



## Outsourcing Hit-to-Lead and Lead Optimization Work: When It Makes Sense to Bring it In-House - Economics and Case Studies.

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# Drug-Discovery Economics

**On average each day in development =**

- **\$37,000 USD in out-of-pocket costs**
- **\$1.1M USD in opportunity cost of missed revenue under patent protection**

*Tufts Center for the Study of Drug Development*

**It can take up to \$100M USD to  
advance a compound to Phase I**



## Changing pharma environment – new models



– You need to find expert help



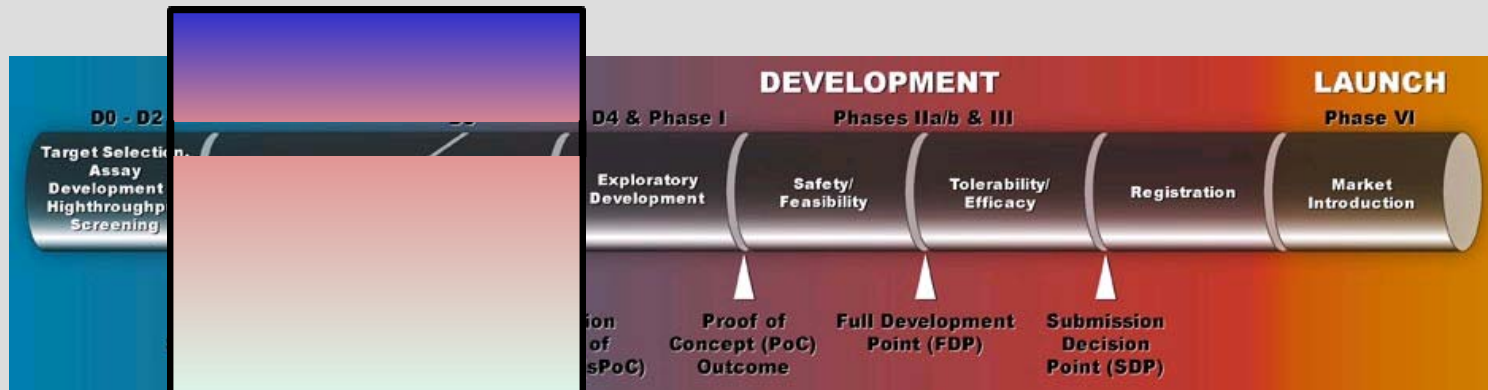
# How can you...



- Get your programs to IND or partnering faster
- Eliminate efforts on compounds that will never become drugs
- Reducing the risk of post-approval problems.



