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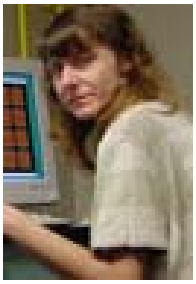

The laboratory is committed to study the mechanism of biomacromolecular assembles with the special emphasis on giant proteases to better understand their role in cancer and aging. To achieve this goal, we blend in our research a unique array of methods from the crossroads of biophysics, enzymology, organic chemistry, cell biology and molecular biology.

In particular, we are devoted to study the proteasome, a multifunctional macromolecular assembly essential in cell cycle progression, signal transduction pathways, immune response and general "housekeeping" in the human cell. The proteasome is currently in the center of attention of clinicians and pharmacologists as a surprisingly promising drug target against multiple myeloma and other types of cancer. The mechanism of action of proteasome inhibitors as anti-cancer drugs is poorly understood, which impedes their truly efficient utilization to battle the disease. One of our goals is to provide an insight into the differences between structure and function of proteasomes in normal and neoplastically transformed cells and in cells in aging tissues. We propose that proteasome, together with other proteases that take a part in the controlled degradation of regulatory proteins in the cell, constitute a functional entity. They form multi-branched degradation pathways enabling a tight control of this irreversible process. We postulate that this web of interactions is dysfunctional in cancer or in aged organisms, creating a "proteolytic instability". Dissecting the web of interaction and aiming at its most vulnerable points would enable to manipulate the activities of the involved proteases to specifically kill tumor cells or to improve an immune response in aging tissue. To better understand "the proteolytic instability" on the cellular level, we are also dissecting the molecular mechanisms of regulation of activity of the proteasome. For this purpose, we developed a model of allosteric regulation of performance of the proteasome. In a small-scale rational drug design fashion, we created a series small-molecule compounds affecting the proteasomal activities. Our goal is that the compounds or their derivatives will become specific and precise drugs against cancer, autoimmune diseases, stroke and other pathological conditions.

The unique capabilities in our laboratory include:

1. atomic force microscopy (AFM), an exceptional technique to study dynamics of biomacromolecules and their interactions with ligands under native conditions. We are employing AFM to study the giant proteases and, in numerous collaborative efforts, to investigate DNA-binding proteins, like ORC (origin recognition complex), MCM (minichromosome maintenance) and helicases, or to examine a structure of drug-treated DNA;
2. spectrofluorometry, currently used to complement the AFM studies of the dynamic structure of the proteasome;
3. expertise in numerous other spectroscopic methods (EPR, ENDOR, mass spectrometry);
4. enzymology, including advanced enzyme mechanism and molecular modeling of enzyme-ligand interactions;
5. development of protein purification techniques designed for giant biomacromolecules;
6. chemistry of peptides: design and synthesis of peptides, peptide derivatives and peptidomimetics, their purification and characterization, computer modeling of their structure and interaction with intended targets;
7. in addition to the above specialized methods and approaches, we are using standard molecular biology methods, yeast genetics and mammalian tissue culture techniques.