Bench to Bedside, Clinical Trials

TRACO-Translational Research : Bench to Bedside, Clinical Trials

Jill P Smith, MD
Professor of Medicine
Georgetown University
jps261@Georgetown.edu

OBJECTIVES

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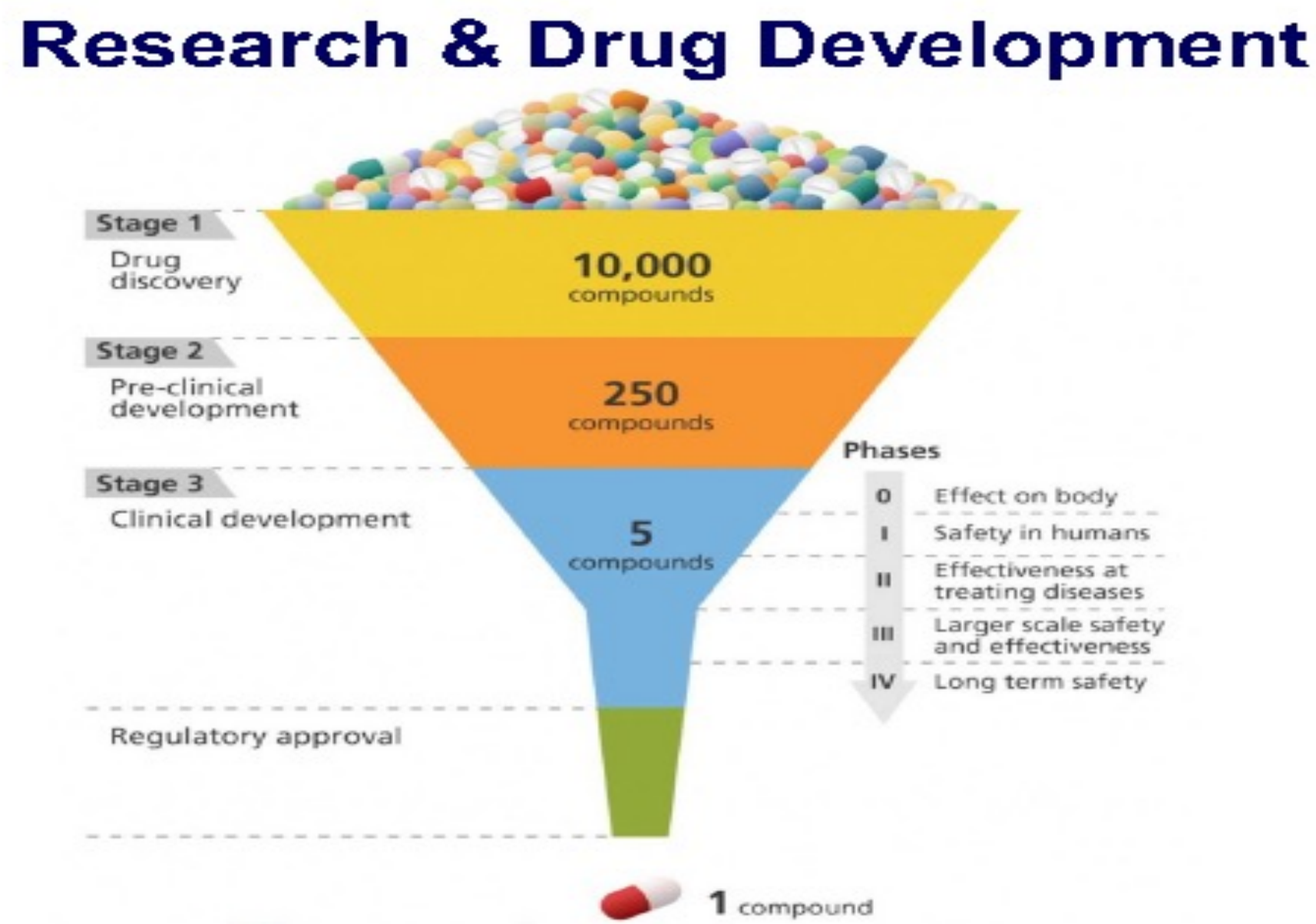
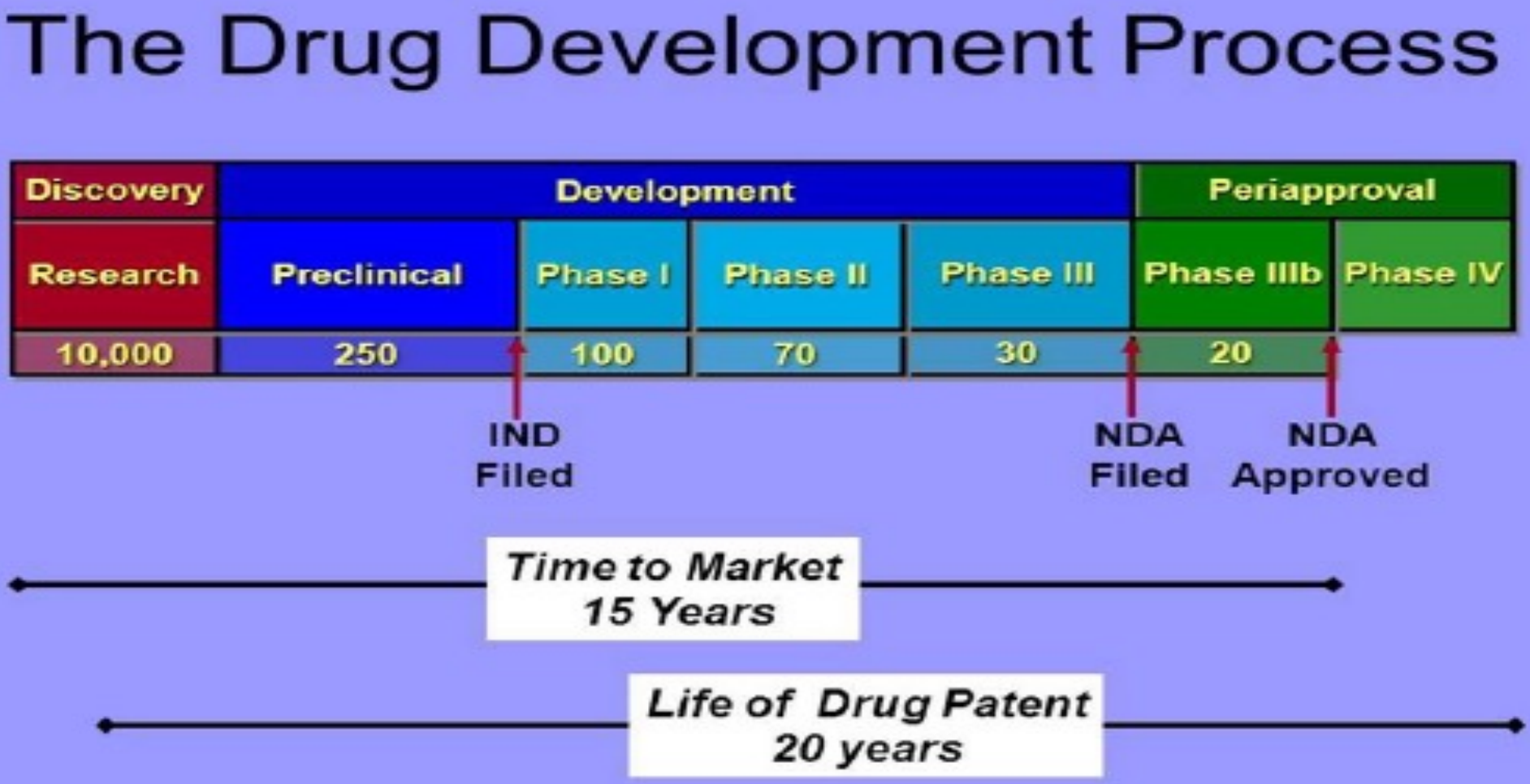
- Understand how an idea is taken from the research lab to patient care.
- Learn the steps in conducting clinical trials
- Understand some of the obstacles to overcome in drug development?
- Examples of my translational projects

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:

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

[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

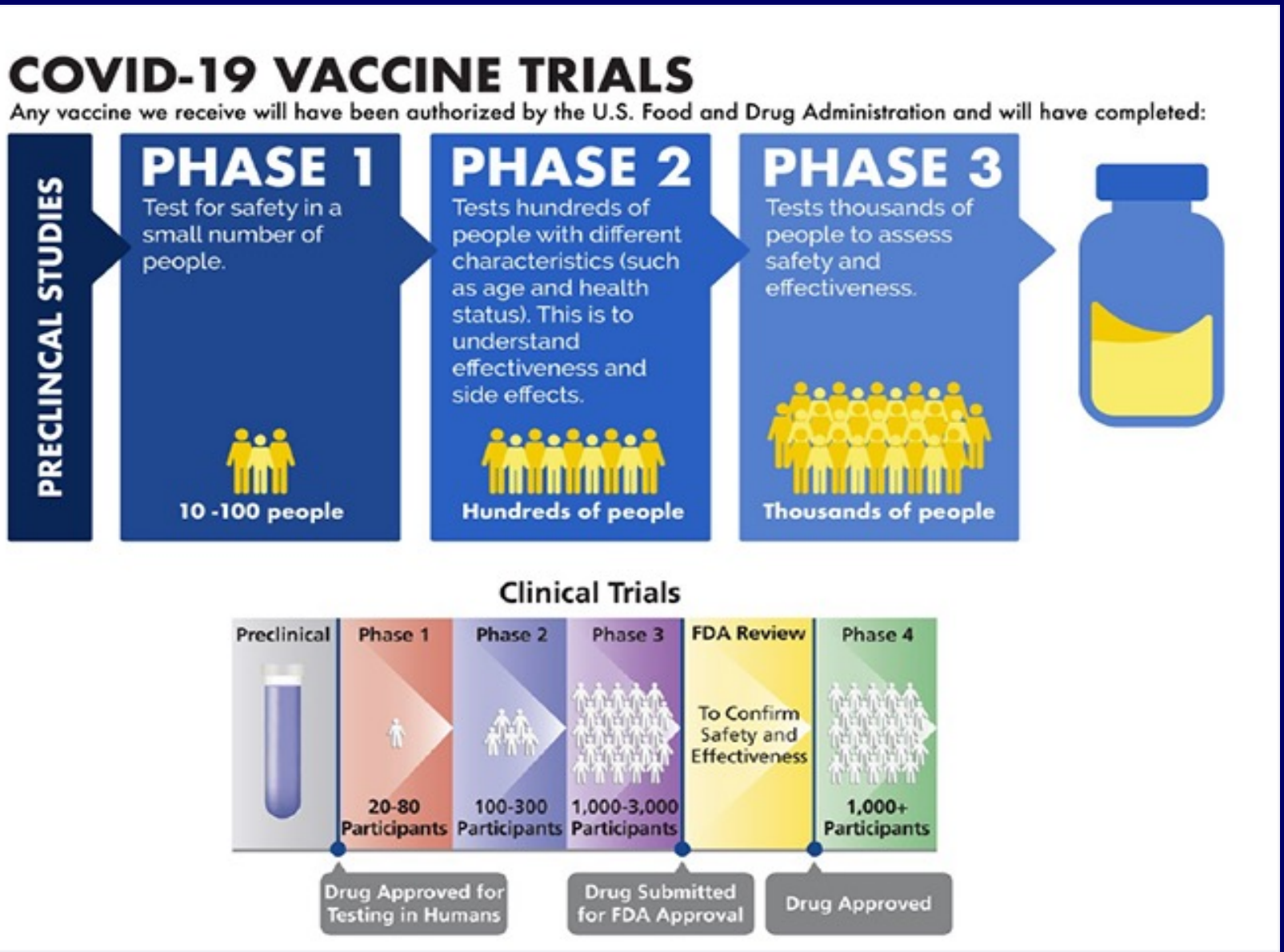
Phase 4

Phase 4

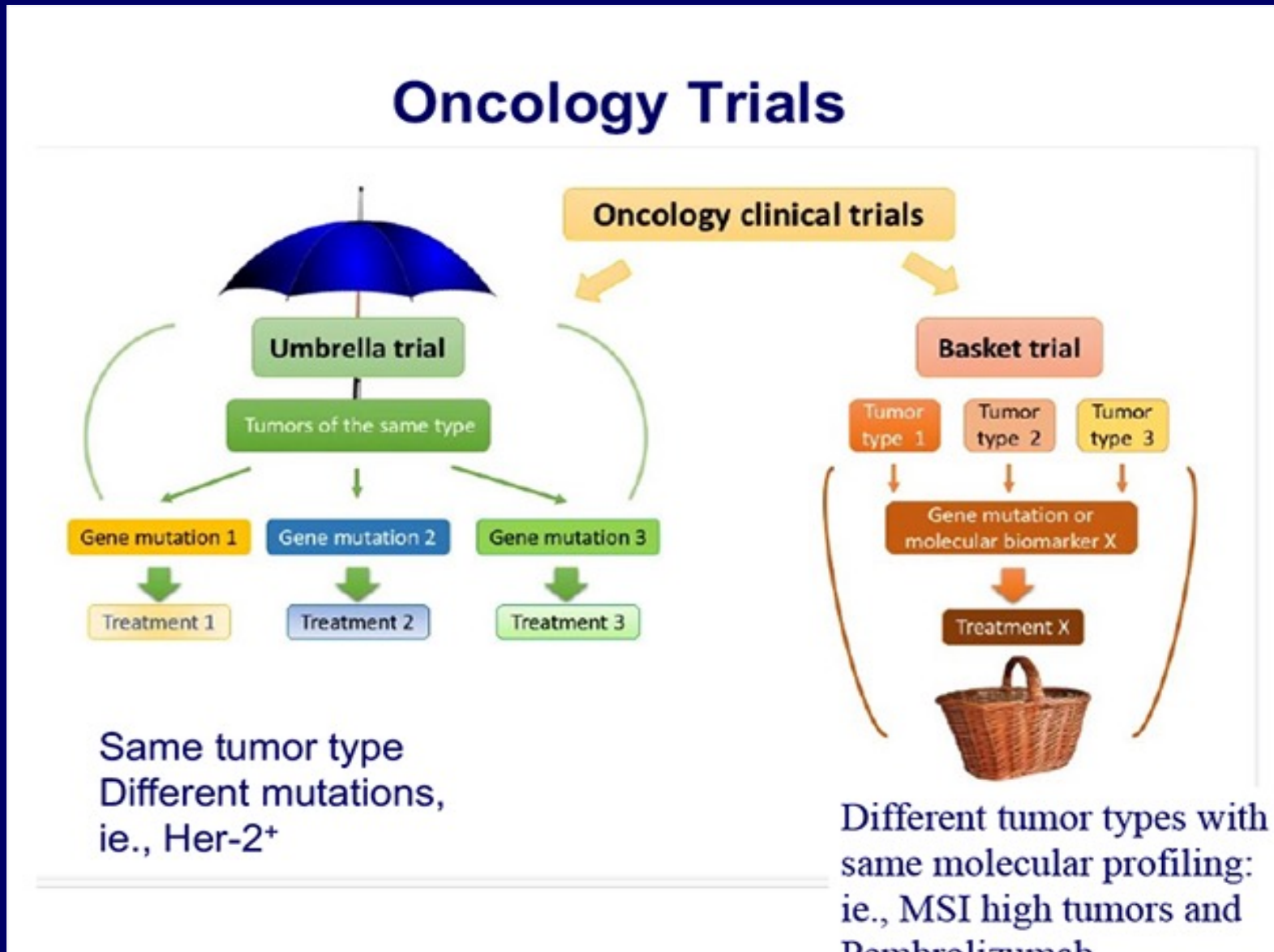
- From hundreds to thousands of people
- Usually takes place after drug is approved to provide additional information on the drug's risks, benefits and optimal use
- Called 'Post-marketing" or

