Fully Human Domain Antibody Therapeutics: The Best of Both Worlds

By combining the therapeutic benefits of small molecule drugs with those of fully human antibodies, Domain Antibodies are expected to have strong therapeutic and commercial potential.

By Robert Connelly at Domantis

Robert Connelly is Chief Executive Officer of Domantis. He has over 22 years’ commercial experience of the life science sector, including that gained in the fields of diagnostics, drug discovery technologies and antibody therapeutics. Prior to joining Domantis, he was CEO of Veritas Pharmaceuticals (Los Angeles, USA), an in vivo imaging start-up company. He spent over five years with IGEN International, latterly as Senior Vice President and General Manager, Life Sciences, where he took part in the company’s IPO and financing rounds, raising $130 million. The first 11 years of his career were spent at Abbott Laboratories in sales, marketing and management positions.

Domain Antibodies (dAbs) are the smallest functional binding units of antibodies. At Domantis, we are applying our proprietary know-how in dAbs to deliver human therapies that address large, unmet medical needs in areas such as inflammation, cancer and autoimmune diseases. Three and a half years after opening our laboratories, we have a dozen proprietary therapeutic programmes underway, and an additional eight therapeutic programmes with partners. A third of these have reached a preclinical stage and several are expected to begin clinical trials in late 2006. They include dAb products to address chronic obstructive pulmonary disease, rheumatoid arthritis, lupus, asthma, solid tumours and multiple myeloma.

In this article, I aim to cover some of the unique characteristics of dAbs, which give them particularly strong therapeutic and commercial potential. This potential is derived from the fact that dAbs combine many of the advantageous characteristics of traditional small molecule drugs and conventional human antibodies, thereby offering patients and clinicians ‘the best of both worlds’.

**DOMAIN ANTIBODIES**

Domain Antibodies (dAbs) are less than a tenth of the size of a full antibody and correspond to the variable regions of either the heavy (VH) or light (VL) chains of human antibodies. Domantis scientists have used the variable domains sequences of human antibodies to create a series of large and highly functional libraries of fully human dAbs, with each library comprising at least 10^10 different dAbs. The dAbs selected from these libraries are both specific for their biological target and are well folded and well expressed.

The Domantis dAb libraries are a rich supply of drug leads, but before I turn to the therapeutic potential of dAbs, I need to underline the fact that they can be made cost-effectively and with relative ease. dAbs express at substantially greater yields than full antibodies or other antibody fragments, like Fabs and scFvs. And unlike conventional antibodies, dAbs are amenable to a wide range of manufacturing processes – including bacterial, yeast and mammalian cell expression. Their small size should also allow for higher molar quantities per gram of product, providing a significant increase in potency per dose. This combination of expression yield, cheaper manufacturing alternatives and dosing flexibility should lead to a significant cost of goods reduction compared with full antibodies and other antibody fragments. Furthermore, the proprietary selection technologies we use ensure that
our dAbs are extremely stable and resistant to harsh conditions, which circumvents some of the delivery, storage and shelf-life issues associated with full antibodies.

The Domantis product engine supports the rapid generation of dAb leads, such that a constant supply of early stage molecules is available to progress into preclinical evaluation. The robustness of our technology allows us to take 15 discovery programs from receipt of target to preclinical development in 18 months or less, with 35 bench scientists. Remarkably, we have had no attrition to date, and have succeeded in all 10 *in vivo* efficacy models performed. We are almost spoilt for choice in terms of the number of drug leads we can take forward and the range of diseases they might address. Hence, our plan is to out-license several of our preclinical leads in the next 12 months, whilst we take several dAbs into the clinic. Our proprietary and partner dAb therapeutics will offer many unique product advantages to doctors and patients, some of which I will outline below.

**DUAL TARGETING DOMAIN ANTIBODIES**

Many human illnesses are multifactorial, involving a number of targets, so the creation of potent, dual action dAbs should lead to better therapies for a broad range of disorders. Conventional antibodies bind strongly to a single therapeutic target. Although attempts have been made to produce antibodies that can bind multiple targets, most have been hampered by manufacturing and purification issues. Domantis has successfully created Dual Targeting antibody molecules that are fully human, bind two separate targets and can be manufactured using industry standard manufacturing processes in dimer, Fab-like or IgG formats.

Natural antibodies have two different variable regions called V\_H and V\_L that come together to bind a single target. At Domantis, we have shown that the V\_H and V\_L regions of natural antibodies can be replaced with pairs of fully human dAbs to create potent molecules that bind two different therapeutic targets.

Dual Targeting dAbs will create new market opportunities by offering novel therapeutic rationales, better efficacy and increased patient coverage. We are currently developing dual targeting dAbs against cytokine targets for inflammatory diseases and respiratory diseases, tumour antigens present on the same tumour cells for improved targeting and growth/angiogenic factors for solid tumours. Our lead dual targeting dAb product has now reached the preclinical stage and a separate dual targeting dAb product has been successfully delivered to Abbott Laboratories for their further preclinical and clinical development.

