Bench to Bedside, Clinical Trials

TRACO-Translational Research : Bench to Bedside, Clinical Trials



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Disclosures

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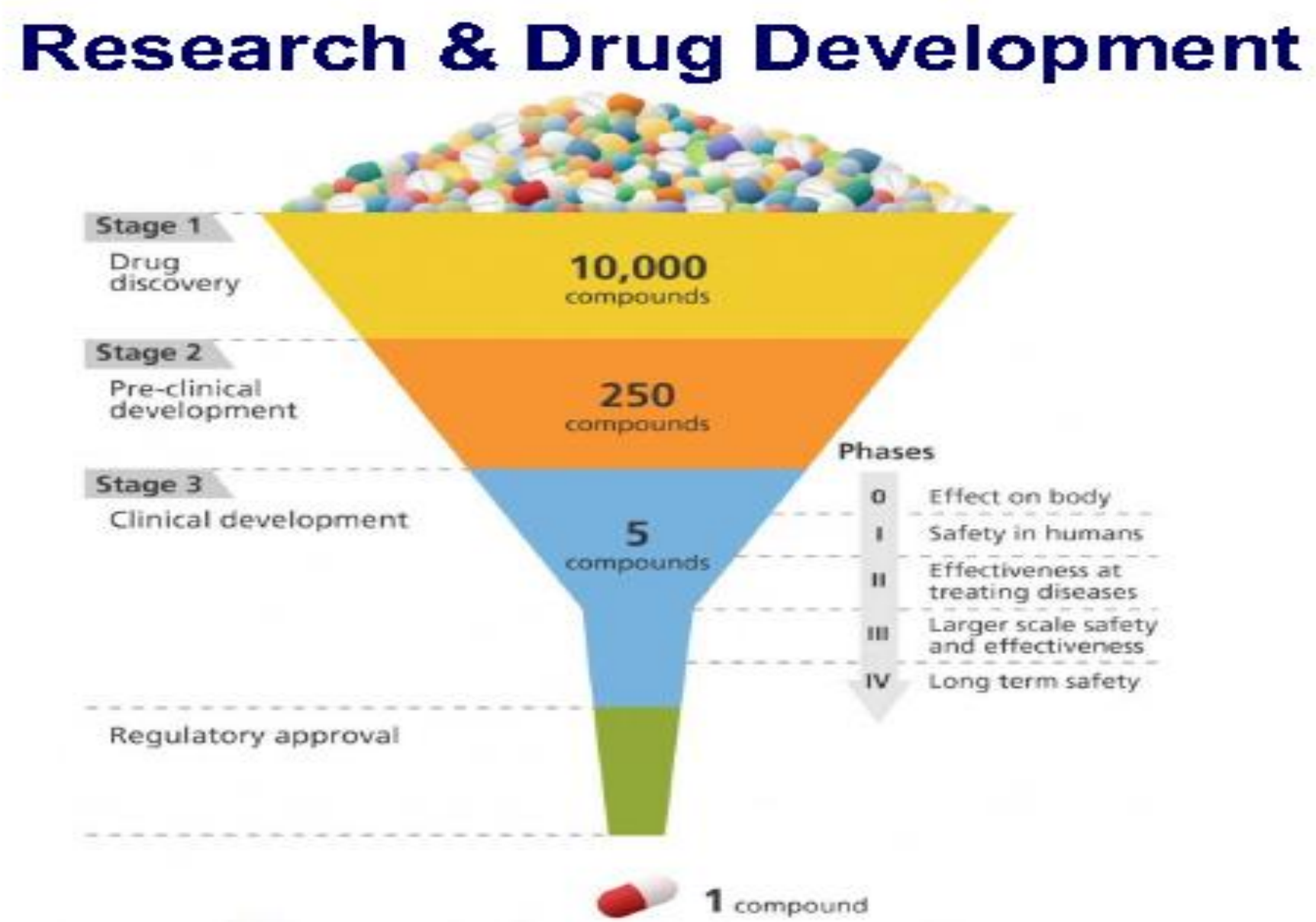
Dr Smith is an co-inventor on an issued patent regarding Proglumide and Pancreatic Cancer.

Dr Smith is employed by Georgetown University and this University is the owner of the intellectual property.

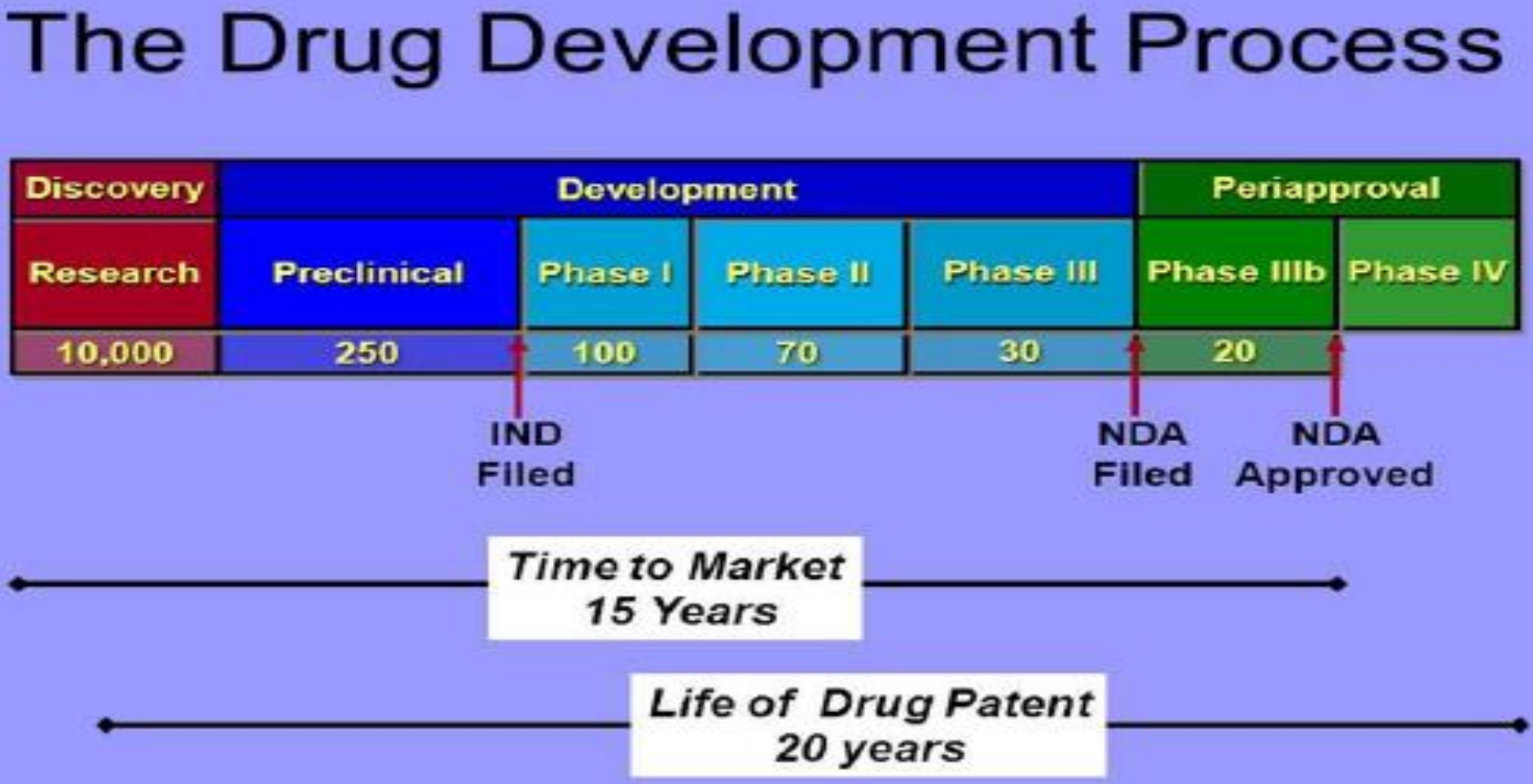


Bench to Bedside and back to Bench again!- Example of translational research

Research and drug development



Drug development process



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.





Ideas

You need an Idea

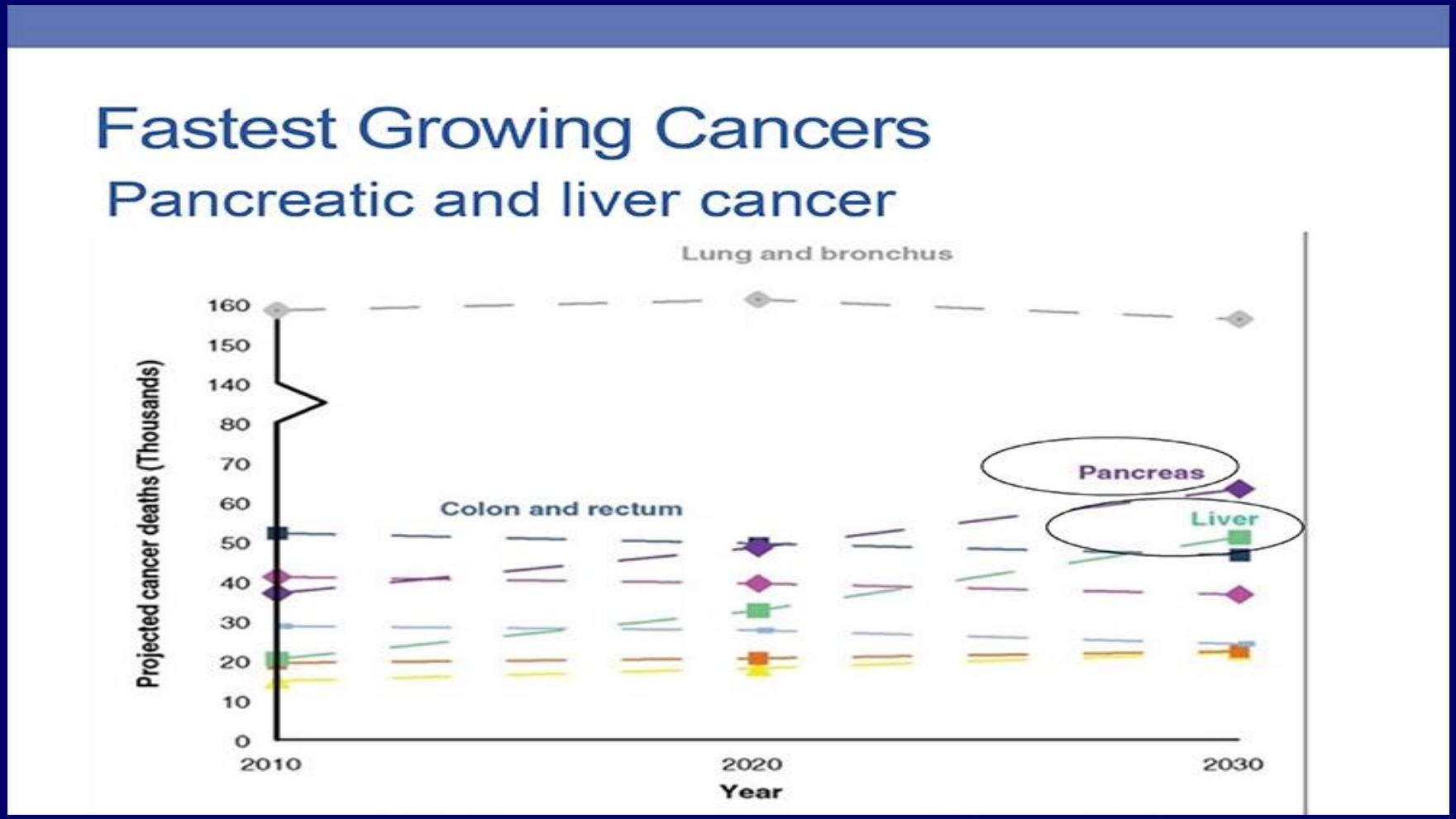


Hypothesis

Passion!!



Fast growing cancers



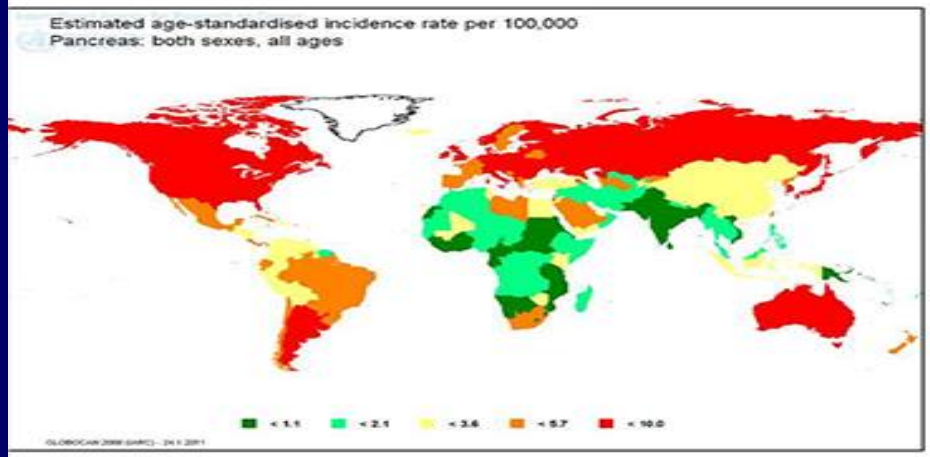
Obese men and cancer



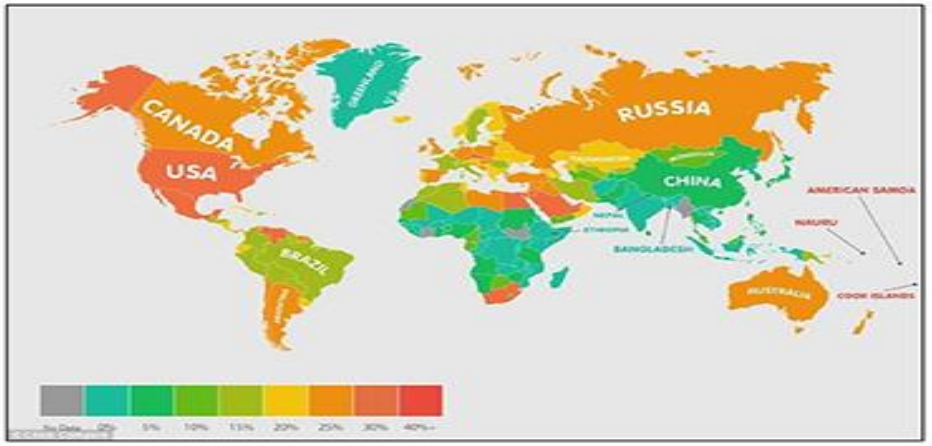
Pancreatic cancer and dietary fat

Pancreatic Cancer and Dietary Fat

There is a direct correlation between dietary fat consumption and the incidence of pancreatic cancer, especially saturated fat.

