So you have a target, now what?

From Targets to Clinical Candidates: Overview and Examples

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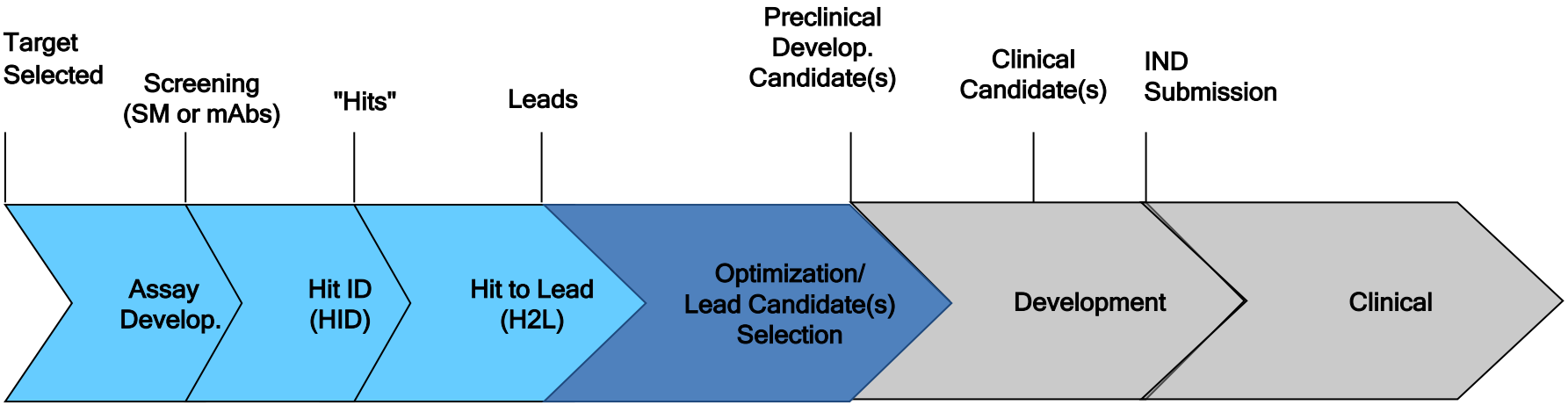
How do you want to approach the target?

- Small molecule:
  → Classical, many examples;
  -Both intra- and extra-cellular targets
  -Targets not amenable (un-druggable)
- Large molecule:
  → Very successful for cancer;
  - Antibodies,
  - Other types of proteins
  -Extracellular targets
- Cell therapy:
  - CAR-T
  →New, more complicated to develop
  -Extracellular targets
- Genetic therapy:
  - Gene therapy,
  - CRISPR
  →New, still being tested
  -Any type of target.

How do you go from a target to potential drug in the clinic?

Hits → leads → preclinical candidate → clinical candidate



How do you find “Hits” to get started ?

“Hits”: small molecules or antibodies that bind to your target and affect target activity.

- Develop and validate an assay
  - An assay is a quantitative method to measure the activity of your target at a molecular or cellular level.
  - Must be specific, sensitive, scalable, and consistent.
- Screen for “hits”
  - Small molecule: large compound library
  - Antibodies: hybridoma, phage display, direct B-cell cloning
- Confirm “hits” using independent assays
- Characterize hits
  - Small molecule: affinity? druggable? Soluble? Specific?
  - Antibodies: Affinity? Isotype? Binning? Epitope?

How do you prioritize your “Hits”?

- Potency: nM to uM, lower number is better, but not always.
- Efficacy: does it completely inhibit or activate your target? Partial vs full agonist/antagonist. Binding only? (antibodies for drug conjugates).
- Specificity: does it also “hit” target paralogs (related receptor/enzyme family members)?
- Druggability (small molecules): soluble? Easy to modify? Stable?

How do you make your “Hits” into “Leads”?

“Leads”: Small molecules or antibodies that have achieved efficacy in vivo.

