CHEMICAL HERITAGE FOUNDATION

# CARLO CROCE

Life Sciences Foundation

Transcript of a Research Interview
Conducted by

Brian Dick

on

12 August 2013

(With Subsequent Corrections and Additions)

CHEMICAL HERITAGE FOUNDATION
Center for Oral History
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## INTERVIEWEE

**Carlo Croce** was born in Milan, Italy and studied medicine at the Sapienza University of Rome. While he initially came to the United States to do medicine at Scripps Clinic and Research Foundation, he ultimately worked at the Wistar Institute with his mentor Hilary Koprowski. There he worked on cell fusion, helping to make the first antiviral and antitumor cell monoclonal antibodies. While at Wistar, Croce, along with Koprowski, Michael Wall, and Ted Allen, formed Centocor, which commercialized monoclonal antibody technology. After leaving Centocor, Croce held positions at Temple University and Thomas Jefferson University, where his research shifted to cloning cancer genes after years of working with cell fusion and tumor viruses. While at Jefferson, Croce and his research teams' focus shifted to microRNAs and their role in the progression of cancer. Croce has also maintained a life-long interest in art and has been an avid collector of Italian Renaissance and Baroque paintings.

## INTERVIEWER

Brian Dick received his PhD in sociology from the University of California, Davis. Before coming to the Institute he was a research associate at the Life Sciences Foundation. His research interests include the history of agricultural biotechnology, the emergence of the biotech industry, and the Human Genome Project.

## ABOUT THIS TRANSCRIPT

Staff of the Life Sciences Foundation conducted this interview, which became a part of our collections upon the merger of the Chemical Heritage Foundation and the Life Sciences Foundation into the Science History Institute in 2018. The Center for Oral History at the Science History Institute edited and formatted this transcript to match our style guide, but as noted, Science History Institute staff members did not conduct the interview.

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bracketed ellipses to indicate the deletion of recorded material. The transcript also includes time stamps at one-minute intervals. We omit without noting most instances of verbal crutches and all instances of nonlexical utterances. We also make small grammatical corrections where necessary to communicate interview participants' meaning. Finally, staff of the Center create the abstract, chronology, and table of contents. With the availability of online full-text searching of our transcripts, the Center for Oral History opted to discontinue the practice of preparing a back-of-the-book index for each oral history transcript in 2020.

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**INTERVIEWEE**: **Carlo Croce**

**INTERVIEWER**: **Brian Dick**

**DATE**: **12 August 2013**

**DICK**: Okay. So this is August 12, 2013. We're in the office here with Carlo Croce. So I have a lot of your background here, and we'll, kind of, go a little bit quickly, just to make sure that we get to the Centocor and Wistar years. You were born in Milan, studied medicine at the University of Rome, and then you were looking towards coming to the United States to do medicine initially with Karl Habel at Scripps, until he—

**CROCE**: Yeah, and he got the [inaudible] redirected to Wistar Institute.

**DICK**: How did that—did they direct you to the Wistar, or—

**CROCE**: Yeah, sort of. It was funny, because I wanted to go with [inaudible] at Salk, and I told my boss, a fellow called Giuseppe [inaudible], that I wanted to go [inaudible]. But it was a very good friend of the head of the Scripps Clinic, it was called at that time, which is now the Scripps Institute. And Frank Dixon was a very good friend of my boss, suggest that I would go to Scripps to work with Karl Habel, because he was doing the same kind of work that Baker was doing. I was interested to work with DNA tumor viruses. So just when I was ready to leave, Habel was bitten by a monkey, developed a viral encephalitis, and went into coma.

So Dixon called my boss, say, "Carlo cannot come here. But in Wistar Institute there is a fellow who is doing the same thing, and was also a friend of Karl Habel, Hilary Koprowski. And I'm sure that if you would contact Hilary Koprowski, Hilary would take him to his lab." And that's what happened.

**DICK**: Now did Koprowski interview you at all, or is it—

**CROCE**: No, no. We chatted for a few minutes at the phone, and then I left, and I arrive here in Philadelphia on June the seventh, 1970. So a long time ago.

**DICK**: Did you discuss art at all with him? Or subsequently? Because I know that he had a lot of interest in music, for example.

