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SPINE: Structural Proteomics IN Europe – the best of both worlds

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The concept of structural genomics arose in the mid to late 1990s in the USA and Japan as a response to the success of high-throughput (HTP) sequencing methods applied to whole genomes (see http://www.isgo.org). It was imagined that similar HTP methods could be applied to obtain three-dimensional structures of all the proteins (the 'proteome') of an organism, which would in particular be an efficient way of filling in the gaps in observed 'fold-space'. This vision led to the investment of substantial sums of money into large-scale structural genomics projects in the USA [*e.g.* nine projects funded by the NIH/NIGMS Protein Structure Initiative (PSI) from September 2000 to June 2005, http://www.nigms.nih.gov/psi/] and Japan (*e.g.* the massive RIKEN project, http://www.rsgi.riken.go.jp/). These were characterized by the concentration of resources into a small number of large centres, the development of novel, automated technologies to permit a HTP pipeline approach to structure determination, and a focus on novel folds as the major target criteria. The US-based projects, in addition, required immediate public deposition of structural data whereas the Japanese RIKEN project also aimed to support Japanese industry, precluding deposition in advance of patent evaluation.

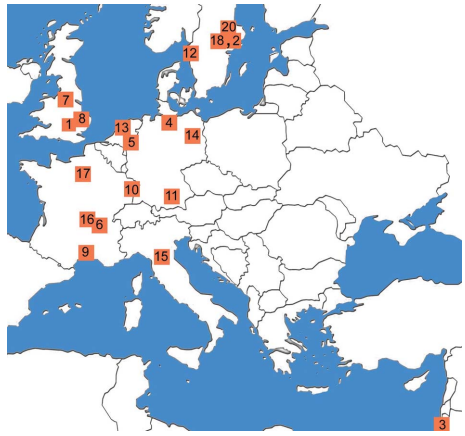
Europe was slower in implementing HTP approaches to structural biology. The Protein Structure Factory in Berlin, Germany (http://www.proteinstrukturfabrik.de/) led the way, followed by the Oxford Protein Production Facility (OPPF) in Oxford, UK (http://www.oppf.ox.ac.uk/) and the Genopoles in France (notably Gif, Marseille and Strasbourg, http://rng.cnrg.fr/). However, it was not until October 2002 that the first Europe-wide project began. This was a three-year project funded by the EU FP5 programme called SPINE: Structural Proteomics IN Europe (http://www.spineurope.org). SPINE, a 'second generation' structural genomics project (indeed purposefully called a Structural Proteomics project to draw a distinction), made some radical departures from the first-generation initiatives, while at the same time obviously benefiting from the experience and technology development of the preceding projects.

The challenge set for SPINE was to push forward with cutting-edge technologies aimed at biomedically relevant targets at the same time as generating a pan-European integration on biomedically focused structural proteomics. The SPINE consortium comprised

Figure 1
Members of the SPINE consortium and SPINE Congress attendees at Montecatini, Italy, 2005.

Table 1
Members of the SPINE consortium.

No.	Partner location	Lead scientist	Contact URL
1	Oxford	David Stuart and Yvonne Jones	http://www.strubi.ox.ac.uk/
2	Stockholm	Par Nordlund	http://ki.se/†
3	Weizmann	Joel Sussman	http://www.weizmann.ac.il/
4	Hamburg	Matthias Wilmanns	http://www.embl-hamburg.de/
5	Utrecht	Robert Kaptein	http://www.bijvoet-center.nl/
6	Grenoble	Stephen Cusack	http://www.embl-grenoble.fr/
7	York	Keith Wilson	http://www.ysbl.york.ac.uk/
8	EBI	Janet Thornton and Kim Henrick	http://www.ebi.ac.uk
9	Marseille	Christian Cambillau	http://www.afmb.univ-mrs.fr/†
10	Strasbourg	Dino Moras	http://lbgs.u-strasbg.fr
11	Munich	Albrecht Messerschmidt	http://www.biochem.mpg.de
12	Gothenburg	Lena Gustafsson	http://www.molbiotech.chalmers.se
13	Amsterdam	Titia Sixma	http://Xtal.nki.nl
14	Berlin	Udo Heinemann	http://www.mdc-berlin.de
15	Florence	Ivano Bertini	http://www.cerm.unifi.it
16	ESRF	Sine Larsen	http://www.esrf.fr/
17	Paris	Pedro Alzari	http://www.pasteur.fr
18	Karolinska	Gunter Schneider	http://ki.se/
19	Uppsala	T. Alwyn Jones	http://www.uu.se/



† Present address

Table 2
A summary of the structure tally of JCSG and SPINE.

Target stage	JCSG	SPINE
Selected	8190	2395
Cloned	3953	15269
Expressed	3639	1344
Crystallized	1182	305
Crystal structure	266	252
NMR structure	8	56
PDB deposited	200	122

19 leading centres in structural biology distributed throughout Europe (Table 1). The project was coordinated from Oxford and organized into a series of workpackages to each of which various combinations of SPINE laboratories contributed. Eight workpackages covered technology development and implementation; the results from each are reviewed in turn in the first eight papers of this volume. These methodological results underpinned the biomedical target based workpackages which were the heart of the project. The structures and biological insights resulting from these workpackages are reviewed in this issue by Fogg *et al.* (for the pathogen target systems) and Banci *et al.* (for the human target systems). Finally, a strong training and networking component was built into the project *via* two further workpackages with the explicit aim of creating an expanding European resource of highly trained structural biologists and technicians to carry forward structural proteomics into the next decade (see Fig. 1).

At a broader level SPINE has been a catalyst for the development of a distributed network of laboratories with HTP capability in many countries and we believe it has helped to establish a democracy in the use of new technologies (*e.g.* affordable nano-crystallization and expression screening robotics). With this emphasis on the development and dissemination of methodologies, the SPINE project perhaps most closely resembled teams such as the Joint Center for Structural Genomics (JCSG, http://www.jcsg.org) in the USA, which also emphasised collaborative technology development perhaps at the expense of sheer numbers of structures in the early stages. At the end of the three-year SPINE project the progress towards its overarching goals can begin to be assessed. The success of SPINE can be measured in terms of an increase in the ability of European structural biologists to enrich the PDB with biomedically relevant protein structures. In numerical terms, SPINE's achievements (Table 2) are compatible with the JCSG (statistics collected for PSI-1 between 1 September 2000 and 31 August 2005; data provided by Raymond Stevens and Ian Wilson), which focused mainly on complete coverage of a bacterial thermophile *Thermotoga maritima* proteome.

SPINE has also pushed forward the development of European standards in several areas of HTP methods, notably LIMS and the handling of frozen crystals (http://www.spineurope.org/page.php?page=protocol_vials). SPINE was driven by the notion of 'human health targets' rather than a bioinformatics based 'fold space'. By its policy of an open, decentralized network and focus on high value targets, SPINE tried to go beyond the potentially divisive dichotomy between the 'traditional' way of doing structural biology ('one post-doc/one project' with in-depth complementary functional investigations) and 'factory-style' structural genomics (multiple parallel projects, abandoning of failures, targets often of unknown function). We believe that modes of work akin to those of SPINE, whereby HTP techniques are exploited for high-value targets, are likely to become the norm for structural biology. Such approaches may be essential if the ability of X-ray crystallography to illuminate biology is to advance fully from isolated protein to the macromolecular complexes central to cell biology.

The SPINE statistics, showing a total of 308 structures solved, reflect novel structures only, the number including ligand- and metal ion-bound isoforms is more than 370.