Ernest Giralt, Uncle Peptide

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This is the second post from Mark Peczuh on the culture of doing science in Spain and, specifically, in Catalunya. (I do owe Mark a big apology for not getting this out sooner.) I really have enjoyed reading this interview with Ernest, and I hope you will too. Lots of great stuff to learn!

"Thank you to […] the perpetually avuncular Ernest whom I hope to grow up to be."

That's the sentence thanking Ernest Giralt in the acknowledgements of my dissertation. Ernest and my PhD advisor began a collaboration in the late 90's that involved my thesis project. Ernest's group used NMR to help us characterize the conformational changes in some α-helical peptides that occurred when a ligand was bound. During that time he visited our lab for a few weeks at a time. I also spent a few weeks in his lab in the summer of 1997 at the University of Barcelona. My first and strongest impression of Ernest – beyond his boundless creativity as a scientist – is the aura of joy that surrounds him. Even though he is always moving at 100 mph and juggling many things, he appears to savor every bit of the process. Whatever he is doing becomes interesting, fun and fulfilling.

Ernest Giralt (Image credit: Mark Peczuh)

Because I enjoy hearing what he has to say on just about anything, and because Xavi Salvatella told me he could give me more of the backstory on ICREA and the formation of the research institutes in Catalunya, I bugged him for a lunch meeting and conversation. Over lunch we caught up on family stuff but then we went back to his office to really do the interview. I explained to Ernest the origin of my idea to share the story of Catalan research and how Xavi really opened my eyes to the ICREA and the research institutes that were started by the Generalitat about 10 years ago.

MP Ernest took it from there, starting with the origins of ICREA…

EG The two things, ICREA and the institutes from the Catalan government, are [the] key things. To the best of my knowledge, they were born independently but more or less at the same time. And they've been very synergistic.

The ICREA program was first. In the 1990's I had co-founded with a colleague an Association of Catalan Scientists for the Promotion of Science. Its objective was to show the connections between science and society. Around that same time, the Generalitiat awarded the Narcís Monturiol Prize to one of the members of this group, Rolf Tarrach [Tarrach won the prize in 1997.]. During the process he had voiced some criticisms of the research situation in Catalunya. Afterwards, the President of Catalunya told him that, if he had ideas about what could be done to improve the situation, he should recommend them. He chose to use our association as a sounding board for discussion and refinement of what would eventually become the ICREA program. I must say that, as usual among a group of scientists, we were not shy with our own criticisms. Together we eventually worked through many of the details to make a plan that we could all support.

The concept behind ICREA is very simple. The institutions that do research in Catalunya, and really all of Spain, especially at that time, were very old ones – in particular CSIC on one hand and universities on the other. From the point of view of recruiting new people, these institutions were not agile enough to attract researchers from outside of Catalunya. So the iCREA program was saying, "Let's invest money in a very meritocratic [way] to select outstanding people and pay the salaries of these scientists." With the salary in hand a scientist could then knock on the door of these traditional institutions and ask for a position. If they had the salary that they secured in a competitive way, then they would likely look attractive enough for these older institutions to "let in some fresh air." An infusion of new ideas through new researchers – new people – was what we thought CSIC and the universities needed at that time. One year after the other, several investigators have been going into the program over the last 10 years. It's a competitive, successful program.

MP And what about the parallel development of the institute system?

EG Independent of this, but again around the same time, Andreu Mas-Colell [currently Minister of Economy and Knowledge in Catalunya] chose to return to Catalunya to be the Minister of Universities, Research and Information Society. Andreu is a world-famous economist; he was a professor at Berkeley and Harvard, and he is a member of the National Academy of Sciences, one of a small group of international members. One thing that Andreu liked to do was host breakfasts with local scientists, including me. At one of the breakfasts, he reported that an idea was circulating that we should have a research institute system in Catalunya and he wanted to discuss this idea. We discussed at first in abstract how institutes should be created. It became clear to many of us discussing the ICREA program that the new positions could fertilize these new institutes. It was certain, though, that ICREA wasn't only going to be used for institutes but was to also to be used by universities and CSIC. Areas of investigation for specific institutes were designated through input from a consulting company and the scientific community and also consideration of the potential economic impacts. The IRB was one of the first institutes to get the designation from the Generalitat. These two things – ICREA and the institutes – have maintained their support in the Generalitat through changing governments over the past 15 years.

MP But there is another piece to the puzzle – the story of the Science Park.

