SARS-CoV-2 Nsp13 Fragments and the Open Chemistry Network

Prof Matthew H. Todd
Chair of Drug Discovery, University College London
@mattoddchem

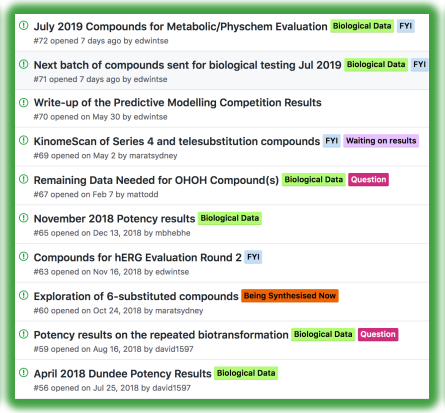
The Basic Approach

1st Law: All data are open and all ideas are shared
2nd Law: Anyone can take part at any level
3rd Law: There will be no patents
4th Law: Suggestions are the best form of criticism
5th Law: Public discussion is much more valuable than private email
6th Law: An open project is bigger than, and is not owned by, any given lab

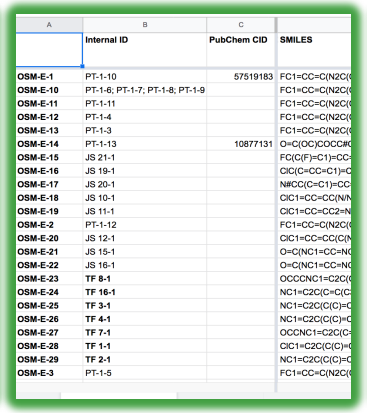
NTDs: *Nature Chem* ***2011****, 3,* 745; *PLoS NTD* **2011**, 5(9):e1260. ***Malaria****: ACS Cent. Sci.* **2016**, *2*, 687; *J. Med. Chem.* **2020**, *63*, 11585; *J. Org. Chem*. **2020**, *85*, 13438; *J. Med. Chem.* **2021**, *64*, 16450. ***TB***: *J. Med. Chem.* **2018**, *61*, 11327. ***Antifungals***: *PLoS NTD* **2018**, *12(4)*: e0006437; *PLoS NTD* **2022**, *16*, e0010159. ***Platform***: *Chem. Sci.* **2015**, *6*, 1614; *Parasitology* **2014**, *141*, 148. ***Laws****: ChemMedChem,* **2019***, 14,* 1804. ***Translation/Policy***: *PLoS Med.* **2017**, *14(4)*: e1002276; Wellcome Open Res. **2021**, *6*:146.

Components

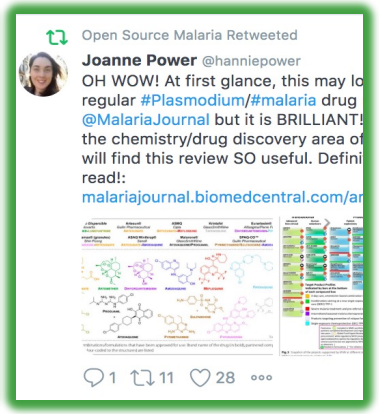
Laboratory Notebooks



Public To Do Lists/Discussion



Open Data



Community

Contributions

Students → *Pharma*

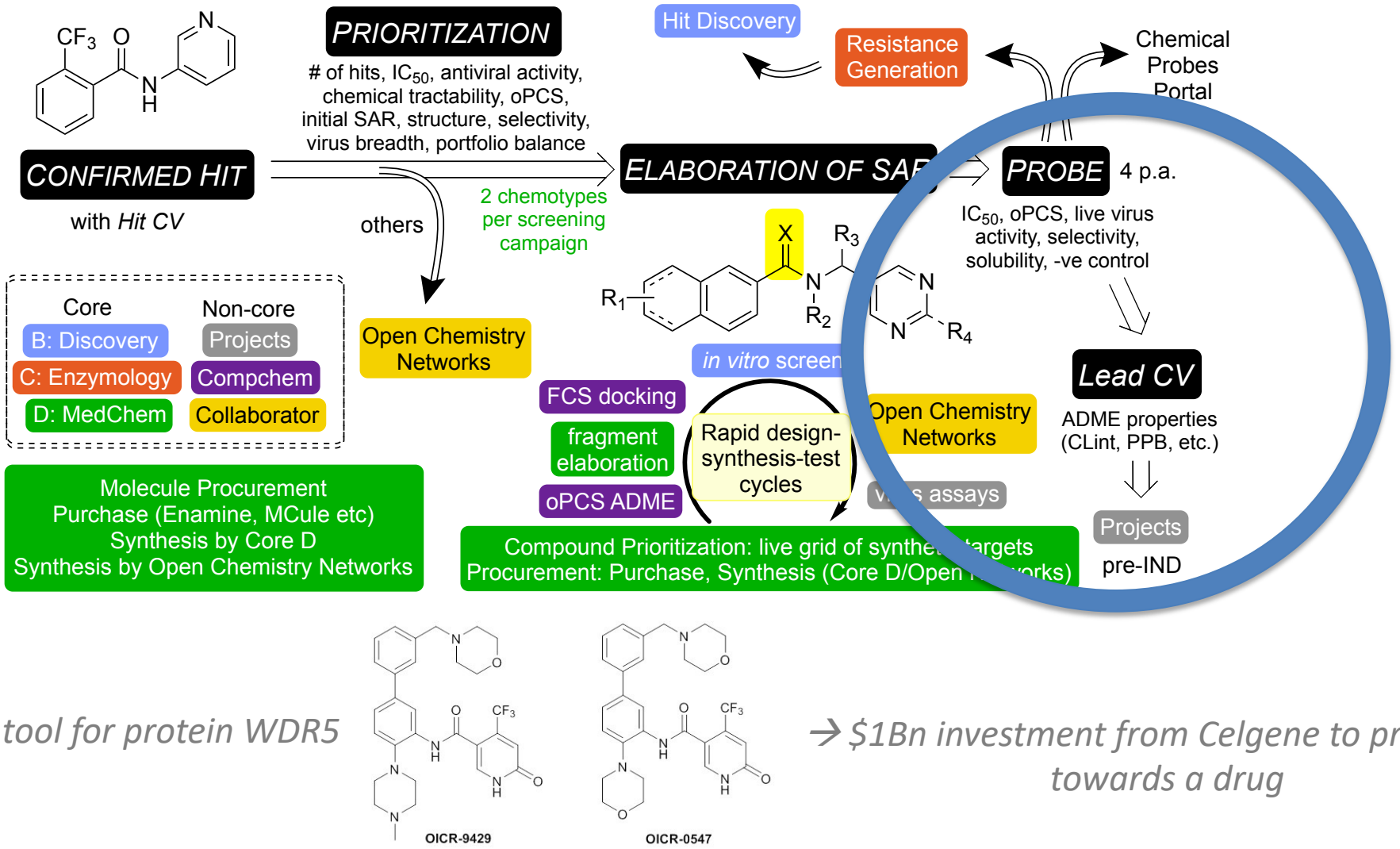
"Open" Needs Clarity re Freedoms

*Open **Access** – to read*
*Open **Data** – to re-use*
*Open **Innovation** – to … what?*
*Open **Science** – something more, like samples, liberal licence*
*Open **Source** – all that, and **full details** and can **participate***

Licences (yawn) define the essential freedoms
e.g. Wikipedia's licence:

READDI-AViDD: All Hit to Probe 100% Open, Providing Translational Options

A biological tool molecule ("probe") can be converted into a drug (which is different)



e.g.: Public domain tool for protein WDR5

→ $1Bn investment from Celgene to progress it towards a drug

https://www.thesgc.org/news/toronto/new-potential-treatment-leukemia-discovered-oicr-scientists-draws-major-industry

Structure of SGC Open Chemistry Networks Projects

SGC Open Chemistry Networks

Parent SGC website
Not community curated
Lists targets, status, rationale
RULES and LICENCE
Links out to project hubs

Raw Data
Managed by individuals
Electronic Lab Notebooks
Essential criteria:
1) Openness/licence; 2) Completeness
3) Permanence; 4) Machine readability

Probe Hubs
Managed by 1) science leads; 2) community; 3) industry mentor;
4) Student Champion
Includes: project status suitable for outsiders, To Do Lists, discussion forum, file store etc

Living Paper
Hosted by a journal
New version released upon milestones
Cleanest version of Project Status
Maintains authorship list
Incentivizes
(We've a journal interested)

Monthly Science Meetings
Each project.
Open to all.
Zoom, recorded.
Placed on Youtube
Linked to Action Items on Hub

SGC Chemistry Networks Social Media
Used by SGC admin, probe leads, contributors
Disseminates new results
Sends out community requests
Advertises through fun posts of contributors

Publicity/Outreach
Promoting project
Route to donations
Logo:
"Proudly Partnering with the SGC"
(click here to find out what this means)
→ Page of terms

OCN
Open Chemistry Networks

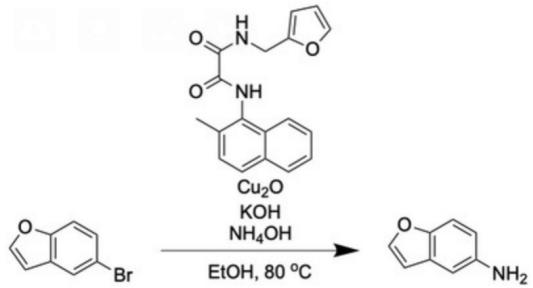
SGC

Open Tech: Simple Technologies Help Dramatically with *Discoverability*

Public Lab Notebooks and Other Data Tools are Available, but Under-used. They'll grow.

