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ESBATech AG
Taking Yeast from the Brewery to Drug Discovery

Dominik Escher* and Alcide Barberis

Abstract: ESBATech AG is specialized in pre-clinical research which comprises the identification of disease-relevant target genes (functional genomics) and lead compounds (drug discovery). For identification and validation of target genes, ESBATech has developed three novel functional genomics technologies. These technologies are currently being applied to the field of Alzheimer's disease, breast cancer and ovarian cancer. For lead compound identification, ESBATech has developed two novel platform technologies which are applied to skin cancer. Furthermore, ESBATech has developed a unique antibody platform technology which can be applied to the areas of therapeutics, diagnostics, and functional genomics. All these platform technologies utilize the model organism yeast which enables the rapid and inexpensive reconstitution of *in vivo* molecular components of human diseases. High-throughput screenings to cure a disease at the molecular level or to identify novel target genes are routinely performed by analyzing more than 10 million candidates in parallel within two weeks.

Keywords: Drug discovery · Functional genomics · Lead compound identification and optimization · *Saccharomyces cerevisiae* · Target gene identification and validation

The Company

ESBATech is a spin-off biotechnology company in its early seed phase derived from the Institute of Molecular Biology of the University of Zürich. The company was founded by Dominik Escher, Alcide Barberis and Adrian Escher in September 1998 as a Swiss joint-stock company (AG). Before the official foundation, ESBATech was a winner of the business plan competition 'Venture 98' organized by the Eidgenössische Technische Hochschule (ETH) of Zürich and McKinsey Switzerland. ESBATech started its research activities at the beginning of February 1999. ESBATech has recently received the KTI Start-up label. ESBATech currently employs four scientists and its facilities are located on the campus of the University Zürich at Irchel.

Yeast as a Model System for Drug Discovery

The early stage of the drug discovery process in the pre-clinical phase starts with the isolation of relevant target genes involved in a certain disease and the subsequent identification of lead compounds that affect the function or the product of such target genes in a desired way. More than 90% of the discovered lead compounds fall out of the development pipeline in late pre-clinical and clinical trials. Therefore, there is a need to have more rapid and reliable screening technologies which identify disease-relevant target genes and effective lead compounds in a short period of time. ESBATech performs screenings in the living organism yeast to meet these needs for the drug discovery process. A very important aspect is that yeast and human cells are very similar at the molecular level. For instance, human proteins which activate a gene in human cells fulfil the very same function in yeast. The same is true for yeast proteins when tested in human cells. Thus, yeast represents an optimal model organism in which screenings can be performed in living cells under conditions very comparable to human cells. In addition, yeast has the unique feature that a human gene can be introduced at any desired location in the yeast genome within one to two weeks. Comparable experiments (gene knock-out or gene re-

*Correspondence: Dr. D. Escher
ESBATech AG
Winterthurerstrasse 190
CH–8057 Zürich
Tel.: +41 1 635 31 59
Fax. +41 1 635 68 11
E-Mail: escher@esbatech.com
http://www.esbatech.com

placement) in mice or human cells take several months up to several years. Thus, putative molecular components of a pathological process of a human disease can be reconstituted in yeast in a very short time.

ESBATech has developed several new platform technologies supporting the whole drug discovery value chain as depicted in Fig. 1. Common to all these platform technologies is the model organism yeast, in which molecular components of human diseases are reconstituted. These transgenic yeast cells can still survive under normal conditions. However, when these cells are subjected to special selection, which is different for each platform technology, they no longer survive and are dependent on the presence of a target gene with the required biological function (functional genomics technologies) or on the presence of a biological active substance which does not have harmful side effects on the cell (lead compound identification technologies). Cells containing the required target gene or lead compound can thus survive and divide to form visible colonies (Fig. 2). With these various platform technologies it is now possible to screen for many disease genes and possible lead compounds in the transgenic yeast cells in parallel (more than 10 millions of candidates within two weeks including a first validation). In the following section the different ESBATech platform technologies are outlined.

