In vivo Pharmacology

What is *in vivo* pharmacology?

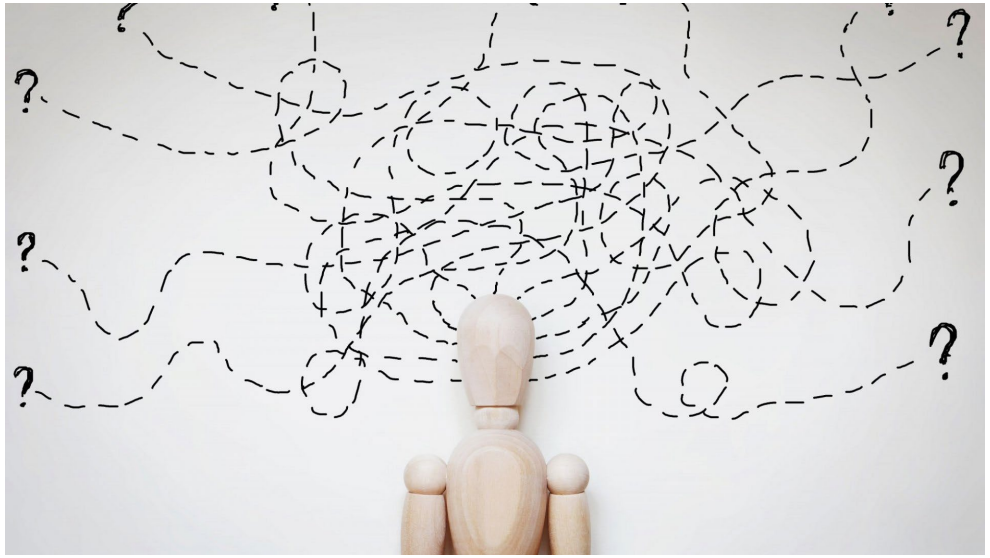
The study of the biological effects of a compound in a living organism

Aspects of Drug Pharmacology

- Efficacy
- Potency
- Dose Response
- Therapeutic Index

Using research animals is

COMPLICATED



AND

EXPENSIVE

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Why is it scientifically important to include in vivo pharmacology in drug discovery?

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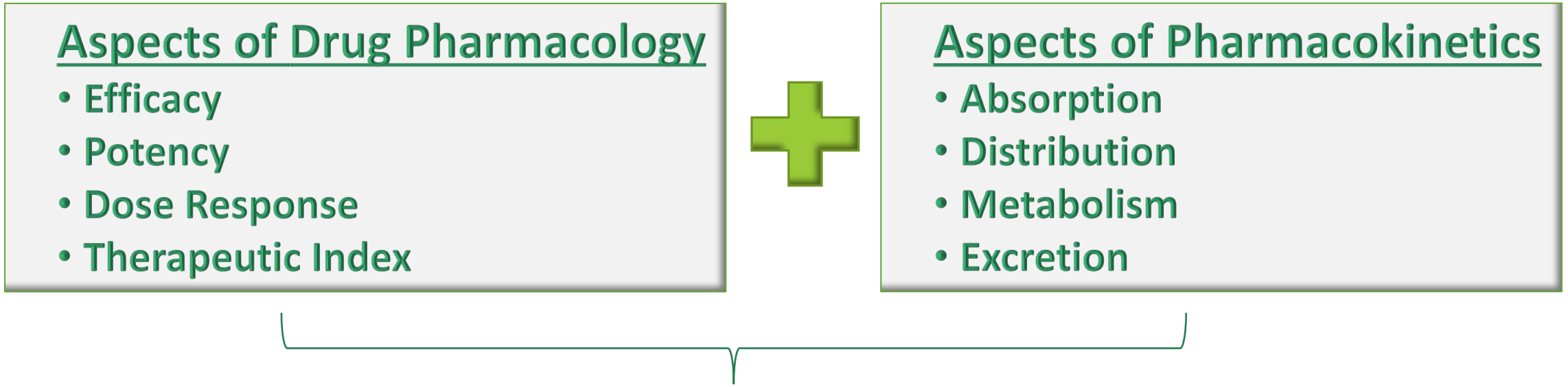
Why is it important to include in vivo pharmacology in drug discovery?



Challenging to reproduce in a test tube

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What is a biotech or pharmaceutical company's primary goal ?

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Answer:

To make money

Poll Question

True or False ?

A good predictor of clinical efficacy (i.e. ,the drug will cure or decrease the effects of the disease) is how it performs in an in vivo disease model ?