Synthesis of benzofuran-5-amine (EGT 517-1)

Edwin Tse - Nov 09, 2020, 9:47 PM



scheme_EGT_517-1.jpeg(29.6 KB)

Strings

BrC1=CC2=C(OC=C2)C=C1

to

NC1=CC2=C(OC=C2)C=C1

InChI=1S/C8H5BrO/c9-7-1-2-8-6(5-7)3-4-10-8/h1-5H

to

InChI=1S/C8H7NO/c9-7-1-2-8-6(5-7)3-4-10-8/h1-5H,9H2

AYOVPQORFBWFNO-UHFFFAOYSA-N

to

GMOLCSICTCPZCU-UHFFFAOYSA-N

Discoverable

Machine-Readable

InChI=1S/C11H11N3/c1-2-6-12-9(4-1)10-8-14-7-3-5-11(14)13-10/h1-2,4,6,8H,3,5

All | Maps | Shopping | Images | News | More | Settings | To

3 results (0.67 seconds)

pubchem.ncbi.nlm.nih.gov › compound

2-(Pyridin-2-yl)-6,7-dihydro-5H-pyrrolo[1,2-a]imidazole | C11H11N3

InChI=1S/C11H11N3/c1-2-6-12-9(4-1)10-8-14-7-3-5-11(14)13-10/h1-2,4,6,8H,3,5,7H2.

Computed by InChI 1.0.5 (PubChem release 2019.06.18). PubChem ...

au-mynotebook.labarchives.com › share

Edwin Tse/OSA Series 2/EGT 467-3 - LabArchives, Your Electronic ...

Edwin Tse/OSA Series 2/EGT 467-3 - created by Edwin Tse on 2020-09-07 17:22:06 UTC. ...

InChI=1S/C11H11N3/c1-2-6-12-9(4-1)10-8-14-7-3-5-11(14)13-10/h1-2,4,6,8H,3,5,7H2. to.

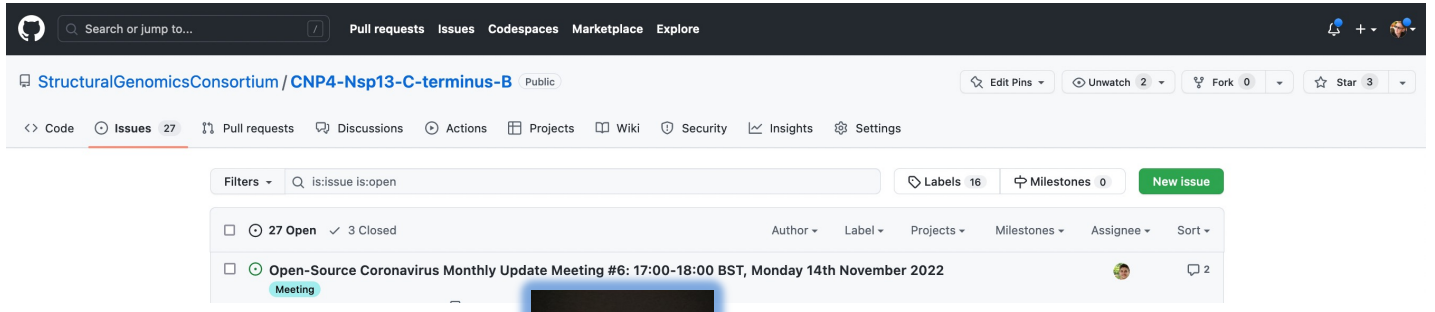
InChI=1S/C11H10BrN3/c12-11-10(8-4-1-2-6-13-8)14-9-5-3-7-15(9)11/h1-2,4,6H,3,5,7H2 ...

au-mynotebook.labarchives.com › share

Edwin Tse/OSA Series 2/EGT 466-3 - LabArchives, Your Electronic ...

Architecture – Some READDI-AViDD Components

Discussion/To Dos
https://github.com/StructuralGenomicsConsortium/CNP4-Nsp13-C-terminus-B



Nsp13 **Pharma Champion**: James Day, Astex

Nsp13 **Student Champion**: Tom Knight (UCL)

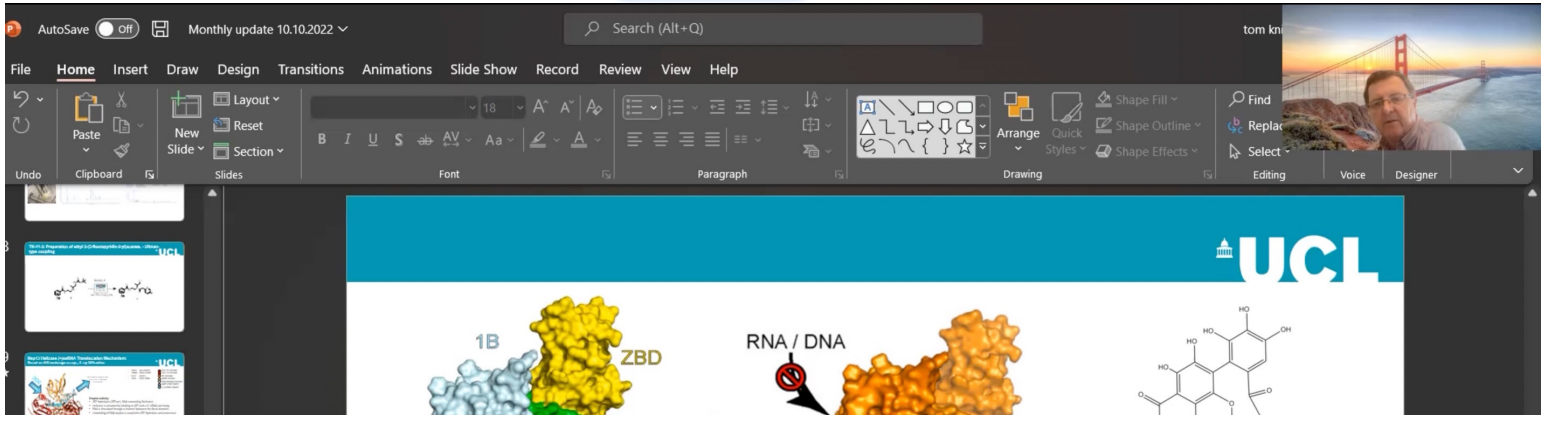
Open lab notebooks, simple compound registration → public data

