Nobel Prize winner Dr. Joachim Frank shares another impressive speech with JOSHA. His speech concluded the international symposium on the occasion of his 82nd birthday, which took place on September 4th, 2022 in the Vagelos Education Center of Columbia University. Among the topics he covered were his first exposure to molecular biology, the accidental discovery that led him into the direction of his research, and advice to young scientists about the importance of “peripheral vision” for success in their careers.
Speech by Joachim Frank
after the International Symposium on September 4, 2022, celebrating his 80th birthday belatedly on his 82nd.
The event took place in the Vagelos Education Center, Columbia University

Dr. Joachim Frank
Professor, Biochemistry and Molecular Biophysics & Biological Sciences; Colombia University; NY, USA & 2017 Nobel Prize in Chemistry

Abstract:
Nobel Prize winner Dr. Joachim Frank shares another impressive speech with JOSHA. His speech concluded the international symposium on the occasion of his 82nd birthday, which took place on September 4th, 2022 in the Vagelos Education Center of Columbia University. Among the topics he covered were his first exposure to molecular biology, the accidental discovery that led him into the direction of his research, and advice to young scientists about the importance of “peripheral vision” for success in their careers.
Dear friends, former and present students, former and present collaborators, and colleagues:

I could not have imagined 50 years ago that I would live to see this dream come true: that my research and the endless times I spent writing and re-writing computer programs, would contribute to the emergence of a powerful new technique of structural biology that sweeps the world now, giving us insights into the minute workings of molecules that are forming the very fabric of life, and allowing us to look at the way viruses interact with the human receptors and find their way into the cell.

My first exposure to the field of molecular biology occurred in the summer of 1964. (Yes, many of you were not born yet!). I was 23 years old, had gotten my bachelor’s degree in physics, or Vordiplom, from the University of Freiburg, and had just moved to Munich to start working on my master’s thesis. And what’s important for what follows, apart from my classes in high school, I had no clue about biology.

I remember sitting in the backyard of my parents’ house in Weidenau, my hometown in the state of North Rhine Westphalia, during the summer break. Not far away was the place, the “Kabäuschen” under the verandah, where I had done my first “scientific” experiments as an eight-year-old. Now, sitting
in the backyard, I was opening a package. The package had been express-mailed to me in advance of a workshop organized by the Studienstiftung des Deutschen Volkes (the German Academic Scholarship Foundation) that had just given me a scholarship award. These workshops were designed to bring students from different disciplines together and featured a variety of topics at the cutting edge of science. The particular workshop I had signed up for was on molecular biology.

[Molecular biology was just in the process of being defined as a field. In fact, the term had been coined only a decade earlier, and it encapsulated the idea that biology can ultimately be reduced to the study of molecules and their interactions. The Journal of Molecular Biology had been founded just five years before, in 1959. The name of a subfield, “molecular genetics,” reflected the fundamental insight that genetics – the basis of heredity – could be explained by the actions of special molecules in the body. Foremost of these was DNA, the physical substrate of heredity].

The express package I opened in the backyard on that day contained a selection of reprints of seminal articles on molecular genetics. Among them was the 1953 Nature paper by James Watson and Francis Crick on the structure of DNA, which had come out only a decade before. It was the one with the famous understated line at the end: “It has not escaped our notice that the specific pairing we have postulated immediately suggests a possible copying mechanism for the genetic material.” Another article I still remember reading was about the one-gene, one-enzyme hypothesis formulated much earlier, in 1945 – the hypothesis, later proven wrong in its rigorous claim, that each gene codes for one and only one protein.
I was electrified when, right then and there, I came to grasp the foundation of molecular genetics, now named the *Central Dogma of Molecular Biology* -- the term Francis Crick had coined. As happens in many highly emotionally charged moments, such as seeing the moon walk in 1969, the Challenger explosion on January 28, 1986, or the collapse of the Twin Tower building on September 11, 2001, the visual scene of where I was precisely at that moment of comprehension of a seminal event is forever etched in my memory, like a photograph: there is still the white paint-chipped wooden chair I was sitting on, the white quartz gravel on the ground, which my father was in the habit of raking every Saturday afternoon, and the slant of sunlight on the large red-brick house that my grandparents had built in 1905. It was a moment of sudden insight, sudden comprehension, where I saw several concepts, Gregory Mendel’s Laws about the inheritance of physical traits, procreation, cell division, protein synthesis -- all coming together in one grand unifying picture.

