KTH International RAE 2008

REPORT PANEL 10: BIOTECHNOLOGY

GENERAL ASSESSMENT OF THE RESEARCH FILED

The Research Field at the KTH is broad and mainly concerns the biotechnology associated with the engineering and applications of the key polymers of life (nucleic acids, proteins and carbohydrates). More specifically this includes gene technology, protein engineering, carbohydrate biosynthesis, nano-technology and bioprocess technology.

The work reviewed has included technology development (in particular high throughput DNA sequencing), and applications that range from mapping the expression of all human proteins in different tissues, the imaging of human tumours with novel reagents, to the creation of new composite materials. Generally the quality of work is at the international level, in some cases at the forefront (UoA *"Protein Atlas"*). Indeed the scale and vigour of the biotechnology activities in the KTH is rare as it covers several of the most important strategic areas of biotechnology. There are also areas where the quality of the research could be greatly improved, for example "*Bioprocess Technology"* and *"Environmental Biotechnology*".

Synergies have emerged from major common elements of technology, particularly gene and protein technologies. This has facilitated collaborative scientific interactions between groups, the development of standard operating procedures and the sharing of expertise and equipment (such as sequencing machines, robots and mass spectrometry). The collaborative interactions have also been driven by inter-disciplinary (and multi-disciplinary) projects and concepts. The UoA "*Protein Atlas"* is essentially an inter-disciplinary project; several disciplines (from nucleic acid technology and bio-informatics to histopathology) have been brought together and used to build a map of the expression of human genes within different tissues of the body (and in different disease states). Likewise the "*Biomime*" concept has brought together different disciplines (biosynthesis of cellulose and the structure of wood fibres with the application of enzymology and chemistry) in the common purpose of making advanced materials; and the *Bioamines* project for industrial enzymatic synthesis of pharmaceuticals is bringing enzyme and bioprocess engineering together. Such common threads of technology or common projects have helped build critical mass and coherence within and between Departments (and UoAs).

The Research Field has been formally assessed as three areas headed *"Medical biotechnology"*, *"Industrial biotechnology*" and *"Protein Atlas"*. We understand that the different Departments and activities within the Research Field were combined into these three UoAs. Generally this had worked well with the UoA *"Protein Atlas"* and *"Medical Biotechnology"* which have a coherent strategy, but perhaps at the expense of the UoA "Industrial biotechnology" which comprises several activities with few common elements. In this UoA attempts have been made to tailor a coherent strategy, for example the *"Biomime"* concept represents one such strategy, but several other groups appear isolated. There is also some evidence of strategic coordination between the UoAs in their future plans (other than

that naturally arising from collaborations and common interests between scientists in the different UoAs).

UoA: Medical Biotechnology

General Assessment

This unit comprises two Departments, the *Department of Gene Technology*, and the *Department of Molecular Biotechnology*. Both departments have focused their research on important areas with huge potential in science and its application (particularly therapeutics and diagnostics). These two Departments provide an excellent resource of expertise and equipment for the Field, perform scientifically at an international level, and collaborate with each other. A unifying element has been the number of staff who previously worked with Uhlèn.

The *Department of Gene Technology* has two main research foci. The first is the development of methodology for massive DNA sequencing, which is applied among others in whole genome bacterial genome sequencing, transcriptome analysis, and mutation studies in cancer and inherited disease. A highlight of this research has been the evolutionary mapping of domesticated dogs. A second research focus is on the development of methodology for DNA analysis of single cells, used for instance for fate mapping in stem cells and drug prediction in autoimmune disease. An interesting application in this area is the analysis of the sensitivity of single skin cells for UV-B radiation damage.

The *Department of Molecular Biotechnology* has a broad focus on the development of protein technology, in particular the development of affibodies as high-affinity reagents for binding other proteins, from human, viral or bacterial origin. An excellent example of this is the use of affibodies to solubilize amyloid-□ peptides. In addition, affibodies are being developed for specific recognition and imaging of certain cancers. Other research lines comprise *in vitro* protein synthesis and labelling, and the implementation of protein fragment complementation assay.

