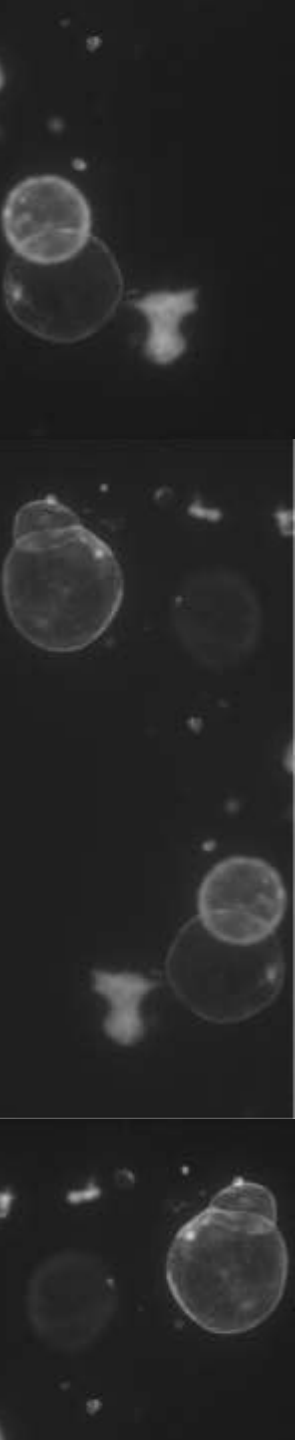


Exploring the Guanine Nucleotide Binding Protein α-sununit(GNAS) mutation in pancreatic cancer

Revenco Iulia

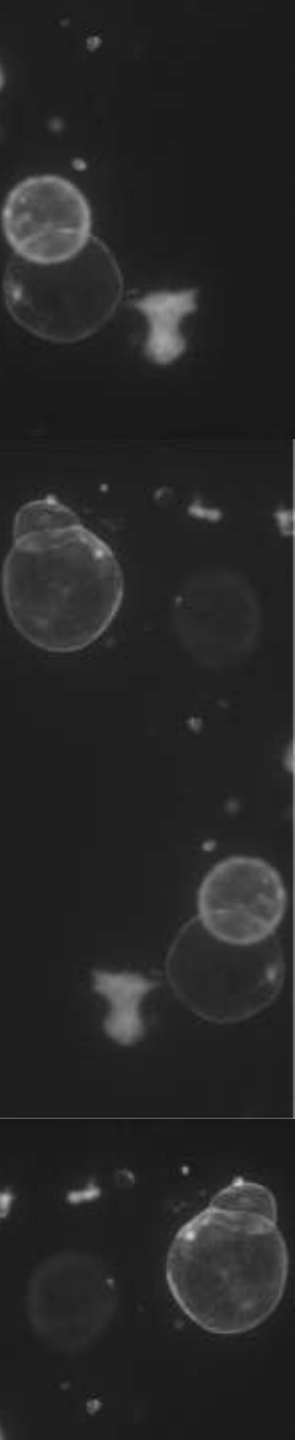
MSc in Oncology

Université Claude Bernard Lyon 1

France

IFPM OHRID

28th July 2018



Latest research experiences

- Scientific context and the challenge
- Methodes
- Conclusion

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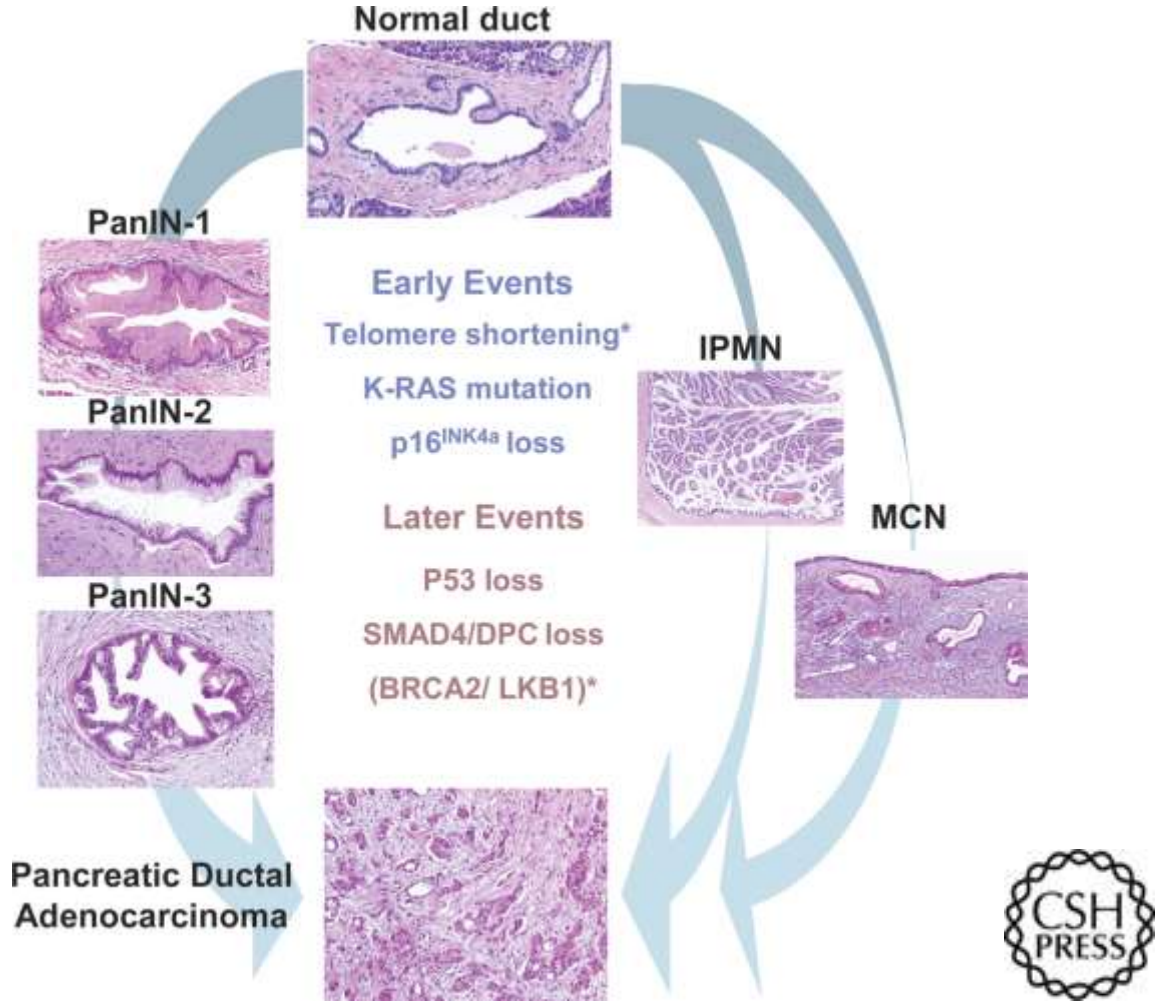
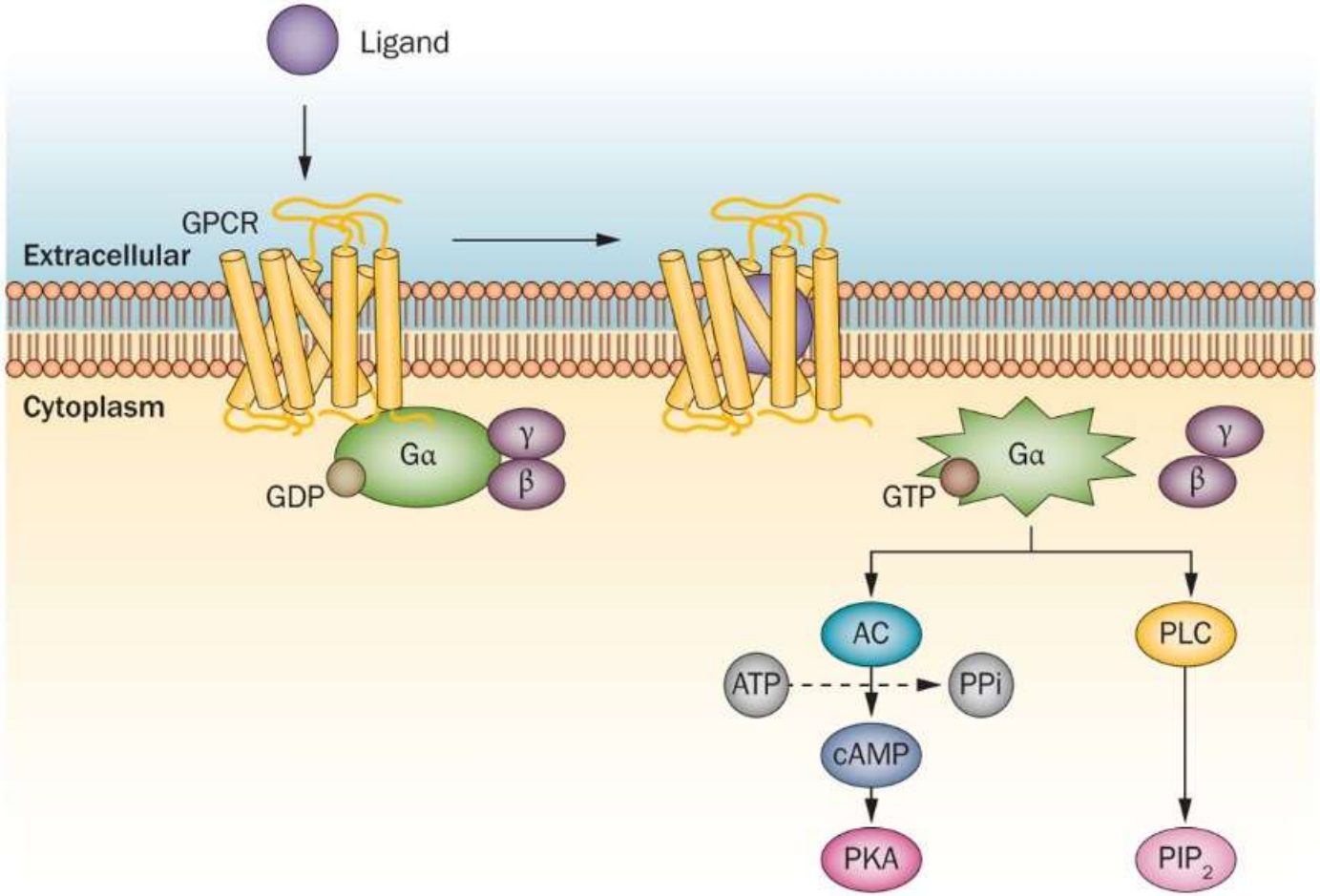
Exploring the Guanine Nucleotide Binding Protein α-sununit(GNAS) mutation in pancreatic cancer

