BlackThorn™ THERAPEUTICS

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September 13, 2016

OUTLINE OF PRESENTATION

1. Problem statement
2. Innovative approaches
3. Policy implications and recommendations

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1958 – "…field of research…accessible for first time by development of psychopharmacology"

THE TREATMENT OF DEPRESSIVE STATES WITH G 22355 (IMIPRAMINE HYDROCHLORIDE)[1]

ROLAND KUHN, M. D.[2]

"Until now only **electroshock therapy** for endogenous depressions and **psychotherapy** for reactive depressions really fulfilled requirements of effective treatment."

Tofranil.
Geigy.
A Milestone in the treatment of melancholy

c.1960, Unknown

"It's mode of action remains for the present completely unknown…appears to us to have a great practical significance in cases in which accidents with bodily injuries lead to obstinate pain and depression…"

In former times, magical visions often dominated the choice of remedy for mental illness – as shown in this depiction of the mandragola (mandrake) from the "Garden of Health" (1485).

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2010 Report

MEDICINES IN DEVELOPMENT FOR

Mental Illnesses

PRESENTED BY AMERICA'S PHARMACEUTICAL RESEARCH COMPANIES

Pharmaceutical Research Companies Are Developing More Than 300 Medicines to Treat Mental Illnesses

2010: > 300 medicines

2014: > 100 medicines

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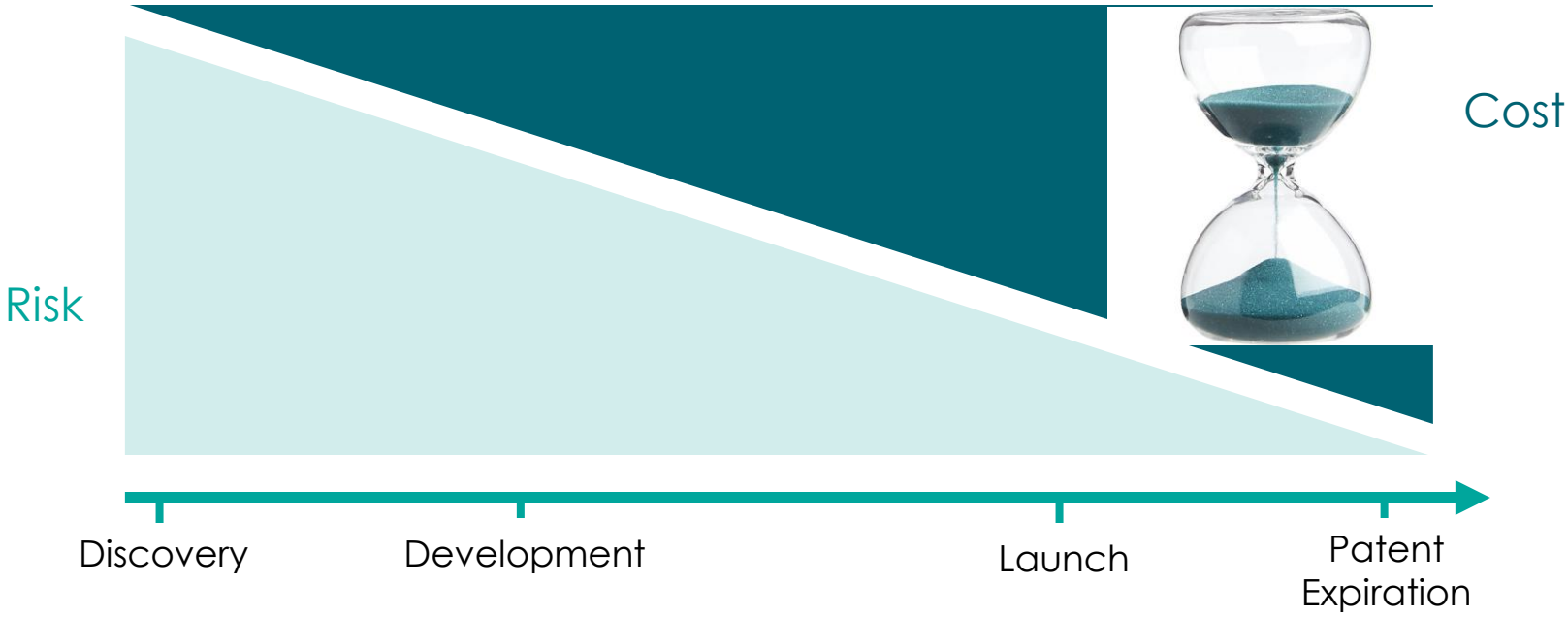
Ambition