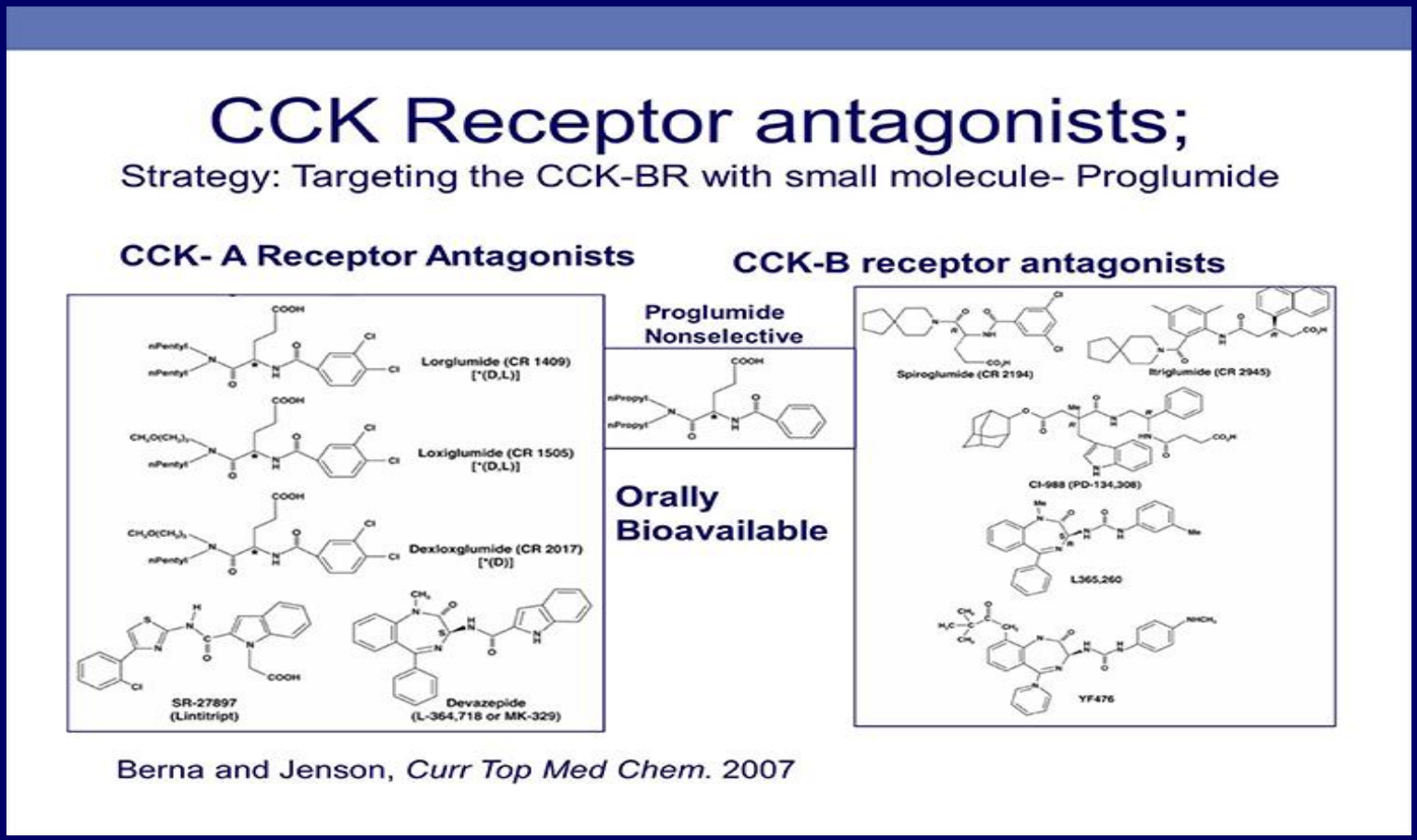


Incidence of Pancreatic cancer World-wide

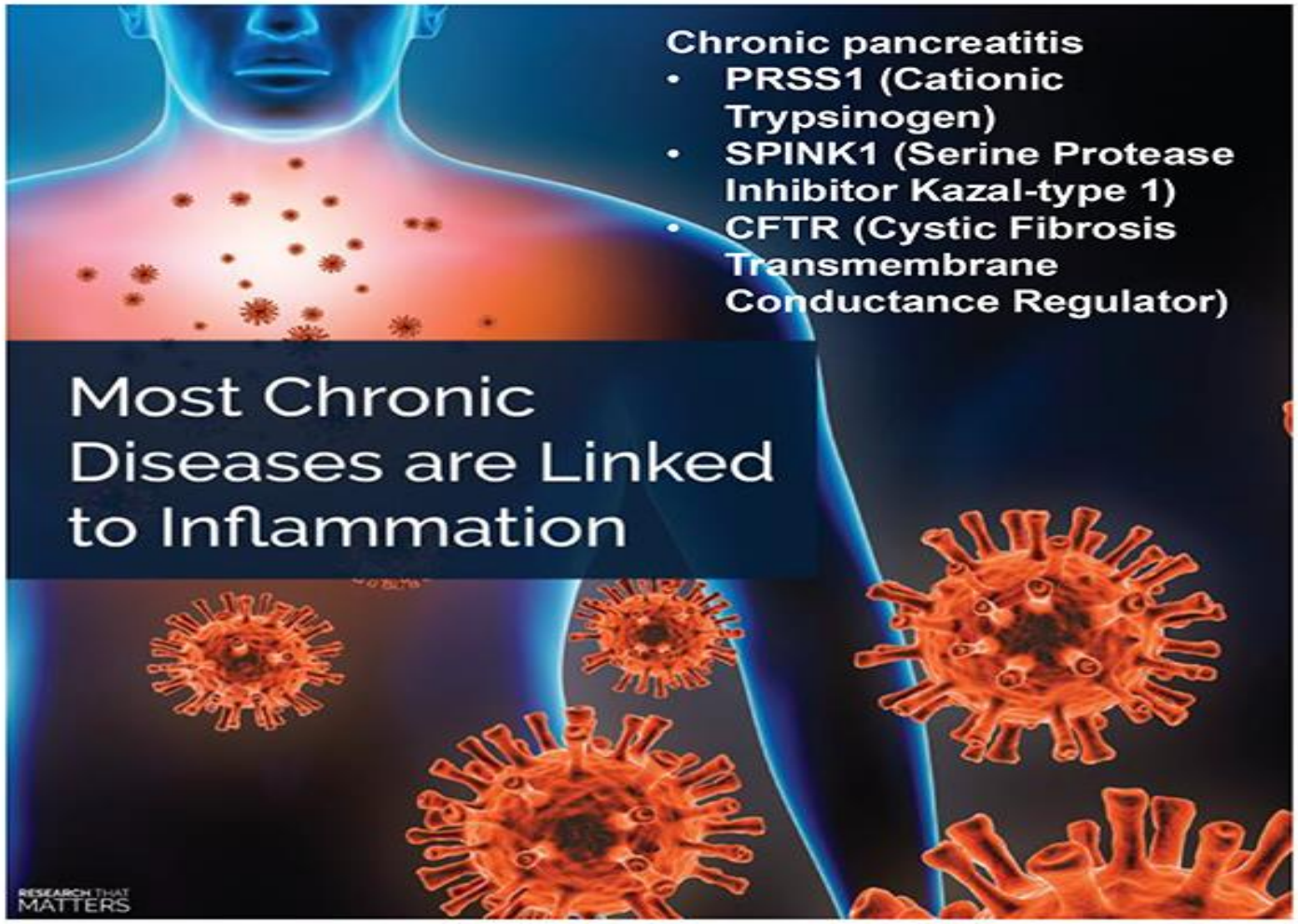


Dietary fat consumption world-wide

CCK receptor antagonists



Inflammation



CCK receptors

Cholecystokinin Receptors: GPCRs

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

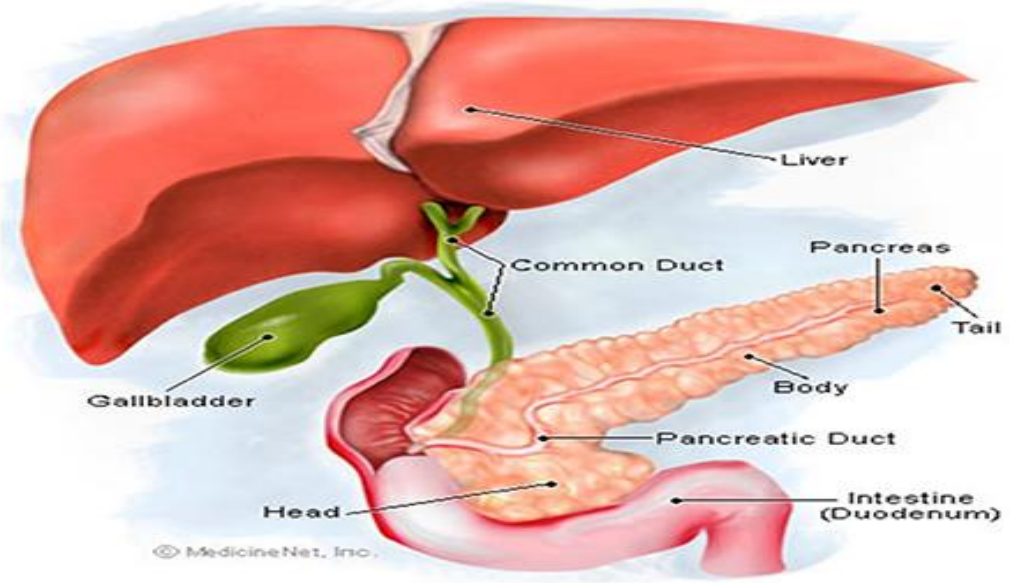
- **CCK-B**: Also called CCK-2R
  brain, stomach
  Binds CCK = Gastrin (1:1)

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

CCK physiology

Normal Physiologic Function of CCK

Bile made in the liver is stored in the gallbladder. CCK causes contraction of the gallbladder so bile can emulsify fat for digestion.

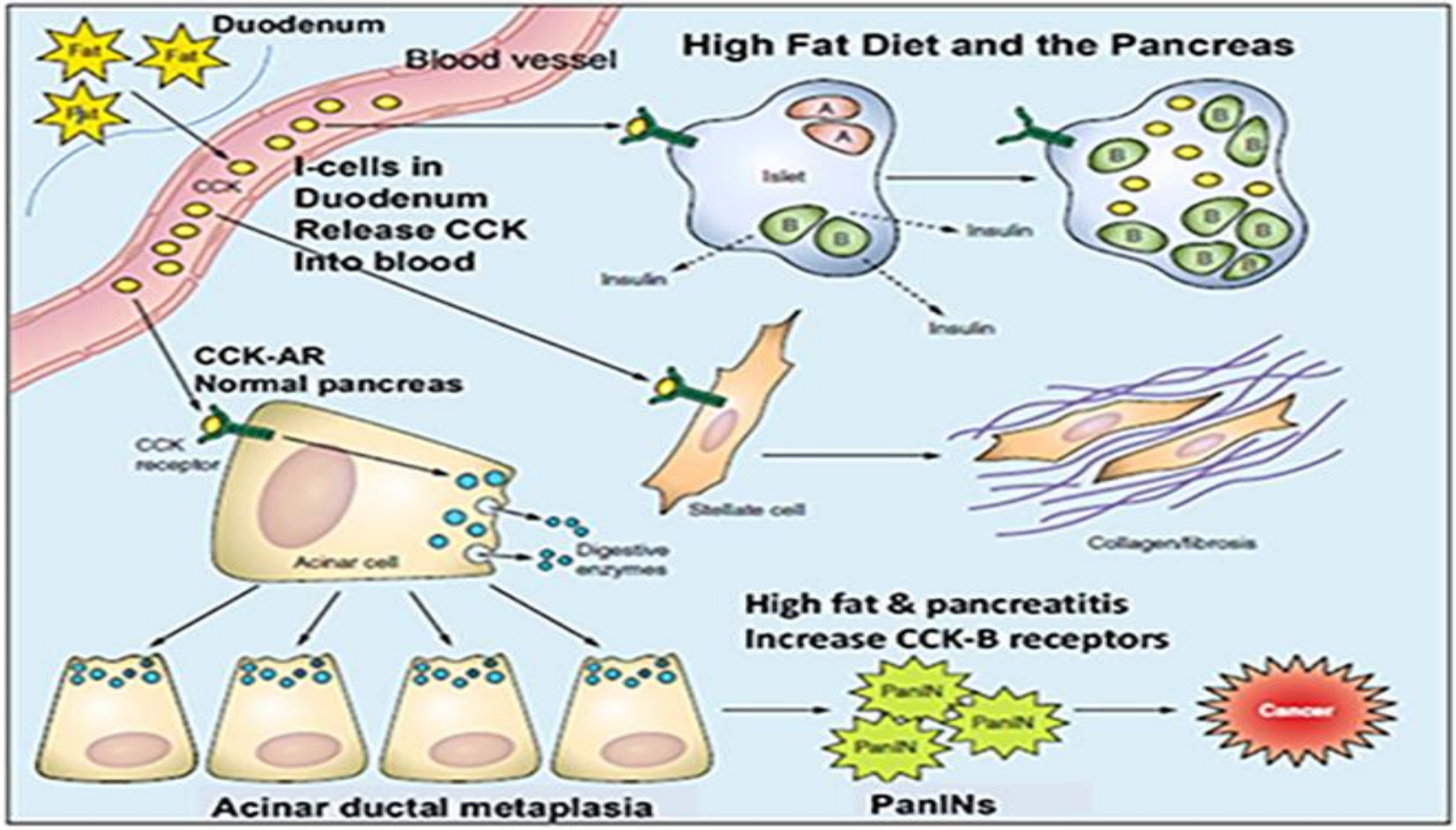


Secretin- releases HC03 from the ducts to neutralize acid

Digestive enzymes Elastase, Lipase, Amylase, Trypsin, chymotrypsin

CCK causes the release of pancreatic digestive enzymes, relaxation of the Sphincter of Oddi and contraction of the gallbladder

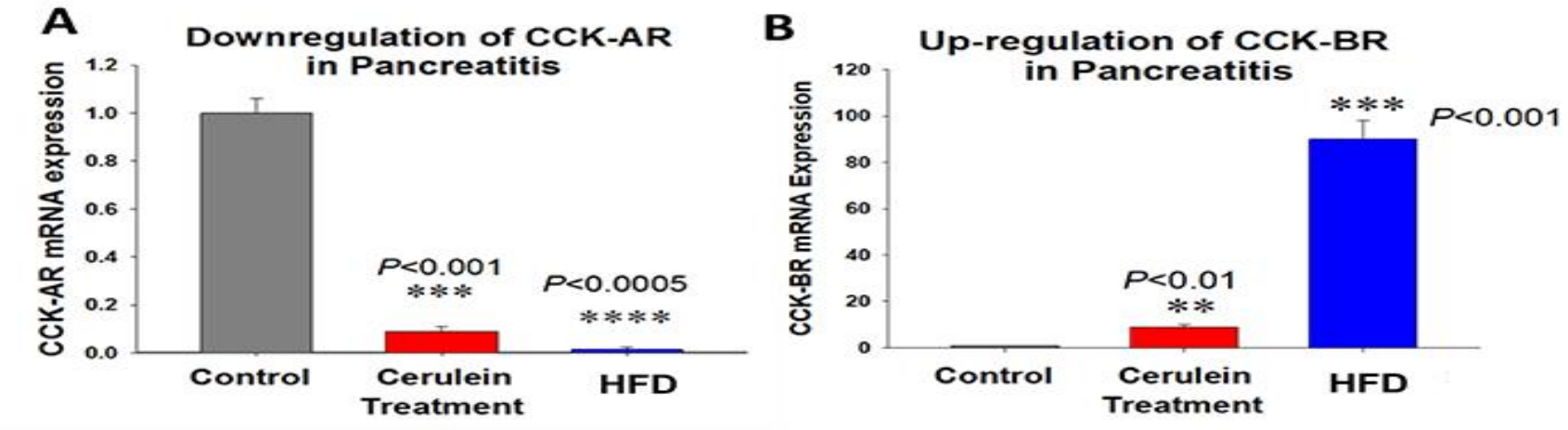
High fat diet



Am J Physiol Gastrointest Liver Physiol. 2014 Jan;306(2):G91-G101

CCK expression

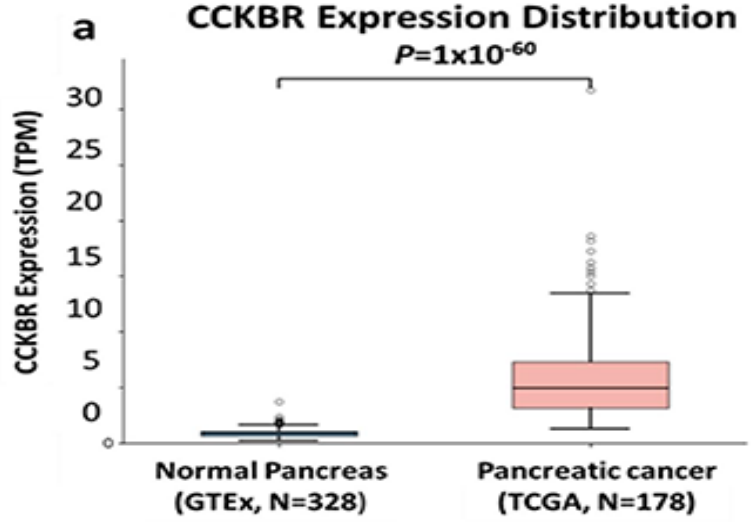
CCK-B Receptor has low expression in normal tissues

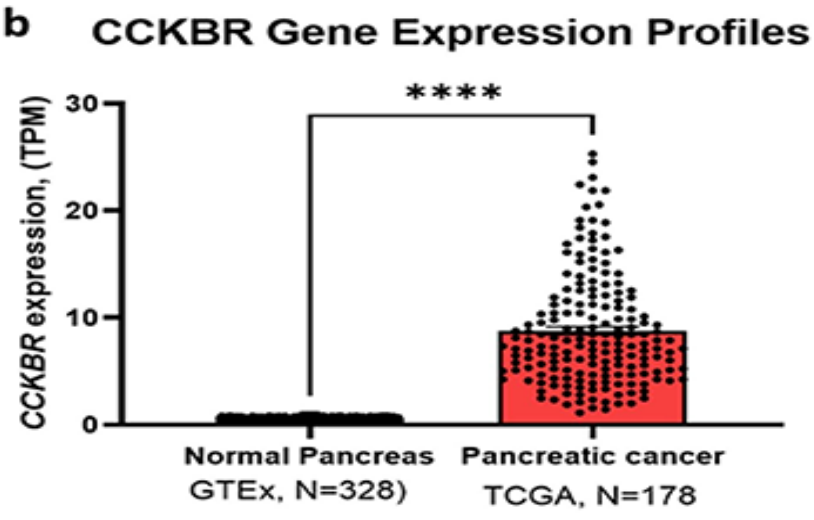


Inflammation (pancreatitis) and high fat diet activates CCK-BR expression.