# ...translate your discovery into a drug



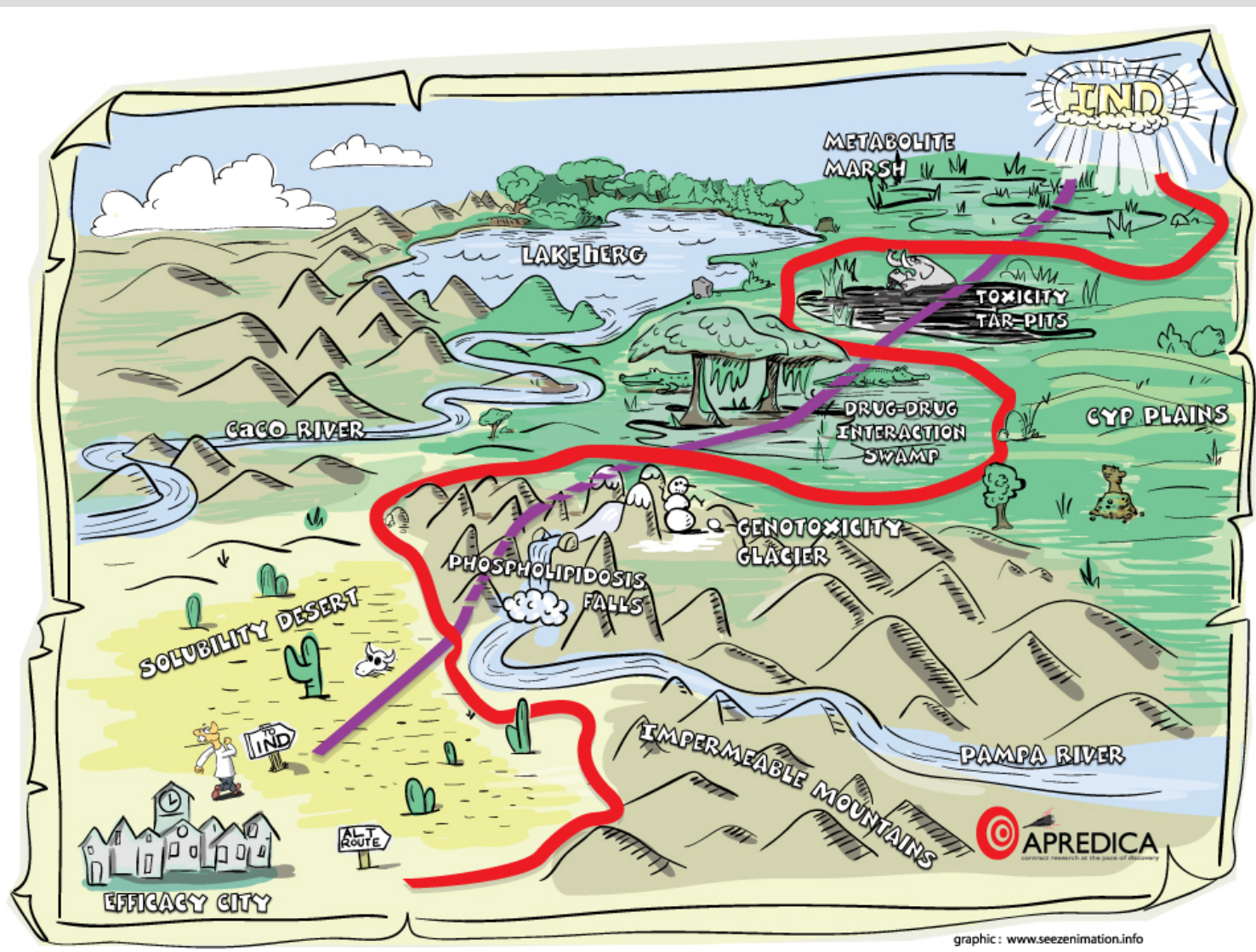
**IND**



**Partnering**



# Efficacy to IND: not a straight line





# Where Can Efficiency Be Improved?

Why is big pharma getting out of discovery?

Can one bridge the Valley of Death between early efficacy and clinical development?

**Is it always more cost-effective to outsource?..  
...Build in-house?**



# Building in-house cost

## FTE

- Ph.D. \$250,000/yr
- MS \$150,000/yr (1 needed)
- BS \$80,000/yr (2 needed)

## Equipment

- \$600,000 analytical equipment
- \$200,000 other lab equipment

## Facilities rent

- \$20-75/sq ft (2,500 sq.ft. lab: \$50,000 - \$187,000 /yr)

**TOTAL: \$1,400,000 to \$1,600,000 /1st year**



# Supporting med chem program (outsourcing)

**Typical: \$100,000 - \$500,000 a year**



# When should you invest in internal?

- **Program have a clear biology, efficacy, chemistry, lead optimization strategy**
- **ADMET is going to support lead optimization 5 days a week for at least 12 months**
- **Program is clearly going to be the foundation for building an organization around it**



## Example: Leads from an academic lab

### Background:

- CNS indication
- Novel structures
- The program has been active for 3 years
- Compounds have *in vivo* efficacy in a new model
- University Technology Development office is interested in partnering the program
- PI wishes to profile 1 lead in suite of ADME + safety + rodent *in vivo* tox



## Example: Leads from an academic lab

### Problem:

- Nothing known about ADMET properties
- Pharma partners want early tox and ADME properties and reevaluating efficacy in accepted model with industry standards

### Solution:

- Consult with client on the program
- Suggested to look at a number of leads in rapid cost-effective assays prior to launching *in vivo* tox



