Bench to Bedside, Clinical Trials

TRACO-Translational Research : Bench to Bedside, Clinical Trials

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Disclosure

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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

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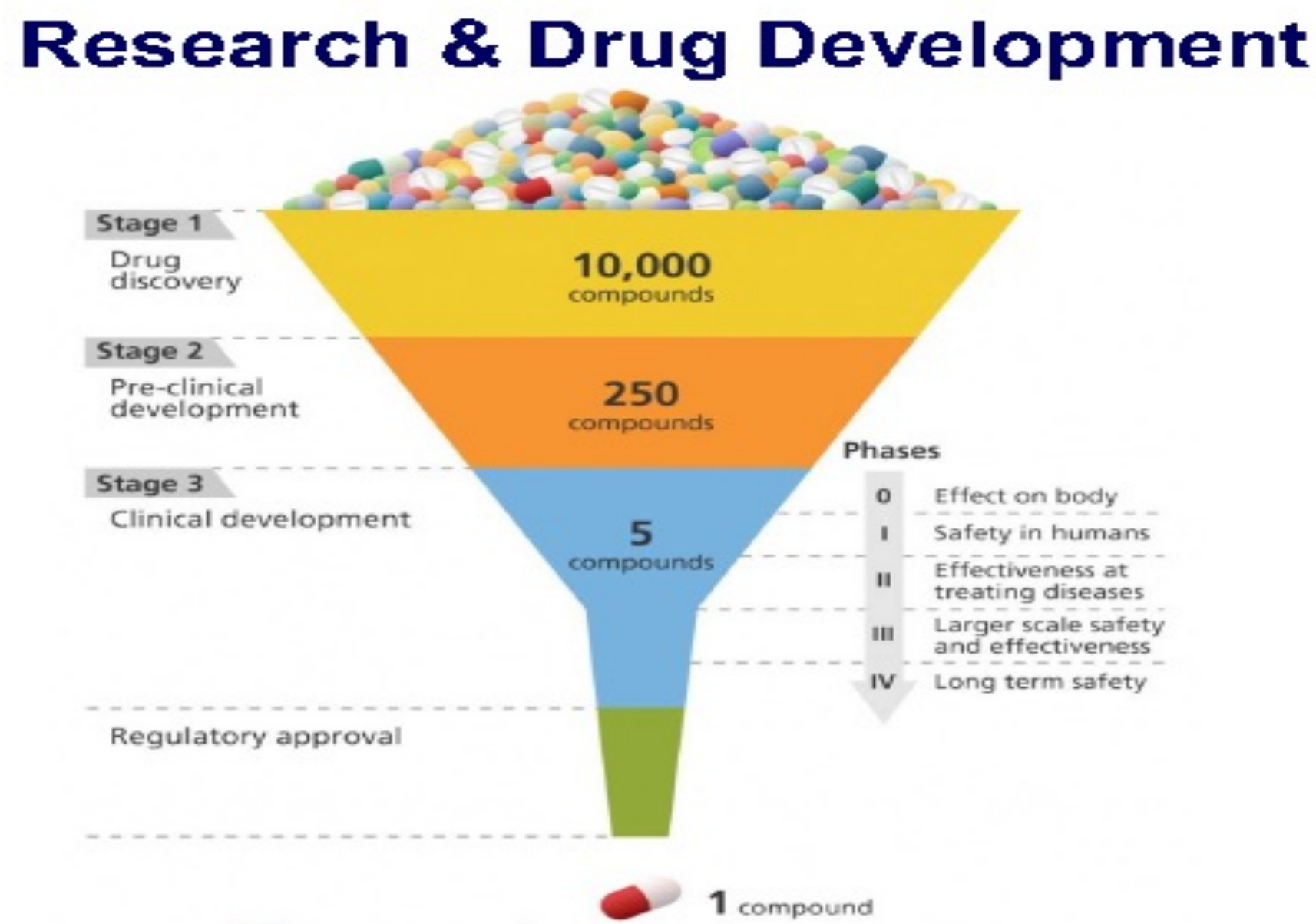
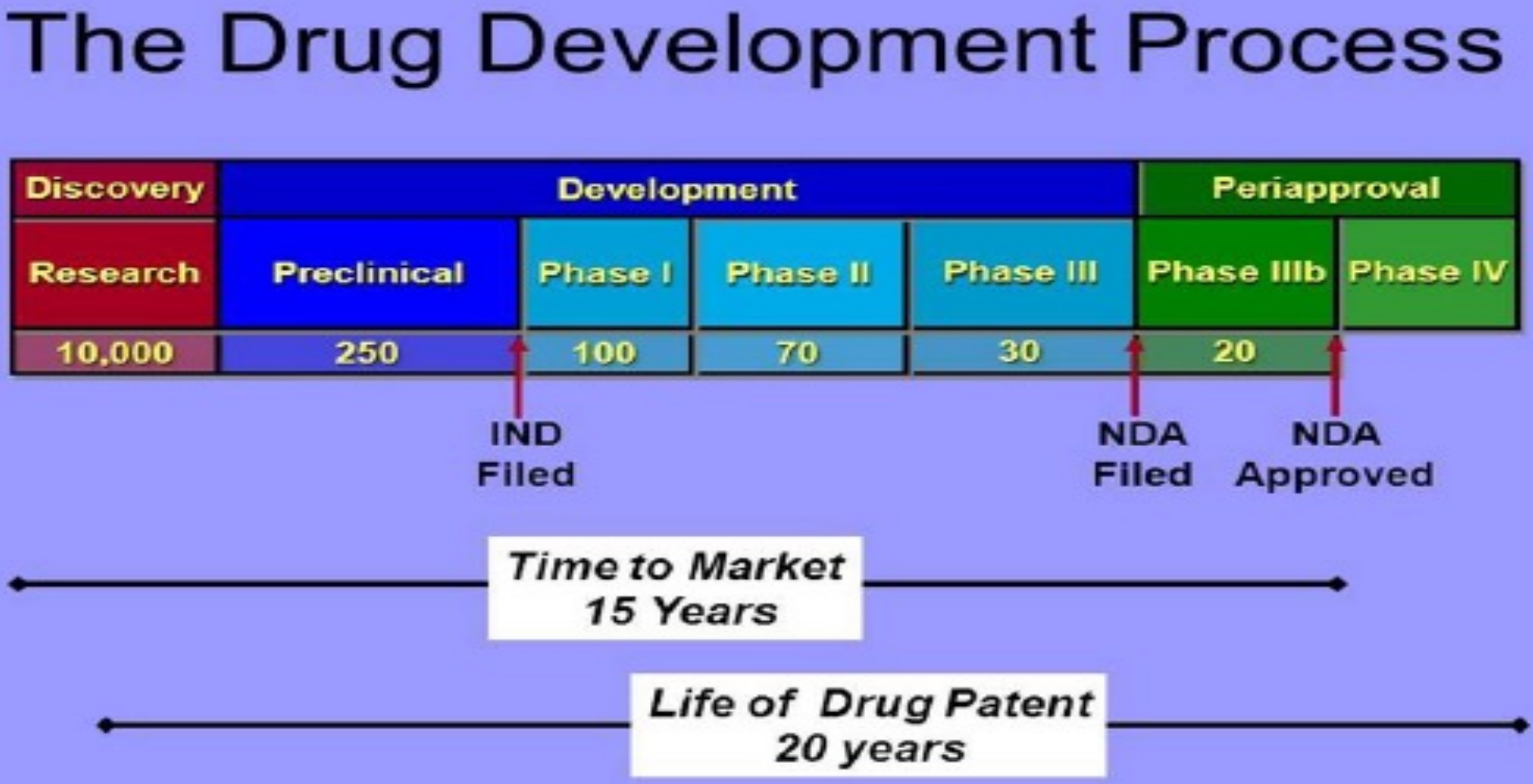
- Understand how an idea is taken from the research lab to patient care.
- Learn the steps in conducting clinical trials
- Understand some of the obstacles to overcome in drug development?
- Examples of my translational projects

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

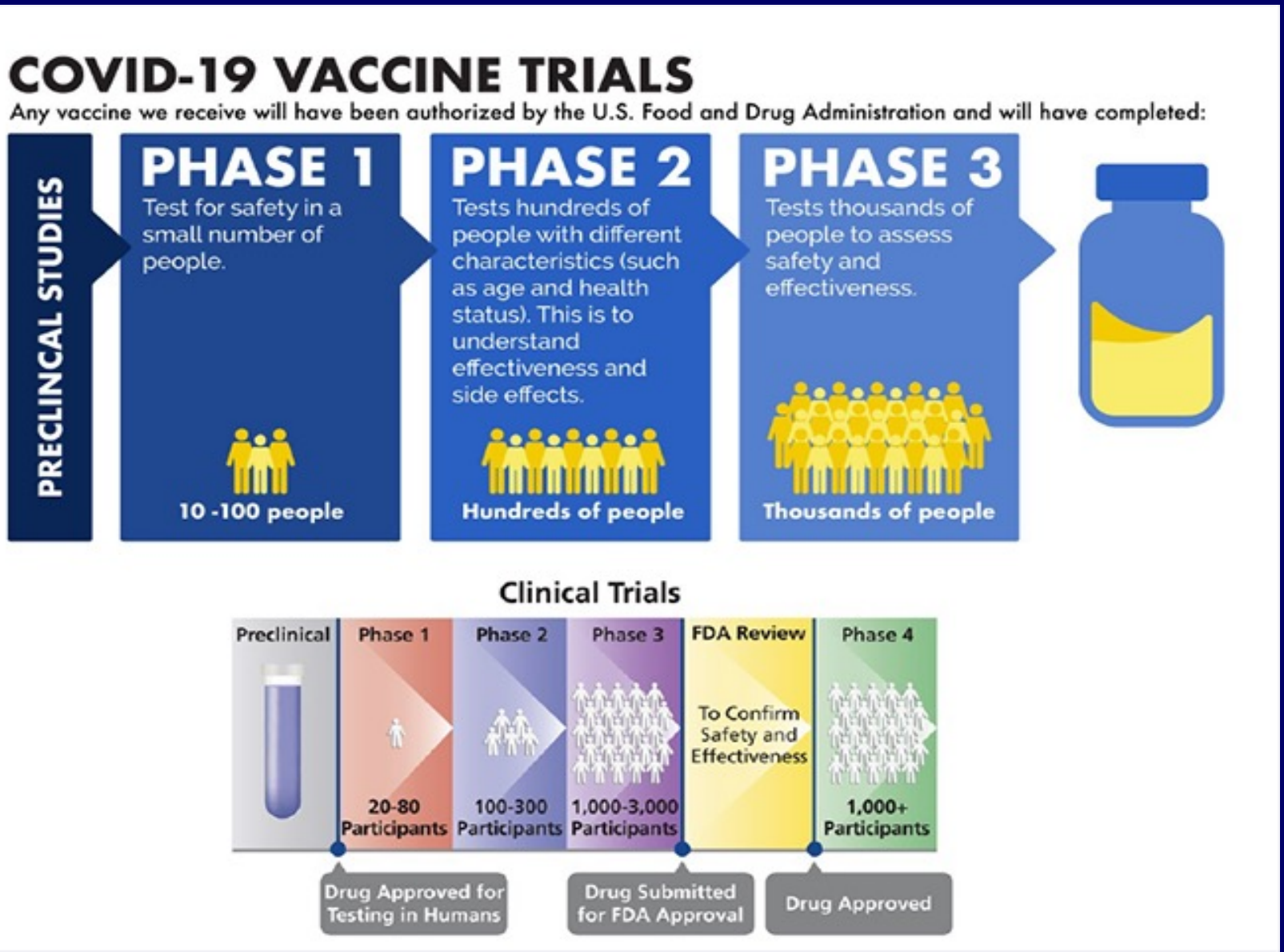
Phase 4

Phase 4

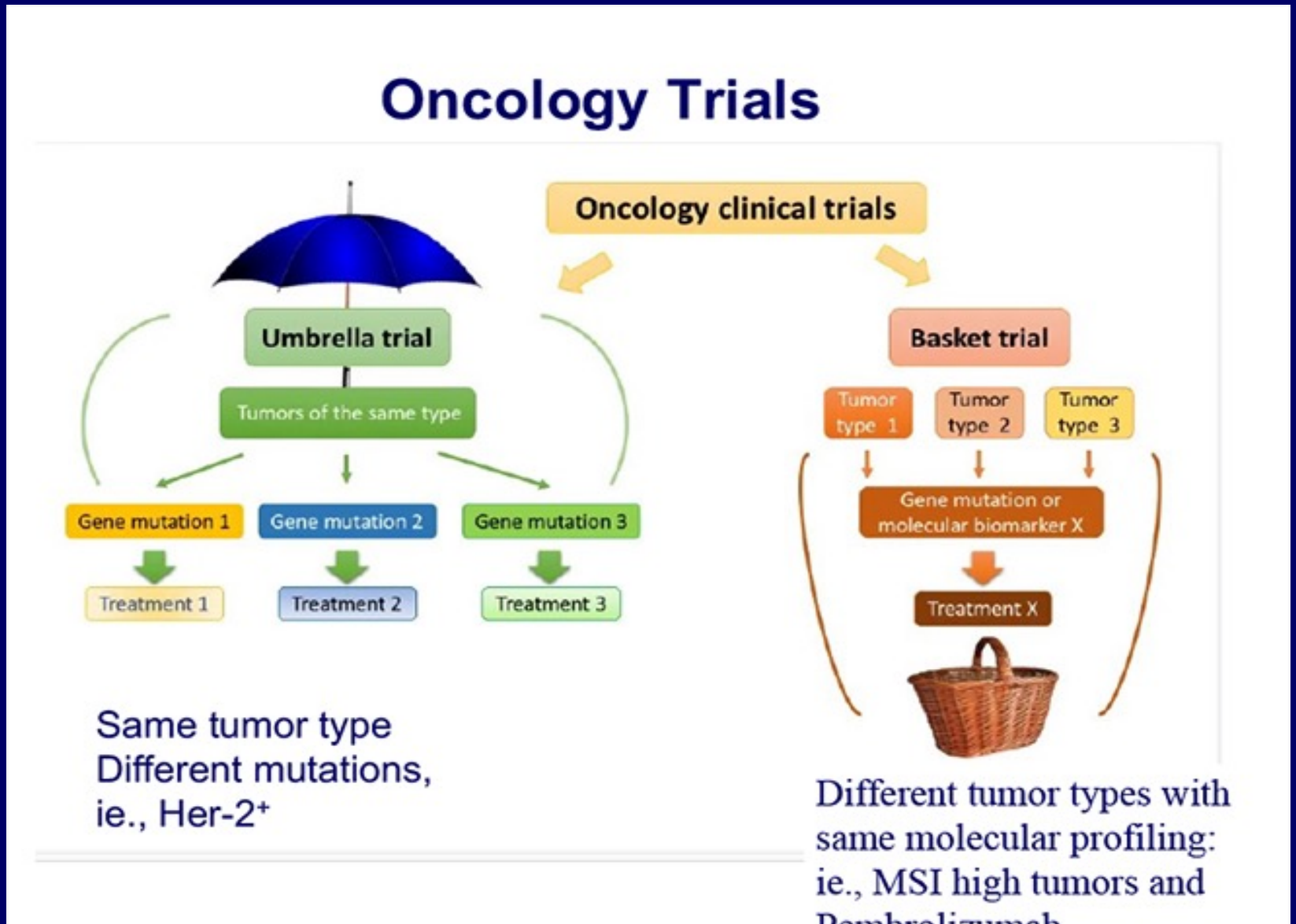
- From hundreds to thousands of people
- Usually takes place after drug is approved to provide additional information on the drug's risks, benefits and optimal use
- Called 'Post-marketing" or

