

Bench to Bedside: The Drug Development Pipeline

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Outline for this session

Introduction

- The goal
- The pathway
- The players
- The challenges

Illustration

- Multiple Sclerosis
- Natalizumab

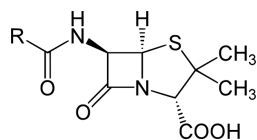
Innovations

- Tissue on chip

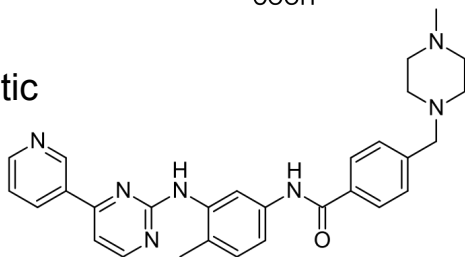
What is a drug?

A product that alleviates, cures or prevents disease, or is intended to affect the structure or function of the body.

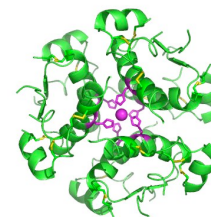
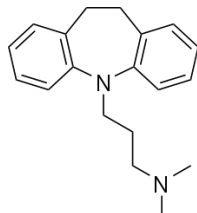
Antibiotics



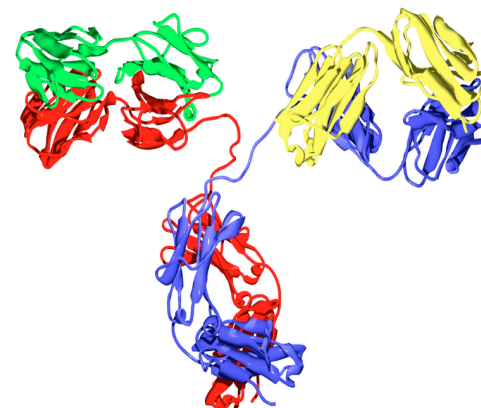
Chemotherapeutic agents



Tricyclic antidepressants



Insulin
(~100x bigger
than antibiotic)



Antibody
(600x bigger
than antibiotic)

Penicillin: Public Domain

Gleevac: Public Domain

Antidepressants: Harbin, Public Domain

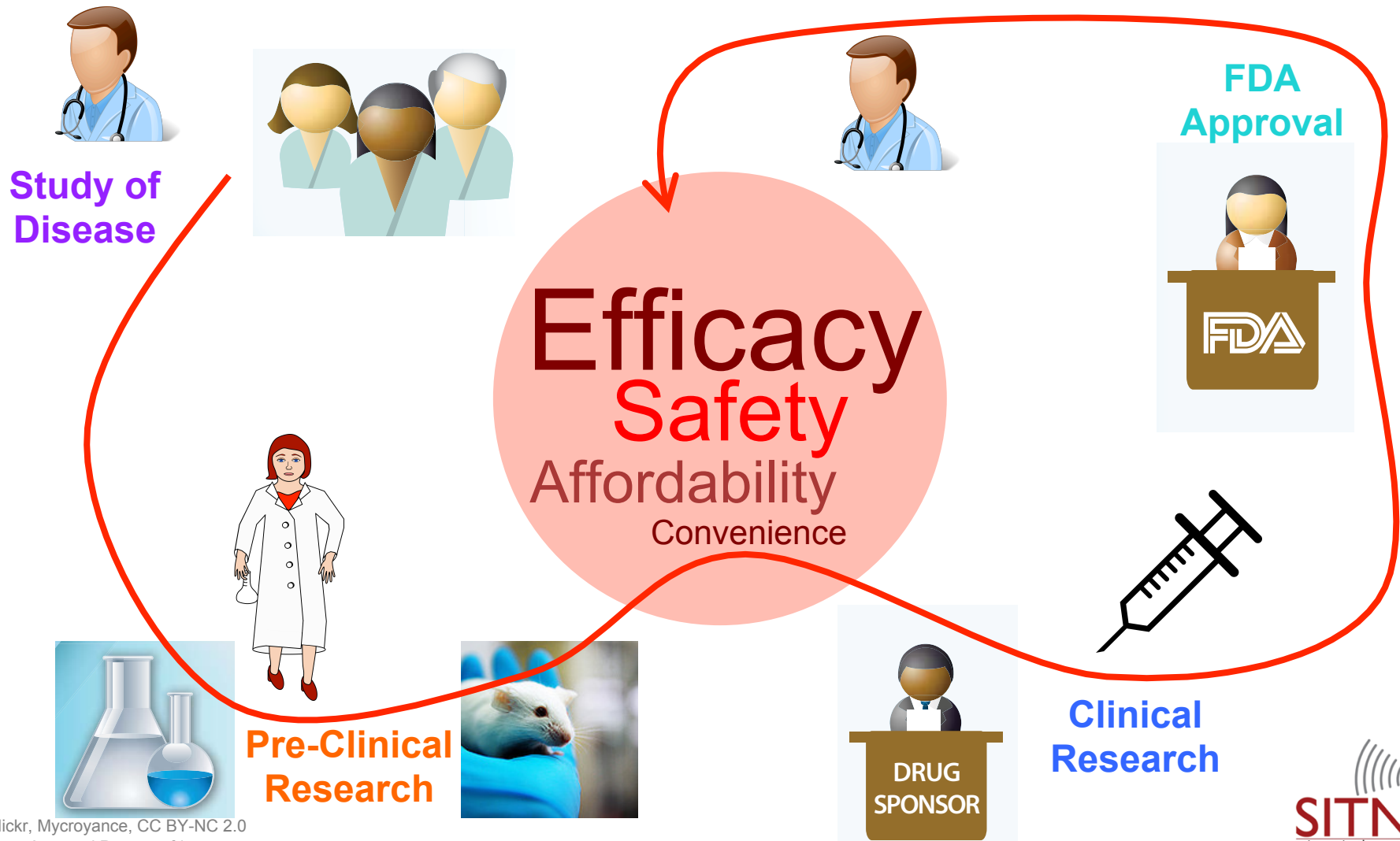
Insulin: Isaac Yonemoto, CC-BY

Antibody: Public Domain

What qualities do we want in a new drug?