# Toxicity Summary of Compounds

	hERG IC50 ( $\mu$ M)	Cytotox and Mitotox IC50 ( $\mu$ M)	Mitotox Potential Yes if >2	CYP Inhibition 2D6	Genotoxic
TA-1	6.1	>250 72	$\geq 3.5$	88% at 10 $\mu$ M	N
TA-15	1.2	132 53	2.5	98% at 10 $\mu$ M	N
TA-19	4.5	>250 196	$\geq 1.3$	61% at 10 $\mu$ M	N
TA-24	2.7	>250 45	$\geq 5.6$	94% at 10 $\mu$ M	N
TA-25	1.2	>250 120	$\geq 2.1$	98% at 10 $\mu$ M	N

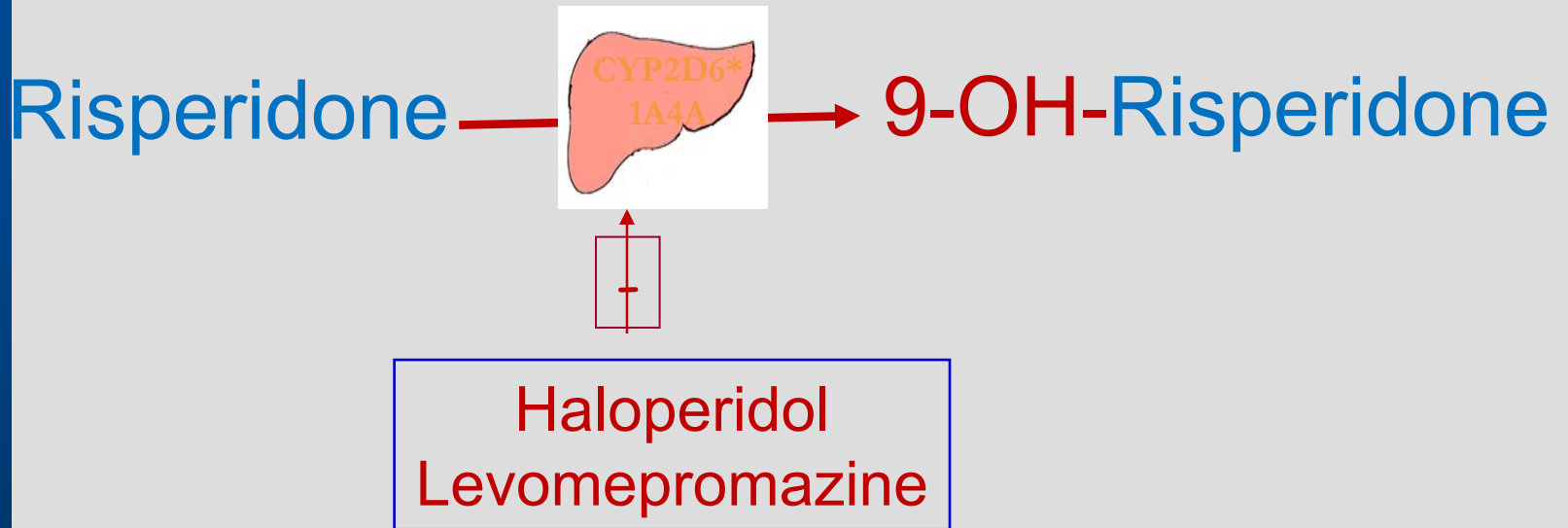


# CYP-2D6 is a problem in the series

Test agent	Test conc (µM)	Cyp1A2	Cyp2C8	Cyp2C9	Cyp2C19	Cyp2D6	Cyp3A4	Cyp3A4
		Phenacetin	Paclitaxel	tolbutamide	S-mephenytoin	dextromethorphan	midazolam	testosterone
a-NF	0.1	68%						
quercetin	2		56%					
sulfafenazole	2			70%				
omeprazole	30				87%			
quinidine	1					97%		
ketoconazole	1						92%	99%
TA-1	10	-13%	-30%	-11%	-37%	88%	2%	-3%
TA-1	100	-7%	-17%	11%	-16%	98%	20%	42%
TA-15	10	-5%	-12%	6%	47%	98%	1%	26%
TA-15	100	13%	-16%	22%	93%	99%	16%	65%
TA-19	10	18%	-6%	17%	6%	61%	-6%	12%
TA-19	100	45%	5%	3%	13%	95%	-12%	44%
TA-24	10	2%	55%	10%	26%	94%	4%	29%
TA-24	100	-11%	51%	4%	56%	98%	-2%	70%
TA-25	10	33%	2%	7%	3%	98%	12%	27%
TA-25	100	-13%	-30%	-11%	-37%	88%	2%	-3%



