UNDERGRADUATE RESEARCH

Understanding Protein Structure Function Relationships

By Ellis Bell, University of Richmond

The projects conducted by undergraduates in the Bell Lab at the University of Richmond all focus on understanding aspects of the role that protein dynamics play in a variety of functions of proteins, from basic kinetics and ligand binding, to allosteric regulation and protein folding. This theme links four quite distinct projects in the lab with groups of students working on i) Oxido-Reductases; ii) Proteases; iii) Protein Kinases; and iv) Ionotropic Glutamate Receptors. In each subgroup, 3-4 students each work on related, but independent projects.

The summer research started around Thanksgiving last year when students expressed interest in joining the summer group- some were returning students, some were new students, and many were finishing up their first semester at the University of Richmond. Work on the summer projects began in earnest in January, with background discussions, the preparation of research proposals, and regular group meetings to discuss both background and experimental approaches. Each student wrote their own proposal to obtain funding, either from NSF research grants, HHMI funded initiatives, or University and Departmental funds.

The official summer research period begins about a week after finals and students start their full time research for ten weeks. During the summer, students are immersed in every aspect of their research project. There are no post-docs, technicians, or graduate students; the undergraduate students take full responsibility for their projects. Each week starts with an organizational meeting so that we can efficiently make use of available equipment. We wrap up each week with a group meeting where each student has to present data and lead a discussion of the rationale of the experiments, the interpretation of the data, and the next steps. In addition, each student is responsible for finding and presenting a paper they have found that has some relevance to their project.

Protein Structure Function Relationships

Our interest in protein flexibility and stability and their relationship to function started some years ago with our work on Malate Dehydrogenase (ref 1) and Glutamate Dehydrogenase (ref 2). Our work has since branched into other proteins as well. While there has been much recent interest and controversy (ref 3) about the role that dynamics play in catalysis, we chose to examine the role dynamics (and related aspects of stability and folding) play in allosteric regulation, partly because of the long focus of the lab on allosteric regulation and partly because of interest in allosteric drug design (ref 4) with its potential to develop very specific modulators of specific protein activity.

Student Projects

This summer DEHYDROGENASE (Angela Tata, Jacqunae Mays and Chun Li) are working on projects involving fluorescence approaches (Chun), Site Directed mutagenesis approaches (Jacqunae), or thermodynamic approaches (Angela) to investigate protein dynamics in their individual projects. They are using techniques as diverse as Multiwavelength collisional quenching, kinetics, ANS fluorescence and CD, and thermal melts to study Glutamate Dehydrogenase and Malate Dehydrogenase (Photo below-left to right: Angela, Jacqunae).

“Before I started research, I would never have imagined myself doing such things- nothing compares to what I have learned by doing hands on lab research.” - Jacqunae Mays
“I am learning how to perform experiments and to complete a research project. More importantly, I am learning how to think critically. By understanding the big picture behind studying certain topics and conducting certain experiments, I learn how to develop new ideas and investigate them.” - SoHo Kim

“Although there are moments when lab can be quite frustrating, finally getting data and understanding it makes the frustration worth it.” - Carol Guzman

SIKE (Clara Kerckhove, SoHo Kim, and Hyejin Park) are examining the effects of multiphosphorylation of SIKE (ref 4), both from the standpoint of how it results from the kinase TBK1 activity (SoHo), to its effect on structure (Clara) and effects on interactions with other proteins (Hyejin) using fluorescence, CD, proteomics approaches, X ray crystallography, and computational modeling (Photo above left: left to right: SoHo, Clara, Hyejin).

iGluR (Forest Barkdoll-Weil, Carlos Metz, Carol Guzman, and Alaina Hyde) are working on the role that either Glutamate binding or steroid binding play on the family of ionotropic glutamate receptors including AMPA, NMDA, and Kainate and are approaching the problem both with fluorescence and with H/D exchange and limited proteolysis approaches (Photo above right-left to right: Forest, Alaina, Carlos, Carol).

The newest project in the lab, PROTEASE (Meron Tarekegn, Kelsey Kines, and David Harry) are developing the tools necessary to investigate two aspects of thiol proteases, precursor activation, and their inhibition by protein based naturally occurring inhibitors, as well as the possible connection between the two (Photo on next page-left to right: Ellis Bell Kelsey, Meron).

To add a little something new to the mix this summer, we are learning how to play with the model organism C elegans with the hope of taking three of the projects (SIKE, PROTEASE and iGluR) in vivo in the future.

Several of the groups are now working on manuscripts where they are not only finishing up work they started last summer, but are writing the first drafts of the manuscripts. We hope 2-3 manuscripts will be ready to submit by the end of the summer, and all of the groups are working towards presentations at this year’s Protein Society meeting and next year’s ASBMB Meeting.

Reaching Out
The group as a whole also engages in a variety of outreach activities over the summer. This year we are working with the URISE program at the University of Richmond to teach a series of modules to incoming first year students such as “Using Standard Curves,” “Measuring and using Rates,” “Visualizing Macromolecules,” “Finding and Using the Scientific Literature,” as well as mentoring several of them on research projects. Jacqnae and Carol work with the
MSI-UAN initiative and mentor high school students in a variety of skills and introduce them to research. The whole group works with our ongoing “Science on Saturday” program for high school teachers and their students from Armstrong Community High School, and helps mentor them in research for a 4 week internship at the end of the summer.

Summer research has engaged these undergraduates in all aspects of the science, helping them develop skills and content knowledge. Their research usually continues during the academic year, allowing these students to grow as independent researchers.

“The exposure and knowledge I’ve gotten from working in the lab is beyond incredible. I wouldn’t change it for anything” - Meron Tarekegn

References:

2. Sarah A. Wacker, Michael J. Bradley, Jimmy Marion, and Ellis Bell “Ligand Induced Changes in the Conformational Stability and Flexibility of Glutamate Dehydrogenase and Their Role in Catalysis and Regulation” Protein Sci. 2010 Oct;19(10):1820-9