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

Oncology trials



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

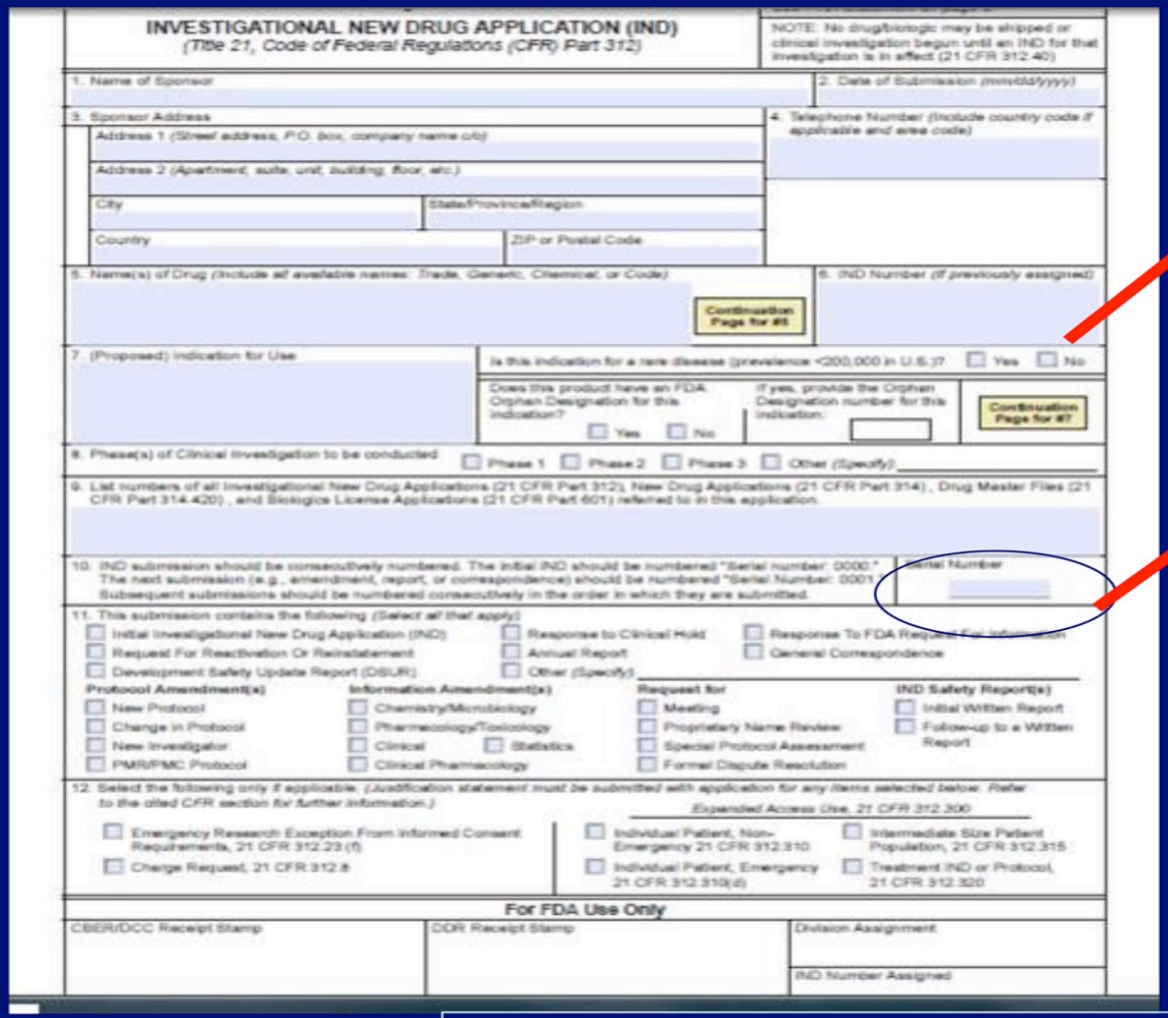
Investigational New Drug (IND) Application

- **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

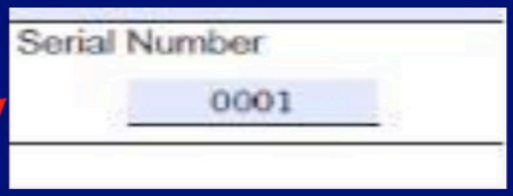
FDA 1571 and 1572 forms, info about sponsor & drug



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

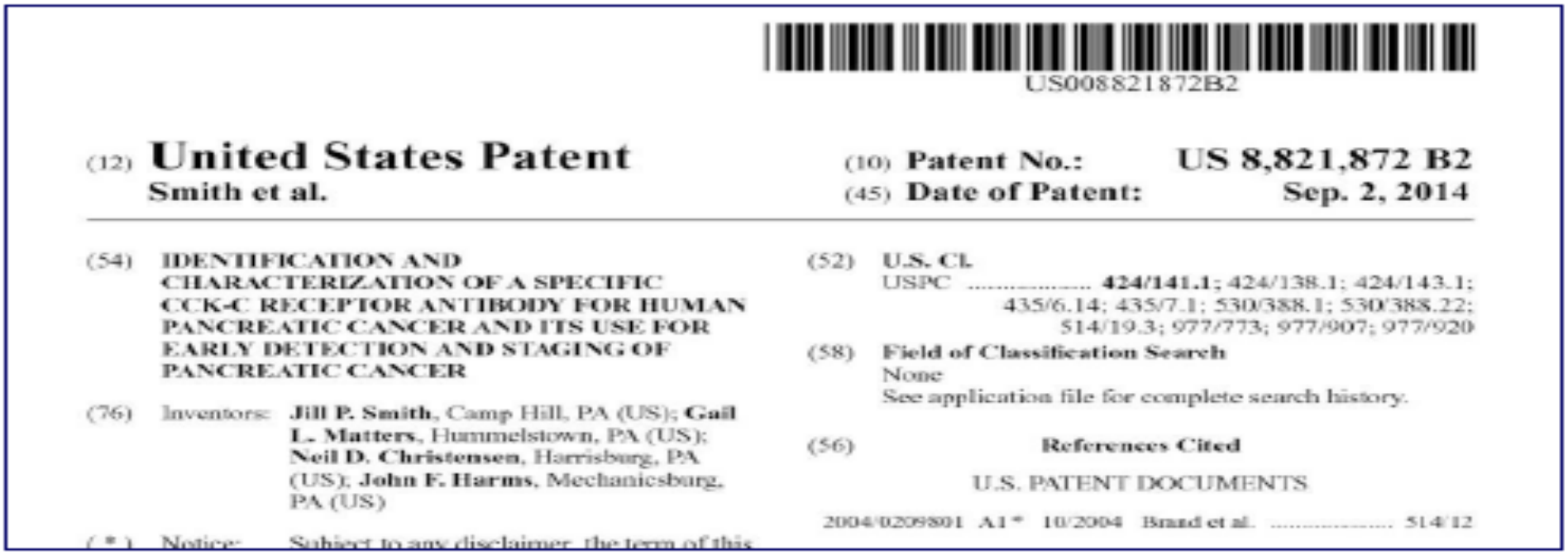


What are you Submitting or requesting In this report

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

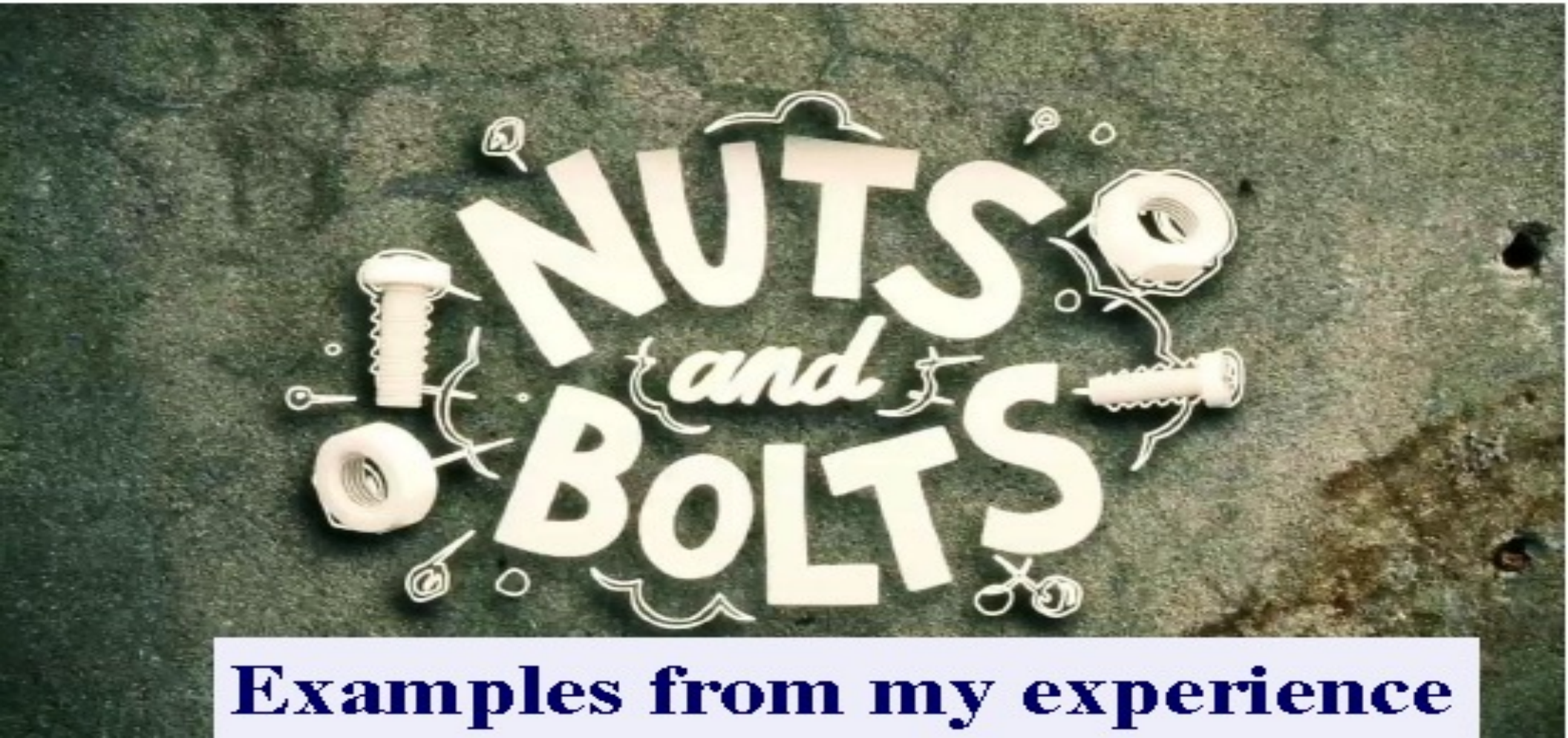
Clinical trials

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

Nuts and bolts

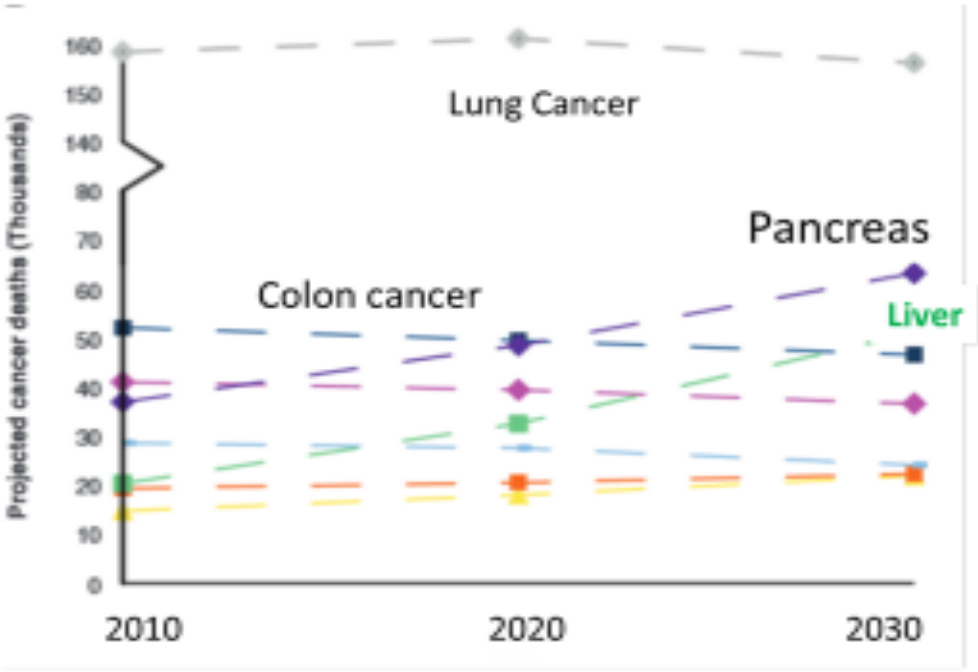
How Do You Do It?



