THE PRESTWICK CHEMICAL LIBRARY® A VALUABLE TOOL FOR SCREENING

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INTRODUCTION

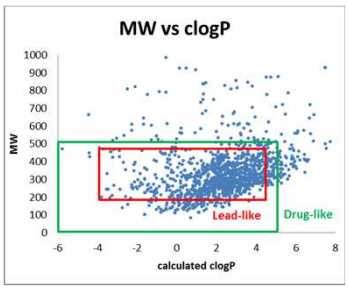
The Prestwick Chemical Library® (PCL) is Prestwick's flagship product dedicated to screening. It is a collection of 1280 molecules comprising 100% approved drugs (FDA, EMEA and other agencies) selected for their high chemical and pharmacological diversity. These off-patent drugs have known bioavailability and safety data in humans are available. The PCL was designed to reduce the risk of "low quality" hits and therefor the cost of the initial screening, and appears to be an efficient smart library for hit discovery. The library is used:

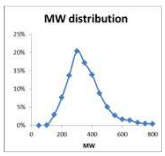
- primarily for molecular and phenotypic screening in order to do repositioning
- for finding hits which may enter an optimization program
- for assay validation
- more recently for the finding of stem cell differentiation modulators

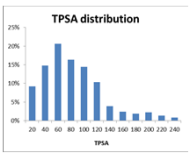
The PCL comes in different formats with a fully-annotated database.

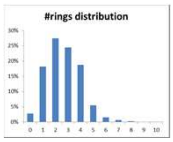
PHYSICOCHEMICAL PROPERTIES AND CHEMICAL DIVERSITY

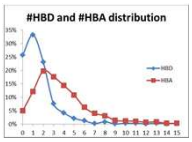
Analysis of the physicochemical properties shows that 83% of the library compounds match with Lipinski drug-like parameters.[1] Whereas clogP and MW cover a large range of value, half of the compounds respect Hann and Oprea lead-like parameters[2] used for the lead selection process. Chemical diversity of a library could be assessed by using the Delimited Reference Chemical Subspaces (DRCS) method.[3-4] The DRCS analysis of the PCL revealed that it covers a well-distributed chemical space compared to other libraries.

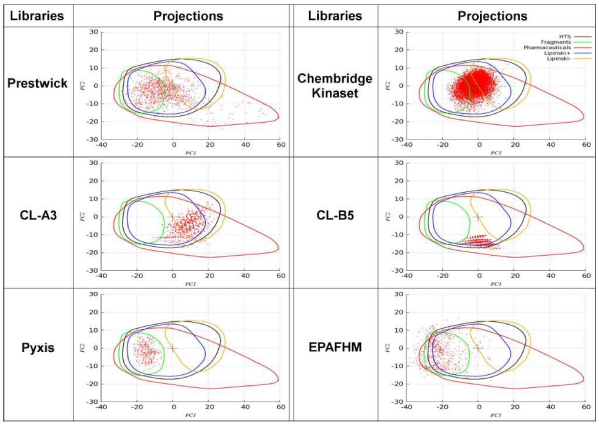






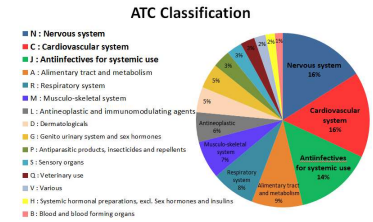


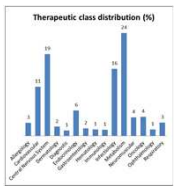


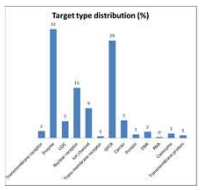


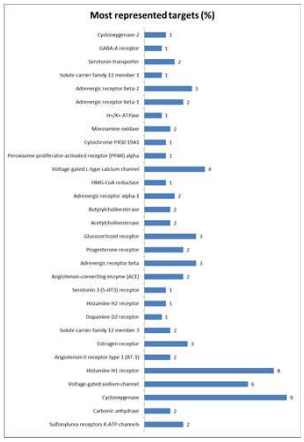
PHARMACOLOGICAL DIVERSITY

Analysis of PCL therapeutic data (WHO ATC classification[5] and therapeutic class distribution) shows that the library covers all main ATC groups. More than half of the drugs within the library are dedicated to CNS, cardiovascular, metabolism and infectiology diseases. Associated pharmacological targets were identified using ChEMBL database[6] and revealed that most of the targets are related to enzymes and GPCRs. More than 100 different targets were found in the PCL: Histamine H_1 receptor, voltage-gated sodium channel and cyclooxygenase were the most represented targets.