- Is the 5th leading cause of death in Europe (IARC)
- In less than 1% the overall survival rate will exceed 5 years
- Age at diagnose between 65-74 year old



Aram F. Hezel et al. Genes Dev. 2006;20:1218-1249

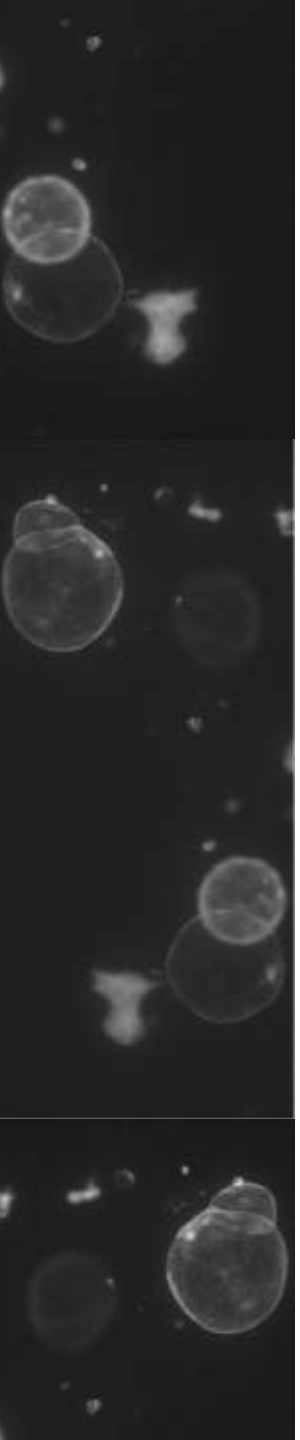
Guanine Nucleotide Binding Protein α-sununit(GNAS) is a critical component of the GPCR signaling



Nat. Rev. Rheumatol. doi:10.1038/nrrheum.2014.62

Normal functions:

- Gluconeogenesis in liver
- Mitochondrial receptor

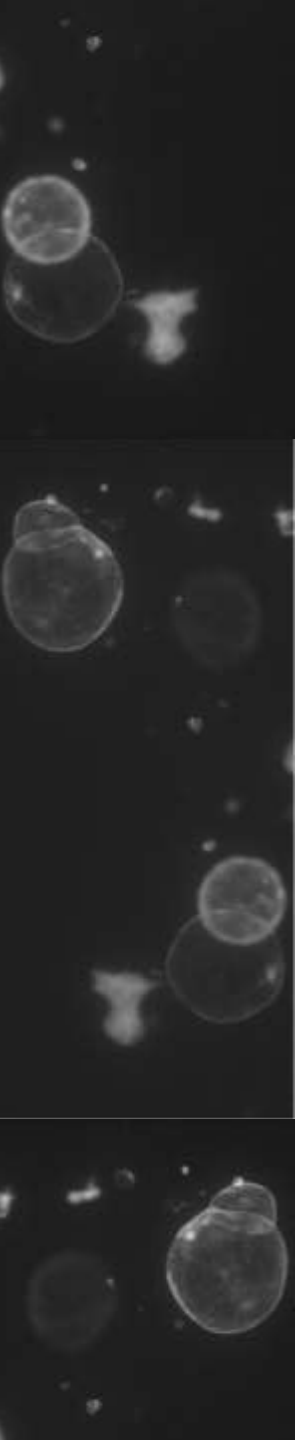


Guanine Nucleotide Binding Protein α-sununit(GNAS) and Cancer

Gαs is a tumor suppressor in Sonic hedgehog-driven medulloblastoma. **Nat Med. 2014 Sep;20(9):1035-42.**

Inactivation of Gαs in skin stem cells initiates basal-cell carcinogenesis. **Nat Cell Biol. 2015 Jun;17(6):793-803**