labarchives
Better Science

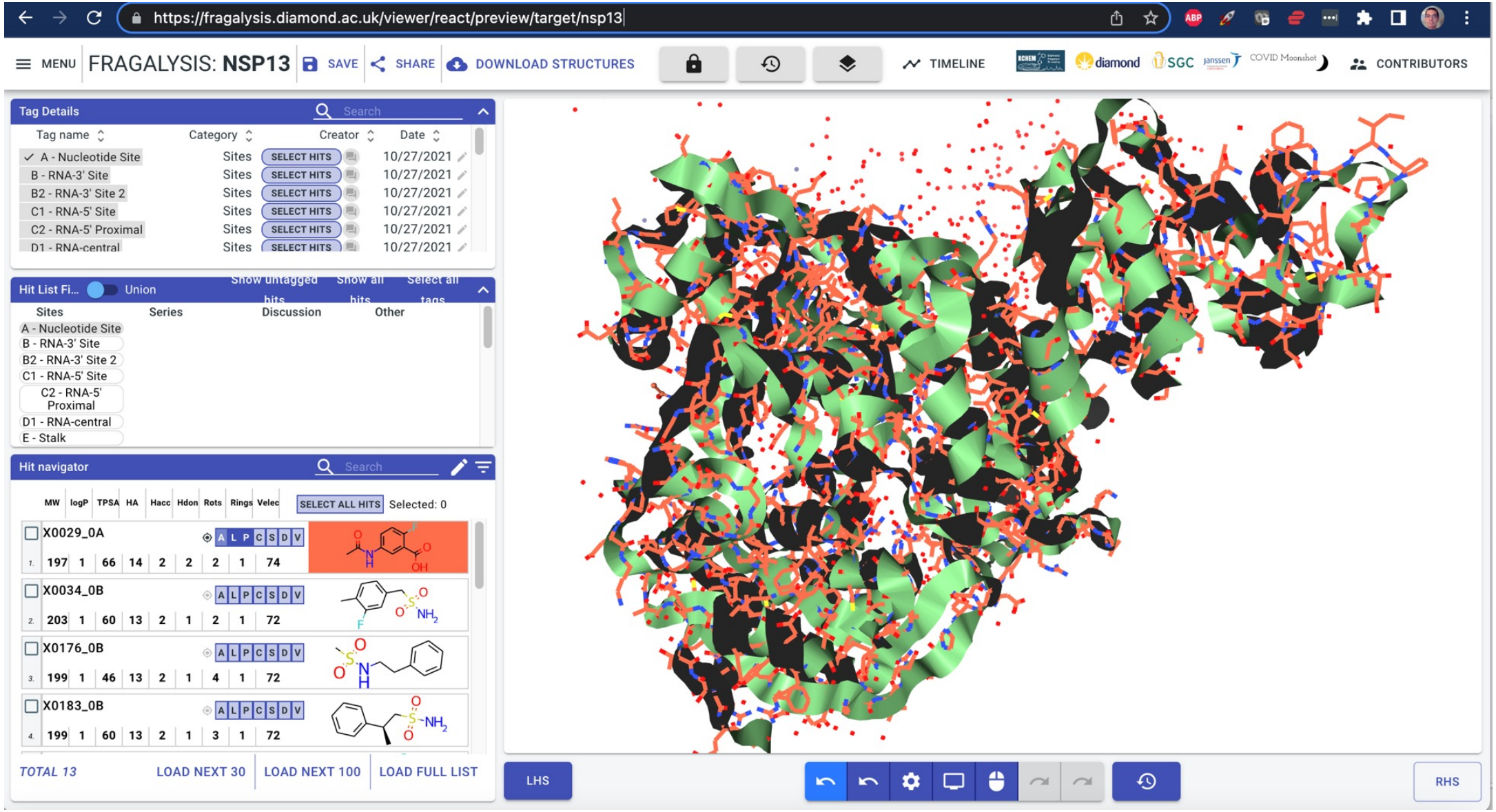
Socmed for community building: @thesgconline, #sgcocn

Recorded Zooms → Youtube

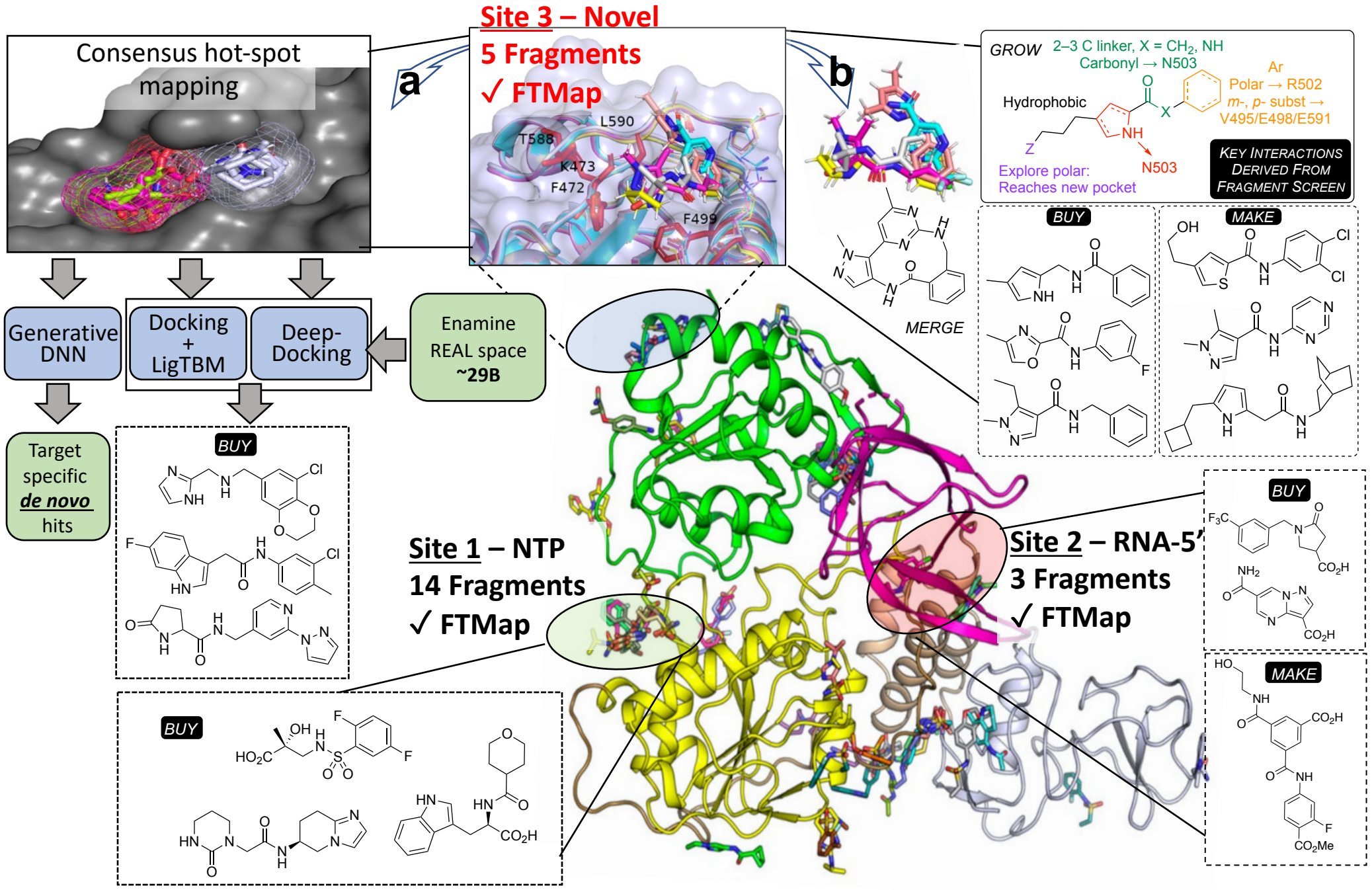
Collaborators incoming, e.g.
https://github.com/StructuralGenomics Consortium/CNP4-Nsp13-C-terminus-B/issues/27