Performance Against Evaluation Criteria

Scientific Quality (basic research)

The UoA is a productive unit group of researchers, with 30-35 publications per year, and with ~5 PhD theses completed each year. From the publication list it is obvious that the UoA performs at an internationally high standard (but generally not at the forefront), with some publications in high impact journals. The broad research profile is perhaps at the expense of the depth of research; to be at the forefront of international research it will probably be necessary to accept bigger challenges (for example as with the Protein Atlas). However, the panel is aware that the system of financing the research at KTH *via* external research grants and using PhD students may make it difficult to tackle bigger problems.

A major feature of the UoA is that it provides a resource in Sweden of high technology and expertise in genetic and protein technology. These have been recognized as the KTH Genome Centre (Wallenberg Foundation funding) and ProNova (the AlbaNova Vinn Excellence Centre for Protein Technology). Although the main focus of the UoA is basic research, it seeks looks for opportunities to collaborate with industry, whether in spinning out technology (as with pyrosequencing), or in technology development (as proposed for the development of a third generation DNA sequencing method) or through consortia (as with the industrial partners of ProNova).

Applied Research Quality

The research of the UoA is clearly inspired by technology development for applications, and parts of the UoA perform applied research at a world leading level. Several spin-off companies have been established based on patents obtained by members of the UoA. In addition, the members of the UoA participate in several EU projects and excellence centre consortia, which involve numerous biotech industries. Consequently the views and vision of the UoA on potential applications are realistic.

A number of practical applications are already in the pipeline, among which are high-affinity affibodies for tumour detection, promising strategies to prolong the serum half-life of recombinant proteins, and solid-phase synthesis of fluorescence-detectable affibodies. This research may also lead to valuable applications in basic research (e.g. tools for selective intervention in cell biology), diagnostics and therapy. In particular the ability to synthesize affibodies on solid phase could provide a market niche that is not available to other protein platforms such as antibodies.

There is a clear synergy with the developments in the *"Protein Atlas"* UoA. In the near future closer ties with the "*Protein Atlas"* may further enhance the quality and potential impact of the research in the *Medical Biotechnology* UoA, as also envisaged in the Strategy of the UoA (see below).

Scholarship

We were troubled with this section. If we take the definition provided as "high quality independent basic and applied research"…"to promote the well being of society", then as the basic and applied research are both high quality (as described in the Terms of Reference), then the only issue to discuss here is whether it "promotes the well-being of society". It is self-evident that work with potential in diagnostics, therapeutics must do so. We thus evaluate the scholarship Excellent in some parts/individuals of the UoA

An example of scholarship (as more usually defined) has been the serendipitous discovery of specific patterns in forensic dog hair mitochondrial DNA samples that, combined with a deep interest in history of the specific researcher, led to a model of the evolution and spread of domesticated dogs on earth, starting about 15,000 years ago. This example shows nicely how scientific results can be developed in a hypothesis that is attractive to the broader public.

Vitality and Potential

The vitality and potential are excellent in some parts of the UoA, good in the remainder. The UoA has succeeded in engaging a large number of PhD students who appear to be lively, questioning and committed. The PI's demonstrated a clear enthusiasm, energy and vision for their research. This contributes to attract research funds and PhD students to further their research. A relatively large number of EU grants have been obtained, which may help to increase the international visibility of the UoA.

Strategy

The strategy of this UoA for its future development is good with real potential to achieve. The strategy is geared towards increasing the synergy within the UoA of Medical Biotechnology, and increasing the synergy of the UoA with the other groups in the School of Biotechnology, in particular the UoA Protein Atlas and the UoA of Industrial Biotechnology. The plans include obtaining both gene and protein information from single cells and to investigate the potential of nanowire-based biosensing systems for biomolecule detection. Such endeavours

will require advanced bioinformatics expertise to be added to the UoA. How the required expertise can be acquired in a sustainable way is unclear at this moment.

