

## Catalysing biomedical innovation

**Babraham Bioscience Technologies Ltd (BBT), the wholly-owned trading subsidiary of the Babraham Institute, is a knowledge transfer (KT) company that leads partnerships to promote successful exploitation of the life sciences to support biomedical innovation. Its activities are focussed around the technology and geographic landscapes of the Babraham Research Campus and it aims to create the premier location for entrepreneurs to establish new and exciting bioventures. In addition, BBT is increasingly reaching out nationally and internationally to promote investment in the life sciences and to generate and sustain growth of the region's healthcare economy. A two-way KT exchange has been generated; it exports technologies derived from the Institute's research programmes and imports and supports exciting new biomedically-orientated companies to the campus.**

BBT's holistic approach is designed to promote the translation of early concepts into commercial reality to ensure that novel discoveries that could be beneficial to society, in terms of health or economy, are exploited. BBT addresses the pinch-points in the commercialisation processes through a flexible approach that adapts to company-specific requirements and the ever changing commercial climate.

BBT's activities promote high levels of interaction between academe, government and industry. The knowledge economy is believed to work best when the three strands come together in particular locations to create dense networks and relationships. As a consequence of this public-private sector axis, BBT is able to commit resources, solve problems, operate independently and look to fund a KT mission and demonstrate increased responsiveness from the publicly-funded research base to the needs of the regional and national economies.

### Core Activities

BBT has created a continuum to promote a culture and environment to stimulate successful outcomes for innovators with exciting new technologies. BBT continues to drive partnerships to translate bio-concepts into commercial reality by bringing together experienced people, finance and the professional and social networks at one geographic location. It is also now networking within the East of England, across the UK and into Europe to further promote international sectoral, rather than geographic or cluster based, support for the life sciences sector.

As BBT has developed its own commercial model, its core activities have come to focus on six themes which it is now looking to take forward:

- Technology/Knowledge Transfer
- Maturation of Technology for investment readiness
- The Babraham Bioincubator
- Promoting Bioincubation
- Finance for the Biotechnology Sector
- Active engagement with policy-makers

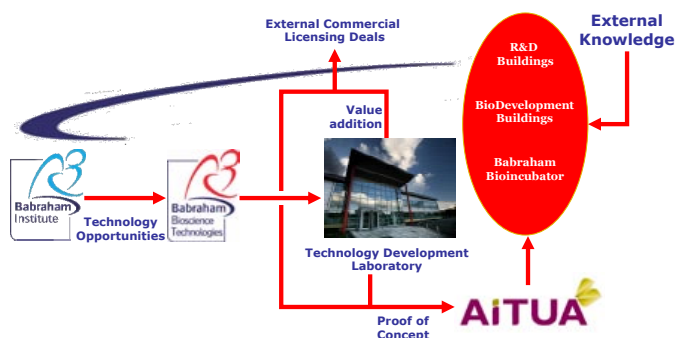
### Technology/Knowledge Transfer:

BBT promotes awareness of KT and supports entrepreneurial spirit within the Babraham Institute, proactively engaging with its user communities; the biotechnology, biomedical, pharmaceutical and healthcare sectors.

BBT manages the Institute's Intellectual Property portfolio, encompassing novel IP and technologies for human healthcare and biotechnology applications. BBT also actively promotes licensing, collaborative development programmes and the creation of spin-out companies. The Institute's Cell Signalling, Developmental Genetics, Cellular Immunology and Neurobiology research is engaged in collaborative projects with national and international companies of all sizes in the pharmaceutical and biotech sectors.

**Maturation of Technology for Investment Readiness:** Translating scientific findings and early stage IPR into commercial opportunities requires technical exemplification to mature it to a point where its application can be readily recognised by industry or the investment community. For biotechnology opportunities, the current financial climate makes this a significant pinch-point in the translation process, a 'Catch 22', where lack of funding prevents exemplification, which restricts value and an ability to raise investment. BBT has addressed this by establishing its own **Technology Development Laboratory (TDL)**. The TDL expanded into new facilities in 2007 to provide fully-equipped molecular biology and chemistry facilities; three full-time development scientists are focussed on translational issues which add value to Institute and external IPR. It offers services and expertise across many scientific fields including molecular biology, protein biochemistry, cell biology and synthetic chemistry. The TDL provides a cost-effective environment for accelerating the translation of technologies by generating proof-of-concept data to exemplify and strengthen patents and add value through exemplification to create investment-ready opportunities.