CCK-BR overexpression

Confirmation of CCK-BR Overexpression in human subjects with public databases

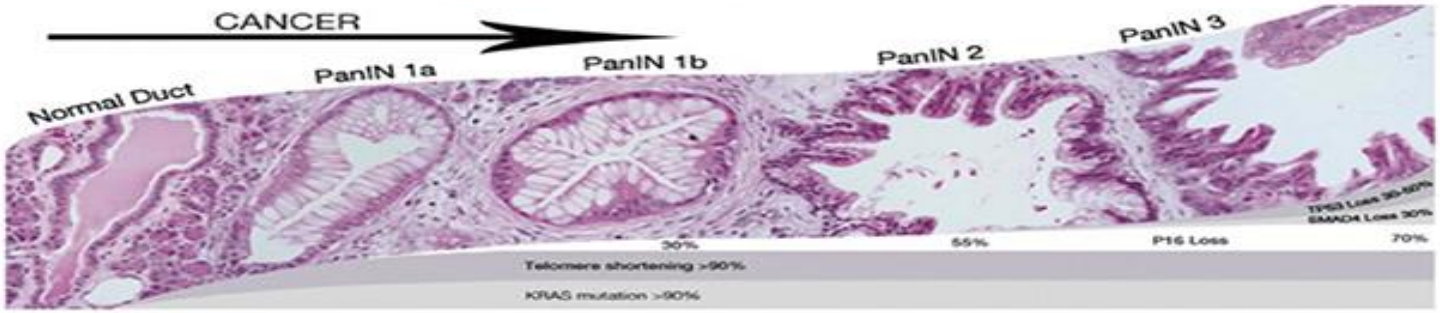




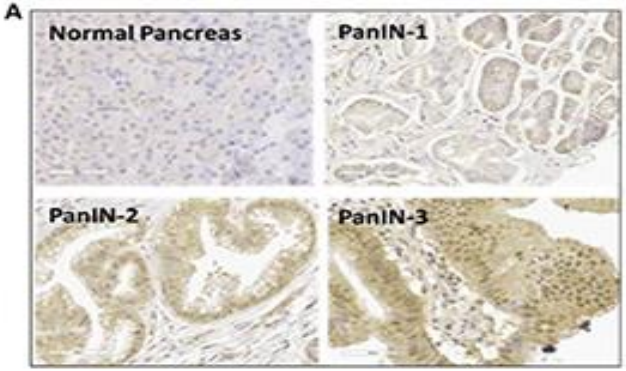
In Press 2026, Smith

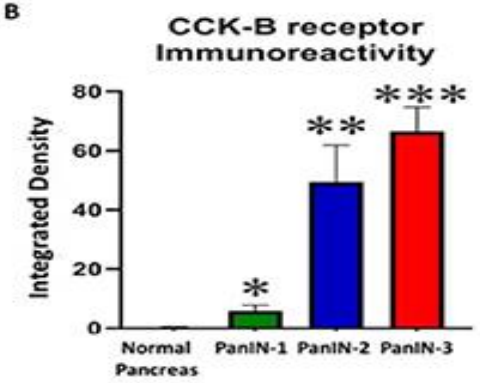
CCK-BR and pancreatic cancer

The CCK-BR is not found in the normal pancreas but is over-expressed in pancreatic cancer



- 90% of pancreatic cancers form from a lesion called Pancreatic Intraepithelial Neoplasia or PanINs.





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

Our hypothesis

Our hypothesis

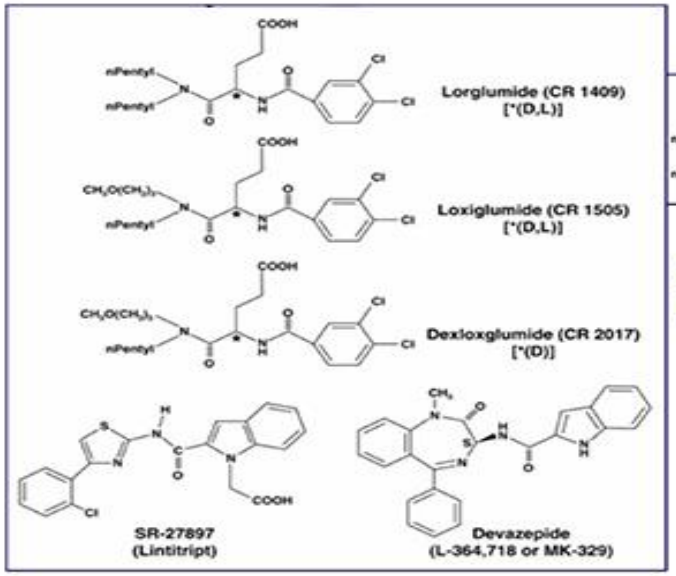
Since CCK-BRs are over-expressed in pancreas and liver cancer, these receptors are good targets for therapy and for imaging (diagnostics).

CCK-R antagonists

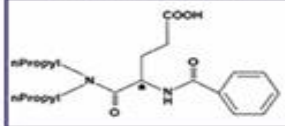
CCK Receptor antagonists;

Strategy: Targeting the CCK-BR with small molecule- Proglumide

CCK- A Receptor Antagonists

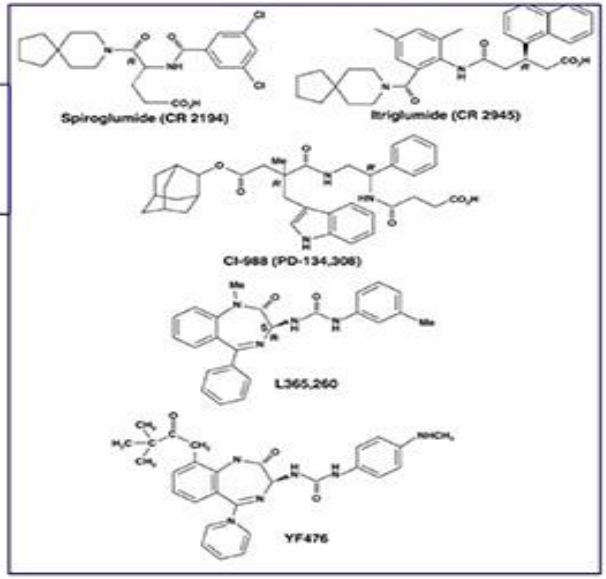


Proglumide
Nonselective



Orally Bioavailable

CCK-B receptor antagonists



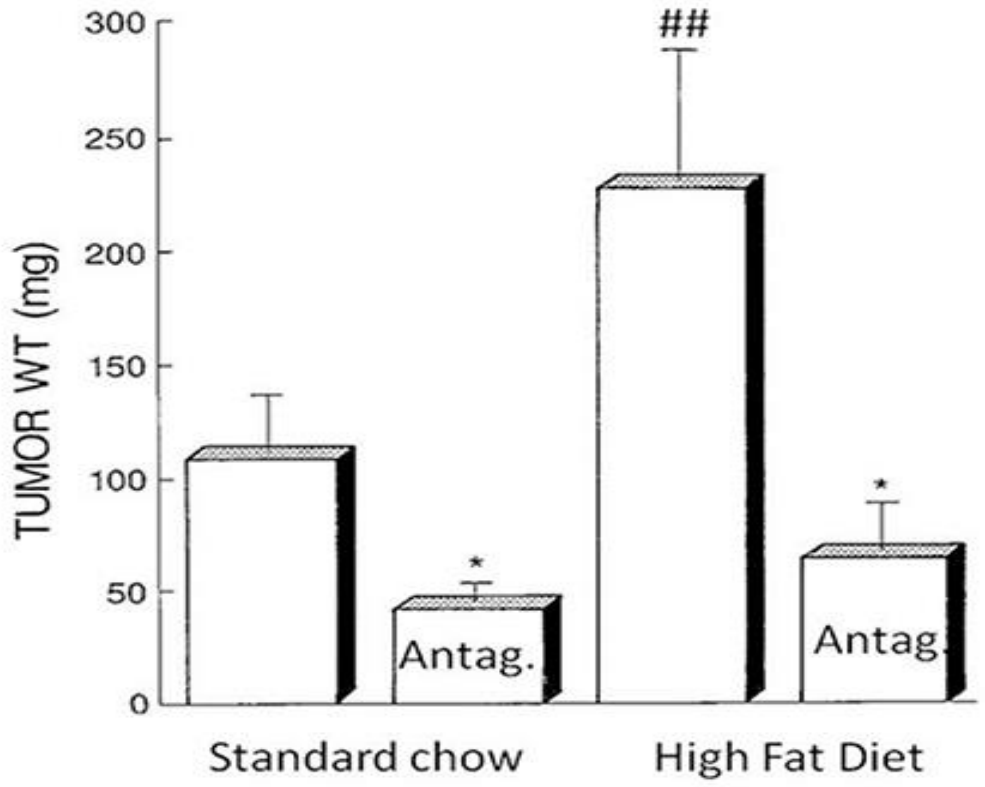
Berna and Jenson, *Curr Top Med Chem.* 2007

Dietary fat

Does Dietary fat increase growth of human pancreas cancer by stimulating the CCK Receptor?



	Low	High
Protein	24.5	20.4
Fat	**4.3**	**20.5**
Fiber	3.7	3.12
Carb	48.4	40.4



Proglumide and chemotherapy

Proglumide Improves Efficacy of Chemotherapy

Cholecystokinin Receptor Antagonist Improves Efficacy of Chemotherapy in Murine Models of Pancreatic Cancer by Altering the Tumor Microenvironment

Treatments: 4 groups
1. PBS control; 2, Gemcitabine monotherapy;
3. Proglumide monotherapy; 4. Combination Gemcitabine & proglumide



C57BL6 mouse
Syngeneic pancreatic cancer
To test tumor infiltrating lymphocytes
To test tumor associated macrophages

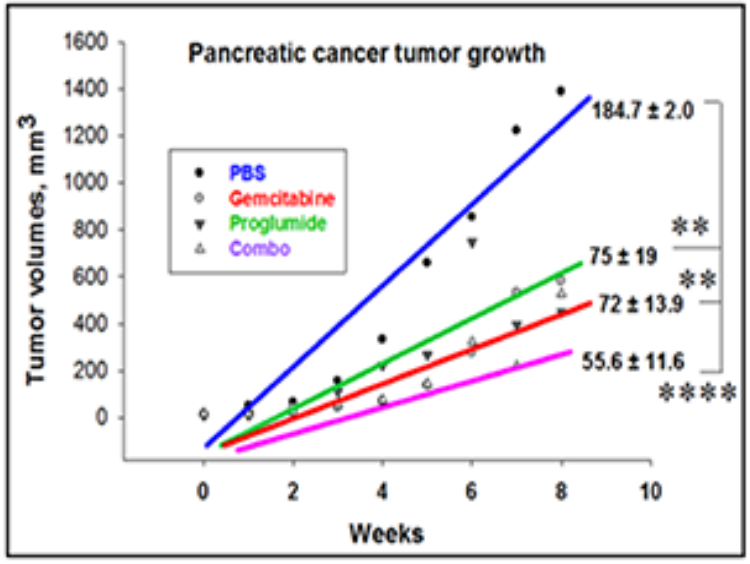


Atyhmic nude mouse
Human pancreatic tumor
Orthotopic
To Study metastases

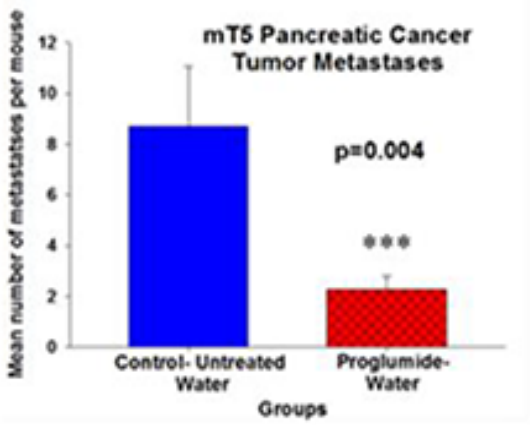
Cancers **2021**, *13*(19), 4949; **https://doi.org/10.3390/cancers13194949**

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.

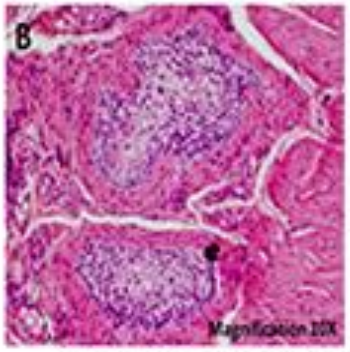


Proglumide decreased growth and the number of metastases in immune competent mice bearing orthotopic syngeneic mT5 pancreatic tumors.
***p=0.00433

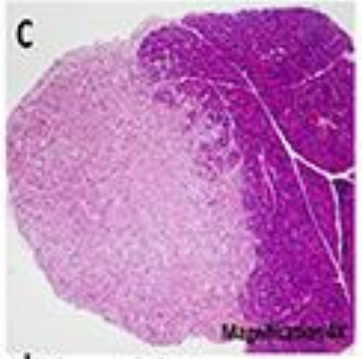
Metastasis

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

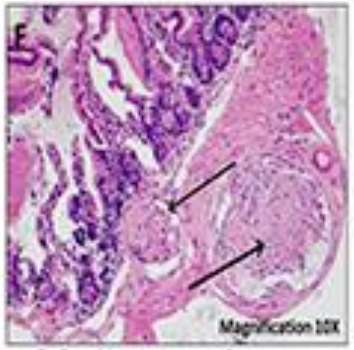
All metastases were confirmed by histology and read by our Pathologist



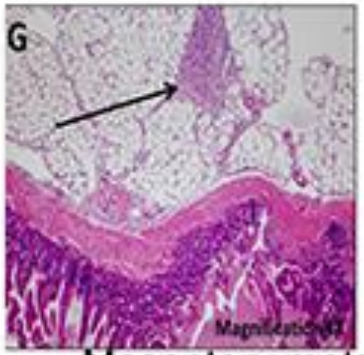
Tumor emboli muscle



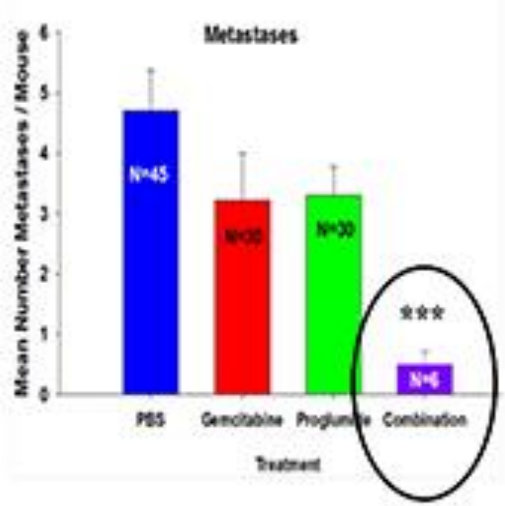
Liver Metastases



Mets to colon



Mesentery mets

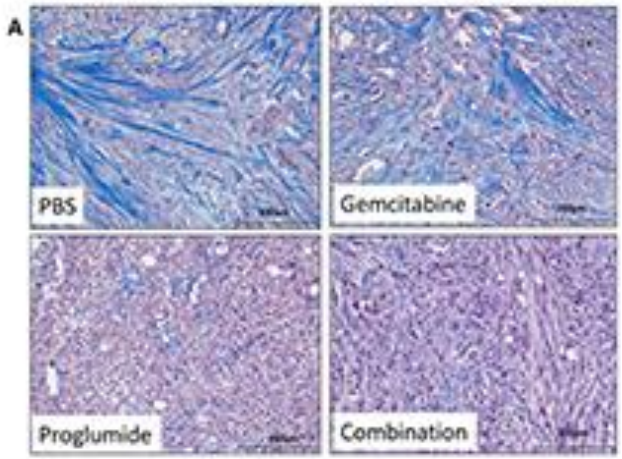


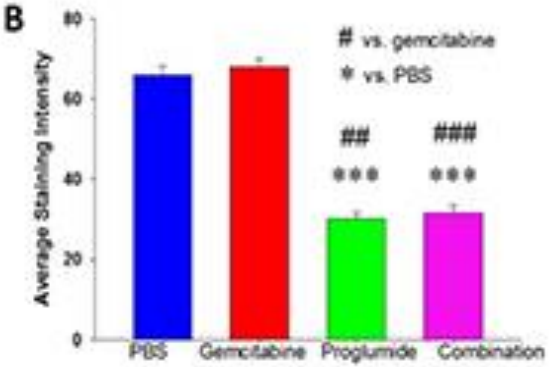
Group	Liver	Mesentery/ Peritoneum	Nodes	Spleen	Diaphragm	Abdominal Wall	Stomach	Colon
PBS	4	22	2	5	1	2	6	3
Gemcitabine	4	12	1	5	0	1	2	5
Proglumide	2	18	2	1	0	2	2	3
Combination	0	3	0	1	1	0	0	1

