# Clinical Trials

## Translational Research : Bench to bedside, Clinical Trials

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# Disclosures

## Disclosures

1. Dr. Smith is a co-inventor on 10 patents – some related to pancreatic cancer.
2. Dr. Smith is the Director of Clinical & Translation Research, LLC, a biotech research consulting company
   - Consultant for Immune Therapeutics, Cytocom, and Cato Research, Inc.

# OBJECTIVES

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

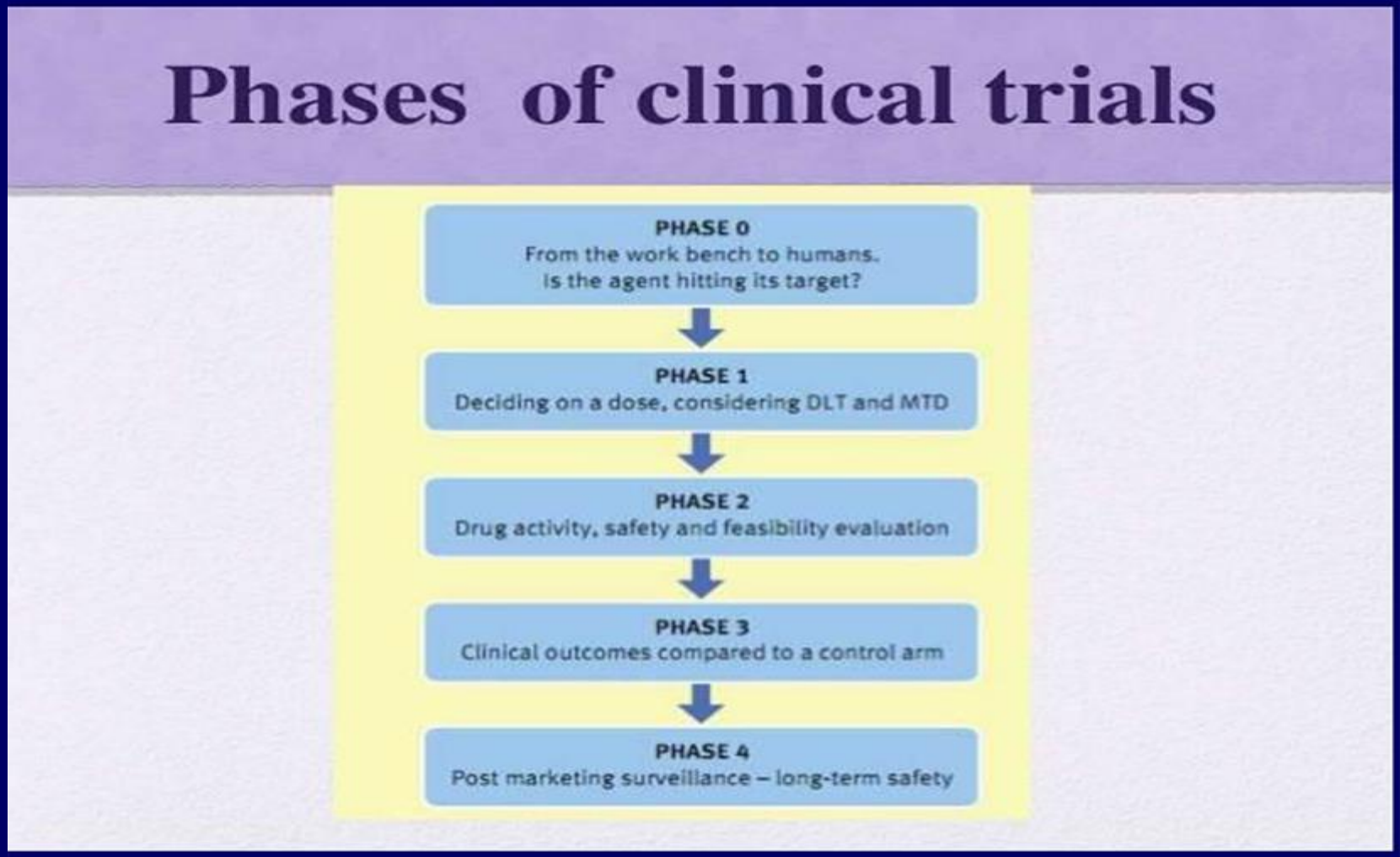
# Research and Drug Development

## Research & Drug Development

Preclinical research

Bottleneck of Drug development

# Phases of clinical trials



# Types of Clinical Trials

- Treatment trials
- Prevention trials
- Early-detection trials/screening trials
- Diagnostic trials
- Quality-of-life studies/clinical benefit studies
- Genetic trials

# 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?

# 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

# 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

# Randomized clinical trials

## Randomized Clinical Trials

- Equal chance to be assigned to one of two or more groups
  - One group gets the most widely accepted treatment (standard treatment) or placebo
  - The other gets the new treatment being tested
- All groups are as similar as possible
- Provides the best way to prove the effectiveness of a new agent or intervention

# 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**

# Research team

Nurse /Study coordinator

## Research Team

Principal Investigator

Statistician

Data manager

Data safety Monitoring Board

Pharmacist

# Drug trials

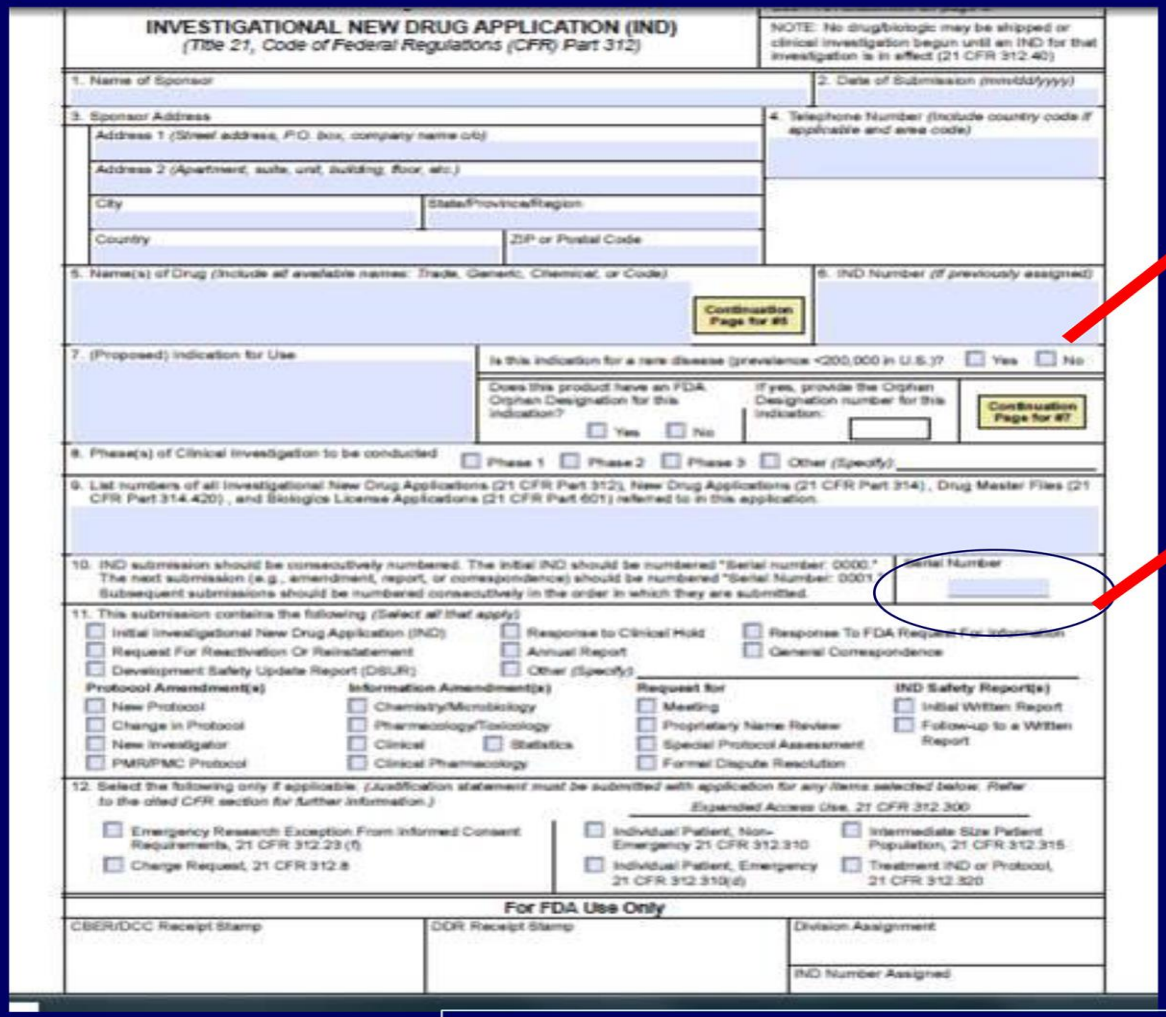
## Before you start (Drug trial)

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

  - 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
  - Research Nurse /Study coordinator
  - Registration of clinical trial on www.clinicaltrials.gov

# 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 |

6. IND Number *(If previously assigned)*

050987

Serial Number

0001

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

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

# Intellectual Property

Intellectual Property

- Submit  an invention disclosure and provisional patent before you present the research results publically (including abstracts).
- The patent belongs to whomever you worked for when you made the discovery. If your employer does not want to file a patent have them assign the rights to you.

# Project format

## Format for the protocol / project proposal

1. **Project title**
   - 1.1 Title page
2. **Project summary**
3. **Project description:**
   - 3.1 – Rationale
   - 3.2 – Objectives
   - 3.3 – Methodology
   - 3.4 – Data management and analysis
4. **Ethical considerations**
5. **Gender issues**
6. Timetable
7. Problems anticipated
8. Budget
9. **References**
10. Curriculum vitae of the investigator(s)

# Clinical study protocol

**Clinical Study Protocol**
**Drug Substance Proglumide**
**Study Number: ESR 17-128**
**Edition Number: 2**
**Date 10 June 2017**

**Study Design:**
This study is an open labelled Phase I/II clinical trial, designed to evaluate the safety and efficacy of proglumide at escalating doses in combination with durvalumab as second line therapy for subjects with metastatic pancreatic cancer.

**Number of Centers: 2**

**Number of Patients:**
12 subjects for Phase 1 and 40 for Phase 2

**Study Population:**
Adults with advanced histologically confirmed pancreatic cancer that have failed one treatment with standard chemotherapy and are not surgical candidates

**Inclusion Criteria:**

**Exclusion Criteria:**

**Investigational Product(s), Dose and Mode of Administration:**
Proglumide will be tested with a classic 3+3 Phase 1 dose escalation will be used to determine the RP2D. Dose levels of proglumide will be: 300mg BID; 600 mg BID; 1200 mg BID.
Proglumide will be administered orally.
In the Phase 2 part of the study, the RP2D will be used (as determined by Phase 1).
Patients will receive 1500mg durvalumab (MEDI4736) via IV infusion Q4W for up to a maximum of 24 weeks (up to 7 doses/cycles) with the last administration on week 24, or until confirmed disease progression, unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met.

**Study Assessments and Criteria for Evaluation:**
**Safety Assessments:**
Laboratory: Urinalysis, complete blood count including platelets. Blood chemistries (electrolytes, glucose, renal profile, liver function tests
**Efficacy Assessments:**

- Survival: OS and PFS
- The overall response according to the irRC is derived from time-point response assessments (based on tumor burden)
- QOL Questionnaire
- Tumor biopsy will be done by radiographic guidance pre-treatment and again after 4 weeks for CCKRs, fibrosis, tumor infiltrating lymphocytes

**Pharmacodynamic / Pharmacokinetic Assessments (if applicable):**
Proglumide plasma

**Statistical Methods and Data Analysis:**
An intent-to-treat analysis will be performed. The secondary outcome measure is PFS and progression will be determined by radiographic imaging. The Kaplan-Meier method will be used to estimate the survival curve for patients on combination therapy compared to historical controls.

**Sample Size Determination:**
The sample size for this study is proposed to be 12 subjects for Phase 1 using the classic 3+3 protocol. Approximately 34 subjects will be needed for Phase 2 including the 6 subjects from the Phase I study. Approximately 46 subjects will be enrolled with an expected drop-out rate of 10-20%.

# Phase 1 Aims

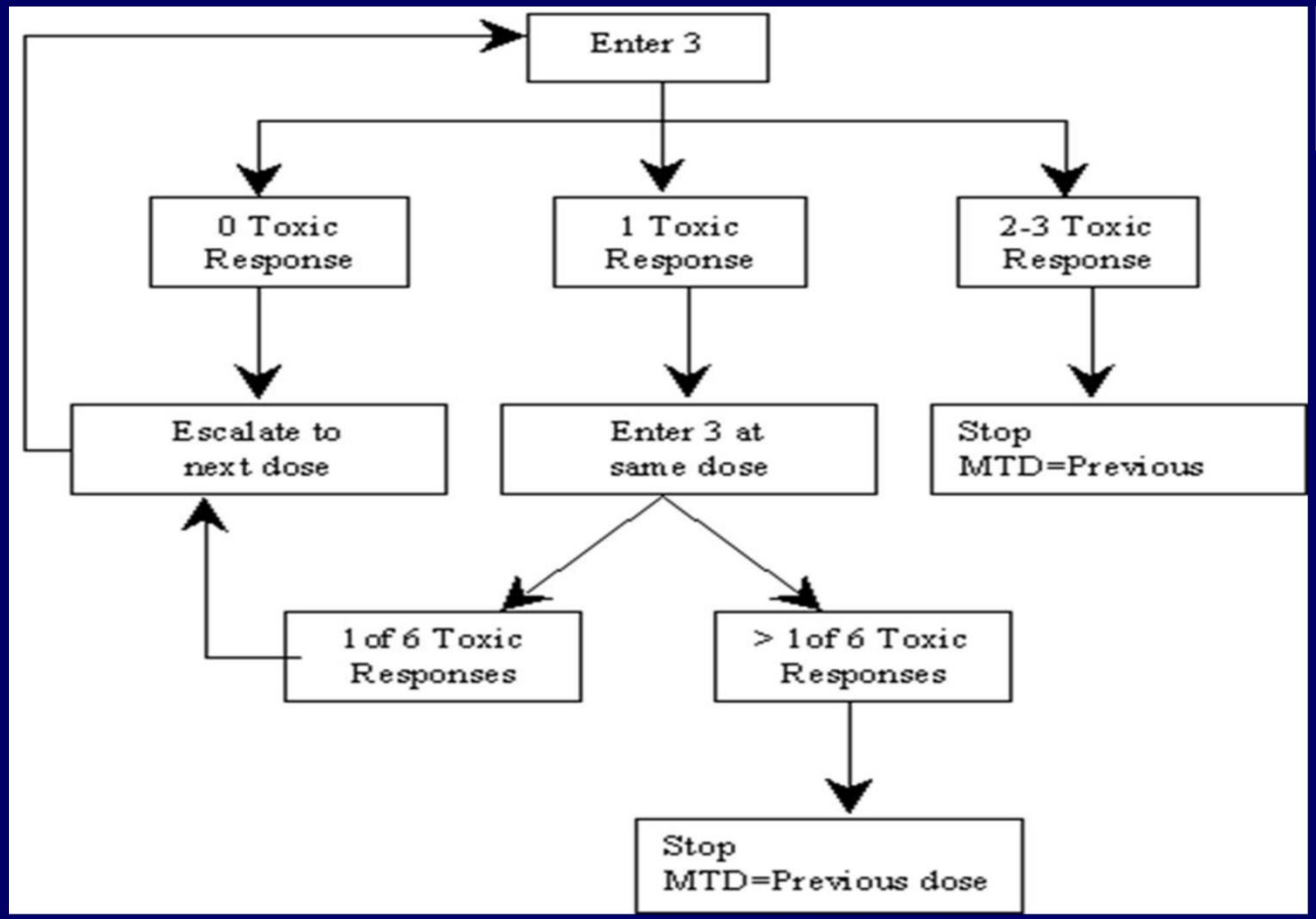
## Aims of Phase 1 Study
### First in Humans Trial

**Study Objectives:**

- Study the safety and toxicity of OGF in humans
- Determine the Maximum-Tolerated Dose (MTD)
- Study the biological kinetics and metabolism of OGF (Pharmacokinetics)
- Study the route of administration

# Dose escalation

## Dose-escalation study
## Classic 3x3 design




**Determine at onset What grade of side effect is acceptable**

**Started at 25 µg/kg**

**50 µg/kg**

**75 µg/kg**

**100 µg/kg**

**150 µg/kg**

**200 µg/kg**

**MTD** **250 µg/kg**

# Pancreatic cancer

## Pancreatic Cancer

- Fourth leading cause of cancer-related deaths in the United States; about 43,000/yr
- The median survival from diagnosis is 3-6 months.
- Five year survival is approximately 5%.
- Most cases are not diagnosed in the early stages.
- There is no effective treatment for nonsurgical cases.