**CROCE**: No, no. I just ended up in his lab. I started working in his lab. And then for one reason or another, I started to—although I was working on—as before, small tumor virus, I also start to work on cell fusion. So I was really the expert on cell fusion. I became that, on cell fusion, at Wistar Institute. And I start to make a lot of hybrids and a lot of somatic cell genetics. So when Koprowski was interested in doing the, sort of, [inaudible] kind of stuff, we had all the technology, all the cells, and so on, so we made the first antiviral and antitumor cell monoclonal antibodies.

**DICK**: Now this was early—like, people like Gerhard and Kleinman were, sort of, working with monoclonal antibodies—

**CROCE**: Yeah, but they were doing these micro wells. So essentially, they were growing clone of B cell. They were not driven by anything. They were just growing in this micro well. So it was not that practical.

**DICK**: They wouldn't last for more than a couple of months, and—

**CROCE**: Never last for a month. But anyway, there was Norman and his former postdoc I think was Walter, and—Walter Gerhard. And so they were working on this growing clones of B cell in micro well, while [inaudible] used the mouse myeloma as a driver. Okay? And we had this mouse myeloma, because I was doing a lot of hybrids with mouse myeloma. So it was very fast. They had an antibody response in mice against influenza virus. And I fuse this cell with mouse myeloma cell. I got hybrid. And they tested them for antiviral monoclonal antibodies, and we got them. And after—

**DICK**: And then that was 1977 that that was published?

**CROCE**: I think it was ’76.

**DICK**: Seventy-six?

**CROCE**: The seventies. I forgot when we apply for patent. Might be ’76, ’77.

**DICK**: Okay. Yeah. I have in my notes ’78.

**CROCE**: The paper?

**DICK**: The patent application.

**CROCE**: Oh, yes, ’78, so might have been when we published. In the tumor cells, it was I'm sure **<T: 05 min>** ’78. Maybe the virus was a little bit earlier.

**DICK**: Yeah. Yeah. How did—because this is, you know, sort of before patenting really begins to take off.

**CROCE**: Oh, yeah. Koprowski was very shrewd. He liked to patent everything he found interesting. So the first patent was Koprowski, Gerhard, and me, on influenza. Then there was rabies. It was Tad Wiktor, Koprowski, and me. I don't know if anybody else. And the antitumor was me and Koprowski.

**DICK**: And how did that go about in terms of, you know, going—I have here that the Wistar—there was the Wistar patent office, that they were working. So Koprowski contacted them and—

**CROCE**: No, no. We had everything—I don't know if they had—I think that they give to some lawyer firm. I think Ballard was the firm of the lawyer. And so we got our patent done. And so we had the patent on monoclonal antibody against virus, influenza. Then we had the rabies. Then we have SV40 transform cell, the monoclonal [inaudible] antigen, the tumor antigen specific for the tumor virus, because—and this—and then Centocor licensed this early patent. We had—I think that our two patents were the earliest ones on monoclonal antibodies, yeah?

**DICK**: Yeah, I think so.

**CROCE**: Yeah. And so they—and then in ’79, we started Centocor.

**DICK**: Yeah, tell me about how that—

**CROCE**: [Inaudible] because Koprowski met [inaudible] he knew already Michael Wall, who like to start a company. And Schoemaker came later, because—I don't know, was the—in 1980 that Schoemaker came along. Could have been ’81. Because the [inaudible] said 1980, but

maybe it was ’81 or ’82. Anyway, Schoemaker came a little bit later, because we fired the former president, a guy called Ted Allen.

**DICK**: Do you know why—you know, again—

**CROCE**: I prefer—

**DICK**: No, not a problem.

**CROCE**: —[inaudible]. We did not respect his sense of whatever. Yeah? So he was fired. He was fired probably within a year. So ’79, we had four share, one Koprowski, one Wall, one me, and one Ted Allen. And then we started this company, and then I believe in ’81 we went public, very quickly. And mainly, the Rockefeller brothers were the investors.

**DICK**: The big—the big investors

**CROCE**: Tony Evnin [inaudible] of the board.

**DICK**: Now what was—you know, it's—Centocor is being started up in ’79. Nineteen eighty, you're bringing people in. I know—how did Vincent Zurawski get involved?

**CROCE**: Well, it became really the technical problem [inaudible] of Centocor. So [inaudible] while we were with Wistar, Zurawski worked for the firm, and he became later on head of research of Centocor. And so he was the technical person at the company. He did not come from the—to the company from our group.

