Laboratory of Biothermodynamics and Drug Design

Dr. Daumantas Matulis
Head of laboratory
Chief Scientist
phone: 370 5 2691884
fax: 370 5 2602116
e-mail: matulis@ibt.lt

Gervydas Dienys, Prof.
Henrikas Šebėka, Ph. D.
Mindaugas Zaveckas, Ph. D.
Asta Zubrienė, Ph. D.
Virginija Dudutienė, Ph. D.
Jurgita Matulienė, Ph. D.

Darius Lingė, M. Sc.
Jelena Jachno, M. Sc.
Jolanta Vanagel, M. Sc.
Vilma Michailovienė, M. Sc.
Lina Mištinaitė, B. Sc.
Milda Gumbytė, B. Sc.

Inesa Tadarovskaja, B. Sc.
Dovilė Makarevičiūtė, student
Jovita Matukaitytė, student
Zigmantas Toleikis, student
Zita Juškaitė, technician

Establishment of the Laboratory of Biothermodynamics and Drug Design (LBDD)

The laboratory was established only recently – January 1, 2006 – a year after its head, Dr. Daumantas Matulis returned from United States where he obtained Ph.D. from University of Minnesota and worked for Johnson&Johnson Pharmaceutical Research and Develompent, L.L.C. The new laboratory is based on the Laboratory of Recombinant Protein Research and retained some of the experienced personnel in this field.

Organizational Structure of LBDD

The laboratory is highly interdisciplinary and consists of four closely interacting groups of biomedical scientists:

1. Recombinant protein production
2. Organic synthesis
3. Biothermodynamics of protein-ligand interaction
4. Computer simulation of protein-ligand interaction

The group of recombinant protein production clones genes of selected target proteins, expresses them in *E.coli*, insect, or mammalian cells, and purifies large quantities of active proteins sufficient for biothermodynamic measurements of binding with synthesized ligands. Several projects involve design of protein domain constructs with targeted mutations in order to demonstrate various amino acid contributions to the energetics of ligand binding. Protein production often involves reconstitution and refolding of proteins from insoluble inclusion bodies.

The group of organic synthesis makes compounds that are anticipated to bind target proteins either by comparison with compounds of similar chemical structure or by computer simulation. Special interest and capabilities of the group are in the field of synthesis of compounds with multiple conjugated aromatic heterocycles.

The group of biothermodynamics of protein-ligand interaction is making measurements by two biophysical techniques, namely, isothermal titration calorimetry (ITC) and protein melting temperature shift (PMTS). The ITC capability has been recently added by the purchase of Nano ITC titration calorimeter from Setaram (France), made by Calorimetry Sciences Corporation (USA). In addition, the binding constants are confirmed by PMTS using fluorimeter with temperature control. Furthermore, the group is involved in the studies of protein denaturation by high pressure using ISS high pressure fluorimeter that has been recently donated to our laboratory by Johnson&Johnson PRD, L.L.C. (USA).

The group of computer simulation of protein-ligand interaction consists of several collaborating scientists that reside outside Lithuania. They are developing software that estimates the energetics of ligand binding to a protein when only the crystal structure of unbound protein and chemical structure of the potential ligand is available.

Lina Mištinaitė, B. Sc.

Jurgita Matulienė, Ph. D.

Research Projects

Since the LBDD has been established so recently, there are no significant results, publications or presentations based on the work performed here. The laboratory selected several protein targets and anticipated several potential ligands of interest to be synthesized.

In the attempt to inhibit signal transduction in the proliferation of cancerous cells, the protein-protein interaction of Hdm2 with p53 is probed with compounds mimicking three hydrophobic amino acids exposed on the surface of p53 that bind to three complementary pockets on the surface of Hdm2.

Second project involves discovering sulfonamides that would specifically inhibit only one or several carbonic anhydrases out of about 15 known carbonic anhydrase isoenzymes. Several of them are known to be involved in the development of various cancers. The project continues building on our previous results.

The former laboratory of recombinant protein research has significant experience in purification and folding of chaperone proteins. One of them, heat shock protein 90 (Hsp90), is an anticancer target. The search and synthesis of compounds similar to well known inhibitors of Hsp90, namely, radicicol and geldanamycin, are underway.

Collaborations

Cathy Royer, Montpellier, France – high pressure fluorimetry.

Matthew J. Todd, Barry Springer, Johnson&Johnson, PRD, L.L.C., Philadelphia, USA – high throughput PMTS (ThermoFluor®) method.

Grants

EC FP6 Marie Curie international reintegration (Daumantas Matulis)

Lithuanian State Science and Studies Foundation (Daumantas Matulis)

EC FP6 Marie Curie international reintegration (Jurgita Matulienė)

Sebastien Durand from Setaram, France.

Publications 2004-2005

1. Matulis D., Kranz J., Salemme F.R., and Todd M.J. 2005. Thermodynamic stability of carbonic anhydrase: measurements of binding affinity and stoichiometry using ThermoFluor. *Biochemistry*, 44, 5258-66.
2. Lovrien R. and Matulis D. 2005. Assays for total protein. *Current Protocols in Microbiology*, Wiley, NY.
3. Budriene S., Gorochovceva N., Romaskevic T., Yugova L.V., Miezeliene A., Dienys G., Zubriene A. 2005. β-Galactosidase from *Penicillium canescens*. Properties and immobilization. *Central European Journal of Chemistry*. 3 (1), 95-105.
4. Pleckaityte M., Mistinaite L., Mistiniene E., Dienys G., Zvirblis G. Biochemical properties of Hsp70 chaperone system from *Meiothermus ruber*. 2005. *Biocatalysis and Biotransformation*, 23(3/4): 191- 200.
5. Mistiniene E., Pozdniakovaite N., Popendikyte V., Naktinis V., 2005. Structure-based ligand binding sites of protein p14.5, a member of protein family YER057c/YIL051c/YjgF. *International Journal of Biological Macromolecules*, 37, 61–68.
6. Matulis D. and Todd M. 2004. Thermodynamics – structure correlations of sulfonamide inhibitor binding to carbonic anhydrase. In "Biocalorimetry 2", eds. Ladbury, J.E. and Doyle, M.L. Wiley. 107-132.