LIFE SCIENCES

Biothermodynamics of small molecule interaction with target proteins for drug discovery

Vilnius University

Keywords: protein-ligand interactions, high-throughput screening, ThermoFluor (thermal shift assay, differential scanning fluorimetry), isothermal titration calorimetry, organic synthesis, recombinant protein production, thermodynamics, kinetics, enzyme inhibition, compound evaluation in cancer cell cultures, carbonic anhydrase, chaperone Hsp90, histone deacetylases.

Research group activities

We are experts in compound library screening to discover compounds that interact / inhibit recombinant human drug target proteins.

We study the thermodynamics and kinetics of protein – small ligand binding and are interested in the fundamental understanding of the protein – ligand molecular recognition process. A system of 12 human carbonic anhydrases and over 900 synthetic sulfonamide-bearing ligands is being studied both energetically and structurally. Nearly 100 protein-ligand crystal structures were solved and deposited to the PDB. Over 5000 reactions were measured yielding the Gibbs energy, enthalpy, entropy, and volume correlations with the chemical and crystallographical structural features of the ligand and protein. Most promising compounds that bound CA IX, an anticancer target, with sub-nanomolar affinity and significant selectivity over other human isoforms, are being tested in cancer cell lines, and in animals for biological development as anticancer drugs.

Proposal

Detailed thermodynamic characterization of the interaction could be performed. Compounds could be screened in cancer cell cultures. Recombinant proteins could be cloned, expressed in bacteria or mammalian cells, and chromatographically purified upon request. Recombinant human carbonic anhydrases (12 isoforms), chaperones Hsp90 (2 isoforms), their various constructs and mutants are available. A library of over 900 synthetic aromatic sulfonamide compounds as CA inhibitors is available.

Meet our team

- More than 30 researchers and students, led by Prof. Dr. **Daumantas Matulis** and allocated to 4 groups:
- molecular and cellular biology headed by Dr. **Jurgita Matulienė**
- organic synthesis headed by Dr. **Virginija Dudutienė**
- molecular modeling headed by Dr. **Vytautas Petrauskas**
- biothermodynamics headed by Prof. Dr. **Daumantas Matulis**

Research outcomes

Most important publications

Over 70 peer-reviewed scientific publications in the journals including: The Journal of the American Chemical Society, Journal of Medicinal Chemistry, Biochemistry, Nucleic Acids Research, Analytical Biochemistry, Biophysical Chemistry and other.

- **Wagner, T. Greschik, H., Burgahn, T., Schmidtkunz, K., Schott, A.K., McMillan, J., Baranauskienė, L., Xiong, Y., Fedorov, O., Jin, J., Oppermann, U., Matulis, D., Schule, R., Jung, M.** 2016. Identification of a small – molecule ligand of the epigenetic reader protein Spindlin1 via a versatile screening platform. Nucleic Acids Research. 44(9): e88.
- **Linkuvienė, V., Matulienė, J., Juozapaitienė, V., Michailovienė, V., Jachno, J., Matulis, D.** 2016. Intrinsic thermodynamics of inhibitor binding to human carbonic anhydrase IX. Biochymica et Biophysica Acta. 1860: 708-718.
- **Kazokaitė, J., Ames, S., Becker, H., Deitmer, J.W., Matulis, D.** 2016. Selective inhibition of human carbonic anhydrase IX in Xenopus oocytes and MDA-MB-231 breast cancer cells. Journal of Enzyme Inhibition and Medicinal Chemistry. In press.
- **Juozapaitienė, V., Bartkutė, B., Michailovienė, V., Zakšauskas, A., Baranauskienė, L., Satkūnė, S., Matulis, D.** 2016. Purification, enzymatic activity and inhibitor discovery for recombinant human carbonic anhydrase XIV. Journal of Biotechnology. In press.
- **Linkuvienė, V., Krainer, G., Chen, W.-Y., Matulis, D.** 2016. Isothermal titration calorimetry for drug design: Precision of the enthalpy and binding constant measurements and comparison of the instruments. Anal. Biochemistry. 515: 61-64.
- **Kazokaitė, J., Aspatwar, A., Kairys, V., Parkkila, S., Matulis, D.** 2016. Fluorinated benzenesulfonamide anticancer inhibitors of carbonic anhydrase IX exhibit lower toxic effects on zebrafish embryonic development than ethoxzolamide. Drug and Chemical Toxicology. In press.

Patents and patent applications:

Synthetic compounds were patented in 6 patents and applications in Europe and USA.

- Benzimidazo[1,2-c][1,2,3]thiadiazol-7-sulfonamides as inhibitors of carbonic anhydrase and the intermediates for production thereof (EP2054420 B1)
- 5-aryl-4-(5-substituted 2,4-dihydroxyphenyl)-1,2,3-thiadiazoles as inhibitors of Hsp90 chaperone and the intermediates for production thereof (US8314132 B2; EP20080766671)
- Fluorinated benzenesulfonamides as inhibitors of carbonic anhydrase (US20150266900 A1; EP2914583 A1)

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