Pancreatic cancer research

My Research in Pancreatic cancer

- 2nd leading cause of cancer-related deaths in the United States; about 58,000/yr
- The median survival with Standard of Care therapy less than 1 year
- Five year survival is approximately 9.3%.
- Most cases are not diagnosed in the early stages- 90% are not resectable.
- 85-90% arise from Precursor PanIN lesions
- 90% have no family history



Rahib L et al. Cancer Res 2014;74:2913-2921

CCK receptors

Cholecystokinin Receptors: GPCRs

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

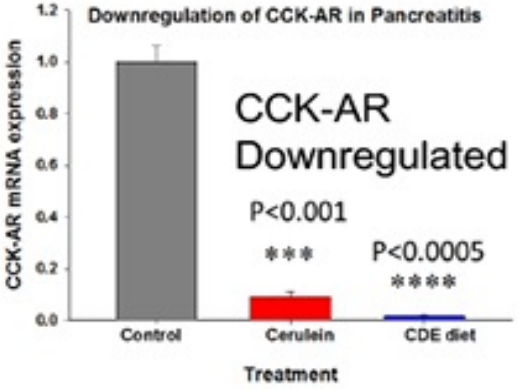
- CCK-B: Also called CCK-2R
  brain, stomach
  Binds CCK = Gastrin (1:1)

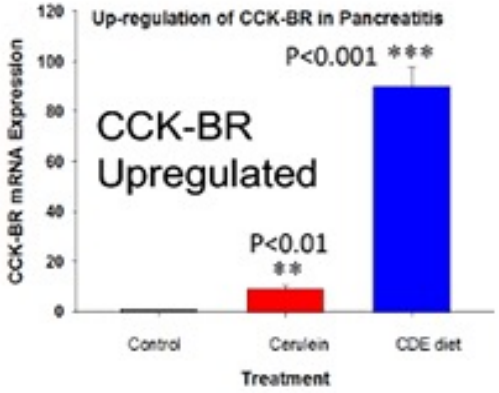
- CCK-C: pancreatic cancer, splice variant of CCK-BR; Only found in human cancer, not rodents. Binds Gastrin > CCK (10:1)

CCK-B receptor

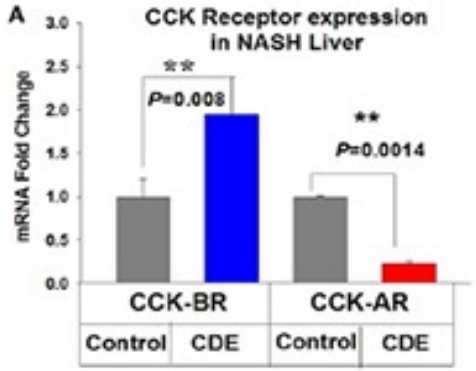
CCK-B Receptor has low expression in normal tissues

Inflammation activates CCK-BR expression- Pancreatitis





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

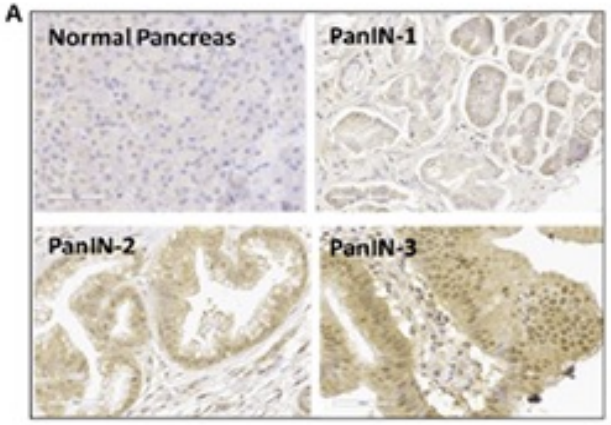


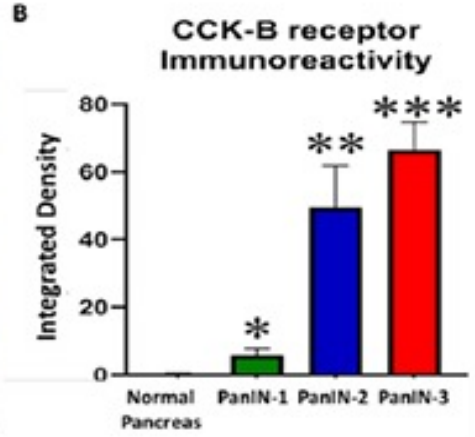
Inflammation activates CCK-BR expression- in hepatitis

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

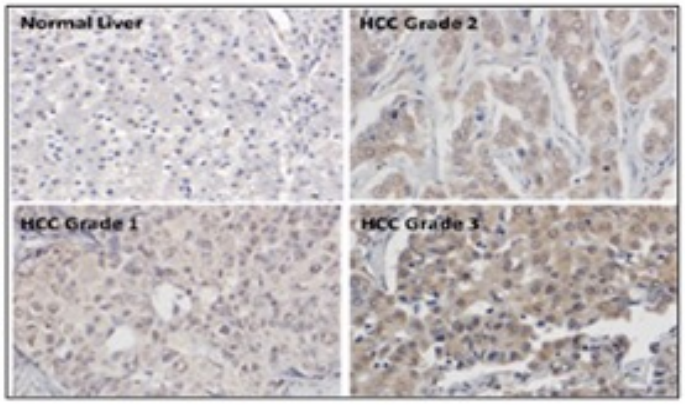
CCK-BR in cancer

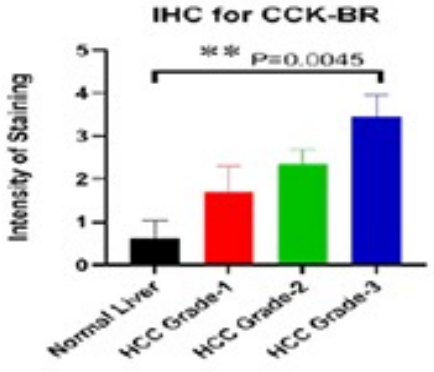
The CCK-BR is over-expressed in HUMAN HCC and Pancreatic





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





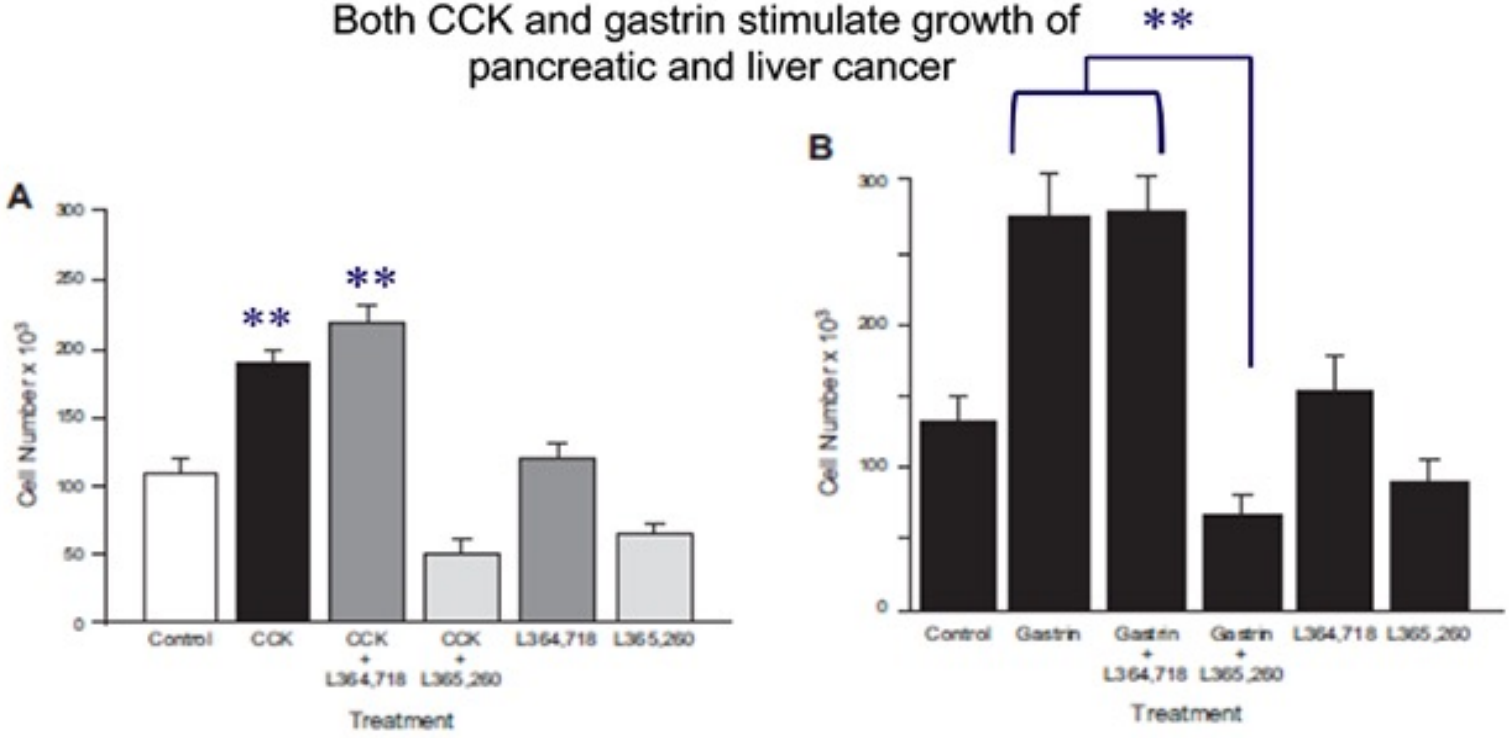
Bottom: CCK-BR is not detected in normal human liver, but is found in HCC and increases with grade of cancer

CCK-BR ligands

Ligands for the CCK-BR

There are two major ligands for the CCK-BR: cholecystokinin (CCK) and gastrin

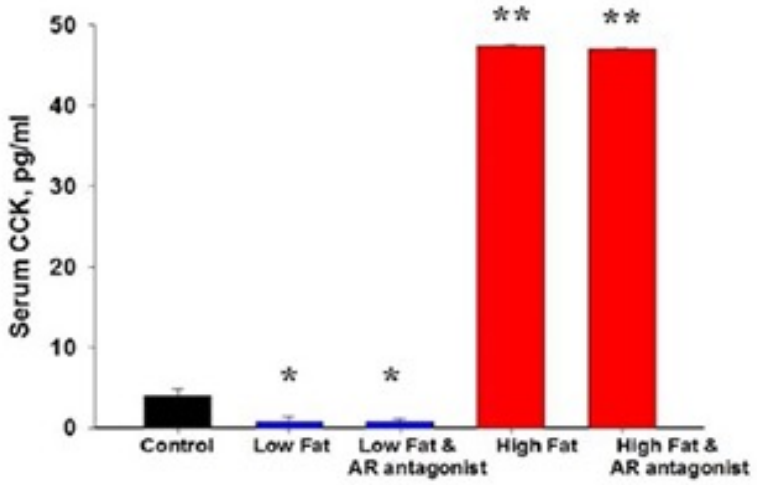
Both CCK and gastrin stimulate growth of pancreatic and liver cancer



Am J Physiol, 2014, PMID: 24177032

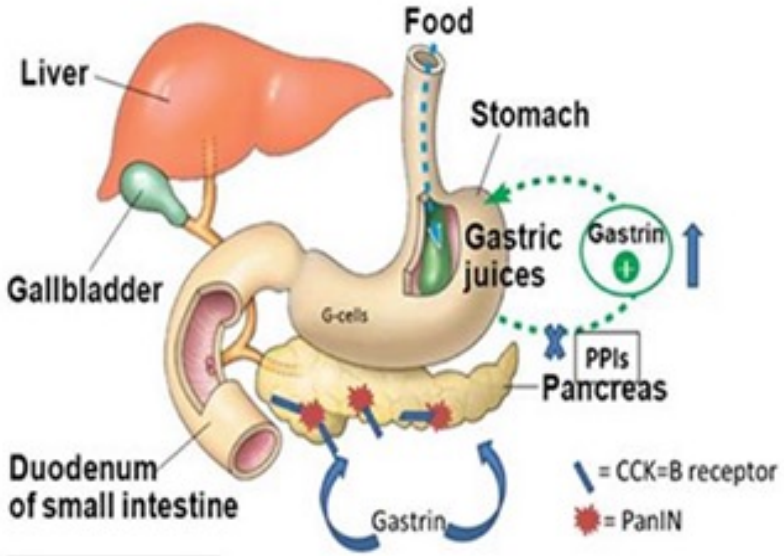
CCK and gastrin

Source of CCK and gastrin



CCK is increased by high fat diet

Am J Physiol 2018,
PMID: 29927319



Gastrin is elevated with high dose PPIs
And also becomes activated in PanIN

Pancreas 2019, PMID: 31268978

Strategy

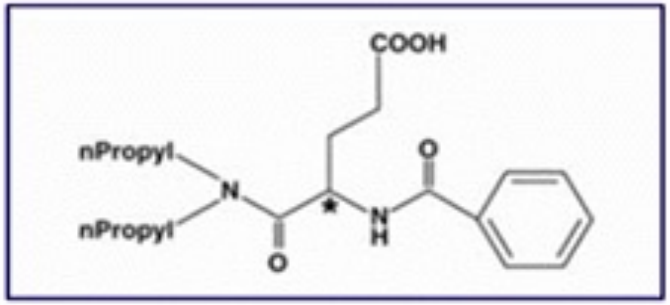
Strategy

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

Furthermore, we have shown that CCK-B receptors are expressed in stellate cells & activated fibroblasts and blockade of CCK-BR decreases fibrosis

Proglumide

Targeting the CCK-BR with small molecule- Proglumide



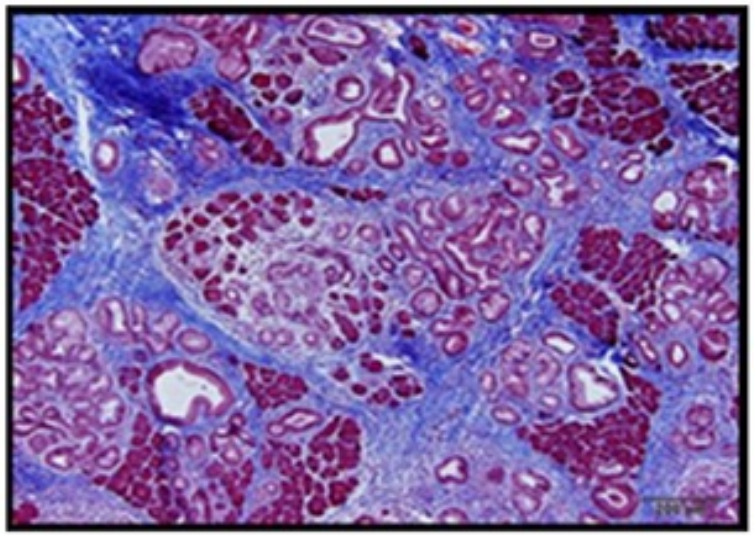
Older drug developed 30 years ago for ulcer disease.