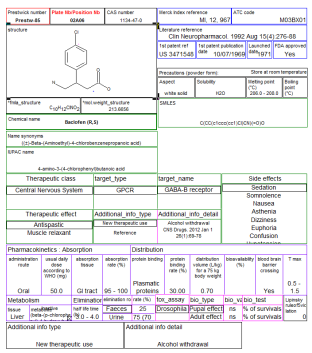






FORMATS AND DATABASE

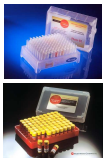
The PCL is delivered with a fully-annotated database available in several electronic formats (SDF, XLS, DB, DWAR). The database includes information such as structure, chemical name, literature reference, physicochemical properties, targets, therapeutic class and effect, pharmacokinetics data and reported side effects. The database has been recently highly updated by using several public sources.[6-9]



Solution in DMSO*:
- Ready for screening
- 96 or 384 well plates
- Volumes: between 200µL and 1mL, special academic format
- Concentration:10mM

*Custom plating available upon request

Powder form:
- Total library or cherry picking
- Delivered in customizable vials
- 10mg or more



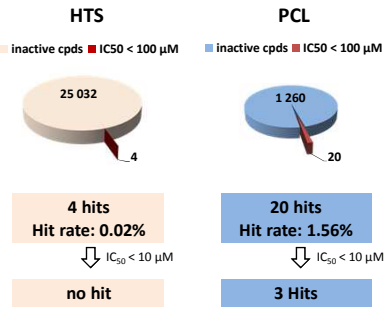
DRUG REPURPOSING

Finding new uses for old drugs can be an effecient strategy in drug discovery/development.[10-11] The significant advantage is that since the repositionned drug has been fully evaluated, safety data are known and so the early cost and time needed to bring a drug to market could be spared. Over the past decade, the PCL use has proven to be a valuable tool for drug development (160+ bibliographic references) and has allowed to identify new indications and mechanisms of action for several PCL compounds (see table).

Old indication	New indication/mechanism
Immunosuppressant	Muscular dystrophy[12]
Antibacterial	Anti-cancer[13]
Vasodilatator	Fungal infections[14]
Cardiotonic	Neurodegenerative diseases[15]
Antihypertensive drug	Anti-prions[16]
Antimalarial drug	Viral infection[17]
Vasodilatator	Immuno suppression[18]
Antimalarial, antihelminthic	Anti-cancer[19]
Antimicrobial, photosensitizer	Anti-cancer[20]

HTS VS SMART LIBRARY

In the course of a hit discovery project (TAKTIC[21]), a primary screening was performed to identify new inhibitors of NF-κB-inducing kinase (NIK), a serine/threonine protein kinase. A HTS approach with a commercial chemical database of 25K cpds considered to be highly diverse was compared with the use of a smart library. The PCL was clearly more favorable and efficient than an HTS library with a hit rate of 1.56% and an higher number of micromolar inhibitors.



CONCLUSION & PERSPECTIVES

The ensuing poster was performed to highlight the benefits of the Prestwick Chemical Library.® The PCL is a screening collection arising from medicinal chemistry expertise that presents a large degree of chemical and pharmacological diversity despite the relatively small number of compounds. Over the past 16 years, the PCL use has shown high efficiency for the identification of new hits and biochemical mechanisms. The PCL database represents so far the best and most annotated database delivered with a screening library.

REFERENCES

1. Adv. Drug Delivery Rev. 1997, 23, 3. **2.** Curr Opin Chem Biol. 2004 (3):255-63. **3.** J. Chem. Inf. Model. 2011, 51, 1762–1774. **4.** J. Chem. Inf. Model. 2012, 52, 327–342. **5.** http://www.whocc.no/atc_ddd_index/. **6.** Nucleic Acids Research, 2014, Vol. 42, Database issue D1083–D1090. **7.** MIMS Drug Information System, Search Drug Information, Interactions, Images, Dosages & Side Effects. https://www.mims.com/. **8.** WIPO - World Intellectual Property Organization. www.wipo.int/. **9.** Vidal. http://www.vidal.fr/. **10.** Drug Discov Today. 2014 19(5):637-44. **11.** Nature. 2007 Aug 9;448(7154):645-6. **12.** Neuromuscular Disorders, 2004, 14, 365-370. **13.** Clinical Cancer Research, 2006, 12, 5557-5569. **14.** Chemistry & Biology, 2005, 12, 973–980. **15.** PNAS 2008, 105 (32), 11218-11223. **16.** Plos One 2008, 3 (4), 1981. **17.** J Virol. 2009, 83(10), 5148-5155. **18.** The Journal of Biological Chemistry 2009 284(14). 9394–9401. **19.** Bioorganic & Medicinal Chemistry Letters 2009, 19, 1592–1595. **20.** PloS One, 2012, 7, 1-14. **21.** TAKTIC (TrAnslational Kinase Tumor Inhibitor discovery Consortium) is a FP7-SME-2012 project (Grant number: 315746).