# Bench to Bedside, Clinical Trials

## TRACO-Translational Research : Bench to Bedside, Clinical Trials

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# Disclosure

Disclosure

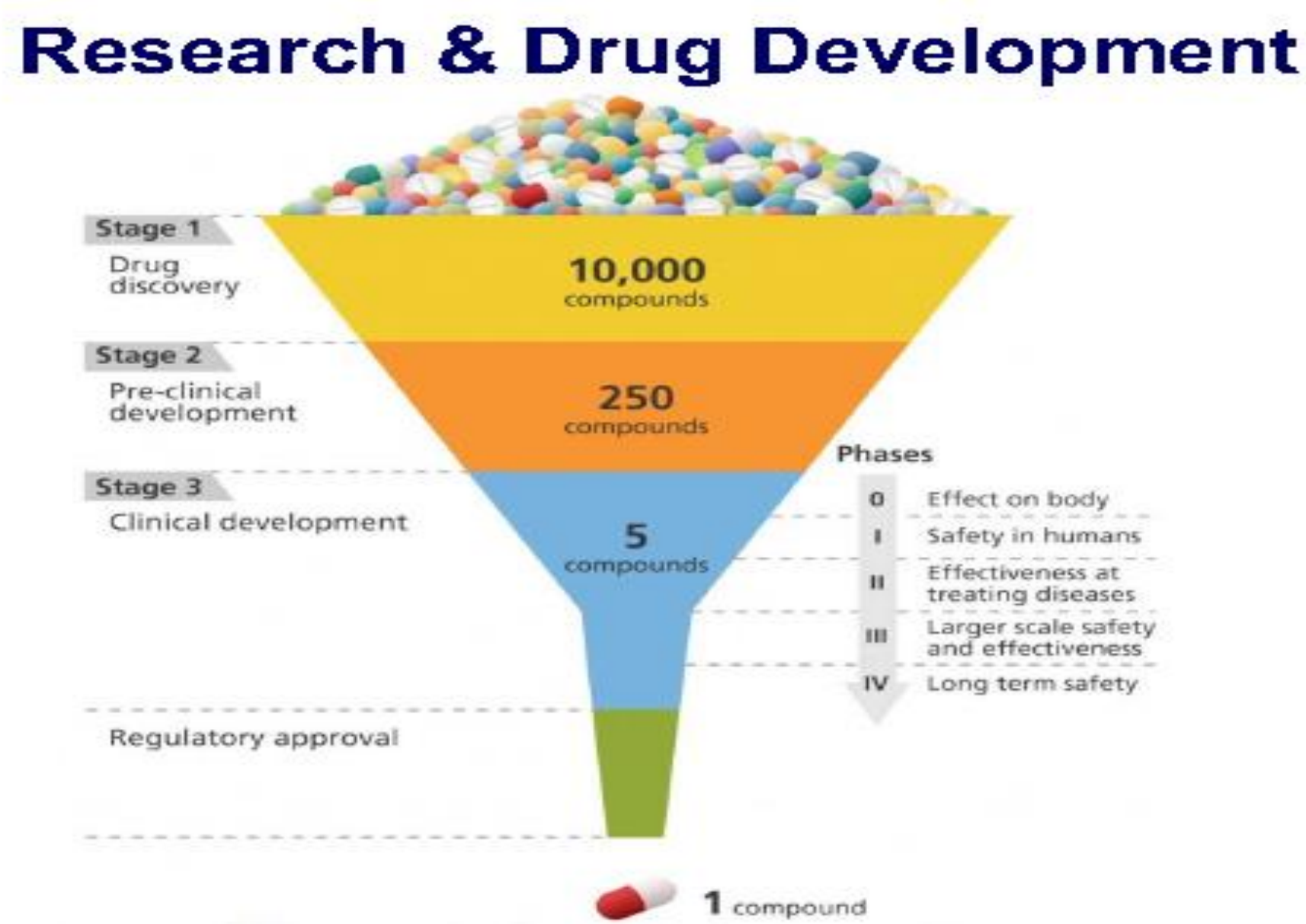
As a child I wanted to become a veterinarian but my guidance counselor told me ‘girls can’t do that.” So I told him I would become a doctor.

# OBJECTIVES

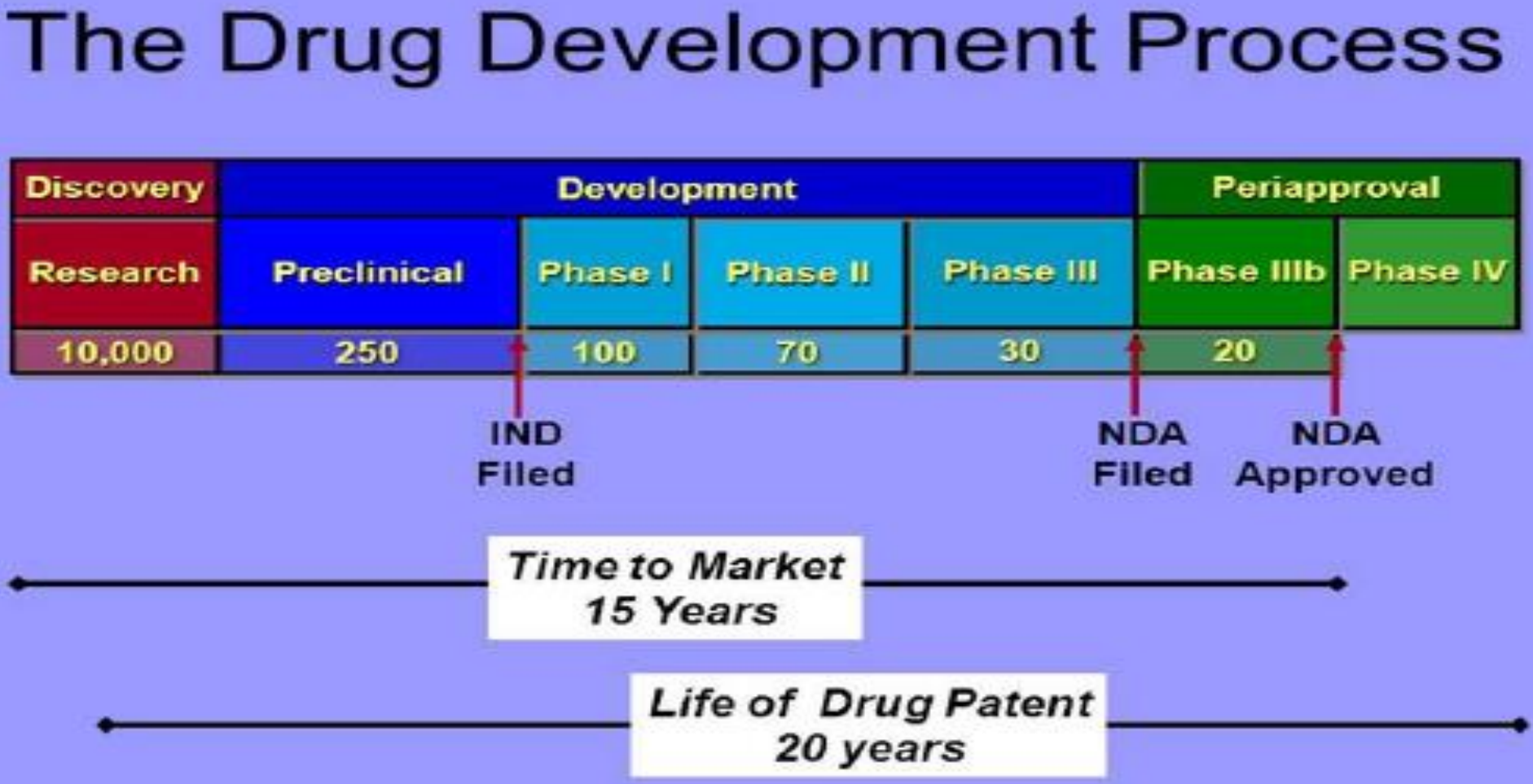
OBJECTIVES

- Understand how an idea is taken from the research lab to patient care.
- Learn the steps in conducting clinical trials
- Understand some of the obstacles to overcome in drug development?
- Examples of my translational projects

# Research and drug development



# Drug development process



# Ideas

You need an Idea

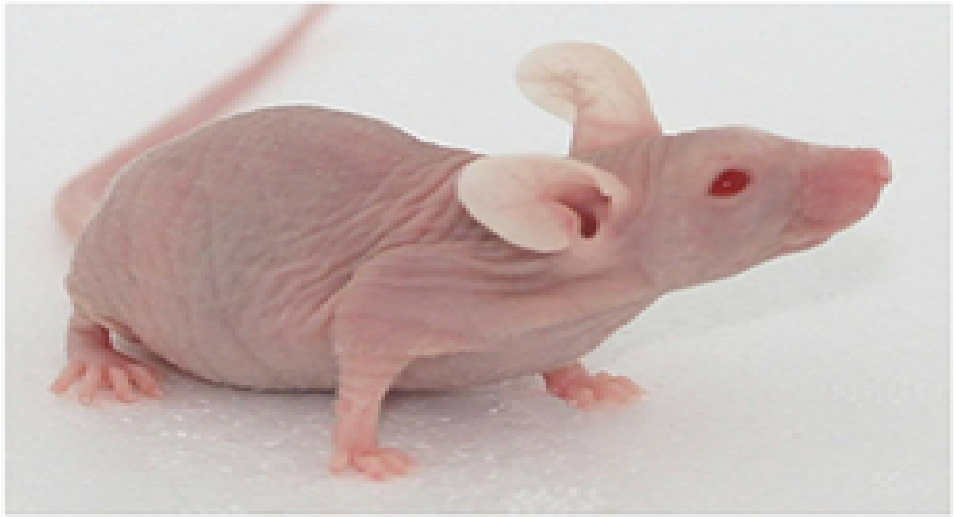
**Hypothesis**

**Passion!!**

# Preclinical studies

## Preclinical Studies

Preclinical Testing: research lab conducts certain studies before the future drug is ever given to a human being. Laboratory and animal studies must be done to demonstrate the biological activity of the drug against the targeted disease. The drug must also be evaluated for safety. These tests take on the average 3 1/2 years.



# Calculating human dose

## Calculating human dose from animal study

Nair AB, Jacob S. Journal of Basic and Clinical Pharmacy. 2016;7(2):27-31.

| Species | Reference body weight (kg) | Working weight range (kg) | Body surface area ($m^2$) | To convert dose in mg/kg to dose in $mg/m^2$, multiply by $K_m$ | To convert animal dose in mg/kg to HED in mg/kg, either | |
|---|---|---|---|---|---|---|
| | | | | | Divide animal dose by | Multiply animal dose by |
| Human | 60 | - | 1.62 | 37 | - | - |
| Mouse | 0.02 | 0.011-0.034 | 0.007 | 3 | 12.3 | 0.081 |
| Hamster | 0.08 | 0.047-0.157 | 0.016 | 5 | 7.4 | 0.135 |
| Rat | 0.15 | 0.08-0.27 | 0.025 | 6 | 6.2 | 0.162 |
| Ferret | 0.30 | 0.16-0.54 | 0.043 | 7 | 5.3 | 0.189 |
| Guinea pig | 0.40 | 0.208-0.700 | 0.05 | 8 | 4.6 | 0.216 |
| Rabbit | 1.8 | 0.90-3.0 | 0.15 | 12 | 3.1 | 0.324 |
| Dog | 10 | 5-17 | 0.50 | 20 | 1.8 | 0.541 |
| Monkeys (rhesus) | 3 | 1.4-4.9 | 0.25 | 12 | 3.1 | 0.324 |
| Marmoset | 0.35 | 0.14-0.72 | 0.06 | 6 | 6.2 | 0.162 |
| Squirrel monkey | 0.60 | 0.29-0.97 | 0.09 | 7 | 5.3 | 0.189 |
| Baboon | 12 | 7-23 | 0.60 | 20 | 1.8 | 0.541 |
| Micro pig | 20 | 10-33 | 0.74 | 27 | 1.4 | 0.730 |
| Mini pig | 40 | 25-64 | 1.14 | 35 | 1.1 | 0.946 |

*Data obtained from FDA draft guidelines.[7] FDA: Food and Drug Administration, HED: Human equivalent dose

The dose by factor method applies an exponent for body surface area (0.67), which account for difference in metabolic rate, to convert doses between animals and humans. Thus, HED is determined by the equation:

$$HED\ (mg/kg) = Animal\ NOAEL\ mg/kg) \times (Weight_{animal}\ [kg]/Weight_{human}\ [kg])^{(1-0.67)}$$

[no observed adverse effect levels (NOAEL) from preclinical research]

# Phase 1

## Phase 1

- 15-30 people
- Determines
  - what dose is safe?
  - How the treatment should given?
  - Pharmacokinetics?
  - How the treatment affects the body?
  - Safety & toxicity

How much?

What route of administration?

