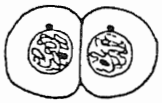

Profile #4
RUTH SAGER, Ph.D.
Professor of Cellular Genetics

BIOGRAPHY

As the discoverer of chloroplast DNA, Dr. Sager had a well-established career in plant genetics when her desire to explore the unknown led her to leave this research for human studies. She moved to England, became a student again, and learned techniques for genetic analysis at the cellular level. Now Chief of the Division of Cancer Genetics at the Sidney Farber Cancer Institute, Dr. Sager discusses the contributions of her research team to the growing understanding of tumor genetics. Dr. Sager compares the life of a scientist to that of an artist or dancer and says that "it gets to the very core of your existence."

VIDEOTAPE SUMMARY

Professionals Portrayed:

Genetists

Research Scientists — (Ph.D.s) — Colleagues, post-Doctoral Fellows

Ph.D. Students

Laboratory Technicians

Medical Equipment and Procedures demonstrated:

DNA Techniques — recombinant properties

Chromosome Studies — kariotype comparisons

Mendelian Ratios

Isoelectric Focusing

Social Concepts Discussed:

The Effect of The Women's Movement on Aspirations and Expectations

Decisions and Factors Affecting Career Advancement

The Challenge of a Mid-Life Career Change

Sharing Profession with Spouse

International Exchange of Scientific Information

Transcript

Interviewer: The most important contribution of your research, what would you consider that to be?

Dr. Sager: Well, I don't think I've made it yet.

Interviewer: The Joint Committee on the Status of Women has created and produced this series on women in medicine with senior women professors at Harvard Medical School. Today we're talking with Dr. Ruth Sager, Professor of Cellular Genetics.

Interviewer: Dr. Sager, could you describe your current research interests?

Dr. Sager: We have three areas. One is the DNA methylation area, the second is the rearrangement areas at the DNA level. The third area is a more genetic approach in which we have been transferring DNA from tumor cells into normal cells and from normal cells into tumor cells to look at changes in expression of knowing pieces of DNA which have been cloned out by recombinant DNA techniques. One technician, Constance Grabowy, has been doing very beautiful methylation studies at the DNA level.

Connie's research involves looking at the effects of a number of what are called "restriction enzymes," enzymes that cut DNA at particular sites in the DNA which they recognize by the sequence, the chemistry of that little location. Some of those enzymes will not cut, are not able to do this breaking of the DNA sequence, if there is a methyl group in the way, and we call them methylation sensitive enzymes. She has been going through all the restriction enzymes that are available, either from commercial source or from one's friends, to find as many methylation sensitive enzymes as possible in order to do a complete study of the positions of these methylated bases in DNA. She has been using chloroplast DNA as a model system for that. Although we're now beginning also to do this with human DNA.

A more fundamental area, I think, are permanent changes that result from rearrangement, and the jumping genes that I talked about earlier are an example of a mechanism for genomic rearrangement; another group in my laboratory have been working on this problem of genomic rearrangements. For example, Dr. Kiyoshi Tanaka has come from Japan and has been in my laboratory for two years. He is a physician and a researcher, both clinical and laboratory researcher in Japan, and in the last two years here he has found some very important clues of short sequences in DNA which seem to have an influence on this rearrangement possibility and the ability of cells to undergo rearrangement. He has found a region of mouse DNA which seems to be responsible for causing rearrangements to occur in a part of a chromosome which is adjacent to this region. He's been able to show that when this sequence is present, then the adjoining region undergoes continual rearrangement, and when it's absent, that region is completely quiet and does not undergo rearrangement at all.

Dr. Inder Ghadi is a talented cytogeneticist who is a postdoctoral fellow in my laboratory. He has been carefully comparing the chromosomes of normal cells and tumor cells to look for systematic changes in chromosome arrangements which may be occurring in the process by which a normal cell becomes a tumor cell. For this purpose, we've mainly been using Chinese hamster cells, but we're also doing some studies now with human cells, and there are a variety of methods. One of the methods is, if you have a recombinant DNA clone carrying a particular sequence of DNA, it can be used as a probe to find out whether that particular gene has undergone some rearrangement, has moved or has become amplified. Here, for example, is a cell in which there has been rearrangement many many fold, amplification of a gene that is involved in the resistance to the anti-cancer drug methotrexate. This is a study that has some direct clinical interest because methotrexate is one of the most popular drugs and very valuable drugs in the study of leukemia.