Fragment Starting Points

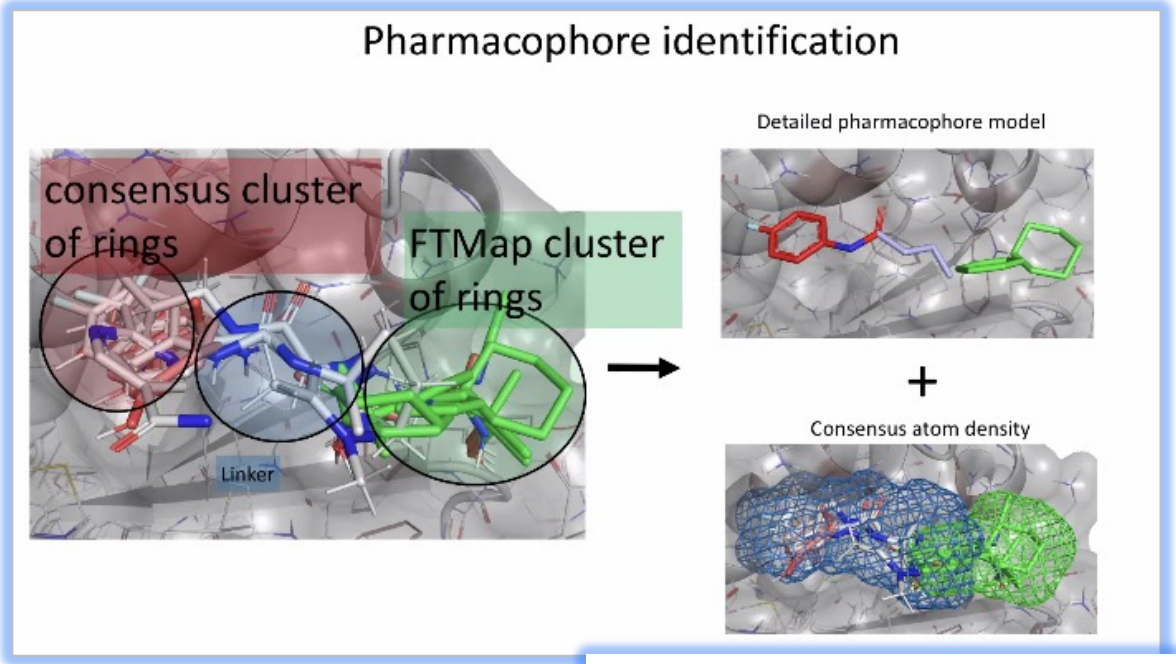


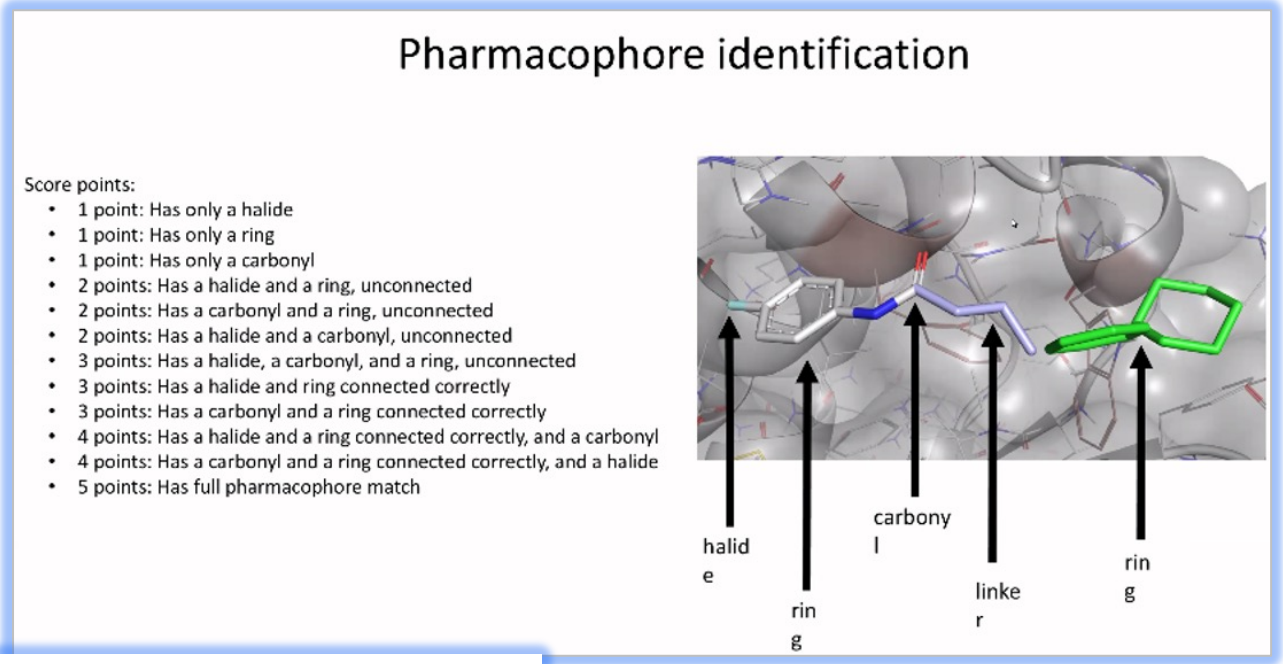
Nat Commun **12**, 4848 (2021). https://doi.org/10.1038/s41467-021-25166-6

