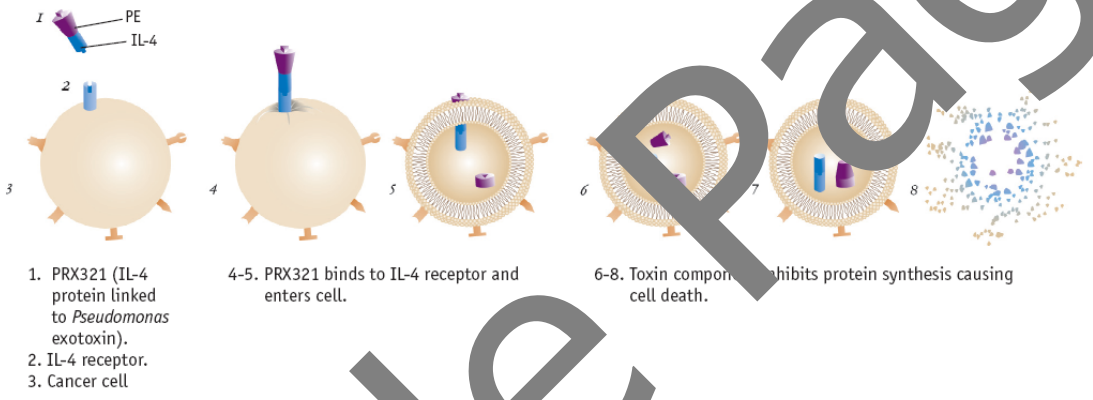
Drug targeting

Targeting fusion proteins

Protox Therapeutics is a leader in advancing novel, receptor targeted fusion proteins. Two novel drug candidates derived from the company's INxin and PORxin platforms are being developed in three clinical programs (Figure 12 and Figure 13).

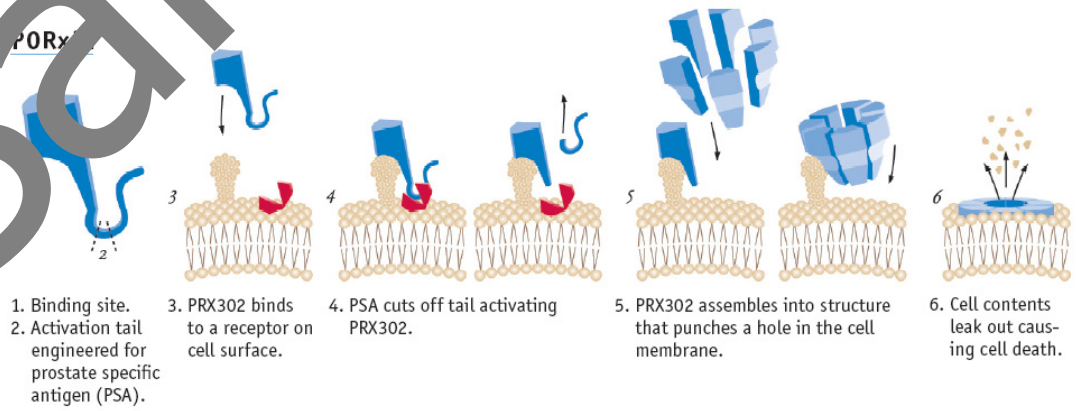
Figure 12: Protox' INxin technology platform



Source: Protox Therapeutics, 2008[i]

A Phase 2a clinical trial valuating PRX321 (INxin) for the treatment of primary brain cancer has been co leted nd the drug has received Fast Track Designation and Orphan Drug Sta s from e US DA.

Figu 13: Protox' PORxin technology platform



Source: Protox Therapeutics, 2008[ii]

Phase 2a clinical trials evaluating PRX302 (PORxin) for the treatment of localized prostate cancer and benign prostatic hyperplasia (enlarged prostate) have also been initiated. PORxin drugs are pro-drugs that are activated by specific proteases produced at elevated levels on the surface of target cells. PRX302 has been generated by engineering the naturally occurring toxin proaerolysin to create a potent agent with a distinct mode of action.

The drug has been engineered so that it is activated by prostate-specific antigen (PSA), an enzyme that is overproduced in patients suffering from prostate cancer and BPH (benign prostatic hyperplasia or enlarged prostate). Once activated, the drug punches holes in the target cells causing the contents to leak out which ultimately leads to cell death. A Phase 2 clinical trial evaluating PRX302 to treat BPH is now underway.

