Summary of PhD Thesis

András Benedek: *Key structural details regulate oligomerization, cellular localization and inhibition of trimeric dUTPases*

The most important publications: (IF: impact factor, IC: independent citation, AC: author contribution among those persons who has not obtained their PhD degree).

1. **Benedek A**, Horváth A, Hirmondó R, Ozohanics O, Békési A, Módos K, Révész Á, Vékey K, Nagy GN, Vértessy BG. Potential steps in the evolution of a fused trimeric all-β dUTPase involve a catalytically competent fused dimeric intermediate. (2016) FEBS J. 2016 Sep;283(18):3268-86. Editor's choice.
IF (2016): 4.237. IC: 1. AC: 100%.

2. **Benedek A**, Pölöskei I, Ozohanics O, Vékey K, Vértessy BG. The Stl repressor from *Staphylococcus aureus* is an efficient inhibitor of the eukaryotic fruitfly dUTPase. (2017) FEBS Open

Bio. 2017 Dec 27;8(2):158-167. Fig. 1A chosen for cover illustration of FEBS Open Bio. IF (2017/2018): 1.782. AC: 95%.

3. **Benedek A**, Temesváry-Kis F, Khatanbaatar T, Leveles I, Surányi ÉV, Szabó JE, Wunderlich L, Vértessy BG. (2019) The Role of a Key Amino Acid Position in Species-Specific Proteinaceous dUTPase Inhibition. Biomolecules. 2019 Jun 6;9(6).
IF (2019): 4.694. AC: 70%.

4. Róna G, Pálinkás HL, Borsos M, Horváth A, Scheer I, **Benedek A**, Nagy GN, Zagyva I, Vértessy BG. (2014) NLS copy-number variation governs efficiency of nuclear import--case study on dUTPases. FEBS J. 2014 Dec;281(24):5463-78.
IF (2014): 4.001. IC: 1. AC: 15%.

The enzyme dUTPase is supposed to prevent uracil incorporation into DNA via hydrolysis of 2'-deoxyuridine 5'-triphosphate (dUTP) into its monophosphate (dUTP), thereby dissipating the amount of energy being stored in the triphosphate group for incorporation of the uracil base. If dUTPase is blocked in a replicating cell, the probability of thymine-less cell death dramatically increases due to increased uracil incorporation into the genetic code. Our aim is to induce this process in therapeutic applications aiming to fight against cancer cells or pathogenic microorganisms via inhibition of dUTPase in a species-specific manner. In order to design species-specific inhibitors a detailed knowledge on structural similarities and differences between dUTPase homologues is needed. Being devoted to reach this goal, on the one hand I successfully characterized the so far unraveled covalent pseudo-heterotrimeric dUTPase structural arrangement using the *Drosophila virilis* dUTPase as a model.

On the other hand, I have investigated the interaction characteristics of two trimeric dUTPase homologues – the *Drosophila melanogaster* and the *E. coli* dUTPase – with protein Stl, a proteinaceous dUTPase inhibitor. I have shown that a remarkable difference may be present in the maximal degree of Stl mediated inhibition among dUTPase homologues. Consequently, the trimeric dUTPase protein sequences involved in binding to Stl are only partially conserved through evolution from bacteria to eukaryotes. I have also made clear that protein Stl may be a universal inter-action partner but not a universally effective inhibitor of dUTPases. The explanation for this lies behind the existence of minor structural differences among dUTPase homologues. These minor differences may serve as a basis for upcoming design of species-specific dUTPase inhibitory peptides.