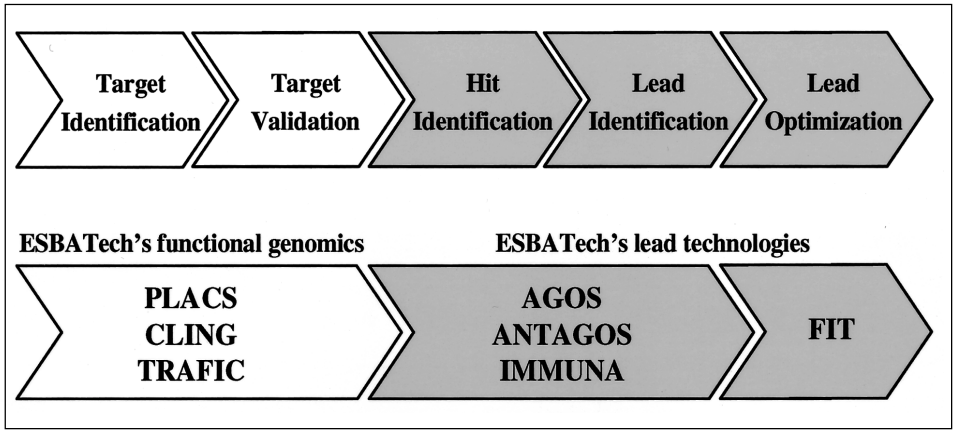

Fig. 1. Value chain of drug discovery aligned with ESBATech's matching platform technologies. Modern drug discovery starts with the identification of disease-relevant target genes (Target Identification). Subsequently the *in vivo* function of the target gene has to be validated (Target Validation). The next step comprises the identification of substances which interact with the protein derived from the target gene (Hit Identification). These hits are then tested whether they also have the required biological activity (Lead Identification). Afterwards these lead compounds are optimized to further improve their activity and to weaken unwanted side effects (Lead Optimization). ESBATech has developed functional genomics technologies for the identification of proteases active in different cellular compartments (PLACS and CLING) and factors involved in gene regulation (TRAFIC). Furthermore ESBATech applies technologies for the direct identification of agonistic (AGOS) and antagonistic (ANTAGOS) lead compounds. Using IMMUNA it is possible to identify single-chain antibodies for intracellular applications. Lead compounds are then further optimized using the FIT technology.

Functional Genomics for Target Gene Identification and Validation

PLACS and CLING Technologies: Several diseases are believed to be caused by the cleavage of cellular proteins by molecular scissors (called proteases). Cleavage could lead to a loss-of-function of the protein or the cleavage product may have harmful effects on the cell. ESBATech has developed PLACS and CLING as novel functional genomics technologies to identify proteases which cleave in different cellular environments (oxidizing and reducing environments). These technologies can also be applied to identify the unknown targets of an already known protease. One of the major

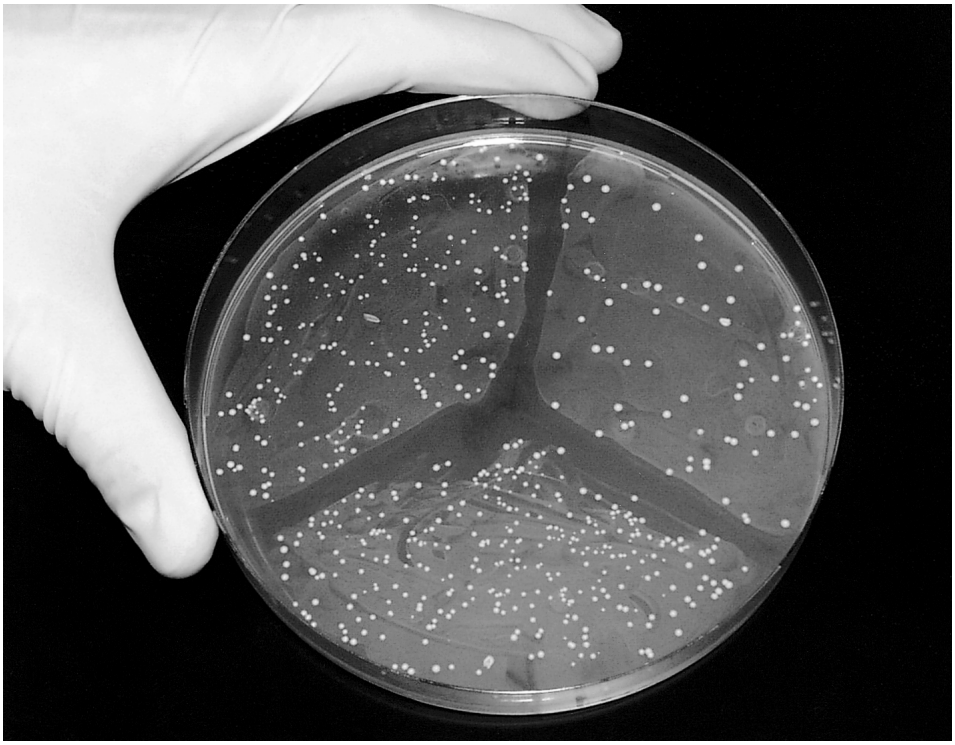

Fig. 2. Transgenic yeast cells containing molecular components of a human pathological process cannot survive under selective conditions. In a screening process, each individual yeast cell tests an independent human gene (for functional genomics) or a different potential lead compound. The cell can only survive if it contains a human gene or a lead compound with the required function, thus allowing replication of the cell which leads to the formation of a visible colony (white dot).