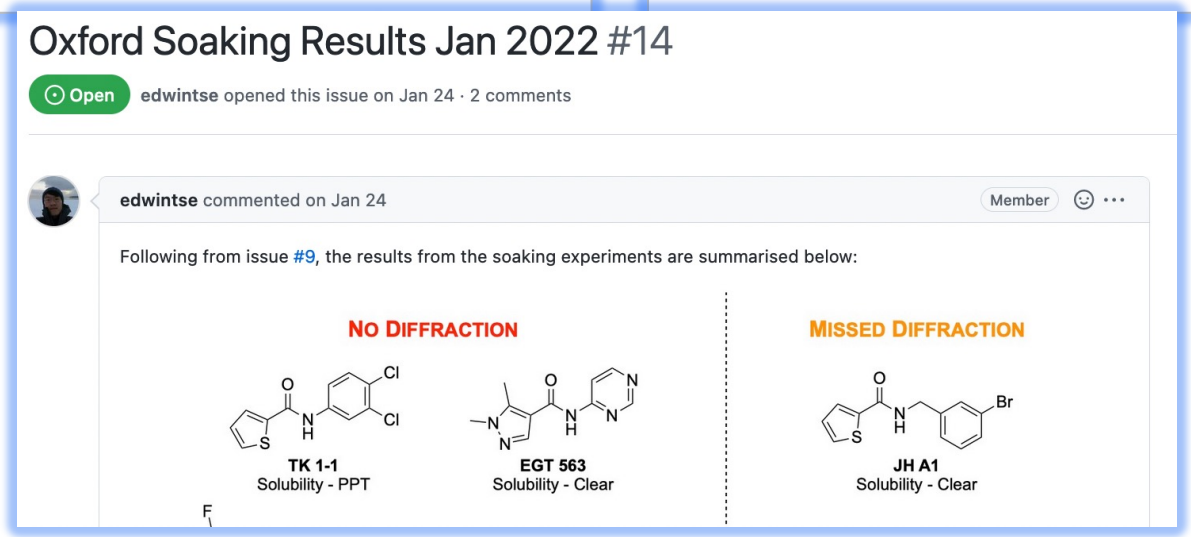


Alex Tropsha, Kostya Popov, Mat Todd, Tom Knight, Heba Agha

Fragment Hits → Pharmacophore Identification/Frag merging

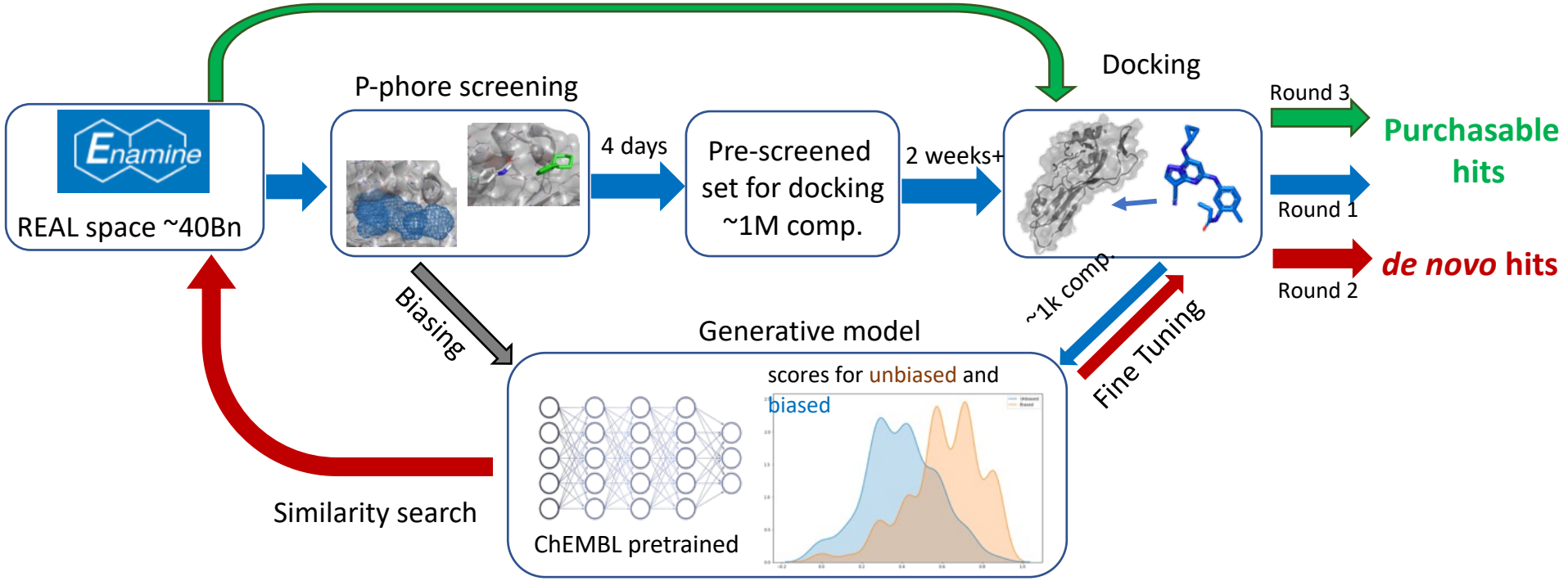


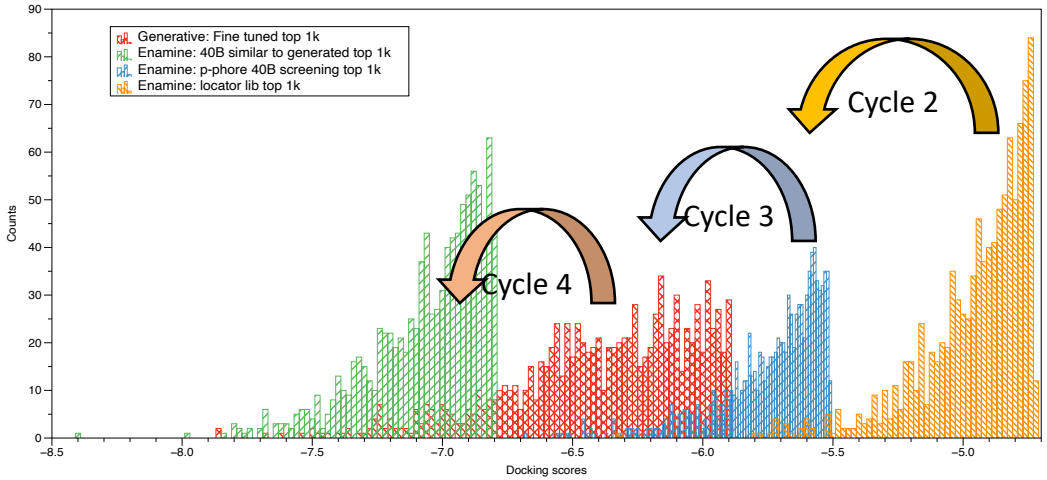




Kostya Popov, Alex Tropsha, Heba Agha, Joe Newman, Ed Tse

Forget the Frags: Structure-based virtual screening workflow

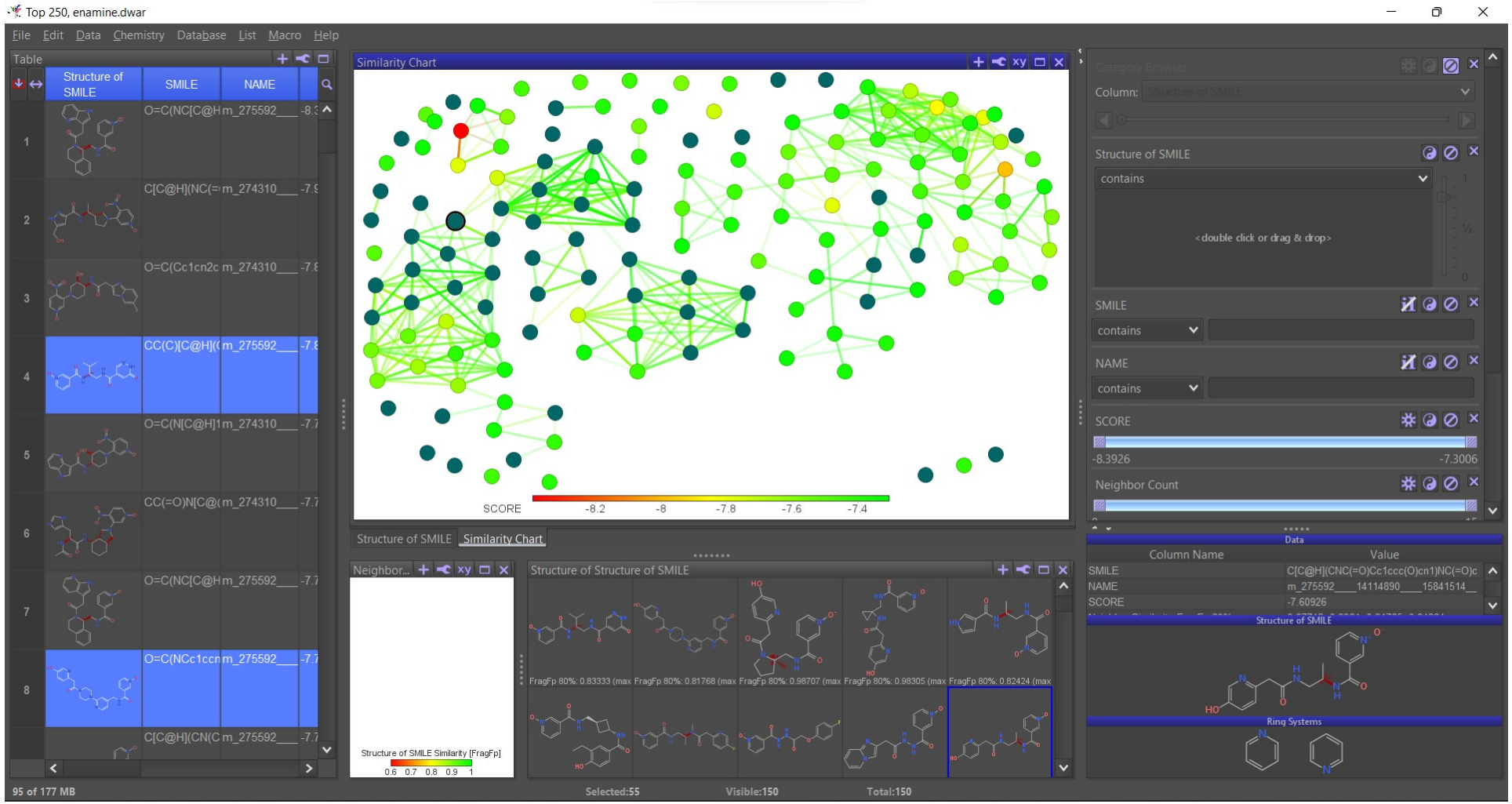




- Pharmacophore screening of 40 Billion analogs.
- Each cycle seeds the next generative model.
- Iterative improvement in docking scores.

Kostya Popov (UNC), Tom Knight (UCL)

Enamine REAL Space, Glide Top Ranked 150 Molecules:
DataWarrior Analysis to Visualise the Covered Chemical Space



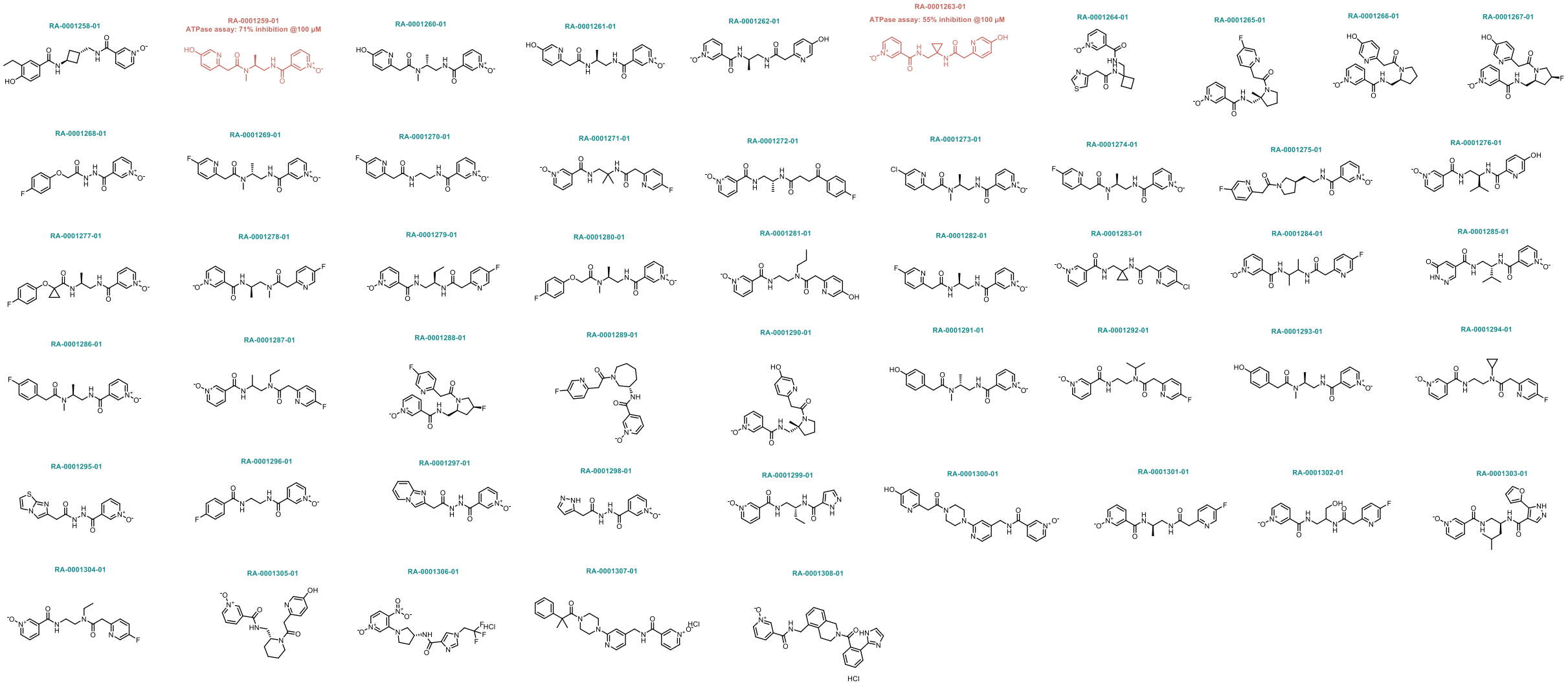
- **Similarity chart clusters molecules based on scaffold similarity.**

Enamine make-on-demand (Buy = 55 molecules).