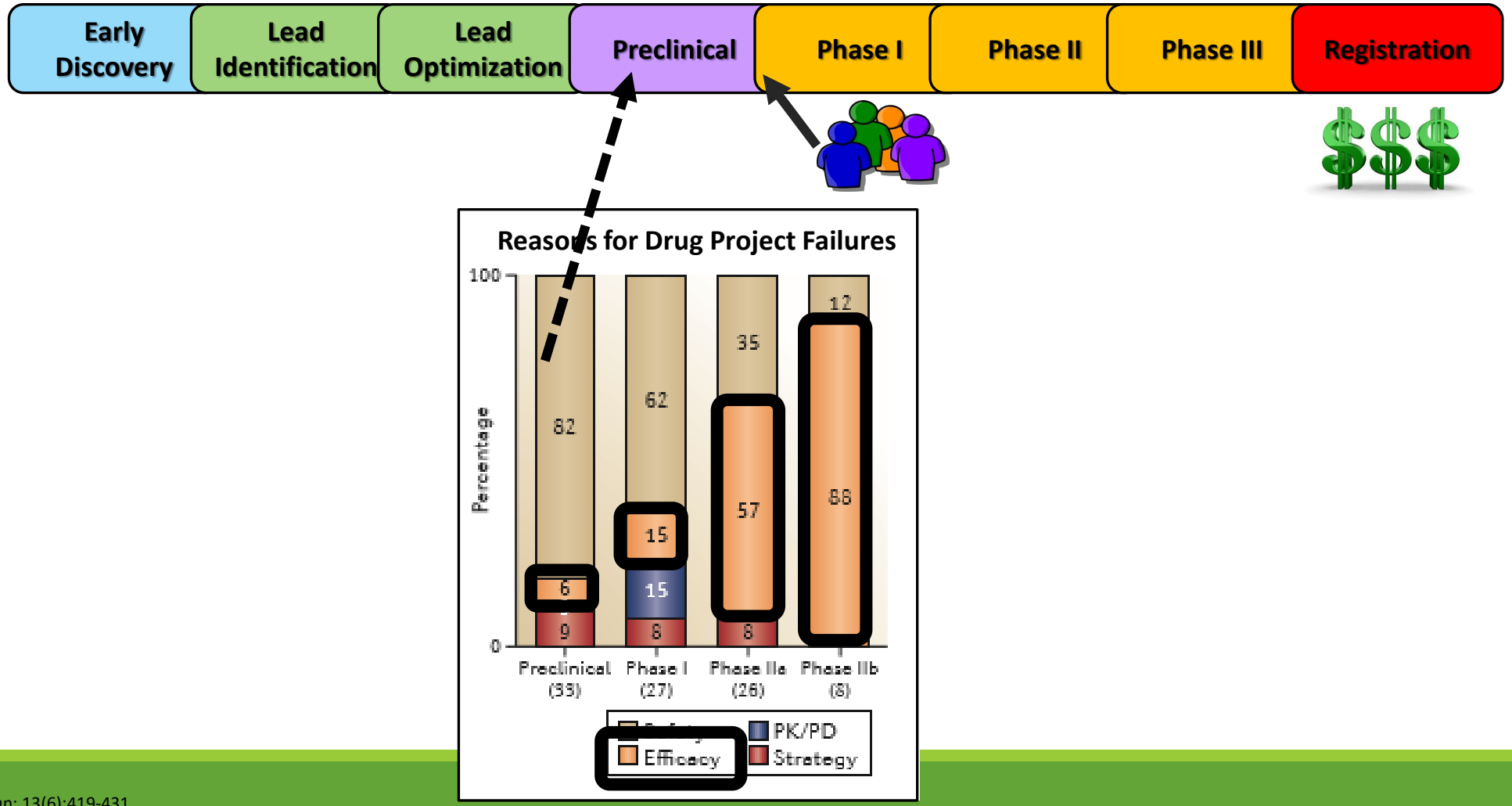
Poll Answer

True or False ?

