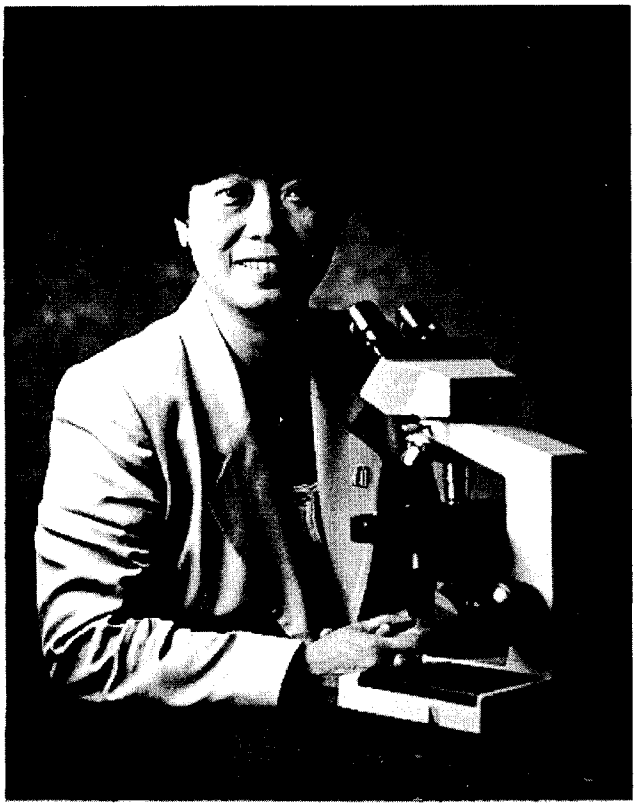
An Interview with a Distinguished Pharmaceutical Scientist

Jessie L.-S. Au[1]

Dr. Jessie L.-S. Au is Distinguished University Professor at The Ohio State University (OSU), Colleges of Pharmacy, Medicine and Biomedical Engineering, and holds the Davis Chair in Cancer Research. Dr. Au received her Pharm.D. (1972) and Ph.D. (1980) degrees from the University of California San Francisco. She was Postdoctoral Fellow and subsequently Cancer Research Scientist at Roswell Park Memorial Institute, until she joined the OSU Pharmacy faculty as Assistant Professor in 1983. Dr. Au was the first woman science faculty at the OSU Pharmacy College and became the first woman full professor in its history. She was co-director of several scientific programs, Director of Translational Research, and Deputy Director of the OSU Comprehensive Cancer Center. Dr. Au was honored with the Research Career Development Award (1990) and the Merit Award (1990) from the National Institutes of Health, the Distinguished Scholar Award (1992), the Dorothy M. Davis Chair (1992) and the Distinguished University Professorship (1998) from OSU, the AAPS Fellowship (1992), and the Swintosky Distinguished Lectureship (1997). Dr. Au has served on numerous NIH Committees, is on the Editorial Board of *Pharmaceutical Research*, and is scientific advisor to several academic cancer centers.



WHAT DO YOU THINK HOLDS THE KEY TO YOUR SUCCESS AS A PHARMACEUTICAL SCIENTIST?

Response: The most significant factors are: (a) curiosity and excitement about science, (b) upbringing and training that challenged me to do more than I thought I could, (c) willingness to enter new fields, learn and apply new methods as needed to solve research problems, (d) ability to integrate multiple disciplines in my work, (e) the good fortune of working with good pre- and post-doctoral students, and (f) a supportive family.

WHAT ARE THE TWO TO THREE ACHIEVEMENTS THAT YOU ARE MOST PROUD OF?

Response: One major achievement relates to my work in pharmacokinetics and pharmacodynamics (PK/PD) of cancer chemotherapy. I believe that my contribution here is two fold. The first is to extend the knowledge base in this area. The second is to develop cellular and molecular PK/PD as new fields of research in pharmaceutical sciences.

