



Managing Internal and External Chemistry for Efficient Drug Delivery

David Hollinshead (*Elixir Software*)

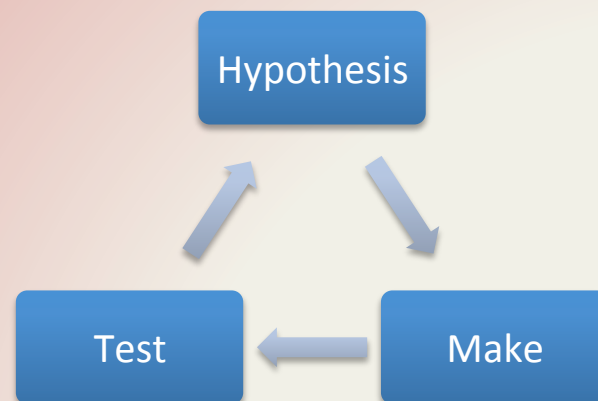
Andrew Griffin (*Praxis Precision Medicines*)

Before Genomics (BG)

- Compounds (up to 1g qty)
- Single compound synthesis
- Animal models
- Structure-effect relationships (ED₅₀)
- Pharmacology
-

(Disease to Target)

Chemistry Workflow



The iterative Hypothesis – Make – Test chemistry workflow was bounded by small compound numbers and relatively few measurements...



Chemistry Drivers

- Improve quality of compounds; reduce attrition
- Deliver more compounds; reduce cycle time

More tools, technologies, data for decision-making...

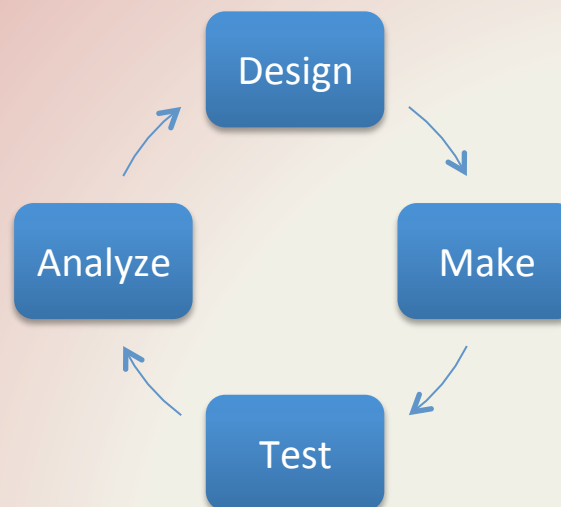
- More and Design tools and design approaches for developing leads
- Chemical technologies to prosecute many compounds simultaneously
- Diverse screening test data to analyze & interpret
- Improving understanding of the reasons drugs fail

Post Genomics (PG)

- Compounds (low mg qty)
- 'Combinatorial' HT chemistry
- HT assays
- Structure-activity relationships (pK_i)
- Molecular biology
-

(Target to Disease)

Chemistry Workflow



Genomics driven changes in HOW chemistry is deployed and what guides it.
 MORE design approaches, compounds, measurements & data analysis...

