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AIMs

Advance **I**nteractive **M**aterials by De**s**ign

Integrated Project

Publishable Executive Summary

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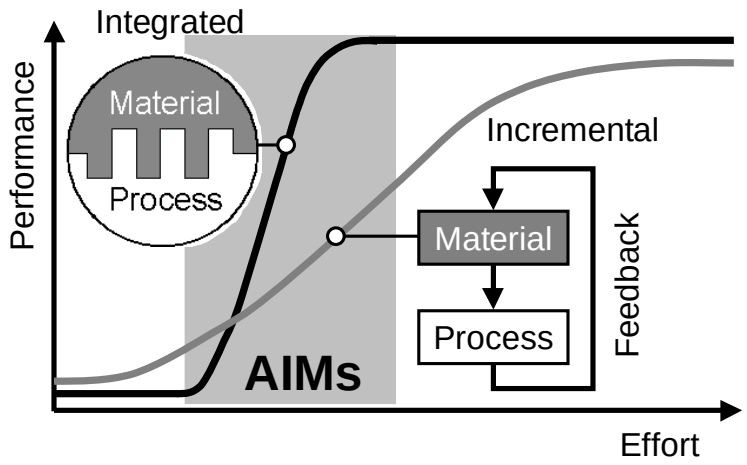
Publishable executive summary

The integrated project AIMs is targeted at the design of a new class of interactive materials for use in the pharmaceutical, chemical and bio-industries. A real breakthrough in the improvement of production processes for complex molecules, e.g. large proteins cannot be achieved by incremental research, as shown by the presentation of material and process design cycles. Only the integration of material sciences and process development can significantly lower the costs for downstream-processing, which accounts for a large part of the production costs and is still considered a bottleneck in the production of bio-molecules. Novel materials for selective purification are composed of functional elements (ligands) that interact with target molecules and structures for separation processes (supports) that are designed to ensure a high efficiency of the related purification techniques (chromatography, membrane separation, extraction). An innovative design approach will allow tailoring the material properties to the customers' needs and perceptions. This will cause a paradigm shift from sole material use to material design within the process development cycle and thus drastically enhance the process efficiency at an early stage.



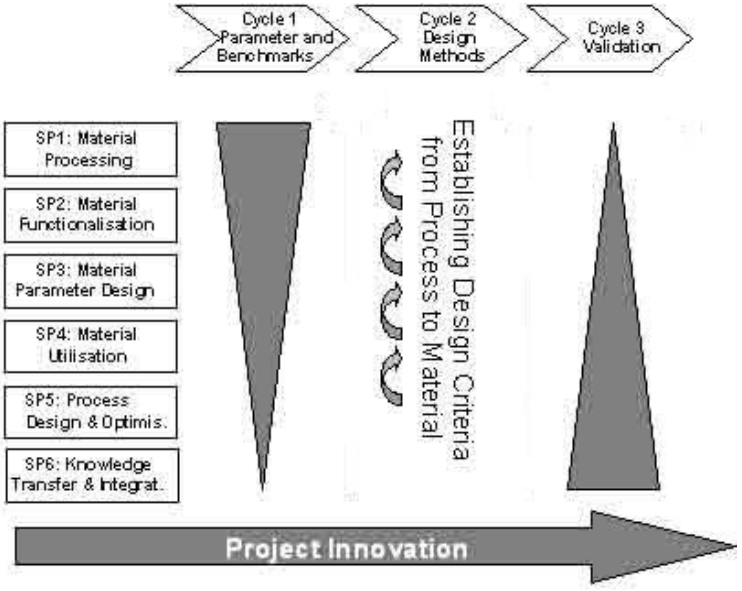
Material and process design cycles

All these efforts are inevitable to meet the demands of an ageing society for new bio-pharmaceutical drugs at reasonable costs. Diseases like cancer, Alzheimer, or rheumatism led to the development of new bio-pharmaceuticals, which show a clear improvement in healing and tolerance. But at the same time, these drugs put new pressure on our health system, since they cannot be produced in reasonable amounts and at affordable costs at the moment. Thus, the project anticipated an urgent need for a dramatic improvement in downstream processing of bio-pharmaceuticals in the near future. The European pharmaceutical and chemical industries have to maintain and strengthen their international competitiveness, to restore European leadership in life science and biotechnology sectors. These expectations date from the project application phase in early 2003 and should therefore be reviewed in the light of new development almost 5 years later.

