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INTERVIEW

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Applications of Traditional Chinese Medicine in Antiviral and Anticancer Drug Development

An Interview with Dr. Yung-Chi (Tommy) Cheng, PhD

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You studied chemistry in Taiwan and then went into a PhD in biochemical pharmacology at Brown University. Can you tell us about how you first became interested in these fields?

I was always interested in chemistry and the biological aspects of chemistry, so my undergraduate major was actually a double major in chemistry and biology. So, when I was deciding what to do after my undergraduate training, I decided to go abroad and applied to universities in Canada. I was at the University of Guelph for one year. My wife was studying at Brown University, so I reapplied to Brown, but they didn't really have a biochemistry department, so I needed to decide what specific specialty of biochemistry I was interested in. I chose to focus on biochemical pharmacology. At the time, they had all graduate students regardless of if you were applying to a PhD or MD program to receive basic medical training. If you were applying to a PhD program, they wanted to train you as an MD-PhD and so I finished the first 2 years of basic training in medicine and then finished my PhD training. That gave me a foundation in medical knowledge.

You then came to Yale for your postdoctoral work and have said this was because pharmacologist William Prusoff was here. What about Professor Prusoff inspired you to come to Yale?

During that period, there was a course offered at Brown University that invited several pharmacology professors from other campuses to teach. Among those was Professor Prusoff who was an expert in antiviral and cancer research. He synthesized the first antiviral drug for the herpes simplex virus (HSV) and I was interested in that subject, so I decided to do my postdoc with him at Yale. I came over after receiving my PhD degree and that was the first time I was exposed to virology. Through bioassays, we identified a nucleoside analog that was highly selective against HSV-1 and then the question was how could this compound have such selectivity? Because before that time, nobody believed that you could come up with an antiviral compound without toxicities since viruses require host proteins to proliferate and replicate.

You have had such a fruitful career thus far, for example, with your research in antivirals and cancer treatment. Can you tell us a bit more about these?

During this time, the pharmaceutical company Burroughs Wellcome (BW), identified a nucleoside analog called Acyclovir. They also didn't know why it was so selective. So, after my post doc training, I decided to take an assistant professor job at the Roswell Park Memorial Institute in Buffalo, NY to work on the underlying mechanisms of antiviral compounds. The paradigm at the time

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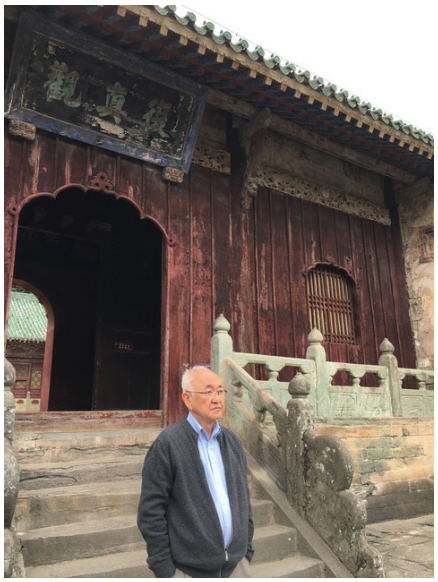
was that there were no selective antivirals, but here were two cases of highly selective antivirals and so the paradigm had to be readdressed. What could be the underlying mechanisms of this selectivity? My work evolved the field and the current suggested use of the viral enzymes by those selective antiviral nucleoside analogs to have selectivity against the virus. This "alternative substrate approach" to develop selective antivirals was proposed. The viral protein identified was thymidine kinase (TK) and it turned out that HSV and other members of the herpes virus family could all induce viral thymidine kinase (TK). The host cells also have TK, but cannot utilize these antiviral nucleosides efficiently, so that's where the selectivity comes in. BW heard about this and examined their guanosine analog; Acyclovir, it turned out, was also utilizing this enzyme to get into viral DNA.