What is the path to get there?



What are the challenges?

14 years

Average length of time from target discovery to approval of a new drug.

85% Failure rate

From Phase I to FDA approval, during clinical trials.

\$2.6 Billion

Cost per successful drug, when all failures are factored in.

Why do these challenges exist?

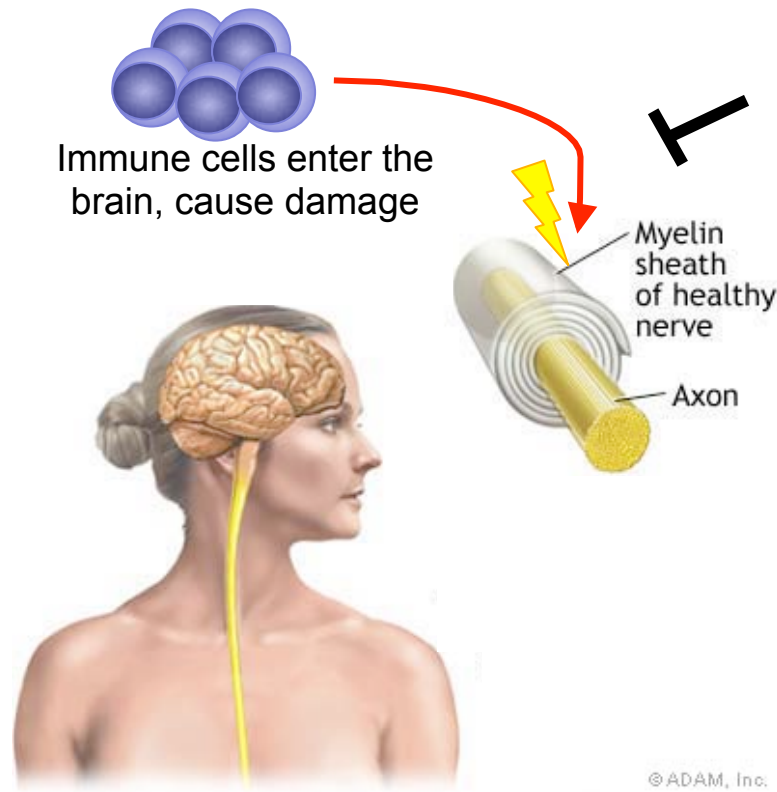
Questions?

Example:

Multiple Sclerosis (MS) and *natalizumab*

Multiple Sclerosis (MS)

- Affects 90 per 100,000 people in the US
- Due to damage to myelin, the insulation for nerves
- Thought to be caused by immune cells



Natalizumab

- Prevents immune cells from entering the brain

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Multiple sclerosis: Identified as disease in 1868

