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ONCE UPON AN ERGANG

AN INTIMATE PORTRAIT INTO
TP MAESTRO ERGANG SHI

AUTOMATION : SLAS2022 / 12 NEW HIRES
TP THROWBACK / TP CELEBRATES
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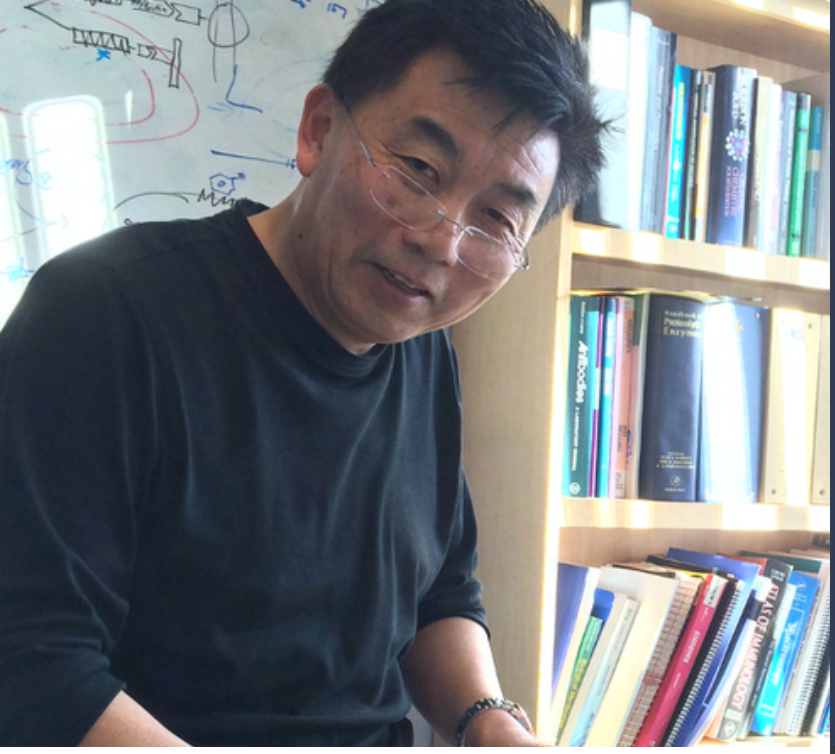
the TP Train Translated to Text

REGENERON



TP:ORIGINS

AN INTIMATE PORTRAIT / ERGANG SHI

"I REALIZE IT'S THE PROFOUND SPIRIT OF TRUTH SEEKING, THINKING BIG, WANTING TO DO GOOD THINGS FOR HUMANITY AND THE WORLD FROM TOP DOWN AND BOTTOM UP OF THE ENTIRE COMPANY THAT INSPIRES ME THE MOST."

With now over 20 years under his belt at Regeneron, we take an in-depth and intimate look into Senior Fellow Scientist of Technology Development, Ergang Shi's tenure. We pose some scientific and personal questions to understand the "man behind the mAb" and get to understand why everyone that works under his tutelage are always engaged, challenged and feel valued. From his humble beginnings in China to an engaging scientist in Tarrytown, this is "Once upon an Ergang"...

MAN BEHIND THE MAB

AN INTERVIEW WITH ERGANG SHI
BY JACQUELINE SISLER AND SHIVRAJ BHOSLE

What was young Ergang like?

I was a latch-key child. Dad was not around. Mom often spoke of me as "the wild boy raised by nature". I was deeply submerged into the wonders of nature, wild woods with birds and small animals, singing creeks with all kinds of small fish, frogs, turtles, and snakes. I was also interested in all kinds of other ventures such as climbing with ropes the 4-story apartment building in which my family was living, organizing snake hunting teams with friends, and turning the space between residential buildings into a vegetable garden. Before college, I went to a remote part of rural China for a few years. It was a harsh new life. I couldn't see what my future was, but I didn't want to be trapped in this place. I started to study English and other useful knowledges besides the regular farming work. I often walked miles across the mountain just to borrow a book. I was able to convince the local village authorities to allow me to build a cave soil lab to help to improve agricultural efficiency. Among other things, I did a survey of the farmland nutrition contents (mainly nitrogen, phosphorous and potassium) of the whole village (see photo). Then the big moment came, when in 1977 Deng Xiao-Ping, the Chinese reformer ordered the restoration of nation-wide college entrance examination, 11 years after its suspension due to the Culture Revolution. I jumped at the opportunity and having passed the exams, enrolled in Tianjin University on the east coast of China to study physical chemistry. Little did I know that this would turn out to be the first step of my career in science.

