Neuroscience Therapeutics Development: Current State And Challenges

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Disclosure: I am an employee of Merck

Finding New Drugs Is Difficult

- In many disorders with unmet medical need,
  - Our understanding of disease biology is incomplete, making it difficult to choose targets that result in effective drugs
  - Even when disease is better understood, finding targets that reliably move biology can be challenging (e.g. tau, α-synuclein)

Background

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- Compared with other disease areas, CNS disorders have been relatively less tractable to finding new treatments as measured by success rates:
  - From 1995 to 2007 the proportion of all new CNS drugs with a first in human dose that ultimately received regulatory approval was 6.2%[1]
  - Benchmarking data suggest that CNS (neurology/psychiatry/pain) success rates are among the lowest of the major therapeutic areas
  - As many new drugs are iterative (e.g. 2nd or 3rd in class, etc.), the success rates for truly novel ('unprecedented') mechanisms may be overstated
  - In recent years, many companies previously active in developing novel CNS drugs have exited the area, despite the large unmet medical need that remains

[1]*Tufts Center for the Study of Drug Development, Impact Report, Volume 16, November/December 2014*

The Challenge

To serve patients well and increase the flow of needed drugs, we will need more efficient discovery and development methods, and improved success rates

The focus today is to explore and discuss paths toward this goal

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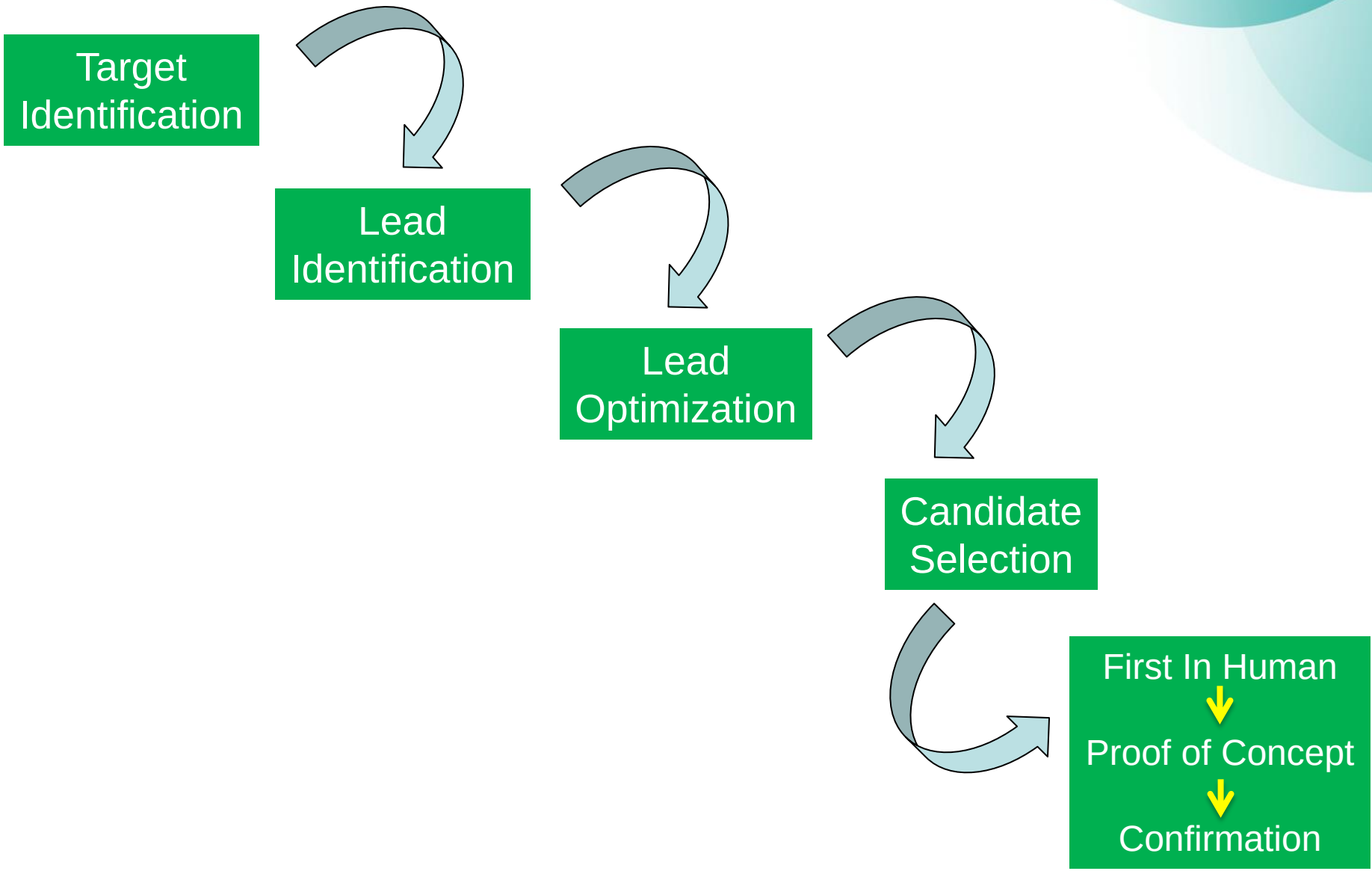
The Path To A Drug



