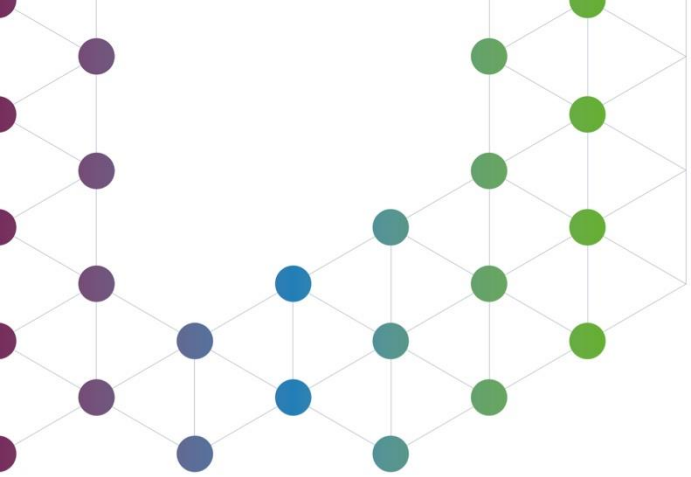


DDF ChemCo

Dementia Discovery Fund

DDF ChemCo
CNS-Biased Small Molecule Library

Contact: DDFChemCo@svlsm.com
Tel: +44 20 7421 7070

SV Life Sciences

The Dementia Discovery Fund & DDF ChemCo

The Dementia Discovery Fund (DDF)

- The DDF is a mission-driven venture capital fund, focussed on discovery and development of novel, effective therapeutics for dementia
- Launched in October 2015, this unique fund was formed by the UK government following the 2013 G8 summit and World Dementia Council meetings, which recognised the need for a new, collaborative funding model to tackle the global challenge of dementia
- In addition to the UK Department of Health, seven leading pharmaceutical companies (GSK, Biogen, Lilly, Takeda, Pfizer, J&J, and Astex subsidiary of Otsuka) and Alzheimer's Research UK invest in the DDF. Heads of Neuroscience and R&D represent these investors on the DDF Scientific Advisory Board
- The DDF is structured as a typical venture capital fund and managed by a dedicated team of neuroscientists nested within SV Life Sciences, which won the competitive bid to manage the fund

DDF ChemCo

- The DDF has set up and wholly owns DDF ChemCo, a small molecule screening company with a CNS-focused library of >500,000 compounds
- **DDF ChemCo will rapidly, cost-effectively enable drug discovery programmes of DDF companies, partners and collaborators, allowing efficient testing of novel discovery hypotheses and so help achieve the DDF goal of increasing the breadth and number of therapeutic approaches in development for dementia**
- The DDF ChemCo library is housed in Basel at the HTS site of Aptuit, an integrated drug discovery CRO with expertise in compound library management, high throughput screening, selectivity testing, and hit characterization. Aptuit will perform and facilitate screens against the library on behalf of DDF ChemCo and its customers
- If you are interested in screening against the DDF ChemCo library as part of a DDF investment in your company/project or on a fee-for-service basis, please contact DDFchemco@svlsm.com

Compound overview

- >500,000 compounds, curated to be CNS-focused and diversity-driven with Lipinski “rule-of-5” filters
- Proven source of HTS hits on diverse targets, from which drug candidates have been developed. 52 screens have been conducted using this library, each identifying effective hits suitable for moving into lead ID efforts

Backgrounds of library compounds:

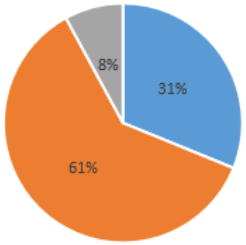
- 30% commercial purchases (med chem and combinatorial),
- 5% de novo synthesis, proprietary compounds
- 65% semi-exclusive combinatorial compounds

Library composition:

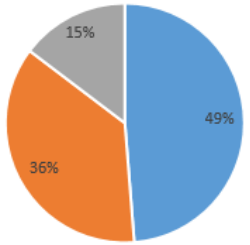
- Reference and novel compounds, including 4,480 compounds that are drugs, clinical candidates and known pharmacologically active compounds
- 1,892 known kinase-targeting compounds, including allosteric modulators, ATP-site compounds, novel and literature compounds
- 175,000 compounds make up the ‘Diversity Representative Subset’, computationally-selected to capture the diversity of the full collection for capacity-limited screens
- Cherry picking of compound subsets from the full library can be performed by Aptuit for targeted screens