I stayed at Buffalo for 4½ years where I moved very quickly through the academic ladder to become a full professor and then moved to UNC Chapel Hill where I stayed for the next 10 years to lead their cancer therapeutics program and continue my research in anticancer and antiviral treatments. In the 1980s, I consulted for a company called Syntex, which was subsequently bought by Roche, that made an analog structurally similar to Acyclovir. Of the herpes virus family, this analog seemed to have no activity in Cytomegalovirus (CMV) in their studies, but I was not convinced it was inactive, so in collaboration with a colleague, Professor E. S. Huang, at UNC Chapel Hill, we found that it was actually the *most* active anti-CMV drug due to CMV-specified TK. However, CMV didn't have much of a market, mostly pregnant women and their children as well as immunosuppressed patients had CMV health issues. Nonetheless, we wanted to help these patients and thus did not pursue a patent of this discovery. Instead, we gave this discovery to Syntex with the promise that they would develop the drug, even if it was an orphan drug at the time. In the early 1980s, Ganciclovir as an anti-CMV drug, was developed. Then in the mid-1980s, HIV started becoming a major issue and at that time there was no effective treatment and many patients were immunosuppressed. CMV related diseases are a major cause of death in these patients. Thus, the market opened up and Ganciclovir became a very profitable drug which Syntex was very happy about. We felt good since our discovery was helping patients.

In the meantime, on the anticancer side of things, I was using a target-oriented approach similar to that of my antiviral work. There were a few nucleoside analogs and natural product derivatives discovered with therapeutic activity in cell culture and *in vivo*, but none of them acted as selectively as I would have liked for anticancer drugs. In the meantime, there were several chemicals shown to have potency against HIV in cell cultures, and those were all nucleoside analogs, so toxicities were expected



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in proliferating tissues. When those analogs developed as HIV drugs and were used in clinic, there were no acute toxicities seen in proliferating tissue at clinically relevant dosage, but they did have delayed toxicities in non-proliferating tissues upon long-term usage. The National Cancer Institute thus asked me, as a leader in nucleoside analog development, to look into why this was the case. One of my graduate students, Norman Chen, found that the delayed toxicities were due to their action on mitochondrial DNA. This led the FDA to test for impact of chemicals on mitochondrial DNA and mitochondrial function as part of toxicity screening for any long-term use drugs. I then wanted to see if I could come up with a drug that goes after viral DNA only and not after nuclear or mitochondrial DNA. At the time, no one really believed in this, but then there was a company, Biochemical Pharmaceutical Company, in Canada who had made a nucleoside analog with equivalent antiviral activity to those used in clinic. But they had difficulty showing its superiority over the HIV nucleoside analogs used at the time. I worked with them to test this drug in a cell culture system against mitochondria and it turned out that in our system it didn't show much anti-mitochondrial activity as other anti-HIV nucleoside analogs. This suggested that this nucleoside analog may not have the delayed toxicity seen in other anti-HIV drugs at the time. They were very excited and quickly the company was bought by GSK to develop this compound as the HIV drug, lamivudine, which has much less delayed toxicity than first generation anti-HIV nucleoside drugs.

I was also interested in the Hepatitis B virus (HBV) which is very prevalent in Asians and is associated with

liver cancer. I gave a lecture at New York University; to give you an idea of the academic atmosphere at the time, Professor George Acs approached me and told me he had just developed an HBV cell line. We had no patent issues and no data transfer agreements, he just gave me the cells he had, and we started testing. At that time, although HBV was a serious problem, not much attention was paid to it in the US. It was likely not a major health issue from a population perspective since it was more so associated with Chinese descendants. We discovered the first anti-HBV drug, L(-)SddC (lamivudine), and it turns out that it was the same drug studied by us for mitochondrial toxicity for HIV discovered by Biochemical Pharmaceutical Company. Chemically, this was a new class of chemicals. L-nucleosides, which were not expected to be active, we discovered potent HBV activity and others discovered HIV activity. Several other L-nucleoside analogs were also discovered subsequently and developed as drugs. Then hepatitis C virus (HCV) came into play. My former Yale colleague, Dr. Andrew D. Hamilton, current President of NYU and previous Vice-Chancellor of the University of Oxford, reached out to me to collaborate on the activity of the compounds he synthesized against HIV and HCV. He had the idea not to inhibit enzyme activity directly, but to inhibit protein-protein interactions of the enzyme to disrupt activity. His student, Kelvin Chou, synthesized two classes of compounds: it turned out one class was very good for HIV and another class was very good for HCV. Thus, we came up with a new concept in designing antibiological compounds by interrupting protein-protein interactions. I want to encourage students – it is important to think outside of the box.