Looking back, I can recognize that my life in science can be divided, more or less distinctly, into four stages.
The first stage ("**Crucible of Ideas**") was an aimless exploration of many ideas, allowed to bounce off one another in the crucible of my mind. I was an unprincipled investigator of sorts, without a group. I got introduced to the electron microscope and its innate hostility to biological samples. Pristine physics met with messy biology. Many ideas were uncooked and got disbanded. I had no sense how I could ever make a difference in science.

This was followed by the second stage ("**Eureka!**") where a singular “idée fixe” emerged – the idea of structure determination from a collection of single molecules in solution, which was quite unorthodox at the time. I spent my time writing programs. The programs invaded my dreams at night. I came to live in my programs – I later compared my situation with the fate of an architect who keeps building and changing a house he is doomed to live in. Fortunately, I found some colleagues and collaborators in real space – among them Martin Kessel, who is here today -- who were supportive, and the first proofs of concept emerged.

Then came the third stage ("**Ribosome as Guinea Pig**"): As newly minted principal investigator, I was able to develop the approach in great detail with the help of many brilliant students. But all that would not have been possible without the use of a fortuitous “guinea pig” molecule, the ribosome. Many collaborators -- ribosome biochemists -- cooked up samples and asked questions they hoped I could answer. I became a structural biologist in the process. It took a long time, but in the end, I came to know the ribosome in and out.

In the fourth stage ("**Apotheosis**"), which is still going on, I saw the development of the technique bloom in the hands of many groups, reaching an unexpected degree of perfection; and saw my idée fixe eventually leading to the award that is every scientist’s dream. But among all the phantasies I have had, I did not foresee that on my 82nd birthday I would be surrounded and accolated by many of my former students and long-term collaborators -- prominent scientists from all over the world!

**Allow me to tell you a bit more about the Eureka stage.** Single-particle reconstruction – How can one even talk about the structure of a molecule if it’s not packed in a crystal? Where did this strange idea come from?

I can tell you this: it all started with a kick.

It started in 1969 with a Polish professor, Antoni Feltinowski, a year after I had begun my Ph.D. work in Munich with Walter Hoppe. He was a refugee with some experience in electron microscopy, and Hoppe had agreed to give him a temporary position in his lab. Feltinowski was a tall man. He was loud, opinionated and quite fidgety. His temperament affected the quality of the micrographs he took, which
tended to be blurry because he kicked the lower part of the instrument habitually during the experiment, causing the column to vibrate.

The Siemens Elmiskop 101 electron microscope.
(Copyright: Science Museum, London| Science & Society Picture Library)

It so happened that at that time a new type of analysis was becoming popular: optical diffraction. When you put an electron micrograph recorded on film into a parallel laser beam and focus it by a lens, one sees a diffraction pattern. It normally shows the signature of the contrast transfer function, in the shape of the so-called Thon rings. [These rings were named after Fritz Thon, and scientist who first described these kinds of patterns in 1964]. When I put Feltinowski’s micrographs into the laser beam, a strange pattern was superimposed; it looked as though the Thon rings were put behind bars. Young’s fringes they were called, as I soon learned.

Optical diffraction patterns showing the Thon “rings” due to the contrast transfer function of the electron microscope, modulated by Young’s fringes. (Here the Thon “rings” are actually elliptic, and even hyperbolic on the right, due to uncorrected astigmatism). The fringes appear when during the exposure the specimen stage has jumped from one
position to another, so that two noisy versions of the same image are superimposed on the recorded film, with a slight shift in between.

