Transcript of Montserrat Interview Part 3: History of CLL Research

Marti: Another organizing principle for our interview was that, I think it seems safe to say that in terms of CLL in Spain, that Barcelona is where it starts, but certainly Salamanca and Madrid and Valencia have present-day CLL interests.

Montserrat: Absolutely.

Marti: Can you comment any about how those came to be?

Montserrat: No, I think that this came out as a result of a personal relationship between me and all these guys.

Marti: Okay.

Montserrat: And then what we had for a number of years was what we called the CLL Spanish group, and we did a number of studies. So, and as a result, there were people in all these places that you have mentioned that became interested in CLL. And, afterwards, I mean, they developed, started developing in a very successful manner, I must say, and they're our brothers. And I think that you are not missing anyone, particularly Salamanca I would say. That's much more than Valencia, vis-à-vis, particularly Salamanca, and Madrid. But Madrid belongs to a kind of different school somehow because whereas we here started to, with internal medicine, and maybe Madrid is much more related to this immunology thing—

Marti: Okay.

Montserrat: —this—yeah. And there is another very important immunologist in Madrid that would provide important information, which is, his name is Nuñez, it's N-U- the famous "N" with a [makes a gesture to represent a tilde]—

Marti: A tilde.

Montserrat: —a tilde, E-Z, Nuñez, and he has been a person very, very important in the world of immunology and in the world of CLL as well.

Marti: Okay.

Montserrat: But, from, a much more basic approach.

Marti: Molecular?

Montserrat: Yeah. I mean, one of the things that I regret, actually, and now is soft in part, but one of the things that I do regret is not having been successful in pushing a much more basic research in CLL, and our research has been basically—

Marti: Clinical.

Montserrat: Now we are participating in the [unintelligible] genome study[1] along with Elias Campo, [unknown name]. As I said to you, there are so many people interested, but in the early days, we kept focused on clinical studies basically, which is according to Winthrop is a mistake.

Marti: Well, I, something that just occurred to me in what you're saying is probably —aside from individual groups, it probably was the CLL Spanish Cooperative Group—

Montserrat: Yeah.

Marti: — that was the network.

Montserrat: It is, yeah. It was.

Marti: And the abbreviation for that is P—

Montserrat: The name of the group?

Marti: Yes.

Montserrat: It's P-E-T-H-E-M-A. This is a group working on all kinds of hematological malignancies, but the Spanish CLL group was incepted in this, at the very beginning, because the Spanish CLL group as such disappeared in the late 90's of, yeah. When, I mean, the different institutions wanted to have their own programs, and so there was not any more cooperation or the cooperation that we established as the Barcelona group was an international cooperation rather than a national cooperation. Yeah?

Marti: That's a good point.

Montserrat: But that's a kind of personal position of mine because I do believe much more—I mean, I need—I'm convinced that cooperation is necessary, but I think that in those days what we really need is international cooperation.

Marti: Now, there is another person—I have to look for the spelling of the name—who has a more molecular, and I think it's a she, and I think that she is in Barcelona. Villamor?

Montserrat: Villamor?

Marti: Villamor.

Montserrat: She is a person that was of flow cytometry.

---

[1] International Cancer Genome Consortium, Genomic study of Chronic Lymphocytic Leukaemia

Marti: Ah, flow.

Montserrat: And she works along with Elias Campo. Campo. You know Campo, right?

Marti: Ah, right. Yes, I recognize that name.

Montserrat: Yeah. But Villamor is our Orfao.

Marti: Oh, okay.

Montserrat: Okay.

Marti: That's good.

Montserrat: That's good?

Marti: Yeah.

Montserrat: Just to define, yeah? In the quickest possible manner.

Marti: Sure, sure. Shorthand. And she is still working?

Montserrat: Yeah.

Marti: Okay, okay. Well, I think that we have covered the history of iwCLL, which was, I think, an important thing, and the history in Spain of CLL. Where will the next workshop be?

Montserrat: Houston.

Marti: Oh, so Keating will be heading up that one. And in terms of cooperative groups, international versus national, makes me think of the CRC in the US versus ERIC. What can you tell me about ERIC?

Montserrat: Well, I think it was created something like six, seven years ago. I am department chairman of the group, and I think it's—there are a number of important differences between ERIC and the CRC. CRC has a blocked cell bank, and ERIC doesn't, and the CRC has performed a number of clinical studies, clinical trials, which is not the case of ERIC. ERIC is much more concentrated in—if I can say, so basic science. And now we are trying to promote and to give more emphasis to clinical studies.

One of the reasons, I mean, this has not been done as yet is because the different cooperative groups for clinical trials in Europe are very, very powerful. The German—

Marti: Are international.