# Pancreatic cancer deaths

## Deaths from Pancreatic Cancer is Increasing

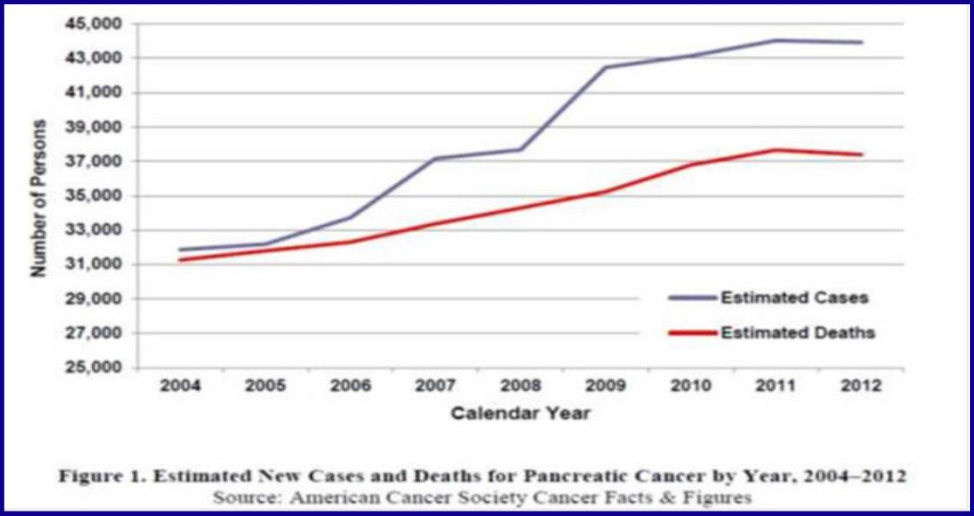
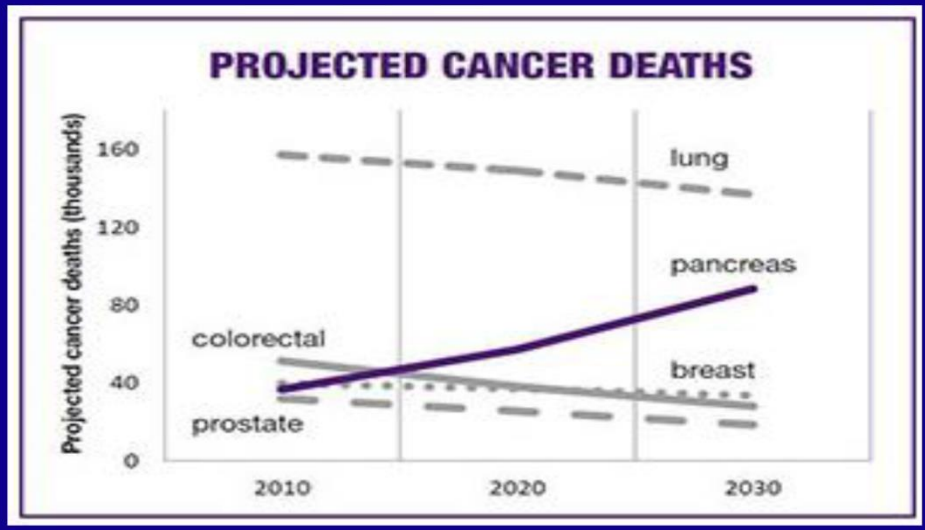


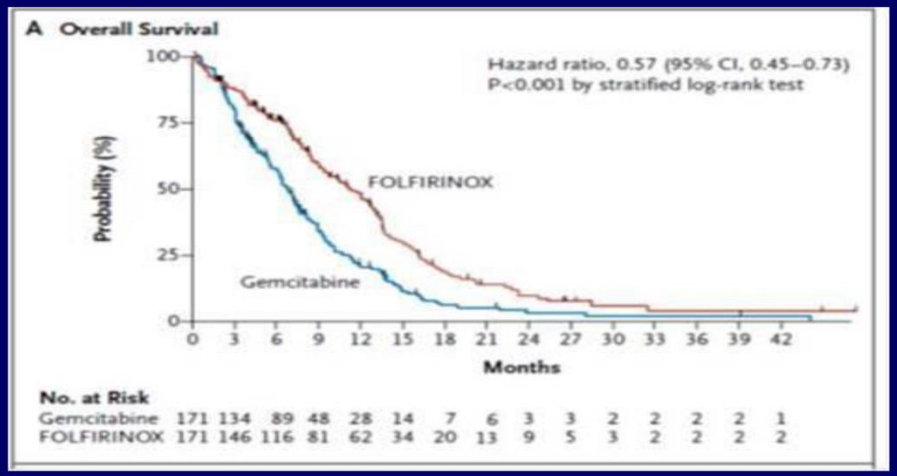

Figure 1. Estimated New Cases and Deaths for Pancreatic Cancer by Year, 2004–2012
Source: American Cancer Society Cancer Facts & Figures

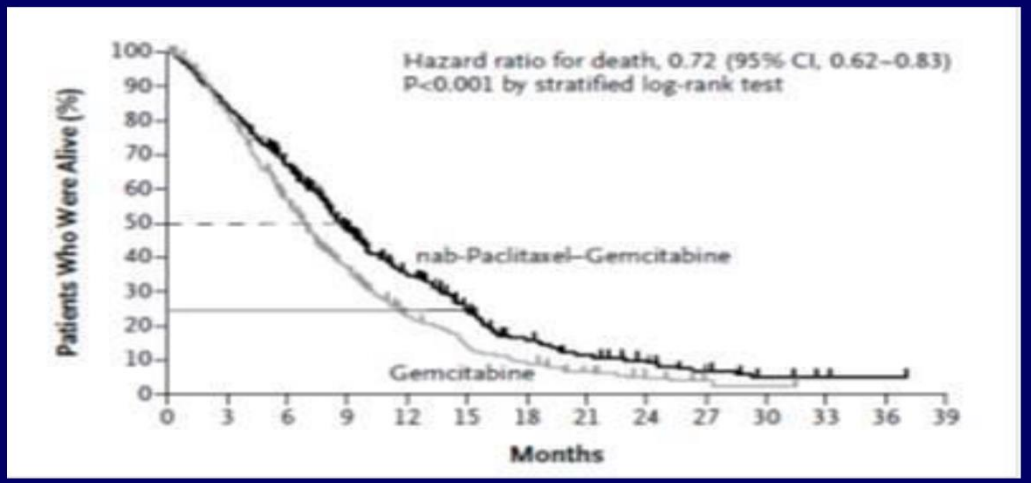



**Pancreatic cancer is projected to become one of top two killers of cancer by 2020.**
**Rahib L et al. Cancer Res 2014;74:2913-2921**

# Pancreatic cancer treatment

## Treatment of advanced pancreatic cancer is poor




N Engl J Med 2011; 364:1817-1825

Survival 11.1 mos

N Engl J Med 2013; 369:1691-1703

**Survival 8.5 months**

# Pancreatic cancer prognosis

## Pancreatic Cancer: Reasons for Poor Prognosis

- No methods for early detection
- No screening tests for high risk subjects
- Resistant to chemotherapy and chemotherapy is toxic and kills normal cells
- We do not understand the biology of this cancer

# Cholecystokinin Receptors:

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

- CCK-B: brain, stomach, human pancreas

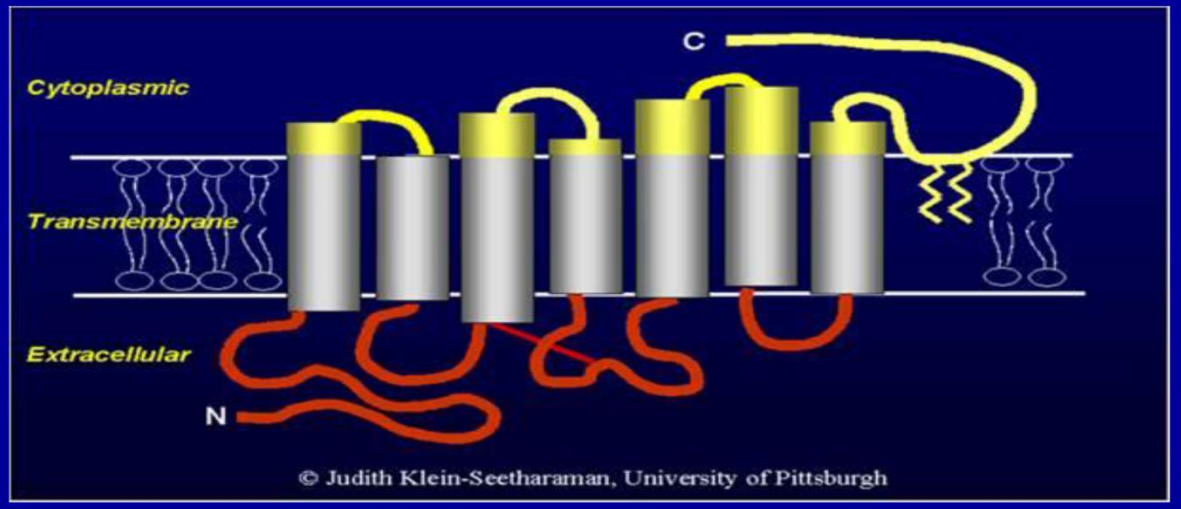
  Binds CCK = Gastrin (1:1)

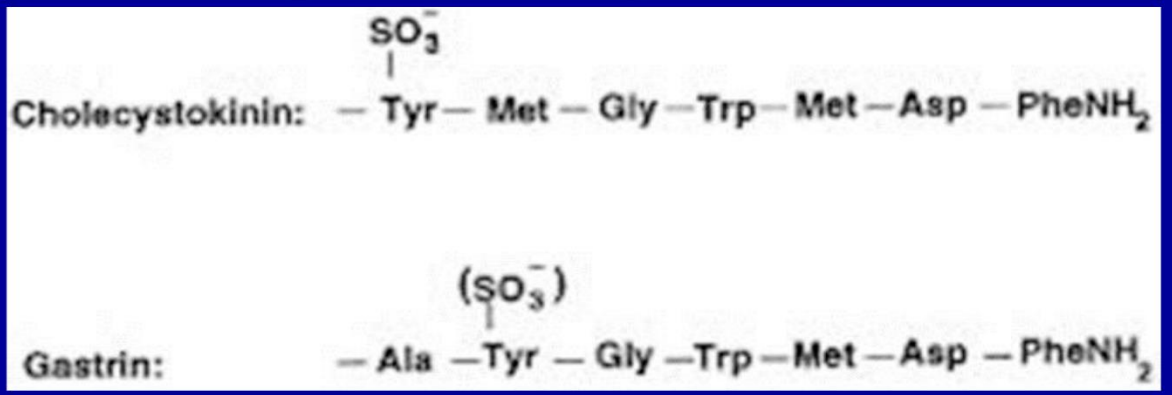
- CCK-C: pancreatic cancer, splice variant of CCK-B; Only found in human cancer, not rodents. Binds Gastrin > CCK (10:1)

# CCK receptors

## Cholecystokinin Receptors and Pancreatic cancer

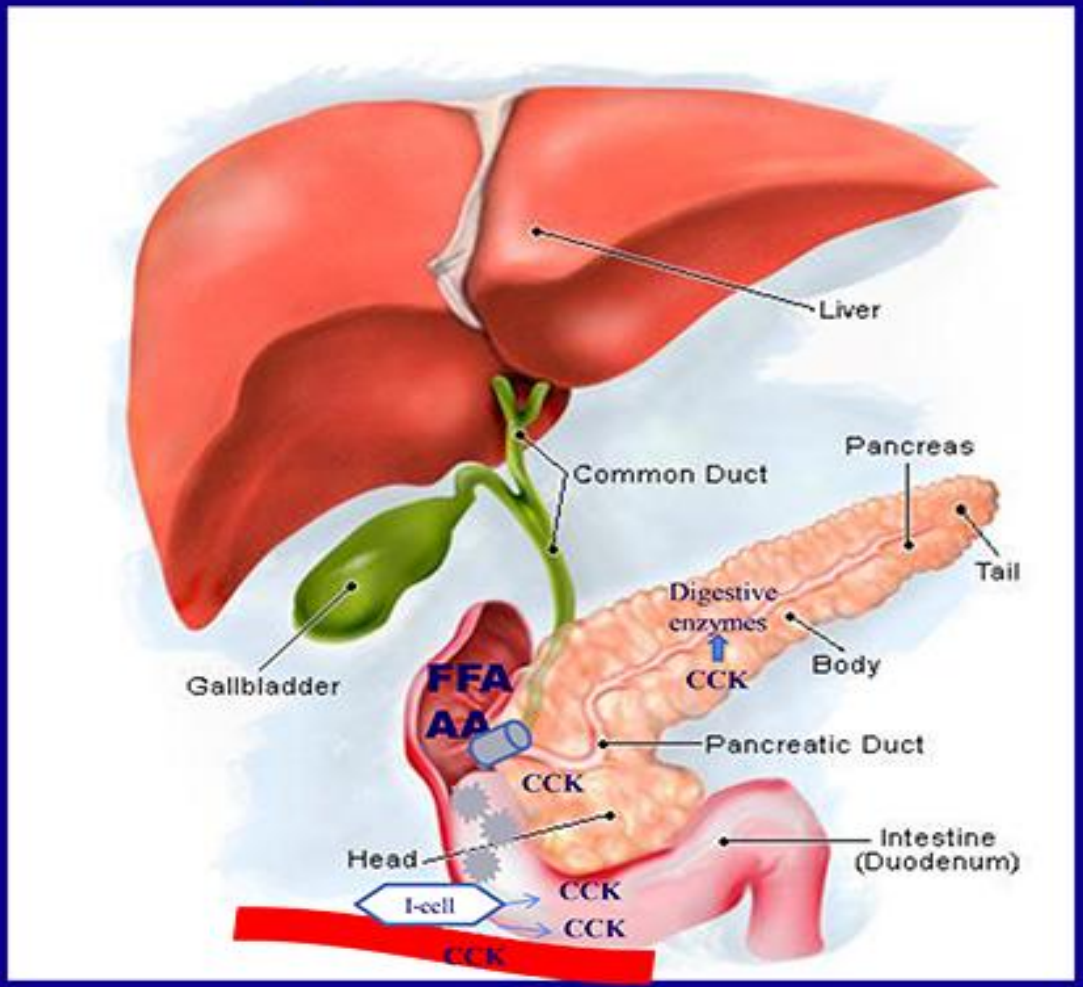
- GPCR: G-protein coupled receptors
- 7-trans-membrane domains
- Ligands: CCK and gastrin