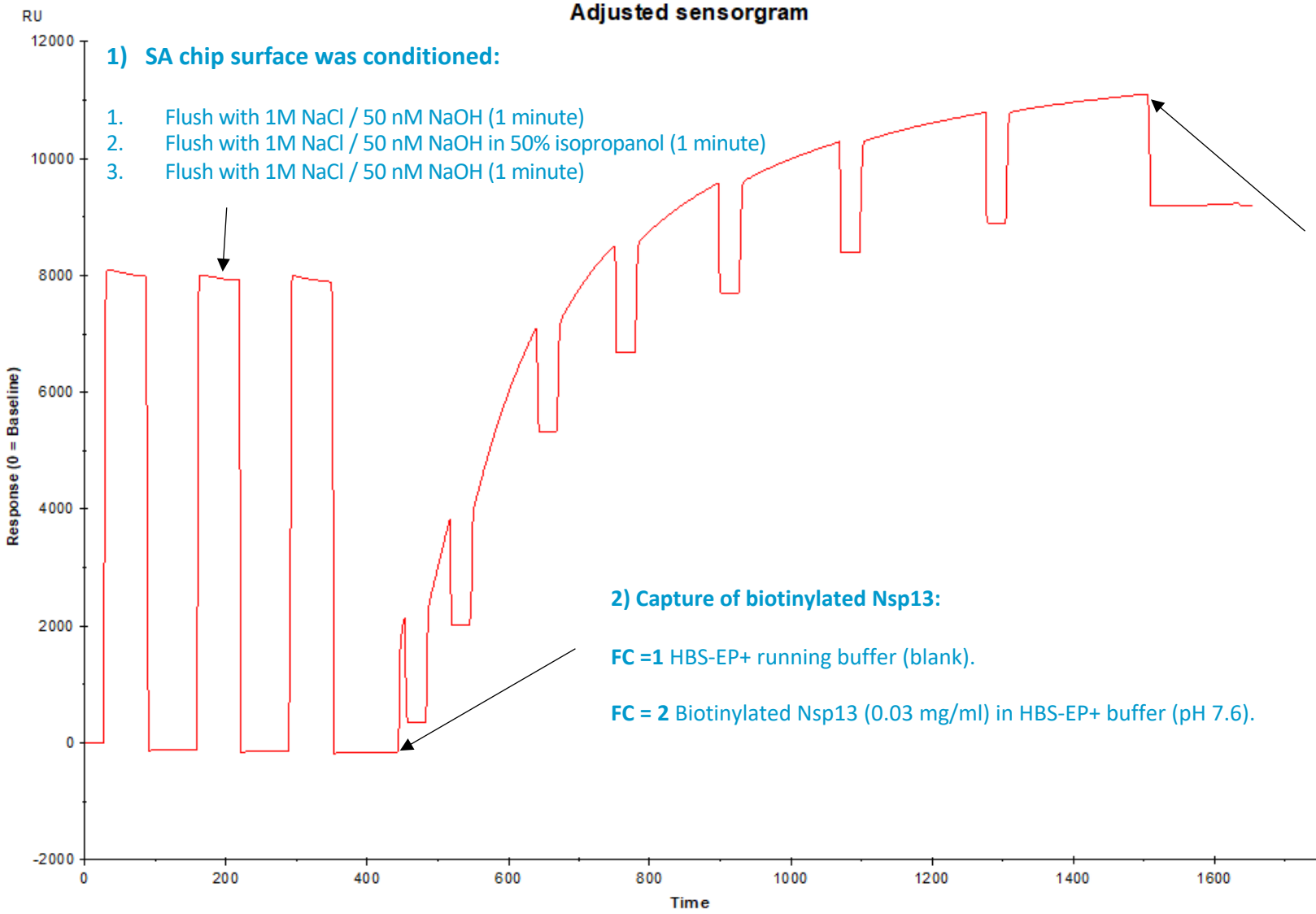
Glide score -8.1 to -7.2 (Make = 95 molecules).

Enamine REAL Space, Glide Top Ranked 150 Molecules:
DataWarrior Analysis to Visualise the Covered Chemical Space

- **Enamine make-on-demand; 51/55 compounds purchased.**
- **51 compounds in DMSO (50 uL, 20 mM) for SPR screen (ongoing).**



Developing an SPR Assay:
High-affinity capture of biotinylated Nsp13 onto streptavidin (SA) chip surface.



1) SA chip surface was conditioned:

1. Flush with 1M NaCl / 50 nM NaOH (1 minute)
2. Flush with 1M NaCl / 50 nM NaOH in 50% isopropanol (1 minute)
3. Flush with 1M NaCl / 50 nM NaOH (1 minute)

2) Capture of biotinylated Nsp13:

FC =1 HBS-EP+ running buffer (blank).

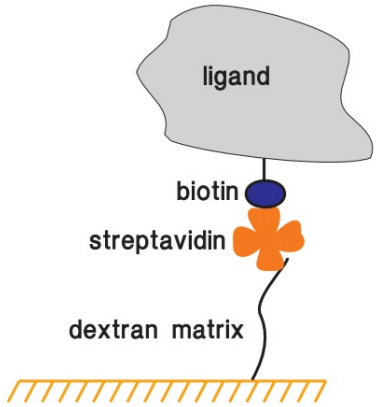
FC = 2 Biotinylated Nsp13 (0.03 mg/ml) in HBS-EP+ buffer (pH 7.6).

Nsp13 protein was coupled to a Cytiva Series streptavidin (SA) chip using the Biocore T100 standard SA-Biotin capture protocol:

https://info.cytivalifesciences.com/Biacore-help-files_Biotinylation-for-streptavidin-biotin-capture.html

