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Man-made enzymes

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Enzymes are biological catalysts with remarkable properties. They perform all the vital tasks of life - process food, produce energy, replicate genes and provide the building blocks for the formation of new cells and organisms. They perform reactions that would otherwise take millions of years in seconds or even milliseconds; they select their specific target molecule from billions of other, often quite similar ones; and they produce a single product out of many possible alternatives.

The enzymes in charge of the basic 'house-keeping' and reproduction of cells seem to have remained virtually unchanged: they are essentially identical in the most primitive bacteria and in humans. On the other hand, more complicated organisms have developed, requiring a vastly wider range of enzymes. Not much is known as to how these remarkable molecules evolved - we lack the fossils and the dinosaurs that have been so useful in studying the evolution of organisms. Nevertheless, biology is united by the rules of Darwinian evolution that explain how organisms as complicated as humans evolved by natural selection operating on wide and genetically diverse populations.

Can we perhaps, in the absence of fossils and dinosaurs, reproduce the evolution of biological molecules including enzymes in the test tube and in real time? This, however, requires the development of new technologies that can apply the principles of Darwinian evolution to genes and enzymes. We have indeed developed such a new technology that my collaborator Andrew Griffiths and I have dubbed Genescis (Gene Selection by Compartmentalised In vitro System). Genescis allows billions of different genes to be placed individually in artificial, cell-like compartments where they are translated to give many copies of the enzyme they encode. The substrates (the target molecules) for the enzyme to be selected and the products of its activity all remain within the same compartment. A selection is applied for the 'survival of the fittest' - only genes that encode an enzyme with the desired activity survive (see Figure). With this system we are now able to reproduce the evolution of existing enzymes and thus get a glimpse of the 'dinosaurs of the protein world' - the inefficient, primitive intermediates that may have led the way to the highly proficient enzymes known to us today. This system, and other systems which make use of combinatorial chemistry and high through-put screening technologies, are also used to generate novel enzyme-mimics ('plastic enzymes') and enzymes for biotechnological and medical applications.

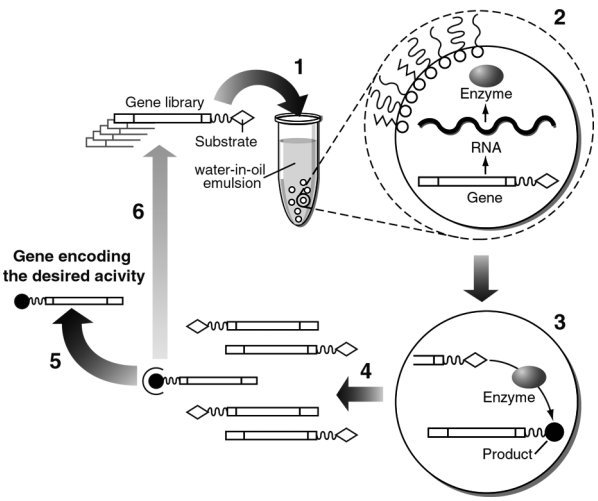

Fig. 1 *Gene selection by compartmentalisation. In Step 1, an in vitro transcription/translation reaction mixture containing a library of genes linked to a substrate for the reaction being selected is dispersed to form a water-in-oil emulsion with typically one gene per aqueous compartment. The genes are transcribed and translated within their compartments (Step 2). Subsequently (Step 3), proteins (or RNAs) with enzymatic activities convert the substrate into a product that remains linked to the gene. Compartmentalisation prevents the modification of genes in other compartments . Next (Step 4), the emulsion is broken, all reactions are stopped and the aqueous compartments combined. Genes linked to the product are selectively enriched, then amplified, and either characterised (Step 5), or linked to the substrate and compartmentalised for further rounds of selection (Step 6).*

Selected Publications

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