EG I have answered your question about Catalunya in general. But now, to complete a triangle, I feel like I should tell you about the science park. This was not in my answer to Catalunya because it is not general. It is specific to the University of Barcelona (UB), the oldest, biggest and premier university in Catalunya. We started work on a Science Park about 12-15 years ago. Back then the area housed several other departments at UB, from history to the humanities. These departments decided to move to different campuses in other areas of Barcelona. That meant that a wonderful piece of land near the Diagonal and coincidentally near several science departments like chemistry, physics and biology [was now unused]. Through some collective brainstorming ("un concurso de ideas"), the idea of a science park was selected. UB understood [that] this be a place where basic science research institutes and labs from companies – both pre-existing companies and spin-offs and start-ups – would be mixed-up together very intimately. To make it more attractive they would provide shared facilities run by the science park itself for emerging technologies such as proteomics, combinatorial chemistry, and nanosciences. In the meantime, some others have been added, like a transgenic mice facility at the IRB. The philosophy is that each institute can build up facilities, but they have to be open to all.

Another set of breakfasts was important for this process too. [Like many places, breakfast can be a power-meal in Barcelona.] Marius Rubiralta, who was research vice-president of UB at that time, held breakfasts on the first Monday of each month here in the area that would become the science park. Typically we were 8-10 people; half were professors from UB and the other half consisted of the owner of the first pharma, the second pharma, and the third pharma and a rep of all the other companies in Catalunya. This group decided that the first center in the Science Park was to be Institute for Bioactive Molecules. This was the embryo for the science park and also for what was to be[come] the IRB. IRB actually started before the Catalan government decided to make the research institutes. When the Generalitat started the program, we instantly notified them that IRB was a functioning institute already and we were then given the "label" of the Catalan Research Institute.

MP You were instantly ready to become an investigator at the IRB then, right?

EG Not exactly. When the science park idea was born I was invited to contribute intellectually to the ideas and design and then, afterwards, I was invited to become an investigator in the institute. Being asked to join gave me the same sensation as if I were preparing to jump into a swimming pool that I knew was empty! (Laughter from both of us.) I was moving from the Department of Organic Chemistry at UB – the department where I had done my PhD studies and had spent all [of] my professional career, except for some parenthetical sabbaticals in France, Scripps, and UCSD. The success of the institute at the time was not a certainty. In some ways, I thought, "That's for the others, not for me."

MP How did you decide?

EG In my case, it was several arguments all together that finally helped me make the decision. The first was the opportunity for interdisciplinary research. At UB we have a great department, but it was too many of the same – Organic Chemistry everywhere. And we were already at the time already working on several interdisciplinary projects on top of our focus on the synthesis of peptides as protein surface binders. We had already begun doing expression of labeled proteins in E. coli for NMR studies and working on more therapeutic uses of our peptides. I must say IRB was the right fit from the perspective [of] our interdisciplinary research questions. This was the main reason for the move. It was an opportunity for real mixing with scientists from multiple disciplines. The second reason is because I've always liked translational science. Here at IRB we're together with companies, and the opportunity for spin-offs was very attractive. Third, because I was involved in the design of this new institute, I thought joining would be an honest show of support. Any one of the three arguments alone would have been insufficient to compel me to move, but, all together, I knew I had to. But, I was afraid. I didn't want to lose what I had achieved after so many years in my department at UB.

MP How is research at IRB different?

EG One thing about research is knowing what you want to do. But another thing that is important is how you will do it. What kinds of experiments can answer your question… that sort of thing. This is the thing that has changed most for my group because to do easy biology in this environment is very, very easy. What I mean is that anyone in my group, even if they have had classical organic training, are able to use a flow cytometer, for example, to measure fluorescence of cells after a few days in the lab. It's because the facility and the technicians are available for this type of experiment at IRB. My group can now do cell culture, confocal microscopy, [and] we've even established a blood-brain barrier model system with epithelial cells and astrocytes isolated from mice. All these were at one time unbelievable experiments for me.

But the goals are the same. We are a molecular recognition group. We want to design molecules that will bind to a target protein and change its function, usually with the intent of interrupting a protein-protein interaction (PPI). Its not the "what" but the "how" that has changed. This is all from the point of view of the intramural research in my lab. The other thing is now it's easier to have substantial, meaningful collaborations with other groups on projects of a grander scale. At IRB we have a strong positive pressure to do projects that are synergistic between groups within the institute. This is easy to say but hard work to do. One of the most talented group leaders at the IRB is Eduard Batlle who is head of oncology program. He is studying some unique stem cell lines from colon cancer patients. He and I have just advertised for a post-doc who will work 50% in my lab and 50% in his lab. The idea is to work on isolation and chemical modifications of some alkaloids as potential anti-cancer agents. We expect the person to leverage the expertise of both groups, a catalyst of a joint project.

MP So what can you tell me about your latest research?

EG Do you want to hear my dream? Ok. My dream is: you go into my lab with a 3D structure of your favorite protein. You put your finger on one spot on the protein, and my group synthesizes a ligand, typically a cyclic peptide, that will bind very tight and, even more importantly, very specifically to that spot. Now what is our research? We work to understand why the scenario I posed is currently a dream and what we can do to make it a reality. We think that taking into account the dynamics

of the proteins is important, so we look at protein dynamics and the μs-ms timescale. This is an area where huge domains of protein are moving. Until recently we were blind to these motions until relaxation dispersion [NMR] experiments had become available. Now we are not blind. We are discovering that more and more proteins have important dynamic behavior and of course if we tried to do all our design on a frozen structure, it's difficult to be successful.

