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United Biomedical, Inc. (UBI) is dedicated to the discovery, development, and commercialization of immunotherapies & vaccines for chronic and infectious diseases and is passionate about delivering science-driven innovation with platform capabilities. Chang Yi Wang is the Chairperson and CSO of United BioPharma (UBP), a member of the UBI group of companies she founded. She discusses her astonishing career, from being the first Asian woman accepted into Rockefeller Universityâ??s Ph.D. program back in 1973, the Nobel Laureate professors or board members she was trained under and worked with, how she leveraged her research and management experience at a young age to establish UBI, and her strategy behind keeping proprietary manufacturing technologies in house, among other key areas.

You have had an enviable career by most peopleâ??s standards, can you briefly introduce your background and the company to our international audience?

I was born in Taiwan and studied chemistry at the National Taiwan University (NTU). After obtaining my bachelorâ??s degree, I went to the United States (US) in 1973 to pursue Ph.D. training in immunology and biochemistry at Rockefeller University. This was quite an enlightening experience. I was the first Asian woman to be accepted into the program and I decided to attend its graduate program due to the institutionâ??s reputation in biomedical research. Furthermore, I was made aware that immunology would be the secret weapon of medicine and this attracted me to the field.

As a first-year Ph.D. student, I joined the laboratory of Dr. Robert B. Merrifield, a 1984 Nobel Laureate in Chemistry for his pioneering work in the establishment of solid-phase peptide synthesis. Under his tutelage, I learned about the many facets of solid-phase peptide chemistry and its application. This is where I had the chance to apply my organic chemistry synthesis skills and branched into peptides. This dedicated one-year synthetic peptide-tool experience laid the foundation for some of my inventions in diagnostics, vaccines and immune-therapeutics later. However, at the time there were not many protein structures and sequences available for design effort, I was attracted to explore the vast sphere of synthetic antigens and their application in biomedical sciences.

I was fortunate to have the chance to learn from Dr. Gerald Edelman, 1972 Nobel Laureate in Medicine for his work with Rodney R. Porter on the immune system and specifically for his discovery of the structure of antibody. He and his colleagues were all instrumental in leading me to the most exciting yet then still primitive field of immunology.

I was also grateful to Dr. Ralph Steinman, 2011 Nobel Laureate in Physiology and Medicine, for being the first teacher at the university to bring me, through many tutorials, to the intriguing field of cellular immunology at a time when he was describing his EM finding of dendrite-like immune cell later known as the dendritic cell, critical for initiating immune responses and its role in adaptive immunity.

For my Ph.D. thesis work, I chose to study in the laboratory of Dr. Henry Kunkel, often referred to as â??the father of immunopathologyâ?•. In choosing the human system, I was the only non-MD in the lab, however, this allowed me to use my chemistry and biochemistry background to study the link between diseases and biomedical sciences.

Due to the solid foundation I gained from the early graduate trainings at the university, I was confident at age 23 in making the move from being a chemist to an immunologist exploring the human immune system, now the central field of Translational Medicine. One could say I was ahead of the curve in this respect. After graduation with my Ph.D. in both Biochemistry and Immunology, I was offered to establish my laboratory of Molecular Immunology by the Arthur J. and Leslie Levine Fund at the Sloan Kettering Institute (SKI) of the Memorial Sloan Kettering Cancer Center (MSKCC), then the largest cancer center in the world. I was the youngest Principal Investigator and head of laboratory at the institute. There, I had the chance to work with Dr. Robert A. Good, a founder of modern immunology who pioneered the first successful bone marrow transplant between non-identical twins.

My work in the early 80s used specific monoclonal antibodies to define several critical lymphocyte surface markers (Leu1, Leu3, Leu4, Leu10, Leu13, Leu14 and idiotypic leukemic T cell marker, also known as the T cell receptor). I was also fortunate to collaborate with Dr. Lloyd Old, one of the founders and standard bearers of the field of cancer immunology, and the National Cancer Institute, which led my laboratory into the tumor immunology and cytokine fields.

How did you leverage your experience in Research when setting up UBI?

When I first started UBI after some serious consideration of becoming an entrepreneur, I was a scientist with some management experience. In the early days of UBI, I wanted to use designer peptides as the tool, which would then combine my expertise in the field of peptide chemistry, immunochemistry, cellular immunology and hybridoma technology for the biomedical application in diagnostics, vaccines and immunotherapeutics. What helped inspire me was my lab experience in the early 1980s when China was opening up to the rest of the world. Initially in my laboratory at the SKI, I had international postdoctoral fellows from Germany, the Netherlands, Japan, Italy, Israel and Taiwan to work with me. However, when China opened to the US, many exchange scholars began to work and be trained at various US research laboratories.