**DICK**: I see. From Massachusetts General Hospital.

**CROCE**: So he was recruited by—in fact, I don't remember from where he was recruited to the company to work in house and start—having lab and so on at the company.

**DICK**: Okay. So you and Koprowski were in—you were on the board of directors.

**CROCE**: Yeah. Until ’85, I believe.

**DICK**: How did that sit with the Wistar board?

**CROCE**: Not well. [Laughter] As you probably know, we had a huge fight with the board, because the president—in fact, the president of the board, who was this guy Eckman, who was—worked for [inaudible]. I remember him screaming, “Scientists do science. Business—businessmen make money.” [Laughter] [Inaudible]. He was very upset that—but the culture was very different at that time—**<T: min>** that some scientists decided to start a company. So we were considered like bad guys, because—now everything considers those guys very good guys. At that time, we were considered bad guys. And so we had—there were threat of lawsuit between us, me and Koprowski and the board. Finally, we came to an agreement. They wanted more shares of ours. And so they had already some shares of the company, but they wanted more share from Koprowski, me, and Gerhard.

**DICK**: I see. So give them more of the money, and then they're okay.

**CROCE**: We became pure again. So I remember I gave them fourteen, fifteen hundred shares from the bank. I had much more than that. That was—Koprowski gave I forgot how many [inaudible]. It was a long time ago.

**DICK**: Now I know, too, that there was, sort of, in 1980, Nicholas Wade writes an article—

**CROCE**: Oh, you know how Nicholas Wade is. I mean, the—Köhler and Milstein developed monoclonal antibody technology. We never argue with that. We never said that we developed monoclonal antibody technology. Okay? We have used that technology to make monoclonal antiviral, anticancer cell.

The problem that Köhler and Milstein did not patent their stuff, but essentially, you know, what they made were monoclonal antibody against sheep red blood cell. So the procedure was okay, but was not particularly interesting from the practical point of view. What was interesting is the technology to make antibodies against specific antigen.

So we never claimed that we developed the technology. We just apply it to those specific areas. So Wade's assertion is that we, sort of, stole, but—the technology from Köhler and Milstein, which was absolutely not true. In fact, if you read our paper, Köhler and Milstein are cited, yeah?

And so we did what we thought that we should be doing, because that was an interesting technology to develop antitumor cell and antiviral monoclonal antibody, yeah? And that's what we patented. So we did not find any—in fact, we threatened to sue Wade, and he came up with sort of—or *Science* came up with some letter saying that they understand that we didn't do anything bad.

**DICK**: Yeah. I heard that you and Koprowski wrote a letter in response to *Science*, and at first, they refused to publish it.

**CROCE**: Yeah. And finally, we brought a lawyer in, and they responded.

**DICK**: And then the editors basically said, oh, you know, after being shared, okay—

**CROCE**: Yeah. We get the lawyer, and then they drafted a letter, that we did not do anything bad, and it was the past.

**DICK**: When Centocor was just starting off, what was the—I know that the focus was going to be on monoclonal antibodies.

**CROCE**: The diagnostic is the big—

**DICK**: Diagnostic?

**CROCE**: We thought that where they had the great potential as drugs, and, you know, in the beginning, biotech needs quite a bit of money. So we are going around, song and dance, saying how great these monoclonal antibodies were. In the beginning, there was a lot of enthusiasm. Then there was the reverse. There was absolutely no—no enthusiasm at all. And I still—the head of Merck Labs, a guy called Schoolnik, he was president of lab, and after we gave a spiel about the greatness of monoclonal antibodies, he got mad and say, "Carlo, monoclonal antibodies will never be drugs." And he was clearly wrong. Now there are some monoclonals that makes billions and billions of dollars.

**DICK**: So you were going on the road show, then, with—say before the IPO?

**CROCE**: Oh, we were going on the road show. It was Koprowski and I, and people from Centocor, to explain why it could be great. At the beginning, some of the—for example, the monoclonal antibody for the antigen expression of ovarian cancer, well, a product from Centocor is still used.

**DICK**: Oh, the hepatitis B?

**CROCE**: No, the ovarian cancer. The monoclonal is still used today for **<T: 15 min>** this, after, what, 1980. So it's thirty years. And so—yeah. So I think that that technology was not only useful for both diagnostics, and Centocor went through up and down. At some point, they had an imbecile as president who put all the eggs of Centocor in something where—that where it should not have been done.