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

Fibrosis

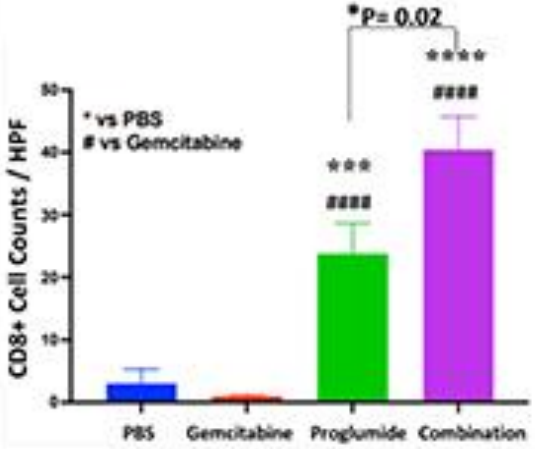
Proglumide decreases fibrosis & alters the immune signature in pancreatic cancer





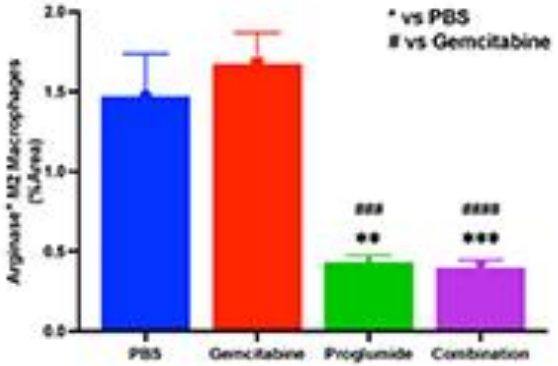
Mouse with pancreatic cancer

Cancers 2021, PMID: 34638432



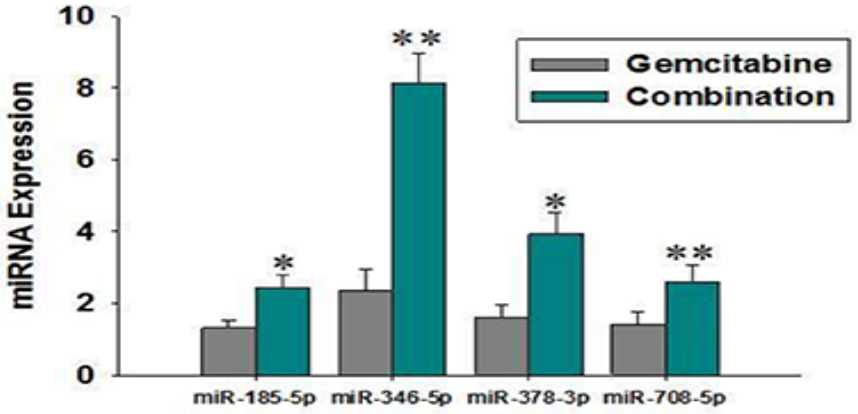
Proglumide increases CD8+ T-cells

Proglumide decreases M2-polarized Macrophages



Blood biomarkers

Development of Blood Biomarker Panel for Tumor Fibrosis

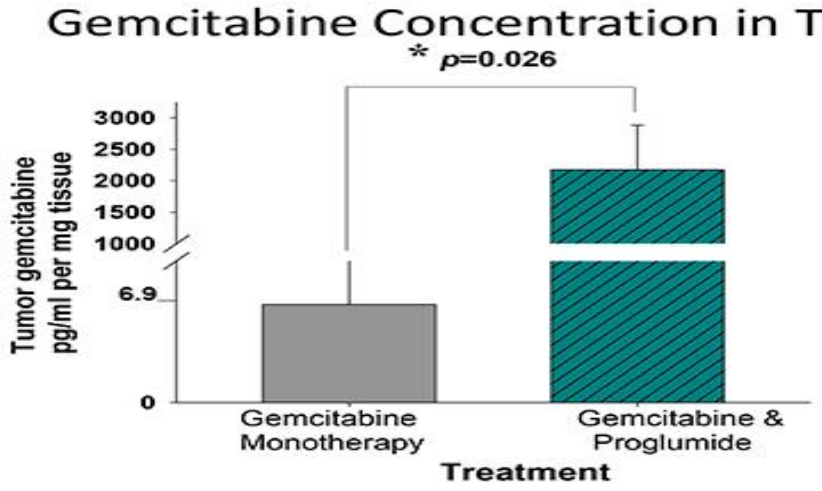


- Peripheral blood was collected from mice to evaluate circulating microRNAs.
- The microRNAs: miR-185-5p, miR-346-5p, miR-378-3p, miR-708-5p are known to inhibit fibrosis from stellate cells.
- Compared to gemcitabine monotherapy, these miRNAs were significantly upregulated in the peripheral blood of mice treated with the combination therapy.

miRNAs that Inhibit Stellate Cells and Fibrosis are Upregulated with Combination Therapy

Gemcitabine

Measurement of Tumor Gemcitabine Levels by Mass Spectroscopy



- Tumor levels of gemcitabine were measured 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.

Based on these findings, we questioned whether proglumide would alter the TME and improve response to gemcitabine in patients with metastatic pancreatic cancer.

Clinical trial

Steps to Starting a Clinical Trial

- 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

Calculating clinical dose



25g

Calculating human dose from animal study



70kg

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]

IND

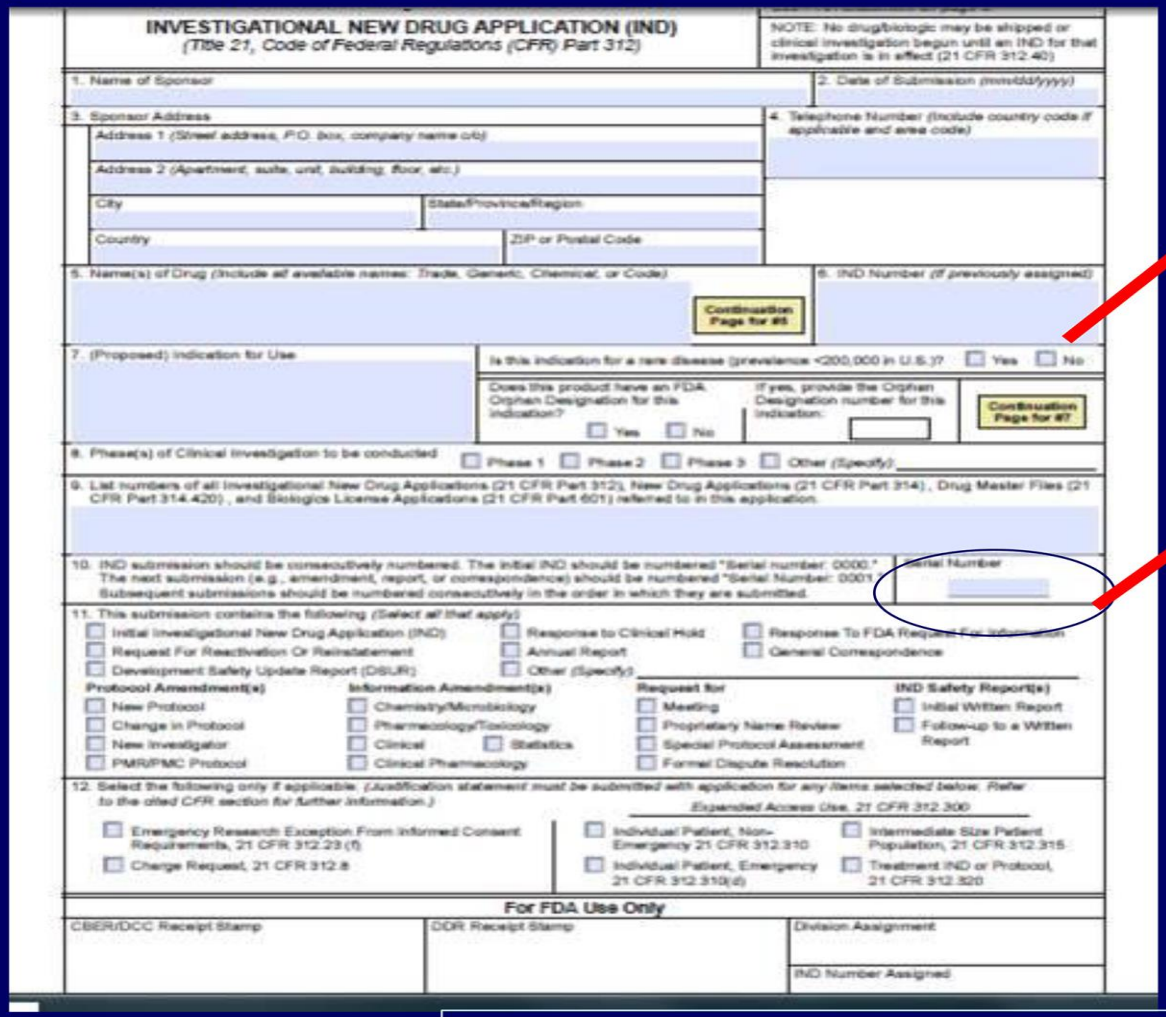
Investigational New Drug (IND) Application

- **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)

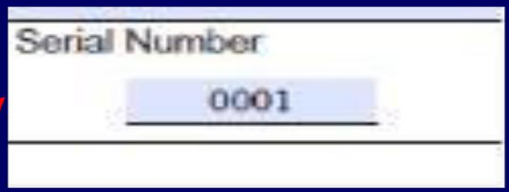
1. Name of Sponsor
2. Date of Submission (mm/dd/yyyy)
3. Sponsor Address
Address 1 (Street address, P.O. box, company name c/o)
Address 2 (Apartment, suite, unit, building, floor, etc.)
City
State/Province/Region
Country
ZIP or Postal Code
4. Telephone Number (Include country code if applicable and area 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

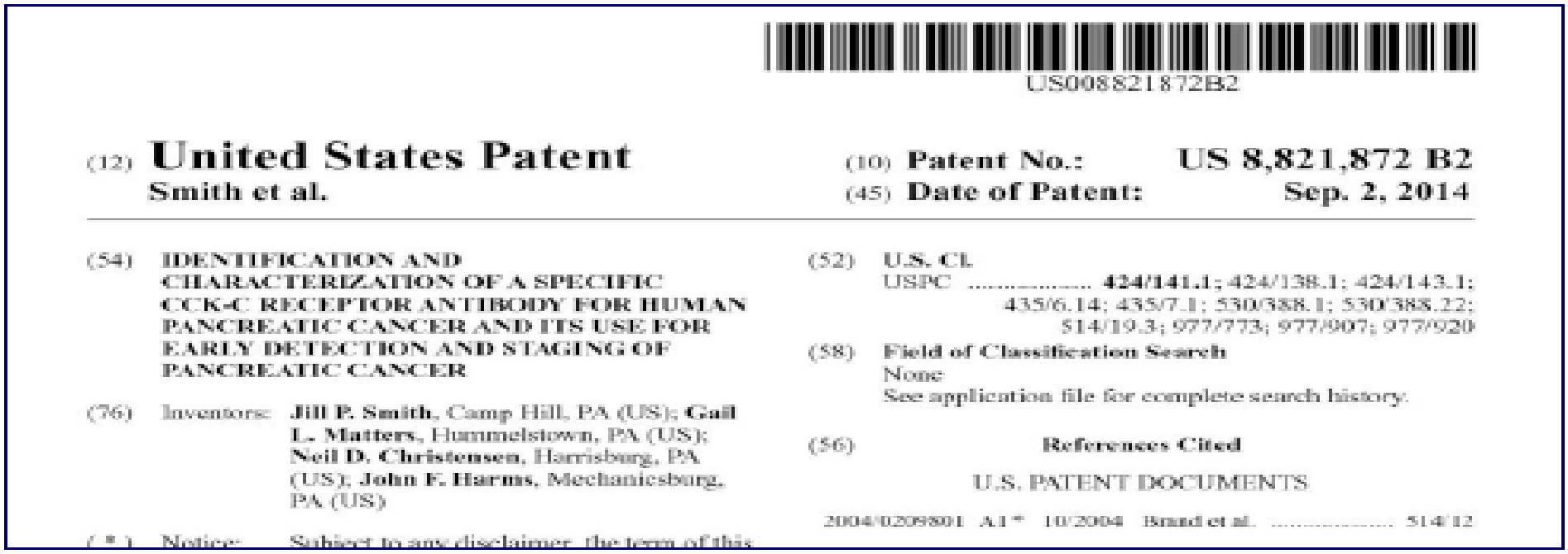
Clinical trials

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

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

Cost

Cost

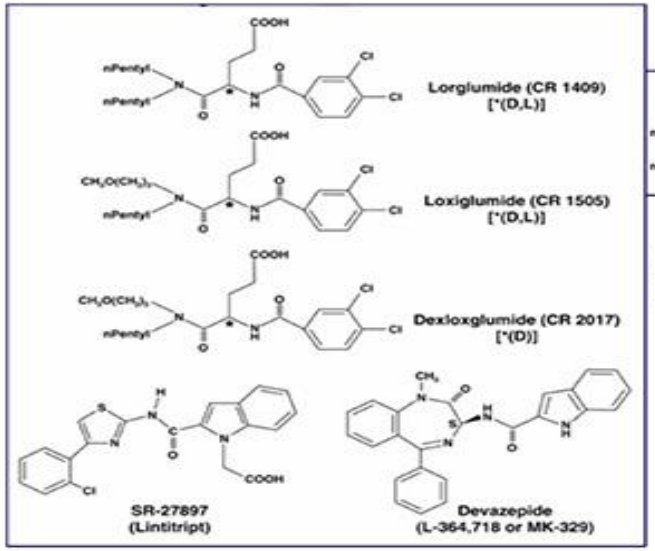
- The NIH will support Phase 1-2 clinical trials.
- Phase 3 Registration trials require an industry partner.
- A ‘registration trial’ is designed to get FDA approval.
- The cost of an FDA New Drug Application (NDA) is greater than $3.0 million today.
- Orphan Drug Designation: a process to lower the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

CCK-R antagonists

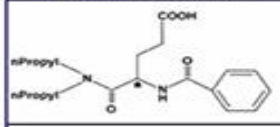
CCK Receptor antagonists;

Strategy: Targeting the CCK-BR with small molecule- Proglumide

CCK- A Receptor Antagonists

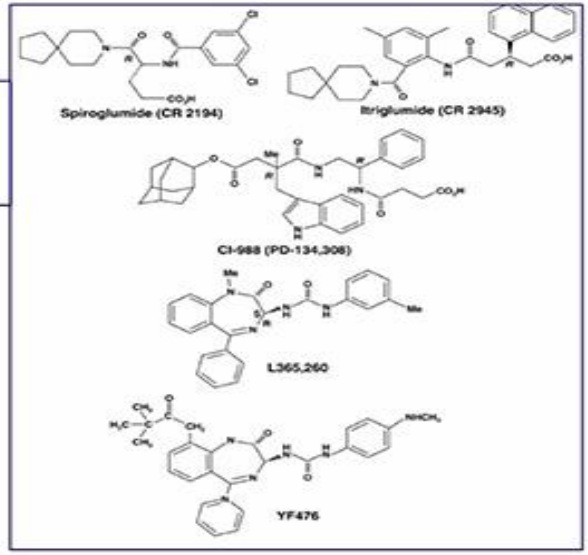


Proglumide
Nonselective



Orally Bioavailable

CCK-B receptor antagonists



Berna and Jenson, *Curr Top Med Chem.* 2007

Phase-1

Phase 1- first in human
Is it safe?

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



How much?

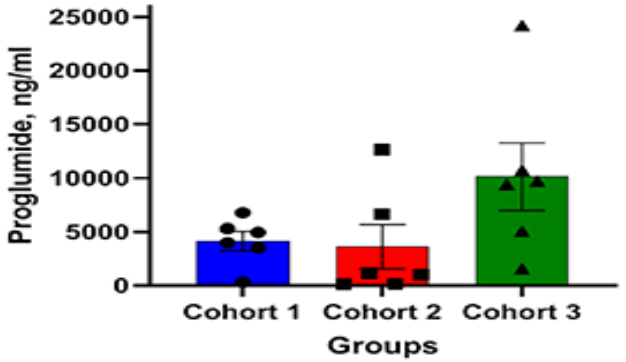


What route of administration?