# Cholecystokinin: CCK

Cholecystokinin: CCK

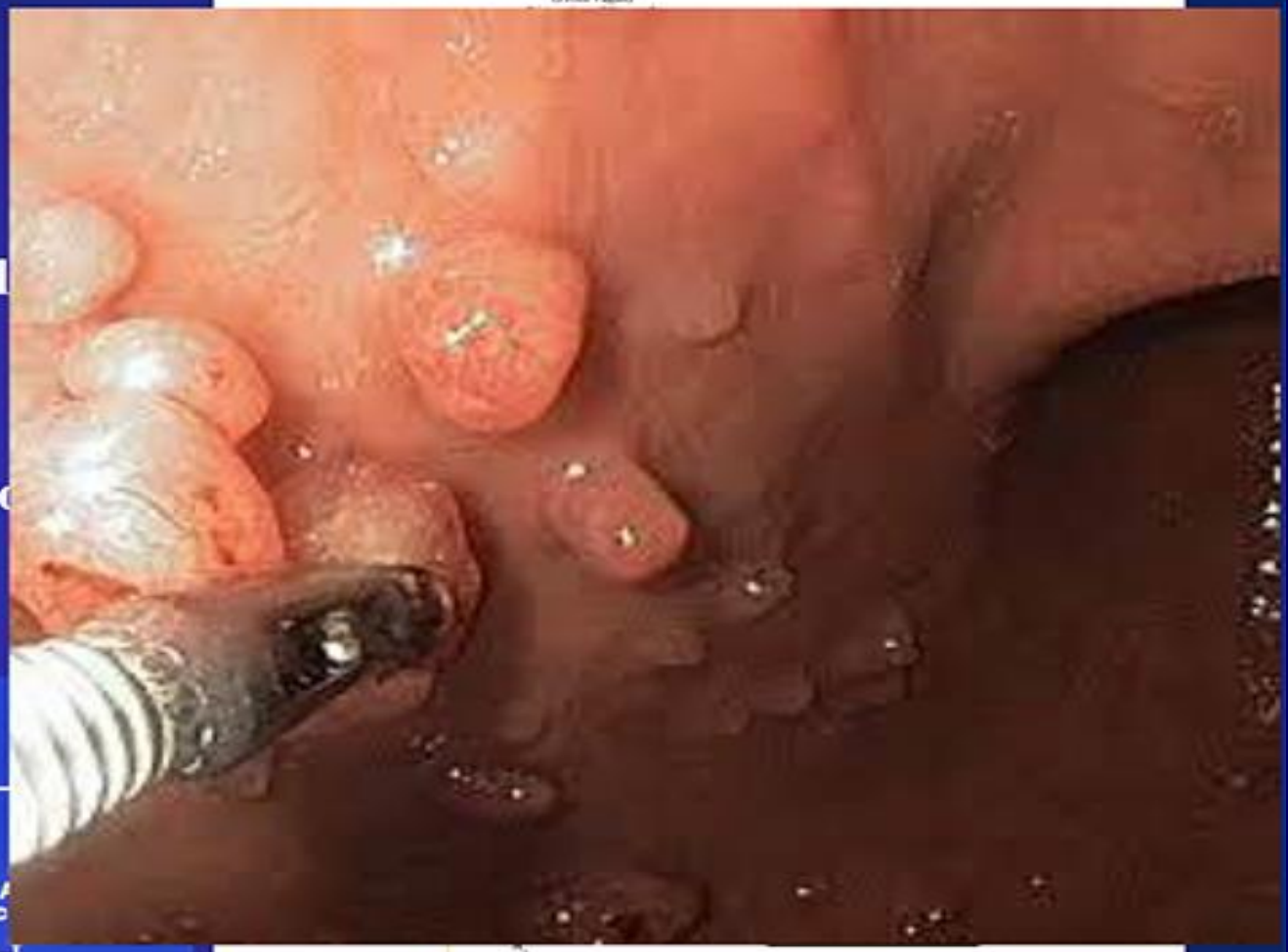


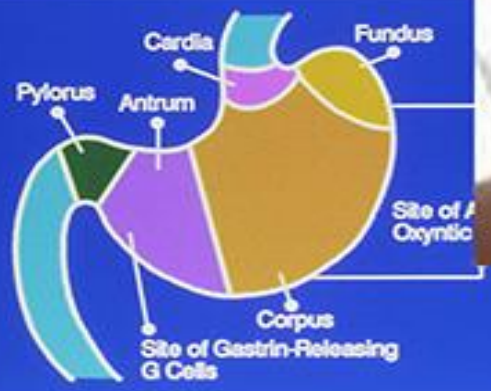
# Gastrin

## Gastrin

- Stimulates rel
of gastric acid

- Stimulates gr
of GI tract





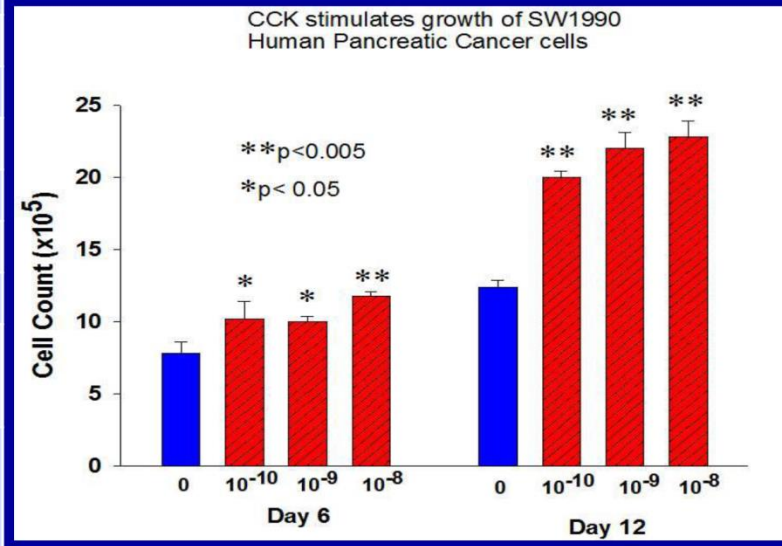
# CCK-B receptor

## CCK-B receptors are over-expressed in pancreatic cancer

Smith. Am J Physiol 2014: 306: G91-101 (review)
Smith et al, Am J Physiol 1994; 266: R 277

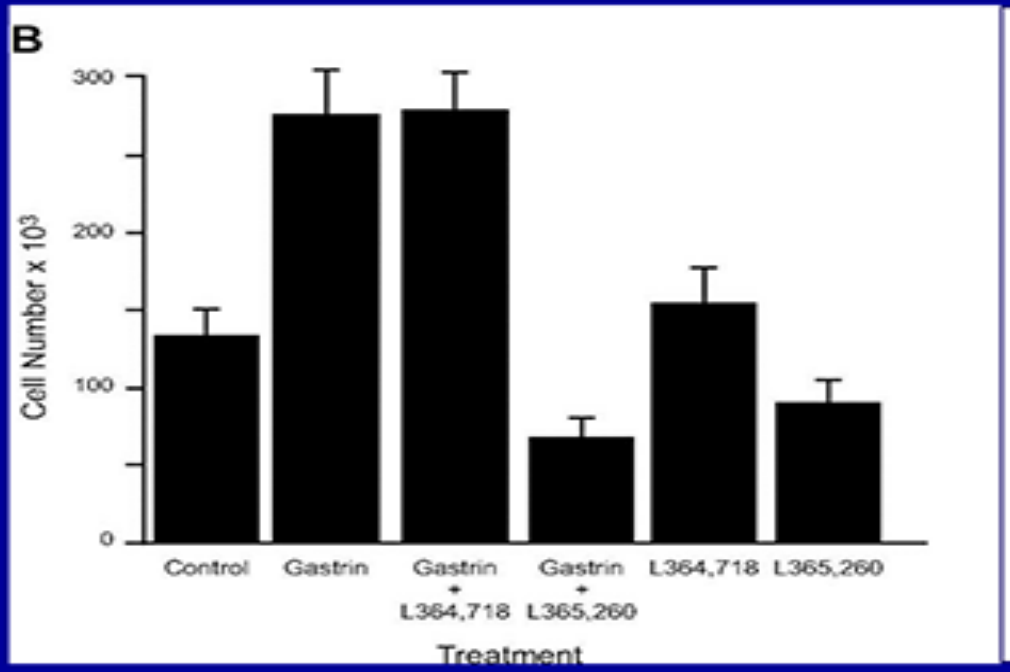
| Tissue /Cell Line | Binding Affinity | Receptor number Bmax |
|---|---|---|
| | Kd, (nM) | (fmol/mg protein) |
| PANC-1 cells | 4.3 ± 0.6 | 283 ± 68 * |
| MDA-Panc-28 | 3.6 ± 0.1 | 273 ± 22 |
| MDA-Amp-7 | 2.0 ± 0.4 | 211 ± 54 |
| MIA PaCa-2 | 3.0 ± 0.7 | 151 ± 12 * |
| Capan-1 | 2.7 ± 1.3 | 149 ± 83 |
| BxPC-3 | 3.4 ± 0.1 | 125 ± 44 |
| Fresh cancer from surgery | 2.3 ± 0.8 | 285 ± 36 |
| Normal human pancreas | 1.8 ± 0.7 | 68 ± 7.2 |

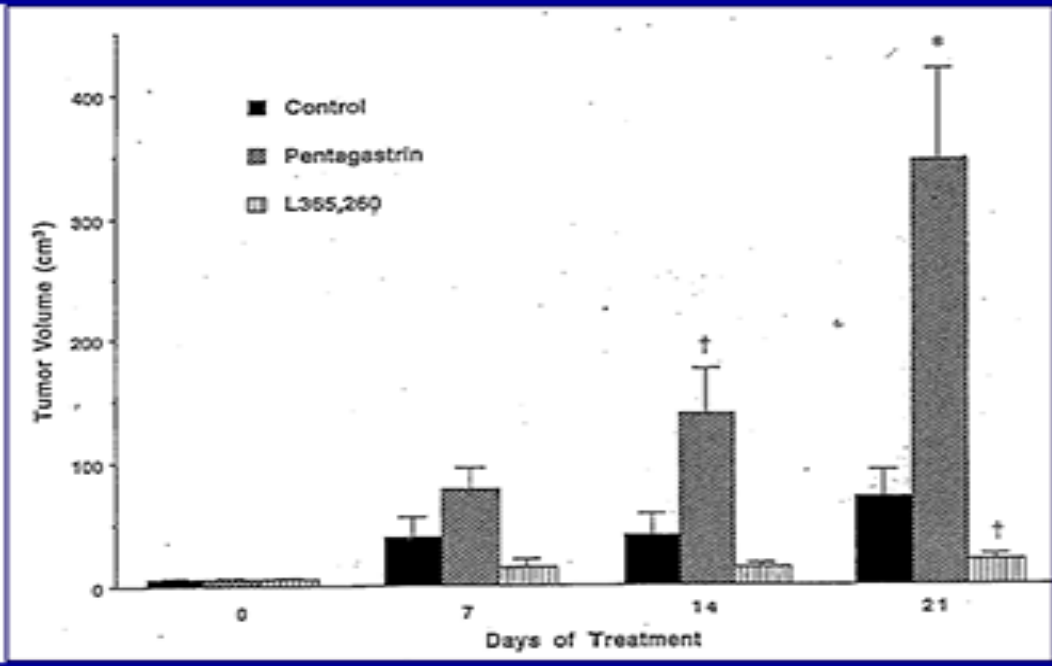
CCK or gastrin stimulate growth of pancreatic cancer



# Gastrin/CCK stimulate growth

## Gastrin /CCK stimulate growth of pancreatic cancer through the CCK-receptor

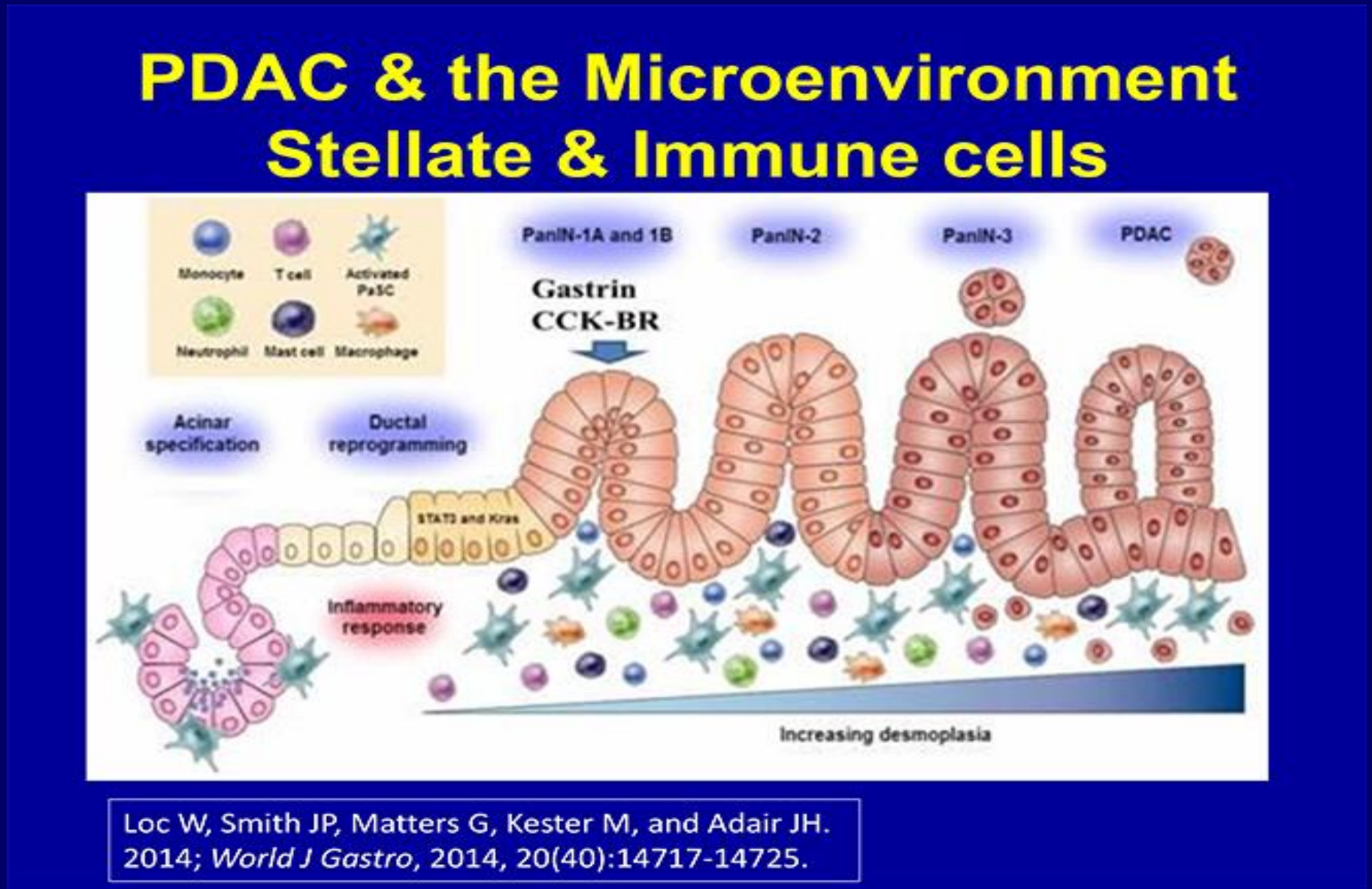



Am J Physiol. 2014 Jan 15; 306(2): G91–G101.

