

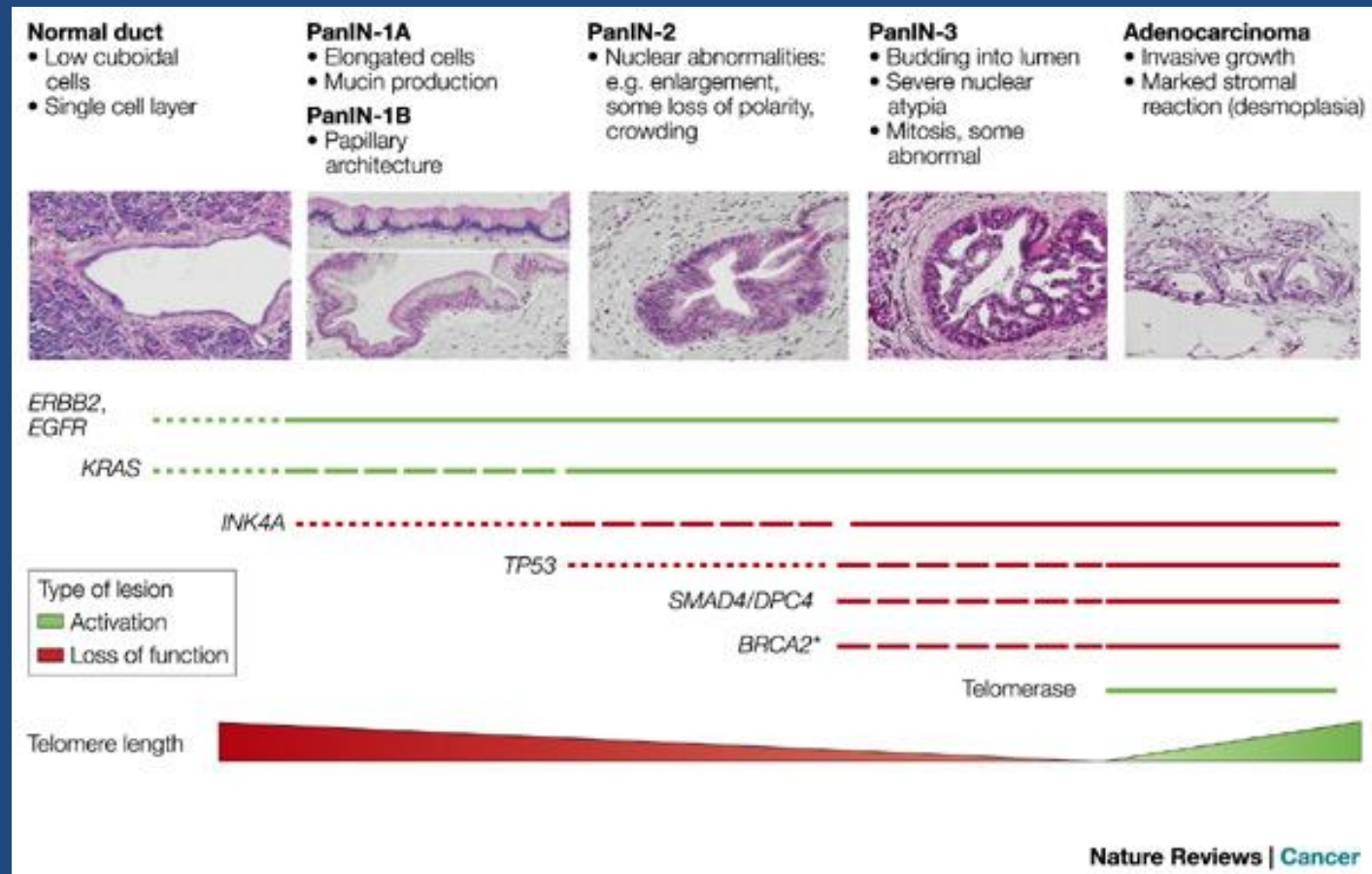
Expression of GRP78 protein is increased in pancreatic ductal adenocarcinoma, pancreatic intraepithelial neoplasia and intraductal papillary mucinous neoplasm