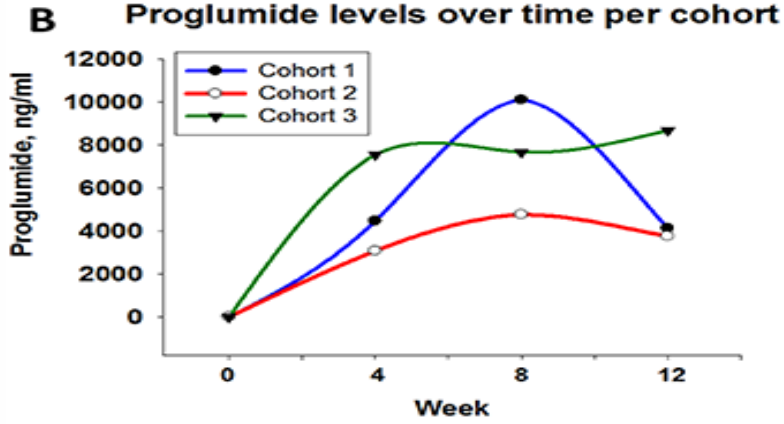
Proglumide blood levels

Pharmacokinetic studies: Proglumide blood levels, From Phase 1 study

A



B



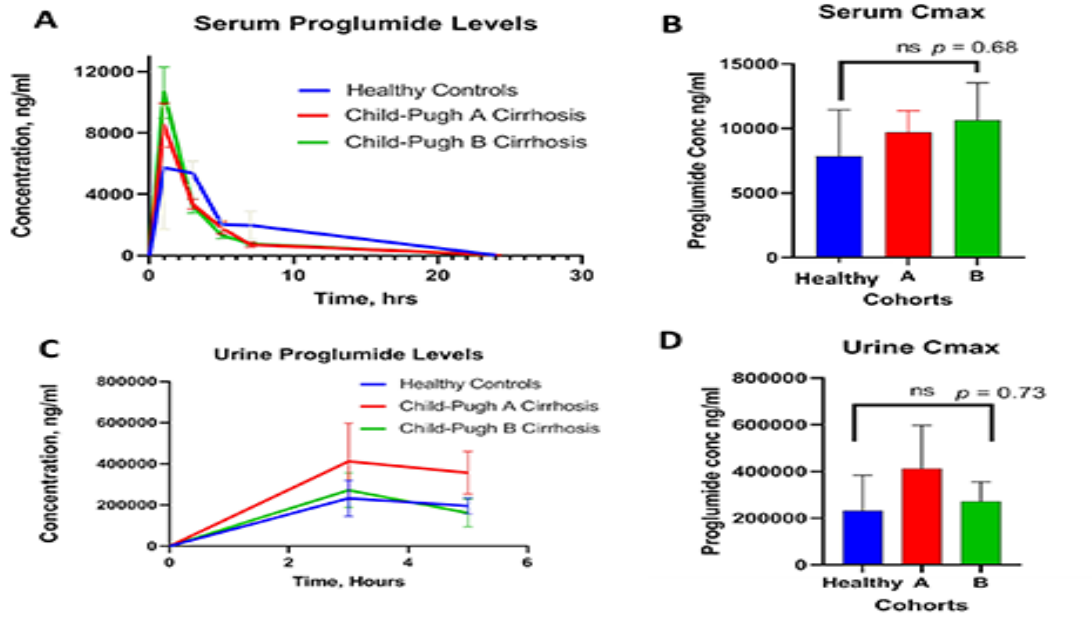
FDA recommended 1200mg starting dose since cohort 3 did not reach cMAX

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

Clinical Pharmacology & Therapeutics 2022

Proglumide safety

Proglumide is Safe in Hepatic Impaired; Child Pugh A& B Cirrhosis



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

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

Study Design



Study Design

Phase 1, Open-labeled Safety and Dosing Study

N=6

FDA IND# 138481
Protocol #001899
Registration #NCT05827055

Inclusion Criteria
Metastatic
Pancreatic Cancer
Biopsy assessible
Gemcitabine naive

Gemcitabine &
Nab-paclitaxel
(SOC) &
Proglumide
1200 mg/d

Outcomes

- Safety
- Dose
- Tumor microenvironment → Biopsy
- Liquid biopsy, biomarkers → Blood miRNA
- Pain Survey; McGill's Questionnaire

Funding: Ruesch
Center & Philanthropy

Secured Orphan Drug designation for proglumide in pancreatic cancer.

Eligibility Critera

Eligibility Criteria:

Inclusion Criteria	Exclusion Criteria
Histologic confirmed PDAC with metastatic disease	Anticoagulants that cannot safely be held for biopsy
Males & Females	Pregnant or nursing
Age ≥ 18	HIV or active Hepatitis B, Hepatitis C
Biopsy accessible tumor	Prior therapy with GEM-NAB-P, Child' C Cirrhosis
Hgb ≥ 9.0g/dL; ANC > 1500/mm^3; Platelets≥ 100,000/mm^3; CrCl>60 mL/min; T Bili <1.5ULN; AST/ALT<2.5 ULN	Known allergy or hypersensitivity to any of the drugs or any drug excipients.
Measurable disease by RECIST	Life expectancy < 3 months
ECOG 0-1; Gemcitabine naive	Other serious medical disease

Methodology

Methodology

1. **Safety** was assessed with adverse events according to CTCAE criteria.
2. **Biomarker analysis by microRNA (miRNA),** a liquid biopsy serum sample was collected at baseline, at week 8, and at the end of treatment (EOT). Changes in miRNA biomarkers in the panel used reflected changes in the TME.
3. **McGill pain surveys** were done at baseline, week 8, and at the EOT.

Methodology

Methodology

4. Tumor biopsies were obtained at baseline and again at week 8 on therapy.

- **Histology**
  - Biopsies were stained with hematoxylin & eosin and also with Masson's trichrome.
  - CCK-BR immunoreactivity was evaluated with CCK-BR antibody (Abcam 77077; 1:200 titer).
- **Tumor microenvironment by Multiplex Immunohistochemistry**
  - Biopsies were reacted with the following antibodies, and Images were viewed and analyzed using PhenoChart and Inform imaging software.

Antibodies

Antibodies for Multiplex Immunohistochemistry:

Target	Antibody	Company	Catalogue #	Opal Fluor
Nucleus	DAPI	AKOYA Biosciences	FP1490	DAPI
Cancer cells	panCK	Agilent	Z0622	Opal 480
Proliferation Index	Ki67	Abcam	ab15580	Opal 520
M2 macrophages	Arginase 1	ThermoFisher	PA5-29645	Opal 570
Natural Killer cells	CD56	Abcam	ab133345	Opal 620
Fibrosis	Collagen1α1	ThermoFisher	PA5-89281	Opal 690
T-lymphocytes	CD8	Agilent	M7103	Opal 780

Patient diagnosis

Results

Subject	Gender	Age (years)	Race	Past treatment	Metastases
001	Male	68	Asian	Yes	Lung
002	Male	72	Black	No	Liver
004	Male	54	White	Yes	Liver
005	Female	72	Black	No	Lung
006	Female	69	White	No	Liver, peritoneum
008	Male	74	White	Yes	Liver, peritoneum

Patient Demographics

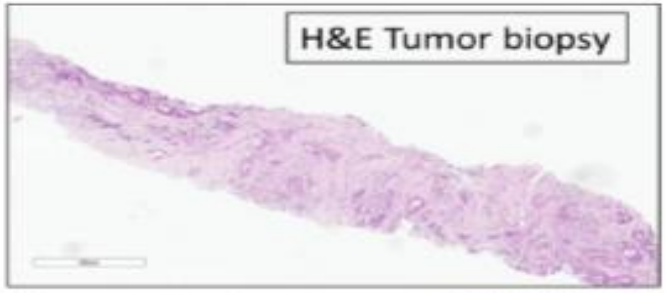
Proglumide trial

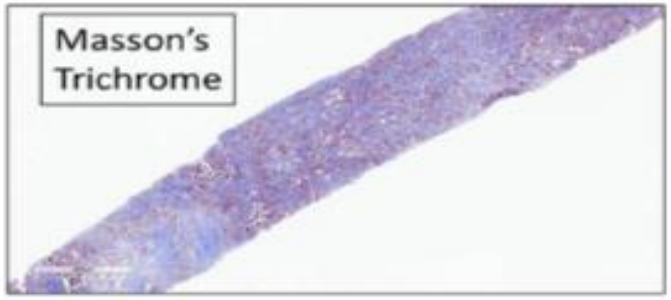
Results

Primary outcomes:
Safety: No Adverse events were reported due to proglumide.
Dose: Proglumide 1200mg/ day (400mg po tid).