**TAILORED SERUM HALF-LIFE**

Domain Antibodies can be engineered to allow precise control over both their biophysical properties and *in vivo* half-life to create the optimal safety and efficacy product profile. In December 2004, Domantis launched its AlbudAb technology, which extends the serum half-life of a therapeutic molecule by several orders of magnitude, from a matter of minutes to several days.
AlbudAbs are fully human dAbs that bind to serum albumin. They can be genetically or chemically conjugated to therapeutic molecules – such as proteins, peptides and small molecules – that would normally have short half-lives in humans. Once injected, the AlbudAb-drug conjugate binds to serum albumin in the bloodstream. Serum albumin has a half-life in humans of three weeks, so drugs with half-lives of minutes can be converted into AlbudAb-drug conjugates with half-lives of several days. AlbudAbs represent a powerful and broadly applicable approach to improving the efficacy of short-lived therapeutic drugs, which we expect to rival the industry gold standards – such as PEGylation, Fc fusion and albumin fusion technologies. Furthermore, they are small and easy to manufacture in microbial expression systems, such as bacteria or yeast. AlbudAb formats for customising the serum half-life of dAbs and other proteins have already been successfully validated through preclinical PK studies and efficacy studies that show enhanced efficacy of proteins formatted in this way.

**DIVERSE DELIVERY OPTIONS**

dAbs are uniquely suited to delivery by injection or (unlike conventional antibodies) non-injectable routes such as pulmonary or oral administration. These options are possible because dAbs are very soluble, stable when freeze-dried or mixed with a range of excipients, resistant to proteolysis in the colon and suitable for encapsulation. After reconstitution, dAbs remain highly soluble, with no loss of functional binding activity. The small size of dAbs should also allow a sufficient dose to be delivered by the pulmonary route to treat topically diseases of the lung (such as asthma) and by oral delivery to treat disorders of the gastro-intestinal tract (such as inflammatory bowel disease). These delivery options should translate into better patient compliance, increased potency and fewer side effects compared with conventional antibodies.

**BROAD THERAPEUTIC RELEVANCE**

Domain Antibodies can address those targets suited to conventional antibodies and other targets which are not. For example, many cell surface receptors are not amenable to antibody therapeutics because conventional IgGs bind dimerically, creating the potential for receptor activation and cross-linking. By contrast, dAbs bind monomerically and do not cause receptor cross-linking, even at high concentration. Furthermore, the compact binding sites of dAbs allow binding to standard antibody targets as well as less accessible targets, such as receptor binding clefts or enzyme active sites. Their small size should also allow for better tumour targeting and tissue penetration, as well as pulmonary delivery to address lung diseases.

**COMMERCIAL OPPORTUNITY**

Therapeutic antibodies are a major commercial opportunity. Over 17 monoclonal antibodies have been approved for use to date and these are expected to generate sales exceeding $9 billion by 2006. As I hope I have demonstrated in this article, fully human dAbs combine the therapeutic benefits of small molecule drugs (formulation and delivery versatility, wide therapeutic target range, low cost) with those of fully human antibodies (enormous diversity, high specificity
and lower toxicity). Thus they have very broad therapeutic relevance.

The commercial potential of dAbs, together with growth of the antibody market, has attracted a good deal of interest from the pharmaceutical industry, and we have already struck a number of collaborative deals – with Abbott Laboratories, ImClone Systems, Tanox and two deals with the Australian biopharmaceutical company, Peptech. A series of dAb therapies derived from these collaborations have moved into preclinical development and should begin clinical trials in late 2006. One of our most recent partnerships is with Argenta Discovery Limited, the respiratory/inflammation drug development company, where we aim to co-develop pulmonarily administered dAb therapeutics for chronic obstructive pulmonary disease (COPD) and other respiratory diseases. The dAbs for this programme are in preclinical testing.

In addition to its commercial appeal, Domantis has also attracted interest from the European Union for several therapeutic collaborations. This year, the company was invited to join the Bloodomics Consortium in a 9 million Euro European Commission funded programme to discover new targets and dAb drugs for the prevention and treatment of cardiovascular disease. As part of this initiative, Domantis will apply its proprietary dAb technology to help validate novel targets identified by other consortium members and to discover dAb-based therapeutics and diagnostics for these targets. The Bloodomics project is dedicated to discovering genetic markers associated with people at risk from atherothrombosis and myocardial infarction. Domantis will receive funding from the EC and will have exclusive commercial rights to any dAbs discovered in the Bloodomics project, as well as an option to license novel targets.

INTELLECTUAL PROPERTY

Domantis has exclusive licences and assignments to an extensive intellectual property portfolio covering dAb libraries and compositions, methods of discovery, formats such as Dual Targeting and AlbudAb, specific dAbs therapeutics, and formulations of dAbs. Today the company has ownership of or license rights to over 200 patents and patent applications.

Much of this patent portfolio is derived from the pioneering work of scientists at the UK Medical Research Council’s Laboratory of Molecular Biology, led by Sir Gregory Winter (founder of Cambridge Antibody Technology (CAT) plc), who published the discovery of Domain Antibodies in 1989. This discovery led to patent rights covering the development and use of Domain Antibodies derived from any species, and led Sir Gregory and Dr Ian Tomlinson to co-found Domantis in December 2000. As a result of this intellectual property position, it is the only company capable of fully exploiting the commercial therapeutic applications of human dAbs.

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LOOKING TO THE FUTURE

Thanks to support from investors and the pioneering work of its scientists, Domantis has made great strides during its short existence, and now boasts a bursting therapeutic pipeline that addresses many huge markets. The best, however, is yet to come. In the next 18 months, our first clinical trials will commence, as will the first trials of our partner dAb programmes and then we can begin to demonstrate the true potential of dAbs in modern medicine. I believe they will have a major role to play in the health of future generations and that they will challenge many preferred treatments currently in use. Domain Antibodies represent the next stage in the evolution of antibody therapeutics – a stage which I believe will see the benefits to patients dramatically expand and their costs decline.

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