**DICK**: Is that Centoxin that—or—

**CROCE**: Yeah. Yeah. The stock dropped from eighty [dollars] to five or four [dollars], I don't know. [Laughter] And finally, went up again. It was bad. And I remember at that time, when we [inaudible] five billion dollars. And frankly speaking, so they sold very well. And I was sitting at the lunch with the president of J&J, and I told him, "Oh, you pay a lot of money for Centocor." He said, "That is the best buy we ever did." And in fact, you consider Remicade, Remicade, it was developed by this friend of ours who work at NYU, that—he was interested in tumor necrosis factor. And Remicade sell, what, three, four, five billion dollars a year.

**DICK**: I know. I was just following ReoPro.

**CROCE**: Yeah. Yeah. And so that was a beginning. Thank God, it was a very successful—but what I like about Centocor, because it—in negation of the way we were, we were not there to make a fast buck. We were interested in developing really a [inaudible], okay, at that time. And now to be true, yeah? We develop—and now Centocor is the right arm of J&J for pharmaceuticals. So the leadership of Centocor became the—you know, Schoemaker died, unfortunately. Because he had the brain tumor. But the rest of the stuff stay with Centocor, stayed with J&J.

**DICK**: With J&J.

**CROCE**: Yeah.

**DICK**: Interesting.

**CROCE**: Develop a very good company.

**DICK**: How were you looking at the field as, sort of, other biotech companies were starting to pop up? Were you aware of, sort of, the other—

**CROCE**: Yeah. We were in competition with a company in San Diego, monoclonal antibody—Hybritech.

**DICK**: Hybritech?

**CROCE**: That was bought by Lilly, whatever, three hundred twenty-six million [dollars], and rapidly discarded. Then some other company, like Idec, et cetera, et cetera. But a few, then two other companies used other company, and so on. But the first two I believe were Hybritech and us. Ivor Royston was involved in Hybritech.

**DICK**: Yeah. Now you were saying that you stayed on the board till ’85, when you—and were you—

**CROCE**: So the Wistar board, the Wistar board was unhappy that Koprowski and me were on the board. So we resigned.

**DICK**: I see.

**CROCE**: We both resigned.

**DICK**: And what was it like working with the board, especially in the early years, the—

**CROCE**: Which board? The Wistar board or—

**DICK**: I'm sorry, the Centocor—

**CROCE**: It was fun. It was fun, because we'd talk about science, and the application of science. We had also on the board a Frenchman who was—I think his photograph is here, who was from Paribas, I remember.

**DICK**: Michael Yagi?

**CROCE**: Yeah. He died. He was [inaudible] talking about strategy and collaboration, and on the board, we had one of the masters of early biotech. That was the guy from Rockefeller Brothers.

**DICK**: Anthony Evnin?

**CROCE**: Evnin. Yeah, Tony Evnin. **<T: 20 min>**

**DICK**: Yeah, how did Tony Evnin get involved with Centocor?

**CROCE**: Oh, he was one of the investors. He knew very well the early investor in Centocor, the guy Michael Wall. And so he financed the early Centocor. And he stayed with Centocor until it was sold to J&J. He was also a good friend of Schoemaker.

**DICK**: Yeah, tell me about—you know, I've read Schoemaker's oral history.

**CROCE**: Well, he was a very—he was [inaudible] graduated from MIT, I believe in chemistry, and he was interested in developing a company. He was a guy who understands science and biotechnology, and he was a very good leader. And when the guy who was—what was his name? I forgot his name now. The president who was fired.

**DICK**: Oh, Ted?

**CROCE**: The one later, was fired, Gerber. Gerber I think was his name. He became the chief technical officer. And that was very good for the company, because the company was able to raise again. And I think he was involved in the early negotiation with NYU to develop Remicade.

**DICK**: Okay, that he—

**CROCE**: Secure Remicade for the company. That was a big boost, because J&J saw the dollar sign, and it was in fact a great choice.

**DICK**: One of the reasons why they paid so much for the company. Okay. And I just want to, you know, cover a few more things while I keep in the time. But at this time, you're doing a lot of work mapping cancer genes, NYC BCL2.

**CROCE**: Yeah, cloning cancer genes. I became a cancer geneticist. So essentially, the evolution, when I start working on tumor viruses, I did a lot of work in cell fusion, somatic cell genetics, then human mapping. Then I did a lot of cloning. I did some [inaudible] cloning, in fact. And then I started working in cancer genetics. And we were in fact involved in the earliest—earliest specific gene alteration in cancer.

