

Exportin 7-Laden Exosomes Unveil Ste-20-like Kinase as a Translatable Therapeutic Target in Cholangiocarcinoma

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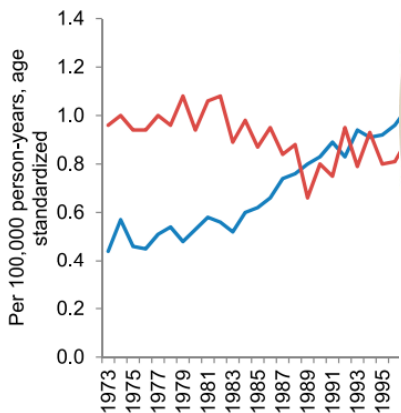
Disclosures

Aveo Pharmaceuticals – Cooperative Research And Development Agreement (CRADA)

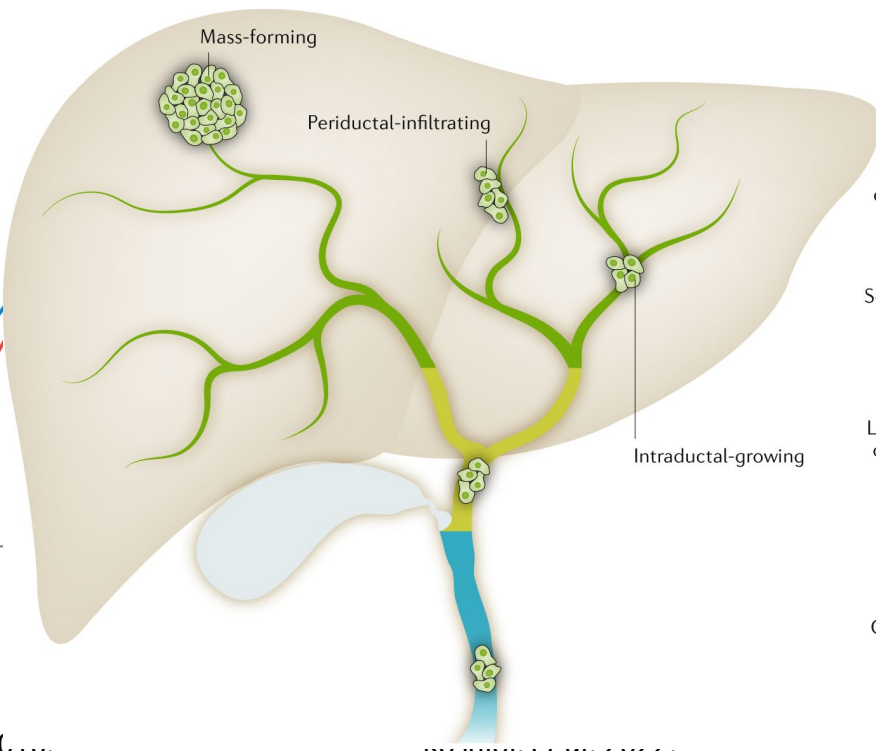
US Patent US2021/060902 Methods for treating bile duct cancers with Tivozanib

Cholangiocarcinoma is a Challenging Malignancy

↑ Incidence

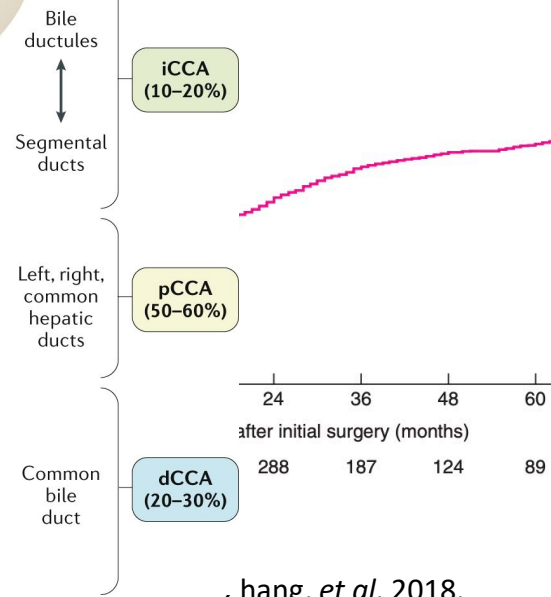


Saha, et al. 2020.



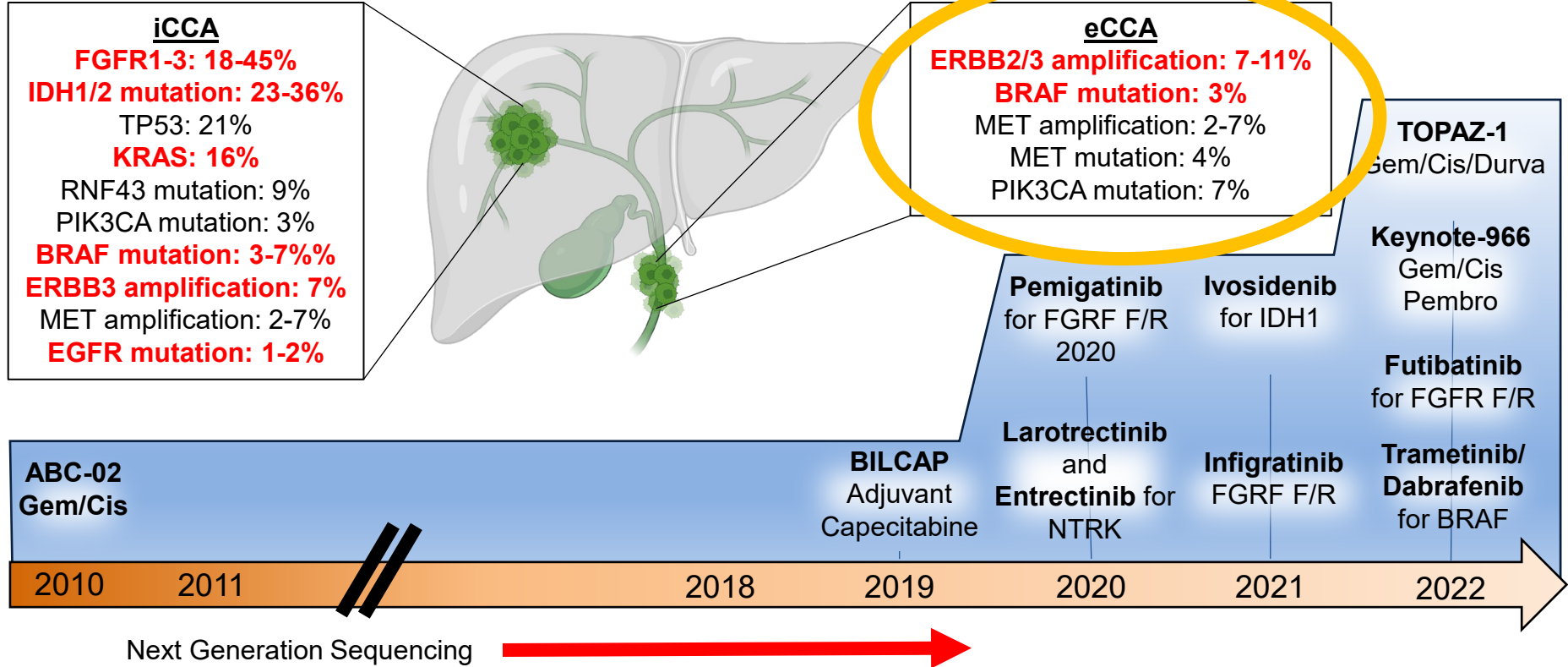
Reisman, et al. 2022.

Prognosis is the Norm

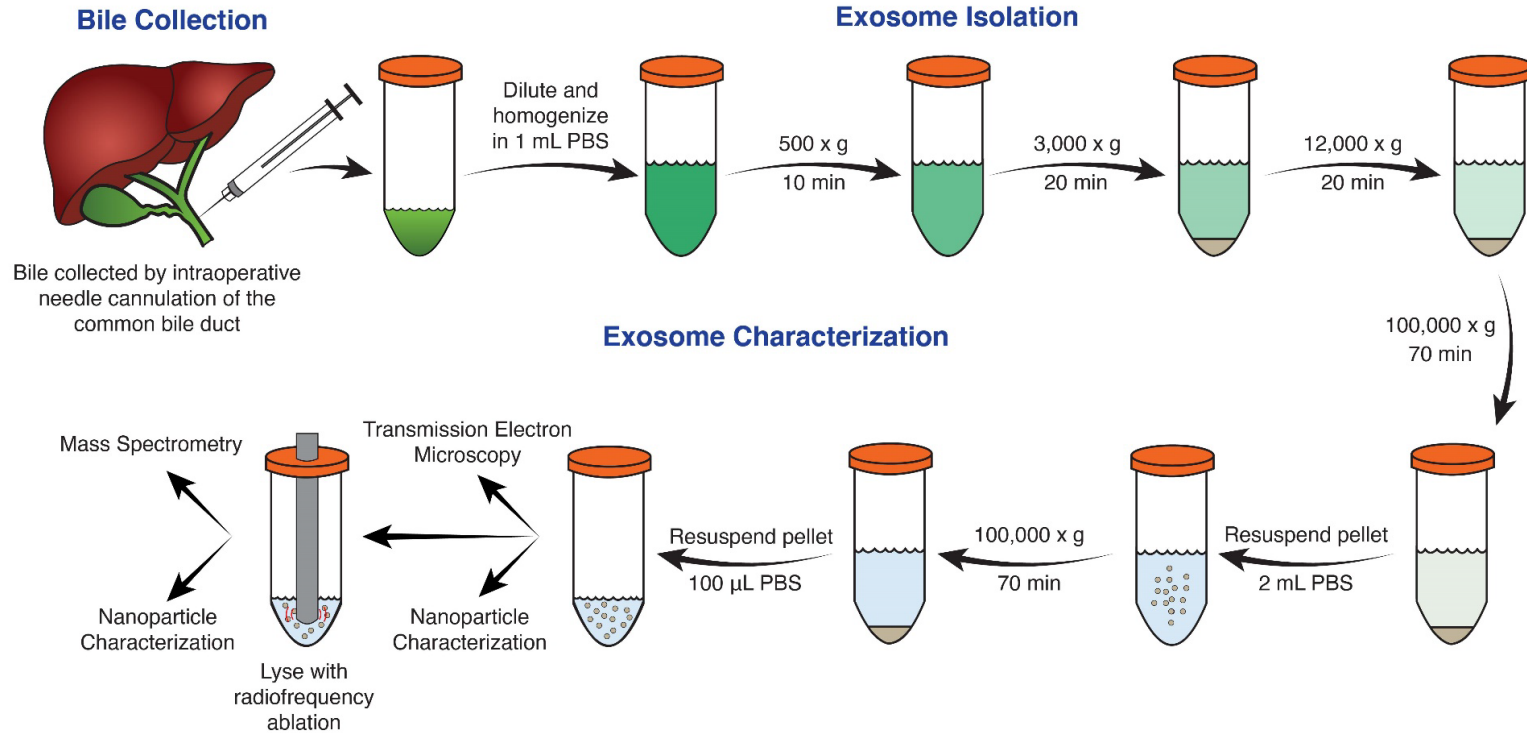


Chang, et al. 2018.