# Pilot Study

## Pilot Study

- A small study that helps develop a bigger study
- A first venture into a particular area
- Used to iron out possible difficulties, and help with design of the bigger, more pivotal study.
- Helps provide ‘tentative response rate’ to estimate the sample size needed in a Phase 2 trial to reach significance over control

# Phase 2

## Phase 2: Efficacy

- Less than 100 people
- Must have a primary endpoint
- Usually unbiased (blinded)
- Determines
  - Does it work?
  - Is it more effective than a placebo?
  - Does not compare with other treatments

# Phase 3

## Phase 3

- From 100 to thousands of people
- Equal chance to be assigned to one of two or more groups
- Determines
  - How the new treatment compares with the current standard
  - Or how it compares with placebo
  - Superiority or non-inferiority trials

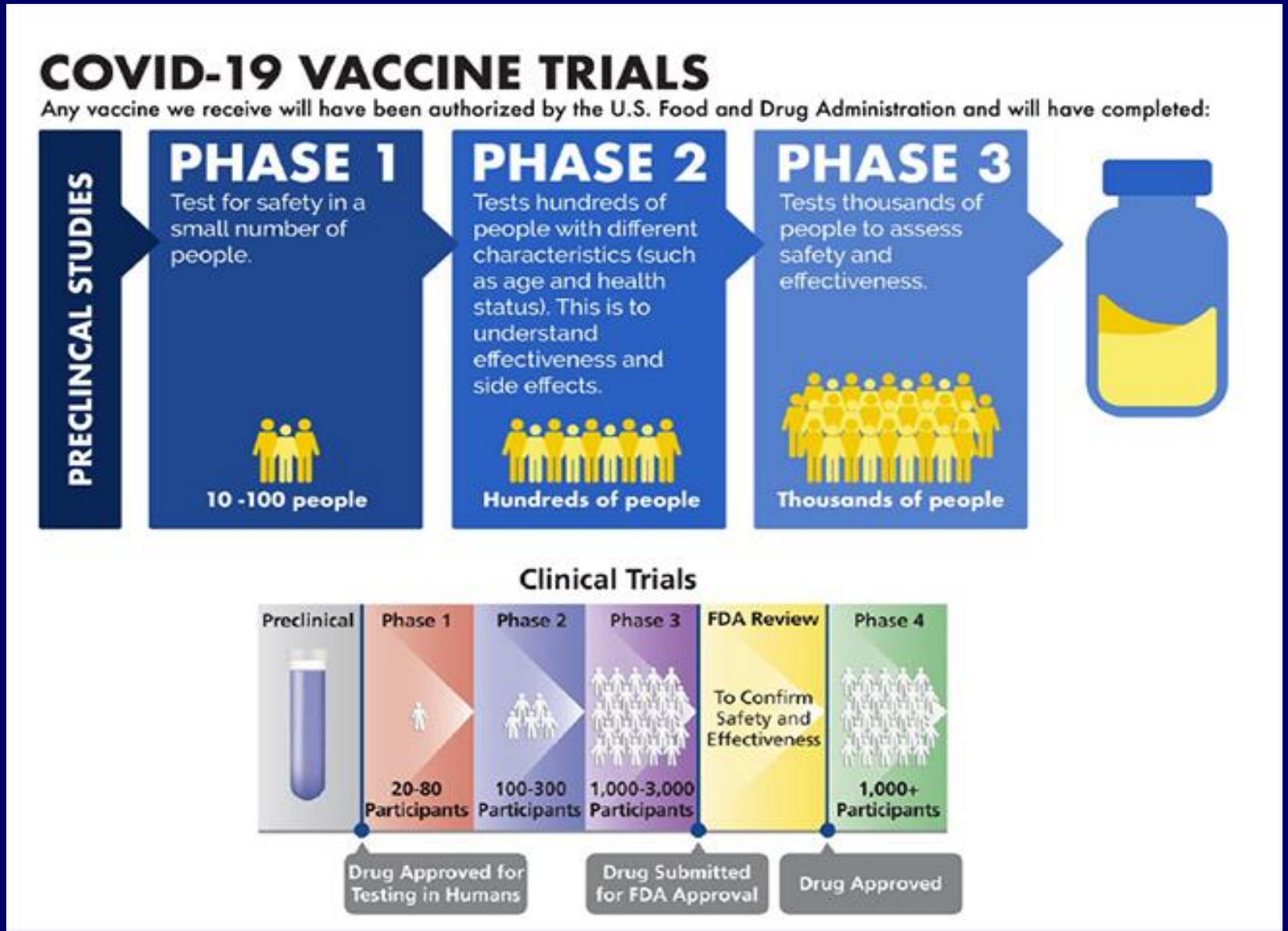
# Phase 4

## Phase 4

- From hundreds to thousands of people
- Usually takes place after drug is approved to provide additional information on the drug's risks, benefits and optimal use
- Called 'Post-marketing" or

Or post-approval trials

# COVID-19

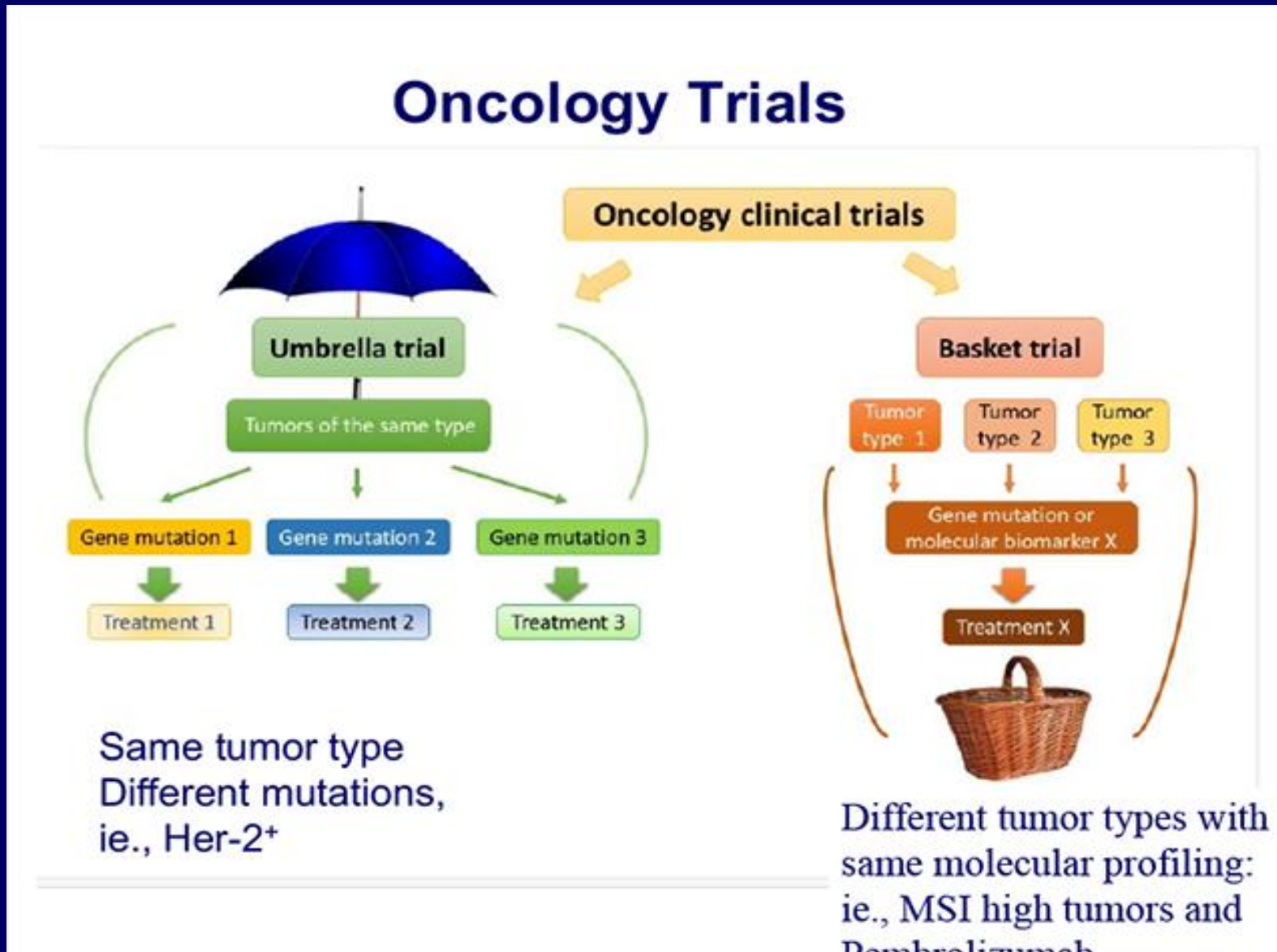

COVID-19 VACCINE TRIALS
Any vaccine we receive will have been authorized by the U.S. Food and Drug Administration and will have completed:
PRECLINCAL STUDIES
PHASE 1
Test for safety in a small number of people.
10 -100 people
PHASE 2
Tests hundreds of people with different characteristics (such as age and health status). This is to understand effectiveness and side effects.
Hundreds of people
PHASE 3
Tests thousands of people to assess safety and effectiveness.
Thousands of people
Clinical Trials
Preclinical
Phase 1
20-80 Participants
Phase 2
100-300 Participants
Phase 3
1,000-3,000 Participants
FDA Review
To Confirm Safety and Effectiveness
Phase 4
1,000+ Participants
Drug Approved for Testing in Humans
Drug Submitted for FDA Approval
Drug Approved

# Adoptive Design Trials

## Adaptive Design Trials

- Group sequential designs allow for prospectively planned interim analyses and possible early stopping due to efficacy, futility, or harm.
- Adaptive Enrichment: provides the ability to drop lower performing subgroups at an interim analysis so that study resources are more efficiently allocated to those with a greater chance of benefit.
- Adaptive Randomization: addresses the limitations of stratified block randomization; allowing for more
- flexibility and options including weighting of covariates.

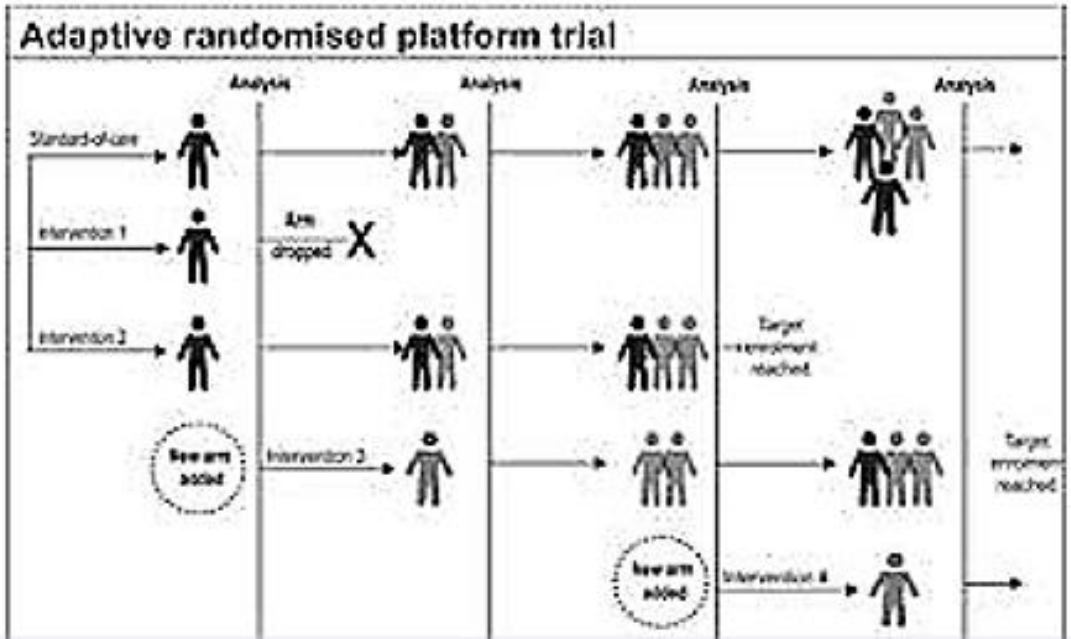
# Oncology trials



# Platform Trials

## Platform Trials

Investigates multiple therapies in one or more diseases in an ongoing manner with arms added or dropped as new data and evidence appear, often using Bayesian methods based on probabilities of treatment success or failure. The Bayesian statistics augments and increases the precision of the information from a current trial by the incorporation of prior information.



# Trial Design Considerations

## Trial Design Considerations

- Unequal randomization: i.e., 2:1 randomization may be preferable if there is prior evidence of a favorable benefit-risk profile.
- Crossover, an intercurrent event, allows patients access to promising agents if they have progressed on the control arm, but may have an impact on the interpretation of endpoints measured later in the
- trial, such as OS.
- Change the p value desired for results.

# Sample Size Calculations

## Sample Size calculations

Cochran's sample size formula

$$n_0 = \frac{z^2 \cdot p \cdot (1 - p)}{e^2}$$

Cochran's sample size formula where "n" is the required sample size, "z" is the z-score based on the desired confidence level, "p" is the estimated proportion of the population with the attribute of interest, and "e" is the margin of error (desired level of precision).

- Level of significance (what is acceptable as an error rate). This is the p-value, such as 95% ($\alpha = 0.05$)
- Power, The power of the study increases with the decrease in the chance of committing a Type II error. Usually 80% is an acceptable level for the power of a study.
- Type 1 error: False positive / Type II error: False negative

# FDA expedited approval

## FDA expedited approval programs for new drugs

- **Accelerated approval:** allows for the approval of drugs that treat serious conditions and fill unmet medical needs
- **Fast track:** expedites the review of drugs that treat serious conditions
- **priority review:** expedited review with the same rigor as standard review
- **breakthrough therapy:** drugs which may demonstrate substantial improvement over available therapy

# Patient rights

## How Are Patients' Rights Protected?

- Ethical and legal codes that govern medical practice also apply to clinical trials
- Informed consent
- Review boards
  - Scientific review
  - Institutional review boards (IRBs)
  - Data safety and monitoring boards

**Genetic testing**
**Add to consent**

# IND

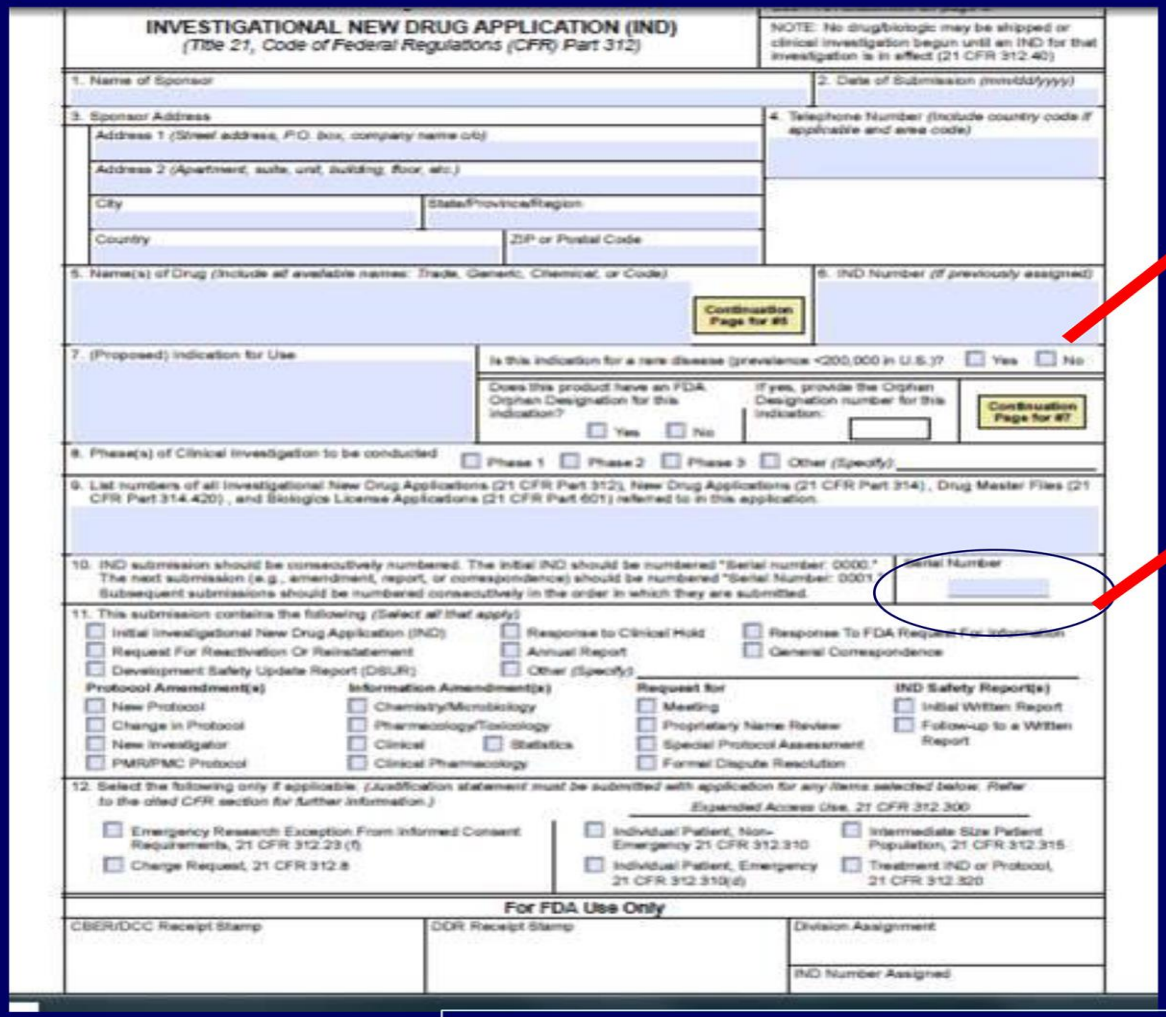
## Investigational New Drug (IND) Application

- **Need approval from FDA**
  - **Apply for and IND# (investigational new drug#)**
  - **1571 and 1572**

The IND becomes effective if the FDA does not disapprove it within 30 days.
The IND must include the following information: the results of previous experiments; how, where and by whom the new studies will be conducted; the chemical structure of the compound; how it is thought to work in the body; any toxic effects found in the animal studies; and how the compound is manufactured. The IND must also be reviewed and approved by the Institutional Review Board where the studies will be conducted.