1868

1960

1970

1980

1990

2000

2010

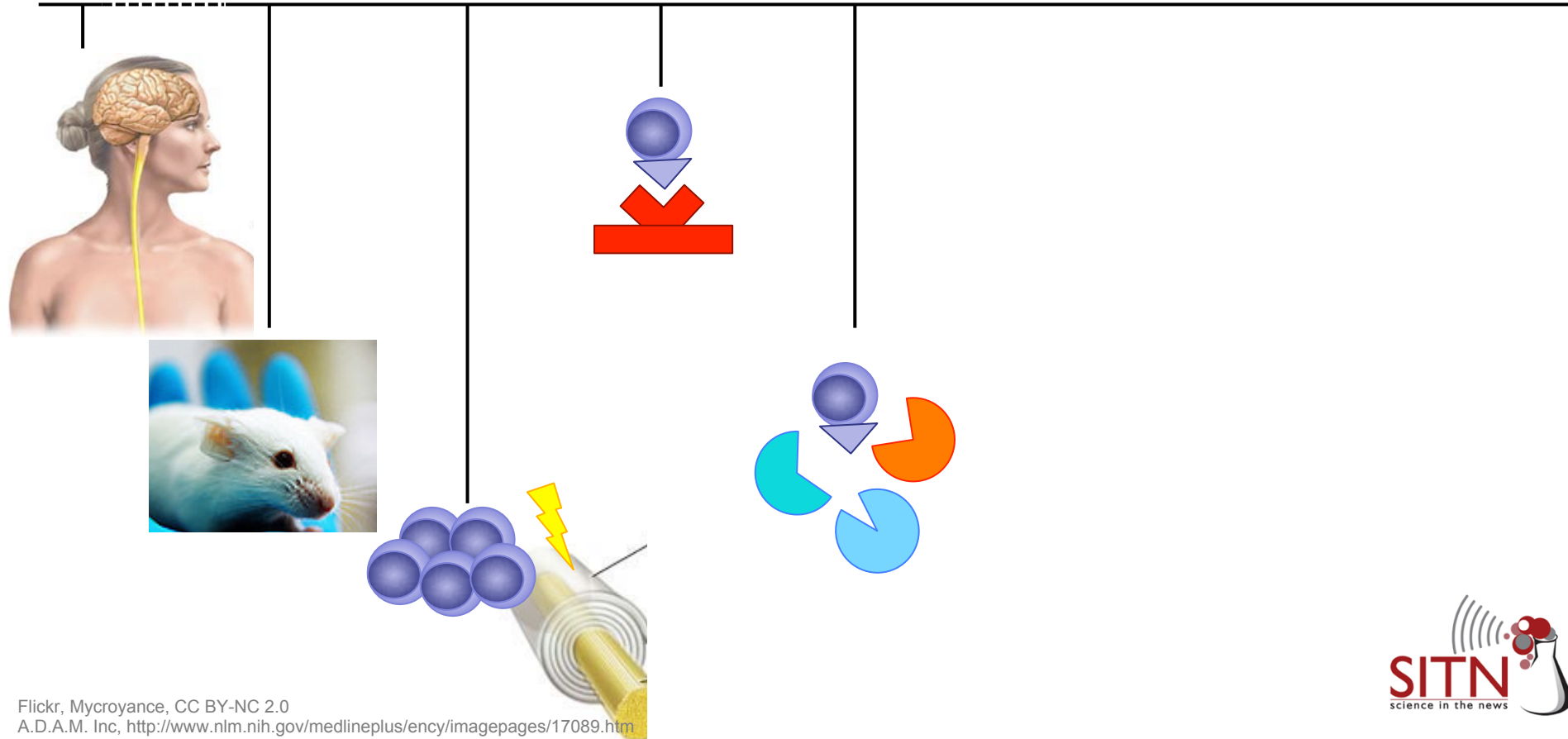
2020



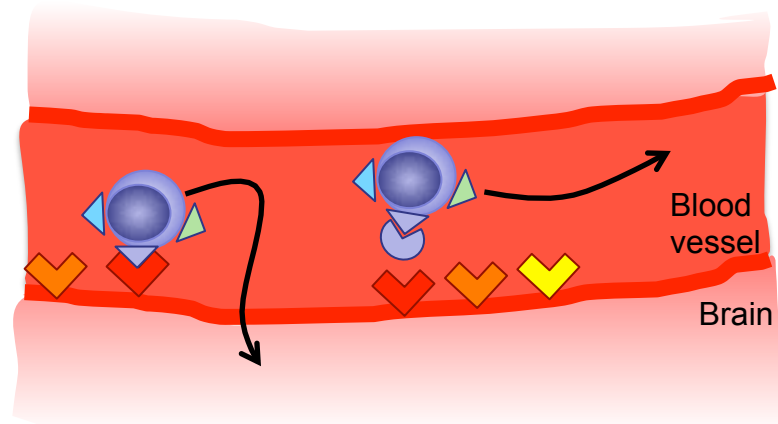
Pre-clinical research: Is there a way to cure multiple sclerosis?

Pre-clinical research

1868 1960 1970 1980 1990 2000 2010 2020



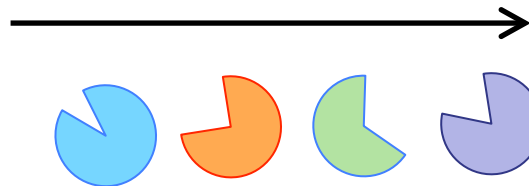
How do immune cells enter inflamed brain tissue?



