Application to the graduate research program (PhD studies)

The research projects at the Department of Biochemistry and Biophysics cover a number of areas of high international interest, such as molecular studies on photosynthesis, mitochondria: biogenesis, structure & function, biochemical toxicology, lipid biosynthesis & function, protein structure, folding & trafficing, membrane protein topology & assembly, DNA-RNA-PNA interactions, bioinformatics, and biological nitrogen fixation. Research at the department involves plants, mammals, yeast, cyanobacteria and photosynthetic bacteria. The department is well equipped and within the projects modern gene technology and computer modelling are used as well as other biochemical, biophysical and physiological methods.

Short descriptions of possible projects are found below. The applicant should state which project (with Ref. No.) the application concerns, and add to the application a "Letter of intent", describing your expectations of the PhD studies. The applicant may apply for more than one position, but in that case, a complete set of documents is required for each position. You are welcome to contact the project leaders for further information (see below).

To be accepted as a PhD student, credits corresponding to four years of full-time studies at the undergraduate level are required, including credits corresponding to at least two years of fulltime studies in chemistry, life sciences or physics, depending on the program. The credits should include courses at the advanced level (second cycle) corresponding to one year and of these one semester should be a degree thesis. In order to facilitate the evaluation of merits and suitability for the PhD studies the *curriculum vitae* (CV) should contain information about the extent and focus of the academic studies. The quantity (as part of an academic year) and the quality mark of courses in chemistry and physics are of particular interest. Please state titles of undergraduate theses and project works.

The selection among applicants will be based on the judgement of their capacity to successfully complete the PhD program. In practical terms, this means that the study merits will be the main selection criterion. The local study merits, such as passed advanced courses or project work at the department, will be given a relatively high weight. Equal opportunity aspects between men and women will be given a certain weight, as well as willingness and ability of candidates to participate in undergraduate teaching.

Economic support is guaranteed during the agreed time in the individual study syllabus (study plan) for the graduate studies, totally for a maximum of 4 years. The department may request that the graduate student takes part in teaching or other departmental work in an activity additional to the graduate studies for up to 20% of full work time in years 2-4.

Additional information can be obtained from the project leaders (see below) and from Astrid Gräslund, head of department (*prefekt*), tel. 08-162450 (astrid@dbb.su.se).

The application together with a CV must reach the department (c/o Haidi Astlind), **no later than May 2, 2008**. Applications should be **on printed paper sent as a letter**

to the department, one set of documents for each position applied for. Address: Dept. of Biochemistry and Biophysics, Stockholm University, Arrheniuslab, 106 91 Stockholm, Sweden.

Short descriptions:

Ref. No. DBB 6-08 (one position): Graduate program biochemistry
Project leader: Susana Cristobal (Susana.Cristobal@dbb.su.se)

Project title: Environmental proteomics in pollution assessment
The world is deeply concerned about the effects of pollution on long-term human and animal health. It is growing in importance the developing of techniques for environmental applications from marine pollution assessment to the risk assessment on chemicals and pharmaceuticals. Differential proteomic analysis using mass spectrometry could decipher protein and peptide profiles, enable the identification of candidate biomarkers that are associated with specific environmental perturbations and offer novel mechanistical approaches to ecotoxicology. (Mol.Cell Proteomics. 2006, 5:1274; Proteome Res. 2007, 6:2094). The project will be focus first on developing proteomics and peptidomics-based techniques to assess antropogenic pollutants. Second, chemical pollution could impair population health over many generations however; gender-specific response to pollutant exposure has been underestimated. This project will explore the biological differences between genders with respect to chemical exposure. Finally, we will apply quantitative proteomic methods to study the impact of nanoparticles on biological systems. Nanotechnology offers a high number of potential commercial and biomedical applications, however, many questions regarding nanoscale materials' potential deleterious effects as yet remain unanswered. The aim of this project is to advance knowledge in the safety, environmental and human health implications of nanotechnology materials and products. Proteomics could provide a global view at glance of the different metabolic pathways affected and the effects of hazardous xenobiotics at on development and reproduction.

Ref. No. DBB 7-08 (one position): Graduate program biochemistry
Project leaders: Martin Högbom (martin.hogbom@dbb.su.se) and
Peter Brzezinski (peterb@dbb.su.se)
http://www.dbb.su.se/research/Hogbom_Martin.htm,
http://www.dbb.su.se/research/Brzezinski_Peter.html

Project title: Structural and biophysical studies of the catalytic mechanism of Cytochrome c oxidase

The respiratory heme-copper oxidases are redox-driven proton pumps, which couple an electron current across the membrane, to a proton current in the opposite direction. One member of the oxidase superfamily is cytochrome *c* oxidase, which is the final enzyme of the respiratory chains in many organisms and is thus an intricate part in the energy-producing machinery.

The coupling of electron transfer to proton transfer in cytochrome *c* oxidase requires control of the pathways and rates of the internal electron- and proton-transfer reactions in order to prevent dissipation of the electronic energy into heat.

In this project we aim to study this mechanism by determining crystal structures of intermediate states in combination with biophysical data and quantum-mechanical calculations. The goal is to bridge the gap between the structural snapshots and produce a continuous "movie" of the mechanism at the atomic level.

