Transcript of Hallek Interview: Part 1

Marti: Michael, thank you very much for coming this morning, and I really enjoyed your talk. I know that you're on a very tight schedule on the basis of the itinerary that I was provided for your schedule. But in terms of trying to capture, in a relatively short period of time, some aspects of the history of CLL, and ultimately the intellectual history of CLL, I would like to start with a couple of questions, if maybe you would comment upon what your medical thesis was about. What did that contain?

Hallek: My medical thesis is actually something that was totally unrelated to what I am doing today. So, I was having a thesis with—there were an observational study in epileptic children, trying to find out whether they had differences in their biological rhythms, a fear that is now molecularly defined. These days it was more an observational study. So, what I did is simply watching these children that had very often behavioral changes that were also spastic, had epilepsies, to find out whether these epilepsies had a daily rhythm that we could use for better treatments.

And I actually went for this thesis for about a year to Paris. So, I did some studies in Paris at that time, which is part of my medical training. And that was my first step into science because my advisor in Paris was a very nice and well-educated professor. And I should actually add one component here, from a very personal point of view, eventually, this was a professor called Alain Reinberg, Reinberg, as the French say, who was actually suffering, tremendously, as far as he told me, from WWII and the Nazi regime. But he accepted me not only like a teacher but as a friend, and you can imagine being a German younger, not really having lived in this generation, during this terrible world war. It was a particular privilege and a very emotional time for me to be in his laboratory at that time.

And so, I started my medical and scientific training with him, but later went to more molecular and clinical things which are totally unrelated. Basically, I think they were—some events were happening by chance and some physician discovered that I was maybe not so bad and asked me to work with him and it was in hematology later.

Marti: Then you went to the Dana-Farber—

Hallek: Yes.

Marti: —to do your graduate studies, and when you came back, you finished, or began and finished your PhD thesis. What was that about?

Hallek: So, I started after this time in Paris, finished medical training and then started doing some pharma research. Basically, modifying agents to stimulate the β_2-adrenoreceptor. And actually, I at that time started doing research on CLL, because we found that stimulation of CLL cells did alter CLL cells by using forskolin or other agents. Actually, they were profoundly separated. Then I realized at that time that my tools to study the molecular events, that might eventually lead to changes in the β_2-adrenoreceptor in CLL were not fit enough. So, then I said, "Well," to my former boss, Dr. Emmerich in Munich, "I have to go somewhere else to get some training in molecular biology." And this is why I decided to go to Jim Griffin's lab at the Dana-Farber, in 1990 to 1992, and worked with him for two years on, as Jim Griffin is known for, myeloid malignancies. But I didn't think it mattered a lot because I wanted to later apply it to CLL, because at that time my interest was already turning into the B cells in the CLL field.

Marti: What would you attribute your interest in B—your interest in B cells led to CLL, or your interest in CLL led to B cells?

Hallek: I would say the major factor that made me stay in CLL was personal and human arguments. The first of all was that my first clinical boss, Dr. Emmerich back in Munich, who he was the one who asked me to come and work for him when I was uncertain to do pediatrics or internal medicine and all these things, and he was interested in CLL. And then second, the second major event was, one of my first international meetings that I organized back in 1994 or 5, I don't remember exactly, where all these big giants in the CLL fields came—field came—Kanti Rai, Michael Keating, Dr. Binet, and all these people that you know so well. And the atmosphere was so positive and nice and supportive, and they actually created—thought it was an excellent idea that we would create a German CLL study group. That these two events, I would say, made me stay in the field because it is not—at that time it was not driven by a certain desire to cure one disease. I could have done it in others, but it was more human arguments that made me stay in the B cell field and in CLL.

Marti: You felt welcomed.

Hallek: Yeah.

Marti: As I indicated to you earlier, when I was reviewing your short biographical sketch, I learned that you were the founder and director and the chair of CLL, I think you say…

Hallek: The German CLL Study Group?

Marti: Deutsche CLL Student Group.