# Clinical relevance: Competitive Inhibition of CYP2D6



	Plasma Levels	Results
Risperidone	↑	↑ Side Effects
9-OH-risperidona	↓	↓ Clinical Efficacy

*1Berecz R, Dorado P, De La Rubia A, Cáceres MC, Degrell I, Llerena A. Curr Drug Targets. 2004 Aug;5(6):573-9.*



# Metabolism Summary of Compounds

	Microsomal Stability % Remaining at 60 min Human	Microsomal Stability % Remaining at 60 min Rat	Plasma Stability % Remaining at 60 min Human	Plasma Stability % Remaining at 60 min Rat
TA-1	90%	12%	109%	97%
TA-15	55%	0%	97%	79%
TA-19	0% No parent remaining in minus NADPH samples	0% No parent remaining in minus NADPH samples	n/d No parent at 0 min	n/d No parent at 0 min
TA-24	2%	0%	97%	105%
TA-25	81%	11%	101%	102%



# Absorption and Distribution Summary

	Caco-2 Permeability Papp A -> B	Caco-2 Permeability Papp B -> A	Active Efflux Ratio	Plasma Protein Binding % Bound Human	Plasma Protein Binding % Bound Rat
TA-1	1.9	4.1	<b>2.2</b>	19.3%	23.3%
TA-15	0.6	13.8	<b>24.2</b>	79.6%	72.8%
TA-19	0.4	0.0	0.0	n/d unstable	n/d unstable
TA-24	0.5	2.8	<b>5.9</b>	49.0%	36.4%
TA-25	1.1	7.5	<b>6.8</b>	45.4%	33.1%



# Questions

Which molecule would you choose to present to partners?

Is there a druggable molecule in this set?

Where do you go from here?

Are there resources left to do lead optimization?

If there are, you can save your program

The earlier you gain understanding of drug-like properties of your hits, the likelier the possibility for you to be able to save and advance your program



## Rest of the story... Round 3.

	hERG IC50 ( $\mu$ M)	Cytotox and Mitotox IC50 ( $\mu$ M)	Mitotox Potential Yes if >2	CYP Inhibition 2D6	Genotoxic
TA-2	> 100	>250 >250	< 2	0% at 10 $\mu$ M	N
TA-3	11.2	>250 >250	< 2	47% at 100 $\mu$ M	N
TA-4	20.8	>250 >250	< 2	55% at 100 $\mu$ M	N
TA-5	8.7	>250 >250	< 2	98% at 100 $\mu$ M	N
TA-6	3.7	>250 >250	< 2	97% at 10 $\mu$ M	N



