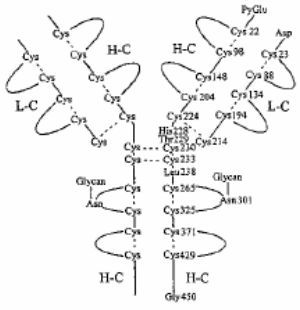
Humanized

Humanization technology is used to generate mAbs in which 90–95% of the sequences are of human origin and 5%–10% are of murine origin. Genetic engineering techniques are used to transfer the murine antigen binding sequences, known as the complementarity determining region (CDR), to a human antibody scaffold. The CDR region is part of the Fab region, which confers the majority of the antigen binding specificity. Humanized antibodies, like chimeric mAbs, carry the ability to effectively induce immune responses because the Fc region is human. The main limitation of this technology is that a mouse mAb with the desired specificity is needed as a starting point.

An alternative approach is called antibody resurfacing but this technique has yet to produce a marketed product. This technique relies on making point mutations in surface residues of the murine antibody, converting the amino acids to those found in human frameworks and thereby 'humanizing' the murine antibody. This process requires alignment of the sequences of the original murine antibody with various human congeners that fulfill requirements of sequence compatibility with the antibody being modified. The first humanized mAb to be marketed was Campath (alemtuzumab, Bayer-Schering), which is used in the treatment of chronic lymphocytic leukemia (**Figure**

Figure 2: Molecular structure of Campath



HC –heavy polypeptide chain; LC light polypeptide chain
Source: FDA[2]

likelihood that Humira will capture sales from Remicade franchise due to superior dosing regime and brand loyalty.

Table 1: Leading monoclonal antibody products in 2009

Product name	Generic Name	Company	Target	2009 Sales (US$ bn)
Rituxan/ MAbThera	rituximAb	Genentech/Roche/Chugai Biogen IDEC, Zenyaku Kogyu	Cancer	3.5
Herceptin	trastuzumAb	Roche/Genentech	Cancer	
Avastin	bevacizumAb	Roche/Genentech	Cancer	4.0
Erbitux	cetuximAb	Bristol-Myers Squibb + Merck Serono (from ImClone)	Cancer	2.0
Remicade	infliximAb	Centocor/J&J Tanabe Sei Schering ugh	Inf tory/ Immu dulatory	4.0 0.5 2
Humira	adalimumAb	Abbo isai	Inflammato Immunomodu y	5.0
Lucentis	ranibizumAb	Roche/Gen & Novartis	Wet age-related macular degeneration	1.5

Source: Company reports, PharmaV imates

Front Runners: pani s

Companies at the top of th Ab ma clude, naturally, those which developed and now ma e leading prod as listed in the above table. Some are from the "big pharma" s le, v thers are ecialist biotechnology businesses, as evidenced by the brief pr es are g address details will be found in an appendix. Often, biotech and p na mpanies join forces in mergers or other forms of alliance.

Abb bora ies

Abbott Lat tories discovers, develops, manufactures and markets pharmaceuticals and medic roducts including nutritionals, devices and diagnostics. The company has expe in the therapeutic areas of animal health, diabetes care, hematology, immunodiagnostics and clinical chemistry, molecular, nutrition, oncology, pain care, point of care and vascular medicine. Abbott has developed a new technology called **DVD-Ig** (dual-variable domain immunoglobulin). This technology could lead to