Hallek: Yes. Yeah, yeah, yeah.

Marti: Please tell me about that in great detail.

Hallek: So, that was, again, in Munich, when I was returning from Boston. And I would say that the training in Boston, Jim Griffin's laboratory was two things: I was more educated in molecular biology and doing experiments in this, and I'm still doing this today. And second, it gave me confidence, because I would never have dared of creating something like a German study group before I went there.

Coming back from Boston, usually you're pumped with self-confidence in a certain way, being at Harvard and all these things, and I basically said to my boss, "Well, there's nobody in Europe except the French, but they're slowing down to do these things. There's a new drug coming up, fludarabine, and we don't know its role in CLL." And since he was interested, he agreed. And basically, I was a young assistant physician, as we call it, and so he took the lead, but asked me very, very soon to actually organize it. And only a year or two later, we assembled all the important German hematologists, including some of the names that you may know, like Wolfgang Hiddemann, Volker Diehl, or Hartmut Döhner, and said we wanted to create this group. And I was actually so young that I expected that anybody of these big figures in Germany would stand up and say, "Well, it's a good idea but I will do it." And yet they didn't.

So, at that time I was, I would say, fairly young. I was not even consultant. I was a simple assistant physician, but I came up with the idea of creating a German CLL study group, becoming one of the most important study groups in the world. I already had this going at that time, I have to admit. And nobody actually came up and shoot me down. So, for some reason, we stayed.

And then, we got a lot of support by the international group, iwCLL, including the people that you know in this country, so, Michael Keating, Kanti Rai. They initially supported strongly that this group would form and gave us initial advice. Also, Emili Montserrat, Guillaume Dighiero were present. We had advisory board meetings in the beginning, and it worked out well. I mean, we liked each other, and despite the fact that I was a lot younger than them, they said, "Well, you should do it." And it is about 12 years ago that we started.

So, it has a lot to do with, I would say, a lot of personal relationships. And I took the courage to just simply say, "Well, we will create the German CLL Study Group." And at this time, it was audacious. I mean, it was something that I shouldn't have said eventually, because how can you dare, of never having done a clinical trial in CLL and called the

first clinical trial the trial of the German CLL Study Group? It's a little bit, uh…

Marti: Audacious.

Hallek: Yes. [Laughs]

Marti: One of the things I noted was that it is described as being not-for-profit.

Hallek: Yes.

Marti: What does that mean in Germany?

Hallek: Well—

Marti: To be a group that's not for profit?

Hallek: So, we don't make any money with the funding or the pharmaceutical industry that we don't use for the clinical trials themselves. We also have, by the way, never written any bylaws. We function as a group of people who respect each other and run the trials. The advantage, I think, in the international comparison of this group is that we always ask ourselves in a peer group of about 20 people who are contributing a lot, "What is the next important question?" And then we design the trial, and then we seek funding. So, we only cooperate with the pharmaceutical company if it goes along with our plans, but we don't run for the money to for—I mean, one of the big disadvantages with the ever increasing bureaucratic burden in pharmaceutical—in clinical research these days, is that you can't finance those things anymore. So, many study groups actually contact the pharmaceutical companies asking whether they could do a trial, whichever it is.

Our strategy is just the inverse. So, we always design our trial first, and then say, "Well, here's a compound that could be interesting. Let's talk to the company." And then we have an open discussion with the budget of all companies involved, which is able to—able or not able to finance the trial. If we are not able to fully finance, we seek support by the German Cancer Aid. So, the strategy is driven by the previous clinical trial and by a medical hypothesis, which drives the next step. And we do this with a self-financed way that is not giving profit to any of us within this peer group of investigators.

Marti: What, if any, relationship is there between the German CLL Study Group and ERIC, the European Research Initiative for CLL?