What was your journey to REGN? Any mentors ?

It's a long story, but I will keep it short. I was working as a teaching assistant of the chemistry department of an institute in Beijing. On a rare occasion, an American biologist, the late Dr. Gordon H. Sato, director of the W. Alton Jones Cell Science Center gave a seminar and had a round table discussion with young teachers. He was interested in me during the discussion and asked if I would like to join his institute for biological research. I said I didn't know biology. He said you know organic chemistry and that should be OK. In the summer of 1985, I joined his institute (Lake Placid, NY) as a visiting trainee along with a few others he had "hand-picked" from China. I was the only one without any prior biological degree or training. I was struggling a lot as I moved from lab to lab trying to fit in the training program. A few months later, Gordon suggested I should join Dr. Wallace McKeenhan's lab to use hybridoma technology and HepG2 cells (which expresses moderate amount of FGR receptors) to characterize and purify the FGF receptors. The beautiful Lake Placid summer environment and my heart wrenching struggles to fit into the advanced biological research requirement formed a stunning contrast. I was voraciously reading all the relevant papers and learning how to do cell culture, membrane preparation, hybridoma fusion and selection. One day I found my hybridoma culture flasks were all contaminated with mold, and I was crying over the

bench. Dr. Sato saw me very sad, and tried to encourage me, "Ergang, I know you want to be good, and I know one day you will". He told me his struggle as a student of Max Delbruck during his Cal Tech days with the theoretical physics class requirement. I later learned that Gordon had made an impact on mammalian cell culture by discovering the serum free system including insights on polypeptide growth factors in the early 70's. He once jokingly told me that he shared a few awards with Stanley Cohen and Rita Levi-Montalcini but not share the last one. Dr. Sato's grand view on life, science and humanity, his passion and persistency had a deep impact on me. Later Dr. Sato initiated a joint graduate program between the Center and Clarkson University. The experience of at the Center turned me into an experimental cell biologist. In 1991, I completed my Ph.D. theses: Purification and Characterization of FGF Receptors.

