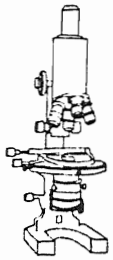

Profile #6
ALICE HUANG, Ph.D.
Professor of Microbiology and Molecular Genetics

BIOGRAPHY

As Director of the Laboratories of Infectious Diseases at Boston's Children's Hospital, Dr. Huang leads a team of physicians and scientists who are exploring virus structure and function. Dr. Huang explains how recent advances in peptide synthesis may lead to the development of vaccines for some of the world's worst diseases. Married to Nobel Laureate David Baltimore and mother of a young daughter, Dr. Huang talks of the decisions and problems involved in combining family responsibilities with a demanding career.

VIDEOTAPE SUMMARY

Professionals Portrayed:

Virologists

Specialist in Peptide Synthesis

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

Ph.D. Students

Laboratory Students

Medical Equipment and Procedures Demonstrated:

Homogenation and Sucrose Gradient Separation of Proteins

Iodination, Electrophoresis and Autoradiography of Proteins

Tissue and Cell Culture

Peptide Synthesis

Social Concepts Discussed:

The Significance of Mentors in Career Development

Decisions and Factors Affecting Career Advancement

The Importance of Collaboration in Scientific Research

Parenting, Day Care and Careers

Changes in Government Funding of Research

Transcript

Dr. Huang: He also said something which I will always remember, he said, "You know you have done very well here in the laboratory and you have a really good thesis." And he said, "Alice, the next few years will be very important and don't think that you are not going to have to work very hard, but I expect to see you a Professor some day." And it is that expectation, I think, which was important.

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. Alice Huang, Professor of Microbiology and Molecular Genetics.

Interviewer: Was there someone at Hopkins that took you under his or her wing in terms of your science career?

Dr. Huang: Well, I have mentioned Barry Wood and he really started this special program and I was in my first year when the program started. There were 21 of us. He and his wife really did look after us very much in the first year, had us out to their home on Sundays, and he would play football with the boys and we'd all sit around and talk about science and medicine and people in science. I hadn't realized it at that time, but his wife was a microbiologist and had gotten a Ph.D. in microbiology while she had a baby in one arm and a toddler in the other hand. She was also the roommate to Polly Bunting and so the connections were very interesting. I think that they must have been extra supportive of women who were trying to make it in that world. After Barry Wood, when I ended up working in a laboratory and going for my Ph.D., my thesis advisor was Dr. Robert Wagner and I must say, I think that he was extraordinarily supportive. I was the first graduate student he ever had, and I think that all preceptors tend to put a lot into their very first student to make sure that things work out for them. He was good in not only showing me the important areas that one should do science in. He was also very good, I don't know if I should really say this but I will anyway, in saying that in science you are really judged purely on what you can do, not what your family was, what your father did, not on your social ability, but more on what you have in your head and how much you can produce. I think that was an important lesson to learn from him. He also said something which I will always remember. He said, "You know you have done very well here in the laboratory and you have a really good thesis," and he said, "Alice, the next few years will be very important and don't think that you are not going to have to work very hard, but I expect to see you a Professor some day." And it is that expectation, I think, which was important because as the next few years went on, I don't think I ever thought very much about where I was really going to end up. But in the back of my mind I remember that "I think you are going to be a Professor some day" and I thought, well, that's not a bad way to go and it sort of gave me a path to follow and aim for.

Interviewer: When did that unconscious career plan turn into something more conscious?

Dr. Huang: I remember that very clearly. It was at MIT. Annamarie Goriani Terrini was a research associate and I was at MIT as a research associate. She, of course, was much more established and well known and many students and post-docs came to MIT because they wanted to work with her. She said, "You may all be very happy doing what you are doing now as post-docs and research associates in labs where you are fairly happy," she said, "but think about it. Should your lab chief move away or die, which is just what happened to me, then you would be nowhere. Since you are in your late 20s and early 30s, it is time to really strike out on your own and build your own lab and establish your own reputation." She said, "Do it now because otherwise it is going to be too late." There I was happily being a research associate at my husband's lab, virtually had all the freedom I wanted, all the money I needed without worrying about it, but I listened to her and decided she was absolutely right. So then I decided that I really had to do it on my own, and I couldn't just stay and enjoy myself and do whatever I felt was easy to do. It was a luxury I think to live and work in an environment in which you had complete freedom but no responsibilities. So then I started job hunting. I interviewed both at Tufts, Boston University and at Harvard. So then I sort of waited around for Harvard and nothing happened at Harvard. Finally, I decided, whom do I know at Harvard? Well, the only person I knew by reputation was Dr. John Enders and so I made an appointment and I went to see Enders. It turned out, circumstances working out ways in which I really had no control, was that the department of microbiology and molecular genetics indeed had an opening for a virologist. But they didn't have space because they were renovating Building D-1. Ed Kass at Boston City Hospital was starting a group of virologists, and he needed someone who was really full time in the laboratory in order to help the fellows who were coming in as virologists. He had just finished off a top floor on the Channing Laboratory Building and needed someone to equip it and to organize it, so that the fellows who were interested in virology would have a place to work. So Enders knew all of this and I think, I am not sure of the exact story, but I think that he ended up putting Kass and the Department of Microbiology together and the Department was willing to give me an appointment and to have me do my teaching function in the Department. Ed Kass was willing to give me a physical location. And so like everyone else in my age group at that time, I put in for a grant for $50,000 for three years and I got it. Ed Kass said, "This is the first time someone here has ever done that; I guess you're fairly independent," and so I started rolling that way.