Xianzhong Ding, Brandon Trac, and Xiuzhen Duan

Department of Pathology
Loyola University Medical Center
Maywood, IL 60153
USA

PANCREATIC DUCTAL ADENOCARCINOMA

- Poor prognosis
- Lack of responsiveness to conventional therapy



Precursor Lesions of Pancreatic Adenocarcinoma

- Pancreatic intraepithelial neoplasia (PanIN)
- Mucinous cystic neoplasm (MCN)
- Intraductal papillary mucinous neoplasm (IPMN)

PANCREATIC DUCTAL ADENOCARCINOMA

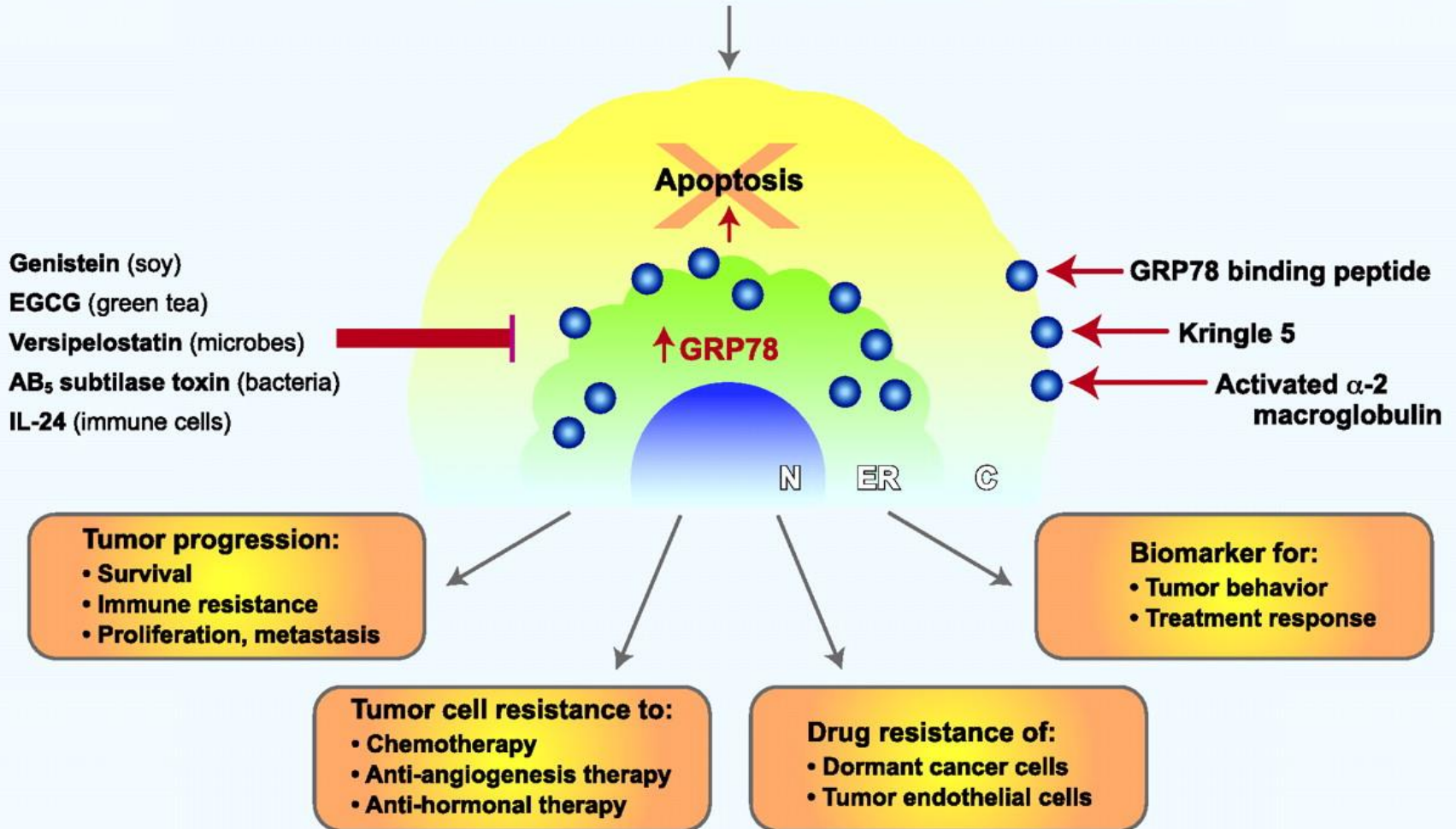
- According to the Response Evaluation Criteria in Solid Tumors (RECIST), for pancreatic cancer patients treated palliatively with gemcitabine and nab-paclitaxel
 - No complete responses were observed
 - Partial response in 37% of patients
 - Progressive disease in 22% of patients