In 1980, I accepted one senior Chinese research fellow from Beijing Cancer Institute to work in my laboratory. In those days, few US trained Chinese scholars wanted to return to China as it was a primitive environment for biomedical research; surely enough, they kept coming and it was not long before my lab was filled with predominantly Chinese research scholars. It was at this point I decided to become an entrepreneur, as these researchers not only needed training but if they wanted to stay in the US they also needed a career and I wanted to create an opportunity for them to thrive.

To become an entrepreneur in the biomedical field, I needed to embark on discoveries and inventions beyond monoclonal antibodies which was my focus at SKI/MSKCC. When I started UBI, our first project was very budget sensitive, furthermore, I needed to be very careful to avoid any conflict of interest with my work at the Sloane Kettering Institute (SKI). Cycling through ideas, I decided to work on an HIV blood screening test system using designer synthetic antigens, which happened to be the easiest area for us to begin with at a time when US NIH and the Pasteur Institute were arguing over who discovered HIV and invented the viral lysate based HIV blood screening test.

I decided that it could be a good time to explore the use of designer synthetic peptide antigens, through extensive epitope mapping to identify the highly antigenic sites on HIV proteins, to replace

the much argued and controversial HIV viral lysate, for detection of HIV antibodies upon infection in a blood and plasma screening test employing antigenic viral peptides, instead of HIV viral lysate, coated ELISA plate. One of the hottest areas in mid 80s was in developing blood screening tests for detection of HIV infection. At that time almost 30 competing players worldwide had strewn the diagnostics field, which demands high precision in both sensitivity and specificity.

Subsequently, I identified a highly antigenic region within HIV gp41 envelope protein suitable for synthetic peptide antigen design and pioneered the first synthetic peptide-based blood screening test kit for detection of HIV antibodies upon infection. This invention along with its serological application in an FDA approved blood screening test data was published in a 1986 article in Proc. Natl. Acad. Sci., sponsored by Dr. Robert B. Merrifield. This first invention brought UBI our first commercial collaboration with Olympus Tokyo, a leading optical and precision instrument manufacturer, with two popular automatic instruments, one for blood typing and one for blood chemistry, which dominated the worldwide clinical laboratories.

I led the UBI team to take on the challenge and brought a never-before synthetic peptide-based blood screening HIV test through a series of FDA approvals for the first non-viral lysate-based HIV blood screening test: from Investigational New Drug (IND), Establishment License to Product License Applications. However, this was a test time for me as I soon found out that commercial market success and FDA product approval, after a 3.5-year painstaking process, are very different kingdoms.

Abbot and Ortho (a J&J company) both had their viral-based test kit approved in 1985; and, ours, though better in seroconversion sensitivity and lack of viral lysate related non-specificity, was approved in 1989. Olympus was keen to market launch due to its predominance in the blood bank operations and clinical laboratories with its fully automated blood typing instrument PK7100 and blood chemistry analyzers; however, Abbott, the number one player in infectious disease screening, had locked up all the microbiology laboratories which conduct the HIV screenings. This culminated being successful at securing regulatory approval due to great scientific invention but failed miserably at the commercial end.

Soon after, we had a second chance to medical diagnostics exploration in the aspect of hepatitis C screening. In 1989, Chiron, the then number three US Biotech player, disclosed that they had cloned HCV. When reading their article and patent filings, I knew I could use everything learned from the past experience in the HIV project and applied the same approach of synthetic peptide antigens to developing a state-of-the-art HCV blood screening test kit when the global field was said to have been monopolized by the triumvirate team of Abbott, Ortho and Chiron. Furthermore, I noticed that the then published Chiron patent application was flawed with missing sequence information from a critical region at the 5â??end of the HCV genome encoding the core protein, therefore, I was confident in our chances to enter the HCV blood screening sphere, as fast as possible, for commercialization.

Within 18 months, we got our synthetic peptides identified, optimized, formulated, kit developed, four patents filed, IND submitted, another scientific paper published in Proc Natl Acad Sci in 1991, and then FDA export license approved, an astonishing pace which broke the industry record for any biologic product commercialization from thought to product market launch. By this point, Chiron, Abbot, Ortho J&J had formed an alliance which gave them a monopoly on the HCV market. After our failed HIV test kit commercialization, we were able to collaborate with a far more adaptive partner in the infectious disease blood screening field, Organon Teknika, number 3 in this field, to launch globally our HCV antibody screening test, banking on our combined experience gained from our respective HIV projects.