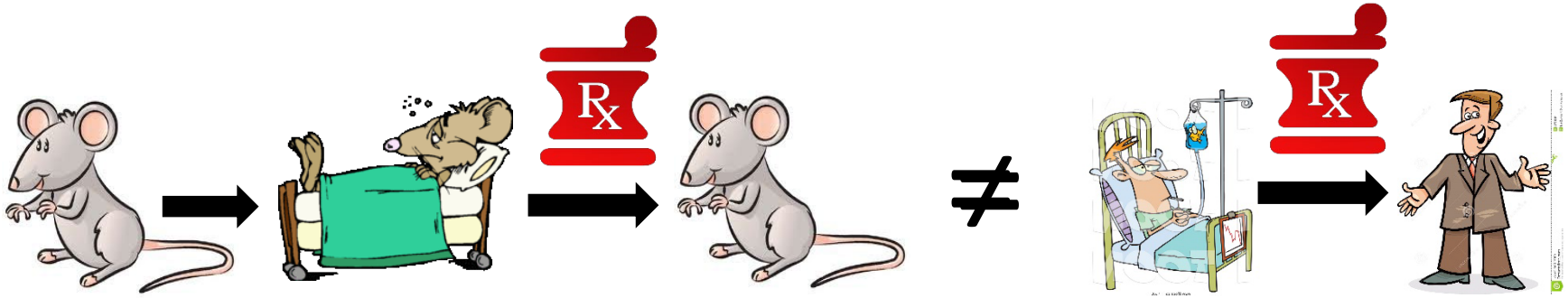
A good predictor of clinical efficacy (i.e. ,the drug will cure or decrease the effects of the disease) is how it performs in an animal disease model ?

FALSE

Animal Disease Models Poorly Predict Efficacy in Humans



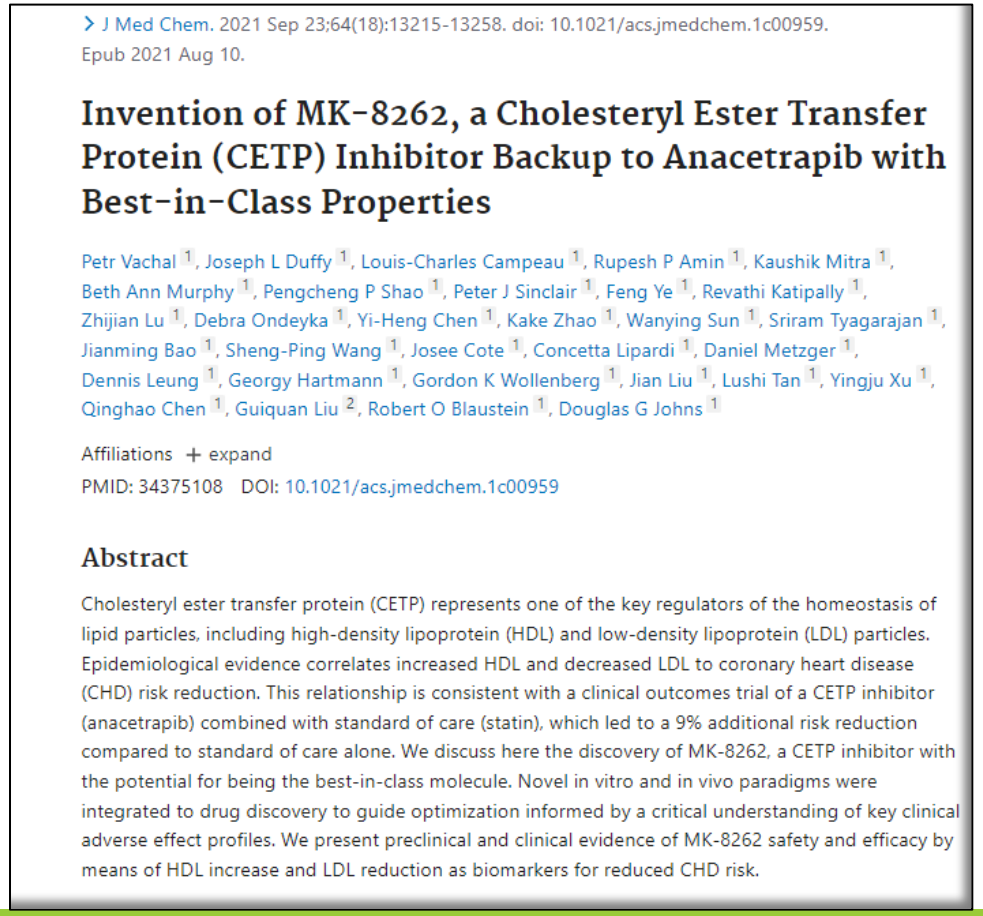
Animal Disease Models Poorly Predict Efficacy in Humans



- Genetic
- Surgical Manipulation
- Mimic a chronic condition in an acute time-frame.
- Apply animal behavior to a human behavior.

? Why use them ?

EXAMPLE: Use of a Mouse Model to Optimize Therapeutic Index.



J Med Chem. 2021 Sep 23;64(18):13215-13258. doi: 10.1021/acs.jmedchem.1c00959. Epub 2021 Aug 10.