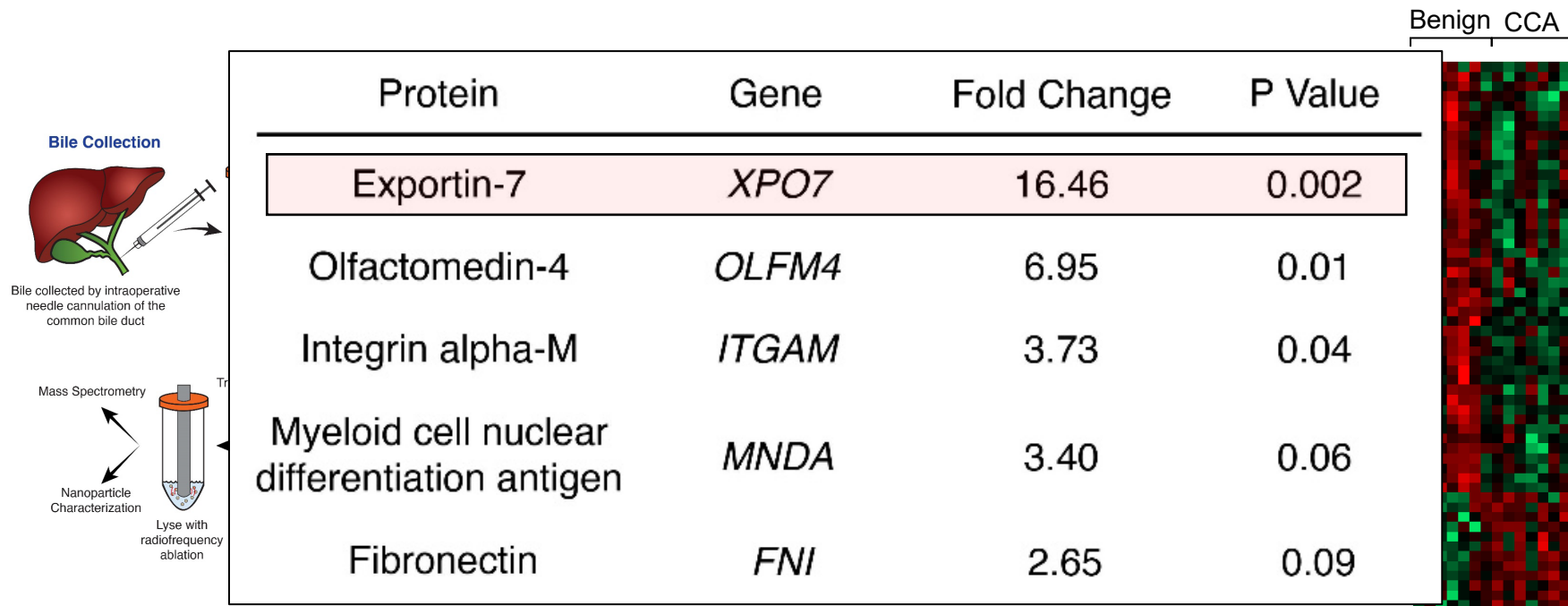
Accelerated Progress in Cholangiocarcinoma



XPO7 is Present in the Biliary Exosomes of Patients with eCCA

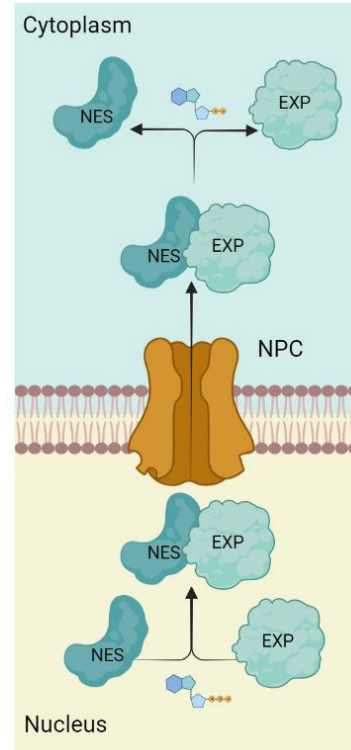


XPO7 is Present in the Biliary Exosomes of Patients with eCCA



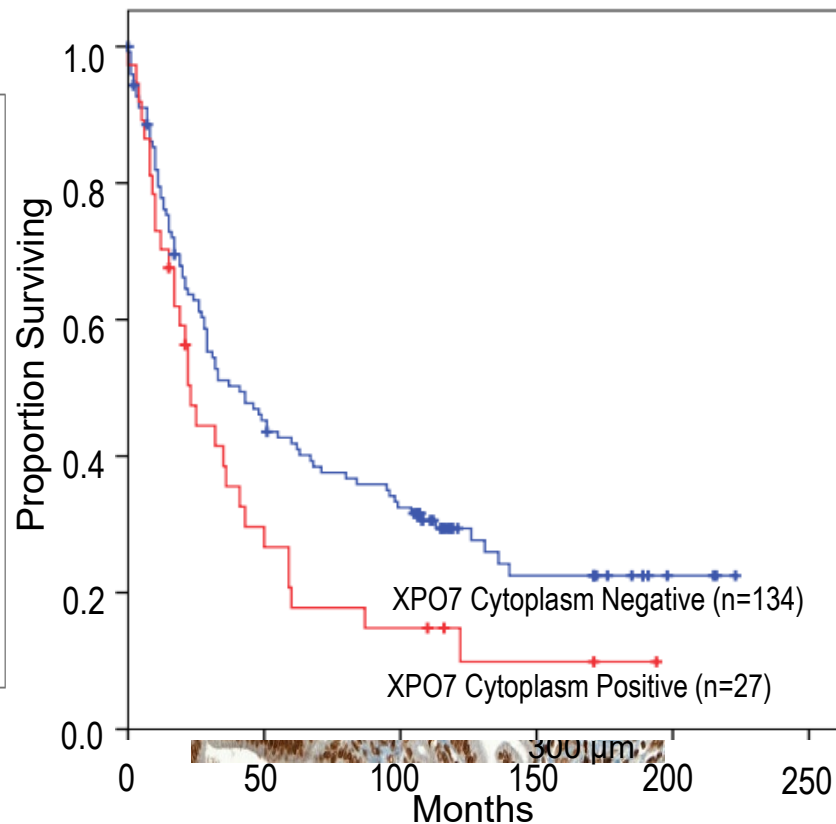
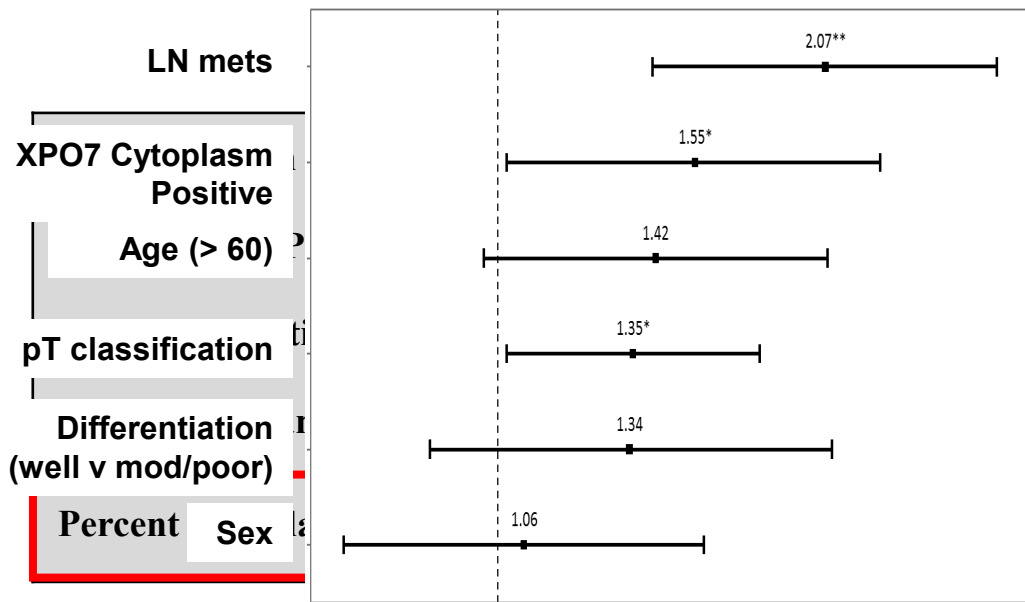
XPO7 is Present in the Biliary Exosomes of Patients with eCCA

- RAN-GTP dependent nuclear export protein.
- Increased expression associated with poor survival in ovarian cancer.
- Necessary for nuclear extrusion during erythropoiesis.