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

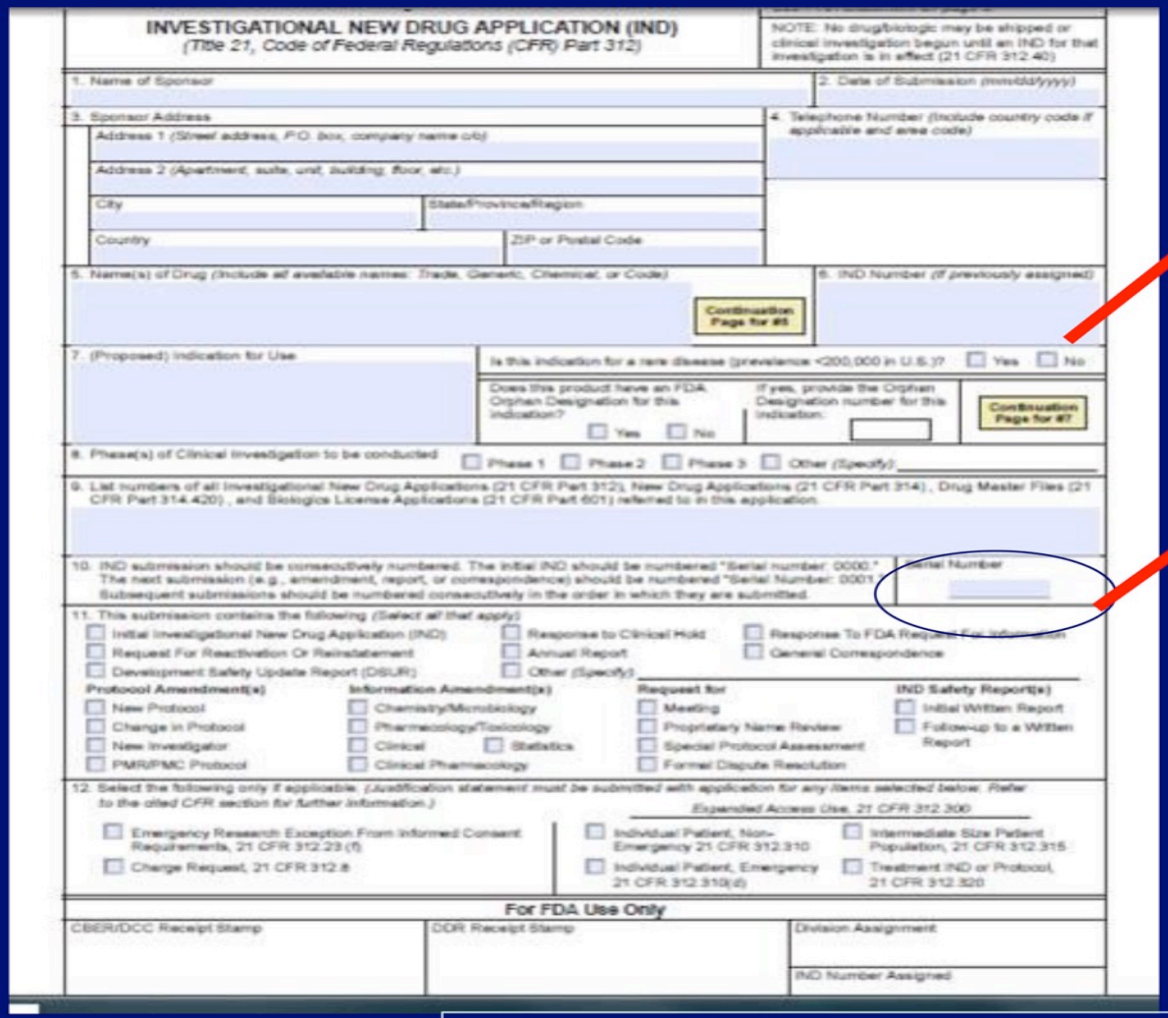
Investigational New Drug (IND) Application

- **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

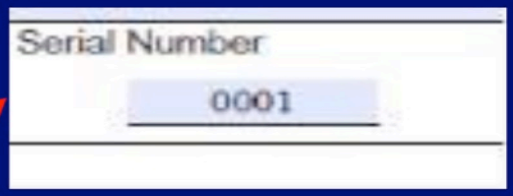
FDA 1571 and 1572 forms, info about sponsor & drug



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

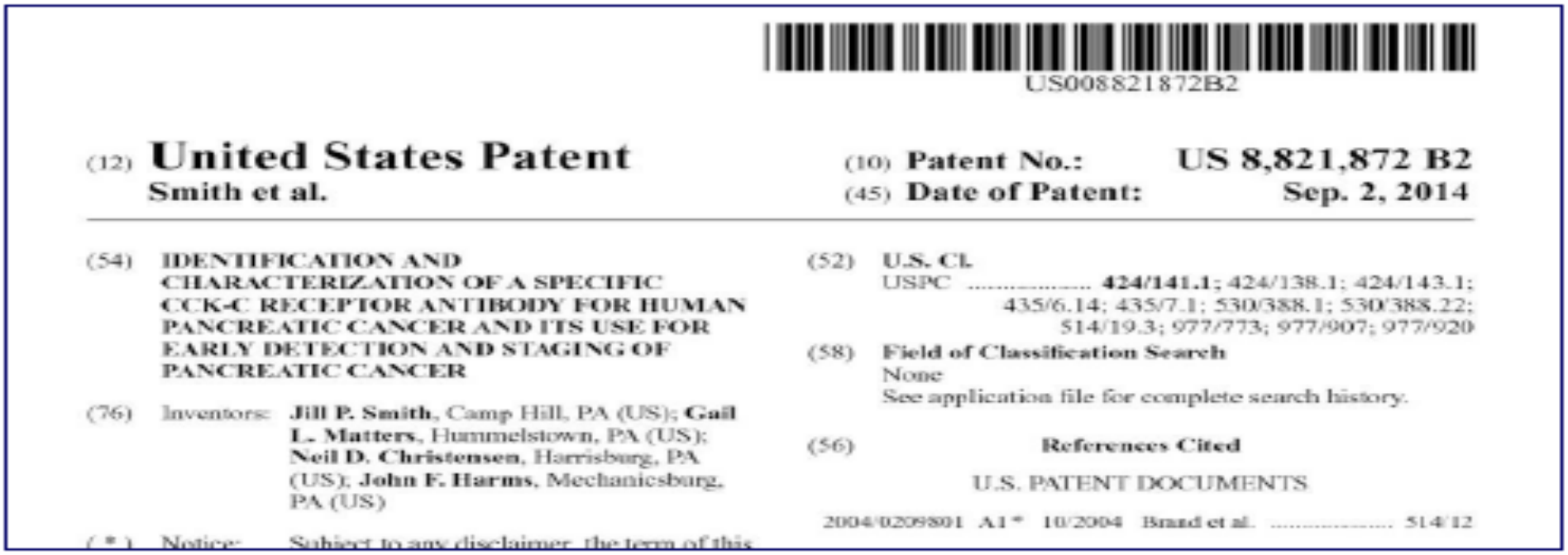


What are you Submitting or requesting In this report

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

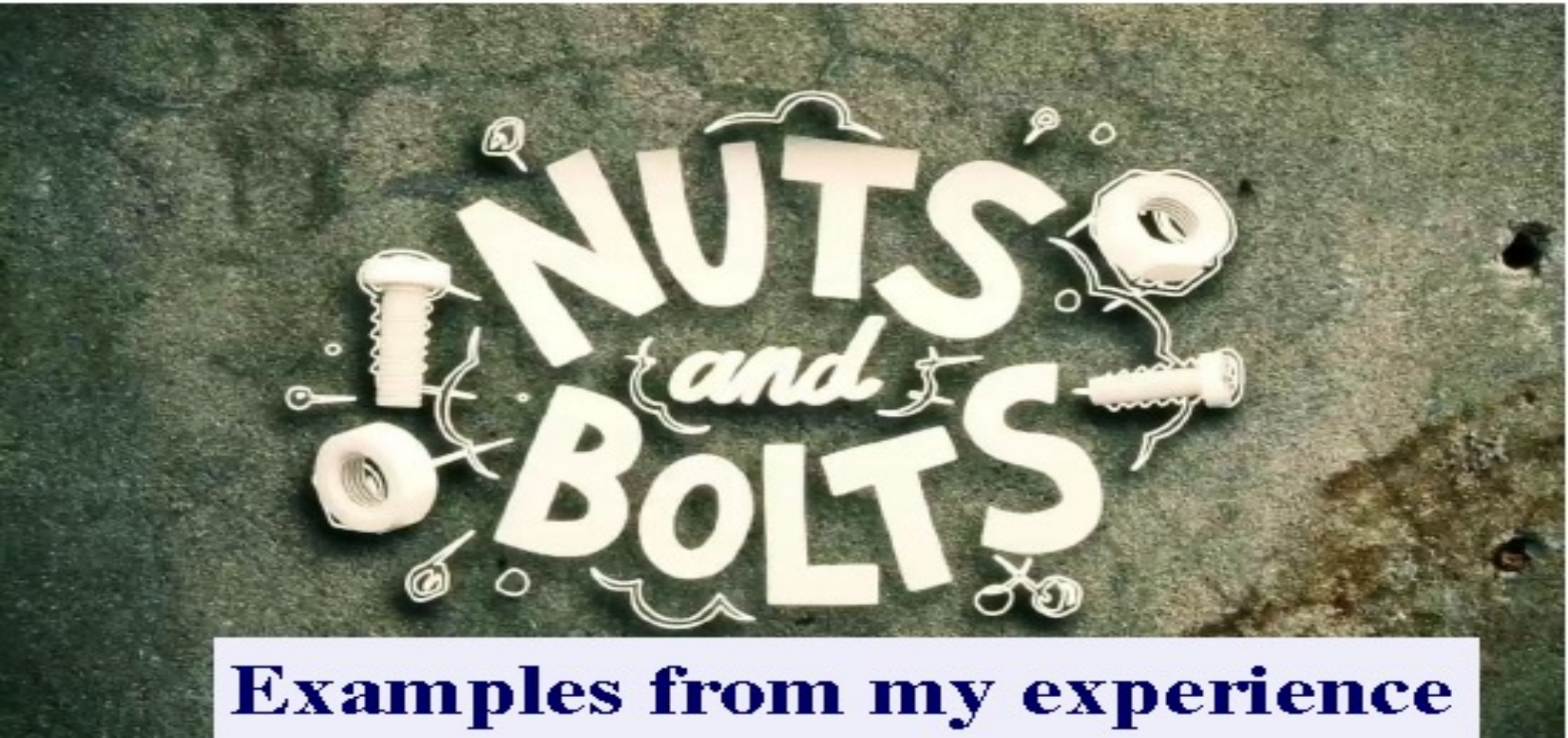
Cost

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

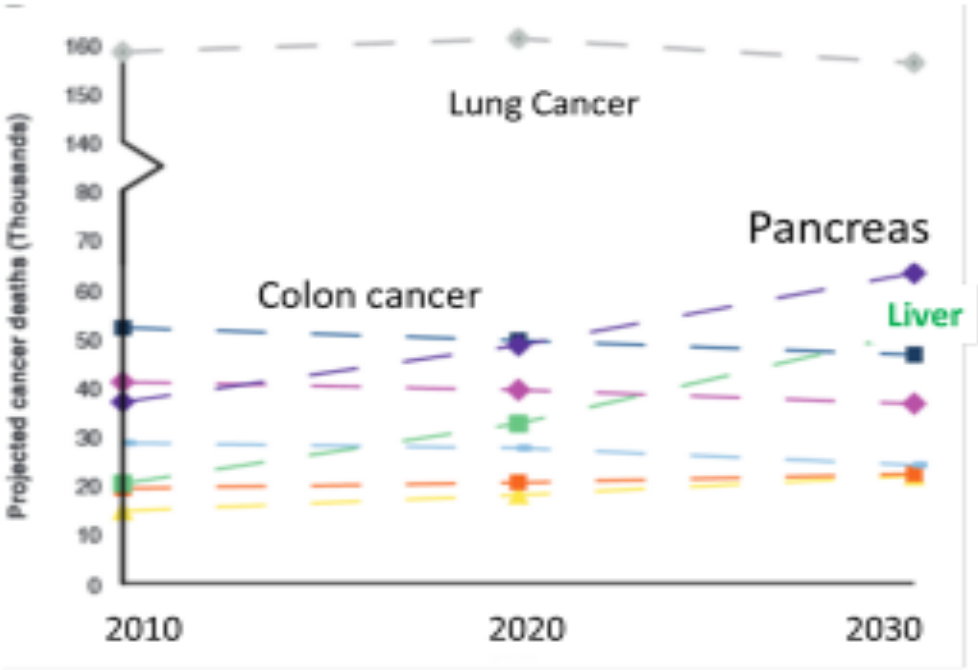
How Do You Do It?



