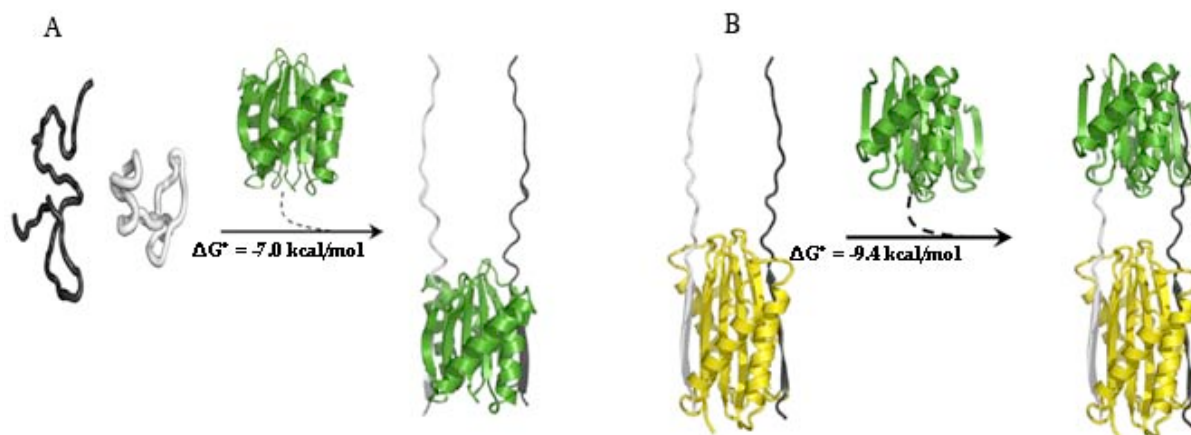


The Barbar lab had a very successful year. The highlights include a new NIH RO1 grant awarded for 5 years to study the role of LC8 as a molecular hub that facilitates dimerization of its disordered partners in various complex systems. Another success on the grants front is a pre-doctoral fellowship from the American Heart Association with a score of 0.6 percentile granted to graduate student Justin Hall. Considering the current tight funding environment, both awards were a major accomplishment and a source of great relief.

I had several invitations to speak at national meetings including in a mini-symposium at the 53<sup>rd</sup> Annual Biophysical Society Meeting, at the 23<sup>rd</sup> Annual Gibbs Conference on Biothermodynamics, and at the Biomolecular Interactions and Methods Gordon Conference. I was also elected to serve as the Program Co-Chair of the Intrinsically Disordered Proteins Subgroup at the 54<sup>th</sup> Annual Biophysical Society Meeting, and as co-organizer of the 24<sup>th</sup> Annual Gibbs Conference on Biothermodynamics .

On the research front we have proposed a new function of disordered protein and that is formation of a poly-bivalent scaffold for multiprotein complex assembly. We showed that assembled dynein intermediate chain is an elongated, flexible poly-bivalent scaffold that is modulated by binding of any of its multiple bivalent ligands. This type of scaffold may be general for assembly of disordered proteins in non dynein systems and thus poly-bivalency is an important general mechanism for constructing stable yet reversible and functionally versatile complexes.



Model depicting bivalency in assembled IC/Tctex1/LC8 subcomplex. (A) Binding of LC8 dimer (green) to two disordered IC chains (monovalent IC, grey). (B) Binding of LC8 dimer to bivalent IC formed upon Tctex1 binding (yellow). Bivalency in disordered IC is manifested when the first dimeric protein binds two disordered chains and creates a bivalent ligand with higher affinity (higher negative  $\Delta G$ ) to the second protein than the monovalent ligand.

### 2009 Publications

1. Benison, G., Chiodo, M.P., Karplus, P.A. & **Barbar, E.\*** (2009) Structural, Thermodynamic, and Kinetic Effects of a Phosphomimetic Mutation in Dynein Light Chain LC8. *Biochemistry*, **48**, 11381–11389.
2. Hall, J., Karplus, P.A. & **Barbar, E.\*** (2009) Multivalency in the assembly of intrinsically disordered dynein intermediate chain. *J. Biol. Chem.* **284**, 33115-33121.
3. Hall A, Parsonage D, Horita D, Karplus PA, Poole LB, **Barbar E.\*** (2009) Redox-dependent dynamics of a dual thioredoxin fold protein: evolution of specialized folds. *Biochemistry* **48**, 5984-93.
4. Benison, & **Barbar, E.\*** (2009) NMR analysis of dynein light chain dimerization and its interactions with diverse ligands. *Methods in Enzymology—Thermodynamic Methods and Applications* (J.M. Holt, M.L. Johnson, and G.K. Ackers, eds.), **455**, 237-58.

