A Proposed ADME Optimization Workflow for Covalent Inhibitors

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Lead Optimization for Metabolism and Safety
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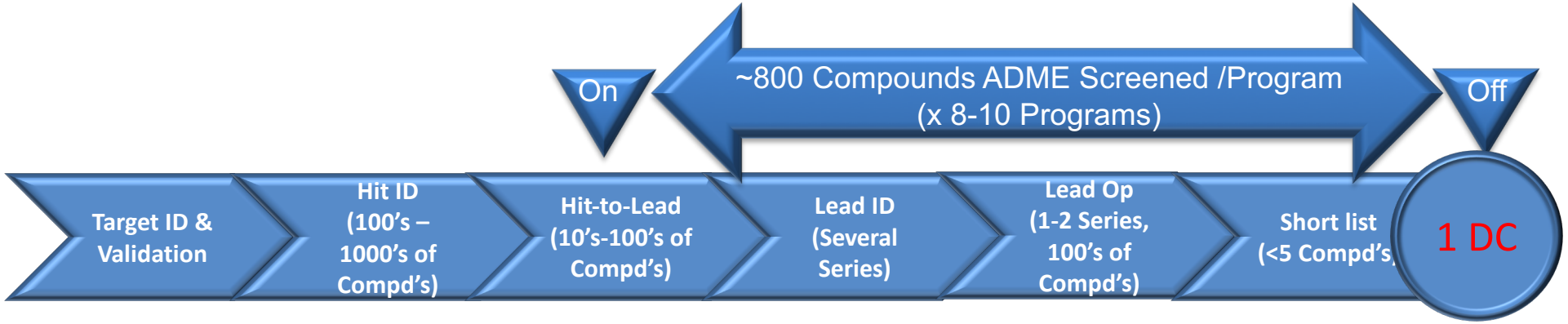
A San Diego biotech start-up dedicated to efficient discovery and development of innovative small molecule drugs to address unmet medical needs in fibrosis and oncology

Central Role of DMPK in Drug Discovery & Development

Thousands of Compounds Enter ADME Screens Per Year

What are the advancement criteria?



1. Ideas
2. Literature
3. Collaborations
4. Development organization

Biochemical triage:

1. ID CC's with desired % Inhibition
2. Generate IC50 and enzyme kinetic data to confirm hits

Chemical triage:

1. Group into series
2. Investigate ease of synth
3. Make a few close analogs to rule out exceptions
4. Investigate patent space
5. Collect some **DMPK** and biological data

Ramp up **DMPK** and biological data collection to narrow down to a few series

Select 1-2 series and optimize in **DMPK**, Pharm, ETox

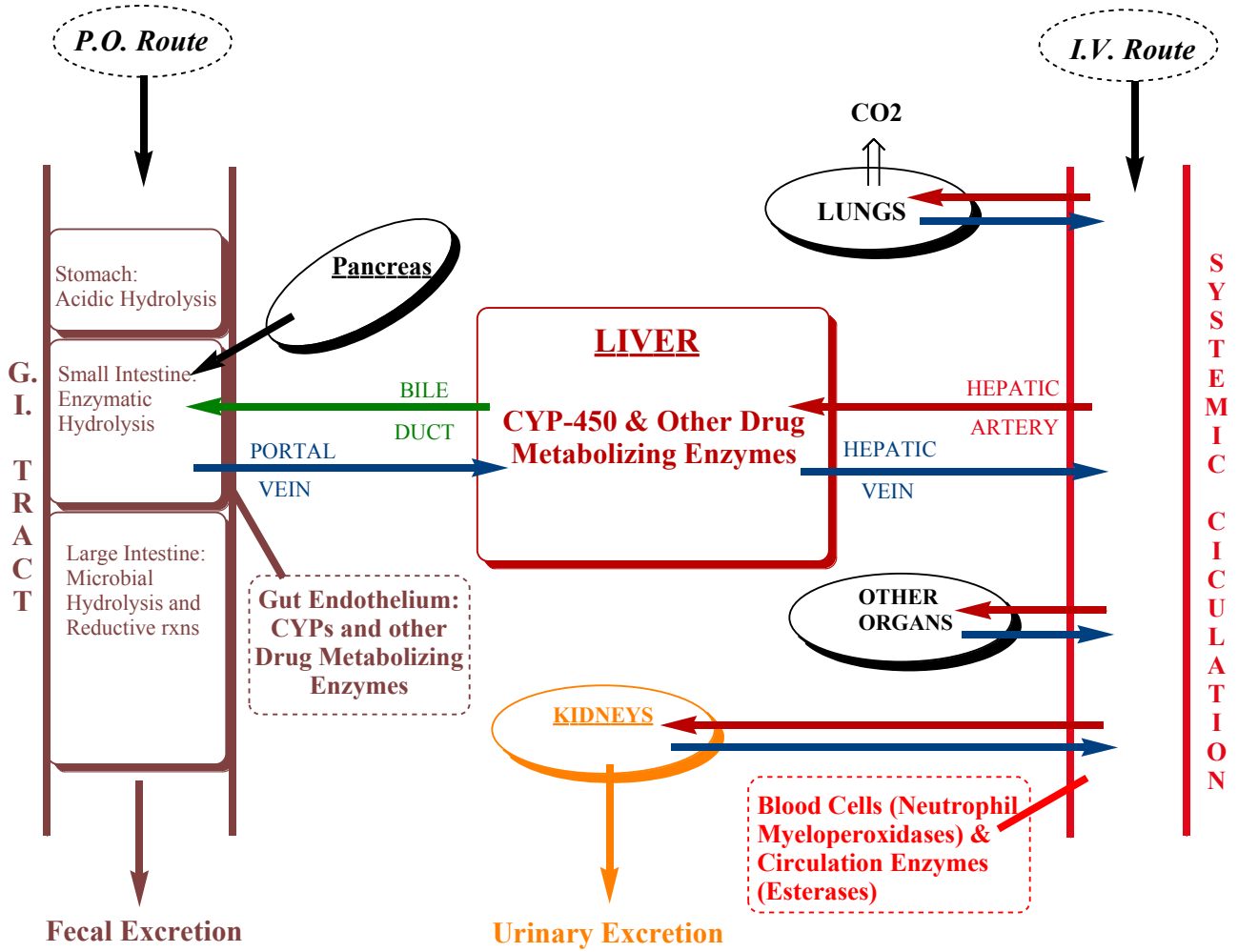
Full characterization in **DMPK**, Pharm, ETox