Interviewer: Can you explain how you made the jump from plant genetics?

Dr. Sager: When I got my Ph.D., I decided to leave corn genetics because by that time it became possible to do genetics with microorganisms, and everything moves so much faster that it was really sort of the threshold of the new era, and I wanted to be part of it. I decided to work on quite a different problem, but still it was a plant problem. I thought it was a plant problem. This had to do with indirect evidence that there were some genes that did not behave as if they were carried on chromosomes. They didn't show those nice three to one Mendelian ratio, and this became something that absorbed me for about the next 20 years of my life. Essentially, I discovered and established the genetics of what we call the second genetic system, which was the DNA located in the chloroplast.

One of the features of chloroplast DNA is that it has a very strange pattern of inheritance. Only the DNA from the female parent is transmitted to all of the progeny; the DNA from the male parent disappears and never reappears. We found that there was a molecular explanation for that, and it had to do with a special biochemical change in DNA, which is the addition of a methyl group; it is called methylation of DNA, which leads to exchange in the properties of the DNA, and when it is methylated it's protected from a particular enzyme. When it is not methylated, that enzyme comes in and just chops it up into little pieces. Methylation of DNA has turned out to be an important mechanism in mammalian cells where the control of gene expression is found. One of the really important things that we learn in the chloroplast work we've applied directly to the cancer problem. But after I had worked on chloroplasts for about 20 years there were lots of problems remaining. I decided to write a book about it and I wrote a book called **Cytoplasmic Genes and Organelles,** and it was hard work.

By the time I had finished the book, I was really tired of the problem, and I felt that I wanted to go on to something else. The problem seemed most challenging, and it still is one of the most challenging problems in biology: "how do normal cells become tumor cells?" That was a complete career change, you might say, because in 1972 I sort of became like a post-doctoral fellow again to start learning about clinical cancer to some extent and about cancer at the cellular level.

I spent a year in London in a wonderful laboratory, The Imperial Cancer Research Fund Laboratory. In Stoker's laboratory I really learned a great deal in the course of that year. Another person in that laboratory was Arthur Pardee, a very well known biochemist who had also switched from bacterial genetics to studying the cancer problem. By the end of that year we had decided to get married and that, I think, was a very important part of this new career of mine, because in the past I had always felt that I wanted to work on something that nobody else was working on and I loved the freedom of not worrying about the competition. But the cancer problem is more serious than that, and you really want all the help you can get, and the whole idea of talking to people who are interested in similar problems was new to me. I never talked to anybody about chloroplasts, just the people in my lab. So it was really very exciting to be married to a man who I could talk to about what I was working on even though our labs are completely independent and our approaches are very different. Still, I think it has been an enormous help to me to get another point of view because his point of view is very biochemical and mine is very genetic, so rather complementary.

Interviewer: Did you do collaborative research with him at anytime?

Dr. Sager: Never, never, no.

Interviewer: I want to talk a little about your climb through the academic ranks, professor. You were a professor at Hunter College. Was that something you actively sought?

Dr. Sager: Well, in a way it was. I was at Columbia University as a research associate supporting myself on my own grant; I guess it was called research scientist. But they would never give me an academic position. They just were not giving jobs to women. Everyone said, "You've written two books and you're internationally known, all that sort of thing, don't you think you ought to have a proper job?" But they were so very very hard to find and I still wanted to stay in New York, so I had a few reasonable job offers from elsewhere which I decided not to take. So the position that came up at Hunter College was really very attractive. The college had just become part of the City University, and they were building a graduate department; most of the people who had been in the biology department were old and retired, so that the department was being built from scratch. I was given a very good position; I only had to teach one course, which was rather unusual for City University, and they mainly wanted me to come and do research and attract more graduate students and faculty.

Interviewer: Do you have any pieces of advice for young women who want to pursue science?