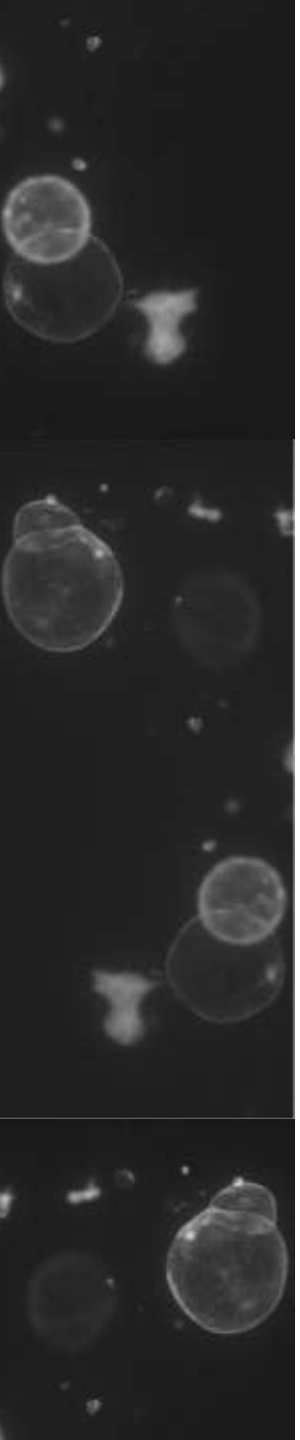
"GNASR201H and KrasG12D cooperate to promote murine pancreatic tumorigenesis recapitulating human intraductal papillary mucinous neoplasm" **K Taki & al. Oncogene 2015**



Aims of project

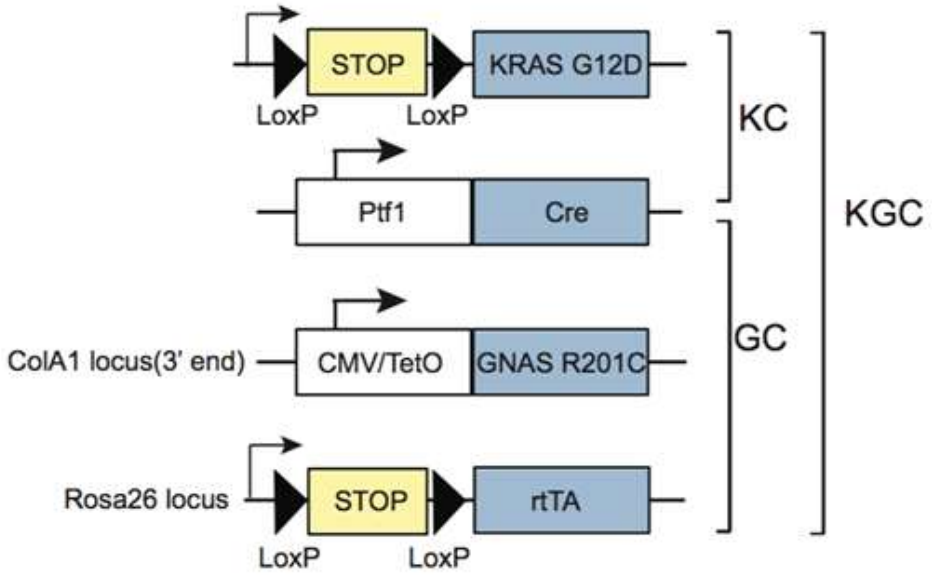
- GNAS mutation influence the Intraductal Pappilary Mucinous Neoplasm tumorigenicity?

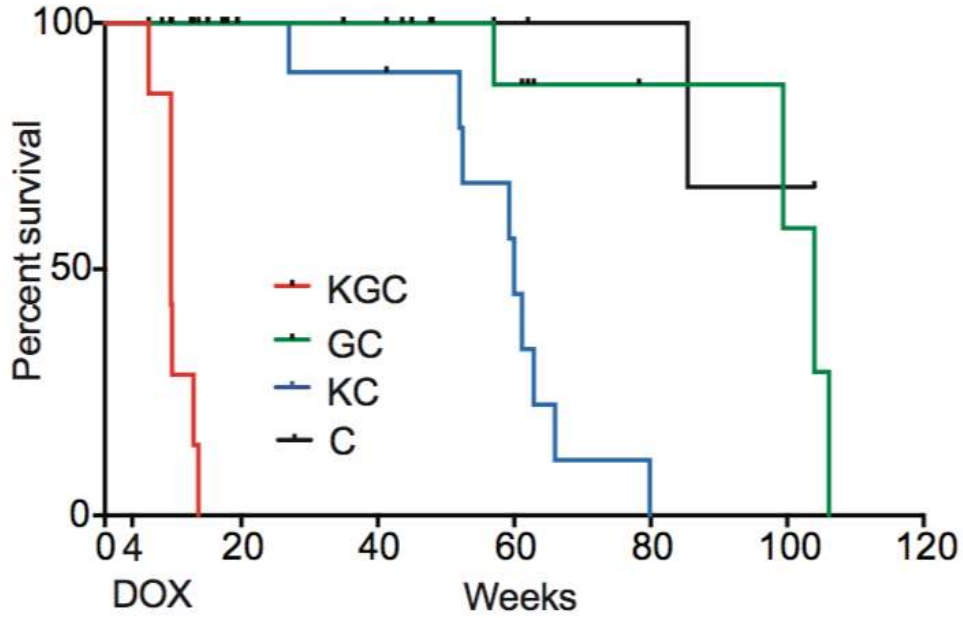
- Characterize the GNAS downstream effectors, what is their role ?



Pancreatic cancer mouse model

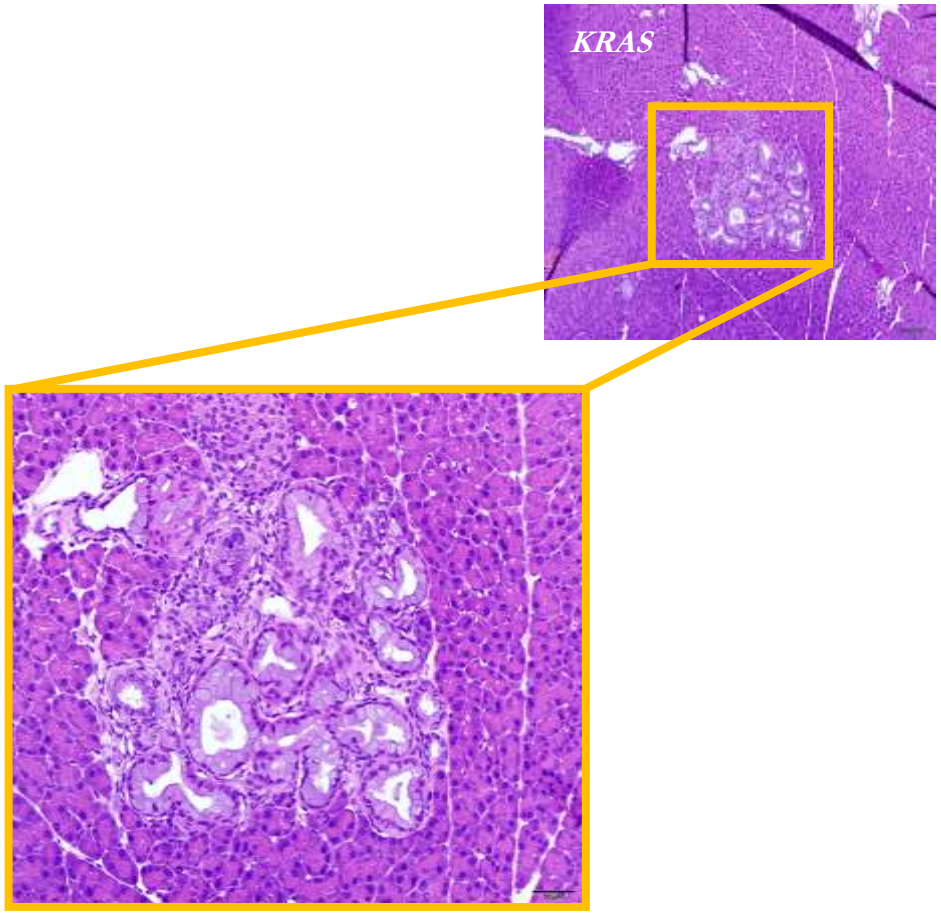
Intraductal Pappilary Mucinous Neoplasm mouse model