**DICK**: With the cloning, what years were you doing the cloning work? Was this the early eighties that—

**CROCE**: That was the early eighties.

**DICK**: How was that? You know, I know this—you don't have PCR or some of the other tools.

**CROCE**: No. It was much tougher. So you had to clone the—the hard way. So essentially, first, we were involved in the resolution of Burkitt lymphoma. We saw that the Myc gene was involved in fusion, in fusion with immunoglobulin [inaudible]. Okay? That regulate the expression of Myc. Then I reasoned that, so we showed that the juxtaposition of Myc to enhance the immunoglobulin gene dysregulates the Myc gene and caused cancer.

Immediately after that, I say, oh, but in this case, we had a known oncogene that's fused—that fuses immunoglobulin gene and gets dysregulated. Thereafter, we can clone a known oncogene by taking advantage of specific chromosomal alteration. And so we cloned BCR-1, that turned out to be [inaudible], and then we clone BCR-2, that turned out to be very important gene, because they represent a new class of oncogene. And that, we clone it in 1984.

And the reason that we were pretty successful, we had phenomenal postdoc, was a great cloner, [inaudible]. He is the senior author on those papers. And he cloned BCR-1, and he cloned BCR-2, and then he continued to work on BCR-2. He became—he left Wistar, became a professor of genetics at Osaka University, and still today is working on BCR-2 family oncogene. [Inaudible] clone other genes and went on to other things.

**DICK**: Wow. Now you were at a number of positions here, and I think, you know, in addition to being—I think you were by 1980 associate director, and then institute professor at Wistar—

**CROCE**: In 1980 I became—so I was the number two [inaudible]. So I was **<T: 25 min>** Koprowski's golden boy, as they call. But I was—I had my research program. He had his research program.

**DICK**: Yeah. How was it, you know, working with—I know that Koprowski could have a strong personality.

**CROCE**: Yeah, but, you know, when he understood that he couldn't go that far with you, and everything was clear, the collaboration was very harmonious. And in fact, I liked him a lot, and he liked me a lot, so . . .

**DICK**: How were—

**CROCE**: But I could tell Koprowski, "No." Yeah? That was an advantage. And he took it well. Yeah. So I did my stuff. I did—the problem—Koprowski, although he loved me very much, he did not want to give up his job. And the board wanted to kick him out, because he was already a little bit senior. And so he sued the board for age discrimination. So they couldn't fire him for a while, yeah? So—but when I saw—so he was like my scientific father. So I thought, the board want to kick him out. I will never be able to take the side of the board, because it would be like going against my own father, okay? So I said, the best thing to do is to get out from—yeah. And so at the time I went to Temple, to—head of the institute there.

**DICK**: I see. And what about just—I know there are stories with—at various faculty parties and what not, that Koprowski would like [inaudible]—

**CROCE**: Oh, Wistar was wonderful. It was the most politically incorrect place in the United States. And to work at Wistar was fun, yeah? Because there was no bureaucracy.

**DICK**: No what?

**CROCE**: Bureaucracy. Very little paperwork. And when you work in such place, you understand that bureaucracy can be reduced to a minimum, and works—the place works much better. Yeah? So order could be fulfilled fast. Take the telephone call, order was placed. Okay? So anything you need to—and we had very good central offices.

So to work at Wistar was easy. It was a pleasure. And then when I had learned that in fact the more bureaucracy you create, the worse things go. So it was—Koprowski was an excellent leader and institute administrator. Excellent. And in addition, he recruited two class of people. One class is the very good people, yeah? And one class was the flunky work that he wanted to be slaves. So—but anyway, that was the way it was.

**DICK**: And—but did it work out? It was a good division of labor, and—

**CROCE**: Yeah. It was very good. His flunky did what he wanted. But the real independent investigator did their own thing, and they were never bothered. And the company, when we needed help, some equipment and so on, Koprowski was very, very helpful. So everything we needed, we got. So Wistar was excellent. And at that time, I must say, Wistar was one of the best places in the United States, if you look at discovery. A lot of important discoveries were done there.

