2018 NOBEL PRIZE IN CHEMISTRY

Exploiting evolution

The diversity and proliferation of life is enabled by evolution. Genetic variation combined with selective pressure can lead to the development of proteins that perform better in different conditions, or enzymes with catalytic activity altered to tolerate new substrates or perform new chemical reactions. Now, the 2018 Nobel Prize in Chemistry has been awarded to recognize the work of researchers who have developed methods to modulate the activity of proteins using the principles of evolution. One half of the prize has been awarded to Frances Arnold "for the directed evolution of enzymes"; the other half is shared between George Smith and Gregory Winter "for the phage display of peptides and antibodies".

Left to right: Gregory Winter, Frances Arnold and George Smith. Credit: Aga Machaj, Trinity College Cambridge; Courtesy of Caltech; University of Missouri

It is hard to rationally determine how a protein sequence should be changed to generate a protein with a desired function. Instead, Frances Arnold, at the California Institute of Technology, uses biology's method for optimizing chemistry. She showed that varying the sequence of an enzyme could be coupled with screening and selection strategies to generate new enzymes that could function in non-natural environments. Her work since has improved this approach, showing that it is possible to develop enzymes that can catalyse reactions completely different to those catalysed by natural enzymes.

Directed evolution requires researchers know which gene encodes the protein they want to modify. George Smith, at the University of Missouri, demonstrated how 'phage display' can be used to physically couple the properties of a protein with the DNA sequence that codes for it. The method involves inserting a DNA fragment — encoding a foreign gene — into a gene that encodes a protein that is 'displayed' on the surface of a bacteriophage. The foreign protein is therefore also displayed on the surface of the 'phage'. Affinity purification using a binding target can then be used to isolate phages that display proteins that bind with high affinity and selectivity (and also the genes that encode them).

Greg Winter, working at the Medical Research Council Laboratory of Molecular Biology, Cambridge, adapted Smith's technique by placing antibody genes inside phages in order to display antibodies on their surface. This enables the direct selection of phages carrying genes that encode variant antibodies evolved to bind a specific target protein with high affinity and selectivity. Combining directed evolution with phage display has enabled researchers to develop several therapeutically useful antibodies. ❐

Kathryn Ashe

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SUPEROXIDE DISMUTASE MIMICS

Redox activity goes organic

Superoxide dismutase mimics can help regulate the levels of $O_2^{\bullet-}$ in the body, but typically rely on redox-active metals that are toxic in their free form. Now, a complex featuring a redox-active quinol moiety complexed to a redox-inactive zinc centre has been shown to catalyse $O_2^{\bullet-}$ dismutation.

Diane E. Cabelli

Superoxide ($O_2^{\bullet-}$) — the reactive oxygen species formed by the attachment of an electron to molecular oxygen — is found in aerobic organisms as a by-product of metabolism. Superoxide is known to have a signalling role in a variety of organisms but, depending on its concentration, it can also be toxic and is suspected to cause various kinds of cell damage when not