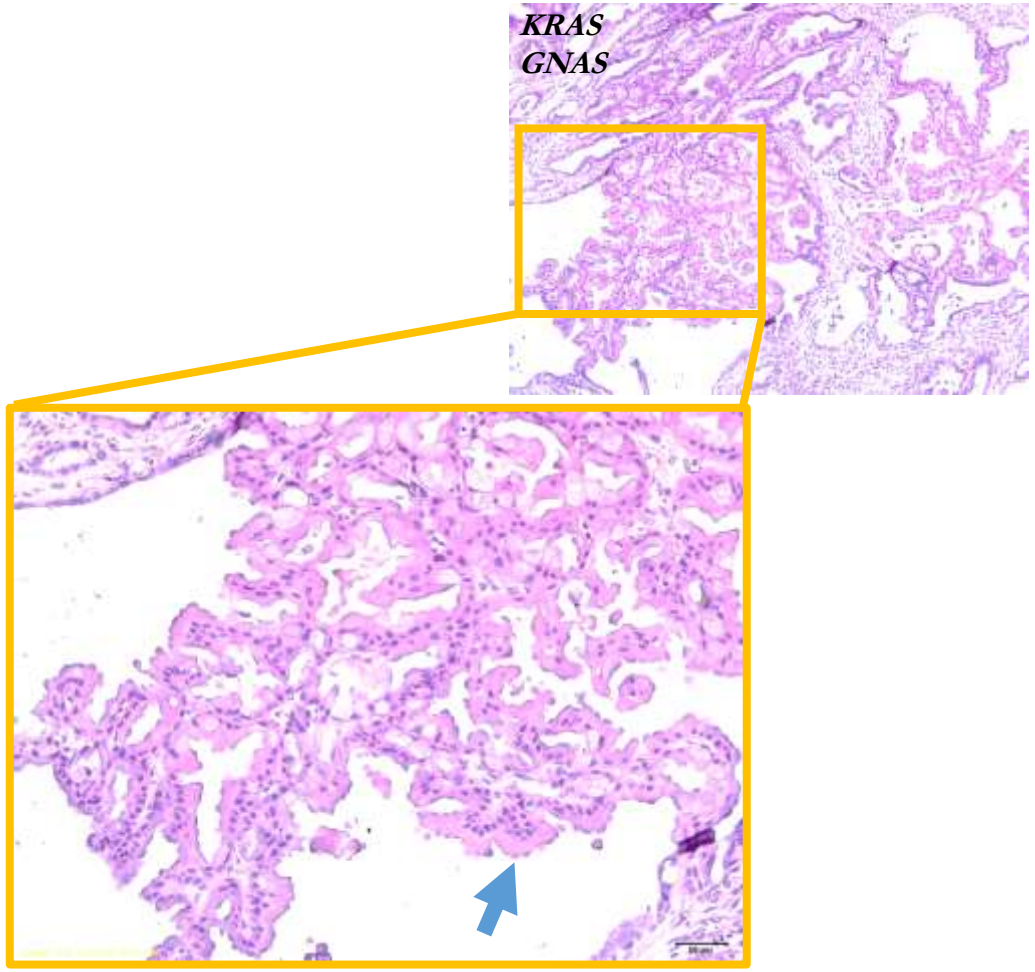




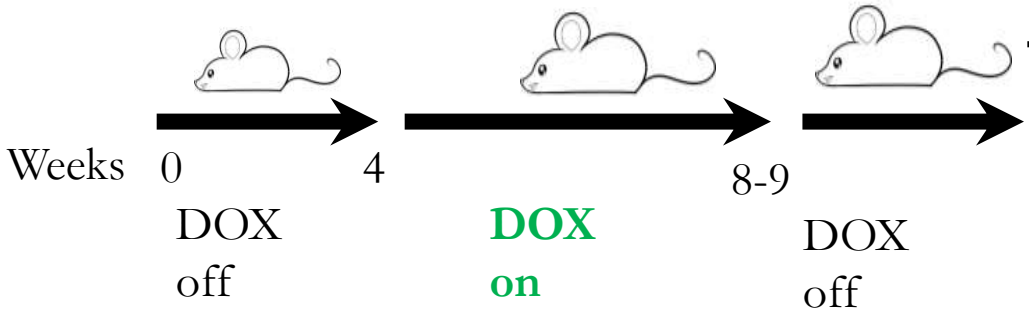
Oncogenic cooperation between mutant KRAS and mutant GNAS

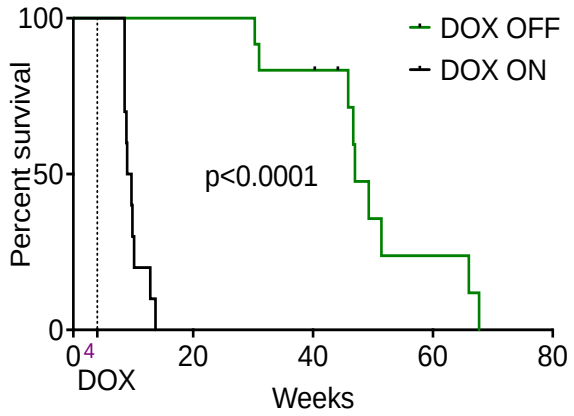
Intraductal Pappilary Mucinous Neoplasm mouse model