Subsets	Size	Use
'High value'	320,000	Widespread screen
Diverse representation set	175,000	HTS 'elite' set
Kinase library	2,000	Kinase specific
Drug library	4,500	'Serendipity' screen

'High value' set (320k)



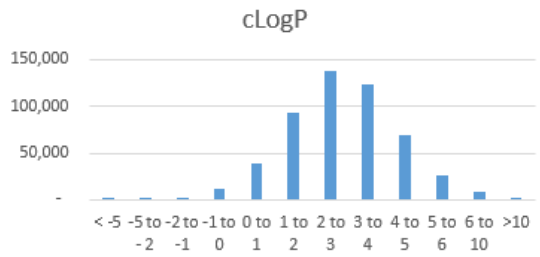
Diversity representative set (175k)

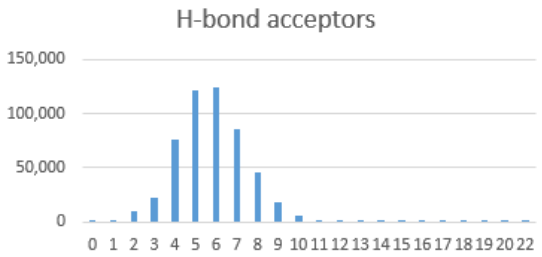


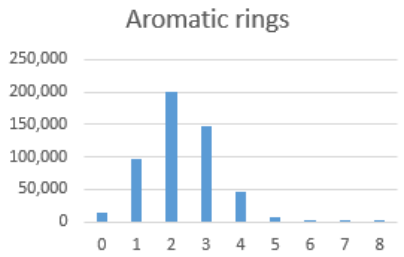
Filters	Category 1 *pass:*	Category 2 *not within Cat 1, but pass:*	Category 3 *not within Cat 1 or 2, but pass:*	Category 4 *outside Cat 1-3*
MWt	150-375	150-475	150-600	
Heavy atom count	11-25	11-32	11-40	
cLogP	1-4	-1.5-5	-2-7	
H-bond acceptors	0-7	0-9	0-11	
H-bond donors	0-2	0-3	0-4	
H-bond acceptors + donors	1-7	1-10	1-13	
Rotatable bonds	0-5	0-8	0-12	
Total polar surface area	0-80	0-120	0-160	
Pos charge	0-1	0-1	0-2	
Neg charge	0	0-1	0-1	
Rings	1-3	1-4	1-6	
Aromatic rings	0-3	0-4	0-5	

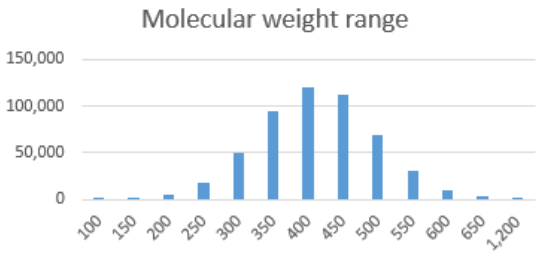
Library characteristics

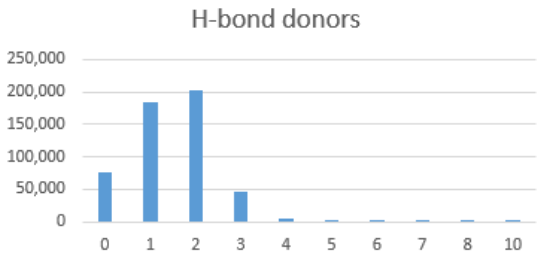
Key properties show good distributions across drug-like ranges