# Case Study Lessons

Original PI's proposal was for \$120,000

- 10-12 weeks duration

Modified approach presented was implemented for \$ 60,000

- First batch results – 2 weeks
- Completed in 6 weeks from start

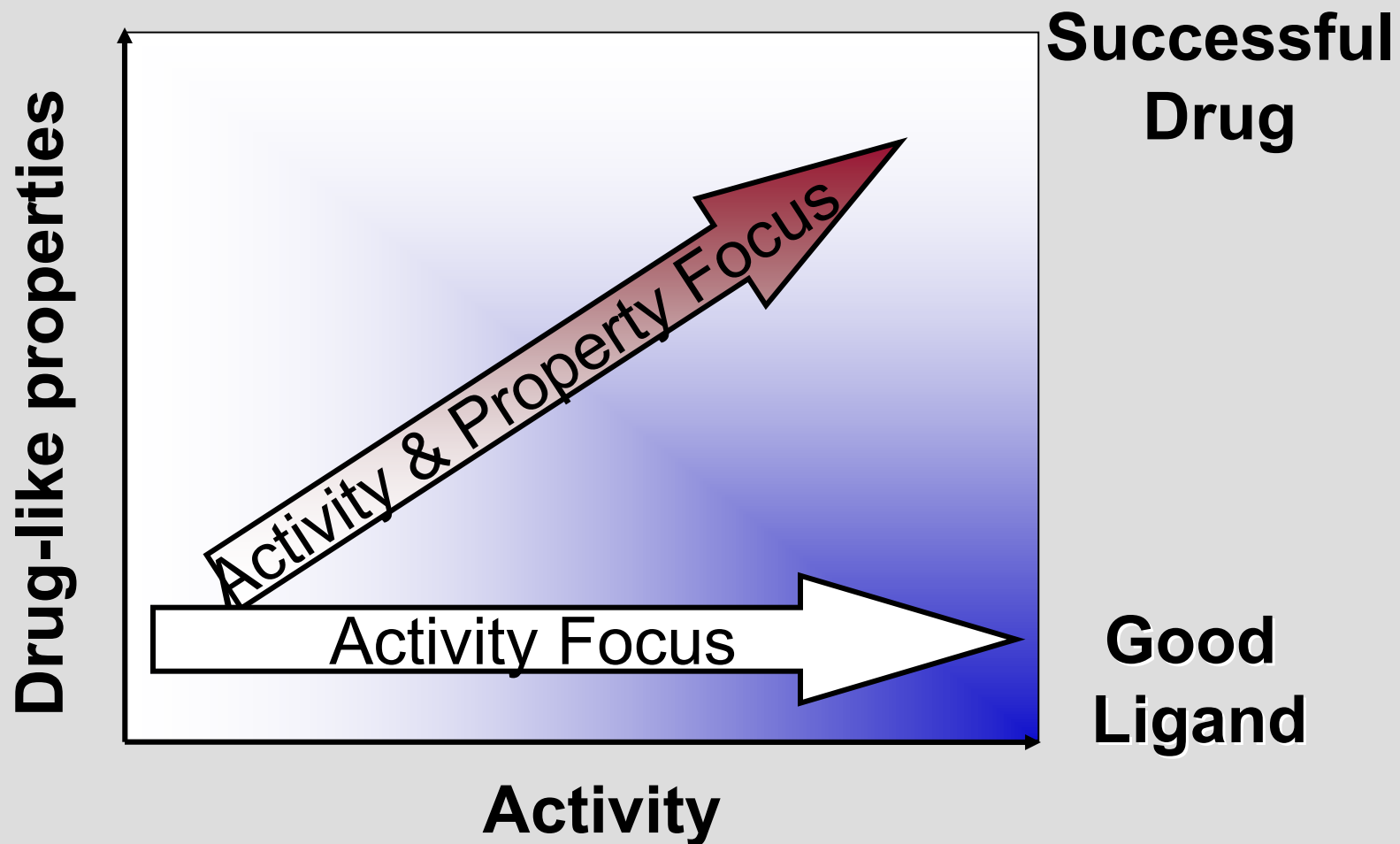
Molecule + backup presented to a partner, who is interested and is going to fund the *in vivo* studies

University and PI's goals achieved:  
Partnering is under way

**University saved \$60,000**



# Stay focused on the goal





## Case Study 1. All In-House R&D

### Approach: Direct to *In Vivo*

- Small number of compounds synthesized
- No *in silico* and minimal *in vitro* ADME Tox
- “Toxicity by sight” assessment by senior scientists
- Lengthy decision process about which compounds to proceed with
- Lengthy, unfocused research, which resulted in negative conclusions



# Case Study 1. Results

## \$500 Million Bonfire

- Funds exhausted. R&D terminated.





## Case Study 2: Additional Studies Needed

### Problem – Failure in Clinical Trials:

- A VC-funded pharmaceutical company received negative results in clinical trials.
- FDA recommended conducting additional *in vitro* ADMET studies to determine the efflux transporters mechanism that may have negatively affected the results.
- Internal R&D had been shut down to conserve resources for clinical trials. No scientists left on staff to manage studies.



## Case Study 2: Results

- Admin staff made no decision on the research.
- Proposed solution not presented to management.
- 6 months later, still “shopping around for a solution.”
- Investors continue to keep company in business.

**Success!**  
**Jobs Protected**



## Case Study 3: The Case for In-Sourcing

### Problem – Early Bad News:

- A newly VC-funded pharmaceutical company outsourced its studies to speed research and reduce costs.
- Initial testing by Apredica identified that their compounds had fundamental structural flaws that made them impossible to use as therapeutic agents.
- The founders' theory did not agree with the objective data provided.