Additional issues

The lack of funding for infrastructure support, in particular technicians to run highly specialized equipment was a problem. To some extent this could be overcome by using PhD students (who were around for several years) to take care of machines, but this had the danger that the students might focus their PhD around the equipment rather than around the scientific question.

UoA: Protein Atlas

General Assessment

This comprises two Departments, *Proteomics* and *Nanobiotechnology*, whose activities are currently focussed on a single project. The project identifies protein reading frames in the human genome, expresses bits of the corresponding protein, and uses these bits to make antibodies to every protein in the human body. The antibodies are then used as reagents to map the locations of every protein in different tissues. The results are made openly available to researchers through the web, and collated with other data (for example expression of specific RNA). The success of the project requires several disciplines to be brought together in a common and highly directed purpose. The project has no international competitors and should prove an immensely valuable resource for researchers and for industry. The project represents the peak of proteomic research today.

Performance Against Evaluation Criteria

Scientific Quality (basic research)

The scientific quality of this unit is world leading throughout. Genomics and proteomics are not traditional disciplines of science. They consist of large-scale comprehensive projects centred around organisms, and have been criticized for their simple mindedness and lack of hypothesis driven inquiry. However, despite these limitations, genome projects have changed the nature of biological science. In this tradition this project to map the protein landscape of the human body, thrills by its mastery of technology, its boldness and broad explanatory scope. Knowing where a protein is in a cell and in which cell types, tissues and organs, can be informative about the general role of that protein, and can guide further drill-down functional work. As the majority of human proteins are of unknown function, this Atlas promises to be a powerful primary resource in the larger quest to find a role for every human protein. The Atlas extends to diseases including cancers and so has a strong and immediate application in medicine.

The scale of the project is huge (more than 80 staff), highly directed, inter-disciplinary (across gene and protein technologies, immunology, histochemistry, histopathology and bioinformatics), and is located at three main sites (KTH, Uppsala and Mumbai). The project has nucleated more 100 academic collaborations nationally and internationally, and five major proteomic programmes funded by the EU, which will serve to amplify its scale and impact even further.

The Atlas contains more than 6000 antibodies corresponding to 5,200 genes and is expanding by more than 60 new antibodies per week. This corresponds to 25% of the human proteome.

The entire proteome should be completed by 2014 if funding is maintained. The results are well documented and promptly published on the web; this helps explain why the number of traditional publications is less then expected for the scale of operation.

Applied Research Quality

Also applied research quality if world leading, the Atlas represents a valuable resource. The essence of a resource is that it should be made publicly available, and indeed this is the case for the information published in the Atlas. However the information on the Atlas is only one aspect of the resource; the protein fragments and the antibodies represent further aspects. These are costly and time consuming to make available to the research community; for this purpose a company has been spun off that distributes the antibody and fragments for a fee. In addition some results of commercial interest are not placed in the Atlas, and these are made available for commercialization. The Committee was impressed by this model, in which the (sometimes) competing requirements of academia and industry are carefully balanced.

The Atlas can be expected to lead to broad and wide ranging medical applications and to advances in the understanding of the causes of diseases and cancers. Several collaborations have been initiated with human geneticists and clinicians to discover biomarkers of disease.

Scholarship

Scholarship is outstanding across the majority of this UoA. The same considerations for the UoA "Medical Biotechnology" also apply here, with the additional consideration that the Protein Atlas is visible in Sweden and represents a trusted source of information (that can promote the well being of society).

Vitality and Potential

Vitality and potential are excellent across the majority of the UoA. By their nature proteomics projects are limited in scope and time - the proteome is finite and the Atlas will be completed, likely by 2014. The Atlas that emerges will, however, be a resource that will be used and refined long after this initial compilation. Assuming that funding continues, the project should be good for another five years at least.

The issue of renewal of human resources is interesting. Certainly the project has provided useful training for young graduate technicians, who usually move on after a year or two. As the project in its current form is finite, and is highly directed, it would be inappropriate to recruit younger faculty simply to "turn the handle". However the Committee believes the project does offer a once-off opportunity for younger faculty to explore the many avenues of protein function that will be opened up by the Atlas. For example, staff could be recruited to explore the biology of proteins that appeared interesting. It is important that this is done in parallel with the compilation work and before its completion and availability to the world at large.