Invention of MK-8262, a Cholesteryl Ester Transfer Protein (CETP) Inhibitor Backup to Anacetrapib with Best-in-Class Properties

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Affiliations + expand

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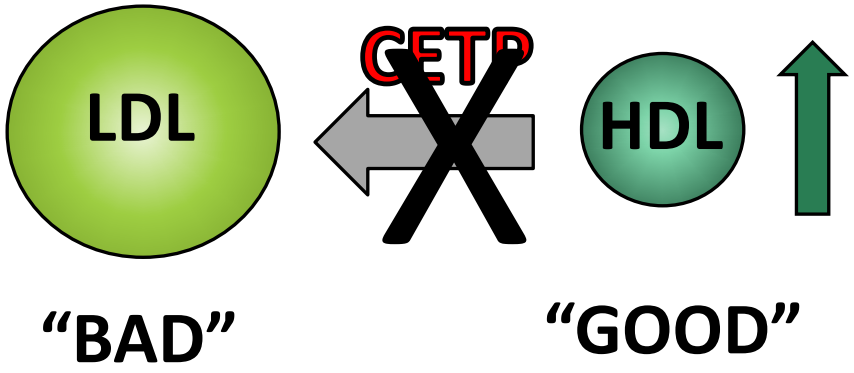
Abstract

Cholesteryl ester transfer protein (CETP) represents one of the key regulators of the homeostasis of lipid particles, including high-density lipoprotein (HDL) and low-density lipoprotein (LDL) particles. Epidemiological evidence correlates increased HDL and decreased LDL to coronary heart disease (CHD) risk reduction. This relationship is consistent with a clinical outcomes trial of a CETP inhibitor (anacetrapib) combined with standard of care (statin), which led to a 9% additional risk reduction compared to standard of care alone. We discuss here the discovery of MK-8262, a CETP inhibitor with the potential for being the best-in-class molecule. Novel in vitro and in vivo paradigms were integrated to drug discovery to guide optimization informed by a critical understanding of key clinical adverse effect profiles. We present preclinical and clinical evidence of MK-8262 safety and efficacy by means of HDL increase and LDL reduction as biomarkers for reduced CHD risk.

CETP-Drug Target Background

Increase HDL → Protect from CVD



CETP Catalyzes the conversions of HDL to LDL

Inhibit CETP → Increase HDL → Protect from CVD

Rodents do not express CETP

ILLUMINATE Trial: 1st CETP inhibitor to Reach Clinical Trials

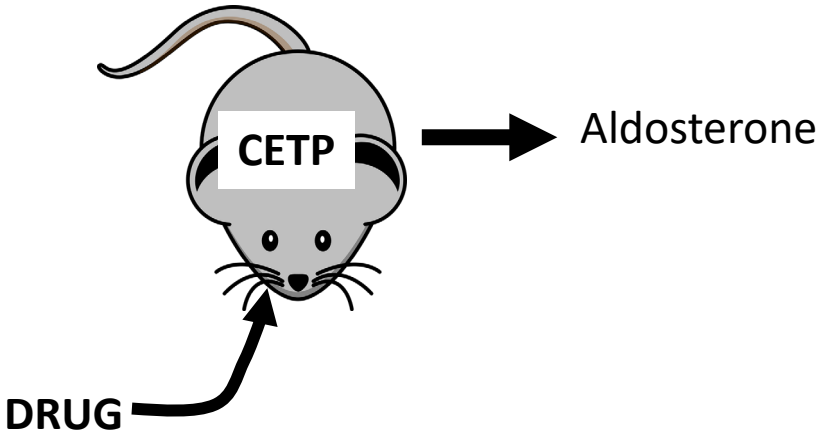
EFFECTS OF TORCETRAPIB IN PATIENTS AT HIGH RISK FOR CORONARY EVENTS.

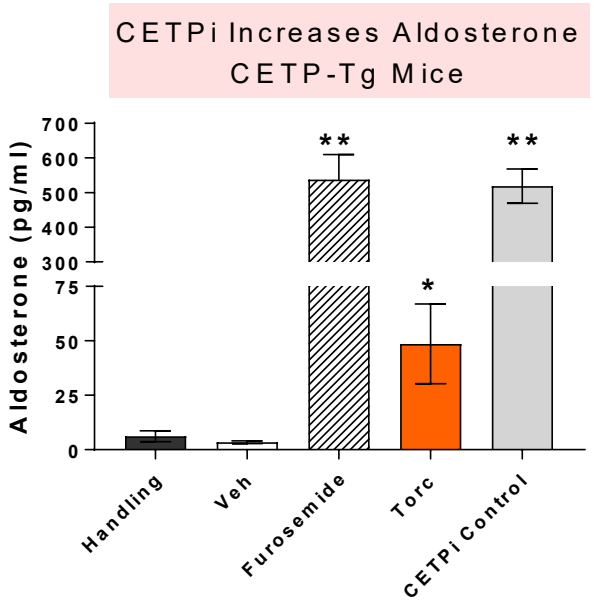
N Engl J Med. 2007 Nov 22;357(21):2109-22. Epub 2007 Nov 5