In cancer chemotherapy, as in other fields, PK and PD are important determinants of the treatment outcome, because tumor response to chemotherapy is affected by the delivery of the drug to its target molecules in tumor cells and the chemosensitivity of tumor cells. At the time we started our work, knowledge and development in cancer PK/PD were primarily on a systemic level. Since over 80% of human cancers are solid tumors, which are known to display regional heterogeneity in drug sensitivity, we felt that it is important to study whether tumor resistance is due to inadequate drug distribution to tumor cells or due to biochemical and/or genetic factors. In this area, a major focus of our work is on intravesical chemotherapy of superficial bladder cancer. By taking into account the spatial relationship of drug delivery and effect, we can examine the different response of tumor cells located in different regions of the tumor-bearing organ due to the differences in drug delivery. Using this research approach, we have determined that inadequate drug delivery is a major cause of treatment failure for bladder cancer patients treated with intravesical chemotherapy. We further determined that the response rate can be substantially increased by using pharmacokinetic interventions to improve drug delivery to tumor cells. This hypothesis is being tested, in collaboration with 15 academic centers in the U.S., Canada and Europe, in a randomized phase III trial. Confirmation of

[1] To whom correspondence should be addressed at Ohio State University, College of Pharmacy, 500 West 12th Avenue, Columbus, Ohio 43210. (e-mail: au.1@osu.edu)

0724-8741/98/1000-1503$15.00/0

our hypothesis will result in an improved treatment outcome in up to 20,000 patients per year. This is very gratifying, especially when considering that this treatment modality has been used for nearly 30 years with only limited success. Another exciting component of this trial is that we have collected tumor specimens to analyze for the expression of the two key enzymes that are responsible for the metabolic drug activation. By comparing the gene expression, the drug delivery and the treatment outcome, we can test the hypothesis that genetic variance is related to the treatment outcome. Confirmation of this hypothesis will enable us to customize drug selection based on genetic information in individual patients.

My other major achievement is a personal one, i.e. succeeding as a woman academic scientist in a male-dominated field, in a major research university. Overcoming the multiple woman-specific barriers and obstacles has been a major challenge. In my own experience as well as from conversation with other women, woman faculty, in addition to having to deal with challenges that are common to all academic scientists, also have to deal with gender-specific problems such as social expectations (e.g. woman's traditional role in the society, obligations as a mother/wife) and being a minority in the academic world. I hope that the achievement of myself and other woman scientists will send a positive signal to other female scientists that consider similar career paths.

WHAT WAS THE TURNING POINT IN YOUR DISTINGUISHED CAREER?

Response: The major strength in my work is the ability to transfer knowledge gained in laboratory research to clinical application. This requires expertise in research on both holistic and reductionist levels, which I acquired in the first half of my academic career. My graduate work focused on the clinical pharmacology of anticancer drugs. I then recognized that systemic pharmacokinetic data alone are not sufficient to determine the sensitivity and resistance of cancer cells to drug treatment, and that studies on a more micro level, i.e. cellular or molecular, are needed. I spent one year in postdoctoral training in biochemical pharmacology where I learned to use cultured cells to study drug effect. The next several years were spent on studying the link between systemic PK, cellular PK and cellular PD. The turning point came when I was able to use my expertise in these different areas (i.e. *in vitro, in vivo*, clinical, biochemical and molecular pharmacology) to forge ahead in translational research.

CAN YOU NAME THE TWO OR THREE INDIVIDUALS WHO HAVE MADE A DIFFERENCE IN YOUR CAREER? HOW SO?

Response: Many individuals have made a difference in my career. In my youth, I was impressed by scientists who have made discoveries that are important to mankind, which was the reason that I chose a scientific career. I was also fortunate to have some of the best pharmaceutical scientists as teachers. In more recent years, I have been inspired by the many outstanding scientists in our field that have advanced the discipline in major ways. The significant accomplishments of these individuals have set the benchmark for me to strive for excellence. On a more personal level, I credit two people, my former professor Wolfgang Sadée and my husband Guill Wientjes. As Guill's former professor Dr. Gerhard Levy says, these are the two most important choices of a scientist. Wolfgang is one of the most versatile scientists that I know; he had instilled in me the idea that science is without boundary. That partly explains my interdisciplinary approach to science. Guill, in addition to being a wonderful collaborator who knows kinetics better than most, has taught me the virtue of patience, which has been very helpful in some very difficult times.

PHARMACEUTICAL SCIENTISTS ARE FACED WITH THE DILEMMA OF HAVING TO PUBLISH IN BIOMEDICAL OR BASIC SCIENCE JOURNALS AND HAVING TO PRESENT IN THEIR SPECIALTY MEETINGS IN ADDITION TO THE PHARMACEUTICAL SCIENCES VENUES. DOES IT MEAN THAT CUTTING EDGE SCIENCE WILL NOT LIKELY BE FEATURED IN THE PHARMACEUTICAL SCIENCES FORUM?

