Deuterated Molecules From Custom Synthesis Facilities- Opportunities and Challenges

THE DEUTERATION NETWORK

Facilitating access to bespoke deuterated materials for your research and promoting deuteration science

DeuNet

Tamim Darwish
Board Chair – DeuNet
Leader – National Deuteration Facility (ANSTO)

Outline

1	Why deuteration? Neutron Scattering, Reflectometry, Diffraction and Crystallography and Others
2	A brief history Deunet
3	DeuNet, refreshed- Vision and Mission- Activities
4	Why do we need deuteration facilities? (cost effectiveness)
5	DeuNet 2022 User Survey Summary

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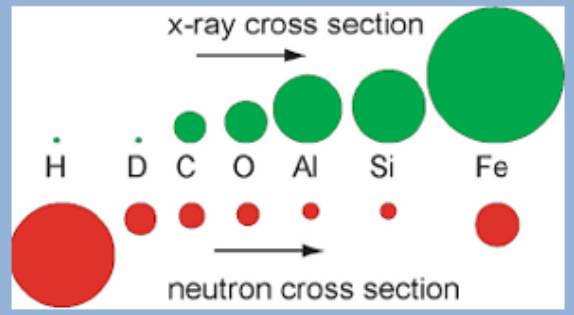
The Deuteration Network

Deuteration as a characterisation tool

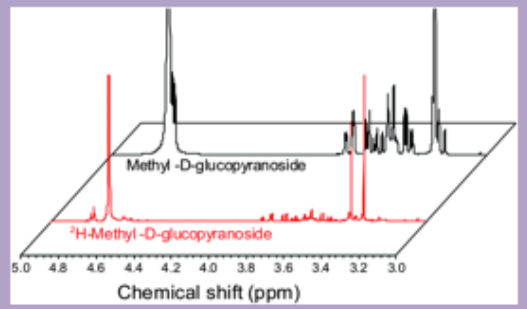
Neutrons

Interact with the nucleus-scattering length



NMR

Nuclear spin properties



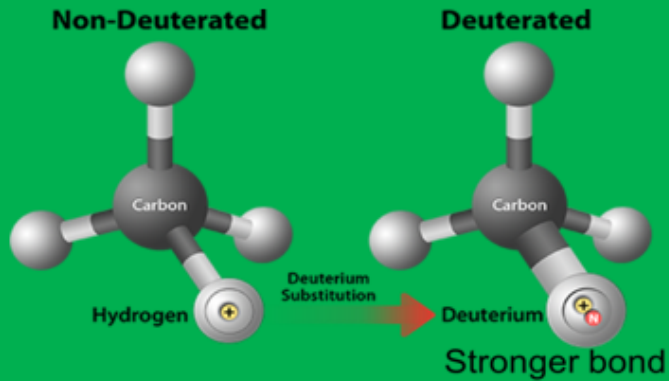
Infra-Red

Vibration frequencies and modes

2800-3000 cm^{-1} (IR)

2000-2200 cm^{-1} (IR)

Kinetic Effect



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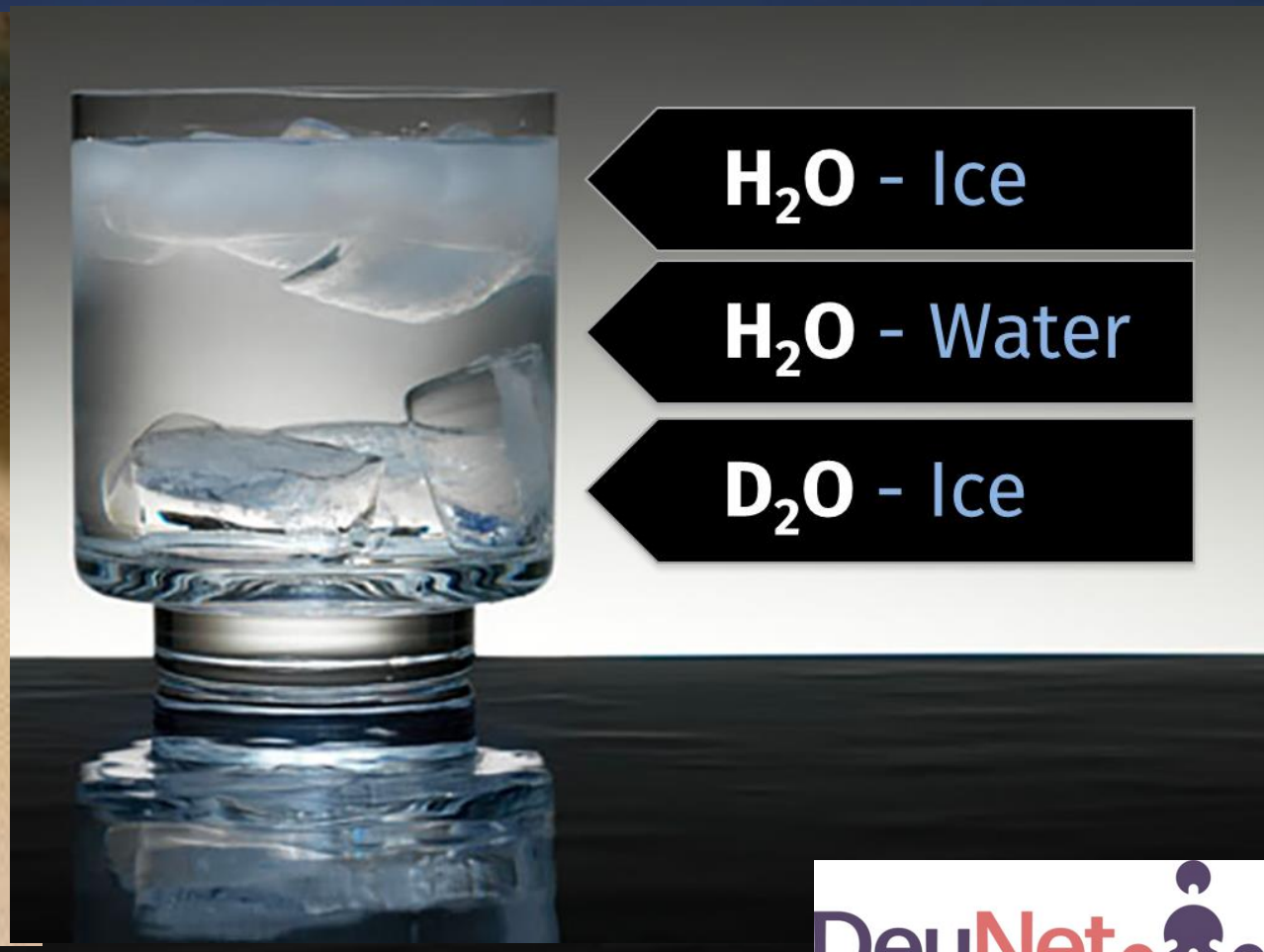
Characterisation Tool & Functional Materials



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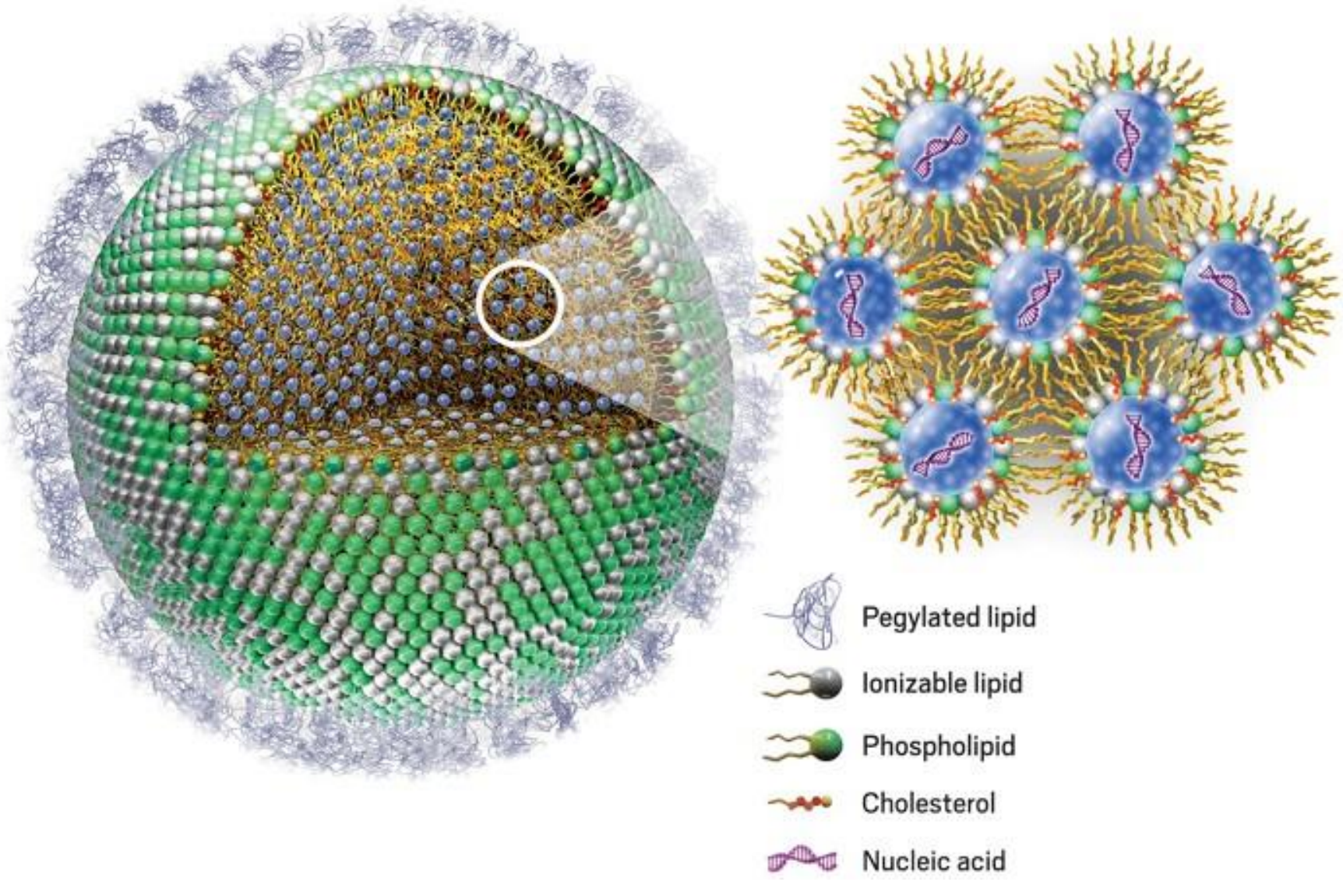
Deuteration to understand complex structures using SANS