Receptors that *might* be involved



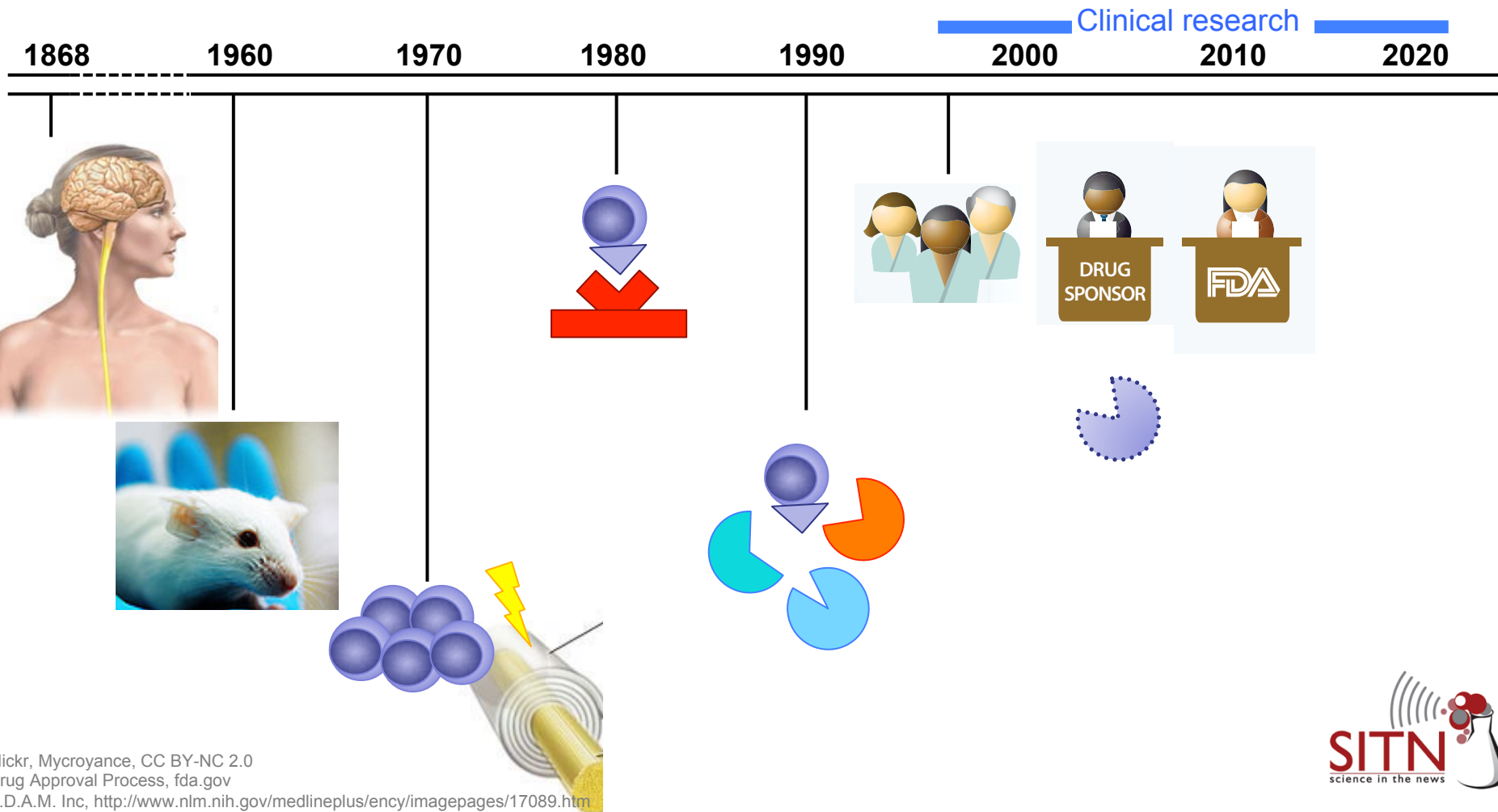
Test antibodies that block each one



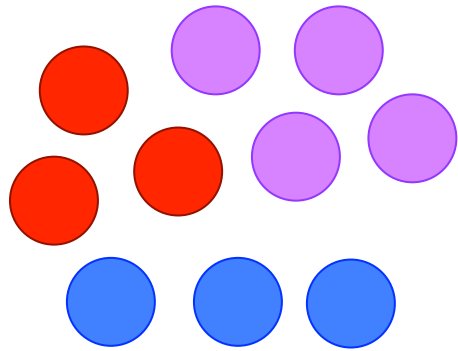
Result



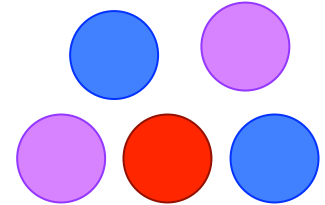
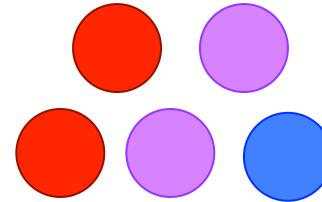
Clinical research: Test a drug in humans