Transdermal delivery

A transdermal drug delivery system (DDS) has many advantages over oral delivery because it bypasses the gastrointestinal tract and the liver, and permits rapid diffusion once the drug passes through the stratum corneum. Transdermal delivery has limitations, however, mostly to do with the poor permeability of the skin to large molecular weight biopharmaceutical and vaccine molecules. Many researchers have explored methods to increase the rate of drug delivery through the skin. These include the use of chemical enhancers, iontophoresis, electroporation, ultrasound and heat, but these have had only limited success.

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[i] http://www.protoxtherapeutics.com/documents/media_kit/ProtoxFactPageMay2008.pdf

[ii] http://www.protoxtherapeutics.com/documents/media_kit/ProtoxFactPageMay2008.pdf

BioGeneriX AG

BioGeneriX AG, part of the ratiopharm group, recognized the importance of biosimilars early on, and has been active in this field since the late 1990s. Establishing BioGeneriX in 2000 was a logical step in the group's business segment strategy. As a wholly-owned ratiopharm subsidiary, BioGeneriX focuses on the biopharmaceutical and clinical development of suitable biosimilar substances.

As a strategic start-up, BioGeneriX AG aims to develop bioengineered drugs for known targets. Backed by a number of functional partnerships and strategic alliances, the unique character of BioGeneriX was shaped in a specific entrepreneurial setting within the existing ratiopharm structure.

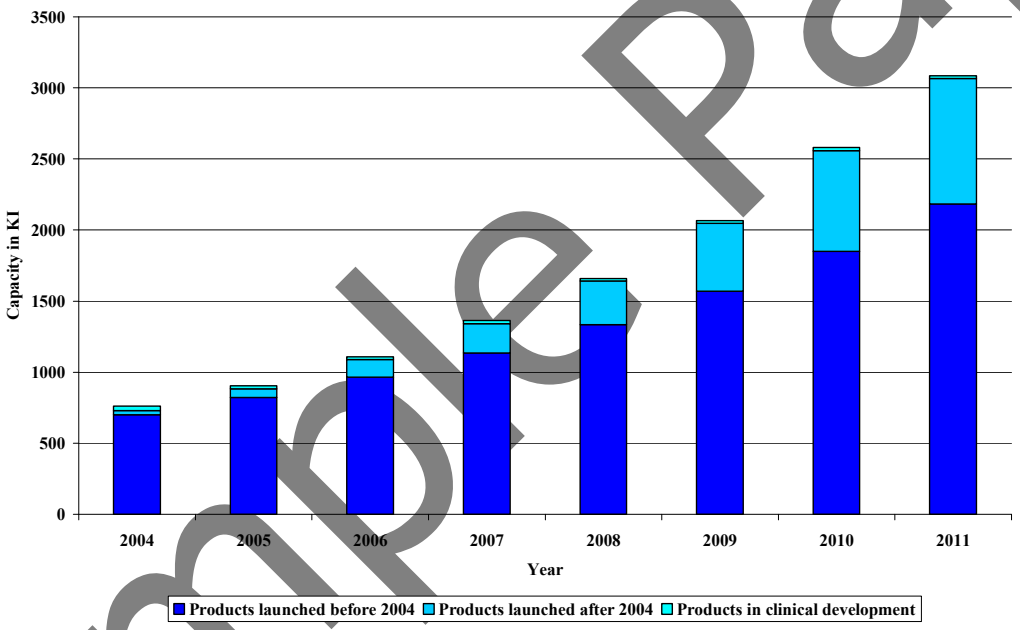
In June 2008 BioGeneriX and Neose Technologies, Inc. announced the initiation of dosing in a Phase 2 trial to evaluate the safety and efficacy of GlycoPEG-GCSF for the treatment of neutropenia associated with myelosuppressive chemotherapy. Neose specializes in using its enzyme pegylation technology to remodel molecules and develop next-generation therapeutic proteins. GlycoPEG-CGSF is being co-developed by the two companies. The multi-country, randomized, double-blind, controlled trial will compare three doses of GlycoPEG-GCSF to the standard, fixed 6 mg dose of Neulasta.

However in September 2008 Neose, which has been struggling, agreed to sell its assets to two drug company collaboration partners for about $43 million. One of these companies is BioGeneriX; the other is Novo Nordisk. The asset sales are the initial step in a contemplated liquidation of Neose.