ADME Advancement Criteria for Orally Bioavailable Reversible Inhibitors

(This may apply to irreversible inhibitors targeting rapid turn-over proteins – need of long half-life)

(Kulkarni, et al., Future Medicinal Chemistry, 2014, 6:131-139)

Factors Affecting Oral Exposure



Factors Affecting Oral Exposure

- pH-dependent solubility
- Dissolution rate
- Lipophilicity
- Permeability (absorption)
- Efflux (exsorption)
- Stability (chemical, acid, blood, metabolic)
- Excretion (bile, urine)

In a fast pace discovery setting, which do you address?

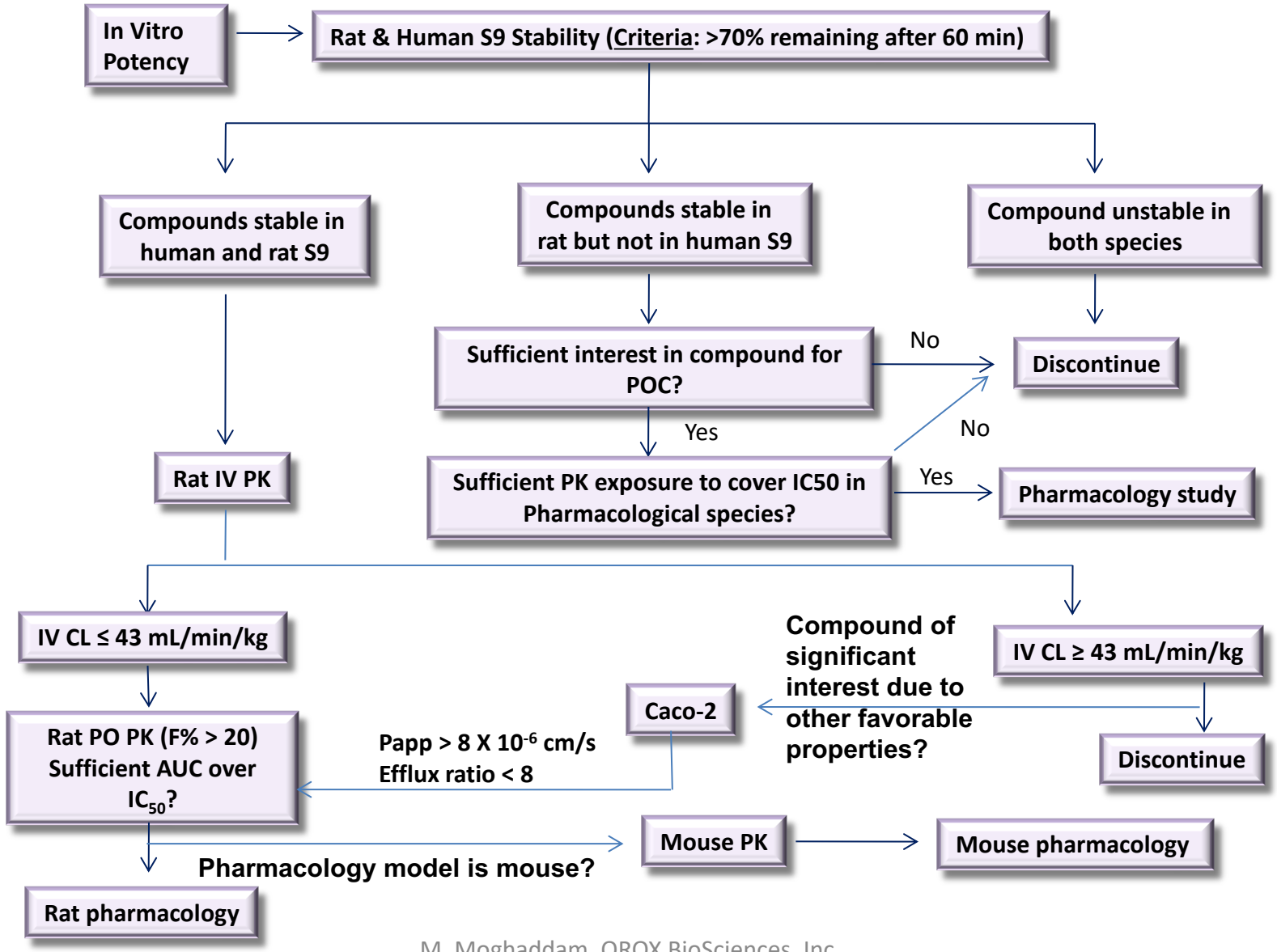
Using what assays, at what stage, and to what extent?

