

Table 1c: Sales of Therapeutic Monoclonal Antibodies and Fc-Fusion Proteins in 2009 with Sources of Information

| Product Name | Target | Company | Indication | 2009 Sales in Original Currency | 2009 Sales in US\$* |
|--|----------------|--|--|--|---------------------|
| ReoPro; abciximab | GP IIb/IIIa | Eli Lilly & Centocor (J&J) | Percutaneous coronary interventions | Lilly 2009 Product Sales Jan 28, 2010 - 2009 sales of US\$ 231.5 mln (- 9.7 %) | 232 mln |
| RoActemra (EU); Actemra; tocilizumab | IL-6R | Roche (Chugai) | Rheumatoid arthritis | Roche PR Feb 3, 2010 - Available in 25 countries, 2009 sales were CHF 146 mln (+ 289 % vs 2008) | 150 mln |
| Nplate; romiplostim; AMG-531 | TPO-R | Amgen | ITP | Amgen SEC 10-K 2009 - 2009 sales were US\$ 110 mln (vs 17 mln in 2008 after approval in 08/2008) | 110 mln |
| CIMZIA; certolizumab pegol; | TNF bound) | UCB Pharma (ex Celltech) | Crohn's disease and RA | UCB PR Mar 2, 2010 - 2009 sales were € 70 mln (+ 600 % vs 2008) | 97 mln |
| Mylotarg; gemtuzumab ozogamicin | CD33 + payload | Pfizer (acquired Wyeth) | CD33+ relapsed AML | PDL Biopharma Product Revenues - 2009 net sales of Mylotarg were US\$ 34.2 mln. Off-market since Oct 15, 2010 | 34.2 mln |
| ARCALYST; riloncept; Il-1 trap | IL-1 | Regeneron Pharmaceuticals | Cryopyrin-associated periodic syndromes (CAPS) | Regeneron Pharmaceuticals PR Feb 18, 2010 - 2009 net product sales of US\$ 18.4 mln (+ 192 % vs 2008) | 18.4 mln |
| Zevalin; ibritumomab tiuxetan | CD20 | Bayer Schering Pharma & Spectrum Pharmaceuticals | B-cell NHL | Spectrum Pharmaceuticals Annual Report 2009 - 2009 US sales of US\$ 15.7 mln (vs US\$ 11 mln in 2008) | 15.7 mln |
| Amevive; alefacept | CD2 | Astellas Pharma | Psoriasis | Astellas Pharma Annual Report 2009 - Sales of fiscal year 2009 ended March 31, 2010 were US\$ 13 mln (vs 16 mln in previous year) | 13 mln |

*Conversion rate as of October 26, 2010: 1 CHF = 1.02749 US\$; 1 € = 1.39272 US\$; 1 Yen = 0.0123106 US\$;

goats (GTC, MAT Pharma, Vivalis, Xori).

5.4 Improving pharmaceutical quality

Pharmaceutical quality is a key characteristic for the successful use of protein pharmaceuticals. Intrinsic features of a mab molecule or chemical modification of sensitive amino acids or sequences can cause issues regarding solubility and stability of a pharmaceutical product. There are approaches to analyze such liabilities and to eliminate them through site directed mutagenesis (Lonza, MilleGen, Xencor).

5.5 Outlook

Most of the listed technologies have been developed to improve existing antibody molecules. Some approaches are redundant (glyco-engineering) and will exist in parallel for reasons of freedom to operate. So far the hypothesis of efficacy improvement by glyco- and protein-engineering has not yet been supported by clinical data and remains without validation. With the emerging diversity for lead discovery of antibodies it may be possible to select suitable molecules from the large number of candidates rather than fix certain disadvantages by engineering.

Table 16: Antibody: Druggability, Cross-reactivity, Target Discovery and Others

| Company | Comments |
|--------------------------|---|
| Epitomics | Rabbit mabs can show cross-reactivity with tox species and animal models |
| Ganymed | Tumor specificity by differential screening of expression patterns |
| Immunocellular | Target discovery approach, glyco-epitopes |
| InNexus | Cross-linking by chemical modification leading to oligomerization after binding or membrane penetration |
| Kalo Bios | Special E.coli strain for expression of Fvs during screening |
| Kolltan | Targeting special epitopes in RTKs |
| Merrimack | Careful analysis of target biology, companion diagnostics |
| MSM Protein Technologies | Can address “difficult targets” |
| Nascent | IL2/Mab IL2 for tolerance induction supportd Treg concept |
| North Coast | Target discovery by functional screens |
| Oxford Biotherapeutics | Screen many targets from OGAP database |
| Symphogen | Use synergy testing |

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Executive Profile:

| | |
|---|---|
| Company Name: | Alligator Bioscience |
| Location: | Lund, Sweden. |
| Website: | http://www.alligatorbioscience.com/Home.aspx |
| Founded: | 2001 |
| Origin of technology: | Lund University. |
| Investors (private/public): | Stena AB, Stiffelsen Industrifonden, Walstone |
| Corporate collaboration partner: | AstraZeneca, AxisShield ASA, Bayer Schering Pharma, Enzymes/Roal, HemoCue, ImmuRx, Wyeth Pharmaceuticals, BioInvent. |
| Antibody Project 1: | ADC-1013. Antibody for cancer indication. In collaboration with BioInvent. In research phase. |
| Technology 1: | FIND [®] (Fragment Induced Diversity) technology. Protein optimization techniques. |
| Advantages of technology 1: | This technology can introduce modifications in the antibody structure, traduced in higher efficacy and potency, improved safety profile and decreased immunogenicity. |

Technology: FIND[®] (fragment induced diversity)

FIND (Fragment Induced Diversity) is an in vitro evolution technology that mimics the natural process of creating protein diversity through recombination. Using **FIND** technology the company creates proteins with the desired properties for the development drug candidates. Properties of proteins such as activity, stability, specificity and other molecular functions can be limiting factors that determine whether a biopharmaceutical drug candidate succeeds in becoming an approved drug.

FIND uses recombination of single-stranded DNA. This is obtained by separating the two strands of naturally occurring DNA in the laboratory and then fragmenting them with exonucleases, which are enzymes that break down single-stranded DNA under controlled conditions. With the aid of DNA and exonucleases, a greater proportion of recombined DNA variants can be achieved than with other in vitro evolution methods. This facilitates the rapid identification of proteins with a number of improved properties.

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FIND technology can redesign characteristics of a protein that can be translated into significant clinical benefits, including higher efficacy and potency, improved safety profile and decreased immunogenicity. In the case of antibodies, depending on the antibody origin the affinity might need to be improved. In cases using murine antibodies and transforming these into human format i.e. humanization, the affinity is often reduced and needs to be restored. Affinities are dependent on complex protein-protein interactions, and are therefore suitable for *in vitro* evolution. **FIND** technology introduces mutations and recombines these into the most favorable combinations, and then the best leads are selected using designed functional screening assays.

Claimed advantages:

- This technology can introduce modifications in the antibody structure, translated in higher efficacy and potency, improved safety profile and decreased immunogenicity.

Comments:

- Concept is adding diversity by a DNA display approach