Dr. Tsung-Ping Su Oral History

September 19, 2022

Shirko: Good afternoon. Today is September 19, 2022. My name is Matt Shirko, and I'm a contractor with the Office of NIH History and Stetten Museum. Today I have the pleasure of speaking with Dr. Tsung-Ping Su. Dr. Su is the chief of the Cellular Pathobiology Section of the Integrative Neuroscience Research Branch, which is part of the National Institute on Drug Abuse (NIDA). Thank you very much for being with me.

Su: My pleasure!

Shirko: To get started, could you tell us a little bit about your background, including where you were born and grew up, your family life, and any formative experiences you might have had?

Su: Yes. I came from an immigrant family that is from Taiwan. My parents immigrated into China from Taiwan in their youth and stayed there for many, many years. I was born in China, and then when I was two years old, my family decided to go back to Taiwan because Chairman Mao Zedong had taken over China. My parents decided not to stay in China. I grew up in a very small town in Taiwan. That small town is now the focus of the whole world when it comes to computer chips. The Taiwan Semiconductor Manufacturing Company Limited produces about 53% of the world's supply of computer chips. They are building two nanometers—the most advanced—computer chips in my hometown. I grew up in the small hometown south of Taiwan and went to high school there, then university in the northern capital city. After graduation from National Taiwan University, I finished the mandatory one-year military service and then came to the State University of New York (SUNY) at Buffalo. I studied biochemistry there and then finished my Ph.D. in the School of Medicine at SUNY Buffalo in 1975.

Shirko: What led to your interest in substance use disorders?

Su: After I got my Ph.D. in biochemistry, a friend of mine suggested to me that chemistry was good, but pharmacology is more practical to society. He suggested that I apply for my postdoc in pharmacology. Most of the interest in pharmacology when I graduated in 1975 was on the opioid receptor. There is an endogenous protein in the brain that may mimic the action of morphine, so that was a huge competition and a very "hot" area. I applied to Stanford's pharmacology chairperson, a professor named Avram

Goldstein. I did my postdoc there and then I started learning how morphine and the opioid receptor works in the brain.

Shirko: How did you end up at NIH?

Su: After two and a half years of training, it's time to move on. This is typical of postdoc training. My professors suggested it was time for me to go to the next step of my experience and that I should write to Dr. William Martin. He was director of NIDA's intramural program by then. He had just hypothesized the three different types of opioid receptors in the brain. I wrote Dr. Martin a letter, and he said yes. So, I joined NIH and NIDA's Addiction Research Center in 1978. I drove from Palo Alto at Stanford University all the way to Kentucky and joined Dr. Martin's laboratory in January 1978.

Shirko: What are some of the roles and responsibilities that you've had over the years at NIH?

Su: I started working on the opioid action in the brain and trying to understand opioid signaling, basically trying to expand the knowledge in the research area. Actually, before I left Stanford, Dr. Avram Goldstein, my mentor, told me that he had demonstrated a new opioid receptor in the brain, which he published in 1971 in PNAS [The Proceedings of the National Academy of Sciences of the United States of America]. He said Dr. Martin suggested that maybe there are three types of opioid receptors—mu opioid receptors, kappa opioid receptors, and sigma opiate receptors. He suggested I study the sigma opiate receptors when I joined Dr. Martin's lab. I thought that was very interesting. That's how we started the study of sigma receptors.

Shirko: You're the chief of the Cellular Pathobiology Section. Can you talk about what specifically that section does and what your role as chief entails?

Su: Basically, we try to solve the problems of drug addiction. That's where we started. The sigma receptor was considered a drug-related receptor, so my section's overall goal was to try to understand and expand the knowledge of the so-called sigma receptor. Is it related to addiction? Is it related to the action of morphine or cocaine or some other things? That is still our fundamental goal, even nowadays.

Shirko: How do you prioritize what kind of studies to get involved with? Is it determined based on specific disorders or types of substances or substance abuse, or do you just follow wherever the science may take you? How do you determine those priorities?

