Berry Chemoprevention of Pancreatic Cancer

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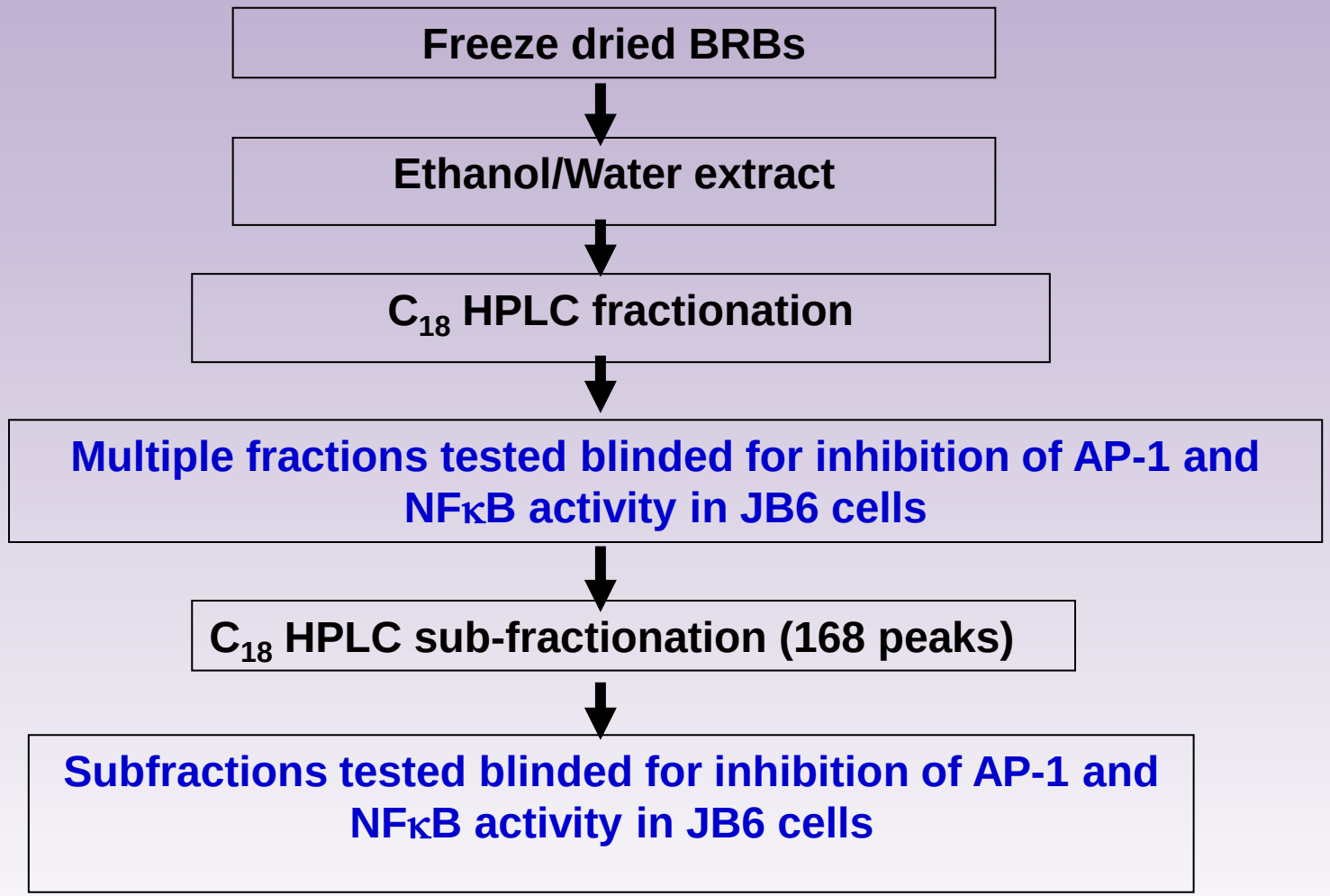
Black raspberries (BRBs)



Freeze-dried powder

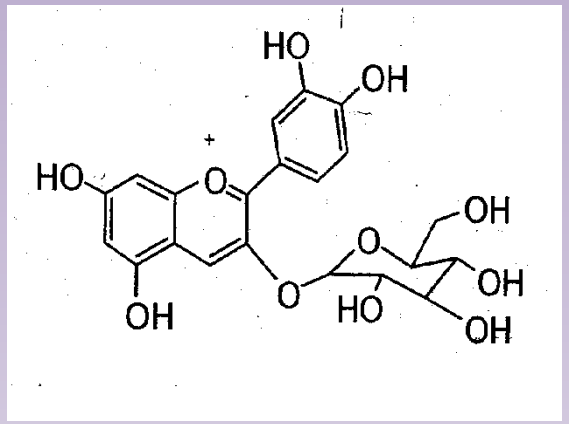


Identification of bioactive compounds in BRBs

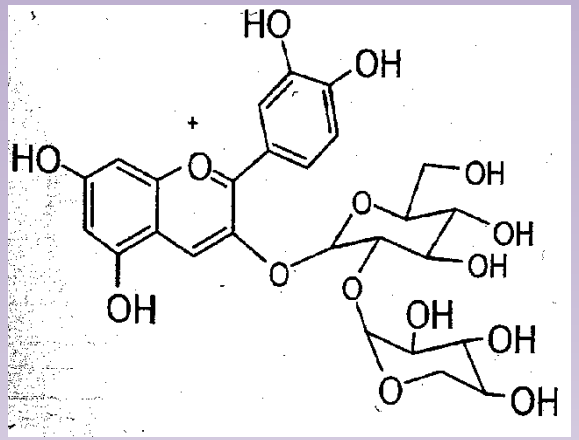


Hecht SS et al., Carcinogenesis 2006;27:1617.

