HOW TO MAKE NEW OUT OF OLD?

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Developing a brand-new drug takes an enormous amount of time, money and efforts. However, there is a wide consensus that new drugs in many therapeutic areas are urgently needed meaning that it is crucial to advance strategies to reduce time frame, decrease costs and improve success rates.

« The most fruitful basis for the discovery of a new drug is to start with an old drug »[1]

Sir James Black, 1988 Nobel Prize

Disillusioned with HTS and struggling to bring new chemical entities to market, many companies are turning back to Sir James' wisdom.[1] In this perspective, to support strategies such as **drug repurposing**, **fragment-based drug discovery (FBDD)** and **selective optimization of a side activity (SOSA approach**), a range of valuable tools based on marketed drugs have been developed at Prestwick. The design, properties and advantages of this tools are presented and discussed in the present poster.

DRUG REPURPOSING
PRESTWICK CHEMICAL LIBRARY® : A HIGH VALUABLE TOOL

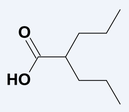
What is drug repurposing?

Repurposing is defined as developing new uses for drug beyond its original approved indication

- Cost effective
- Preclinical safety studies already completed
- Reduced timeline
- De-risked strategy

Selected by a team of medicinal chemists and pharmacists for high chemical and pharmacological diversity, as well as for known bioavailability and safety in humans, the Prestwick Chemical Library® is a unique collection of **1280 off-patent small molecules, 95% approved drugs**.

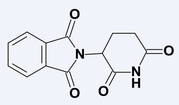
REPURPOSING IN MULTIPLE THERAPEUTIC AREAS



Valproic acid[2,3,4]
(Prestw-1482)

1978 FDA approved Antiepileptic **CNS** ⇨ 1995 FDA approved Antimanic / Bipolar disorders **CNS** ⇨ Phase II, 2017 Head and neck cancer **Oncology** ⇨ Phase II, 2018 HDAC inhibitor **Anti-infective**

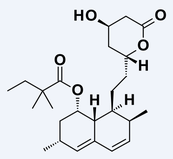
REPURPOSING OF A WITHDRAWN DRUG



Thalidomide[5]
(Prestw-192)

Approved in 1950s Antihistaminic, Sedative ⇨ **Teratogenic effects Withdrawn (1962)** ⇨ 1998 FDA approved Treat leprosy ⇨ 2012 FDA approved Multiple myeloma

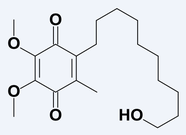
REPURPOSING AS ORPHAN DRUG



Simvastatin[6]
(Prestw-865)

2008 FDA approved
Cholesterol lowering effects

⇨ **Duchenne Muscular Distrophy** (phase III) ⇦



Idebenone[7]
(Prestw-1288)

2007 EMA approved
Leber's hereditary optic neuropathy

SOSA (SELECTIVE OPTIMIZATION OF SIDE ACTIVITY) APPROACH[11]
PANEL OF PRESTWICK DRUG LIBRARIES : KEY TOOLS

What is the SOSA approach?

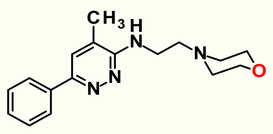
Transformation of the observed "side activity" into the main effect with simultaneous strong reduction of the initial pharmacological activity

- Time and cost shortened
- Increased probability of obtaining safe, soluble and oral bioavailable leads
- Free space for patenting

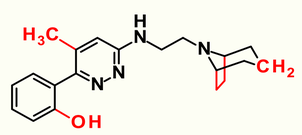
Prestwick Chemical has developed a range of valuable drug libraries :

- **Prestwick Chemical Library®** : 1280 drugs with high pharmacological diversity
- **Prestwick CNS Drug Library** : 320 drugs with proven pharmacological effects on the central nervous system
- **Prestwick GPCR Drug Library** : 265 drugs interacting primarily with GPCRs
- **Prestwick Ion Channel Drug Library** : 106 drugs interacting primarily with ion channels

EXAMPLE : INVERSION OF THE ACTIVITY PROFILE OF MINAPRINE[12]



Minaprine (Cantor®) = Prestw-66
Dopaminergic: +++
Serotoninergic: +
Cholinergic: ½+



Modified Analogue
Dopaminergic: 0
Serotoninergic: 0
Cholinergic : ++++

CONCLUSION

In drug discovery process, starting with approved drugs or fragments of approved drugs increases hit quality and the probability of obtaining safe, soluble and oral bioavailable leads. To support this strategy, Prestwick chemical has developed a wide panel of compound libraries with the Prestwick Chemical Library® and the Prestwick Drug Fragment Library as flagship products.

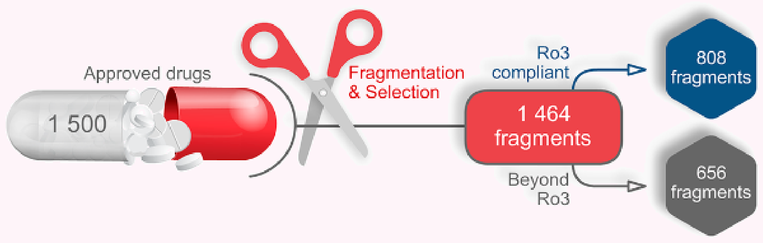
FRAGMENT BASED DRUG DISCOVERY
PRESTWICK DRUG-FRAGMENT LIBRARY : AN INNOVATIVE TOOL

What is FBDD?

