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Discussion cards

What is it good for? Basic versus applied research

Discussion card for proposal 1: The mRNA vaccine revolution

Proposal number 1 describes how *in vitro* mRNA could be used to deliver instructions to produce a protein of interest in a mammalian host cell. Instead of using this to simply study protein function in vivo, this technology can also be used to produce proteins of interest for therapeutic use, e.g., virus spike proteins as an mRNA vaccine. Considered a game changer in the fight against COVID-19, the work that underpinned this technology was begun by a Hungarian scientist more than 25 years ago. What is remarkable is that Dr Katalin Kariko, working first with Dr Elliot Barnathan and subsequently in collaboration with Dr Drew Weissman, could not get funding for this research, yet she persevered. At the time people assumed that mRNA would not be stable in a host; that it would be recognized as foreign by the immune system and degraded, thus rendering it ineffective. Drs Kariko and Weissman discovered that the incorporation of synthetic nucleosides (mRNA building blocks) as part of the mRNA code could protect the RNA from the host response. Dr Kariko is a senior vice president at BioNTech, the originators of the Pfizer vaccine, and her research has also formed the basis of the Moderna vaccine, a relatively new biotech company that has adopted mRNA therapeutic technology. One wonders where we would be at this moment in time if Dr Kariko had not persevered, in spite of funding rejections.

Discussion card for proposal 2: Synchrotrons and the structure of SARS-CoV-2

With the urgent need to combat SARS-CoV-2 infection, synchrotrons around the world have been widely used to determine the structure of this new coronavirus. With this technique, scientists have been able to determine the structure of the virus proteins. Synchrotrons have also been used to study how the SARS-CoV-2 spike binds with the cell membrane of human cells during infection. This structural information was then used to build computational models to study the virus further. For example, these simulations have allowed the comparison of SARS-CoV-2 and similar viruses, to help predict whether existing antiviral drugs could treat COVID-19. They have also been used to predict the best antigens to trigger immunity. Structural data and simulations have had a big impact on providing information about the spike protein, analyzing all the potential shapes it could take through its folding/unfolding movements. Computer simulations based on the solved structures have even been used to predict possible changes (mutations) to this protein. This can give us the opportunity to test the efficiency of current vaccines, as well as to anticipate the design of new ones.

Discussion card for proposal 4: Lipid nanoparticles and COVID-19 vaccines

Lipid nanoparticles are crucial (yet little recognized) components of modern COVID-19 vaccines, since they protect vulnerable mRNA fragments from degradation and allow them to be delivered into cells for translation into protein, which is what triggers the immune response. Since mRNA has a net negative charge, it would not be able to pass through non-polar cell membranes so it is necessary to incorporate complementary positive charge into the carrier system. This was achieved by adding amine groups to the molecular structure of lipid nanoparticle carriers. Having permanent positive charges would lead to toxic entities that would be attacked by the human immune system, so fine-tuning of the chemical structure was necessary. This was achieved by synthesizing and testing thousands of ionizable lipids. This shows how basic research is necessary to learn about the fundamental properties of new materials before these materials can be used during a time of need, such as a global pandemic. The newly developed mRNA-based vaccines (Pfizer-BioNTech and Moderna) exploited this knowledge; they didn't have to develop new nanoparticles but just adapt and refine the existing ones, which made rapid roll out of these vital vaccines possible.