Reality

RISK:COST TRADE-OFF INFORMS CLINICAL DEVELOPMENT



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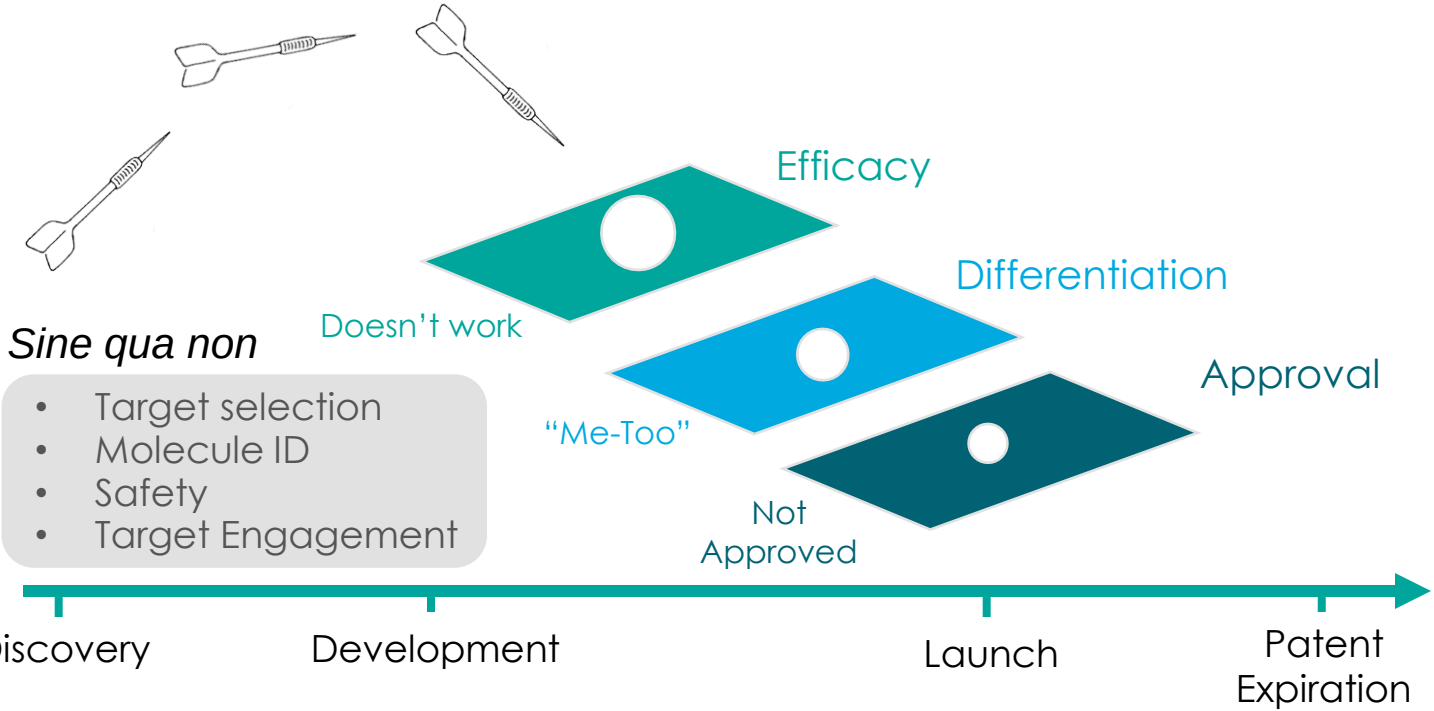
UNIQUE AND COMMON FEATURES OF CNS DRUG DEVELOPMENT



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BALANCING INNOVATION AND INVESTMENT

Stage	Objective	Dimension	Response
Efficacy 	Higher probability of success	Scientific: • Will it work?	Converge on same molecular targets to mitigate target validation risk
Differentiation 	Return on investment	Clinical: • Better than alternatives?	Pursue unmet needs or incremental improvements within existing indications
Approval 	Predictability	Regulatory: • Path to approval?	Invest in novel endpoints or follow regulatory precedent