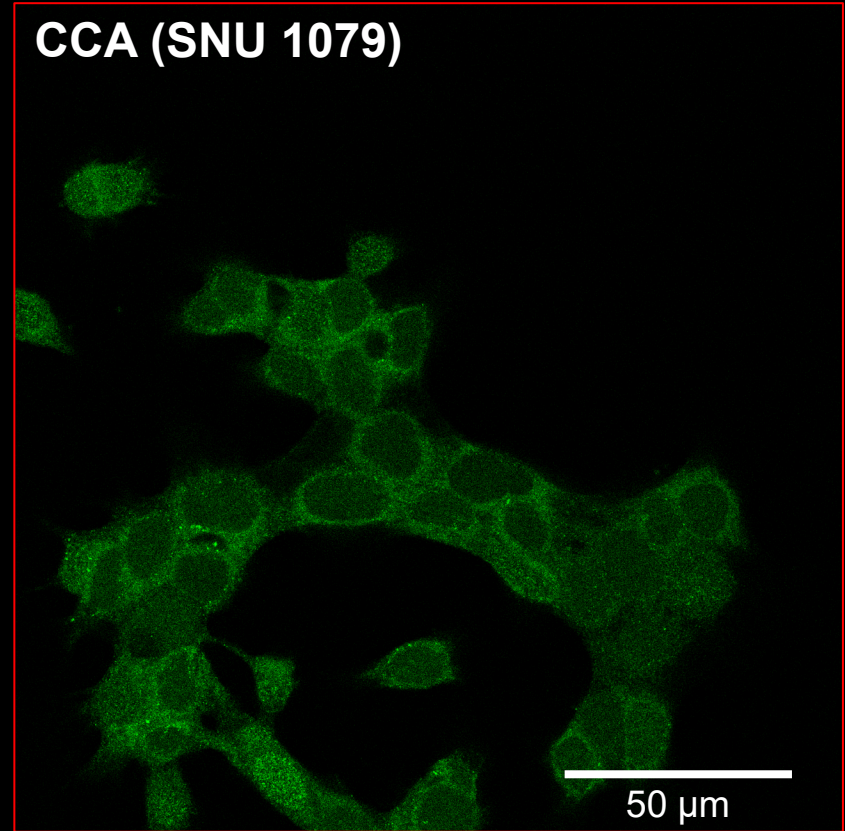
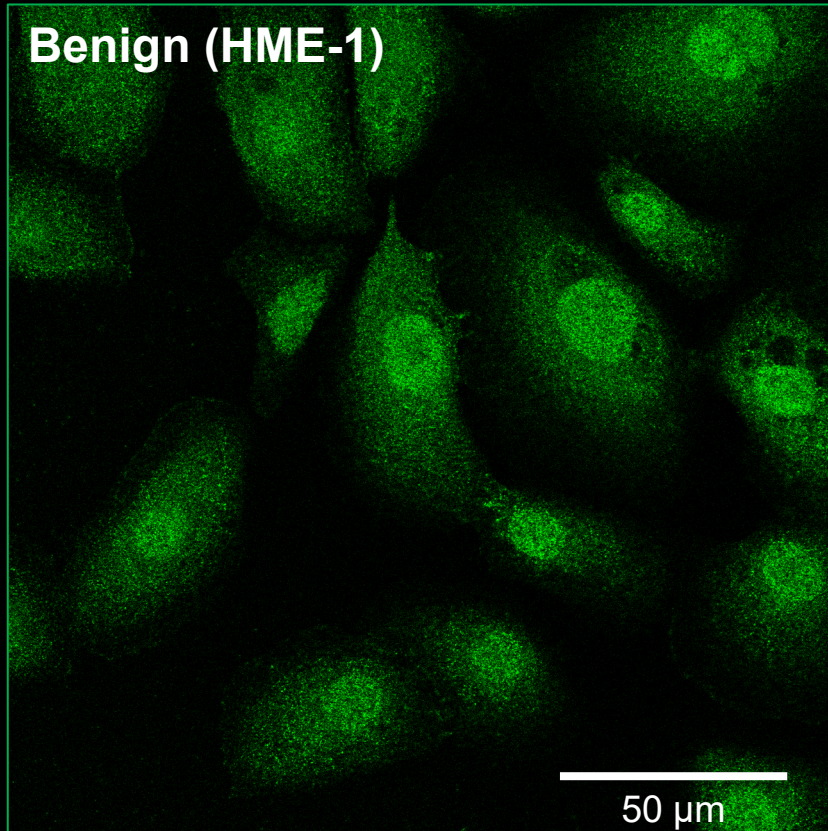


Protein	Gene	Fold Change	P Value
Exportin-7	<i>XPO7</i>	16.46	0.002
Olfactomedin-4	<i>OLFM4</i>	6.95	0.01
Integrin alpha-M	<i>ITGAM</i>	3.73	0.04
Myeloid cell nuclear differentiation antigen	<i>MNDA</i>	3.40	0.06
Fibronectin	<i>FNI</i>	2.65	0.09