Hallek: So, the idea was in the, I think the year 2000, or around that time to create a network of European investigators in CLL that Guillaume Dighiero, Emili, and myself had at that time to make the knowledge

that we accumulate accessible to everybody. The next step, or the next reason for creating the ERIC was to have a discussion forum in Europe to avoid that we would do overlapping trials. So many things that need to be solved in CLL that I would like, that I wanted to avoid, that we would do competing trials and competing investigations rather than putting everything on the table, openly discuss it, and then decide who is doing what. And usually it was very easy. And that is exactly what happened.

The ERIC has very little money. Our role model, in the beginning, was to create something similar to the CRC in the United States. For several reasons, we did not get funded because the European funding mechanisms are more complicated. Usually, you don't get a lot of funding for research, more for traveling. But we then decided because we didn't get a lot of funding, let's do things that are—that we have to do anyway. And we created projects on the harmonization of prognostic markers. So, for instance, one paper came out from this group on the harmonization of IGVH mutational assessment, so that we have now a standardized method that everybody uses and difficult cases are reviewed by an expert committee in the ERIC.

A second thing was to say, well, there is a lot of uncertainty how to correctly assess MRD levels. And therefore, there was a project led by Andy Rawstron and Peter Hillmen within the ERIC to simply seek for harmonization, and that was actually later joined by Tom Kipps, Laura Rassenti, and all the people here to have an international standardization of MRD assessment.

And so, we did a couple of things that worked out quite well. The ERIC still is in the same, let's say, mode of action. With little money, we achieve much, or I would say. And it now has been transferred to Emili Montserrat's direction. So, I led this group for 6 years, I would say, between 2000 and 2006. Then I handed off to Danny Catovsky, who was second president, and now it's Emili Montserrat. And it's a truly European operation.

Marti: I have to confess ignorance. I didn't realize that in addition to the CLL study group you played this role in ERIC.

Hallek: Yeah.

Marti: And as much as I sometimes like to think I know Danny Catovsky, I did not realize his role in ERIC, although I'm not surprised. And Montserrat, his involvement in CLL of course is, as you say, before yours.

Hallek: Yes.

Marti: He was actually one of the people who was very adamant that I conduct these interviews on tape, rather than just pen and pencil. In terms of the IGVH and MRD, I think I understand quite well the role they are playing presently. One thing that I would ask about prognostic factors you did not talk about so much in your presentation this morning, and that is the status of, say, ZAP-70—

Hallek: Yes.

Marti: —in Germany or Europe.

Hallek: Mmhmm. So, the markers are frequently used clinically because most laboratories that assess the B cell phenotype in CLL or the typical CLL phenotype always concomitantly assess CD38 and ZAP-70. In clinical practice, it is—so, it's overused, I would even say, because there's no standardized methodology yet. It seems again—that has been an ERIC project, one that I didn't mention because it is not fully finished yet, but it seems that with a specific antibody, I forgot the name, by the way, they seem to get more reliable results. I mean, you know, better than I do, actually, that you have to do all the tricks to assess the cytoplasmic expression correctly.

The problem with ZAP-70 is we have to resolve the reliability of the test, or to improve the reliability of the test to avoid misinterpretations. And until that's not done correctly, we—it won't be in broad clinical use in the future. CD38 is much more reliable, however, it may not be as strong as a prognostic marker. And this is where we are. So, usually we would recommend to actually not use them in clinical practice or general practice, but in clinical trials. My experience, and I think that's the same here, in both continents I would say, is that they are both increasingly used because flow cytometry is done and then you had an another antibody and get some result, whatever it's worth.

Marti: But it does seem that both FISH cytogenetics, molecular genetics, and the IGVH are the two most important prognostic factors that are being used in Europe, or in Germany.

Hallek: Yes, with I think a clear preponderance of cytogenetics, because now everybody is convinced that they have immediate clinical consequences when it comes to treatment while for IGVH it's less clear. So, I don't see any of the two subtypes, mutated or unmutated, that I would treat differently at the present time, given the information that they are unmutated or mutated. That's different for cytogenetics, because as we've discussed this morning, deletion 17p means you have to choose another treatment option, otherwise they will do poorly. So, it is for these immediate consequences on the

management that we are doing those systematically in Europe or in Germany, at least, while IGVH is certainly not as frequently assessed in the clinical routine. It is sometimes done when you want to know whether the patient is having—going to have an aggressive disease, but not as a systematic evaluation as it is for cytogenetics.