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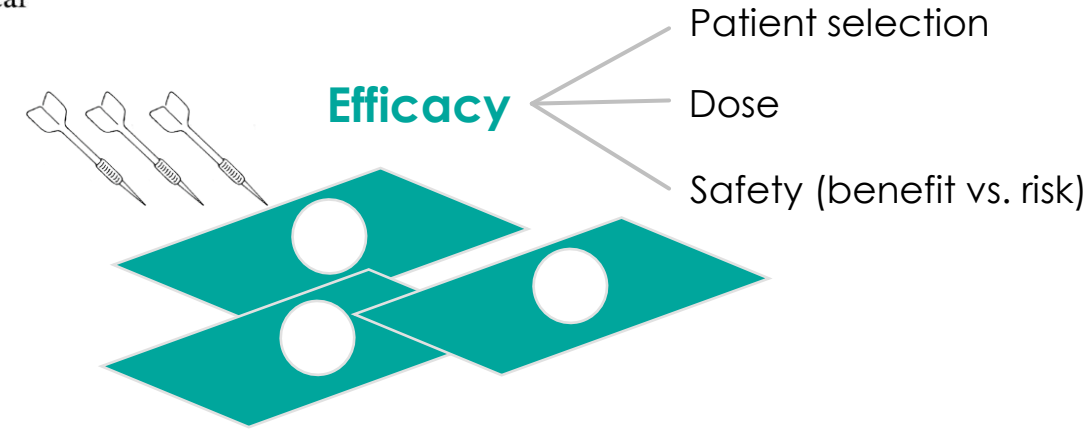
A RETURN TO "LEARN AND CONFIRM" MODEL

CLINICAL PHARMACOLOGY & THERAPEUTICS
VOLUME 61 NUMBER 3 MARCH 1997

COMMENTARY

Learning versus confirming in clinical drug development

Lewis B. Sheiner, MD *San Francisco, Calif.*



Phase 2 is a phase, not a single study

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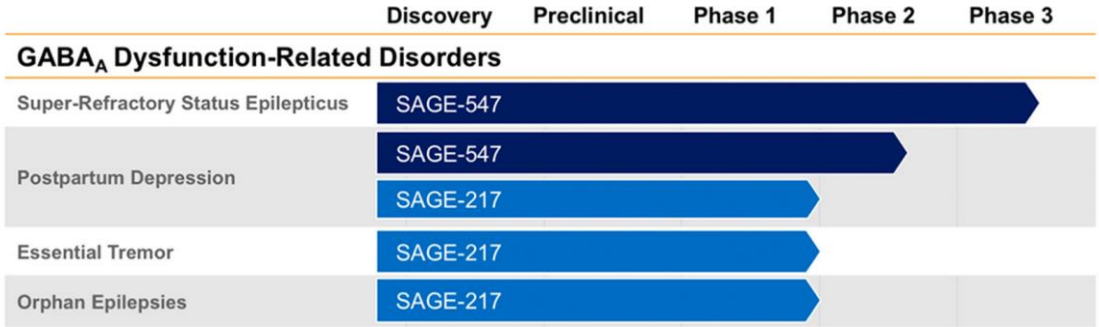
HYPOTHESIS-DRIVEN TESTING IN HUMAN SUBJECTS

- **Hypothesis:** parvalbumin-positive (PV+) interneurons dysfunctional in schizophrenia
- **Target:** Kv3 potassium channels control PV+ interneurons
- **Model:** Acute doses of ketamine in healthy volunteers induce schizophrenic-like positive and negative symptoms that resemble schizophrenia
- **Explore:** Kv3 modulators as new target for the treatment of schizophrenia using "ketamine challenge model" in human subjects

"LEARN & CONFIRM" IN TARGET PATIENT POPULATION

- **Multiple indications pursued per molecule**

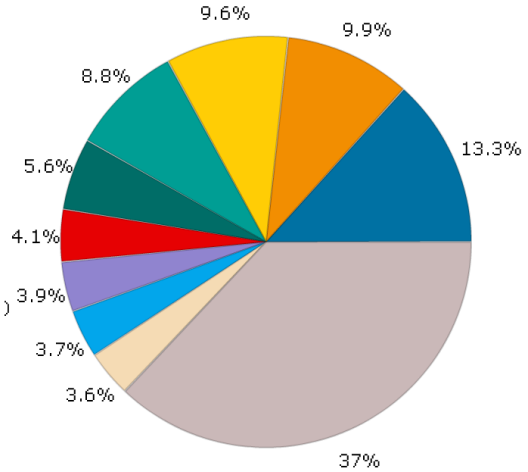


- **Small, targeted trials**
  - 4 patient exploratory open-label efficacy study in post-partum depression (PPD)
  - 21 patient placebo-controlled Phase 2a trial in PPD
- **Aggressive timelines, within regulatory guidelines**
  - ~15 months from initial clinical signal to "breakthrough therapy" designation
  - Hamilton Depression Scale