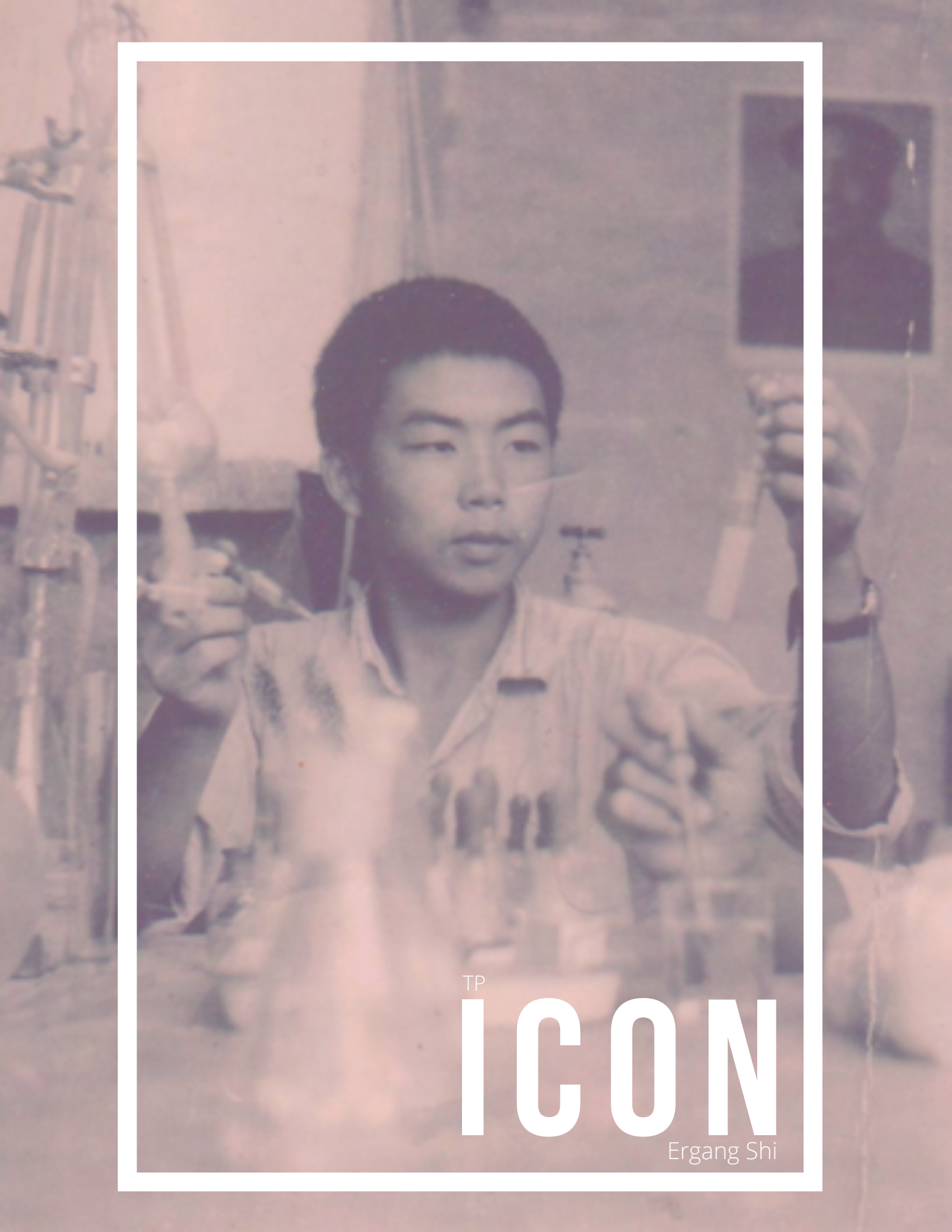
A few years into my postdoc training in Vanderbilt University, I got distracted and left academia, and got involved several business activities and small biotech start-ups and turning into a salesman for a while. I returned to Vanderbilt in late 1996, having realized that my true passion was in science. I worked as a scientist consultant to study a group of monoclonal antibodies raised against CM101, a complex bacteria polysaccharides and key component of GBS toxin, under Dr. Carl Hellerqvist in the Biochemistry Department. While I was making some interesting discoveries on the epitopes of the mabs to CM101, Carl urged me to use a new instrument available in the department called BiaCore SPR sensor. Apparently, some PI's grant funding enabled to purchase the machine, but no one seemed interested in using it. I was so engaged in my work and kept postponing to try BiaCore. One day, Carl looked at me, curling him arms, said: "you're like a chicken. Cluck! Cluck!". I felt ashamed and went to the core lab to figure out how to use BiaCore. I loved it and have used it all the time ever since. Later I joined the hybridoma and phage display group as an instructor for conducting BiaCore services for Vanderbilt faculties. I got a call one day from Regeneron HR recruiter asking if I was interested in joining the company. I followed it up and came to join Regeneron in March 2001.

What would be one of the best accomplishments you have working in Regeneron / TP?

It would be the discovery of the mab epitope binning idea and method. It is a general and simple method to classify any given numbers of mabs raised against any antigen according to their epitope binding features in a very short time.