Highlights of ILLUMINATE TRIAL :

- **Stopped ~1 year increased risk of mortality and morbidity**
- Torcetrapib + atorvastatin (Lipitor), **raised HDL-C by 72%** and reduced LDL-C 25% vs. atorvastatin alone
- **25% increase in CV death, 58% increase in overall mortality**
- **Increase in aldosterone following three months**
- Increase in serum sodium and decrease in serum potassium.
- **Could not rule out that CETP inhibition was not the cause of the adverse events of torcetrapib.**

Experiments to Establish a Mouse Aldosterone Platform using CETP Transgenic Mice



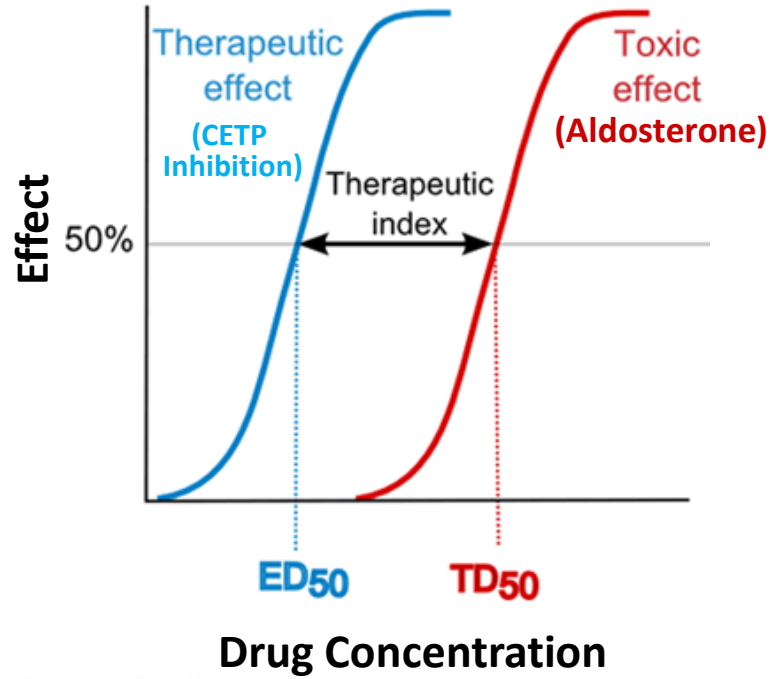


Able to measure changes aldosterone in CETP-tg mice using a protocol suited to support the scale of a lead optimization drug discovery program.

Therapeutic Index

The difference between of the amount of drug that causes the <u>therapeutic</u> <u>effect</u> to the amount that causes <u>toxicity</u>.

- **Therapeutic effect= CETP inhibition**
- **Toxicity= aldosterone NOEL**



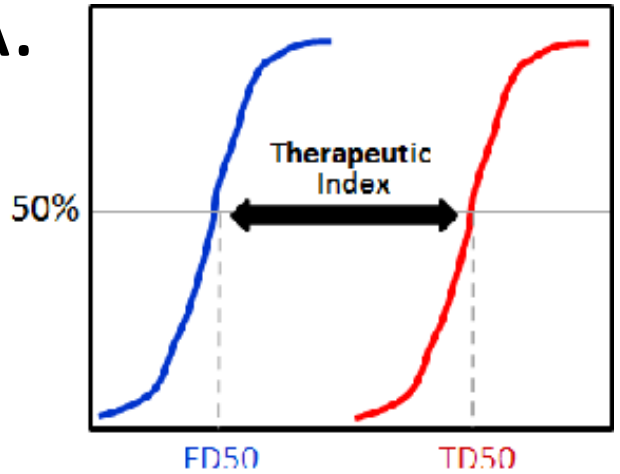
<u>ED 50</u>: The amount of drug that causes a therapeutic effect in 50% of a population.

<u>TD 50</u>: The amount of drug that causes a toxic effect in 50% of the studied population

Poll Question #2

Which is the less risky drug candidate?

A.



