



Synthesis of compounds with antituberculous activity

(STCU project 4932)

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Antituberculosis drugs

- **inhibitors of synthesis of fatty acids** (isoniazid, pyrazinamide, ethionamide, prothionamide, thiacetazone, RA-824, ORS-67683)
- **inhibitors of biosynthesis of peptidoglycan and arabinogalactan** (ethambutol, D-cycloserine, amoxicillin, clofazimine)
- **inhibitors of protein synthesis** (streptomycin, kanamycin, amikacin, capreomycin, viomycin, clarithromycin, linezolid)
- **inhibitors of synthesis of nucleic acids** (rifampin, rifapentin, fluoroquinolones)
- **inhibitors of dihydrofolate reductase**
- **inhibitors of ATPase**
- **inhibitors of mycobacterial cytochrome p450 mono-oxygenases**
- **FtsZ targeting compounds**
- **inhibitors of synthesis of amino acids, monophosphate kinases, signal kinases**
- **inhibitors with the mixed or unknown mechanisms of action**



Modified from Larkman and Adhikari, 1997; and Ma et al., 1996

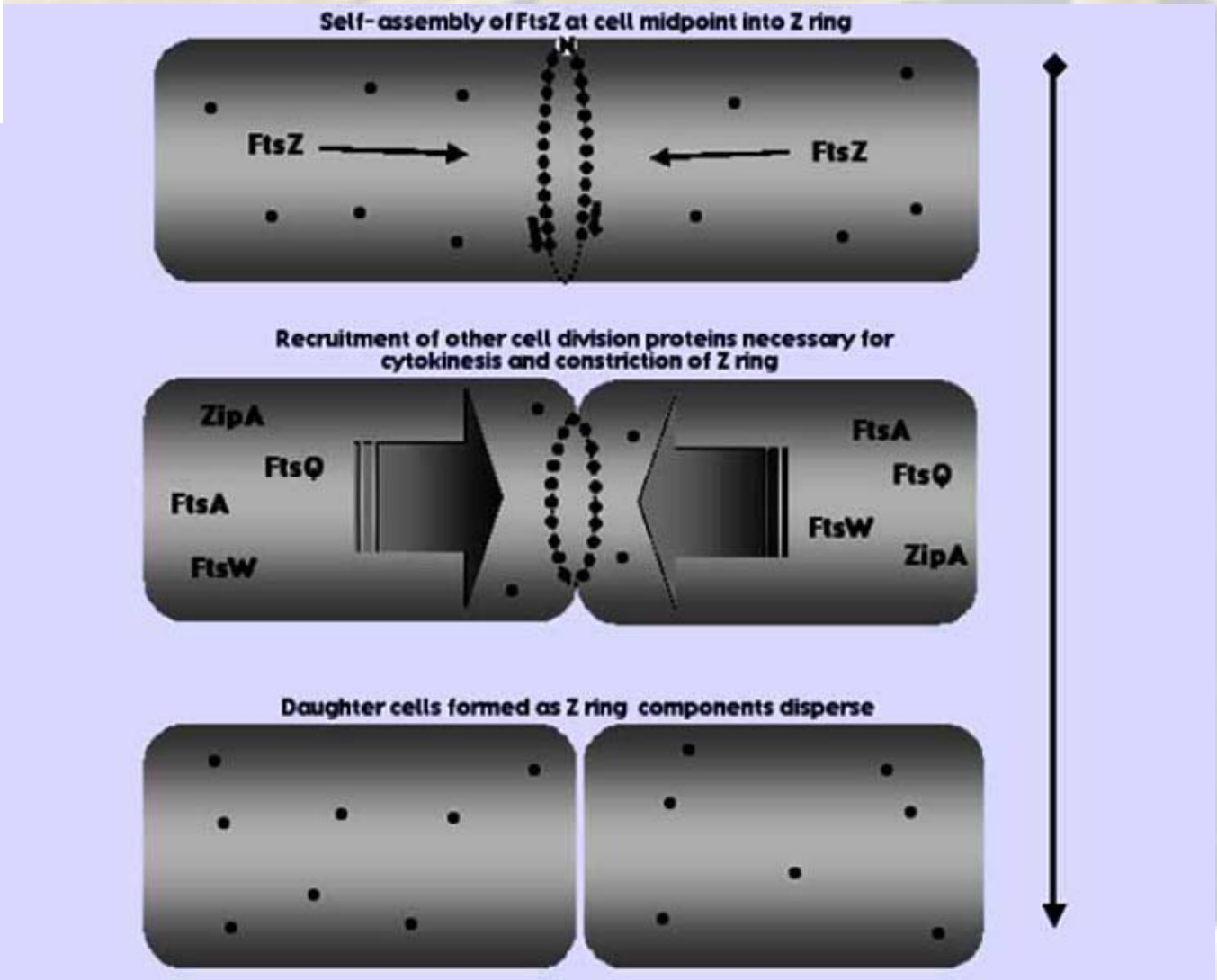
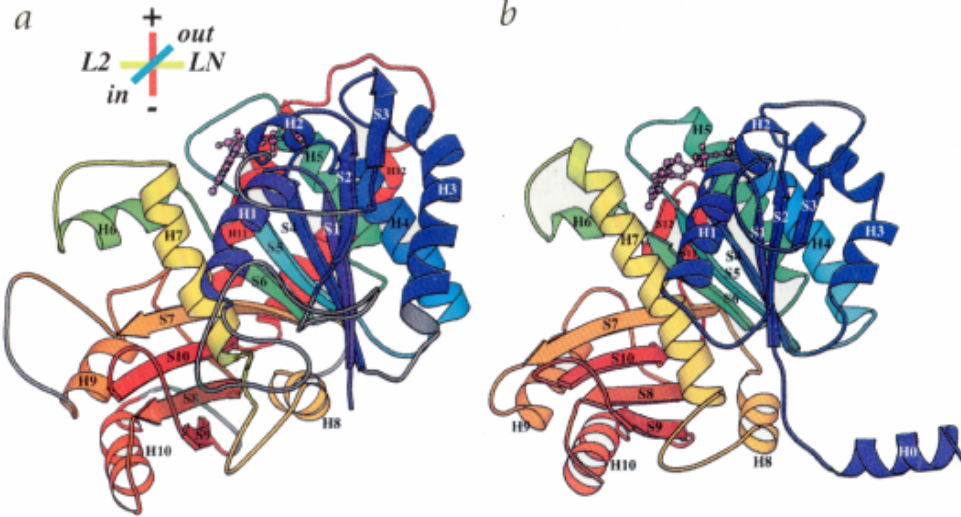
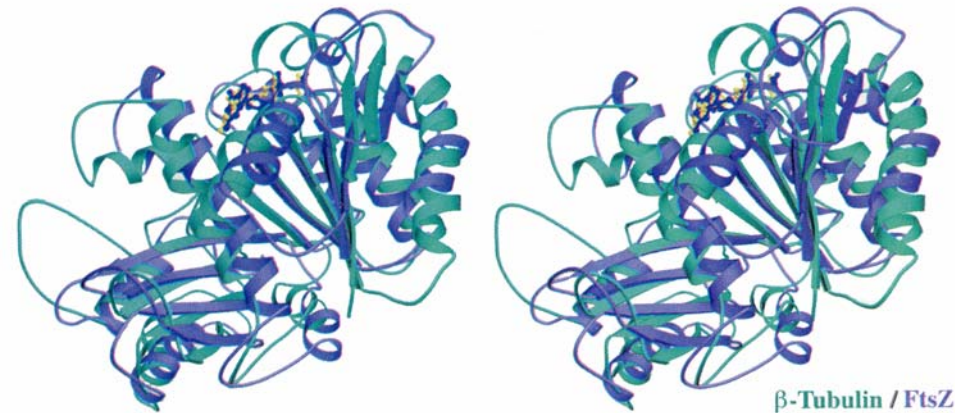