Cytoplasmic XPO7 is Associated with a Poor Prognosis

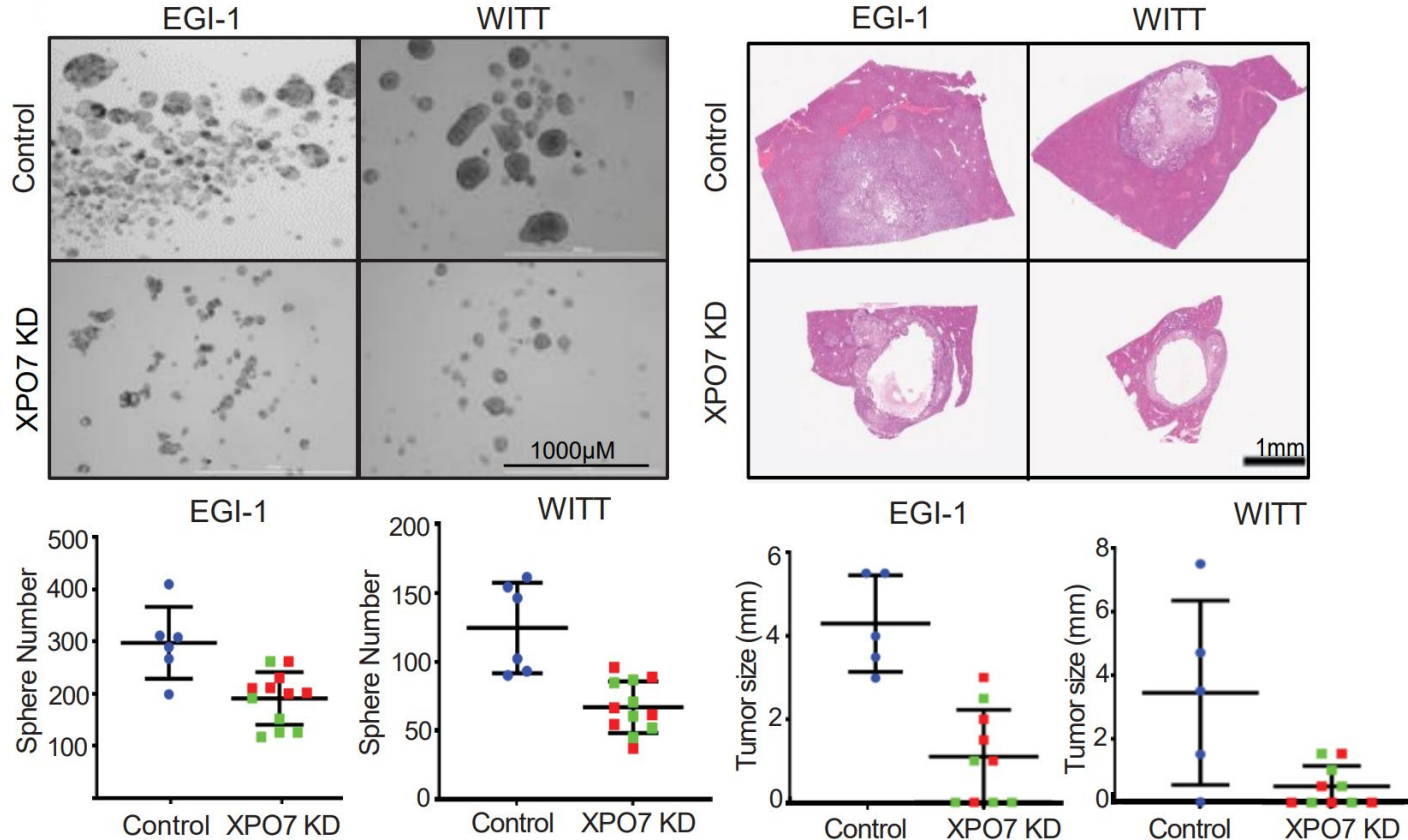


XPO7 Localizes to the Cytoplasm in CCA Cell Lines

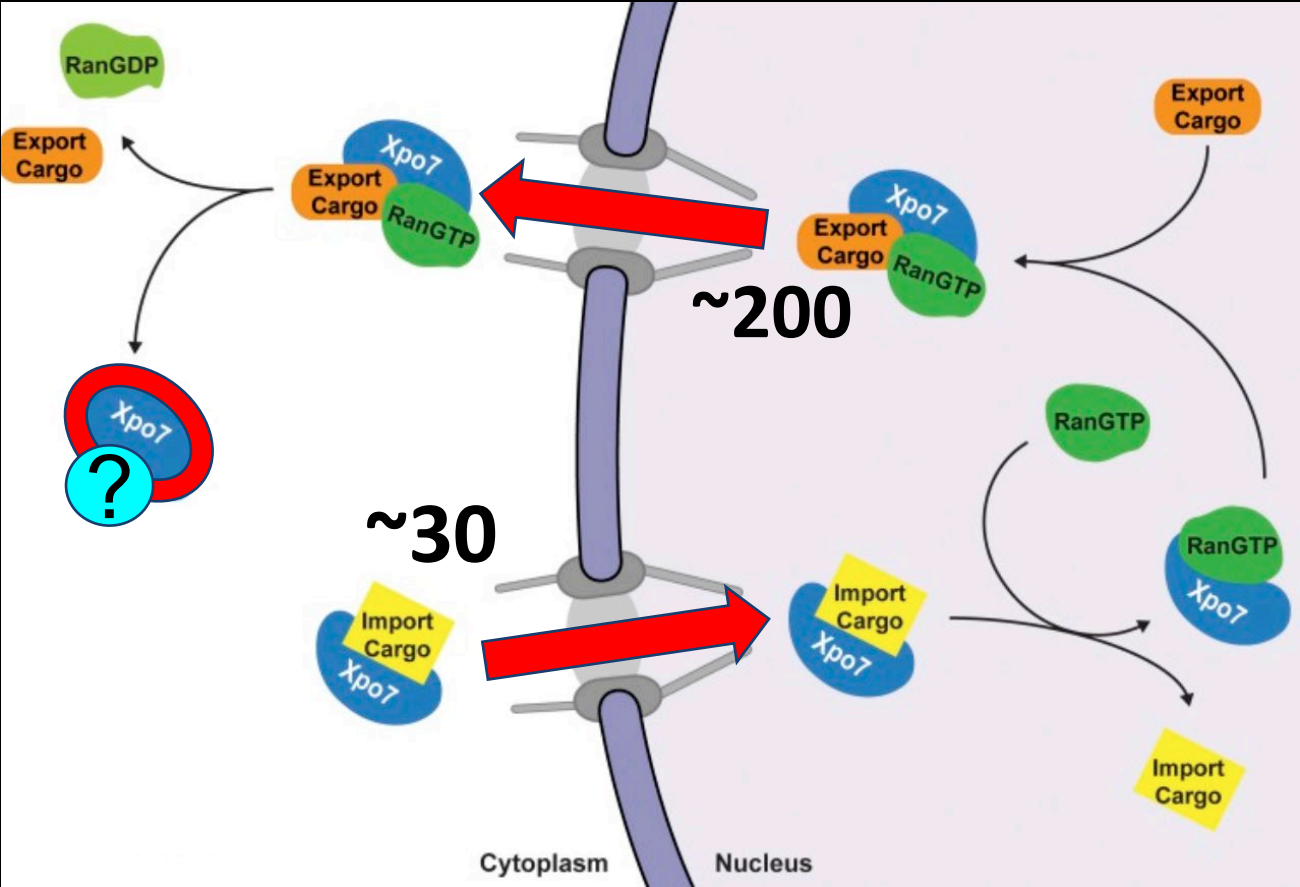


XPO7

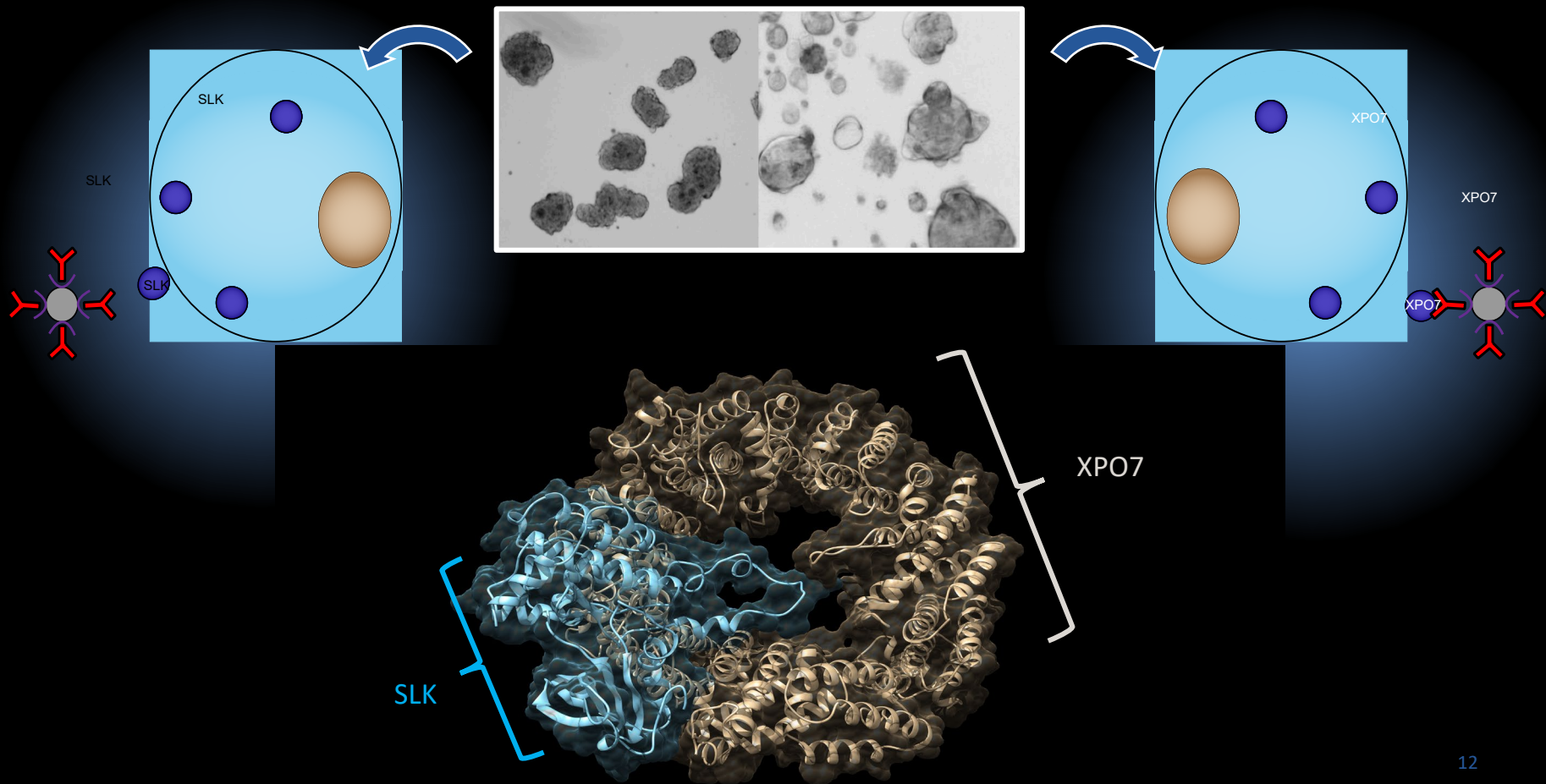
XPO7 Knockdown Alters Cell Phenotype



Exportin-7 (XPO7)