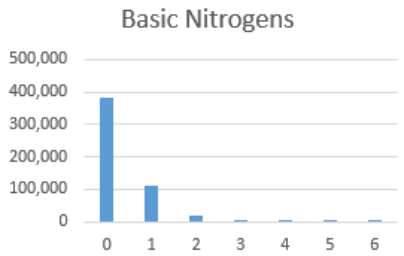


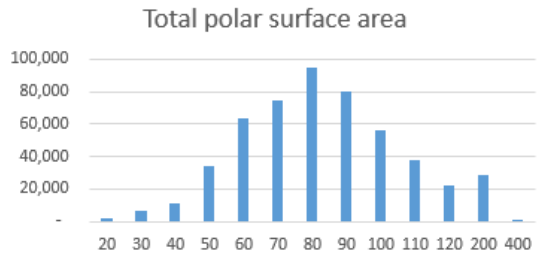


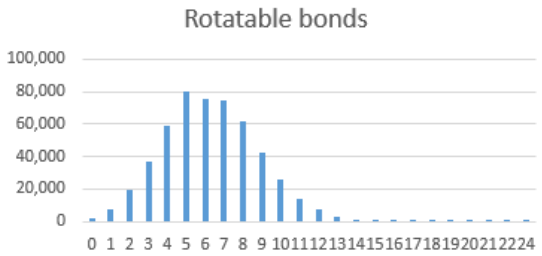


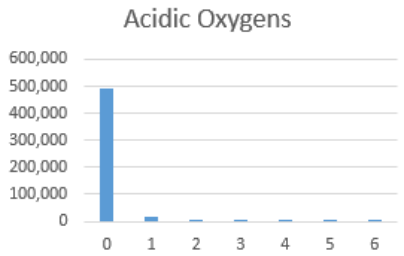








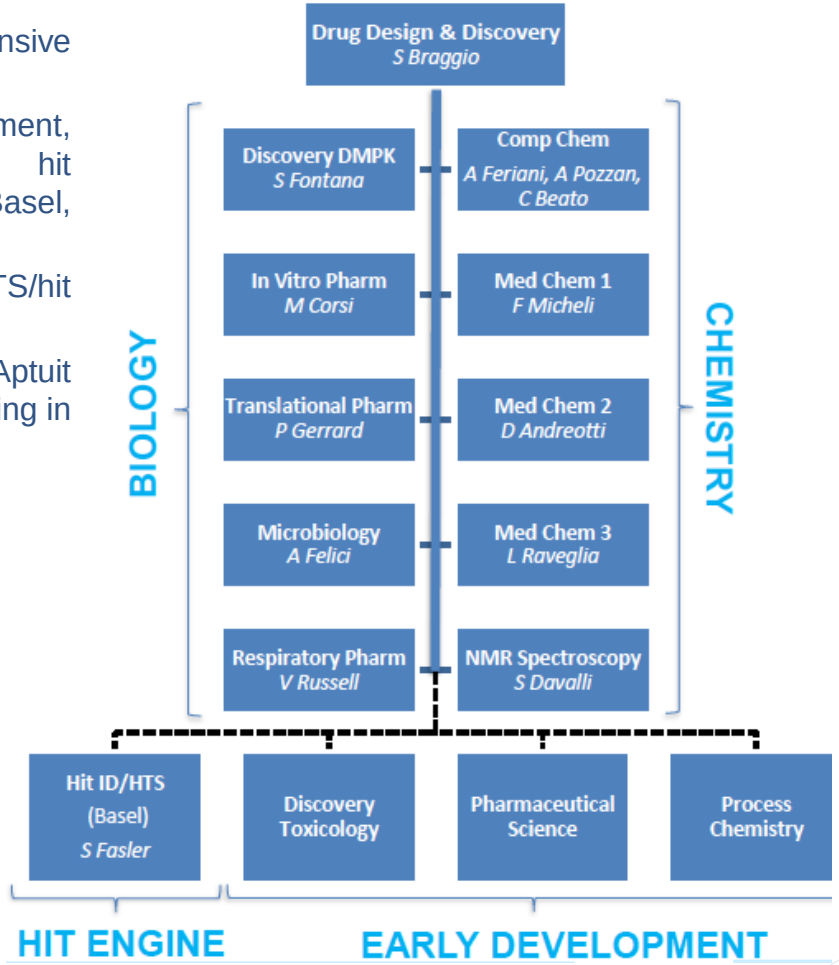




The library is housed at Aptuit

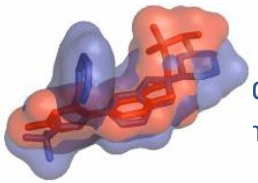
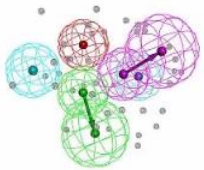
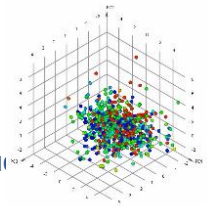
About Aptuit:

- Aptuit is an integrated drug discovery CRO with extensive experience in CNS-targeted approaches
- Aptuit provides expertise in compound library management, high throughput screening, selectivity testing, and hit characterization via its Exquiron Biotech subsidiary (Basel, Switzerland)
- DDF ChemCo library is housed and used for HTS/hit confirmation in Basel
- Follow on assays can be developed and executed in Aptuit Verona, where expertise in DMPK and CNS biology, including in vivo assays, resides (former GSK CNS R&D site)