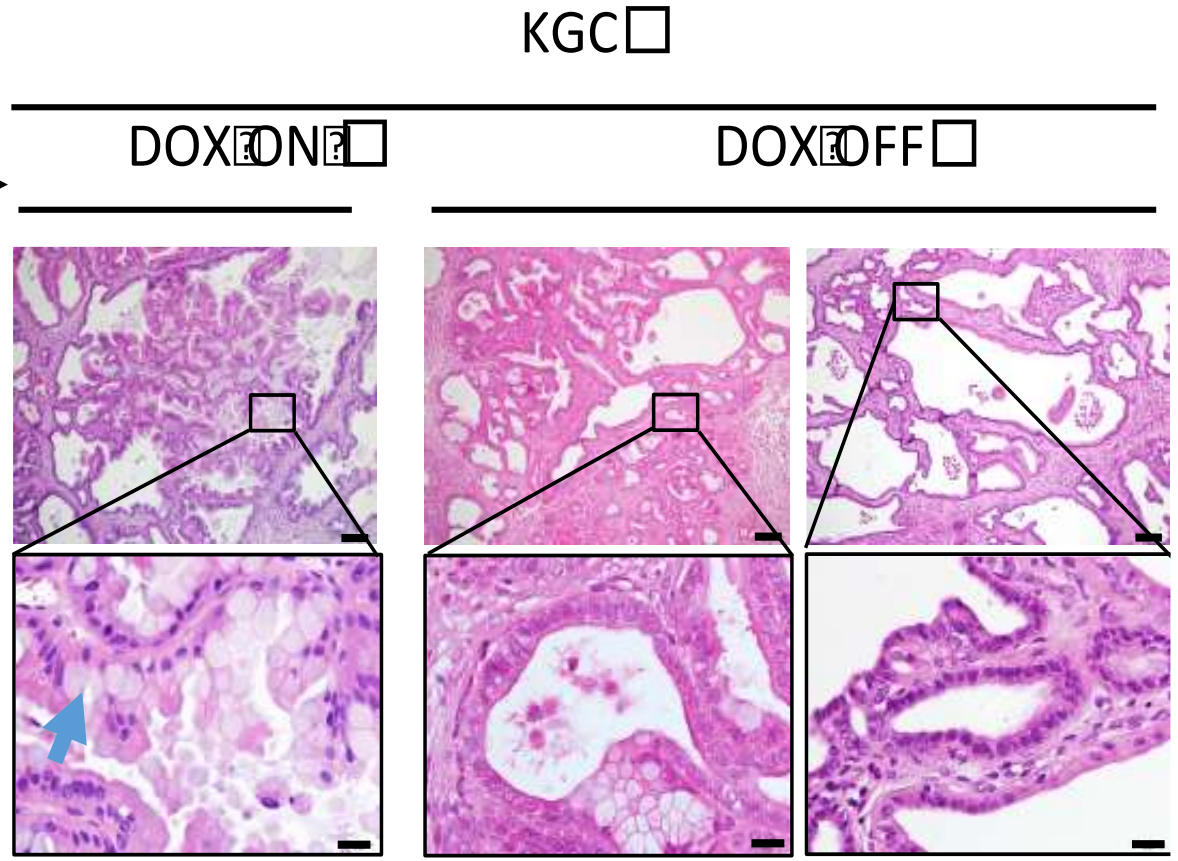




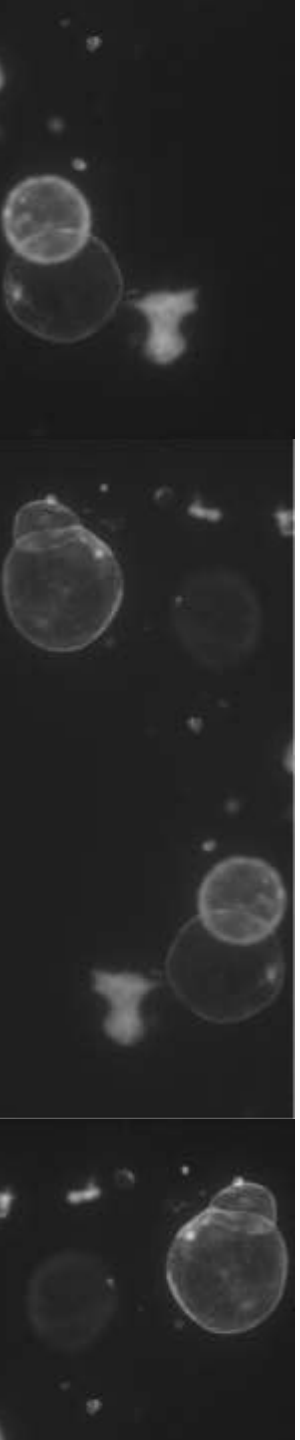
Deactivation of mutant GNAS expression inhibits the proliferation and progression of tumors





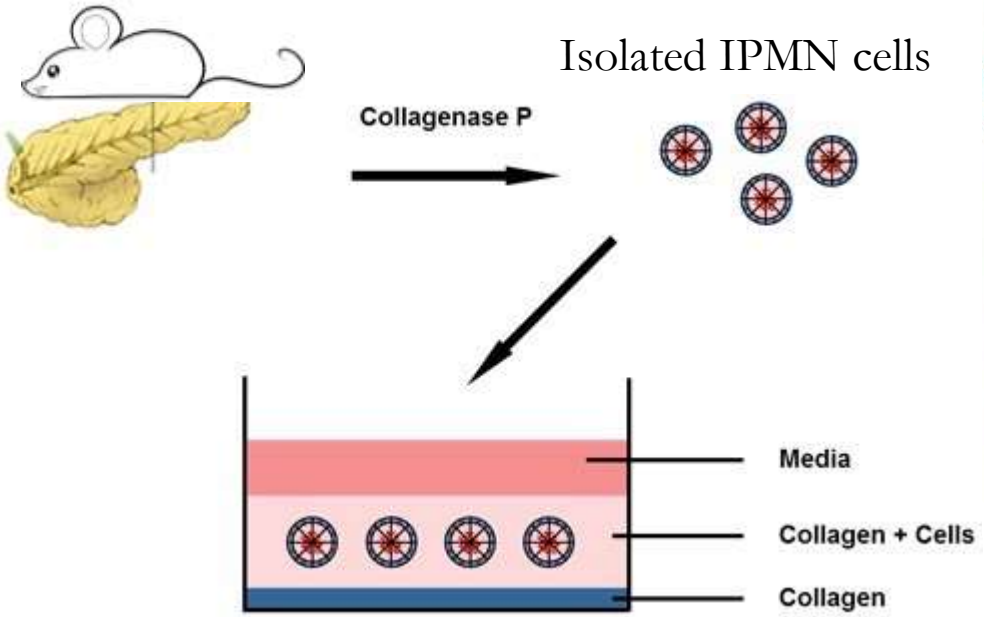


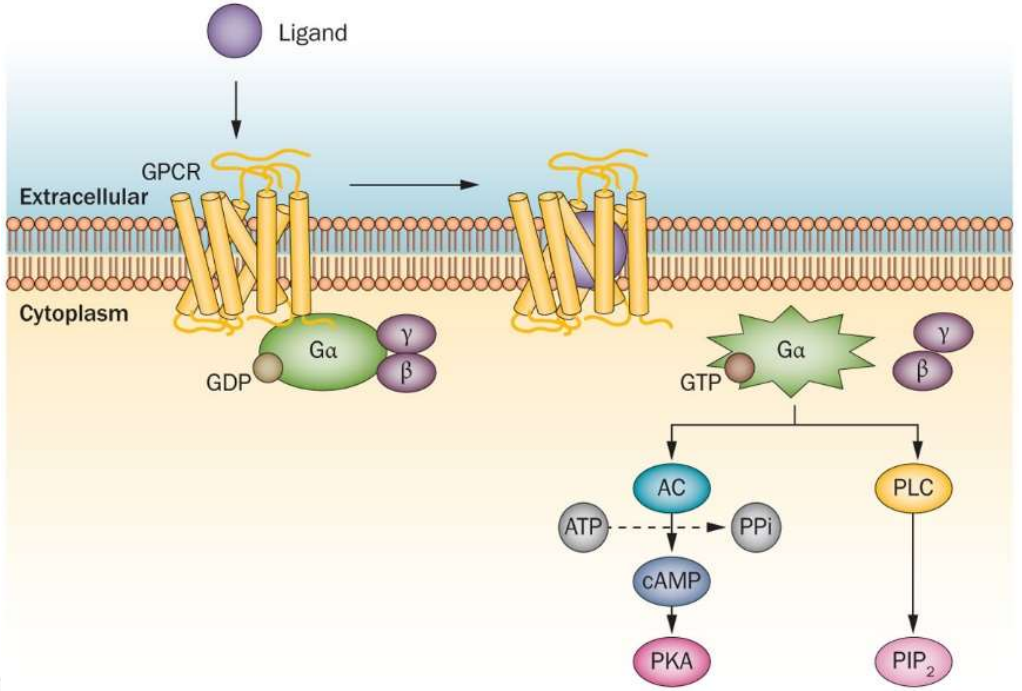
GNAS-R201C mutation is necessary for tumor maintenance in KRAS-G12D pancreatic murine tissu