This UoA can also be seen as the current KTH face of "*Human Proteomics*" rather than a large project with a finite end. If viewed in this light, it will be necessary to undertake recruitments in new areas of proteomics. The Committee noted with approval the development of the newly established "*Nanobiology Group*" with a focus on micro-fluidics, which over the next few years is likely to become central to human proteomics (and other projects involving analysis of large numbers of samples).

Strategy

The strategy of this unit is outstanding with real potential to achieve. The high level of thought that has gone into every phase of the work is most impressive. The project is a series of linked operations each of which has posed significant challenges for mass processing, whether production of recombinant human proteins and high quality polyclonal antibodies, or immunocytochemistry and image analysis. At the same time the costs have been brought down. Not least have been the challenges of managing such a large operation on three sites and with labour mainly from unskilled technicians.

Further plans to compile an Atlas of model mammalian systems such as the rat and mouse will allow access to powerful genetic information to complement the resource, for example, through knockout mice or RNAi knockdown approaches.

During the next few years it will be necessary to plan for the longer-term evolution and maintenance of the Atlas as a database on the Web, following its compilation. In particular, how will the Atlas be curated as the user community refines the information within it?

Actions for Development

The "*Protein Atlas"*, while well known to those in proteomics, and to molecular biologists in Sweden, is surprisingly unknown among biologists and clinicians elsewhere. The Committee believe that there is a need for a high profile research paper or even a paid advertisement to promote the existence and availability of the *Protein Atlas* as a resource to the human biomedical community internationally.

This project is a jewel and its successful completion will have a huge impact. There is much to be gained in maintaining the current momentum of the project which would enable the Atlas to complete a first draft by ~ 2014.

Note the suggestion under "Vitality and Potential" for recruitment of younger faculty to study biology of a selected set of proteins from the Atlas.

UoA: Industrial Biotechnology

General Assessment

Under the heading "Industrial Biotechnology" four very disparate Departments are collected: *Bioprocess Technology, Environmental Microbiology, Biochemistry, and Wood Biotechnology.* Thus the research of the *Department of Bioprocess Technology* research is directed towards the small-scale high-throughput of proteins, particularly in bacteria. It also has a state-of-the-art pilot plant which can be used for both research and teaching of KTH students (the only installation in Swedish universities). The research in the *Department of Environmental Microbiology* is directed towards waste-water treatment and included the isolation of a coagulant protein to replace chemicals. The research in the *Department of Biochemistry* is directed to understanding enzyme catalysis, and developing enzymes for synthetic and analytical applications, and included the development of the pyrosequencing of DNA. The research in the *Department of Wood Biotechnology* is directed towards understanding how extracellular polysaccharides are formed, remodelled and degraded, and how this knowledge might be used to create new materials.

It was difficult to review this UoA as it is in a state of flux with recent retirements of key-faculty members (*Bioprocess Technology*) and impending retirements (*Environmental*

Microbiology and Biochemistry). Furthermore the Head of the *Department of Biochemistry* was not available for interview (although a junior colleague presented some of the work). We therefore had some difficulties in fully understanding the likely future direction of the work in three of the four Departments of this UoA.

Performance Against Evaluation Criteria

Scientific Quality (basic research)

Some of the work on biocatalysis and pyrosequencing was of high international standard; likewise some of the work on carbohydrate enzymology, cell wall polysaccharide synthesis and fiber technology. The Committee particularly liked the work on the xyloglucan endo-transglycosylase, including its use to modify the surfaces of fibers. However the work in the *Departments of Bioprocess Engineering* and *Environmental Biotechnology* was not at this level. The *Departments of Biochemistry* and *Wood Biotechnology* had a variety of international academic collaborations, including collaborative EU projects.