# FDA forms

## FDA 1571 and 1572 forms, info about sponsor & drug



**INVESTIGATIONAL NEW DRUG APPLICATION (IND)**
*(Title 21, Code of Federal Regulations (CFR) Part 312)*

NOTE: No drug/biologic may be shipped or clinical investigation begun until an IND for that investigation is in effect (21 CFR 312.40)

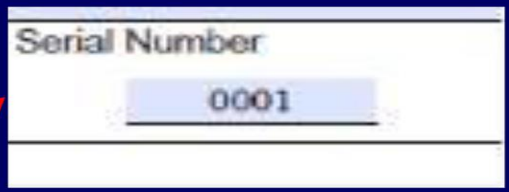
1. Name of Sponsor
2. Date of Submission (mm/dd/yyyy)
3. Sponsor Address
Address 1 (Street address, P.O. box, company name c/o)
Address 2 (Apartment, suite, unit, building, floor, etc.)
City
State/Province/Region
Country
ZIP or Postal Code
4. Telephone Number (Include country code if applicable and area code)
5. Name(s) of Drug (Include all available names: Trade, Generic, Chemical, or Code)
Continuation Page for #5
6. IND Number (If previously assigned)
7. (Proposed) Indication for Use
Is this indication for a rare disease (prevalence <200,000 in U.S.)? Yes No
Does this product have an FDA Orphan Designation for this indication? Yes No
If yes, provide the Orphan Designation number for this indication:
Continuation Page for #7
8. Phase(s) of Clinical Investigation to be conducted: Phase 1 Phase 2 Phase 3 Other (Specify)
9. List numbers of all Investigational New Drug Applications (21 CFR Part 312), New Drug Applications (21 CFR Part 314), Drug Master Files (21 CFR Part 314.420), and Biologics License Applications (21 CFR Part 601) referred to in this application.
10. IND submission should be consecutively numbered. The initial IND should be numbered "Serial number: 0000." The next submission (e.g., amendment, report, or correspondence) should be numbered "Serial Number: 0001." Subsequent submissions should be numbered consecutively in the order in which they are submitted.
Serial Number
11. This submission contains the following (Select all that apply):
Initial Investigational New Drug Application (IND)
Request For Reactivation Or Reinstatement
Development Safety Update Report (DSUR)
Response to Clinical Hold
Annual Report
Other (Specify)
Response To FDA Request For Information
General Correspondence

| Protocol Amendment(s) | Information Amendment(s) | Request for | IND Safety Report(s) |
|---|---|---|---|
| New Protocol | Chemistry/Microbiology | Meeting | Initial Written Report |
| Change in Protocol | Pharmacology/Toxicology | Proprietary Name Review | Follow-up to a Written Report |
| New Investigator | Clinical Statistics | Special Protocol Assessment | |
| PMR/PMC Protocol | Clinical Pharmacology | Formal Dispute Resolution | |

12. Select the following only if applicable. (Justification statement must be submitted with application for any items selected below. Refer to the cited CFR section for further information.)
Expanded Access Use, 21 CFR 312.300
Emergency Research Exception From Informed Consent Requirements, 21 CFR 312.23 (f)
Charge Request, 21 CFR 312.8
Individual Patient, Non-Emergency 21 CFR 312.310
Individual Patient, Emergency 21 CFR 312.310(d)
Intermediate Size Patient Population, 21 CFR 312.315
Treatment IND or Protocol, 21 CFR 312.320

**For FDA Use Only**

| CBER/DCC Receipt Stamp | CDR Receipt Stamp | Division Assignment |
|---|---|---|
| | | IND Number Assigned |

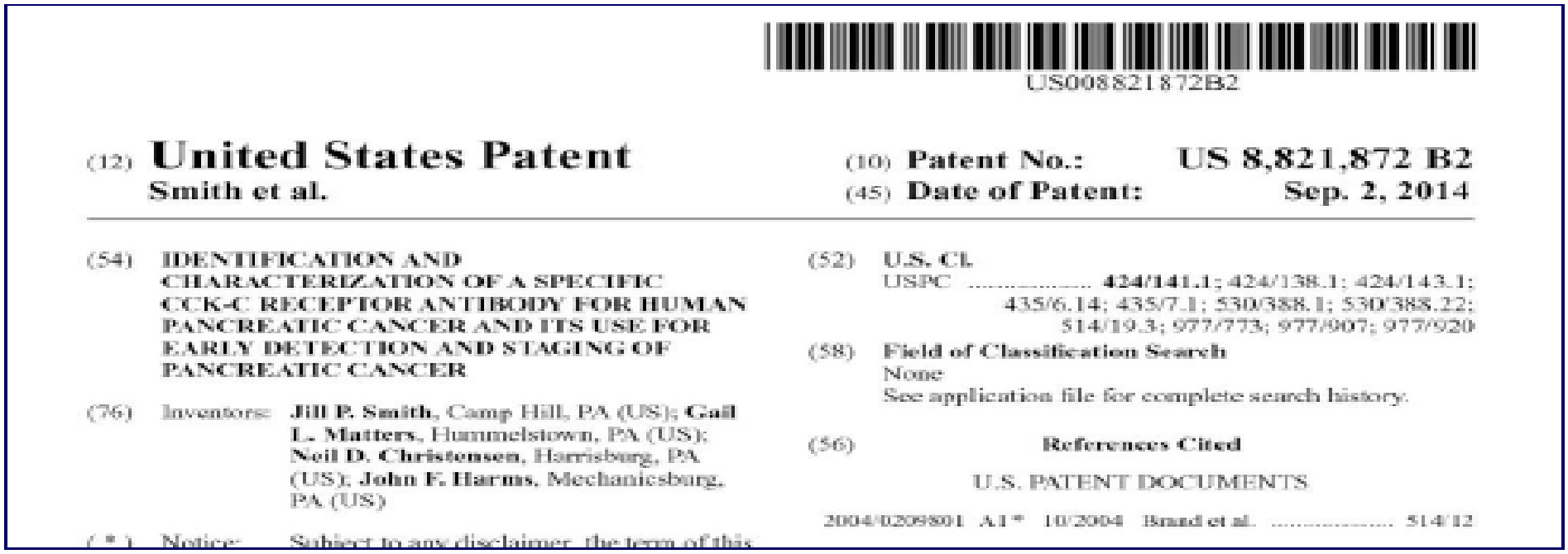




**What are you Submitting or requesting In this report**

**Must be submitted with <u>every</u> communication to FDA**

# Intellectual property

## Intellectual Property



US008821872B2

(12) **United States Patent**
**Smith et al.**

(10) **Patent No.: US 8,821,872 B2**
(45) **Date of Patent: Sep. 2, 2014**

(54) **IDENTIFICATION AND CHARACTERIZATION OF A SPECIFIC CCK-C RECEPTOR ANTIBODY FOR HUMAN PANCREATIC CANCER AND ITS USE FOR EARLY DETECTION AND STAGING OF PANCREATIC CANCER**

(76) Inventors: **Jill P. Smith**, Camp Hill, PA (US); **Gail L. Matters**, Hummelstown, PA (US); **Neil D. Christensen**, Harrisburg, PA (US); **John F. Harms**, Mechanicsburg, PA (US)

( * ) Notice: Subject to any disclaimer, the term of this

(52) U.S. Cl.
USPC ..... **424/141.1**; 424/138.1; 424/143.1; 435/6.14; 435/7.1; 530/388.1; 530/388.22; 514/19.3; 977/773; 977/907; 977/920

(58) **Field of Classification Search**
None
See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

2004/0209801 A1* 10/2004 Braud et al. ..... 514/12

- Before you present your work publically -IP
- License the patent when it issues

# Clinical trials

## Other things to do for a Clinical Trial

- Write a protocol- study design with outcomes
- Write a consent form
- Obtain IRB approval
- Find a Sponsor - Get Funding support-$
- Responsibilities of the Principal Investigator (CITI training)
- Research Nurse /Study coordinator
- Registration of clinical trial on www.clinicaltrials.gov

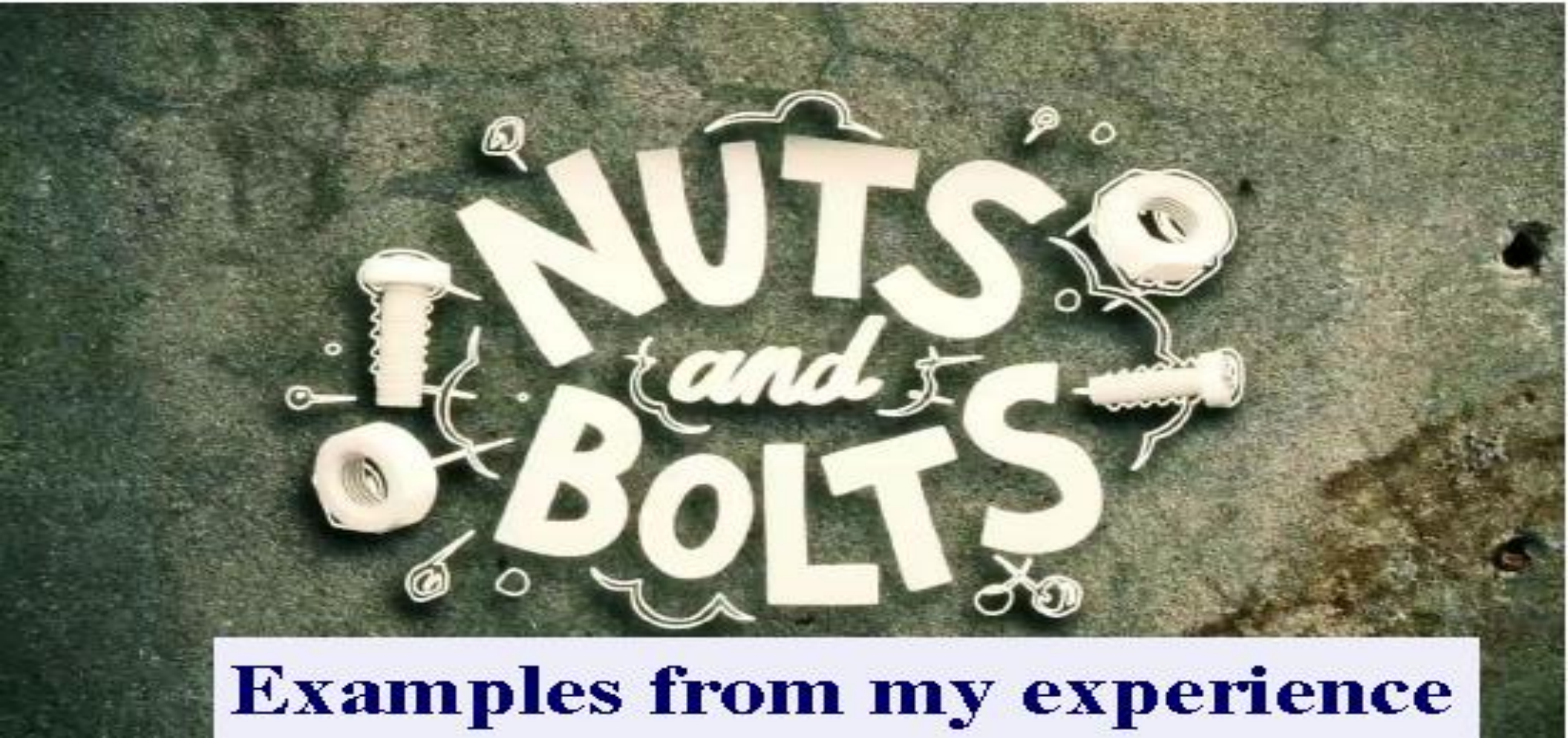
# Cost

## Cost

- **The NIH will support Phase 1-2 clinical trials.**
- **Phase 3 Registration trials require an industry partner.**
- **A 'registration trial' is designed to get FDA approval.**
- **The cost of an FDA New Drug Application (NDA) is greater than $3.0 million today.**
- **Orphan Drug Designation: a process to lower the cost for rare diseases (Prevalence <200,000). With Orphan Drug Designation the application fee is waived and sponsors receive additional exclusivity rights**

# Nuts and bolts

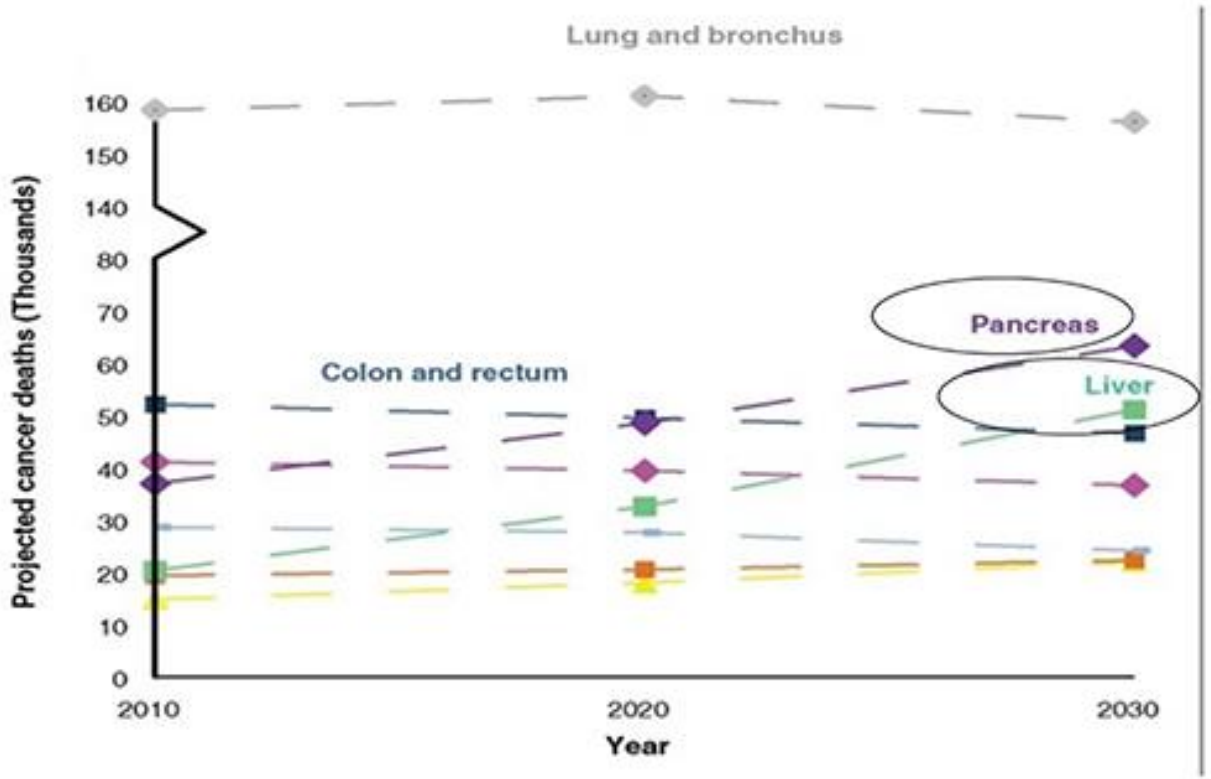
## How Do You Do It?