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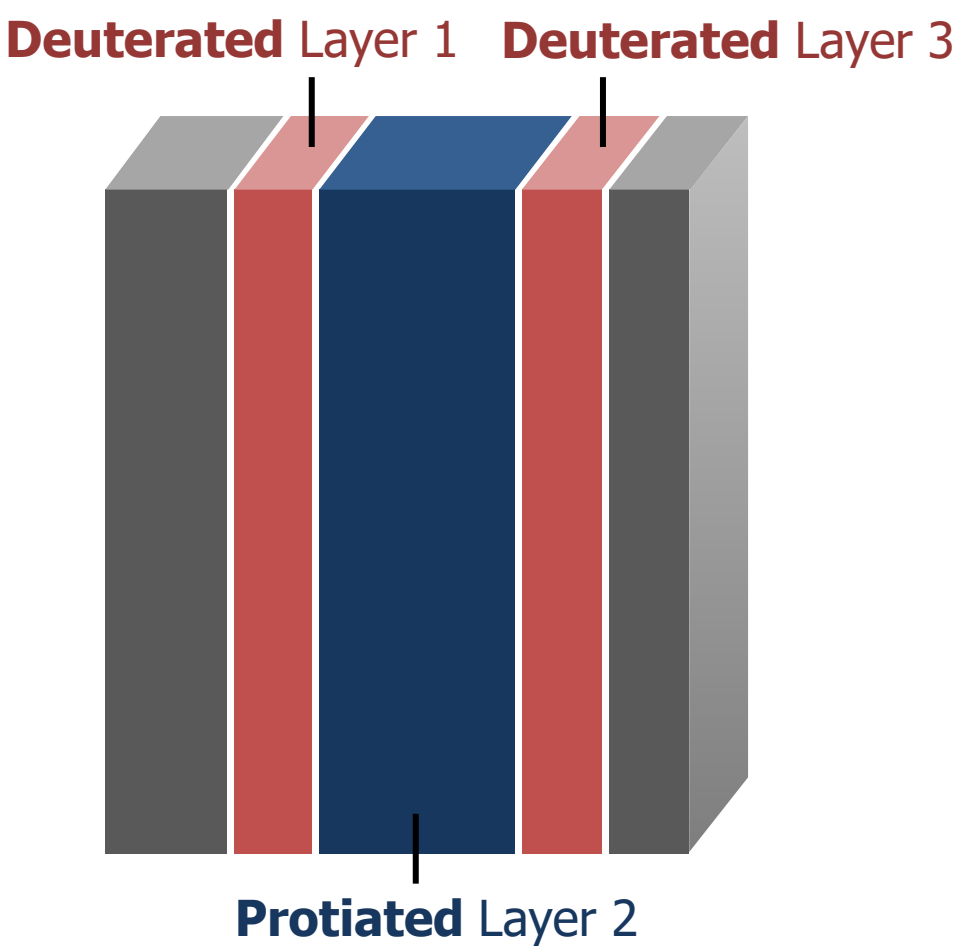
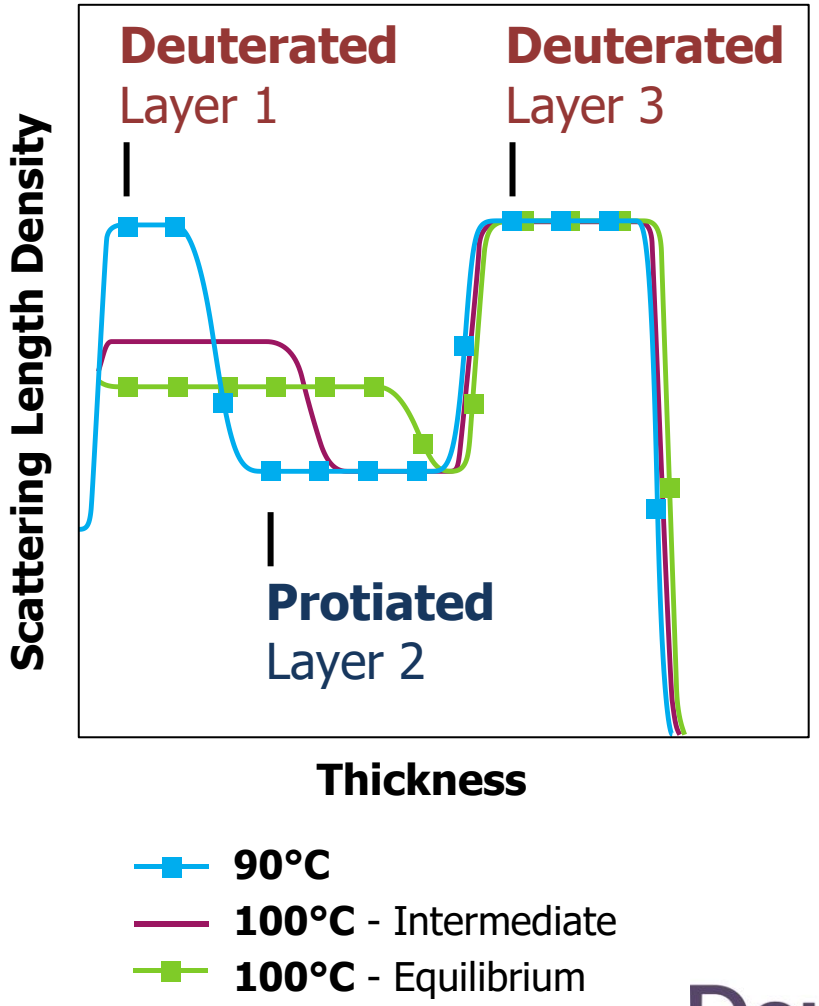
Deuteration for contrast between layers in neutron reflectometry (NR)





Smith et. al. Adv. Funct. Mater. 2011, 21, 2225

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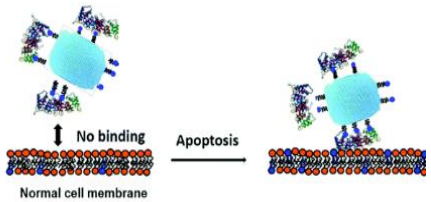
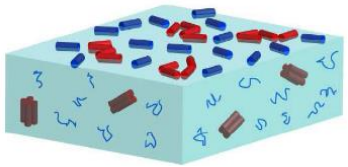
Partially Deuterated Proteins

Partially deuterated proteins are useful for various biological investigations. Deuteration of the proteins provides **contrast for neutron scattering** experiments which can be utilised for research areas, including:

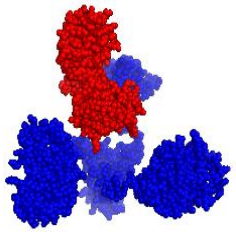
1. Human Health



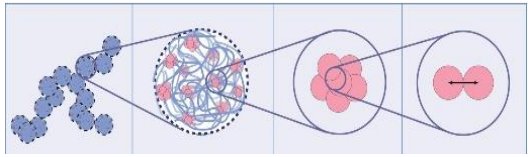
2. Understanding Bacteria



3. Protein Behaviour



4. Food Products



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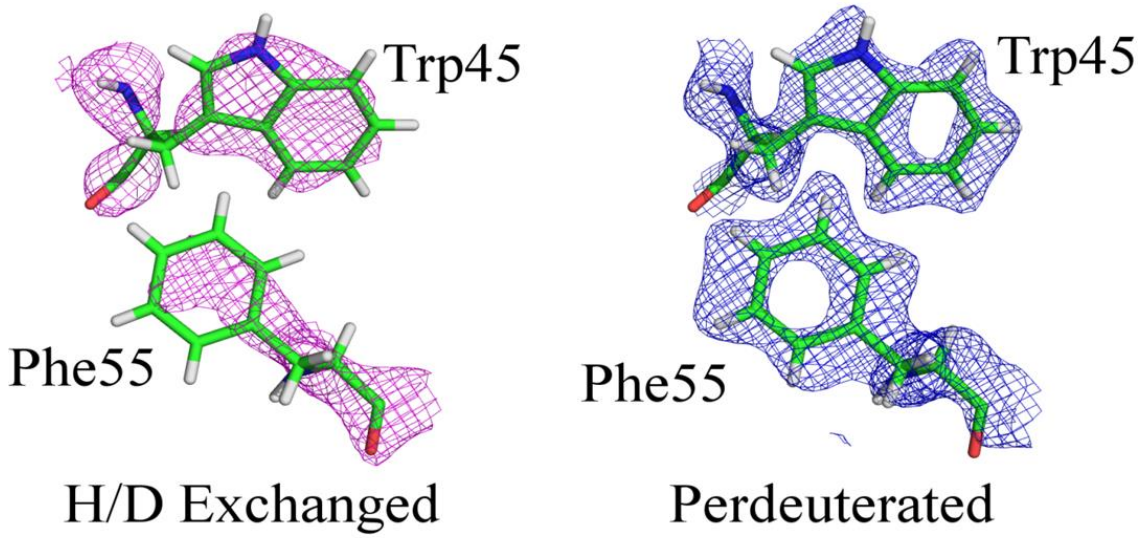
Deuteration to reduce the incoherent scattering of hydrogen in neutron diffraction

Removing ^{1}H from the crystal reduces incoherent (noise) scattering, and thus allows for:

- Smaller crystals
- Shorter diffraction time
- Weak neutron source / detector



Nuclear density maps, 2.1Å resolution, of H/D exchanged (left) and perdeuterated (right) cholesterol oxidase (Golden, Duff, Meilleur, Vrielink, unpublished figure)
Non-exchangeable hydrogen atoms bonded to positively scattering carbon atoms results in cancellation of density as can be seen on Phe55 and Trp45 of the H/D exchanged structure. Density cancellation is near-complete for CH_2 groups.

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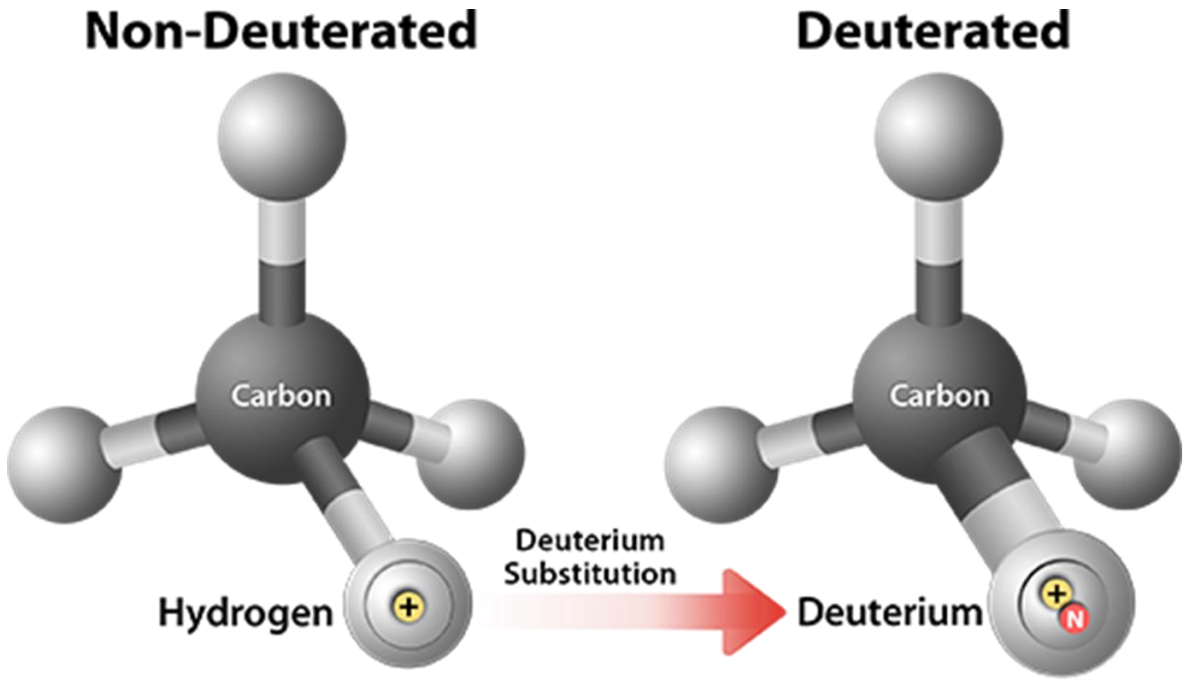
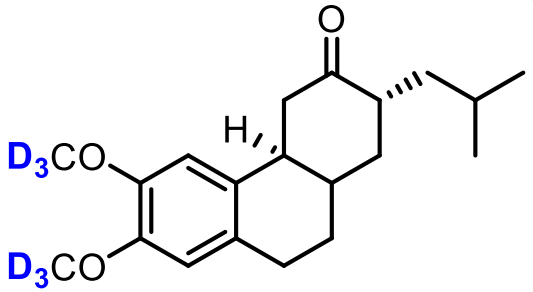
Superior Properties of Deuterated Drugs