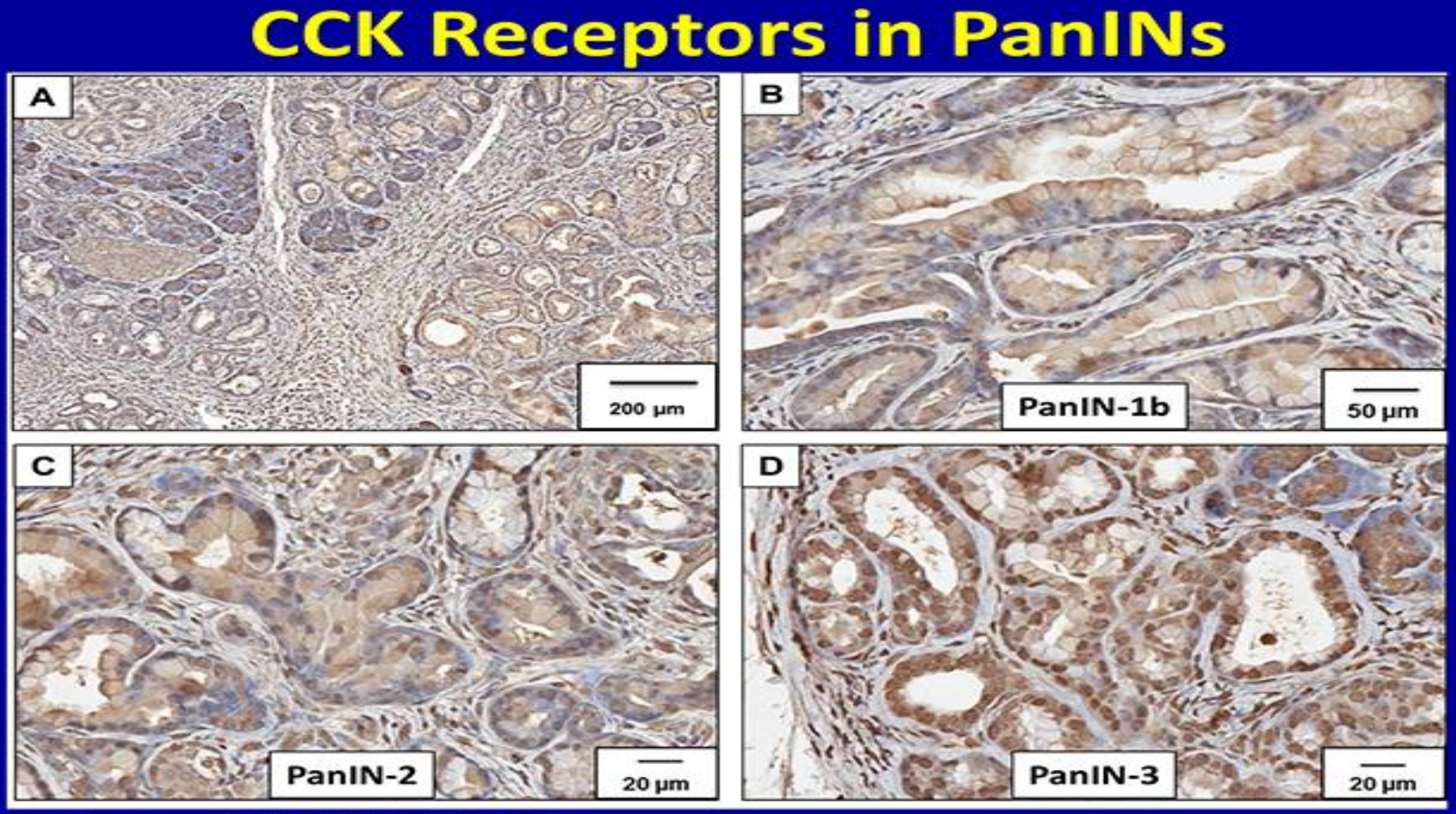
Smith et al *Amer. J. Physiol.* 268:R135-R141, 1995

# PDAC & the microenvironment stellate and immune cells




Loc W, Smith JP, Matters G, Kester M, and Adair JH. 2014; *World J Gastro*, 2014, 20(40):14717-14725.

# CCK receptors in PanINs




Pancreas. 2014 Oct;43(7):1050-9.

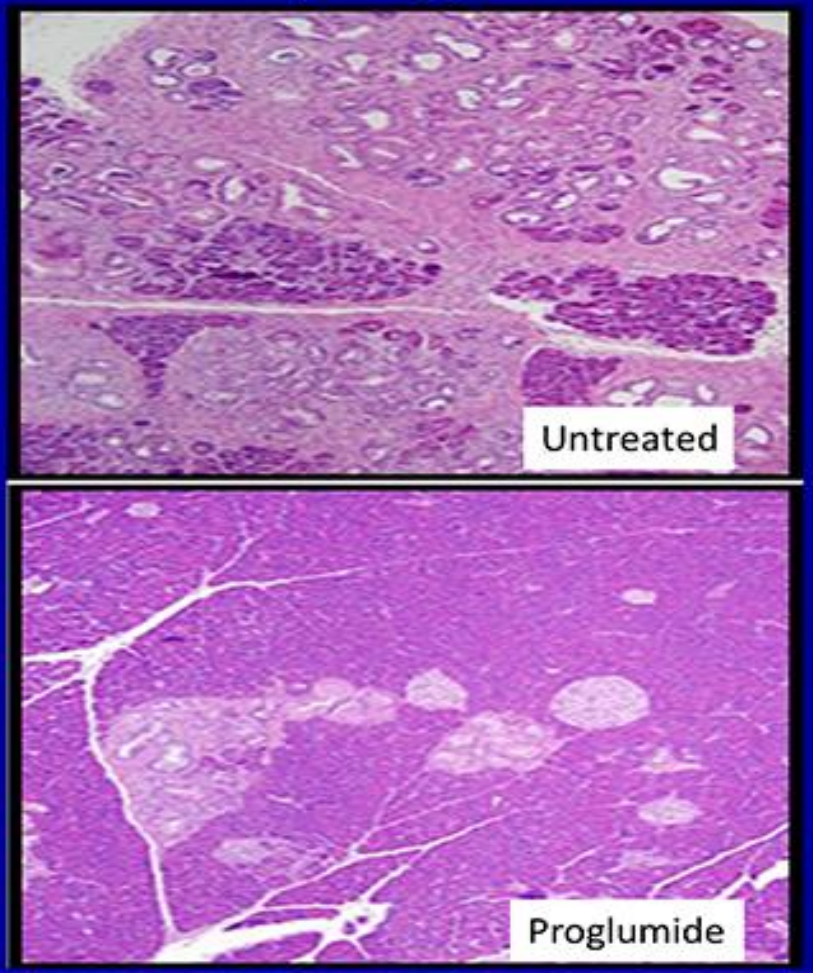
# CCK-R and PanIN progression

## CCK receptors and PanIN progression

CCK receptor blockade

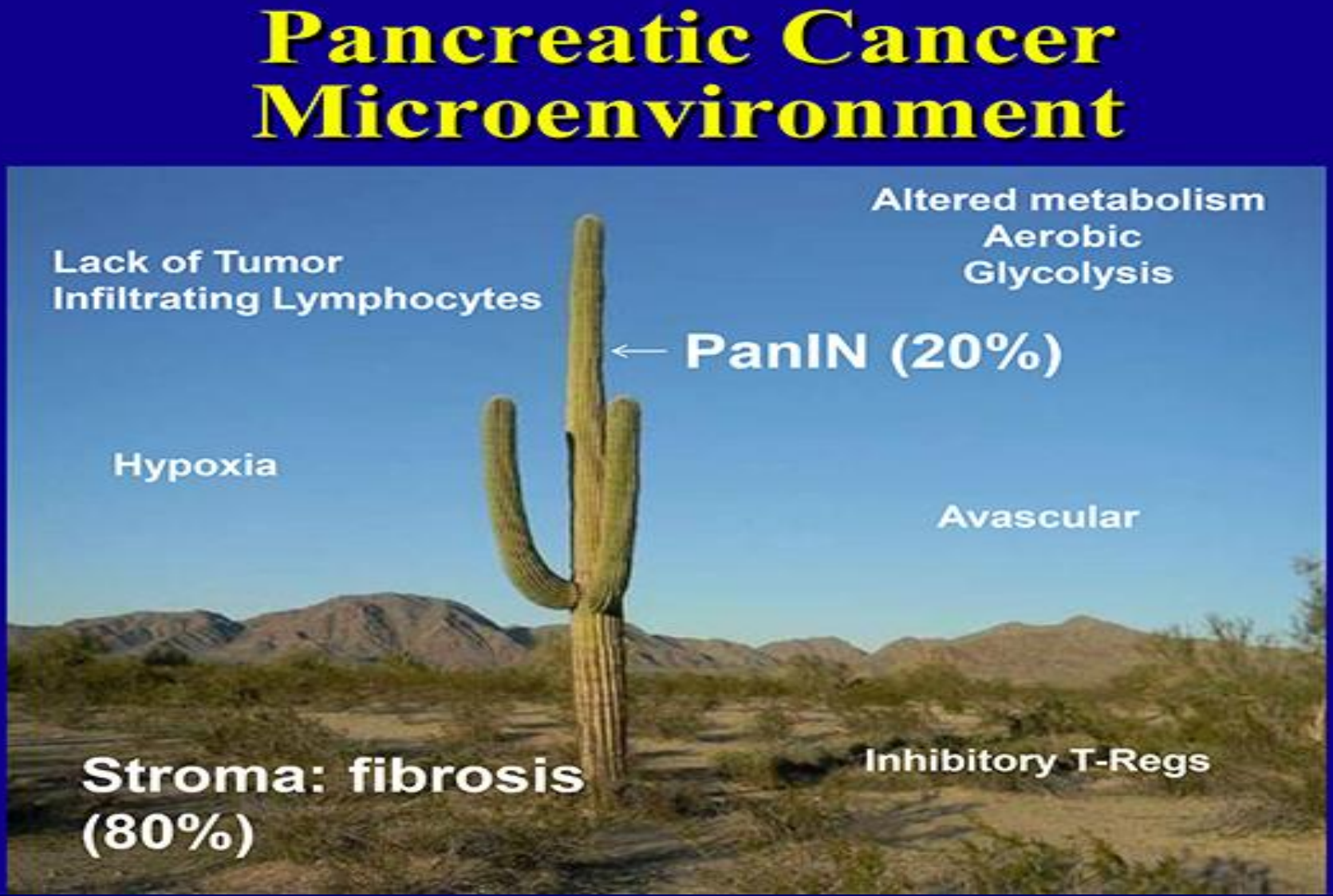
(Proglumide)

Halts progression of PanIN lesions in KRAS transgenic mice



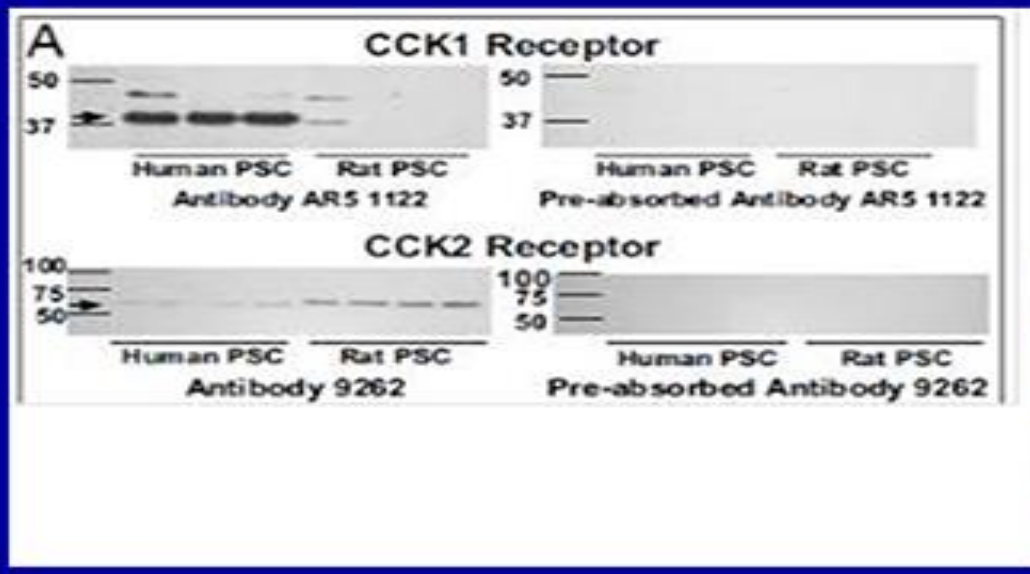

Pancreas. 2014 Oct;43(7):1050-9.