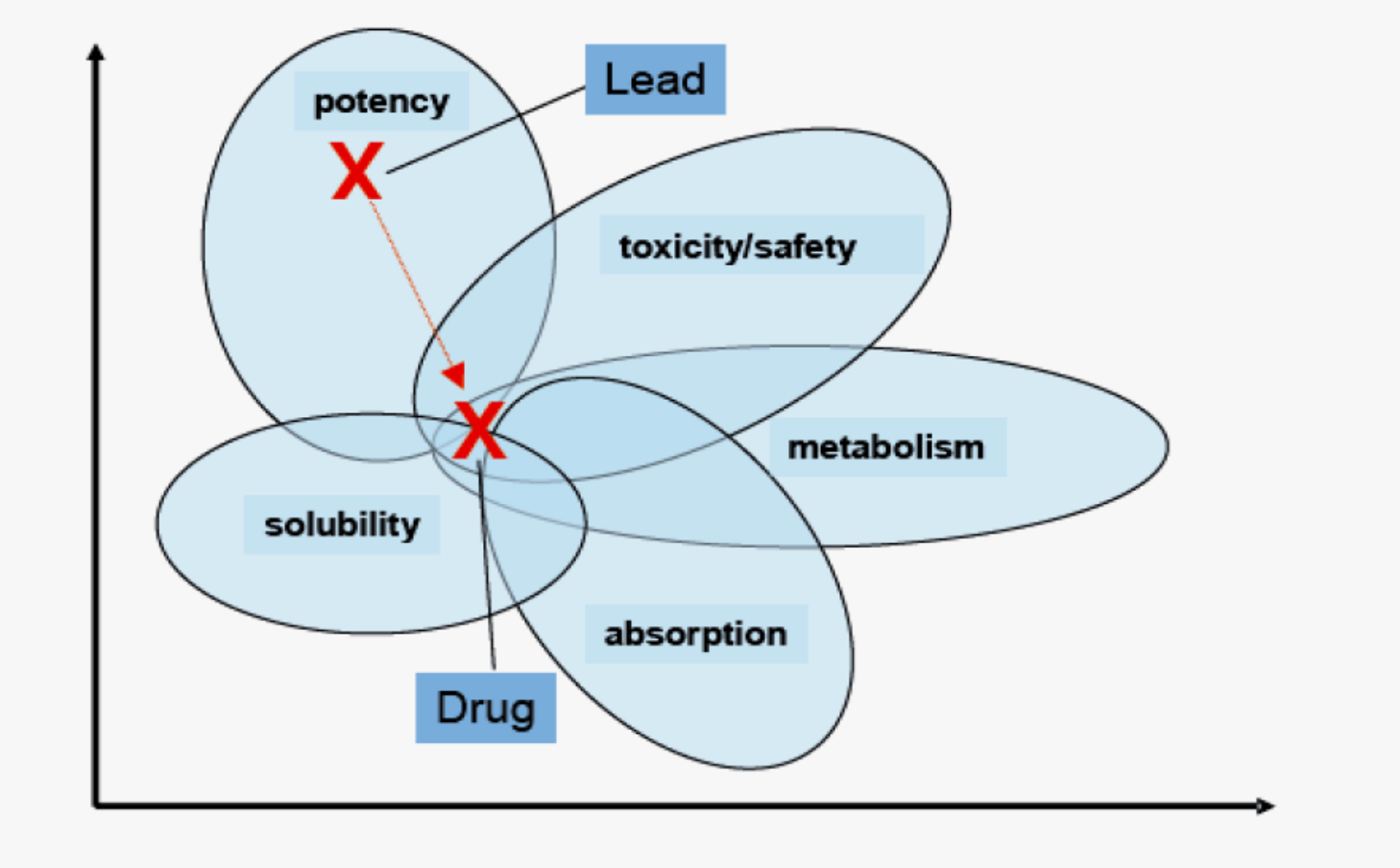
- Antibody “Hits” may be tested in vivo directly out of screening, and achieve efficacy.
  - If not, improve affinity by affinity maturation
- Small molecules often need improvement in potency and efficacy before achieving efficacy in vivo.
  - Chemists make modifications on the “Hits”.
  - You test the new compounds for potency and efficacy with in vitro assays
  - Compounds with sufficient potency and efficacy will be tested in vivo.
    - Compound stability in vivo (pharmacokinetics) needs to be determined for dosing regimen designs.