"LEARN AND CONFIRM" EXTENDED BETWEEN COMPANIES

- **Fragile X Syndrome: mechanism vs. trial methodology**

mGluR5 antagonists



Thomson Reuters Integrity 2016

Seaside Therapeutics

STX107 in Adults With Fragile X Syndrome
Estimated Enrollment:16; 2 week duration

FRAGILE X SYNDROME

NOVARTIS

Mavoglurant in fragile X syndrome: Results of two randomized, double-blind, placebo-controlled trials

Total of 175 adult and 139 adolescent patients randomized into 4 treatment arms; 12-week duration

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LEARNING FROM NEGATIVE TRIALS: FRAGILE X SYNDROME

	NOVARTIS	neuren pharmaceuticals
Mechanism	mGluR5	IGF-1
Subjects	314	70
Doses	3	2
Duration	12-week	4-week
Clinical scales	Regulatory precedent for Autism	Focus on FXS-specific behavioral domains
Functional measures	None (suggested including markers of central responses)	Eye-tracking, cognitive measures
	Berry-Kravis, *Sci. Trans. Med.*, 2016	Company Website, Investor presentation, 2016 Clinicaltrials.gov, 2016

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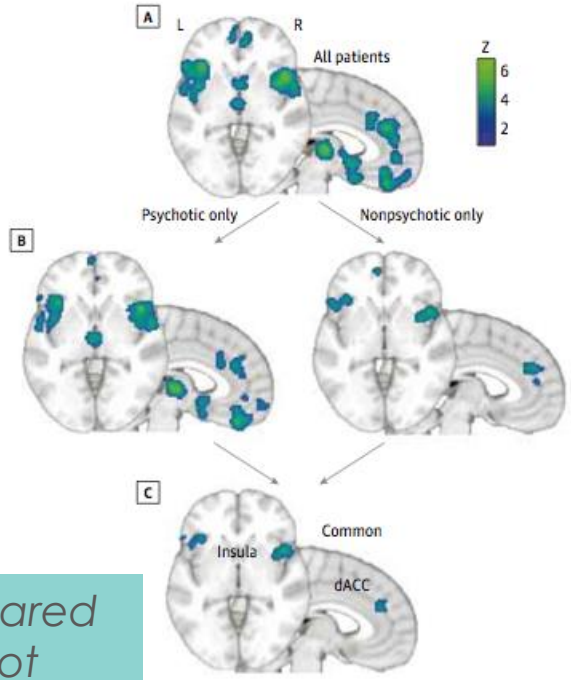
LEVERAGE EXISTING DATA FOR HYPOTHESIS GENERATION

Original Investigation | META-ANALYSIS

Identification of a Common Neurobiological Substrate for Mental Illness

- Voxel-based morphometry meta-analysis of ***193 studies*** comprising **15,892 individuals** across six diagnostic groups
  - Gray matter loss converged across diagnoses in 3 regions
  - Few diagnosis-specific effects, distinguishing only schizophrenia and depression from other diagnoses



Goodkind et al., 2015

➢*"Organizing model that emphasizes the import of shared endophenotypes across psychopathology, which is not currently an explicit component of psychiatric nosology."*