GRP78

- Glucose-Regulated Protein 78 (GRP78)
- Heat Shock Protein 70 (HSP70) family
- A major endoplasmic reticulum (ER) chaperone protein
- Critical for protein quality control of ER
- GRP78 is preferably required for
 - cancer cell survival
 - Promotes tumor progression
 - Enhances drug resistance

Endoplasmic Reticulum Stress in the Tumor Microenvironment

(glucose starvation, hypoxia, protein misfolding)

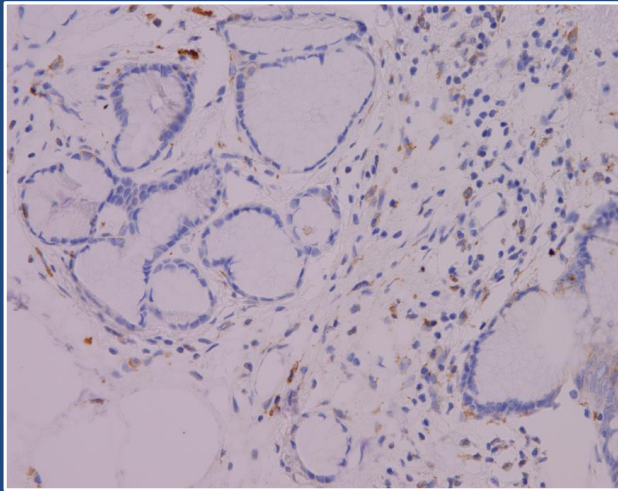


AIMS

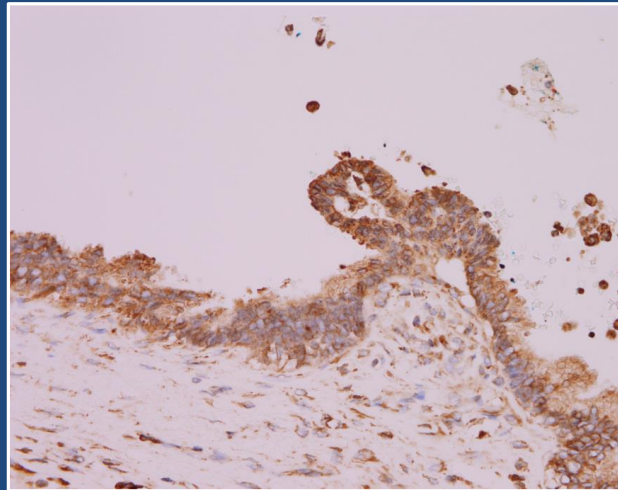
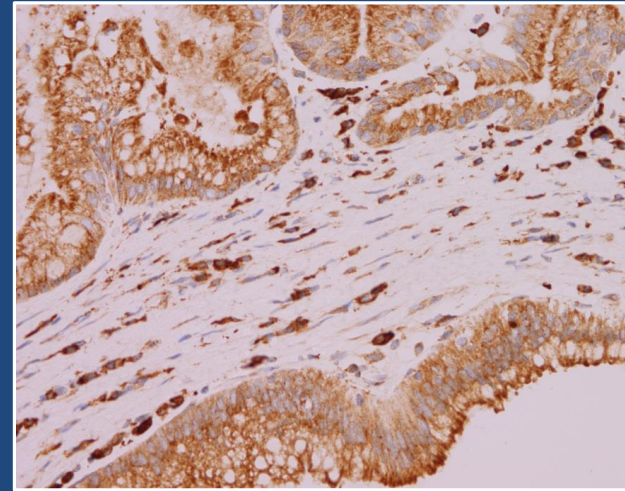
- **GRP78 expression in human pancreatic ductal adenocarcinoma**
- **GRP78 expression in precursor lesions of human pancreatic ductal cancer**
 - Pancreatic intraepithelial neoplasia
 - Intraductal papillary mucinous neoplasm
- **GRP78 and pancreatic cancer growth**