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

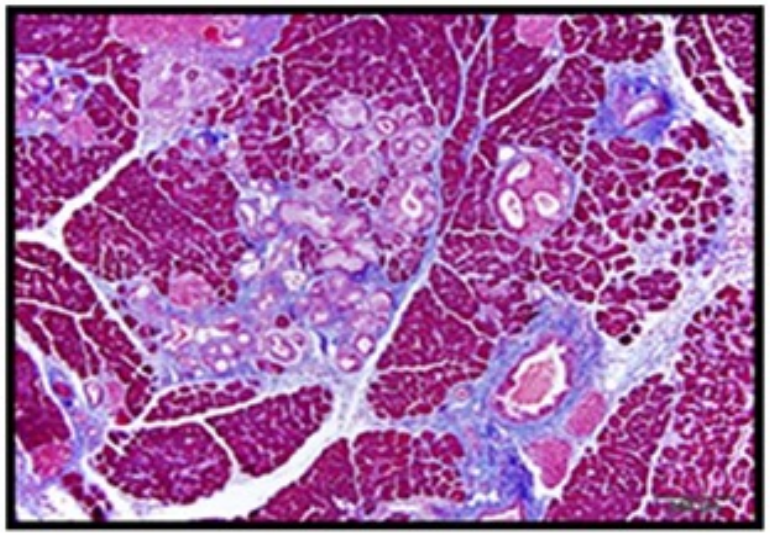
Proglumide

Proglumide prevents pancreas PanIN progression and fibrosis, Kras mouse model

Vehicle control



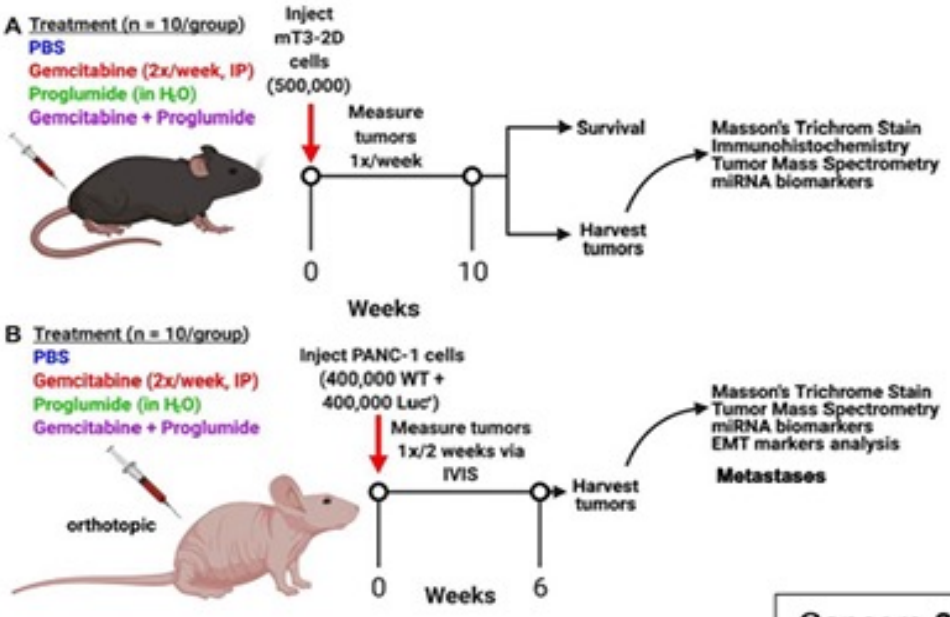
CCK receptor Blockade



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

Mouse models

Methods & Models for Studying Proglumide & Pancreatic Cancer



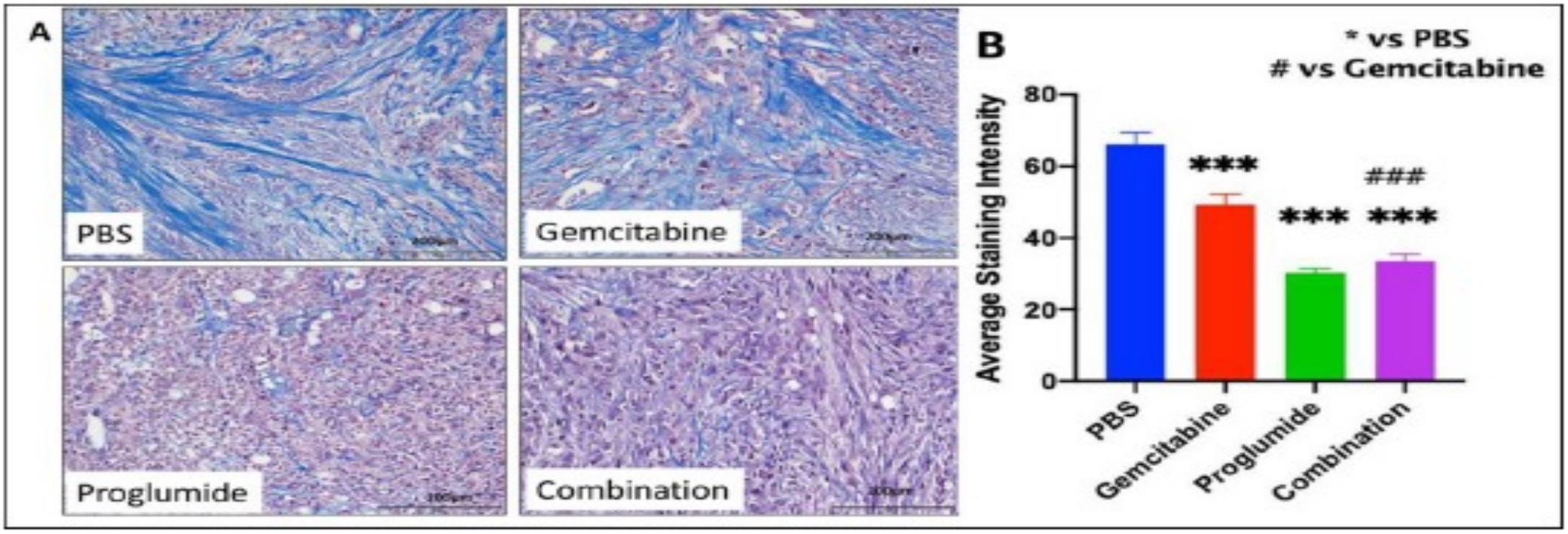
Immune Competent: mT3 murine PC cells grown subcutaneously in C57BL/6 mice to examine role of proglumide & gemcitabine on the TME & immune cells.

Immune deficient: PANC-1 human PC cells grown orthotopically in nude mice to examine the role of proglumide & gemcitabine on metastases and survival.

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

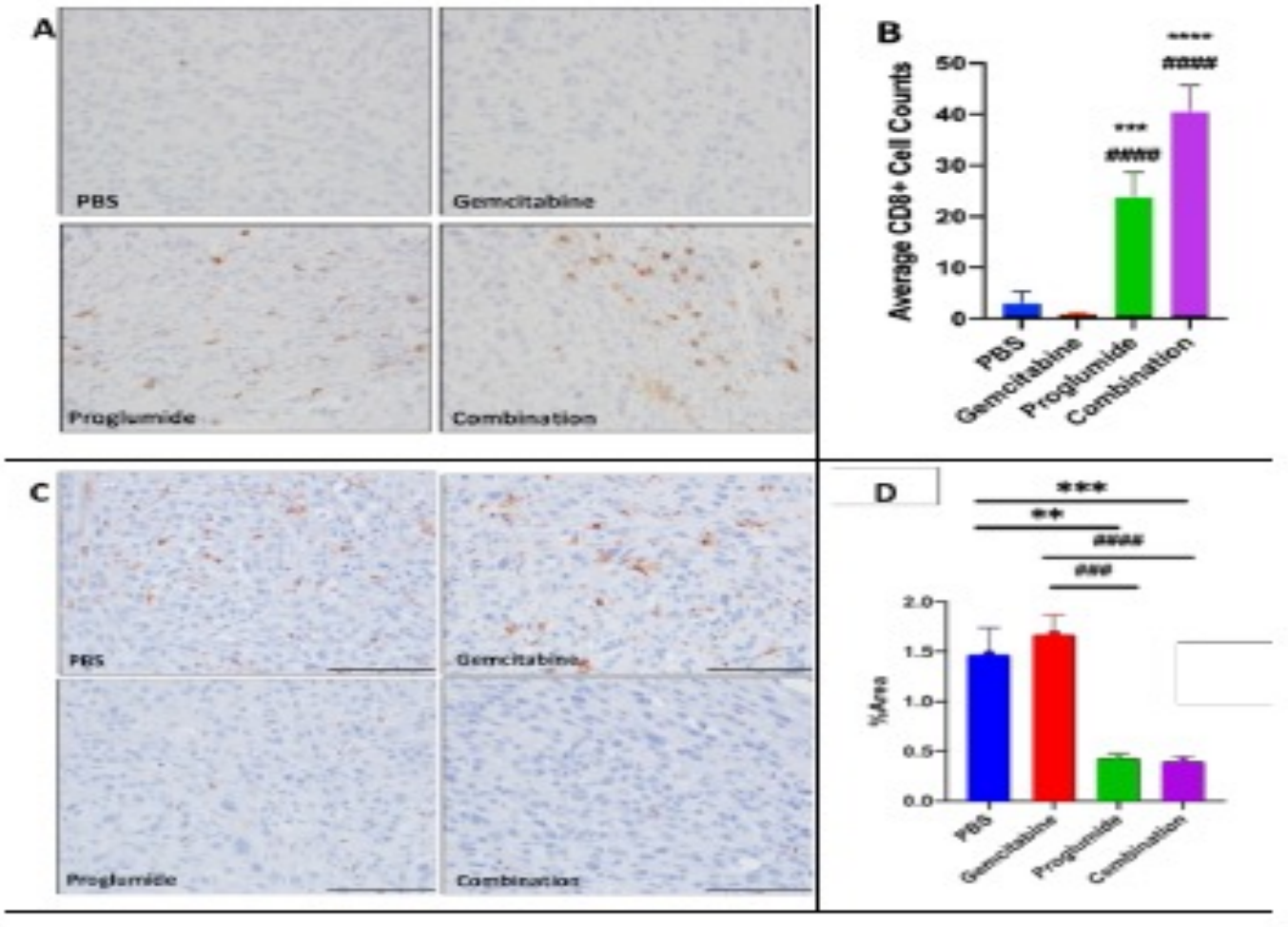
Proglumide reduces fibrosisTumor growth rate

Proglumide Decreases Fibrosis in TME



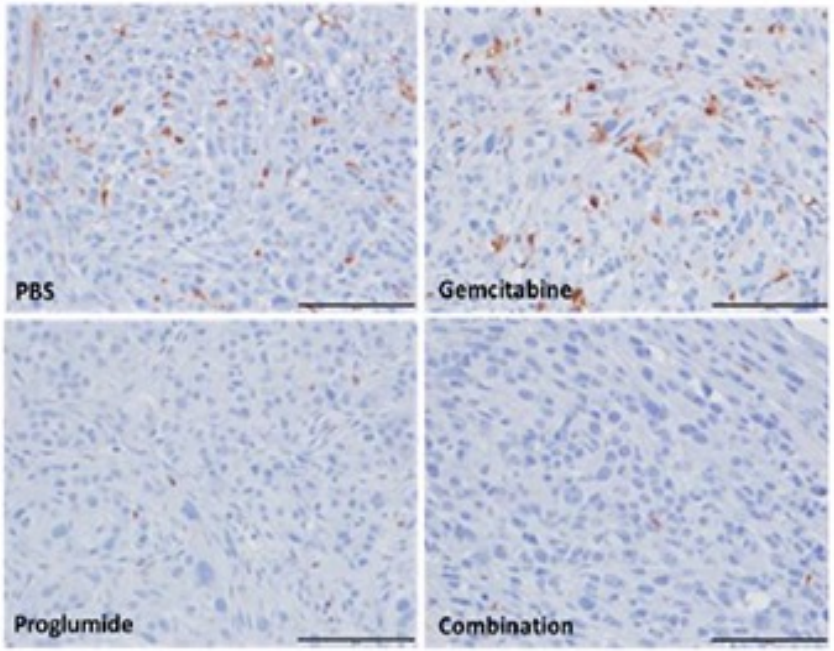
Proglumide

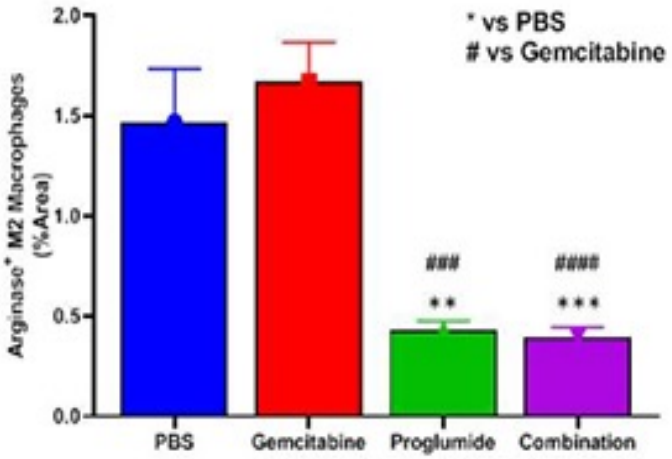
Proglumide increases influx of CD8+ cells and decreases M2-polarized TAMs



TAMS

Proglumide Alters the Tumor Immune Cell Signature: M2-polarized Tumor Associated Macrophages (TAMS)



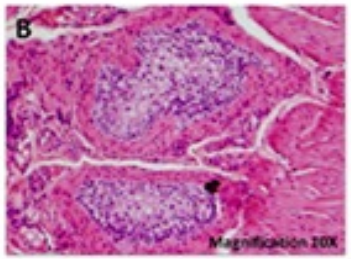


Representative tumor sections from each treatment group stained with arginase to show immunoreactive M2-polarized macrophages. TAMs are abundant in the TME of controls and mice treated gemcitabine. TAMs were significantly decreased in tumors of mice treated with proglumide or the combo; ** $P < 0.005$; *** & ### $P < 0.001$; **** & #### $P < 0.0001$).