Su: That's a very good question. Although we are focusing on solving the health problems of America—specifically the addiction problem in America—and trying to disseminate out findings to the American people, with basic science sometimes we are working on something we really cannot predict. If we can predict it, there's not much point to what you're doing, is there? You hypothesize to some extent, and then you see what the data is telling you. That is so-called fundamental basic science. This fundamental basic science often leads to very unexpected things—epitomizing the mission of NIH by "solving" diseases. But disease solving is not something easy. It needs a very strong fundamental knowledge of the basic cellular molecular understanding, in order to solve the big problem of human health and brain disease and addiction. Otherwise, it's very difficult. So, in other words, the fundamental principles may not be realized before what you're doing, and you have no previous knowledge at all. You're trying to come up with something. That is a fundamental mission of our agency, to differentiate it from others—say, a university's mission. NIH is encouraged to ask some non-targeted questions and that's almost exactly what I did in the beginning in search of the so-called sigma receptor. My section is expanding our basic understanding of this protein action over the years to many, many different diseases—including addiction.

Shirko: In 2020, you published a study on endocannabinoids' role in cocaine addiction. Can you give us some background on what endocannabinoids are and what their role is in terms of cocaine addiction and possibly other substance use disorders?

Su: Yeah. Marijuana has many psychoactive components and one of the major components is cannabinoids. The cannabinoid structure is very interesting because it's highly lipid soluble. In 1970, the endogenous protein mimicking the action of morphine was hypothesized and was pursued. Almost around that time, maybe ten years later, a woman scientist in Eastern Kentucky University hypothesized that maybe there is an endogenous protein or substance that is working. She hypothesized that in the brain there may be a receptor for cannabinoids. Cannabinoid is from the marijuana plant. On top of that, people began to realize the story of the endogenous protein in the brain that mimic morphine. Could there also be in the brain an endogenous compound mimicking the action of cannabinoids? They call it an endogenous cannabinoid. That's what it is. Endogenous cannabinoid is not a cannabinoid but is structurally similar. They found it, they purified it, and they found that, yes—there is endogenous compound in the brain that mimics the action of cannabinoid on the brain's cannabinoid receptor. They call it endocannabinoid. This endocannabinoid is very lipid-like. They don't exist in a water environment—they cannot. My question was why? Why am I interested in this endocannabinoid's very lipid compound? There is a fundamental problem in the signaling mechanism action of endocannabinoid in the brain. This endocannabinoid is called 2-AG. The fundamental understanding is 2-AG can be secreted from the brain neuron into another neuron in a reverse direction and then work on that upstream neuron to cause a secondary release of another neurotransmitter to again go back to the original neuron that is sending the 2-AG up. We have B and A. and first of all B is secreting 2-AG to A and then A is sending another signal to B. It's called a "cell feedback." This 2-AG, in order to translocate from B to A, is in an all-water environment—a majority of the brain is a water environment—so how can a lipid travel from B to A through this ocean of water? That is a fundamental question that existed in the endocannabinoid research area, and nobody has an answer. The idea from myself was the sigma

receptor is a very interesting protein. It can exist in a lot of places and maybe it can exist also in a vesicular form—in a physical form. That physical form can be secreted, including the endocannabinoid 2-AG in it, and then translocate in this extracellular vesicle into the A neuron, therefore carrying the 2-AG in this extracellular vesicle to A, and then merge into the membrane of A and that may be the action. That was a hypothesis, and we prove it in this publication you just mentioned.

Shirko: You've looked at the sigma-1 receptor's role in some other disorders, including dementia and schizophrenia. Are there any other disorders that this could potentially play a role in and are the mechanisms any different?