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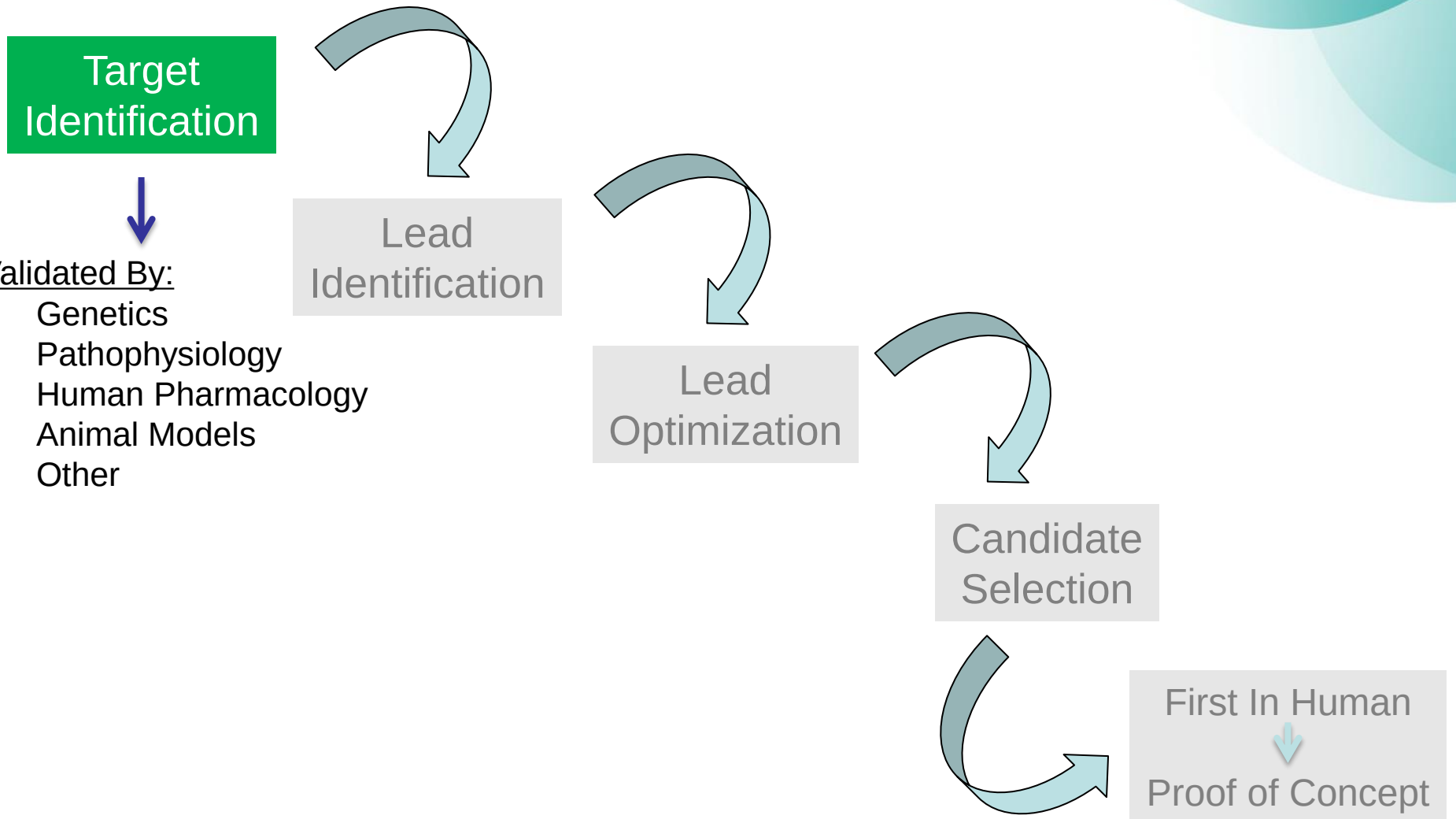