Montserrat: They are basically international. So, it is still—I am convinced that for, let's say, some particular phase II studies, I mean, to have an individual phase II study center in which other groups can participate

in, so this is one of the rules, yeah. But there are, this—there are, it's funny, iwCLL, I mean, it is a group of friends. Actually, there is no structure. Then you have the CLL Global Foundation,[2] which is based in America, which is Mike Keating project. You have the CRC, again in America, which is my understanding, which is basically the leading person is Tom Kipps, I think. That's my feeling. And then you have the cooperative groups, which are probably, well, you know them much better than me, but they are probably not as active as the European groups are.

And in Europe, what we have is ERIC. I defined a little bit ERIC a minute ago. And then we have these very, very strong cooperative groups, the German—basically the German, I think that the dominant group is the German. And we are doing now many, many studies with the Germans, and so Michael Hallek deserves a lot of credit for the effort and for putting all of us together. So, he is leading in strong personality. Oh, you know him very well.

Marti: Yes. Yeah. Actually, when Dr. Hallek visited the NIH about a year ago, I was able to conduct an interview with him similar to this one. And I've made a copy of his interview and gave it to him, and I recently met Dr. Rai. I wanted to give him a copy because Dr. Hallek is very appreciative of what you spoke about earlier, about the core friendship. He was so impressed by that core friendship because it was extended to him, and he attributes that to the beginning and success of the German CLL study group.

Montserrat: Well, I mean, it's—I think that maybe, I mean, he's too modest from the side of Michael Hallek. I think that Michael Hallek would have succeed anyhow. I mean, I'm sure of that.

So, at the same time, I mean, he asked for the support of the iwCLL, and he built up a kind of consulting committee or advisory board, whatsoever, and it was basically people from the iwCLL. And Michael, when he was still in Munich, he organized them. He was not yet full professor of medicine. He organized a number of meetings in nearby Munich in a monastery. That's—and he invited us. And, yes, I mean, somehow, I mean, he had our blessing, to say so.

Marti: Sure, sure.

Montserrat: To say so. But, still, I mean, he would have been—he's a successful person. I mean, it's because he is a hard, a very hard worker. But now he's a little bit the opposite. I mean, now he's taking the lead of the iwCLL. At the iwCLL, I think that the fact I knew iwCLL very well from

[2] CLL Global Research Foundation

the very beginning. It's a long-standing story of mutual interest and friendship. I mean, it's—for me, I mean, to be completely honest, not only is it not exactly the same as it used to be 20 years ago, I mean, for many reasons. I mean, we are competing for grants, we are competing for events, we are competing—there's much more competition. But, 20 years ago, I mean, we are so open, I mean, each other. I mean, there were no secrets. There were nothing.

I mean, now, it's—well, life changes.

Marti: I also think—

Montserrat: I hope that you edit this.

Marti: Oh—

[Laughter]

Marti: Yeah, we'll be very careful. But, I think that, at each level of the group formation or a group enlargement, that the same process of becoming comfortable with each other and trusting each other, that was present from the beginning, but I think each successive group has to learn that. I think that we don't necessarily start out that way. We start out more with, you know, I want the drugs, I want the funds, and then when we find out that—

Montserrat: But, yeah, no you're right, but since the very beginning, these things were nonexistent. I mean, there was no problem at all. I mean, I do remember that when I organized the meeting here in Barcelona, the fifth, I mean, the problem was to get the company, the pharma, interested in giving us some money, and I got some money because of a friend of mine whose interest was not CLL at all, but there was a good relationship, and he said, "Well, I mean, how much do you need?" And he said, well, eventually, "It's not a big amount of money, so I will give it to you as a kind of personal thing." I mean, he said [unintelligible] grants, so do it.

I mean, now when we organize the meetings, I mean, the pharma is knocking on the door. I mean, and giving, willing to give us money, so this is completely different story. And it is a competition.

But, since, I mean, to become a member of the iwCLL, there are no rules. I mean, and just by appointment, it's by invitation. I mean, then I think that somehow you are completely right. I mean, the people joining the iwCLL is the core group. I mean, they have a profile. I mean, they have a kind of profile.

Marti: One of the things that Rai likes to point out in the early history of iwCLL is that, until the discovery that CLL was a B cell, there wasn't

much interest. It was kind of backwater for CLL, and I don't know if it was Rai, but somebody went so far as to say that, "Well, the whole reason iwCLL was founded was just so they could stay alive, because they were drowning in CLL." And then, perhaps, I think, when fludarabine came, that was another big surge—

Montserrat: Absolutely, indeed, absolutely.

Marti: Then treatment was driving interest.

Montserrat: Absolutely.

Marti: And now I might be so bold as to say that not only did the classification and treatment continue to grow, but now the advent of the molecular. And I'm kind of chagrined to say that I think an even newer era now is going to be this whole understanding of the microenvironment. That seems—which is such an old idea from, you know, 20 years—I don't know how far back you can trace the—

Montserrat: Since history repeats itself, when I organized the meeting in Barcelona, 1980, whatever—

Marti: '91.