Pathology

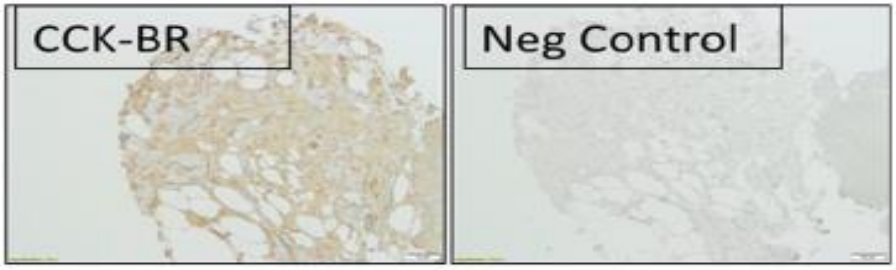
Tumor Biopsies Confirmed by Pathology







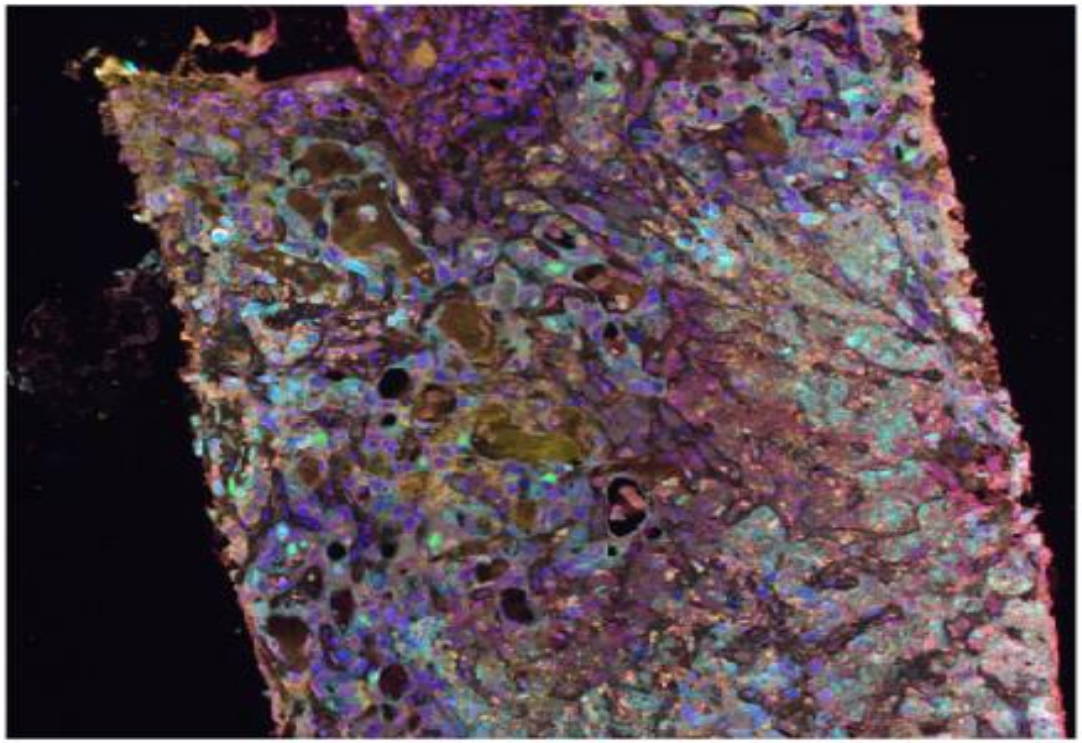
Bhaskar Kallakury, MD



Biopsy

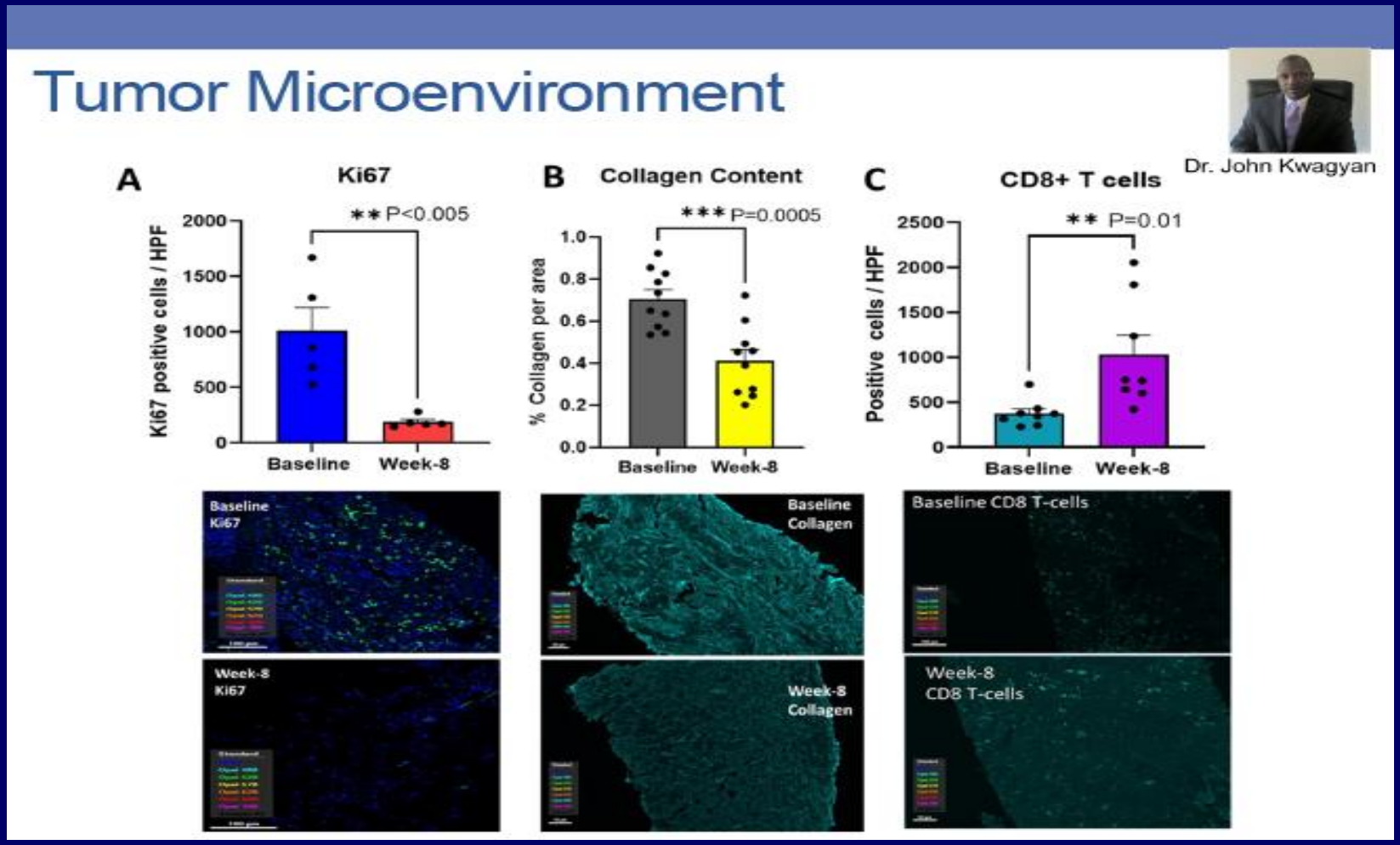


Anju Duttargi



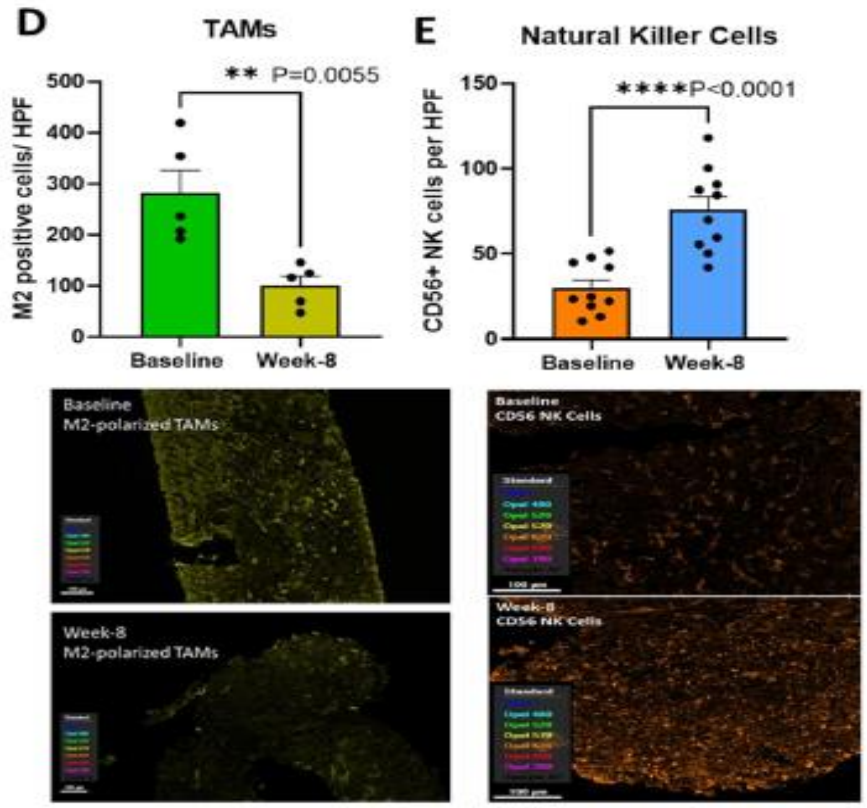
Tumor Biopsy By Multiplex IHC

Tumor microenvironment



Microenvironment

Tumor Microenvironment





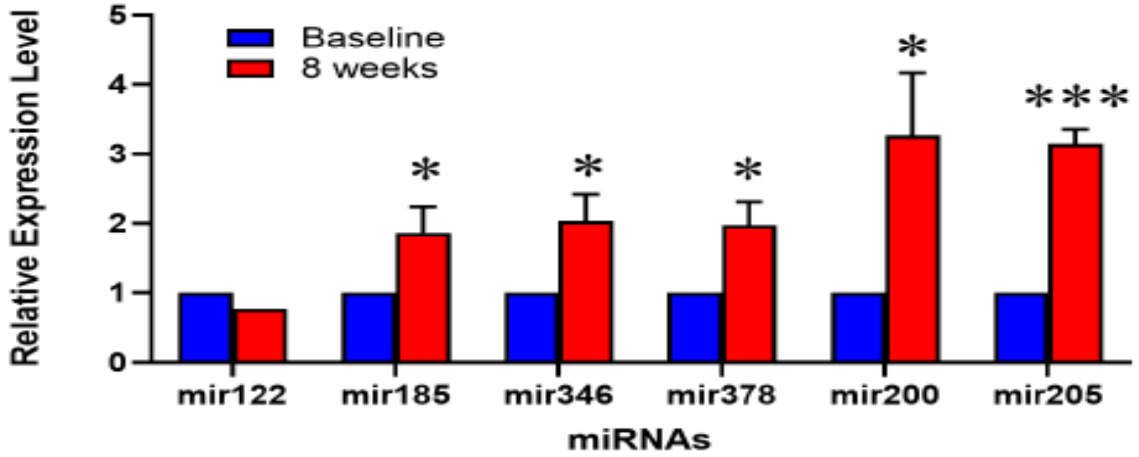
Dr. John Kwagyan

Liquid biopsy

Liquid Biopsy



Gakiza C. Nkulikiyimana



Average miRNA values in all patients at baseline and at week 8. Columns represent means ± SEM. Week-8 values are significantly different from baseline *P<0.05 and ***P<0.0001.

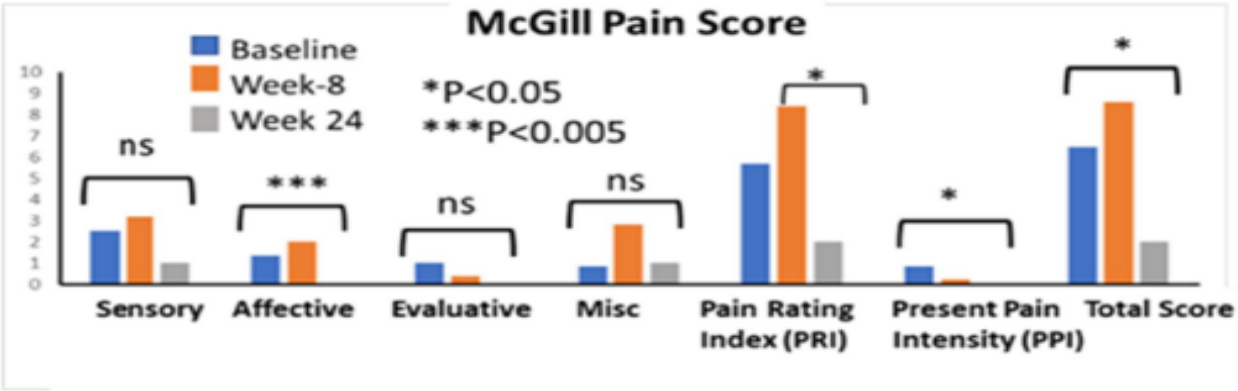
miRNA	Function	Cancer Role	Expected result	Why it matters
122	Cell Cycle Regulation	Upregulated in tumors	Decrease or downregulated	Restore control of proliferation
185	Inhibits proliferation & promotes apoptosis	Downregulated in tumors	Increase /upregulated	Promote cell death, anti-tumor
346	Inhibits growth & migration & fibrosis	Downregulated in tumors	Increase /upregulated	Decreases fibrosis
378	Inhibits fibrosis	Downregulated in tumors	Increase /upregulated	Decreases fibrosis
200	Inhibits EMT, blocks metastasis	Downregulated in tumors	Increase /upregulated	Decreases metastases
205	Inhibits EMT, supports epithelial phenotype	Downregulated in tumors	Increase /upregulated	Decrease metastases

Pain management

Pain management

Wenqiang Chen, MD, PhD





McGill pain scores for each pain category and total score. No differences were observed at week 8 compared to baseline, but a significant improvement in pain overall was seen at week 24 or at the end of treatment compared to baseline. *P<0.05; ***P<0.005.

Pancreatic cancer study

Conclusion of Pilot Pancreatic Cancer study

1. These results showed that proglumide is safe in combination with chemotherapy for subjects with metastatic pancreatic cancer.
2. The findings suggest that proglumide remodels the pancreatic cancer TME by decreasing fibrosis and immunosuppression, while enhancing T-cell infiltration.
3. The parallel shifts in circulating miRNA profiles offer a promising non-invasive biomarker panel for monitoring treatment response.
4. Cancer pain improves after 8 weeks on proglumide.
5. These results support further investigation of proglumide's role in pancreatic cancer therapy and in future Phase II clinical trials.

Published: Pharmaceutics. 2026 Mar 19;18(3):379.

Phase 2

Phase 2: Efficacy Proof of Concept

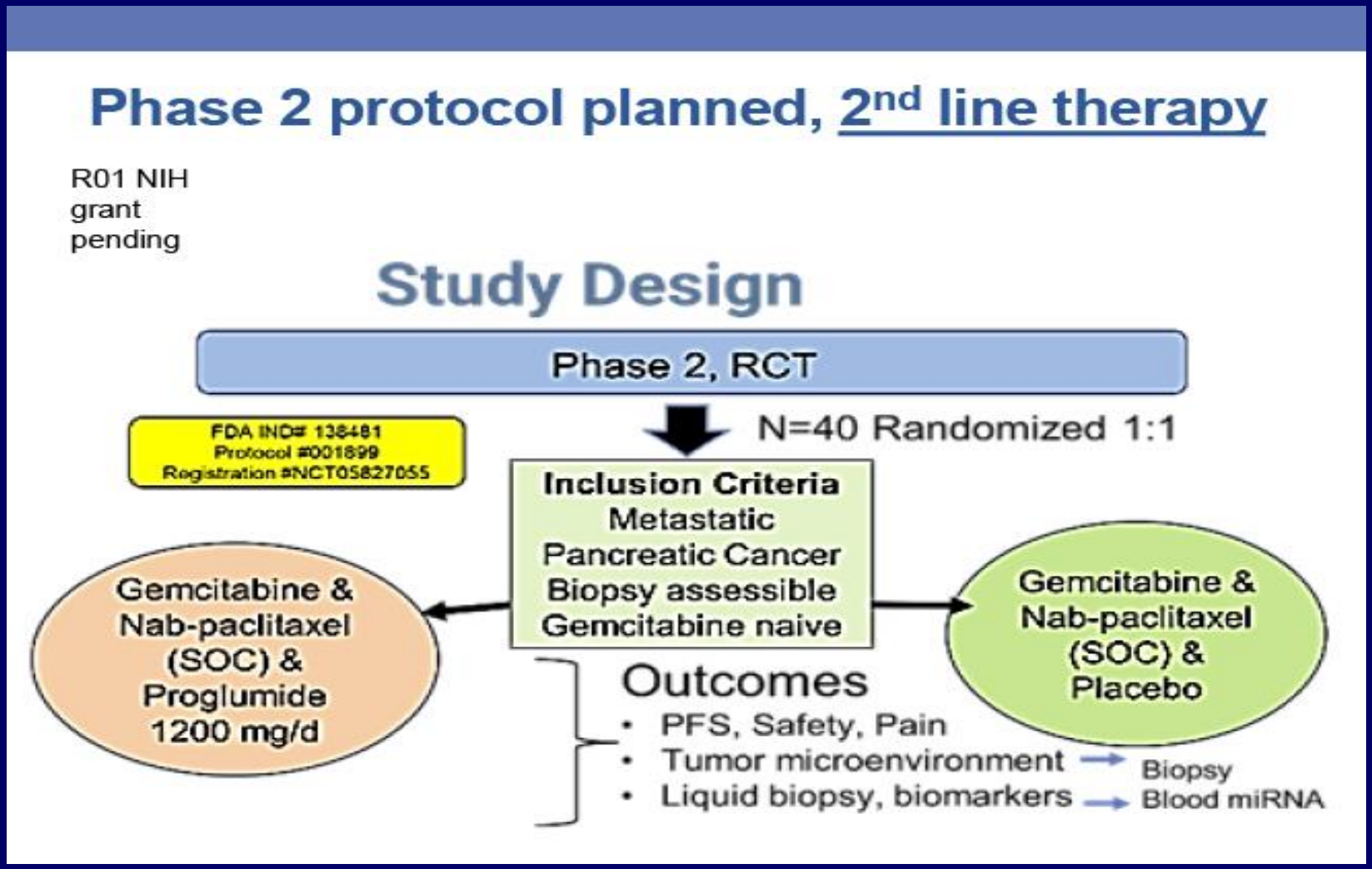
- May be less than 100 people
- Must have a primary endpoint
- Usually unbiased (typically it is double-blinded; neither the subject or investigator know)
- Equal chance to be assigned to one of two or more groups
- Determines
  - Drug Efficacy?
  - Is it more effective than a placebo?



Randomized, double blinded



Phase 2 protocol



Phase 3

Phase 3 – requires an industry partner



- From 100 to thousands of people
- Equal chance to be assigned to one of two or more groups
- Required for new drug applications to FDA (NDA) not funded by NIH or DOD
- Determines
  - How the new treatment compares with the current standard
  - Superiority or non-inferiority trials

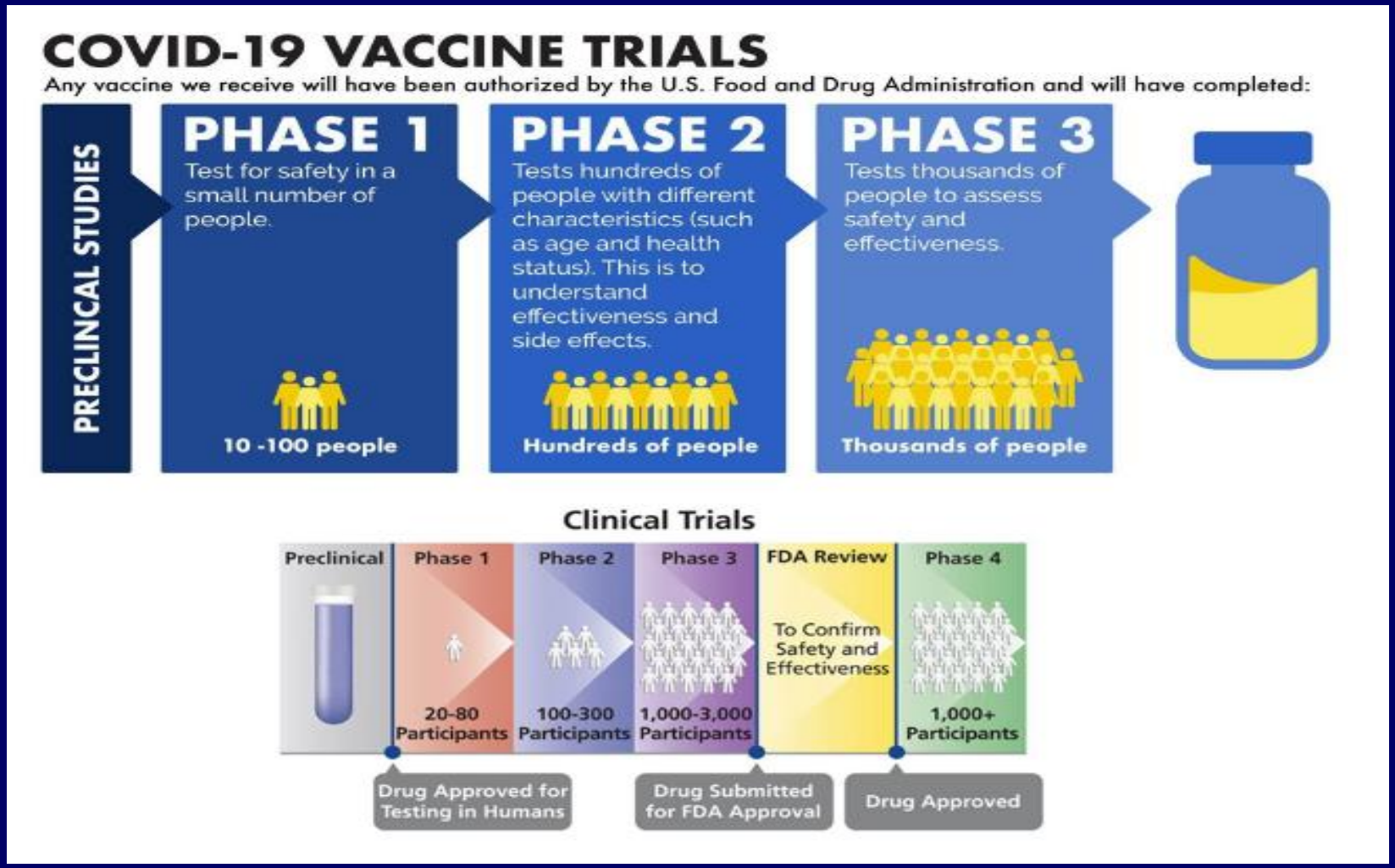
Phase 4

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 post-approval trials
- Long-term safety



COVID VACCINE



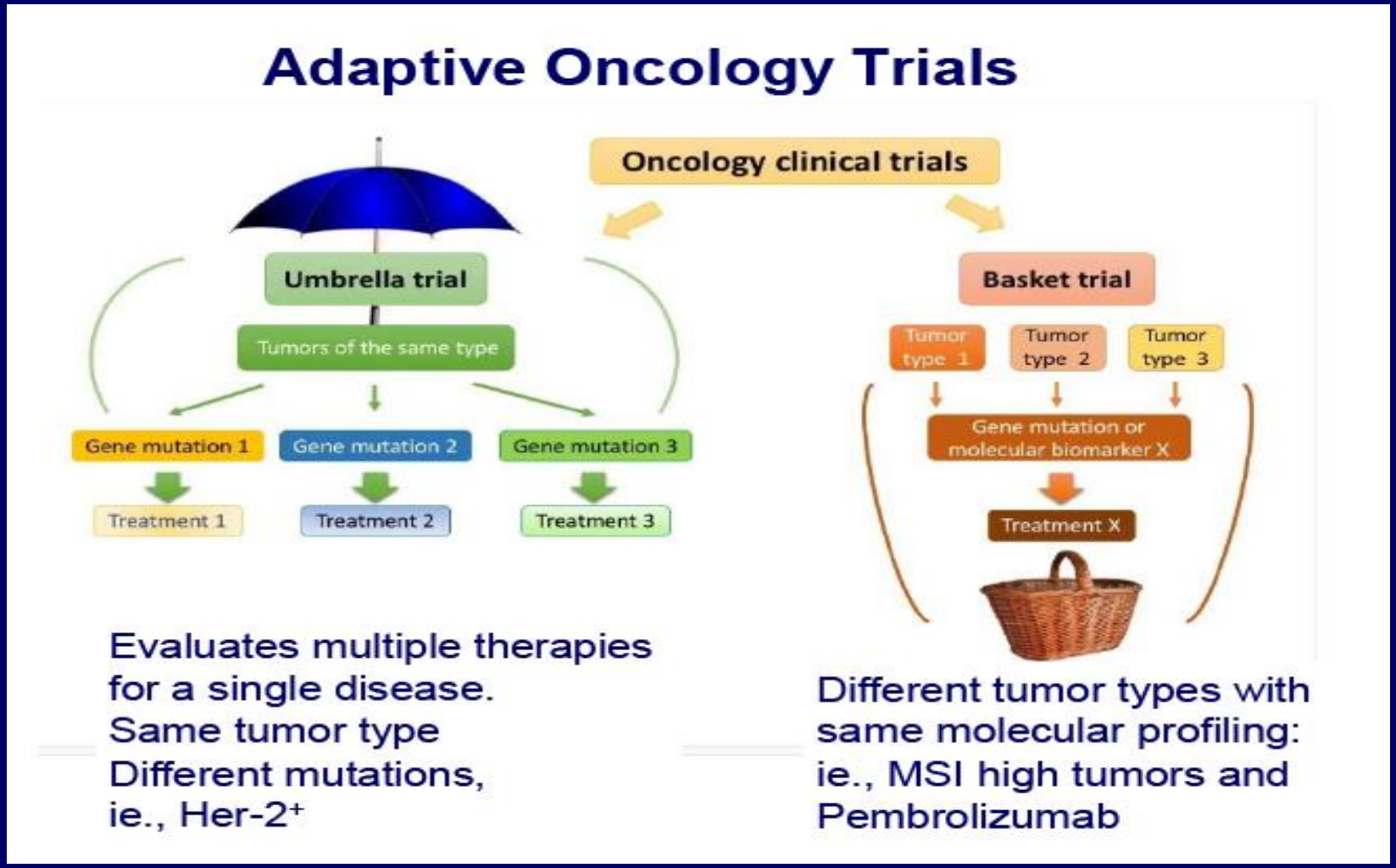
Adaptive design trials

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.