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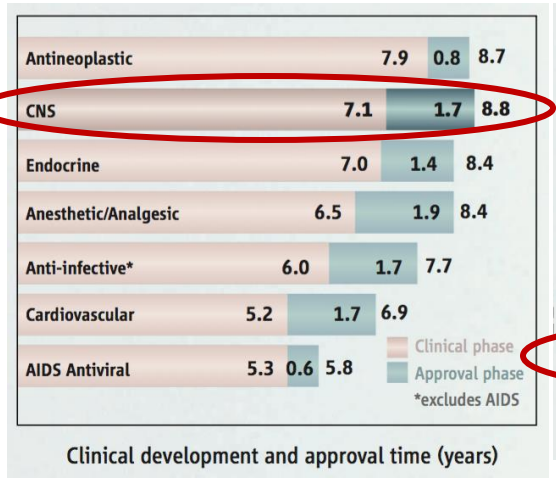
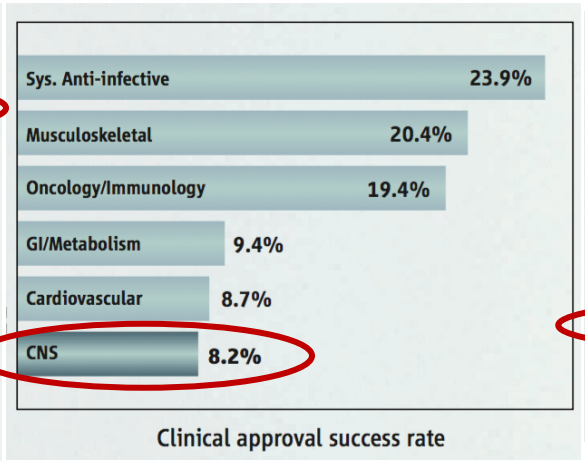
THRESHOLDS FOR INVESTMENT

- **Scientific:**
  - Is discovery and early development path informed by novel mechanistic insights that do not rely solely on animal "efficacy" models?
- **Clinical:**
  - Can a hypothesis be tested in a human subject model or a targeted clinical population?
- **Regulatory:**
  - Is unmet medical need sufficiently high to justify following a path without regulatory precedent?

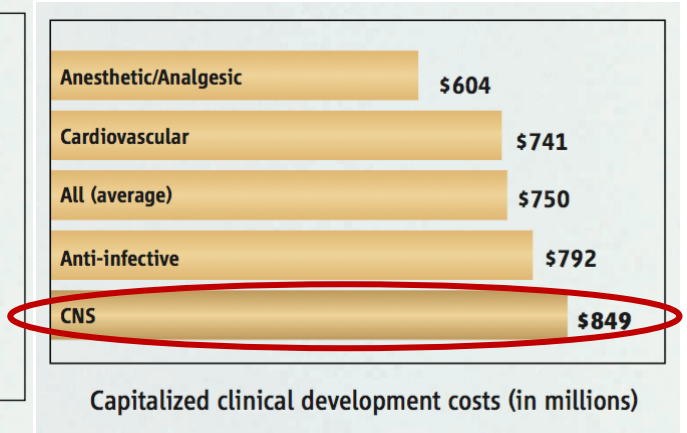
CNS DISORDERS: R&D INVESTMENTS ARE NOT PROPORTIONAL TO UNTREATED DISEASE BURDEN



Clinical development and approval time (years)



Clinical approval success rate



Capitalized clinical development costs (in millions)

Miller, *Science*, 2010

- Clinical development and approval = 8.8 years
- Clinical approval success rate = 8.2%
- Capitalized clinical development costs (2010) = $849M

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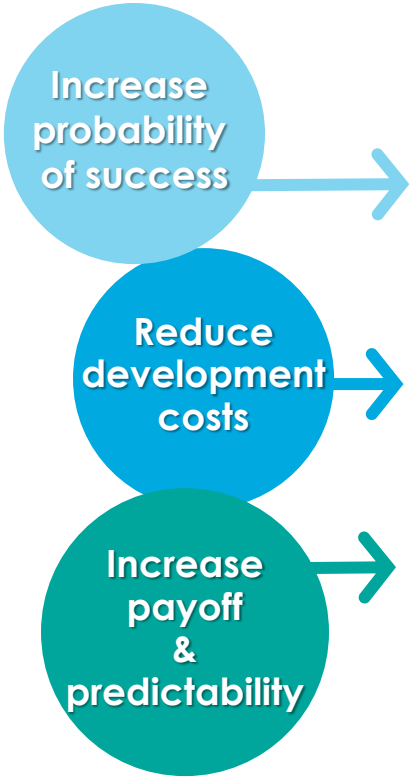
POLICY CONSIDERATIONS



1. Create risk-sharing models to target validation
2. Improve access to clinical data
3. Simplify clinical study requirements
4. Invest in Regulatory Science
5. Extend patent protection

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