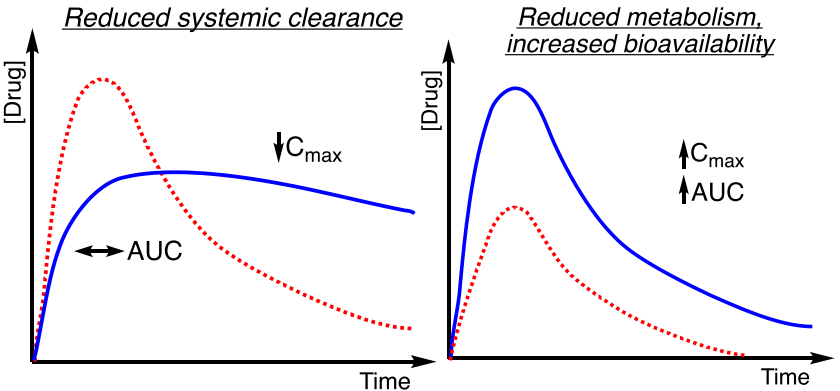




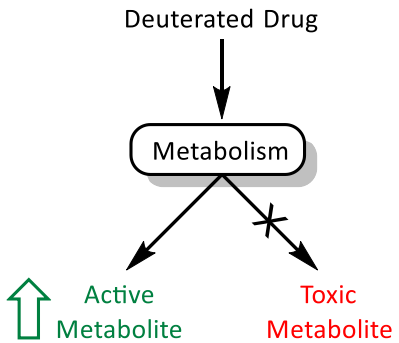
Deuterabenzine
FDA approved 2017

- The half-lives of tetrabenazine-d6 and its active metabolites are almost twice as long as those of the undeuterated compounds

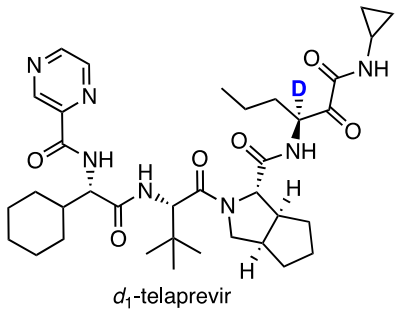
Improve Pharmacokinetics



Reduce Toxicity



Modulate Epimerisation



d_1-telaprevir

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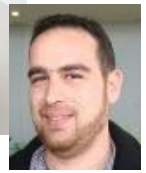
A Brief History- Deunet

EU-infrastructure project funded by SINE2020

EUROPEAN SPALLATION SOURCE

Peter



Tamim

European chemical deuteration platform

- 4-year EU project 2015-2020

ESS, ILL, ISIS and JCNS, with ANSTO NDF as an observer member.

Goals:

- Benefit from **methods, expertise and resources** at all facilities
- **Form a cost effective platform** to share materials
- **Include University, international and industrial partners**
- **Offer user access** to existing products and services of the labs
- **Coordinated access** for all European neutron users

NEUTRONS FOR SCIENCE

Science & Technology Facilities Council

JÜLICH FORSCHUNGSZENTRUM

Australian Government
Department of Education, Science and Training

Deunet in SINE2020 – an EU project

Main achievements of SINE2020:

- Establishment of a new chemical deuteration laboratory at ESS
- European User Survey (2017) on deuteration use and needs
- Access to STFC deuteration facility to European users
- Development of methods for lipid deuteration, and separation from cell cultures at ILL
- Joint R&D and new collaborations in e.g. enzymatic + chemical synthesis of chiral biopolymers at FZJ and ESS.
- JCNS starts deuteration service
- Participation in broader infrastructure collaborations (e.g. LENS, ARIE)
- Several new international members joined the Deunet

This project received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 654000

League of advanced European Neutron Source

Working group 3 : Synergies in technological development and operation
Subgroup on Deuteration Technologies (Chem, Bio, Xtal) ESS, ILL, STFC, FZJ

4 Pillars:

- chemical deuteration
- biological deuteration
- macromolecular crystallisation
- networking and synergies

Priorities aligned to outcomes of SINE2020 (Sustainability report):

1. Identifying new R&D projects and collaborations aligned to future research themes and priorities in Europe
2. Networking with international deuteration facilities
3. Cross-facility working group on deuteration user access in Europe

Activities: Webinar series, Pilot Action on Global Health Challenges

Brightness^2 EU project 2019-2022 (finished):

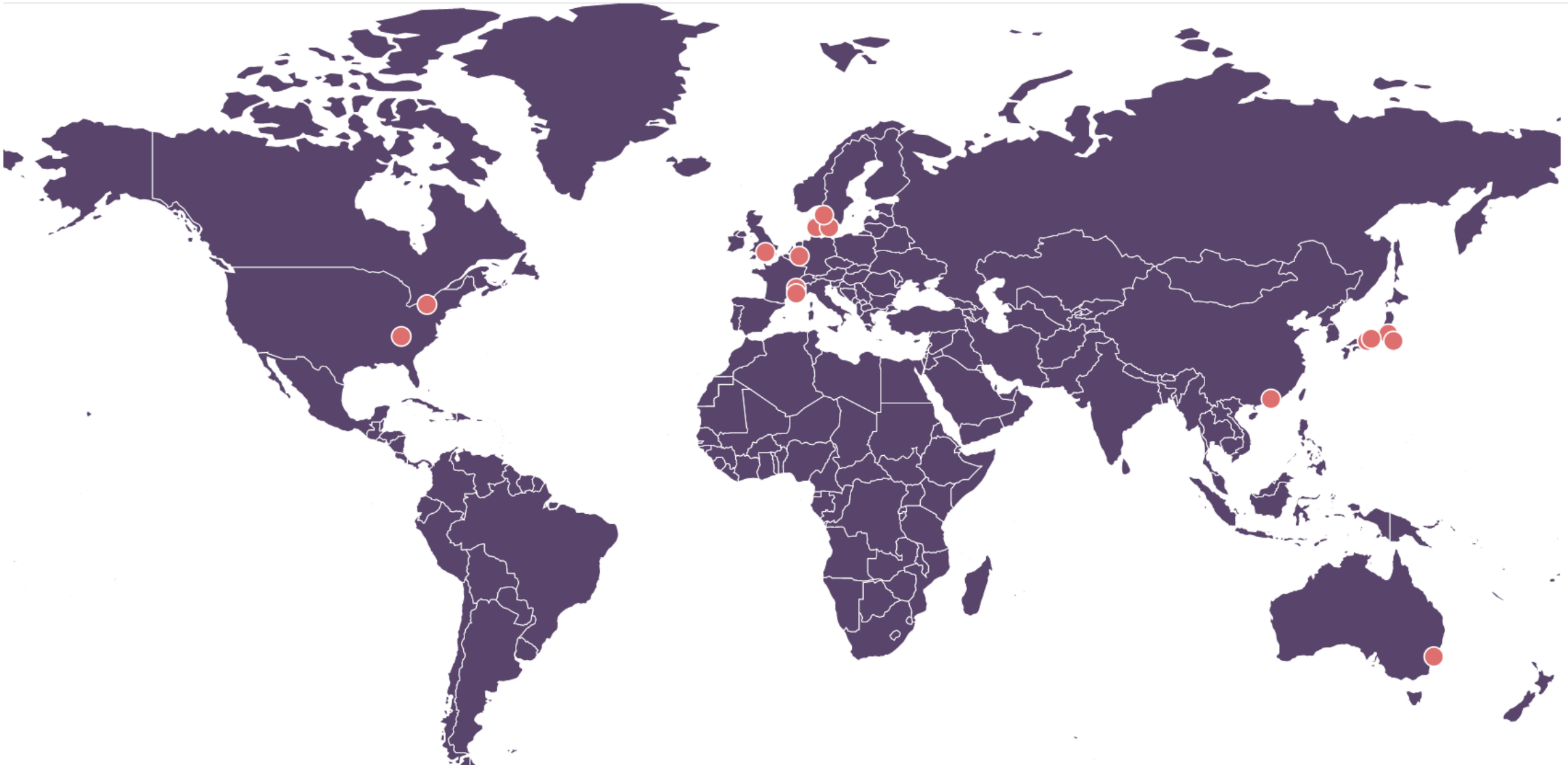
WP2 Task 2.3B: Deuteration For Soft Matter and Life Sciences (ESS-STFC)

- i) chemical and/or microbial production of perdeuterated fatty acids and lipids
- ii) enzymatic synthesis of complex novel deuterated compounds.

Deuteration subgroup = European members of DEUNET, Lead: John Wester (STFC)

BrightnESS^2 is funded by the European Framework Programme for Research and Innovation Horizon 2020, under grant agreement 823867

DeuNet Labs and Facilities in 2023



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DeuNet Board

Executive Board

Tamim Darwish, NDF (Chair)

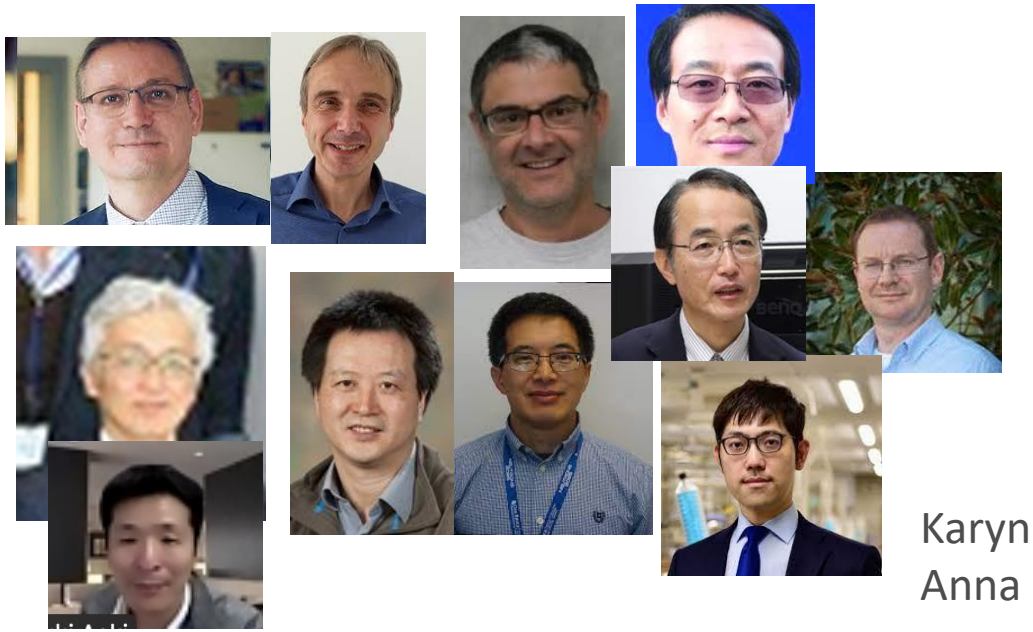
Zoe Fisher, ESS

Giovanna Fragneto (ESS/ILL)