Dr. Sager: I think the first thing is to be sure of your own abilities. Science is very demanding; you have to be able to think very well and also have a very good memory. You have to really love it; I think it all comes from inside; you feel that this is the way you want to live because doing science is a way of life. It really gets to the very core of your existence. It's not a profession like many other professions, its much more like being an artist or being a dancer. It's something that really demands everything from you that you are capable of. So you have to start with a fairer degree of assurance that that's what you like. But once you really feel that that is what you want to do, then you have to really stick with it.

Dr. Ruth Sager
Vocabulary

chloroplast. A plant cell inclusion body containing chlorophyl.

cytogeneticist. A specialist in a branch of genetics concerned with the structure and function of the cell.

DNA. Abbreviation for dioxyribonucleic acid.

DNA hybridization. Procedure used to identify DNA or RNA sequences by allowing separated known DNA strands to join with complementary areas on the unknown strands.

DNA methylation. Process to add a methyl group to any of the DNA bases; associated with regulation, expression and enzyme degradation procedures.

enzyme. A protein, secreted by cells, that acts as a catalyst.

Mendelian ratio. Mendel's law of dominance — where recessive traits only appear in individuals possessing only recessive genes, thus when two pairs of genes, one dominant pair and one recessive pair, are combined in a random manner, only one of the four possible gene combinations will yield an individual with the recessive trait.

methyl group. A group of the radical — CH3, present in a variety of compounds.

recombinant DNA. DNA produced by recombination or crossing-over between two homologous chromosomes.

restriction enzymes. enzymes which are able to recognize and break off specific sequences of the DNA chains; associated with identification: mapping techniques.

Dr. Ruth Sager
General Questions

1. What personal traits does Dr. Sager reveal that have aided her career as a scientist? For example, what does she, an internationally known scientist, mean when she says that she has not yet made her "most important contribution to research?

2. How is the team effort of research shown in Dr. Sager's work?

3. What direct clinical implications does the research in this lab have?

4. Dr. Sager says that she undertook "a complete career change." Why? How?

5. Describe the pattern which emerges in the development of Dr. Sager's career.

6. How does she illustrate the saying "publish or perish"? What influence did her publishing experiences have on her career?

7. What does Dr. Sager say about discrimination against women in academic medical research? How did she confront this discrimination?

8. What advice does she give to young women who want to pursue a science career? What does she mean when she says that "you really have to love it"?

9. How has the decision to marry influenced her career? To what extent does her husband's work relate to hers?

Dr. Ruth Sager
Science Questions

1. What area of research is Dr. Sager involved with?

2. What is recombinant DNA? Why are recombinant DNA techniques useful?

3. What is a restriction enzyme? What do they allow the research to do?

4. What is gene rearrangement?

5. Dr. Inder Ghadi, a cytogenticist, has been comparing the chromosomes of normal cells to tumor cells. He is looking for systemic changes in chromosome arrangements. What is the significance of these chromosome rearrangements?

6. Dr. Sager made a jump from plant genetics to cancer research. What were her reasons for making this shift?

7. Dr. Sager has made an important contribution to molecular biology. What was this discovery?

8. What does Dr. Sager consider to be one of the most challenging problems in biology today?

9. How might gene rearrangements on a particular chromosome be related to cell transformations? What might cause some of these gene rearrangements?

10. Dr. Sager is married to a biochemist. His lab is completely independent of hers. Do you feel that being married to a researcher in a similar field is an asset? Or is it detrimental?

11. What are the moral/ethical issues involved with recombinant DNA research? Should recombinant DNA research, because it has special risks, be allowed to be controlled in a self-policing manner, or, because of the magnitude of the safety issues, should this area of science fall under governmental regulation? What implications does this have for the researcher with a tradition of freedom of inquiry?

12. How responsible should scientists be for the consequences of the application of their research? In what areas of science and medicine are these concerns most evident?

Dr. Ruth Sager
Social Studies Questions

1. Whose responsibility is it to discern if discrimination exists in a profession or business? Whose responsibility is it to bring about change? Why? How?

2. What dilemmas arise in combining a career and marriage? Does medicine present special dilemmas? Explain.

3. Why might an established person choose to make a complete career change? Who might be affected by such a decision? How would a person make such a change?