CHEMICAL HERITAGE FOUNDATION

TIMOTHY J. McDONNELL

The Pew Scholars Program in the Biomedical Sciences

Transcript of an Interview
Conducted by

Steven J. Novak

at

University of Texas MD Anderson Cancer Center
Houston, Texas

on

17, 18, and 19 June 1996

ACKNOWLEDGEMENT

This oral history is part of a series supported by a grant from the Pew Charitable Trusts based on the Pew Scholars Program in the Biomedical Sciences. This collection is an important resource for the history of biomedicine, recording the life and careers of young, distinguished biomedical scientists and of Pew Biomedical Scholar Advisory Committee members.

From the original collection at the Center for Oral History Research, UCLA Library, UCLA.

The following oral history, originally processed at the UCLA Center for Oral History Research, has been reformatted by the Chemical Heritage Foundation. The process involved reformatting the front matter, adding a new abstract, replacing the table of contents, and replacing the index. The paragraph spacing and font of the body of the transcript were altered to conform to the standards of the Oral History Program at the Chemical Heritage Foundation. The text of the oral history remains unaltered; any inadvertent spelling or factual errors in the original manuscript have not been modified. The reformatted version and digital copies of the interview recordings are housed at the Othmer Library, Chemical Heritage Foundation. The original version and research materials remain at the Darling Library, University of California, Los Angeles and at the Bancroft Library, University of California, Berkeley.

REFORMATTING:

Holly Polish, Program Intern, Oral History, Chemical Heritage Foundation. B.A. History, American University.

David J. Caruso, Program Manager, Oral History, Chemical Heritage Foundation. B.A., History of Science, Medicine, and Technology, Johns Hopkins University; PhD., Science and Technology Studies, Cornell University.

UNIVERSITY OF CALIFORNIA, LOS ANGELES

Oral History Interview Agreement No. R960620

This Interview Agreement is made and entered into this 19th day of July, 1996 by and between THE REGENTS OF THE UNIVERSITY OF CALIFORNIA, a California corporation, on behalf of the Oral History Program at the UCLA campus, hereinafter called "University," and TIMOTHY J. MCDONNELL having an address at University of Texas, M.D. Anderson Cancer Center, Department of Molecular Pathology, Box 89, 1515 Holcombe Blvd. Houston, TX 77030, hereinafter called "Interviewee."

Interviewee agrees to participate in a series of University-conducted tape-recorded interviews, commencing on or about June 17, 1996, and tentatively entitled "Interview with Timothy J. McDonnell". This Agreement relates to any and all materials originating from the interviews, namely the tape recordings of the interviews and a written manuscript prepared from the tapes, hereinafter collectively called "the Work."

In consideration of the mutual covenants, conditions, and terms set forth below, the parties hereto hereby agree as follows:

1. Interviewee irrevocably assigns to University all his copyright, title and interest in and to the Work. This assignment applies to University, its successors, and assigns, for and during the existence of the copyright and all renewals and extensions thereof.

2. By virtue of this assignment, University will have the right to use the Work for any research, educational, or other purpose that University may deem appropriate.

3. Interviewee acknowledges that he will receive no remuneration or compensation for his participation in the interviews or for the rights assigned hereunder.

4. Interviewee will receive from University, free of charge, one bound copy of the typewritten manuscript of the interviews.

5. To insure against substantive error or misquotation, Interviewee will have the right to review the manuscript before it is put into final form. University therefore will send Interviewee a copy of the edited transcript for review and comment. Interviewee will return transcript and comments to University within 30 days of receipt of the transcript. In the event that Interviewee does not respond within 30 days, University will assume that Interviewee has given full approval of the transcript.

6. All notices and other official correspondence concerning this Agreement will be sent to the following:

If to University:

Office of Research Administration
University of California, Los Angeles
P.O. Box 951406
Los Angeles, California 90095-1406

Attention: Ms. Carli V. Rogers
Copyright Officer

If to Interviewee:

Timothy J. McDonnell
Department of Molecular Pathology
University of Texas
M.D. Anderson Cancer Center
Box 89
1515 Holcombe Boulevard
Houston, Texas 77030

University and Interviewee have executed this Agreement on the date first written above.