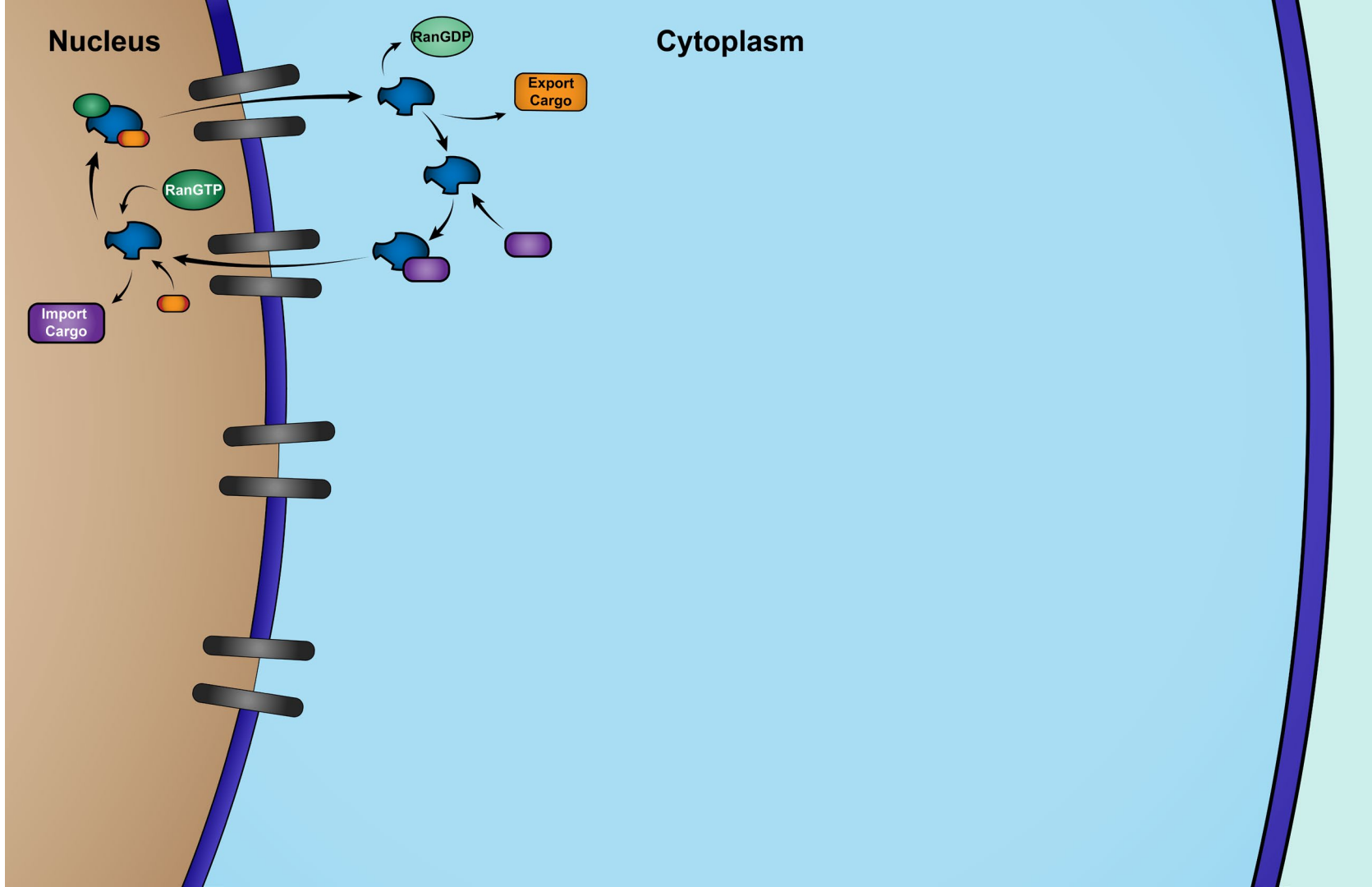


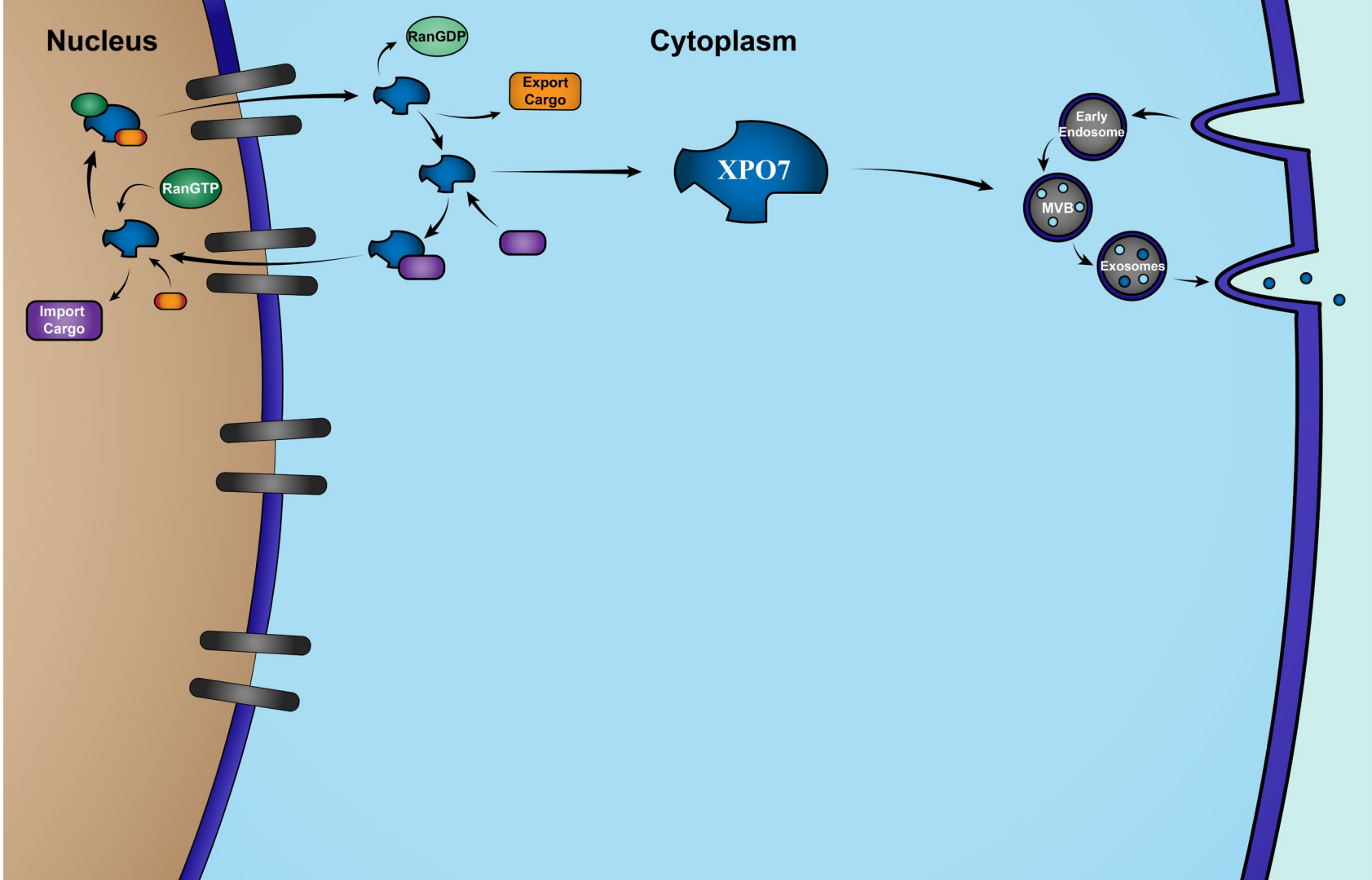
Cytoplasmic XPO7 binds SLK

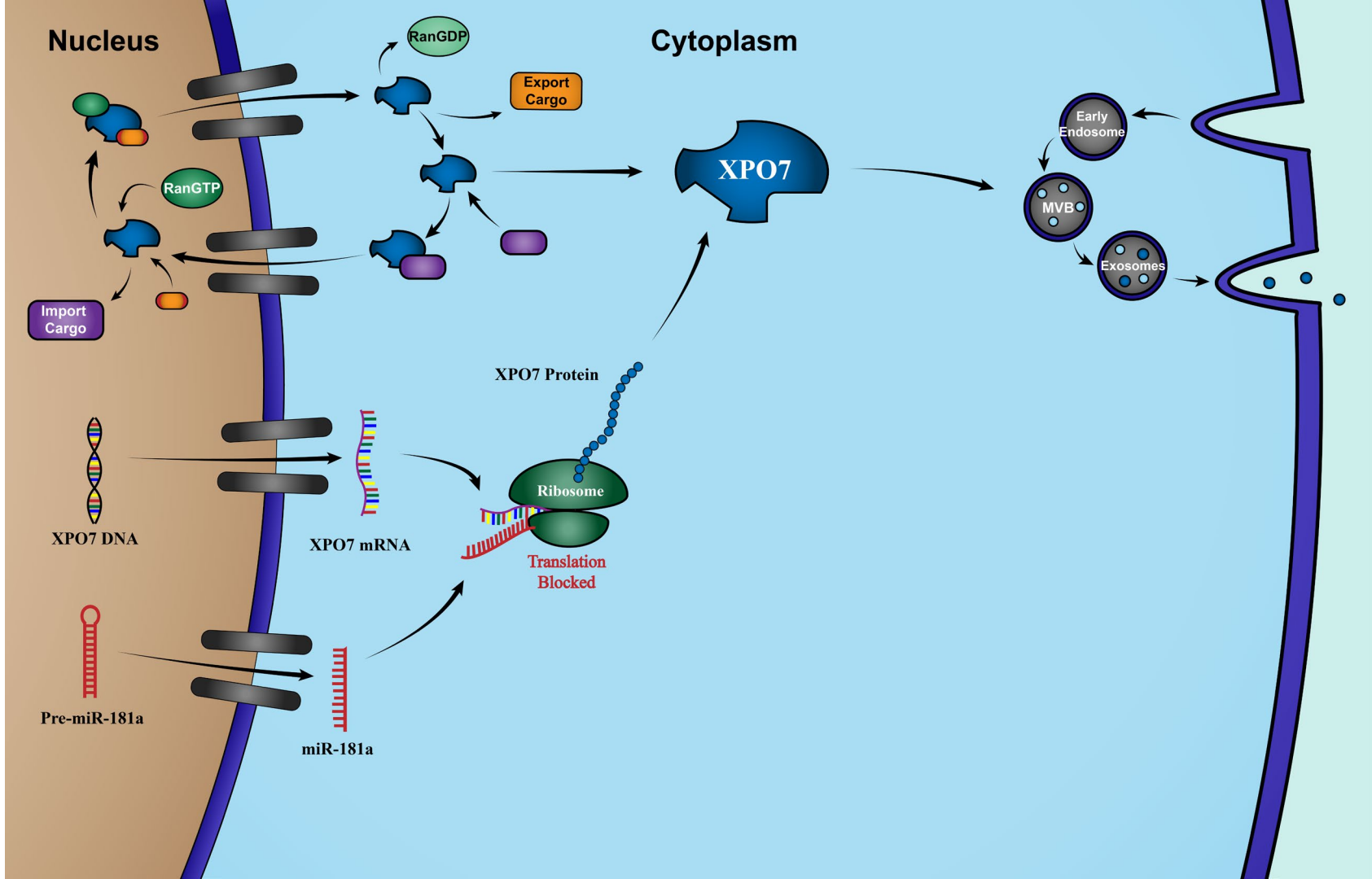


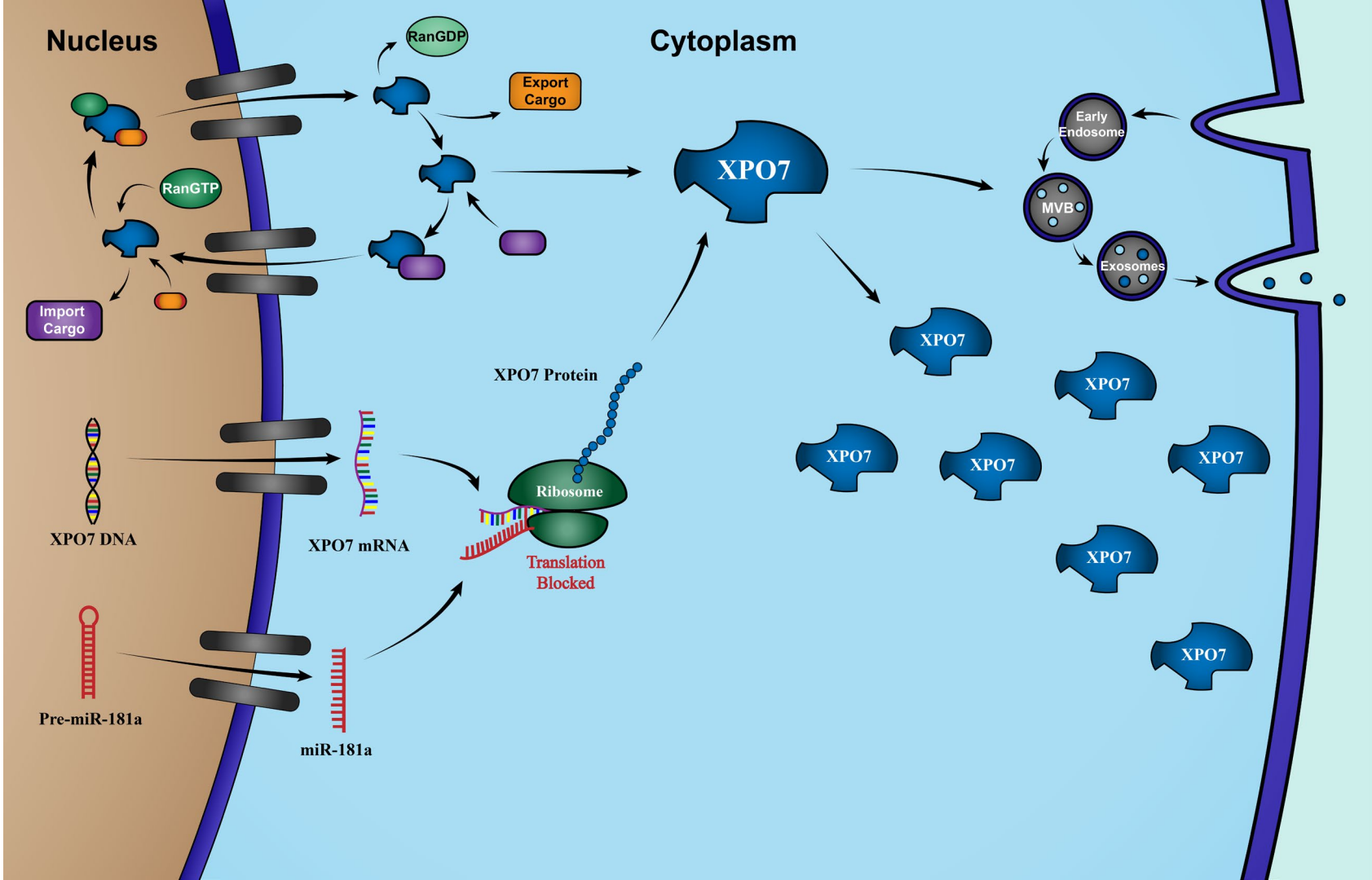
Nucleus

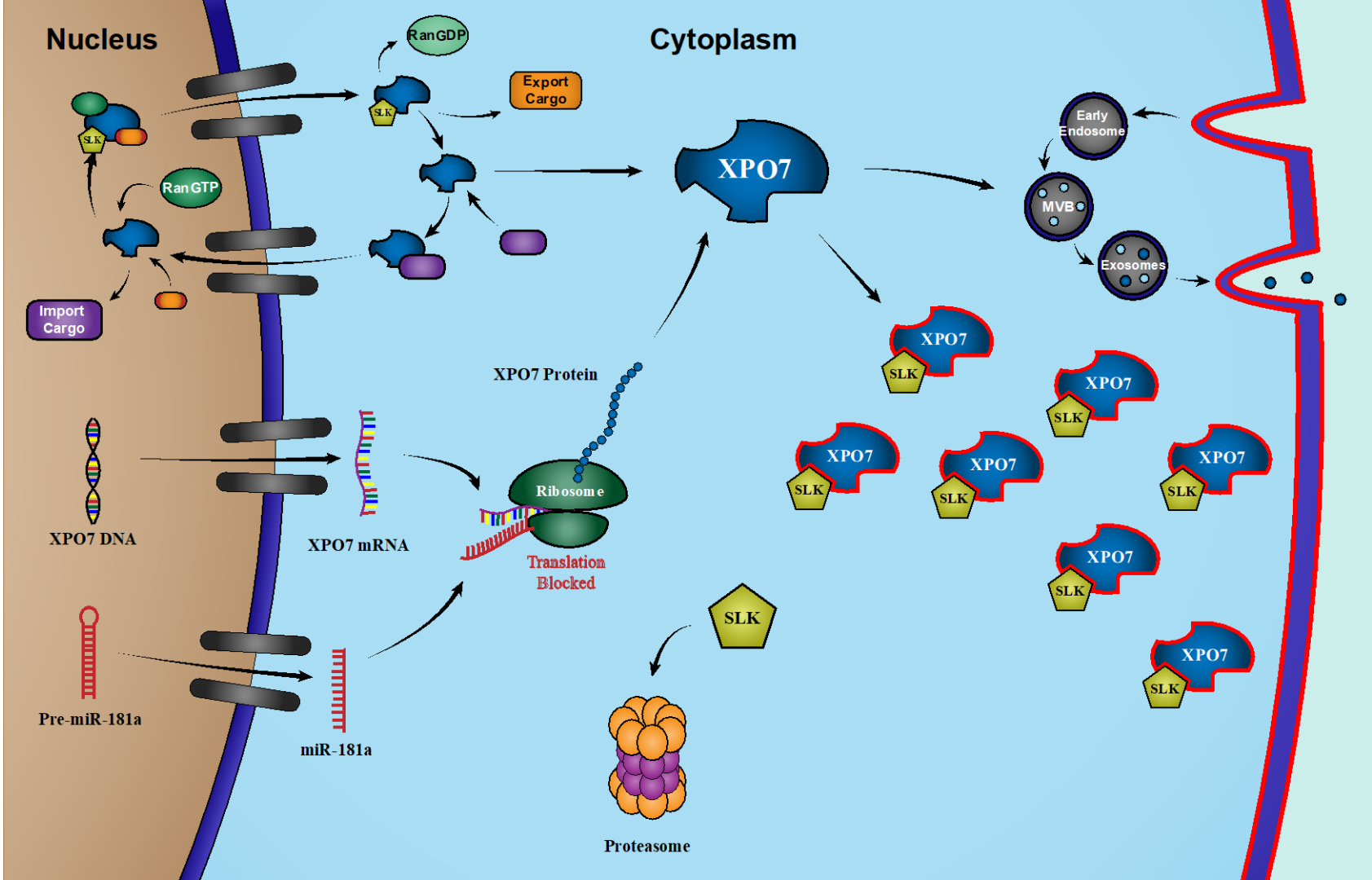
Cytoplasm

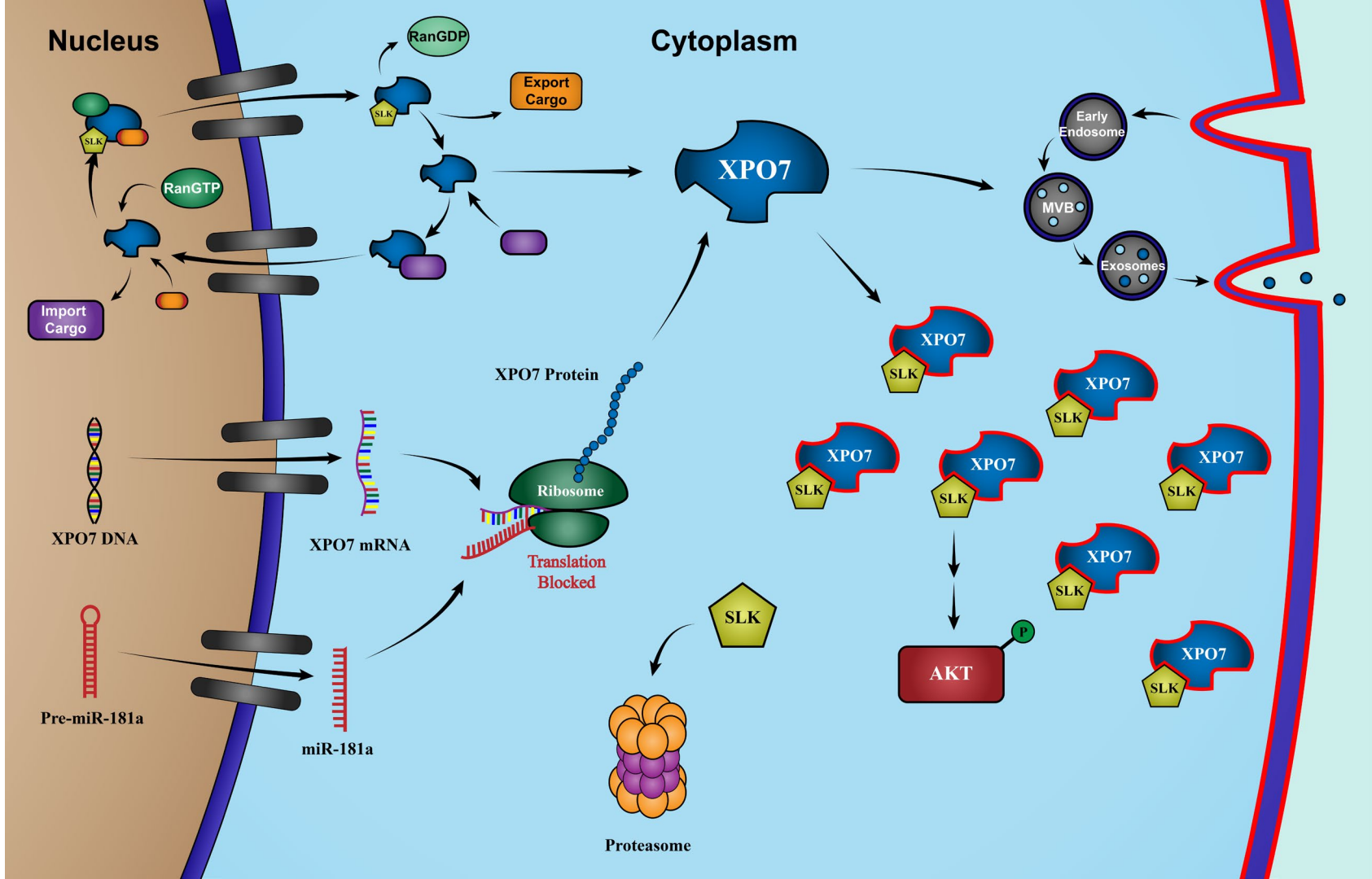


