

# THE ILL ENDURANCE PROGRAMME



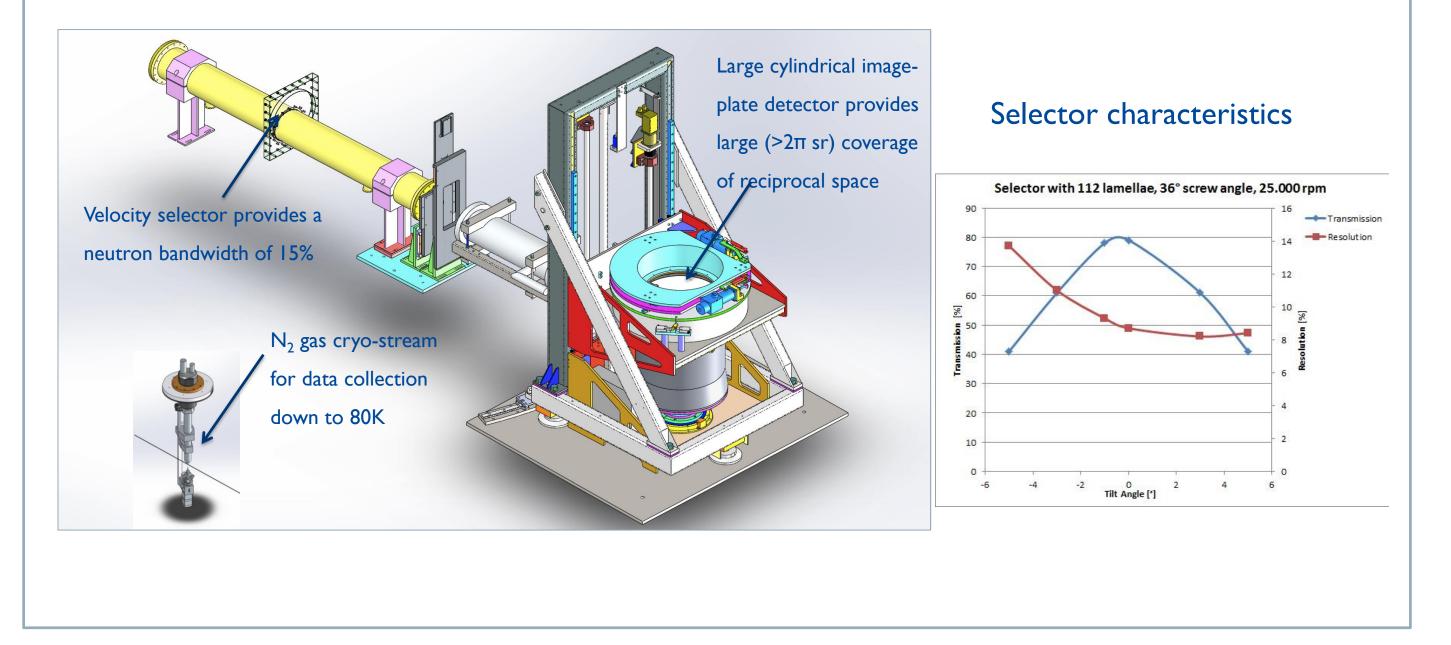
# **DALI** – Extending the capacity and capability for neutron macromolecular crystallography

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# THE INSTRUMENT

#### DALI will extend the range of systems to those with larger unit cells (>100Å)

- Combines quasi-Laue data collection with a large cylindrical detector
- Utilizes a narrower neutron bandwidth ( $\delta\lambda/\lambda = 10\%$ ) compared to LADI ( $\delta\lambda/\lambda = 30\%$ )
- Data collection will be possible at room- or low-temperatures (down to 80K)



# THE SCIENCE

#### H-atoms & protons (H<sup>+</sup>) play key roles in numerous biological systems and processes

- Knowledge of their positions is essential e.g. in elucidation of enzyme mechanisms and for improving drug-design
- Neutron crystallography is the only approach to locate mobile H-atoms/protons and without radiation damage issues

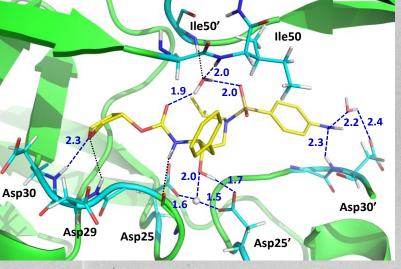
HIV drug design studies An immature HIV virus particle during the process of maturation. HIV protease (A) cleaves proteins required for virions to mature and become infectious, and thus is a. target in HIV therapy.



