CA21111 - One Health drugs against parasitic vector borne diseases in Europe and beyond (OneHealthdrugs)

Modelling of binding affinity constants of a potential new class antiparasitic drugs

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"Novel leads and drugs for vector borne diseases: Targets and off targets (toxicity and ecotoxicity) and mechanism of action"

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Current breakthrough in research of nucleoside drugs (1)

Target: Adenosine kinase (ADK; EC 2.7.1.20) is phosphotransferase type of enzyme that converts the purine ribonucleoside adenosine into 5′-adenosine-monophosphate.

$$\text{Adenosine} + \text{ATP} \xrightarrow{Mg^{2+}} \text{5′-adenosine-monophosphate} + \text{ADP}$$

- ADK is an upstream regulator of adenosine,
- extremely short plasma half-life (<1 s),
- ADK Inhibition increase intracellular adenosine which passes out of the cell via passive diffusion or via nucleoside transporter(s) to activate nearby cell-surface adenosine receptors.
- ADK inhibition in alternative mechanism for activation of adenosine receptors and production of adenosine-associated potential inhibitors.

Current breakthrough in research of nucleoside drugs (2)

- Parasitic protozoa are incapable of *de novo* synthesis of the purine rings
- Biophysical and biochemical characteristics of ADK isolated form *Leishmania Donovan* are different then ADK from other eukaryotic sources regarding to the mode of action.
- *T. brucei* and *Leishmania* differences: Adenine amidotransferase, a *Leishmania*-specific enzyme that does not exist in other studied trypanosomatids or in mammalian cells in deamination of adenine

Objective:

- *In silico* molecular modelling based on docking study for testing binding affinity of antiparasitic nucleoside drugs such tubercidin and other lead compounds testing the hypothesis whether ADK of Leishmania is less effective in phosphorylation reaction of nucleoside analogues then *Tb*ADK.

Methodology:

Target site: Adenosine Kinase (AK) L. Mexicana (LmexAK) T. brucei AK (TbAK) Both, tested on cell toxicity.

No available experimentally resolved structure of TbAK and LmexAK

Leads, testing drugs: AK inhibitors (nucleoside analogues drug class)

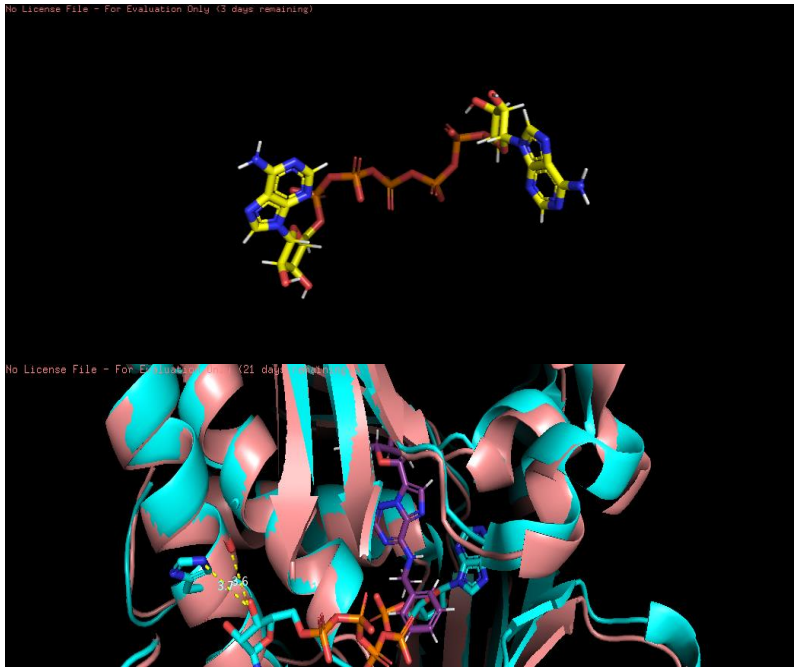
Utilizing amino acid sequences from genes of TbAK and LmexAK (TriTrypDB) https://tritrypdb.org/tritrypdb/app Generated structures for TbAK and LmexAK (amino acids sequences in software package) https://alphafold.ebi.ac.uk/

Optimizing the protein structures (PyMol software package) https://www.pymol.org/

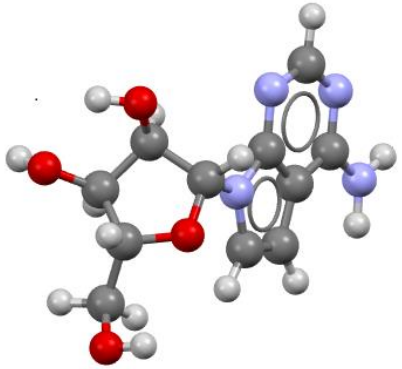
Docking testing: interaction AK with lead compounds (drugs): Software package https://github.com/gnina/gnina

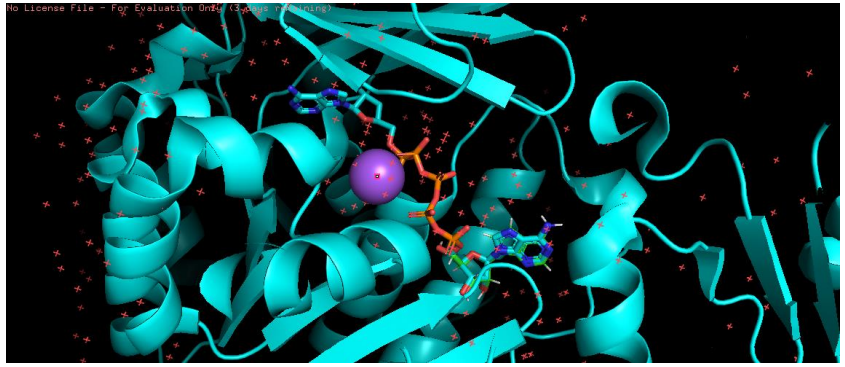
Results (*in process of publishing…)*:

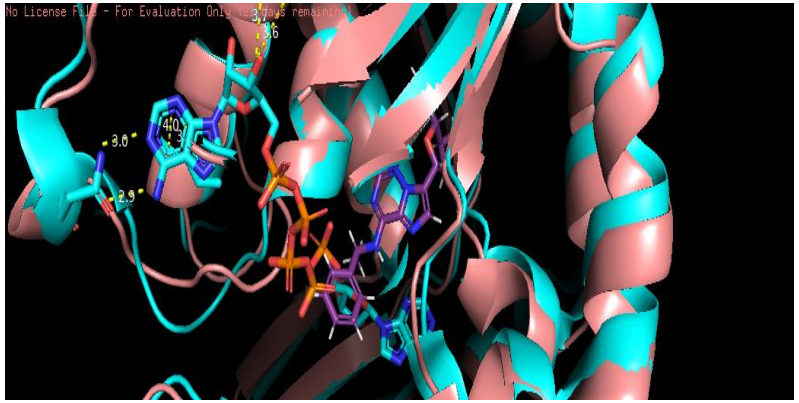
Optimized structures based on drug – protein interactions, affinity binding constants based on binding energy minimal values,
structural –activity relationship



Tubercidin appears to be the strongest binder, in addition to the co-crystallized ligand 3otx (TbAK)







Thak you for your attention

Thank for STSM CA 21111