Ones to Watch: Companies

Agennix AG

Agennix AG was formed by the merging of GPC Biotech AG wi[th] Agennix Incorporated in November 2009. Agennix is developing an oral [for]mulation of talactoferrin for a number of indications including non-small cell l[ung] cancer (NSCLC) and renal cell carcinoma (RCC), as well as other possible non-cance[r] [indica]tions such as severe sepsis and diabetic foot ulcers. Talactoferrin is a unique recom[bi]nant form of human lactoferrin, an important immunomodulatory protein, which acts by [tar]geting key components of the human immune system. The c[om]pany's other drug candi[dates] include **satraplatin** for treating various diseases includi[ng] prostate cancer, ovarian cancer and small cell lung cancer, and **P[X]-2866**[6], a multi-t[arg]eted kina[se] inhibitor, indicated for solid tumours. **Talacto[fer]rin** has recei[ved] Fast Trac[k] [desig]nation from the FDA for its indication and a Special Protocol Assessment (SPA) was completed with the FDA for the FORTIS trial. The c[om]pany entered into a license agreement with Yakult for satraplatin in Jun[e].

Akebia Therapeut[ics], Inc.

Akebia Therapeutics, In[c.] develo[ps] small molecule therapies for the treatment of anemia and vascular disease[s] was found[ed] in 2007. It is engaged in the development of **HIF-[PH]** (hypoxia inducible factor prolyl hydroxylase) inhibitors and **human protein tyrosine phosphatase beta** (HPTP beta) inhibitors targeting Angiopoietin-2. The HPTP beta inhibitors modulate Angiopoietin-2 activity and are useful in the treatment of retinopathy and cancer. Akebia's product pipeline consists of 1) **AKB-6548** and **AKB-4924**, selective oral HIF-PH inhibitors for the treatment of anemia; 2) **AKB-9778**, human protein tyrosine phosphatase beta, for vascular leak syndrome peripheral artery disease.

Biovitrum AB

Biovitrum AB was established in 2001 as a spin-out from Pharmacia. Its research expertise is focused on development and production of biotechnology therapeutics in the areas of haemophilia, inflammation/autoimmune diseases, cancer supportive care

recombinant myelomas or hybridomas. CHO cells and myeloma cells have proved more attractive for large-scale production as they produce larger quantities of antibody and are more stable than hybridomas.

Therapeutic Proteins: Production Challenge

Although post-translational modification (PTM) has been discuss[illegible] as an engineering approach in protein production, recombinant proteins are pro[illegible] several types of unwanted PTMs that can reduce their effi[illegible]y and limit shelf life. [illegible]ome cases these modifications can also lead to unwanted si[illegible]ffects, such as triggering an immune reaction against the therapeutic prote[illegible]

The ability to perform complex PTM[illegible] one of the m[illegible]or reasons [illegible] majority of biotherapeutics are manufactured in ani[illegible]ells. Ind[illegible], only a few biopharmaceutical proteins such as albumin (Rec[illegible]bumin, mad[illegible]ovozymes) and insulin (e.g. Insulin Lispro made by Lilly and Novo[illegible]rgo simpl[illegible]difications such that they can be manufactured using yeast or ba[illegible]ria. [illegible] most [illegible]valent modifications include variable glycosylatio[illegible]isfolding [illegible]nd ag[illegible]ation, oxidation of methionine, deamidation of asparagi[illegible]nd g[illegible]e, and proteolysis. Detecting and preventing these m[illegible]ifications has bec[illegible]a major c[illegible]llenge for the biotechnology industry.

PTM glyc[illegible]ylati[illegible]

Glycosylatio[illegible]represe[illegible] th[illegible]ost complex protein PTM, and much research has centered on [illegible]easurement and modification of the *N*-glycosylation process. However, there [illegible]a need for fast and high-throughput assays to detect different [illegible]lycoform[illegible]uch [illegible]s the Procognia system that uses an array of lectins linked to MALDI ma[illegible]spectrometry. Another area for improvement is the reliability of *in vitro* biologic[illegible]ssays for therapeutic glycoproteins. For example, poorly sialylated glycoforms of erythropoietin (EPO) actually perform better *in vitro*, but the effect of clearance by the asialoglycoprotein receptor outweighs the EPO receptor binding advantage, with the result that highly sialylated glycoforms are more effective in humans. Indeed, the half-life of the natural EPO molecule has been improved by