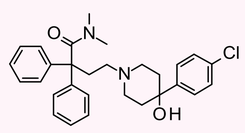
It starts with identification of small molecules that bind with weak affinity but high quality interactions to the target. It is followed by optimization to lead compounds with high affinity and selectivity.[8]

- Higher hit rate compared to HTS
- Reliable technique for wide range of targets
- Hits with higher ligand efficiency
- 2 approved drugs and 30+ in clinical development

Prestwick Chemical medicinal chemists designed a unique collection of **1464 small molecules (MW<300)** arising from the smart **fragmentation of 1500 approved drugs** (up to year 2016).



Example:

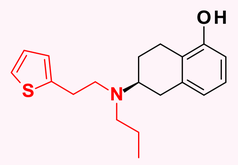


Loperamide

⇨ **Prestw-Frag-1453** **Prestw-Frag-1193** **Prestw-Frag-1365**

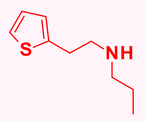
SPECTACULAR OCCURRENCE OF PRESTWICK FRAGMENTS IN 2017 FDA-APPROVED DRUGS

85% of the 2017 FDA-approved[9,10] drugs contain at least one of the Prestwick Drug-Fragments confirming that expansion of drug fragment hits is likely to give molecules with appropriate ADMET properties during lead optimization.



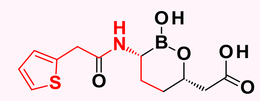
Rotigotine
2007 FDA approved
Parkinson's disease

fragmentation process ⇨

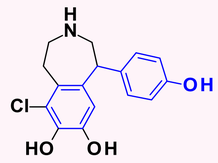


Prestw-Frag-3251
Exclusive Prestwick Fragment

present in a 2017 approved drug ⇨

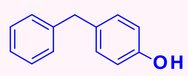


Vaborbactam
2017 FDA approved
Antibacterial



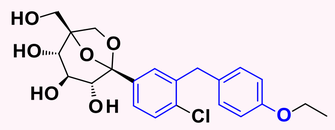
Fenoldopam
1998 FDA approved
Antihypertensive

fragmentation process ⇨



Prestw-Frag-3455
Exclusive Prestwick Fragment

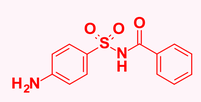
present in a 2017 approved drug ⇨



Ertugliflozin
2017 FDA approved
Type 2 diabete

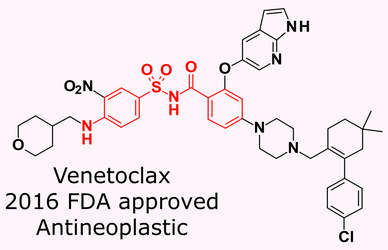
SPECTACULAR OCCURRENCE OF PRESTWICK FRAGMENTS OVER THE TIME

Small antibacterial drug Sulfabenzamide (**Prestw-Frag-2345**), FDA approved in 1945, is present as core fragment in Venetoclax, an antineoplastic agent approved by FDA in 2016.



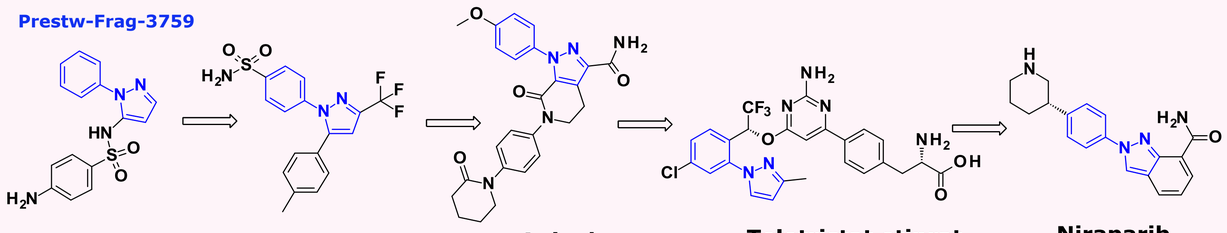
Prestw-Frag-2345 = Sulfabenzamide drug
1945 FDA approved
Antibacterial

present in 2016 approved drug ⇨



Venetoclax
2016 FDA approved
Antineoplastic

Phenyl-pyrazole core (**Prestw-Frag-3759**), fragment of Sulfaphenazole, is retrieved over time in many approved drugs in different therapeutic areas.



Sulfaphenazole
1974 approved
Antibacterial

⇨ **Celcoxib**
2001 FDA approved
Anti-inflammatory

⇨ **Apixaban**
2002 FDA approved
Antithrombin

⇨ **Telotristat etiprat**
2017 FDA approved
Carcinoid syndrome diarrhea

⇨ **Niraparib**
2017 FDA approved
Ovarian cancer

1. Innovations in Pharmaceutical Technology, issue 42, 10-12 **2.** World Psychiatry, **2018**, 17:1, 28-29 **3**. Chem. Biol. Interact., **2018,** 25, 280, 51-58 **4**. Cancer Research, **2017**, 77(13), 4058 **5**. Nat. Rev. Drug Discov., 2012, 11, 191-200 **6**. Current Opinion in Pharmacology, 2017, 34, 36-48 **7**. Journal of Inborn Errors of Metabolism & Screening, **2017**, 5, 1-8 **8.** Curr. Med. Chem. 2012, 19(30), 5128-5147 **9.** FDA: http://www.fda.gov/Drugs **10.** C&EN, January 22, **2018**, 26-30 **11.** Drug Discov. Today **2006**, 11, 160-164. **12.** Il Farmaco **1993**, 48, 253-274.