**DICK**: Yeah. It seems like Koprowski, when he came in 1957, really sort of turned it around and—

**CROCE**: Yeah. Plus the museum. And he changed it. He made it essentially a virology institute. Then with cancer [inaudible], but virology was probably the major emphasis. After I developed the Myc, etcetera, cancer would become the major, major emphasis. But virus was—were always emphasis. They develop a lot of vaccine, and Wistar still benefit, because they still get a lot of money from some of the vaccines.

**DICK**: Yeah. I wanted to just make sure—just a couple of the coworkers there, like Barbara Knowles. Did you know her?

**CROCE**: Barbara Knowles, the development biology. She went to Singapore. She was—I found her in Koprowski's lab when I got there.

**DICK**: And what was she working on? I know that—

**CROCE**: On somatic cell hybrids. Yeah.

**DICK**: And was she helpful in terms of—

**CROCE**: She was a very pleasant person, and she was working in the Koprowski group. And she also, sort of, spin off and became her own scientist. And then we recruited Davor Solter, who was **<T: 30 min>** one of the best [inaudible] biology in Europe and in United States. And Barbara Knowles form alliance with him, with Davor Solter, and developed a program in developmental biology.

**DICK**: And can you tell me, too, just a little—I know we mentioned Walter Gerhard, but just a little bit as background on him?

**CROCE**: On him?

**DICK**: Yeah.

**CROCE**: Him, he was a Yugoslav, and he did some pretty good development biology in Yugoslavia. And Koprowski heard of him and met him at some meeting, and he recruited him. So he recruited him for development biology, but one of the best in embryology, he was a great embryologist. He hired Trinchieri, who was—formed a big group on cytokines, discovering interleukin 12 and several other interleukins, and now he's at NCI, after he became director of an institute in France.

So then he recruited Peter, who [inaudible] for H2 restriction. And he was really—he went—was away from Wistar when he got the Nobel Prize, and he got the Nobel Prize for some work that he did in Australia with the Swiss. And then we got a lot of other people to—who had some pretty good [inaudible].

**DICK**: Great. Now when you went to Temple University. There's the—sort of, the tension with the board at Wistar.

**CROCE**: Oh, no, not with me. Oh, tension, well, with Koprowski.

**DICK**: With Koprowski, yeah, which—

**CROCE**: Not with me. Not with me. And so then I got intense relationship with Temple's board, and finally I had enough, and I say goodbye, and I went to Thomas Jefferson University. And when I was at Thomas Jefferson, they fired Koprowski, so I said, "Come over." And so he started working at Jefferson. He brought his group to Jefferson.

**DICK**: Okay. Now did they—the way I've read it, they, sort of, gave him just a title that didn't really mean anything, but he sort of—

**CROCE**: Yeah. No, it was the title—a big title. He was [inaudible]. Yeah, but he could bring all his group. He got some good space. And he stayed at Jefferson for a number of years. In fact, I think he was fired about two years ago from Jefferson, when he was '90 to'94 or '93.

**DICK**: He wasn't ready to quit at any time.

**CROCE**: No, I guess not. He did not want to quit.

**DICK**: And it's at this time, or around this time, that you're beginning to look at how oncogenes are activated by translocation, or both activated and suppressed?

**CROCE**: And we look at suppressor, and maybe at activated oncogene. And I think that that, it turn out to be a great area of research, because essentially, that is the base of targeted therapy. So [inaudible] the expression of an oncogene, and then you use a drug to inhibit the action of the oncogene, if the oncogene is [inaudible]. So that—so those—the early genetics of cancer, but in fact, [inaudible] targeted therapy.

**DICK**: So eventually from diagnostics it went—

**CROCE**: Yeah.

**DICK**: —to therapeutic applications.

**CROCE**: So the idea that this alteration, this genetic alteration in cancer, dysregulates an oncogene, yeah, specifically. So the oncogene, it dysregulate the oncogene in the cancer cell. It allows the development of targeted therapy. One of the gene involved in translocation was ABL. ABL oncogene. So you know that Novartis developed an anti-ABL small molecule that gets a nominal result in the treatment of [inaudible]. But the principle, the basic scientific principle, were already established through the discovery of the activation of an oncogene due to those specific **<T: 35 min>** [inaudible].

**DICK**: And this was first—really the first time that that was understood in terms of—

**CROCE**: Nineteen eighty. Two, 1982. It's [inaudible] book. And the second was BCR-2, and the third was the BCR-ABL, that was targeted by [inaudible]. That was '85. So in the progression of '82, they make translocation. Eighty-four, they clone BCR-2 that is involved in translocation and activates BCR-2. In '85 was the BCR-ABL fusion. And then while this developed, the anti-ABL—now later, after several years, Abbott developed anti-BCR-2 small molecule.