# Fastest Growing Cancers

## Fastest Growing Cancers &

Pancreatic and liver cancer are unmet



# CCK receptors

## Cholecystokinin Receptors: GPCRs

- **CCK-A**: Also called CCK-1R
  alimentary tract, gallbladder, pancreas.
  Binds CCK > Gastrin (1,000:1)

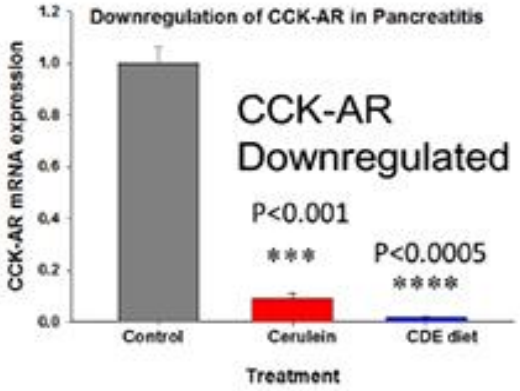
- **CCK-B**: Also called CCK-2R
  brain, stomach
  Binds CCK = Gastrin (1:1)

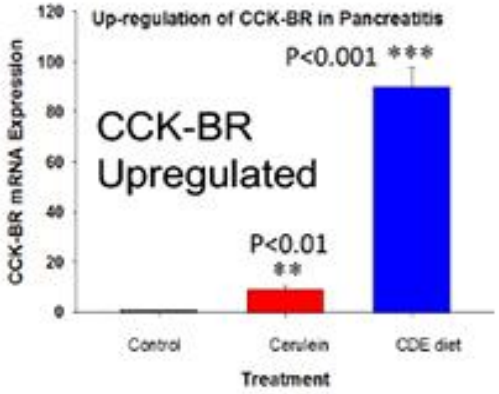
- **CCK-C**: pancreatic cancer, splice variant of CCK-BR; Only found in human cancer, not rodents. Binds Gastrin > CCK (10:1)

# CCK-B receptor

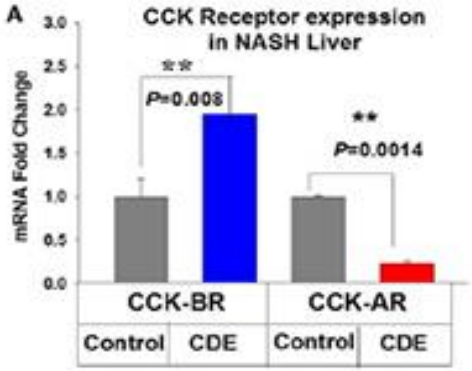
## CCK-B Receptor has low expression in normal tissues

Inflammation activates CCK-BR expression- Pancreatitis




The CCK-BR becomes upregulated in two different animal models of pancreatitis

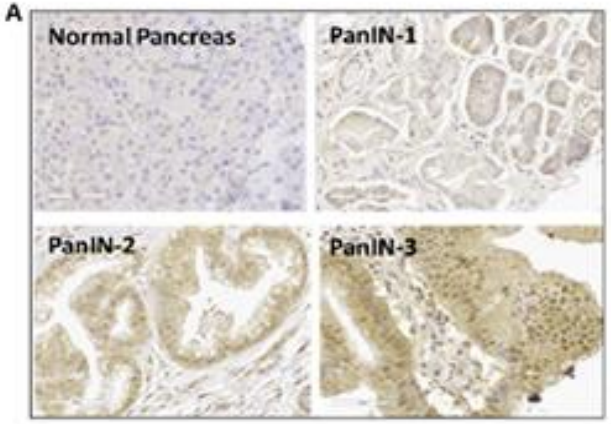


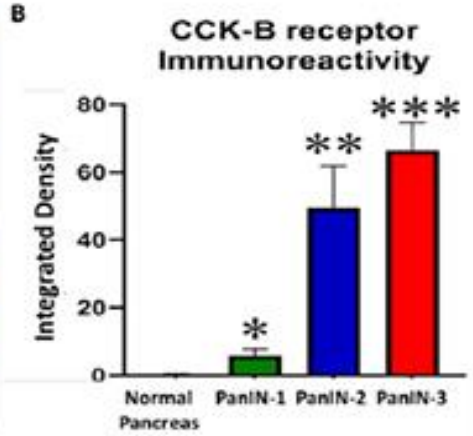

Inflammation activates CCK-BR expression- in hepatitis

In Nonalcoholic Steatohepatitis (NASH) The CCK-BR is also upregulated and the CCK-AR is downregulated

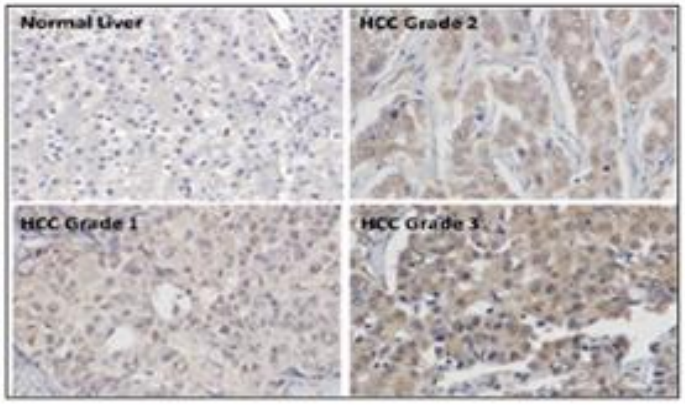
# CCK-BR in cancer

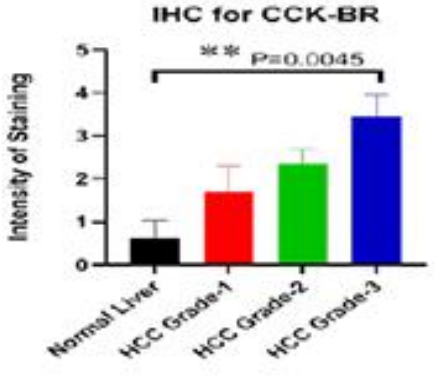
## The CCK-BR is over-expressed in HUMAN HCC and Pancreatic




Top: CCK-BR is absent in human pancreas but becomes expressed in precancerous pancreatic intraepithelial neoplasia (PanINs). Biomolecules, 2021 PMID: 34944412




Bottom: CCK-BR is not detected in normal human liver, but is found in HCC and increases with grade of cancer

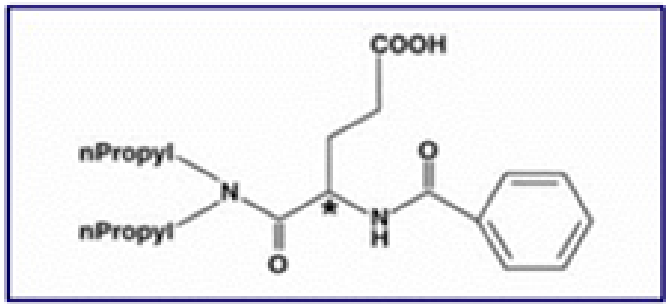
# Our hypothesis

Our hypothesis

Since CCK-BRs are over-expressed in pancreas and liver cancer, these receptors are good targets for therapy and for imaging (diagnostics).

# Proglumide

## Targeting the CCK-BR with small molecule- Proglumide

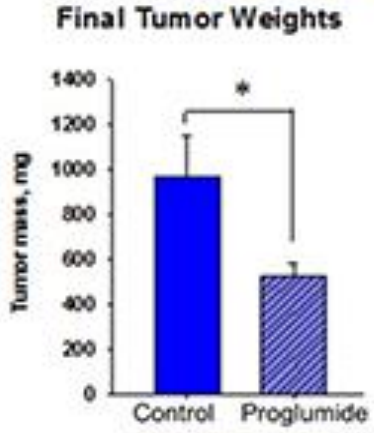


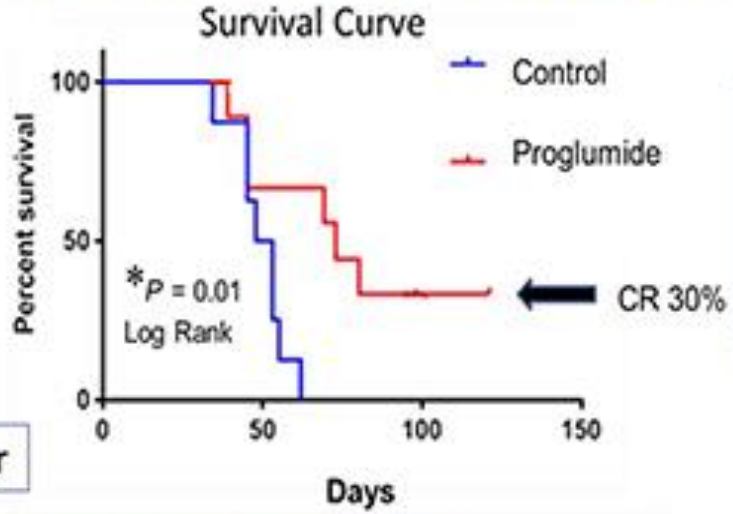

Older drug developed 30 years ago for ulcer disease.

Broad safety profile
Orally bioavailable
Minimal to no toxicity
Decreases growth of pancreas and liver cancer in mice, inhibits fibrosis, increases influx tumor CD8+ T-cells

# Proglumide

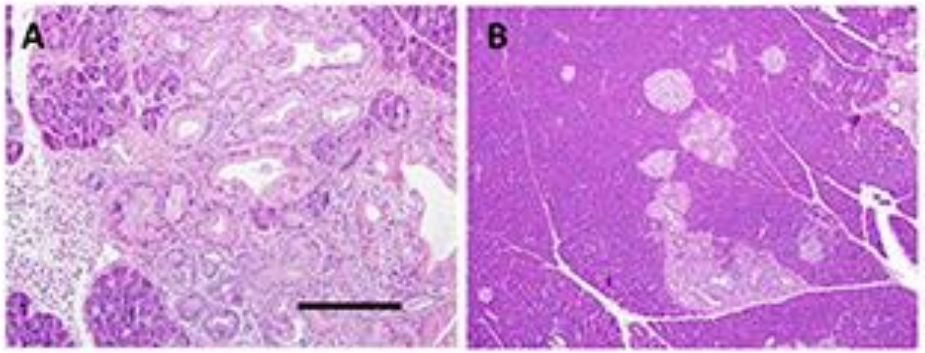
## Proglumide inhibits growth of pancreatic cancer and PanIN progression