Features of clinical trials



Randomization



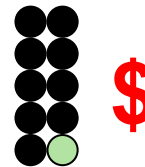
Placebo



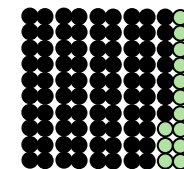
Blinded



Study size



\$

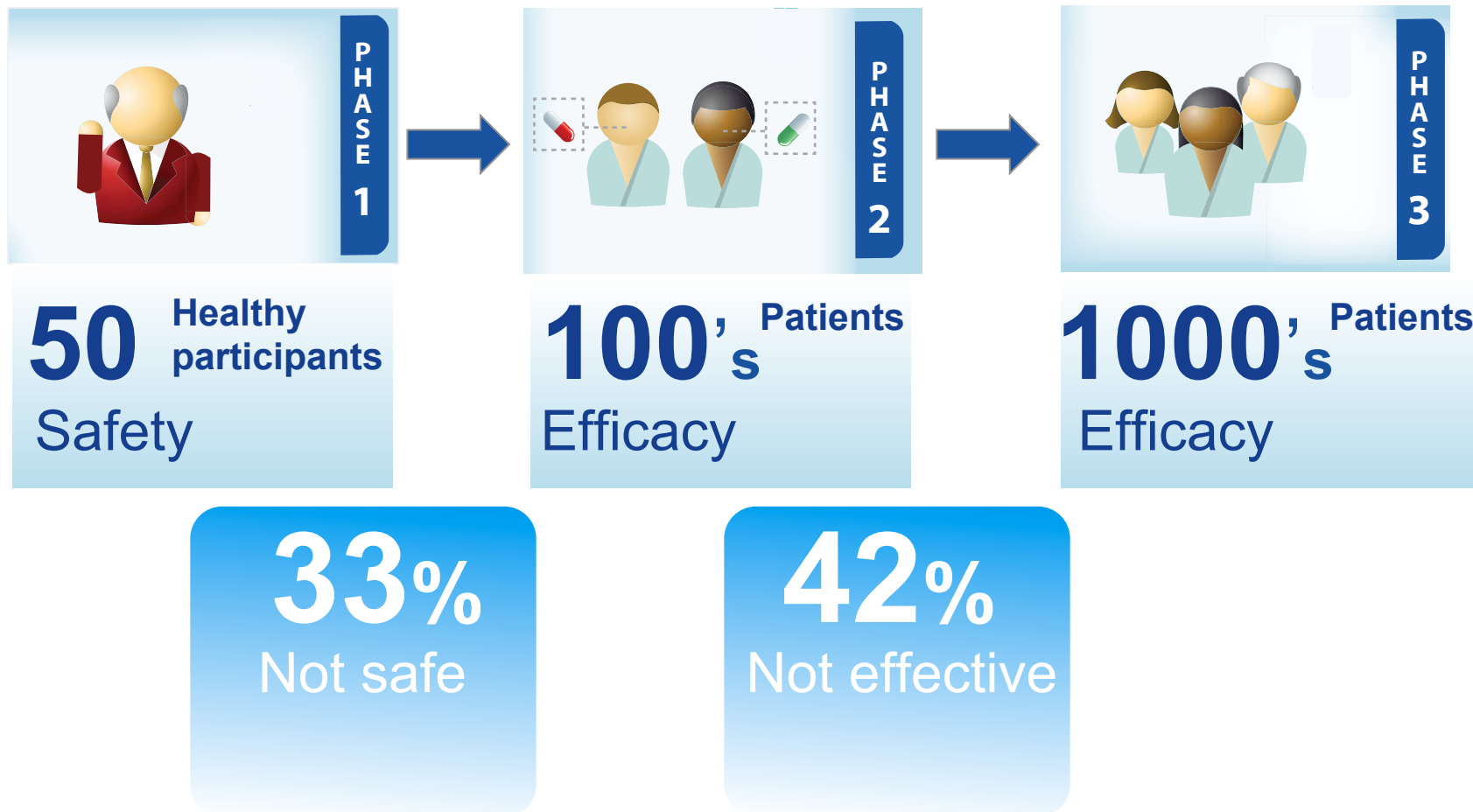


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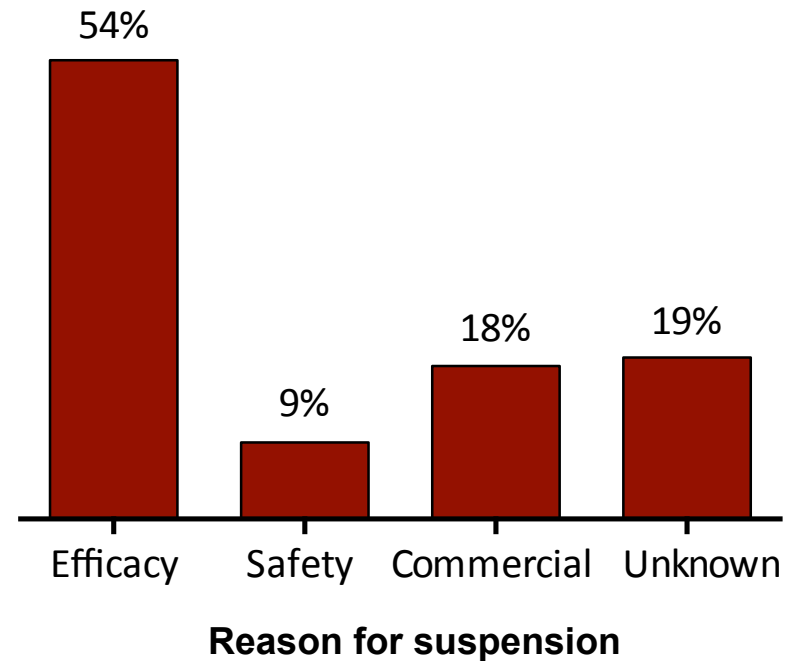
Clinical trials are run in phases



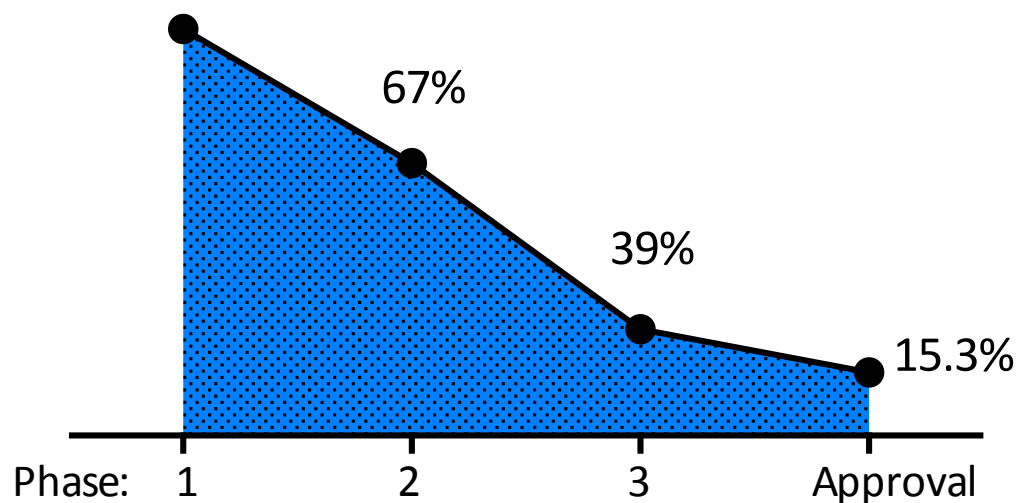
At each phase, many drugs fail



60% of trials in Phase 3 are suspended



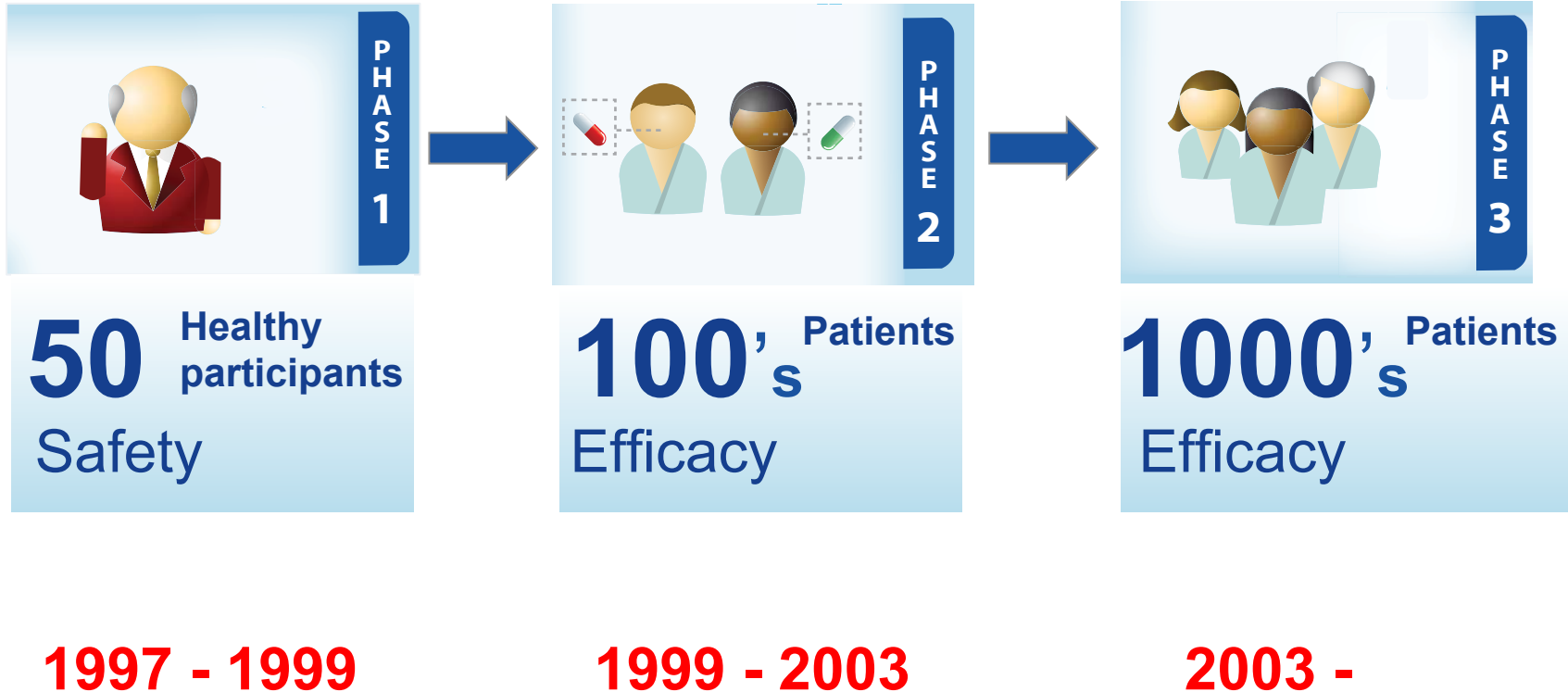
Why are safety and efficacy hard to predict?