Determination of Advancement Criteria in Absence of PD Data

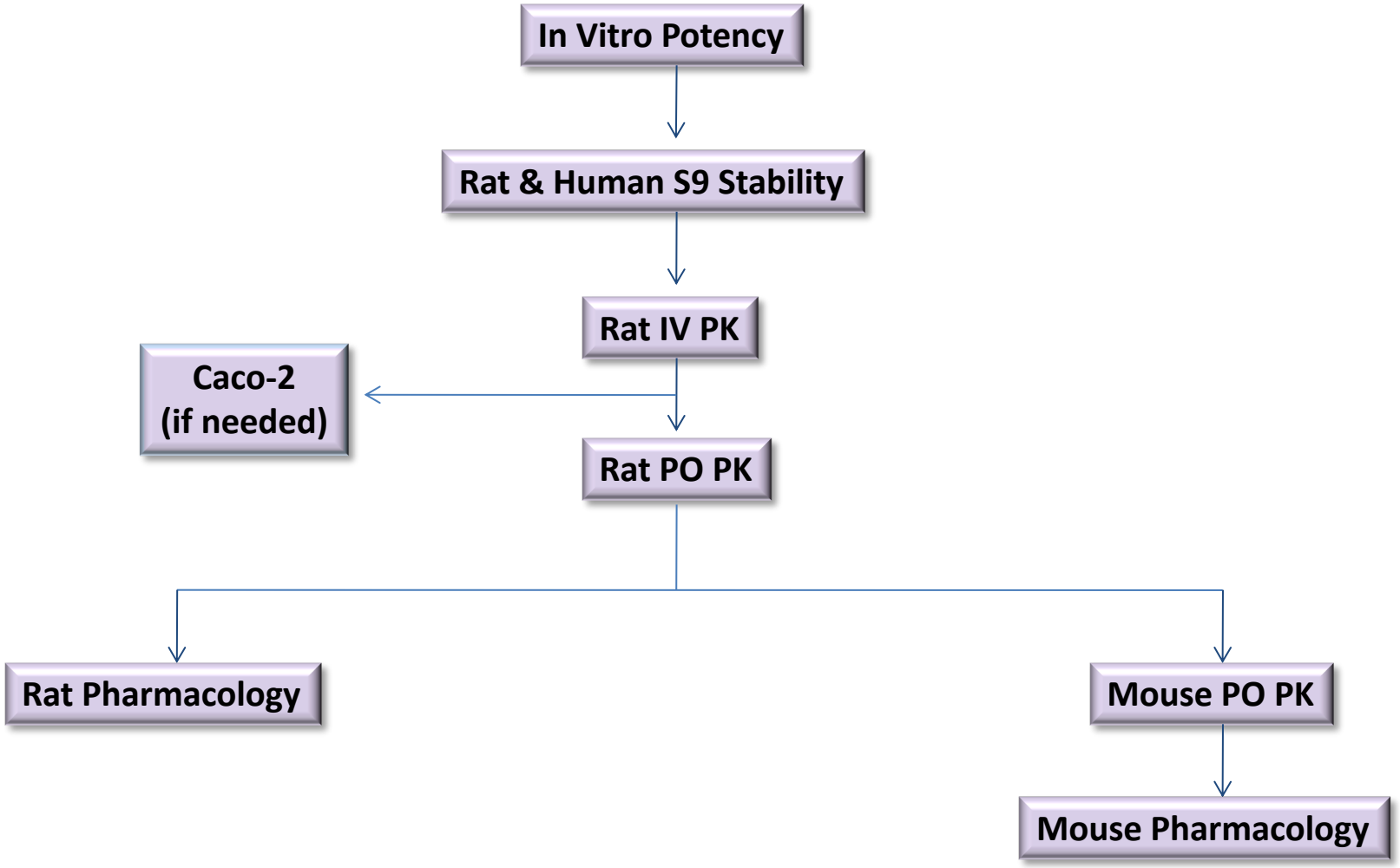
How do you decide what is "good PK" in absence of PD data?