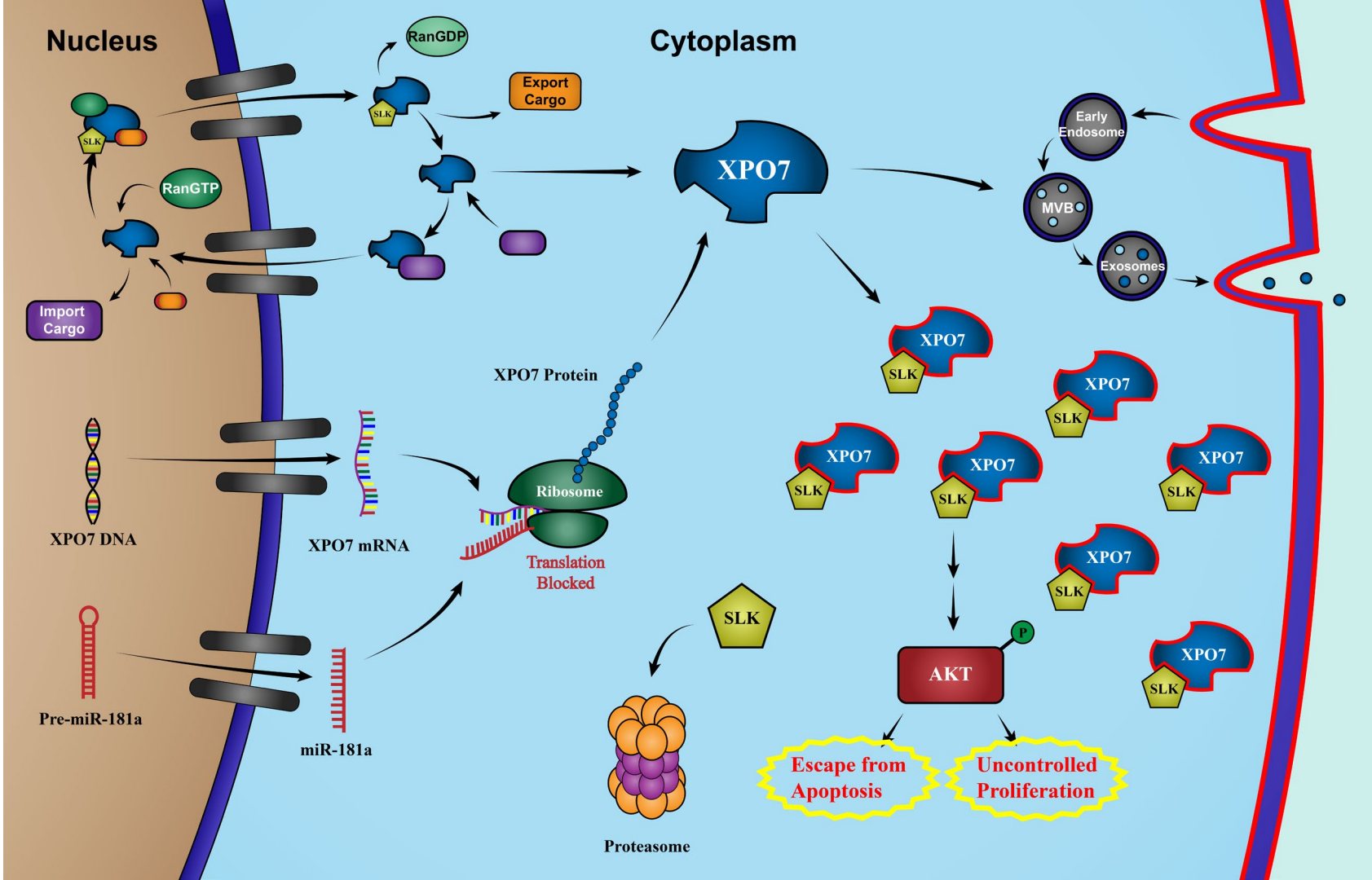


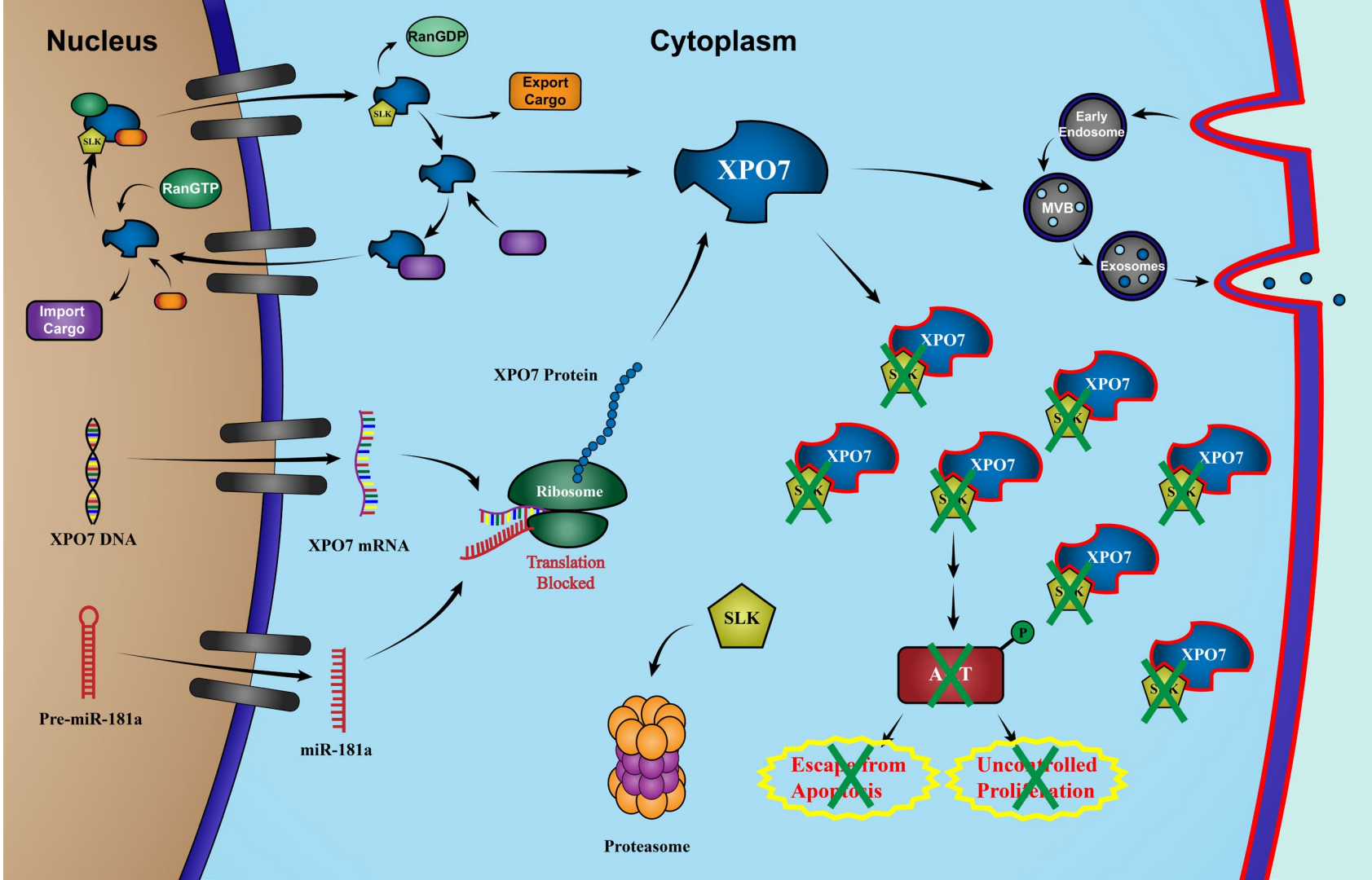




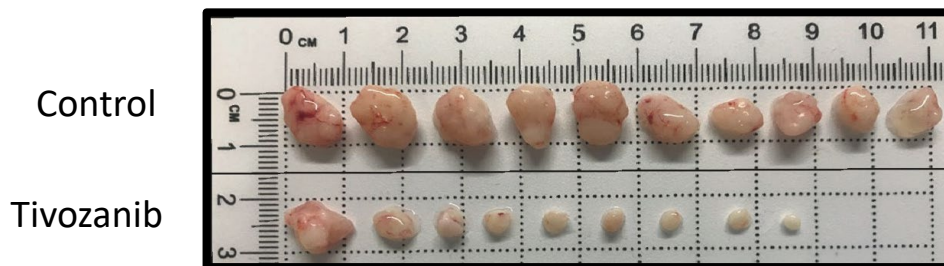
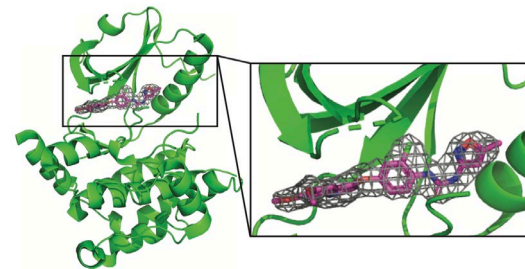
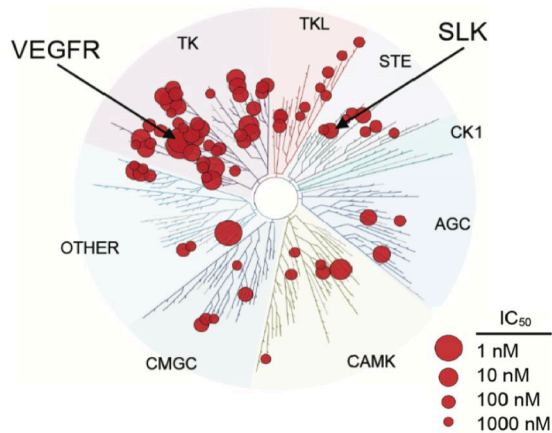
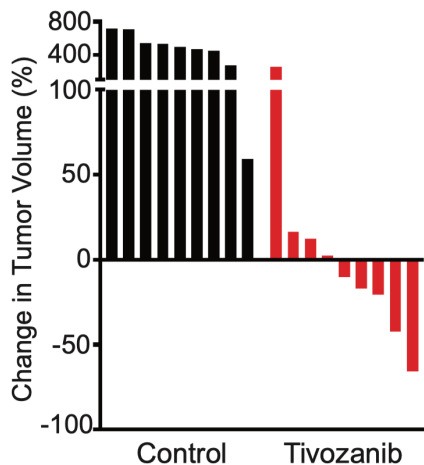
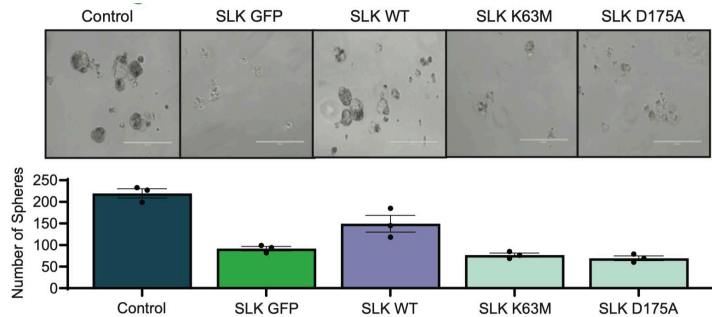




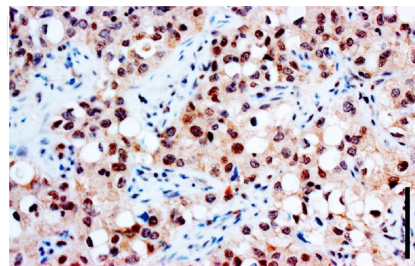