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)

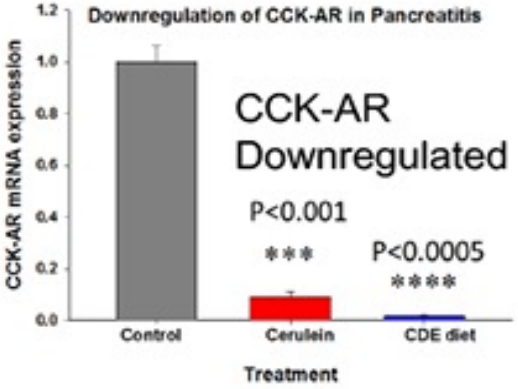
- CCK-B: Also called CCK-2R
  brain, stomach
  Binds CCK = Gastrin (1:1)

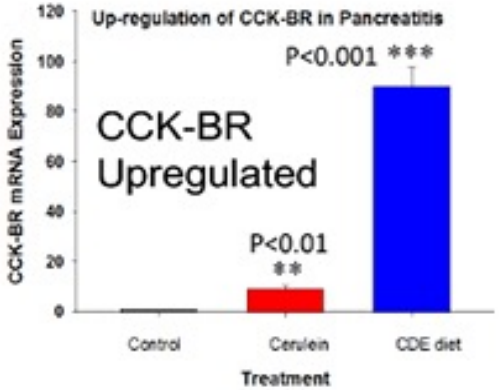
- CCK-C: pancreatic cancer, splice variant of CCK-BR; Only found in human cancer, not rodents. Binds Gastrin > CCK (10:1)

CCK-B receptor

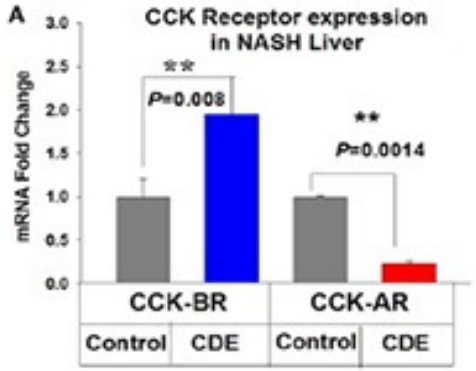
CCK-B Receptor has low expression in normal tissues

Inflammation activates CCK-BR expression- Pancreatitis





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

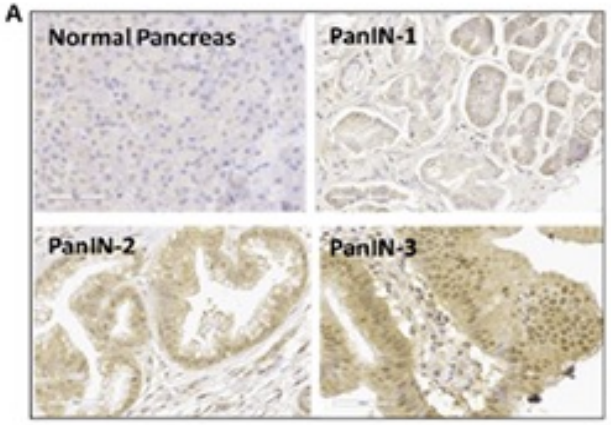


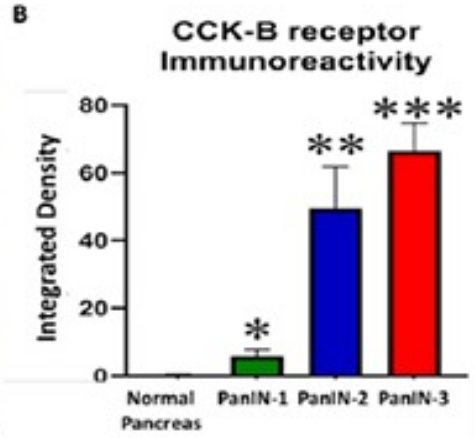
Inflammation activates CCK-BR expression- in hepatitis

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

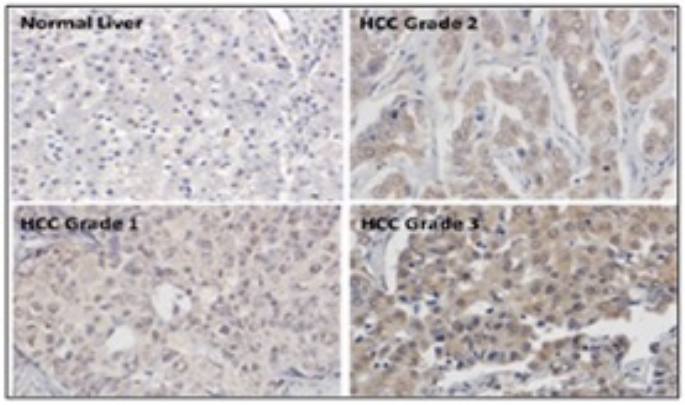
CCK-BR in cancer

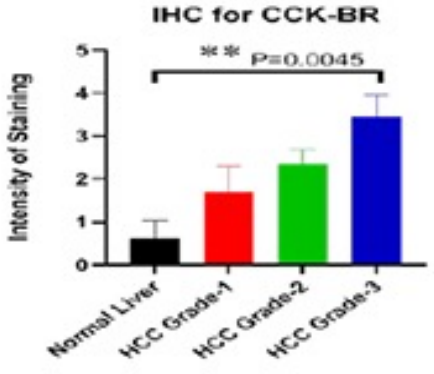
The CCK-BR is over-expressed in HUMAN HCC and Pancreatic





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





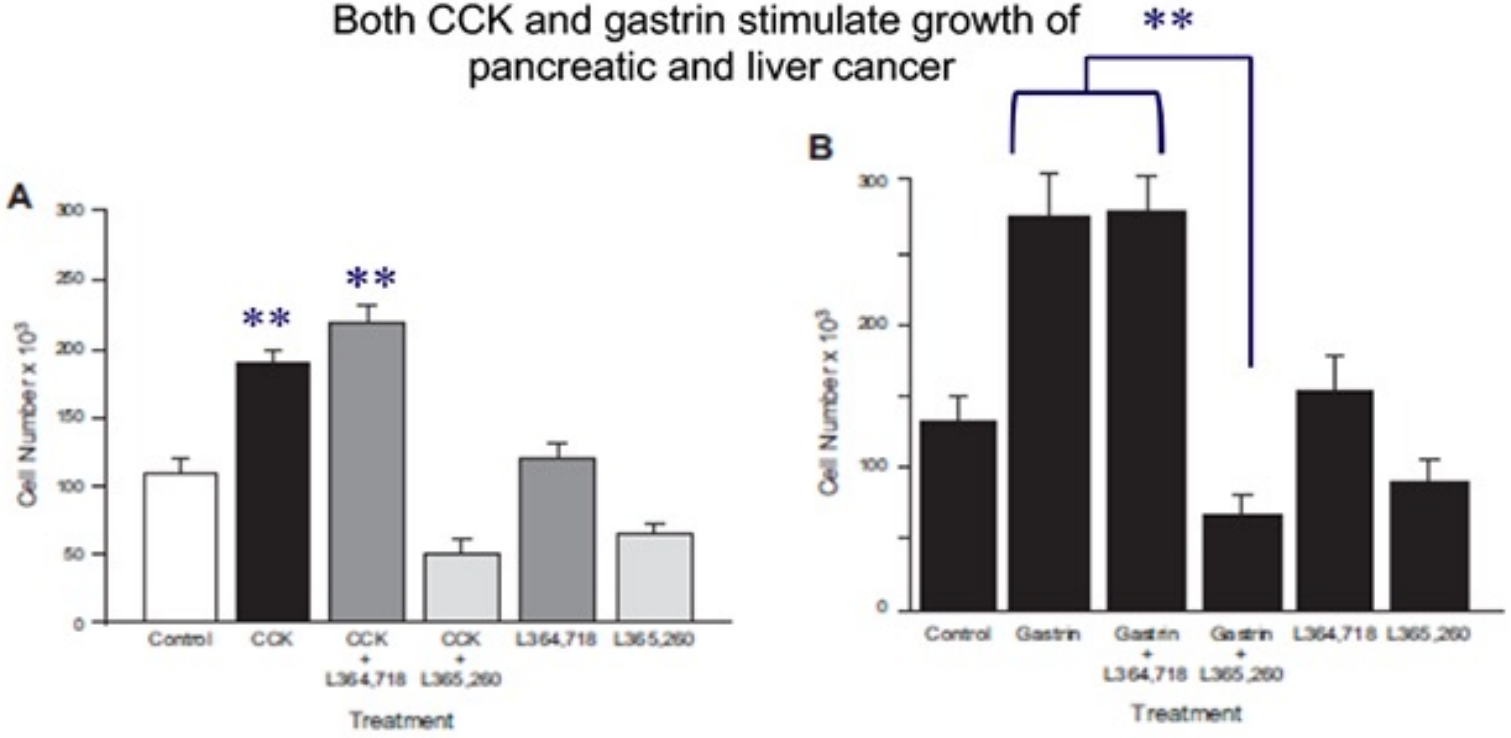
Bottom: CCK-BR is not detected in normal human liver, but is found in HCC and increases with grade of cancer

CCK-BR ligands

Ligands for the CCK-BR

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

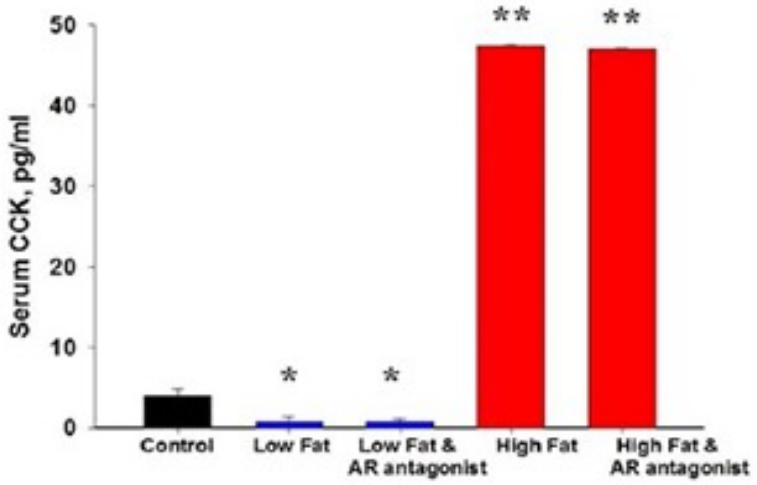
Both CCK and gastrin stimulate growth of pancreatic and liver cancer



Am J Physiol, 2014, PMID: 24177032

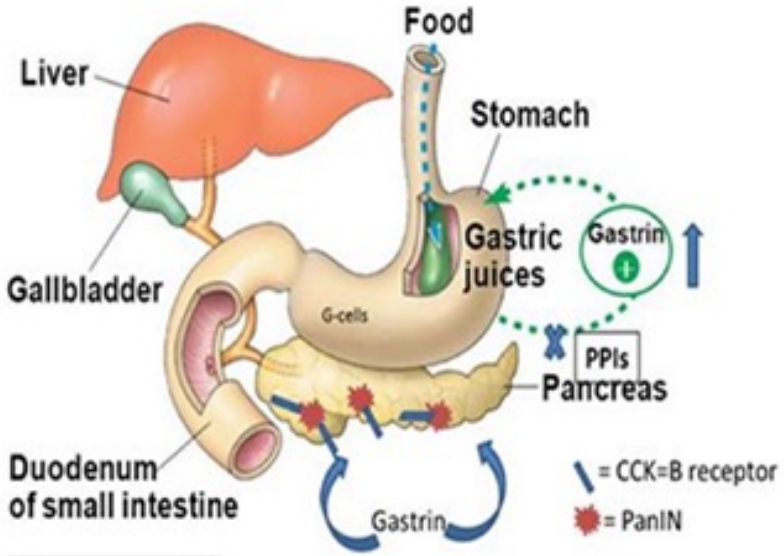
CCK and gastrin

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

Problems

What is the problem?

Pancreatic cancer:

1. Dense fibrosis around the cancer prevents penetration of T-cells and chemotherapy.
2. There is no screening test to diagnose Pancreatic cancer in early stages

Liver cancer:

1. Fibrosis (cirrhosis) is the major risk factor
2. Can fibrosis be reversed to prevent cancer

Strategy

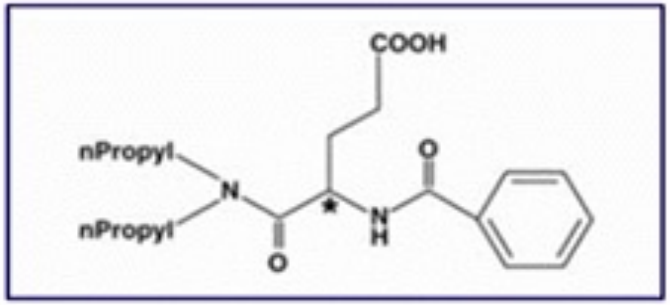
Strategy

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

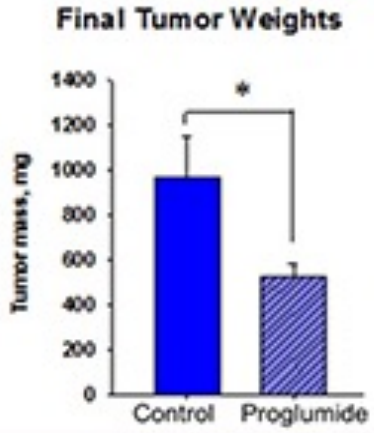


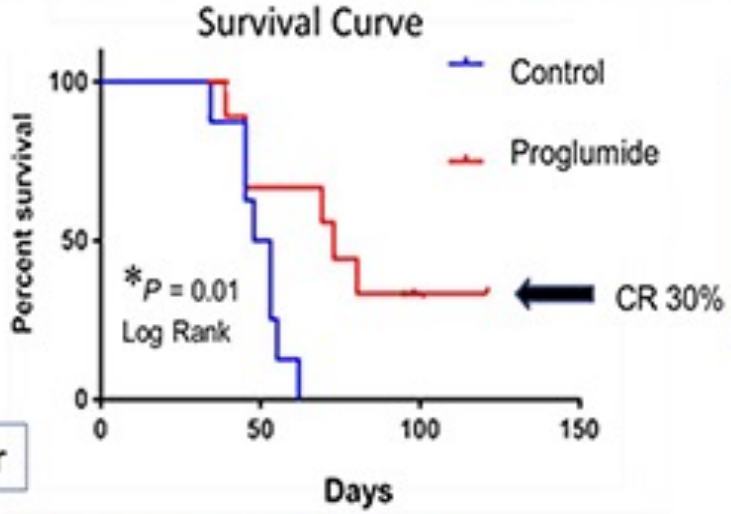
Older drug developed 30 years ago for ulcer disease.