The BBT facility, which has received funding from East of England Development Agency (EEDA) and the BBSRC, enables BBT to take projects out of the Institute's research laboratories and provide a commercial focus to the development programmes. The facilities also offer third party access to the equipment in the facility and the laboratories themselves as an economic option for innovators to try out their concepts before establishing a company or indeed for companies to move their technologies into new areas which their facilities cannot currently support.



The TDL services offer a new dimension to the Institute's science programmes, particularly through the chemistry services and expertise offering. Promoting more effective translation of Institute science into biomedical products and to date the facilities have helped develop four new technologies, two of which are now forming the basis of new ventures and two are being developed as licensing opportunities.

**The Babraham Bioincubator:** The Bioincubator was established in December 1998 which represented the start of the development of the Babraham Research Campus. It is one of the oldest true bioincubators in the UK and over the last ten years has seen more successful bioventures through its doors than any other facility. Whilst the laboratory and office accommodation on offer has been expanded, the facilities at Babraham have remained fully occupied since 2001. A menu of services is offered to tenants designed to help start-up and early stage companies as they mature over a five to seven year timescale by providing ways to reduce cash-burn during these formative and cash-restricted years.

For those establishing their first company, BBT has in-house business expertise and is linked to a wide network of business service providers in the Cambridge region so that it can offer guidance in the establishment of new ventures. Tenants benefit from access to the Institute's science and technology support services, the TDL as well as administrative, IT and corporate services, providing a supportive environment in which nascent scientific enterprises can flourish.

Until recently most of the new ventures establishing at Babraham derived from the Greater Cambridge Region with others relocating from London, Bristol, Manchester and Scotland. However we now accommodate two international companies, one from China and the other from Austria. In November 2007, BBT signed a Cooperation Agreement with the Japan External Trade Organisation (JETRO) London Centre to promote bioscience-based business, trade and direct investment between Japan and the UK. Under the terms of this Agreement, JETRO will select Japanese individuals or companies that express their intention to enter into the Babraham Bioincubator. If these start-up or early stage ventures are accepted, JETRO will provide the finances to lease facilities and provide consultation for the new companies for up to one year, with the possibility of a further one-year extension. During this time BBT will aid the establishment and growth of the new companies to create viable new businesses in the region.

**Promoting Bioincubation:** BBT, recognised by EEDA as an Enterprise Hub, is working with the other Hubs in the region to promote and support collaboration promoting the region's Life Sciences' Intellectual Capital. That said, BBT is also promoting the need for sector rather than regional support initiatives to promote the bioscience-driven knowledge economy through UK and/or European Bioincubator networks. We have led the establishment of the UK Bioincubator Forum which could provide a ready-made infrastructure through which a UK-wide strategy of support for early-stage life-science businesses could be delivered. The Forum could provide a dynamic and catalysing interface to create an additive social network. The Bioincubators could bring multidisciplinary expertise to interface effectively with national and regional government departments, RDAs, the Research Councils, academe, private sector life science industry and the investment community.

The potential for Bioincubators to network obviously extends to interactions with EU counterparts. The European network creates international connections to nodes that can feed into national networks to promote the internationalisation of the early stage ventures in all the Bioincubators. BBT is working with partners in the Council of European BioRegions (CEBR) Bioincubator Special Interest Group creates the means to develop this 'hub and spoke' model across Europe.

**Finance for the Biotechnology Sector:** The inherent risk associated with investment in the life sciences sector and the biomedical (Red Biotechnology) sector in particular, manifests itself in the paucity of investment capital available to early stage bioventures. BBT addresses this by providing direct links between the investment community and bioventures via the twice yearly Biotechnology Investment Forum. The events bring together start-up and early stage ventures looking to secure investments of £K100 to £M5 and those groups and individuals in the Business Angel and Venture Capital communities interested in the sector.

In a more proactive way BBT has established and invested in Aitua Ltd ([www.aitua.com](http://www.aitua.com)), formerly Babraham Bioconcepts Ltd. This 'investment vehicle', directed at the commercialisation of Intellectual Property in the life science sector, has a 10-year pipeline agreement with the Babraham Institute. It creates value for its shareholders and partners by actively designing, nurturing and growing companies, building them around novel and defensible IP with products that address a significant market need. Aitua drives early commercial activity and ensures management and shareholder interests are aligned to achieve an early exit.