Applied research quality

Elements within the *Departments of Biochemistry, Wood Biotechnology and Bioprocess Engineering* had filed patents, and engaged with industry including spin offs. The Pyrosequencing methodology had led to a fast commercial DNA sequencing machine; the *Biomime* concept could lead to advanced materials; and the Bioprocess Engineering had a significant external funding from industrial contracts for fermentation. The Committee particularly liked the *Biomime* concept to make advanced materials based on wood fibers; it is highly interdisciplinary and included several of the research groups of *Wood Biotechnology* with other Departments of the KTH and Umeå.

There were few interactions between these Departments of the same UoA: the project *Bioamines* (between *Bioprocess Technology and Biochemistry*) to immobilize enzymes on the surface of bacteria for biosynthesis of pharmaceuticals being one such interaction.

Scholarship

Similar considerations as applied to this section of the UoA of Medical Biotechnology indicate that elements of this UoA show evidence of scholarship. In particular as the basic and applied science of *Biomime* are of high quality, and the development of "green" advanced materials would be to the benefit of society, we conclude that this element of the UoA shows scholarship.

Vitality and Potential

The *Department of Wood Biotechnology* had some excellent younger faculty (in particular Brumer) and a lively collection of postdoctoral and PhD students. The future of this Department seems in safe hands. The three other Departments with impending retirements were more difficult to assess. We did not see any evidence that a new appointment would be made to head the *Department of Environmental Microbiology*; we understood that an appointment to the Head of Bioprocess Technology was in progress; and it was not clear whether an external appointment would be made to the Head of Biochemistry.

Strategy

The strategy of this unit as a whole was weak. However, there are present and latent synergies between the elements of this UoA. For example *Bioprocess Technology* and *Biochemistry* propose to develop the BIOAMINES project; similarly it should be possible to develop interactions between *Biochemistry* and *Wood Biotechnology* on the enzymology of carbohydrate synthesis and modification. *Bioprocess Technology* also proposes to develop

collaborations with the Protein Atlas and *Medical Biotechnology* UoAs for production of proteins in mammalian systems. The impending retirements and new appointments offer the opportunity to reinforce or re-engineer these synergies. The UoA therefore has considerable power at this stage to shape its future by the nature of the appointments it will make. It is therefore important that a wider vision is developed for the UoA in which there can be greater interactions between the parts. One possible vision is described below in which the revitalization of *Bioprocess Technology* could be engineered have a wide impact.

In this assessment exercise, we were asked NOT to take teaching into account. However with this UoA a consideration of the teaching responsibilities is quite helpful in deciding on the direction of its research. In a University teaching and research are ideally intermeshed, with the key areas of teaching supported by research in the same areas. In turn this requires research in quantitative analysis of metabolic networks and regulatory networks, as well as the scale-up issues of modern Bio-Industry (both as regards to fermentation (with mixing, mass-and heat transfer) and down-stream processing). If the research of *Bioprocess Technology* were revitalized in this manner, the key-subjects from metabolic pathway-analysis, bio-reactor performance and downstream processes could be applied equally well to give quantitative solutions to environmental problems. Thus the research and teaching of both *Bioprocess Technology* and *Environmental Microbiology* could be directed to include common elements, and develop synergies.

The other UoAs within "*Biotechnology"* could also benefit by revitalization of *Bioprocess Technology*, e.g. by delivery of materials form the pilot-plant as well as analytical thinking as regards to optimization of analytical methods, data-processing and the like. For example there are excellent opportunities for synergies with the *Biochemistry Department*, in the construction of analytical fermentation protocols, in analysis of pathway fluxes and enzyme activities etc. There is no reason why bio-companies might not entrust KTH with the development of new production processes based on bio-catalysis, but the process must be studied as a whole from laboratory to pilot plant. Likewise the *Department of Wood Biotechnology* unit would benefit by a revitalization of *Bioprocess Technology*. Questions regarding rheology, mass transfer (to or from solid substrates), kinetics of break-down or synthesis of biopolymers etc. are well suited for the expertise of a *Bioprocess Technology* unit that works astride the frontier between the engineering and the bio-sciences.