Diagram of prokaryotic cell division and the Z-ring
(Ojima et al. Current Topics in Medicinal Chemistry, 2007, Vol. 7, No. 5)



**Ribbon diagrams for β -tubulin (pig) (a)
and FtsZ (Methanococcus jannaschii) (b)**



**Stereo view of the superposition
of the tubulin (pig) and FtsZ (Methanococcus jannaschii)**

Compounds targeting FtsZ

Viriditoxin

Zantrins

GTP Analogue BrGTP

Sanguinarine

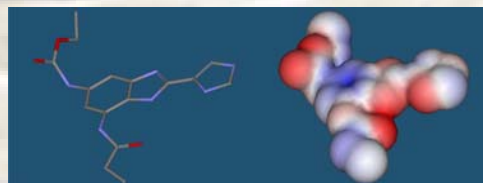
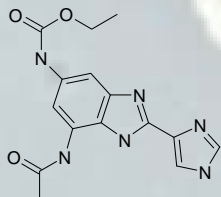
Bis-ANS

Thiabendazole and Albendazole

2-Alkoxy carbonylaminopyridines

Taxanes

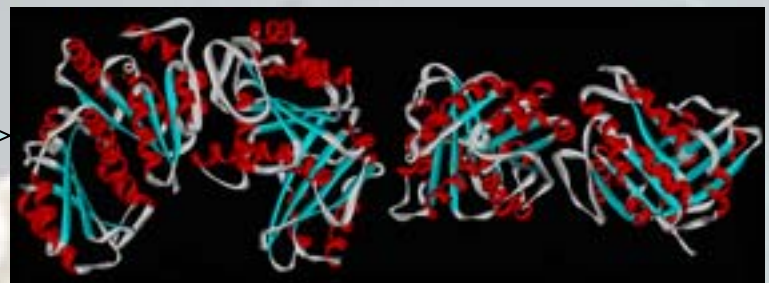
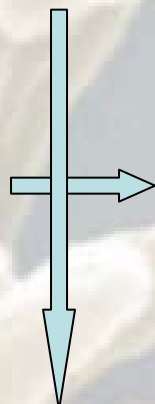
ethyl[6-amino-2,3-dehydro-4-phenyl-1H-pyrido(4,3-b)(1,4)diazepin-8-il]carbamate



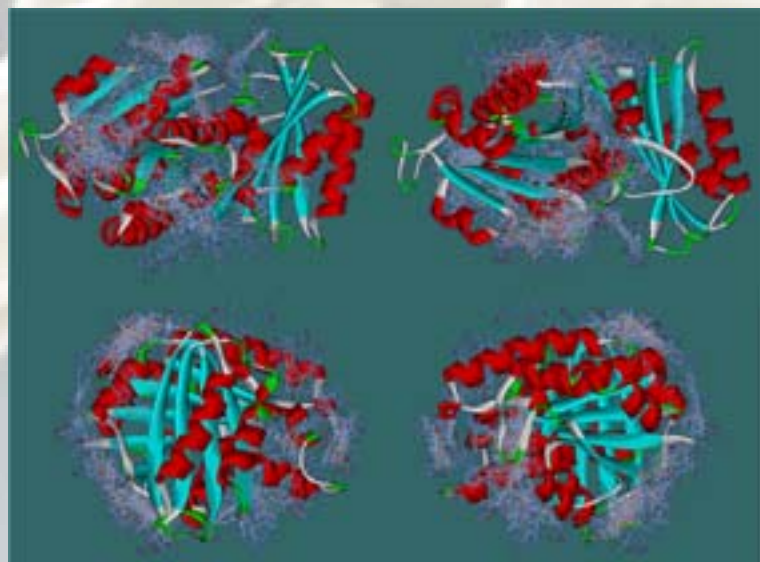
Three-dimensional structure of ethyl[6-amino-2,3-dehydro-4-phenyl-1H-pyrido(4,3-b)(1,4)diazepin-8-yl]carbamate

1	10	20	30	40	50	60	70	80	90	100
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PfzNdeI	G G G T G T G G A P P V A S I A R K G A L T V G V T R P F S F E G R R S N Q A D G I A A L R E S C D L I V I P M D L L Q M D K A A V L M D A P F S A G E F L L G S Q G I T G L I T F P									
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Alignment of FtsZ protein sequences (*Mycobacterium tuberculosis*), obtained from different sources



Preliminary three-dimensional model of FtsZ (*Mycobacterium tuberculosis*)



Docking of ethyl[6-amino-2,3-dehydro-4-phenyl-1H-pyrido(4,3-b)(1,4)diazepin-8-yl]carbamate with FtsZ (*Mycobacterium tuberculosis*)

Strategy of the project

Development of the improved model of spatial structure *Mycobacterium tuberculosis* FtsZ



Development of spatial models of different benzimidazoles/phenylcarbamates with next identification of their structural parts directly responsible for interaction with FtsZ



Screening of mycobacterial FtsZ to identify appropriate binding site, based on a homology between tubulin and FtsZ surface



Docking of studied compounds into identified found interactive sites and analysis of interaction features: an estimation of complexes stability, refinement of results of the stage 2 concerning the benzimidazole/phenylcarbamate active groups



Design of new drugs with increased activity against mycobacterial FtsZ by the way of replacement of groups-deputies in the structure of benzimidazole/phenylcarbamate



Chemical synthesis of the developed compounds



Experimental verification of activity of synthesized drugs on *in vitro* polymerization models of *Mycobacterium tuberculosis* FtsZ

Next steps in the framework of this project

- Patenting of rational methodology of design of benzimidazole and phenylcarbamate antimicobacterial drags;
- Patenting of the benzimidazole drugs, synthesized during a project, and show strong depolymerising effect in relation to the *Mycobacterium* FtsZ protein;
- Entering into cooperation with new partners from Ukraine and abroad, with the purpose of comprehensive testing of the synthesized drugs on living cultures of *Mycobacterium tuberculosis*;
- Marketing research and contract negotiations with agents of the pharmacological companies' in relation to commercialisation introduction of described methodology, or/and developed by us drugs, in dependence on market requirement.