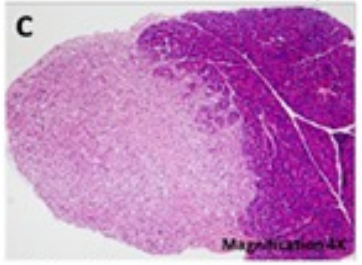
Metastases

Metastases were Significantly Decreased in Mice with PANC-1 Tumors Treated with the Combination Therapy

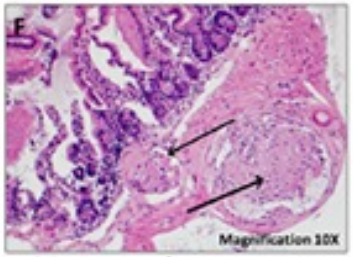
All metastases were confirmed by histology and read by our Pathologist



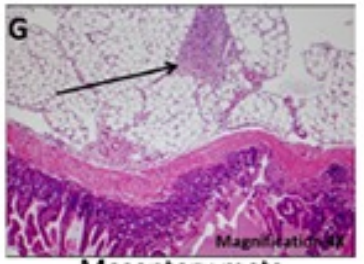
Tumor emboli muscle



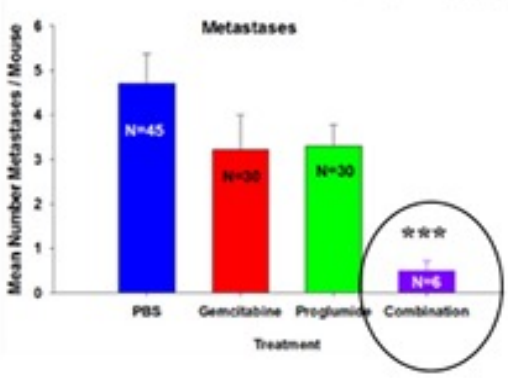
Liver Metastases



Mets to colon



Mesentery mets

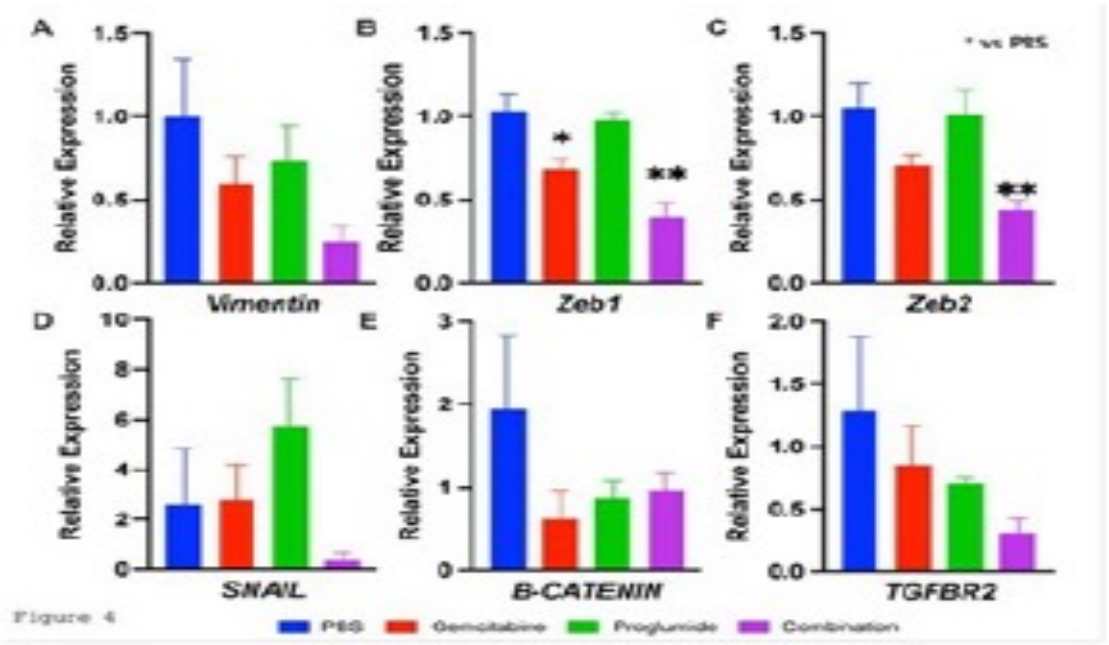


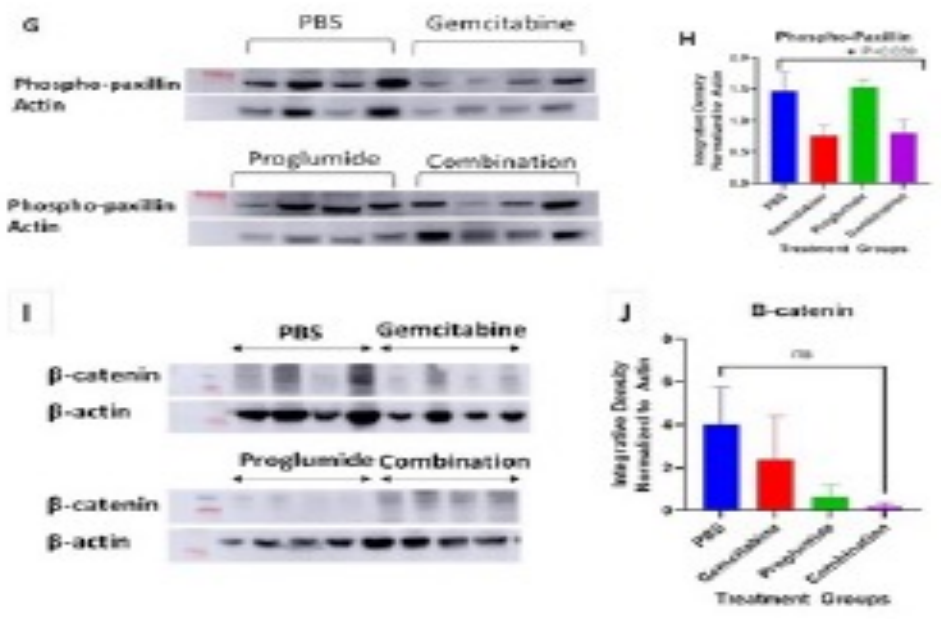
Group	Liver	Mesentery/ Peritoneum	Nodes	Spleen	Diaphragm	Abdominal Wall	Stomach	Colon
PBS	4	22	2	5	1	2	6	3
Gemcitabine	4	12	1	5	0	1	2	5
Proglumide	2	18	2	1	0	2	2	3
Combination	0	3	0	1	1	0	0	1

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

Proglumide and gemcitabine

CCK receptor blockade prevents metastases by blocking EMT

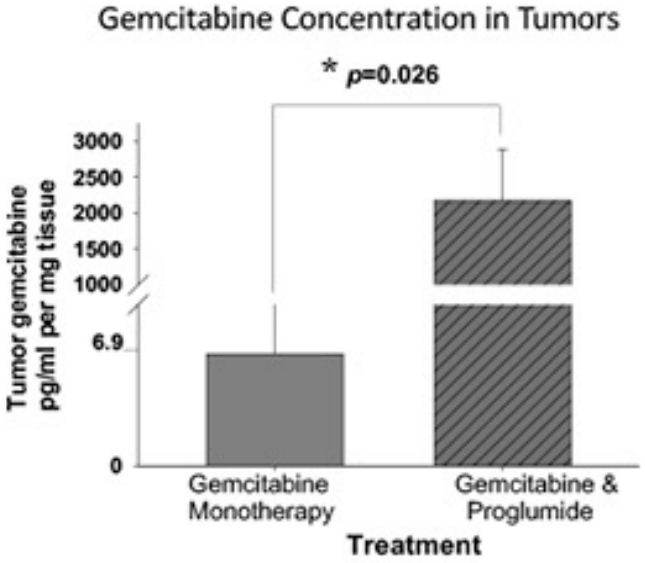




Plans: Proglumide approval as orphan designation in pancreatic cancer IND files and approved. IRB protocol approved. Clinical trial planned to add proglumide to standard of care therapy. Funding- grant being reviewed.

Gemcitabine levels

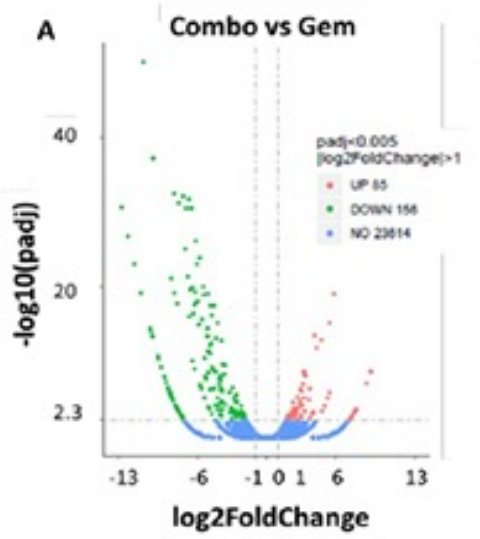
Measurement of Tumor Gemcitabine Levels by Mass Spectroscopy



- 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.

Differentially expressed genes

Differentially Expressed Genes by RNAseq between Gemcitabine monotherapy compared to combination therapy with proglumide



B

Down Regulated	Myl4	Cancer Cachexia
	Pvalb	Activation PSC
	Actn2	Tumor invasion
	Prkag3	mTOR signaling
	Rgs7	G-protein regulator
	Il-10	Promotes tumor immune escape
	Wisp2	Migration & metastases
	Hoxa3	Promotes tumor growth
	Fbln7	Pro-angiogenesis
Up-Regulated	Cldn7	Tumor Suppressor
	Gc	Vit D binding protein
	Reg1	Inhibits PSC activation
	Pcdhga7	Tumor Suppressor

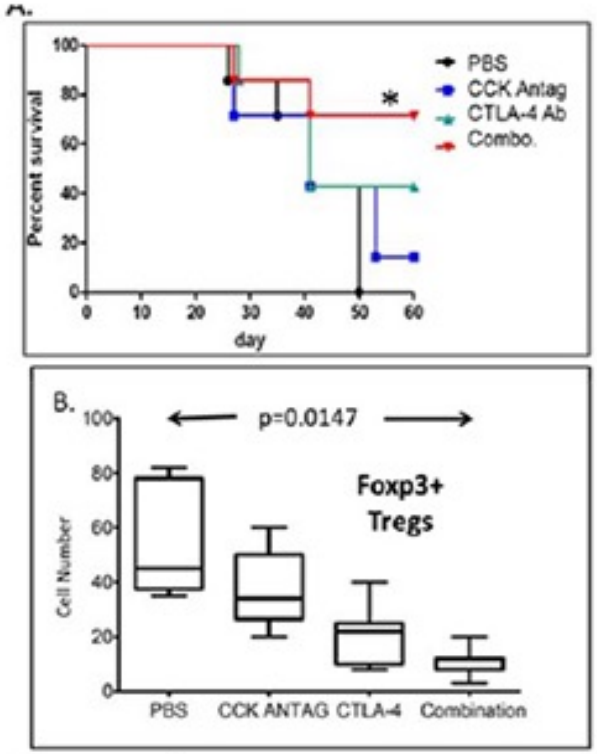
A. A volcano plot shows 85 genes that are upregulated Log2-fold and 156 genes that are downregulated in the combination therapy group compared to gemcitabine monotherapy.

B. Thirteen novel genes were identified that previously have not been reported

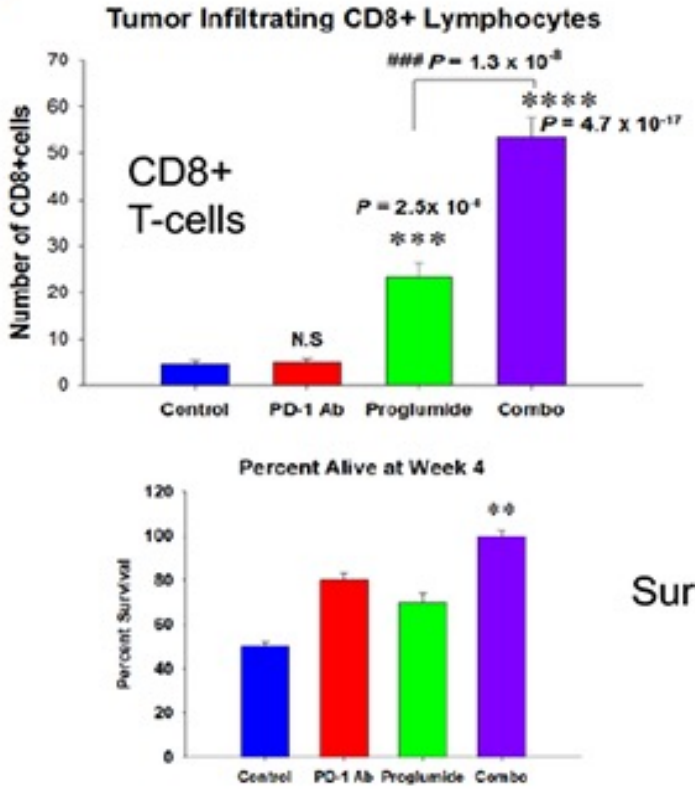
Total RNA was extracted from tumors of gemcitabine- treated and Combination-treated mice and subjected to RNAseq.

