# Meet Dr. Joachim Frank, Nobel Laureate

***Our editors Vikas Chelur CC'21 and Maria Trifas CC'21 interviewed Dr. Joachim Frank in December 2017. Dr. Frank is a professor in Columbia's Biological Sciences department who recently won the Nobel Prize in Chemistry in 2017 with Jacques Dubochet and Richard Henderson for their research in cryo-electron microscopy. Here is a snippet of the interview where Professor Frank explains his research at different levels.***

**VC (Vikas Chelur):** Could you give us a brief explanation of your research in cryo-electron microscopy, as it pertained to you winning the Nobel prize from first how you'd explain it to a toddler?

**JF (Joachim Frank):** Molecules are very tiny, tiny things that we have all over our body. And they bounce against each other and sometimes they recognize each other and say hi. And we want to know exactly what they're doing and how they do this and how they say hi and why they want to get together and how this all makes our body work. This particular method that we developed makes it possible to see these molecules with very, very super microscopes that are better than light microscopes.

**MT (Maria Trifas):** What about for a middle schooler?

**JF:** Everybody knows that life processes are constituted by interactions of molecules. We have thousands of molecules of different kinds in each cell. And in a normal cell they function properly. In a deceased cell, there are many difficulties in these interactions, problems. And that's how disease processes are developed.

From that it follows that we need to have as complete a knowledge of all our proteins in the cells as possible. The existing technique for determining the structure of molecules to the atomic level (which means the highest resolution level) was by x-ray crystallography.

For decades now, x-ray crystallography has been used to determine structures of biomolecules. And there are in fact more than a hundred thousand structures in the public database. They make possible what we call molecular medicine, because medicine nowadays is molecular medicine. It is based on the extensive knowledge of molecular structures. So, this whole database has a huge, huge gap. That gap exists because not all molecules can be crystalized. That's essentially where electron microscopy jumps in.

Electron microscopy can visualize molecules in a particular method that the three of us (Nobel laureates) got our prize for. It is a method of obtaining the structure of molecules from molecules in solution. And we call it single not because there is only one, but single because they are not attached to each other. So, we can simply look at many, many molecules that are randomly oriented in solution and on that basis, on the basis of the projection, we see the surface structure.

There are two important methodologies involved. One of them is the way how all the information from the different projections have to be related to one another in order to find the orientations and then develop the three-dimensional visualization. That technique I developed long before the 'cryo' part came along. So, I developed this with a very poor contrasting method that existed at the time which is called negative staining – so molecules were badly treated but they were still in some way propped up by the negative stain. And the images received their contrast essentially received their contrast as stain exclusion. So, one didn't see the molecules, but one saw the stain, and what the molecules excluded. With this kind of visualization, I developed the algorithms, the computational techniques, to get all the way to the 3D structures.

When I was just about finished with that, this other technique came along which allowed us to embed molecules in vitreous ice. That's the contribution by Jacques Dubochet. The existing attempts to keep molecules in water by quickly freezing the sample in liquid nitrogen – that method doesn't work, because on the interface between the grid and the liquid nitrogen, gas bubbles form, very quickly. These gas bubbles don't transmit heat very efficiently, and that allows the ice to form crystals. Crystalline ice is dangerous for molecules; it sort of destroys them because it expands. And besides, it also has its own structure which interferes with the structures that we are looking at. So vitreous ice is really an invention that came along in 1980.

And then Dubochet discovered, along with his mentor, that the formation of crystalline ice can be prevented by substituting ethane for liquid nitrogen. So now we have this little vessel of liquid ethane suspended in a bath of liquid nitrogen. And when the grid with the sample on it is plunged in there, then the ice that is formed is glasslike, and hence vitreous. So it is a very simple concept, but it is an ingenious idea, and all of a sudden, there was a way of freezing the molecules as if they were in liquid water, they stayed in liquid water.