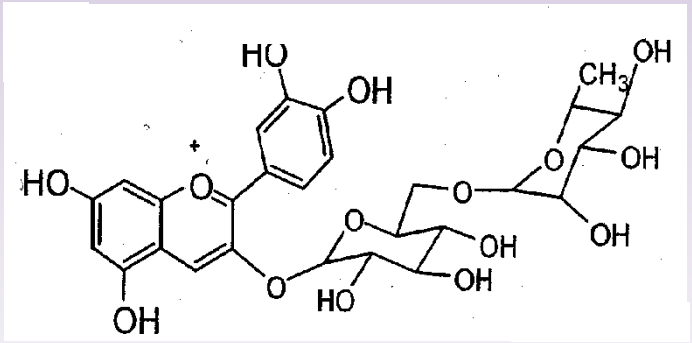
Anthocyanins in black raspberries



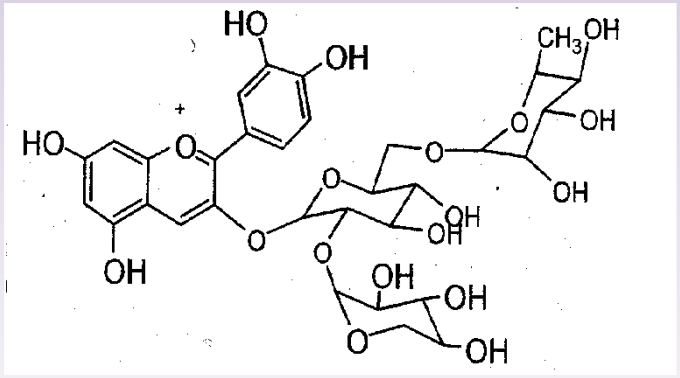
Cyanidin 3-O-glucoside



Cyanidin 3-O-sambubioside



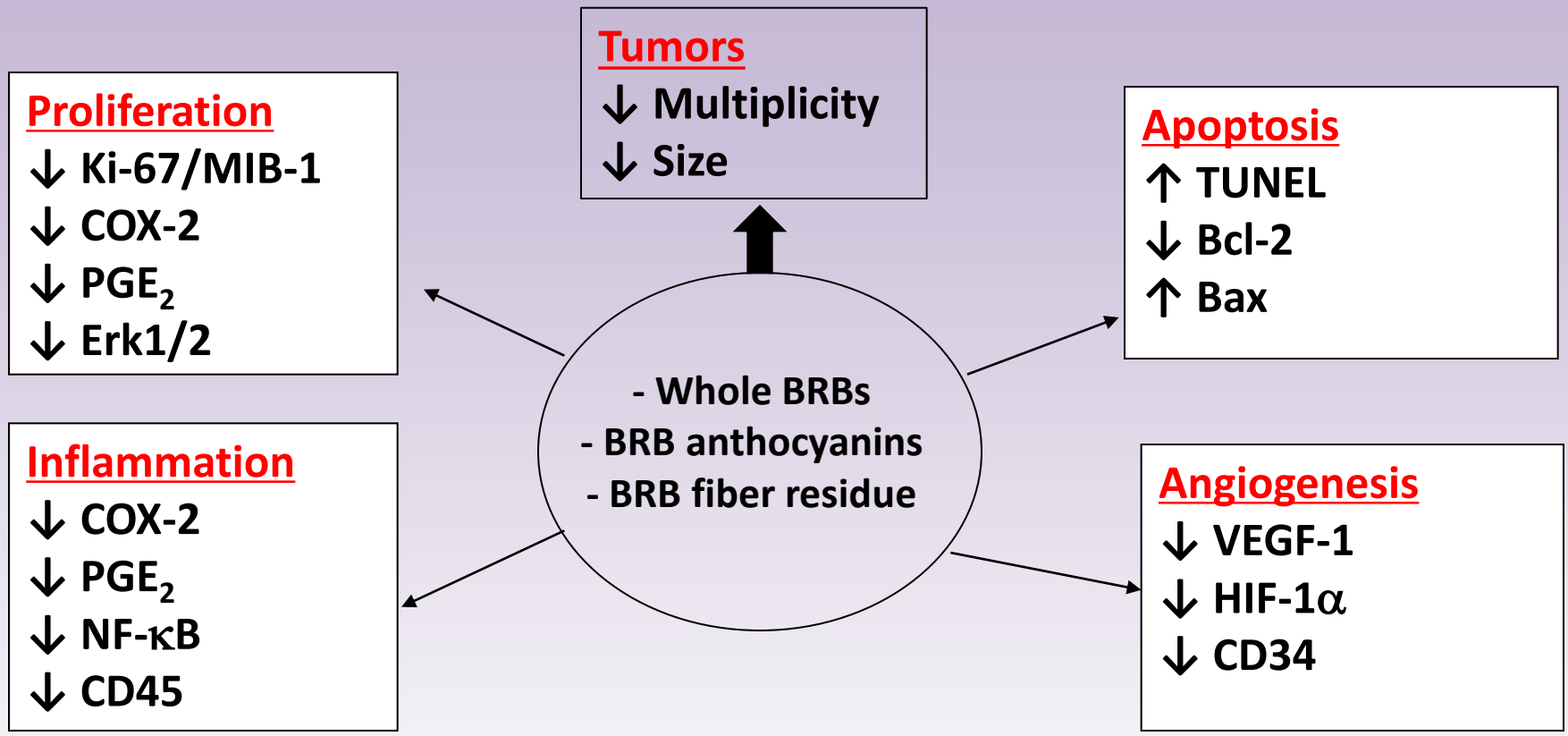
Cyanidin 3-O-rutinoside



Cyanidin 3-O-(2^{G}-xylosylrutinoside)

SS Hecht et al., Carcinogenesis 27:1617, 2006

Effects of whole BRBs and BRB anthocyanins on cellular events and associated genes in carcinogen-treated rat esophagus



CD45 – leukocyte common antigen, CD34 – Microvessel marker

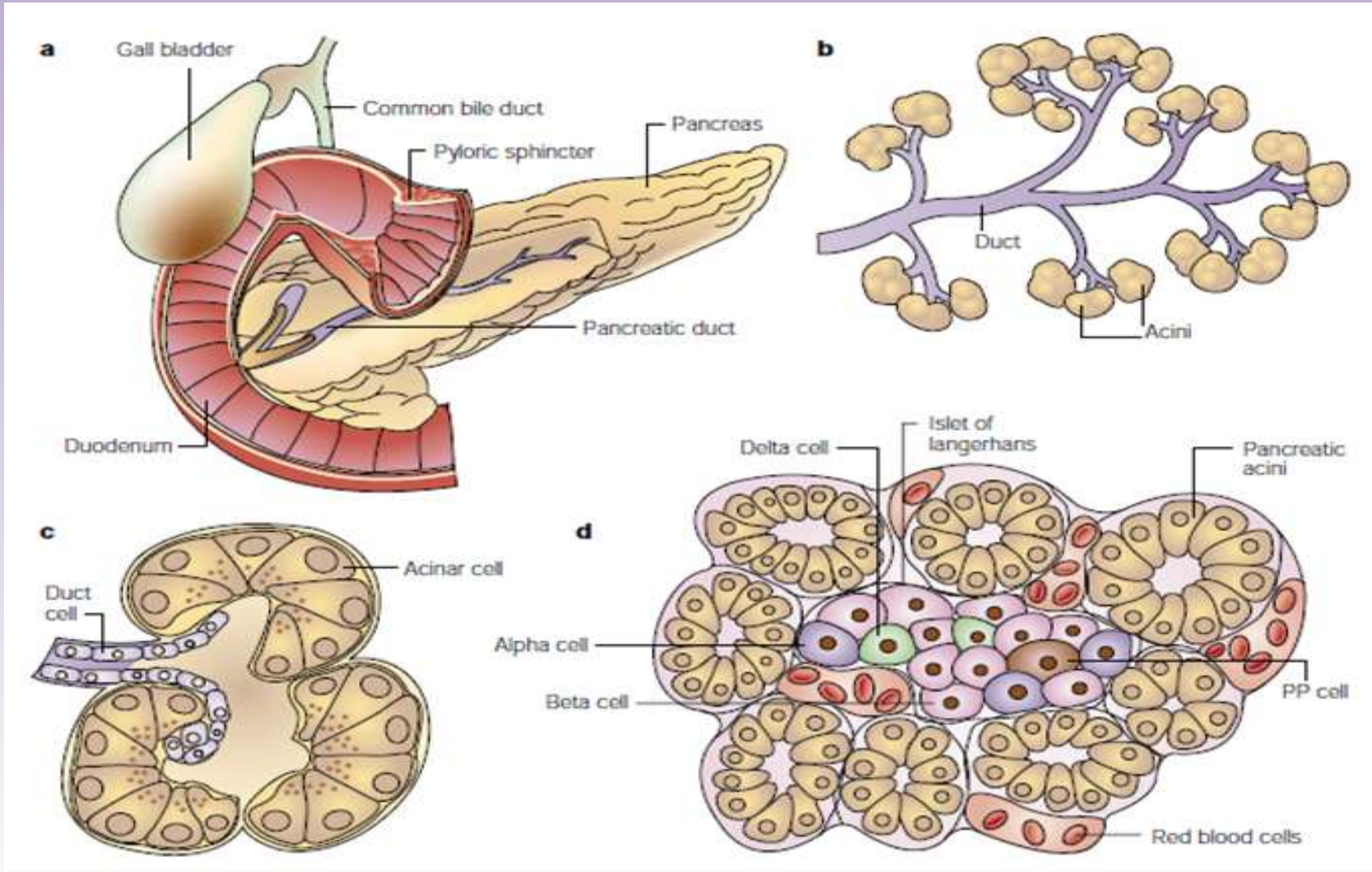
Wang LS et al., Cancer Prev Res 2009;2:84.