MP What is the implication on those movements in a lock and key versus an induced fit model for binding?

EG The implication is significant. Within the lock and key paradigm, if you have a flexible ligand you will have to pay an entropic cost when binding to the target protein. This idea has guided medicinal chemistry for 100 years. It's based on the assumption that the protein, too, is rigid. But, if you have a protein that is opening and closing with a rigid molecule that is like a "palo en las ruedas" (stick in the wheels) – freezing this movement – then you pay a huge entropic cost on the side of the protein. My view, but I have not been able to prove this experimentally, is that if you could maybe tune the dynamics of the protein with the dynamics of the ligand then both could move together – a dynamically tight binder.

My group can now look at the affinity of ligands with proteins in the gas phase and in solution and rank order families to look for the importance of solvation in these interactions. We'd like to understand how solvation plays a role. Molecular recognition at protein surfaces is the focus of the group. We select proteins for investigation not because they are easy to work with or they are good models, but because we are in a biomedical institute so we choose targets that are therapeutically relevant or at least biologically relevant. For instance, we have been working on protein dynamics related to a protein important to schizophrenia and also on amyloid fibrils (Alzheimers), p53 and growth factors related to cancer. Our recent paper in Angewandte [It's the cover graphic!] reports on a peptide that is able to disrupt a PPI important to endocytosis called clathrin-mediated endocytosis. The key is that the peptide (a modified β-arrestin sequence) must be able to adopt an α-helical conformation to bind to the target protein – the β-appendage domain of the AP2 complex. For one sequence, a diazobenzene is linked to the peptide at two points (alkylation of cysteine thiols) along the peptide spaced three turns apart. The diazobenze is a photo-switch. Irradiation of the peptide with visible light favors the trans form of the diazobenze and consequently the α-helix (go). Irradiation with UV light switches the diazobenzene to the cis form and the a-helix can not form (stop). The beauty is that the shape of the peptide can be modulated in either direction based on the cis-trans switching of the diazobenzene and the spacing of the linkages to the peptide, whether it's two or three helix turns. We call them traffic light peptides. Then if you have a cell culture and you add a one of these peptides and you irradiate with the appropriate light (UV or Vis), endocytosis will stop and, when you switch wavelengths, endocytosis will go back again.

MP Do you envision this as a tool compound?

EG Yes, we envision this as a tool for confocal microscopy. On a single cell basis, [a] scientist can choose whether endocytosis is operative or not. And then they can be compared for [determining] what the effects of endocytosed material [are] for example. Therapeutically, we are limited currently because UV-Vis light is poorly absorbed in tissue, but we envision retinopathies, though. Melanoma In the future we envision using the same strategy but with near IR chromophores to help with better tissue penetration.

MP Do you have still have responsibilities at UB?

EG Of course. I love university life, I love my university and I love teaching a lot. One the conditions of coming here [to IRB] was that I could keep this aspect of my academic activity. For example, this year I taught a course on the application of spectroscopy with stereochemistry and conformational analysis to elucidate the configuration and conformation of molecules. Students like this course because it's like molecular Sudoku, "What is a compound that has this MW, with these spectra…," I participate also on committees for the teaching activities. But my research labs are all at IRB.

MP How do you identify as being a Catalan? You are a son of Barcelona. What kept you here?

EG I am traditional for this point of view. It is a very common practice for people here to live abroad but to come back.

When my mother recently passed away (at 92), all four of her sons and her nine grandsons without exception were living in Barcelona. But this doesn't mean we don't move. I have lived for periods in France, the US, and the UK; one of my brothers has also lived abroad. One of my sons lived in Italy for several years and another has lived in the US and China. This means we like to go abroad, but we come back. It's more a question of the style of life. We keep very close to family and friends. I like music. When I was young, say from 16-20 years old, I sang in choir with a group of about 40 singers. That's been some time ago! Nonetheless, every first Tuesday of the month I have dinner with that group; sometimes we are all 40, and sometimes only 15-20 can make it. I, like the others, sometimes have other plans that can't be broken or I'm out of town or whatever. I know that if I want, I can go and spend time and talk with those people that I've know for all these years and we can sing together if we choose. These roots – and here when I talk about roots I mean people – all these people that were my friends when I was 16 and we sang together, or friends I made during the summer when I was young, or friends from school. Many of these people are still around and I can enjoy spending time with them. Of course on top of this is family; once a week while she was still alive, my brothers and I together had lunch with my mother. For me this is very important. It's about people and relationships.

MP More that a decade after we first met, Ernest continues to inspire and teach me. His life is filled with the same day-to-day challenges as any academic, but he remains focused on what's important like ideas and relationships. In the end those things provide the greatest joy. Now, just like when I was a grad student, I'm hoping to follow his lead.

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