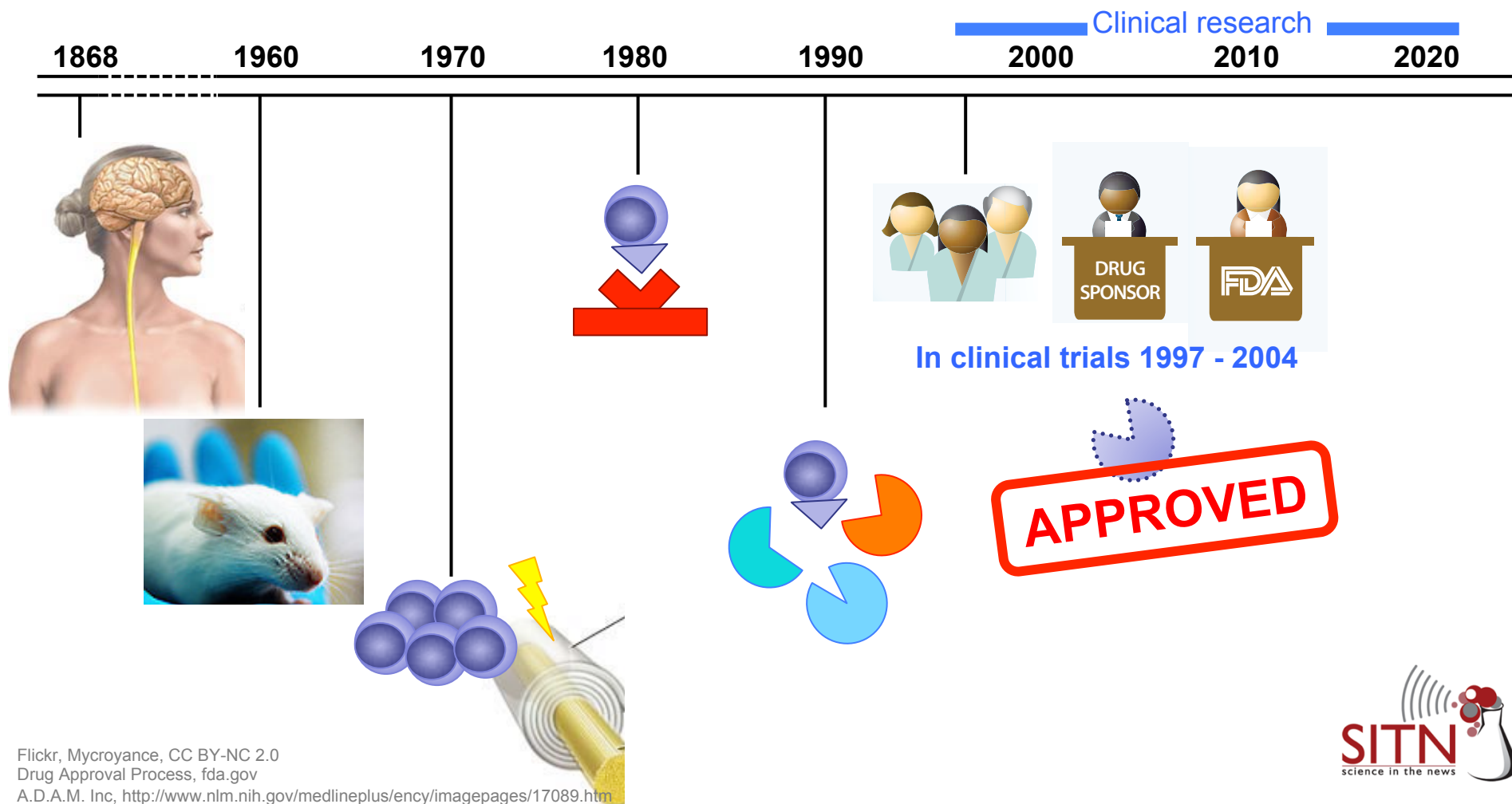
- Research models of disease are not the same as humans
- Studies of humans are limited by available materials
- A new drug needs to be better than current drugs

Questions?

Natalizumab had very promising results



Expedited FDA approval, in 2004



Natalizumab suspended 3 months later: Two cases of fatal brain inflammation (PML: Progressive multifocal leukoencephalopathy)

During multiple sclerosis:

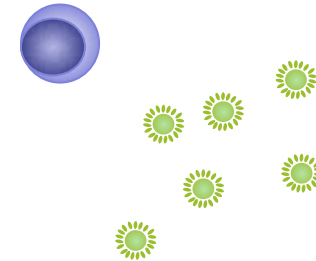
Immune cells enter brain, cause damage



Natalizumab prevents immune cells from entering the brain

During infection with JC virus:

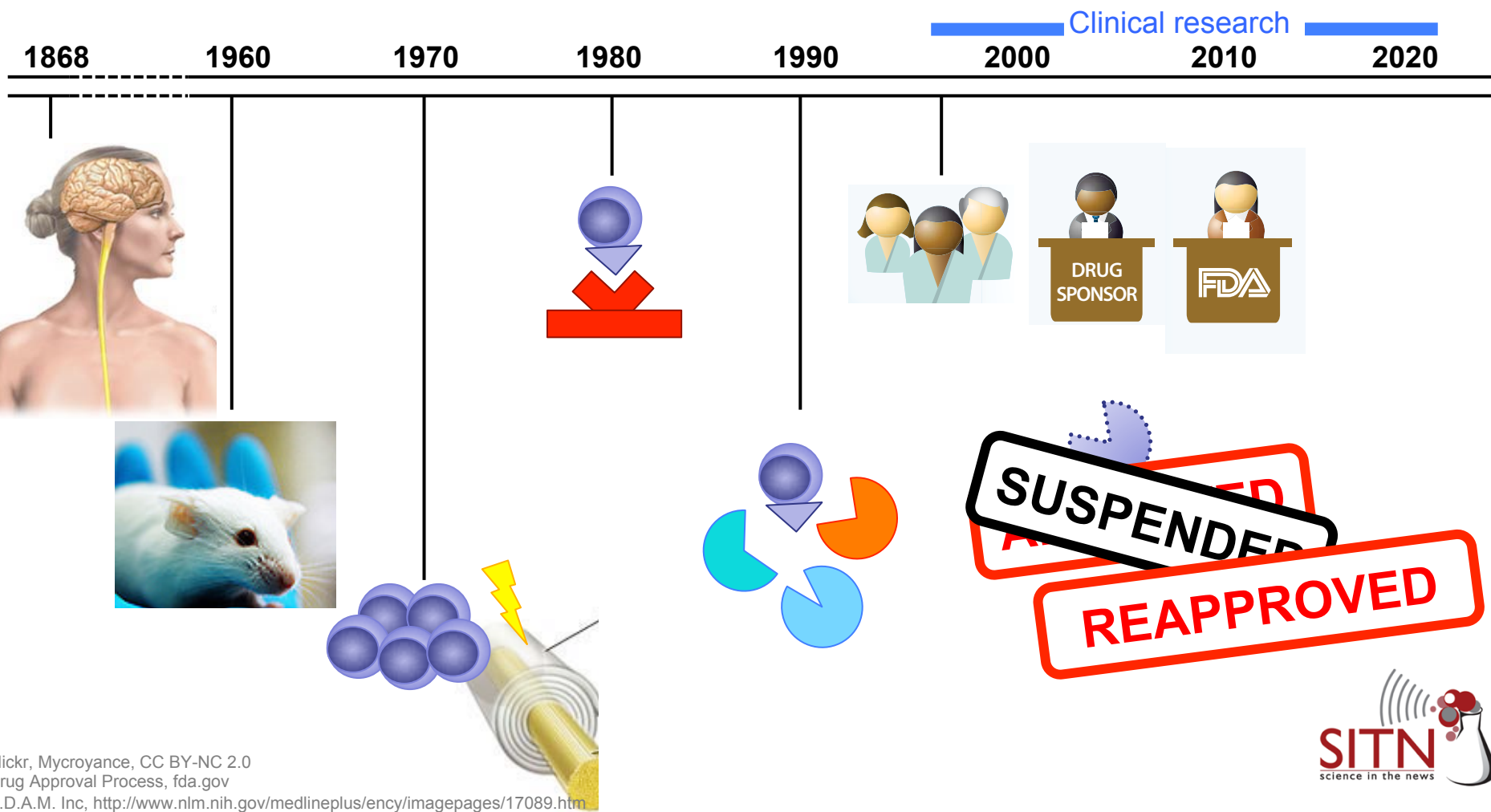
Immune cells enter the brain, stop the spread of virus, and protect brain tissue



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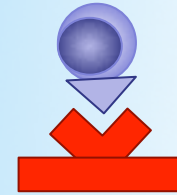
Reapproved 1 year later