How do you make your “Leads” into preclinical development candidate?

This is commonly called “lead optimization”

- Small molecule:
  - Modify compounds to improve potency, efficacy, pharmacokinetics, toxicity, solubility, etc.
  - This is the most challenging phase of small molecular drug discovery.
- Antibodies
  - Affinity maturation to improve affinity and potency, and specificity.
  - Antibodies tend to have similar PK. But off-target toxicity could be a problem. Also, potential of anti-idiotype antibodies must be tested.

Lead optimization – finding the balance of drug-like properties



Pelkonen et al.: *Pharmacokinetic Challenges in Drug Discovery*. Springer-Verlag, 2002.

How do you make your preclinical candidate into a clinical candidate?

Preclinical development: the formal process of assessing a drug candidate for safety and manufacturing control. The data are used for the filing of IND (Investigational New Drug) application.

- Safety/toxicity
  - Two species (small molecule: rats and dogs; large molecules: rats/monkeys)
  - Systematic evaluation of PK, potential toxicity, and maximum tolerated dose with single and repeat dosing.
  - All studies must be done under GLP conditions.
- Chemistry, manufacturing, and controls (CMC)
  - Manufacturing process and facility
  - Quality control
  - Specification and stability of the product
  - All must be done under GMP/GLP conditions

If the candidate passes safety/toxicity standards and CMC, it becomes a clinical candidate.

From Assay Development to Clinical Candidate

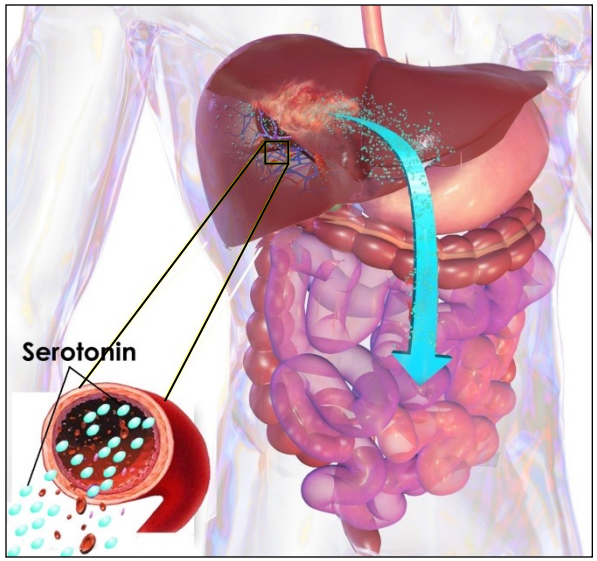
The case of discovering and developing inhibitors of tryptophan hydroxylase for the treatment of carcinoid syndrome