Su: The action of sigma-1 receptor is it can maintain the client protein—it's called a "chaperone." It has a client protein. For the client protein, functional conformation—the three-dimensional conformation—rely on sigma-1 receptor. Sigma-1 receptor's major role is to chaperone the client protein in its correct conformation to perform its action. Receptors, ion channels—the sigma-1 receptor can protect them and can maintain them in the right conformation. That's the first action of sigma-1 receptor. Secondly, sigma-1 receptor action can be regulated by ligand, by drugs, or by compound. The compound can enhance this chaperoning activity of sigma-1 receptor to perform its chaperoning function on the clients in a negative and positive way. That is a fundamental action of sigma-1 receptor. The second point of sigma-1 receptor is it can translocate upon stress or some drug stimulation. It can translocate from its original place to the place where it can meet the client and the client needs help. That's what the fundamental action is. Now back to the central point of the action of the sigma-1 receptor. Sigma-1 receptors are originally existing somewhere, but it can translocate to the nuclear membrane. Nucleus has a membrane and in that nuclear membrane there are holes allowing proteins to come in or come out through the tunnel to exchange the material—very important genetic information or gene control—through cytosol into the nucleus. This is where one of the most important actions of sigma-1 receptor is at this moment. This interesting location of sigma-1 receptor at the nuclear core serves to regulate material changes between cytosol and nuclear. If you look at the Nature Reviews recently, just a couple years ago, the title of that review is "Gateway to Neurodegeneration: Nuclear Core." In other words, this nuclear core is serving very interesting role in many neurodegenerative diseases, including dementia, including Lou Gehrig's disease, muscle dysregulation, Huntington disease, and also Alzheimer's. Those are the major three neurodegenerative disease that are currently under investigation from the point of view of the sigma-1 receptors. This nuclear core localization and action of sigma-1 receptor also related interestingly to the action of cocaine. We published three papers on this action of sigma-1 receptor in terms of cocaine and the drug abuse area so there again is back to the basic side. Originally, I did not know what the function of sigma-1 receptor is, although my boss at Stanford told me to do that research, but I did not know what happened. But now we have an interesting picture here. Sigma-1 receptor plays a very interesting and pivotal role. It can affect not only drugs of abuse, but also neurodegenerative diseases.

Shirko: I wanted to ask specifically about the sigma-1 receptors and their role in depression as they relate to antidepressants. There were some studies that evaluated the role of the current

antidepressants and how maybe the sigma-1 receptors could make some differences here. Could you talk about that?

Su: There are animal studies which suggest the sigma-1 receptor is involved in depression. Agonists can reverse the depressive symptoms in rat behavior. The major discovery was from the fact that some of the main antidepressant drugs have affinities for the so-called 5-HT2 receptors. That's okay; that's a major action of Prozac. But lo and behold, those famous antidepressants, some of them have higher affinity at sigma-1 receptors than at the 5-HT2 receptors. This was discovered by the Japanese group, and so people began to wonder whether the sigma-1 receptor drug agonists can be an antidepressant or not. They are starting—the publications are coming out. Further, on a second note, the most famous anti-depressant right now is ketamine, the child anesthesia agent. But now the great notion over the past five or ten years is that low doses of ketamine can be used as an antidepressant. It's in use in a clinical setting now. Ketamine's mode of action is still not clear. We still don't know the major molecular target of ketamine when it enters into the cell and into the neurons or what the ketamine is binding through to work on depression. We still don't know, even though it was published in Nature etc. But we still don't know the molecular target of what ketamine is doing. There is a paper published by a famous professor at the California Institute of Technology (CIT) that showed that after entering the neuron, ketamine can find some specific target—including sigma-1 receptors. Even more interesting is the big news in antidepressants now—the psychedelic drug called psilocybin, the "magic mushroom" component used ritually by the Brazilian aborigines. Hopkins University—Dr. Roland Griffiths, right next door [to NIDA in Baltimore]—showed that in humans it can be an antidepressant. The structure is just a phosphoric acid adduct to another structurally similar compound called N,N-dimethyltryptamine, a trace amine active in the brain. This trace amine in the brain has been shown by the University of Wisconsin group to bind to sigma-1 receptors, so this psilocybin may bind to sigma-1 receptors, defining whether it's the main reason for its antidepressant qualities. Psilocybin has been in clinical trials for antidepressants. I even saw on Twitter yesterday that it can work against alcohol withdrawal as well. People are crazy about using this psilocybin and trace amine analog with additional modifications to see whether it can work or not. It's potentially highly possible that it may bind to sigma-1 receptors, but we don't know yet. What I mean is that, yes, sigma-1 receptor's relation to depression is a very intriguing question.

Shirko: It sounds like your research takes you different places beyond just substance abuse. Are there any other sort of studies that you're involved in that maybe are exploring some of these non-addictive processes—neurological issues, psychiatric disorders, etc.?

