Enabling synthesis in FBDD

*Dial-a-Molecule Annual Meeting 2018*

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FBDD – Fragment Based Drug Discovery

**Fragments:**
- **Low MW, polar molecules** are used to identify binding pockets on a target protein

**Structure-led design:**
- Increased target affinity is achieved by designing chemical probes to interrogate protein architecture

**Specific growth vector elaboration:**
- Fragments are elaborated in **specific directions** along well-defined **vectors** to generate **bespoke** lead compounds
FBDD – Synthetic considerations

• **Fragments:**
  – Low MW, polar molecules are used to identify binding pockets on a target protein

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• **Specific growth vector elaboration:**
  – Fragments are elaborated in specific directions along well-defined vectors to generate bespoke lead compounds

*Minimal pharmacophore* can present regioselectivity and reagent compatibility issues

*Growth vectors* can be difficult to access synthetically

Design rationale vs Synthetic tractability
Traditional vs cutting edge synthesis techniques

Traditional vs cutting edge synthesis techniques

\[
\text{traditional} \quad 3 \text{ steps}
\]

J. Org. Chem, 2016, 81, 6980
Problematic heterocycles

- Aliphatic heterocycles
  
  - [Chemical structures]

- Nitrogenous heteroarenes
  
  - [Chemical structures]
Bespoke synthetic toolbox for FBDD

- At Astex we are exploring the use of liquid handling robots for optimisation and reaction discovery
- C–H functionalisation techniques e.g. Hydrogen Atom Transfer (HAT) catalysis can permit direct elaboration on native fragments
**Bespoke synthetic toolbox for FBDD**

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**Single electron transfer processes:**

- Tolerate polar motifs – good for heterocycles!
- Performed in polar solvents – good for liquid handling robots
- Ambient temperature – good functional group tolerance
- High value couplings (e.g. sp²-sp³ coupling, nitrogen-rich compounds)

*Highly accessible thanks to revolution in photoredox catalysis!*
HTE Workflow

**Source plate dosing**
- Andrew Alliance LHR
- Flexibility of Consumables
- Free X,Y,Z movement

**Reaction plate dosing**
- Mosquito® LHR
- 125 nmol scale
- 2.5 µL reaction volume
- ~40 mg substrate/plate
- 100-1000s combinations

*Science, 10.1126/science.aar6236 (2018); Science, 2015, 347, 49*
HTE Workflow

Analysis
- Reformat into 384 well plate with Mosquito®
- Semi-quantitative hit analysis by LC-MS
- μmol scale up to confirm structure by NMR
New reaction discovery – Heteroarylation of amines

- Reaction conditions elucidated on nanogram scale in MTP
- Photoredox mediated cross-dehydrogenative coupling (CDC)
- $\alpha$-amino radical Minisci-type addition to heteroarenes
- 112 substrates screened (56% hit rate)
  - explored Structure Reactivity Relationship (SRR) of methodology
- Reaction performed on gram scale in flow
  - in collaboration with Prof. Steven Ley and Dr. Fabio Lima (University of Cambridge)
Examples of Substrate Scope

\[ \text{PG} \text{H}_{\text{et}} + \text{PG} \text{H}_{\text{et}} \xrightarrow{\text{DMSO}} \text{PG} \text{H}_{\text{et}} \]

- 40%  
- 80%  
- 90%  
- 42%  
- 81%  
- 58%

\[ \text{Boc-N} \text{CO}_2\text{Me} \]
- 30%

1.3g, 2h  
\( \tau = 10\text{min} \)

- 58%  
- 83%  
- 41%  
- 63%  
- 69%  
- 56%

\[ (\alpha:\beta) 1.5:1 \]

Manuscript in preparation
Summary

- New synthetic methodology developed using cutting edge chemistry technologies
  - Photoredox heteroarylation of amines
  - HTE screen on ng-scale
  - Valuable sp²-sp³ CDC
  - g-scale reaction in flow
- Explore Structure Reactivity Relationships (SRR)
  - Standardised data…reaction prediction
- Enabling fragment growth vectors and improving fragment kinship
- Need to overcome analytical bottleneck!
Sustaining Innovation Postdoc Scheme at Astex

- Propagation of Astex’s scientific culture
- Exploratory research in a multi-disciplinary team
- Academia in Industry – focus on publication
- 5 postdocs/year
- 3 year contract
- Focus on internal and external collaboration
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