Proglumide improves survival in immune competent mice

Mouse Pancreatic cancer



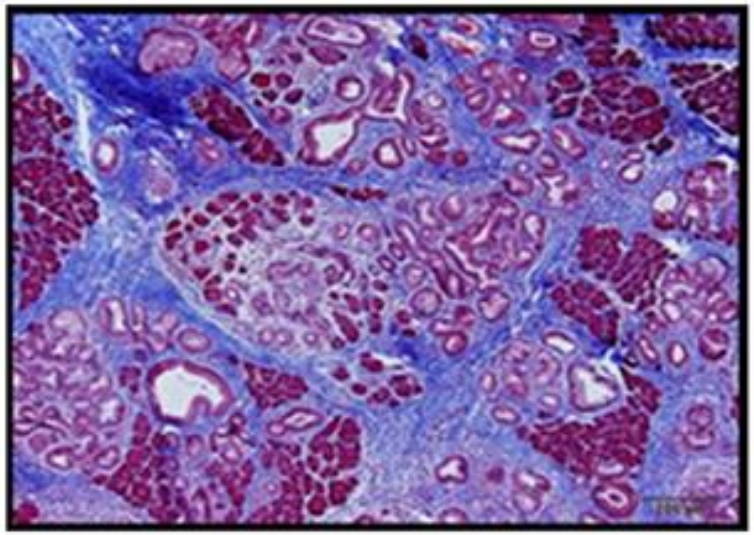

LSL-Kras$^{G12D/+}$; *P48-Cre* (KC) mutant KRAS transgenic mice

A. Control mouse untreated
B. Mouse treated for 4 months with proglumide in drinking water

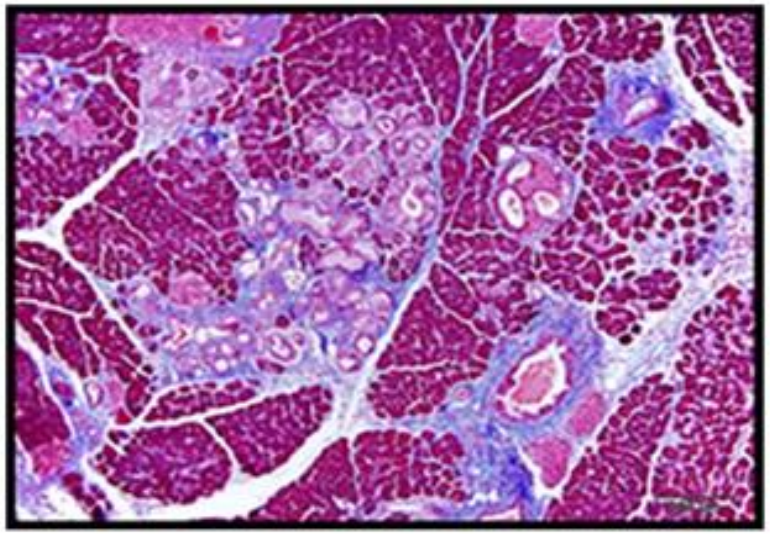
# Proglumide

## Proglumide prevents pancreas PanIN progression and fibrosis, Kras mouse model

**Vehicle control**



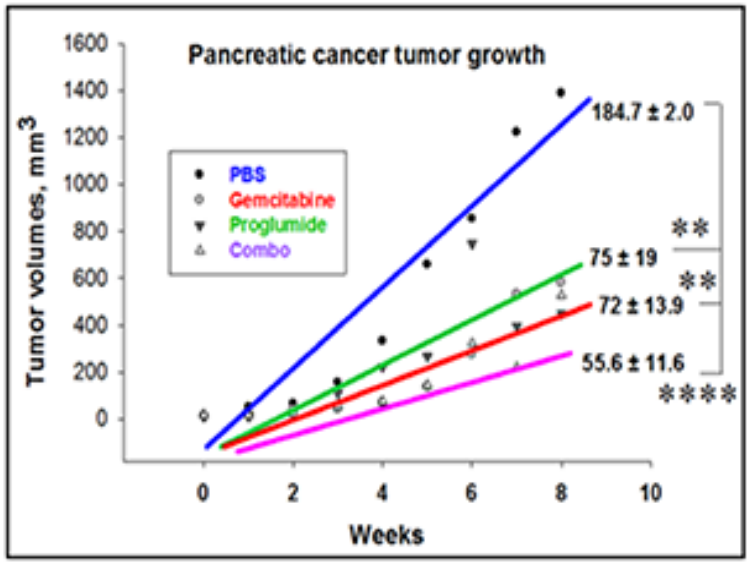
**CCK receptor Blockade**



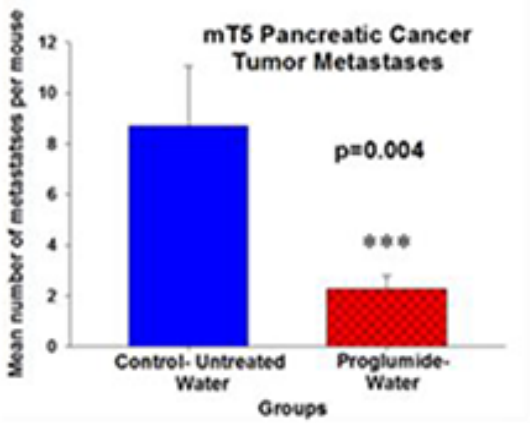
Smith et al. *Pancreas* 2014; 43: 1050–1059

# Pancreatic tumors

## Proglumide decreases Pancreatic cancer growth- syngeneic mouse



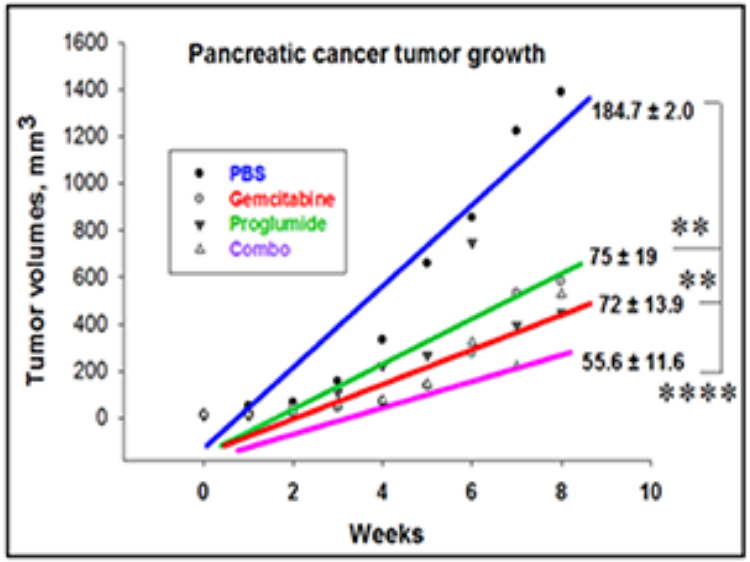

Proglumide monotherapy decreases tumor growth rates of pancreatic cancer in immune competent mice. There is an additive effect when combined with gemcitabine.



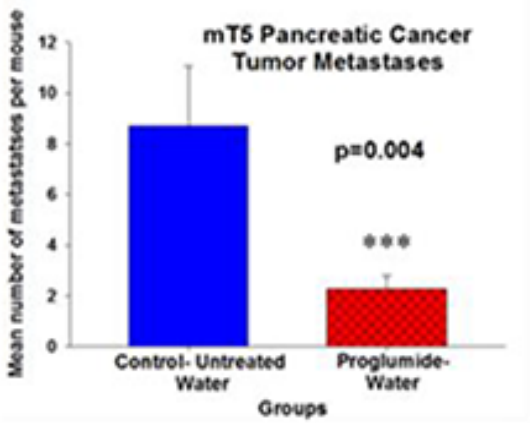

Proglumide decreased growth and the number of metastases in immune competent mice bearing orthotopic syngeneic mT5 pancreatic tumors.
***p=0.00433

# Pancreatic tumors

## Proglumide decreases Pancreatic cancer growth- syngeneic mouse



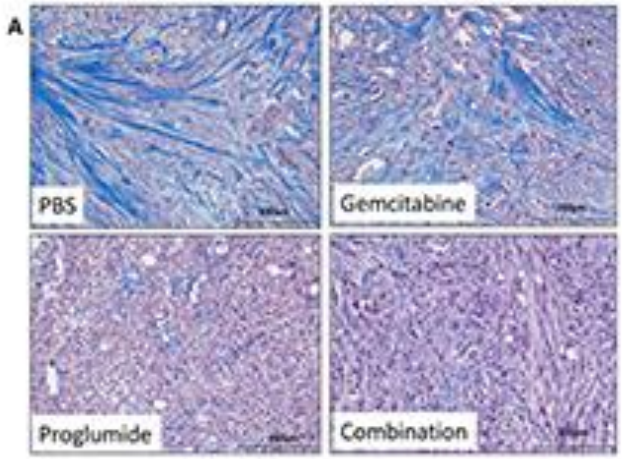

Proglumide monotherapy decreases tumor growth rates of pancreatic cancer in immune competent mice. There is an additive effect when combined with gemcitabine.

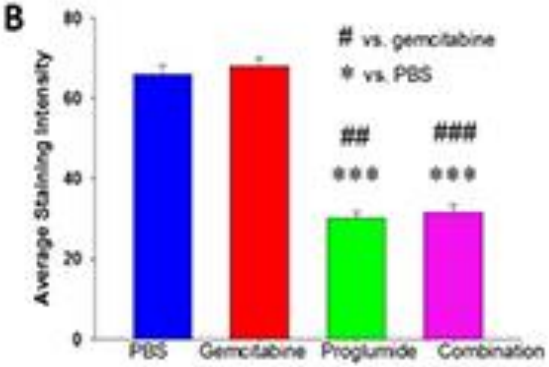



Proglumide decreased growth and the number of metastases in immune competent mice bearing orthotopic syngeneic mT5 pancreatic tumors.
***p=0.00433

# Fibrosis

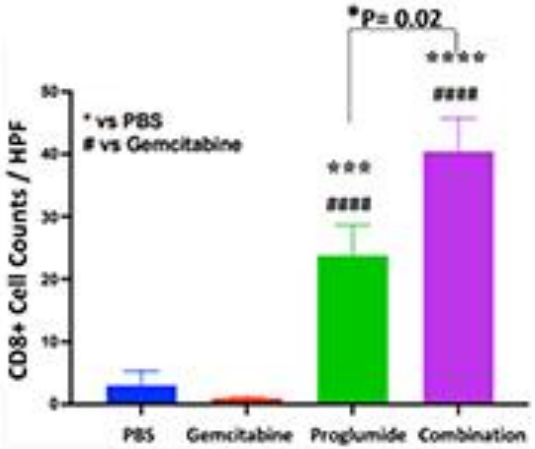
## Proglumide decreases fibrosis & alters the immune signature in pancreatic cancer



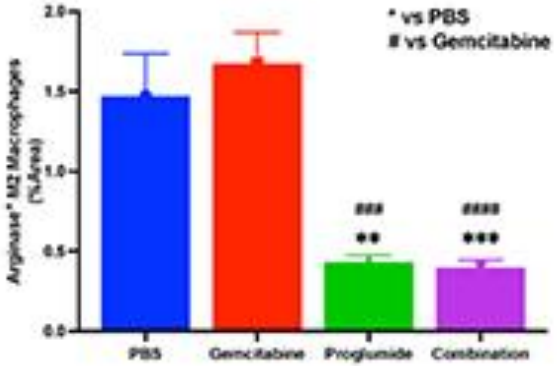

Mouse with pancreatic cancer

Cancers 2021, PMID: 34638432




Proglumide increases CD8+ T-cells

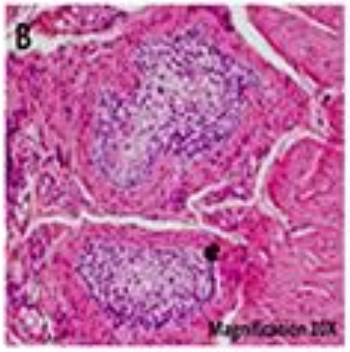
Proglumide decreases M2-polarized Macrophages



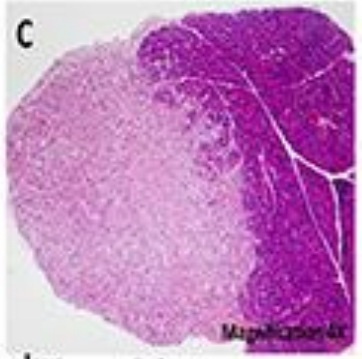
# Metastasis

## Metastases were Significantly Decreased in Mice with PANC-1 Tumors Treated with the Proglumide &Gemcitabine

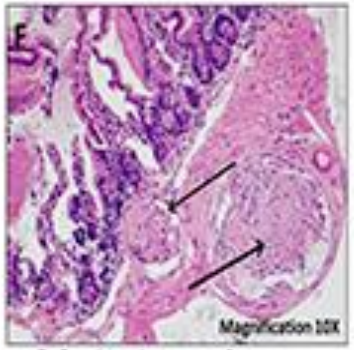
All metastases were confirmed by histology and read by our Pathologist



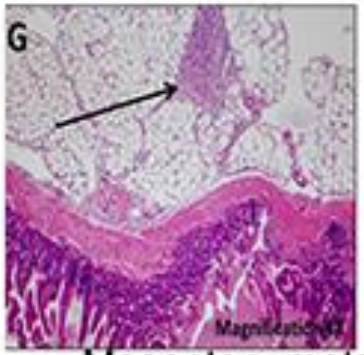

Tumor emboli muscle



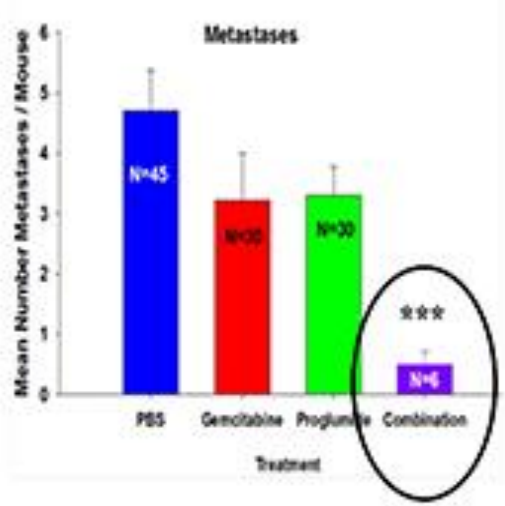

Liver Metastases




Mets to colon




Mesentery mets

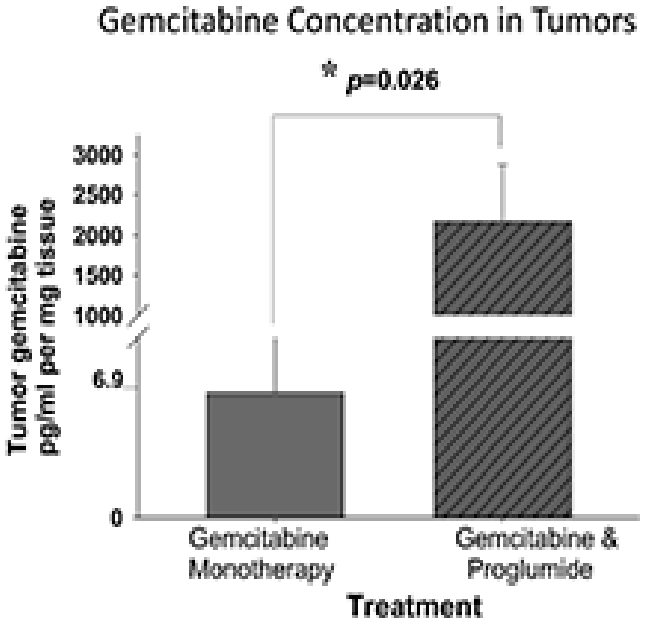



| Group | Liver | Mesentery/ Peritoneum | Nodes | Spleen | Diaphragm | Abdominal Wall | Stomach | Colon |
|---|---|---|---|---|---|---|---|---|
| PBS | 4 | 22 | 2 | 5 | 1 | 2 | 6 | 3 |
| Gemcitabine | 4 | 12 | 1 | 5 | 0 | 1 | 2 | 5 |
| Proglumide | 2 | 18 | 2 | 1 | 0 | 2 | 2 | 3 |
| Combination | 0 | 3 | 0 | 1 | 1 | 0 | 0 | 1 |