The objectives of AIMs as outlined above have not only been affirmed but also reinforced by recent developments in pharmacy and biotechnology. Recombinant proteins are considered as ideal therapeutics for numerous diseases. This potential, together with recent problems of small molecule pharmaceuticals like VIOXX or Baycol which had to be removed from the market, led to a growing number of recombinant proteins in the development pipeline. Most of these proteins will be new monoclonal antibodies (MABs). At the same time, new production techniques and cell lines with higher yields have alleviated the shortage in bio-

manufacturing capacity, but this holds only for the upstream part. The downstream part is still considered as a bottleneck that can undercut some of the advances in cell line productivity being achieved through molecular biology. The market for monoclonal antibodies grows with an annual rate of 20% and thus confirms the selected process example of the AIMs project.

The integrated project AIMs comprised 24 partners with a different cultural, social and scientific background, including 4 industrial partners from different sectors (Bayer Technology Services GmbH, DSM Biologics, Merck KGaA, and Sartorius AG) and 4 innovative SMEs (GVS S.p.a., Prometic Biosciences Ltd., Syncom B.V., and Xeptagen S.p.a.). The academic world is represented by 14 outstanding partners from all essential disciplines (ABO Akademi University, Budapest University of Technology and Economics, Central Institute for Labour Protection, CNRS-Université de Provence, ETH Zürich, Instituto Superior Técnico Lisboa, Montpellier University, Politecnico di Milano, Slovak University of Technology in Bratislava, Technical University of Lodz, University of Bologna, University of Dortmund, University of Twente, and University of Vienna). Additional expertise in publishing and dissemination of knowledge is provided by two stakeholders (Elsevier Ltd and Dechema e.V.). Those 24 partners are needed over a period of at least 4 years with manpower amounting on the whole to approximately 150 person-years. RTD with a multi-disciplinary character is performed on a European level, and the strong involvement of SMEs in innovation intensive areas of the project promote the take-up of promising but not fully established technologies for integrated material / process design. The project is led by the University of Dortmund, represented by Prof. Andrzej Górak who is an experienced coordinator and enjoys the trust of all partners.



AIMs RTD approach

To reach the overall objectives described above, AIMs is divided into 6 individual sub-projects and 3 different cycles presented in the picture on the left.

The sub-projects are linked to ensure an optimum exchange of knowledge and technology. **SP1: Material Processing** deals with support structures, sorbents and the scale-up of material production. **SP2: Material Functionalisation** comprises the different aspects of material-product interaction like ligand design, processing and immobilisation. The cross-linking project **SP3: Material Parameter Design** creates the necessary interface between material and process by relating structural material parameter with material performance. It implies up-to-date methods, such as molecular modelling, kinetic studies or mass transfer phenomena, to predict an optimum material texture. **SP4: Material Utilisation** considers the three different unit operations chromatography, membrane separation and extraction, to ensure a variety of options for both, material application and process optimisation. **SP5:**

Process Design & Optimisation deals with a final experimental evaluation of the overall material performance under process conditions and the formation and validation of a generic method for process development, design and optimisation. It also acts as a link to the consumer by providing an optimised process with materials, tailored to its special needs. **SP6: Knowledge Transfer & Integration** generates appropriate links between the technical sub-projects on various levels. The main focus is to ensure proper knowledge management (incl. IPR) inside the consortium, to disseminate project results, and to evaluate the wider social impacts of the AIMs project.

Communication has already been established during the project preparation phase and all partners were brought to the same level of understanding. Clear interfaces were defined to ensure the unobstructed exchange of information between the different groups of the project. To allow all scientists to become acquainted with the different techniques, training courses have been carried out that deliver insight in both, theory and experimental techniques. Especially the exchange of PhD students between different partners is often used to foster the collaboration on a European level. The establishment of a web-platform at www.aims-eu.de with a secure area provided a powerful tool for internal communication, which allows an easy exchange of documents, the announcement of upcoming events, the provision of up-to-date mailing lists, and the access to all project deliverables. The website is continuously updated according to the demands of the project.