Carcinoid Tumor

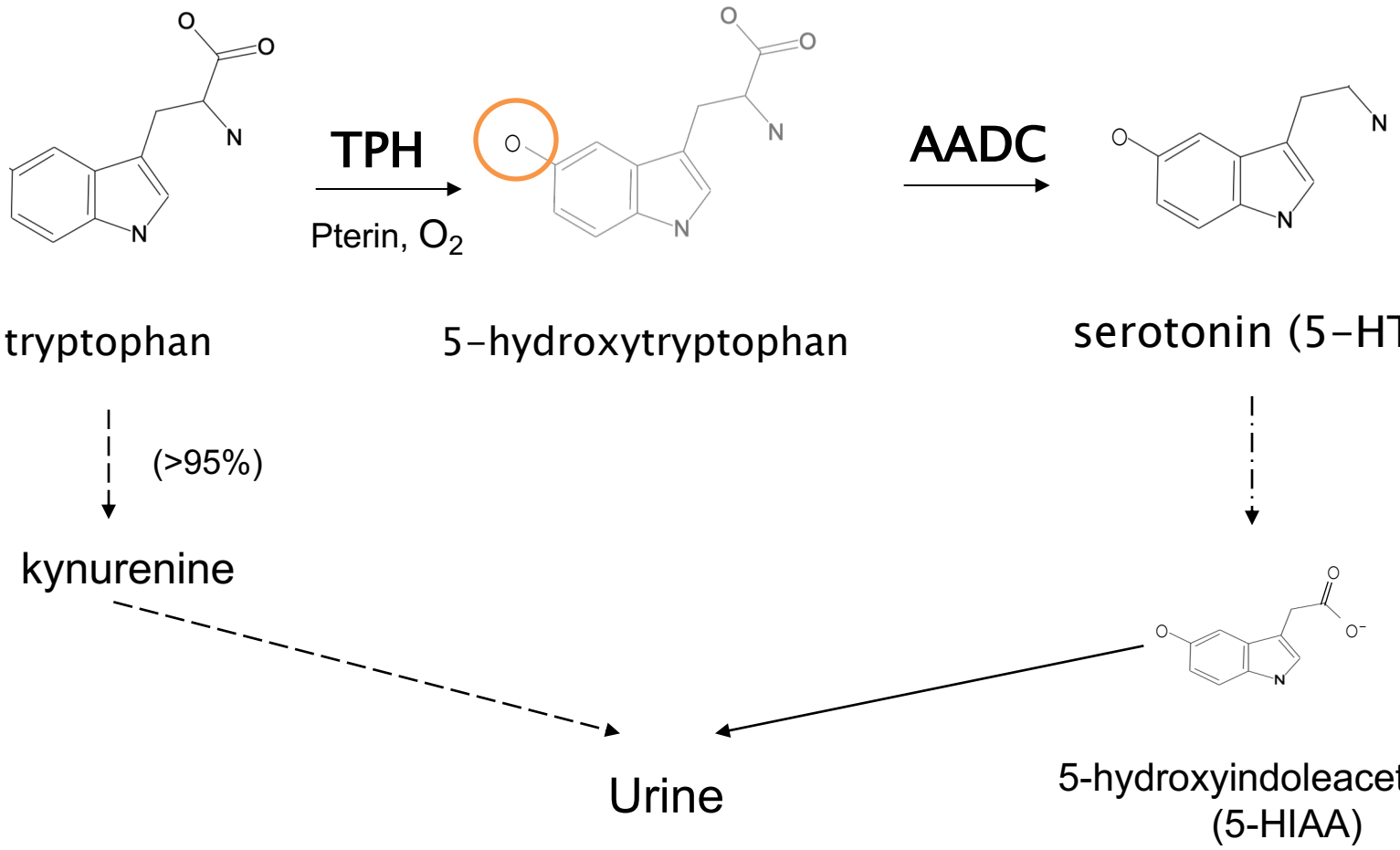
- Carcinoid = cancer-like, originally believed to be indolent and slow-growing
- One type of neuroendocrine tumor
- Most commonly found in the mid-gut
- Incidence = ~4/100,000, with steady increase.
- Often secret biologically active substances, such as serotonin, histamine, substance P
- 10% of patients with carcinoid tumor will progress into carcinoid syndrome

Carcinoid Syndrome

- Metastasis of serotonin-secreting carcinoid tumors to the liver leads to carcinoid syndrome
- Clinical symptoms:
  - Cutaneous flushing: upper part of the body (80%)
  - Watery diarrhea and abdominal cramp (80%)
  - Bronchospasm
  - Endocardial fibrosis(30-40 %): arrhythmia. Right heart insufficiency.
- Excessive serotonin production by the tumors is believed to be responsible for the diarrhea and endocardial fibrosis
- Current treatment
  - Somatostatin analogs for symptomatic relief.
  - However, almost all patients will eventually escape from such treatment