**DICK**: And I know that into I think the late nineties, you're looking for the genes involved in CLL.

**CROCE**: Yeah.

**DICK**: And that it was, kind of, a very difficult—

**CROCE**: Oh, yeah. Yeah. In fact, my postdoc left to get an MBA from Wharton. But we were very—so I was lucky in some way. I was unlucky in another way. Because in 1993, they discovered the first microRNA, but they discovered it in *C. elegans* [*Caenorhabditis elegans*], and after that, there was no interest whatsoever. You don't see any paper on microRNA. After—

**DICK**: Just, sort of, a curiosity kind of thing?

**CROCE**: Yeah. It was—there was no interest. Ninety-three, you look after '93, there were no papers. But then, '98, siRNA were discovered, and since they are small, like microRNA, there was a new interest in microRNA, [inaudible] '98, yeah? In '99—oh, no, 2000, it was found that *Drosophila* [*melanogaster*] has microRNA genes. It was found [inaudible] microRNA was discovered in '91, and in 2001 was found the [inaudible] has microRNA gene.

So we look at whether this region where we found the gene had to be, but we couldn't find any gene. We found in fact there were two microRNA. That was the—so essentially, that indicates that alteration in microRNA is involved in disease, was the first discovery of the involvement of non-coding RNA in disease. And we found that in fact in cancer, there is—there are alteration in this microRNA gene. That was a very fruitful investigation, because we—so I come—I had always a huge lab. I convert most of my lab to study microRNA gene.

**DICK**: And this was, like—you were collaborating with George Calin?

**CROCE**: George Calin was my postdoc.

**DICK**: Okay. And—

**CROCE**: Who was in fact the first author of the first paper of microRNA in disease.

**DICK**: I see. And, you know, I've read, too, that it wasn't a technological limitation in terms of discovering the role that these micro [RNAs] play—the genes coding for the micro [RNAs], but, sort of, a intellectual barrier. You know, why weren't people searching for this, I guess, and—

**CROCE**: Well, it's a natural barrier, okay? This was a new way to look at things. I give you an example of this. So people believe that all the genes involving cancer were oncogene and [inaudible] gene [inaudible] gene, okay? Nobody was prepared to accept the fact that genes involving cancer included for non-coding RNA. In fact, when I submitted the paper to *Science*, the first paper, it was [inaudible] was rejected within twenty-four hours.

**DICK**: Wow.

**CROCE**: See, because it's—what is this? [Laughter] But they did not realize that in fact it was something revolutionary. It of course was not described before. So I sent it to *PNAS*. But I just tell you how biases are so negative in science. In ’89 I publish a paper in *PNAS*, ’89, **<T: 40 min>** so four years before microRNA were discovered in *C. elegans*, yeah?

And I clone a breakpoint and—between chromosome 8 and chromosome 17. And I found that this alteration fused two genes. One was Myc, and the other, I call it BCL-3, okay? And this include a [inaudible] 1.7 kilobit transcript that is expressed at very high [inaudible] lineage. We clone it from a leukemia.

And we publish in *PNAS*, BCL-3 code, the 1.7 kilobit messenger RNA, and overexpressed, *blah blah blah blah*. Then we sequence it. [Inaudible]. And we stop working on it. It was a [inaudible] of miR-142, which is in fact the microRNA that is most highly expressed in [inaudible] cell.

**DICK**: And is that why there wasn't the O.R.—the open reading frame?

**CROCE**: Yeah, because this gene had no coding. But they code it for small RNA. I miss a bigger opportunity there. I had it in my hand. I have it first. But yeah, then when I look back, I say, "I have been a fool. My postdoc was a fool." Probably if I had a guy like Sugimoto working on it, probably we will have worked it out. But it did not happen. We got it—once in a while we get it right, but once in a while we make some big miss.