Some chemopreventive agents in black raspberries

- **Vitamins:** A, C, E, folic acid
- **Minerals:** calcium, selenium
- **Simple phenols:** ellagic acid, ferulic acid, coumaric acid, quercetin
- **Complex phenols:** anthocyanins
- **Phytosterols:** β-sitosterol, campesterol, stigmasterol
- **Fiber**

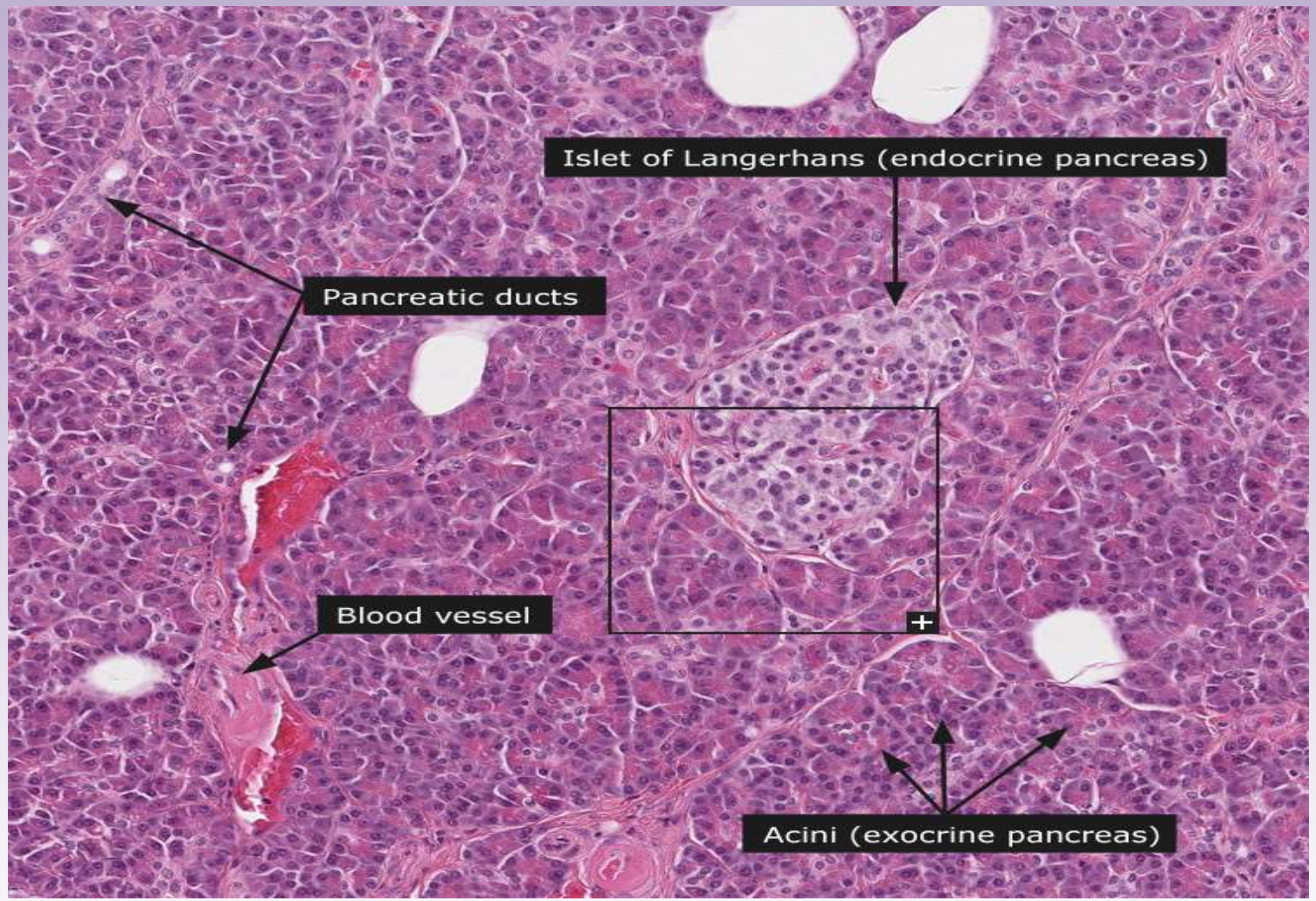
Stoner GD, Cancer Prev Res. 2009;2:665.

Anatomy of pancreas



Nabeel Bardeesy and Ronald A. DePinho. Pancreatic cancer biology And genetics

Normal pancreas



http://www.proteinatlas.org/learn/dictionary/normal/pancreas/detail+1

Prevalence of pancreatic ductal adenocarcinoma (PDAC)

