

GENETIC ENGINEERING

GEN NEWS

CORPORATE PROFILE

UniTargetingResearch Enhances Protein Production

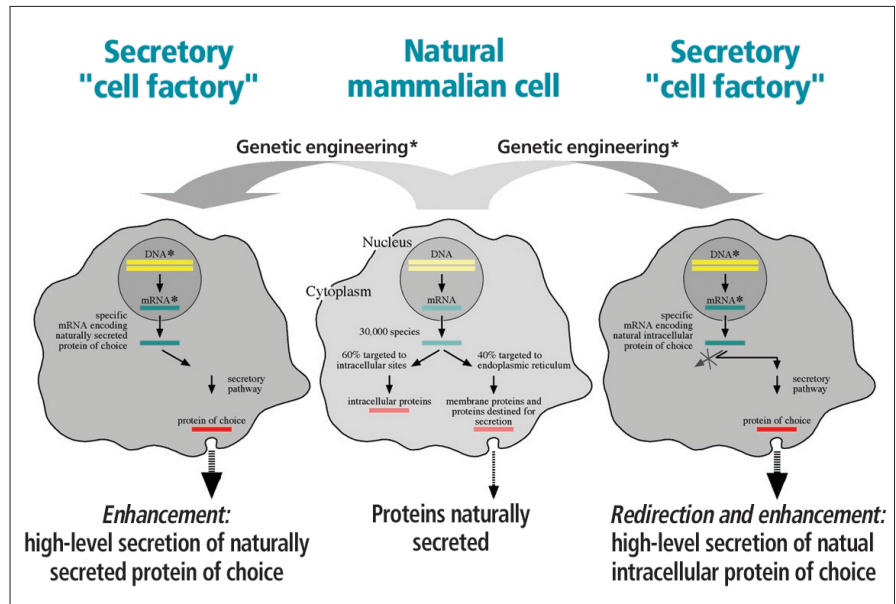
Cell Factories Secrete Intracellular Proteins and Enhance Normal Protein Secretion

Candida Savage

UniTargetingResearch (UTR; Bergen, Norway) produces native proteins using its patent-pending technology designed to exploit the cell's natural mechanisms, to significantly enhance amounts of protein secreted and to promote secretion of naturally intracellular proteins.

By generating genetically engineered cell factories containing selected targeting information for the encoded protein of interest, UTR aims to recover native proteins on a commercial scale without destroying the cells or having to perform multiple purification steps.

UTR's approach to protein production differs from conventional approaches in that it exploits the cell's secretory pathway to enhance protein secretion, as opposed to increasing the



UniTargetingResearch uses a genetic engineering approach to generate novel "cell factories" for protein production by mammalian cells.

scale of production.

Enhancing Protein Production

Traditionally, companies using mammalian systems to produce recombinant proteins seek to scale up production principally by the use of high-expression vectors and modulation of cell-growth conditions. In contrast, UTR aims to increase yield of high-quality proteins by

using a unique genetic engineering approach based on the cell's natural secretory pathway.

"By inserting genetically modified vectors into cells, we can enhance secretion by a factor of more than 10, thus achieving 'supersecretion,'" claims Beate Stern, Ph.D., CSO of UTR.

The company reports that it has discovered key signal elements, the interaction of

which plays a major role in targeting messenger RNA (mRNA) to the endoplasmic reticulum (ER) and directing the encoded protein to the cell's secretory pathway.

This discovery is the subject of pending patent applications and the founda-

tion of UTR's technology platform. UTR works with customers to determine the best set of these key elements for the particular protein of interest and then genetically modifies cells to optimize the protein production.

Proteins possess intrinsic signals that govern their localization within the cell. It is well established that signal peptides located on nascent polypeptide chains of certain proteins direct the synthesis of these proteins to the endoplasmic reticulum, for later export of the protein from the cell.

Researchers at UTR have demonstrated that different signal peptides vary greatly in the efficiency with which they direct secretion of a reporter protein, with one particular class of signal peptides being surprisingly efficient. (The efficiency also varies depending on the type of protein used.)

Particularly striking, the firm says, is its additional discovery that specific areas within the mRNA are also important players during mRNA targeting to the ER. Consequently, by using these areas together with a member of the key class of signal peptides, any naturally secreted protein can, in principle, be exported out of the cell with increased efficiency, UTR asserts.

"Using this method of inserting appropriate targeting elements into the genetic material coding for the protein of interest, both the efficiency of its synthesis and its secretion can be significantly enhanced," iterates Dr. Stern.

To insert the elements, UTR says it has developed a "seamless" cloning method that does away with linkers that could affect the functionality of the signals and/or encoded protein.

Intracellular Proteins

UTR's technology has two major fields of application: high-level secretion of naturally secreted proteins, and secretion of

proteins normally retained within the cell. UTR is currently producing genetically engineered cell lines to achieve its so-called supersecretion of specific proteins for disease application where expertise already exists.

"Naturally secreted proteins are the subject of increasing medical interest and many are already used in therapeutic intervention," says Farzaad Abdi-Dezfuli, Ph.D., UTR's business coordinator. He lists insulin, growth factors, and interferon as examples.