You've also based some of your work in traditional Chinese medicine (TCM), such as with PHY906. Can you tell us more about this and how you first become interested in TCM?

Based on the heterogeneity of tumor cells, I started to wonder that the treatment of cancer should include not just the tumor cells, but the microenvironment of the tumor and the whole body of cancer patients. This eventually led me to think about Chinese medicine because it evolved through human experience and has been used in the treatment of many diseases even today. Modern drug discovery methods did not take advantage of and even ignored these experience-based medicines. Unlike other traditional medicines, TCM is still a large part of medical care in China and many Asian countries. It is not seen as "alternative" medicine in countries which have more people taking herbal medicines than "Western" medicines, particularly for disease or symptom prevention or treatment. It often has multiple claims due to its poly-chemical nature. In my lab, to improve the current therapeutics of drugs, we take the approach either to increase anti-tumor activity or to decrease toxicity or side effects associated with the usage of antitumor drugs. To explore the potential of TCM, initially, I tried to deal with their potential on the relief of side effects of therapeutic drugs. If I could improve chemotherapy by decreasing their side effects, then I could help patients in terms of quality of life and potentially help to increase the dosage of chemotherapy without the associated side effects. At that time, I was interested in a drug called irinotecan used for treatment of colon cancer. The major side effects were GI-related, so I decided to explore decreasing this drug side effect by using TCM. Long story short, together with Dr. Shwu-Huey Liu and Zaoli Jiang in the lab, we found a formula which was written over 1800 years ago and still in use today, "huang qin tang," that may have this potential due to its claim for treating diarrhea, nausea, and vomiting. In mice, this formula did not compromise the anti-cancer activities of irinotecan – it actually enhanced it and also decreased irinotecan GI toxicity. The mechanisms underlying this protective GI effect related to anti-inflammation and promotion of stem cell growth to help repair damaged colon tissue. Interestingly, for the enhancement of anti-cancer activity of irinotecan, this formula enhanced the inflammation in the microenvironment of tumors triggered by dead cells by attracting more monocytes to differentiate to type-1 macrophages. This observation, followed with subsequent studies, suggested that this TCM formula could be used with other chemotherapy drugs, radiation, or immunotherapy regimen as long as these treatments triggered dead tumor cells in the tumor microenvironment. A potentially broad-spectrum anticancer adjuvant, PHY906, was thus evolved.

Can you talk about your experiences with the intersection between TCM and Western medicine?

One argument against the value of TCM is the inconsistency of preparation and lack of evidence claim. It is correct that if you don't have consistent preparation, you cannot expect to have reproducible pre-clinical or clinical results. The TCM formula we focused on consisted of four herbs, in which if you took any one of them out, it was not as effective. For this formula to be used for preclinical and clinical studies, we decided to make consistent preparations by controlling the source of the herbs and making the final product under CGMP standard operating procedures. For the past 16 years, we made six preparations and demonstrated we can make consistent preparations. Our product is based on "huang qin tang" which is also made by other companies but using different sources of herbs and processing techniques. To differentiate our preparation from others, we specifically called ours PHY or YIV 906. We purchased "huang qin

tang" from other vendors on the market and tested their properties. They all behaved differently and couldn't do the job as effectively as PHY906 had *in vivo*. We have completed six Phase 1 and Phase 2 studies in the US and now we are doing a randomized multi-center international clinical trial with a target population of HBV associated hepatocellular carcinoma (HCC), which is the major type of liver cancer in Asia. In order to develop PHY906 as a drug, we formed a company called Yiviva, in which Yale is a co-founder. So Yiviva is going to handle the logistics to run a clinical trial which I can't do as a Yale professor – industry needs to come in and take over the development.