INTERVIEWEE

X _____
(Signature)

Timothy J. McDonnell
(Typed Name)

University of Texas
(Address)

M.D. Anderson Cancer Center

1515 Holcombe Boulevard

Houston, Texas 77030

Date 6/17/96

THE REGENTS OF THE UNIVERSITY OF CALIFORNIA

_____
(Signature)

Carli V. Rogers
(Typed Name)

Copyright Officer
(Title)

Date 7-19-96

Chemical Heritage Foundation
Oral History Program
315 Chestnut Street
Philadelphia, Pennsylvania 19106

TIMOTHY J. McDONNELL

1956 Born in Long Beach, California, on 27 February

Education

1974 A.A., United States International University
1977 B.A., Biology, University of California, San Diego
1982 Ph.D., Anatomy, University of North Dakota
1986 M.D., Washington University School of Medicine

Professional Experience

Washington University School of Medicine, St. Louis, Missouri
1986-1991 Resident in Pathology

University of Texas MD Anderson Cancer Center, Houston, Texas
1991-present Assistant Pathologist, Division of Pathology
1991-1996 Assistant Professor, Department of Molecular Pathology
1996-present Associate Pathologist, Department of Molecular Pathology, Division of Medicine
1996-present Associate Professor, Department of Molecular Pathology, Division of Medicine

Honors

1991 United States and Canadian Academy of Pathology Stowell-Orbison Award
1992 Wilson S. Stone Memorial Award
1992-1996 Pew Scholar in the Biomedical Sciences
1993 United States and Canadian Academy of Pathology Benjamin Castleman Award

Selected Publications

McDonnell, T.J. et al., 1989. *Bcl*-2-immunoglobulin transgenic mice demonstrate extended B cell survival and follicular lymphoproliferation. *Cell* 57:79-88.

McDonnell, T.J. et al., 1990. Deregulated *Bcl*-2-Ig transgene expands a resting but responsive immuno-globulin M and D-expressing B-cell population. *Molecular and Cellular*

Biology 10:1901-7.
McDonnell, T.J. and S.J. Korsmeyer, 1991. Progression from lymphoid hyperplasia to high-grade malignant lymphoma in mice transgenic for the t(14;18). *Nature* 349:254-56.
Nunez, G. et al., 1991. *Bcl*-2 maintains B cell memory. *Nature* 353:71-73.
McDonnell, T.J. et al., 1992. Expression of the protooncogene *bcl*-2 in the prostate and its association with emergence of androgen-independent prostate cancer. *Cancer Research* 52:6940-44.
McDonnell, T.J. 1993. Cell division versus cell death: A functional model of multistep neoplasia. *Molecular Carcinogenesis* 8:209-13.
Marin, M.C. et al., 1994. Evidence that p53 and *bcl*-2 are regulators of a common cell death pathway important for *in vivo* lymphomagenesis. *Oncogene* 9:3107-12.
Marin, M.C. et al., 1995. The functional basis of c-*myc* and *bcl*-2 complementation during multistep lymphoma-genesis *in vivo. Experimental Cell Research* 217:240-47.
Hsu, B. et al., 1995. Evidence that c-*myc* mediated apoptosis does not require wild-type p53 during lymphomagenesis. *Oncogene* 11:175-79.
Marin, M.C. et al., 1996. Apoptosis suppression by *bcl*-2 is correlated with the regulation of nuclear and cytosolic Ca^{2+}. *Oncogene* 12:2259-66.
Roth, J.A. et al., 1996. Retroviral-mediated wildtype p53 gene transfer to tumors of patients with lung cancer. *Nature Medicine* 2:985-91.
Beham, A. et al., Bcl-2 cell death suppression is accompanied by selective inhibition of p53 nuclear import following DNA damage. (Submitted).

ABSTRACT

Timothy J. McDonnell spent his first six years in Indiana and Spain; then the family moved to San Diego, California. His father was a mechanical engineer in the Navy and then the Air Force. His mother had been a weather forecaster in the military during the war and then became a police officer. She gave up work to be a housewife when her children were born. McDonnell was always fascinated with the natural world, wanting first to be a veterinarian and later a herpetologist or an oceanographer; he even worked as a bat bander for a time. He attended public schools; his grade school was very good, but his junior high and high schools less so. In fact, he felt his performance worsened the longer he stayed in school, so after his sophomore year he left high school without having been graduated and entered the United States International University. There he majored in biology, which he continued when he transferred to University of California, San Diego, although his interest shifted from organismic to cellular biology, as exemplified particularly by an interest in the causes of cancer.

McDonnell then attended graduate school at the University of North Dakota, where he taught anatomy in addition to doing his own research. He entered the John O. Oberpriller laboratory; there his research on cardiac muscle demonstrated that differentiated cells are not necessarily postmitotic. After receiving his Ph.D., McDonnell stayed at the University of North Dakota to study for an M.D. degree. Because he had already had most of the first two years' medical school classes he was able to be a research assistant, teaching anatomy and doing his own research. He decided to transfer to Washington University in St. Louis for his residency in diagnostic pathology. He wanted to specialize in pathology in order to combine research with practice, so he accepted a postdoc in the Stanley Korsmeyer lab, searching for cancer-causing genes in mice.