Su: Beyond the substance abuse area of research mainly it's on the neurodegenerative diseases and also mental health—depression as we have mentioned. Those are the major things right now. Although, sigma-1 receptors exist in the liver. What its action is on the liver is still unclear. There was only one paper published about twenty years ago. The sigma-1 receptor in the liver is important for the survival of the hepatic cell—a little cell. That was the only one. Sigma-1 receptor actually exists not only in the brain and in the liver, as I mentioned, but also in the cardiomyocyte in the heart. It also exists in the

adrenal glands. The adrenal glands are very important when facing the stress response. We need the adrenal glands and we need to suppress the release of corticosteroids through adrenal glands in order to be able to either flight or escape. The sigma-1 receptor is also in the pineal gland, for example, and the pancreatic gland as well. It's not only in the brain but also in other tissues. We still don't know why they are there. Beyond the neurological disorders, there's the heart—there are many publications on the sigma-1 receptors playing a very important role in the survival of the cardiomyocyte—in the cardiac heart diseases. Last year we had a collaboration with King's College of London. There's a collaborative publication with us showing that the location where sigma-1 receptor is is critical to the survival of myocardial—the heart. So that's very interesting, beyond the neurological diseases and drug abuse.

Shirko: Changing focus a little bit to your lab and your work during the COVID-19 era. How did the pandemic impact your work? Was anything paused or did anything change focus?

Su: That's very interesting—the impact of the COVID-19 pandemic. Actually, it's affected the progress of one of my most important projects right now. Beyond the neurological disorders and neurodegenerative diseases, on the back burner all the time is drug abuse. We have a study on cocaine, a study on morphine, and a study on methamphetamines. Those are the three major topics that I'm asking questions on. How can we contribute to understanding the action of sigma-1 receptor on those drug abuse issues? Let's talk about cocaine. We have a project that was largely affected and slowed down by COVID-19. In this particular study, we need rats with a specific bodyweight. We need them to be consistent with our previous data. But the rats couldn't be shipped in enough numbers. COVID-19 has largely slowed down the speed of the specific project and my poor fellow has been waiting and waiting. Unfortunately, I don't know whether she can finish this project or not. It's a very important project. Cocaine use can cause a major problem. As we struggle from cocaine, people lose their ability to judge. They become compulsive. They just don't care. They just want something, and they want it regardless of whether it's good or bad—it doesn't matter. It's a typical disruption—it's seen in the cocaine addicts after their withdrawal. We found in the behavior model and also the electrophysiological model, that the sigma-1 receptor antagonist can block this disruptive action of cocaine. It can normalize it. So, if you treat with sigma-1 receptor antagonists those rats that are doing cocaine, after withdrawal those rats will not be compulsive anymore. COVID-19 has slowed us down, so therefore we have not reached the scientifically important statistical level. We are at the critical point to reach the statistically significant level of these behavior changes, and we are trying to finish this project. That is a very terrible thing, but on the other hand, we kept the other projects going because it does not involve animal behavior, so that was not really as miserable as this one particular project. To answer your question, yes, COVID does negatively impact my projects.

Shirko: Is there any kind of movement within NIDA to evaluate how some of these substance use disorders may have changed or increased during the pandemic? You sometimes hear that drinking or drug use increased as a result of the economic and sociological changes during the pandemic.

Su: The NIDA Headquarters may have answer for this specific question. My project does not involve the effect of sigma-1 receptors on COVID-19 directly or indirectly, although it was published in Nature that sigma-1 receptor is involved in the survival of COVID-19. It was big news, even in the abstract. It was done by the University of California San Francisco group. They were proposing the sigma-1 receptor antagonists may be used to fight against the COVID-19 virus' survival inside the cell, but then they found that it may not be a correct mechanism, so they sort of quieted down later. I know there are some other laboratories working on the sigma-1 receptor in terms of its regulation on the virus messenger RNA [ribonucleic acid]—those viruses are RNA viruses, so sigma-1 receptors may relate to this RNA. This is an interesting scientific point. Sigma-1 receptor is a protein. It can bind to other proteins. It can also bind to RNA. We published that in Nature Communications in 2021. I thought sigma-1 receptor protein itself may bind RNA. It may bind to the COVID-19 virus' RNA as well. It may sequester the activity of the viral RNA to block them from replication. That was just a hypothesis. I did not go into that detail to prove that possibility, but it remained a potential possibility. I wasn't expecting that.