- Retrospective analysis of global Celgene DMPK and Chemistry data
- Approximately 1000 internal compounds spanning various projects and chemical series
- Supporting statistical analysis
- What did the more successful compounds behave like in ADME assays?

Celgene Discovery DMPK Flowchart



General DMPK Flowchart



Conclusions

- The following cutoff criteria were obtained from our statistical analysis:
  - ✓ S9 >70% Remaining at 60’
  - ✓ CL < 43 mL/min/kg
  - ✓ Papp > 8 X 10^{-6} cm/sec
  - ✓ Efflux ratio < 8

- Using our advancement criteria we obtained:

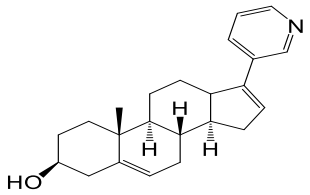
  - ✓ ~10% reduction in unnecessary rat IV PK studies
  - ✓ ~40% reduction in unnecessary rat PO PK Studies
  - ✓ >60% of compounds entering rat PO PK have AUC > 3μM·hr

Advancement Criteria for Orally Bioavailable Covalent Inhibitors

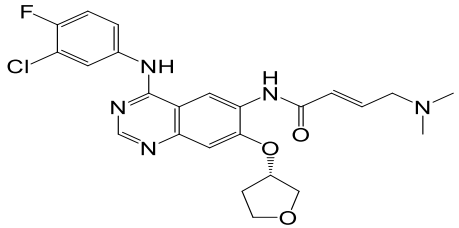
(This may apply to reversible inhibitors with favorable inhibition kinetics (Km/Vmax) or long PD half-life)

(Moghaddam, et al., Drug Metabolism Letters, 2014, 8, 19-30)

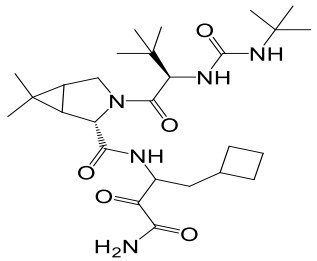
10 Late Stage or Marketed Irreversible Drugs



