<u>Multiple UROP Openings with the Sasisekharan Laboratory</u> at the Harvard-MIT Division of Health Sciences and Technology, Koch Institute of Integrative Cancer Research, and Department of Biological Engineering, Massachusetts Institute of Technology

Project #1 Project Title: A Novel Approach to Structure-based Protein Design and Engineering

Project Description: The rational design of proteins is central to the engineering of novel molecules for a broad-spectrum of biotechnology and medical applications. However, design-based protein engineering has been rife with challenges arising from misfolding, instability, and dysfunction of the designed molecules. In recent years, our group has been actively decoding the rules governing folding, stability, and function for diverse human and pathogen proteins, owing to our development of powerful in-house structural and sequence analysis tools (e.g. see our recent publications in Nature Biotechnology 2009 and PLoS ONE 2010 at the following links -- http://www.nature.com/nbt/journal/v27/n6/full/nbt0609-510.html and http://dx.plos.org/10.1371/ journal.pone.0009391). Towards furthering the decoding of rules governing design-based protein engineering and applying such knowledge for creating novel proteins with important therapeutic applications, we are currently seeking an undergraduate student with keen interest in both the computational and experimental aspects of molecular structural biology. Specifically, this UROP is ideally suited for students with interest in both

(i.) learning state-of-the-art molecular modeling (e.g. Discovery Studio, PyMol) and programming (e.g. MATLAB) tools for the de novo design of novel proteins; and (ii.) performing guided bench work for experimental validation of the designed protein's functions. The UROP student will benefit from working with senior researchers in a fast-paced group and is expected to co-author significant journal publications emerging from this research (as has been the norm with all of our past and present UROPs). The UROP engagement is expected to commence during the Fall 2010 term, or earlier if a suitable candidate expresses interest.

Prerequisites: Strong analytical abilities and an active interest in experimental protocols are both desirable skills for this UROP research.

Contact: Dr. Venky Soundararajan (<u>http://web.mit.edu/venk/www/</u>) by e-mail at venk@mit.edu with a copy to Prof. Ram Sasisekharan <u>http://hst.mit.edu/public/people/faculty/</u><u>facultyBiosketch.jsp?key=Sasisekharan</u> at rams@mit.edu -- Further information is also available from the Sasisekharan Laboratory website at <u>http://web.mit.edu/tox/sasisekharan</u>/

Project #2

Project Title: Engineering a Database of Influenza Virus Surface Protein Molecular Models to Decode Patterns of Antigenic and Functional Site Evolution towards Developing Novel Therapeutic Solutions

Project Description: This UROP will involve the use of in-house molecular modeling tools to compute a database of influenza surface protein molecular structures from NCBI bioinformatics

databases. The main goal of this constructed massive database will be to develop protocols for analysis and mining of novel biomedical signatures that will facilitate important biomedical and biotechnological applications. Specifically, the determinants of (i.) glycan receptor-binding specificity of viral hemagglutinin protein and (ii.) antigenic evolution; will be determined by utilizing techniques from our recently published studies (see our Nature Biotechnology 2009 and PLoS ONE 2010 papers at the following links --

http://www.nature.com/nbt/journal/v27/n6/full/nbt0609-510.html and

<u>http://dx.plos.org/10.1371/journal.pone.0009391</u>). Significant biological and therapeutic value is anticipated for the results emerging this analysis, which is expected to lead to important scientific publications. The UROP engagement is expected to commence during the Fall 2010 term, or earlier if a suitable candidate expresses interest.

Prerequisites: Strong analytical abilities, with an active interest in database construction and data mining, are desirable for this UROP research.