Shirko: Is there anything additional about your work that you'd like to talk about or mention for the record? Any forthcoming projects or studies?

Su: My main mission at NIH is related to drug abuse, there's no doubt. I published only two major papers on neural degeneration. One is in Nature Communication showing the sigma-1 receptor binds the RNA and that RNA causes Lou Gehrig's disease. Another one is just recently published in Autophagy. Autophagy means "self-eating" when cells are under stress. They begin to use their own body to survive—they eat part of their body to survive. It's called "autophagy." "Phagy" means eat, "auto" means "self"—so "cell eating process." In neurons, this is a very important process. Alzheimer's disease, Huntington's disease, Parkinson's disease, Lou Gehrig's disease—they all show impairment in autophagy. This impairment in autophagy is a major issue in neurodegenerative diseases. Sigma-1 receptor agonists can reverse that process. This is one focus, but that's not my main mission at the NIH. My main mission is to understand basic science. That's what differentiates NIH from extramural research. We can focus on non-targeted, very basic science and we don't have to worry about the grant review processes. That's what epitomizes the NIH research. Meanwhile, while we're doing that, I never lost my primary mission related to drug abuse. In my laboratory, one of the important projects is to see the impact on the baby when the mother was using morphine. When they are born, they were withdrawing from morphine. They call it neonatal abstinence syndrome. Currently there is no drug. NIDA has been trying to solve that problem. The newborn baby is experiencing morphine withdrawal—hyperactivity, painful neuronal excitation, etc. We still don't have a drug for that. My laboratory has data showing that, in rats, if you give them the sigma-1 receptor antagonist, this terrible withdrawal syndrome in babies is gone. The baby will not have overexcitability in their neurons and behaviorally they act normal. Further, in sigma-1 receptors knockout mice they don't have this neonatal opioid withdrawal. We have found that sigma-1 receptor plays a very important role in the morphine abstinence syndrome in the newborn babies. We're still working on that. Another project is also related to opioids. When adults are using morphine for a long time, they begin to develop a very low threshold for pain. They are hypersensitive to pain stimulation. We call it opioid-induced hyper pain, or in scientific terms, opioid induced hyperalgesia. Hyperalgesias are terrible for anyone who has to take morphine for

medical reasons. We found that in a mouse that has no sigma-1 receptor, they don't have this morphine induced hyperalgesia. In other words, this is a fascinating discovery, and we are working on the mechanism. Without a mechanism, we cannot publish it. We need to know why. That's what we are working on. And cocaine, of course. We are working on the decision making. We are also working on the initial single dose of cocaine. The neurological changes upon that first dose of cocaine are very important because it causes the subsequent later neuronal changes in the reward area—the nucleus accumbens. This gate control action of cocaine is fascinating. We are working on that. We found that without sigma-1 receptors, there's no problem. Cocaine does not cause a terrible effect on these neuronal changes. In other words, sigma-1 receptor is working against opioids but is "hijacked" by cocaine. We are looking forward to finishing those projects.

Shirko: Sounds like some pretty interesting and important work that you're doing and I'm curious to hear how things turn out as you move along. Thank you for sharing all of this with us and explaining a little bit about what you do.

Su: My great pleasure. I hope, with the Lord's blessing, that this will come out to be beneficial to the American people and to the world. That's our sincere hope as NIH researchers—that's our basic mission. We hope, with the Lord's help, we can help the American people through this fantastic research environment of intramural research at NIH. People are asking me why I do research at NIH. I'm going to quote our previous NIDA director, the great Dr. William Martin, who hypothesized the multiple opiate receptors—mu, kappa, sigma. When I was working with him in Lexington, Kentucky at the original location of NIDA intramural, I said "Dr. Martin, you are retiring from the NIH and you're going to University of Kentucky as a chairperson. Can I join you as an assistant professor or something?" He said, "Dr. Su, you know what? Don't. You don't know that you are in the heaven of research." And he was correct. So, I enjoy NIH very much because it's a heaven for research!