Overview of the experimental and computational approaches to protein design session at the 19th IUPAB congress and 11th EBSA congress

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Protein design is an interdisciplinary field in which biologists, chemists, physicist and computer scientists work together to attempt to solve the problem of how to design an amino-acid sequence that will successfully fold to a specified 3-dimensional structure. The field is now, perhaps, reaching its adolescence, with sophisticated computational methods, including the ubiquitous Rosetta Design, enabling the design and redesign of protein folds without the years of painstaking experience with individual proteins that was a prerequisite for success in the early days. In spite of the overall success of these approaches, there is still plenty to be resolved in the field with the success rate for a given novel sequence still far from perfect, and with new methodologies and concepts being continually developed.

Ivan Korendovych (Syracuse) began by showcasing the power of designed short peptide sequences in assembling into robust beta-sheet assemblies that can be modified to catalyze a variety of reactions. The ability of such structures to perform multiple reaction steps without dissociation of the substrate was particularly promising for applications in multistep synthesis.

Anna Peacock (University of Birmingham) brought us up to the cutting edge with the incorporation into redesigned coiled coils of novel chemistry from the lanthanide series. By utilizing different binding positions within the structure, she demonstrated that selectivity of metal binding can be produced, and work is ongoing to increase the affinity of binding for exciting new applications in medical imaging.

Daichi Yamada (Ochanomizu University) presented an attempt to functionally redesign two different photolyases to adopt each other's specific function. While (6-4) could be mutated to take on the action of CPD photolyase, the reverse could not be achieved. The inference was made that it is easier to return a protein to a function it had previously had in its evolutionary history than to add the new, more complex function present in the more recently evolved (6-4) photolyase.

Vikas Nanda (Rutgers University) introduced us to the 'Pareto frontier', a concept from economics that he discussed in the context of the design of mutually exclusive collagen peptide interactions. He explained the necessary tradeoff in design between stability and specificity and introduced a protocol for discovering if you had optimized your design or if further improvement was possible. He gave us a useful warning to not be too narrow in the areas of the specificity/stability phase space we investigate during design, suggesting that local minima were deep and optimization was, therefore, a difficult task.

Finally, Cristina Martina (University of Liege) brought us the design of an artificial TIM-barrel using the Rosetta Design protocol. This talk gave us great insight into the successes and failings of the approach. While, overall, a sequence was developed, many of the trial sequences failed to be expressed, were truncated, or could not be refolded from inclusion bodies. The talk highlighted clearly the additional challenges of producing stable, soluble, proteins suitable for X-ray crystallography that lie beyond finding a sequence that can fold with low energy to the desired target structure.

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