The structure of HIV protease with an inhibitor bound in the active site. Drug design has been led by structures of enzyme-protease inhibitor complexes, determined using X-ray diffraction.



Neutron diffraction allows direct location of H-atom and H<sup>+</sup> positions, revealing the Hbonding interactions in the active-site.



J. Med. Chem. (2013) 56, 5631 Angewandte Chem. (2016) 55, 4924 J. Med. Chem. (2017) 60, 2018

## AN EXPANDING FIELD

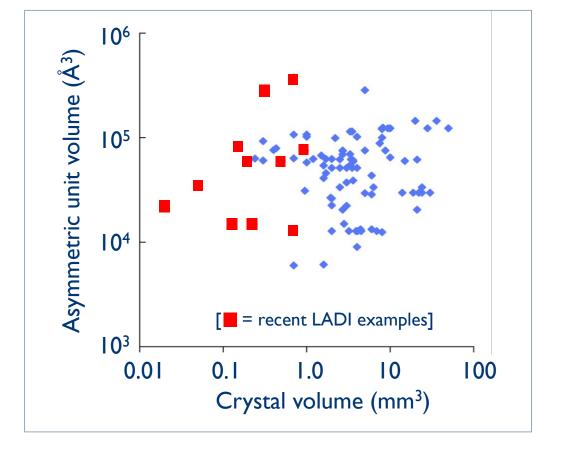
### **HIGH-IMPACT**

 Improvements to LADI at HI43, along with new instruments online (MLZ, ORNL etc) has led to an expanding field with >50% (86/166) structures determined since 2015

#### Number of proposals, days requested and overload rate all increasing for LADI

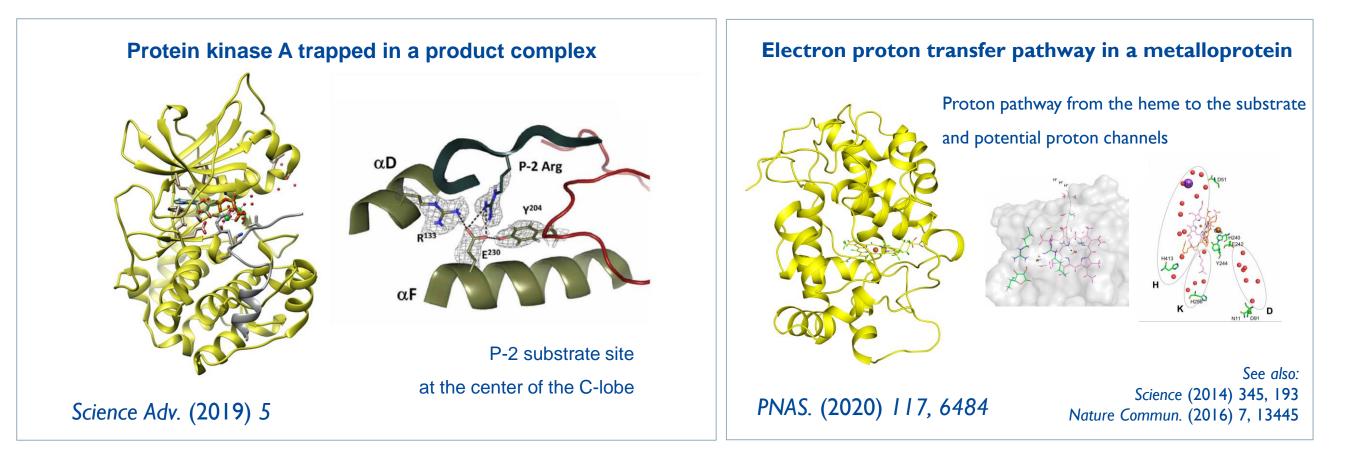
Year	Proposals	Days requested	Overload
15/16	50	713	2.9
17/18	35	478	2.3
19/20	50	379	3.4