**Active engagement with policy-makers:** As BBT has developed the interface between the Public, Third and Private Sectors as a means of delivering a successful KT remit, we are now well placed to address policy issues within the region and nationally. BBT will be looking to engage the representational groups from the Biotechnology sectors, Regional Development Agencies, National Agencies and Government to promote the bioscience-based Knowledge Economy. BBT is leading the UK Bioincubator Forum and discussions in Europe, with a view to generating infrastructures that promote larger geographies to support life sciences-specific networks transcending regional/national boundaries. These infrastructures will provide interconnecting webs to create an innovation ecology that reaches out from current centres of excellence to generate connectivity between clusters and cities.

**The Babraham Research Campus:** The Babraham Institute and BBT, supported by the BBSRC and EEDA, are engaged in a £130 construction programme to remodel the site to develop the Babraham Research Campus. The objective is to make the campus the location of choice for those establishing bioscience enterprises in the UK. The campus already provides a unique and highly successful research and commercial environment, one that actively fosters innovation and plays a pivotal role for biomedical start-up companies in the Cambridge region.

The Babraham Research Campus is a true Science Park, linking the blue skies academic research of the Babraham Institute with commercial excellence. The juxtaposition of companies with the Babraham Institute allows synergistic relationships to flourish between the academic and business communities. Synergy is key to the Babraham Bioincubator concept; ventures must be developing technologies or products that are of relevance to human healthcare and the biotechnology and pharmaceutical sectors.

As part of the UK Science Base, the Babraham Research Campus contributes to the wealth creation, quality of life and public understanding of science objectives of Government. Consequently, BBT has established a reputation for successfully translating good science and technology into sound business opportunities through developing partnerships for wealth creation.



Mr Phil Willis MP, then Chair of the House of Commons Science and Technology Select Committee, officially opened Babraham's first BioDevelopment building, Minerva, in June 2006 and is pictured with Dr Richard Dyer, former Director of the Babraham Institute and Non-Executive Director of BBT Ltd.

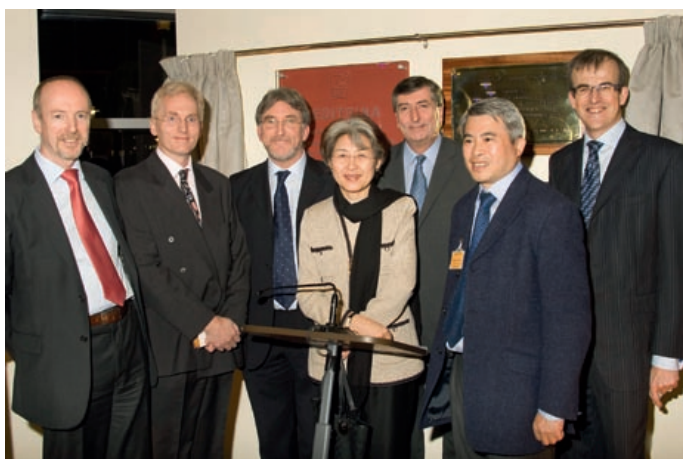
The exceptional commercial facilities, offered at flexible and competitive rates, have been fully occupied since 2001. Around 30 companies, employing over 300 staff, currently reside on the campus, occupying 72,500 sq ft of bioscience facilities provided within our Bioincubator Buildings and our two BioDevelopment Buildings, Minerva and Meditrina.

BBT's latest building, Meditrina, was completed on 24th August 2007 and offers purpose built office and laboratory accommodation - fully fitted units of 1,000 sq ft. BBT commissioned this building to meet the incubation demands on the campus and the building was fully leased within three months to tenants either growing out of our existing facilities or relocating to the Babraham Research Campus.