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

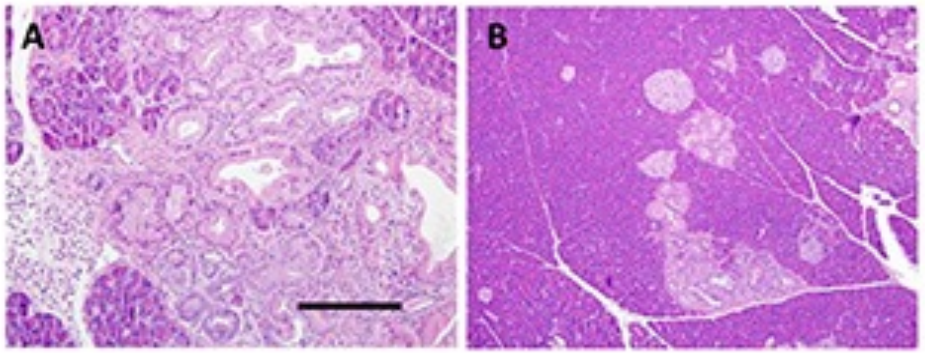
Proglumide inhibits growth of pancreatic cancer and PanIN progression





Mouse Pancreatic cancer

Proglumide improves survival in immune competent mice



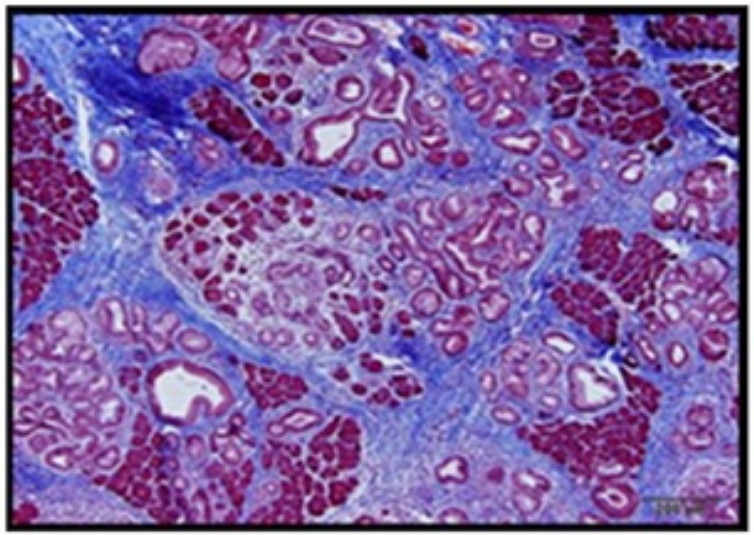
LSL-Kras$^{G12D/+}$; *P48-Cre* (KC) mutant KRAS transgenic mice

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

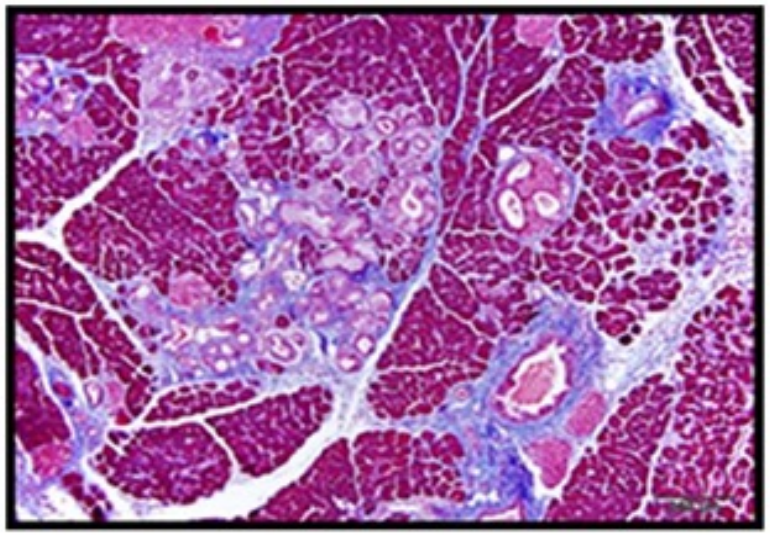
Proglumide

Proglumide prevents pancreas PanIN progression and fibrosis, Kras mouse model

Vehicle control



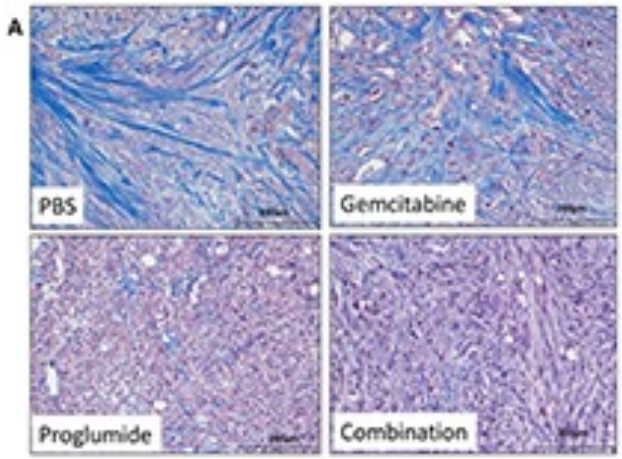
CCK receptor Blockade

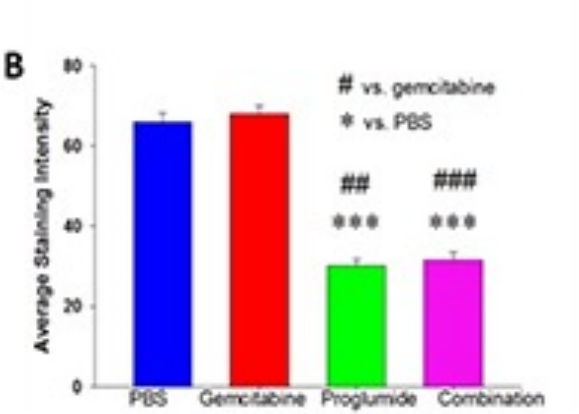


Smith et al. *Pancreas* 2014; 43: 1050–1059

Fibrosis

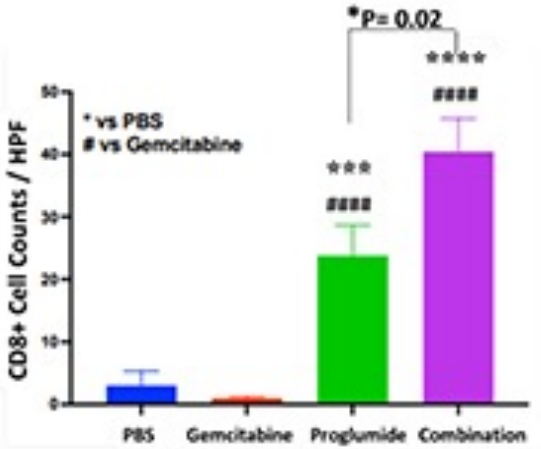
Proglumide decreases fibrosis & alters the immune signature in pancreatic cancer





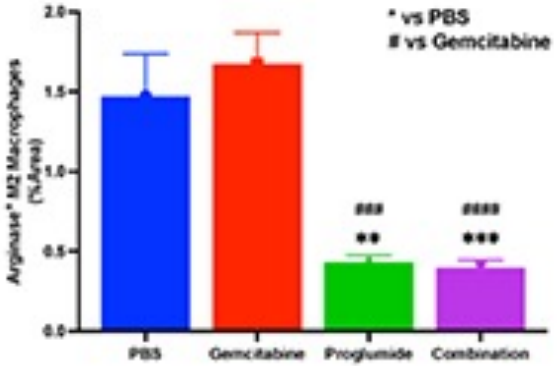
Mouse with pancreatic cancer

Cancers 2021, PMID: 34638432



Proglumide increases CD8+ T-cells

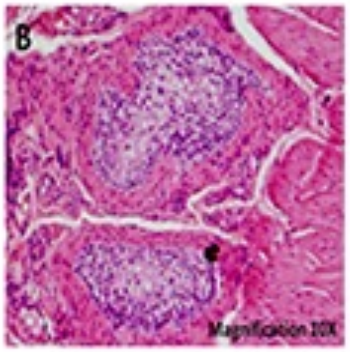
Proglumide decreases M2-polarized Macrophages



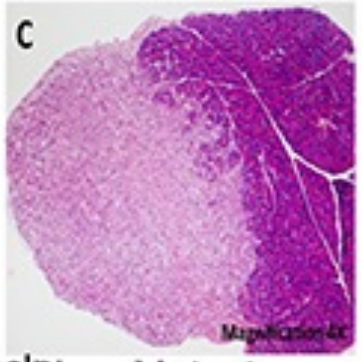
Metastasis

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

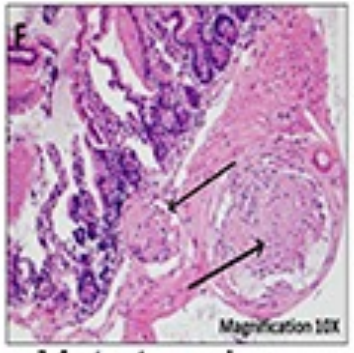
All metastases were confirmed by histology and read by our Pathologist



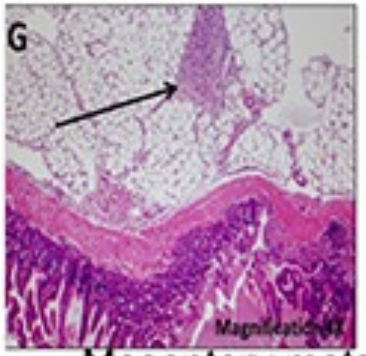
Tumor emboli muscle



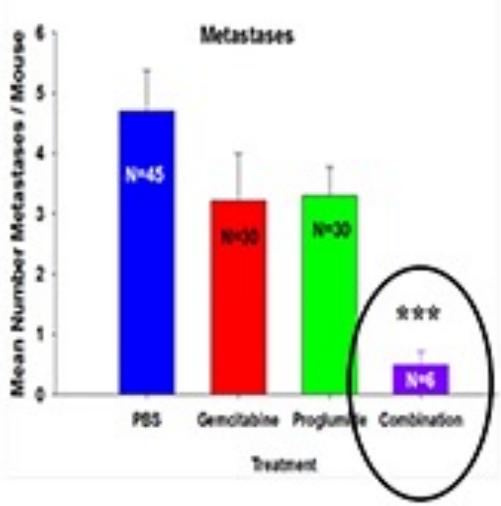
Liver Metastases



Mets to colon



Mesentery mets

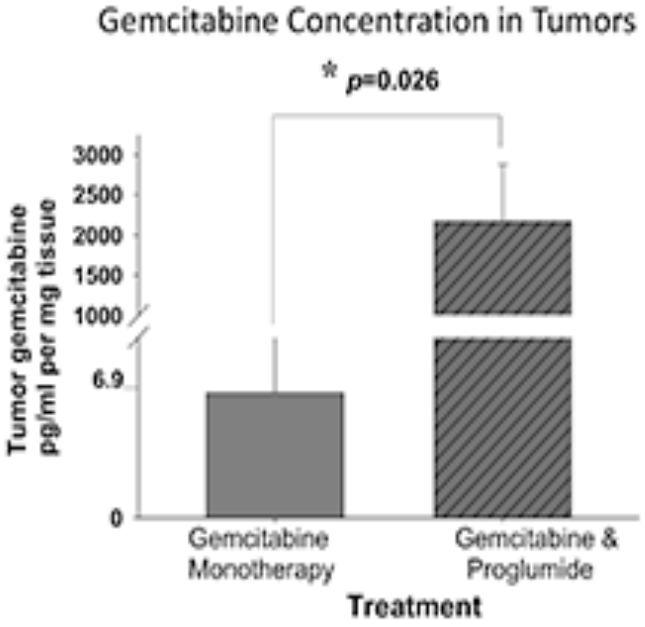


Group	Liver	Mesentery/ Peritoneum	Nodes	Spleen	Diaphragm	Abdominal Wall	Stomach	Colon
PBS	4	22	2	5	1	2	6	3
Gemcitabine	4	12	1	5	0	1	2	5
Proglumide	2	18	2	1	0	2	2	3
Combination	0	3	0	1	1	0	0	1

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

Gemcitabine

Measurement of Tumor Gemcitabine Levels by Mass Spectroscopy

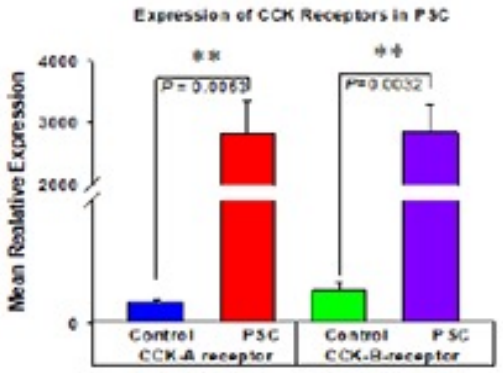


- A method was developed to measure tumor levels of gemcitabine using Mass Spectroscopy.
- Mean gemcitabine levels (pg/ml per mg of tumor tissue) were significantly higher in the tumors of mice treated with the combination therapy compared to gemcitabine monotherapy.
- These results indicate that proglumide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

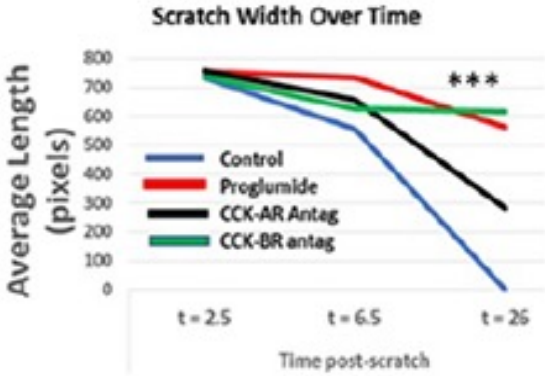
Fibrosis

Stellate Cells – Fibrosis - Proglumide

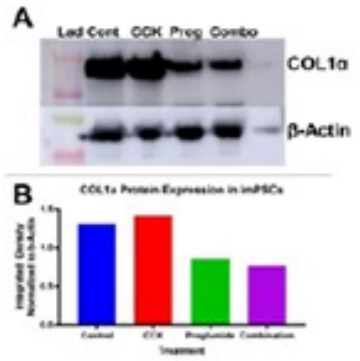
Do not Post



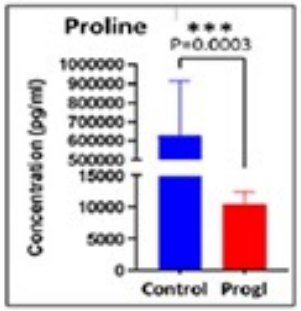
Pancreatic stellate cells express both CCK-AR and CCK-BRs (Unpublished).



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



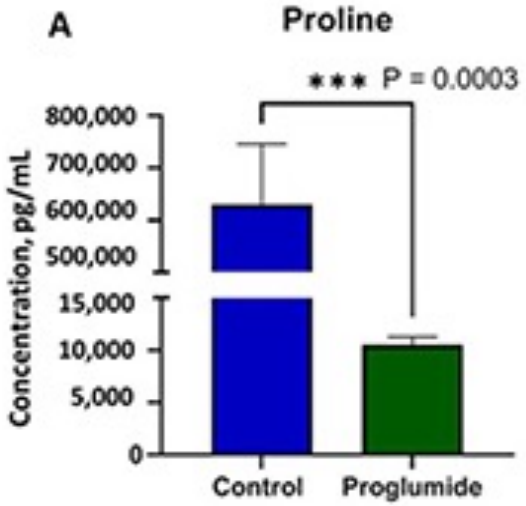
Collagen-1α protein is decreased by proglumide in PSCs.

