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Controlling drug design through 'unnatural' selection

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Darwin probably never envisaged that, 150 years after 'Origin of the Species' was published, scientists would be adapting his ideas to improve drug design, but new research from the University of Leeds is doing just that.

Enzymologist Alan Berry and chemist Adam Nelson used 'directed evolution' to adapt a natural enzyme to make analogues of the anti-flu drug, Relenza™. The scientists – from Leeds' Astbury Centre – created enzymes able to control the three-dimensional construction of the drug-like molecules they produced. Controlling the shape of drugs at this level is essential since many therapeutics only work when in one format and, in some cases – such as Thalidomide – the wrong format can have serious side effects. This is the first time that the technique has been used in this way.

Directed evolution mirrors natural evolution, except that the researchers control which properties are passed on to the next 'generation'. Dr Berry and Professor Nelson made thousands of copies of their target enzyme, each subtly different to the 'parent', and then selected the ones that suited their purpose best. They then repeated the process, until, step by step, they had the final enzymes they were looking for.

Dr Berry said: "Enzymes can be engineered using rational design, but it takes a lot of time to amass enough information to use that approach. With directed evolution, you pick randomly from a huge number of copies of the enzyme to find the properties you want. It's fully

automated and very high throughput. Syntheses of anti-flu drugs are complicated, but using this technique you can cut out some of the process – often generating enzymes which are much more efficient than their natural 'parents'."

Professor Nelson said: "Directed evolution could help simplify the production process for many drugs already on the market, but it's unlikely to be used in this way as a new method of synthesis requires approval even for an existing drug. However, in the future, drug design is likely to focus more and more on directed evolution, with a big increase in the number of bio-engineered catalysts created for drug development."

Dr Berry added: "It is surprising that chemical manufacturers don't use enzymes more widely as catalysts, as they are environmentally friendly. The main stumbling block has been that enzymes will only carry out very specific reactions. However, we've shown that directed evolution allows us to modify natural enzymes as required, opening up the possibility of creating tailored catalysts for a range of industrial chemical syntheses."

The research was funded by the BBSRC, EPSRC and the Wellcome Trust. The scientists have secured further funding from these agencies to look at adapting enzymes to create more complex sugars, such as di- and tri-saccharides.

Source: University of Leeds