The companies on the campus today are developing a range of exciting new biomedical products including:

- Drug discovery with core interests in the treatment of pain, inflammation, obesity, Alzheimer's disease;
- Novel antibacterial agents to address multiple drug resistance;
- New biologics-based platforms for drug development;
- DNA amplifications and sequencing technologies to permit the analysis of entire genomes in days and other technology to generate sequence information from thousands of genomes for use in the discovery of genetic variations affecting common diseases and the development of safer more effective drugs;
- Medical diagnostics for mass screening for colorectal diseases;
- New vaccines for infectious diseases with an initial focus on TB;
- Display, array and molecular evolution technologies to promote drug discovery and improvement;
- Biomaterials and stem cell biology for regenerative medicine and tissue engineering.

The development of the Babraham Research Campus is the Babraham Group's approach to driving an effective and substantial socio-economic impact from the curiosity-driven research-base and R&D facilities associated with the Babraham Institute.



Babraham's latest Bioincubator, 'Meditrina', was officially opened by Her Excellency Madame FU Ying, Ambassador of the People's Republic of China (pictured centre) in November 2007, pictured with: (left to right) Richard Ellis, Chair EEDA; Paul Whiteway, Head of International Sales, UKTI; Prof Michael Wakelam, Director Babraham Institute; Sir Robin Young, Chair East England International; Mr Wang Yonghui, Chairman of the Board of Guangzhou Xiangxue Pharmaceuticals Co.; Dr David Hardman, CEO BBT Ltd.



## Accelerating technology translation

The Technology Development Laboratory's (TDL) mission is to accelerate the translation of technologies into commercially exploitable opportunities. While it is proving to be an asset in developing the technology arising from the Babraham Institute's research, it also offers scientific services to the wider 'bio-community' including academic groups, virtual or established companies, investors and technology transfer organisations. Access is then on a fee for service basis and ownership of the results and associated intellectual property remains with the client. It is particularly designed to support bio-entrepreneurs at the steep and early steps which raise an immature technology to the level where it can form the basis of a fundable business. This is achieved by providing either or both bench space and scientific development services. In keeping with this mission the master word regulating the interaction of the TDL with the technology originator is 'flexibility'.

### Capability

The TDL comprises fully equipped chemistry and biology facilities and provides services and expertise across many scientific fields including molecular biology, protein biochemistry, cell biology, medicinal chemistry and synthetic chemistry. The laboratory provides an environment where biological/medicinal concepts can be developed cost effectively. We are therefore particularly adapted to provide help at the vital 'proof of concept' stage of developing a technology. Because the data the TDL generates could serve as patent exemplification, the laboratory uses patent-safe electronic laboratory books. TDL scientists also understand the strict requirement for confidentiality and the time and cost pressure which accompanies early stage innovation. The TDL also provides services from some of the central facilities of the Babraham Institute on a commercial basis such as custom monoclonal antibody production.

*"I have this great idea for commercial exploitation of our results but it needs to be tested in a novel setting and my lab can not divert resources to do this..."*

*"I have developed an assay to follow a biological process as part of my research, I think it has wider applications and could be commercialised; however, it would need evaluating in these other applications as well as standardising before approaching a commercial partner..."*

*"We recently set up a company to exploit a novel technology, but we are still operating virtually and need to generate proof of concept data to raise more funds before we can invest in our own lab space and human resources..."*

BBT's drivers for creating the Technology Development Laboratory (TDL)



Typical projects performed by the TDL include steps such as DNA cloning, mutagenesis, protein expression in bacterial, insect or mammalian cells, protein purification, enzymatic or cell based assays, screening (low to medium throughput), cell culture, transfection, cell sorting, cloning or imaging; chemistry modelling, library assembly, chemical synthesis and analysis.

The East of England Development Agency (EEDA) recognised the important role that the TDL plays in supporting small enterprises and awarded it a £300K grant to develop its screening facility in May 2008.

### Case study

During their studies on fertilisation (see page 29), Dr Roy Jones' laboratory identified a compound that, in addition to inhibiting sperm-egg binding, had potential as an anti-cancer reagent. Based on the sulfation code concept, it was hypothesised that quercetin-B-D-glucoside sulfate might have anti-angiogenic activity. Blocking neo-angiogenesis is a target of choice in many cancer therapies as it starves tumours of a blood supply as well as preventing metastasis. The TDL played a crucial role in bringing this idea to fruition. The TDL's Head of Chemistry, who brings over 11 years' experience as a chemist in industry, was involved from the early stages and devised a novel series of compounds based on Dr Jones' findings. The TDL biology facility and its Development Scientist then implemented in-house an industry standard cell based assay measuring angiogenesis. This assay was used to screen and evaluate the properties of compounds generated by the chemistry. The data provided by the TDL during this collaboration were included in a Patent Application, strengthening the initial filing and extending its protection to a wider range of compounds.