Even though the Protein A benchmark technology significantly advanced since the start of the AIMs project and is even declared as a well-established industrial standard for purifying monoclonal antibodies by the major provider of Protein A resins, concern of pharmaceutical companies increase to be depended on the availability of Protein A materials. Alternative purification technologies that are a not using Protein A are thus becoming higher importance, especially on a fast growing and highly competitive market. By following the concept of mimetic affinity ligands, ion-exchange materials and alternative purification concepts such membrane separation and different extraction technologies, AIMs is fully in line with the demands of the pharmaceutical industry.

The development of new materials started with commercially available benchmark materials, which have been evaluated to allow an assessment of the progress in terms of material and process improvement. Three generations of improved affinity materials have been developed for all different unit operations. Thorough investigation of the materials with a real cell supernatant led to a continuous improvement of material performance and created a database that can be used for the development of new affinity materials. The development of a new SartoAIMs Protein A affinity membrane has to be highlighted since it shows a manifold improved capacity for IgG in comparison to commercially available benchmark materials. Affinity materials with mimetic ligands also reached a maturity comparable to benchmark materials available at the beginning of the project and thus represent an alternative to Protein A.

Reliable quantitative correlation between material structure and performance were established for ion-exchange materials. Together with the availability of a new chromatographic resin FractoAIMs, which possesses a higher mechanical stability and can be produced according to target structural parameters bead size, pore size, surface area and ligand density, this facilitates a real “material-by-design” approach to tailor the material properties to

the needs of the individual application. This approach has successfully been applied to the specific design of an ion-exchange material for the continuous chromatographic purification.

In addition to the development and evaluation of new materials, the modelling strategies for the individual purification technologies improved significantly. All three unit operations have been modelled successfully and the level of detail and accuracy in predicting the process behaviour reflect the technical maturity of the technology. Suitable software interfaces have been developed which allow for an easy exchange of data between the detailed unit operation models and the generic process model. An experimentally validated molecular model allows assessing the interaction of support, linker, ligand, and product and is thus ideally suited to promote the design of new materials.

Two continuous alternatives to the current Protein A technology have been considered for the purification of monoclonal antibodies within the AIMs project. The Multi Column Solvent Gradient Purification process shows a performance that is comparable with purification concepts that use Protein A as a capture step but uses much cheaper ion-exchange resins as the stationary phases. These results led to the foundation of the company ChromaCon AG (www.chromacon.biz), as a supplier of high performance chromatographic process solutions. Aqueous two-phase extraction is also on the way to become a real alternative to existing purification technologies. Even without using an affinity system, a counter-current multistage extraction process has reached a global recovery yield of 80% at a removal of 79% of the impurities and leaving room further improvements.

New process concepts have been developed that exploit the full potential of the new materials and purification technologies. These concepts were tested under real process conditions in a mini-plant set up not only to assess their performance as an alternative to the existing Protein A platform technology, but also to give valuable information for a generic process design methodology that considers all successful AIMs technologies. The combination of two MCSGP units that operate with different stationary phases allows to complete the required MAB purification with only two steps excluding virus inactivation. This goes along with a reduction by a factor of 3 in the total purification costs.

Socio-economic studies revealed the influence of the project outcome on the society and economy in two example countries (Poland and Germany). Dissemination of project results has attracted higher attention, since alternatives to conventional purification technologies could be announced.

Taking monoclonal antibodies (MABs) as an example, the proof of the following process improvements as a result of the projects' new approach is expected within the next six years:

- Process development time cut in half.
- Cost of goods in MAB production decreased to 100 up to 1,000 €/kg, representing a reduction by a factor of 10 to 100.
- Technical feasibility and reliability of product quality in new large scale MAB productions (100 to 1000 kg/year), representing an increase of production capacity by a factor of 10 to 50.