IMPROVING CELL LINES FOR YOUR INDUSTRIAL SUCCESS

acib

ANIMAL CELL TECHNOLOGY & ENGINEERING

Content

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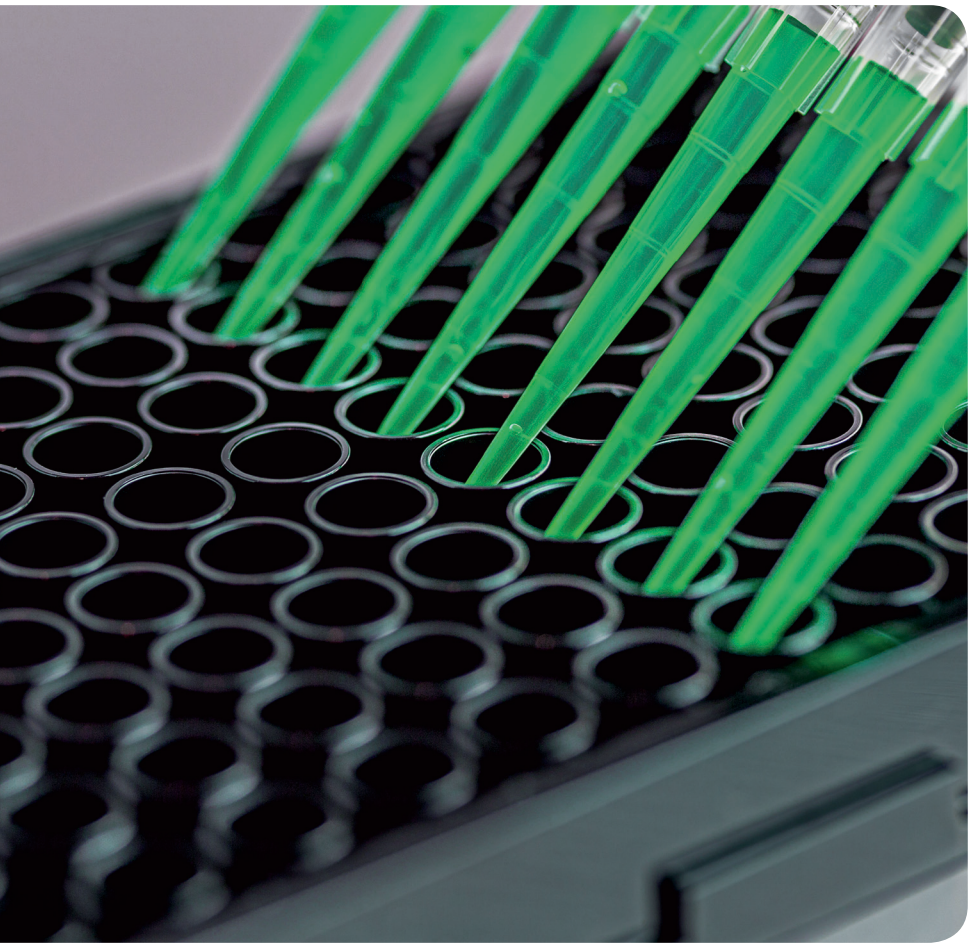
Animal Cell Technology & Engineering

THE STATUS QUO

Over the last years the biologics market has been growing at an ever increasing rate with monoclonal antibodies established as leading products, but with other, innovative formats emerging. Today, therapeutic proteins are mostly produced in Chinese hamster ovary cells, as these CHO cells are able to synthesize proteins with characteristics similar to those in humans.

Despite dramatic improvements, the development of both production cell lines and processes is still time-consuming and challenging. Further enhancements require a detailed understanding of the mechanistic details of how a cell is able to handle high production rates of foreign proteins and sophisticated methods of selecting or engineering cells that manage to do so in an optimized way.

Until these are available, cell line development and robust production processes remain major hurdles for the industry to overcome.



The Challenges

Mammalian cells like CHO are extremely complex, with many layers of regulation and control present. Challenges we have to face when working with CHO include high genomic and phenotypic variation, instability of production, and secretory bottlenecks. These issues lead to high screening efforts to identify the best producer clones, and consequently to high manpower, the necessity for automation, resulting high costs and delays in time to market.

Thus, a major goal of acib is the identification of patterns of gene expression, protein activities and metabolite fluxes that correlate to process relevant properties of production cell lines. Based on these, we design both new engineering strategies to generate cells with optimal performance and process monitoring protocols that reflect the state of the cells.

Our Solution

acib establishes new bioinformatics tools, statistical analyses and mathematical models which enable the identification of relevant parameters to identify the best performing subclone, and subsequently better prediction of cell behavior during bioprocesses. This will lead to reduced costs for R&D, monitoring and control. To reach this goal, one of our exploratory tasks is to expand and improve existing -omics data sets and *in-silico* models.

A major focus of acib lies on the improvement of CHO cells as production platform in key aspects such as enhanced growth rate, productivity and product quality. Established tools include methods to control the epigenome, to analyze and characterize the stability of the genome, as well as CRISPR/Cas9 and other genome editing tools for targeted cell engineering. Based on our knowledge and tools, acib deepens the understanding of complex cellular regulation to enable design and control of processes with increased reliability for industrial applications.

> Our goal is to achieve *in-silico* modeling of cellular processes and metabolism at a level of detail that will allow prediction of cellular behaviour. Therefore, we are co-ordinating a concerted effort of the scientific community to establish detailed databases and bioinformatics tools for the interpretation and use of -omics results.