Contact: Dr. Venky Soundararajan (<u>http://web.mit.edu/venk/www/</u>) by e-mail at venk@mit.edu with a copy to Prof. Ram Sasisekharan <u>http://hst.mit.edu/public/people/faculty/</u><u>facultyBiosketch.jsp?key=Sasisekharan</u> at rams@mit.edu -- Further information is also available from the Sasisekharan Laboratory website at <u>http://web.mit.edu/tox/sasisekharan</u>/

Project #3 Project Title: Construction of a Universal Protein Sequence-to-Structure Database for High-throughput Mining of Structure-Function Relationships

Project Description: This UROP research will commence with building on the in-house, highthroughput sequence-to-structure mapping protocol developed recently by our group (http:// dx.plos.org/10.1371/journal.pone.0009391), to enable the construction of a universal protein structural database. Post construction of the database, an appropriate Graphical User Interface (GUI) is to be developed, to showcase the bioinformatics information content relating to the modeled protein structures. Our vision is to create an easy-to-mine database of the universal set of molecular models built, using which resource, specific biological applications such as sequence-to-function mapping will be explored. There is a rich plethora of protocols already implemented by our past and present UROPs, and the new UROP is expected to quickly adapt to working with our group to further these goals. Based on the interests of the UROP, several follow-up applications may be explored, in the post-database-construction phase, including de novo identification of glycan-binding properties from amino acid sequence. This project will involve significant analytical and computational skills. Journal publications are already being compiled and it is expected that this UROP student will contribute to these papers as a coauthor. The UROP engagement is expected to commence during the Fall 2010 term, or earlier if a suitable candidate expresses interest.

Prerequisites: Strong analytical abilities, with a vivid and creative imagination, general appreciation of structures/geometry, and an active interest in molecular modeling and computational biology are all desirable traits for this UROP research.

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Project #4 Project Title: Pattern Recognition on Protein Structural Surfaces: Applications to Decode the Glycosylation Machinery

Project Description: This UROP is a very fundamental biological project with broad applications that are expected to provide significant insight into the biomolecular mechanisms facilitating the glycosylation of proteins. Glycosylation is one of the most common post-translational modifications and is performed by numerous enzymes with poorly defined specificity. The goal of this UROP is to build on the in-house protein structural analysis protocols developed by us recently (e.g. see our recent publications in Nature Biotechnology 2009 and PLoS ONE 2010 at the following links -- <u>http://www.nature.com/nbt/journal/v27/n6/full/nbt0609-510.html</u> and

<u>http://dx.plos.org/10.1371/journal.pone.0009391</u>) for recognition of 'signature glycosylation patterns' on the molecular surfaces of diverse protein structures. The findings that emerge from this analysis are expected to have major implications for furthering our understanding of the glycosylation machinery, thus opening the doors for novel biotechnological applications involving prediction and modulation of these fundamental processes. If successful, similar protocols may be more broadly explored for predicting signatures of other biologically and biomedically important post-translational modifications, as well. The advances enabled by this UROP study are expected to result in major publications in pioneering journals that will have a profound impact on molecular biology at large.

Prerequisites: Strong analytical abilities with some previous MATLAB experience is desirable for this UROP research.

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Project #5

Project Title: Mining Protein-Protein Interfaces for Understanding Biomolecular Interaction Specificity and Furthering Design-based Therapeutic Engineering

Project Description: This UROP research involves the development of a protocol for mining of protein-protein interfaces from the PDB, by building on our recently-showcased and novel

protein structural analysis tools (e.g. see our recent publications in Nature Biotechnology 2009 and PLoS ONE 2010 at the following links -- http://dx.plos.org/10.1371/journal.pone.0009391). The goal is to compute the signatures of protein-protein interaction specificity and affinity. Novel analytical approaches have been envisioned to enable the mining and analysis aspects of this research. The ideal UROP student would have an inherent ability to recognize patterns from analysis of data-rich signals. Prediction of protein-protein interactions is a significant biological advancement with major biotechnological implications. Important scientific and technological publications are hence expected from this UROP research.

Prerequisites: Strong analytical abilities with some previous MATLAB experience is desirable for this UROP research.

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