Interview with Xavier Salvatella – by Mark Peczuh

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This is the first of several posts from Mark Peczuh that I am hosting. In this post, Mark interviews Xavier Salvatella on his research (protein-protein interactions and their implications for disease) and why he works/lives in Barcelona. Enjoy!

"It is a bit like Janelia Farm on the Diagonal"

We met, unexpectedly, at the entrance to his building in the Barcelona Science Park on the University of Barcelona campus. His building is literally in the shadow of Camp Nou, the home stadium of the famed Football Club of Barcelona better known simply as "Barça". He was hurriedly arriving to make our appointment in the same way I was. Although it has been a few years, I instantly recognized **Xavier Salvatella** by his characteristic gait with the torso slightly askew and the welcoming smile. Xavier had reluctantly agreed to be the subject of my first interview – a guinea pig. I am currently in Barcelona on a Fulbright Fellowship. As part of this fellowship I will be interviewing interesting scientists here in order to understand the practice of science/research in the context of place.

Xavier Salvatella (Image Credit: Mark Peczuh)

MP: So tell me about your research.
We have two sides of the lab. One side has been focusing on methods development to characterize the flexibility of proteins. Everybody is aware of the importance of flexibility, but it's very hard to characterize. Right now only simulations are undergoing a revolution. [This revolution] is based on a change of approach on how computers are built. Rather than building supercomputers that can do many different tasks, people have said, "Perhaps it's better to build them for a specific task." Computers have been optimized to do molecular dynamics on a much longer time scale, up to microseconds. The simulations still cannot be done with very large and complex flexible proteins and many things can not be studied with simulation.

MP: I'm expecting you to tell me something about how your group uses NMR as a tool for characterizing dynamics of proteins. How does the time scale of the experiment – either simulations or NMR – fit with the dynamics of the protein?
That's a good question. By NMR you can look at dynamic processes at any time scale. Processes from nanoseconds, using relaxation times, to seconds or more, by doing experiments in real time, can be studied. Simulations can only look at the fastest time scales but there are many, interesting, dynamic processes that are so slow that they're beyond the current reach of simulations. The encouraging thing is that on the fastest time scales, there is good agreement between the two. This has led to improvement of both of the methods (NMR and simulation).

MP: Where do protein dynamics come into play in biochemistry? Protein-protein interactions, catalysis, what?
Protein dynamics are definitely important to catalysis, but we're focused on protein associations – either protein-protein interactions (PPIs) or protein oligomerization. Usually when PPIs are modeled via docking, they're treated as two rigid bodies and the complementarity of their surfaces is interrogated. In reality, however, the two proteins are fluctuating; they are flexible. When they associate, there are often subtle conformational rearrangements in both proteins. We've been

collaborating with a computational team at the Barcelona Supercomputing Facility regarding this. We reported earlier this year on a strategy to improve prediction of binding partners and docking modes between ubiquitin and several of its partners. The task of ubiquitin is to bind proteins. If you try to predict complexes with it you have to take into account the flexibility. We used NMR experiments to define a conformational ensemble for ubiquitin; this is a collection of all the conformations that have a certain probability of being populated by the protein. It's multimodal, and when all the conformers are probed in the simulation, you get accurate complexes. The collection of conformers agrees with the experimental data better than the crystal structure. So protein flexibility, when accounted for by conformational ensembles, improves the performance of docking methods.

MP: What about the other side of the lab?

The other side of the lab is working on a project that also involves a question related to PPIs because it involves the association of a protein with itself. Flexibility often makes proteins more probable to aggregate and form plaques as a consequence of that flexibility. We are interested in this relationship: more flexibility – more aggregation, more flexibility – faster aggregation, different types of flexibility – different types of aggregates, these sorts of questions. But we were using a protein that is not particularly important to biomedicine.

MP: And then?