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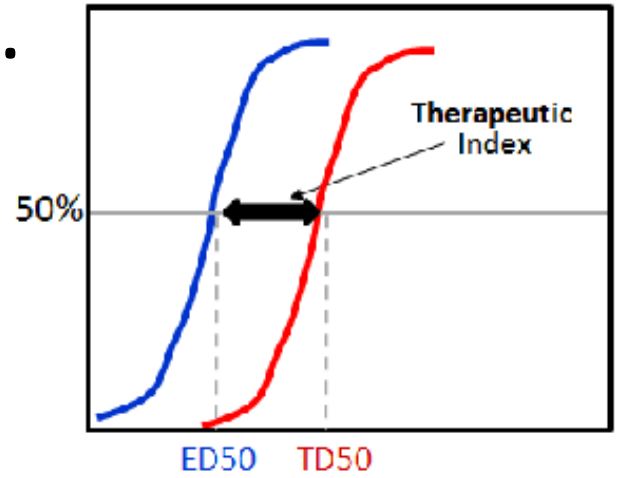
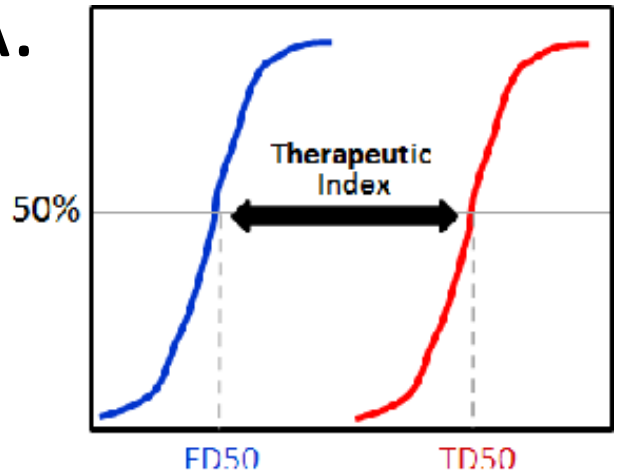


Poll Answer

A.