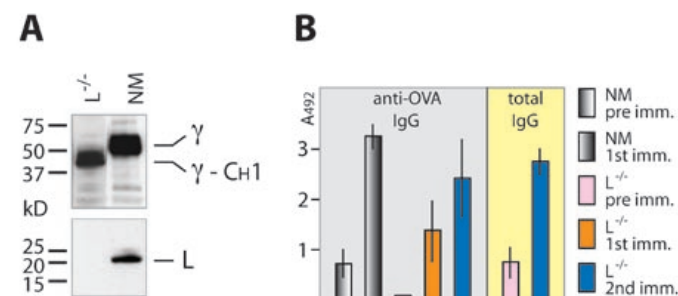


## Spontaneous production of heavy-chain-only antibodies

**Classical antibodies or immunoglobulins (Igs) are produced in all jawed vertebrates and consist of multiple pairs of heavy(H)- and light(L)-chain. The release of single chain antibodies from the cell is normally prevented by chaperone association and degradation. Exceptions are found in camelids (dromedary, camel and llama only) and lower vertebrates (e.g. cartilaginous fish) which release modified H-chain Ig lacking one exon. In camelids, immunisation with viral epitopes can generate high affinity H-chain-only antibodies, which, because of their small size, recognise clefts and protrusions not readily distinguished by conventional antibodies. We have identified a method of producing H-chain-only antibodies in mice, which will allow the generation of single chain antibody repertoires for biomedical evaluation.**

Antibodies are vital for immune defence and various *in vitro* systems have been established to select, modify and produce large quantities for therapeutic use. These include hybridoma technology and phage or ribosome display, which involves specificity selection and obtaining binding domains by PCR. As the most beneficial antibodies have been produced in immunised rodents, 'humanisation' by sequence exchange or CDR-grafting has been applied. In addition, transgenic mice and, more recently, cattle have been derived that produce large repertoires of fully human Ig. Naturally produced human antibodies are seen as most compatible and beneficial for human therapy, for example, the anti-EGF antibody Vectibix for the treatment of certain cancers. Despite this success many antigens, most crucially perhaps viral structures and enzymes, are poorly recognised by conventional antibodies. However, evidence from camelids indicates that these could be detected by H-chain-only antibodies.

The lack of L-chain in the mouse was found to result in expression of particular H-chain-only antibodies. We have analysed the antibodies produced and identified a possible mechanism that leads to secretion of such incomplete but nevertheless diverse and antigen-specific H-chain Ig. Mouse H-chain-only antibodies have a molecular mass of about 96 kD and consist of 2 identical paired  $\gamma$  H-chains (~48 kD each) covalently-linked and lacking the first constant (C) region exon  $C_H1$  (Figure 1A). In size and configuration they closely resemble camelid H-chain antibodies. In serum and B-cells from  $L^{-/-}$  mice a diverse repertoire with many different variable (rearranged  $V_H$ -D[diversity]-J[joining]) and C genes is found. Immunisation, with for example ovalbumin, produced a repertoire of specific IgG H-chain antibodies and generally increased antibody titers (Figure 1B).

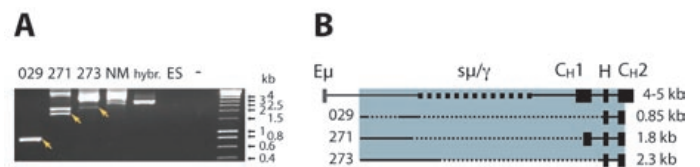


**Figure 1.  $L^{-/-}$  mice produce H-chain IgG without L-chain.** (A) Serum from L-chain deficient ( $L^{-/-}$ ) and normal (NM) mice was separated on SDS-PAGE under reducing conditions, which identified  $\gamma$ -chains lacking  $C_H1$ . (B) Specific IgG antibody responses against ovalbumin (anti-OVA) and total IgG titer, before immunisation (pre imm.) and after the first (1st imm.) and second immunisation (2st imm.).