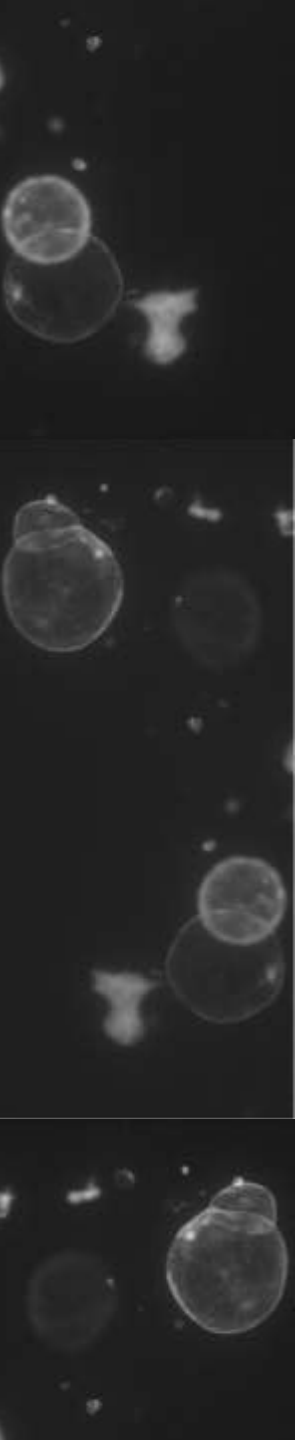
3D *In vitro* model to decipher the molecular pathway GNAS

KGC model



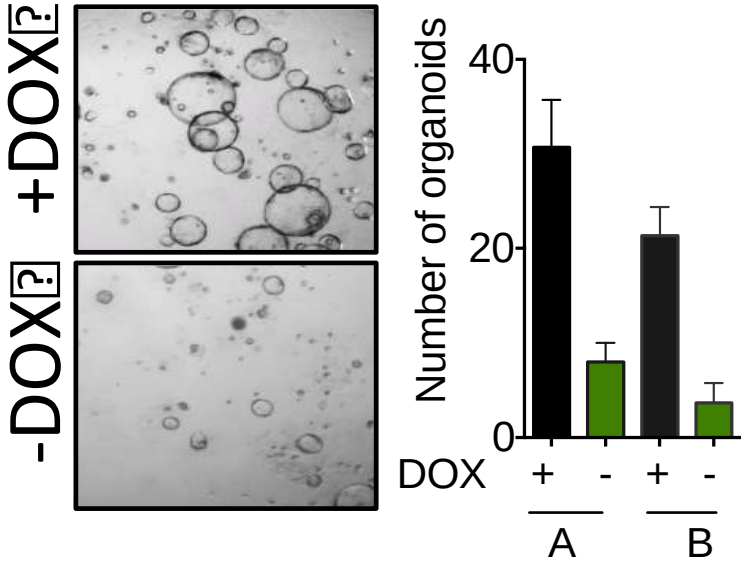


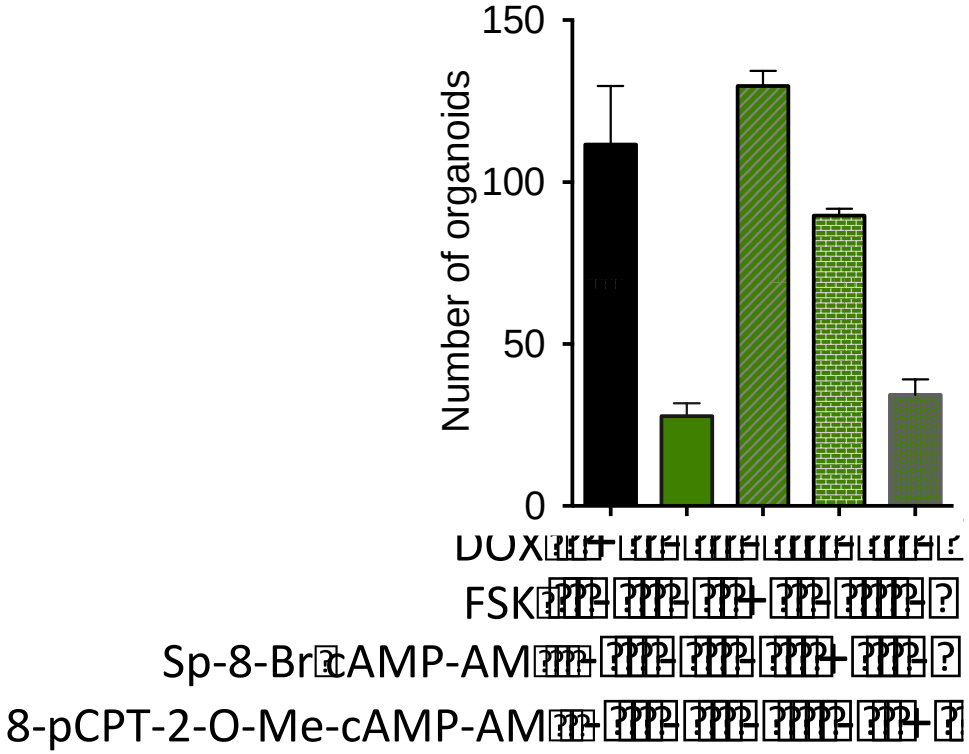
Nat. Rev. Rheumatol. doi:10.1038/nrrheum.2014.62