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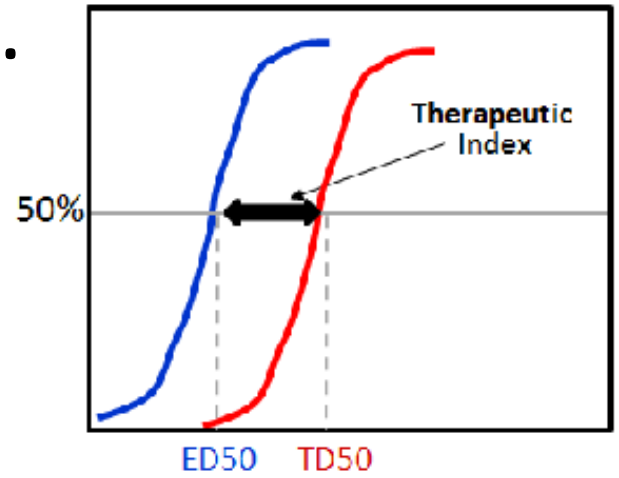
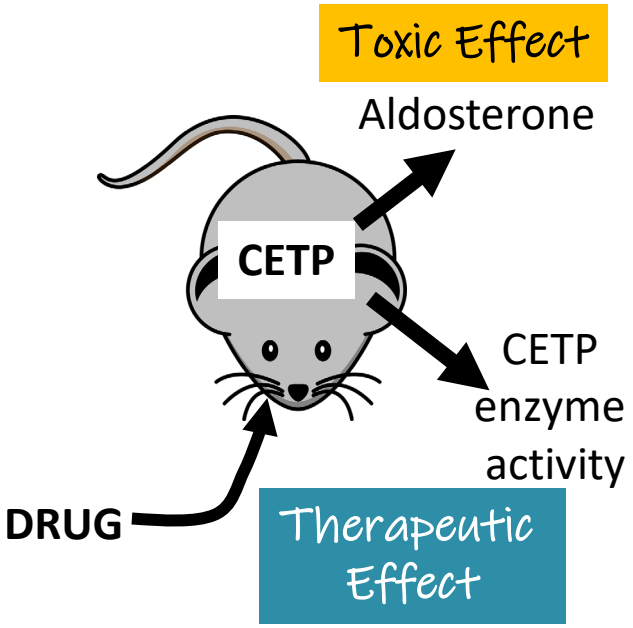
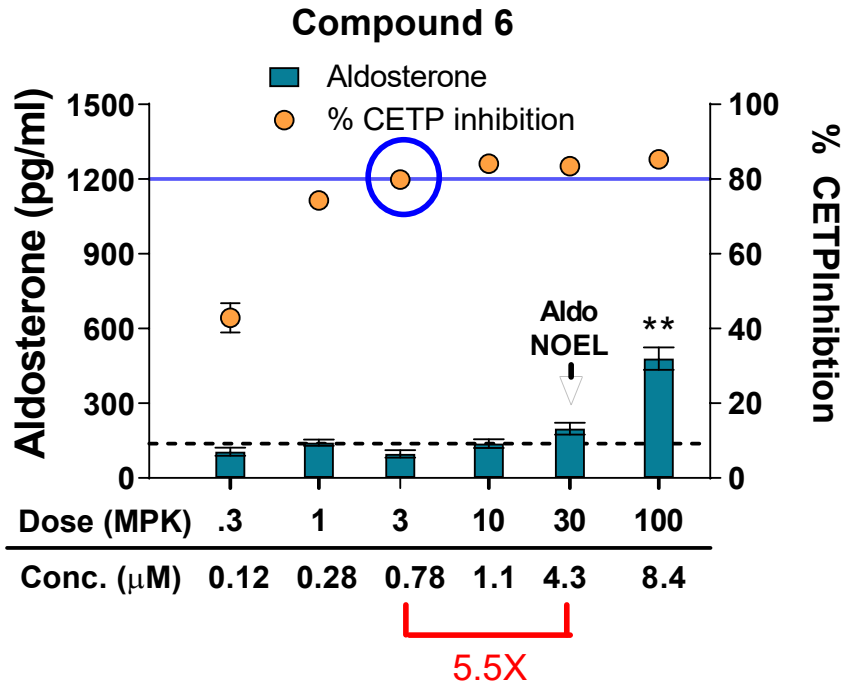
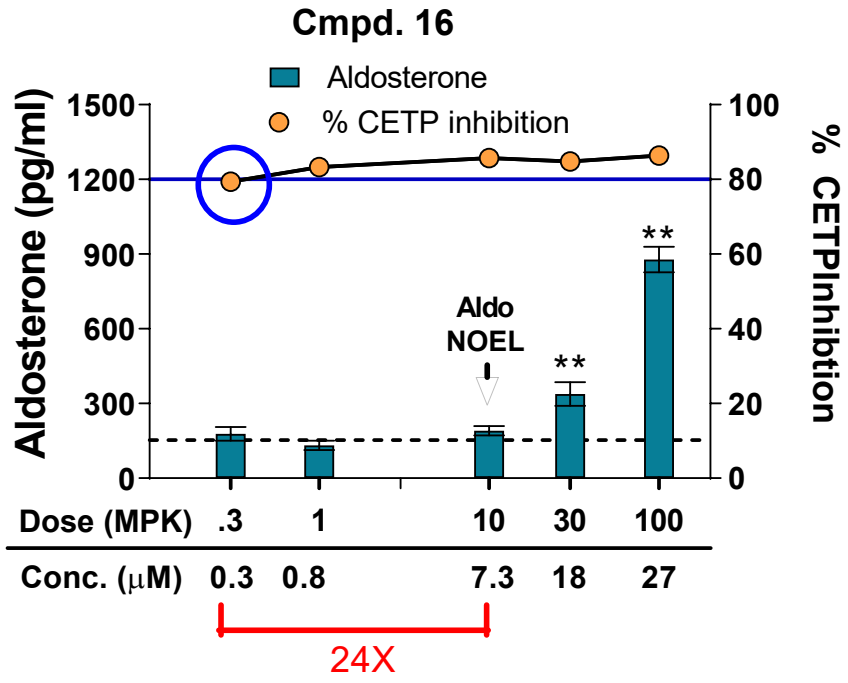
B.



Example: Use of in vivo pharmacology to determine therapeutic index







NOEL (No Observed Effect Level): smallest amount of a drug that causes an adverse effect

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Which is less risky to move forward in the drug discovery process?