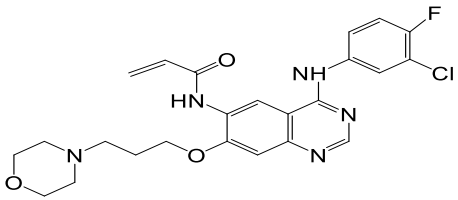
Abiraterone



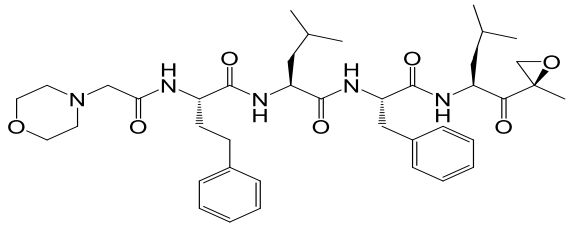
Afatinib



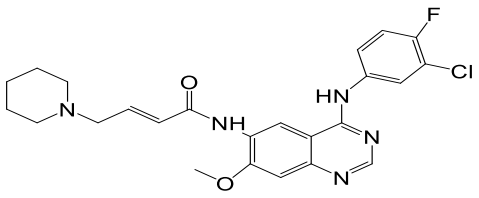
Boceprevir



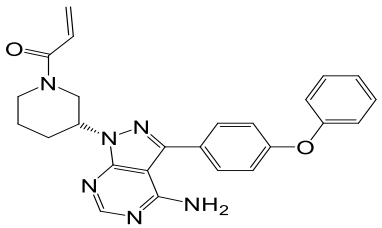
Canertinib



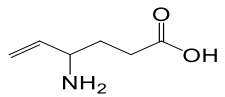
Carfilzomib



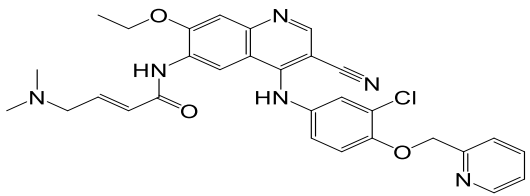
Dacomitinib



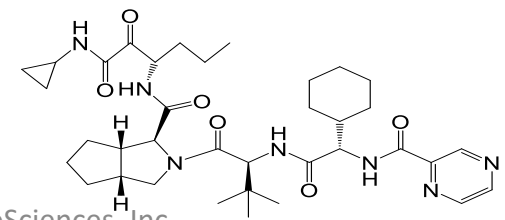
Ibrutinib



Vigabatrin



Neratinib



Telaprevir

10 clinically late-stage or marketed covalent inhibitors

Clinically Relevant Information

Compound	Corporation	Dosing Route / Therapeutic Indication	Clinical Dosing Regimen	Target (De Novo Synthesis Half-life)
Abiraterone®	Johnson & Johnson	Oral / Prostate Cancer	1000 mg/day	CYP17A1 (12 – 33 hr)
Afatinib®	Boehringer Ingleheim	Oral / NSCLC, Prostate Cancer, Head and Neck Cancer, Glioma	40 mg/day	EGFR (16 – 24 hr) and Her-2
Boceprevir®	Merck & Co.	Oral / Hepatitis C	800 – 2400 mg/day	HCV Protease (> 16 hr)
Canertinib®	Pfizer Inc.	Oral / Cancer	≥ 200 mg/day for a week, every other week	EGFR (16 – 24 hr)
Carfilzomib®	Onyx Pharmaceuticals	Intravenous / Myeloma	~1000 mg infused in 2-10 min, 2 days/week, for 3 weeks, followed by 12 day drug holiday	20S Proteosome (Unknown)
Dacomitinib®	Pfizer Inc	Oral / NSCLC	150 mg/day	EGFR (16 – 24 hr) and Her 2, Her-4
Ibrutinib®	Pharmacyclics	Oral / CTL, Myeloma, Lymphoma, Autoimmune Diseases	420 mg/day	Btk (16 – 24 hr)
Neratinib®	Pfizer Inc	Oral / Breast Cancer	160 – 240 mg/day	EGFR (16 – 24 hr) and Her-2
Telaprevir®	Vertex Pharmaceuticals	Oral / Hepatitis C	2250 mg/day	HCV Protease (NS3 > 24 hr)
Vigabatrin®	Lundbeck Inc	Oral / Antiepileptic	2000 – 4000 mg/day	GABA Transaminase (Unknown)

Summary of Preclinical In Vitro and Rat PK Data for 10 Covalent Drugs

In Vitro			
	Liver S9 Stabitlity	Rat	3 - 97%
		Human	3 - 90%
	Blood Stability	Rat	32 - 100%
		Human	52 - 100%
	3A4 Inhibition (uM)	No NADPH	0.5 - >10
		With NADPH	0.2 - >10
	3A4 Inhibition Fold Shift		2 - 3.5

In Vivo	
CL (mL/min/kg)	11.1 - 350
V_{ss} (L/kg)	0.67 - 115
MRT (hr)	0.52 - 7.40
[Blood]/[Plasma]	0.59 - 2.93
Cmax (μM)	0.01 - 77
PO $AUC_{(0\text{-inf})}$ (μM·hr)	0.03 - 106
F%	0.23 - 91

Valid PK screening assays require the following in vitro data:

1. Approximately, what level of target silencing (as well as Inhibitory Concentrations) do you need?
2. Approximately, how long (x minutes) does it take to get to that level of inhibition?

Irreversible Inhibitors - POC Effort

Enzyme Potency

Cell Assay (Target occupancy, target resynthesis rates)

Warhead Optimization

Effective Screens

Iterative

Residue-Mod Confirmation (non-screen)

Mass Modification (>70% in 1 hr incubation)

Iterative

Exploratory "E-PK" (IV, IP, or PO) in Mouse or Rat on the Most Potent CC's with >70% Mass Mod

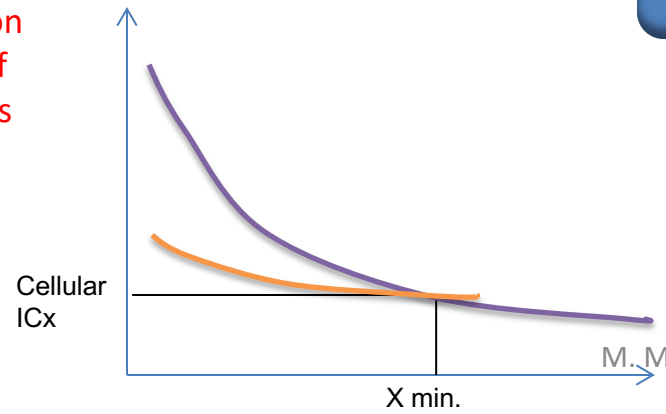
Stop POC PK

Iterative

Biomarker/Pharm Readout

POC Obtained

If after a reasonable effort, adequate in vivo exposures are not achieved, limited diagnostic DMPK assays can be deployed on limited # of compounds