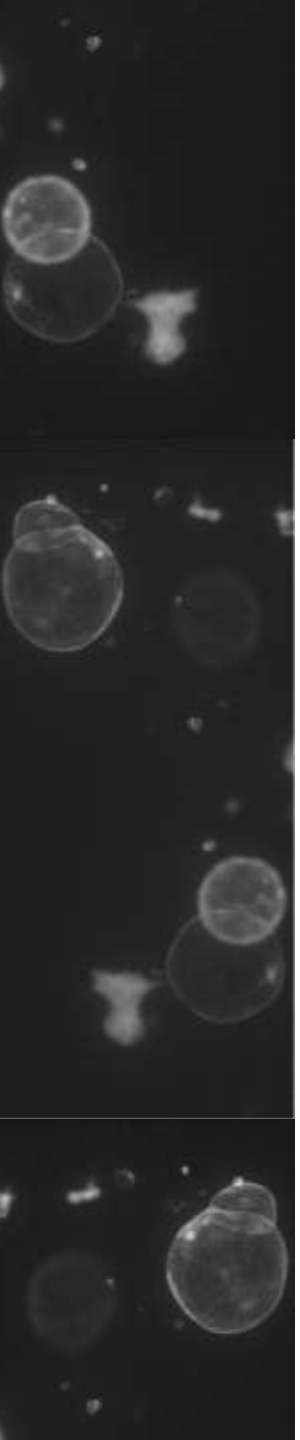


cAMP/PKA signaling is involved in mutant GNAS driven organoid formation

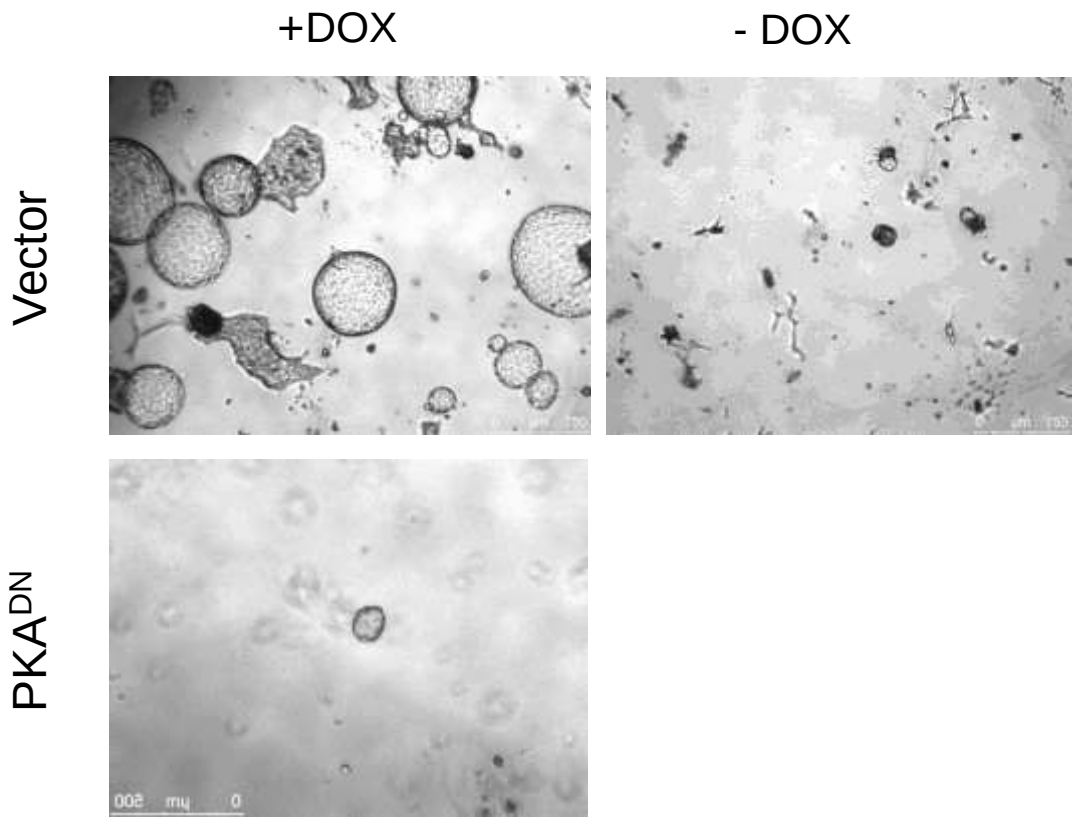
- Forskolin – Adenylate Cyclase Agonist
- Sp 8 Br – cAMP analogue
- 8pCPT – EPAC specific agonist

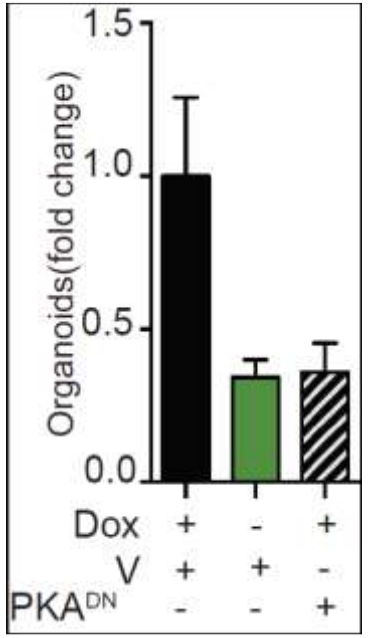




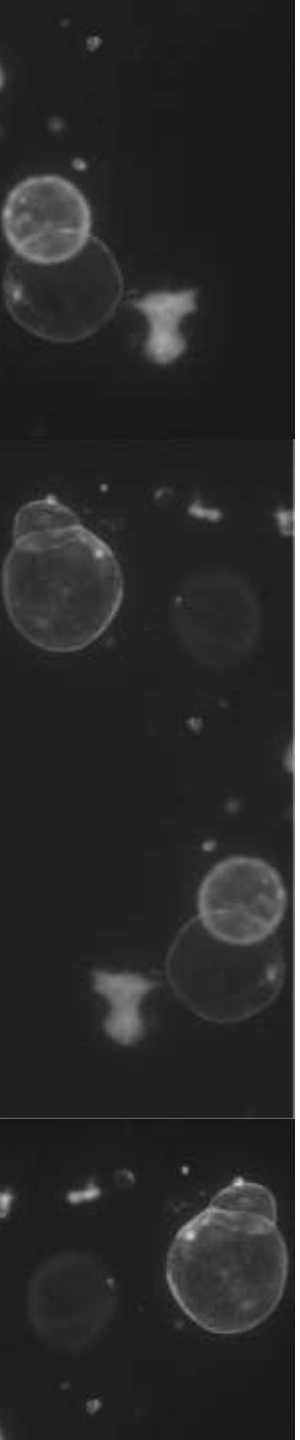


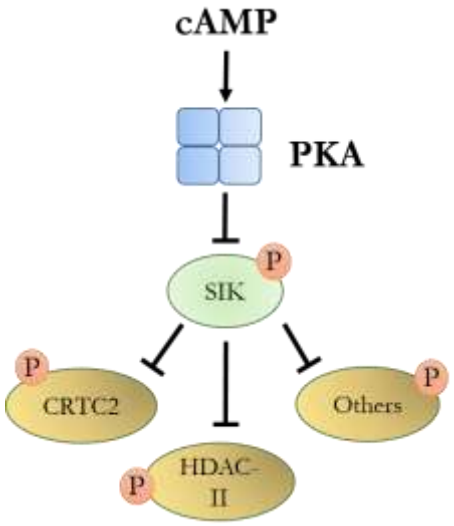
cAMP/PKA signaling is required for mutant GNAS driven organoid formation