Celebration of NIH funding of RO1: *Dynein Light Chain as a Dimerization Hub for Natively Disordered Proteins*.

Picture shows members of the Barbar and the Karplus labs. (Andy Karplus, center, is a collaborator on this grant).



More reasons for celebrations....

Justin Hall received the Nellie Buck Yerex Graduate Fellowship, an award given to outstanding graduate students who are pursuing study in a scientific field.

Andrea Hall received the Bayley Graduate Fellowship, an award given on the basis of academic performance and promise for the future.

Pictured also besides me is Dr. Chris Mathews, one of the nominators.



### **Major equipment addition: Surface Plasmon Resonance**

Our lab has been successful in securing funding for a Surface Plasmon Resonance instrument, Pioneer from ICX Technologies, as part of a multi-user equipment grant.

### **Visitors and Outreach**

Our lab also had the pleasure of hosting a couple of visiting speakers: *Bill Skach* from OHSU and *Tracy Handel* from UCSD.

I offered, with the help of Justin and Andrea Hall, a Saturday academy module to High School Students focused on Protein Structure Function.

## Undergraduate Student Researchers

1. *Christine Schneider* (Fall 2008 – Spring 2009) – presented a poster in the Celebrating Undergraduate Excellence poster competition
2. *Jonathan Yih* (Su 2009-present) HHMI and NSF REU
3. *Brian Phan* (Su 2009) HHMI and URISC
4. *Jamil Barbar* (Fall 2009-present) NSF REU
5. *Sam Albeke* (Su 2009-Fall 2009)

## Current lab members

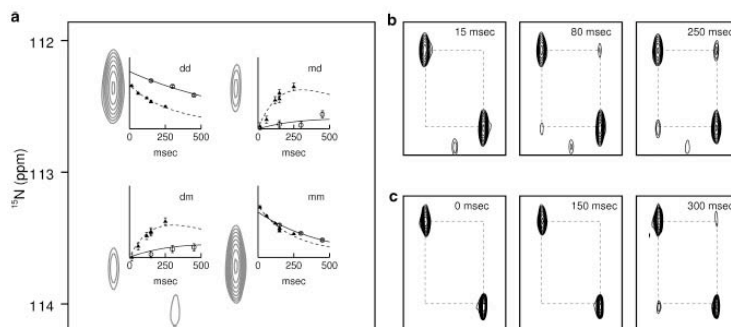
From left to right: Elisar Barbar, PI, Justin Hall, Yujuan Song, Jessica Morgan, Afua Nyarko and Sam Albeke. Not pictured lab members are Greg Benison, Jamil Barbar and Jonathan Yih.



## Paper Highlights

*Benison, G., Chiodo, M.P., Karplus, P.A. & Barbar, E.\* (2009) Structural, Thermodynamic, and Kinetic Effects of a Phosphomimetic Mutation in Dynein Light Chain LC8. Biochemistry, 48, 11381–11389.*

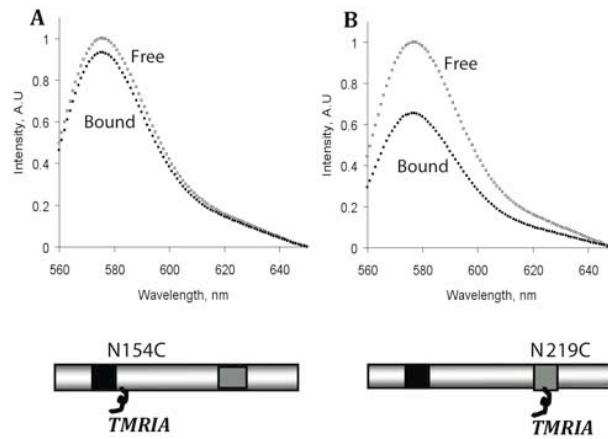
First author *Greg Benison* with the help of undergraduate student Marcus Chiodo, and in collaboration with Professor Andy Karplus, published a paper that characterizes the linkage between phosphorylation and dimerization of LC8 using both NMR and crystallography. We infer from this study that phosphorylation of one subunit of wild-type LC8 raises the dimer dissociation constant by at least 400 fold to prevent dimerization of LC8 at physiological concentrations. Some LC8 binding partners may bind tightly enough to promote dimerization even when one subunit is phosphorylated.