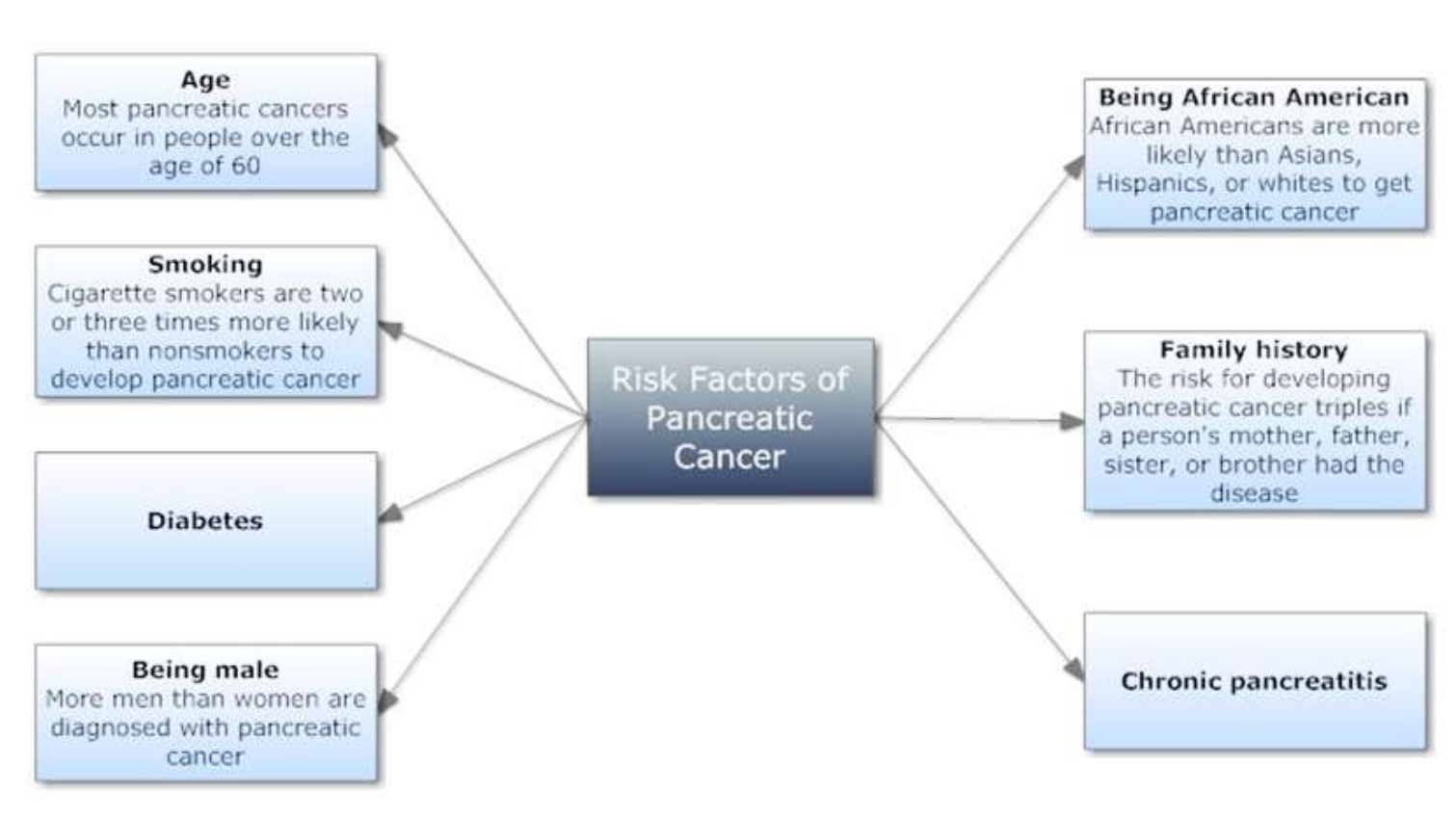
- **Worldwide - the 12th most common cancer with 338,000 new cases diagnosed in 2012.**

- **United States - estimated 48,960 new cases and 40,560 new deaths in 2015, 4th leading cause of cancer deaths.**

- **5-year survival rate - 4.1%**
- **Highest 1-year and 5-year mortality rate**

http://www.wcrf.org/int/cancer-facts-figures/data-specific-cancers/pancreatic-cancer-statistics
Siegel, R.L., et al. (2015) Cancer statistics, 2015. CA Cancer J Clin, 65, 5-29.

Risk factors



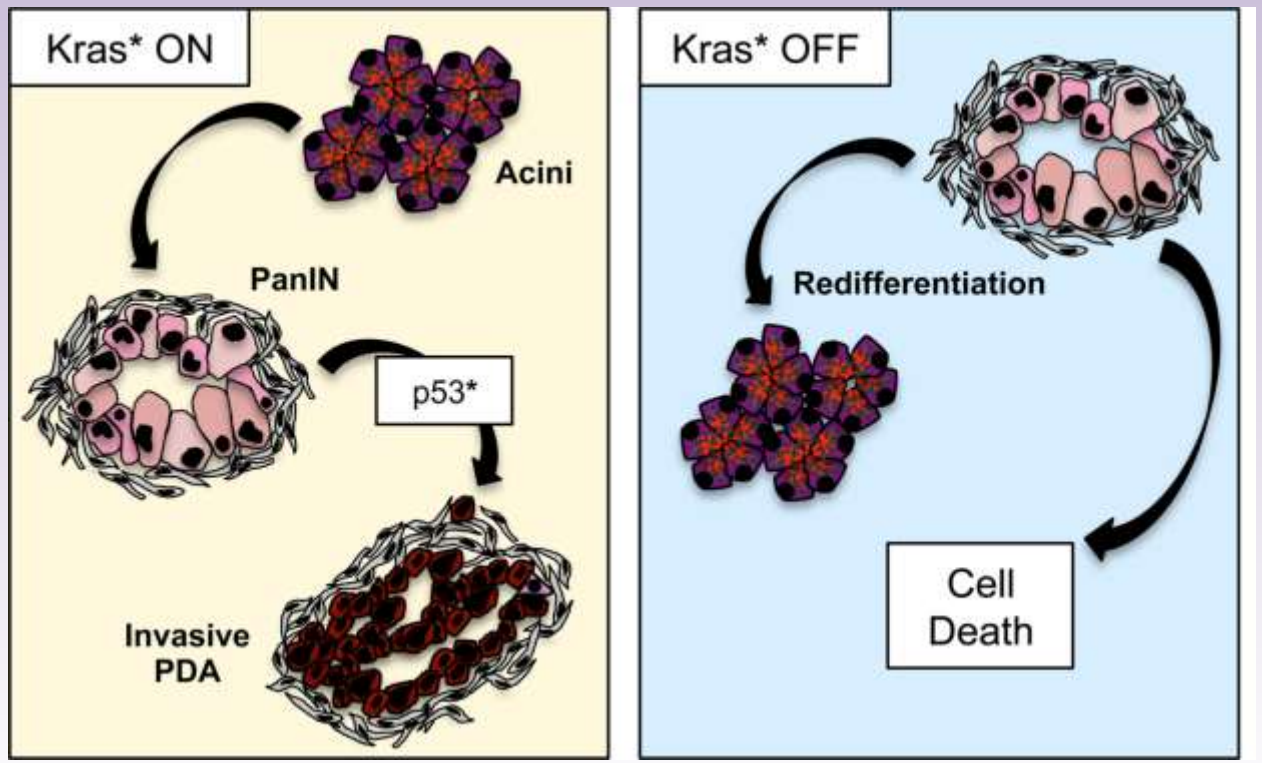
- **Diet – High intake of red meat and processed meat, and low intake of Fruits and Vegetables**

http://www.vwmin.org/risk-factors-tobacco-national-cancer-institute.html

Wiseman, M. (2008) The second World Cancer Research Fund/American Institute for Cancer Research expert report. Food, nutrition, physical activity, and the prevention of cancer: a global perspective. Proc Nutr Soc, 67, 253-6.