In 1991, it was a time when UK and the world public health agencies had a serious problem to contend with, due to the perceived HCV sequence monopoly, from recently approved blood screening tests to preventive vaccines. The per test price was far higher than that for HIV blood screening, and most of the public health agencies were lacking funds to purchase the very expensive HCV blood screening test to safeguard the blood supplies. We took this opportunity to collaborate with the best liver disease laboratory and HCV clinic worldwide during this period by sending out UBIâ??s newly developed state-of-theâ??art HCV test for extensive testing, validation, and assessment in comparison with the then approved first generation and its next generation Chiron/Ortho/Abbot HCV tests. To the surprise of most laboratories, our HCV antibody screening test was highly competitive with Chironâ??s yet to be launched second generation HCV test, surpassing in both sensitivity and specificity to its first generation which was just approved HCV test.

This pleasant finding afforded our HCV test to be quickly approved by the UK medical agencies for participation in at least 1/3 of the UK blood screening market. Thereafter, we quickly secured almost one-third of the European market as well before international patent disputes arose, which was another lesson learned. Our HCV blood screening test, through several of its generations, was sold in some world markets for the following 25 years with revenues and profits, along with other financial resources, plowed into the development of technology platforms and biological products derived therefrom within the UBI group which brought us to our current status.

What are the capabilities of UBI Group today?

The foundation for our achievements and potential is the integration of several advanced platform technologies focused around **functional antigenics** which first identifies with high precision the â??functional sitesâ?• from selected target molecules, then design around that for optimized peptide immunogens along with the **vaccine formulations for active immunization**, which was encouraged by UBIâ??s former board member Dr. James D Watson, a 1961 Nobel Laureate in Medicine and Physiology for his discovery of the double helix structure of DNA; and for carefully screened **antibodies for passive immunization,** for the treatment and prevention of diseases. We have harnessed the power of functional antigenics to **invent â??matters of compositionâ?•** through our proprietary platform technologies.

Functional antigenics is supported at UBI by our team of **chemists** skilled in the disciplines of peptide chemistry, organic chemistry, immunochemistry and polymer chemistry; team of **molecular and structural biologists** for molecular modelling and design of **peptide immunogens and humanized antibodies;** and team of **virologists, cell biologists, cellular immunologists** and **formulation scientists**, skilled in the establishment of functional assays and animal models, and adjuvant technology for development of optimized vaccine, long acting protein and antibody drug formulations. UBI scientists emphasize the coordination of the requisite technologies to rapidly convert research findings into biological product candidates and products. **These products are categorized below as immunotherapeutics which include proprietary monoclonal antibodies, long acting proteins and high precision designer vaccines, matching immunodiagnostics, and veterinary designer vaccine products.**

Specifically, several platforms including (1) UBITh platform technologies which would enable the creation of high precision designer immunogen and vaccine formulations to mount immune responses against infectious pathogens at specific target sites or against the degenerative form of pathogenic self-proteins, through active immunization for immunotherapy; (2) mAb development platform technologies including a proprietary de-fucosylation technology to enhance ADCC activity of anti-tumor antibodies, sophisticated protein structure analysis techniques, and proprietary protein

manufacturing process development know-how to allow high yield protein production from engineered CHO cell lines; and (3) long acting protein drug development platforms including proteoglycan fusion protein platform and single chain Fc-fusion protein platform; and (4) microsphere technology platform for peptide drugs.

Our solid R&D and robust technology platforms are the cornerstone of our long-term business competitiveness. It is the driving force to the growth and continuous sustainability to our new pipeline generation. Our cutting edge clinical research laboratories with the most advanced equipment settings demonstrate our incessant effort to enhance our R&D capabilities. For more details of our UBI group capabilities, the reader can refer to our website.

You also have invested in neuroscience. According to studies by the EMA, CNS medicines have a higher rate of failure compared to other therapeutic areas â?? proven by the recent big pharmaÂ´s move to pull out of this area. In this regard, how is UBI prepared to mitigate the higher risks incurred with the development of CNS/Alzheimer products?

At United Neuroscience, we have successfully optimized our high-precision designer vaccines for a few well known neurodegenerative, disease-causing target proteins such as Abeta, Alpha Synuclein, and Tau, and ventured into various clinical programs of different stages. Based on UBITh vaccine platform, our vaccines would elicit antibodies preferentially bind to their denatured oligomeric or fibril forms.

Meanwhile, we are also expanding our mission to **democratizing health, not just brain health, and have re-conceptualized our strategy from neuroscience company to becoming a â??platformâ?• company. This allows us to expand and mitigate risk within our portfolio across the existing emerging neurodegeneration pipeline and new targets with a more clear and proven biology**.

We have trained and built a core team in the high precision designer vaccine area employing our UBITh platform where our experienced designers, CMC, preclinical and clinical team members have both specific skills and also a broader set of accomplishments and capabilities to meet additional needs as we grow. They have a passion, mindset, and knack for hunting drugs and are our core, our heart and our future.