For the current COVID-19 pandemic, no matter if you believe in the effectiveness of Chinese medicine or not, China is able to get infections under control using herbal medicine. Many of the herbs used are traditionally used to treat respiratory diseases. We noticed that they all have herbs with anti-inflammatory properties. It is highly possible the formula used could mitigate pneumonia or respiratory issues of the lung by decreasing lung inflammation caused by viral infection. The optimal treatment for COVID-19 is to have proper combinations of antiviral agents together with those anti-inflammatory TCM formulas. The future of medicine should appreciate different approaches and merge together to become one word: "WE." What does that mean? Togetherness and also "West and East." That's what I'm aiming for.

You've talked about poly-chemical medicine and "systems biology." Can you expand on this?

Cancer cells in cancer are so heterogeneous, not just the mutations of the cancer cell, but also the different microenvironment of each cancer cell that influence cancer cell behaviors. One single chemical that kills all the cancer cells in a tumor without toxicity is next to impossible, so I began to think about the potential of poly-chemical medicine targeting multiple sites and chemicals. Chinese medicine often has multiple herbs per formula and multiple claims for usage. It is holistic in concept, so it came into my mind as the lead to explore in the paradigm of poly-chemical and systems biology drug discovery.

In the evolvement of current medicine, attempts are ongoing to take a systems biology approach and be more holistic. In addition, the treatment is moving towards precision medicine for complicated diseases. TCM has always focused on holistic approaches and has always prescribed drugs depending on the unique situations of patients. Preventive medicine is also a new emphasis in the current medical research field, but this was long-practiced in TCM. Finally, the practice of combining different disciplines such as the use of immunotherapies with chemotherapy or radiation is ongoing. TCM has always used combined approaches. As you can tell, "Western" medicine and "Eastern" medicine principles have started to merge. I think the future of medicine isn't "Western" or "Eastern" medicine, but we should have only one united medicine, "WE" medicine, by merging these two schools of thought. That's what we should aim for.

What current or upcoming work are you excited about right now?

I am continuing to focus on developing YIV906 as a pan adjuvant for cancer treatment. I also started getting interested in one of the real causes of death in cancer patients. I realized it's not only because cancer grows to the extent where there's too many cancer cells everywhere but it's also because patients are easily infected when their immune system is so weak. Among those infected, pneumonia is the cause of death in many patients and microbial triggered inflammation is the major cause of pneumonia. A lot of Chinese medicine claims to be good for the control of inflammation. Herbs categorized as "qing re yao," are "medicine that removes heat" where heat symptoms strongly resemble inflammation. In order to support this hypothesis, we studied this class of herbs and found that they were indeed related to anti-inflammation and uniquely hit multiple mechanisms of inflammation in comparison with other categories of herbs. With the herbs in this category, we started to explore their ability alone or in combination to decrease inflammation and its downstream fibrosis of lung tissue, including virally caused pneumonia. It is known that antiviral drugs and antibiotics may be sufficient to treat pneumonia when inflammation is not serious, but when inflammation exacerbates, anti-infectious agents are not as effective. Combination treatment of antimicrobial and anti-inflammatory drugs could be better. Also, current existing anti-inflammatory treatments for pneumonia consist of glucocorticoids, but they have undesirable side-effects and others such as IL-1 or IL-6 antibody or other biologic approaches can be very costly. It is highly possible to come up with herbal medicine based on historical claims and modern knowledge as anti-inflammation drugs for pneumonia. This herb medicine is as or more effective and affordable than current treatments. So far in our animal studies, combinations of several selected herbs with different mechanisms were shown to have the desirable anti-inflammatory properties. Once we optimize the combination, we would like to initiate a clinical trial to test the formula. This is one of the focuses of my lab in addition to PHY906 as a pan adjuvant for cancer treatment. We would like to develop a new herb formula as a pan anti-pneumonia drug.