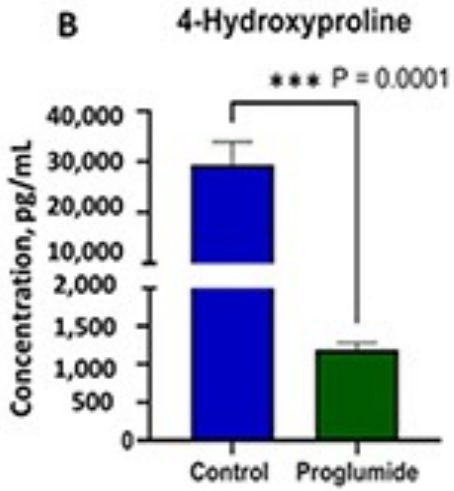


Proline is decreased in PSCs with proglumide.

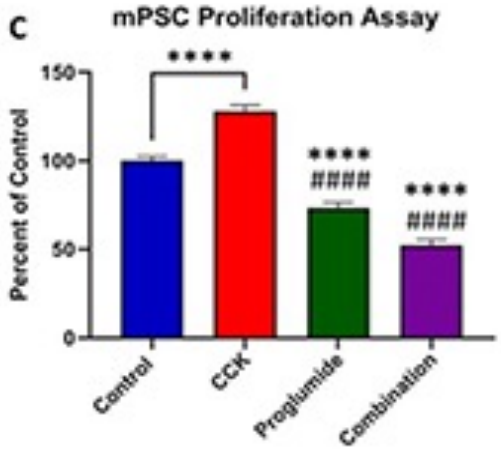
Proglumide decreases collagen and motility of stellate cells: Mechanism of action how proglumide decreases tissue fibrosis.

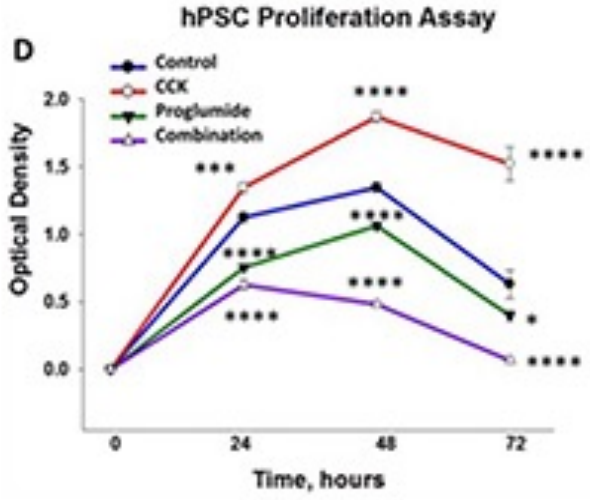
Proglumide





Effects of proglumide treatment on proline and 4-hydroxyproline levels, and proliferation of pancreatic stellate cells



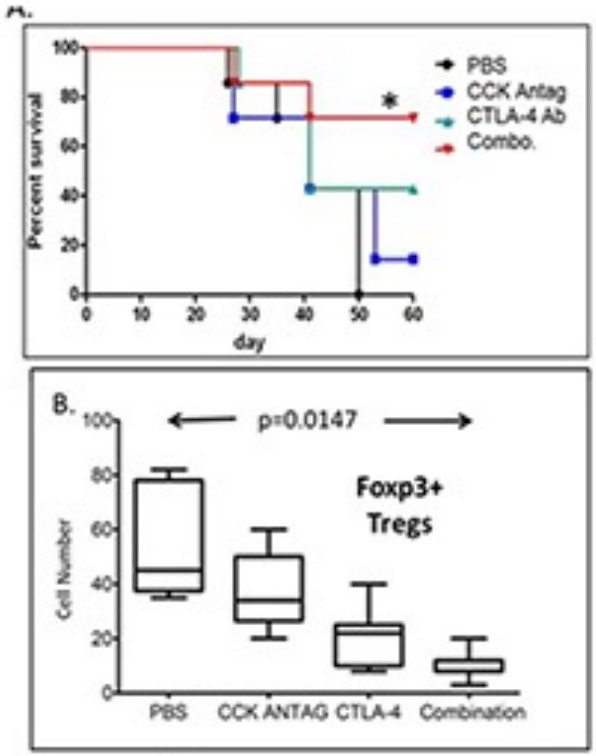


Proglumide blocks fibroblast proliferation in mouse (C) and human (D) Cells

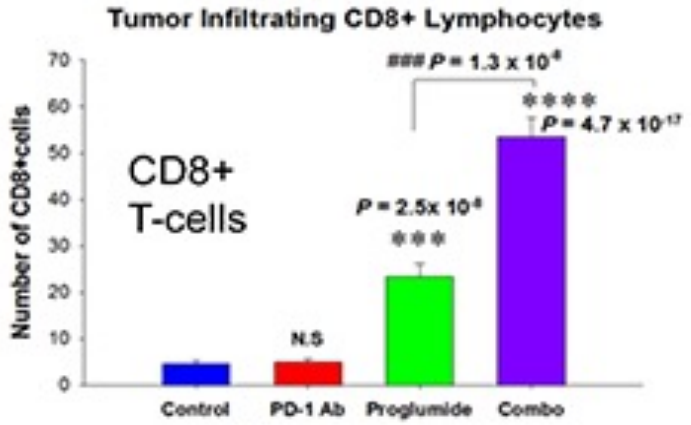
Published: Cancers 2023

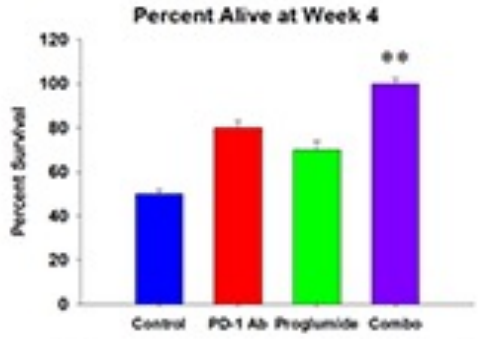
Immune checkpoint

Proglumide Improves Efficacy of Immune Checkpoint Abs



Pancreatic cancer
Cancer Immunol Immunother. 2018
PMID: 29043413



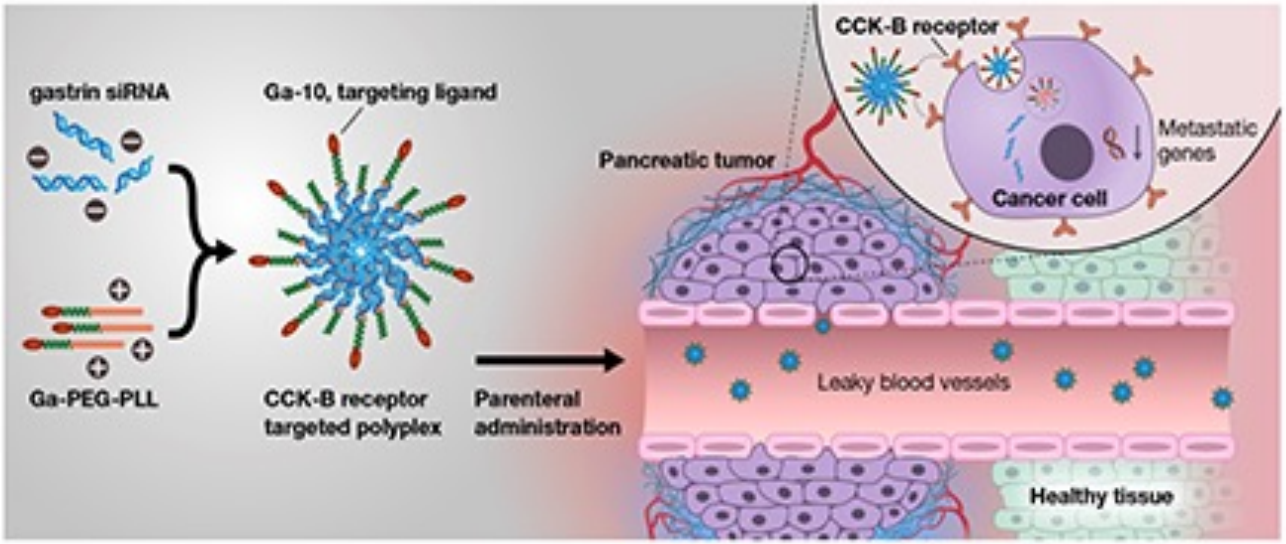


Survival

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

Nanoparticles

Targeting the CCK-BR with Nanoparticles



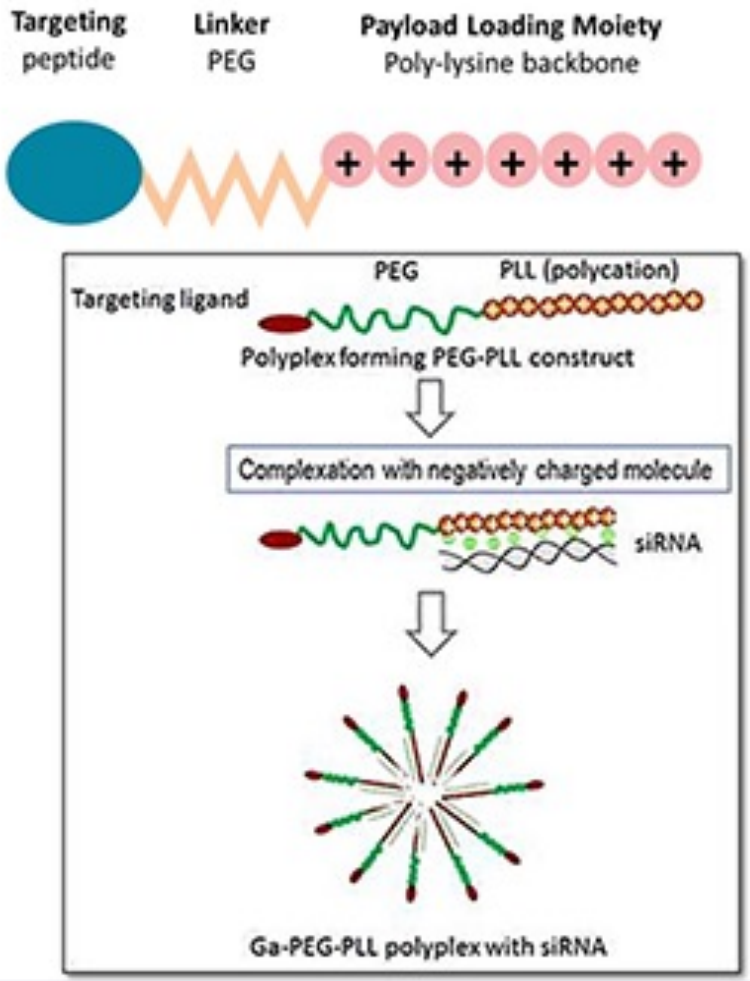
Nanoparticles were used for COVID-19 vaccines to deliver mRNA

Our strategy is to use nanoparticles to deliver siRNA

To knockdown 2 Driver genes: Gastrin & mutant KRAS

Nanoparticle construct

Nanoparticle Construct



1) CCK-B Receptor Targeted NP

Self-Assembly: Poly-lysine backbone self-assembles into a micelle with negatively charged siRNA

Specific Targeting: CCK-BR is overexpressed in PC

Protected Therapeutic Delivery: 45-48 nm nanoparticle size allows for increased penetration into the highly desmoplastic pancreatic tumor microenvironment

2) Therapeutic Application

Therapeutic Payload: siRNA targeting gastrin slows cancer growth and metastasis

Cancer Specificity: CCK-BR + gastrin siRNA combo only effects tumor cells and reduces off-target toxicity

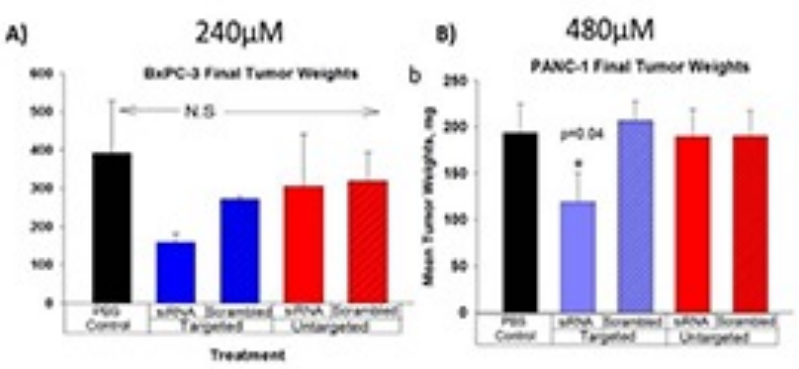
3) Imaging Diagnostic Application

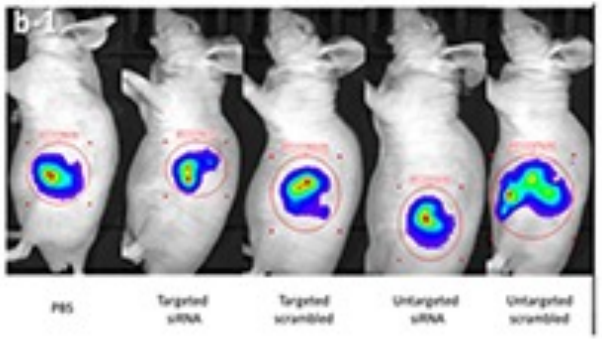
Imaging Payload: siRNA conjugated to a fluorescent or PET radiotracer

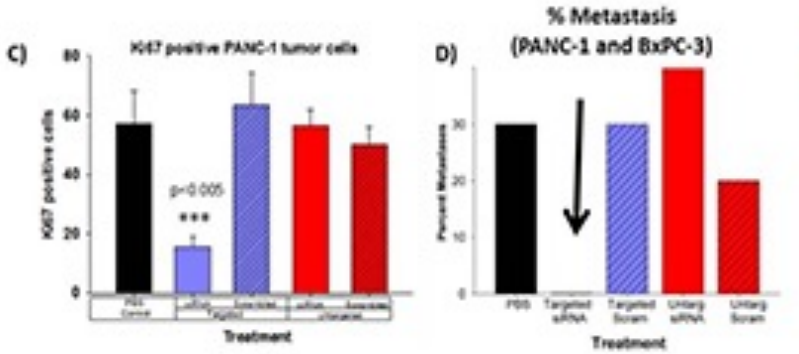
Pre-Cancerous Detection: In PanIN-3 lesions

CCK-BR nanoparticles

CCK-BR targeted nanoparticles







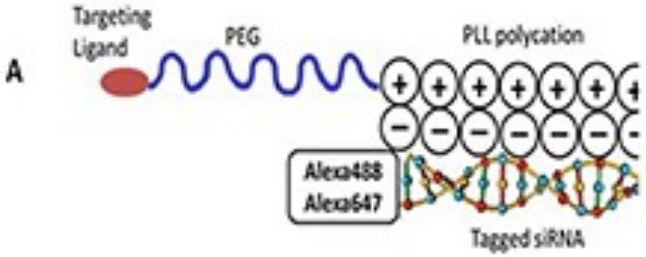
CCK-BR-Targeted siRNA Delivery for Pancreatic Cancer The y