## Case Study 3: Solution

- “Problems” with the CROs.
- Disparage the data.
- Long, fruitless search for “competent” CROs.

**Shoot the Messenger**



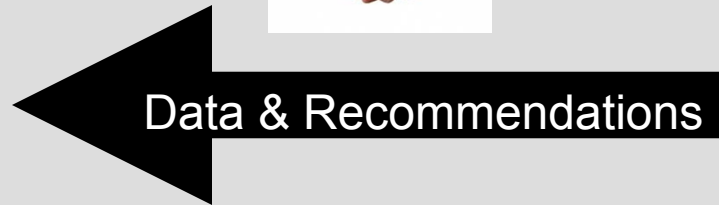
## Case Study 3: Results

- Investors were convinced the company had to build internal capabilities as no CROs were competent.
- Additional funding obtained to build internal development infrastructure.
- 18 months later, founder finally admits failure on initial approach.
- Small initial cost turned into large, hard-to-walk-away-from sunk cost.
- Investors continue to fund the company.

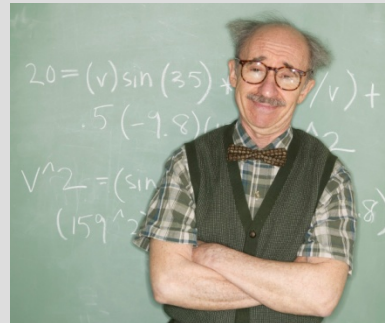
# Company Saved!



# Evolving Pharma Model



Scientific Ideas





## Case Study 4: Investors De-Risked

- **Problem – Large Up-Front Investment Risk:**
  - A VC firm was planning to invest in 3 companies @ ~\$5M USD each, but still had doubts.
- **Solution – Extended Due Diligence:**
  - Assess the drug-like properties of the proposed compounds.
  - \$15,000 USD cost per program.
  - Data in 3 weeks.
- **Results – Bad Investments Averted:**
  - 2 of the 3 opportunities found to be excessively high risk due to poor initial drug-like properties.
  - 2 poor investments avoided. \$10M USD saved.



## Factors to Consider When Building a Successful ADME Program

**Relevance to therapeutic area (Patient)**

**Desired/feasible route of administration**

**Knowledge base about the program**

**Biological activity** (Potency *in vitro* and animal model, selectivity)

**Efficacy**

**Chemical series**

**Expertise in drug discovery and development**



## Advantages of Bringing in a Specialist Partner

- ▣ Lets you focus on advancing programs
- ▣ Gets your programs off the ground faster
- ▣ Allows to test multiple hypotheses without distracting internal teams
- ▣ Access to external ADMET expertise
- ▣ External validation



## When selecting a partner CRO

- ▣ **Project manager education and role**
  - ▣ **Scientist or bus dev person?**
- ▣ **Historical percent of studies on time**
- ▣ **Percent personnel with experience and advanced degrees**
- ▣ **Personnel turnover in last 24 months**
- ▣ **Observe behaviour and response time**
- ▣ **Observe right sizing rules**
- ▣ **One-stop shops are not always the best way to go for your needs**
- ▣ **Do not delegate CRO selection to non-scientists**



## Outsource To:

- **De-risk programs**
- **Help make better decisions, earlier in the game.**
- **Add third-party validation**



## In-Source when:

- **Program have a clear biology, efficacy, chemistry, lead optimization strategy**
- **Assay is going to support lead optimization 5 days a week for at least 12 months**
- **Program is clearly going to be the foundation for building an organization around it**



# APREDICA

**Your early ADMET partner**

Better decisions. Earlier in the game.

**Katya Tsaoun, Ph.D.**

President

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617-812-1911



# Why Apredica?

## Expertise:

- 80% Ph.D. ratio on the bench
- Extension of internal discovery teams

## ADMET Passion and Focus:

- 7 posters/talks presented in 2008
- Wiley & Sons' book *ADME for Medicinal Chemists* to be published in 2010