Interviewer: So getting an independent grant was a very important step for you?

Dr. Huang: Oh, I think it was and I think you know it is unfortunate these days that it is much harder for a young person to start. I mean, in the late 60s and early 70s, it was assumed that someone in my field would get a grant as an assistant Professor, get almost all their major equipment which would be between $30,000 to $60,000 and just start going and set up a lab de novo, out of nothing. And that was just what everybody did. Now I think that the institution has to come up at least with starter funds and some heavy equipment.

Interviewer: Could you describe some of the problems that people in your lab are working on?

Dr. Huang: I would be happy to. One of the problems that is being worked on is the continuation of the questions involving defective particle interference, defective interfering virus particles, and this is work being done by Dr. David Cave. The project that we thought would be best, would be to isolate DNA molecules that were copies of RNA sequences of the defective interfering virus particles that we know about, and taking that DNA ask, "If you can use it as a probe against the products that were made in living animals, such as mice. To look at the products that were made of brains or spleens or anywhere else and ask what the DNA would do, would they hybridize and light up sequences if they were identical?" So in this way we can ask the question, "Do defective interfering virus particles alter the course of a given disease?" Will it ameliorate the disease? Will it cause it to be more persistent rather than acute and to really prove it by showing how the genetic information is being replicated in these animals and in the particular time frame. So what he has had to do in the last year or so, is to be able to handle DNA in plasmids, to grow them up in bacteria, to be able to translate them so that they will be labeled with P32 in vitro and then to develop the methods of hybridization in the laboratory that would be useful for his purposes. He has actually been very good in reading the literature and adapting new methods — the brain is not the easiest organ to work with. He has been highly successful now in getting nucleic acids of the right size so that we can actually prove whether defective interfering particles are there or not there. So I am very pleased with what he is doing. That is Dr. Cave.

Then I have had a post-doc named Dr. Lynn Little who has been with us for a year now. His background was really in viral pathogenosis and he has done mostly animal work. He started working on growing vesicular stomatitis virus in human tumor cells. We have had the collaboration of Dr. Judah Folkman, who has supplied us with primary cultures of human tumors that he has actually gone in and taken out of patients. This particular work is getting to the point at which we think we have our hands on the tumor specific human antigen which is found on HeLa cells but is related to neuroblastoma and rhadomyosarcomas in children, so we are fairly excited about that.

I have been very lucky in our lab to have had a chief technician named Trudy Lanman who has been with me since 1975. One of the most professional technicians that I have ever seen and not many laboratories really of my size, have only one technician. She is the one who does all of the ordering, all of the maintenance of the laboratory and besides she keeps up the tissue culture and the virus assays in the laboratory.

We have a new venture that is going on in the laboratory now and it is sort of fun! In fact, it comes in the appearance of a big machine and it is called the peptide synthesizer. It is an automated computerized system that really does simple organic chemistry reactions. The reason that we have it is because there has been a new, let's say, a new discovery of an old discovery, that has happened in the past two years and this has really accelerated by discoveries made out in San Diego. Now what they found was that you can make a peptide of several amino acids hooked up. It doesn't have to be very big. It could be anywhere from six amino acids long, up to 20, and these amino acids are actively hooked together, can be then injected into rabbits and elicit antibodies. That antibody will be able to find the big protein molecule of which the peptide is just a part of. So what that says, is that just for molecular biology, you can now begin to map out specific domains of that protein. You can also use the antibody to purify the protein out of a gamisch of other things.