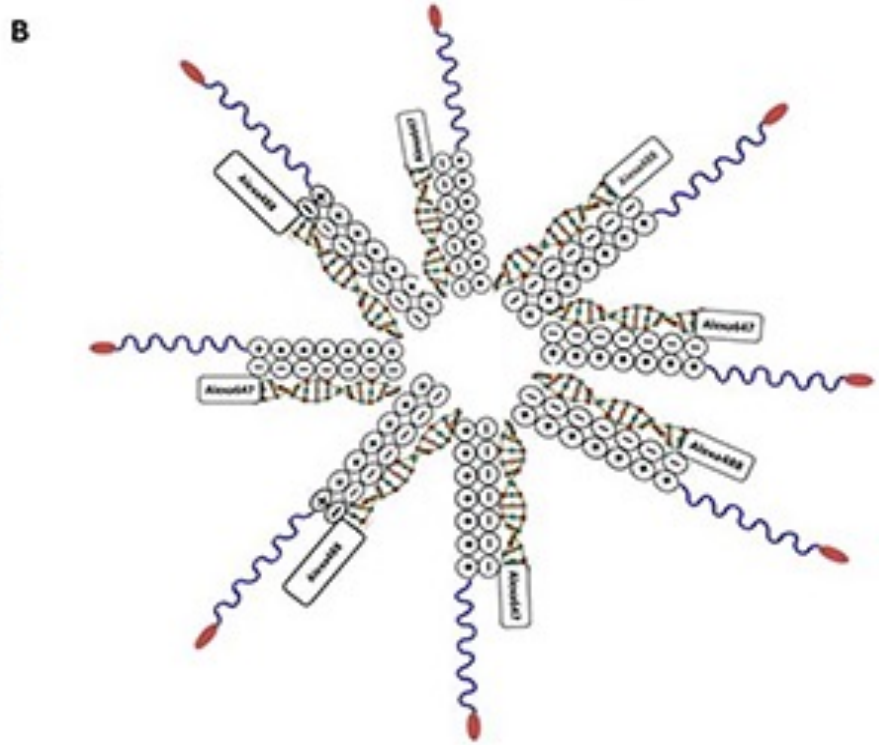
- **Reduced Tumor Weight:** Targeted gastrin siRNA treatment led to reduced tumor weight in BxPC-3 and PANC-1 orthotopic xenograft models- dose dependent fashion.
- **Ki67 Proliferation index:** Significantly decreased in tumors of mice treated only with targeted gastrin siRNA NPs
- **Gastrin Silencing in PC Prevented Metastasis:** Mice treated with targeted siRNA against gastrin prevented metastatic spread

Diagnostic NP

Early, Pre-cancer Diagnostic NP

Since PanIN-3 express CCK-BR can we use it for imaging and precancer diagnosis?



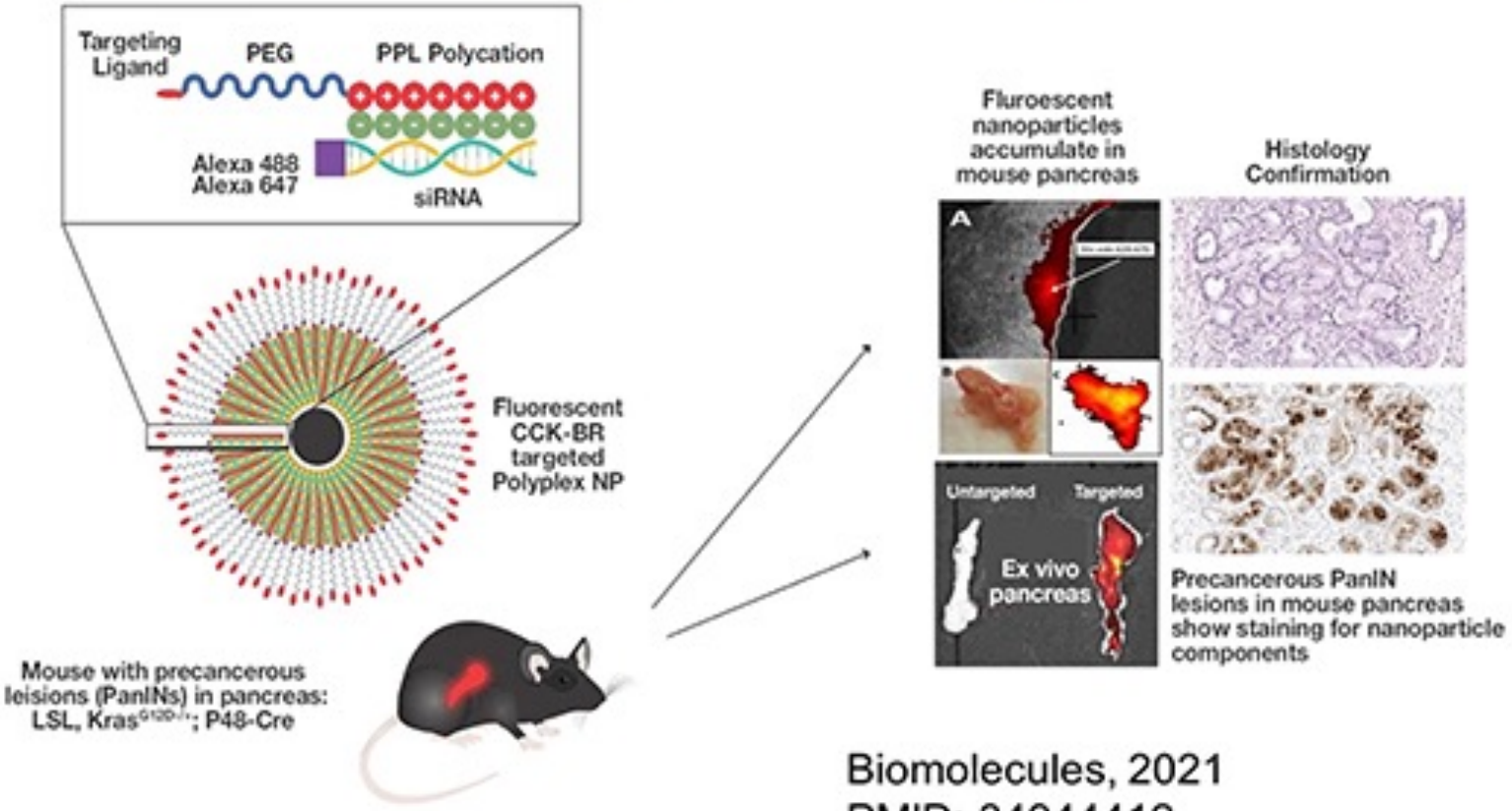


Imaging Application

- Far infrared fluorescent probes can be conjugated directly to the targeted siRNA
- Complex self-assembles to form a CCK-BR targeted-specific polyplex nanoparticle micelle

CCK-BR as a target

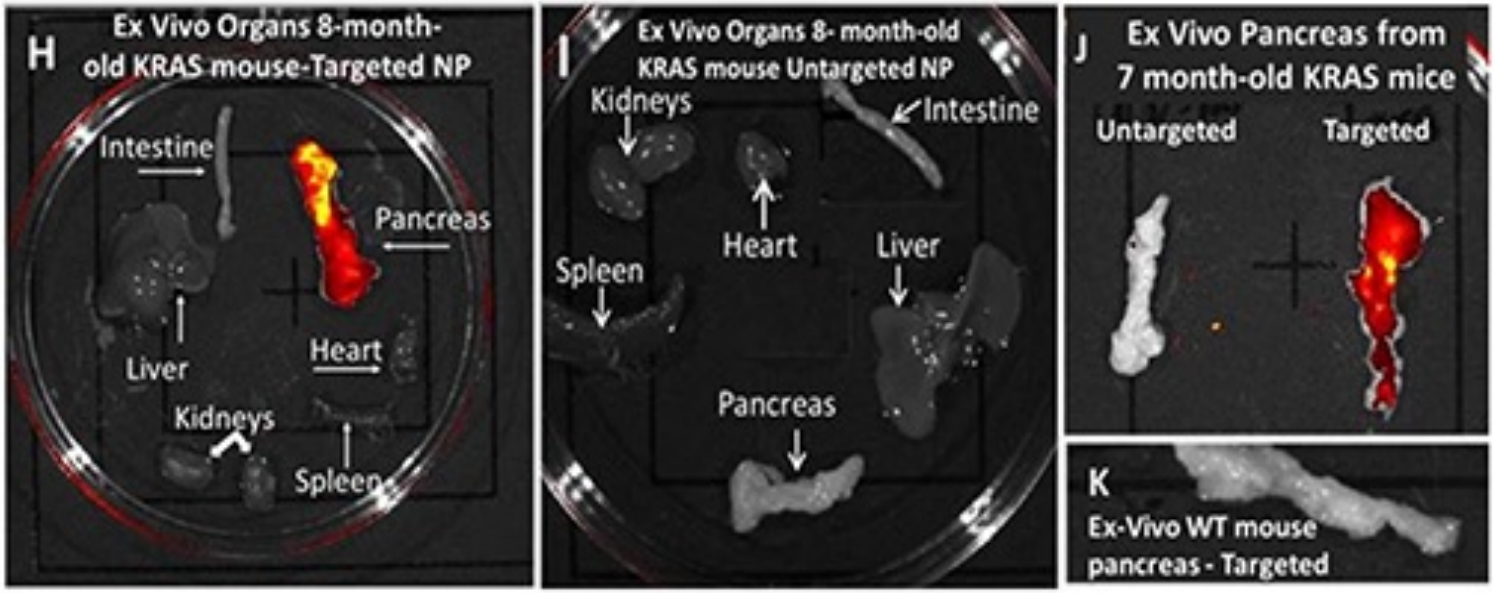
Using the CCK-BR as a Target for imaging and therapy



Biomolecules, 2021
PMID: 34944412

Nano imaging

Nano-imaging Precancerous Pancreas Lesions



Targeted NP

Untargeted NP

Biomolecules, 2021
PMID: 34944412

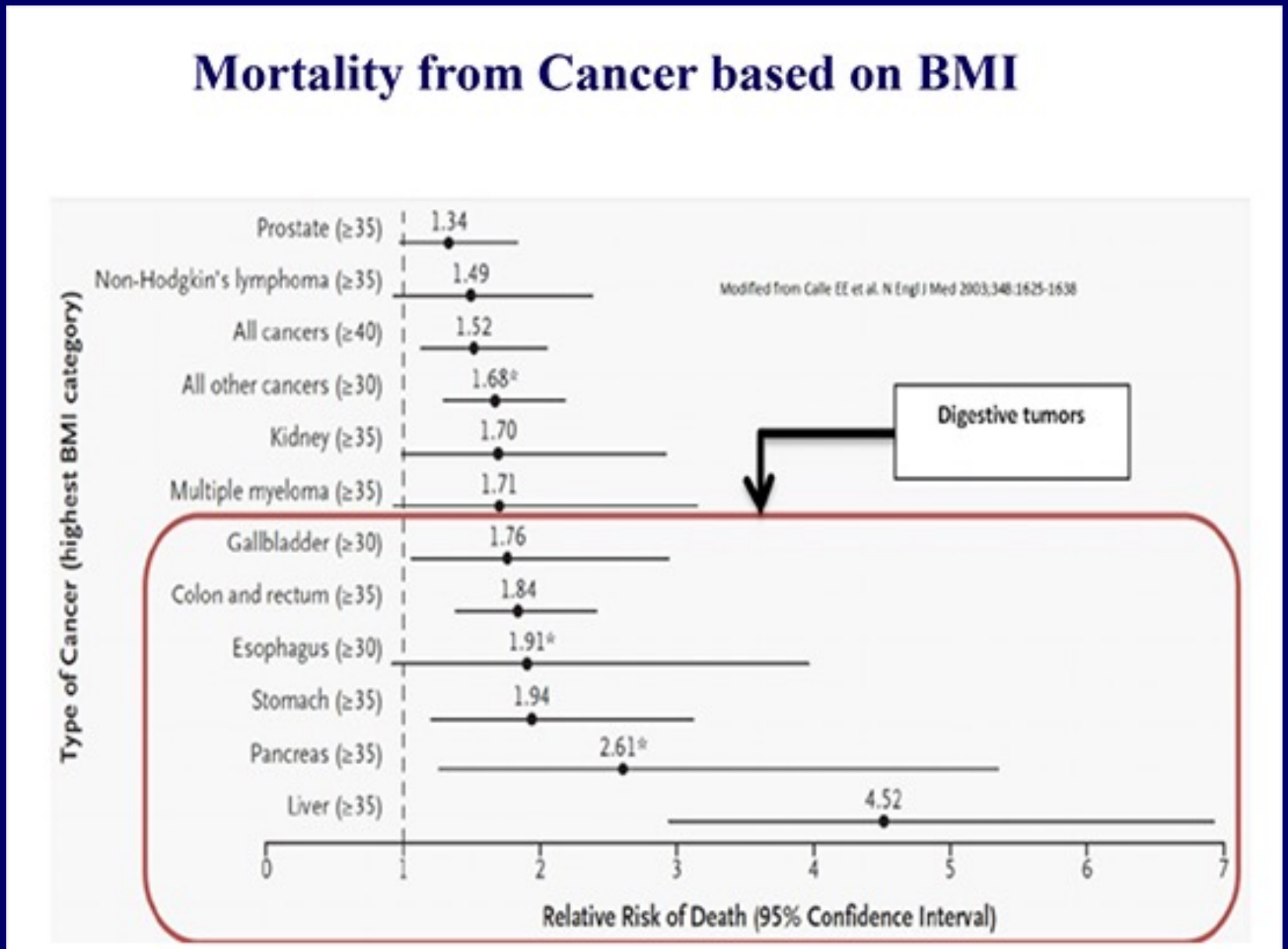
Developing a nanoparticle that targets the CCK-BR in early cancer or PanINs – An imaging tool PET scan.