Montserrat: Oh. Yeah. I mean, David Galton didn't make it, and David Galton was a real fantastic personality. He said to me, well, we have had that *Festschrift,* remember the book—

Marti: That was for Daniel.

Montserrat: No, no, no, no, no—that was for Daniel. No, no, no, no, no. No, but we have, but we had the celebration for David, and David said, "Well, listen. It's what is over is over," so it's, uh. And I remember that I invited him to come to Barcelona, but he didn't make it. And he wrote to me a letter that should be somewhere, and saying, because I sent to him the abstracts. He was mentioning, because history repeats itself, and he was saying exactly the same thing as you were quoting Kanti Rai. He said, "Oh, Emilio, I realize that most likely the meeting has been successful. I am very glad and happy because of you," blah blah blah. "On the other hand, it's amazing to see how this disease is changing so quickly and so rapidly." So that's—

Marti: That is a difference.

Montserrat: That's a difference.

Marti: And things are moving faster.

Montserrat: And I think that now we are in an era, to me, which is very similar to maybe 10 or 15 years ago, 20 years ago, exactly in terms of

morphology in the same position as we were with AML. And, so, I mean, to me, it's quite clear that, I mean, CLL is not a single disease. It is different diseases.

So, one of the things I don't understand, maybe because of my biological background is not good enough, is why people in this saying that microarray signature, which is similar for mutated and non-mutated, indicates that this is a single-cell with two varieties, and so this is something that I simply don't understand, because, I mean, if there are critical genes that make a difference, then it could be different.

But, I mean, if you take—I think it's appropriate now to talk about 17p minus CLL, 11q minus CLL. So, I think it's appropriate. I mean, these are completely different diseases with completely different natural histories and completely different treatments. What do you think?

Marti: Oh, I couldn't agree with you more, but I think I sense a shared frustration in that you were right that the microarray expression analysis says that we have to think about it as one disease or as one common signature, yet the minute that we divide the, in the mutational status into unmutated and mutated, then a new picture begins to emerge. We have to accept that. What I find even more frustrating is, if I understand it, as much as we think that the deletional pattern, the chromosomal deletional pattern, which is deletional in CLL and not translocation like in other lymphomas, the microarray people tell us, oh, there's no pattern there. They can't see any difference. And yet, we know biologically and clinically there is.

So, I suspect that once we make the mutation and unmutated split, we then have to decide about whether or not the chromosomal differences will express itself along those lines, and there's also a new bevy of prognostic markers post-ZAP-70 that I think are coming on the scene, but how to use them, or, maybe not even necessarily how to use them clinically but how to understand them and interpret them in terms of different biological subgroups. I don't think that's clear yet, either, or at least in my mind maybe. Maybe someone else understands.

Montserrat: Well, my point of view, I mean, and I wrote a paper about that, I mean, many, but one that very specific paper about that, is that maybe prognostic factors as understood historically. I mean, it's all useless and devoid of interest nowadays in CLL. I mean, if we have the prognostic factors at diagnosis and those are only useful, I mean to have an idea of how frequently you have to see the patient. That's period. No more than that. And what is very important, it's to have good biomarkers to predict response to therapy. I think that that's—this is what is really makes the difference.

So, back to CLL people and core group, and the definition, and what is the common background of this person's—I would also say, and I wouldn't [unintelligible] as an [unintelligible] person, which is I think that all of them somehow, they try to understand.

So, I will qualify a little bit what I have meant to say. I mean, to me, nowadays, I mean, with the technology we have, it is very easy to accumulate information, to accumulate data, okay? I mean, the only thing that you need is a big lab, is money, is researchers, is students, is the technique and the samples, and then you can really generate and generate and generate and accumulate material. But this is one thing, and the other thing is we need to understand what's going on, and which is completely different to me. So much of the stuff, I received to for—

Marti: Review.

Montserrat: I mean, to me, it's completely nonsense. I mean, you eventually accept it because it's part of the game and it is part of how the science is built up. That's for sure. But many or most of these stuff doesn't contribute to a real understanding of the disease, that's my personal bias, doesn't contribute to a real understanding of progress of the disease. There are very, very few things—but that's my particular bias. Differences between—I think that you and I already spoke about that in when we met in Bethesda about differences between—maybe these differences are much clear-cut in using Spanish words between knowing and understanding.

So, we have in Spanish a word which is *comprender* which is the biggest—it's comprehensive, I mean, it's the same thing. *Comprender* is when you make something alien, you incorporate this into you [gestures at heart]—I mean, it's an, and you really know that that's—that's why clinical judgment continues being important.

Marti: And improves.

Montserrat: And improves, yeah.