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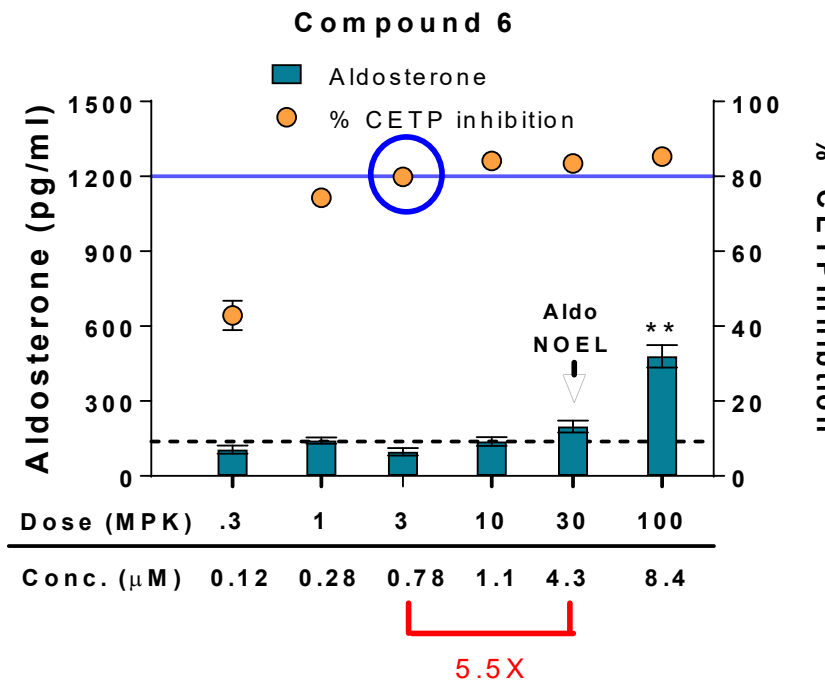
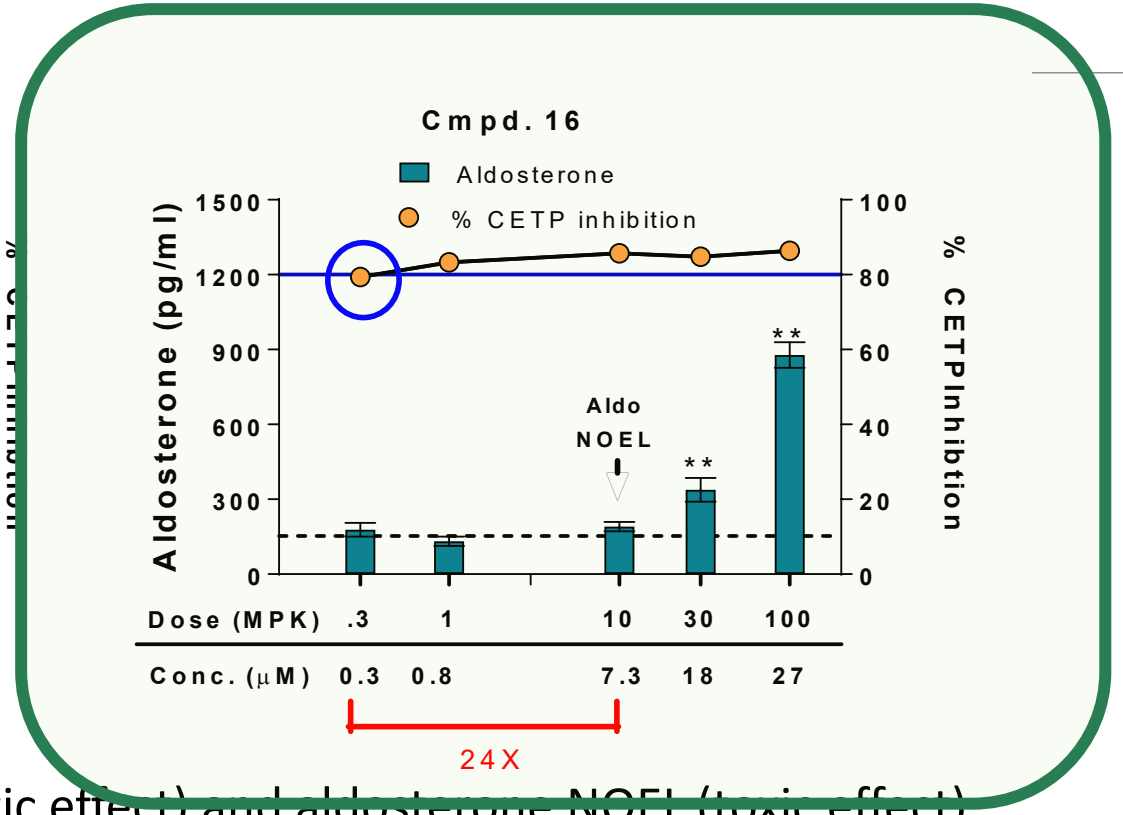
Estimate TI by Incorporating CETP inhibition measurement





- Estimate index between CETPi (therapeutic effect) and aldosterone NOEL (toxic effect).
- Index used to prioritize compounds.
- >250 compounds screened using this methodology.
- Program reached milestone 3 months ahead of schedule.

How did in vivo pharmacology help to advance the CETP inhibitor drug program?

- Prioritize compounds based on their CETPi-Therapeutic Index.
- Reduce the risk that a preclinical candidate would not carry the unwanted properties of torcetrapib.