Irreversible Inhibitors – (Oral) Lead Optimization Effort

Enzyme potency

Cell potency (Target occupnacy, target resynthesis rates)

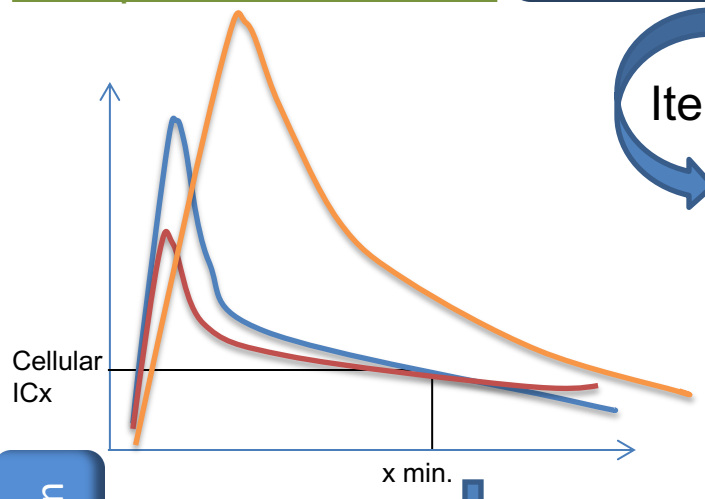
Mass modification (>70% in 1 hr incubation)

Iterative

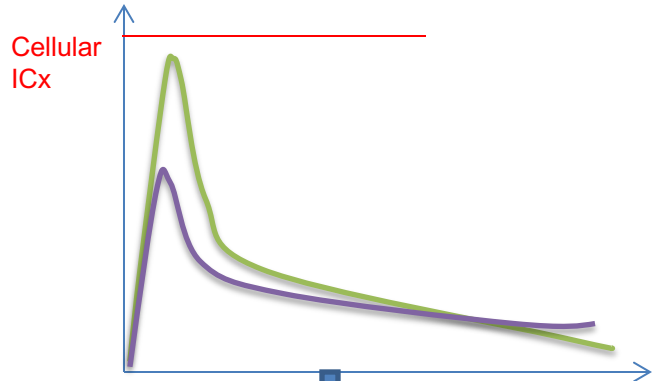
Exploratory "LO PK" in rodents on most potent CC's with >70% mass mod

Iterative

Acceptable Rat PO PK



Poor Rat PO PK



Reactivity (non-screen, Occasional): Rat & human blood reactivity (1-2 hrs), GS H reactivity w/ & w/o S9

CYP Inhibition

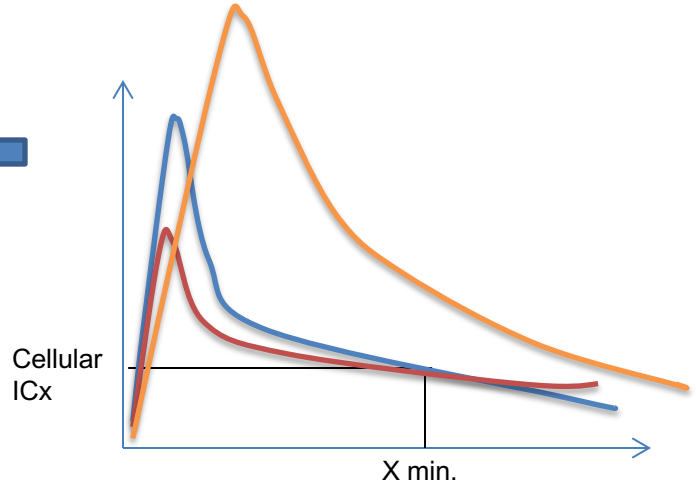
Biomarker/Pharm readout

Diagnostic Studies

1. Rat blood reactivity (>70% in 1 hr) & S9 stability (>70% in 0.5 hr) & met ID,
2. Caco-2 (Perm/Efflux)
3. Portal vein absorption (Dissolution/Gut metab)

Irreversible Drug Late Stage to Shortlist Oral Lead Optimization

Acceptable Rat PO PK



DMPK Profiling

- Rat IV PK (CL, Vss, MRT, F% Calc)
- Microsomal CYP Inhibition/Induction
- Full met ID – Cross species hepatocytes to guide HS PK

Pharm/Tox profiling

- Efficacy models
- Tox profiling

Reactivity (non-screen):
Dog, monkey, rat & human blood stability (1-2 hrs), GSH reactivity w/ & w/o S9

PK/PD modeling and human dose prediction (Leftover experiments)