Hanna Wacklin-Knecht, ESS

John Webster (STFC)

Board members

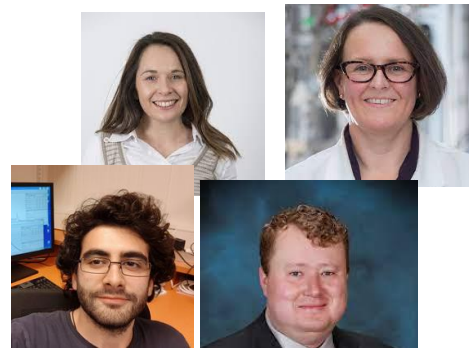


- Peixun Li, STFC
- Zvi Kelman (NIST/IBBR)
- Wolfgang Knecht, LP3/PPS
- Hiroyuki Aoki, J-PARC
- Hugh O'Neill, ORNL
- Hiroshi Naka, Deut-Switch (Kyoto)
- Jürgen Allgaier, JCNS
- Kunlun Hong, ORNL
- Howard Wang, SLAB
- Masaaki Sugiyama, KIDS
- Hironao Sajiki, Gifu Pharma Uni
- D-Lab (ILL)

Communications/Web Sub-Group

Karyn Wilde, NDF (Chair)
Anna Leung, ESS

Brad O'Dell, NIST/IBBR
Hiroshi Naka, Deut-Switch
Giacomo Corucci, ILL



DeuNet Vision and Mission

An international network of deuteration facilities and laboratories which aims to facilitate access to deuteration services and customised deuterium labelling of molecules and biomolecules for use in neutron research and in other characterisation techniques.

Endeavours to become a central hub for access to deuteration research around the world, deuteration information and research outcomes that are enabled by deuterium labelling.

DeuNet Aims

Promote collaborations between deuteration facilities and laboratories- Complementarity and steer away from duplicating efforts

Increase visibility of its members to researchers and research facilities that benefit from deuteration science

Facilitate the development of new methods for deuteration

Facilitate communication between each of the DeuNet members and their collaborators through regular meetings and user workshops.

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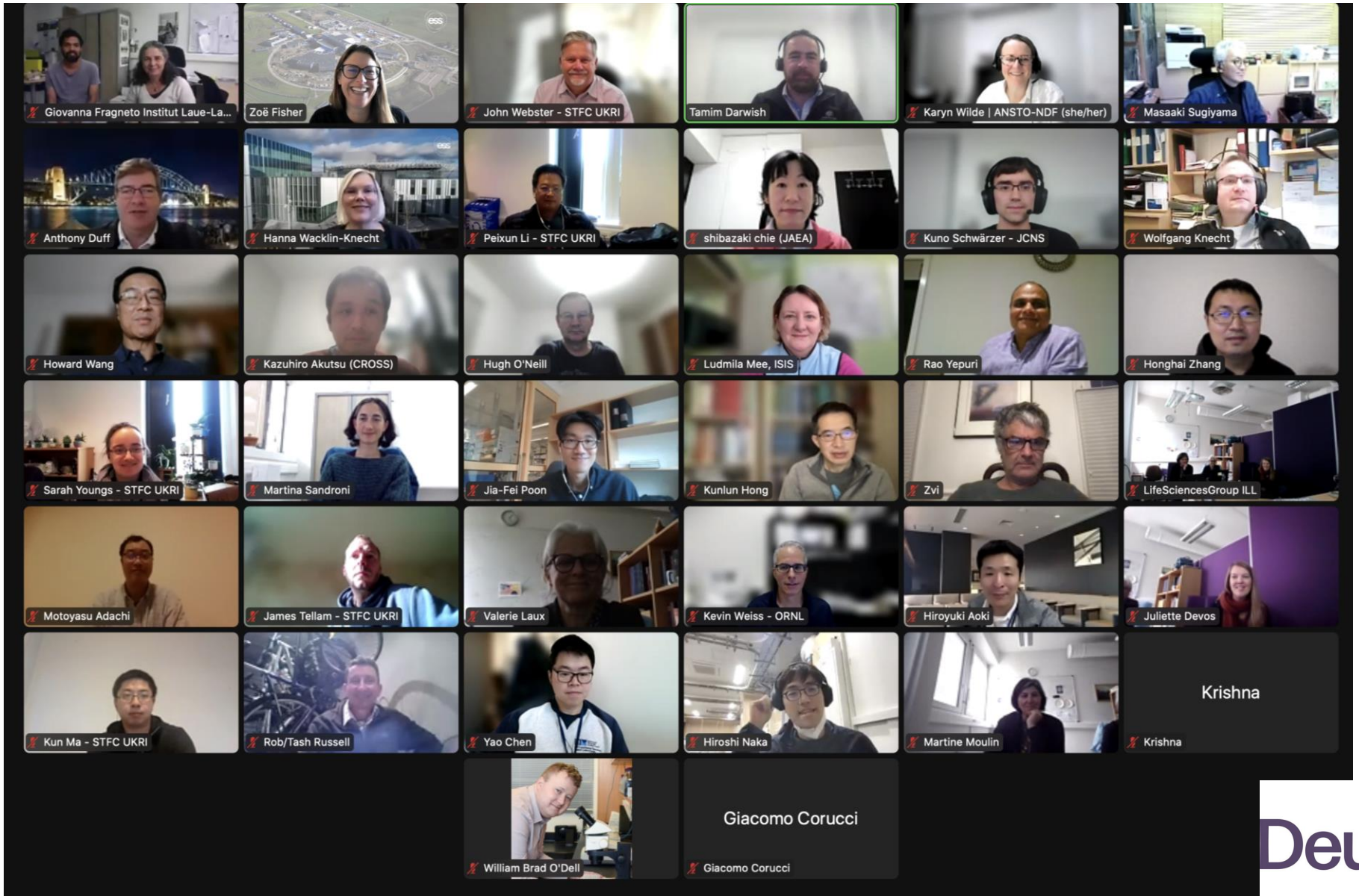
DeuNet Facilities Meeting, Nov 2022



J-PARC Deuteration Workshops

2017 Tamim Darwish, NDF
Anna Leung, ESS

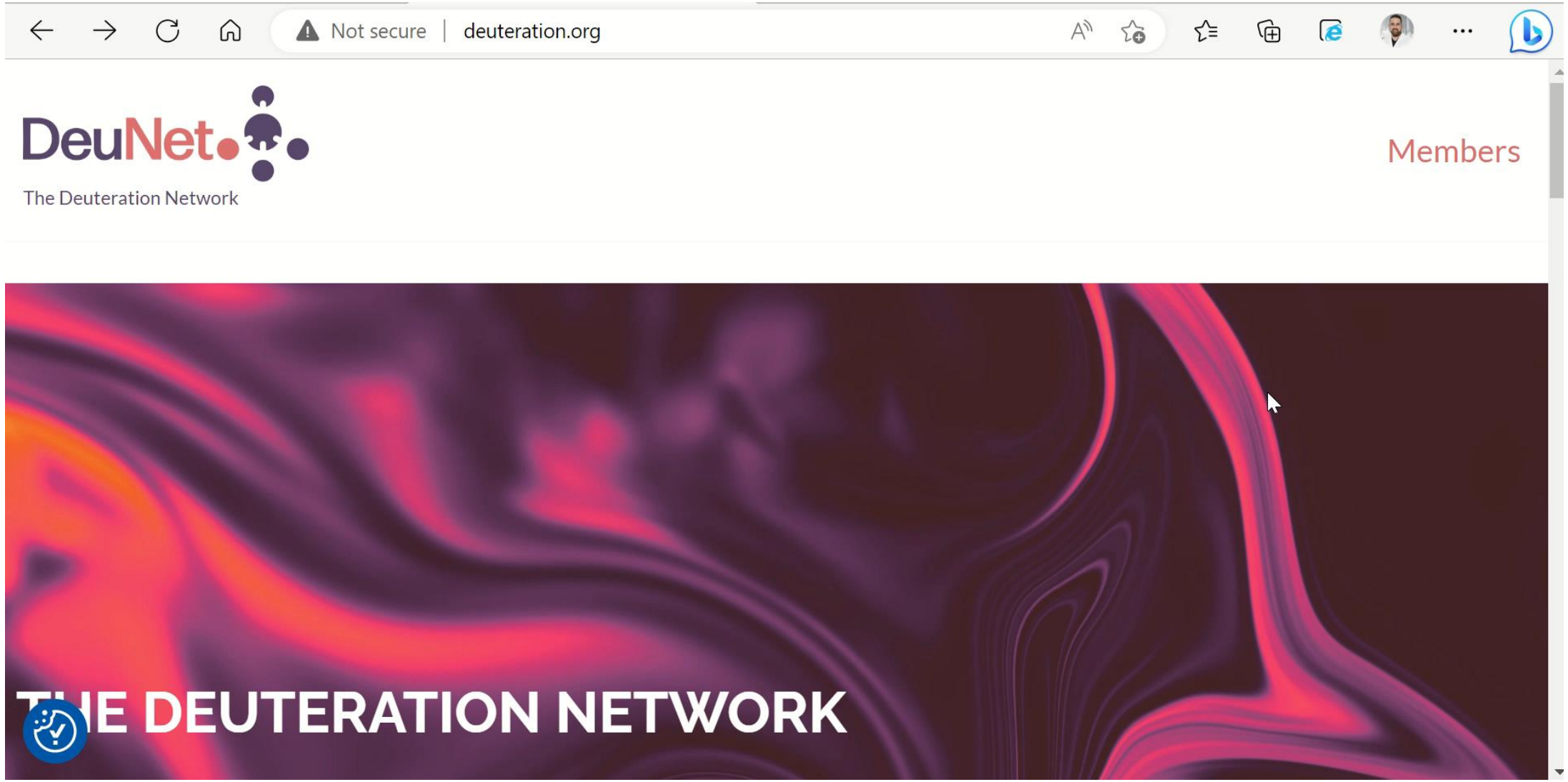
2018 Tamim Darwish, NDF
Kunlun Hong, ORNL