SUMMARY

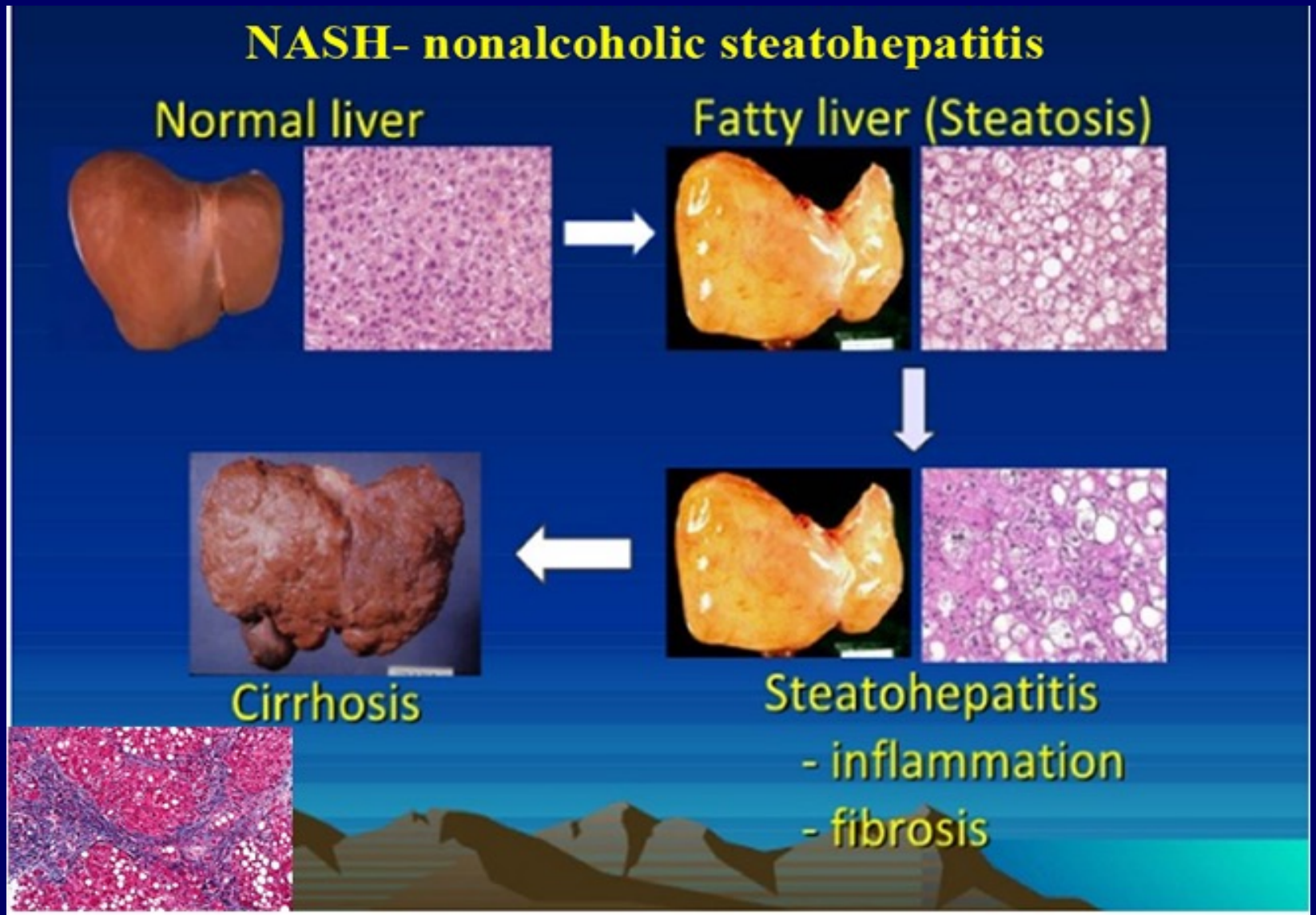
Summary Targeting the CCK-BR in Pancreatic Cancer

1. Proglumide inhibits pancreatic & liver cancer growth by blocking signaling at the CCK-BR.
2. Proglumide therapy potentiates the efficacy of chemotherapy and immune checkpoint abs by decreasing fibrosis and changing the immune signature of the tumor microenvironment.
3. Our CCK-BR targeted biodegradable nanoparticle can image precancerous PanIN lesions in the pancreas and treat cancer without toxicity.

Mortality and BMI

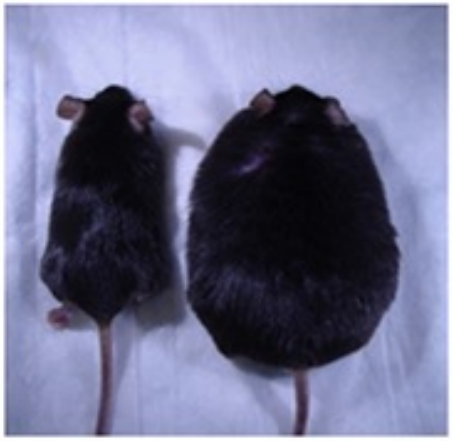


NASH


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

Animal Models

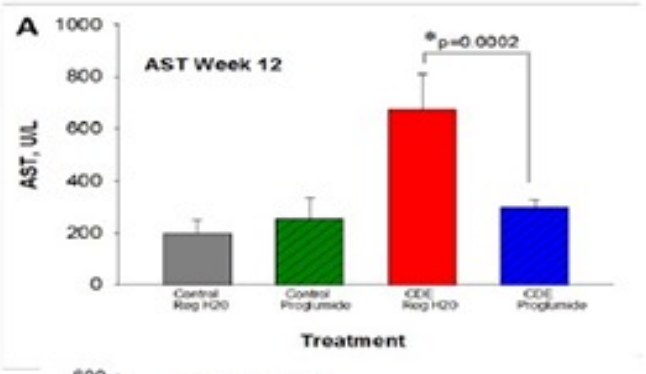
High Fat Diet Animal Models

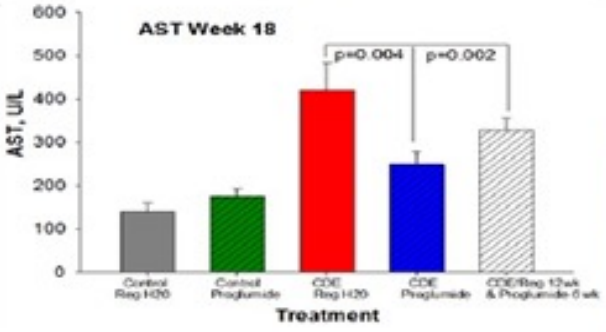


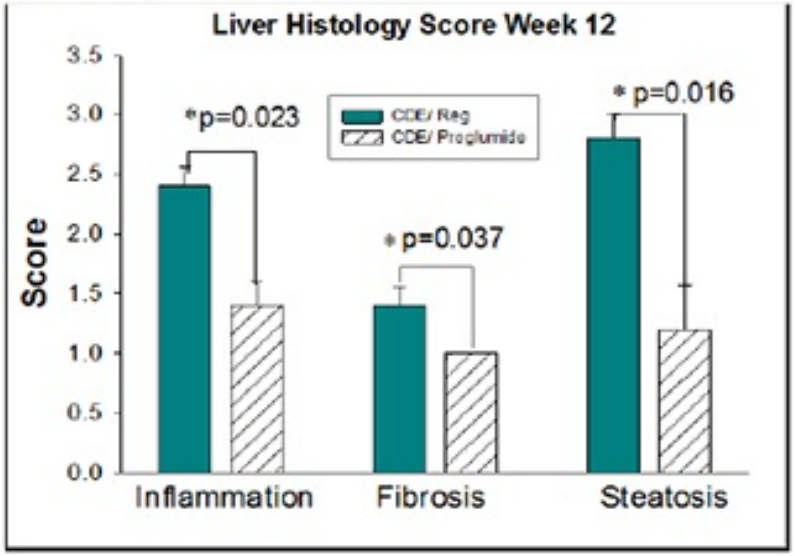
Low Fat Control High Fat

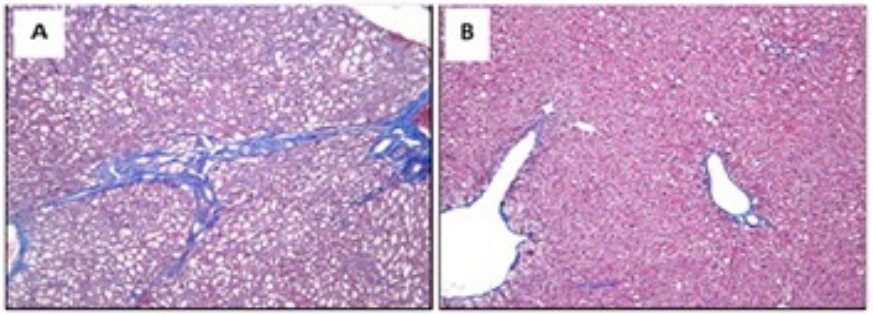
Proglumide reverses NASH

Proglumide reverses NASH in High Fat CDE mouse model









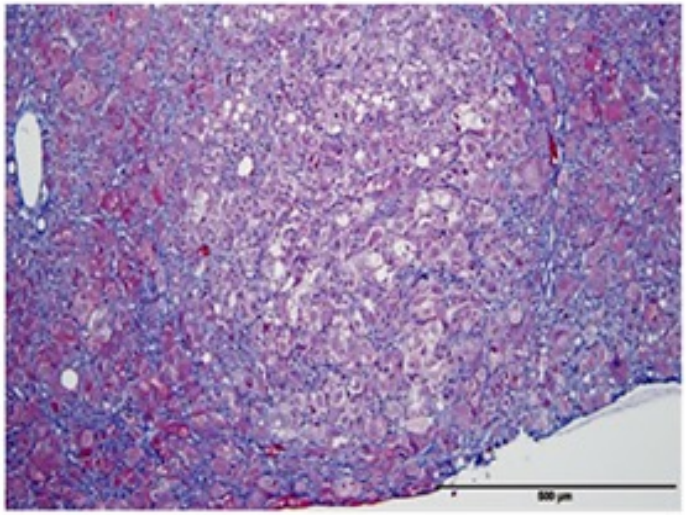
Control Proglumide

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

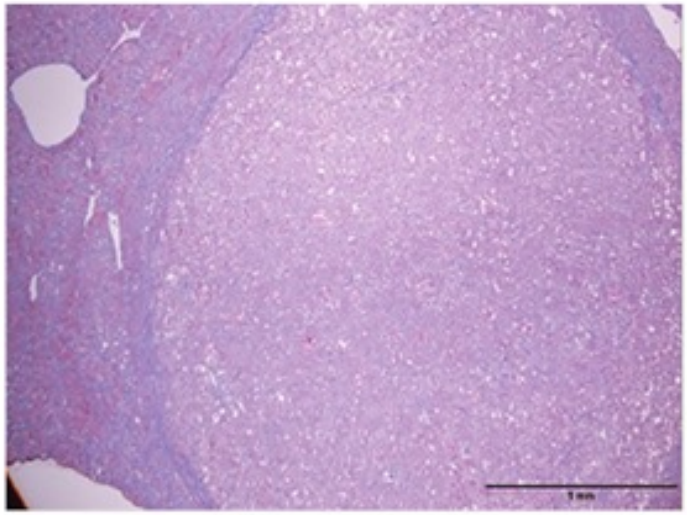
HCC prevention

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

Clinical studies

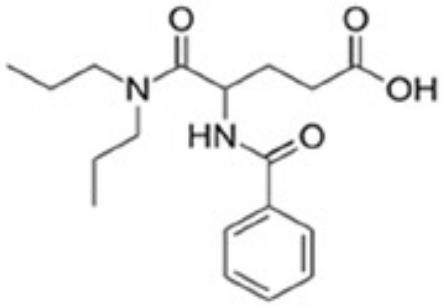
Clinical studies Bench to Bedside
Human Clinical Trials

1. Treating NASH - nonalcoholic steatohepatitis to prevent liver cancer -Completed
2. Safety study in cirrhosis patients to reverse fibrosis- Completed
3. Pancreatic cancer study- proglumide with chemotherapy
4. Chronic pancreatitis study – ongoing
5. Liver cancer study- proposed