## Avoid the Build & Liquidate Cycle:

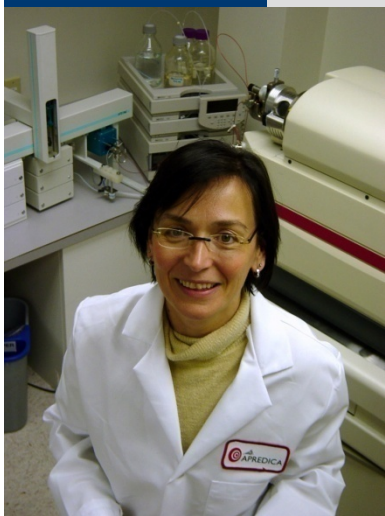
- Most drug-discovery programs fail
- Many remaining successful programs shut down R&D to focus resources on clinical trials



# Aprelica's Founder and President

## Katya Tsaoun, Ph.D.

- 15 years' biotech experience, 9 years ADMET:
  - NitroMed
  - Surface Logix
  - GPC Biotech (Mitotix)
  - OPTA/Enzytech
- Ph.D. (Biochemistry), Tufts University
- Post-doc (Neurochemistry), Harvard Primate Center
- Designed and led programs in:
  - Oncology, metabolic, CV, infectious diseases
- Experience in:
  - HTS
  - lead optimization
  - clinical-candidate selection





# Aprelica's Scientific Leadership

**Robert Annand, Ph.D. – Director of Biology**

**17+ years' experience:**

- Surface Logix
- GPC Biotech
- Parke-Davis

**Ph.D. in Medicinal Chemistry**

**Post-doctoral training in Mechanistic Enzymology**

**Expertise in Discovery Biology:**

HTS, secondary assays, *in vivo* studies, drug metabolism

**Early development**

**Project Management**





# Apredica's Resources and Capabilities

- **State-of-the-art analytical chemistry (2xLC/MS/MS, 1xHPLC/UV, plate readers), cell-culture, and biology lab**
- **65+ customers worldwide**
  - Academic laboratories
  - Virtual companies
  - Mid-size pharma
  - Large pharma





# Apredica Scientific Staff

- ▣ Every scientist with 10+ years' experience in drug discovery
- ▣ Project management and team leadership
- ▣ Breadth of expertise:
  - Metabolic disease
  - Anti-infectives
  - Oncology
  - Inflammation
- ▣ Advanced Training in:
  - ▣ Biochemistry
  - ▣ Medicinal Chemistry
  - ▣ Biology





# Apre dica's Approach

- ▣ Outsourcing with an in-house ambience
  - Collaborative
  - Consultative
- ▣ Strictly fee for service
- ▣ Develop ADMET strategy as part of overall program goals
  - **Start** from simple mechanistic systems
  - **Gather data** on potential issues within series
  - **Support lead optimization** on a few assays important for the series
  - **Advanced lead optimization/development:**
    - Move to complex systems and organisms when mechanism is understood
    - Repeat the optimization loop



# Apredica's History

- **2005**
  - Nov. – Incorporated
- **2006**
  - **May**
    - North Shore Business Plan Competition - Won
    - Raised \$0.2M USD in friends & family round
    - Obtained 600 sq. ft. lab & equipment sublet
  - **June**
    - Open for business
    - First customer served
    - WPI Business Plan Competition – Runner Up
  - Oct. – Moved to 1,600 sq. ft. lab.
- **2007**
  - Jan. – Cash-flow positive
  - June – 2<sup>nd</sup> triple-quad mass spectrometer
  - July – Profiled in *Money* magazine.
  - Oct. – Moved to 4,400 sq. ft. lab.



# Apredica Today

- ▣ **65+ customers and rapidly growing (32 in 2008)**  
(companies, government, academia, non-profits, VC firms)
- ▣ **Planning to add GLP capabilities and additional locations**
- ▣ **Strong network of niche expert partners:**
  - Partnerships with several *in vivo* labs
  - Partnership with a Russian med chemistry CRO
- ▣ **Privately held**



# Some Customers

- **AdipoGenix**
- **Boston University**
- **Cambria Pharmaceuticals**
- **Cellicon Biotechnologies**
- **CoNCERT Pharmaceuticals**
- **MaxThera**
- **Mercury Therapeutics**
- **Vanderbilt University**



# Our Customers Are Funded By

- **Flagship Ventures**
- **Brookside Capital Partners Fund**
- **New Leaf Venture Partners**
- **Three Arch Partners**
- **TVM Capital**
- **Skyline Ventures**
- **Greylock Partners**
- **QVT Fund LP**