2023 Tamim Darwish, NDF
Zoe Fisher, ESS (couldn't attend)

Next Year J-PARC Deuteration Workshop mid-2024

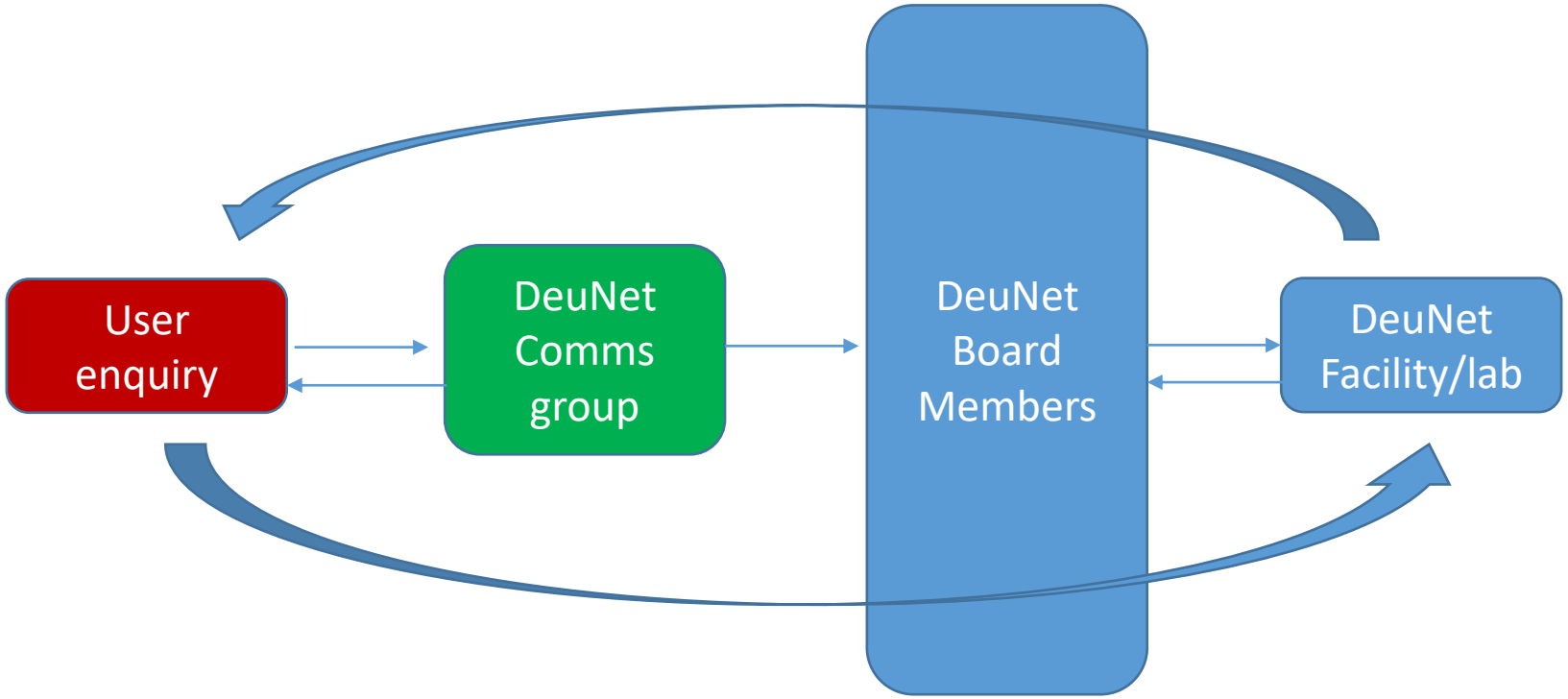
International Deuteration Workshop!

DeuNet Webpage



DeuNet Webpage and communication flow

- http://deuteration.org
- contact@deuteration.org
- News and stories
- Publications
- Chat channel (members only)



DeuNet on Social Media

DeuNet

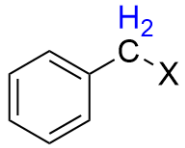
Why do we need deuteration facilities?

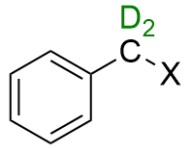
- Customizing molecules to fit the users needs is more productive and cost effective

Cost/variety of deuterated materials

It is no secret that labelled compounds are expensive and available in lower chemical diversity than native materials. Site-specific deuteration is a cost multiplier. In the case below, -d_5 and -d_7 are also available, and more cheaply.

Talk to us!





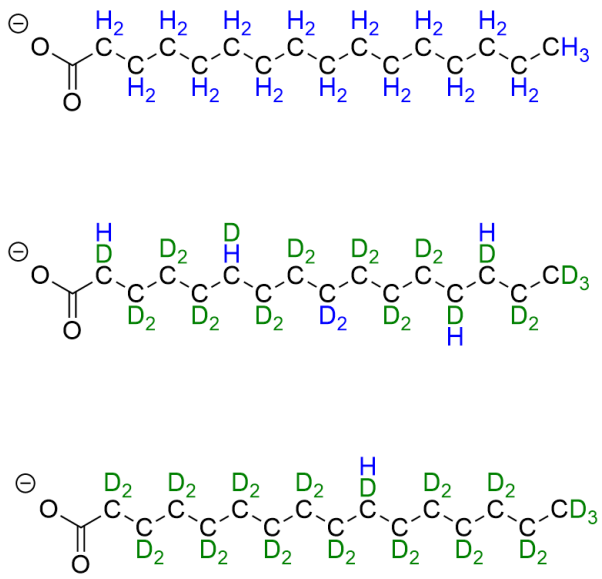
X =	Lowest listed price (USD/g)	Lowest listed price (USD/g)
Cl	0.04	980
Br	0.18	275
I	31	N/A

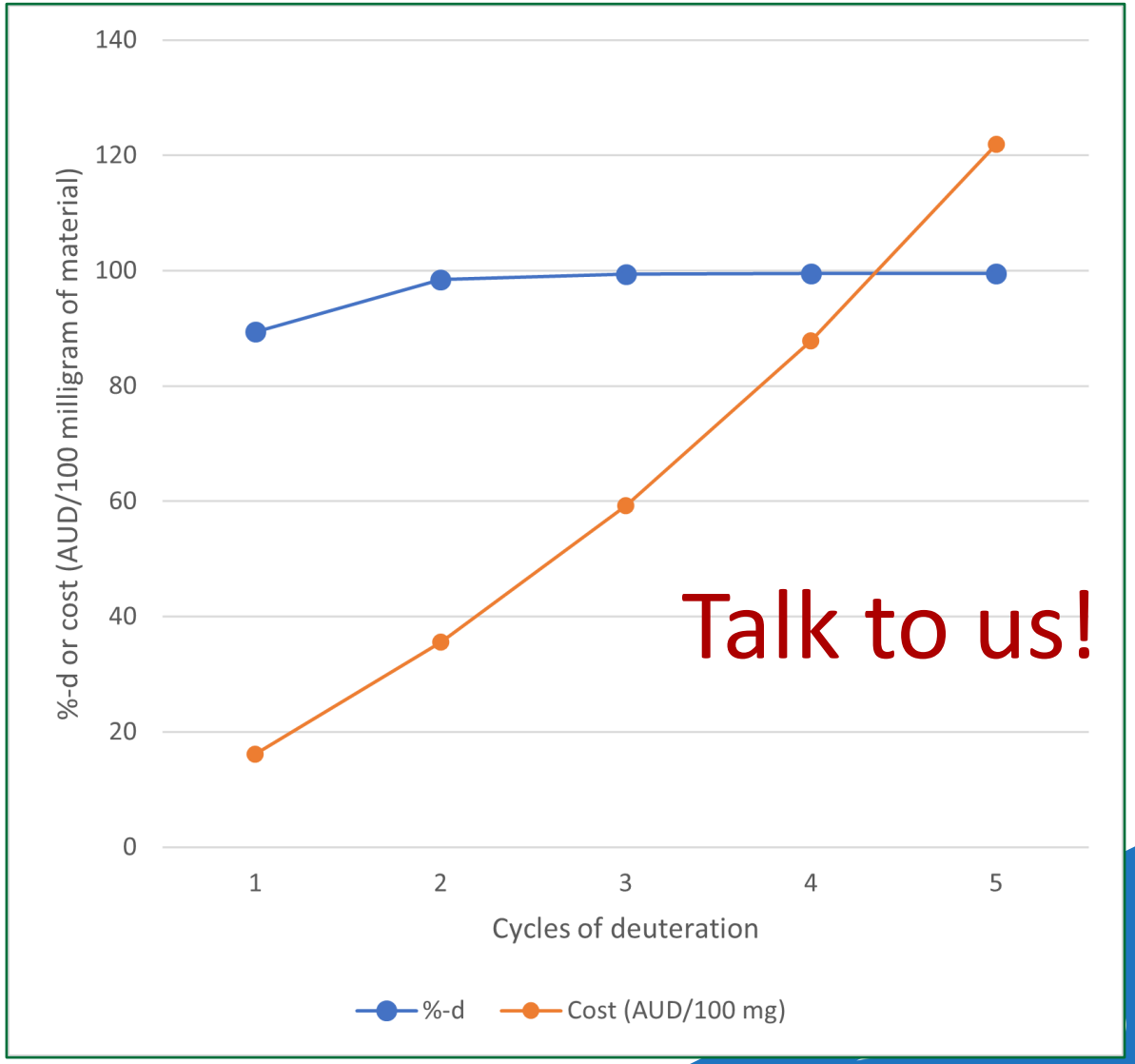
Dr Carl Recsei

ANSTO

Cost *vs* isotopic purity

- Hydrothermal deuteration is a process of catalysed H/D exchange – hydrogen atoms are redistributed between the D_2O solvent and the molecule to be deuterated with the aid of precious metal catalysts.
- Moderate deuteration is straightforward to achieve, with increasingly stark costs associated with the highest levels of isotopic purity.

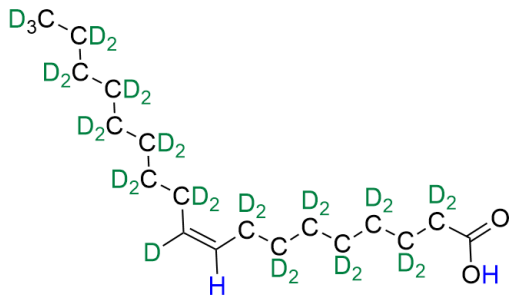


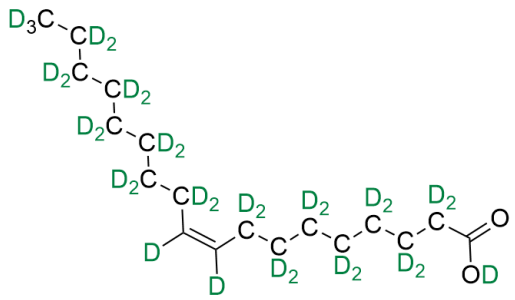


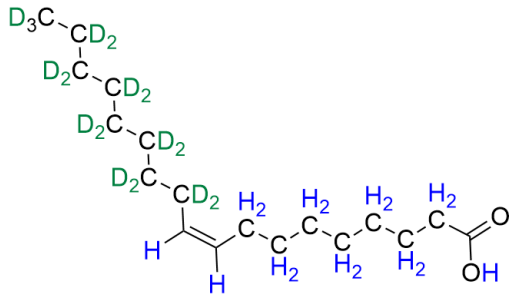
Searching for deuterated materials (i)

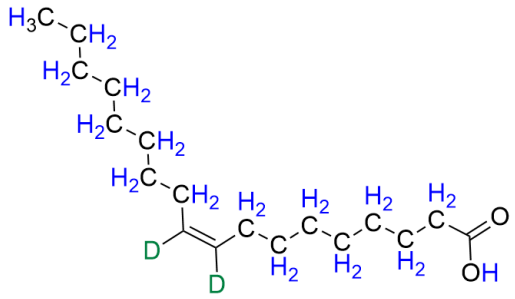
Oleic-d_{33} acid

The CAS database contains these compounds:









Options for potential buyers of these deuterated oleic acids:

Supplier	Lowest listed price (USD/mg)	$-d_x$	%-*d*
Non-NDF	30	2	6%
Non-NDF	82	17	52%*
Non-NDF	31	33	100%*
NDF	3.2	33 (32)	94%

*exact level is lower – these are theoretical maxima based on the reported structure

Talk to us!