Manufacturing Opportunities

The realities of devising and executing manufacturing systems for biopharm products were discussed in Chapter 4. For any company capable of addressing those realities and interested in exploiting the market potential, there is an exponentially-growing opportunity (4 times the capacity from 2004 to 2011) in the marketplace, as illustrated by Eric Halioua of the Arthur D Little organization in a presentation made in 2006 (Figure 31).

Figure 31: Global production capabilities, 2004-2011



Source:: Eric Halioua, Arthur D Little Health Care Practice, 2006

Dr Halioua explained that the demand for production capacities, as indicated in the chart, includes antibodies and other biological products already on the market in 2003; antibodies and other biological products marketed after 2003; and products in development. Assumptions as to the annual sales growth of the products marketed before 2003 were 11.6%, and 20.0% for products marketed later. Also, it was assumed that the time required for penetration of the new products introduced on the market would be 2 years.

FDA regulation of biosimilars

For the US market, an abbreviated New Drug Application (ANDA) pathway, used for small molecule generic drug applications, does not yet exist for the majority of biologics, which are marketed under Biologic License Applications (BLAs). However, as pointed out by Griffiths (2004) some biotechnological products have been approved under new drug applications (NDAs) and therefore such drugs could be threatened by generic versions.

In the US, the legislation covering generic substitutes draws on the Drug, Price Competition and Patent Restoration Act of 1984, commonly known as the "Hatch Waxman Act". This is a federal law which provides incentives to support the development of generic versions of off-patent drugs. The approval of generic versions of marketed drugs that are not exactly identical to the original product are allowed via a regulatory route known as a 505(b)(2) filing. The section 505(b)(2) pathway may also serve as a way to obtain regulatory approval of generic versions of certain biological products originally approved under a new drug application (NDA). The section 505(b)(2) applicant must also provide any additional clinical data needed to demonstrate that differences between the original drug and its generic version have not changed the safety and efficacy profile of the product.

The scientific, regulatory and legal framework for the approval of small- molecule generic drugs is well developed, and a regulatory system for approving FOBs (follow-on biologics) was established in Europe in 2006. However, no regulatory pathway currently exists for FOBs, commonly referred to as biosimilars or biogenerics, in the US.

On May 30, 2006, the FDA approved Omnitrope, recombinant E. coli-expressed somatropin (human growth hormone) from Sandoz/Novartis. Omnitrope, itself, is not particularly significant; it now joins many other E. coli-expressed somatropin products in the US market. Omnitrope's approval is significant, because it is the first biopharmaceutical product (follow-on protein) to be discussed in the courts and receive a much-publicized approval as a generic drug under 505(b)(2) regulations.

Prior approvals of somatropins had been based on full NDAs, including traditional-

type safety and efficacy trials, while Omnitrope was approved primarily based on comparisons, including clinical studies of bioequivalence, with Genotropin from Pfizer, the current market leader among somatropin products in the US. Omnitrope's approval does not establish new precedents, since the FDA has recently granted other abbreviated 505(b)(2) generic drug approvals to other biopharmaceuticals, e.g., calcitonin, glucagon and multiple hyaluronidase products, including a recombinant form. The FDA has yet to issue guidelines, either for the "simpler" biopharmaceuticals or the more complex entities however, work is in progress and is currently open for discussion[i].

Approving copycat versions of more complex biologics, such as monoclonal antibodies, vaccines, pegylated proteins and coagulation factors, will be a more arduous undertaking. Many factors, such as culturing, purification and processing conditions, lead to subtle variations in the protein product. As already noted, a key variable of biologics is immunogenicity, which can dramatically affect a patient's response to a biopharmaceutical drug. Even if the same gene is expressed in the same host cells using similar production methods, a follow-on biologic cannot be assumed to be the same as the innovator product.

"What constitutes a biosimilar monoclonal antibody is going to open up a completely new discussion," according to Huub Schellekens, Director of the Central Laboratory Animal Institute at the University of Utrecht, and national expert at the EMEA. The very manner in which monoclonal antibodies are first generated and then selected - by fusing tumor cells with mammalian cells - raises questions over whether it would ever be feasible to consider a monoclonal antibody as a follow-on drug. ""In my view you always need to consider them as a unique protein," Schellekens says[ii].

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[i] http://www.fda.gov/cder/news/biosimilars.htm & http://www.fda.gov/cder/meeting/followOn/Cooney.ppt

[ii] Huub Schellekens, How similar do 'biosimilars' need to be? *Nature Biotechnology* 22, 1357 - 1359 (2004)