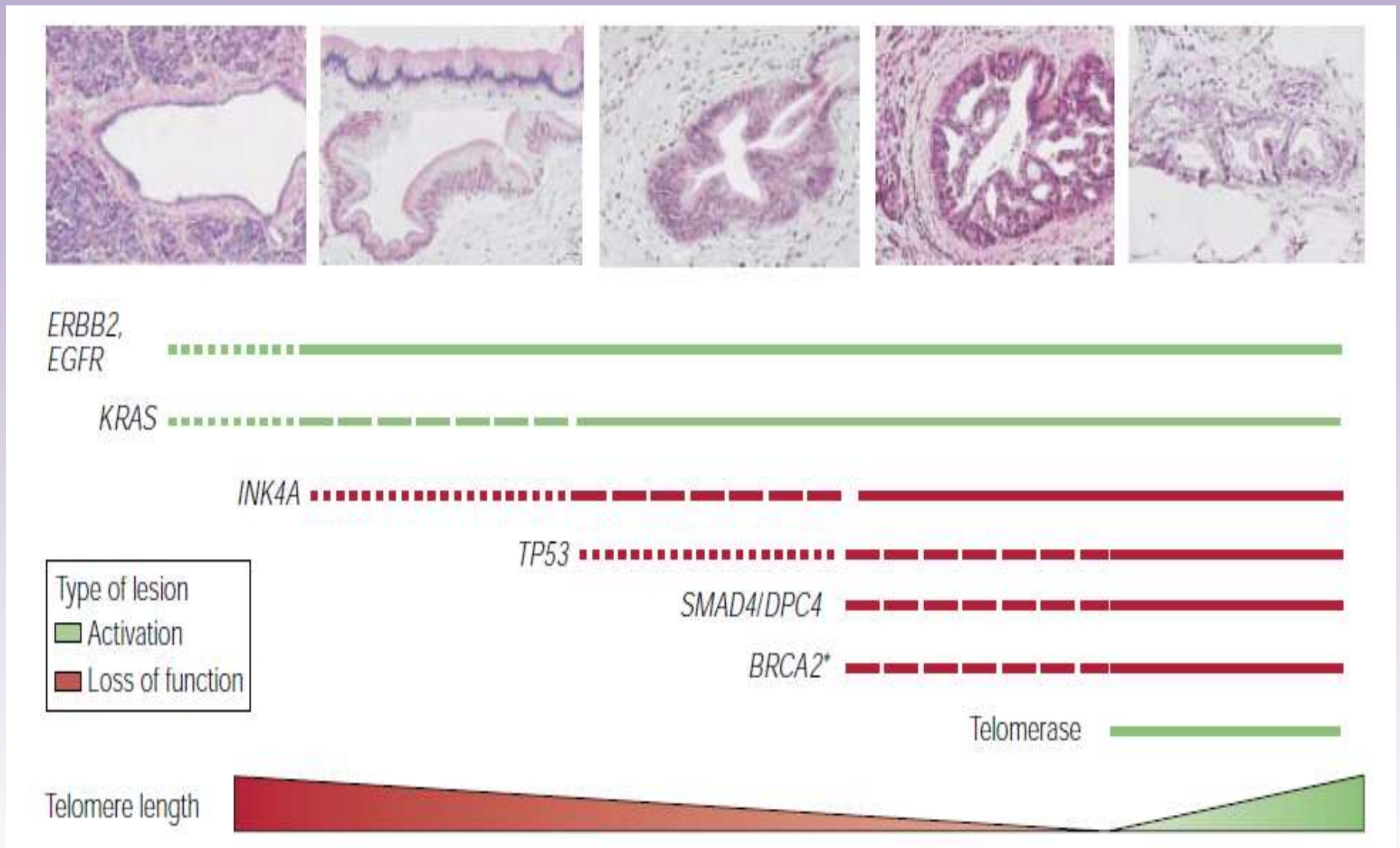
Molecular genetics: PDAC

- Oncogene *K-ras* - Activation >90%
- *Tumor suppressor gene Trp53*- Loss-of-Function 50-70%



Meredith A. Collins and Marina Pasca di Magliano. Kras as a key oncogene and therapeutic target in pancreatic cancer

Pathology of PDAC



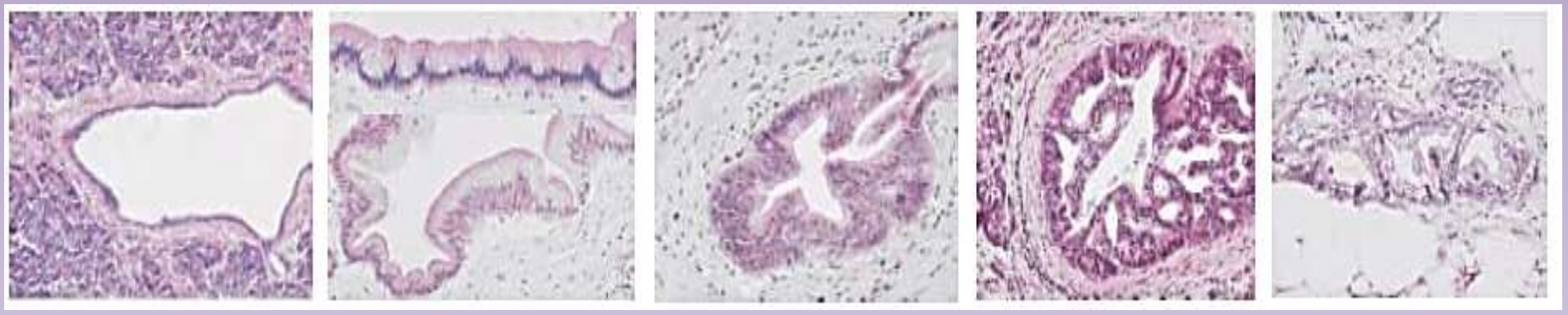
Nabeel Bardeesy and Ronald A. DePinho. Pancreatic cancer biology And genetics

Genetic models

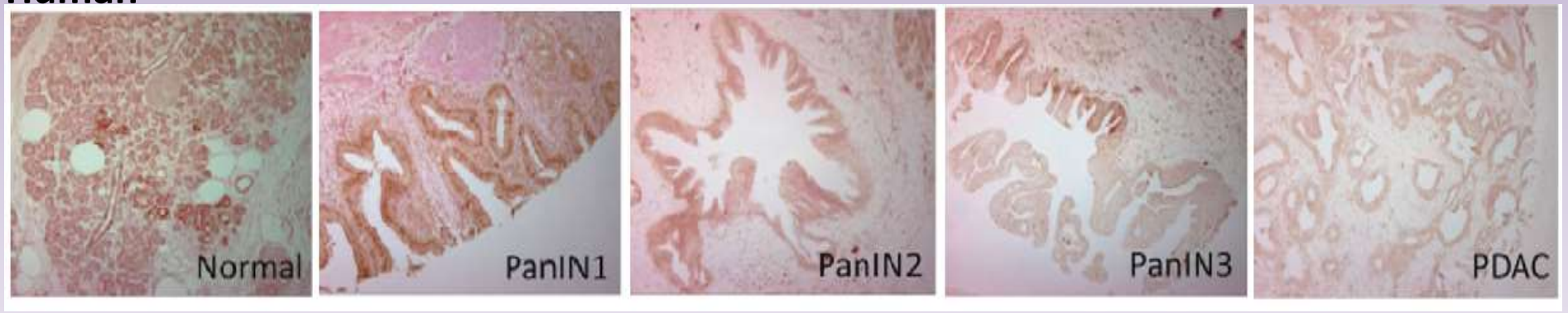
Genotype	Time of tumor development (mo)	Survival (mo)
PDX-1-Cre; LSL-KrasG12D	6	16
PDX-1-Cre; LSL-KrasG12D; LSL-Trp53R172H/-	2-3	5-6