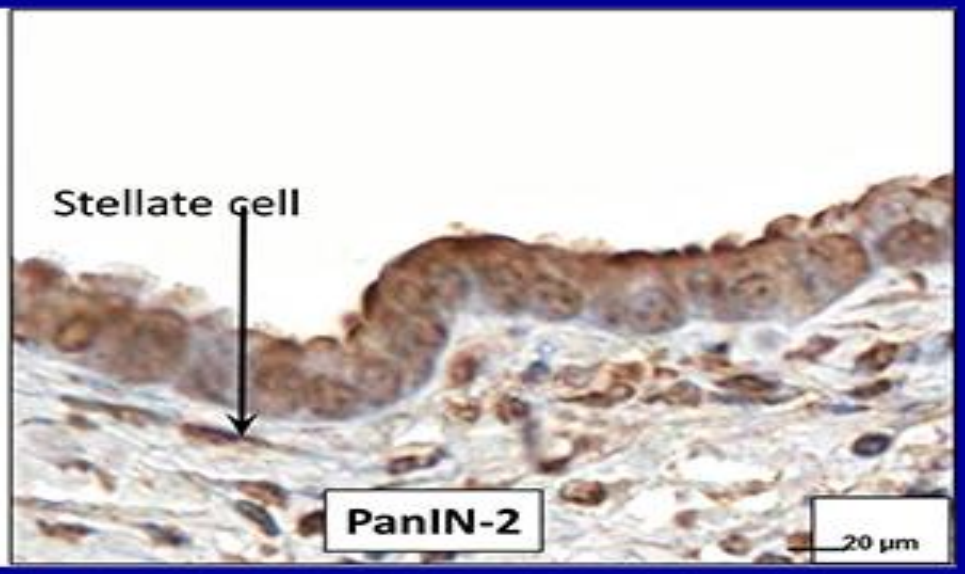
# Pancreatic cancer microenvironment



# CCK-R and Pancreatic stellate cells

## CCK Receptors are also on Pancreatic Stellate Cells



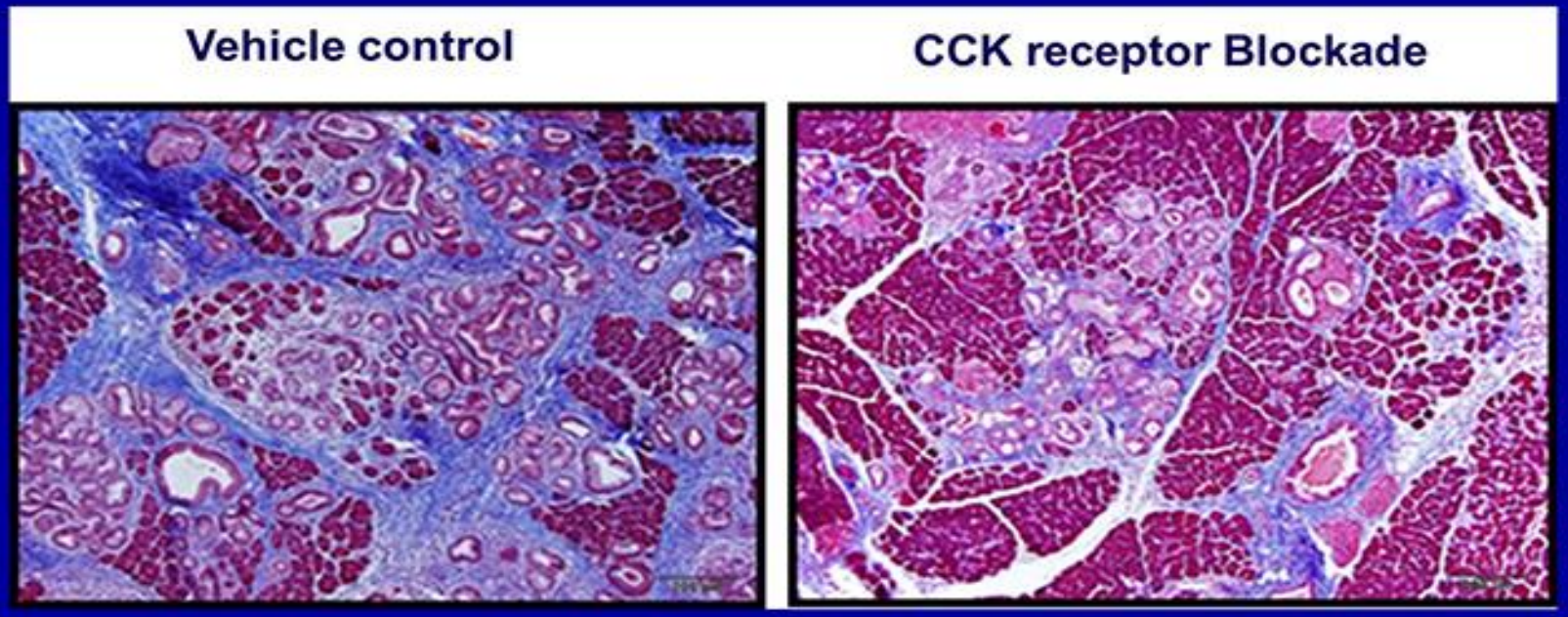




Berna. J Biol Chem. 2010, 285, 38905

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

# CCK-R blockade prevents fibrosis

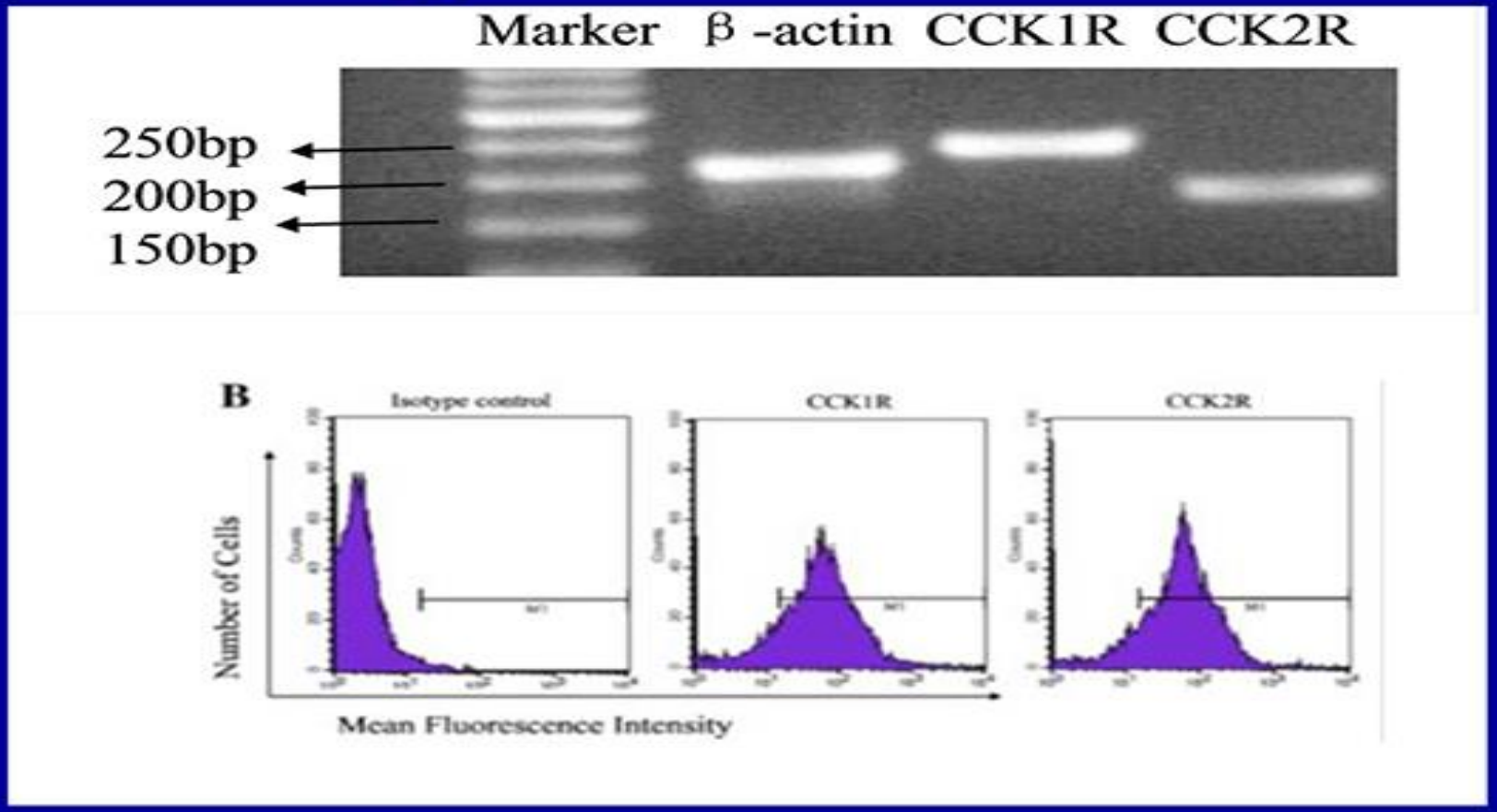
## CCK Receptor Blockade Prevents Fibrosis in KRAS mouse



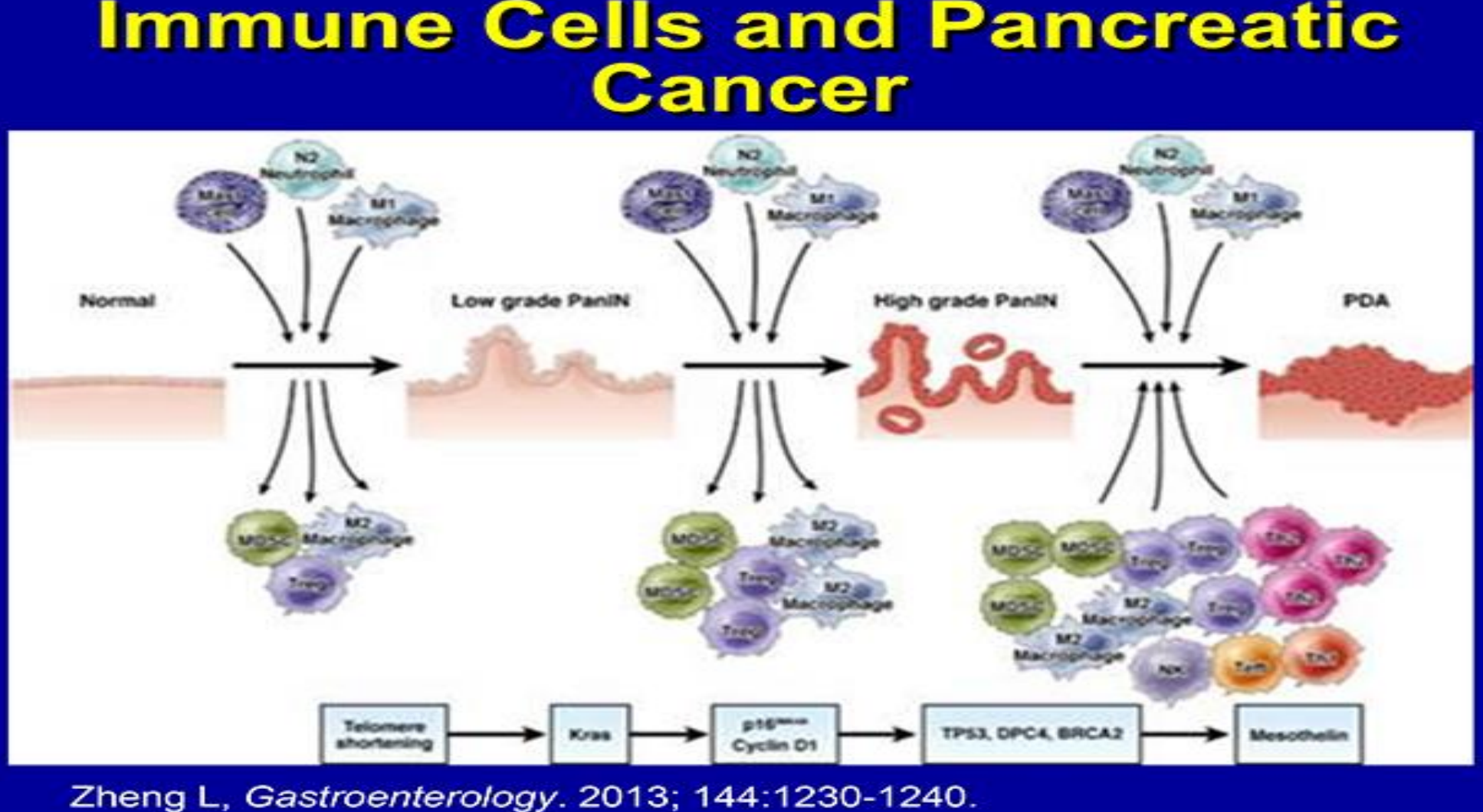

Pancreas. 2014 Oct;43(7):1050-9.

# CCK-R and immune cells

## CCK Receptors are on Immune cells



# Immune cells and pancreatic cancer




Zheng L, *Gastroenterology*. 2013; 144:1230-1240.

# Immune therapy

## Role of Immune Therapy in Pancreatic cancer

Athymic Nude mice/ SCID
Immune Deficient

C57BL/6 mice or $Kras^{G12D}$ Transgenic mice
Immune Competent

**Must use immune competent mice and syngeneic cancer models. We use mT3 and mT5 murine pancreas cancer cells derived from KRAS transgenic mice.**

# Pancreatic cancer and immunotherapy

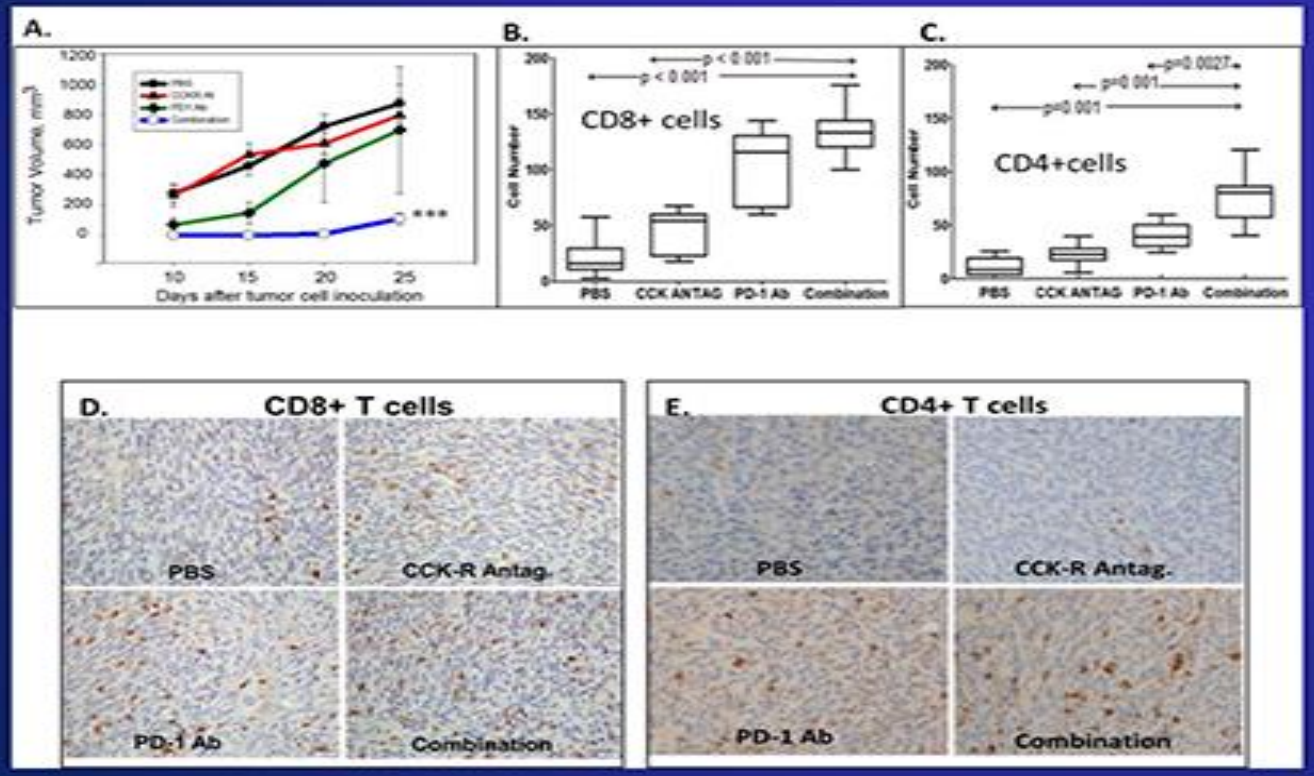
## Problem #1

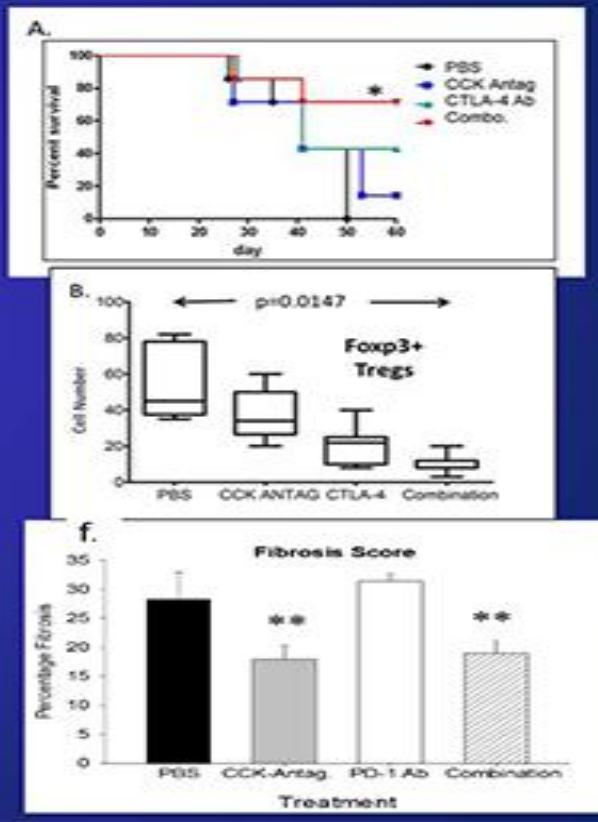
- Pancreatic cancer does not respond to immunotherapy
- The fibrosis and immune suppressive cells of the microenvironment make therapy difficult