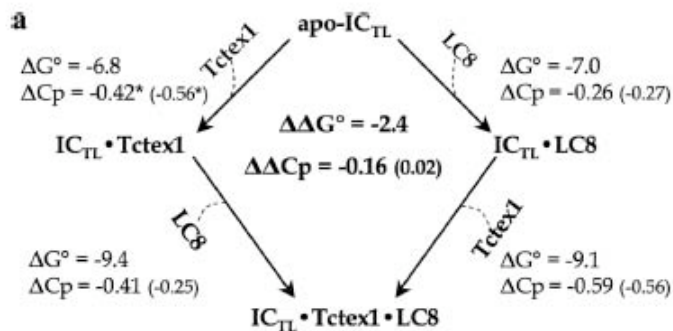
**Barbar, E. & Nyarko A. (2010) Regulatory Roles of Dynein Light Chains in Dynein Assembly. *Dynein Handbook, in press.***

**Afua Nyarko** wrote a review focused on the regulatory roles of dynein light chains. In this figure she illustrates the method of fluorescence quenching to probe regions that undergo self-association as a result of LC8 and Tctex1 binding.



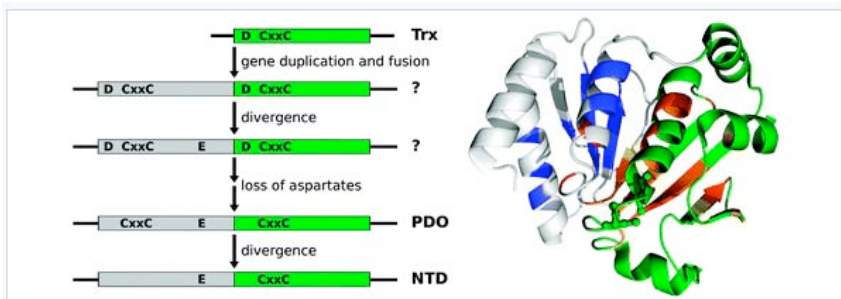
Hall, J., Karplus, P.A. & **Barbar, E.\*** (2009) Multivalency in the assembly of intrinsically disordered dynein intermediate chain. *J. Biol. Chem.* **284**, 33115-33121.

First author Justin Hall determined the energetics for each step in the thermodynamic cycle to demonstrate multivalency effects in the assembly of IC with light chains LC8 and Tctex-1. For the wild type complex, there is a 50-fold multivalency enhancement of affinity for the second light chain binding.



Hall A, Parsonage D, Horita D, Karplus PA, Poole LB, **Barbar E.\*** (2009) Redox-dependent dynamics of a dual thioredoxin fold protein: evolution of specialized folds. *Biochemistry* **48**, 5984-93.

First author Andrea Hall shows differences in dynamics between the two folds of the NTD indicating that each has a specialized function that may have allowed evolution of the a fold to enhance catalysis and specificity.



## Alumni contacts in 2009

*Jim Gould (Su 2000)*



I was delighted to hear from Jim after all these years, pictured above with his 3 year old daughter Lucy in front of his poster at a FASEB meeting. Jim spent the Summer of 2000 in our lab and he remembers this time fondly in spite of *"it was a frustrating summer but opened my eyes to the realities of research and potential of grad school"*. Jim is now a postdoc in Michael Dean's lab at NCI trying to understand the Hedgehog/Gli pathway and its relation to carcinogenesis and cancer recurrence.

*Crystal Hammer (Su 2006-Spring 2007)*. I received a package of wonderful and extremely tempting homemade cookies from Crystal this year with news about her being now in the MD program at OHSU.

More alumni news will be coming in the next newsletter, please stay in touch.

For now, I will end and wish you all a very fruitful and happy new year.