Transcript of Rai Interview Part 7: Research Partnership with Chiorazzi

Gerald Marti: I know very well in our first meeting, we went in great detail about how the origin of the Rai staging system. I recall that you saw four or five patients in one afternoon, and two of them were CLL and they had the same findings, but one was near death and the other was doing well. And you went on to get the medical records and you had a room that was about 10' by 10' and you hung up little abstracts, synopsis of each of the patients and I think some people thought you might be going crazy in that room staring at all those abstracts until you figured it out. But I wanted to jump ahead much further in your career back to Long Island and the relationship with Dr. Nicholas Chiorazzi, if you would talk about that.

Kanti Rai: Yes. Well, I became somewhat well known in CLL circles. And my hospital, Long Island Jewish, is practically next door to North Shore Hospital. Now, the two hospitals have merged and they're called the North Shore LIJ Health System. And as it happens, Nick Chiorazzi, Nicholas Chiorazzi, was a first-class scientist and he is an M. D., he's not a Ph. D., but he's really been out of clinical medicine for about 10, 12 years. He was—I first met Nick when he was at the Rockefeller University, 20, 25 years ago, working with a legendary immunology scientist, Henry Kunkel. And Nick and I worked on a hairy cell leukemia project. He was studying lymphocytes, B-lymphocytes, and was intrigued by whether or not there are abnormalities in T-lymphocytes of patients with hairy cell leukemia.

So, from there, Nick came to North Shore and became the Chief of the Division of Rheumatology and Immunology. And I was happy to hear that he was there. And in the course of the next 10, 12 years we would collaborate. I would have a patient about whom I would ask him a question from immunology point of view. And slowly Nick became a full-time bench researcher with NIH grants and had become a very, very well-known person in B-lymphocyte physiology and ontogeny. So, we would correspond or talk to each other from time to time. And then he started to work on the project of determining the importance of somatic hypermutation in the CLL lymphocytes, IgVH, immunoglobulin variable region heavy-chain gene.

And the field had just been opened a couple of two, three years earlier by a landmark paper by Harry Schroeder and Dighiero[1] showing that somatic hypermutation is not unusual in CLL, and Nick was intrigued by that. And I started to send my patient samples to Nick. And lo and

[1] Schroeder HW Jr, Dighiero G. The pathogenesis of chronic lymphocytic leukemia: analysis of the antibody repertoire. *Immunol Today*. 1994 Jun;15(6):288-94.

behold, within a matter of two, three years, this work was put together and it really changed the entire face of CLL because it showed, in a reasonably large sample size, that approximately half the number of patients with CLL had mutation in their IgVH gene and the other half did not. And at that time, it was considered that CLL lymphocytes are immunologically naïve, that they have not passed through germinal center and therefore they do not function effectively as B-cells.

And then the observation that the 50% of CLL population which have mutated IgVH gene are the ones which must have passed through germinal center or else how do you explain the mutation. And those were the patients who had clearly a better survival time, longer survival time,[2] and many of those never required any treatment. Well, when I saw that work, then he and I started to ask a number of other questions related to this adding to or making the clinical staging and prognosis so much more sophisticated because the clinical staging that we had proposed was totally clinical-based. And now we are bringing some science into it rather than just physical examination and we became partners.

And this is something like marriages, successful marriages made in heaven, because most of us as you know who are clinicians have a large number of patients and we have questions about the disease, but we have no counterpart with whom to collaborate at this basic science level, and similarly a number of our colleagues have excellent lab, excellent ideas but they have no resource for getting patient samples and clinical support. So, each institution suffers from these disparities and we were fortunate that within one institution we have the clinical part and basic science part.[3] And we recognized that, and we said, let us proceed.

And that partnership has borne a lot of good fruit in terms of contribution to the field of CLL at basic science level and integrating that at the clinical level and we are still active collaborators and partners.

Marti: Do you think that had anything to do with the founding of the CRC, that idea that you just mentioned about getting the clinical and the basic science together?

Rai: Yes. That certainly had the roots there but not because of the Chiorazzi and Rai partnership. Chiorazzi had no role at all in the initial formation of CRC but the concept was exactly what you just said. And

---

[2] Dr. Rai's clarification: longer survival time than the survival time of patients who had unmutated IgVH

[3] Dr. Rai's note: This might seem simple or natural but in truth this is a rarity.

that was—there I give full credit to Bruce Cheson, who had pulled a group of us together when he was at the National Cancer Institute of CLL working group. And we met a few times. Bruce was able to get the support from the director of NCI to sponsor this working group. We formulated guidelines for diagnosis, criteria for response, criteria and indication for treatment, and all that.

And during those meetings, the idea struck to Bruce that if we, the non-NCI people, would try to put together a group and propose to NCI development of a consortium where basic science and clinical sciences would collaborate and move the field of CLL forward. And that exactly happened that way and we elected by acclamation Tom Kipps as our leader, and Michael Keating and a number of other people who are participants. And Lee Nadler was in the original members and Michael Grever who was then at Hopkins and then moved on to Columbus, and a number of other people, Carlo Croce, and at the clinical level it was really Mayo Clinic[4] joined later on.

But Dana-Farber because Lee was there and Lee brought in John Gribben and M. D. Anderson, San Diego, and eventually Ohio State, and I at Long Island Jewish. We formed a very, very good relationship, mutual trust and a very deep commitment to participate in correlated sciences of bench and clinics.

Marti: Perhaps the biorepository is the greatest strength of that group?

Rai: Yeah, the tissue bank, absolutely. Every one of us who sees CLL patients have informed consent signed by our patients to participate in tissue bank research, and we send our samples, if it is bone marrow, if it is blood, to the headquarters in San Diego. And that has become an enormous repository of resources because none of the work that we see today conducted by John Reed at the Burnham Institute, Carlo Croce and now in Columbus and number of other, and M. D. Anderson and the San Diego group itself, and now Mayo Clinic would have been possible if it had not been for large numbers of samples to test anybody's hypothesis.

[4] Dr. Rai's note: Neil Kay from Mayo Clinic