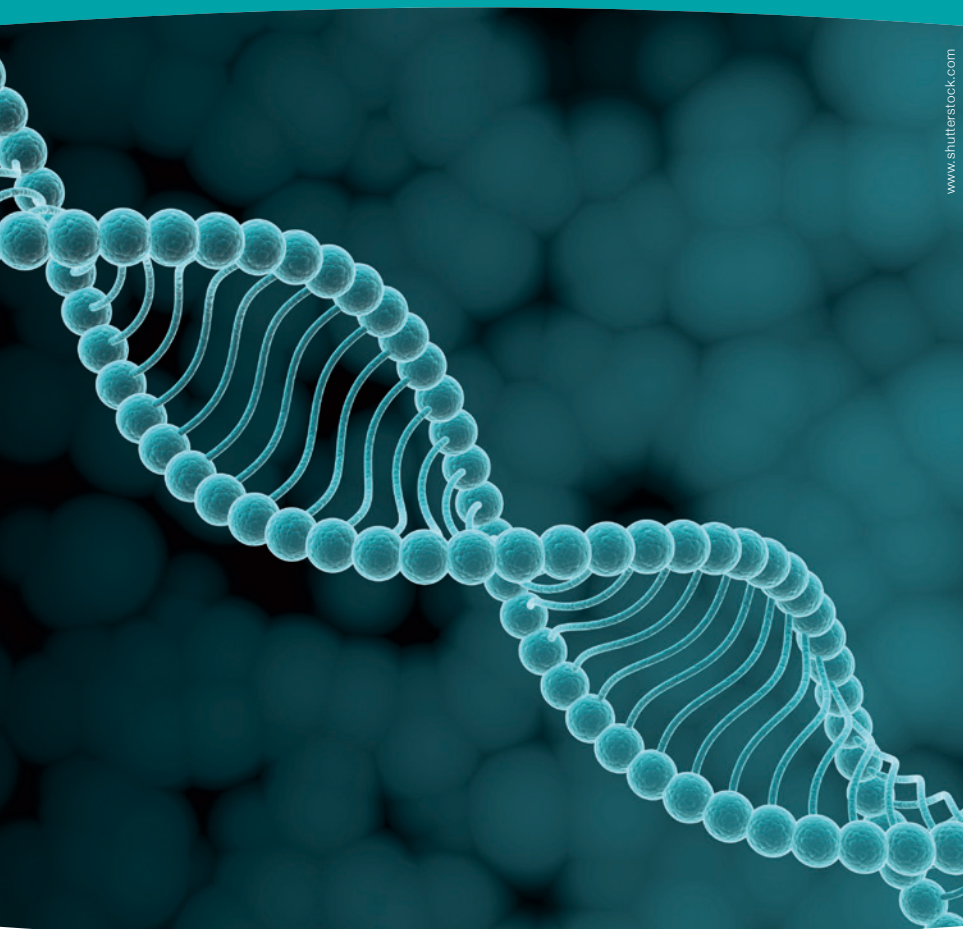




# Animal Cell Technology & Engineering

Improving cell lines  
for your industrial success



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# Animal Cell Technology & Engineering