Stringent restrictions for use

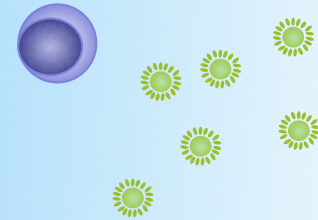


Key points from the natalizumab story

Discoveries in different fields led to the development of natalizumab



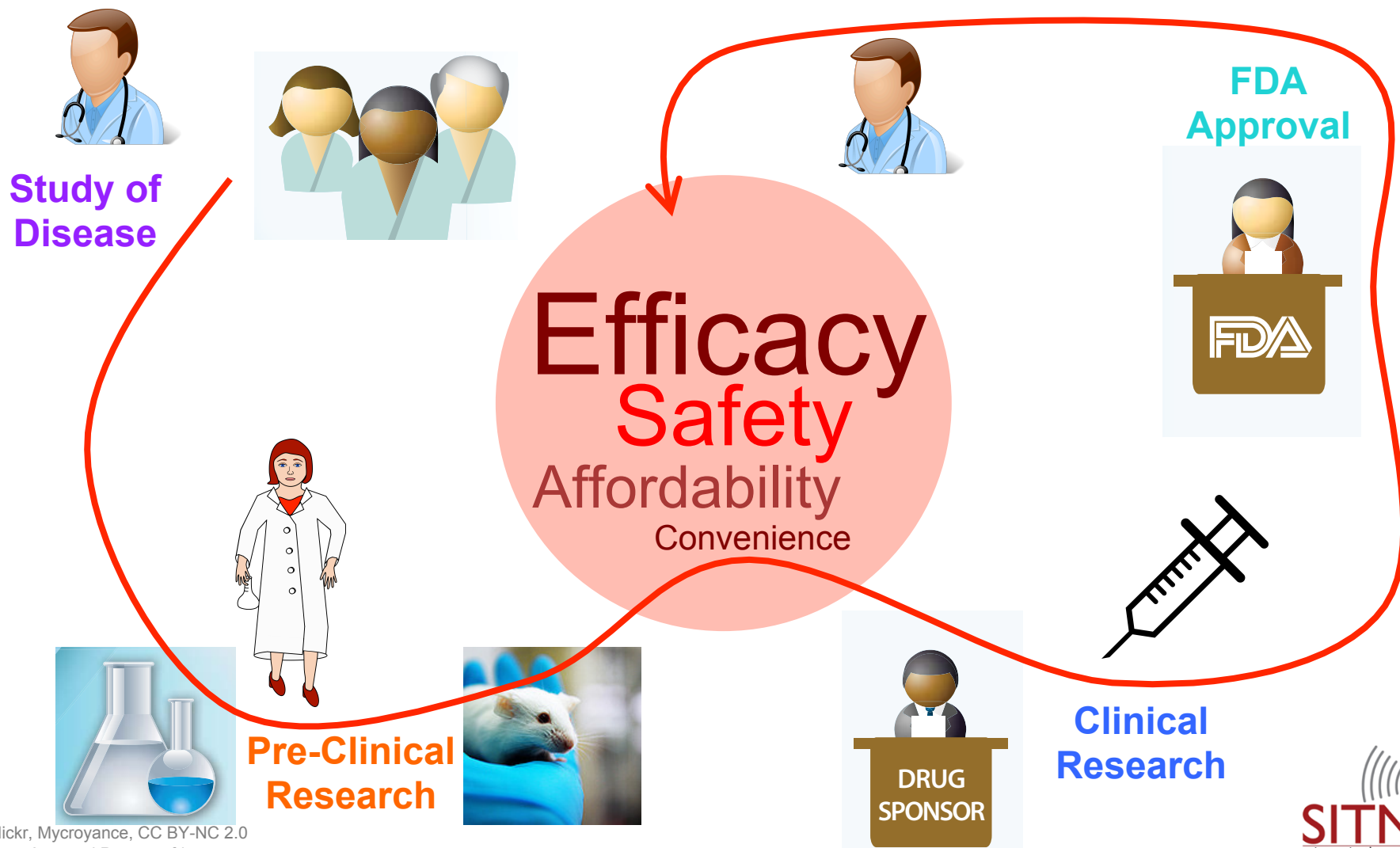
Pre-clinical studies could not predict complications due to JC virus infection



The FDA wants to make SAFE drugs available to patients



Summary



To address the challenges

Repurposing of approved drugs

- Use drugs already approved for safety
- Test in other candidate diseases

Improve laboratory models of disease

- Better understand the current models
- New models

New technology: do more with less

- More data from small clinical samples
- Allows better study of human biopsies, blood

Innovative approach: Tissue chip for drug screening

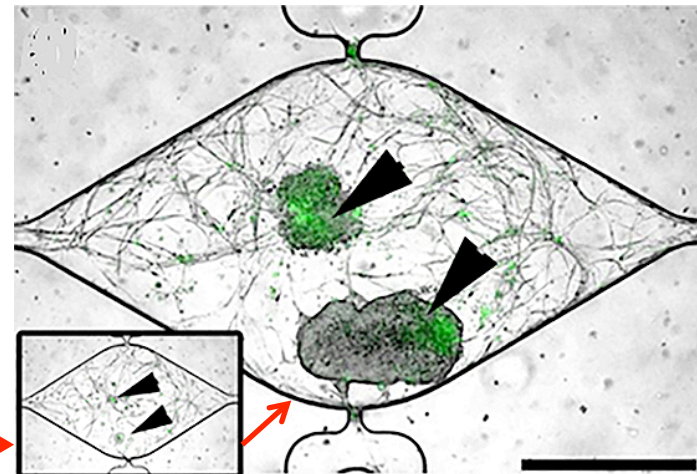
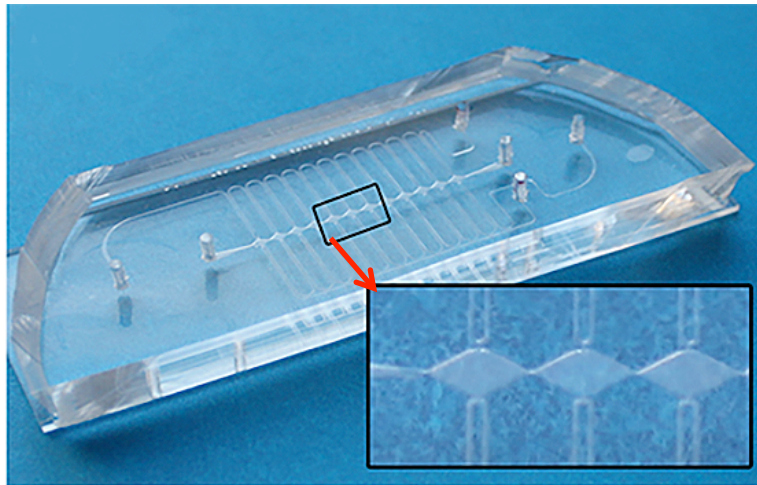
Tissue chips

- Mimic human tissues
- Screen drugs before testing in humans

Pre-Clinical

Tissue Chips

Clinical



Summary

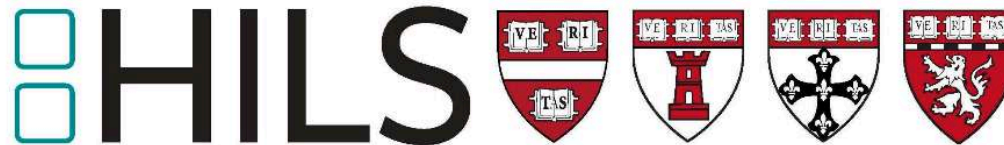
The drug development pipeline

- The goals
 - Safety, Efficacy, Affordability
- The pathway
 - Long, expensive, challenging
- The players
 - Scientists...Pharma...FDA...Patients
- The challenges
 - Difficult to understand how the body works
 - Difficult to predict how a drug will act in humans
- Innovations
 - Facilitated by growing scientific knowledge
 - Facilitated by new technology

Thank you!

SITN would like to acknowledge the following organizations for their generous support of this event.

Harvard Integrated Life Sciences



The nonprofit plasmid repository



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