Christoph Benedikt Westphalen, Kenneth P. Olive. Genetically Engineered Mouse Models of Pancreatic Cancer
Marta Herreros-Villanueva, Elizabeth Hijona, Angel Cosme, Luis Bujanda. Mouse models of pancreatic cancer

KPC mice



Human



Elongated cells
Papillary architecture

Nuclear abnormalities

Severe nuclear atypia
Mitosis
Budding into lumen

Invasive growth

PanIN: pancreatic intraepithelial neoplasia
PDAC: pancreatic ductal adenocarcinoma

Xidi Ma, Kelly R. Pekala, Christine P. Petersen, and Maureen A. Gannon. The Role of HNF6 on Pancreatic Cancer

5% BRBs prolong survival of *K*-ras$^{LSL.G12D/+}$, *p*53$^{LSL.R172H/+}$, Pdx*Cre* mice

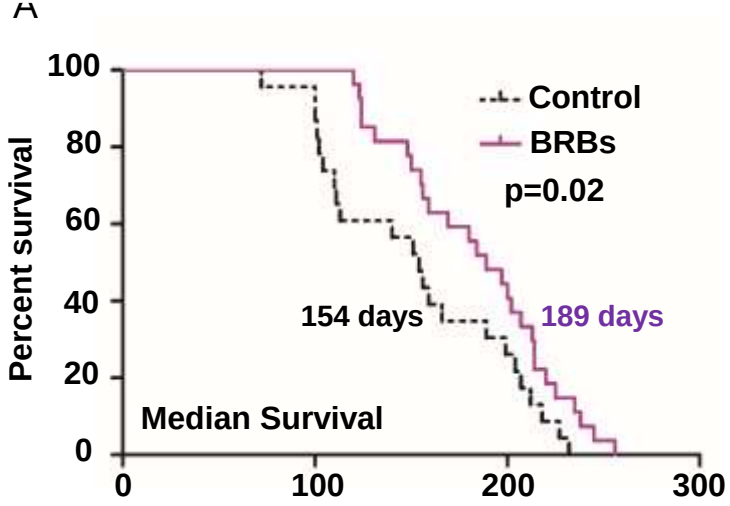
4 wks old

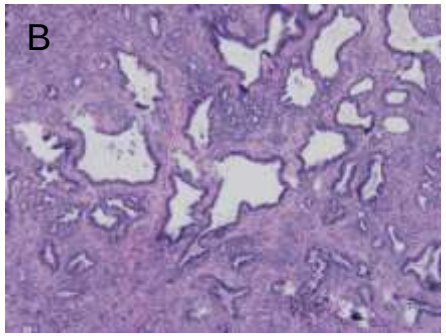


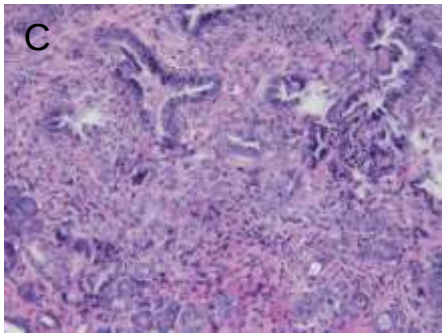


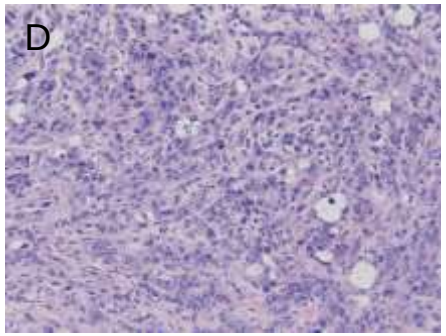
Control or 5%BRB

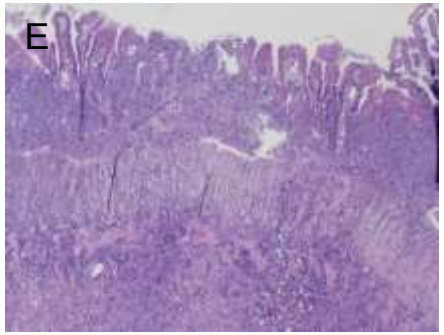
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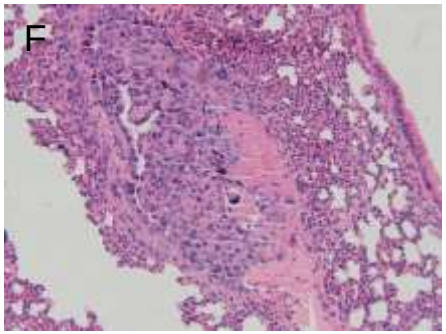