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Target Identification

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- Target validation can come from a number of different sources—genetics, pathophysiology, clinical observation, animal models, etc.
- The limitations of animal models have been increasingly recognized, and emphasis is shifting towards validating targets with human data

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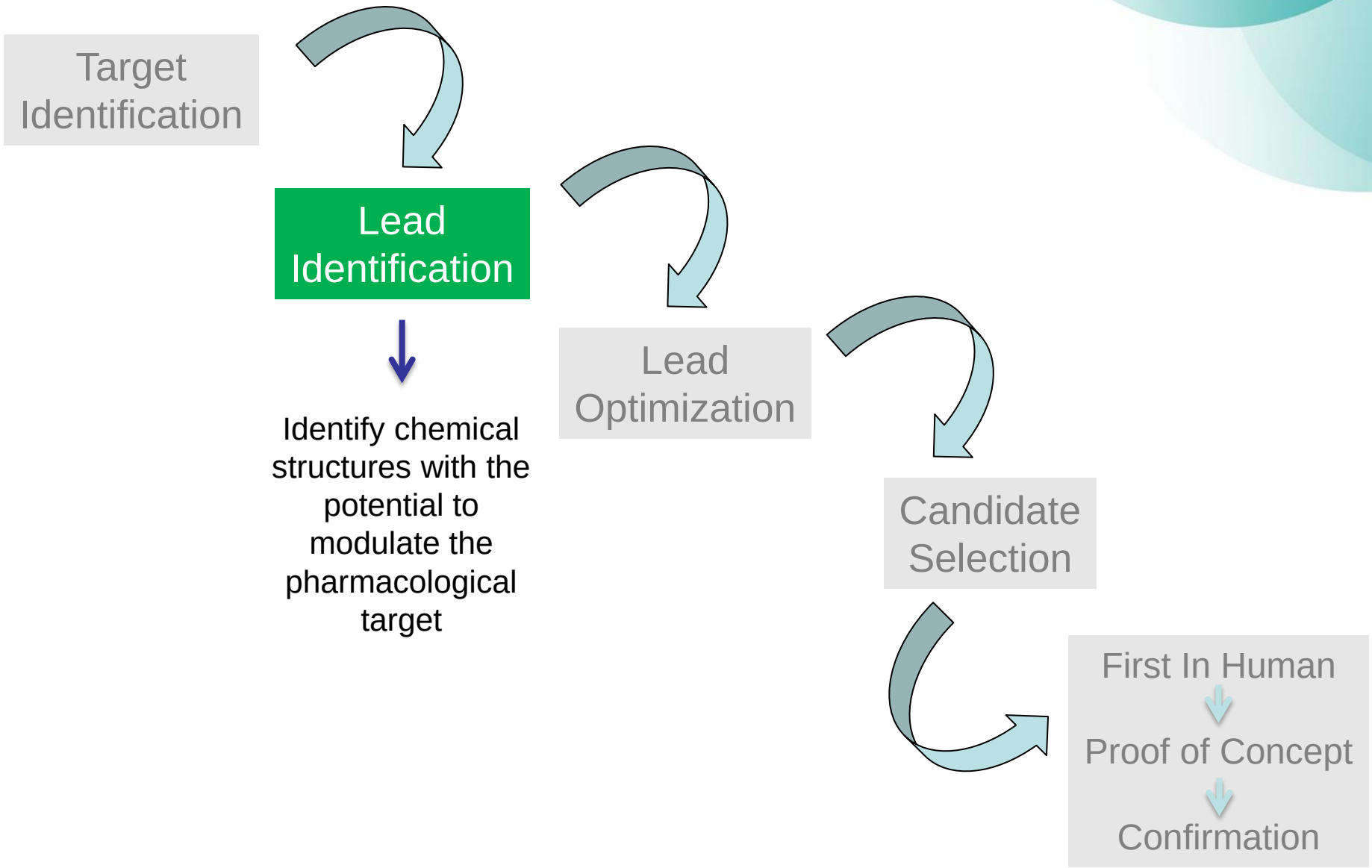