J Clin Transl Sci. 2023; 7(1): e125.

Adaptive Oncology Trials



Trial design

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.

FDA 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

Back to the Bench

Back to Bench



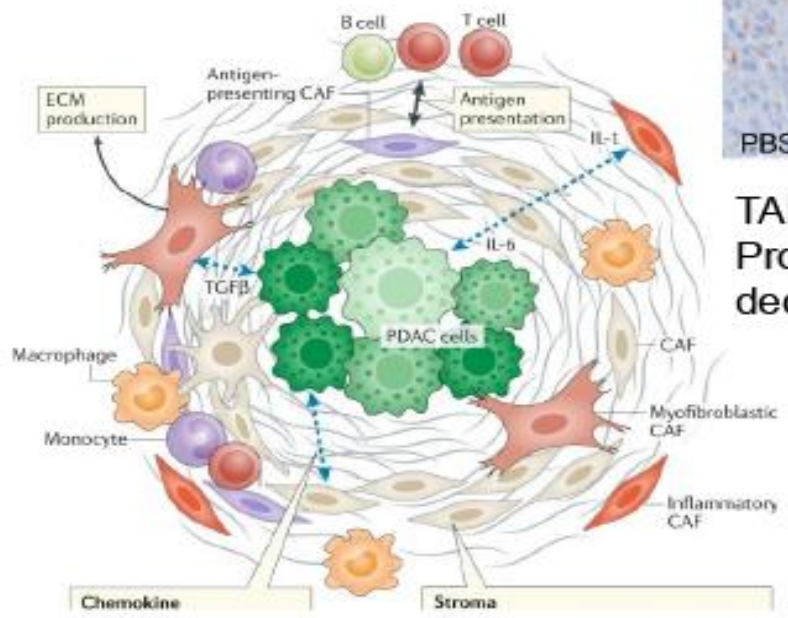
Bench to Bedside and back to Bench again!- Example of translational research

Research takes a team, collaboration, and a village. No man (woman) is an island!

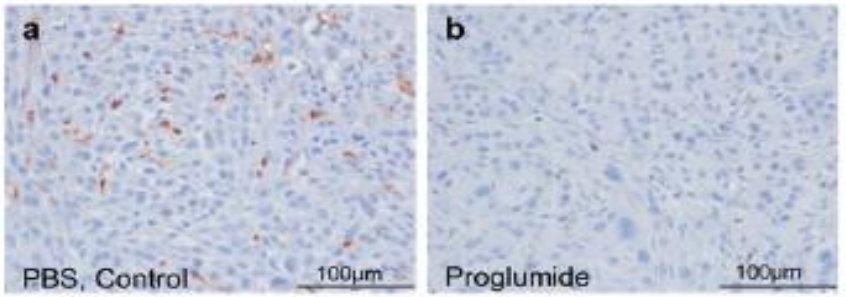
Tumor microenvironment

Mechanism of Action- How does proglumide alter TME? Focus on TAMs

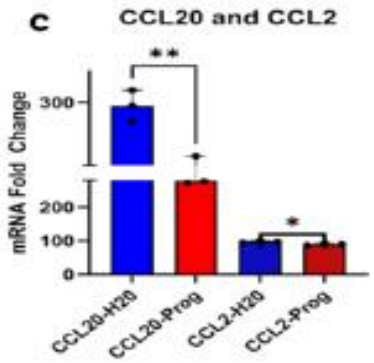
Tumor-associated macrophages



Nature Reviews Clinical Oncology **volume 17**, pages527–540 (2020)



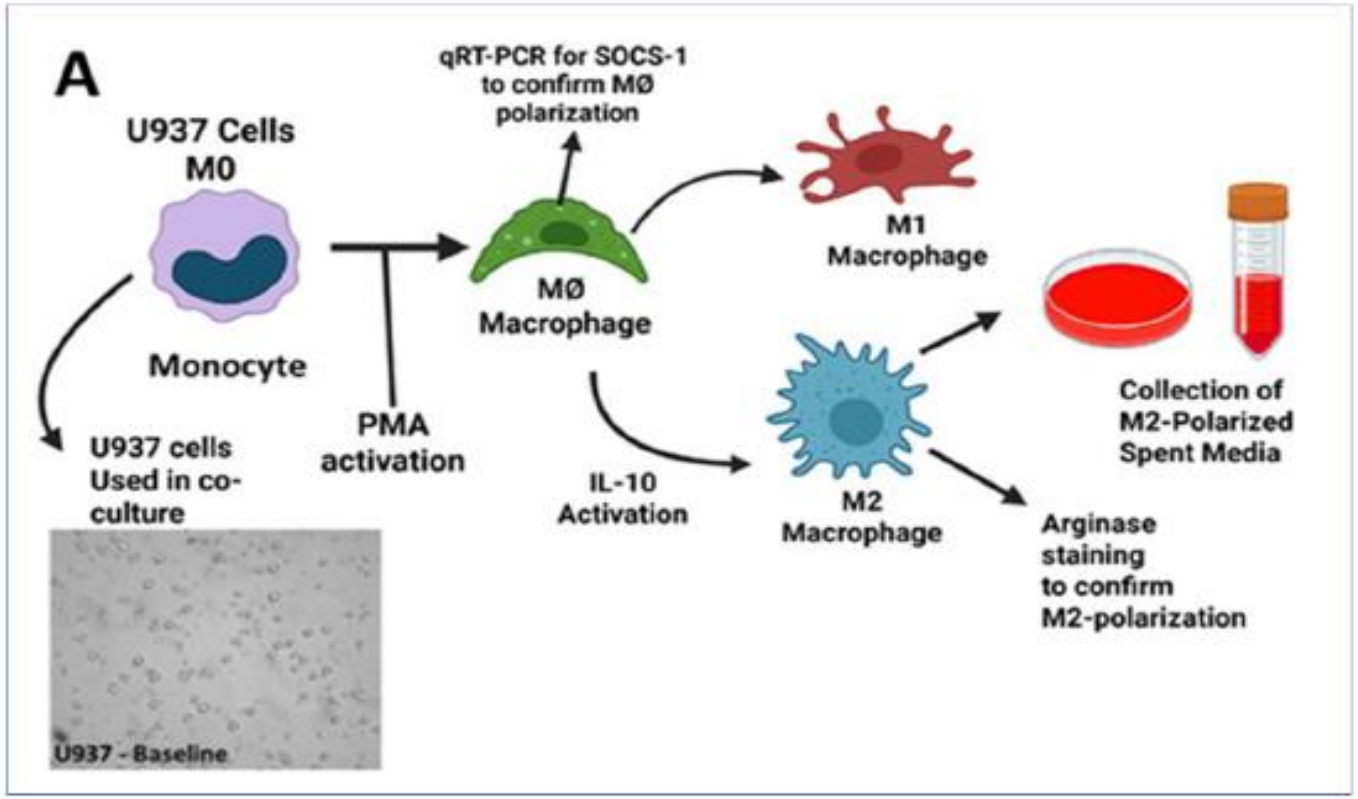
TAMs are abundant in pancreatic cancer. Proglumide, a CCK-B receptor antagonist, decreases TAMs.



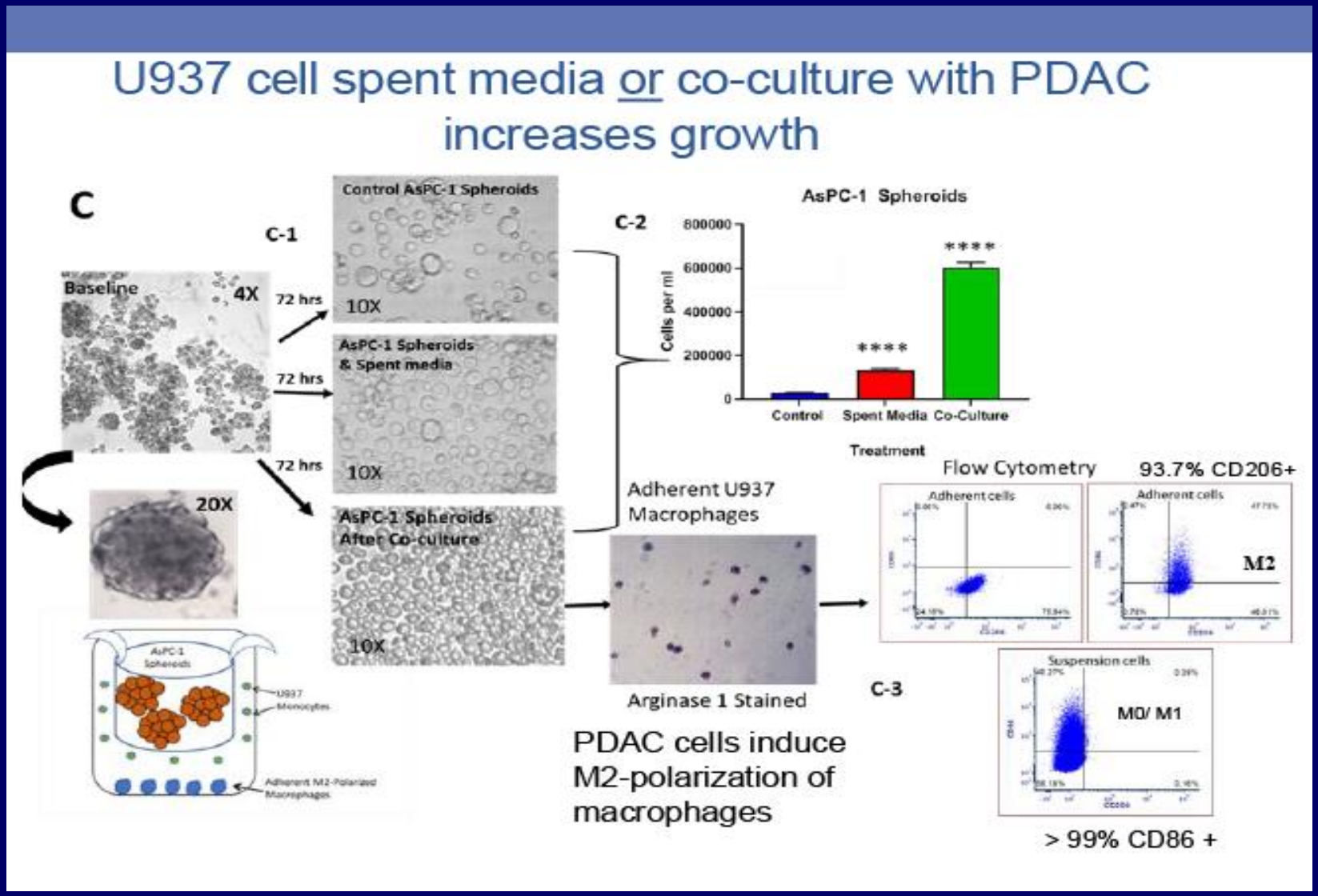
Chemokines, CCL20 and CCL2, are released from Activated TAMs to attract other Immune cells.

The Pancreatic Cancer Tumor Microenvironment

Macrophage polarization

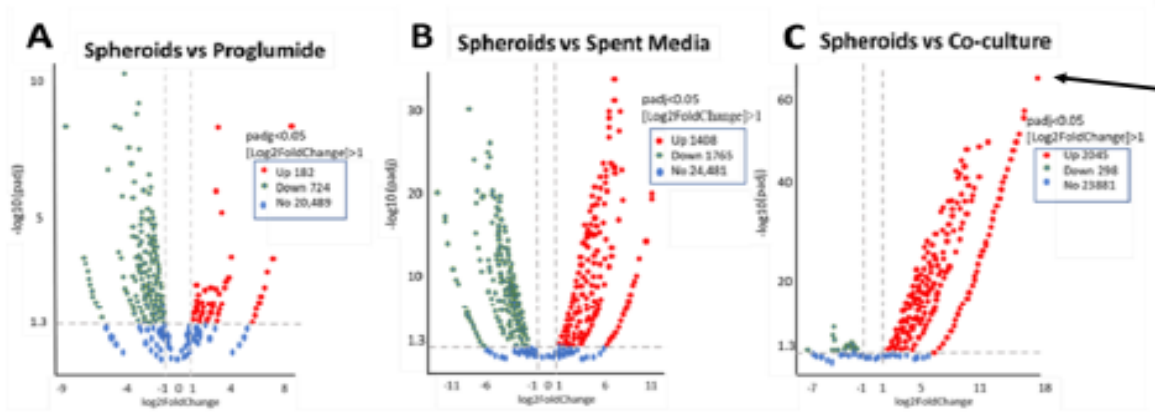


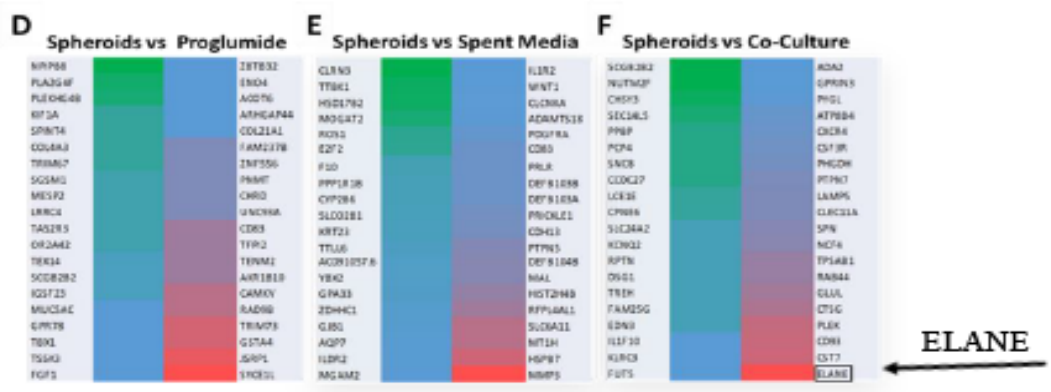
Growth effects

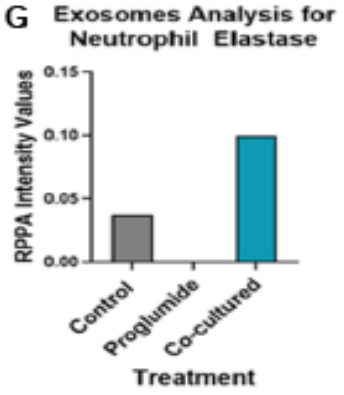


Differentially expressed genes

Differentially Expressed Genes with Crosstalk by RNAseq





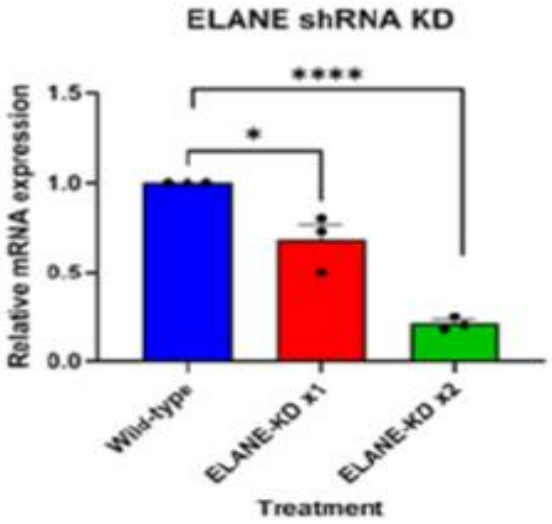


gene_id	Co-culture	Control	log2FoldChange	pvalue	padj	gene_name
ENSG0000	23840.09	1.39E-17	17.54337676	6.96E-71	1.82E-66	ELANE