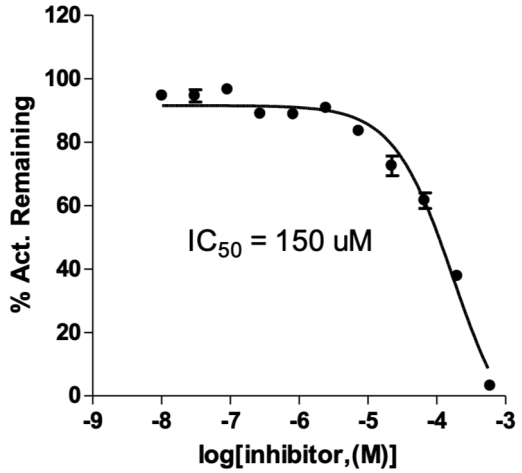


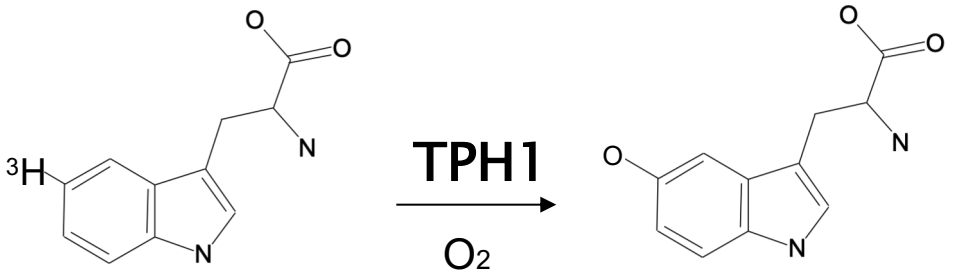
Synthesis of Serotonin (5-Hydroxytryptamine, 5-HT) Is Initiated by Tryptophan Hydroxylase (TPH)



HTS Assay Was Developed Using Purified Recombinant Human TPH1

Human TPH1
(650 nmole/min/mg)





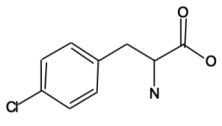
(absorbed by charcoal)

+ ^{3}H O H

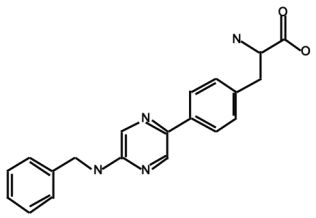
(NOT absorbed by charcoal)

(Vrana *et al*., 1993, J. Neurosci. Methods, 48:123-129)

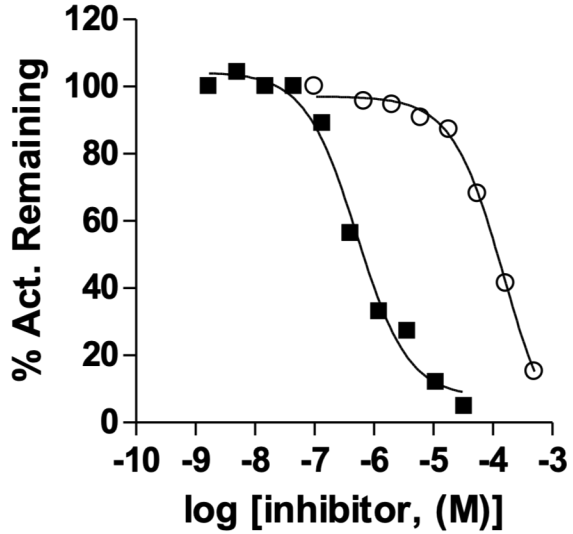
Screening of 200,000 Compounds Identified Several Series of Novel, More Potent TPH1 Inhibitors



pCPA



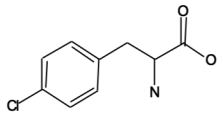
Compound 1a



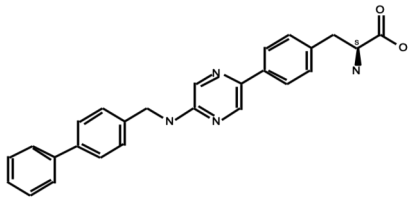
○ pCPA
(IC_{50} = 150 uM)

■ Compound 1a
(IC_{50} = 0.6 uM)