Enhance team-working & communication within the **DMTA** cycle

Design

Capture design hypotheses & objectives



Make

Track progress with delivery of agreed synthesis targets



Test

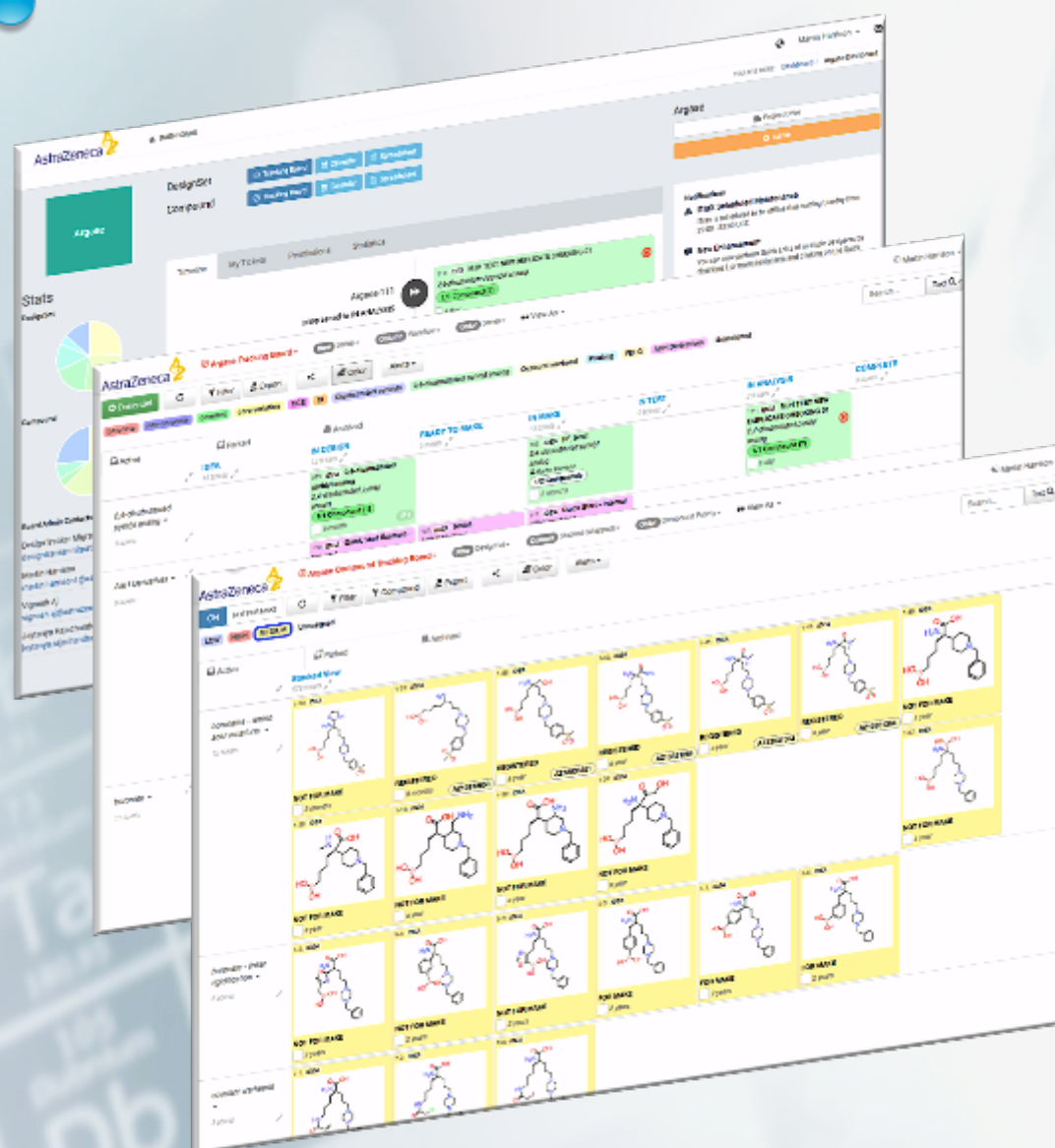
Know when biological evaluation is completed



Analyze

Trigger analysis – was the design objective met? Capture learning...





Project Dashboard

Design Tracking

Compound Tracking



Project Dashboard

- Flexible functionality to view project design sets in many ways
- We view the information with workflow as the 'process' and rowed by 'priority'
- Extra dimension to the data using coloring, in the example below color by chemical series
- Filtering of information to enable focussed views