Immune checkpoint Abs

Proglumide Improves Efficacy of Immune Checkpoint Abs



Pancreatic cancer
Cancer Immunol Immunother. 2018
PMID: 29043413



Survival

Liver cancer and PD-1 Ab
ASCO GI, Abstract 2022

Summary

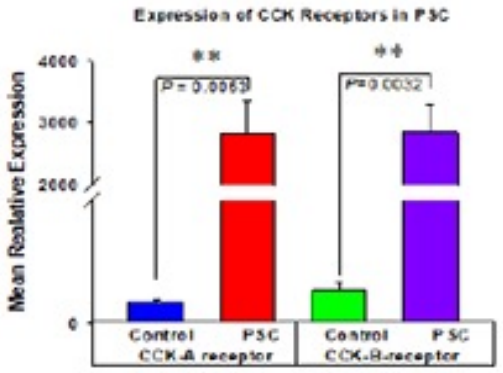
Summary Proglumide and Cancer

1. Proglumide inhibits pancreatic & liver cancer growth by blocking the actions of CCK and gastrin at the CCK-BR.
2. Proglumide therapy potentiates the efficacy of chemotherapy and immune checkpoint abs by decreasing tumoral fibrosis and rendering the tumor microenvironment less immunosuppressive.
3. Georgetown holds IP for combination therapy with proglumide
4. Also have Orphan Designation of proglumide in pancreatic cancer

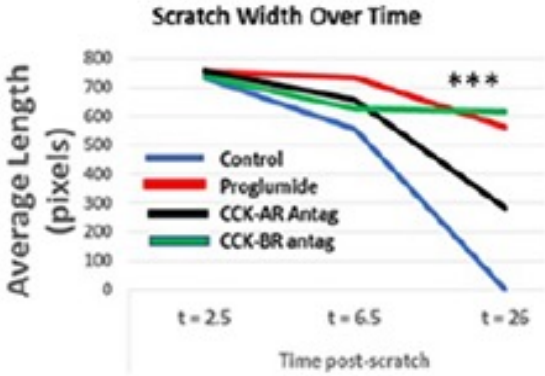
Fibrosis

Stellate Cells – Fibrosis - Proglumide

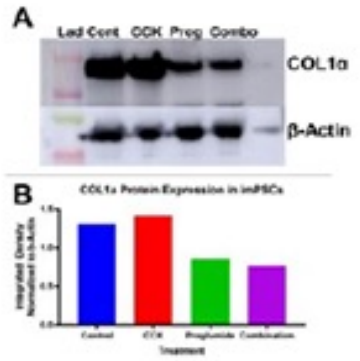
Do not Post



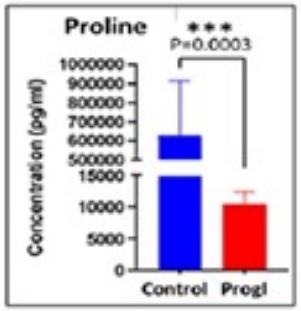
Pancreatic stellate cells express both CCK-AR and CCK-BRs (Unpublished).



Proglumide and the CCK-BR antagonist prevent PSC migration. *** P<0.0001.



Collagen-1α protein is decreased by proglumide in PSCs.

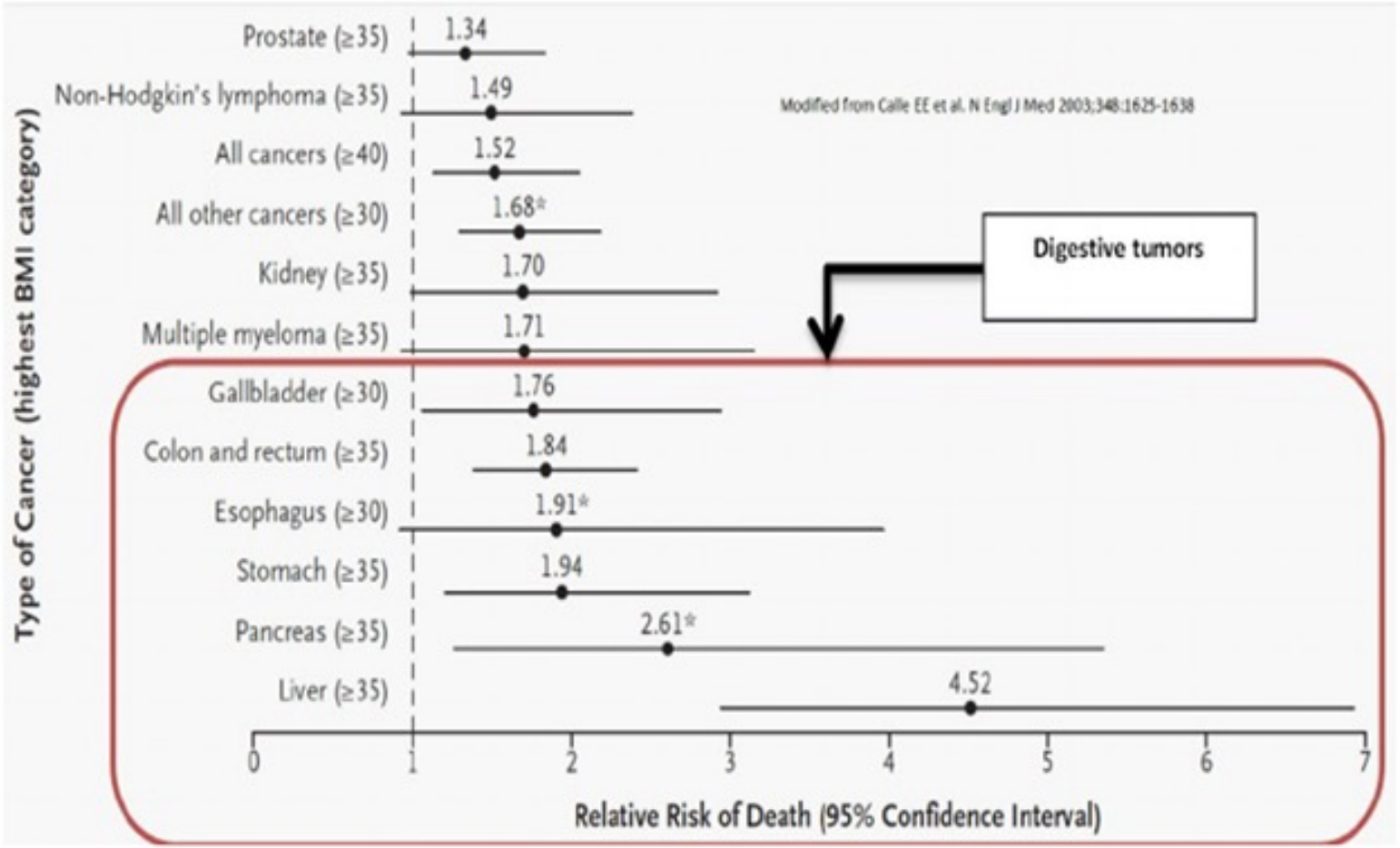


Proline is decreased in PSCs with proglumide.

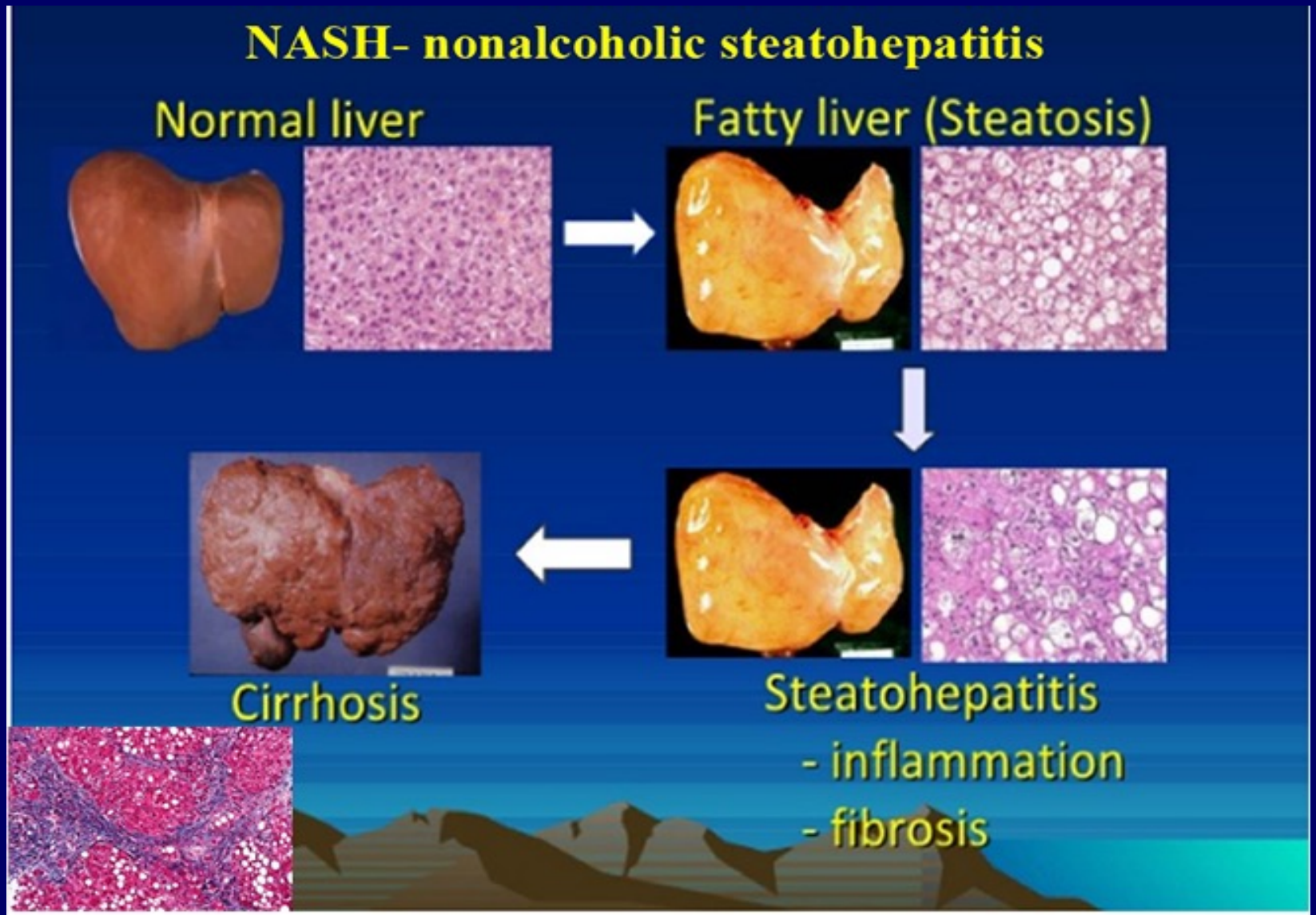
Proglumide decreases collagen and motility of stellate cells: Mechanism of action how proglumide decreases tissue fibrosis.

BMI

Mortality from Cancer based on BMI

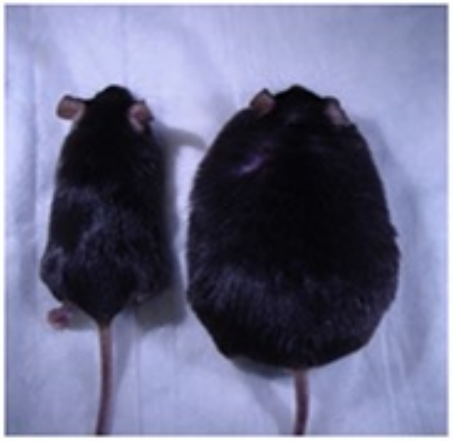


NASH


NASH- nonalcoholic steatohepatitis
Normal liver
Fatty liver (Steatosis)
Steatohepatitis
- inflammation
- fibrosis
Cirrhosis