To identify the process that leads to H-chain release from the cell without L-chain we identified the Ig transcripts produced in spleen cells. Interestingly, both normal size and shorter size products were found. However, only certain B-cells, stained for the plasma cell marker syndecan, produced exclusively the short transcript lacking  $C_H1$ . In combination with sorting these cells by flow cytometry (FACS) and fluorescence *in situ* hybridisation (FISH) we identified H-chain antibody secreting cells and their developmental generation.

A major task was, however, to define the changes in the DNA that produced the shorter RNA transcripts. The strategy used was to amplify, by long range PCR, the region from  $V_H$ D $J_H$  or  $J_H$  to C, which includes the  $E\mu$  enhancer region and the switch sequence to permit IgM to IgG isotype change. This first amplification, using total DNA from cell extracts providing fragments of sometimes over 10 kb, is not readily visible in ethidium bromide stained gels. However, a second nested PCR shows these large genomic amplifications (Figure 2A), which can be cloned and sequenced (Figure 2B). The smaller bands identified large deletions, with the loss of  $\mu$  and  $\gamma$  switch regions and part or all of the  $C_H1$  exon, possibly due to imprecise class-switch recombination events.

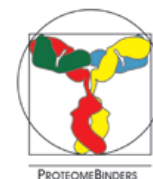
In summary, H-chain-only antibody repertoires can be readily produced in L-chain deficient mice. This finding paves the way for expressing human H-chain-only antibodies in mice. Thus it may be possible to derive new, highly advantageous, antibody-based reagents for the treatment of infections and for therapy considerations not accessible by conventional Ig.



**Figure 2. Class-switch recombination removes  $C_H1$ .** (A) Nested PCR amplifications from 3' $E\mu$  to  $C_H2$  after initial  $V_H$ D $J_H$  (029) or  $J_H$  (271, 273) to  $C_H2$  amplification of sorted spleen cells. The numbers, 029, 271 and 273, indicate different clones (marked by arrows). DNA from normal mice (NM), a hybridoma (hybr.) and (germline) ES (embryonic stem) cells, as well as no DNA (-) served as controls. (B) Map of the clones with  $E\mu$  and  $C\gamma$  exons,  $C_H1$ , hinge (H) and  $C_H2$ , indicated by boxes. The deleted region is represented by dotted lines, the switch region,  $s\mu/\gamma$ , by the broken line and the size of the normal (top) and shorter products shown in kb.

### Publications

- Zou X *et al.* (2007) Heavy chain-only antibodies are spontaneously produced in light chain-deficient mice. *J Exp Med* **204** 3271-3283
- Brüggemann M *et al.* (2007) Selection strategies III: transgenic mice. In: *Handbook of Therapeutic Antibodies* (ed. Dubel S) 69-93 Weinheim, Germany: Wiley-VCH
- Brüggemann M *et al.* (2006) Heavy-chain-only antibody expression and B-cell development in the mouse. *Crit Rev Immunol* **26** 377-390



## Protein characterisation, selection, evolution and arraying

Our group applies proprietary technologies and expertise in protein structure, engineering and display to the characterisation and optimisation of antibodies and protein interactions. We have developed ribosome display as a cell free technology, which allows the selection of binding molecules from very large libraries. We have introduced *in situ* protein array technologies to address shortcomings of conventional array methods. We have collaborated in high resolution structure determinations of autoantibody complexes, such as the rheumatoid factor of rheumatoid arthritis. We are involved in largescale EU projects and coordinate efforts under the 6th and 7th Framework Programmes to establish comprehensive resources of affinity reagents covering the human proteome, together with tools for their use and application in analysis of biobanked samples. Our research is translated on the Babraham Research Campus within Discerna Ltd. ([www.discerna.co.uk](http://www.discerna.co.uk)).

Ribosome display is a cell-free technology which we pioneered for the selection and evolution of antibodies and other proteins encoded by DNA libraries. Individual nascent proteins are linked physically to their corresponding mRNA in stable protein-ribosome-mRNA complexes, followed by selection for binding to specified targets (Figure 1). By associating proteins with the genes encoding them, selected candidates can be readily refined in further rounds of targeted mutagenesis and selection (molecular evolution). Freedom from the constraints of cell-based systems allows enormous libraries of diverse sequences to be generated by PCR, maximising the chances of identifying a functionally relevant protein as a product lead. We use novel ribosome display methods to maximise efficiency of selection of recombinant human antibody fragments and improve them by directed molecular evolution.