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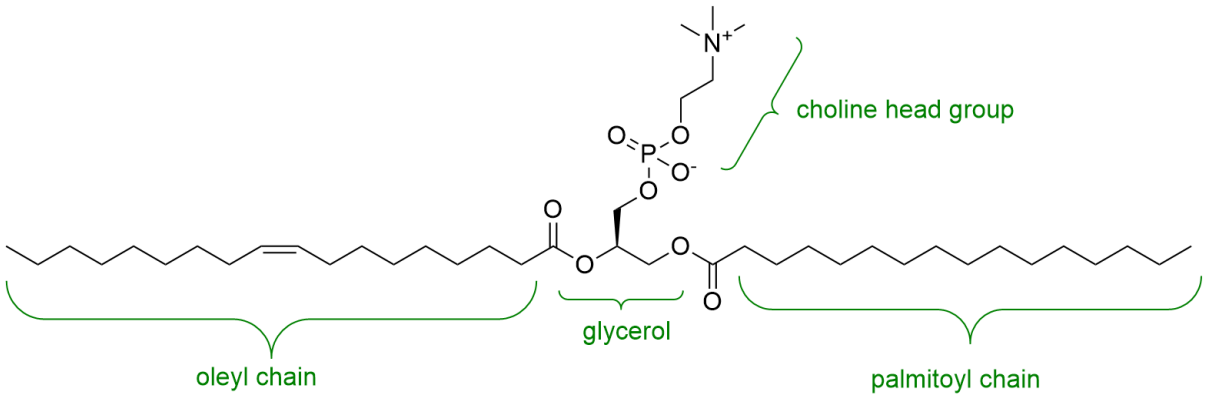
Searching for deuterated materials (ii)

POPC-d_n

$31 < n < 82$



Supplier	Choline head	Glycerol	Palmitoyl chain	Oleyl Chain	Lowest listed price (USD/mg)	%-*d*
Non-NDF	h_{13}	h_5	h_{31}	h_{33}	3.1	0%
Non-NDF	h_{13}	h_5	d_{31}	h_{33}	33	38%*
NDF	h_{13}	h_5	d_{31}	d_{33}	7.0	75%
NDF	d_{13}	h_5	d_{31}	d_{33}	48	90%
Non-NDF	d_{13}	d_5	d_{31}	d_{33}	484	100%*

*exact level is lower – these are theoretical maxima based on the reported structure

Talk to us!

ANSTO

DeuNet 2022 User Survey Summary

305 responses received *(as of 1st September 2022)*

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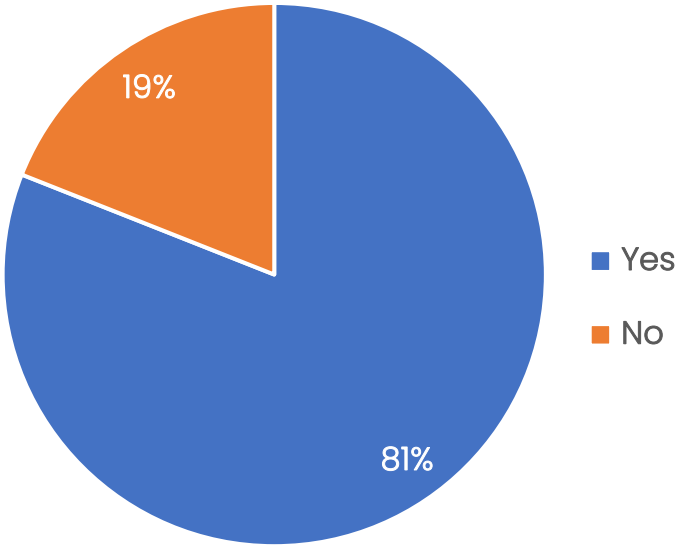
The Deuteration Network

Do you currently use deuterated materials in your research?



How dependent is your research on access to deuterated materials?

~50% (of current users of deuterated materials) responded their research either **very dependent** or **impossible without** deuterated materials

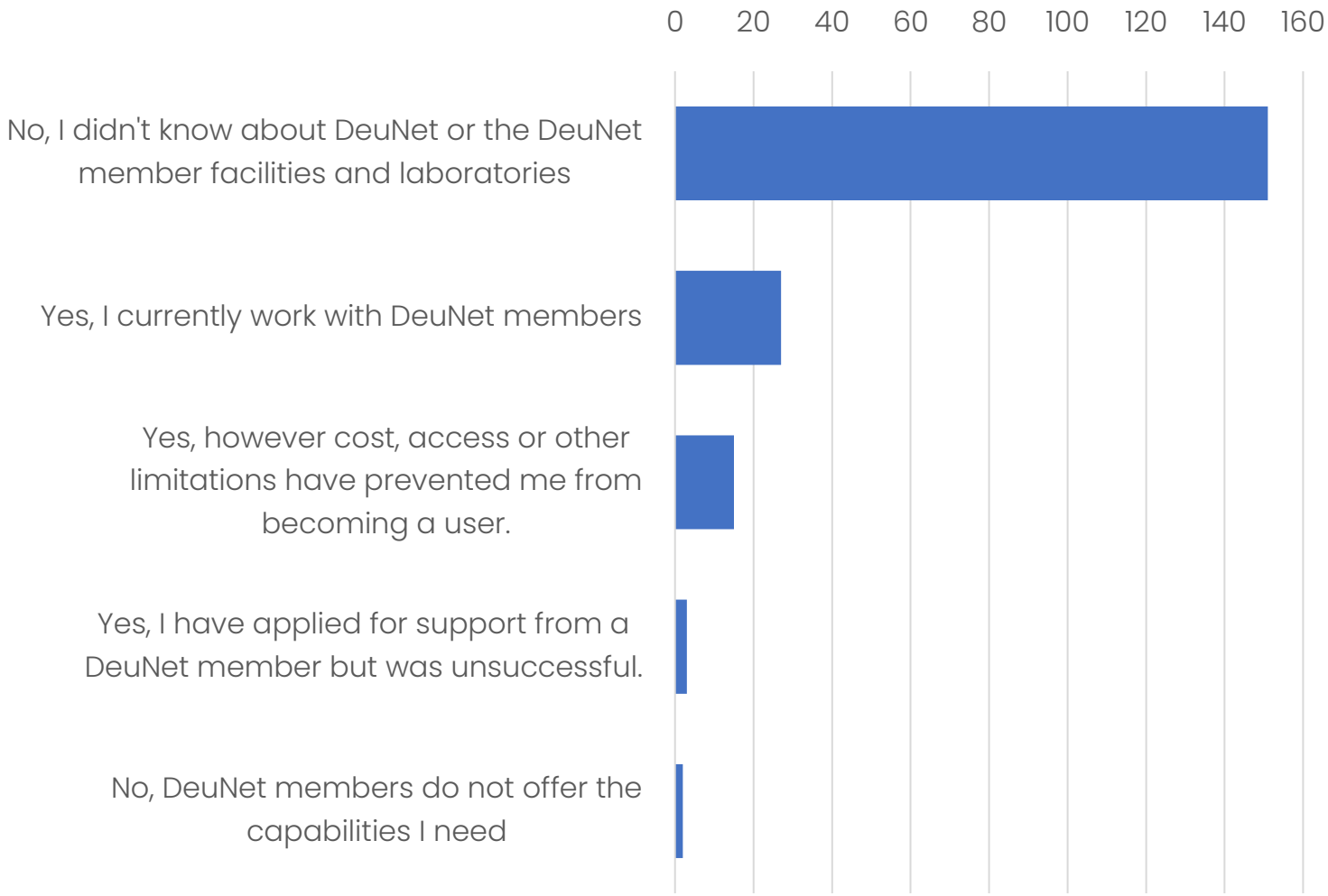
~83% responded **dependent** and above

Have you considered becoming a user of a DeuNet member facility/laboratory?

Question for responses indicating “Non Deuteration Facility User or In-House Deuteration”

Only 1 response possible

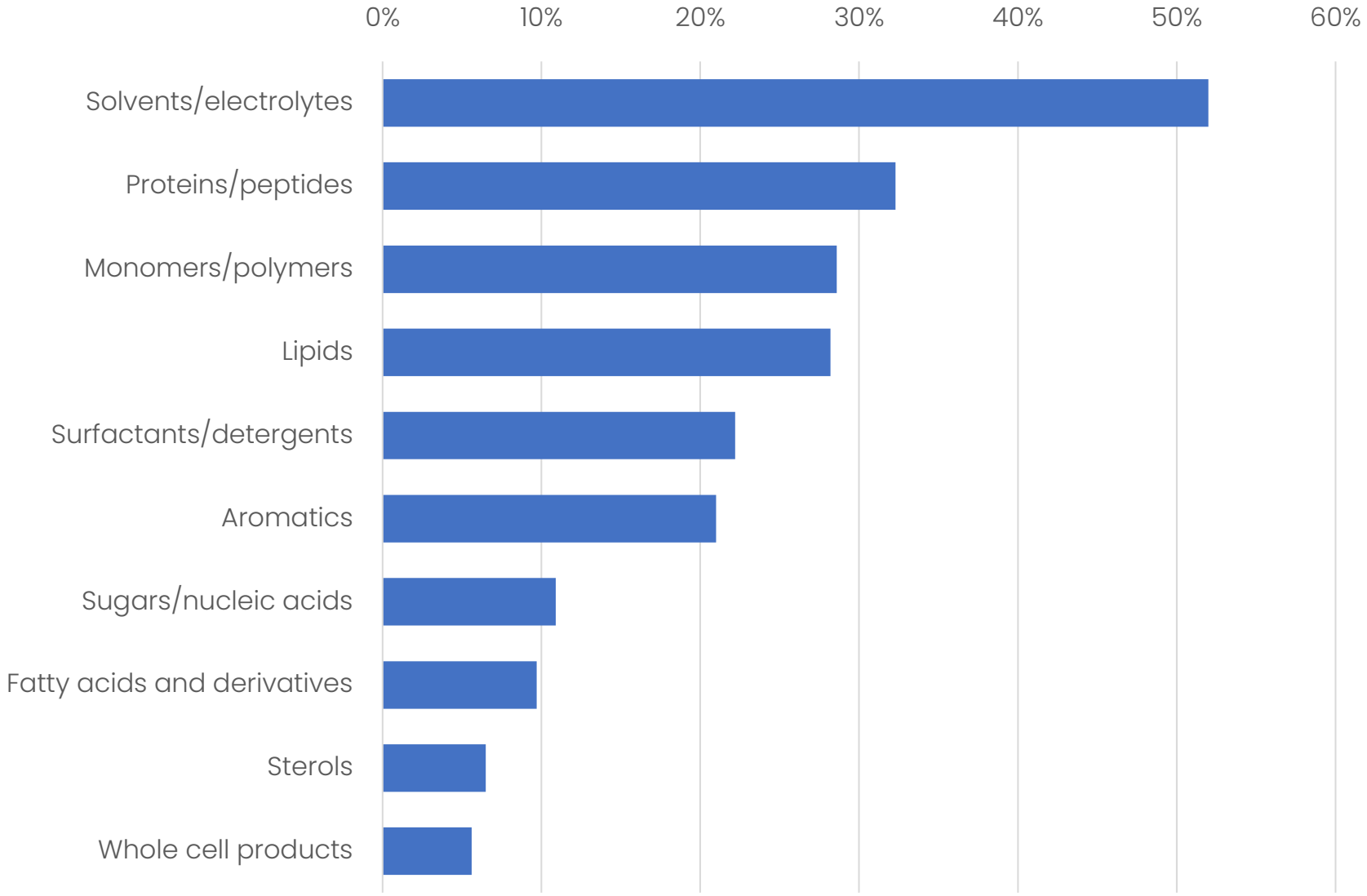
~50% (of total survey responses) didn’t know about DeuNet or the DeuNet member facilities and laboratories



Which groups/types of deuterated molecules do you currently use?

