

## PLENARY LECTURE P2

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### High throughput technologies in structural biology

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During the past 5 years significant progress has been made in developing novel high throughput structural biology technologies for protein cloning, expression, purification, crystallization, crystal imaging, synchrotron beamline data collection, NMR analysis, and structure determination/analysis. These developments are largely a result of the U.S. NIGMS Protein Structure Initiative, and efforts in Europe (e.g. SPINE) and Japan (e.g. Protein-3000). At The Scripps Research Institute, we have been able to miniaturize, automate and parallelize the structural biology processes using nanoliter volume technologies (see <http://stevens.scripps.edu/webpage/htsb/> for examples). The majority of these developments have now been commercialized and are being used by both traditional structural biology labs and structural genomics centers. Accordingly, significantly smaller amounts of materials can be used at all steps, and more parallel experiments can be engineered (genetically and mechanically) within the same space and time constraints, at lower costs.

Application and results from these efforts towards entire proteomes (e.g. *T. maritima*, SARS), enzyme pathways/families (e.g. catecholamine biosynthesis, botulinum neurotoxins), and high value drug targets (e.g. DPPIV, PAL) are now starting to emerge and will be presented. Furthermore, lessons that we have learned from the past 5 years leads us to conclude that integration of the new individual technologies will significantly increase the levels of structure determination successes and throughput than is currently possible today. For example, integration of a laboratory-based compact light source with novel microcapillary crystallization (< 50 nL) and large-scale *in-situ* diffraction screening will enable new science. These new experiments will have to be done with tight feedback loops between crystallization, imaging, screening and data collection as well as protein sample preparation, in a fashion similar to DNA sequencing with the ABI3700. In addition, new approaches to protein sample preparation, such as gene synthesis and cell-free expression, coupled with rapid expression analysis feedback will be essential. Initiatives currently in place at TSRI are exploring these approaches with the challenging targets such as eukaryotic membrane proteins and large protein assemblies.

**Acknowledgements:** I am grateful for the incredible cooperation between technology development efforts including: JCSG, SPINE, Joint Center for Innovative Membrane Protein Technologies (JCIMPT; NIH Road Map Initiative GM073197), Accelerated Technology Center for Gene to 3D Structure (ATCG3D; NIH PSI-2 GM074961), Genomics Institute of the Novartis Research Foundation, The Scripps Research Institute, and Syrrx.