Phase 1 Study

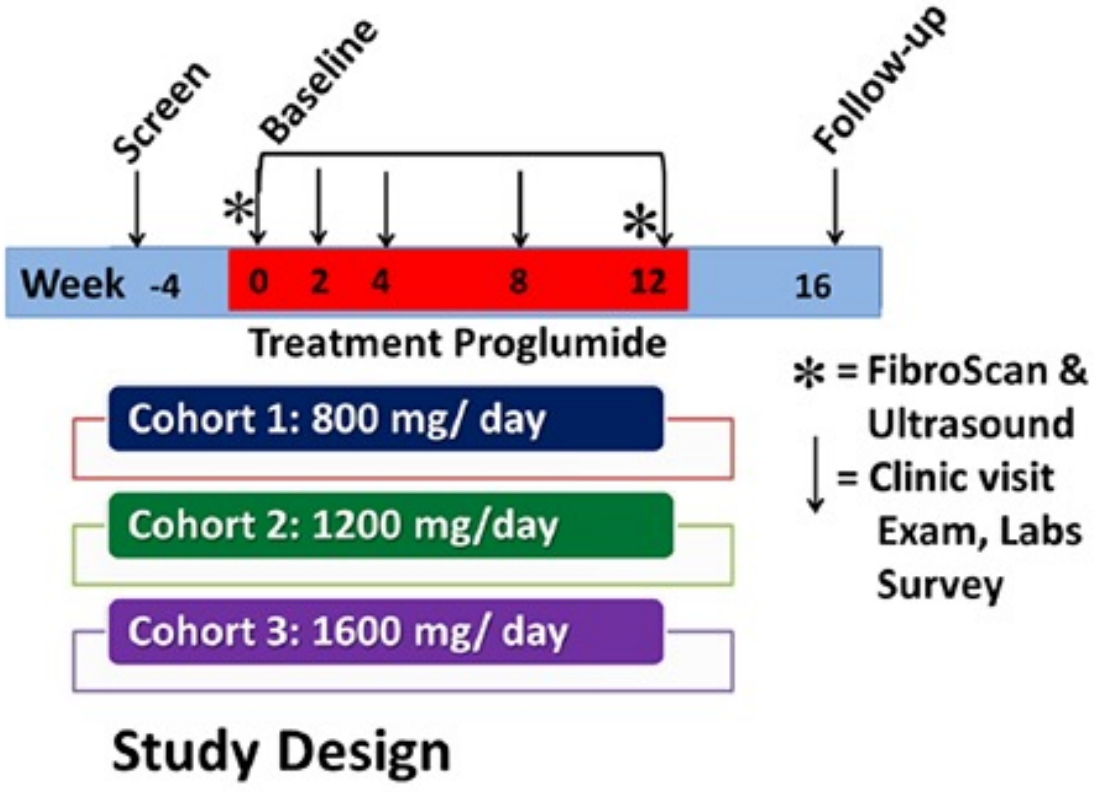
Phase 1 Study in NASH

Published Clinical Pharmacology & Therapeutics



Proglumide

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



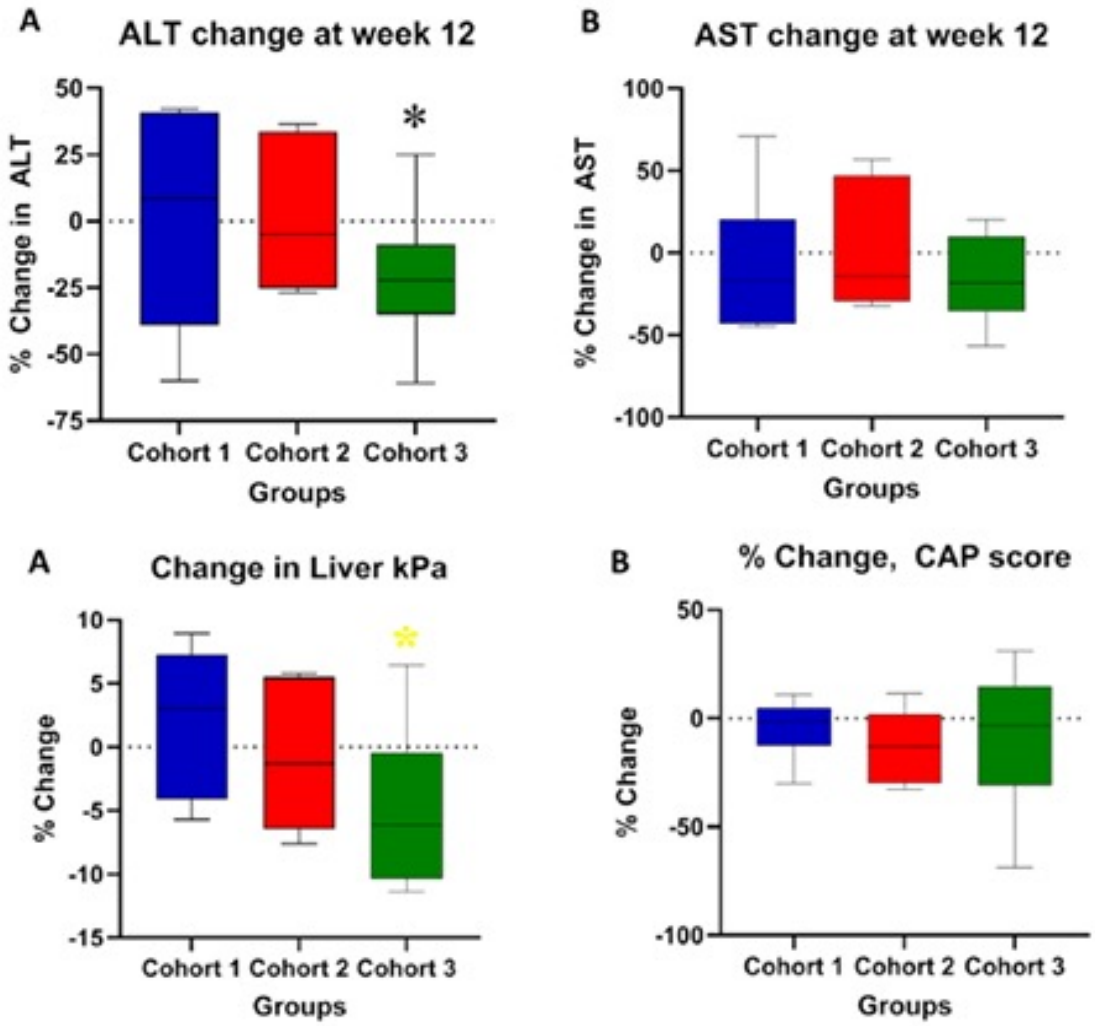
Study Design

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

Proglumide in NASH

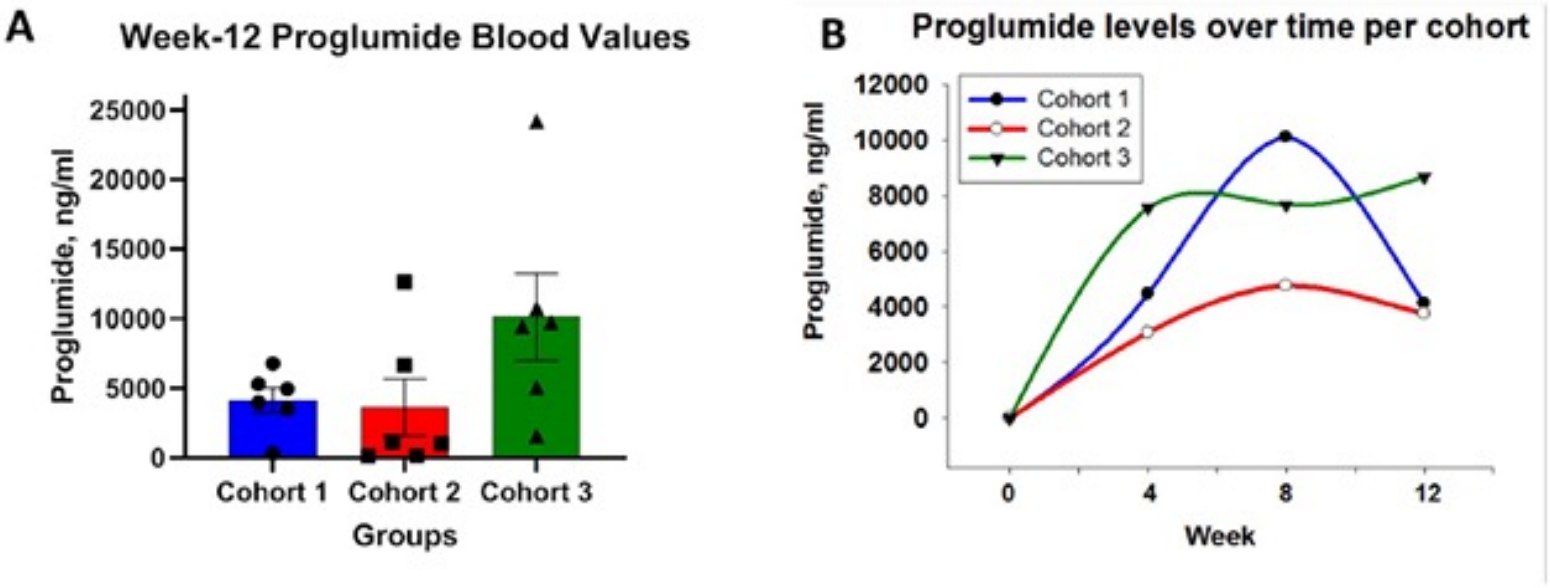
Proglumide in NASH

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



Proglumide blood levels

Proglumide blood levels
From Phase 1 study

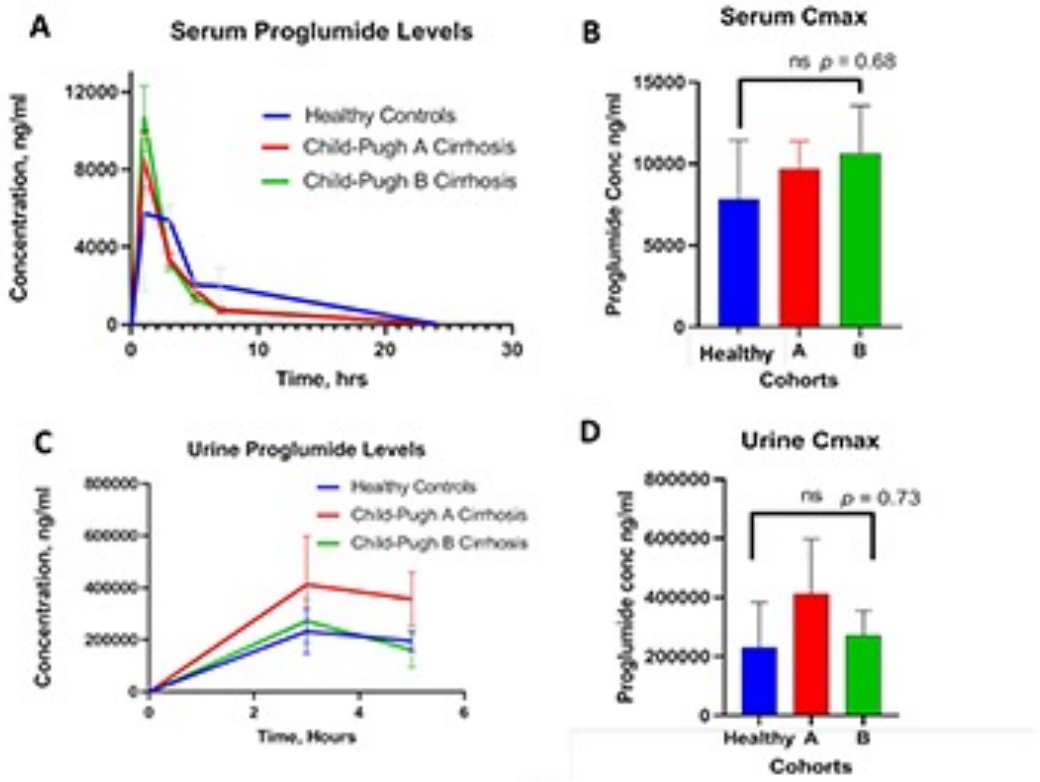


AEs: Only mild, none in Cohort 3 and no one had to discontinue drug

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

Proglumide in hepatic impaired

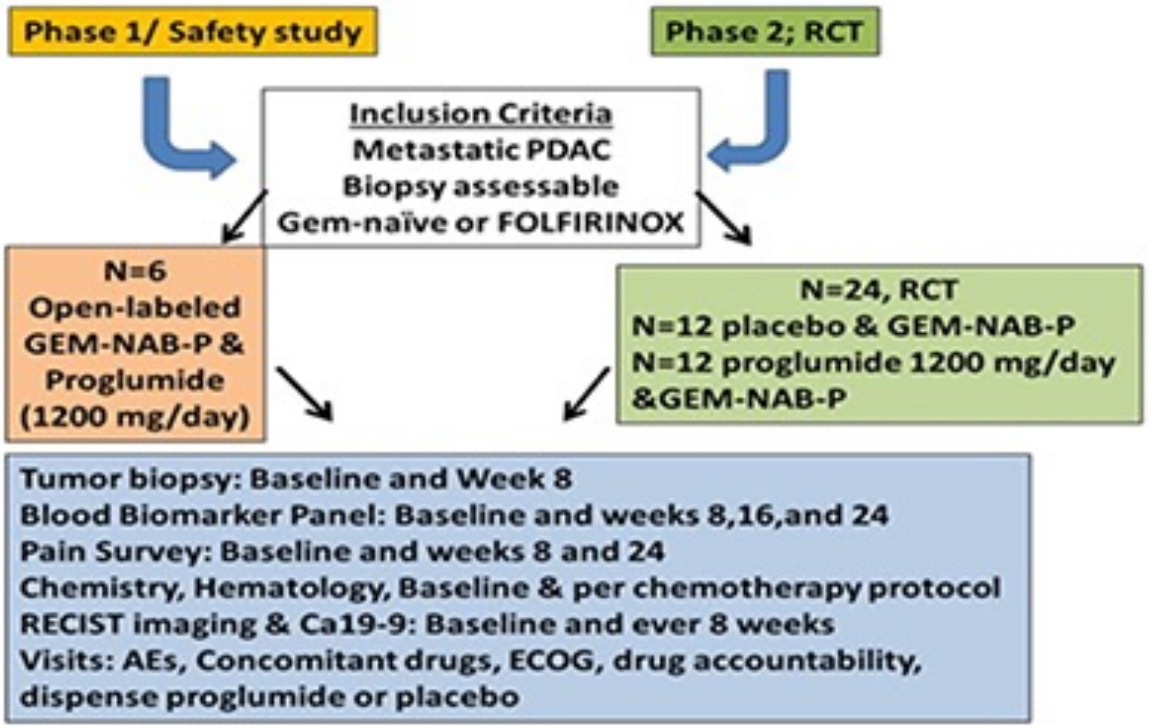
Proglumide in Hepatic Impaired; Child Pugh A& B Cirrhosis



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

Pancreatic cancer clinical studies

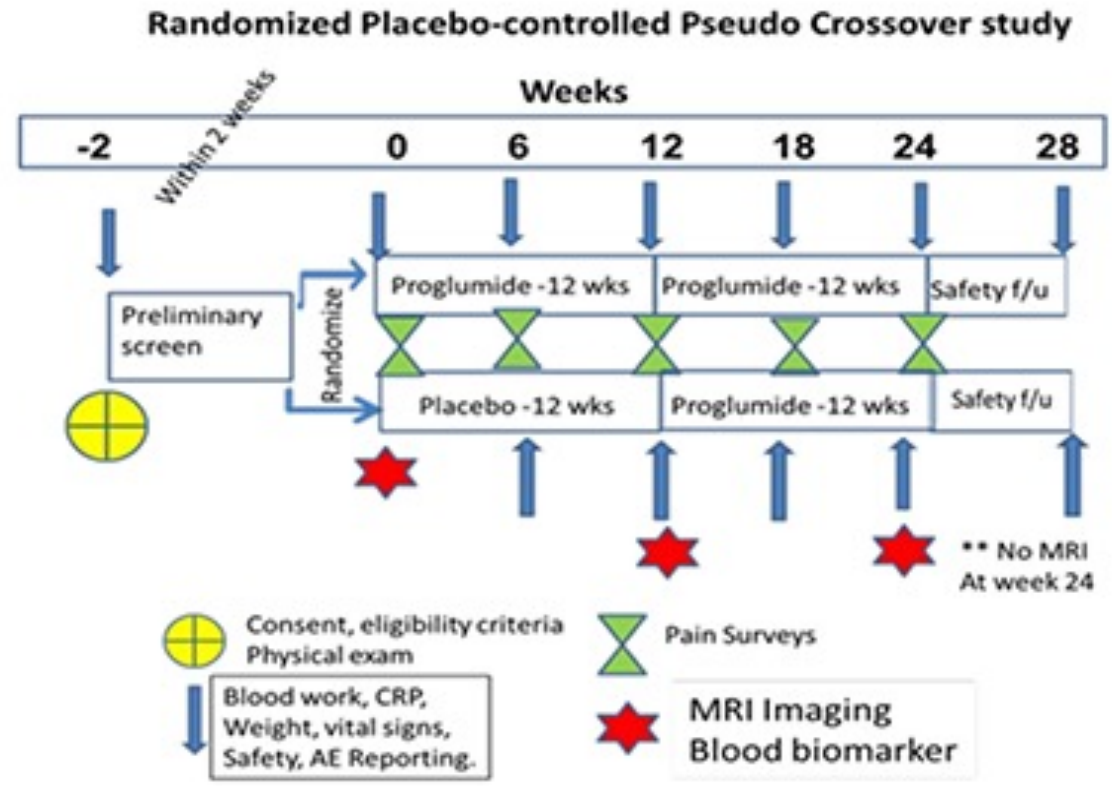
Current clinical studies — Pancreatic cancer



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

Current clinical studies

Current Clinical Studies- Chronic pancreatitis



Chronic pancreatitis is a risk factor for pancreatic cancer

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

Pancreatic cancer patients

Pancreatic cancer patients
(with permission)

Bobbie

Acknowledgements

Acknowledgements: Funding

NCI- R01, Plasticity of the CCK-BR
Pancreatic Cancer Action Network
Gap Institutional Funding
Harrington Discovery Scholar Award

Thanks to
Our mouse
volunteers

Smith lab