Aptuit capabilities

- State of the art liquid handling capabilities
- High throughout cherry picking and serial dilution capabilities
- Automated and modular screening stations
- Acoustic dispensing capacity
- Barcode-tracked sample management and assay data
- Broad computational chemistry expertise applied at all stages of the hit identification process
  - Ligand-based virtual screening
  - 2D similarity searches incl. Turbo similarity
  - 3D shape/pharmacophore searches, field-based methods
  - Structure-based virtual screening
  - Virtual docking of tangible and virtual compound collections into enzyme and receptor active sites
  - Active site derived pharmacophore searches
  - Bio- and cheminformatics, including in silico ADME
  - Machine learning model generation and search using machine learning methodologies
  - Cluster-based analysis and re-mining of complex HTS data sets
  - Extensive use of chemigenomics database
- Lead Optimization capabilities
- dli
  nce
  (flu
  ity,
  fluorescence polarization, time-resolved fluorescence, HTFC)
  - Ca^{2+} mobilization assays, on channel activity by FMP dye
  - Absorbance- and luminescence-based readouts, AlphaScreen®
  - Radioisotopic assays (binding, filtration, or scintillation proximity using 3H-, 33P-, 35S-, or 125I-tracers)
  - Biosafety level 2 whole-cell screening assays (microbial and mammalian)
- IND enabling platform optimized to reduce time & cost (INDiGO platform)
- Biological assay expertise
  - Adaptation and optimization of client- provided protocols
  - Mammalian/insect cell-based model systems
  - Biochemical enzyme or interaction assays
  - Receptor binding, transporters, uptake studies
  - Microbial viability assays (bacteria, fungi, parasites)
  - De novo assay development and miniaturization
  - Complementation by counter, selectivity & orthogonal assays
  - Enzymatic MoA studies
- Expertise in target areas/biology (GPCR, ion channels/ electrophysiology)

Working with DDF ChemCo and Aptuit

Client to contact DDF ChemCo with non-confidential outline of proposed screen*

DDF ChemCo and Client implement a standard authorisation agreement setting out scope of work with the ChemCo library and related terms

With authorisation agreement, Client and Aptuit directly discuss details of work to be performed by Aptuit (screening or plate preparation and shipping), including the cost of such work

After screening, any further optimization work requested of Aptuit to be negotiated directly between Client and Aptuit

*Contact **DDFchemco@svlsm.com**

Useful information to include:

- Whether screening requested to be run at Aptuit or elsewhere (i.e. request for plated compounds to be shipped)
- Nature of the assay (e.g. biochemical, phenotypic, current format/throughput)
- Screening of entire library or selected subset

FAQs

- **What is the origin and nature of the library? Sources, size of full collection, size of diversity subset and any other specialized subsets? (e.g. fragment sets or compounds aligned with specific classes or targets**) – see slides 3 & 4

- **How have the CNS credentials been determined?** See slide 5

- **Screening practicalities**
  - **Can we cherry pick compounds of interest to be plated for screening?** – Yes – Aptuit has the capability to cherry pick compounds for targeted screens. If Clients wish for chosen compounds to be plated and shipped they must bear the associated costs.
  - **How much stock is there and at what concentrations?** For a fee, you may request a daughter set of echo-compatible plates at 10mM in 100% DMSO with sufficient volume to create assay ready plates for an HTS, hit confirmation, and follow on dose response curves. Assay ready plates at the appropriate concentrations (as high as 100uM) may also be requested
  - **What are the limits to the number of times we could screen as part of a collaboration?** ChemCo will function as a fee-for-service company, in principle with no limit to the number of screens any customers may request
  - **What are the considerations for stock depletion by various groups using the library?** There is sufficient stock for ChemCo to run dozens of HTS per year; we will re-synthesise as required
  - **What sort of plating is available? Assay ready or daughter plates requiring further dispensing?** Either can be made available
  - **Does Aptuit have the capacity for acoustic dispensing?** Yes

FAQs, cont.

- **Hit follow-up**
  - **What is the down-stream process should a series be identified from the library? What happens if two groups independently find the same compounds and wish to optimise, and ultimately create CoM patent applications?** The DDF ChemCo library is a non-exclusive resource and we do not plan to remove compounds that have been identified as hits from the library. We would consider offering reasonable lead time to enable both parties to achieve their goals should two groups independently identify the same hit compounds and wish to optimize them

- **Finances and costing**
  - A Client may be able to screen the ChemCo library whether or not DDF is an investor. On a case-by-case basis, Clients can use the library on a DDF-investment or fee-for-service basis, with the aim of enabling access to the library on attractive terms
  - Follow on work at Aptuit would be negotiated directly between the Client and Aptuit
  - To discuss potential cost implications of your project, please contact **DDFChemCo@svlsm.com**