DMTA Pharma DMH DesignSet Tracking

Row DesignSet Priority Column Workflow Color Series View As

DesignSet Refresh SSS Filter Export Color Alerts

Active Parked Archived

	PROPOSED 4 tickets	IN DESIGN 2 tickets	DESIGN COMPLETE 1 tickets	IN SYNTHESIS 4 tickets	IN TEST 2 tickets	IN ANALYSIS 2 tickets
HIGH 10 tickets	<div>038: IDEA stuff Pyridine 0/3 Compounds 5 months</div> <div>022: IDEA Marvin Test Miscellaneous Kiera Knightley 1/5 Compounds 2 years</div>		<div>025: IDEA S28 4[H]-Furyl- Amide Selectivity Pyrrolo-Pyridine 0/7 Compounds Sept Review 3 months</div>	<div>013: IDEA Pyrazolo-Pyridine Exploration #1 Pyrazolo-Pyridine Pat Ploughman, Kiera Knightley 3/6 Compounds Rev in Aug Progress</div> <div>003: IDEA Pyrazolo-Pyrimidine Motif Pyrazolo-[1,5-a]- Pyrimidine Martin Harrison, Pat Ploughman 3/6 Compounds Rev in Aug 5 months</div>	<div>012: IDEA S55 Amides with Amino-alkyl 4-Carboxy-Quinoline Kiera Knightley 3/4 Compounds Partner Labs Inc Rev Mtg Aug a year</div>	<div>005: IDEA S43 Amides with 6- Bn-ethers 4-Amido-Quinoline Martin Harrison, David Hollinshead 4/6 Compounds Info. Required Partner Labs Inc Alert</div> <div>011: IDEA S28 4[H]-Furyl Amides Pyrrolo-Pyridine Martin Harrison, David Hollinshead 4/8 Compounds Partner Labs Inc Rev Mtg Aug a year</div>

High level data shown:
Title, series, number of
Compounds, chemist
Hover over shows more info

What Information Do We Capture Within A Design Set?

DMH-3 Summary ▾ Edit 0 Design Comments 0 Design Attachments Compounds ▾ Full screen Share

DesignSet **Pyrazolo-Pyrimidine Motif** DesignSet Priority **HIGH** Status **IN SYNTHESIS**

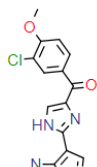
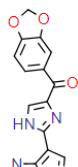
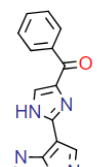
Chemistry Information

Title	Pyrazolo-Pyrimidine Motif	Current Position	IN SYNTHESIS
Chemistry Type	Project	DesignSet Priority	HIGH
Required By	16-Jun-2017		
Series	Pyrazolo-[1,5-a]-Pyrimidine	Sub Series	2-Imidazole Amide

Issue / Hypothesis

Issue	Cell Penetration, New Lead Finding, hERG Binding		
Hypothesis / Rationale	Novel motif suggested by protein modelling and overlay with indole series. The motif is a new pharmacophore based upon modelling/overlay. This design is for the purpose of screening tools for NMR fragment-based screening in parallel with the design for testing.		
Contributor(s)	Harrison, Martin	Concept Date	31-Jan-2017

Compound Overview

Summary Stats NOT FOR SYNTHESIS 0 FOR SYNTHESIS 0 IN SYNTHESIS 0 SYNTHESIS COMPLETE 3 SYNTHESIS FAILED 0	3-5 IDEA 	3-4 IDEA 	3-2 IDEA 
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- **Not just a list of compounds**
- Information captured can be tailored to each organization's needs
- Capturing of hypothesis, issue to solve and outcome of design set can also be captured
 - Knowledge capture and sharing
- Sensitive information like 'hypothesis' can be hidden from external partners



Realtime Team Communication (Internal and External Members)

DMH-5 Summary | Edit | 4 Design Comments | 1 NEW Design Attachments | Compounds ▾

DesignSet: **S43 Amides with 6-Bn-ethers** | DesignSet Priority: **HIGH** | Status: **IN ANALYSIS**

+ Comment

Anders Nystrom
October 17, 2018, 11:16

We've had some interesting data on this series. David - Please could you direct efforts now at a remake of 5-8? The requirements are highlighted in the new Remake ticket

5 users alerted and are still to view
Partner Labs Inc

Martin Harrison
May 29, 2018, 14:33

Thanks

Partner Labs Inc

David Hollinshead
July 26, 2017, 13:25

I had synthesis problems with the urea in this design set, but the other 2 compounds have been made now

Partner Labs Inc

Martin Harrison
June 1, 2017, 23:10

Can you take on the assigned cpds in this designset?

