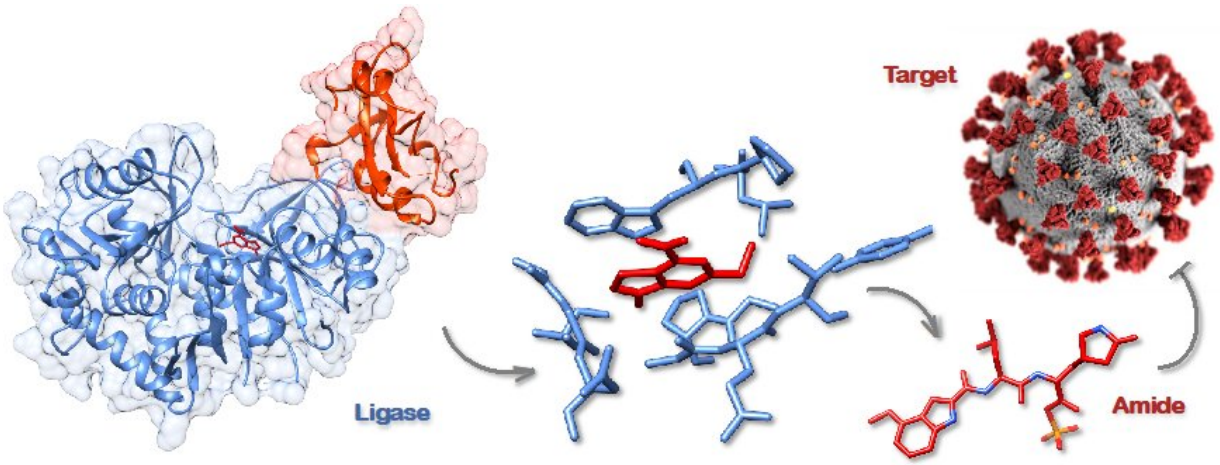
Scientists accelerate path to drugs for COVID-19

May 20 2021, by Ben Robinson



Credit: University of Manchester

Scientists at The University of Manchester have developed a more efficient method to produce medicines that are in development for the treatment of COVID-19, cancer and other diseases that affect many of the world's population.

New research published today, in *Nature*, describes a new family of enzymes (ligases) which can assemble the key chemical building blocks required for pharmaceutical production. The newly discovered enzymes can effectively enable different molecules to be stuck together by creating what is known as amide bonds. This discovery paves the way to

more efficient and sustainable production of pharmaceuticals and other valuable chemicals.

The new findings have demonstrated that the ligase enzymes can accept many substrates, but in some cases proved too unstable for practical use. To overcome this problem, the researchers mutated the enzymes to create more robust and stable variants which were shown to have important practical applications and could be used to make pharmaceuticals. They were able to make key amide containing precursors of various antiviral agents, including a drug from Pfizer that is currently in clinical trials for the treatment of COVID-19. They also made the key amide component of an anticancer agent in clinical trials for leukemia. Finally, they showed how the ligases could be used to generate derivatives of ibuprofen which are being developed as potentially improved anti-inflammatory agents.

Amide bonds are very important in nature. For example, the protein molecules that control the functions of all living organisms are held together by amide bonds, which form a link between the carbon and nitrogen atoms of amino acid building blocks.

The amide bond can also be used to construct a raft of synthetic, non-natural, molecules including many of the most important pharmaceuticals that we rely on today and agrochemicals that can boost crop yields to feed the growing population. In addition, the amide bond is also very strong and is used to construct hard wearing materials (polyamides) including, textiles and carpets.

Prof Jason Micklefield who led the Manchester team said: "We are confident that our ligase enzymes offer many advantages over the existing methods used to make amides. We are also optimistic that our enzymes can find real word applications in the manufacture of new medicines and other useful products."

"The ligase enzymes provide a cleaner more efficient and rapid way to construct amide bonds. This could enable pharmaceuticals to be produced in fewer steps, with less waste and at lower costs than the typical chemical processes used today."

For many years, scientists have sought to develop new synthetic methods to construct amide bonds. To date most of these methods have relied on toxic chemical reagents and dangerous volatile organic solvents which are damaging to the environment. Most of the existing methods also lack selectivity and result in by-products. Consequently, amide containing molecules, including pharmaceuticals, often require multi-step manufacturing processes which make these products expensive.

The team in Manchester, went searching for natural catalysts (enzymes) that could construct amide bonds in a cleaner, more efficient and sustainable manner using water as a solvent. They investigated pathways used in bacteria to produce amide containing molecules (natural products). They found a family of ligase enzymes that bacteria use to make amide containing toxins that kill plants.

Initially the team explored the use of these ligases to make herbicides, which might be deployed in farming to improve crop yields. However, when they used X-ray crystallography to determine the structure of one of the ligase enzymes, they realized that the enzyme active site was relatively open and could accommodate a much wider range of substrate building blocks for production of pharmaceuticals.

More information: Michael Winn et al, Discovery, characterization and engineering of ligases for amide synthesis, *Nature* (2021). DOI: 10.1038/s41586-021-03447-w

Medical Xpress

Provided by University of Manchester

Citation: Scientists accelerate path to drugs for COVID-19 (2021, May 20) retrieved 25 April 2024 from https://medicalxpress.com/news/2021-05-scientists-path-drugs-covid-.html

This document is subject to copyright. Apart from any fair dealing for the purpose of private study or research, no part may be reproduced without the written permission. The content is provided for information purposes only.