Animal Models

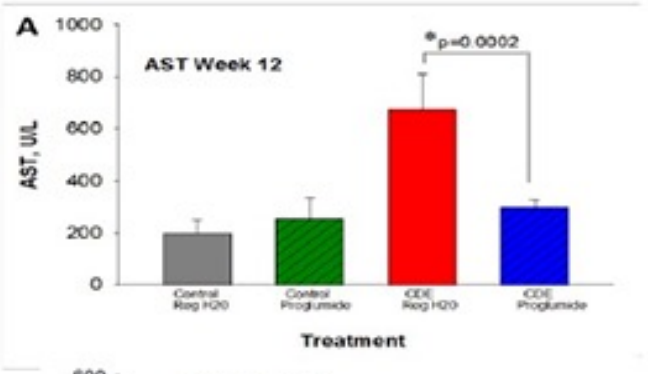
High Fat Diet Animal Models

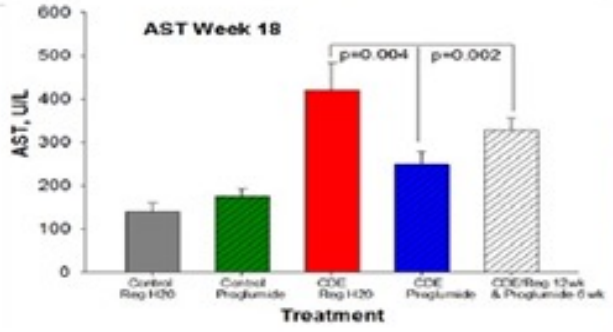


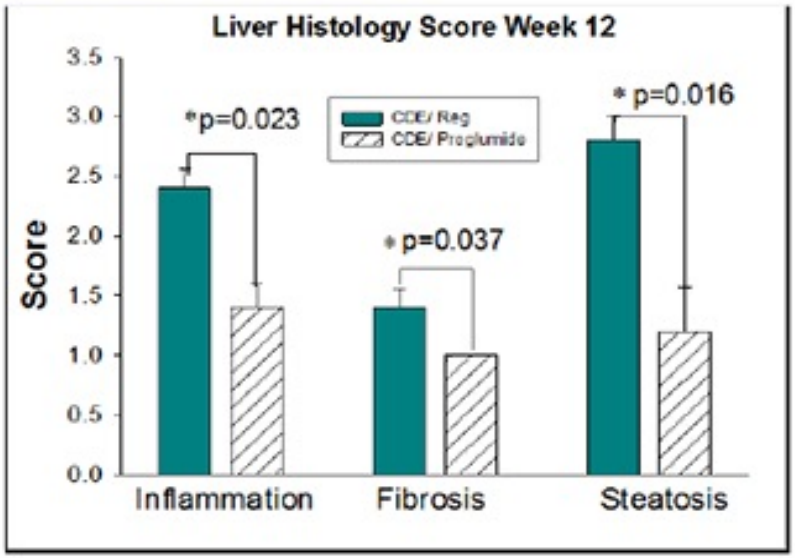
Low Fat Control High Fat

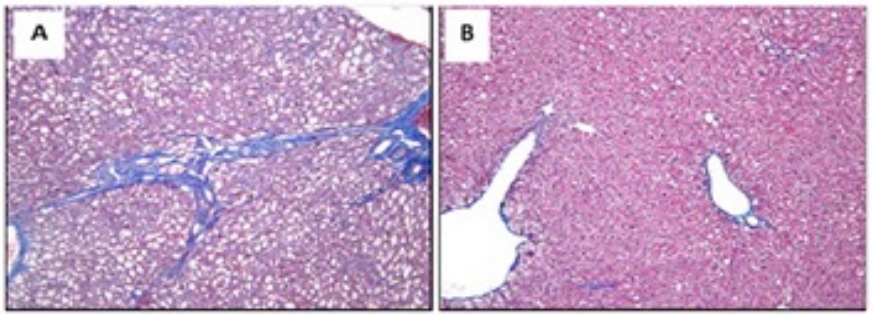
Proglumide reverses NASH

Proglumide reverses NASH in High Fat CDE mouse model









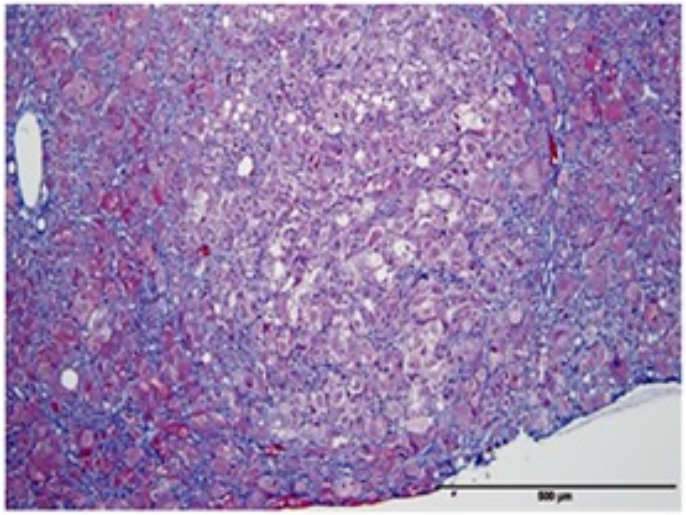
Control Proglumide

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

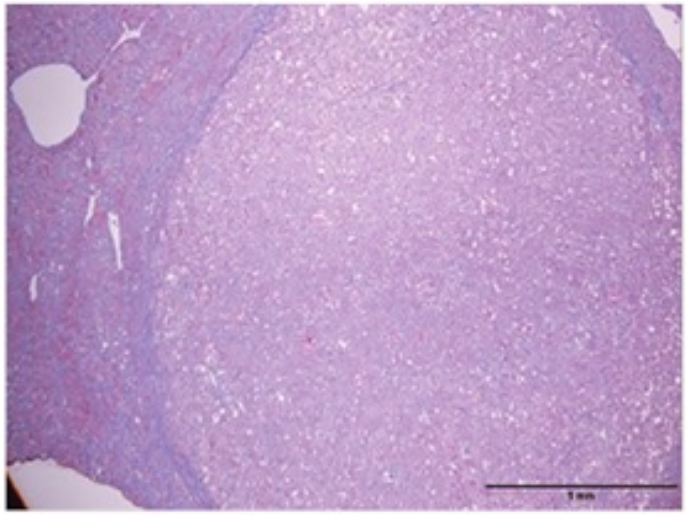
HCC prevention

Proglumide Prevented HCC

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



Week-18, CDE/Reg 10X
Dysplastic Nodule



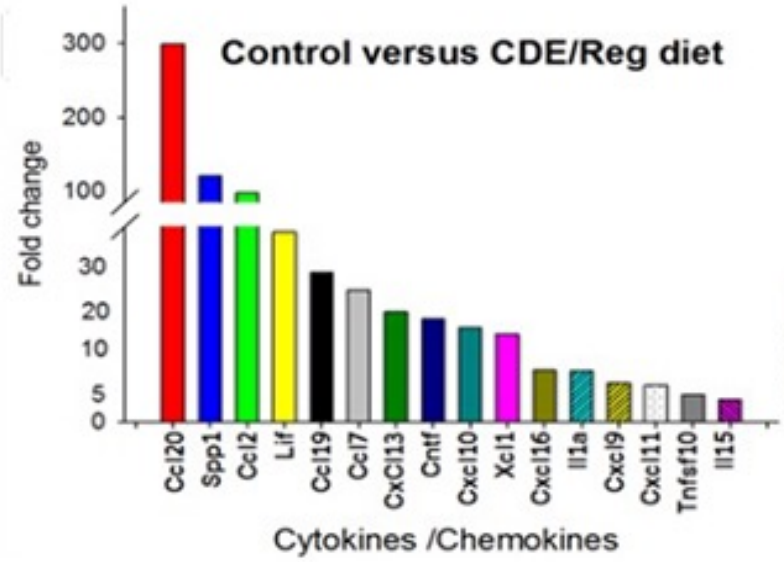
Week-18, CDE/Reg 4X
Hepatocellular Cancer

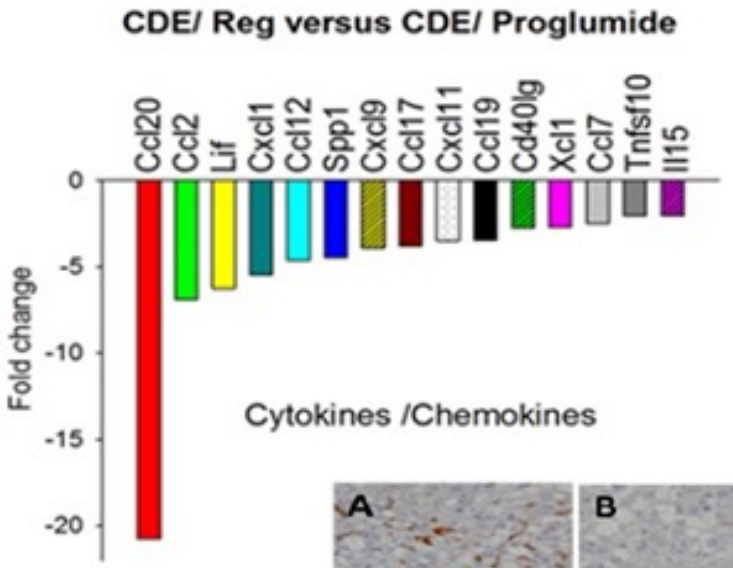
Normal Mouse
Liver

Mice on CDE diet show
several foci of HCC

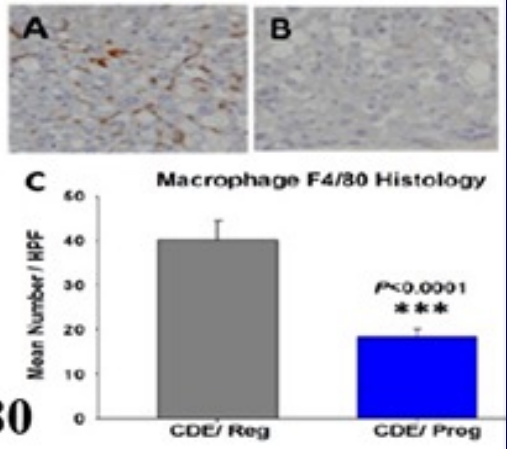
Cytokines

Proglumide decreases hepatic cytokines & chemokines





Proglumide decreases liver cytokines & chemokines, and decreases liver Activated macrophages.