Compound Overview

Summary Stats	5-7 IDEA	5-4 IDEA	5-3 IDEA
NOT FOR SYNTHESIS 0			
FOR SYNTHESIS 1			
IN SYNTHESIS 0			
SYNTHESIS COMPLETE 0			
SYNTHESIS FAILED 1			
REGISTERED 4			
REFERENCE 0			

‘Comments’ to share updates with external partners and for external partners to share information back to the client

‘Attachments’ to share externally (e.g. synthetic procedures) or internally only (e.g. comp chem docking poses)

elixir Targets Within The Chemistry Tab

Workflow view of compounds in a design set

DMH-3 Summary Compound Views Row Compound Type Column Workflow Color Compound Workflow Full Screen

DesignSet Pyrazolo-Pyrimidine Motif DesignSet Priority HIGH Status IN SYNTHESIS

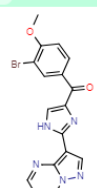
NO SYNTH OFF 0 Compounds Compound Export Color Alerts Search... Text C

Active Parked Archived 2

FOR SYNTHESIS	IN SYNTHESIS	SYNTHESIS COMPLETE	SYNTHESIS FAILED	REGISTERED
0 tickets	0 tickets	2 tickets	0 tickets	2 tickets

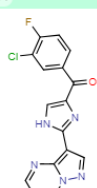
IDEA
6 tickets

3-16: IDEA



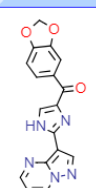
SYNTHESIS COMPLETE
Ploughman, Pat
5 months

3-15: IDEA



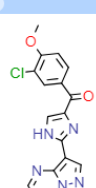
SYNTHESIS COMPLETE
Harrison, Martin

3-4: IDEA



REGISTERED
Ploughman, Pat
5 months Complete

3-5: IDEA



REGISTERED
Ploughman, Pat

- Priority can be give to individual compounds
- Compound drag and drop to update status
- Compounds can be assigned to individual chemists if required (manage workload)

elixir Spreadsheet View of Compounds

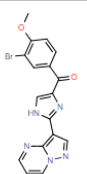
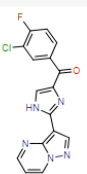
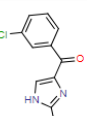
DMH-3 Summary Compound Views

DesignSet Pyrazolo-Pyrimidine Motif DesignSet Priority HIGH Status IN SYNTHESIS

Compounds Compound Export

Active Parked Archived

Drag here to set row groups

I ↓	Type	Structure Depiction	W...	Cor...	label	RDKit ...	RDKit ...	RDKit T...	RDKit L...	RDKit L...	RDKit ...	Ad...
<input type="checkbox"/> DM...	IDEA		SYNT...			3.1	398.2	85.2	1	6	4	Martin ...
<input type="checkbox"/> DM...	IDEA		SYNT...			3.1	341.7	75.9	1	5	3	Martin ...
<input type="checkbox"/> DM...	IDEA		SYNT...			3	323.7	75.9	1	5	3	Martin ...

1 to 6 of 6 First Previous Page 1 of 1 Next Last

Calculated properties (generated when compounds loaded into ChemTrax)

Compound status (for synthesis, in synthesis etc)

Filters

- ☒ label
- ☒ RDKit MolLogP
- ☒ RDKit MW
- ☒ RDKit TPSA
- ☒ RDKit Lipinski HBD
- ☒ RDKit Lipinski HBA
- ☒ RDKit N Rot Bonds
- ☐ SMILES
- ☒ Added By
- ☒ Workflow

Row Groups

Drag here to set row groups

Values

- avg(RDKit MolLogP)
- avg(RDKit MW)
- avg(RDKit TPSA)

- Easy view of basic calculated properties for each compound
- Quick edit to prioritize/down prioritize compounds
- Popular with Praxis users