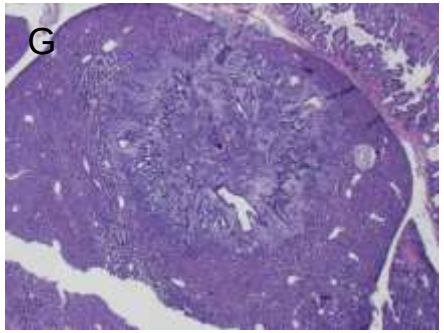




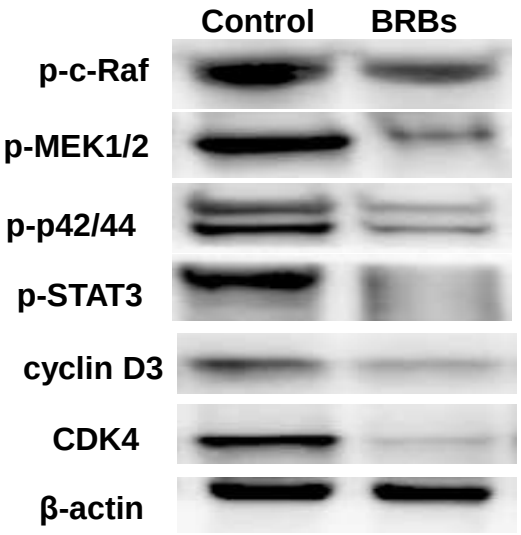


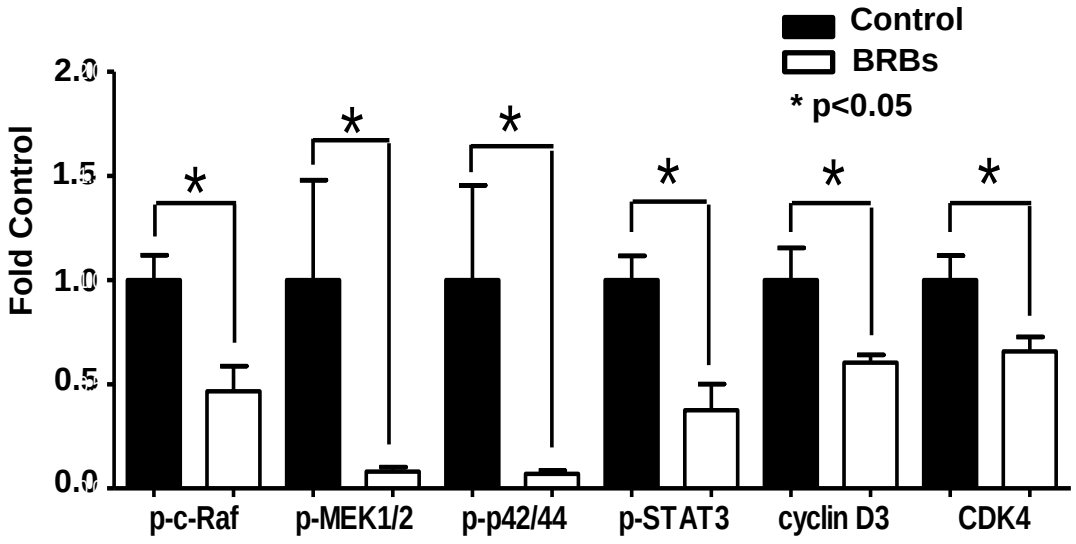


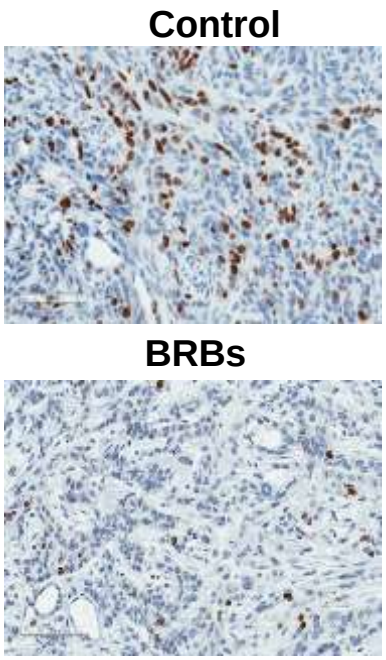


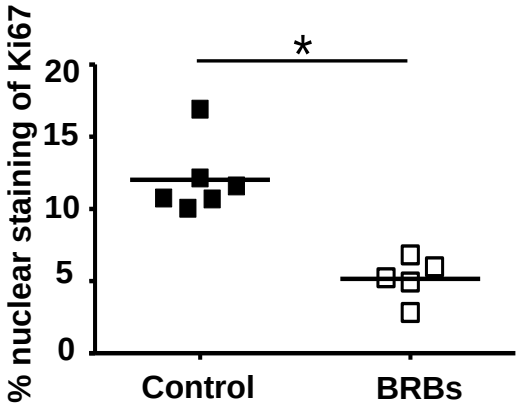


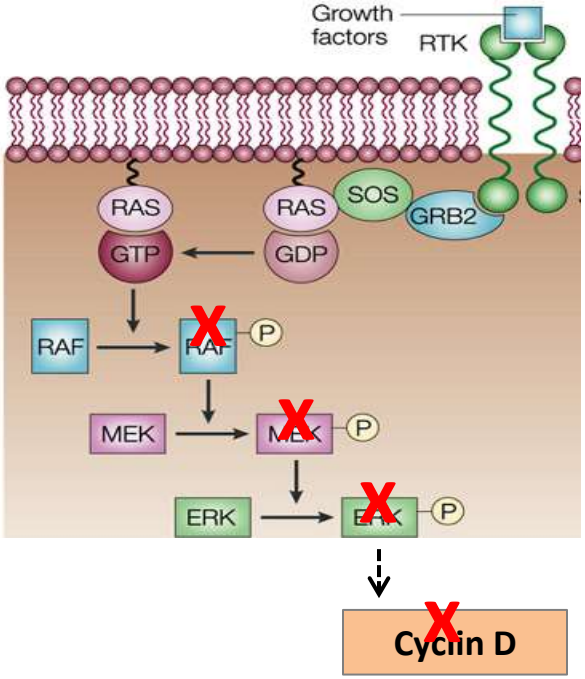
5% BRBs prolong survival of *K*-ras$^{LSL.G12D/+}$, *p*53$^{LSL.R172H/+}$, Pdx*Cre* mice



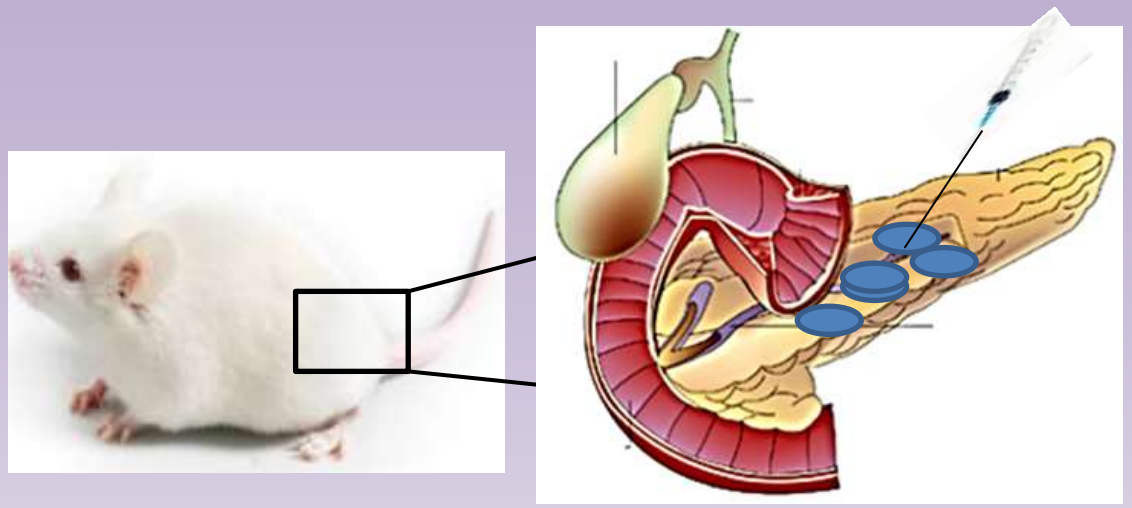








Orthotopic xenograft



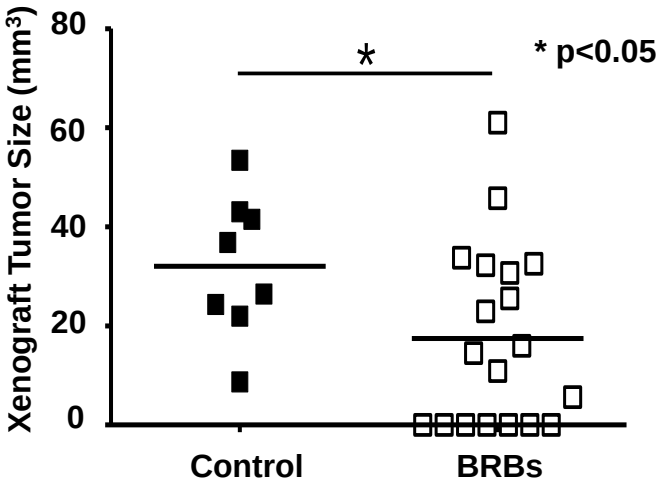
- **Injection**
  Luciferase-transfected Panc-1 cells
- **Imaging** - confirming Panc-1 tumor establishment in the pancreas
- **Imaging**
- **Euthanization**