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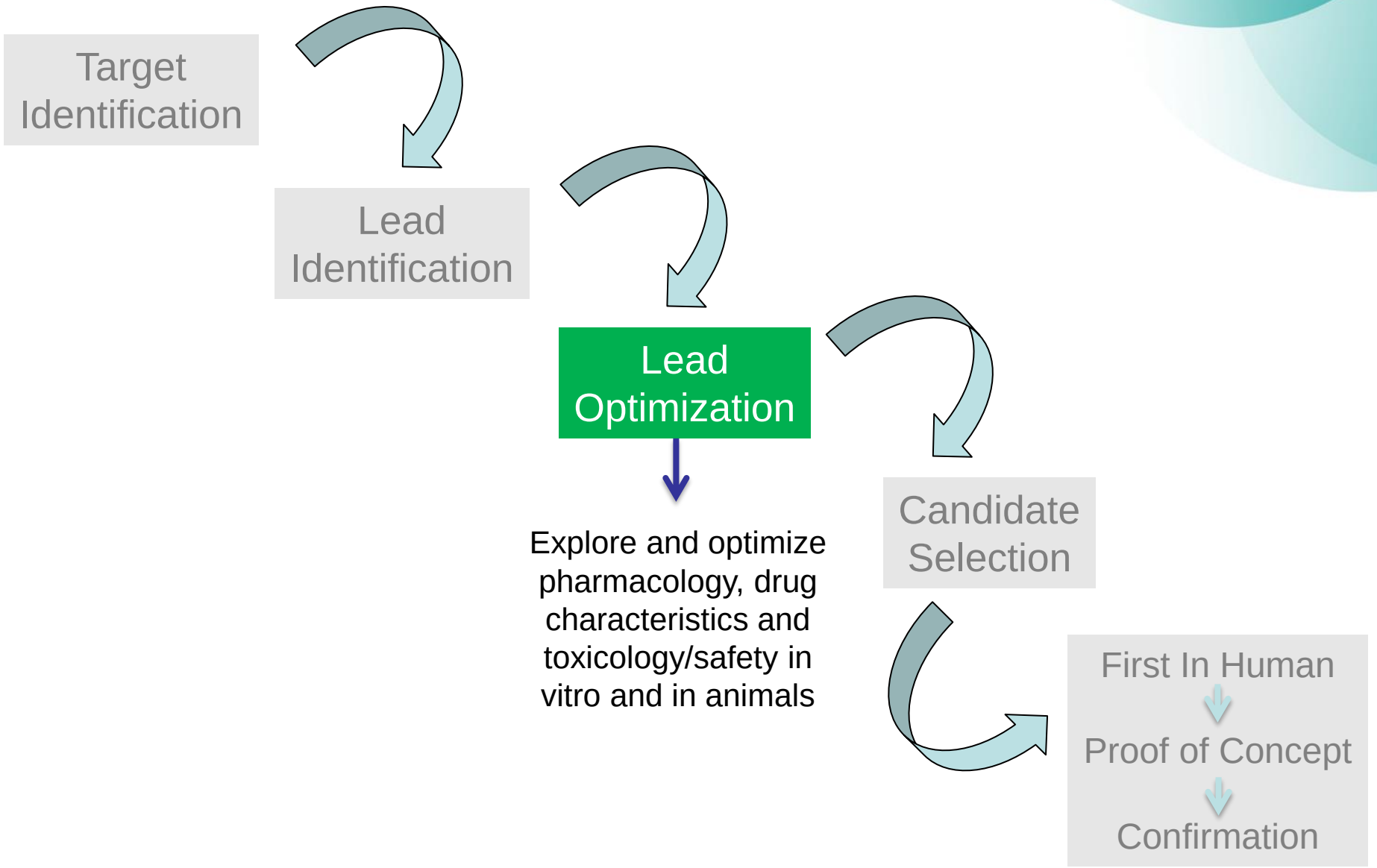