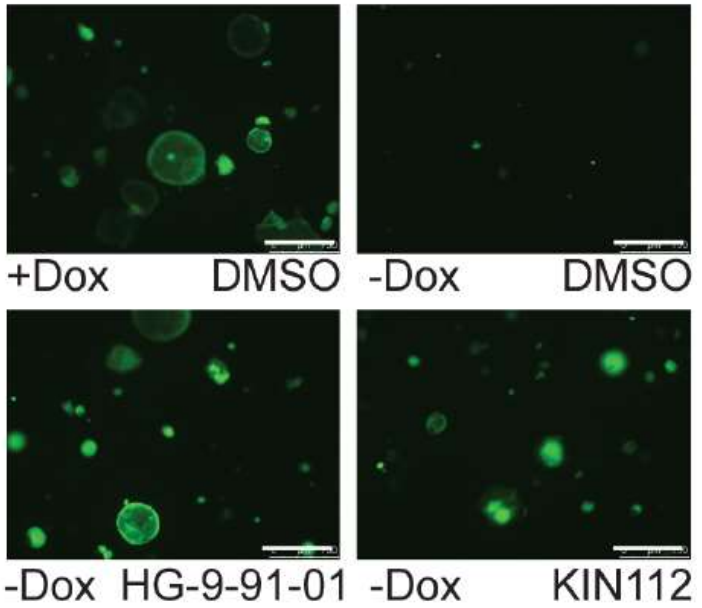


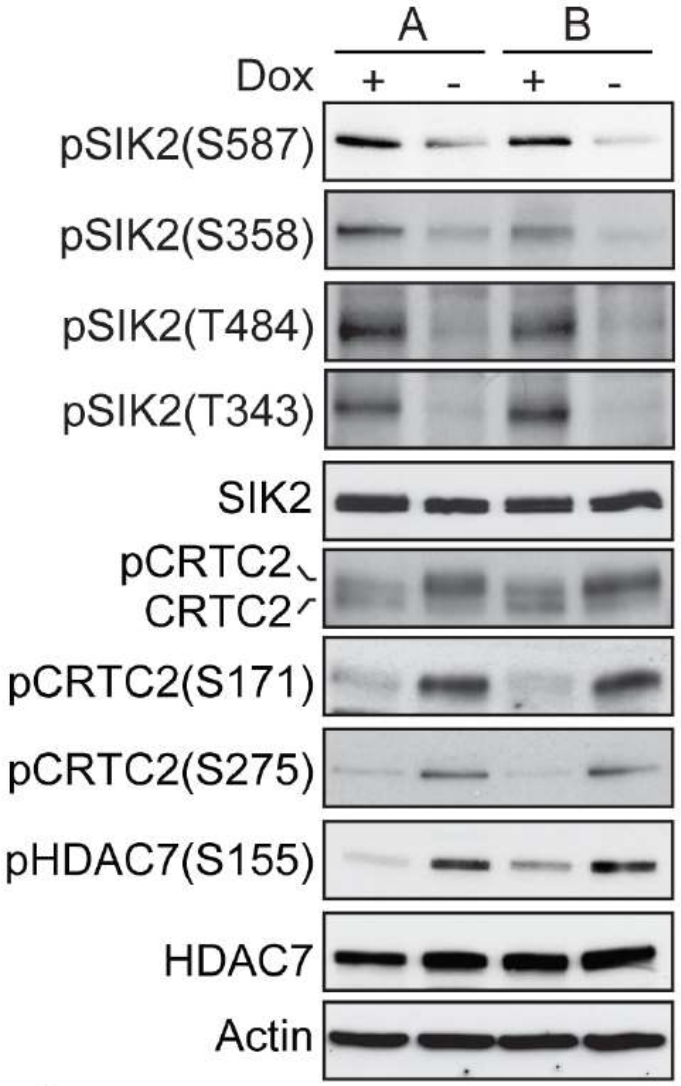


cAMP/PKA axis regulates organoid growth via Salt Induced Kinase (SIK) in IPMN



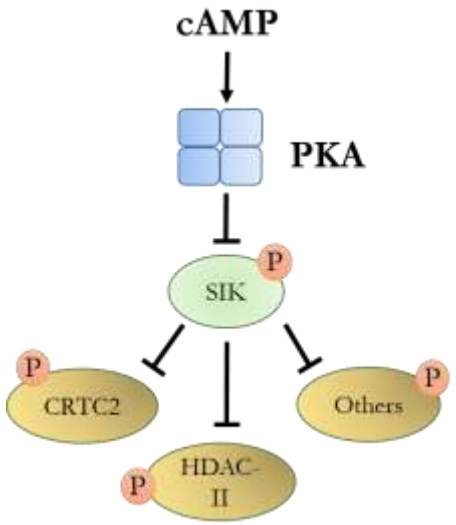


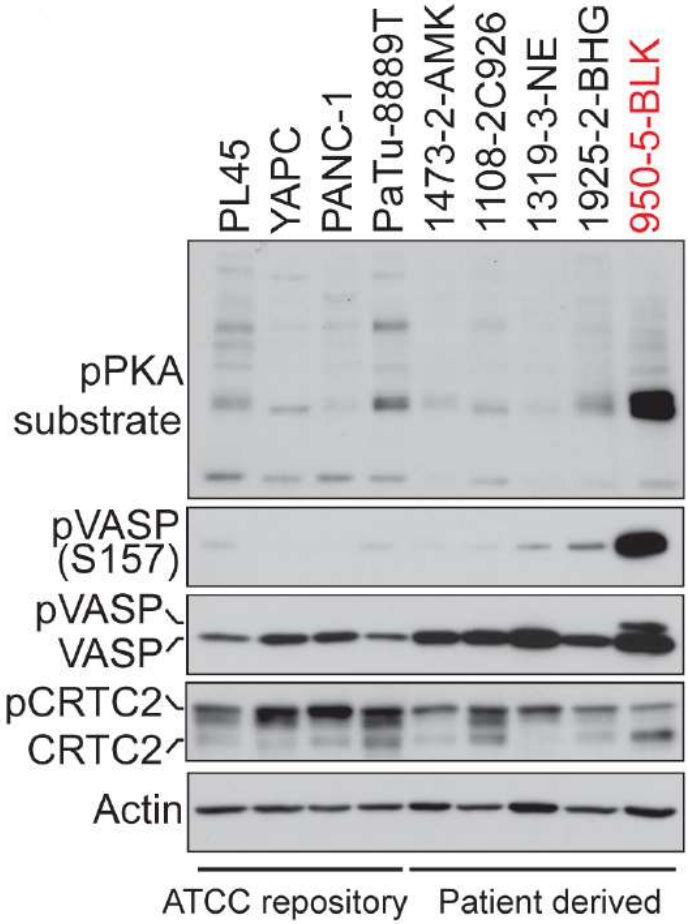


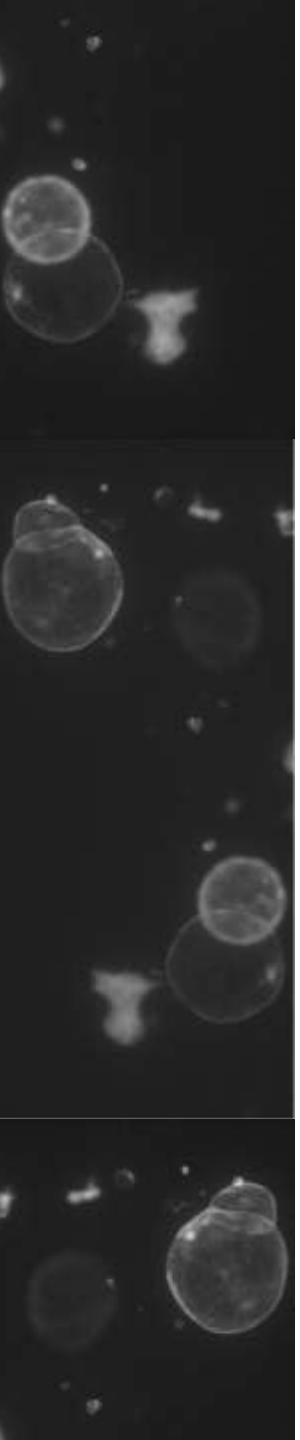


HG-9-91-01 & **KIN112** = pan-SIK inhibitors

cAMP/PKA axis regulates tumorigenic activity via Salt Induced Kinase (SIK) in IPMN







Conclusion

- Mutant GNAS induces IPMN progression and maintenance
- PKA plays an important role in the mutant GNAS driven tumor devellopement
- This pathway introduces consequent metabolic shift

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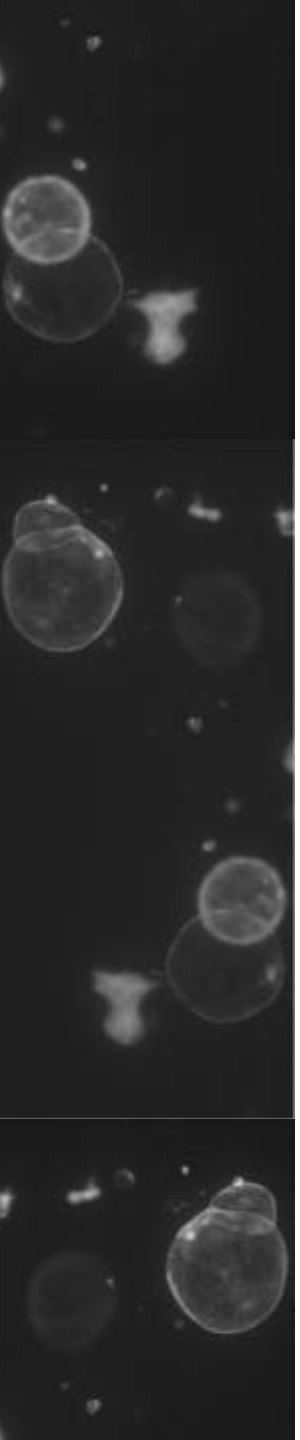

Thank you!

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