Conclusions

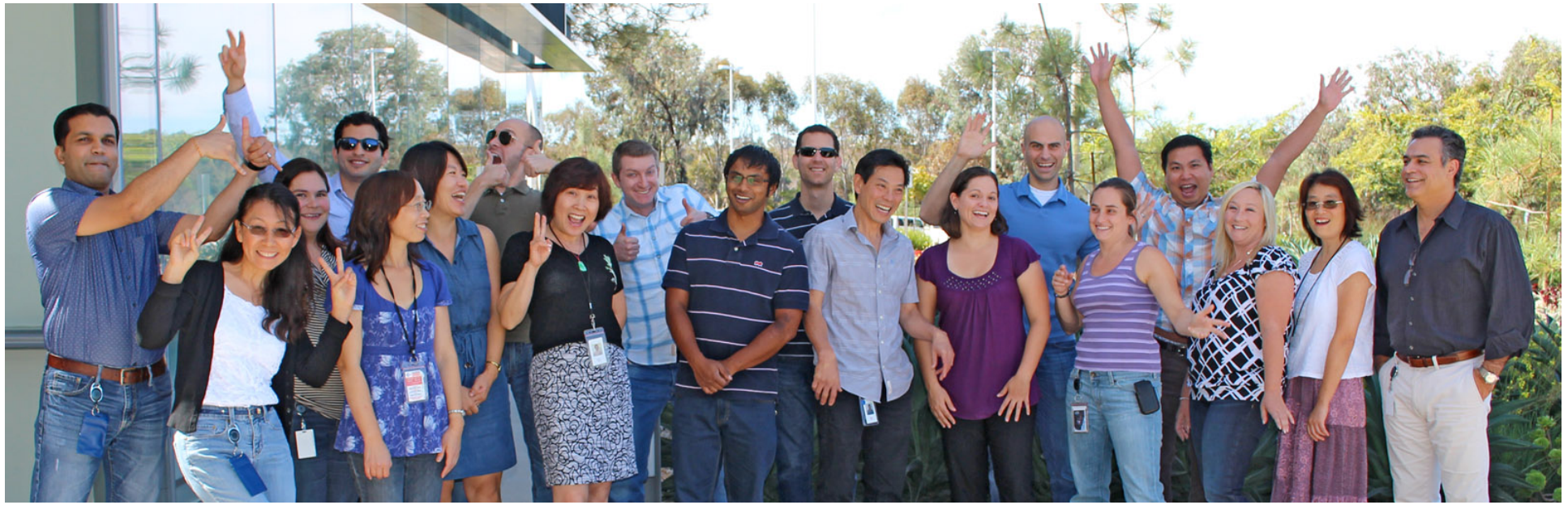
- ADME triage criteria are better defined for non-covalent compounds & their relevance to covalent inhibitors needs careful considerations:

- Slow CL remains a big factor in reducing dose and should not be overlooked

- Traditional ADME considerations do not seem to differentiate high and low potential covalent inhibitors (ADME not a filter)

- For covalent inhibitors, “Good PK” for modifying targets with long turnover time = *Adequate exposure at site of action for adequate length of time to silence the target at a desired level, followed by rapid decline in circulating concentrations to minimize un-intended consequences*

Acknowledgments



Appendix

10 clinically late-stage or marketed covalent inhibitors

In Vitro Stability

Compound	*% Remaining at 30 min*		*% Remaining at 60 min*	
	Rat Liver S9	**Human Liver S9**	**Rat Whole Blood**	**Human Whole Blood**
Abiraterone®	46	3	67	70
Afatinib®	82	85	100	82
Boceprevir®	90	65	32	58
Canertinib®	39	70	72	69
Carfilzomib®	9	1	67	63
Dacomitinib®	87	90	76	100
Ibrutinib®	3	25	79	56
Neratinib®	59	69	NA	85
Telaprevir®	97	80	96	52
Vigabatrin®	100	99	NA	NA

10 clinically late-stage or marketed covalent inhibitors,
CYP Inhibition

Compound	*REVERSIBLE INHIBITORY POTENTIAL*						
	Mean % Inhibition following co-incubation with 5 µM compound						
	CYP1A2	**CYP2C8**	**CYP2D6**	**CYP2C19**	**CYP2B6**	**CYP2C9**	**CYP3A4/5**
Abiraterone®	52.0	43.5	62.8	20.8	19.7	18.1	36.8
Afatinib®	6.0	6.0	25.6	2.4	28.5	29.1	1.1
Boceprevir®	6.2	0.0	5.6	21.9	18.3	15.7	40.8
Canertinib®	4.8	0.0	11.8	40.0	20.8	19.3	1.0
Carfilzomib®	4.0	41.6	18.9	36.1	25.4	15.2	68.6
Dacomitinib®	2.7	1.3	78.5	47.6	30.7	12.6	24.3
Ibrutinib®	0.0	58.1	16.4	34.7	61.2	48.6	38.7
Neratinib®	5.7	31.3	11.2	28.9	26.1	33.3	19.1
Telaprevir®	6.5	1.5	10.1	37.8	20.0	13.2	69.6
Vigabatrin®	3.5	6.7	4.7	12.9	15.8	3.9	4.0

