Highly pure bioactive proteins will be needed beyond the current applications in biomedical diagnostics and therapeutic applications. Such proteins must become affordable for low- and medium-income countries so that they also could benefit from the progress of modern medicine. Pure recombinant proteins are also needed as food supplements and alternative non-animal nutrients. The rising global demand for such proteins is creating a need for economical and fast manufacturing method. The goal of the Concrys project is to develop a new crystallization-based method for efficient production and purification of proteins in a sustainable and highly efficient manner with much better economics in comparison to the core technology chromatography, which is currently required to achieve the quality limits. Chromatographic processes are highly selective, but often represent a bottleneck and a cost-driver of the whole production due to high prizes of chromatographic resins and low throughput, which is limited by resin adsorption capacity.

The advantages of crystallization are: low costs, high recovery and purification efficiency. Though the proteins are often structurally unstable when stored in solution, they can be successfully stored in dry crystalline form for long periods of time. This allows reducing bulk storage costs and obtain longer shelf life compared to the conventional formulation techniques. Nevertheless, the development of bulk protein crystallization is still at an early stage, and the process is far from being a routine operation. This stems from the complexity of the protein solid-liquid behavior and the diversity of dense phases that can be formed and a complex mechanism accompanying their formation, which is influenced by a number of variable parameters. Therefore, the design of protein crystallization is still based on trial-and-error methods and it is not transferable to other protein types. The process is usually performed batchwise in stirred tank crystallizers, where nucleation and growth of protein crystals is induced in the presence of a crystallization agent. Such an approach has a limitation related to imperfect mixing between the solution of protein and crystallization agent, which generates a high degree of supersaturation at liquid-solid interface. This causes a risk of precipitation of amorphous solids or formation of inactive aggregates. On the other hand, too rigorous stirring induces high shear stress, which inhibits growth of the protein crystals. Moreover, that method suffers from difficulties in the control of the operating parameters, it is also lacking efficient design procedures. Therefore, the research group in Rzeszów University of Technology (PRz) has developed a new concept of forced convection crystallization (FCC) technique as an alternative to commonly used crystallization techniques. In that process, the desired crystallization condition is achieved by controlled water removal from the protein solution under mild temperature conditions. Until now, the process has been realized only in a lab-scale batch system, which cannot be applied in industrial production. The concept of FCC will be extended to a continuous mode, in which mechanical stirrers will be replaced with an Archimedean screw, which allows simultaneously effective and gentle mixing of the protein solutions. The potential of continuous FCC (CFCC) relies on its efficient coupling with continuous production recombinant protein from bacterial cell cultures (CRPP). The continuous integrated operation shall outperform batch processes, which have been used so far, in terms of the most important performance indicators, such as protein stability, yield and productivity. Up to now, CRPP has not been achieved due to inherent instability of *E. coli* cell lines. In the frame of Concrys, a new technology based on growth-decoupled production will be derived by the experts from University in Vienna (BOKU). With the new bacterial expression technology, it will be possible to continuously produce proteins using inexpensive culture medium.

In the Concrys project, the concept of continuous CFCC (CFCC), its design framework, and its integration with CRPP shall be developed. The design framework shall be based on a detailed model of the process dynamics, which will be developed by the experts from Magdeburg University (OVGU). The model shall account for the most important phenomena affecting the process: mass and heat exchange, hydrodynamic conditions, crystallization thermodynamics and kinetics, and crystal size distribution. The model and its calibration procedure shall be applicable for various proteins after the specificity of their crystallization mechanism is accounted for. Therefore, the project realization shall bring another important benefit that is gaining a better insight into the mechanism of protein crystallization, which is not well understood.

To achieve these goals complementary expertise from PRz (knowledge of protein crystallization process), BOKU (knowledge of bacterial expression technology) and OVGU (knowledge of complex technological processes) are brought together.