Protein Structure Initiative (PSI) Annual Joint Meeting of the Research Directors and the PSI Advisory Committee (PSIAC) and Meeting of the Network Steering Committee, December 8-10, 2009

Report of the PSI Advisory Committee

Introduction

This report deals with the "wind-up" annual meeting for Phase 2 of the Protein Structure Initiative (PSI-2). There was much overlap between the material presented this year and that discussed at least year's meeting. For this reason the present report will be brief and will focus on areas where there are changes relative to the Year 2008 report.

Large-Scale Centers

Progress of the four large-scale centers was reviewed by the respective directors, Stephen Burley, Andrzej Joachimiak, Gaetano Montelione and Ian Wilson. Each of these centers is continuing to contribute around 200 structures per year to the PDB and there seems little doubt that the goal of 3000 unique structures during PSI-2 should be reached. There continue to be advances in the efficiency of structure determination, although the rate of improvement is less than that which characterized the early years of PSI-2.

Specialized Centers

1. PSI-Nature Structural Genomics Knowledgebase (Helen Berman)

For a number of years the PSIAC had expressed concern at the need to better disseminate to the community at large the benefits of the PSI. The highly efficient establishment of the Knowledgebase by Dr. Berman and her group, together with ongoing improvements, go a long way to alleviate this concern. The establishment of the Knowledgebase has been one of the big successes during the past two years.

2. Protein Modeling (Roland Dunbrack; Adam Godzik)

Drs. Dunbrack and Godzik reviewed recent activities by their respective groups.

3. PSI Materials Repository (Joshua LaBaer)

Subsequent to last year's meeting, the PSI Materials Repository has been relocated from Harvard to Arizona State University. Dr. LaBaer reassured the meeting that, notwithstanding this disruption, the repository is ready and able to continue to receive materials. Nevertheless, with the pending termination of PSI-2 in 2010, the PSIAC expressed concern that there is little time remaining to ensure that all of the appropriate materials generated by PSI-2 be archived in an appropriate fashion. There was also discussion regarding the development of efficient procedures for checking and verifying deposited materials. The NIH staff is urged to ensure

that all of the PSI-supported groups are taking appropriate steps to have their materials checked and deposited.

4. Membrane Proteins (Wayne Hendrickson; William Harries substituting for PI Robert Stroud)

The presentations given this year tended to reinforce the conclusions stated in last year's report, namely that it is very difficult to obtain high-quality crystals of intrinsic membrane proteins and that it is usually necessary to "tune" the crystallization conditions for each protein to take into account its functional characteristics. (By years 4-5 of PSI-1 it was very clear that pipelines could be established to efficiently determine the structures of unique soluble proteins. This has not been the case for membrane proteins during PSI-2.) As stated last year, there is no question that structural biology of membrane proteins is a critical area that needs ongoing support. It is also very encouraging that an increasing number of important membrane protein structures are appearing in the literature. For the reasons given above, it does not appear optimal to have large-scale "pipelines" for membrane protein structure determination similar to the PSI-2 large-scale centers for soluble proteins. Rather, it would seem more productive to have a larger number of smaller centers, each focused on a biological theme.

5. Other Specialized Centers (John Markley; Lance Stewart; Tom Terwilliger; Michael Malkowski substituting for PI George DeTitta)

The reports of Drs. Malkowski, Stewart and Terwilliger covered and updated material presented a year ago.

In contrast, Dr. Markley used his time to address the three questions which participants in the meeting had been asked to consider, namely the following.

i. What have we learned through the PSI?

ii. What would the current state of structural biology be if the PSI had not occurred?

iii. How has the PSI changed attitudes and perceptions about large-scale biological science?

It seems worthwhile to restate Dr. Markley's conclusions here, as they serve as a useful summary for the final PSI-2 Annual Meeting.

Summary (adapted from John Markley)

i. The PSI has shown that structures of eukaryotic proteins can be solved in pipeline fashion (albeit with success rates lower than for prokaryotic proteins).

ii. The PSI has developed effective ways of exchanging information so as to avoid duplication of effort, share protocols, compare different approaches, and profit from the products of each other's research.

iii. The PSI has demonstrated the importance of capturing detailed information on a complex project in machine-readable formats.

iv. The PSI has shown the importance of rigorous protocol development.

v. The PSI has demonstrated the utility of bioinformatic tools to assess the likely biomedical importance of a structural target and the likelihood that a target sequence will yield a structure.

vi. The PSI has demonstrated that costs can be cut through the development of flexible protocols and inexpensive screens that accurately predict downstream success.

vii. The PSI has demonstrated the value of complementary approaches to protein production and structure determination.

viii. Technology developed through the PSI and other structural genomics projects has greatly lowered the costs of protein NMR structures and enlarged the range of accessible targets.

ix. The PSI has developed and implemented improved technology for X-ray structure determinations.

x. The PSI has shown how biologists and biochemists can carry out mutually-rewarding collaborations that utilize high-throughput approaches.

xi. The PSI has demonstrated the value of functional follow-up studies for targets of high biomedical importance.

xii. The PSI program has been an engine for promoting scientific interactions and dissemination.

xiii. The PSI program is changing how biochemists and biologists carry out their research.

Committee Members Present: David Davies, Lila Gierasch, Jack Johnson, Brian Matthews (Chair)

Report Submitted: December 22, 2009