**Hypothesis: CCK-receptor blockade decreases fibrosis and alters the immune signature of the tumor microenvironment**

# CCK-R antagonist

## CCK Receptor antagonist therapy improves response to immune checkpoint antibodies



# Clinical trial: Phase 1/2

## Clinical Trial: Phase 1/2

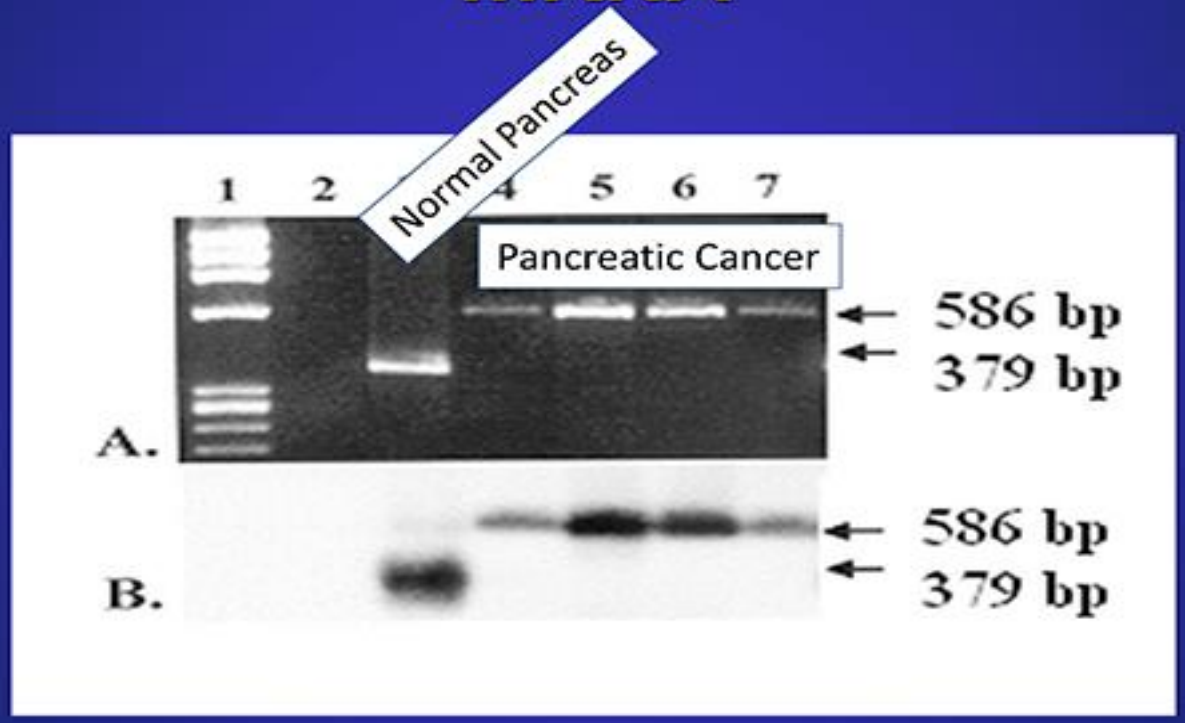
- Use of CCK receptor antagonist and immune checkpoint blockade in pancreatic cancer: Proglumide
- Intellectual property- secured
- Source of GMP grade CCK antagonist
- Apply for IND# -pending
- Industry partner
- Funding- pending

# Problem #2

**No biomarkers or means to screen high risk individual.**

# RT-PCR of CCK-B-R

## RT-PCR of pancreas cancer for CCK-B receptor revealed larger mRNA

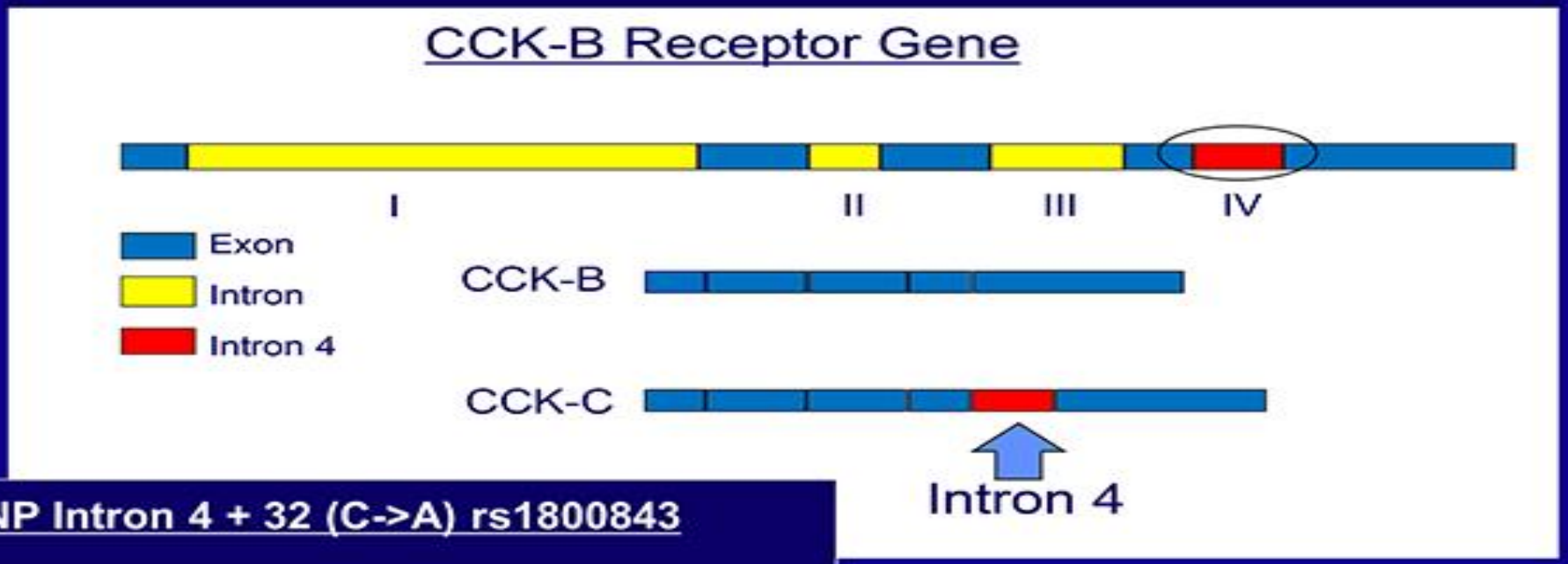



Smith JP. Characterization of the CCK-C (cancer) receptor in human pancreatic cancer. *Gastroenterology* 116:, 1999

# Alternative mRNA splicing

## Alternative mRNA splicing in cancer cells creates a novel, CCK-C Receptor

Occurs in ~35% patients with pancreatic cancer and predicts risk $p = 7.5 \times 10^{-8}$

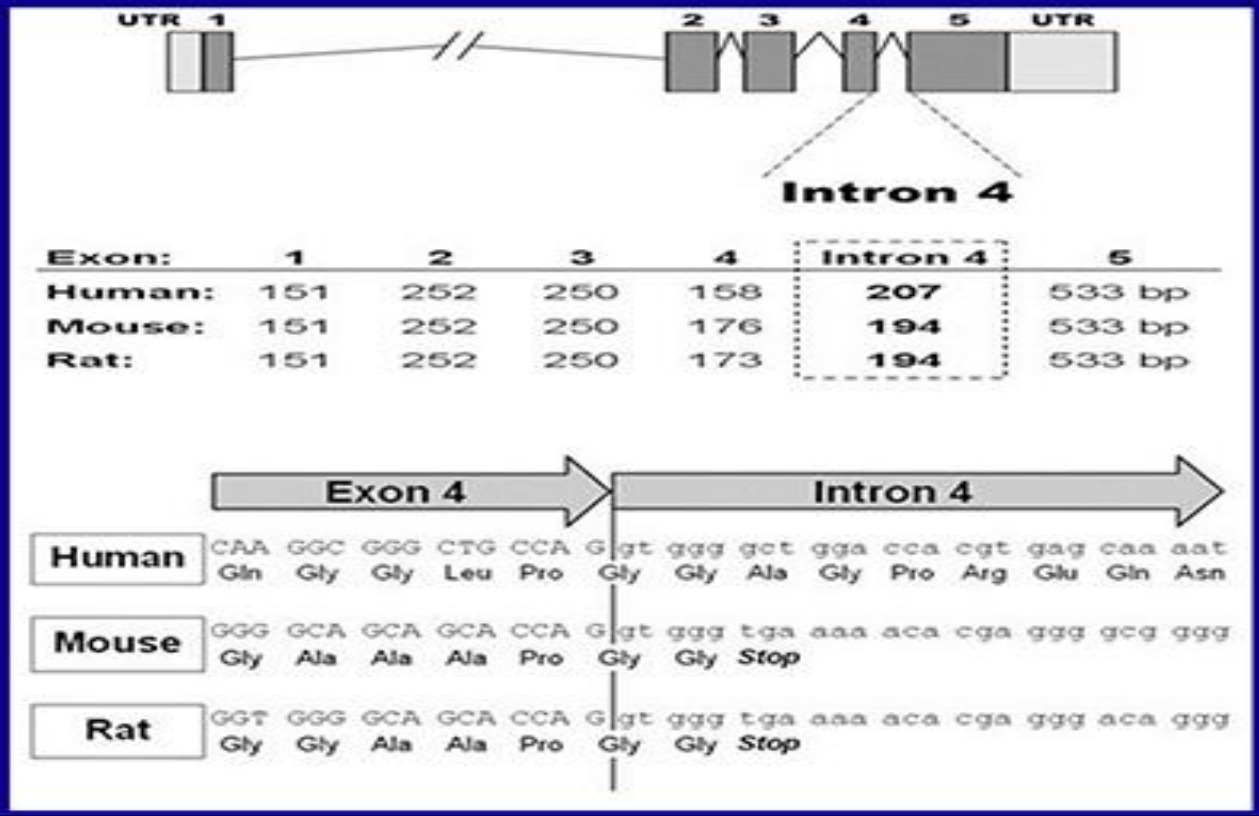



**SNP Intron 4 + 32 (C->A) rs1800843**

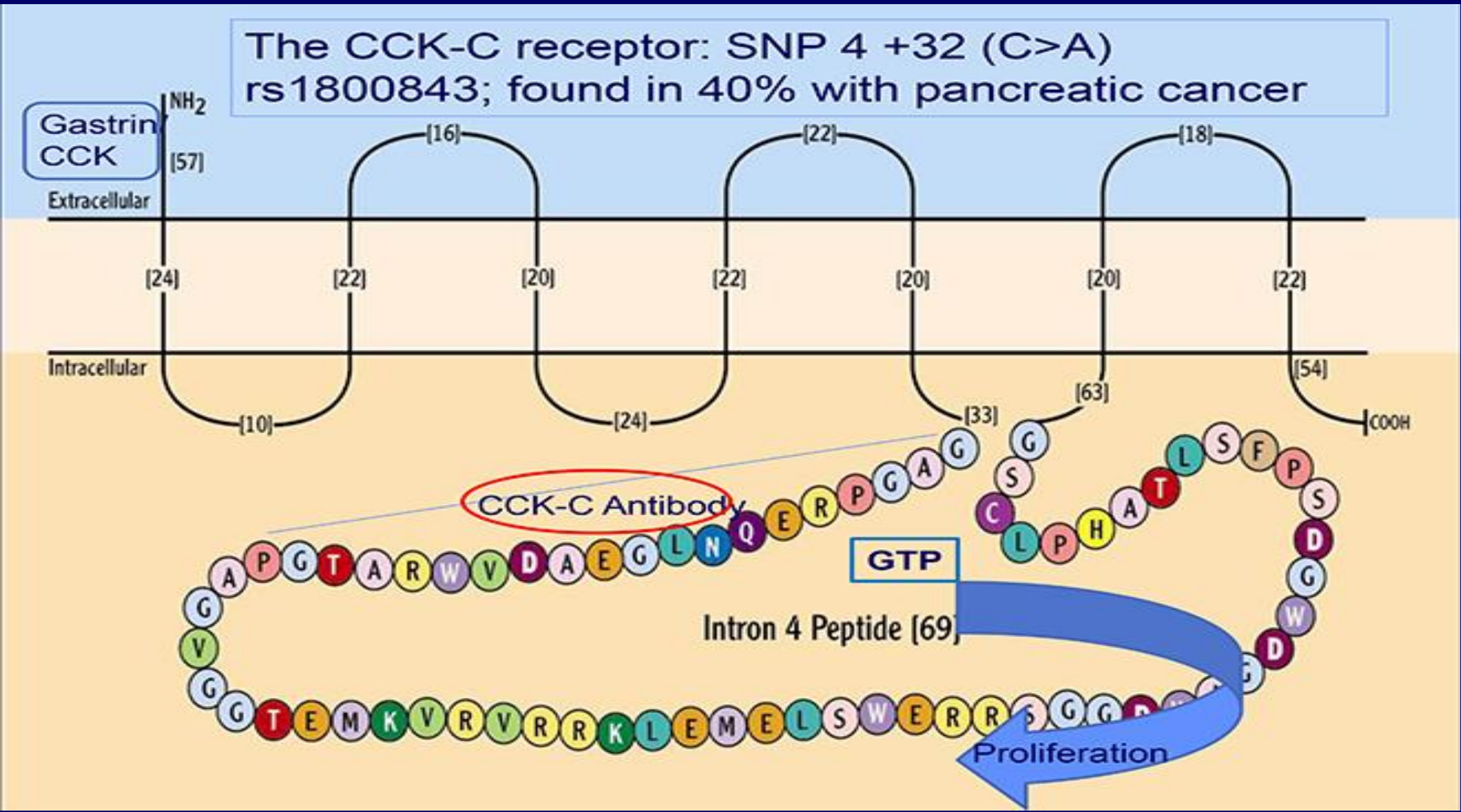
**Smith et al,** Pancreas 2015;44: 236–242
**Smith,** J.P., 2002. Characterization of the CCK-C (cancer) receptor in human pancreatic cancer. *Int. J. Mol. Med.* 10:689-694.