The story is quite funny, actually. Shortly after I had arrived at the IRB, while we were in the midst of the methods development project, my wife's friend asked me to describe our research to her. The incident coincided with a real effort on our part to try and adapt our research to what we have here [at the IRB]. I realized that it would be attractive to get into a biomedical problem. Rather than working only on the methods for their own sake, we wanted to apply the methods to an important protein. I was explaining our research about aggregation to her when she said, "I have a family member that has a disease that is similar to this, it's called Kennedy's disease." I looked up Kennedy's disease on Wikipedia and found out it's a rare familial genetic disease of which not much is known. But it had to do with aggregation of a protein called androgen receptor, a protein that is responsible for the male phenotype. In the cytosol it is in an inactive state and then upon binding testosterone large conformational changes occur. This leads to translocation into the nucleus and the protein then acts as a transcription factor to upregulate specific genes.

MP: Wow. So it was a project that was perfectly suited to your program, right?

Yes. Around that same time there was a call by Catalan funding agency that targeted rare diseases. So I quickly wrote up an application and got about 400.000 euros (shared with two other groups) to work on the androgen receptor aggregation project – [in order] to characterize how it aggregates, etc.

MP: Isn't androgen receptor linked to prostate cancer too?

Yes, it is also the main target in prostate cancer. The normal state of prostate cells is to be turned "on" via testosterone through the androgen receptor. Unless there is constant activation by testosterone, the cells will go into apoptosis. So a common pharmacological treatment for prostate cancer is to stop the activation of androgen receptor. But in a certain fraction of patients that undergo this therapy, [after] two to three years, they stop responding to the treatment. This recurrence is called castration resistant prostate cancer. Here the receptor is able to activate itself even in the absence of testosterone. We're trying to look into this process using our methods. The reason being that the protein sequences (via sequencing of the patients' DNA) for the androgen receptors have mutations. They are all in a domain that is totally flexible, and there are many hints that this is the domain that drugs should really target. So crystallography can't give much information here but our NMR methods can….and do, because we can look at these "intrinsically disordered" proteins.

MP: So it's methods development to look at protein flexibility and its implications for aggregation and the application of the methods to therapeutically important proteins?

Yes, and the upside is that, if you look at the IRB website we have five research program areas: chemistry and molecular pharmacology, structural and computational biology, cell and developmental biology, oncology, and molecular medicine. Out of those five, three or four of the program areas are in this one project. These two projects related to androgen receptor –

Kennedy's disease and prostate cancer – have been well received by my colleagues and students.

MP: I haven't asked about the IRB itself. How would you describe it?

For me, right now, the reasons I joined IRB were that I could solve two [problems]. It was here I knew I would "be where I belong." I am from here and I have friends and I like to live here. And there was a place I could [perform] the type of research I wanted with the resources that I think are necessary. Because the two things happened in the same place, I took [the position]. It was very pragmatic.

(Image Source: Institute for Research in Biomedicine)

MP: What resources, maybe beyond the obvious instrumentation, etc.?

At the IRB, all the resources necessary to ask broad, impactful questions are provided. In return there is an expectation that investigators are ambitious about their science; big ideas are encouraged. By design, there is no process for tenure at the IRB, and investigators are reviewed every five years. This creates a certain urgency or an intensity that that defines the environment here. It is quite effective for motivating everyone.

MP: It sounds like Janelia Farm on the Diagonal.

Yes, it is a bit like Janelia Farm on the Diagonal. (La Diagonal is a huge boulevard in Barcelona where the IRB is located.) When I left to do a post-doc in Cambridge, I thought, "I am going to a great place in a very important group who try to solve huge fundamental problems. I will not be able to do this in Barcelona ever so I may as well enjoy it and if I do well I will look for positions elsewhere – in the US or the UK to run a research group." And then, I realized it was possible to do it here in Barcelona at the IRB, so I applied to the job and I got it.

MP: What made this possible?