Why have you decided to build a fully integrated group in the era of cost containment and outsourcing?

As an inventor, it is very important to have a deep sense for the physical and biomedical characteristics of the molecules we are creating, be that antibodies, long acting proteins or designer vaccines. We put these invented baby â??moleculesâ?• into multiple *in vitro* and *in vivo* testing systems for efficacy assessment, and then to cost-effectively and timely bring them into pre-IND and IND phases for clinical trials. There is plenty of proprietary â??know-howsâ?• involved throughout these processes. Yes, it has been a long way as I look back from the day when I made my first invention of a much-needed HIV peptide antigen-based blood screening test. Now decades later, it is more a dream come true as an inventor who has focused mainly on immunology-based biologicals where molecular and cellular engineering designs, small and large scale peptide synthesis, and multiple unique formulations involved in our CMC activities are executed in-house.

Of course, we work closely and extensively with many CROs in preclinical/toxicology studies and clinical trials to create synergies for timely development of all our products. I am particularly excited about our UB-421 mAb which is going through several proof of concept trials involving functional cure of HIV infection, and multiple phase II and III trials in other clinical applications of this unique anti-CD4 monoclonal antibody. I am also very enthusiastic about our Allergy program where our monoclonal antibody UB-221 directed against IgE with far superior properties than Xolair would open up many allergy treatment options beyond Xolair.

Our vaccine UB-211, targeting a membrane proximal domain of IgE (or IgE-EMPD), is now entering its phase I trial in allergic rhinitis patients, which should also bring us a much-anticipated clinical outcome for patients with unmet medical needs. So we have a strong clinical program for treatment of allergic diseases in this much needed biomedical field. I am also quite excited about our anti-Abeta, -Alpha Synuclein and -Tau vaccines targeting patients with neurodegenerative diseases despite the many dropouts by the major biopharmas. Immunology and serology have many subtleties to go with them. Even targeting the same molecule, one antibody or one high precision vaccine formulation is not to be lightly equated to another similar product.

Having in-house operations can afford us the opportunity to quickly adapt improvement in manufacturing processes to arrive at later successes in product advantages due to cumulative know-how gained over the years. This would also allow many of the patent and technology â??know-howsâ?• to be kept in-house without having to spread those pearls to outside firms which would ultimately be controlled externally.

What have you achieved over the last five years and what would you like to achieve over the next five years for the UBI group?

After establishment and further improvement of monoclonal antibody drug, long-acting protein drug, and high precision designer peptide vaccine platforms, the UBI group with a global footprint has developed many critically selected proprietary immunologicals that are entering various phases of clinical trials. Much larger financial resources are required to allow respective product development efforts based on individual platform technologies. We have thus executed the spinoffs of technology platform-based companies with the respective platform-derived products during the last five years. These included United BioPharma (UBP) for monoclonal antibody-based products, UBI Pharma (UBIP) for improved version of long acting protein drugs and injectable pharmaceuticals, and United NeuroScience (UNS) with the high precision designer peptide vaccines for treatment of neurodegenerative diseases.

UBI has successfully transitioned into an innovation-driven biomedical group with independent subsidiary companies with each of them focusing and nurturing around a core technology derived product pipeline. Such a transformation coupled with establishment in both Taiwan and China, besides the original site in Hauppauge, New York, the respective state-of-the-art PICS compliant GMP manufacturing facilities has allowed timely transition from research to IND enabled clinical development for the respective technology platform based products. This is quite an accomplishment during the last five years for UBI to evolve as a multinational, multiplatform and multiple immunotherapeutic products group of companies, from its early commercialization of its proprietary peptide based blood screening diagnostics (HIV, HCV and FMDV) and animal health vaccines (swine FMDV and LHRH for immunocastration).

We have currently more than ten proprietary biological products in various stages of clinical development. We are focusing on pushing **at least five of these products through clinical trials into regulatory approvals for global commercialization** in the coming five years to become a fully

integrated group of biomedical companies. This has been a long way from the time I started UBI in New York as an entrepreneur scientist based on inventions and early product revenues, without any financial support from either US venture capitalists or Wall Street investment bankers. This situation is to be changed as we are now beginning to tap into various capital markets beginning with the first IPO approval for our animal health vaccine company ShenLian Biomedical (aka UBI Shanghai Animal Health) to be listed next month on the Shanghai SciTech Security Exchange. Additional IPOs on the HK Security Exchange, Taiwan Security Exchange, and Nasdaq would be explored for United BioPharma, UBI Pharma and United NeuroScience, respectively.

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