# Human vs animal CCK-C-R

## Human vs animal research CCK-C receptor

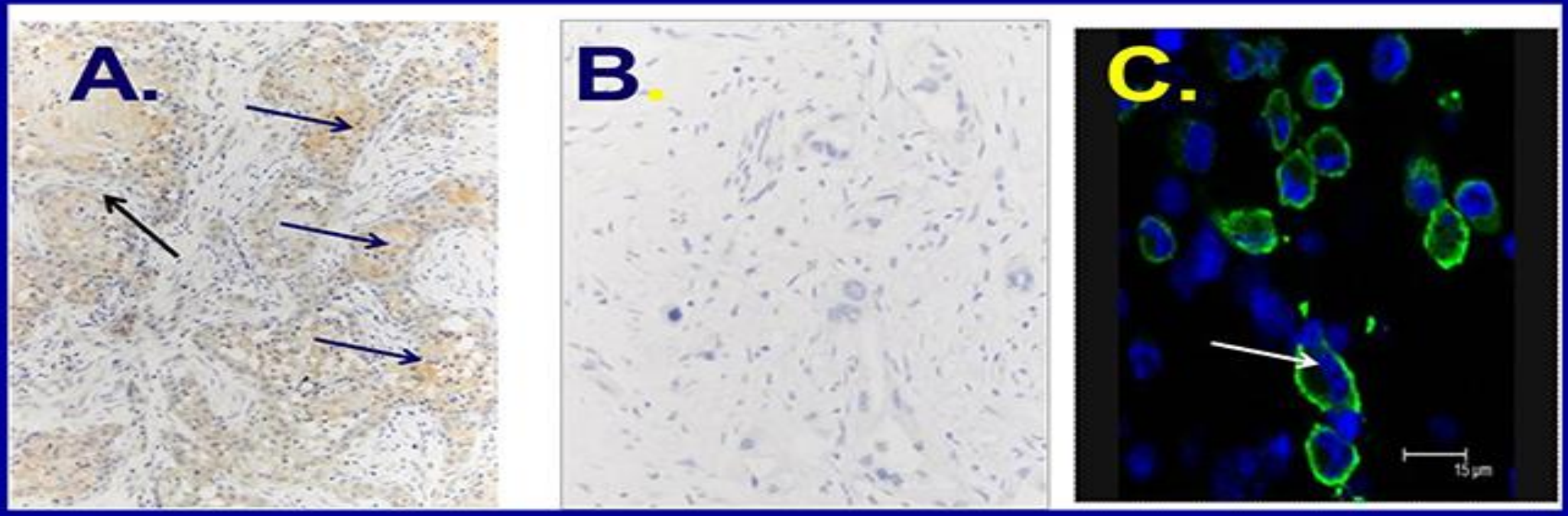


# CCK-C-R


The CCK-C receptor: SNP 4 +32 (C>A)
rs1800843; found in 40% with pancreatic cancer
Gastrin
CCK
NH2
[57]
Extracellular
Intracellular
[16]
[22]
[18]
[24]
[22]
[20]
[22]
[20]
[20]
[22]
[10]
[24]
[33]
[63]
[54]
COOH
CCK-C Antibody
GTP
Intron 4 Peptide [69]
Proliferation

# CCK-C-R expression

## Not all Pancreatic Cancers Express the CCK-C Receptor




Smith JP, Cancer Biology & Therapy 13:, 2012

# Patient study

## Patient Population Study

### Small pilot trial

- 110 subjects
- Genotyped their CCK receptor.
- Survival significantly different in those with the SNP p=0.0001 HR= 3.36

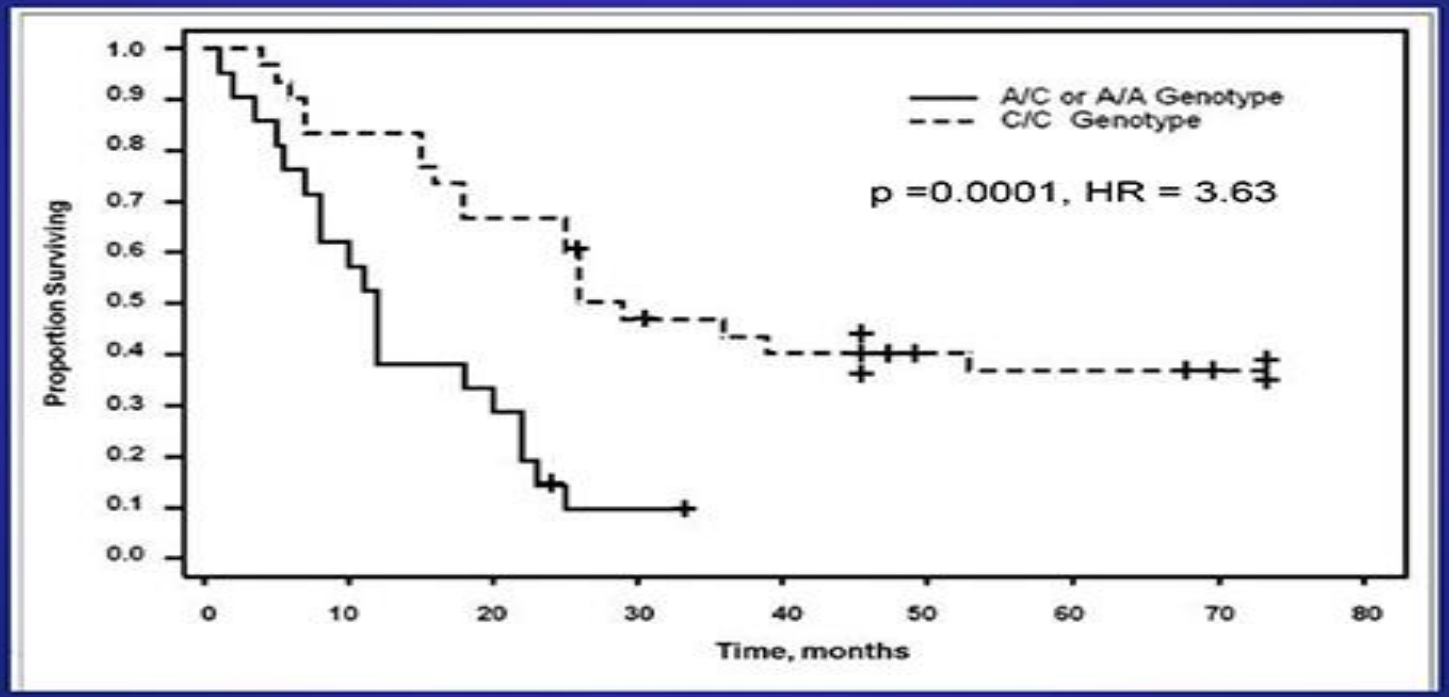
### Validation study

- Larger cohort of different patients 931 patients
- Even after adjustment for stage of disease, survival of subjects with the minor allele was significantly shorter than those with the wild-genotype (hazard ratio, 1.83; P = 3.11 10−11).

** Antibody has patent rights and currently under negotiations

# Survivor curve

## A-SNP of the CCK-B receptor causes an aggressive phenotype

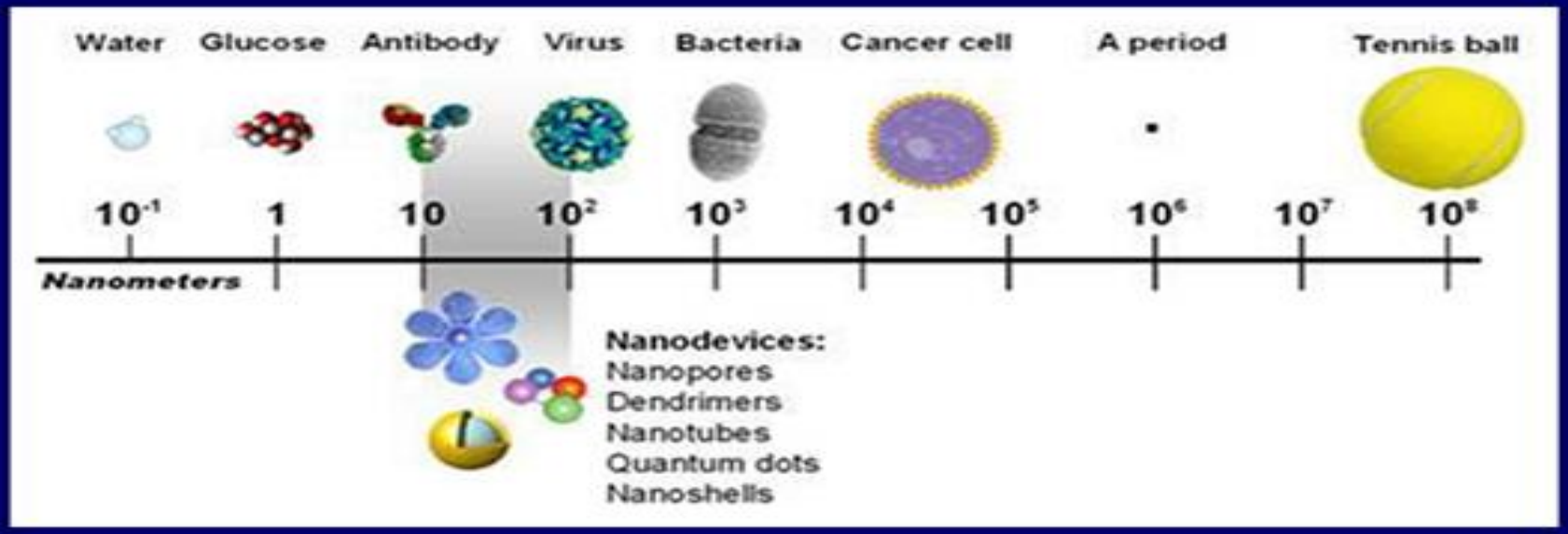



Small pilot trial

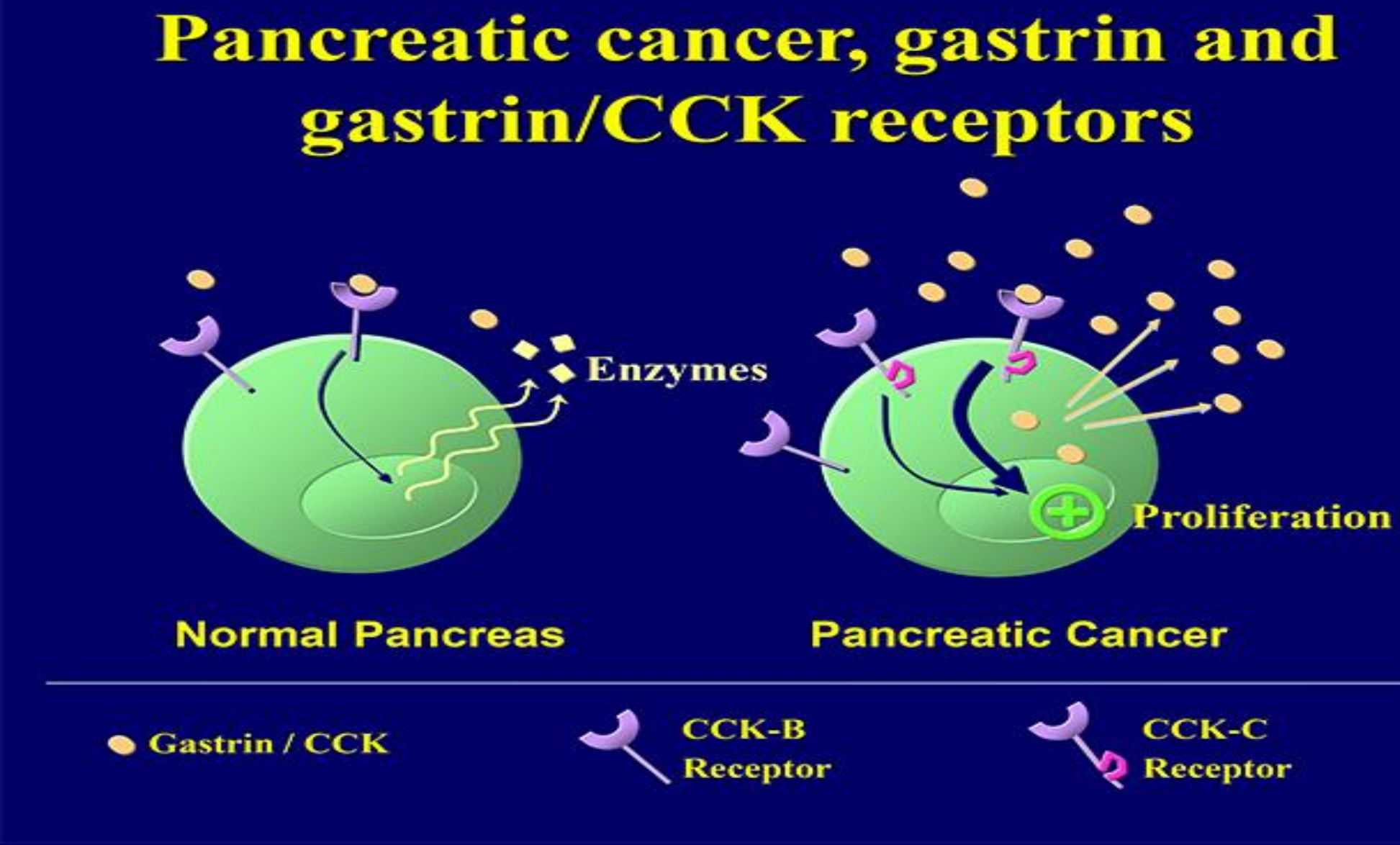
# Problem #3

- Chemotherapy has toxicity because it is not target specific
- There is no sensitive radiographic imaging tests for early cancer diagnosis

# Nanotechnology and Cancer



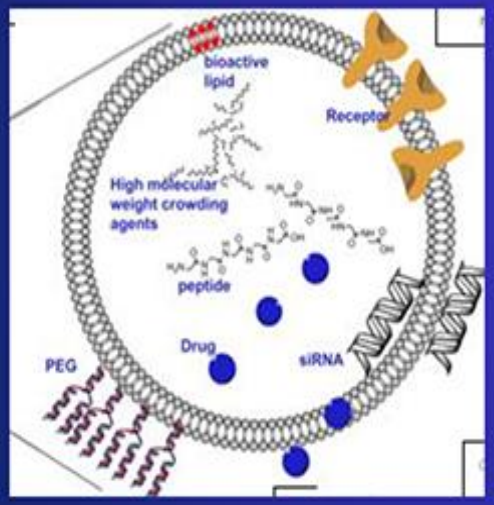
# Pancreatic cancer gastrin



# Nanotechnology

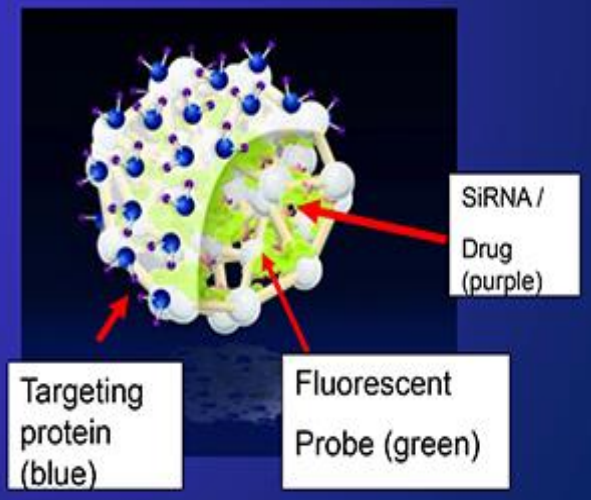
## Nanotechnology: Delivery Vehicles for Cancer Therapy

- Nanoliposomes



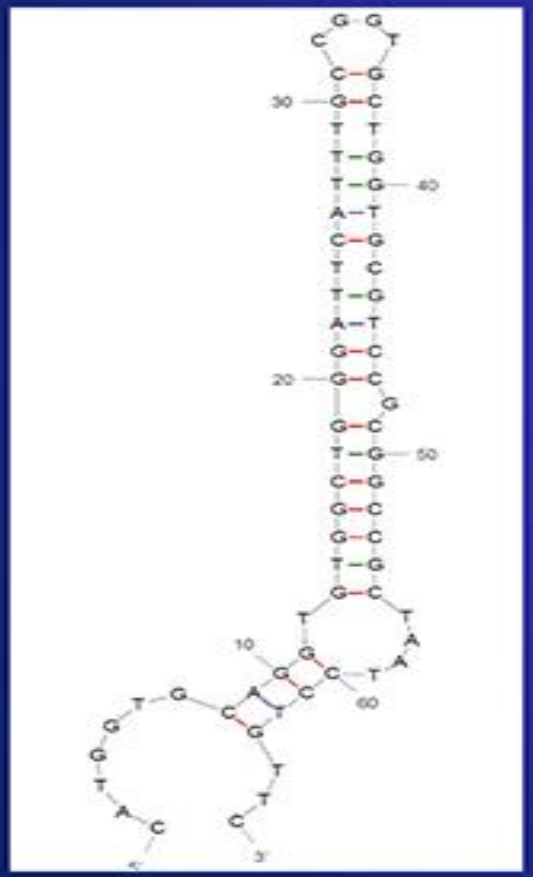

1,2-Dioleoyl-3-Trimethyl- ammonium-propane (DOTAP, MW 774.19), 1,2-distearoyl-snglycero-3-phosphetanolamine-N-[methoxy (polyethylene glycol)-2000 (PEG, MW 2,805.54), and 1,2-Dioleoyl-sn-Glycero-3-Phosphethanolamine (DOPE, MW 744.04)