Responses in order

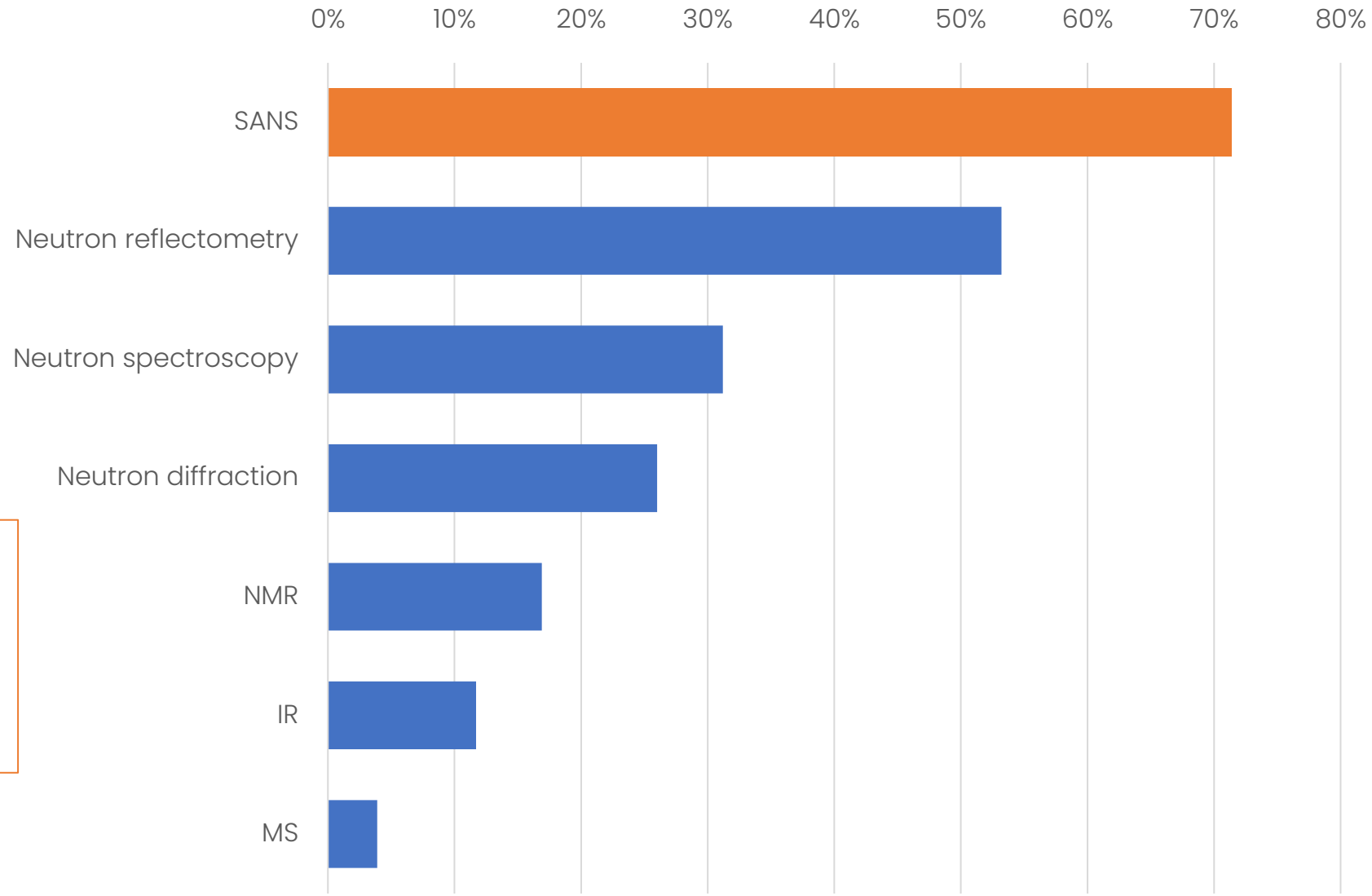
Multiple options possible



Which experimental techniques do you currently use with deuterated materials?

Responses in order

Multiple options possible

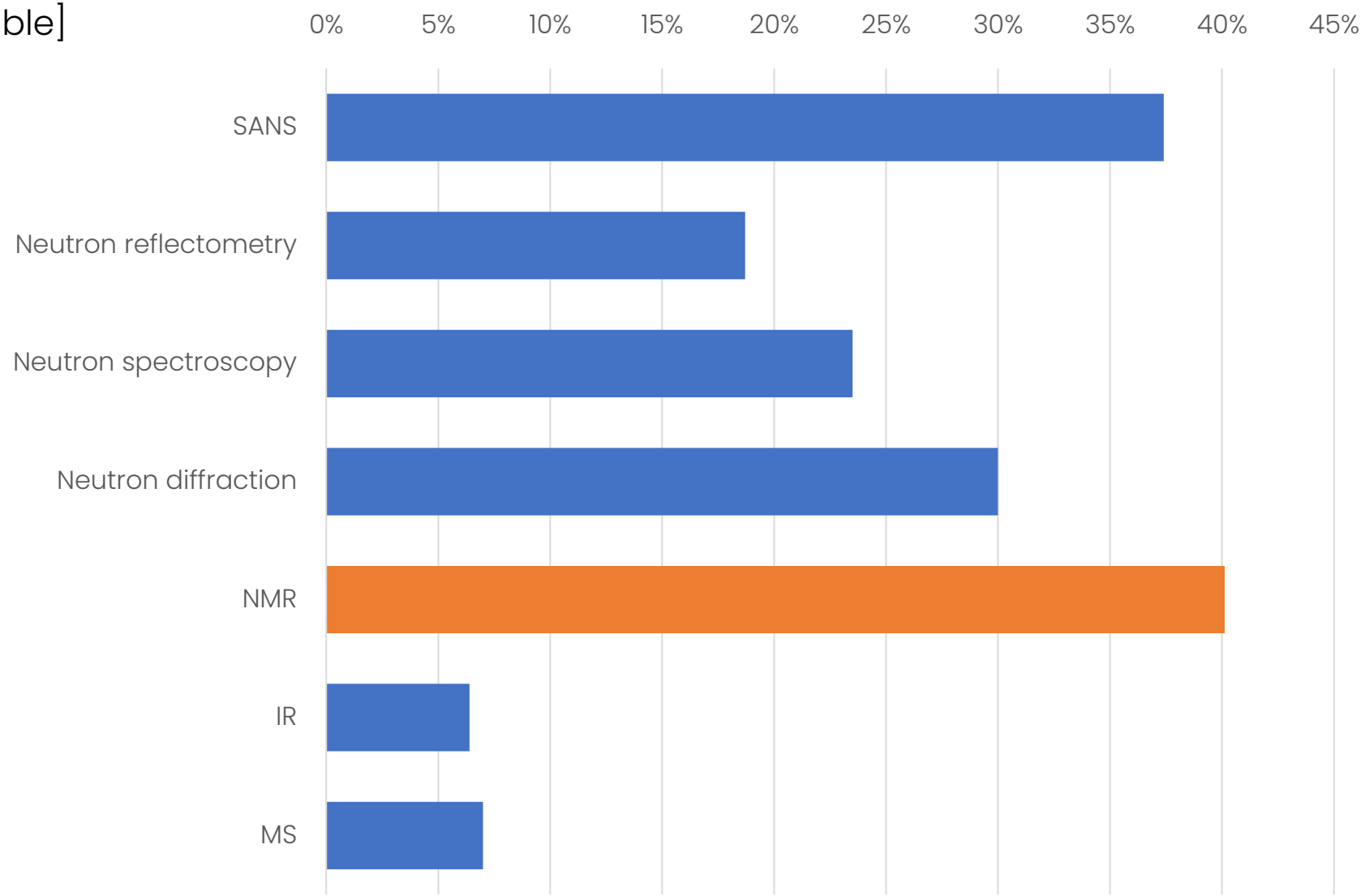


SANS and other neutron most commonly used experimental techniques using deuterated molecules currently

Which experimental techniques would you use with deuterated materials?

[If more available or accessible]

