DRUG DESIGN

PHARMACOLOGY

New vistas in anti-retroviral HIV drug design

HIV-1 protease is an enzyme which is essential for the replication of HIV, the retrovirus that causes AIDS. **The enzyme is a key drug target** for HIV/AIDS therapy; understanding its structure and function at the atomic level, including **the location and movement of hydrogen atoms, is vital for understanding drug resistance and guiding rational drug design.**

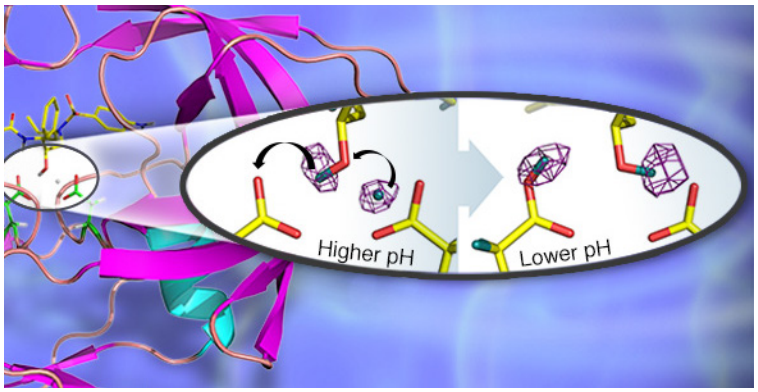

Fig. 1 - A 3D structure of the HIV-1 protease in cartoon representation with bound clinical drug darunavir (shown as sticks). The catalytic site contains two closely positioned aspartic acid residues. The insert depicts the hydrogen transfer reaction in the catalytic site, captured for the first time by neutron crystallography. Credit Jill Hemman and Andrey Kovalevsky (Oak Ridge National Laboratory).

The use of X-ray crystallography to study the structures of HIV-1 protease and drug complexes has led to the design of effective, commercially available drugs, but x-rays cannot determine the positions of mobile hydrogen atoms and protons. Neutron crystallography, however, can reveal these hydrogen-bonding interactions, which play a key role in how effectively a drug binds to its target.

Researchers used neutron crystallography to probe the structure of HIV-1 protease in complex with the clinical inhibitor darunavir, allowing details of the hydrogen-bonding interactions in the active site to be determined and revealing ways to enhance drug-binding and reduce drug-resistance. The group was also able to shed light on the sensitivity to pH of the enzyme's catalytic activity. These details will help in the design of new more effective antiretroviral therapy drugs.

These results highlight that neutrons represent a unique probe to obtain structural details for proton transfer reactions in biological systems.

REFERENCE

Long-Range Electrostatics-Induced Two-Proton Transfer Captured by Neutron Crystallography in an Enzyme Catalytic Site, Gerlits et al., Angewandte Chemie International Edition 55, 4924-4927, 2016 and ILL news.

Neutrons for Industry

http://sine2020.eu/industry.html

Neutrons for Industry

industry@sine2020.eu

SINE2020 Industry Consultancy is now open for requests.

Proof-of-concept experimental beam time is being offered to Industry!

RAPID ACCESS

Fast-stream processing for industrial applications, optimising result lead times.

CONFIDENTIALITY

Activity covered by non-disclosure agreements. Only company name and measurement type to be published.

FLEXIBLE SERVICES

In many cases industrial processes and conditions can be re-created in the test laboratory. Final data analysis and reporting are provided.

SINE2020

EXPERT CONSULTANCY

Industrial R&D professionals in collaboration with experienced specialists from European neutron centres.

PARTNERS FROM:

Czech Republic, France, Germany, Hungary, Netherlands, United Kingdom.

BNC

Science & Technology Facilities Council ISIS

ILL NEUTRONS FOR SOCIETY

HZB Helmholtz Zentrum Berlin

MLZ Heinz Maier-Leibnitz Zentrum

GEMS German Engineering Materials Science Centre Helmholtz-Zentrum Geesthacht

Orphée Laboratoire Léon Brillouin

TU Delft Delft University of Technology

SINE2020 receives funding from the European Union's Horizon 2020 research and innovation programme under grant agreement N° 654000