The Path To A Drug

Target Identification

Lead Identification

Lead Optimization

Candidate Selection

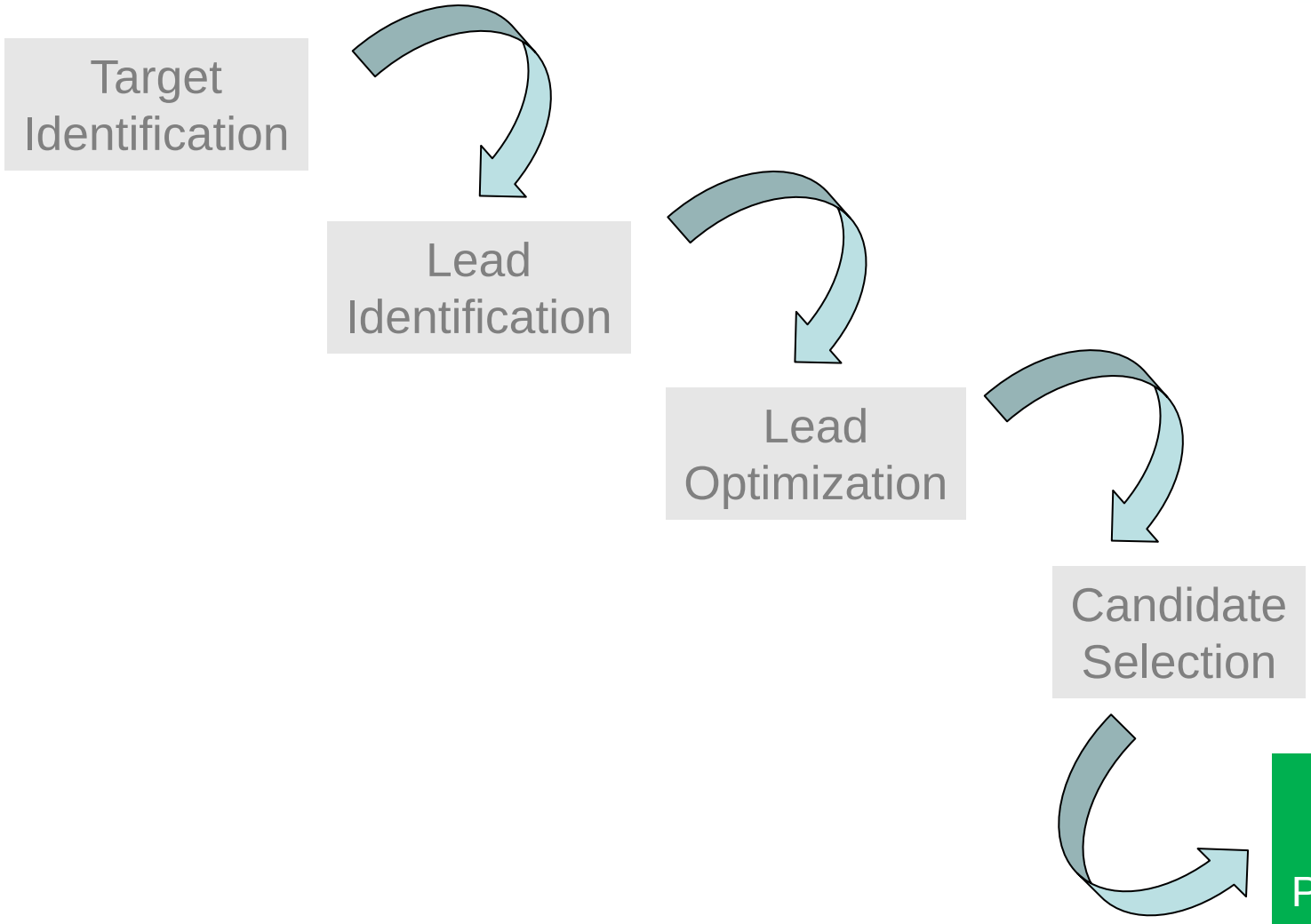
GLP toxicology and other work required to enable human studies