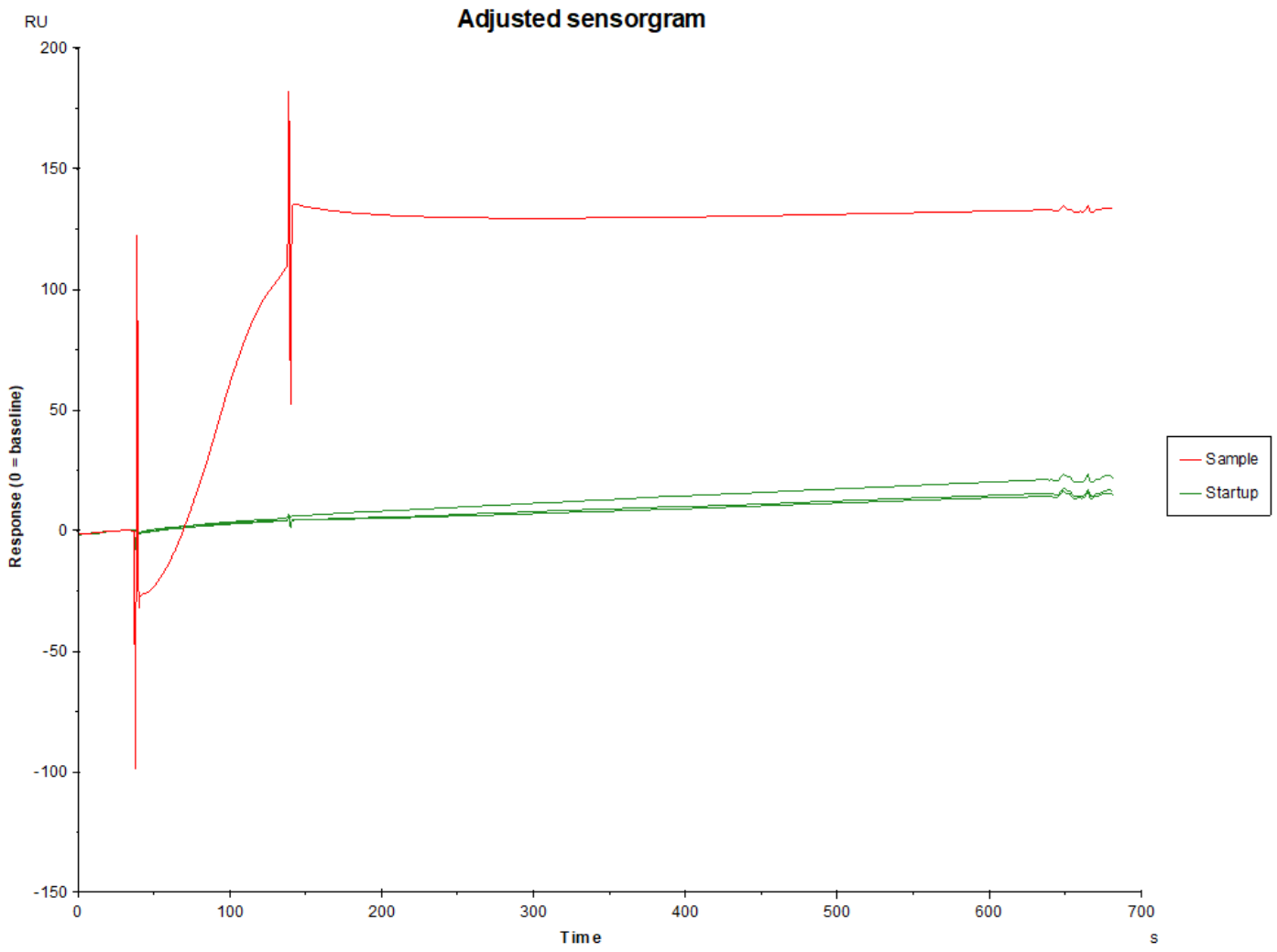
3) Capture of biotinylated Nsp13 reaches near saturation:

Biotin capture was successful, just under 10'000 RU was reached.



https://github.com/StructuralGenomicsConsortium/CNP4-Nsp13-C-terminus-B/issues/25

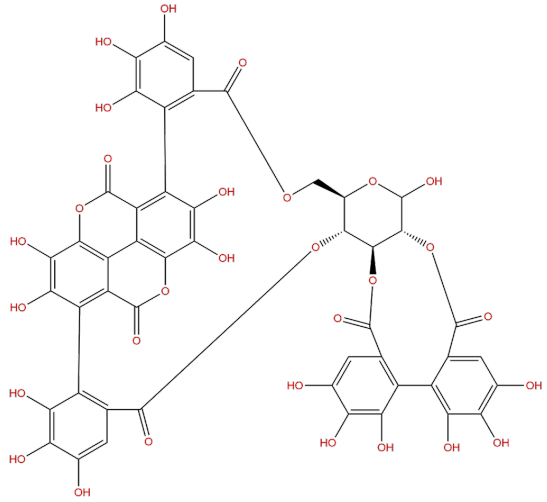
SPR: Screening of control compound #1 (Punicalagin)



A positive control binder (Punicalagin, a.k.a. PUG, KD = 21.6 nm) was flowed over the capture protein to confirm it as a nanomolar binder to Nsp13; https://github.com/StructuralGenomicsConsortium/CNP4-Nsp13-C-terminus-B/issues/22#issuecomment-1270191492

1. PUG, [CAS-No: 65995-63-3] (1.5 mg) was diluted into DMSO (1 mL) to give a 1.3828 mM stock solution.

2. This stock was then diluted to 216 nM (10X KD) by dissolving 1.5 uL of the stock solution up to 10 mL with phosphate-buffered saline (PBS, https://info.cytivalifesciences.com/Biacore-help-files_Buffers-for-small-molecule-screening.html) with 2% DMSO.



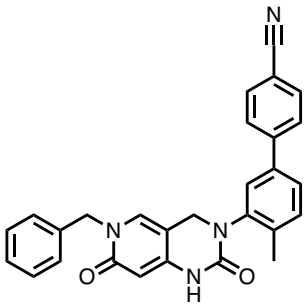
- PUG showed irreversible binding to Nsp13.
- Spikes likely due to mismatched composition of buffers (HBS-EP+ vs PBS).

Ref: https://doi.org/10.1016/j.antiviral.2022.105389

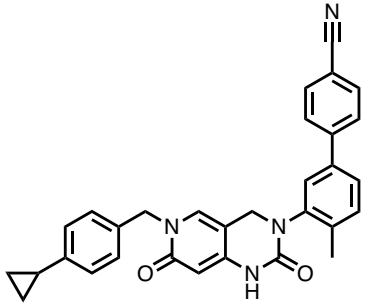
SARS-CoV-2 Nsp13 First Hits! Targeted Library and Docking of Enamine Real

Targeted Library Designed for Nsp13 (but different site)*

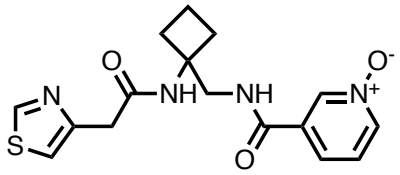
From the docking of 40B compounds (designed for “site 3”)



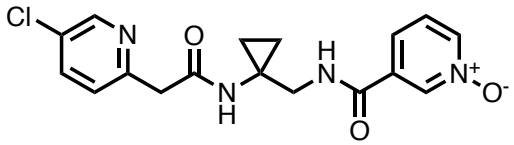
RA-0001313-01



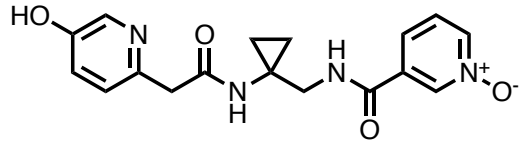
RA-0001335-01



RA-0001264-01



RA-0001283-01



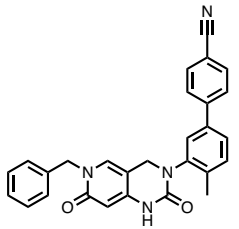
RA-0001263-01

SARS-CoV-2 SPR KD (µM)	3	3	6	8	11
MERS SPR KD (µM)	4	3	5	7	11
SARS-CoV-2 ATPase IC_{50} (µM)	83	NT	48	NA	12

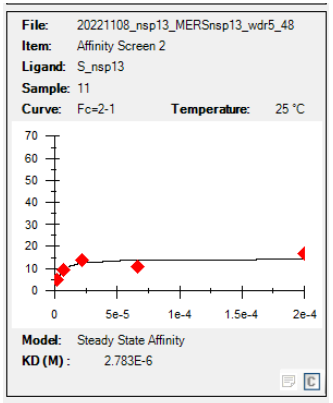
Sumera Perveen, Anwar Hossain, Konstantin Popov.

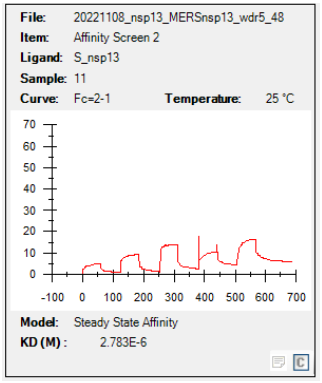
*Based on allosteric Inhibitors targeting the spliceosomal RNA helicase Brr2, 10.1021/acs.jmedchem.7b00461.