By luring cells to secrete proteins that are normally retained intracellularly, the proteins can be obtained without multiple purification steps. In other methods, intracellular proteins are commonly harvested after destroying the cell and purifying the cellular contents to extract what is often less than a few percent of the total cell content. Apart from being destructive, it is also time-consuming and costly.

This is where UTR's approach may offer an attractive alternative. Customers may use the technology to export a candidate protein out of the cell. Of the approximately 30,000 different proteins produced in humans, on average 90% are synthesized for internal use. "We are thereby dramatically extending the range of recombinant proteins that can be produced," says Dr. Stern.

The company is currently developing methods to efficiently secrete intracellular proteins of potential commercial interest.

Intracellular-protein secretion could be applied to lead-identification and development stages of the drug R&D value chain. Enhancement of secretion of proteins normally released from the cell holds potential for almost all drug development phases and can significantly increase the amount of drug protein available for preclinical, as well as clinical trials, UTR notes.

AT-A-GLANCE

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NUMBER OF EMPLOYEES

10

FOCUS

UniTargetingResearch develops technologies to optimize synthesis of proteins and their secretion from mammalian cell lines. The firm says its platform technology exploits the cell's secretory mechanisms to generate bulk secretion of high-quality proteins for diagnostic and therapeutic applications.

Mammalian Cell Factories

An upsurge in interest in protein-based pharmaceuticals means that mammalian proteins are becoming increasingly important.

Most recombinant proteins are produced using bacterial or other nonmammalian expression systems. These cells, however, do not possess the appropriate posttranslational-processing machinery to ensure proteins are made with accurate structure and full functionality.

In addition, concerns about contamination of proteins expressed in prokaryotes, especially for proteins destined for the therapeutic and diagnostics market, has increased interest in safe mammalian expression systems.

UniTargetingResearch uses mammalian host cells to address these issues. "By generating novel mammalian cell factories, we ensure production of proteins for which native processing and activity are imperative, such as anti-angiogenic proteins and cytokines," states Dr. Stern.

Company Background

UniTargetingResearch was founded in May 2001. The company commercializes technology stemming from an EU-funded project between Profs. Ian Pryme (University of Bergen), John Hesketh (University of Newcastle-upon-Tyne; Tyne, U.K.), and Albert Tauler (University of Barcelona).

A major strength of UTR is its intellectual capital based on the continuing involvement of the inventors, with their scientific know-how and technical expertise. Furthermore, the three scientists bring an important international dimension to the company and provide a base for R&D activities at sites across Europe, UTR says.

The company is jointly owned by private and venture capital investors. The primary shareholder is Forinnova (Bergen), the technology-transfer subsidiary of Sarsia Innovation (Bergen), which provides project development and seed capital financing for firms with promising projects, with a focus on Norwegian biotechnology.

As Erlend Skagseth, UTR's CEO and Forinnova's managing director, explains, "Forinnova uses its industrial competence to develop technology platforms from the laboratory bench to a proof-of-concept stage. At this point, preseed financing is provided by Sarsia Innovation, among other investors, to assist the company to grow to a stage where it can attract venture capital and industry investors."

Young biotech start-ups usually have strong intellectual capital but suffer from a lack of industrial and business experience to commercialize their platform technologies. A strategic decision to offer about one third of UTR shares to **Biosense Laboratories** (Bergen) has given UTR the advantage of tapping into a biotech's commercial expertise.

Biosense Laboratories was established in 1996 to produce biotechnology-based diagnostics for environmental and food-safety testing. The company supplies kits using biomarkers, bioassays, and immunoassays, particularly for industrial-product testing, effluent testing, environmental monitoring, and ecotoxicological research.

Currently, six kits are commercially available, with a further 13 kits in the development pipeline. "Partnerships with **Japan EnviroChemicals** (Osaka) and **Paracelsian** (Ithaca, NY) in 2002, and with **Abraxis Kits** (Warminster, PA)

in 2003, illustrate our international-market penetration," says Prof. Anders Goksøyr, founder and CSO of Biosense Laboratories.

"Having Biosense acting in an advisory capacity for UTR should facilitate the commercialization and global market penetration of its platform technology."

Partnership Opportunities

UniTargetingResearch works with companies to customize solutions for protein production. "We aim to produce proteins that present a challenge in terms of the procedure currently available and the quantity and quality of a specific protein obtained," states Dr. Abdi-Dezfuli.

As starting material, UTR needs, for example, the cDNA containing the coding sequence of the candidate protein and the assay system for the product of interest. UTR then sets to work generating the most appropriate genetic constructs and transfected cell lines to express the gene encoding this protein and, finally, harvesting it on a laboratory scale.

"There is no single model for inducing supersecretion of proteins," notes Dr. Stern. "Based on our experience, we will work to achieve optimal production of our partner's protein," she continues. The process usually takes six to nine months, depending on the type of starting material supplied.

UTR's novel approach to enhancing protein secretion may offer a significant improvement in the protein-production processes. "Several global key pharma players involved in therapeutic and diagnostic proteins have shown an interest in our technology, and negotiations are currently under way," says Dr. Abdi-Dezfuli.

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