Taking a data driven approach to drug discovery

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The process by which new medications are discovered

Biology relevant to disease  |  Target based phenotype  |  Drug-able by any modality  |  Therapeutic index  |  Right patients

Target discovery  |  Screening  |  Lead generation  |  Optimization  |  Preclinical development  |  Clinical development

Target Discovery
• Novel therapeutic hypotheses in diseases with validated therapeutic biology (first in class)
• Develop clinically differentiated drugs from existing clinical/marketed therapies (best in class)
Multiple drug discovery projects advance in parallel

Within Immunology we usually have 6 projects in Lead Optimization and 12 projects in the Target Selection phase.

Stage gates
- Target Selection (0 – 1 year)
- Lead optimization (1 – 3 years)
- IND

Functions
- Tool compound identification
- In vitro assay development
- Design & Synthesis
- ADME
- Pharmacology
- Safety/tolerability
- Process Chemistry
- GLP Toxicology

Requires working effectively and efficiently
Drugs are ‘designed’ by medicinal chemists – typical process

**In vitro screen**

- Potency of compounds
- Series identification
- Chem draw 2D overlay
- Core hopping
- Cross over compounds
- Matrix of compounds
- Synthetic accessibility

**Synthesis leads design**

(we hire synthetic organic chemists to be medicinal chemists)
Medicinal Chemistry: implementation of Design-Synthesis paradigm - a productive division of labor

- What to make (design)
- How to make (synthesis)

- Abbvie Bioresearch Center in Worcester, MA switched to a Design/Synthesis model in 2013
- The split in design and synthesis allows for specialization in each discipline
  - Designers and synthesizers share project team goals, and take joint ownership of compound decisions
  - Designers and synthesizers refine chemical plans: add, modify and deprioritize targets
  - Designers and synthesizers are collocated for optimal interactions
Specialization in each role leads to enhanced use of modern software - Tools generate more data and exacerbates the problem of tracking and archiving information.
Chemtrax encompasses all aspects of Design/Synthesis

- Enables integration of design synthesis cycles and promotes a transparent and collaborative working environment

• Chemtrax is an Amazon web-based service that tracks all phases of compound design and synthesis and facilitates meetings in organized manner

• Chemtrax eliminates wasted time on PowerPoint slides and searching for past ideas, and allows for teams to retain and organize project information from idea conception to compound registration
Tracking workflow
Displays overview of all target compounds at each stage of synthetic execution

- Compound tracking board provides transparent visual overview of entire chemical program for each project
- Intermediates and resynthesis of lead compounds are easily displayed
- Captures input from project members at multiple sites including external collaborators
BTK project – coordinated effort allows refinement of properties

- Clear trend into more optimal drug like space over time in parallel with achievement of project goals.
Effective: design/synthesis allows a focus on drug like compounds for TNFi

"... but we didn't need umpteen years of upheaval to tell us that making compounds that weight 910 with logP values of 8 are less likely to be successful. Did we?"


Jeremy J Edmunds, Lab of the future, November 2019
Effective: design/synthesis allows a focus on drug like compounds for TNFi

What you work on is just as important as what you won’t work on:

Chemists working in Design/Synthesis mode

Date

“... but we didn't need umpteen years of upheaval to tell us that making compounds that weight 910 with logP values of 8 are less likely to be successful. Did we?”


Jeremy J Edmunds, Lab of the future, November 2019
To measure efficiency:
Quantifying, Visualizing, and Monitoring Lead Optimization  Andrew T Maynard et al., GlaxoSmithKline

Statistical framework to quantify and visualize the progress of LO projects

JAK1 inhibitor project

Interleukins (IL-2, IL-4, IL-7, IL-9, IL-15 and IL-21)

Type I cytokine receptors

IL-6

Type II cytokine receptors

GM-CSF

Erythropoietin

Type I interferons (e.g. IFNα, IFNβ)

Interleukins (IL-10, IL-20, IL-22 and IL-28)

IFNγ

JAK1

JAK2

TYK2

STAT1

STAT3

STAT5

STAT1

STAT2

STAT3

STAT5

Type I activation:

- Lymphocyte proliferation and homeostasis
- T-cell differentiation
- Inflammation
- Erythropoiesis
- Myelopoiesis
- Platelet production
- Innate antiviral defense

Type II activation:

- Transcription
Janus kinase inhibitor (JAK) project
Project goal: achieve selective JAK1 clinical candidate

- During the course of the project 58 different assays were utilized to measure JAK family member selectivity
- 12 enzyme and cellular assays dominated data collection
**iSCORE: favorably increasing score with time**

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**Clinical candidates**

Missing values replaced by average values across project compounds
JAK project compounds exist in drug like space

ClogP

Molecular Weight

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Comparison of Shannon entropy and ECFP6 NxN mean matrix for 1674 JAK inhibitors

Similar trends in degree of similarity/dissimilarity calculated by moving average for Shannon Entropy or ECFP6 fingerprints
JAK clinical candidates align with higher scoring peaks

Graph showing the alignment of clinical candidates with higher scoring peaks.
Clinical candidates identified by profiling a diversity of Compounds in rat/dog/monkey toxicity studies

Clinical candidates

Compounds with appropriate JAK1/JAK2 selectivity; efficacy; PK; CV safety; to warrant toxicity studies to allow selection based on therapeutic index

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This is what it takes to move a project from idea to approved drug - large amount of data/information/knowledge is generated

RINVOQ example

- > 1700 Compounds
- > 8500 in vitro assays
- > 750 in vivo studies
- > 12 years

- > 5 series
- Multiple synthetic steps
- JAK Enzymes
- Cellular
- Selectivity
- Pharmacodynamics
- Pharmacokinetics
- Efficacy
- Preclinical safety
- 5 years preclinical development
- 8 years in clinical development
Summary

Design-Synthesis paradigm allows for expertise in each discipline; resulting in higher quality design concepts and excellence in synthesis to enable proficient synthetic routes to complex targets

- Appropriate application of design tools improves the quality of compounds that are prepared
- Expertise in synthesis enables the preparation of preferred compounds
- With focused specialization in each area, project teams can take advantage of new approaches
- Software like Chemtrax integrates the design and synthesis cycles and promotes a transparent and collaborative working environment
- Chemtrax allows for teams to retain institutional knowledge in an organized manner that can be leveraged by future projects
- Tractability and trajectory of a project can be measured and then assessed
- Multiple parameter optimization in parallel requires an integration of wisdom/knowledge/information/data that is enabled by informatics

If you think you can walk from the lab and do design in your office for a couple of hours and then go back to synthesis, you don’t understand the complexity of design or synthesis

You manage what you measure
Backups
Quantification of the similarity of compounds: Shannon Entropy

- Fragmentation signature created for each compound
- Merged fragment population created and occurrence recorded
- For each compound the specific fragment occurrence is compared with the fragments distribution in the merged fragment population
- Quantify fragment overlap as a measure of similarity
- The higher the SE the more similar the test compound is to the total population

\[ SE = - \sum_{i=1}^{n} p_i \log_2 p_i; \quad p_i = c_i/n \]

Asinex Project compounds
A maximal score of 1 is only achieved when the measured value is better than the desired value by 6 standard deviations.

Illustrates how calculated $P_{FP}$ binding Score varies with pIC50.

Threshold of 0.05 uM specified for $P_{FP}$ binding and Error of 0.1.

- 50 nM, pIC50 = 7.3
- 12.6 nM, pIC50 = 7.9

$P_{FP}$ binding Score
- 0.5
- 1.0
With increasing error, convergence (score 1) is achieved with IC50 < 1 nM

Threshold of 0.05 uM specified for P_{FP} binding and Error of 0.3

Illustrates how calculated P_{FP} binding Score varies with pIC50

- 0.05 uM, pIC50 = 7.3, P_{FP} binding Score 0.5
- 0.0008 uM, pIC50 = 9.1, P_{FP} binding Score 1.0
Evaluate Maynard methodology

- AIDEAS Platform: Biovia’s Pipeline Pilot/Tibco Spotfire:
  1. Murcko clusters
  2. ECFP6 similarities and Shannon entropy
  3. iSCORE
iSCORE: Multi-Parametric Score

- Teams define properties/parameters and weight required in scoring
- Project teams set the desired value/thresholds
  - Includes error margins

\[
iScore = 1 - \left( \prod_{i=1}^{n} (1 - P_i)^{w_i} \right)^{1/\sum Wi}
\]

**Example Function**

User value = desired value : then P=0.5
User value = desired value +/- 6SD: then P=1