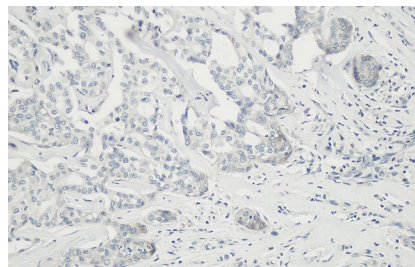
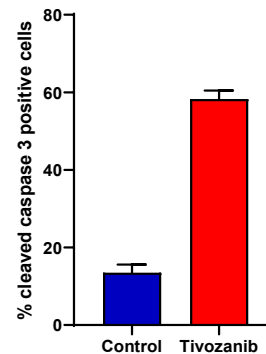
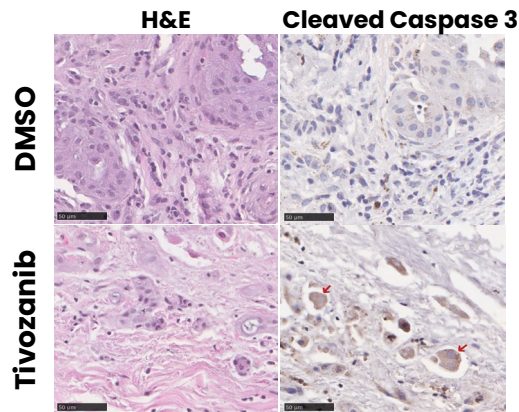
Tivozanib Blocks SLK Kinase Activity



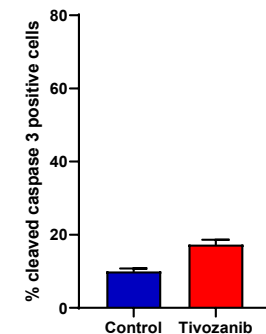
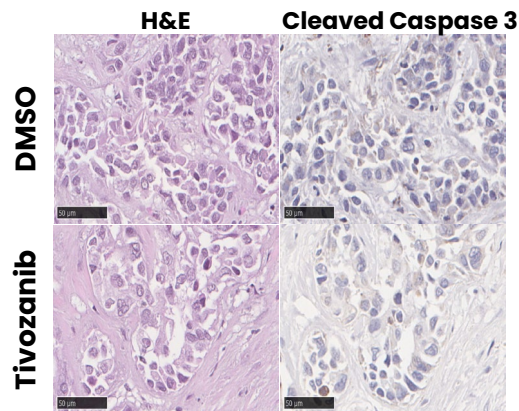
Tivozanib Causes CCA Cell Death Ex Vivo



