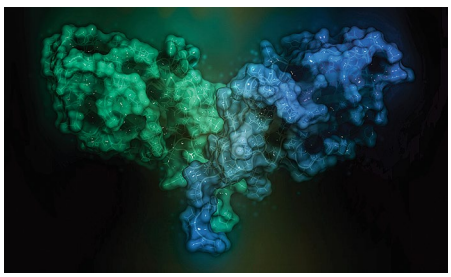
# Awards for manipulating technologies

The 2018 Nobel prizes in chemistry and medicine celebrate tools for engineering biological materials.

It may seem that there is little connecting the 2018 Nobel Prize in Chemistry, awarded to Frances H. Arnold, George P. Smith and Sir Gregory P. Winter for the directed evolution and phage display of proteins, and the 2018 Nobel Prize in Physiology or Medicine granted to James P. Allison and Tasuku Honjo for cancer immunotherapy. Notwithstanding, both prizes celebrate engineering technologies to generate enzymes, antibodies and cells with novel properties to tackle some of the world's current problems.

Nearly 30 years ago, after unsuccessful attempts to create new enzymes using traditional engineering, Frances Arnold devised a novel protein engineering tool termed directed evolution of proteins[1]. This approach, inspired in the events that define natural evolution, might be regarded as a biochemistry equivalent of selective breeding. It uses random mutagenesis to generate a pool of protein mutants that are tested for desired properties or substrates. The mutant with the higher activity is then selected for additional cycles of random mutagenesis and in vitro selection until the wanted features are attained. In its first demonstration, Arnold evolved a subtilisin variant, an enzyme that breaks down proteins, whose activity in a water/organic solvent mixture was hundreds of times higher than the original one[1]. Since then, this protein-engineering technology has been widely used, and nowadays directed evolved enzymes are found in modified organisms that break down environmental pollutants and transform carbon biomass into biofuels. Others are employed as greener and more efficient alternatives to synthetic metal catalysts used in industrial chemistry, in the production of non-toxic pesticides, cosmetics and detergents, as well as drugs to treat diabetes and cancer.

Directed evolution of proteins can also be done with the phage-display technique awarded with the other half of the Nobel Prize in Chemistry. In 1985, George Smith reported that peptides fused to the gene of the coat protein of bacteriophages (viruses that infect bacteria to proliferate) are expressed at the phage's surface as part of its capsule protein[2]. He later demonstrated that these phage-displayed peptides can be selectively purified from a mixture of phages using antibodies in a process known as biopanning. Gregory Winter realized the potential of such approach for the directed evolution of therapeutic antibodies. He generated a library of phages with billions of antibodies at their surface, selected those that recognized particular proteins and used random mutations to create a new library, from which he selected antibodies with increased selectivity and affinity for their target[3]. In collaboration with others, Winter further developed this technology to produce pharmaceuticals, leading to the first fully human monoclonal antibody (adalimumab) approved by American and European drug agencies to treat rheumatoid arthritis in the early 2000s. Its therapeutic applications have now been extended to several other autoimmune diseases, such as Crohn's disease and psoriatic arthritis. This success sprouted the use of phage-display technology in drug discovery, which has produced antibodies to treat distinct cancers, such as gastric and colorectal tumours, as well as vision loss and anthrax infection.



Three-dimensional representation of CTLA-4, a T-cell surface receptor involved in immune regulation. Credit: molekuul.be/Alamy Stock Photo

The 2018 Nobel Prize in Physiology or Medicine recognizes an immune cell-modulation technology that uses antibodies targeting the cell surface proteins of T-cells, cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) (pictured) and programmed cell death protein 1 (PD-1), to relieve the inhibition of the immune system and elicit an attack on tumours. In independent studies[4,5], James Allison and Tasuku Honjo demonstrated that CTLA-4 and PD-1 are negative regulators of T-cell activation, each through different inhibition mechanisms. T-cells initiate immune responses and thus their activation is tightly regulated to guarantee that a response is only triggered in the presence of pathogens or diseased cells. CTLA-4 and PD-1 are fundamental components of that regulation mechanism. Motivated by previous evidence suggesting that the activation of the immune system could be harnessed to attack tumours, James Allison looked for a general strategy to fight cancer by relieving CTLA-4 inhibition of T-cell activation. He used monoclonal antibodies to block CTLA-4 and found that this treatment had cured mice carrying tumours[6]. Honjo and collaborators followed this concept and showed that targeting PD-1 inhibition also resulted in an immune attack of tumours in mice[7]. These studies established a new type of cancer immunotherapy that uses antibodies (checkpoint inhibitors) to engineer a response from the immune system against tumours. Monoclonal antibodies targeting CTLA-4 or PD-1, such as ipilimumab, pembrolizumab and nivolumab, are now approved therapies against metastatic melanoma and bladder cancers. Ongoing clinical trials suggest that this therapy seems promising against lung and prostate cancers. Nonetheless, being based on the induced overstimulation of the immune system, adverse autoimmune side effects are common. This is currently being tackled with the development of new checkpoint inhibitors that, by increasing efficacy and reducing side effects, will hopefully contribute to make this type of cancer immunotherapy more effective and safer.

The technologies awarded with the 2018 Nobel prizes in chemistry and medicine have significantly contributed to new biological tools to address some of mankind's present challenges. As new biomaterials are made available by these engineering approaches, further benefits are expected. ❐

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