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advantages of PLACS and CLING is that the screening for the unknown protease or its targets occurs in the same subcellular compartment in yeast cells as in human cells. The different compartments within a cell show remarkable differences in terms of acidity, oxidizing environment and composition of factors, and therefore many proteins are only functional in their correct location in the cell. Thus, PLACS and CLING are powerful functional genomics technologies which uncover novel disease-relevant proteases or their targets for subsequent drug discovery. ESBATech currently applies PLACS and CLING in a collaboration with Hoffmann-La Roche in the field of Alzheimer's disease.

TRAFIC Technology: An important task of future drugs will be to specifically modulate expression of genes involved in human diseases. To this purpose, the factors regulating gene expression must be characterized. Up to now, there was no technology available which allowed broad screenings in a living organism to identify new factors regulating gene expression. The unique feature of the TRAFIC technology is that extensive screenings (more than 10 million different candidate genes) can be performed in parallel (within two weeks). This opens up the possibility to uncover networks of factors regulating expression of genes which are involved in a certain disease. Cancer is a typical example of a disease caused by aberrant gene expression. The identification of novel factors involved in aberrant gene expression adds important puzzle pieces to the picture of cancer biology and provides potential new drug targets. At present, ESBATech applies TRAFIC to the fields of breast and ovarian cancer.

Lead Compound Identification and Optimization

AGOS Technology: In several pathological processes, important proteins are modified so that they lose their original function. A consequence of these mutations is, for example, that cells can divide and grow fast, thus leading to cancer. Drugs reverting this modification would therefore restore the original activity of the protein and prevent further growth of cancerous cells. Such a drug would act as an agonist. The ESBATech AGOS technology identifies agonistic lead compounds which show the required biological activity. AGOS is currently applied to identify agonistic lead compounds for factors involved in gene regulation. However, AGOS technology can be applied to any target in the cell.

ANTAGOS Technology: A form of skin cancer (invasive neoplasia) is believed to be initiated by the interaction between two proteins (derived from so-called oncogenes). Many other pathological processes might also be caused by the interaction between two critical proteins which normally does not occur in healthy cells. A drug which can prevent this interaction, thus blocking the two critical proteins, would act as an antagonist and would have the potential to stop the disease. The ANTAGOS technology identifies lead compounds which block interactions between proteins, both inside the cell and on the cell surface such as between receptors and ligands or viruses. ESBATech currently applies ANTAGOS to the field of skin cancer in a collaboration with Prof. Gerard Evan from the University of California in San Francisco.

IMMUNA Technology: Antibodies are preferred tools for biochemical and molecular biology research, diagnostics and medical applications due to their high affinity and specificity to the antigen and due to their high stability. Single-chain antibodies are a shorter version of natural antibodies and basically have the same biological activities. Single-chain antibodies expressed within the cell (*e.g.* cytoplasm or nucleus) are called intrabodies. ESBATech has developed the IMMUNA technology which allows direct screening for antibodies against targets within the cell. This opens up broad applications for the IMMUNA technology: IMMUNA-derived intrabody can be expressed in a transgenic model organism (*e.g.* Drosophila, mice) to specifically interact with a defined part of the target protein, thus knocking out the specific function associated with this part of the protein, while leaving intact the rest of the protein (functional genomics). For therapeutic purposes the antibody can be applied in gene therapy as a highly specific agonist or antagonist of a protein within the cell. Furthermore, IMMUNA-derived antibodies can be applied to the field of diagnostics.

FIT Technology: Immediately after a lead compound has been identified through the application of ESBATech's platform technologies AGOS, ANTAGOS and IMMUNA, it can be optimized using the FIT technology. The required biological function is further enhanced while, at the same time, unwanted interactions which can cause side effects are eliminated. ESBATech has successfully applied FIT to further improve single-chain antibodies for intracellular applications that were identified by the IMMUNA technology.

Outlook

ESBATech aims to become a world leader among the biotechnology companies specialized in yeast-based functional genomics and drug discovery. ESBATech seeks to start collaborations with pharmaceutical companies. The ability to enter into such collaborations, in addition to generation of the required revenues, provides a due-diligence process for which ensures validation and further improvement of the various ESBATech platform technologies. For example, the collaboration with Hoffmann-La Roche was initiated at the blueprint stage. Within a short period of time (less than six months), ESBATech succeeded in integrating this blueprint into the PLACS and CLING technologies and has recently shown the feasibility of the screening systems to Hoffmann-La Roche. This achievement shows the high level of competence and know-how for yeast-based technologies at ESBATech. ESBATech will, besides further applications of the existing platform technologies, also develop novel platform technologies, thus allowing us to occupy a leading position in yeast-based functional genomics and drug discovery.

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