

SPINE 2-Complexes

Title: From receptor to gene: structures of complexes from signalling pathways linking immunology, neurobiology and cancer

Thematic area: Life Sciences, Genomics and Biotechnology for Health

Instrument: Integrated Project

Co-ordinated by: University of Oxford

EC contribution: 12m€

Duration of project: 42 months from July 2006

Number of partners: 19

Subject of case study: Dr Susan Daenke, University of Oxford

susan@Strubi.ox.ac.uk

Project website: <http://www.spine2.eu/>

The Challenge

The Framework Programme 5 project SPINE (Structural Proteomics in Europe) has been highly successful in its goal to pioneer a collaborative, high throughput approach to structural biology. This initiative in solving 3-dimensional protein structures required integration of protein target selection, recombinant protein production, purification, crystallisation, and analysis by NMR spectroscopy and X-ray crystallography. SPINE progress in establishing new technology infrastructure and activity in structural biology across Europe is generating significant advances in the characterisation of “high value” protein targets implicated in human disease – opening up new opportunities to understand disease and to develop novel diagnostics and therapeutics.

One of the next challenging frontiers in structural biology is the characterisation of large macromolecular (protein-protein) complexes to determine function within important human cell signalling pathways. These more difficult protein targets are now coming within range in consequence of the expertise built and disseminated in SPINE.

SPINE – its achievements and impact

An earlier case study analysis of the initial two years of the first SPINE project described success in three main areas: (i) Protein structure characterisation; (ii) Technology development and transfer; and (iii) Support for training and mobility. These achievements grew throughout the project. A total of 308 novel protein structures were solved by the consortium and later notable successes included:

- Immunological proteins (T-cell receptor and major histocompatibility antigen complexes) relevant to disease and the development of T-cell vaccination strategies;
- Comprehensive set of nuclear receptors (for a range of ligands) involved in cancer – which may now be made available for commercial screening purposes.

Other technology transfer successes, in or near commercialisation, include systems for crystal imaging and for image-recognition software. In addition, the objective to

develop standardised structural proteomics capabilities widely across Europe has inspired a major open access initiative at EMBL whereby crystallography samples can now be submitted, conveniently and affordably, for automated and computerised synchrotron assessment and data interpretation.

In summary, the impact of the first SPINE project can be valued in two ways.

- First, with regard to the excellence of the science – illustrated by dedication of a recent issue of the leading peer reviewed journal *Acta Crystallographica Section D* (October 2006) to the achievements of SPINE.
- Secondly, by the pan-European dissemination of the high throughput, robotic, nanolitre-scale technologies integrated within the standardised structural proteomics pipeline process.

This work has enabled the EU to catch up with (and in some respects surpass) the previous world leaders, USA and Japan. The European added value was accomplished by capitalising on the complementary expertise across Europe to develop a comprehensive test-bed to standardise the new technology – and at relatively low cost by comparison with the international competitors. The value of this first SPINE project can also be judged in terms of the enthusiasm of the partners to tackle more difficult challenges in SPINE-2.

SPINE-2 – The Project

The Framework Programme 6 project uses the expertise and momentum built in SPINE-1 to apply the pipeline approach to more demanding targets in systems of demonstrated biological importance. The focus is on characterising structure-function in key human signalling pathways:

- (i) Ubiquitination and de-ubiquitination;
- (ii) Cell cycle and apoptosis;
- (iii) Synaptogenesis and neuronal signalling;
- (iv) Kinases and phosphatases involved in signalling and regulation;
- (v) Transcriptional receptors and regulation;
- (vi) Innate and acquired immune receptors and inflammation;
- (vii) Viral subversion of cellular signalling and immune modulation.

Some of these cellular processes involve similar components and pathways, enhancing the opportunities for interaction among the scientists in the consortium.

Building the Consortium

In building the consortium, the project coordinator retained the core of expert groups from SPINE-1 and aimed to bring in extra partners with experience in the desired biological target areas. As the core partners remained in place, it might be assumed that building a second consortium was easier than the first time. However, there were a significant number of new laboratories now wishing to join (a measure of the success of SPINE-1) – a challenge for the coordinator, who recognised the importance of keeping the consortium at a manageable size. This challenge was addressed by instituting an informal selection process whereby potential participants disclosed what value they could contribute to the consortium in terms of protein targets or technologies. For example, the UK SME Domainex became a partner

because of their technology enabling identification of protein regions that are tractable targets for structure determination.

Lessons learned

The “tips for success” derived from the case study analysis of the early experience in SPINE-1 – relating to the needs to ensure added value across the consortium, democratic discussion and the development of ongoing European Commission support (without micro-management) – have been reinforced by subsequent experience. In addition, the project coordinator emphasises two points that are receiving particular attention in SPINE-2:

Communication within the consortium

The core members have developed an effective, collegiate working relationship in SPINE-1 and this ensured that SPINE-2 could start rapidly, without a lag phase. Because the scientific targets in SPINE-2 are more demanding, there is an expectation of more joint action among partners. This provides a greater challenge for the project coordinator to ensure integration across the consortium and central monitoring of individual scientific interactions between partners. In order to address these coordination needs, the project is developing web-based software to document the status of each partner’s contribution and keep the communication channels open.

Active training programme

The internal training budget for SPINE-1 had been found insufficient to satisfy all of the training and networking opportunities emerging in this fast-moving area. The SPINE-2 Integrated Project application was accompanied by a successful bid for a SSA programme to cover a range of training activities including laboratory-based workshops, scientific meetings and exchange activities. These are anticipated to be of particular value in exposing the newer Member State consortium partners (Czech Republic, Hungary) to the advanced technologies and, more broadly, in educating the next generation of scientists.

Looking to the future

There will be increasing research possibilities to use structural proteomics to characterise higher levels of organisation within the cell, for example in organelles and membranes and to capitalise on advances in technology to provide detail at the atomic scale. It is essential to continue to build EU leadership in the area of structural biology and there will be significant opportunities coming into range for strategic support, which should be considered in Framework Programme 7.