Prof. Nicole Borth
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EXAMPLES OF OUR PARTNERS

BIOCRATES LIFE SCIENCES The Deep Phenotyping Company

SANDOZ

gsk GlaxoSmithKline

GE Healthcare

sanofi aventis

HOCUS LOCUS

MilliporeSigma

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Chinese Hamster Ovary Cells

TOOLS

BIOINFORMATIC TOOLS

→ Next-generation sequencing
→ ChIP-seq / RNA-seq
→ CHOmine
→ Genome scale metabolic model
...

CELL ENGINEERING TOOLS

→ Genome editing tools / CRISPR
→ FACS
→ RNA-based selection systems
→ Plasmid design
→ Gene-knockout libraries
...

ANALYSIS

→ Genomics
→ Epigenetics
→ Transcriptomics
→ Metabolomics
→ Proteomics
→ Non-coding RNAomics
→ Genomic Stability
→ Karyotype analysis
→ Product quality
...

OPTIMISATION

→ Growth rate
→ Productivity
→ Glycosylation
→ Medium composition
→ Process optimisation
→ Secretion capacity
→ Minimal cell line
...

CONTROL

→ Autologous CHO promoters
→ Enhancer elements
→ Stabilization of phenotype
→ Genomic / epigenetic modifications
→ Defined integration site
→ Defined glycosylation pattern
...

GENOME SCALE INFORMATION
OPENS NEW POSSIBILITIES

In cooperation with leading academic institutions, acib is working on the reference genome of the Chinese Hamster and has also sequenced several cell lines and subclones, made available in the online database http://cho-epi-genome.boku.ac.at and at https://borthlabCHOresources.boku.ac.at. These genome data sets open a new era of possibilities for CHO cell line development and bioprocessing.

CHARACTERISATION / ANALYSIS
DESCRIBES STATUS QUO

Besides genomics, acib is working in the fields of transcriptomics, proteomics, metabolomics and non-coding RNAomics to characterize cells under different process conditions and adapted or selected for different phenotypes. Further, we have established methods to analyze the stability of the genome of a given cell line, such as chromosome painting technology to enable visualization of large scale genomic rearrangements.

GENE / FUNCTION
PROVIDE UNDERSTANDING

acib is trying to identify patterns of gene expression that enable a more thorough understanding of the function of genes, specifically with respect to recombinant protein production. A comprehensive resource of chromatin states has been gathered, which enables to investigate the relative contribution of epigenetic modifications towards phenotype evolution. Besides, acib is working on full gene knockout libraries using paired gRNA-CRISPR technology which might lead to deeper understanding of gene function.

PREDICTION
CONNECTS COMPLEX DATASETS

All -omics based methods generate large data sets that then require statistical and mathematical tools to enable reduction to the relevant and controlling parameters. This interplay between large data sets and learning algorithms for their analysis will finally result in predictive tools that then allow either the design or engineering of a cell factory with just the right properties. So far the first genome scale metabolic model for CHO was generated and verified in cooperation with acib and proved to be useful for diverse applications.

SELECTION OR ENGINEERING
TRANSFERS KNOWLEDGE INTO CELL BEHAVIOUR

The predictive models also allow for the development of tools for specific selection of cells that exhibit beneficial functionalities by random evolution. Alternatively, the gained knowledge can be used for targeted engineering approaches to design cells with desired properties, such as high production capability or enhanced product quality attributes.

We offer years of expertise & the most sophisticated tools

Our expertise covers both bioinformatics tools, including established pipelines for NGS data analysis, development and maintenance of a publicly available CHO database (CHOmine) or the first genome scale metabolic model for prediction of cellular properties, as well as cell engineering tools, including genome editing tools like CRISPR, cell sorting via FACS or novel RNA-based selection systems.
Our expertise spans the fields of large-scale -omics studies such as genomics, transcriptomics, proteomics, meta-bolomics or non-coding RNAomics. Based on these data we are working on the optimisation or control of key parameters of the CHO production platform, like enhanced growth rate and productivity or the stabilization of a desired phenotype.

YOUR BENEFITS

Our expertise enables you to better control the molecular basis of productivity and product quality in mammalian cells to achieve

reduced production costs

of valuable therapeutic compounds and will give you an edge over your competitor.

The Austrian Centre of Industrial Biotechnology

ABOUT ACIB

The Austrian Centre of Industrial Biotechnology (acib) is a top-class international research institution in the field of industrial biotechnology. Since its foundation in 2010 the center of excellence has specialized on the development of innovative, eco-friendly and economical processes for the biotech-, chemical- and pharmaceutical industries using the methods and tools of nature. Presently 200+ coworkers are carrying out research in more than 175 research projects.

OUR RESEARCH DOMAINS

acib carries out research in all field of industrial biotechnology. Its extensive expertise covers 12 research fields from biocatalysis and recombinant protein production to modelling and engineering and bioprocessing.

OUR NETWORK

The non-profit organization with its headquarters in Graz has additional sites in Innsbruck, Tulln, Vienna, Linz (AUT), Bielefeld, Heidelberg and Hamburg (GER), Pavia (ITA), Barcelona (ESP), Rzeszów (POL), Canterbury (NZL) and Hsinchu (TWN) and bundles a consortium of 200 academic and industrial partners. Among the partners are renowned companies such as BASF, DSM, Sandoz, Boehringer Ingelheim RCV, Jungbunzlauer and VTU Technology.

Watch our **blog** & listen to our **podcast** at www.acib.at/news

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