LADI continues to be world-leading e.g. most
structures [36], largest cell [125kDa], lowest crystal-to-cell
volume ratio [15 x 10<sup>14</sup>], fastest data collection [14h]



- Results are often medically relevant and of high-significance
- Reflected by publications in high-impact journals e.g. Science, Nature Commun., Angewandte Chem.

#### • Average impact-factor per publication = 6.8



# **DALI SITING**

**DALI** will be sited in front of LADI at the end-position of cold **neutron guide H141** 

LADI at HI43

• Planned to be in place for **commissioning by the last cycle of 2020** 

# **EXTENDING THE LIMITS**

**DALI** will allow us to do **extend the capacity and capability for neutron MX** 

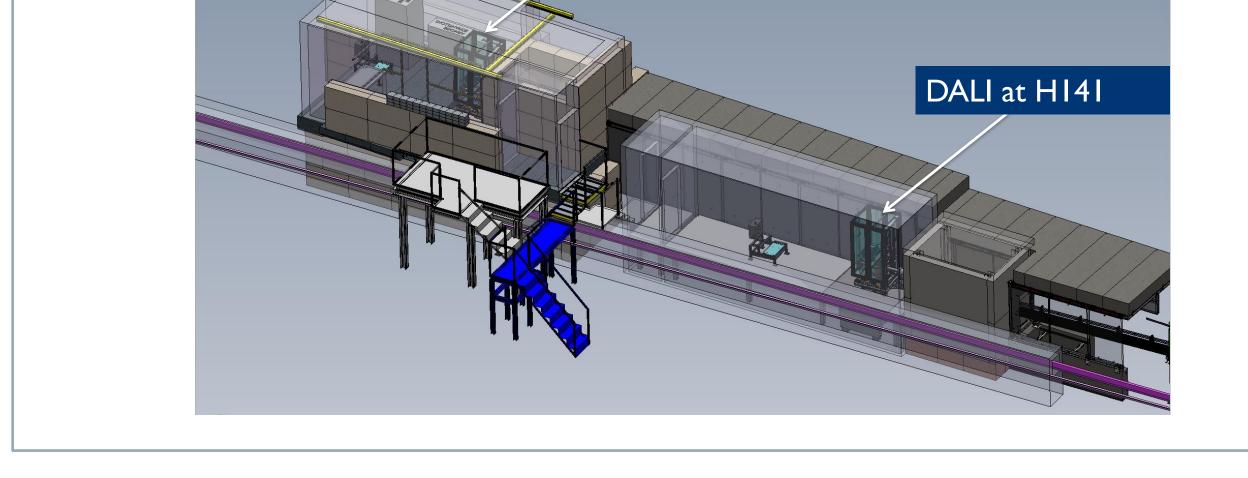
 Reduced bandwidth of DALI (cf. LADI) will (i) improve data completeness for large cells (i.e. 80 - 100Å on edge) and (ii) allow us to extend the limits to >100 Å on edge

#### **DNA** polymerases

AcetylcholinesteraseAcetlycholinesterases catalyze the breakdown of theneurotransmitter acetylcholine. They are the target of inhibition bynerve agents and pesticides.Unit-cell = 126, 126, 134 Å ( $P3_1$ 12) $\delta\lambda/\lambda$ =10% <12% of reflections</td>spatially overlapped

#### INSTITUT LAUE LANGEVIN - THE EUROPEAN NEUTRON SOURCE





DNA polymerases play a central role in cell division, duplicating DNA and passing it to new cells. Unit-cell = 93, 108, 150 Å  $(P2_12_12_1)$  $\delta\lambda/\lambda = 10\% < 8\%$  of reflections spatially overlapped