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RESEARCH CONFERENCES

ESF-EMBO Symposium

Molecular Perspectives on Protein-Protein Interactions

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Hotel Eden Roc, Sant Feliu de Guixols, Spain

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Conference Highlights

Specific interactions between proteins are the basis for the spatio-temporal organization of the cell. This four day conference gathered scientist from different disciplines with the common interest to explore protein-protein interactions from a molecular perspective, i.e. with a common understanding of a protein as a chemical entity. In order to account for the broad spectrum of this topic, the conference was organized in ten thematic sessions. The conference was opened by a keynote lecture, which already covered several major important concepts, which further emerged during the conference: the role of protein structure and dynamics for interactions, specificity and promiscuity of recognition as well as the challenge to detect highly transient protein complex. These issues were taken up in the following sessions, which were more specifically devoted to:

- The understanding of the physicochemical basis of protein interactions in order to quantitatively predict protein complex formation
- The evolution and rational design of interaction partners and interaction properties for biological and medical applications
- The role, identification and characterization of special protein complexes involving intrinsically unstructured proteins or membrane proteins
- Emerging techniques for identifying and probing protein interactions.

Strikingly, this rather broad spectrum of topics proved to be thematically highly interwoven, and a number of common questions emerged during the conference:

- What is the molecular basis of specificity and promiscuity?
- What is the role of the structural dynamics and structural plasticity of proteins for complex formation?
- How can we better identify and characterize very transient interactions?

The topic and the format of the conference were very much appreciated by the scientific community. The number of applications substantially exceeded the maximum number of participants, and the quality of the applications was very high. About 60% of all oral presentations were selected from abstracts for short talks (20 minutes). Thus, young scientists did not only present their work in two very stimulating poster presentation sessions, but also had the chance to contribute to the main sessions. These short talks nicely complemented the in total 23 talks given by invited lecturers. The meeting was truly international with a good mix of scientists from more than 25 countries from all continents. Both genders were well represented both as speakers and young scientists. Upon conclusion of the conference, emerging topics of the field as well as minor possible improvements of the conference format were identified in a very positive and productive “Forward Look” discussion.

☒ I hereby authorize ESF – and the conference partners to use the information contained in the above section on ‘Conference Highlights’ in their communication on the scheme.

Scientific Report

Executive Summary

One basic property of proteins is the ability to specifically target and to form non-covalent complexes with other proteins. Interactions between proteins are the basis for the spatio-temporal organization of the cell. Recent analysis of cellular protein-protein interaction networks (interactomes) have identified an average of 5 interaction partners for each protein. Thus, the complexity of protein-protein interaction networks goes far beyond the complexity of genomes. Understanding the principles of protein-protein interactions from a molecular perspective is absolutely vital for understanding the numerous processes based on protein interactions in the cell. Within this conference, the challenges in the field of protein-protein interactions were addressed from different perspectives. While we understand some basic physicochemical principles of protein interactions, there are numerous unresolved issues which require a multidisciplinary approach. The aim of this conference was to shed light on these issues from different perspectives, which have in common a molecular view on proteins and protein interactions. During the 4 days of the meeting with ~160 participants, a total of 56 talks were delivered in 10 topical sessions as well as close to 100 posters were presented in two evening poster sessions. A rather broad spectrum of topics were covered in the following sessions:

- Theory & Computation
- Kinetics & Thermodynamics
- Protein-protein interactions in disease and drug development
- Protein interaction networks
- Membrane protein complexes
- Emerging and single molecule techniques
- Intrinsically unstructured protein complexes
- Signalling complexes
- Evolution and design
- Multi-protein complexes

Strikingly, several common key concepts, questions and challenges emerged in spite of this rather multidisciplinary approach:

- The specificity and promiscuity of interactions and interaction partners
- The role structural dynamics and intrinsically unfolded proteins for the physicochemical properties of protein complexes
- The importance of highly transient interactions, which are extremely difficult to identify and to quantitatively characterize
- The impressive methodological advances for screening protein interaction networks and for generating specific binding proteins
- The promising capabilities of single molecule spectroscopy and single molecule imaging for probing protein conformations and interactions in the native environment.