Here McDonnell talks about how he learned molecular biology techniques; established that *bcl*-2 is an oncogene and discovered that *bcl*-2 functions not by enhancing cell growth but by preventing cell death. He discusses the concept of apoptosis, programmed cell death; the slow growth rate of most cancer cells; searching for factors which supplement *bcl*-2 in causing cancer; Korsmeyer's research background and lab management style; and the creation and patenting of transgenic mice. McDonnell continued to be interested in cardiac muscle biology. After his second year he married Sherry Wetsch, at that time a law student. Being newly married and moving to a new city and university was challenging during his third-year, but his fourth-year internship in pathology, diagnosing frozen tissue sections, went well and was well suited to his meticulous personality. Here he explains the technique of flow cytometry. Then it was time to apply for academic positions. McDonnell accepted an appointment at the University of Texas M.D. Anderson Cancer Center and began staffing his laboratory. He talks about his start-up package and lab space. He shifted his research focus to prostate cancer. He discusses areas of overlap between his own and Korsmeyer's research interests; he goes into his focus on the regulation of cell death and how the disruption of regulation contributes to cancer; he explains his interest in *bcl*-2's role in regulating transmembrane traffic. McDonnell gives a critique of traditional prostate cancer treatment and discusses the therapeutic potential of apoptosis research. He believes he has insights gained by being a combined M.D./Ph.D. He explains the degree to which cancer is associated with infectious diseases and the role of the environment in causing cancer, explaining the difference between cancer cells and normal cells. He tells why mice are models of human disease and of biological systems. Mostly he thinks

experiments with animals are ethical, provided they are for health benefits—specifically cancer—but he is a vegetarian.

UCLA INTERVIEW HISTORY

INTERVIEWER:

Steven J. Novak, Senior Editor, UCLA Oral History Program. B.A., History, University of Colorado; Ph.D., History, University of California, Berkeley; M.B.A., UCLA Graduate School of Management.

TIME AND SETTING OF INTERVIEW:

Place: McDonnell's office, University of Texas M.D. Anderson Cancer Center.

Dates, length of sessions: June 17, 1996 (126 minutes); June 18, 1996 (123); June 19, 1996 (91).

Total number of recorded hours: 5.65

Persons present during interview: McDonnell and Novak.

CONDUCT OF INTERVIEW:

This interview is one in a series with Pew scholars in the biomedical sciences conducted by the UCLA Oral History Program in conjunction with the Pew Charitable Trusts's Pew Scholars in the Biomedical Sciences Oral History and Archives Project. The Project has been designed to document the backgrounds, education, and research of biomedical scientists awarded four-year Pew scholarships since 1988.

To provide an overall framework for Project interviews, the director of the UCLA Oral History Program and three UCLA faculty consultants developed a topic outline. In preparing for this interview, Novak held a telephone pre interview conversation with McDonnell to obtain written background information (curriculum vitae, copies of published articles, etc.) and to agree on an interviewing schedule. He also reviewed prior Pew scholars' interviews and the documentation in McDonnell's file at the Pew Scholars Program office in San Francisco, including his proposal application, letters of recommendation, and reviews by Pew Scholars Program national advisory committee members.

For technical background, Novak consulted J.D. Watson et al., *Molecular Biology of the Gene.* 4th ed. Menlo Park, CA: Benjamin/Cummings, 1987 and Bruce Alberts et al., *Molecular Biology of the Cell.* 3d ed. New York: Garland, 1994.

The interview is organized chronologically, beginning with McDonnell's childhood and education in Southern California and continuing through his graduate and medical education at University of North Dakota, his residency and postdoc at Washington University, and the establishment of his own laboratory at the University of Texas M.D. Anderson Cancer Center. Major topics discussed include cell differentiation, the characteristics of cancer cells, clinical treatment of cancer patients, apoptosis research, and the function of the *bcl*-2 gene.

ORIGINAL EDITING:

Gregory M. Beyrer, editorial assistant, edited the interview. He checked the verbatim transcript of the interview against the original tape recordings, edited for punctuation, paragraphing, and spelling, and verified proper names. Words and phrases inserted by the editor have been bracketed.

McDonnell reviewed the transcript. He verified proper names and made minor corrections and additions.

Novak prepared the table of contents and index..

Beyrer assembled the biographical summary and interview history.

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