**DICK**: But in the long run, though—

**CROCE**: In the long run, it's fine. In the long run, it's fine. That was a big miss.

**DICK**: And—now, you know, just the last few minutes here, I see that you've been involved in a few other companies more recently. Ciphid—

**CROCE**: I was in [inaudible] involved in GenPro.

**DICK**: GenPro?

**CROCE**: Yeah, those turned out to be okay. I was on the scientific advisory board. And that had been—is doing very well now. It was bought by the Japanese Chugai, and then Chugai, when it was bought by Roche, had to divest from it. And now has a very high quotation in the stock market. And then, more recently, I developed this Chlorgen, microRNA. We will see if it will be successful or not. Time will tell. I believe in microRNA for diagnostic and therapy, so I hope that that will work as well as Centocor.

**DICK**: [Yes]. What are your thoughts, just, sort of, reflecting on how both I guess the life sciences and commercial biotechnology have changed over the years? Is there any sort of things that you note or pick up on in terms of what's—

**CROCE**: No, in most cases, it's still bullshit, in the sense that a lot of companies are based on [inaudible], but there are companies that are serious, and are based on some new technology, and some new methodology. And [inaudible] the medicine will depend [inaudible]. Now since pharmaceutical companies are ultra-bureaucratic, can't get anything done, the only way they can operate is—to develop a pipeline, is to buy small companies. So small companies are there to last, and they will be bought by big companies. Some will make on its own, but mainly they will be bought. And they will provide a pipeline that big pharmacy are incapable of generating.

**DICK**: It just seems like a lot of the internal R&D has been outsourced.

**CROCE**: They don't know how to do it. I mean, Pfizer was spending, what, seven, eight billion dollars a year in developing drugs. Probably I develop more drugs than them in my own lab. Yeah? So it's [inaudible]. So big pharma is—they are banks. They have a lot of cash. And they can buy what they need. So when they see a product that can fill their pipeline, they buy it.

**DICK**: And is that in large part due to the bureaucratic structures that—

**CROCE**: Yeah, it is. So they have lost any imagination. And they are sort of scientists which are not first-class scientists, yeah, who can **<T: 45 min>** generate new knowledge. That's the problem with the big pharma, with the exception of few, like Genentech. Genentech is still good. But the big ones are not that good. Nevertheless, they can develop the drug which they buy. And they will continue to do that for a while.

**DICK**: Division of labor, where the small startups are doing the innovative research, and then the—

**CROCE**: And then they are bought, and they will die.

**DICK**: Right. [Laughter] And just the, you know, last minute here with you, you want to just mention your interest in art?

**CROCE**: Yeah.

**DICK**: Because I see that, you know, it goes back to when you were a young child.

**CROCE**: I have a huge collection. I love Old Master paintings. And since I have been involved in this thing for over—I bought my first painting when I was twelve years old. And then, you know, I study artistry a lot. I look at thousands of pictures. And so I can more or less find who the others are, or have an idea who the others are. And so I buy when I can buy, and I have a huge collection.

**DICK**: What led you to medicine instead of say, you know, art history?

**CROCE**: Now medicine—I love always science. When I was a kid, I wanted to become famous, to become a neurophysiologist. But—so I always loved science. I also love art. I have no talent. So I can't paint, or I can't draw. But at least I have an appreciation for paintings [inaudible] the Great Masters. So when I can, I buy. I buy a lot, in fact. I buy probably four, five, six paintings a month.

**DICK**: Oh, wow. It's just like auctions and—

**CROCE**: Yeah, mainly auction. Mainly auction. Once in a while gallery, but mainly auction. And actually, I try to pay as little as I can, but sometimes I have to pay then for their value.

**DICK**: And sometimes they don't know who the artist is, right?

**CROCE**: Oh, no. So we have still a lot of leverage, because since, again, in the field of art, there are some great experts, but they are very few. And the auction houses, they have some people who are experienced, but they are not that terrific. So there is still—

[Interruption]

**DICK**: The only other thing, would it be okay if I contacted you just to—there's, you know, a lot of other people we'd love to get in touch with.

**CROCE**: Sure. No problem.

**DICK**: You know, people like Vincent Zurawski or Michael Wall.

**CROCE**: Yeah. No problem.

**DICK**: Can I send you or Sharon an email, and, you know, and if you happen to have any contact information for them—

**CROCE**: Yeah. That's no problem.

**DICK**: Wonderful.

**CROCE**: Okay?

**DICK**: Great. Well, thank you so much.

**CROCE**: Thank you [inaudible].

**DICK**: I really appreciate you taking the time.

**CROCE**: Yeah. Very good. Yeah.

[END OF AUDIO, FILE 1.1]

[END OF INTERVIEW]