There is another virtual institution, called iCREA that hired me from Cambridge to work at the IRB; they gave me a salary for five years. Let me give you some background. Before I left for Cambridge, there were two places where you could do research: as a university professor or as a CSIC investigator. CSIC is a national research institute all across Spain – it's similar to the CNRS in France – one institution devoted to many different types of research. But there was [an] interesting development in Cataluña around the time when I left [for Cambridge] in which the government decided that those two institutions were not appropriate for doing cutting edge, high impact research for many reasons – the rigidity of the hiring system, tenure – which can cause people to relax, bureaucracy, etc. etc. etc. Two instruments were created by the Catalan government to solve this problem. One is the creation of iCREA; it is a very small agency that recruits good scientists and negotiates a salary with them and assesses their performance every 3-5 years. This instrument is open to all institutions (universities, CSIC) as a way to support salaries for their staff. This was a way that many talented scientists have moved [back] to Barcelona. The big thing is that the selection of the iCREA researchers is done by committees of experts that couldn't care less about anything except the quality of the science of the applicants. There was a huge emphasis on that. Each year there is a huge competition for 20 positions in iCREA. I was brought in to the IRB on a (now discontinued) junior iCREA program. In parallel to this was the creation of centers of excellence. The government created a number of research institutes of varying sizes in areas of science that were considered important to Cataluña. Of the many centers that were created, IRB is one of the biggest. They are totally different than a university or CSIC – more intensity, more resources. Both university faculty and CSIC researchers can be investigators at an institute along with iCREA researchers… or in fact "no ones" – investigators that are sponsored directly by the institute. We have all of these varieties at IRB. These two instruments have been very successful, so successful that the competition is quite intense. They have changed the panorama completely – now we have in Cataluña research centers that are top quality in Europe, top quality in the world.

There's something about this neighborhood of Barcelona that encompasses Camp Nou and the IRB. The motto of Barça is visible from an arial view of the stadium, "Més que un club (More than a club)." Perhaps the same can be said for the IRB, "Més que un institut."

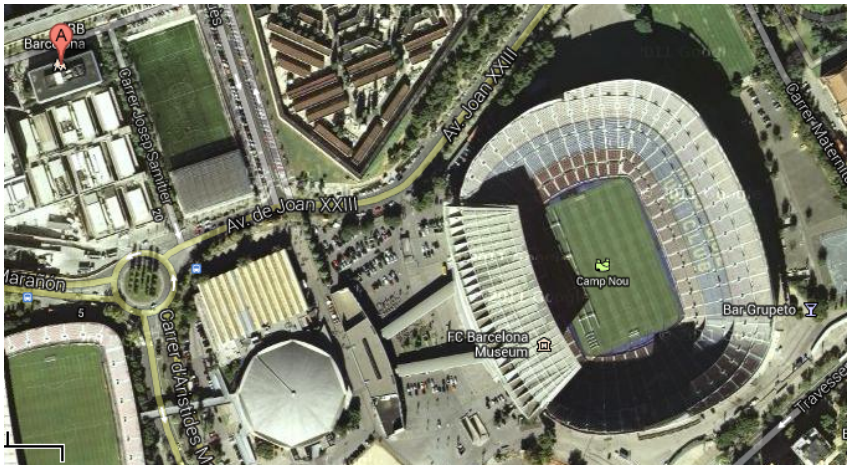

Image from Google Maps. **A** indicates the Institute for Research in Biomedicine.

*Name: Xavier Salvatella
Position: Investigator at the Institute for Research in Biomedicine (IRB) in Barcelona.
Research: Characterizing the flexibility of proteins and the implications of this flexibility for biology
Important: Married, father of son Lluc (2 years) and daughter Maria (4 months)
Why Barcelona? I am from here and I have friends [here] and I like to live here
Why IRB? And [in Barcelona] there was a place I could [do] the type of research I wanted [and] where there [were] resources that I think are necessary [for that research]. Because the two things happened in the same place, I took [the position]. It was very pragmatic.
Quirky: [I have] a peculiar fascination with pens and personal office supplies.

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