GRP78 IMMUNOHISTOCHEMISTRY

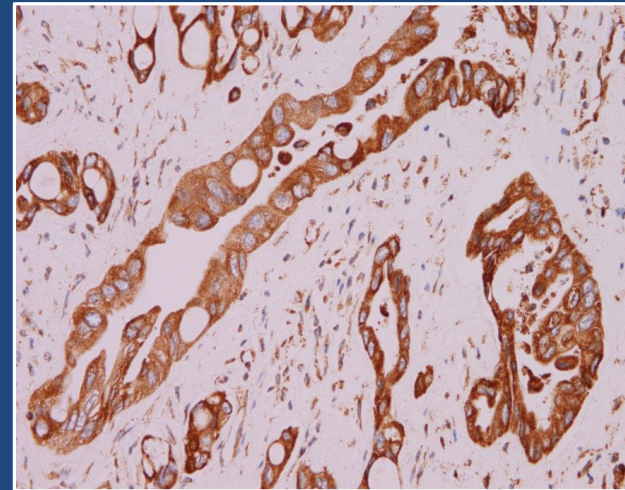
Benign pancreatic ducts



Low grade IPMN



High grade IPMN

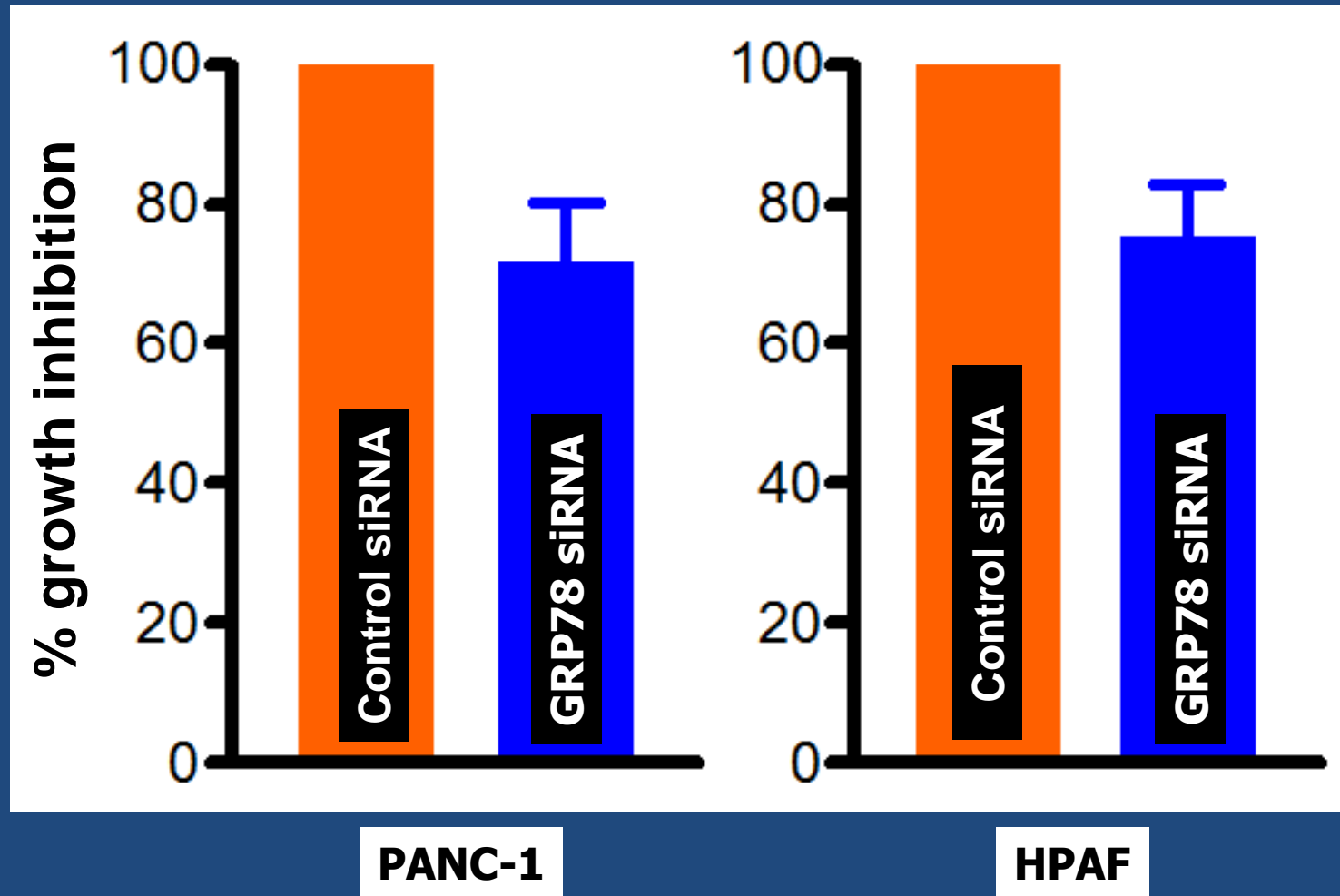


Invasive ductal adenocarcinoma

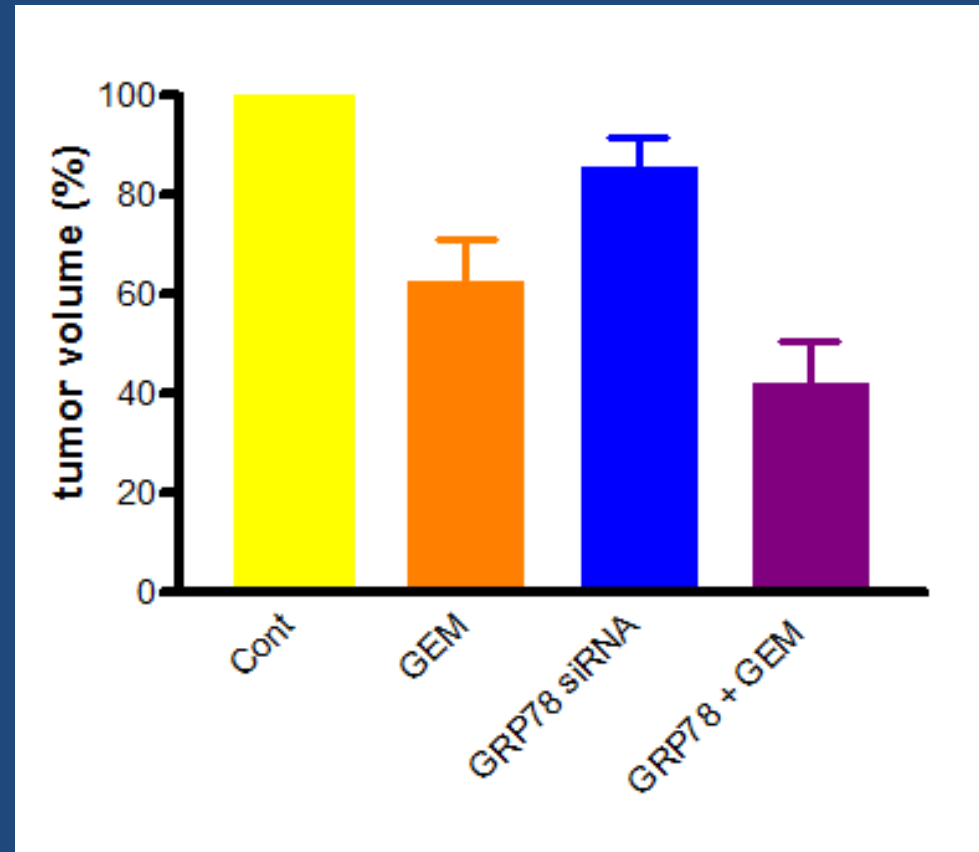
GRP78 PROTEIN EXPRESSION LEVEL

	Normal ducts	IPMN-LG	IPMN-HG	<u>panIN-HG</u>	PDAC
Total	38	26	9	32	20
No or weak staining (0-1+)	37	7	0	0	0
Strong staining (2-3+)	1	19	9	32	20
% of strong staining	3%	73%	100%	100%	100%

GRP78 siRNA INHIBITS PANCREATIC CANCER CELL PROLIFERATION



GRP78 KNOCKDOWN ENHANCES ANTICANCER EFFECT OF GEMCITABINE



SUMMARY AND CONCLUSIONS

- **GRP78 is up-regulated in human pancreatic ductal adenocarcinoma and its precursor lesions**
- **Blockade of GRP78 inhibits pancreatic cancer cell proliferation**
- **GRP78 knockdown enhances anti-cancer effect of gemcitabine**
- **Prognosis?**