First In Human

Proof of Concept

Confirmation

The Path To A Drug



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- Animal models often can usefully explore whether a given pharmacology can effect desired biological changes

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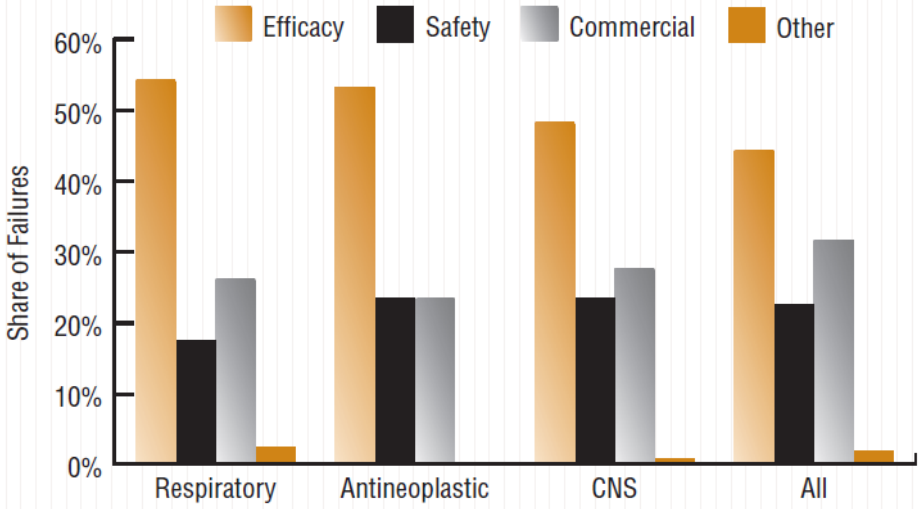
- Thus better approaches and paradigms are needed

The Most Common Reason For Failure Is Inefficacy: The Drug Candidate Does Not Demonstrate The Desired Therapeutic Benefit

Efficacy issues leading to failure dominated for certain therapeutic classes

Therapeutic Classes with Relatively High Efficacy Failure Shares



Source: Tufts Center for the Study of Drug Development

- For investigational drugs that first entered clinical testing in 2000-09, more than half of the respiratory and antineoplastic indications (54.3% and 53.3%, respectively) that failed did so primarily for efficacy reasons.

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To encourage increased efforts to find and develop new CNS therapeutics there are several potential 'levers'

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Today's Focus