- Calcium $PO_4$ Nanoparticles

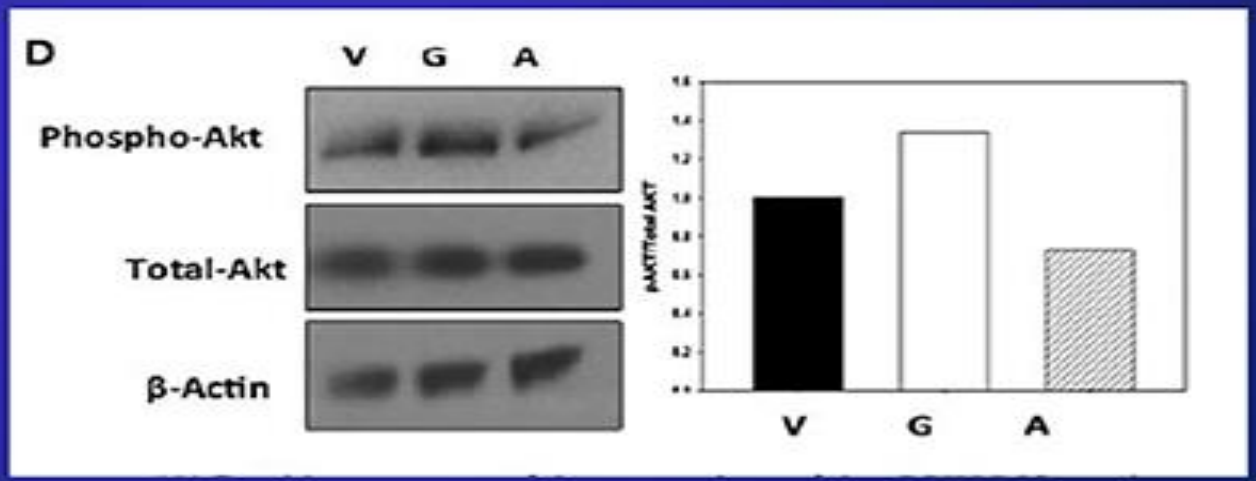


# DNA Aptamers

## DNA Aptamer to the CCK Receptor targets Pancreatic cancer

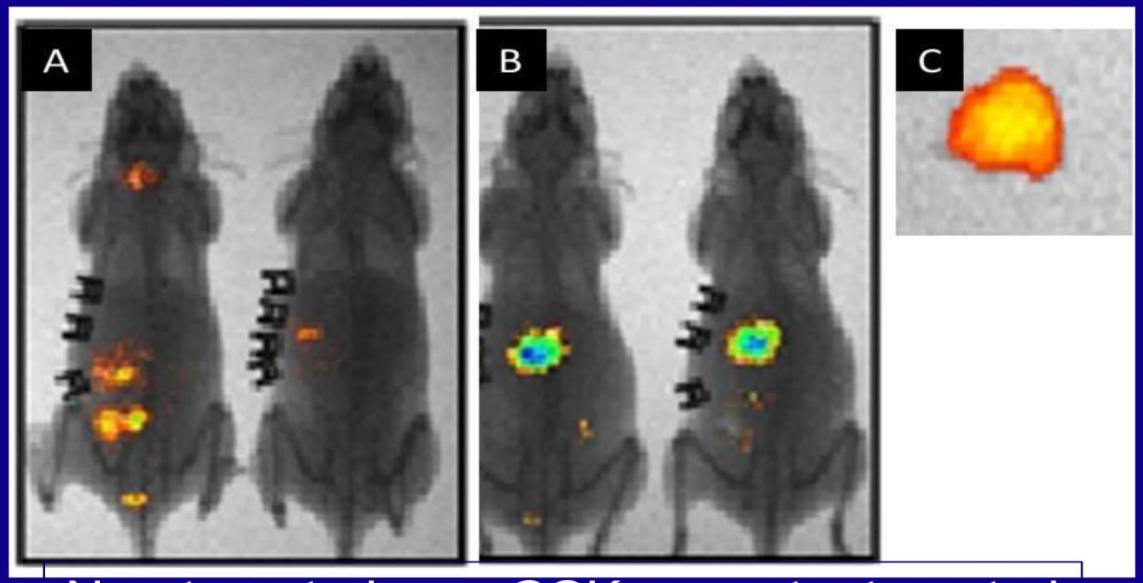


Using SELEX, Systematic evolution of ligands by exponential enrichment , selection against an "exposed" CCKBR peptide and CCKBR-expressing PDAC cells we identified thousands of DNA aptamers



# Molecular targets

## Target-specific nanoparticles to pancreatic tumor cells *in vivo:* Using the CCK receptor as a target




Non-targeted CCK- receptor targeted

Nude mice bearing orthotopic human pancreatic cancer cell tumors

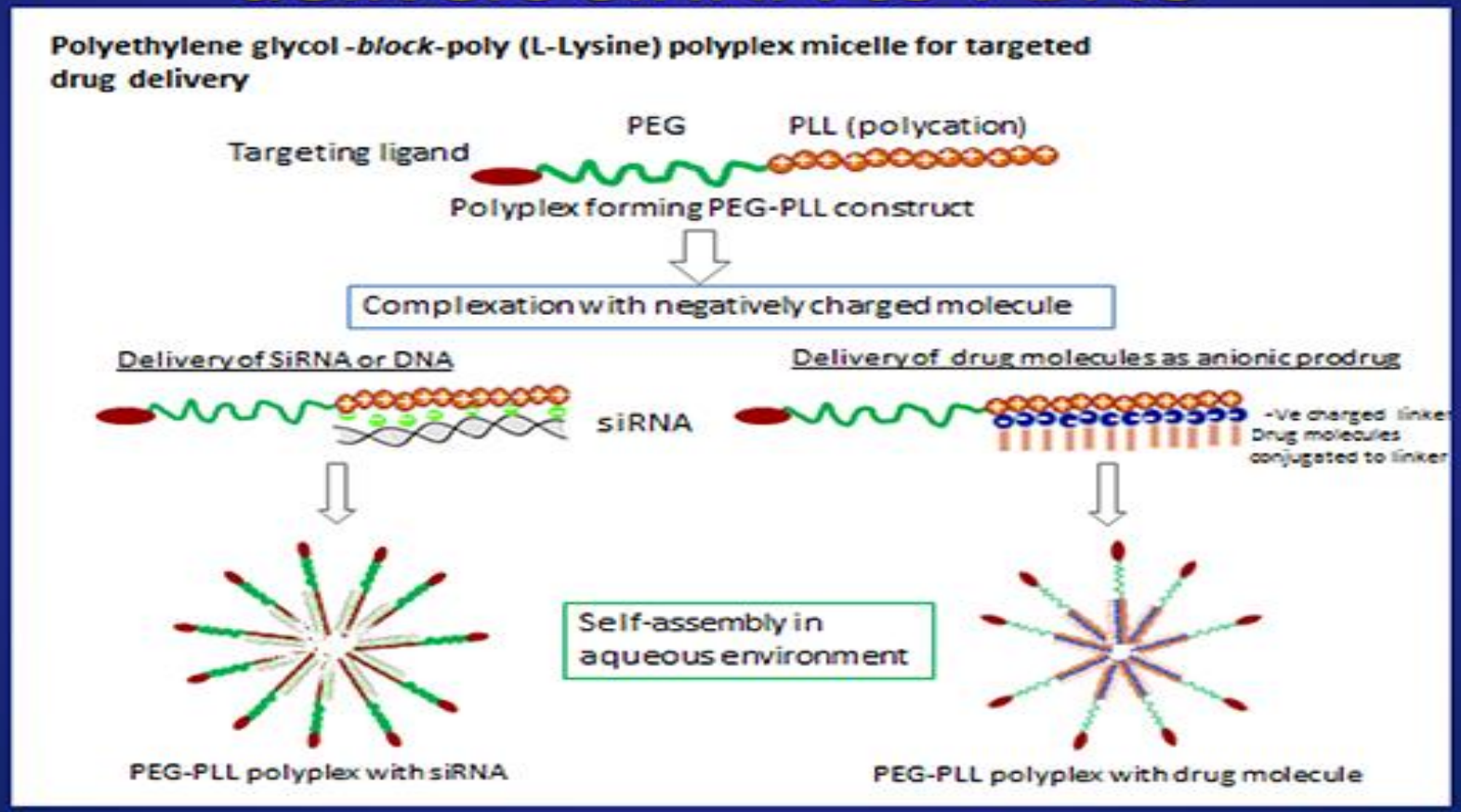
A. Mice injected with untargeted, ICG loaded CPNP at 7 hrs (left) or 24 hrs (right) post-injection

B. Mice injected with gastrin-targeted CPNP at 7 hrs (left) or 24 hrs (right) post-injection showing enhanced CPNP uptake into the orthotopic tumor

C. Excised pancreatic tumor 24 h post-injection

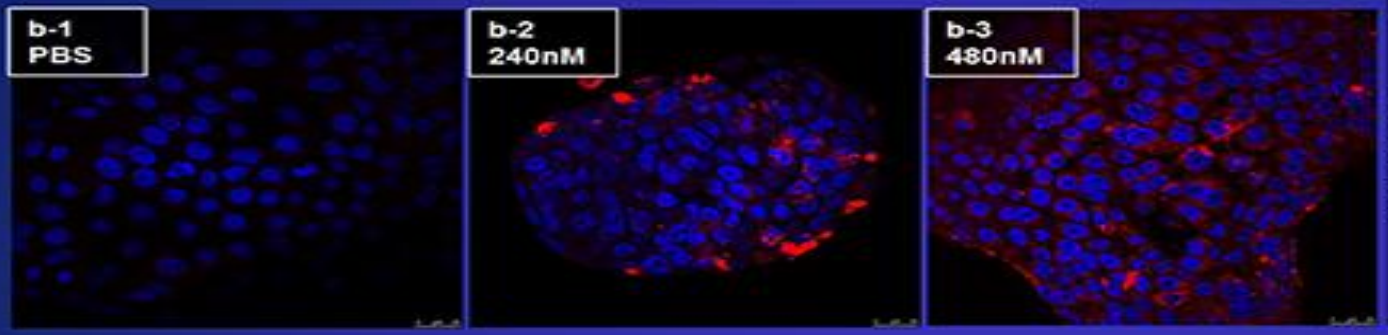
Barth, ACS Nano, VOL. 4 · NO. 3 · 1279–1287 · 2010

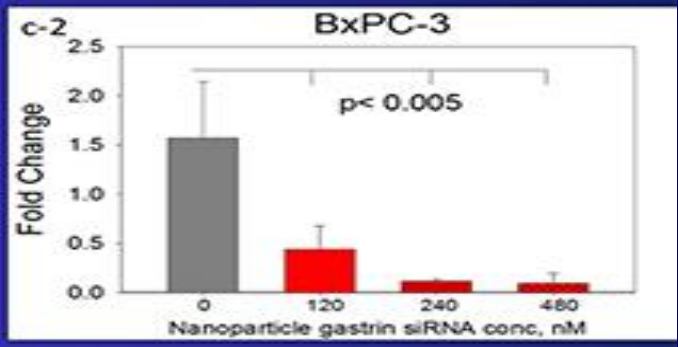
# Target specific polyplex NP

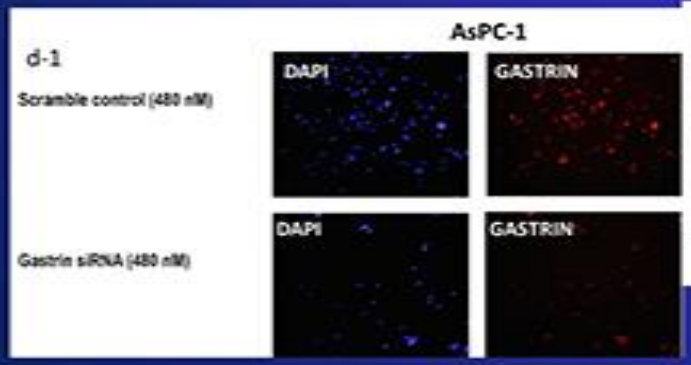


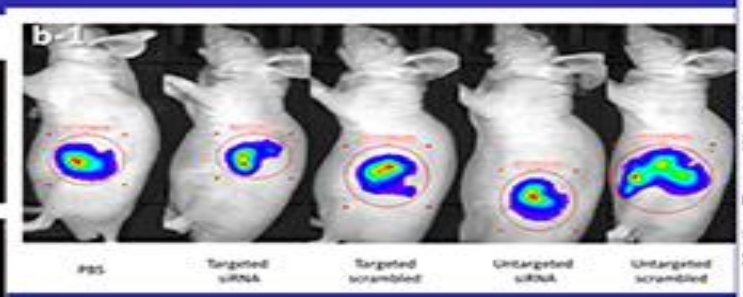
# Polyplex NP

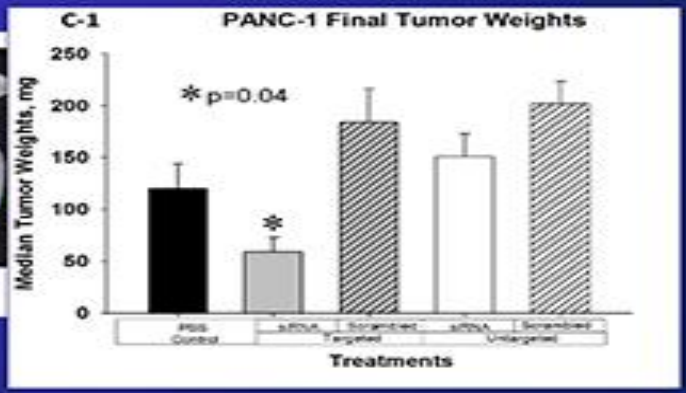
## Polyplex NP Targets the CCK Receptor and knocks down gastrin




Targeted gastrin siRNA treated mice had smaller tumors and no metastases

# Nanoparticles Are "Theronostic" (Therapeutic and Diagnostic)

AACR Dream team: Stand-up-2 Cancer

Clinical scientist

Oncologist

Material science engineer

Imaging engineer

Pharmacologist

Toxicologist

Project manager

Patient advocates

# Research Obstacles

## Obstacles with Translational Research Today

1. **$$$$$** Is the problem a lack of funds, misuse of funds, or disparity of funds?
2. Clinicians do not get protected time to do translational research.
3. Chiasm between industry and NIH /academia
4. Problems with patient accrual into research studies.
5. No more –one man bands, we need team science. PhDs must work with MDs. Team science

# Pancreatic cancer patients

**Bottom Line:**
**Does the research have**
**Clinical relevance to**
**Help people?**

**Bobbie** (with permission)
**Pancreatic cancer patient**

**Vickie** (with permission)
**Pancreatic cancer patient**

# Side effects

## Potential Side effects of CCK receptor blockade



No More Heartburn!!!

# Collaborators

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Julian Burks, PhD

Sandra A Jablonski, PhD

Louis Weiner, MD

Smith Lab & Collaborators

Shangzi Wang, PhD

Funding: NIH / NCI, Donner Foundation, Ruesch Foundation