Cancers **2021**, 13, 4949. PMID: 34638432

# Gemcitabine

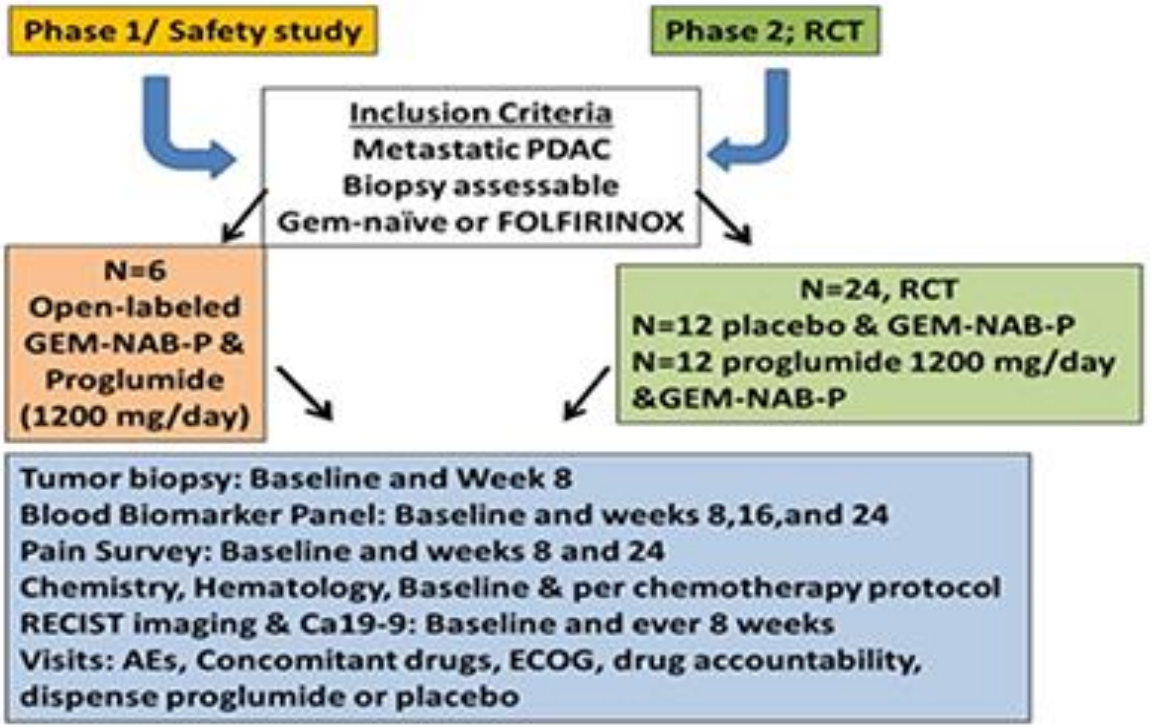
## Measurement of Tumor Gemcitabine Levels by Mass Spectroscopy




- A method was developed to measure tumor levels of gemcitabine using Mass Spectroscopy.
- Mean gemcitabine levels (pg/ml per mg of tumor tissue) were significantly higher in the tumors of mice treated with the combination therapy compared to gemcitabine monotherapy.
- These results indicate that proglumide therapy enhances the uptake of gemcitabine into pancreatic tumors possibly by decreasing the fibrosis in the pancreatic TME.

# Pancreatic cancer clinical studies

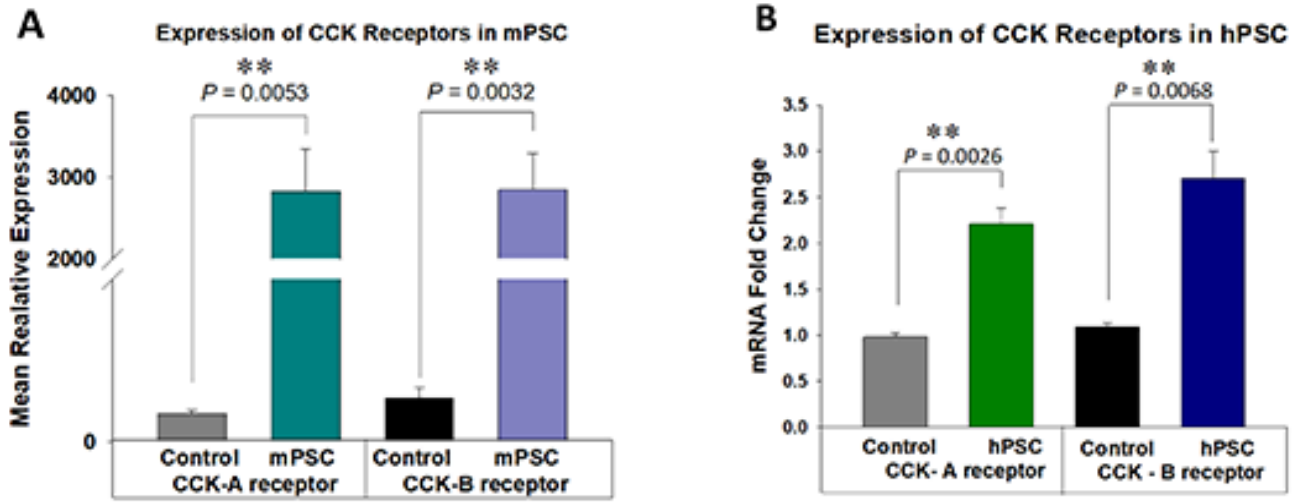
## Current clinical studies — Pancreatic cancer




Secured Orphan Drug designation for proglumide in pancreatic cancer. The drug has been licensed to a company for development.

# Fibrosis

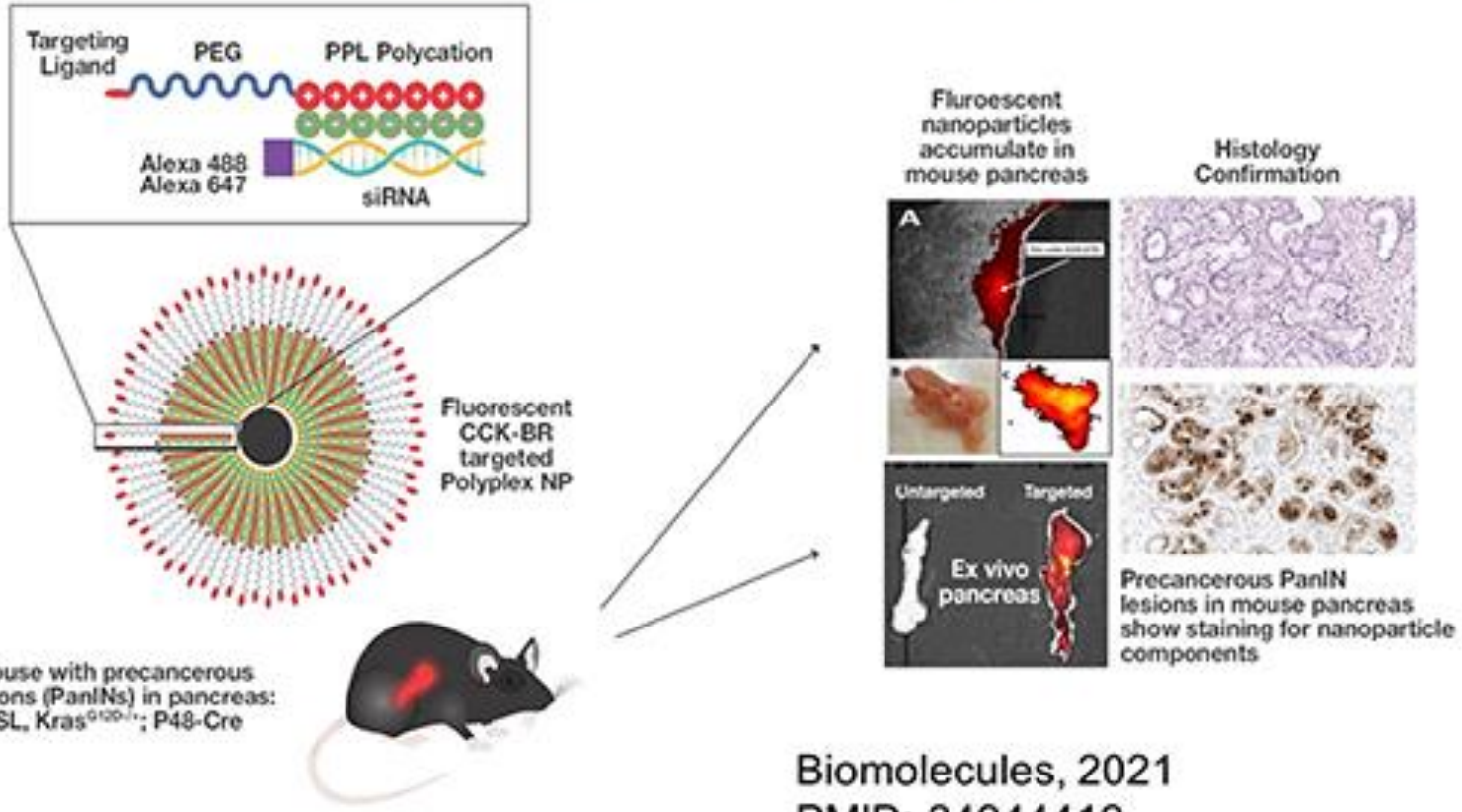
## How does proglumide decrease fibrosis? CCK receptors on fibroblasts




Mouse (A) pancreatic stellate cells and (B) human pancreatic activated fibroblasts Express both the CCK-AR and the CCK-BR

# CCK-BR as a target

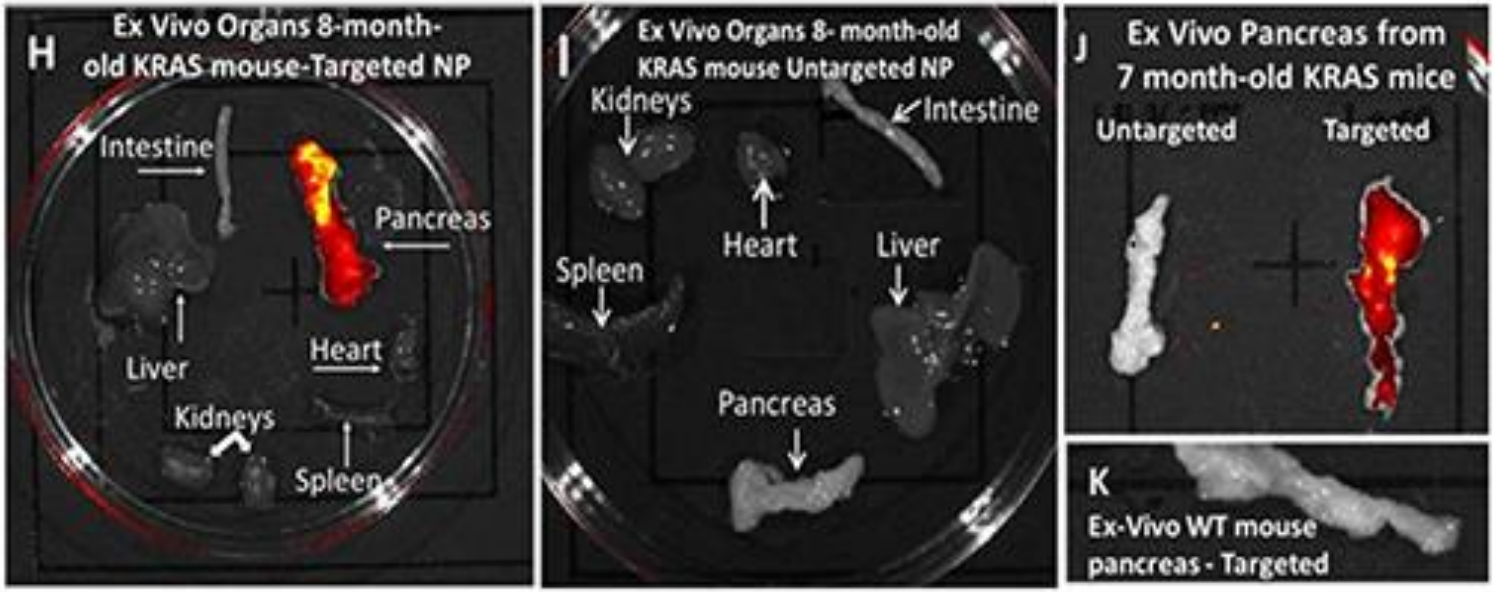
## Using the CCK-BR as a Target for imaging and therapy




Biomolecules, 2021
PMID: 34944412

# Nano imaging

## Nano-imaging Precancerous Pancreas Lesions




Targeted NP

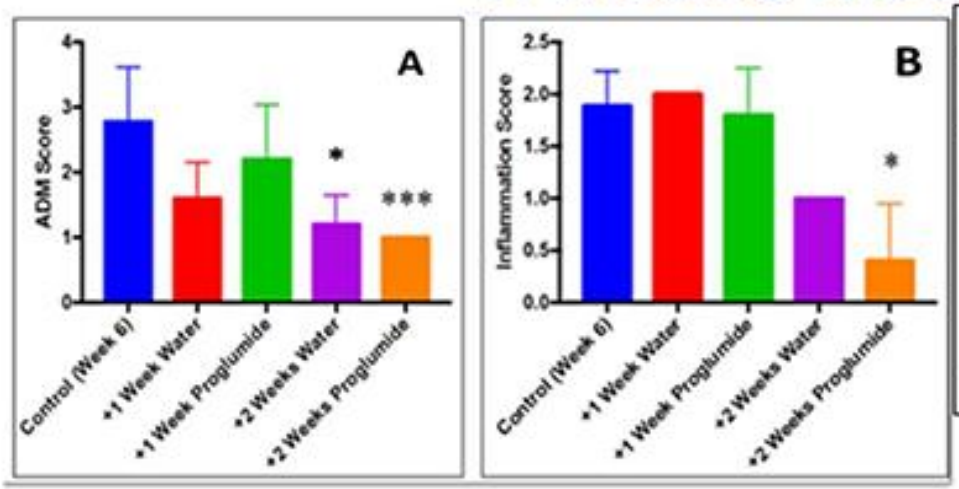
Untargeted NP

Biomolecules, 2021
PMID: 34944412

Developing a nanoparticle that targets the CCK-BR in early cancer or PanINs – An imaging tool PET scan.