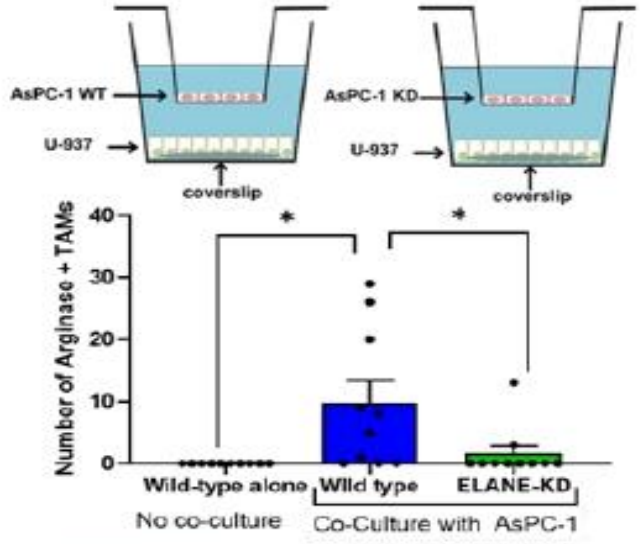
Exosomes from cancer spheroids Contain neutrophil elastase/ ELANE

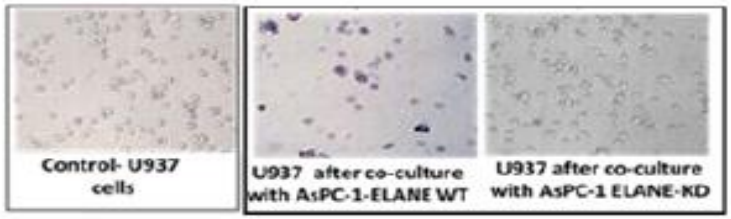
ELANE knockdown

ELANE Knockdown in Pancreatic Cancer cells



shRNA Knockdown transfection of AsPC-1 pancreatic cancer cells to downregulate *ELANE* expression

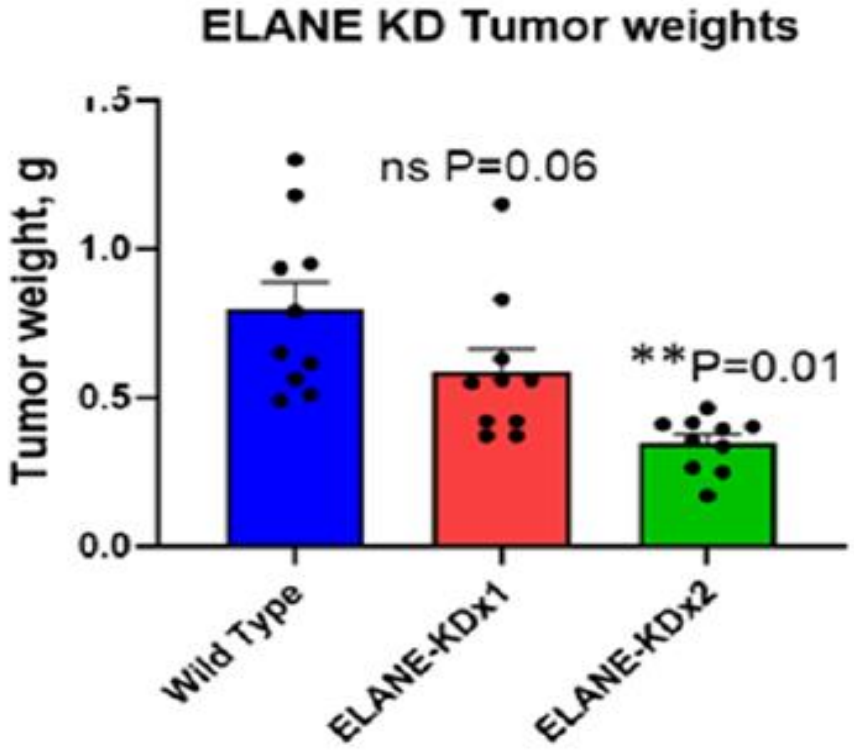




U937 cells polarize to M2-TAMS only with Wild-type cells, not *ELANE*-KD cells

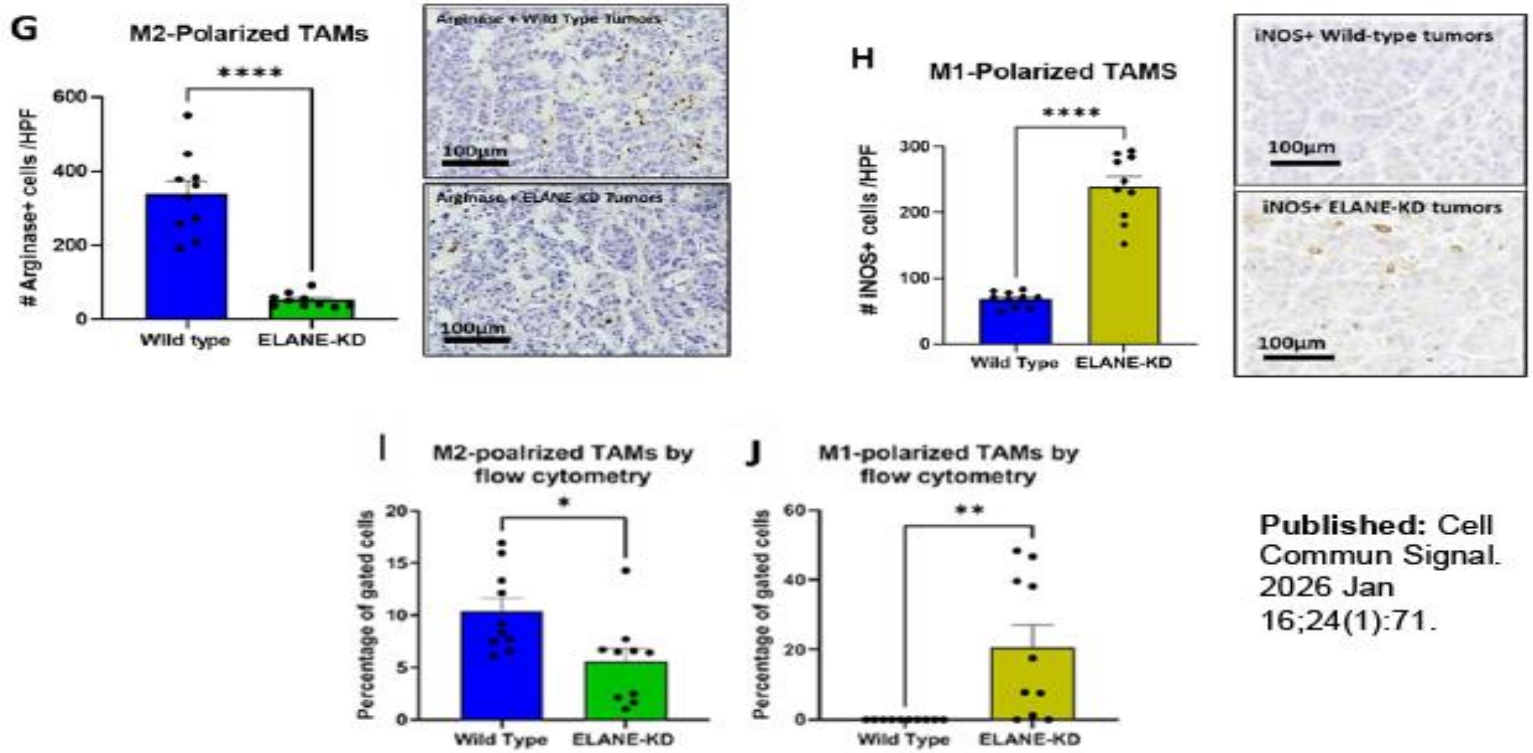
Growth effects

Downregulation of *ELANE* decreases growth of pancreatic cancer



Downregulation

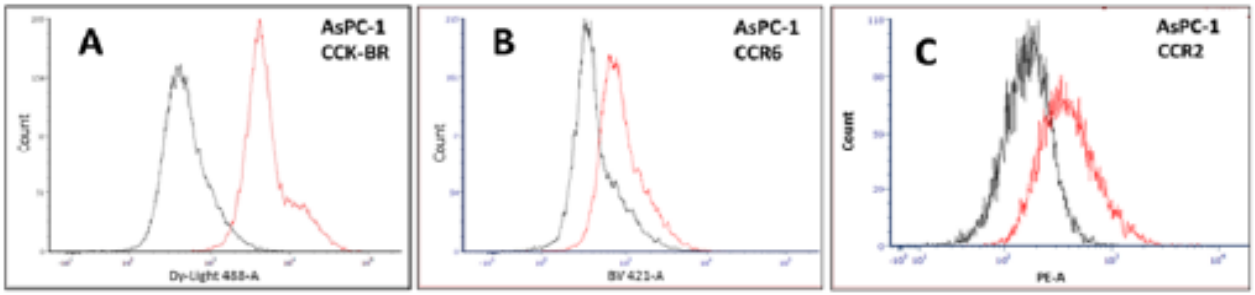
Downregulation of *ELANE* decreases M2 and increases M1 TAMS in tumors

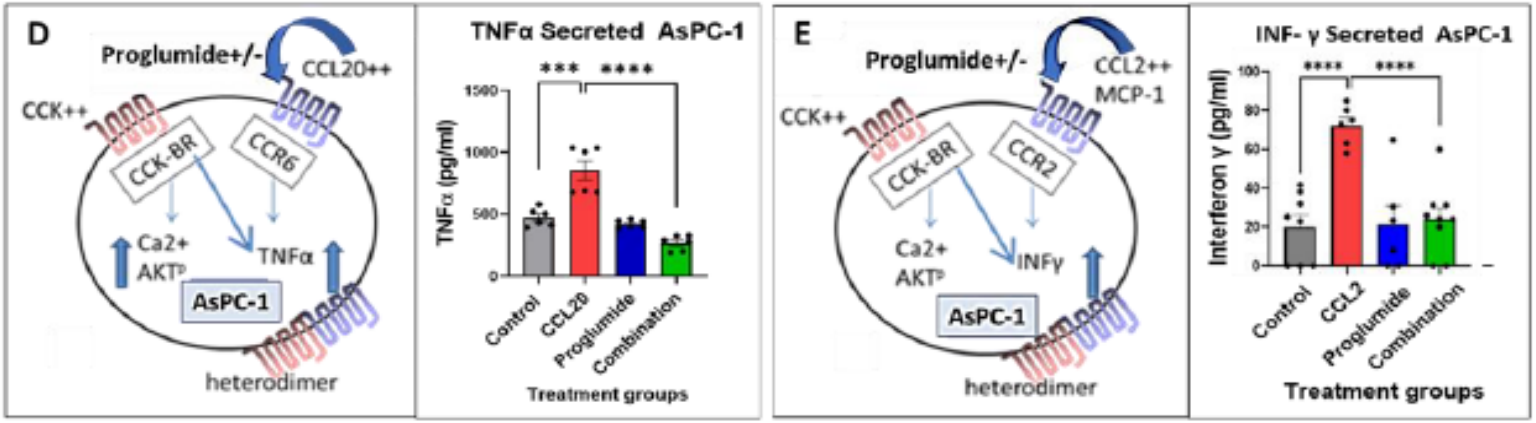


Published: Cell Commun Signal. 2026 Jan 16;24(1):71.

Receptor crosstalk

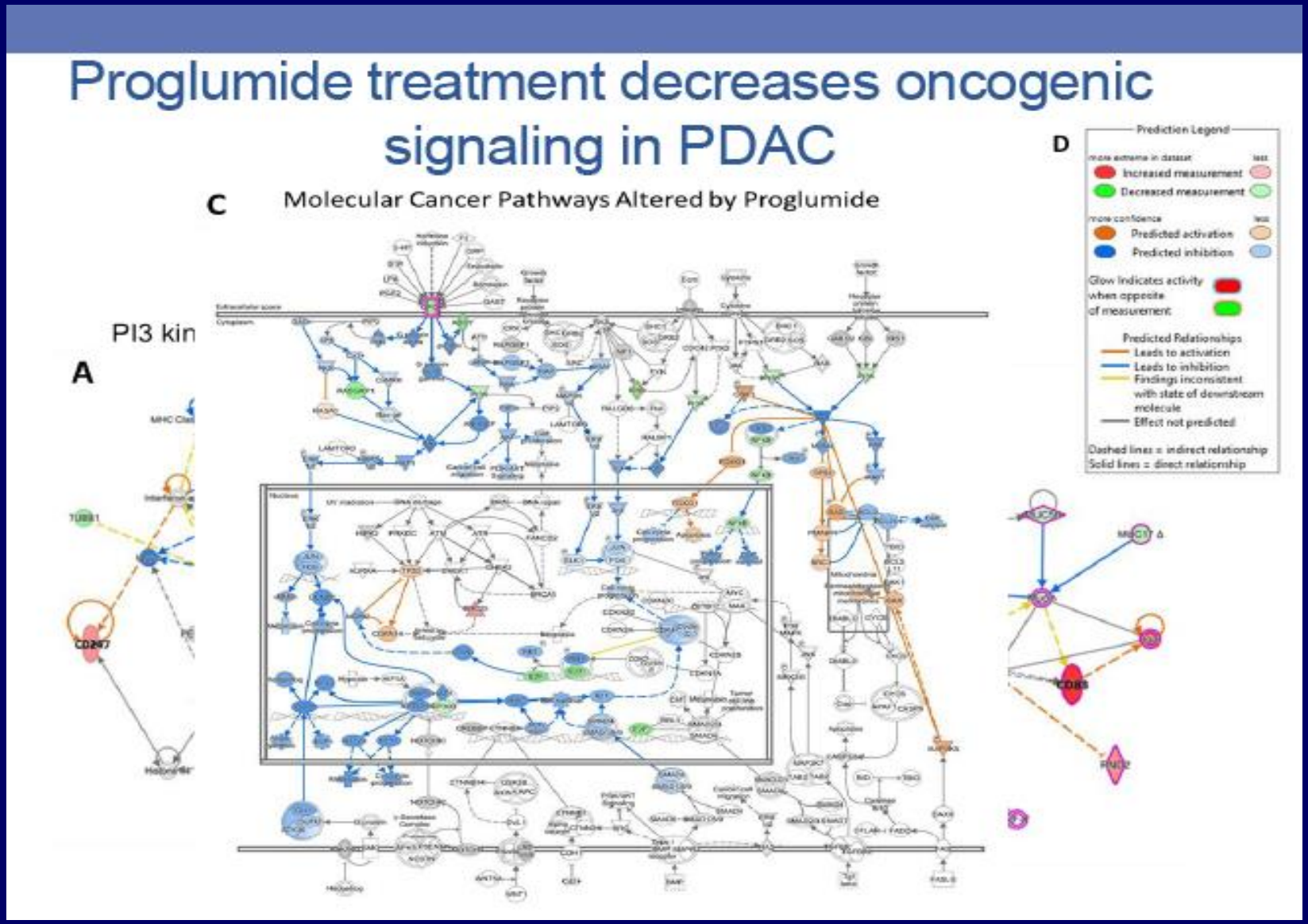
Crosstalk of GPCR: CCK-B Receptor and Chemokine Receptors





Proglumide interrupts chemokine receptor activation by intracellular crosstalk between GPCRs.

Proglumide decreases signalling



Funding

This research was funded by

- The Ruesch Center for the Cure of Gastrointestinal Cancers and by a philanthropic gift to Georgetown University.
- NIH /NCI grant: R01 CA277680
- NIH/ NCI grant R21CA241007
- The Pancreatic cancer Action Network

Words of Wisdom

Words of Wisdom: Have Passion and Don't Give up

- "The only way to do great work is to love what you do"- Steve Jobs
- "Choose a job you love, and you will never have to work a day in your life." - Confucius.
- "If you can't figure out your purpose, figure out your passion. For your passion will lead you right into your purpose." - Bishop T.D. Jakes
- "If you don't believe in yourself and your dreams, no one else will believe you either. Believe in yourself, have faith in your work and DON'T GIVE UP!" - Jill Smith, MD