XPO7+ CCA



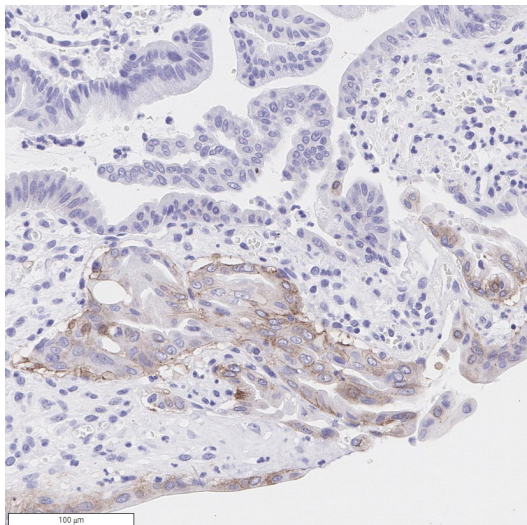
XPO7- CCA



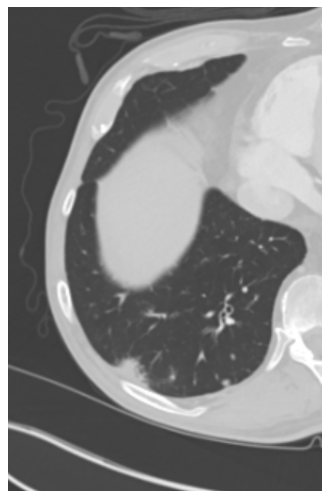
Evaluating Efficacy of Tivozanib (AV-951) in Biliary Tract Cancers

Disease stability with Tivozanib treatment

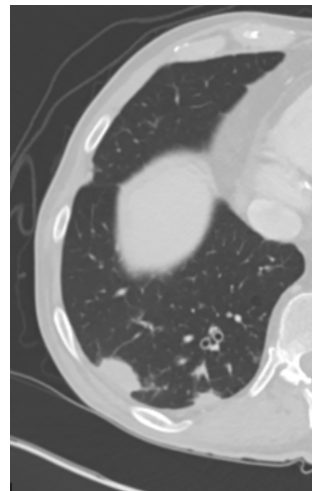
NCT04645160 Pt#3
XPO7+



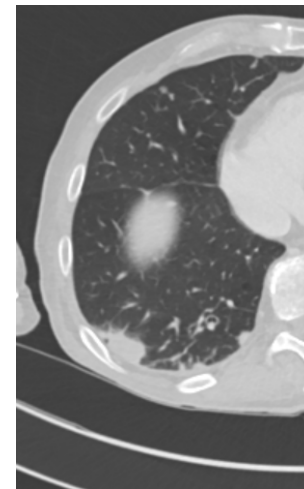
Gem/Cis



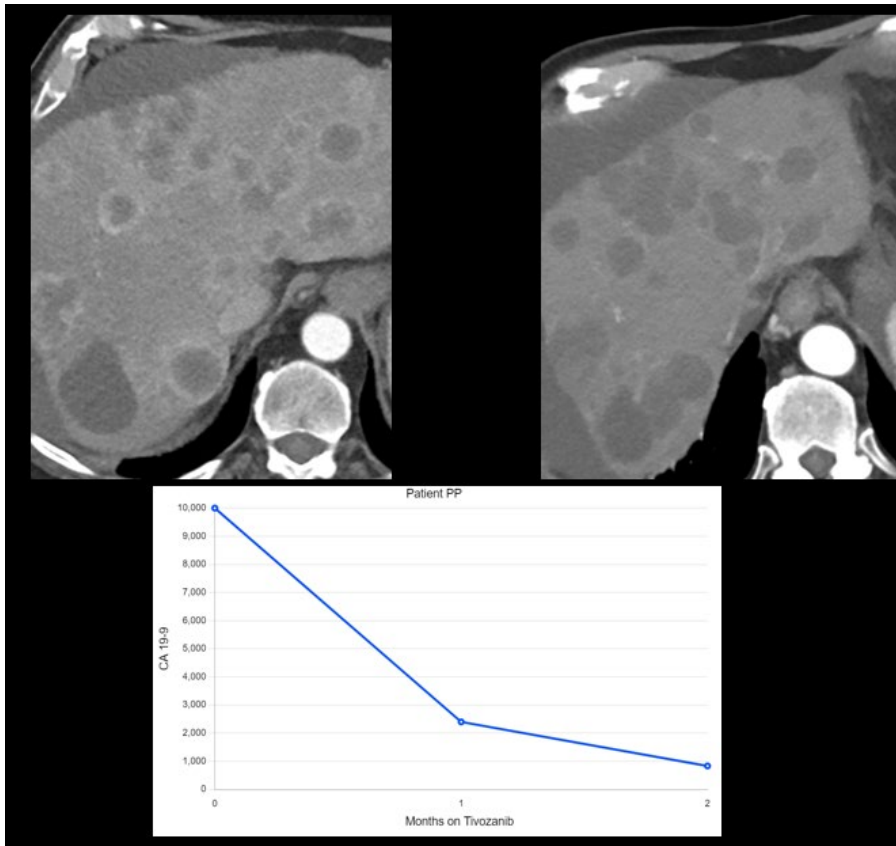
Capecitabine



C2 Tivozanib



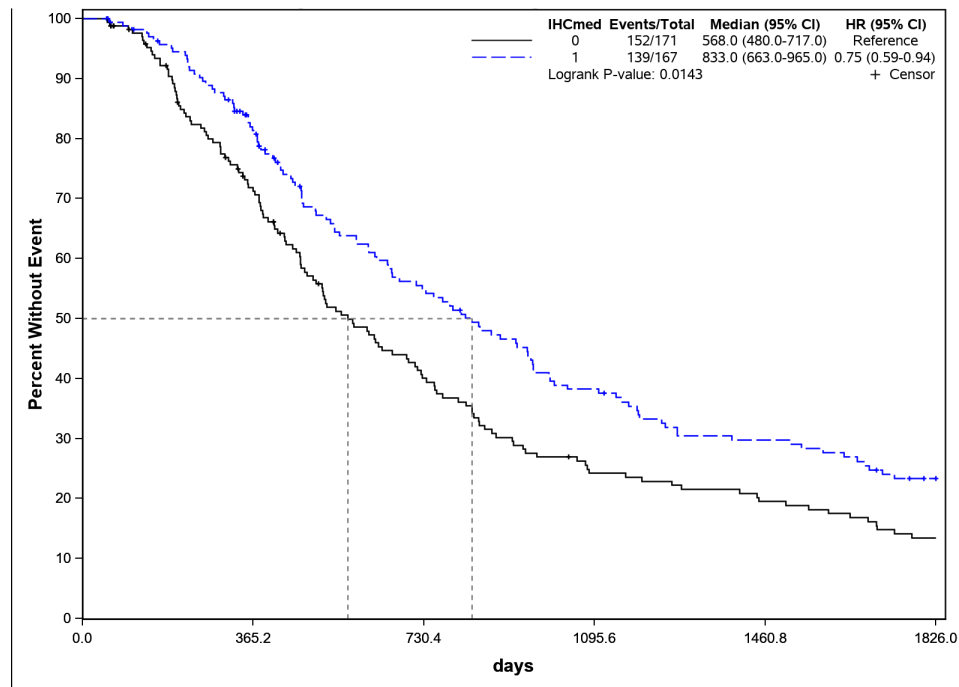
Reduction in CA 19-9 with Tivozanib Treatment



Similar Biology in Pancreatic Adenocarcinoma?

N=339 PDAC in TMA
stratified by cytoplasmic
staining for XPO7

HR 0.75 (95CI 0.59-0.94)



Conclusions

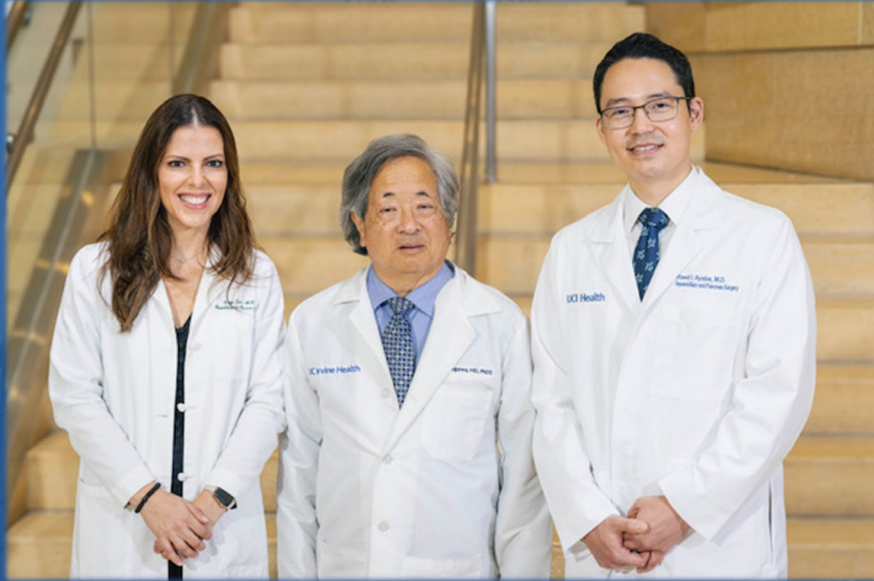
CCA remains a challenging disease with limited effective treatment options.

XPO7 is a liquid biomarker for CCA and is linked to an aggressive phenotype through SLK.

SLK is an effective therapeutic target *in vivo* and *ex vivo*.

The XPO7/SLK/AKT axis may be at play in other tumor types, including pancreatic cancer.

UCI Division of Hepatobiliary and Pancreas Surgery

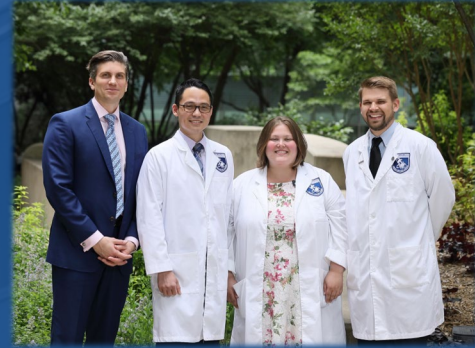


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Thank You

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