Multiple options possible

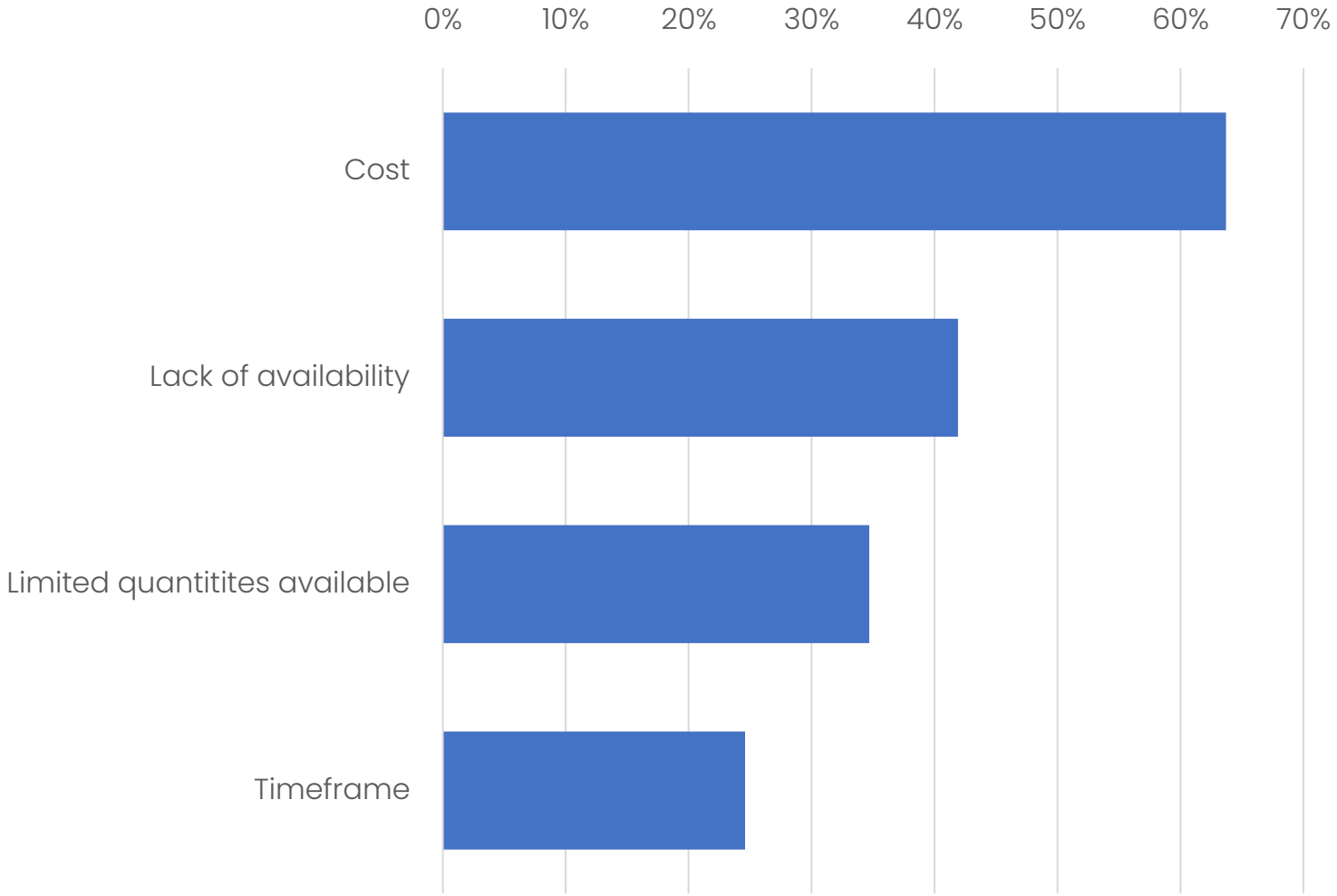


NMR precedes the order of experimental techniques that the users would use with deuterated molecules

Do you face challenges in accessing deuterated materials?

Responses in order

Multiple options possible

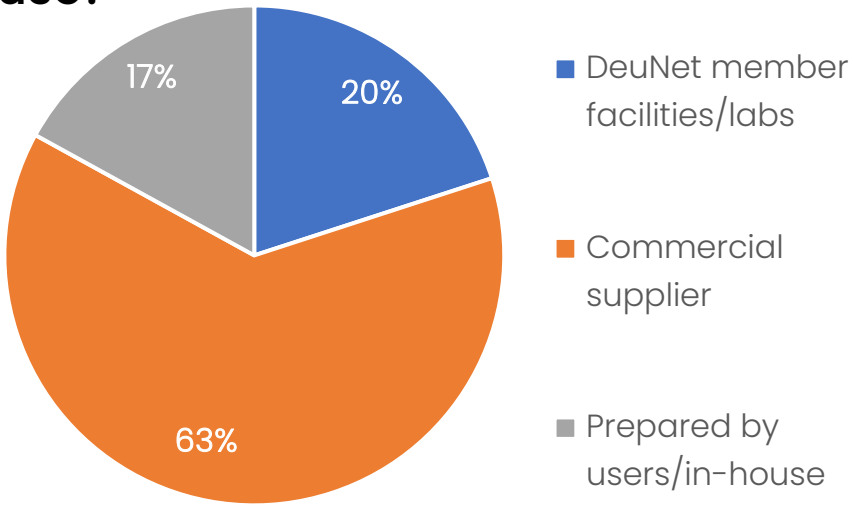


Same trend observed in responses from current and prospective deuteration users

Where do you most often obtain the deuterated materials you use?

Only 1 response possible

20% current deuteration users "most often" obtain their deuterated materials from the DeuNet member network – due to lack of visibility (knowing who to contact, available information on DeuNet members and access options)



Majority of those aware of DeuNet find no challenges in accessing deuterated molecules from DeuNet members

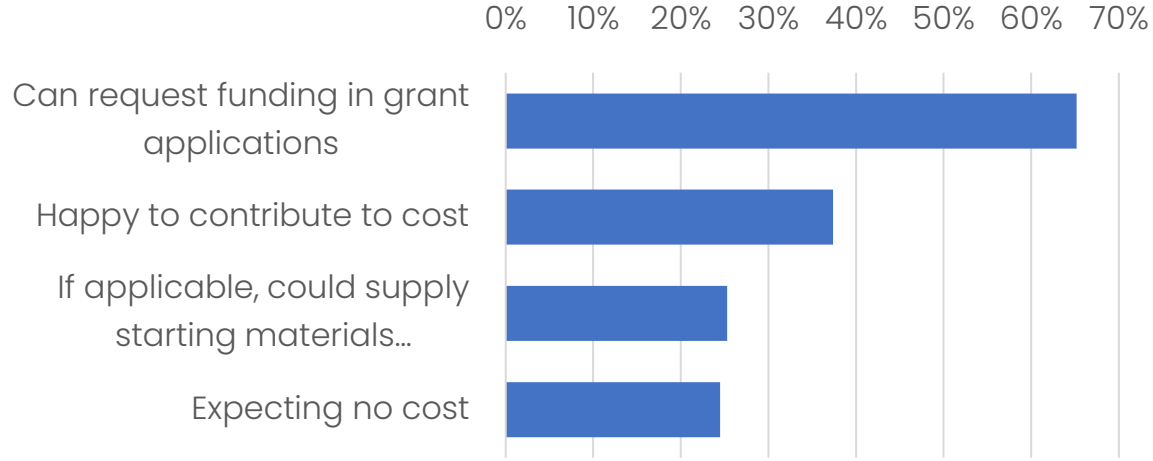
Most common requests from users:

- More publicity and advertisement about the services
- Common website
- Access to catalogues

Responses to question regarding cost of production of deuterated materials

Responses in order

Multiple options possible



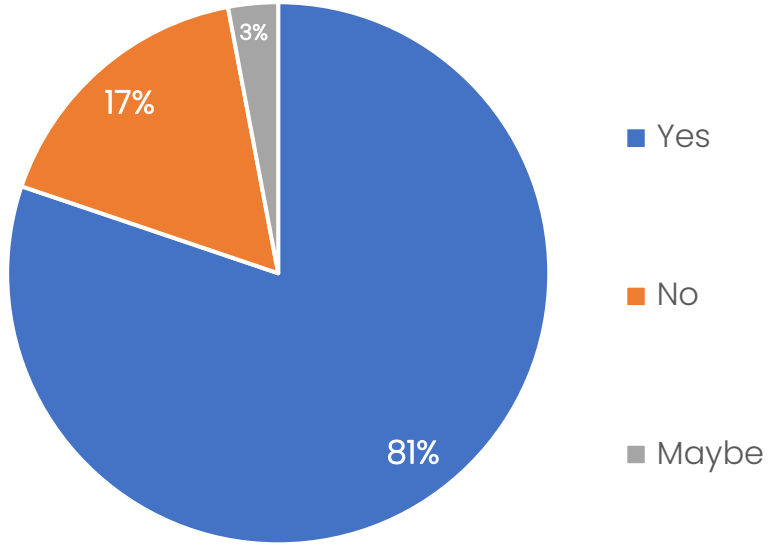
Responses to question regarding co-authorship of DeuNet member staff on publications arising from work utilising supplied deuterated materials

"Yes - provided the chemical is produced by the DeuNet laboratory as a specialist synthesis of a product that cannot be sourced commercially."

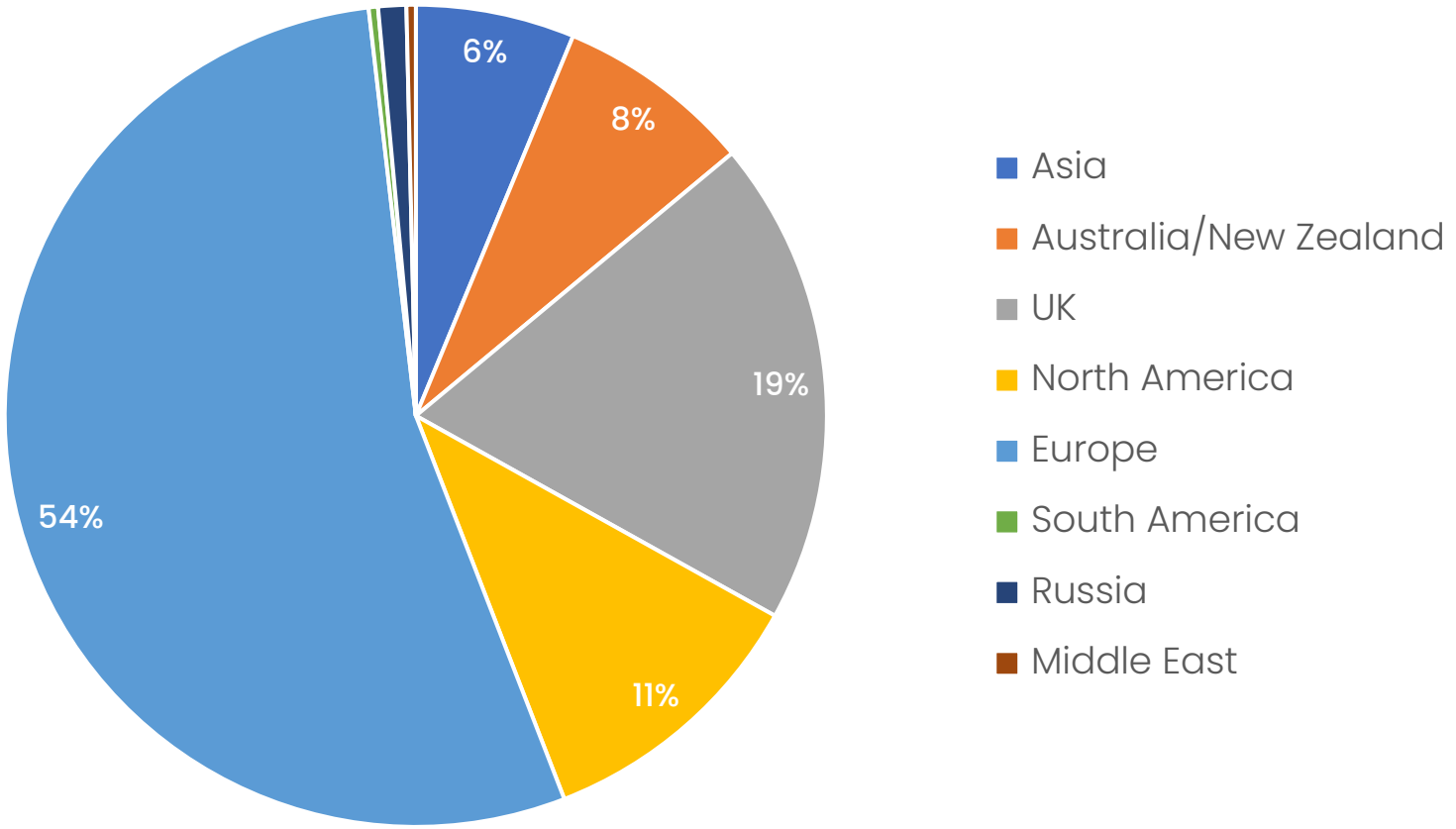
"Depends on the nature of the collaboration"

"I am happy to add the person who actually prepared the material used for the experience but adding the lab PI as well does not seem justified to me"

"Acknowledgments for sure, co-author would depend on the situation"



Respondee/User Origin by geographical region



Thank you