All at once the pattern I saw revealed a lot about the experiment: first, the contrast transfer function, and second, how much the image had shifted during the exposure in response to Feltinowski’s kicks, and third, the resolution of the electron microscope, which could be judged by how far out the fringes could be seen. But the most important insight was the realization that it was possible to align molecules shown in two noisy images with an accuracy, on the object scale, of 3 Angstrom and better. [One angstrom, for the non-specialist, is ten-millionth of a millimeter, a one behind six zeros behind the decimal point].

Here are the results of related experiments. In this case, I took two separate images of the same area of a thin carbon foil and recorded them on photographic films, and then superimposed the two films outside of the electron microscope, where I could shift them against each other by any amount. The pictures in the lower row show the optical diffraction patterns obtained in three such experiments when the two images are perfectly aligned. In the upper row are the corresponding diffraction patterns when a small horizontal shift is applied. The larger the shift, the narrower and more numerous the Young’s fringes become. In each case, the extent of the patterns of Young’s fringes demarcates the information limit, and hence the best possible resolution that could be achieved once the CTF has been corrected. And the fringes are intrinsically, by a Fourier theorem, related to the cross-correlation function, which is instrumental in efforts to align images computationally.

I got my first paper out of this, which was published in 1969 in the journal Optik. Quite to my surprise, my mentor didn’t want his name listed on the paper. He wanted me to get all the credit, as single author.

And from there everything else followed.

(Sometimes I wonder about Dr. Feltinowski, what happened to him? Is he still kicking?)
I’m aware that many students and young investigators are here, looking for some hints on what they could do to be successful in science. For instance, during the visit in 2018 to my alma mater, the University of Freiburg, I was asked to give a presentation to students, entitled “How to become a Nobel laureate.”

Looking back, I see that a lot of serendipity was at work, which cannot be taught. The Feltinowski effect, if you will. If I should give advice, it could be expressed in one catch phrase: peripheral vision. Look out for hints that come along outside your narrow field of vision. Every unexpected outcome in an experiment may have the seed for an explanation involving a new concept, a new mechanism. Sometimes obstacles are overcome by occupying your mind with something completely unrelated, even outside of science. In Richard Feynman’s words: “Study hard what interests you the most in the most undisciplined, irreverent and original manner possible.”

And be sure to have emotional support to bridge the vast periods of non-success, experimental mishaps, scoops, and other disasters. I was very lucky to have the support of my wife Carol, through thick and thin, for almost 40 years.

Before I come to the end, the official end of this fantastic Symposium, I need to say big thanks. First of all big thanks again to the speakers and chairs for the presentations of cutting-edge results, thoughtful reviews of their areas of research, and personal tributes. It was an unforgettable day joining us in appreciation of science and the fabric of life.

Thanks to the Organizing Committee for the fantastic work they have been doing in preparation of the event, for over a year – actually three years, to be more precise -- Rajendra Agrawal (Wadsworth Center, Albany), Bob Grassucci (Columbia Cryo-EM Core), Bridget Carragher (Simons Electron Microscopy Center), my wife Carol Saginaw, Jose Maria Carazo (University of Madrid, CNB-CSIC), Masgan Saidi (Columbia BMB & Cryo-EM Core), Ruben Gonzalez (Columbia Chemistry), and Yaser Hashem (University of Bordeaux).
The Organizing Committee, plus one.

From left to right: Yaser, Ruben, Jose-Maria, Bob, Joachim, Raj, Masgan, Carol, and Bridget.

Special thanks to Columbia University Medical Center, Agouron, Gatan, Genentech, Hitachi, Merck, MiTeGen, SPT Labtech, Structura, and Thermo-Fisher Scientific for their generous contributions. Without their support none of this would have been possible. We would have had no party last night, only zoom sessions today with speakers from out of town, and most unfortunately, everybody would be sent home immediately after this talk.