Also, there is tremendous potential for this peptide as a vaccine because instead of having to take a whole organism, whether it is a virus or a bacteria and try to kill it in some way, or to

attenuate it and inject it into people as a vaccine to protect them against the more virulent kind, we now can just synthesize the peptide of the region that we are particularly interested in. That, we know, will elicit protective antibodies in the human host and just use that clean preparation, inoculate it into people and protect them. In fact, over the last few years, the last two years, there have been reports for both hepatitis B virus and for foot and mouth disease virus that such peptide vaccines work very well. These results now are in animals, but I see no reason that they won't be extended to humans very shortly, so for an infectious disease division it makes good sense to get into this particular area.

Now I have have been very lucky in the person I found, the people who know organic chemistry and know solid phase peptide synthesis are actually very few in this country and I was lucky to find Dr. Janice Young who had been doing this ever since her days at Berkeley when she was a post-doc. She, in fact, has coauthored a book called **Solid Phase Peptide Synthesis** with John Stuart, so she comes highly equipped to run the facility, to trouble-shoot and to really take care of it.

Interviewer: I would like to talk a little about your family life, your life outside of the medical school here. You are married and you have a child. Was that a difficult decision, to have a child?

Dr. Huang: Oh not at all. I think that, well my reasoning went this way: That you only live once and there are so many experiences in life that one should try to have as many as possible.

Interviewer: How has that affected your career development?

Dr. Huang: That is a very interesting question. I think that before I had a child I would always look at women and say, these women who just quit after having their first child and said, "I am dropping out and I am going to raise a family," that they were just using it as an excuse and that they really did not enjoy what they were doing to begin with. When I had my first child, I realized that that was a rather snap judgement. The hormones do an amazing job on one's head and you are just not in control of what you feel and what you think. I was lucky enough not to have had my child until I was about 35, so my career was fairly well established. I had a functional laboratory with several people who were actively involved and so it wasn't necessary for me to be at my 100% best. So even though I think at times I found it very difficult to concentrate, and to be perfectly honest, I don't think I really got my head back under my own control for two years after the birth of my daughter.

Interviewer: Would you advise women in science to delay child bearing until their career is well established?

Dr. Huang: I think that would certainly help. I think that there are two, well there are several things. One is that financially one should be in a position where one has enough money to know that you can hire the best care or put your children in the best day care centers and not try to pick up babysitters here and there and try to make do. I think having that stability just makes life a lot easier and then you never have to worry about what is happening to your baby when you are at work.

Interviewer: Do you encourage young women to pursue science and to stick with it?

Dr. Huang: I encourage young women to find themselves and to use whatever potential they have to the fullest. Since I know science best, I tend to use that as a jumping off point. I can at least show them how exciting an area it is, how much fun I have had doing what I am doing, and I think that is one area that I do push.

antibody. In any broad sense any molecule, soluble or cellular, which is evoked by the stimulus provided by the introduction of antigen and which reacts specifically with that antigen in some demonstrable way; specifically, one or other of the classes of globulins present in the blood serum or body fluids of an animal as a result of antigenic stimulus or "naturally."

attenuate. To reduce, by heat or chemical action, the virulence of a pathogenic microorganism, prior to use as a vaccine.

defective interfering virus particles. Imperfect or malfunctioning virus particles which otherwise would produce superinfection, mutual extinction or cell blockade when exposed to another virus in a susceptible cell, in some instances at the same time and in other instances at different times.

DNA. Abbreviation for deoxyribonucleic acid: the large protein containing deoxyribose as the sugar component and four bases: adanine, quanine, thymine and cystosine. These are arranged as two long chains which are twisted into a double helix. DNA is found principally in the nuclei of animal and vegetable cells, usually loosely bound to protein is considered to be the autoreproducing component of chromosomes and of many viruses, and the repository of hereditary characteristics.

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.

Foot and mouth disease virus. A picornavirus (very small ether-resistant virus having RNA nucleic acid composition) causing foot and mouth disease of cattle, swine, sheep, goats, and wild ruminants.