Marti: Would you consider using the immunoglobulin gene mutational status and/or cytogenetics to determine the frequency of follow-up visits during a wait-and-watch?

Hallek: No.

Marti: No. You just go by the CBC and the clinical findings?

Hallek: Yes. So, here's one of the most interesting things right now in both research and clinical practice with the earlier discovery, even from MBL's and then CLL, the early phases. There's some patients who benefit from early information. I recently—an example is a typical young person who wants to create a company and asks me whether he will actually be without treatment for a longer period. And this—I cannot answer, so I usually answer, "Well, we will watch and then see, whether the disease is becoming dynamic." But in this situation, it can be very helpful to some of the patients to have more information and to make educated decisions later on. And in those situations I actually put them into the full array of potential tests, including ZAP-70, CD38, and mutational status, because if they are favorable in terms of their prognosis, that will help them, and if they are not, they may make different choices. But that's rare cases. For all the rest, I don't do it. I just watch. The longer I do it, the more I realize that usually you see everything you need to see from the dynamics of the disease.

Marti: As part of your presentation this morning, you talked about when you did the comparison, I believe it was CLL—I can't remember, was it—the comparison of Cytoxan and fludarabine versus CRF, the addition—

Hallek: Yeah, the CLL 8 protocol?

Marti: That was CLL 8. I was very surprised, as I think you were, that the overall survival for Binet A and B was statistically—

Hallek: Superior.

Marti: Superior to C. And when you did the analysis of the Binet C to see what you could possibly find out, you really didn't find anything, minimal residual disease, prognostic factors weren't that different. That was my impression.

Hallek: Yes.

Marti: That you really didn't know what it was. The question I wanted to ask about that, in Binet B, how do you make a decision to treat someone? Does the protocol just allow the acquisition of so many patients with Binet B? Because they would be asymptomatic.

Hallek: Yeah. So, the inclusion in our protocols is they have to have symptomatic disease. So, it's not enough to have Binet B and no symptoms, they have to either have very large lymph nodes or rapidly growing lymph nodes or subjective symptoms, strong symptoms to actually make the treatment indication. And with this, it's still the largest group of patients that we have included in the trial.

Now, this is what we did in the past, and I think we should continue doing so until we know solidly from our trial that this is the truth. It may change, though, because when we now have these survival differences with a first-line treatment choice in Binet stage B, it may change our paradigm in these patients and in CLL in general, because this may be the best situation to start treatment, the Binet B patients, where they have large enough lymph nodes but not cytopenias.

And this is only because we've seen our survival differences, as I told this morning, survival differences for combination treatments. We see it for FC versus F, and when we put out all the high-risk patients, and we see it for all patients combined for FCR versus FC. So, FCR may prolong, or is prolonging, from our data, the survival of the patients when we do it.

And we don't see that benefit in the Binet stage C patients, so it may have several consequences. One is to really challenge our study and see whether the Binet stage C patients were treated correctly, because there was one big difference and that was treatment delays and dose reductions. We had the dose reduced more for the Binet stage C patients with FCR than for FC, so there is a difference.

Marti: And they had more cytopenias?

Hallek: They had probably more cytopenias and therefore the careful physicians delayed treatment a little bit—a little longer. And so, we may just have underdosed the three components or maybe even the rituximab for that reason. So that may—it's currently maybe one of the best explanations although we are not totally sure yet.

And the second lesson to be learned eventually is, well, maybe it's not a good idea to wait on the stage C and start a little earlier. When you have a chance to reduce the tumor, because that is where you create survival differences. So, that's a fascinating paradigm to arise right now. I'm uncertain about it because it is in the process of being

evaluated, and one should never make too strong statements while doing that, but it’s fascinating to see that.