Compound	*TIME DEPENDENT INHIBITION POTENTIAL*						
	Mean % Inhibition following pre-incubation with 5 µM compound (Fold-Shift)						
	CYP1A2	**CYP2C8**	**CYP2D6**	**CYP2C19**	**CYP2B6**	**CYP2C9**	**CYP3A4/5**
Abiraterone®	57.9 (0.9)	67.8 (0.6)	67.0 (0.9)	7.0 (0.3)	17.4 (0.9)	17.2 (0.9)	52.0 (1.4)
Afatinib®	0.0 (0.0)	10.7 (1.7)	1.7 (0.1)	**5.4 (2.3)**	16.3 (0.6)	18.5 (0.6)	0.0 (0.0)
Boceprevir®	**57.9 (9.3)**	0.0 (0.0)	0.0 (0.0)	20.4 (0.9)	6.2 (0.3)	1.4 (0.1)	**81.4 (2.0)**
Canertinib®	3.7 (0.8)	0.0 (0.0)	2.8 (0.2)	15.4 (0.4)	28.2 (1.4)	12.4 (0.6)	**7.7 (7.7)**
Carfilzomib®	2.9 (0.7)	5.0 (0.1)	0.3 (0.0)	21.1 (0.6)	27.3 (1.1)	11.1 (0.7)	83.8 (1.2)
Dacomitinib®	0.0 (0.0)	**40.4 (31.1)**	75.1 (1.0)	12.2 (0.3)	29.8 (1.0)	13.8 (1.1)	19.7 (0.8)
Ibrutinib®	0.0 (0.0)	41.9 (0.7)	2.2 (0.1)	4.1 (0.1)	40.4 (0.7)	30.5 (0.6)	52.1 (1.3)
Neratinib®	1.5 (0.3)	8.0 (0.3)	0.1 (0.0)	17.6 (0.6)	24.2 (0.9)	34.6 (1.0)	29.8 (1.6)
Telaprevir®	0.0 (0.0)	**21.2 (14.1)**	0.0 (0.0)	15.1 (0.4)	14.7 (0.7)	12.3 (0.9)	86.6 (1.2)
Vigabatrin®	1.5 (0.4)	**19.5 (2.9)**	0.04 (0.0)	3.7 (0.3)	8.0 (0.5)	0.4 (0.1)	**11.7 (2.9)**

10 clinically late-stage or marketed covalent inhibitors

Permeability and Efflux

Compound	*Caco-2 Assay*		*Plasma Protein Binding*	
	P_{app} A→B (X 10^{-6} cm/s)	**Efflux Ratio (B→A / A→B)**	**Rat (% Bound)**	**Human (% Bound)**
Abiraterone®	NA	NA	100	100
Afatinib®	1.8	30	100	98
Boceprevir®	1.0	20	98	98
Canertinib®	5.8	2.0	NA	86
Carfilzomib®	0.6	18	100	99
Dacomitinib®	12	2.0	99	98
Ibrutinib®	31	0.4	100	99
Neratinib®	0.9	6.0	NA	100
Telaprevir®	1.5	12	99	90
Vigabatrin®	2.4	0.2	NA	90

10 clinically late-stage or marketed covalent inhibitors

Rat IV Pharmacokinetic Parameters

Compound	CL (mL/min/kg)	Vss (L/kg)	MRT (hr)	B/P Ratio
Abiraterone®	144	22.6	2.5	1.2
Afatinib®	182	35.7	3.2	1.5
Boceprevir®	353	11.0	0.52	1.3
Canertinib®	53.7	7.27	2.3	NA
Carfilzomib®	297	115	6.4	0.80
Dacomitinib®	69.2	24.7	6.0	2.9
Ibrutinib®	41.6	18.8	7.4	0.62
Neratinib®	9.72	1.13	2.0	0.59
Telaprevir®	21.2	0.882	0.69	0.95
Vigabatrin®	11.1	0.666	1.0	0.75

10 clinically late-stage or marketed covalent inhibitors

Rat PO Pharmacokinetic Parameters

Compound	C_{max} (μM)	T_{max} (hr)	$AUC_{0\text{-}inf}$ (μM*hr)	F%
Abiraterone®	0.0296	2.0	0.106	3.1
Afatinib®	0.0856	2.7	0.586	31
Boceprevir®	0.134	0.33	0.267	29
Canertinib®	0.255	2.3	0.878	14
Carfilzomib®	NC	NC	NC	NC
Dacomitinib®	0.282	4.7	4.30	69
Ibrutinib®	0.627	0.75	1.49	16
Neratinib®	0.634	4.0	5.13	16
Telaprevir®	0.00547	0.83	0.0273	0.23
Vigabatrin®	76.6	0.42	106	91