The participants not only very much appreciated the unique and timely scientific topic of this conference, but also the format, which ensured a vibrant exchange between young and more established scientist from diverse disciplines in protein interaction research.

Scientific Content of the Conference

In order to account for the broad spectrum of approaches in protein interaction research, the conference was organized into ten topical sessions. The conference was opened by an extremely stimulating keynote lecture from Peter Wright about structural and functional studies on interactions of intrinsically unstructured proteins. This impressive lecture already raised several key concepts of the meeting such as dynamics, promiscuity and transient interactions.

Session 1: Theory & Computation

In this first half-day session, not only the impressive progress in the simulation of protein association and binding was demonstrated (Rebecca Wade), but also in the ability to design proteins in *silico*, which tightly bind their interaction partners (Tanja Kortemme). A common theme was to exploit secondary structure motifs to design small binding entities (Amy Keating, Ora Schueler-Furman). The important role of computer-aided design at the interface to experimental approaches was impressively highlighted.

Session 2: Kinetics & Thermodynamics

In the second half-day session, experimental and computational approaches towards understanding the physicochemical basis of protein-protein complexes were discussed. Important topics included to the role of the crowded cellular environment on the kinetics of protein complex formation (Gideon Schreiber), the important role of local structural dynamics of proteins for the thermodynamic properties (Anthony Kossiakoff) and the distinct properties of transient protein complexes in transfer reactions (Marcellus Ubbink, Lucia Banci). The important physicochemical concepts set in this session were revisited throughout the meeting.

Session 3: Protein-protein interactions in disease and drug development

Session 4: Protein interaction networks

In these two short sessions, fundamental and applied aspects of protein-protein interactions in biology and medicine were raised. These included generic approaches for design and modification of binding proteins for medical applications (Arne Skerra) and elegant structural insight into the intimate relationship of the evolution of virus and host proteins (Leo James). The power of protein engineering and selection for developing tools to interfere with protein interactions was highlighted (Sachdev Sidhu). Another concept covered by these sessions were interactome-wide approaches (Stephen Michnick, Patrick Aloy). This topic yielded into a lively discussion on the amount of “trash” interactions and the resulting problems for interactome analysis (Stephen Michnick). Despite of the rather broad scope of these two sessions, many important concepts raised in the previous, more fundamental sessions were taken up, thus underscoring the highly interdigitated perspective of this conference.

Session 5: Membrane protein complexes

Membrane proteins make up ~30% of the total proteome, but much less is known about their structure and their interactions. For this reason, this session was largely focused on methods for exploring protein interaction in their native membrane environment. Next to highly automatized screening and validation of interaction partners for membrane protein targets (Igor Stagljar), advanced biophysical techniques for probing membrane protein interactions were topic of this session (Roland Brock, Dimitrios Stamou). Some further presentations demonstrated the intricate

Session 6: Emerging and single molecule techniques

This session was dominated by the application of single molecule techniques for probing conformations and interaction of proteins. A key advantage of single molecule compared to whole ensemble spectroscopy is the possibility to probe heterogeneous, non-synchronized samples. Applications presented in this session involved interactions at the ribosome involved in translation explored by single molecule imaging (Joseph Puglisi), conformational dynamics explored by multiparameter single molecule fluorescence spectroscopy (Claus Seidel) and the detection of interactions between membrane protein complexes by atomic force microscopy. Another important technique discussed in this session was the application of vibrational spectroscopy for monitoring conformational changes in protein ensembles (Klaus Gerwert).

Session 7: Intrinsically unstructured protein complexes

An important general concept of the conference was the role of intrinsically unstructured proteins as interaction partners. In this session, the importance of intrinsically unstructured protein domains as preferred interaction sites were further corroborated by a genome-wide analysis (Madan Babu). Moreover, some unique features in the structure and dynamics of complexes formed with unstructured protein domains were presented (Carlos Bertoncini, Flemming Poulsen) as well as the characteristics of intrinsically unfolded chaperones (Dana Reichmann).