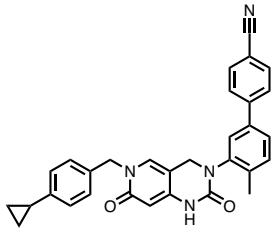
SARS-CoV-2 Nsp13 SPR Sensograms



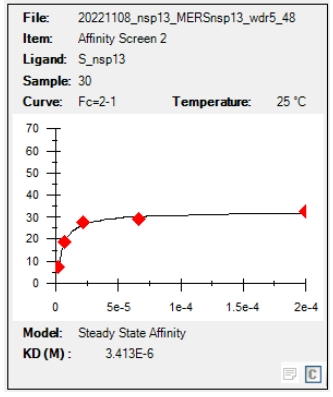
RA-0001313-01

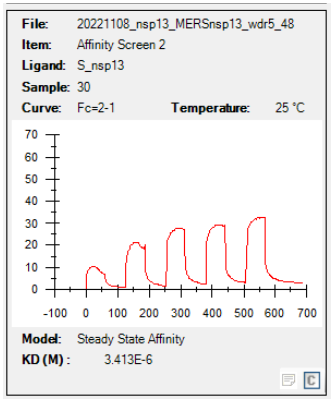


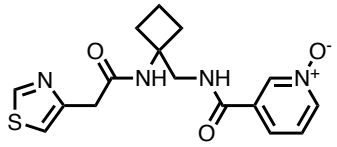




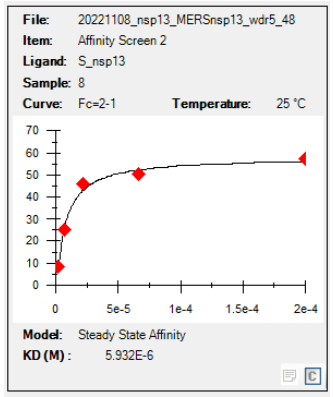
RA-0001335-01

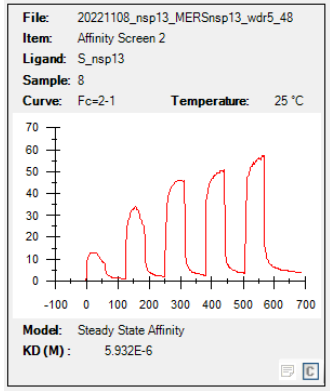


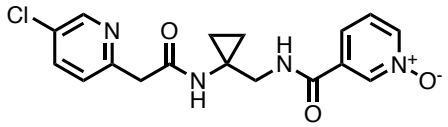




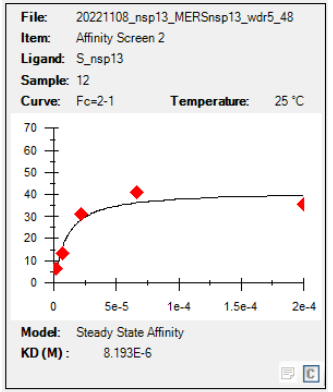
RA-0001264-01

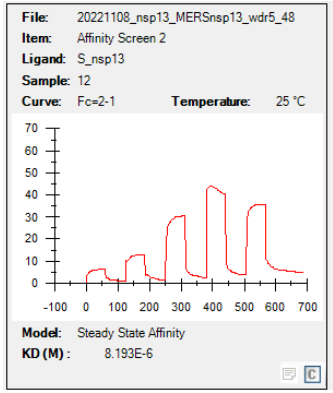


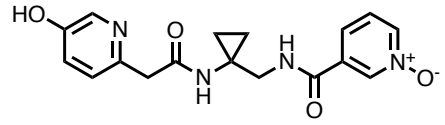




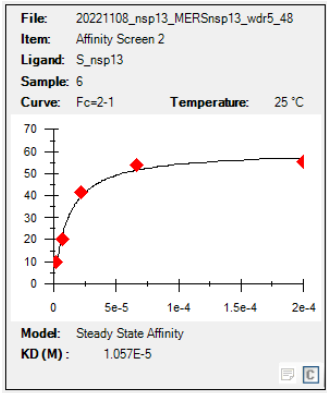
RA-0001283-01

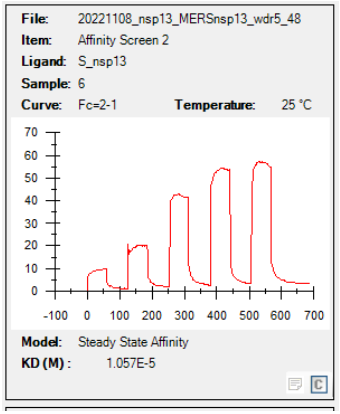






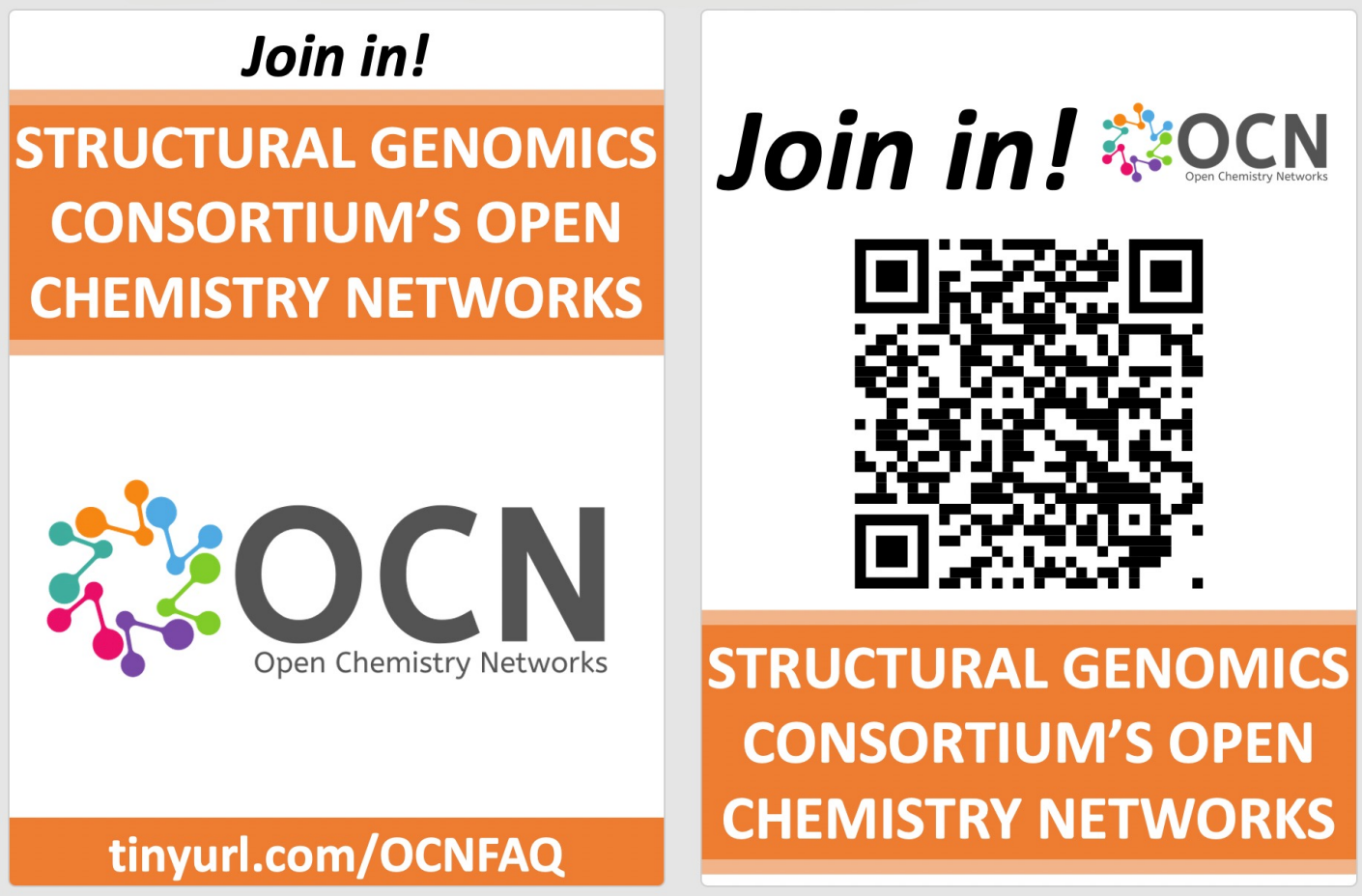
RA-0001263-01





You're Invited

CC-BY-4.0 applies to all hit discovery and hit to lead – i.e. essential freedoms baked in



https://github.com/StructuralGenomicsConsortium/Chemistry_TechOps_HowTo/issues/2

Hiring Soon at UCL

Postdoc Chemistry Champions
PDRA Screening/Assays
Lab manager
Ex-Pharma Project Coordinator
Website/Data developer

Volunteer Pharma Champions for all series (time commitment: 3 hrs per month)

See how it works:
Next open, online meeting: December 12th at https://ucl.zoom.us/j/97172937586
(https://github.com/StructuralGenomicsConsortium/CNP4-Nsp13-C-terminus-B/issues)

Some Nsp13 People and Funders

UCL: Tom Knight, Ed Tse, Kangping Liu, Jemima Haque, Linda Patio, Robin Ketteler, David Selwood, Clara Gathmann
Chapel Hill: Tim Willson, Nat Moorman, Alex Tropsha, Konstantin Popov, Heba Agha, Peter Brown, Anwar Hossain
Toronto: Cheryl Arrowsmith, Sumera Perveen and team **Diamond/Oxford**: Joseph Newman, Daren Fearon **Astex**: James Day
And others and the rest of the READDI-AViDD team