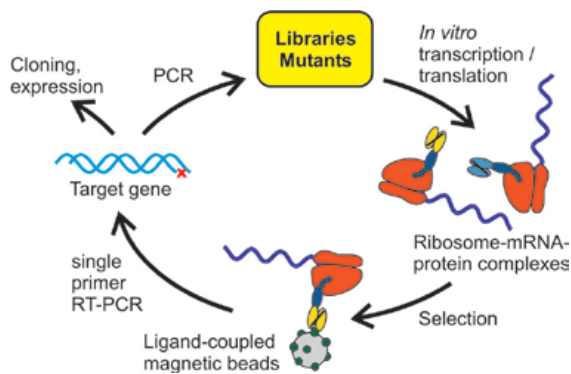


Figure 1. Schematic of ribosome display cycle.

DAPA (DNA array to protein array) is a new protein array technology originating from our group, which allows the 'printing' of replicate protein arrays directly from a reusable DNA template array (Figure 2). DNA template arrays are generated on glass slides by spotting of PCR products encoding the proteins of interest with an immobilisation tag. When a protein array is needed, the DNA array is assembled into a 'sandwich' with a membrane, soaked with a cell-free protein expression system, and a second glass slide functionalised with a tag capture substrate. Protein synthesis originates from the DNA array spots and proteins are immobilised on the capture slide. This allows protein arrays to be made directly prior to their use. Moreover, repeated copies of the protein array can be made from a single DNA array. DAPA is complemented by our recent developments of an optimised double hexahistidine tag for immobilisation and a fusion strategy with the immunoglobulin C $\kappa$  domain for enhanced *in vitro* expression of protein. The arrays will be used to characterise binders and identify protein interactions.

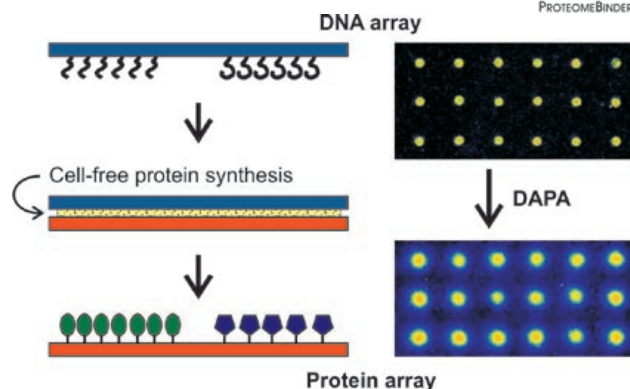


Figure 2. Schematic (left) and example (right) of DAPA, showing an array of GFP protein after immunofluorescent detection.

Our group has also pioneered the structure determination of human autoantibody complexes. A recent example is the crystal structure of the human rheumatoid factor RF61 as a complex with IgG Fc (Figure 3), a collaboration with King's College London, CNRS and CEA Gif-sur-Yvette (France) and the University of California Irvine (USA).



Figure 3. Structure of the RF61 / Fc complex showing two RF61 Fab binding to human IgG1 Fc.

There is a widely acknowledged need for comprehensive generation of well validated protein affinity reagents in the proteomic era. We coordinate pan-European efforts for the creation of a resource of binding reagents for characterisation of the human proteome. ProteomeBinders ([www.proteomebinders.org](http://www.proteomebinders.org)) is an EU FP6 infrastructure coordination project, which will be complemented from 2009 by AffinityProteome, an FP7 health project linking academic and SME partners. Jointly with Uppsala University, we also coordinate biomolecular resources in the new FP7 Biobanks and Biomolecular Resources Infrastructure ([www.biobanks.eu](http://www.biobanks.eu)).

### Publications

- He M *et al.* (2008) Printing protein arrays from DNA arrays. *Nature Methods* **5** 175-177
- He M & Taussig MJ (2007) Eukaryotic ribosome display with *in situ* DNA recovery. *Nature Methods* **4** 281-288
- Taussig MJ *et al.* (2007) ProteomeBinders: planning a European resource of affinity reagents for analysis of the human proteome. *Nature Methods* **4** 13-17
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