Cancer Prev Res 2021;14:17–30 PMID: 33115780

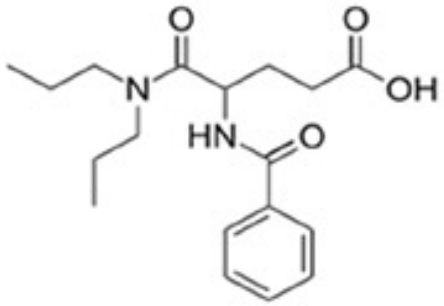
Clinical studies

Clinical studies Bench to Bedside

Phase 1 Study

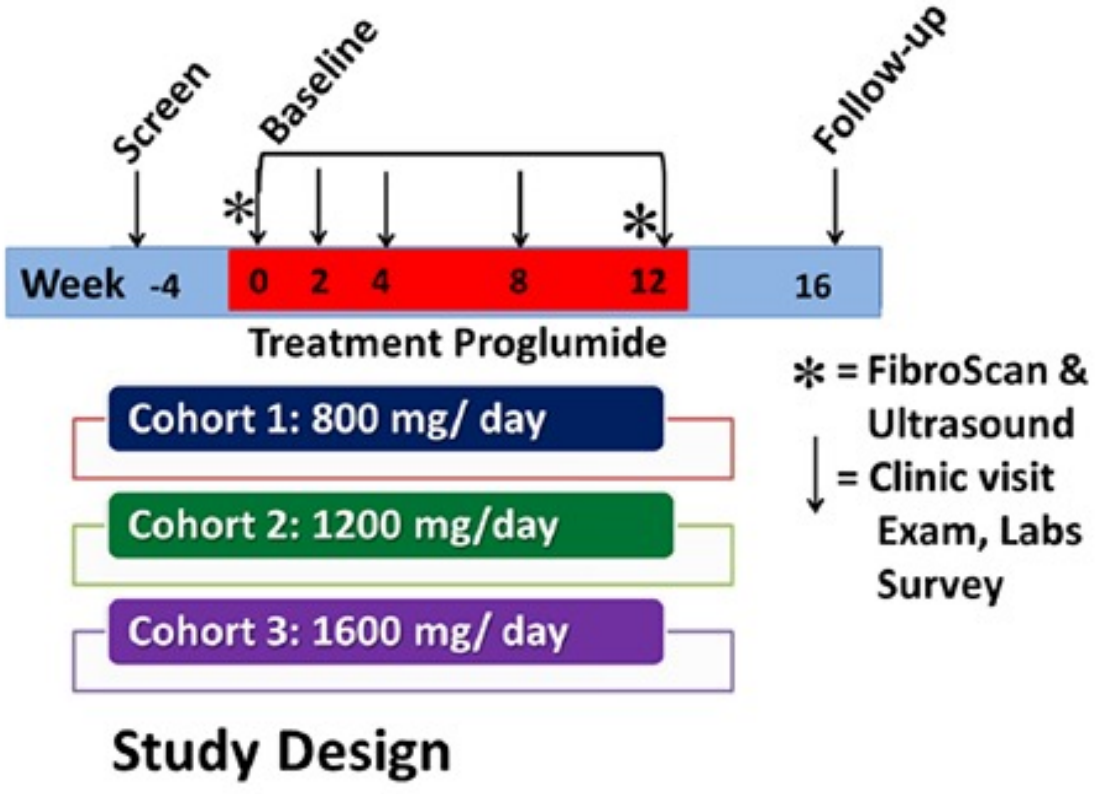
Phase 1 Study in NASH

Published Clinical Pharmacology & Therapeutics



Proglumide

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



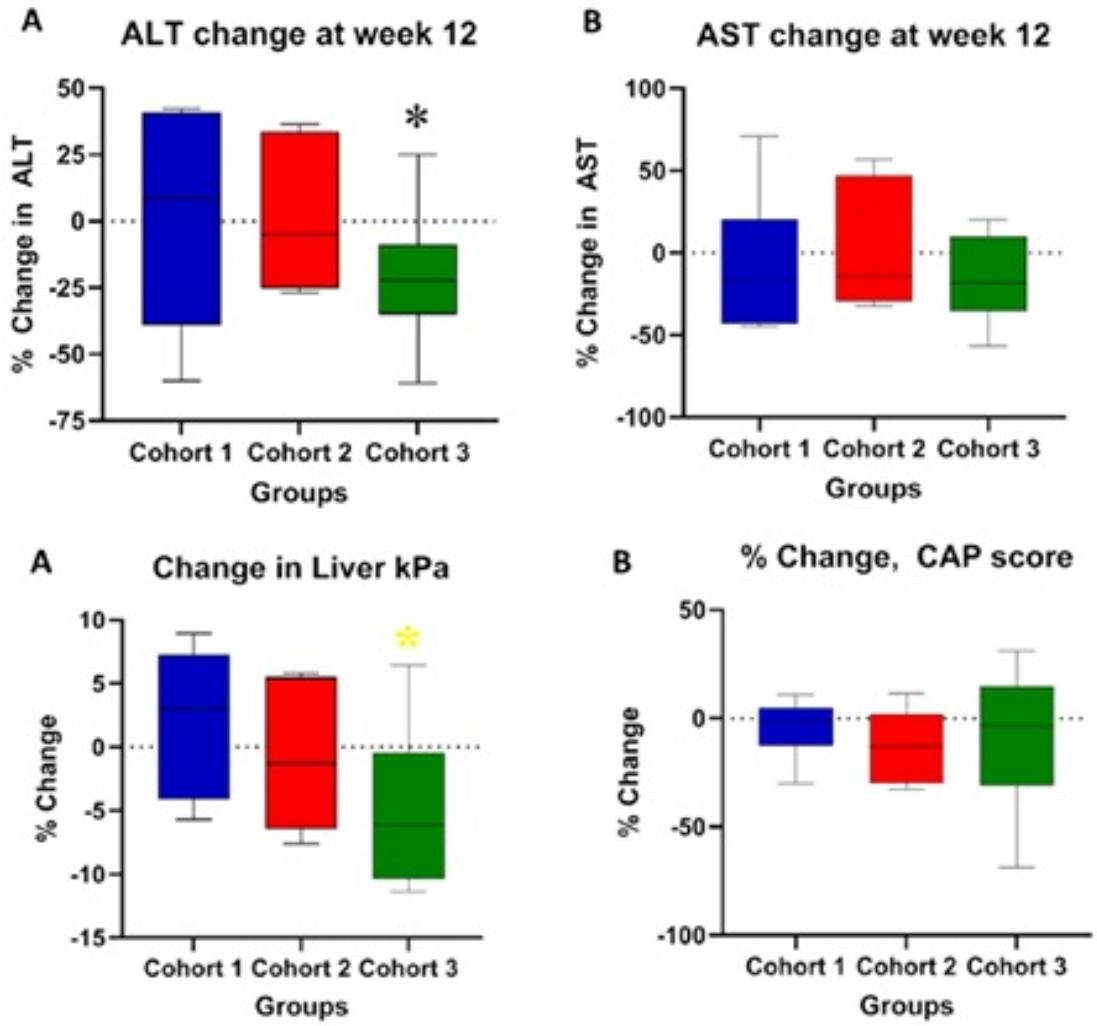
Study Design

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

Proglumide in NASH

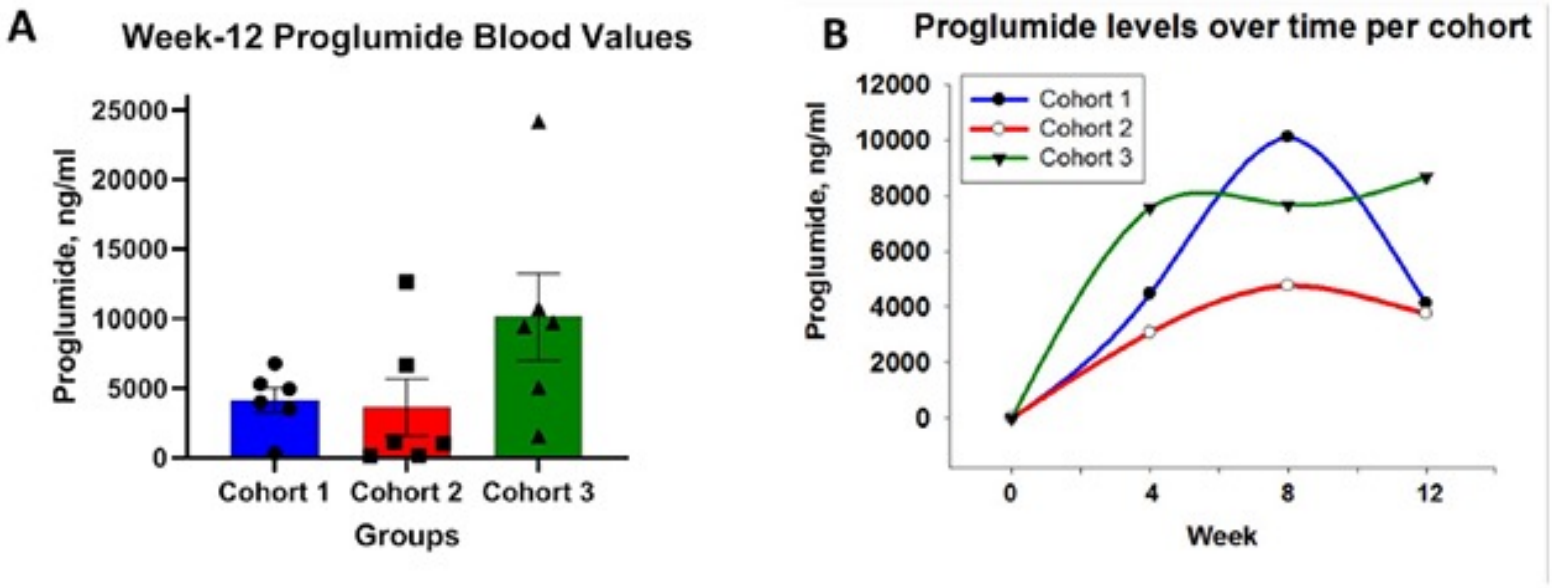
Proglumide in NASH

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



Proglumide blood levels

Proglumide blood levels
From Phase 1 study

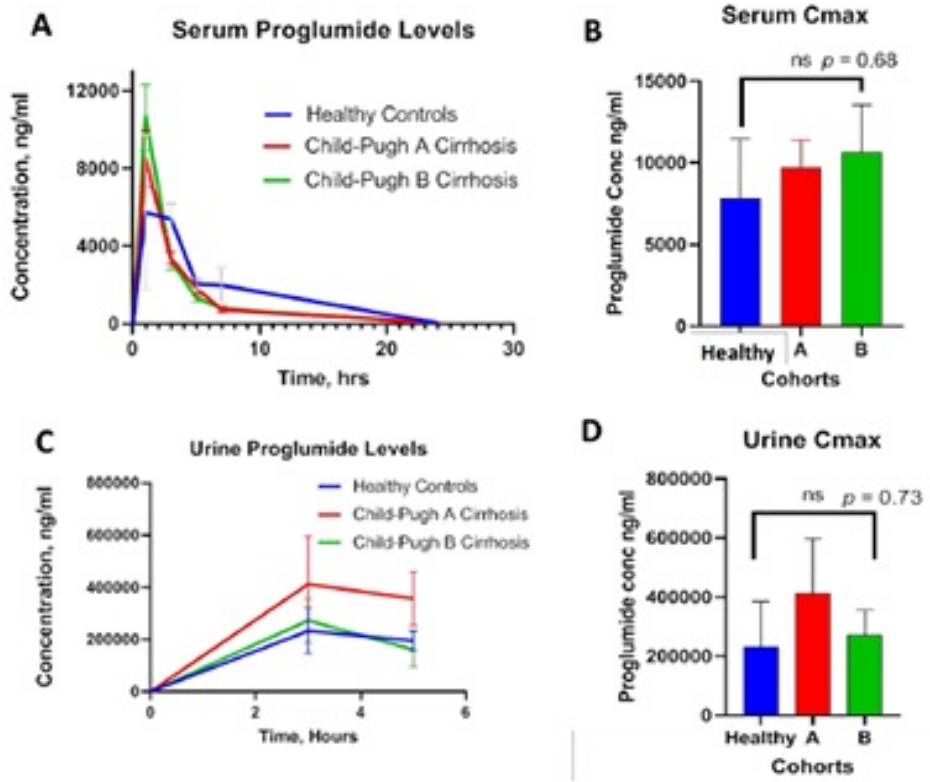


AEs: Only mild, none in Cohort 3 and no one had to discontinue drug

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

Proglumide in liver impaired

Proglumide in Hepatic Impaired; Child Pugh A& B Cirrhosis

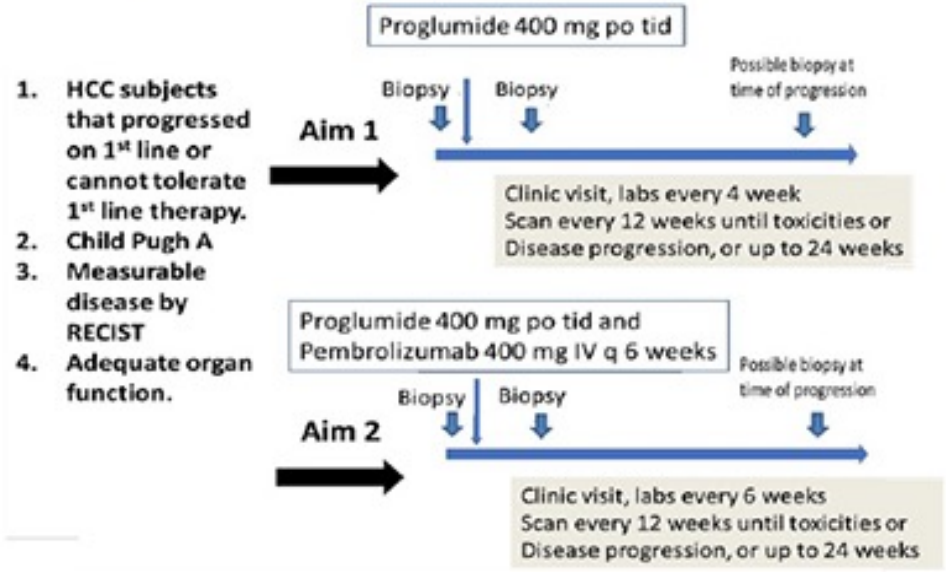


Pharmaceutics. 2022 Mar 12;14(3):627. PMID: 35336003;
www.clinicaltrails.gov (NCT04814602)

Proposed studies

Proposed studies

1. HCC subjects that progressed on 1st line or cannot tolerate 1st line therapy.
2. Child Pugh A
3. Measurable disease by RECIST
4. Adequate organ function.



HCC Clinical study
± PD-1 Ab

SOC chemotherapy for pancreatic cancer
+ proglumide 1200mg/day N=6
+ proglumide 1600 mg/day N=6
Outcomes: Safety, survival, tumor biopsies

Pancreatic cancer study

Which way to go?

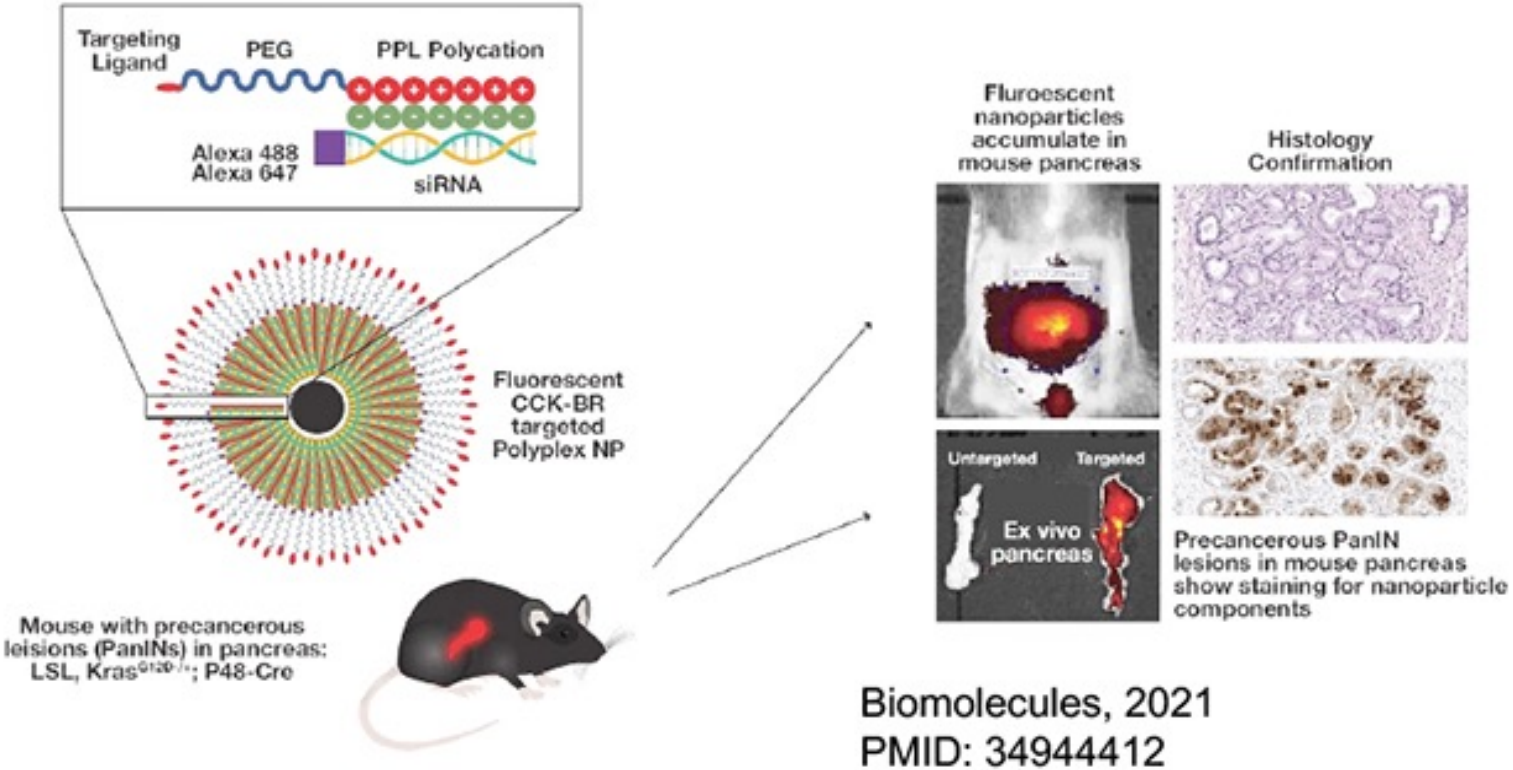
Which way to go?

Explore the anti-fibrotic effect in other diseases (cirrhosis, chronic pancreatitis)

Nanoparticle that targets the CCK-BR

CCK-BR imaging

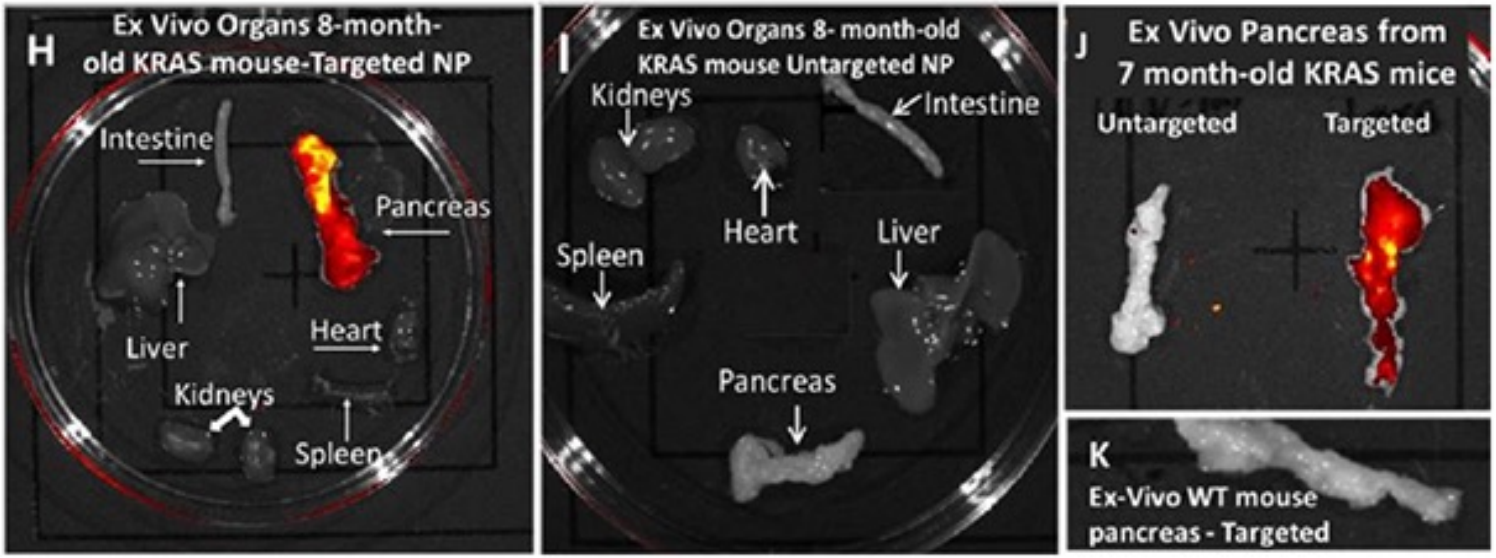
Using the CCK-BR as a Target for imaging and therapy



Biomolecules, 2021
PMID: 34944412

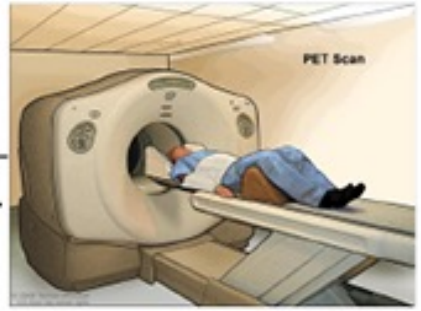
Nano-imaging

Nano-imaging Precancerous Pancreas Lesions



Biomolecules, 2021
PMID: 34944412

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



Smith lab