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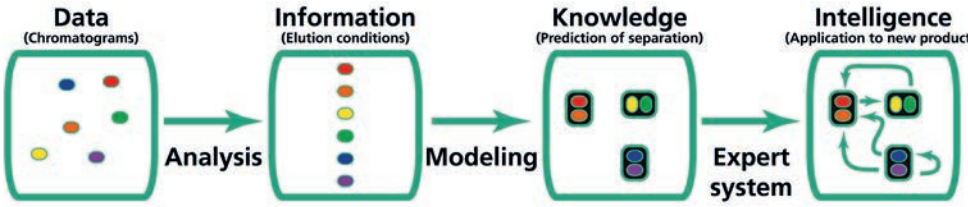
IME

FRAUNHOFER INSTITUTE FOR MOLECULAR BIOLOGY
AND APPLIED ECOLOGY IME

INTEGRATED PRODUCTION PLATFORMS

PROCESS DEVELOPMENT, SCALE UP, GMP-COMPLIANT PRODUCTION AND CONSULTING



Process modeling workflow

HIGH-THROUGHPUT PROCESS DEVELOPMENT AND MODELING

Process development can be expensive and laborious if pilot-scale or even laboratory-scale optimization experiments are needed. Therefore, massively parallelized small-scale systems that facilitate HTS have attracted much recent attention. The Fraunhofer IME IPP Department (Integrated Production Platforms) is establishing a fully-automated and integrated platform that will facilitate the screening of gene variants encoding protein-based APIs using our proprietary PCP and cell-free systems as well as in customer-selected expression hosts, combined with parallelized chromatographic purification schemes and protein analytics such as capillary electrophoresis (CE) on the same device. This platform will be complemented by commercial HTS cultivation systems allowing the screening of batch and fed-batch conditions in microtiter plates and 250-mL scale for microbial and cell culture-based processes. The experiments are typically built around a design-of-experiments (DoE) strategy that provides rich information, and the generation of descriptive models for the complex influences of different process parameters, which in turn facilitates rapid process optimization. This approach is complemented by mechanistic models describing protein expression and chromatographic purification, allowing many conditions to be screened *in silico*. The most beneficial conditions can then be tested and confirmed using the HTS platform before the process is scaled-up, supporting the quality-by-design (QbD) approach recommended by the regulatory authorities. We therefore encourage you to challenge our current HTS capacities and help us to push this technology forward!

Filtration process development

EVERYTHING STARTS WITH YOUR BRILLIANT IDEA

Biotechnology is a key 21st century technology. As such, biotechnological products are already changing our lives, for example as active pharmaceutical ingredients (APIs) in new medicines that facilitate the treatment of challenging diseases such as cancer. The number of such biopharmaceuticals has increased over the last year, accounting for about 30% of all new medicines approved by the regulatory authorities. But before any such medicines enter the market, they must undergo an extensive development process comprising API design, proof of concept, process development and scale up, production under good manufacturing practice (GMP) conditions, clinical trials and regulatory approval. Although such processes may involve different steps and unit operations, they all trace back to a common origin: a brilliant idea for a new API. In the past, global pharmaceutical companies were not only the manufacturers but also the developers of APIs, and thus covered the entire development chain. This approach has changed more recently because recombinant DNA can now be used routinely in even the smallest laboratories, and the associated costs have fallen dramatically. Tremendous creative and intellectual potential has therefore been unleashed, enabling academic research groups, start-ups as well as small and medium enterprises (SMEs) to fuel the biopharmaceutical development pipeline with their own ideas.

We accelerate your biotechnology research towards clinical trials

If you have an idea, the Department of Integrated Production Platforms (IPP) at the Fraunhofer Institute for Molecular Biology and Applied Ecology IME offers a partner-

Nicotiana tabacum grown under controlled conditions

ship to transform the idea into a product candidate for clinical testing. Why would you need a partner? As an API developer you belong to an elite group requiring product design and proof of concept studies, but many organizational, regulatory and technical questions are likely to arise before manufacturing can begin. For example, the milligram to gram quantities of API required for characterization and preclinical/clinical testing can be difficult to produce in typical molecular biology laboratories under regulated conditions, and quality criteria such as residual DNA or host cell protein (HCP) levels may be difficult to define. The Fraunhofer IME's comprehensive expertise as a contract research organization, and our consulting services covering process development, GMP-compliant production and quality management, can therefore provide valuable assets. As an application-driven, nonprofit organization, we offer the highest degree of flexibility, ranging from small specific optimization or feasibility studies to complete process development strategies spanning gene design, expression system selection and optimization, downstream process development, scale up, GMP-compliant production and API release by our Qualified Person (QP). Process development and GMP-compliant API production can thus be undertaken by a single partner, saving you time and the costs of process, data and technology transfer, and reducing the time to market for your product. You will also benefit from our highly motivated and experienced senior scientists, engineers and technicians, who are permanent members of our project teams.

Development and production capacities at the Fraunhofer IME

Fraunhofer IME has more than 15 years of experience with different expression systems for recombinant protein production including *Escherichia coli* (bacteria), *Pichia pastoris* (yeast), Chinese hamster ovary (CHO) cells (mammalian cell lines) as well as *Nicotiana tabacum* (tobacco) and

Äkta pilot in clean room environment

N. benthamiana as intact plants and cell cultures. Using the latter approach, proprietary plant cell pack (PCP) and cell-free systems are available for high-throughput screening (HTS), and transient expression in plants facilitates protein manufacturing from gene to pilot-scale protein production in less than 4 weeks. All operations can be conducted in safety level 1 and 2 environments according to the German GenTSV. Our upstream fermentation capacity offers small-scale bioreactors of 1–100 L and GMP-compliant reactors up to 350 L. Conventional stainless-steel and single-use bioreactors (SUBs) are available. Plants can be cultivated in a 450 m^2 greenhouse facility with either individual or hydroponic fertilization. Alternatively, a completely isolated vertical farming unit is also available, with another 550 m^2 of cultivation area and fully-defined environmental conditions including light, fertilizer and humidity. The equipment available for downstream processing includes homogenizers for cells and plant tissues, bag and depth filtration devices ranging from laboratory to process scale, ultrafiltration/diafiltration (UF/DF) devices for process volumes of 100 mL to 1000 L, and diverse chromatography systems. A fully-equipped and quality-monitored GMP facility is available for the production of clinical-grade APIs, backed by dedicated quality control (QC) laboratories as well as the corresponding pharmaceutical quality assurance (QA) system. In March 2009, Fraunhofer IME was granted a manufacturing license for the production of biopharmaceutical APIs in microbial systems for phase I clinical trials. In November 2009, the license was extended to include monoclonal antibodies (mAbs) manufactured in transgenic plants, and in 2012 another extension allowed the production of API for use in phase II clinical trials. More than 20 successful campaigns, inspections by competent authorities and customer audits have been completed, so we are confident we can help with your upcoming projects. Our process development and GMP services are described in detail in our brochures and online.

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