# Proglumide reverses pancreatitis

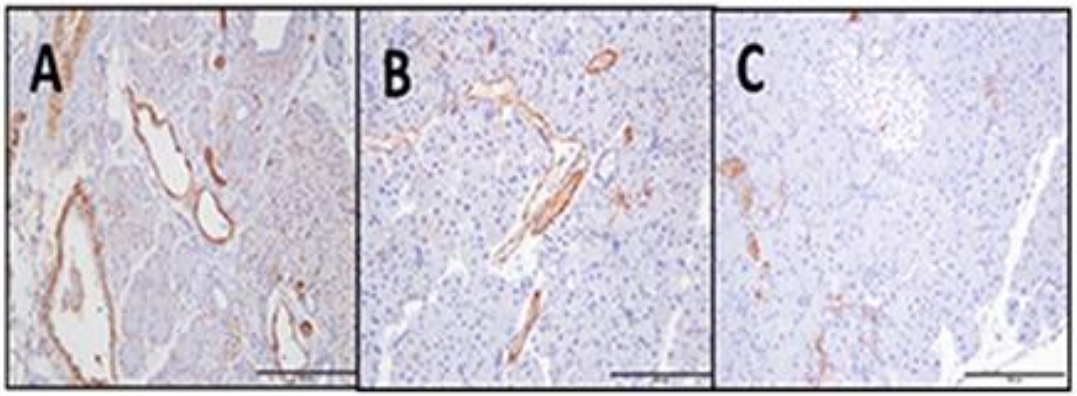
## Proglumide Reverses Chronic Pancreatitis in Mouse Models







**A.** Acinar ductal metaplasia (ADM) scores decreased with proglumide compared to control water-treated mice. *p=0.013; ***p=0.0002. **B.** Inflammation scores improved in proglumide-treated mice.* p<0.0001




Proglumide therapy decreases pancreatic fibrosis **A.** Baseline αSMA staining of fibrosis. **B.** αSMA immunoreactivity in pancreas of control mice. **C.** αSMA staining is reduced in mice treated with proglumide

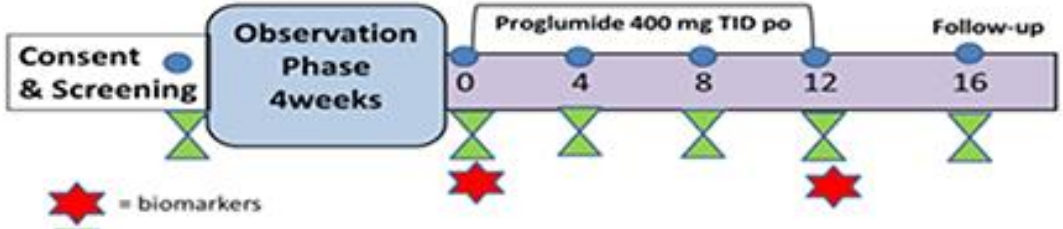
**Dig Dis Sci. 2020 May; 65(5): 1376–1384**

# Pancreatitis

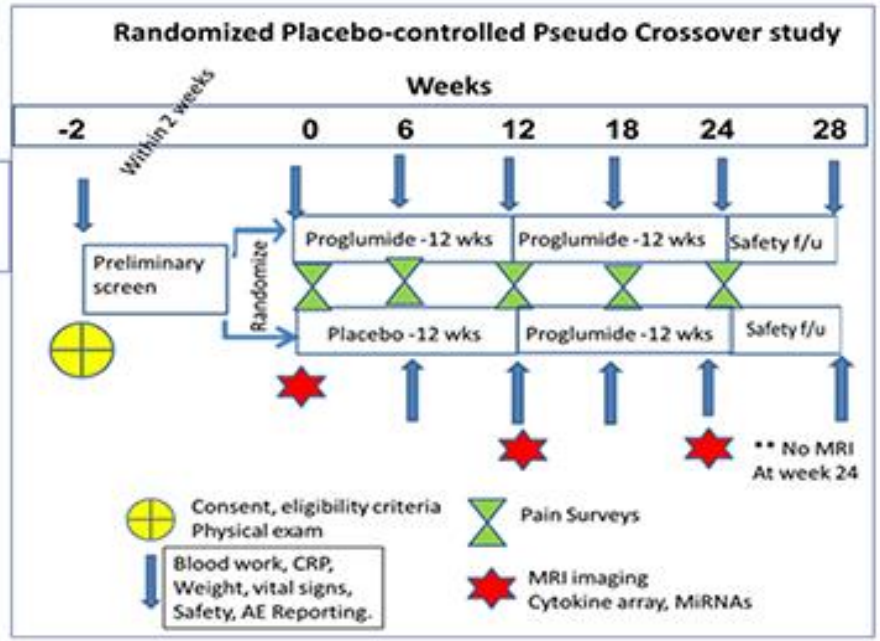
## Chronic pancreatitis

**LEAD-IN Open-Labeled study**

Lead-in
Open Labeled




Phase 2 randomized
Placebo controlled

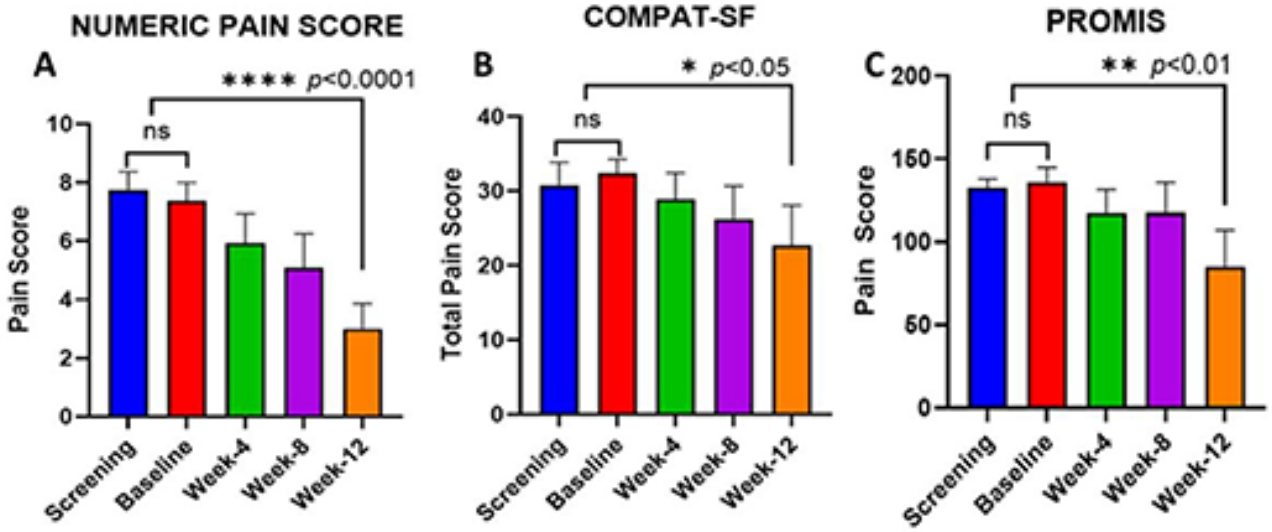



IRB# STUDY 5063
FDA IND#161920
Clinical trials registration
# NCT05551858

Publication:
*Pharmaceutics* **2024**, *16*, 611

# Proglumide decreases pain

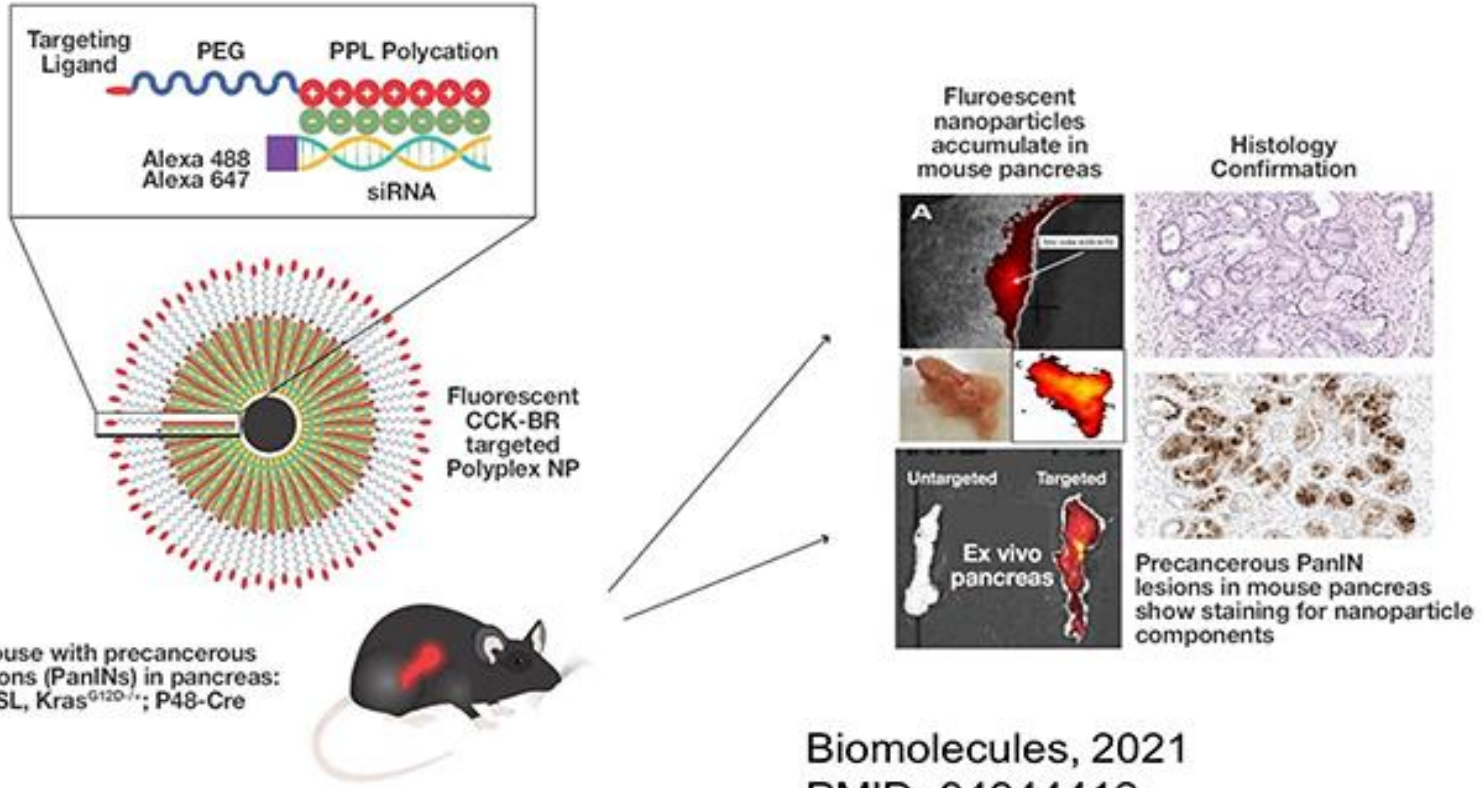
## Proglumide decreased Pain in Chronic Pancreatitis




Compared to baseline pain scores; there was significant improvement in pain at week 12 of study as measured with (A) Numeric Rating Scale, (B) COMPAT-SF, and (C) NIH PROMIS. Columns represent means ± SEM with N = 8 samples per column. Ns = not significant; * p < 0.05; **p < 0.01; and **** p < 0.0001.

# Targeting CCK-BR

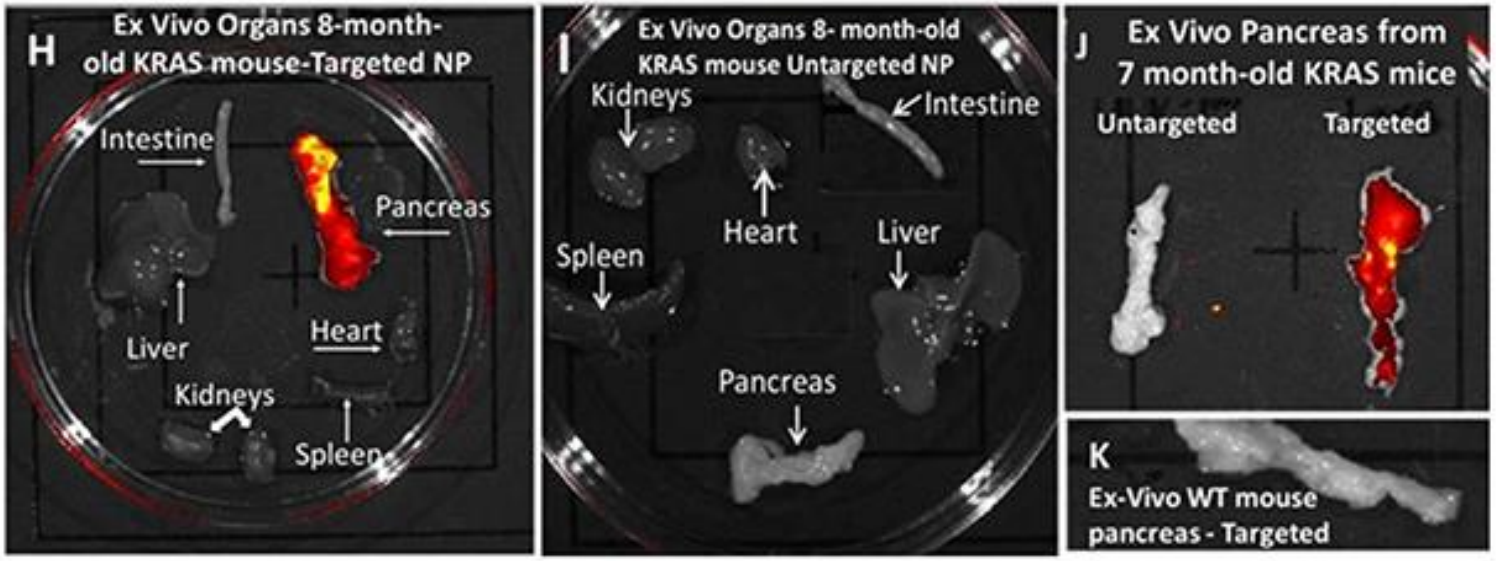
## Using the CCK-BR as a Target for imaging and therapy




Biomolecules, 2021
PMID: 34944412

# Nano-imaging

## Nano-imaging Precancerous Pancreas Lesions




Targeted NP

Untargeted NP

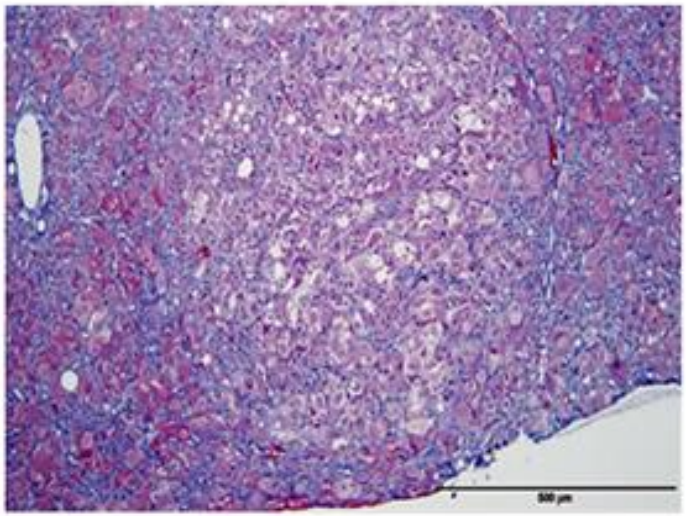
Developing a nanoparticle that targets the CCK-BR in early cancer or PanINs – An imaging tool PET scan.