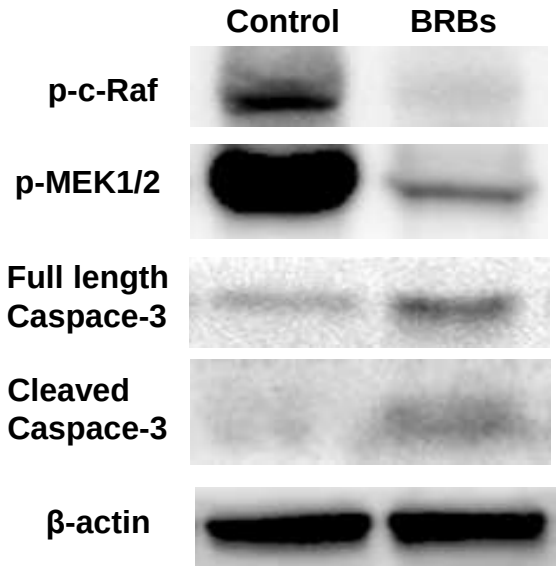
4 weeks

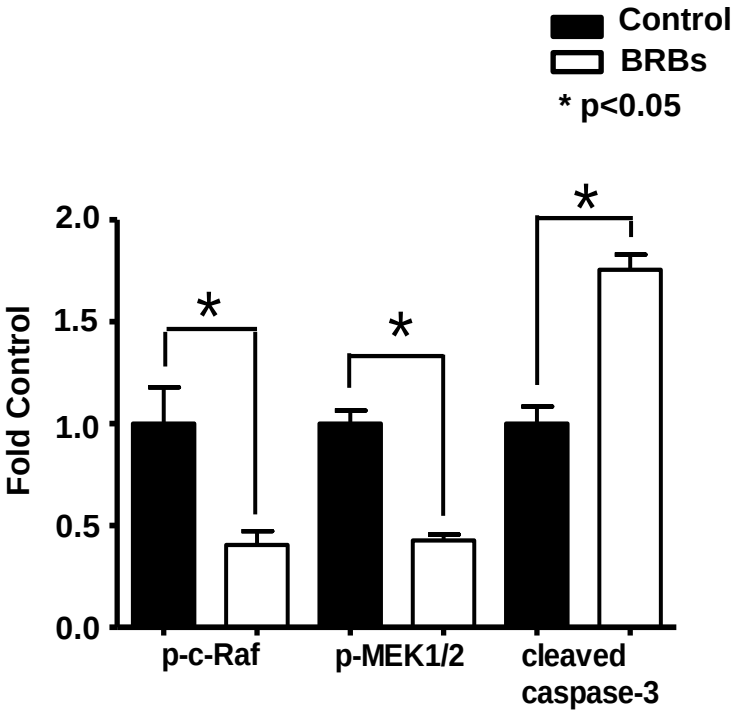
6 weeks

Control or 5% BRB diet

5% BRBs suppress Panc-1 tumor growth

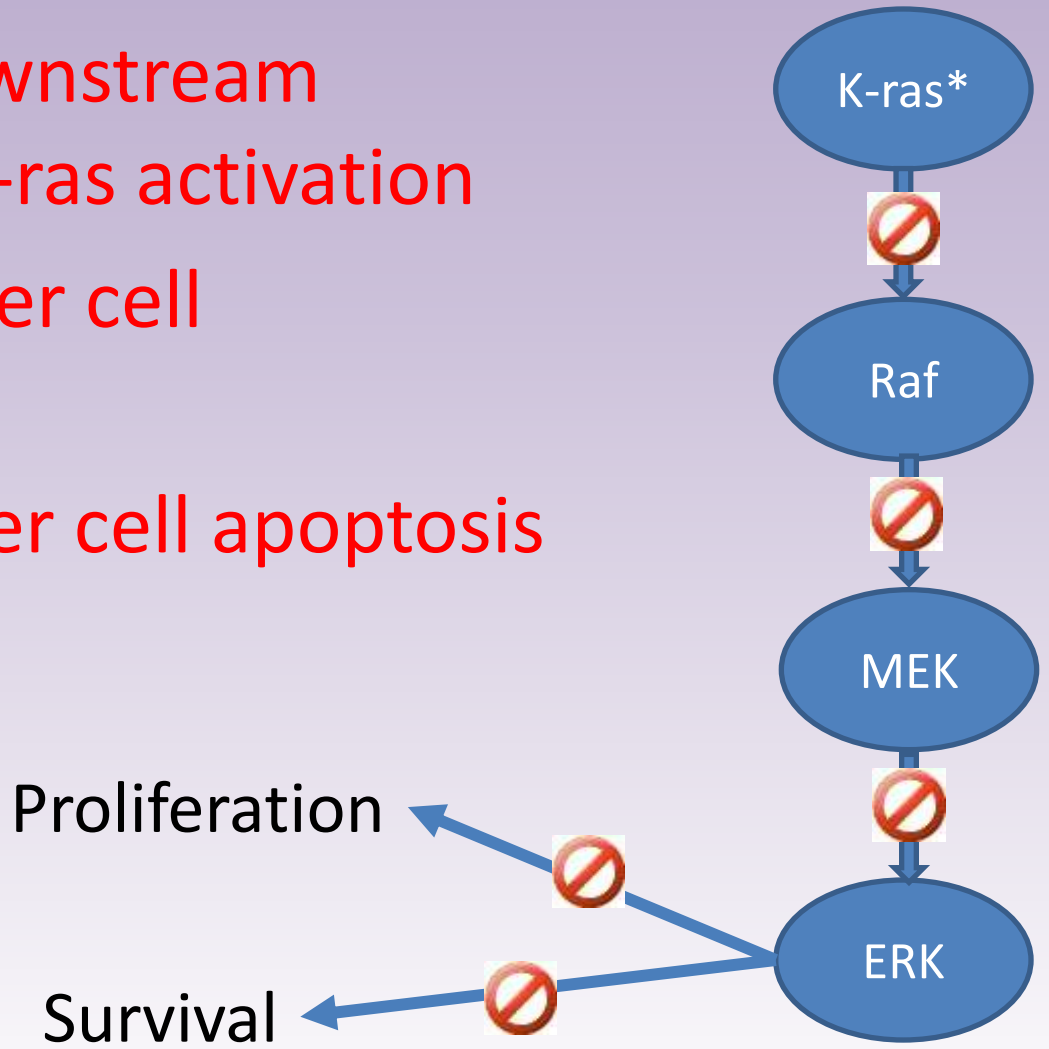






How do black raspberries protect against PDAC?

- Inhibit the downstream pathways of K-ras activation
- Suppress cancer cell proliferation
- Promote cancer cell apoptosis



Acknowledgement

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