Response: This is a very important issue. Without cutting edge research, science becomes technology. There is some truth in your supposition, although I think the reasons are more complex. One has to do with the applied nature of the pharmaceutical disciplines. Take for example the field of PK/PD. Industrial scientists represent a majority of the members in the AAPS. Their expertise and work, as dictated by the FDA, focuses on the more traditional aspects of PK/PD such as systemic PK and bioavailability issues. Cellular and molecular PK/PD, which I consider cutting edge science, are not popular topics in the AAPS meetings. This factor makes it less attractive and difficult to present this type of work at the AAPS meetings. In fact, I would like to see the AAPS leadership address this issue.

WHAT IS YOUR VIEW ON THE CURRENT STATE OF RESEARCH IN CANCER DRUG PHARMACOKINETICS AND PHARMACODYNAMICS?

Response: Most of the research in cancer drug pharmacokinetics are done by pharmaceutical scientists and clinical pharmacologists, and are the typical pharmacokinetic studies, e.g. plasma half-life and clearance. Most of the research on cancer drug pharmacodynamics are done by cancer pharmacologists, and focus on elucidating the mechanisms of drug sensitivity and resistance. Integrated pharmacokinetic and pharmacodynamic studies are rare, and represent under-developed research areas, and a tremendous opportunity for those who are interested and equipped.

WHAT ARE THE FUTURE CHALLENGES IN CANCER DRUG PHARMACOKINETICS AND PHARMACODYNAMICS?

Response: Future challenges in these areas are to bring together the two diverging fields, so that the plasma pharmacokinetics can be related to drug effect on cellular and molecular levels. There are exciting research areas waiting to be explored. Recent advances in molecular biology and genetics have opened up many avenues of research. Cancer pharmacologists, by nature of their training, usually are more qualitative than quantitative. Pharmaceutical scientists, with their quantitative orientation,

are uniquely qualified to move these fields forward. Another area that warrants attention is the kinetics of intracellular events. For example, many processes involved in apoptosis, a process that is important for multiple human diseases, have been identified. These processes are regulated by dynamic interaction between the protein products due to the expression of apoptotic and anti-apoptotic genes. Pharmacokinetics, by delineating the kinetics of these events using computational approaches, can identify the relative importance of the different interactions. To meet these challenges, the graduate curriculum needs to incorporate courses on molecular biology and genetics.

YOU ARE ONE OF THE LEADERS IN TRANSLATIONAL RESEARCH. WHAT IS TRANSLATIONAL RESEARCH AND HOW CAN ONE BE TRAINED FOR IT?

Response: Translational research is loosely defined as translating laboratory findings to clinical application and *vice versa*. An example for the former is the development of a drug or formulation in order to apply it for human use. An example for the latter is to take a clinical observation to develop laboratory studies. For example, based on the clinical observation that metastatic cancer is more resistant to drugs compared to primary cancer, we have designed studies to examine the mechanisms of resistance of metastatic tumors, and use this information to develop novel therapeutic strategies. One is best prepared for translational research by having both clinical and basic science training, by having collaborators in both fields, and most importantly by having an open mind, ears and eyes. Pharmaceutical scientists, because of their orientation to applied research, are born translational researchers.

AS YOUR RESEARCH IS TAKING ON INCREASINGLY MOLECULAR AND CELLULAR THRUSTS, ARE YOU CONCERNED THAT OVER TIME, THERE WILL BE NO ONE TRAINED IN THE TENETS OF CLASSICAL PHARMACOKINETICS AND PHARMACODYNAMICS?

Response: This is a complex issue. Classical pharmacokinetics are very much needed for advancing the goals of pharmaceutical industry, and are necessary training for students in pharmaceutics graduate programs. On the other hand, pharmacokinetics alone usually cannot solve the research problems, which have become increasingly molecular in nature and therefore must be addressed by molecular research approaches. This is particularly true for academic scientists such as myself whose research and graduate student funding is from the National Institutes of Health, where cutting edge research is mandated. From the student's development as a modern day scientist, he and she also need to pursue cellular and molecular research, in addition to learning classical pharmacokinetics. I am concerned that over time, neither the academicians nor the students can afford to be trained as a classical pharmacokineticist. I would like to see academic and industrial leadership to begin to address this issue. One possible solution would be to establish a Pharmaceutical Technology Institute, funded by the industry and staffed by academic scientists, where students are taught the necessary technologies for advancing the goals of the industry.