HeLa cells. The first continuously cultured human malignant cells, derived from a carcinoma of the cervix; used in the cultivation of viruses.

hepatitis B virus. Serum hepatitis virus; the causative agent of viral hepatitis type B, a virus disease of the liver.

in vitro. In the test tube, referring to chemical reactions, fermentation, etc. occurring therein.

microbiology. The science dealing with microbes (microscopic and ultramicroscopic organisms).

molecular genetics. The branch of science that deals with heredity at the level of the molecule.

peptide. A compound of two or more amino acids in which the carboxyl group of one is united with the amino group of the other, with the elimination of a molecule of water, thus forming a peptide bond, --CO--NH--.

peptide synthesizer. An automated system that produces specific small peptide bonds, by joining the carboxyl group of one amino acid with the amino group of another amino acid, with the elimination of a molecule of water.

plasmids. A paragene or replicating unit, other than a nucleus gene, that contains nucleoprotein and is involved in various aspects of metabolism in organisms; extra-chromosomal hereditary determinants.

rhabdomyorsarcoma. A tumor, usually highly malignant, of striated muscle.

neuroblastoma. A malignant neoplasm or tumor characterized by immature, only slightly differentiated nerve cells of embryonic type.

pathogenesis. The mode of origin or development of any disease or morbid process.

RNA. Abbreviation for ribonucleic acid, a macromolecule/protein consisting of ribonucleoside residues connected by phosphate from the 3′ hydroxyl of to the 5′ hydroxyl of the next nucleoside, involved in the basic processes of protein synthesis.

tumor specific human antigen. Any of various sorts of material (e.g., microorganisms, toxoids, exotoxins, foreign proteins, foreign cells or tissues and others), specific to various tumors in humans, that, as a result of coming in contact with the appropriate tissues, after a latent period, usually of from 8 to 14 days, induces a state of sensitivity and/or resistance.

vaccine. Any preparation intended for active immunological prophylaxis — preparation of killed microbes of virulent strains or living microbes of attenuated (variant or mutant) strains; microbial, fungal, plant, protozoal, or metazoal derivatives or products.

vesicular stomatitis virus. Apparently an RNA virus, agent causing vesicular stomatitis in horses, cattle, sheep and pigs, with lesions similar to those of foot and mouth disease but milder clinical reaction.

virology. The study of viruses and of virus diseases; **virologist**, a student of virology.

virulent. Extremely dangerous; denoting a markedly pathogenic microorganism.

virus. A term for a group of **microbes** which with few exceptions are capable of passing through fine filters that retain bacteria and are incapable of growth or reproduction apart from living cells.

Dr. Alice Huang
General Questions

1. Define the term "mentor." Who were the mentors in Dr. Huang's career?

2. How did mentors set the expectations, point the way — or, as Dr. Huang says, give her "a path to follow and to aim for"?

3. What specific female role models did she have? Why were they especially helpful?

4. What personal traits helped her to advance in a research career and to make important personal decisions about marriage and family?

5. Dr. Huang made an important career decision while she was still young. What was this decision? Why was this early decision such an important one in terms of developing a career in academic medicine?

6. Dr. Huang had a misconception about women who leave their careers after having their first child. What was this misconception? Why did she reconsider her perception of women's commitment to their careers?

7. According to Dr. Huang for what reasons should women in science consider child-bearing?

8. What steps to success are revealed in the career pattern developed by Dr. Huang? How did she position herself for advancement? How did she use networking?

9. Why does she describe her work as "fun"? Why is that significant?

10. Using the information Dr. Huang gives about her career development, write a set of guidelines on how to advance.

11. How important is it to enjoy one's career work or even to find it fun? List the characteristics of your ideal career income, status, etc. Where would you rank enjoyment of work? Why?

Dr. Alice Huang
Science Questions

1. What are viruses? How do they cause disease? How are they transmitted?

2. Why is there difficulty in showing a cause and effect relationship between specific viruses and certain diseases, such as cancer?

3. What does her work show about the team effort of research?

4. How does Dr. Huang illustrate the personal traits suitable for leading a medical research term? What are these traits?

5. The peptide synthesizer is an automated system designed for the production of very specific small peptides. Vaccines for particular viral infections could be developed using this piece of instrumentation. Elaborate upon this procedure.

6. Using DNA hybridization techniques, how might one determine the presence of a viral genome in a transformed cell? How could autoradiographic labeling with P^{32} aid this problem?

7. What are the current research problems being dealt with by Dr. Huang's lab team? Why will information acquired in this area provide immediate and long term benefits?

8. Medical research needs financing. Where does the money come from that supports current medical research? What are the current problems with financing medical research?

9. What is the significance of showing the presence of defective interfering particles in transformed cells? How might this be accomplished?

Dr. Alice Huang
Social Studies Questions

1. Why are role models so important to success? When role models are limited, how can a person set about building new opportunities? How can school, education, or families help people who are trying to break out of stereotypes as seen, for example, in "Women In Medicine"?

2. What conflicts can arise when combining a medical career and family? How might these conflicts be resolved?