Session 8: Signalling complexes

Many cellular signaling pathways are based on a chain of interactions, which are switched by posttranslational modification. Many interactions discussed in other sessions were involved in signaling. In this very short session, some aspects of signal activation by membrane receptors were discussed. This included the application of single molecule imaging techniques for probing diffusion and interaction dynamics of receptor complexes (Jacob Piehler) as well as a computational approach for unraveling the specificity of RGS proteins (Mickey Kosloff).

Session 9: Evolution and design

The ability to engineer high affinity protein interaction sites has important implications for fundamental research and for medical applications. In this session, the evolution of protein binding sites was discussed from basic and applied perspectives. Next to improving binding affinities by rational (Julia Shifman) and evolutionary techniques (Eric Sundberg, Katja Arndt), an approach for de-novo grafting binding sites onto functionally unrelated but structurally related protein scaffold was presented (Luhua Lai). Moreover, the capabilities to gain insight into protein interaction network by topology analysis were discussed (Natasa Przuly). In a special highlight presentation, a total quantitative description of a simple bacterium was presented (Luis Serrano).

Session 10: Multi-protein complexes

In this last, methodology oriented session approaches to explore large, multiprotein complexes were presented. These included high-resolution structural analysis by NMR (Marius Clore, Paul Rösch) as well as techniques for probing the composition of large complexes by mass spectrometry (Michal Sharon, Helena Barysz). Moreover, novel techniques for screening for multiprotein complexes (Kristian Müller) and for assessing the stability of protein complexes within large assemblies (Frederic Cazals) were presented.

Forward Look

An impressive group of experts was enlisted to present invited talks on a broad, yet well balanced selection of topics. Not only the invited talks were uniformly of very high quality, but also the presentation selected from the abstract (nearly 60% of the total number of talks) very nicely complemented the spectrum of topics. The main results mentioned above were of high scientific standards. Several important common concepts and challenges in protein-protein interaction research successively emerged during the conference:

- The specificity and promiscuity of interactions and interaction partners
- The role structural dynamics and intrinsically unfolded proteins for the physicochemical properties of protein complexes
- The importance of highly transient interactions, which are extremely difficult to identify and to quantitatively characterize
- The impressive methodological advances for screening protein interaction networks and
- The promising capabilities of single molecule spectroscopy and single molecule imaging for probing protein conformations and interactions in the native environment.

The final look forward discussion fostered these emerging topics within the field of protein-protein interactions, some of which should be considered more explicitly in a future meeting.

▪ Is there a need for a foresight-type initiative?

Not at this time.

Atmosphere and Infrastructure

▪ *The reaction of the participants to the location and the organization, including networking, and any other relevant comments*

The location, the hotel facilities, the service as well as the quality of the meals was much appreciated by the participants. The. The warm and personal, yet professional organization and management by the ESF during the conference was received very positively by virtually everyone and contributed a lot to very good atmosphere during the meeting.

In total the participants were very enthusiastic about the conference. Most of them considered the scheduled presentations at the ‘cutting edge’ of science, clearly defining and analyzing the most important problems and opportunities in the field of protein-protein interactions. The speakers’ presentations were mostly considered as well delivered, often conducive to vibrant discussions following the talks. However, several participants suggested to reserve more time for these discussions, which often were very extensive and therefore were terminated by the chairmen in order to keep the schedule. Despite of the dense scientific program, there was ample opportunity for informal exchange of information was available during the relatively long lunch and dinner breaks and at the two evening poster sessions. These vibrant poster sessions were extremely positively received and persisted until late night.

The atmosphere was very positive, most considered the conference as very special and highly stimulating due to the broad range of topics presented from a unifying perspective. All participants took all their meals together, which encouraged casual interactions. During the coffee breaks in the morning and afternoon sessions, participants were intensively interacting and discussing. According to the participants, the conference aims were timely, clearly and efficiently communicated, and in the end fully realized, ultimately making for a very successful conference. Virtually everyone felt that the conference should be repeated within the next 2-3 years in a similar format. Prof Marcellus Ubbink (Leiden University) was suggested as the chair for the next meeting, and he accepted. Prof Ubbink participated at all three PPI meetings and he will be an excellent chair. It was suggested that the next meeting will be held in spring 2013.

Date & Author:

07/02/2011 **Jacob Piehler & Gideon Schreiber**