Project staff

Project manager

Prof. Yaroslav Blume

Modeling, docking and chemical design

Dr. Pavel Karpov

Dr. Alexej Nyporko

Chemical synthesis (Inst. of Organic Chemistry, Kiev)

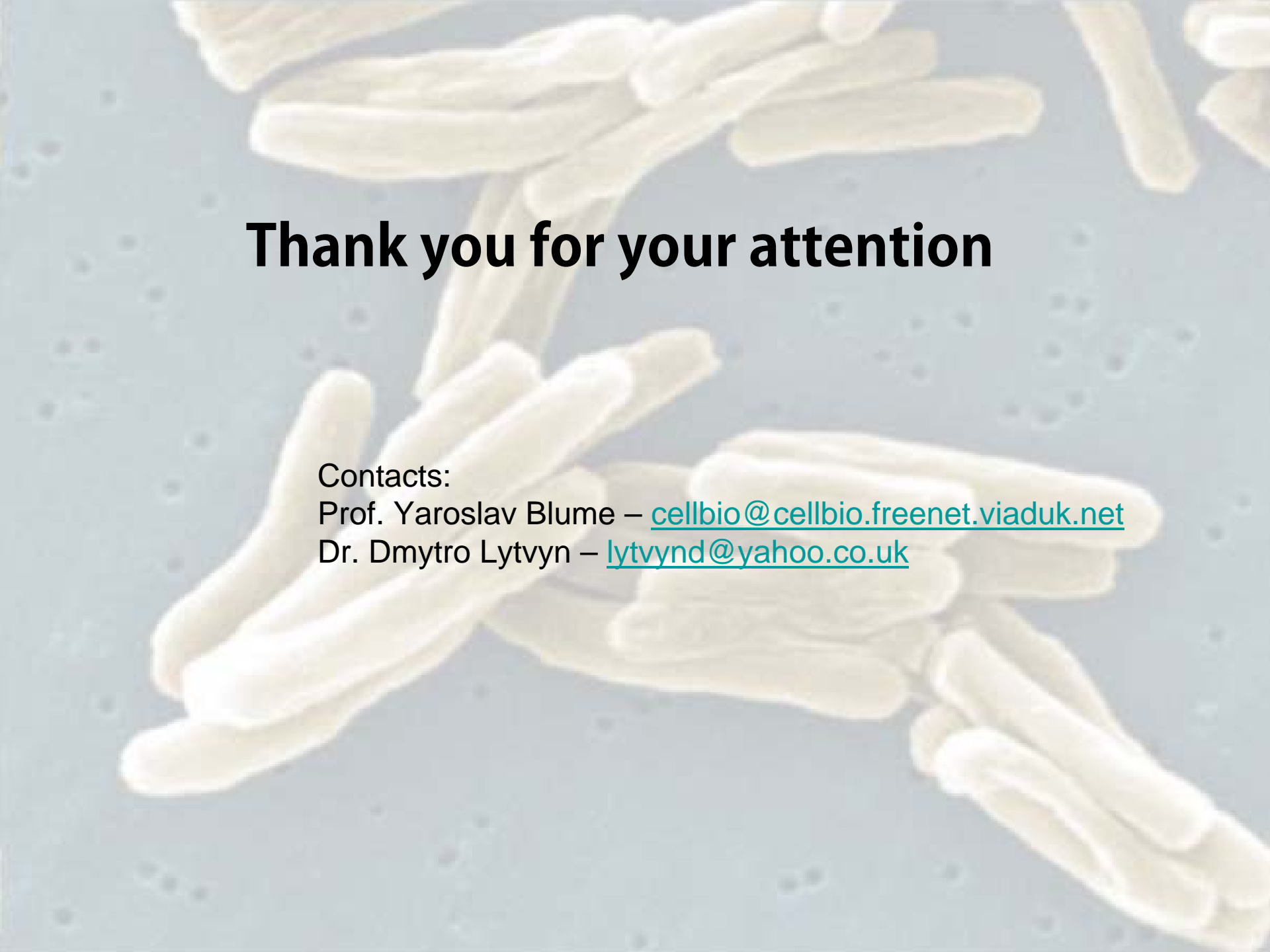
Prof. Myron Lozynskij

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Screening of new compounds

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Thank you for your attention

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