Biomolecules, 2021
PMID: 34944412

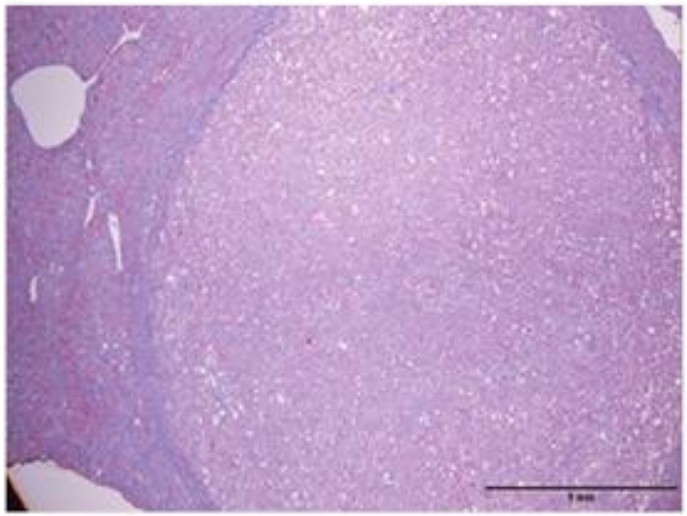
# HCC prevention

## Proglumide Prevented HCC

- *Dig Dis Sci*. 2020;65(1):189–203. PMID: 31297627



Week-18, CDE/Reg 10X
Dysplastic Nodule



Week-18, CDE/Reg 4X
Hepatocellular Cancer

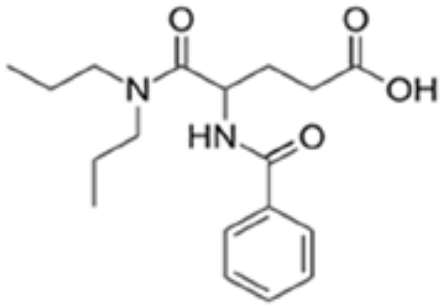
Normal Mouse
Liver

Mice on CDE diet show
several foci of HCC

# Phase 1 Study

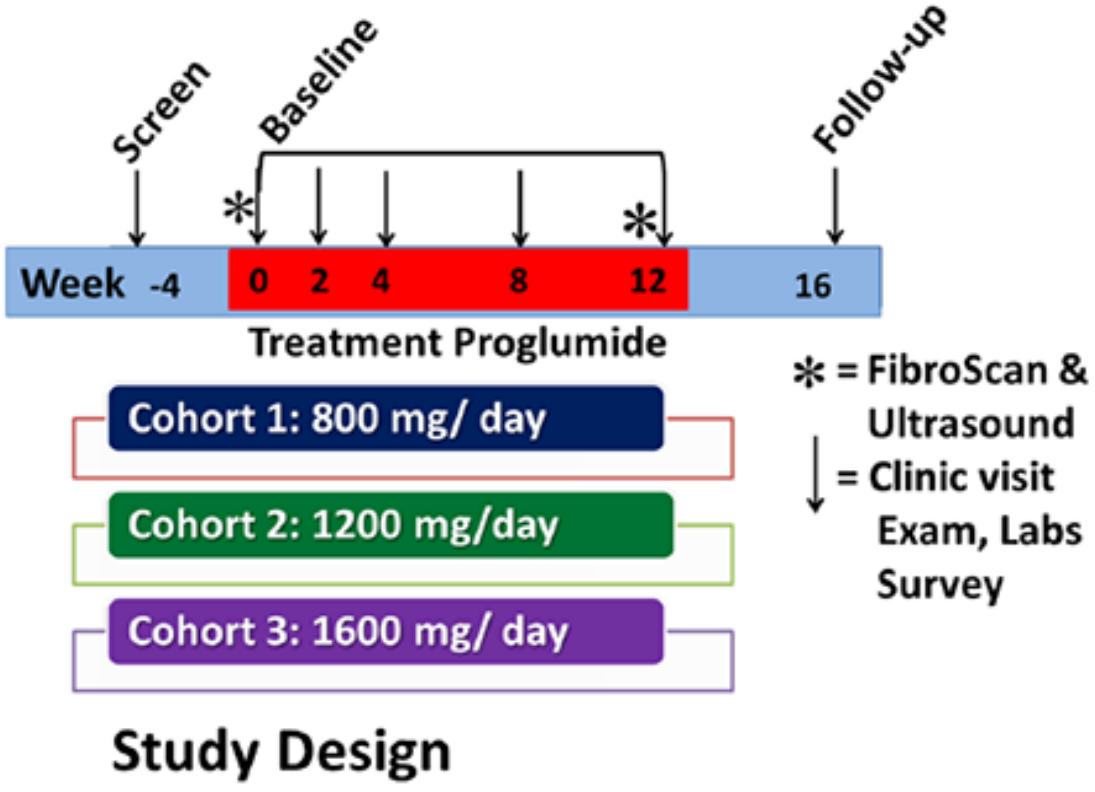
## Phase 1 Study in NASH

### Published Clinical Pharmacology & Therapeutics




**Proglumide**

FDA IND#: 143696
www.clinicaltrials.gov
NCT # 04152473
Vegan capsules: 400 mg
Funded by NCI grant

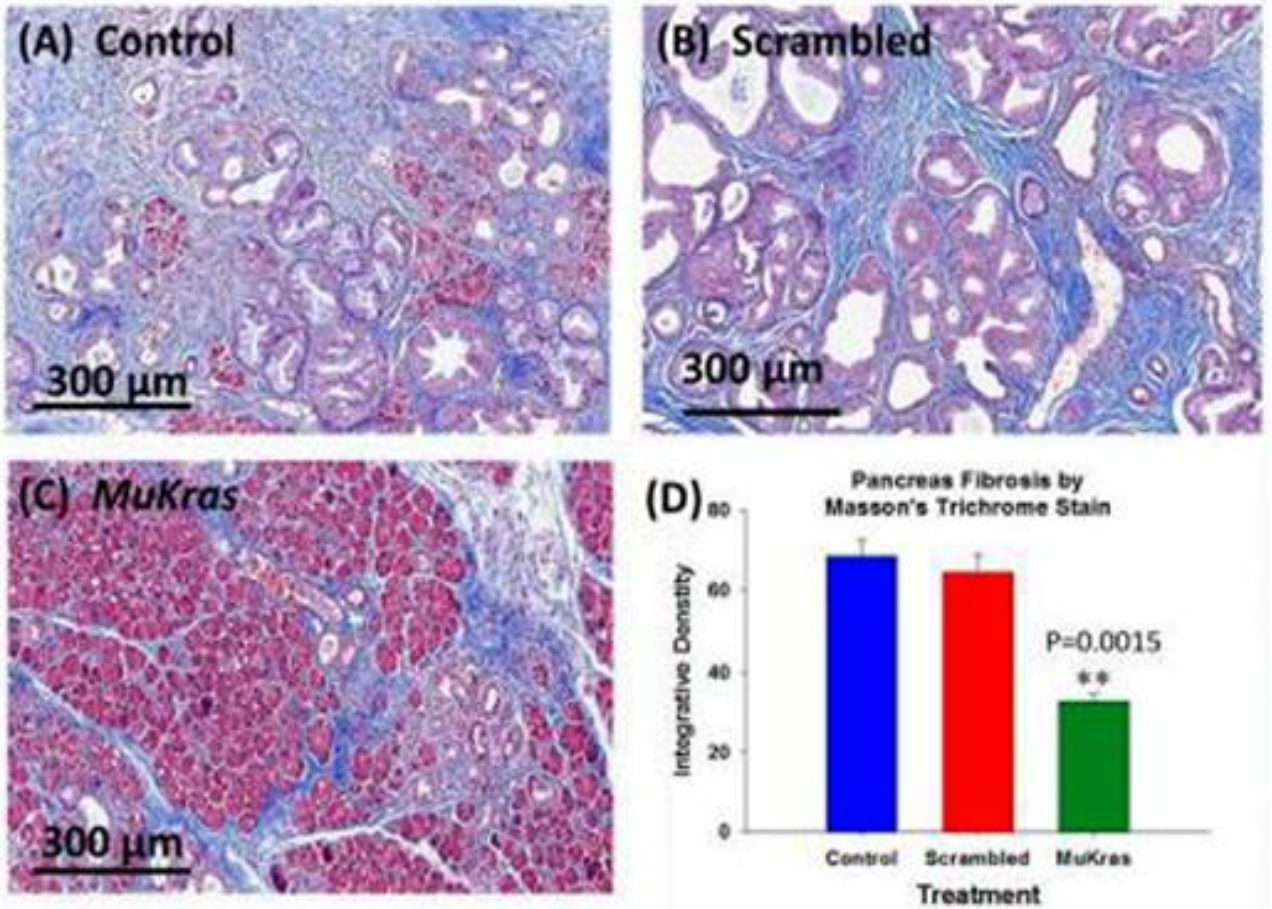



**Study Design**

https://doi.org/10.1002/cpt.2745

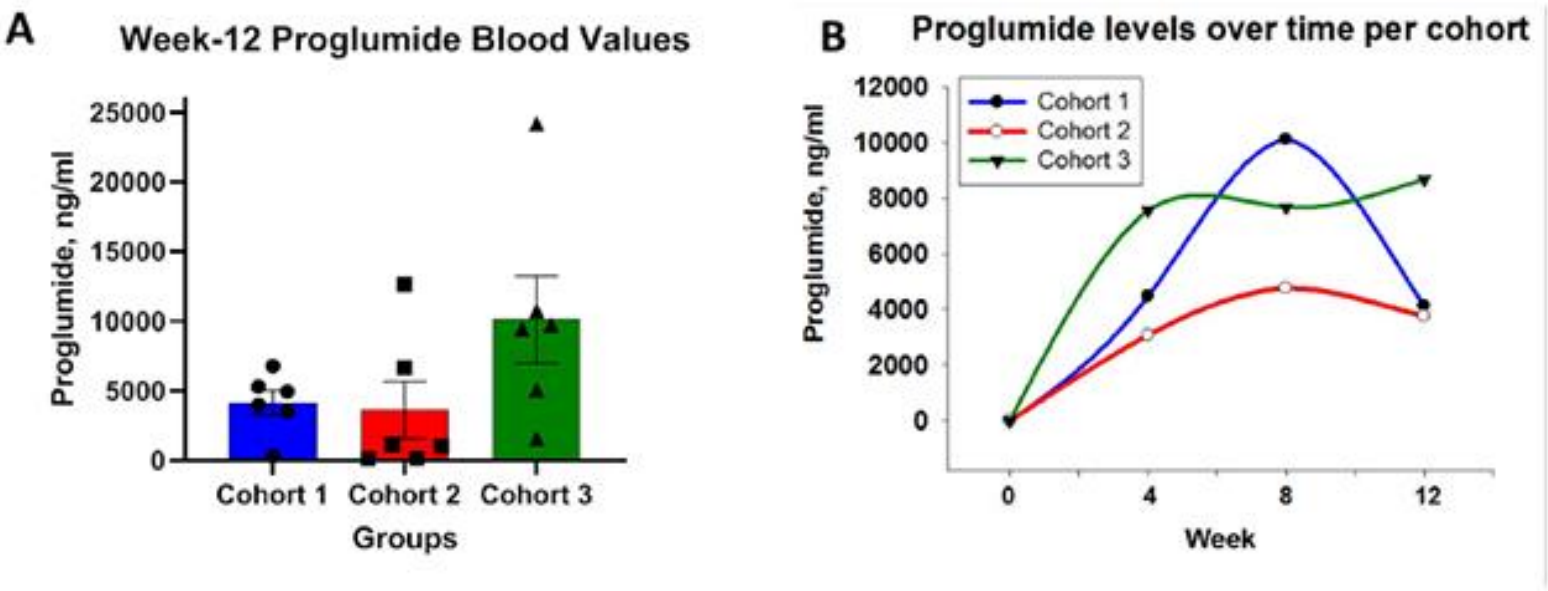
# CCK-BR targeted NP

## CCK-BR targeted NP decreases Fibrosis in Kras Mouse pancreas



# Proglumide blood levels

## Proglumide blood levels
## From Phase 1 study

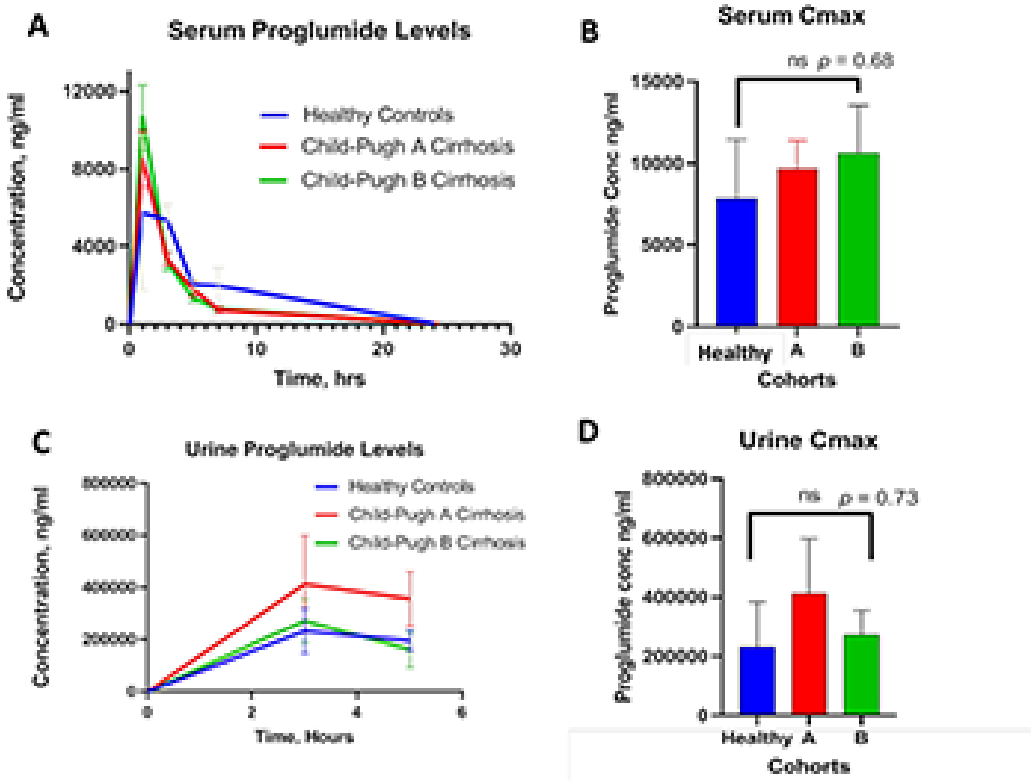



**AEs: Only mild, none in Cohort 3 and no one had to discontinue drug**

https://doi.org/10.1002/cpt.2745

# Proglumide in hepatic impaired

## Proglumide in Hepatic Impaired; Child Pugh A& B Cirrhosis




Pharmaceutics. 2022 Mar 12;14(3):627. PMID: 35336003;

www.clinicaltrails.gov (NCT04814602)

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Thanks to
Our mouse
volunteers

# Smith lab