A few months after I joined Regeneron as a scientist in the BiaCore group, Gang Chen asked me if I could determine how many distinct mabs were among 79 FACS sorted anti hTie2 hybridoma soup samples? At the time, their group was developing the FACS-sorting technology for antibodies and CHO production using hTie2 as POC. I knew it would be very challenging to run the usual BiaCore pair-wise competition matrix with so little soup (about 5-10 ml each) and so little time. As I was planning the experiment, one evening I was sitting by the reservoir on my way home, the binning idea came to mind like a bright flash of light in the night sky. I was so excited and rushed back to the lab. I worked tirelessly for 3 days and nights to conduct the first binning test and it worked. It was such an exuberant feeling -like a curious young boy who queried the majestic nature and she answered back. The epitope binning experiment found there were 7 distinct mabs in those soup samples and later confirmed by sequencing. I later developed the method into Luminex, a multiplex beads binding system superbly suited to the idea and learned bioinformatic data analysis with the help of Wen Fury. The Luminex based epitope binning method became a robust assay providing the first view of the available "epitope land scape" for most of the therapeutic antibody screenings, from a few hundreds to a few thousands of individually captured mab clones.

It is the BiaCore SPR instrument that allowed me, in a unique situation, to intimately interact with nature (protein molecules) while holding a singular thought of how to disrupt surface coupled antigen molecules with various distinct agents (proteases, reactive chemicals etc.), then using this panel of structurally



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Ergang Shi

disrupted antigen plus the intact antigen to "see" how many unique mabs in the testing set by surveying their binding pattens. It is the label free features of SPR (surface plasmon resonance) sensing capability without any indirect agent involved (such as secondary detecting antibodies) in real time where the operator can directly see nature's feedback on the query (the setting condition) in front of his own eyes. It is the directness and real time to see what's going on I found so intriguing and amazing in the discovery process. Today Luminex based mab epitope binning is still used to provide an antibody diversity view on most of the therapeutic mab up-stream screening, even though robust sequencing methods provide CDR gene usage diversity. I hope I can work on improving the current epitope binning method and even leverage it for a deeper understanding on the potential "molecular linguistics" among protein-protein interactions in general.

What do you think about the path that REGN and your group (in particular) is heading?

Thinking back on my 21 years journey in Regeneron to this point, I feel tremendous joy and satisfaction. I truly believe that Regeneron has made who I am today. Yes, there were mistakes I made and deeply regret. Yes, there were many attempts I made with good intent and pure heart but did not bear fruits. I realize it's the profound spirit of truth seeking, thinking big, wanting to do good things for humanity and the world from top down and bottom up of the entire company that inspires me the most. I also realize what a wonderful career it is to work in the field of life science: that the work itself is directly related to the ultimate question - what is life- that has been pursued since antiquity by the great minds down to every thinking person. A tremendous honor, satisfaction, and responsibility fill my heart. Right in front of my eyes, Regeneron, an unstoppable winner leads the field into the future. With my current challenging medical condition, I start to think more seriously about how to live a meaningful life. I realize that besides my family and friends, my work at Regeneron, and the passion I share with so many of my Regeneron colleagues provide significant meanings in my life and I'm very grateful.

Our leader George once said that "protein is our sweet spot". I often think about it. Protein in some sense, is the molecular essence of life. All the rest- DNAs, RNAs, carbohydrates, lipids, myriad of small molecules, and water- are "dancing around" this life's functional executioner in this symphonic wonder of life. The very name of our department, Therapeutics Proteins, reveals the work of honor and prestige. It's an honor for me to realize how fortunate it is to be part of this remarkable group. I also feel a great fortune to have had Bill Olson as my manager in the past 8 years. He has provided a firm ground and guidance for me to grow my unique strengths and become a better manager. His dedication, hard-work, and magnitude of professional knowledge as well as compassion have always been an inspiration.

Metaphorically speaking, if every therapeutic drug program is like launching a space probe to its successful designation, TP with its close allies like PES, will provide the ignition and the first powerful upwards push to its designation during that process. The protein operation led by Ray is one of the most vital components for a successful launching. Reagent design, material qualities, and timing all matter. I envision that in the near future of the group there will be a well-balanced modern working place where creative and dedicated people work in harmony with an automation environment of sophisticated information and material flow processes, while enabling each individual to grow on his/her unique strength and interest to evolve with the company's bright future, which will enable every willing heart in the lab enjoy both pipetting and thinking.

-Erqang