YOU ARE EXTREMELY WELL FUNDED. WHAT HAS CONTRIBUTED TO YOUR SUCCESS IN THIS ARENA?

Response: Several factors have contributed to our good fortune. First, our research approach of using mathematics and biology to solve problems related to cancer chemotherapy distinguish us from most cancer pharmacologists. Second, we have selected projects that are likely to have high significance (e.g. clinical implications, opening up new fields) and/or have longevity. The other factors relate to grantmanship, such as (a) provide sufficient preliminary data to convince the reviewers that we can accomplish the tasks, (b) able to convey the excitement of the research to the reviewers, and (c) able to anticipate questions and skepticism from the reviewers and address the potential concerns up-front. Lastly, it has been tremendously helpful that I have served on NIH Study Sections, which enable me to think like a reviewer.

DO YOU FEEL THAT WE ALL HAVE AN OBLIGATION TO BE A VOLUNTEER IN SCIENTIFIC ORGANIZATIONS? IF SO, WHY?

Response: Yes, I think we do need to volunteer, either in a scientific organization, or in other parts of the scientific community. It is simply part of good citizenship.

WHAT WOULD BE YOUR ADVICE TO OUR FEMALE PHARMACEUTICAL SCIENTISTS WHO ARE ABOUT TO EMBARK ON THEIR CAREERS?

Response: My first advice is to choose the right academic mentor and a supportive spouse. Second, it is important to identify and obtain support from a mentor (male or female) who understands the unique issues woman scientists have to deal with. Third, do not give up, do good and good things will happen.

WHAT WOULD BE YOUR ADVICE TO OUR JUNIOR PHARMACEUTICAL SCIENTISTS WHO ARE ABOUT TO EMBARK ON THEIR CAREERS?

Response: The next decade should be a very exciting time for pharmaceutical scientists. There are unprecedented opportunities waiting to be explored. Furthermore, the NIH has increased its funding of research grants, which should give a boost to research activity. My general advice is to stay excited, learn and enjoy science, and stretch when things seem out of reach. My further advice is as stated above for woman scientists.

WHAT WOULD BE YOUR ADVICE TO OUR SENIOR PHARMACEUTICAL SCIENTISTS IN THEIR RELATIONSHIP TO THEIR JUNIOR COLLEAGUES?

Response: I believe that an important role of senior scientists is to mentor junior and developing colleagues. This includes (a) guiding them through processes that are critical to their development, such as establishing strong research programs, teaching skills, obtaining funding, and achieving tenure, (b) serving as a role model and demanding excellence, and (c) providing a nurturing environment so that they can succeed.

WHAT ARE THE FUTURE CHALLENGES TO THE PHARMACEUTICAL SCIENCES?

Response: A major challenge is to remain as an identifiable scientific discipline, as opposed to being a technology-driven discipline. A solution to this challenge is to continue to explore cutting edge research areas. For drug delivery, this includes fields such as gene therapy and drug transport on a cellular level. For biopharmaceutics, this requires a broadening from classical PK/PD to quantitative biological sciences, to include some of the emerging fields such as the kinetics of intracellular events and regulatory mechanisms. In all this, we should maintain the unique quantitative orientation of our research approach and graduate training. We should preserve our identity, i.e. an applied science, but yet stay competitive.

WHAT IS THE PLACE FOR ENTREPRENEURSHIP IN ACADEMIA?

Response: Entrepreneurship has some value in academia. Entrepreneurial efforts have led to major advances in sciences and technologies in general and US economy is particular. This is in part because our society is driven by entrepreneurship, and in part because scientists are driven by the desire of making significant discoveries. However, I do see potential conflicts between entrepreneurship and academic missions. The risks of entrepreneurship include restricted publications for graduate students which interfere with their training and dilution of academic pursuits for faculty. My thinking is that entrepreneurship should be permitted with restraint and appropriate level of institutional oversights.

HOW HAS YOUR PHILOSOPHY OF EDUCATING GRADUATE STUDENTS BEEN CHANGED OVER THE YEARS?

Response: My philosophy in training graduate students has not changed fundamentally over the years. In my opinion, students are best helped by being asked to do more than they think they can do, learn that science has no boundary, learn to identify significant research problem and design appropriate experiments, pay attention to details, learn to be critical of their results, learn to communicate their results verbally and in writing, and acquire the level of confidence that is appropriate for their accomplishments and ability.