mechanism/physiological role
Understanding drug action and antibiotic resistance; development of novel agents

DNA topology & DNA topoisomerases

Various biological processes lead to DNA topological problems, e.g. introduction of unwanted supercoiled and catenanes



Transcription

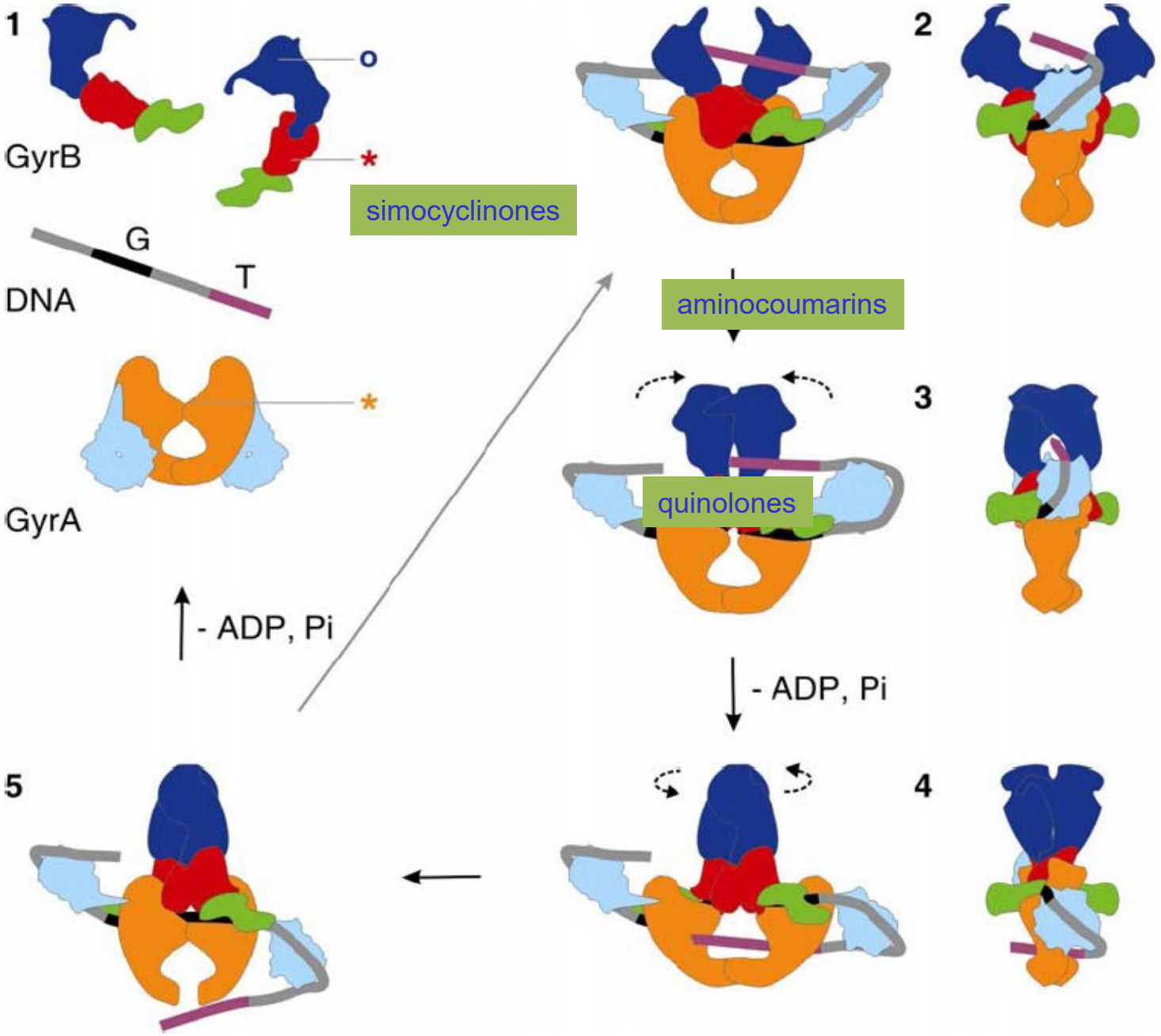


Replication elongation

Topos, two types:
I → single-strand breaks
II → double strand breaks

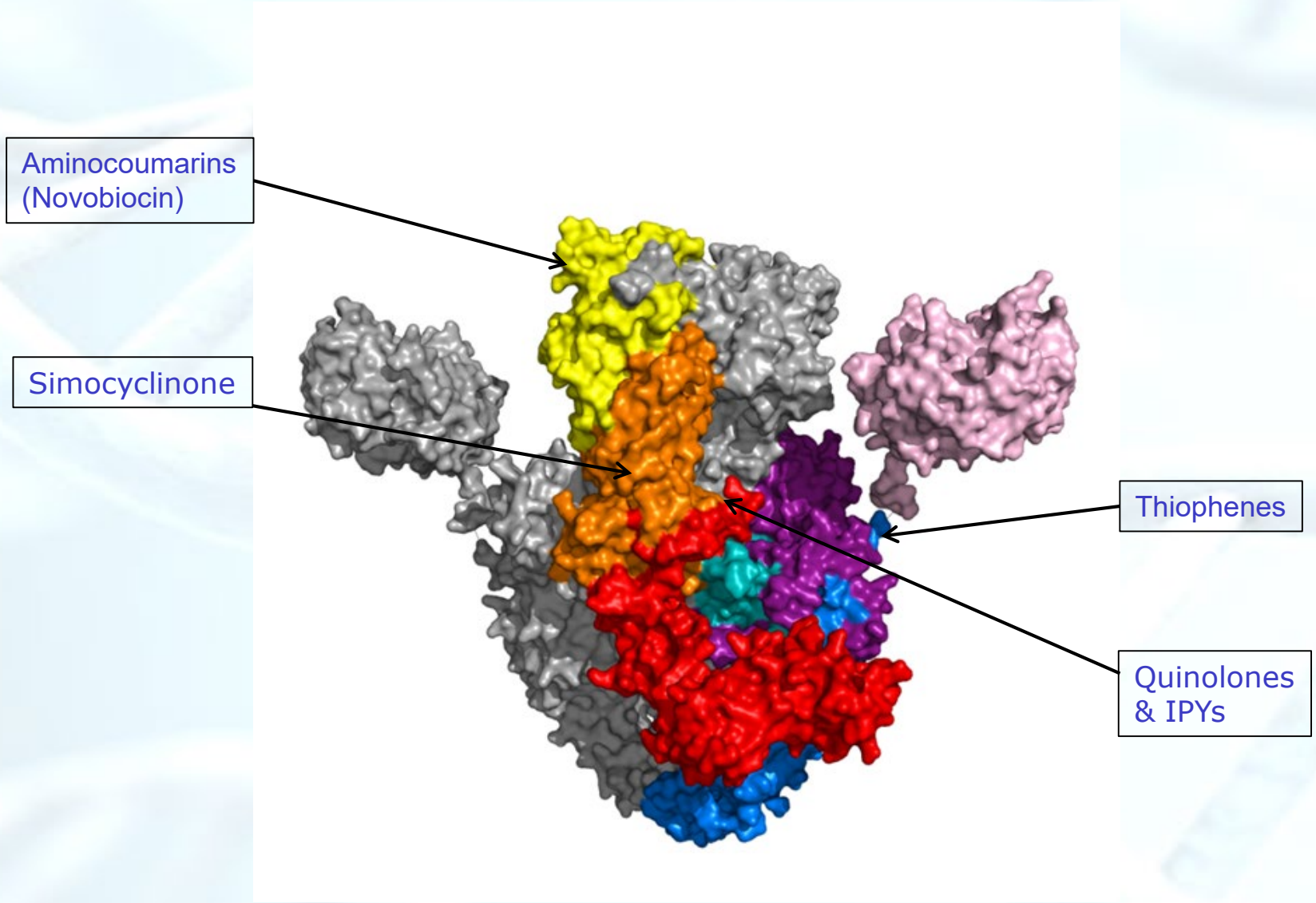
- Currently no antibiotics targeted to type I topos.
- Type II topos, DNA gyrase & topo IV highly successful antibiotic targets

Mechanism of DNA supercoiling by gyrase



Costenaro, *et al.* (2007). *Structure* ***15,*** 329-39.

Sites of drug action on DNA gyrase



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- Germe *et al. Nucleic Acids Res*. 2018; **46**:4114-28.
- Bush *et al. The Biochemist*. 2018; **40**:26-31.
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- Chan *et al. Proc Natl Acad Sci U S A*. 2017; **114**:E4492-E500.

Funding & Consortium/Collaboration Activities

- ENABLE – EU: IMI (ND4BB) consortium
- Mm4tb – EU consortium; now finished; 2 TB drugs in clinal trials
- AMR on the NRP
- Screening services and provision of reagents (via Inspiralis)
- Scientific Advisory Board of Antibiotic Action

Bottlenecks

What we do is a very small slice of a very big cake and our contribution to the AMR effort has to be collaborative. We need:

- Novel compounds
- Funding (at the appropriate scale)
- Ready access to appropriate collaborators

Proposed screening cascade for discovery of new antibacterials