The project involves expression of wild-type and mutant proteins, purification, crystallization and structure determination by X-ray crystallography as well as optical biophysical studies. Experience in these fields is a merit.

Ref. No. DBB 8-08 (one position): Graduate program biochemistry
Project leader: Peter Brzezinski peterb@dbb.su.se, tel. 163280
http://www.dbb.su.se/research/Brzezinski_Peter.html

Project title: Mechanisms of proton transport across membranes

Ion-translocating integral membrane proteins are involved in a wide range of functions in living cells such as signal transduction, energy conversion and nerve conduction. The project is centered around one class of these proteins - those in which ion translocation is driven by electron transfer (eT). We use of a wide range of biochemical and biophysical techniques to investigate and understand the structure and function of these proteins at a molecular level. The Ph.D. project involves preparation of mutant forms of the eT driven proton pump cytochrome c oxidase, purification of the protein and mechanistic studies using a number of biophysical techniques.

Ref. No. DBB 9-08 (one position): Graduate program biochemistry
Project leader: Pia Ädelroth (piaa@dbb.su.se), tel 164183.
http://www.dbb.su.se/research/Adelroth_Pia.html

Project title: Functional studies of membrane proteins involved in nitric oxide detoxification

Nitric oxide (NO) is a toxic gas produced in a variety of biological processes; e.g. as a host defense mechanism during bacterial infections, or as an intermediate during the process of denitrification, a bacterial process in which nitrate is step-wise turned into nitrogen gas. In bacteria capable of reducing NO to the much less toxic gas N_2O (laughing gas), there is an NO-reductase (NOR), an integral membrane protein which is present in denitrifiers as well as some pathogens where its role is to detoxify the NO produced by the hosts immune defense. Some bacteria are capable of NO-reduction through a recently discovered side-reaction of another protein; the cbb_3-type oxidase, whose main physiological role is to couple O_2 reduction to proton pumping as the terminal reaction in the respiration process. The Ph.D. project involves the use of a combination of biochemical and biophysical techniques to investigate the mechanisms of NO- (and O_2-) reduction and its coupling to proton translocation by the NORs and cbb_3-oxidases; e.g. sequence alignments and homology modelling, site-directed mutagenesis and protein purification, laser-induced optical spectroscopy and redox potentiometry.

Ref. No. DBB 10-08 (one position): Graduate program biochemistry
Project leader: Martin Högbom (martin.hogbom@dbb.su.se)
http://www.dbb.su.se/research/Hogbom_Martin.htm,

Project title: Structural biochemistry of integral membrane proteins

High-resolution protein structures constitute a very powerful tool to understand the function and evolution of proteins and they are becoming increasingly important as a basis for drug design. In our group we use X-ray crystallography to determine protein structure at atomic resolution.

Membrane proteins are targets for the majority of drugs on the market and perform a remarkable number of cellular processes including signaling, transport, energy transduction and enzymatic reactions. Still, there are only high resolution structures for some 150 unique membrane proteins, compared to ~15 000 for soluble proteins.

This project aims to determine crystal structures of certain membrane proteins of particular medical and scientific value. The structural information will be used to design further biochemical experiments to obtain an in-depth functional understanding.

The project involves cloning of genes as well as protein expression, purification, crystallization and structure determination by X-ray crystallography. Experience in these fields, especially membrane protein expression, purification and crystallization is a merit.

Two projects for European non-Swedish students as a part of the TransSys ITN
These two position are funded by a EU grant and can only be applied for by students who are residents in (citizen of) a EU or EU-affiliated country other than Sweden. For details and questions contact AE or GvH

Ref-No: DBB-08-Gvh-01 (one position): Graduate research program biochemistry
Project leader: Gunnar von Heijne (gunnar@dbb.su.se)
http://www.dbb.su.se/research/Von_Heijne_Gunnar.html

Project title: Membrane protein interactions: modelling and experiment
Most integral membrane proteins are part of larger complexes. However, the interactions that drive protein-protein interactions in membranes are poorly understood. In this project, theoretical and experimental techniques (cloning, site-directed mutagenesis) will be combined to analyze and possibly predict interactions between membrane proteins, mainly using model proteins expressed in *E. coli*. Wet-lab experience of molecular biology work is required. The position is funded by a EU grant and can only be applied for by students who are residents in a EU country other than Sweden.

Ref-No: DBB-08-AE-02 (one position): Graduate research program biochemistry towards bioinformatics)
Project leader: Arne Elofsson (arne@bioinfo.se)
http://bioinfo.se/

Project title: Membrane protein interactions: bioinformatics or experimental studies
So far the insertion of helices by the translocon has mainly been studied by artificially designed single helices. However, as noticed many helices do not seem to be hydrophobic

enough to be inserted without the help of neighboring helices. Therefore, the insertion of such marginally hydrophobic helices in vivo and in vitro is important to provide insight into how membrane helices are inserted. In this project, theoretical studies of membrane proteins will be combined with experimental techniques (cloning, site-directed mutagenesis) to analyze the insertion, folding and interaction of TM-helices. We seek outstanding PhD candidates with knowledge of bioinformatics and/or wet-lab molecular biology techniques. The position is funded by a EU grant and can only be applied for by students who are residents in a EU (associated) country other than Sweden.