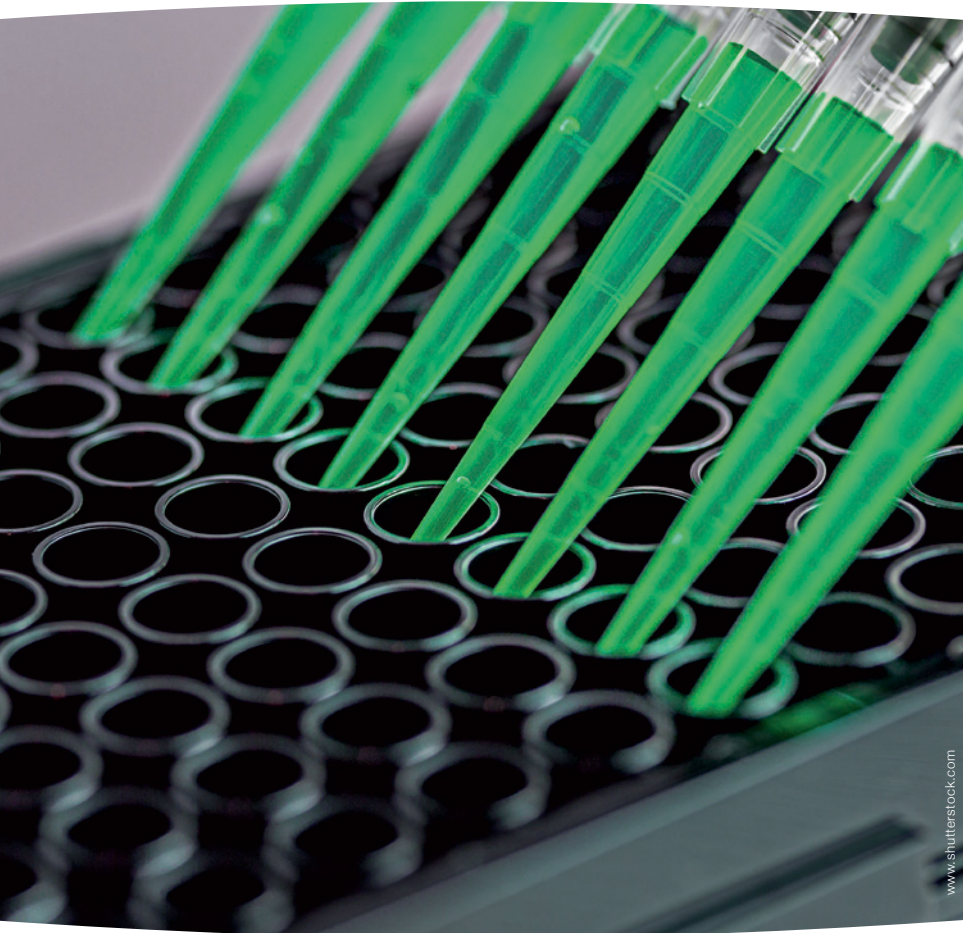
## THE STATUS QUO

Over the last years the biologics market has been growing at an ever increasing rate with monoclonal antibodies emerging as leading products. 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.

Improvements require a detailed understanding of the mechanistic details of how a cell is able to handle high production rates of foreign proteins. Until this is available, cell line development and robust production processes remain major hurdles for the industry to overcome.





## The Challenges

The main problem is that 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, 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, which will deliver both new engineering strategies and process monitoring protocols that focus on the state of the cells.



# Our Solution

**acib** establishes new bioinformatics tools, statistical analyses and mathematical models which enable the identification of relevant parameters and in the following better prediction of cell behaviour 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 with key aspects on increasing the growth rate, the productivity and the 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 prediction 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**  
BOKU Vienna  
acib GmbH

## EXAMPLES OF OUR PARTNERS



# 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
- ...

## OPTIMISATION

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

## ANALYSIS

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

## CONTROL

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

## MAMMALIAN CELL FACTORY OPENS NEW POSSIBILITIES

In cooperation with leading academic institutions, **acib** is working on the reference genome of the Chinese Hamster. Besides the Chinese Hamster, **acib** has sequenced 6 related CHO cell lines, made available in the online database <http://cho-epigenome.boku.ac.at>. These epigenome 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, including 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 the establishment of full gene knockout libraries using CRISPR technology which might lead to deeper understanding of gene functions and in the future to a minimal cell line to enable faster growth and enhanced genomic stability, due to the smaller genome size.

## PREDICTION CONNECTS COMPLEX DATASETS

All -omics based methods generate large data sets that then require statistical and mathematical tools to enable again 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 transferred to targeted engineering approaches for designing cells with desired properties, like high growth rate and production capability.

## 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, metabolomics 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

**acib** uses the concepts of nature to replace traditional industrial methods with new, more economic and ecological technologies. The international non-profit research centre for industrial biotechnology has locations in Vienna, Graz, Innsbruck, Tulln, Linz, Hamburg, Bielefeld, Heidelberg, Pavia, Ljubljana, Rzeszów, Barcelona, New Zealand and Taiwan.

**acib** is an international network of 150+ international universities and industry partners, including Lonza, G.L. Pharma, DSM, Sandoz, Boehringer Ingelheim, Patheon or Shire. Owners are the University of Natural Resources and Life Sciences (Vienna), University of Technology (Graz), Universities of Innsbruck and Graz and Joanneum Research.

At **acib** 200+ scientific employees with up to 30+ years of experience in industrial biotechnology work in more than 150 research projects.

The competence centre **acib** is sponsored within COMET (Austrian Competence Centres for Excellent Technologies) by the BMVIT, BMWFW and the provinces of Styria, Tyrol, Lower Austria and Vienna. The COMET program is handled by the FFG.



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