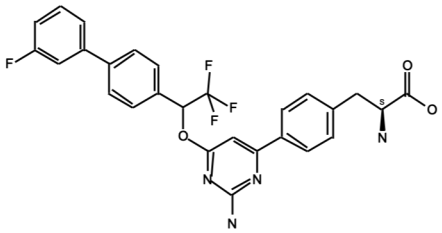
Cell Based Assay Is Critical to Differentiation of Compounds



pCPA

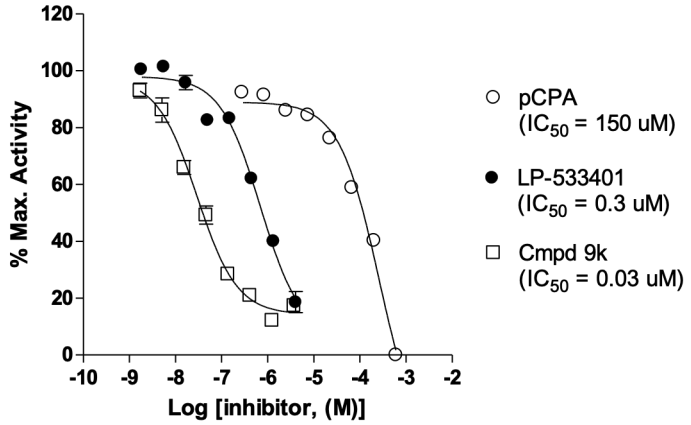


Compound 9k

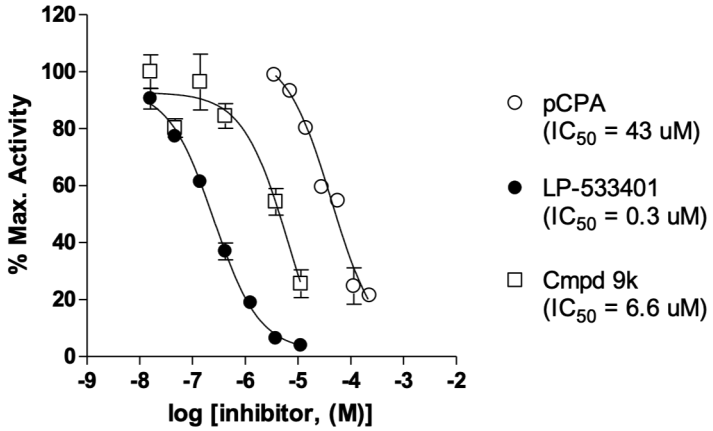


LP-533401

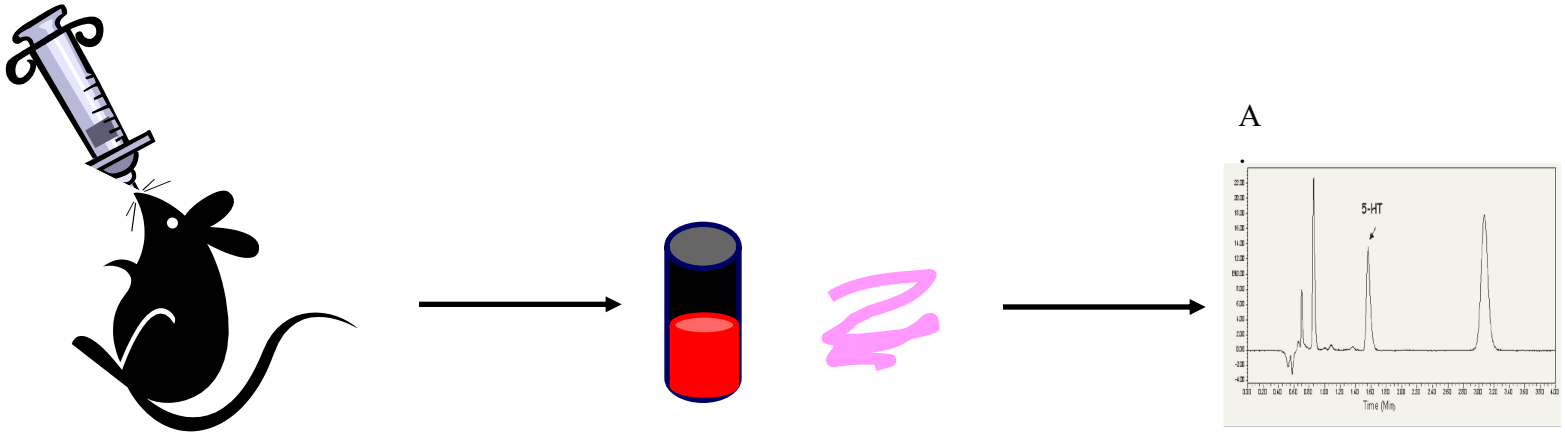
Enzyme assay



RBL-2H3 Cell Assay



Compounds Were Evaluated *in vivo* for Serotonin Reduction

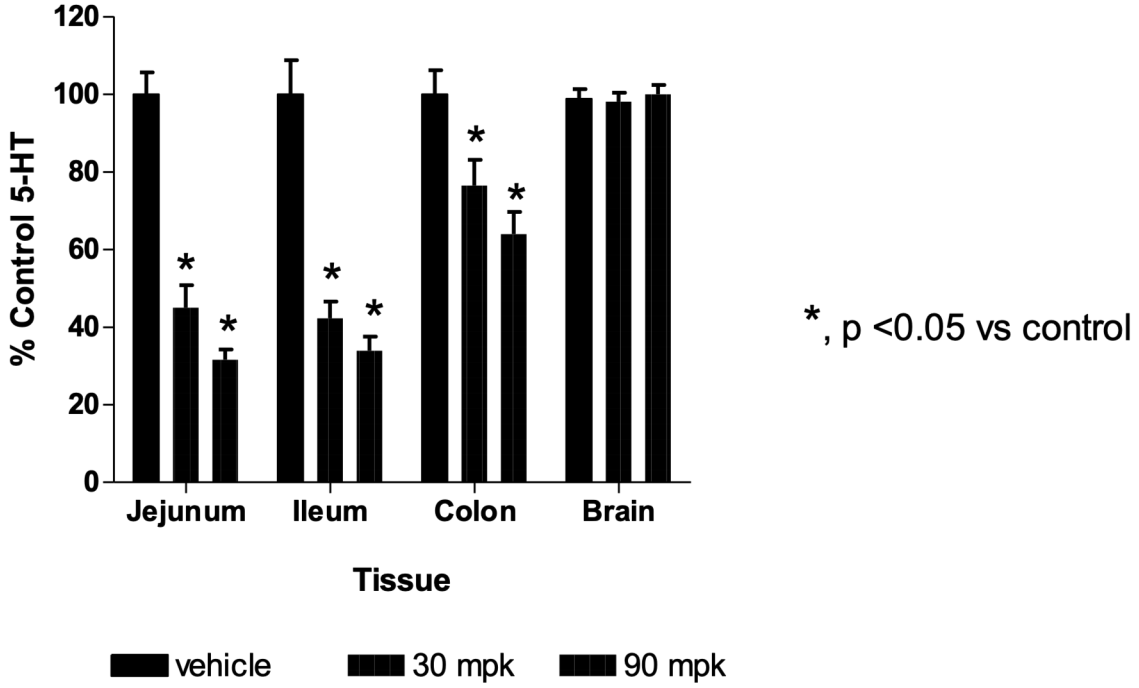


Oral gavage, daily, 3-4 days

Necropsy

Serotonin analysis

LP-533401 Reduces Serotonin Levels In the Gut But not In the Brain



(Liu et al., J Pharmacol Exp Ther. 2008, 325:47-55)

LX1032 (Xermelo™) Was Approved by FDA

FDA News Release

FDA approves Xermelo for carcinoid syndrome diarrhea

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For Immediate Release

February 28, 2017

Release

The U.S. Food and Drug Administration today approved Xermelo (telotristat ethyl) tablets in combination with somatostatin analog (SSA) therapy for the treatment of adults with carcinoid

- Phase 2-3 clinical trials of LX1042 (Telotristat etiprate) were completed successfully
- On March 30, 2016, Lexicon Submitted New Drug Application (NDA) to FDA for Telotristat Etiprate for the Treatment of Carcinoid Syndrome.
- On May 31, 2016 Lexicon Announced FDA Priority Review of NDA for Telotristat Etiprate for the Treatment of Carcinoid Syndrome.
- On Feb. 28, 2017, FDA Approved Xermelo for carcinoid syndrome.
- On Mar. 1, Xermelo was available.