Role of Na,K-ATPase in Gastrointestinal Cancer

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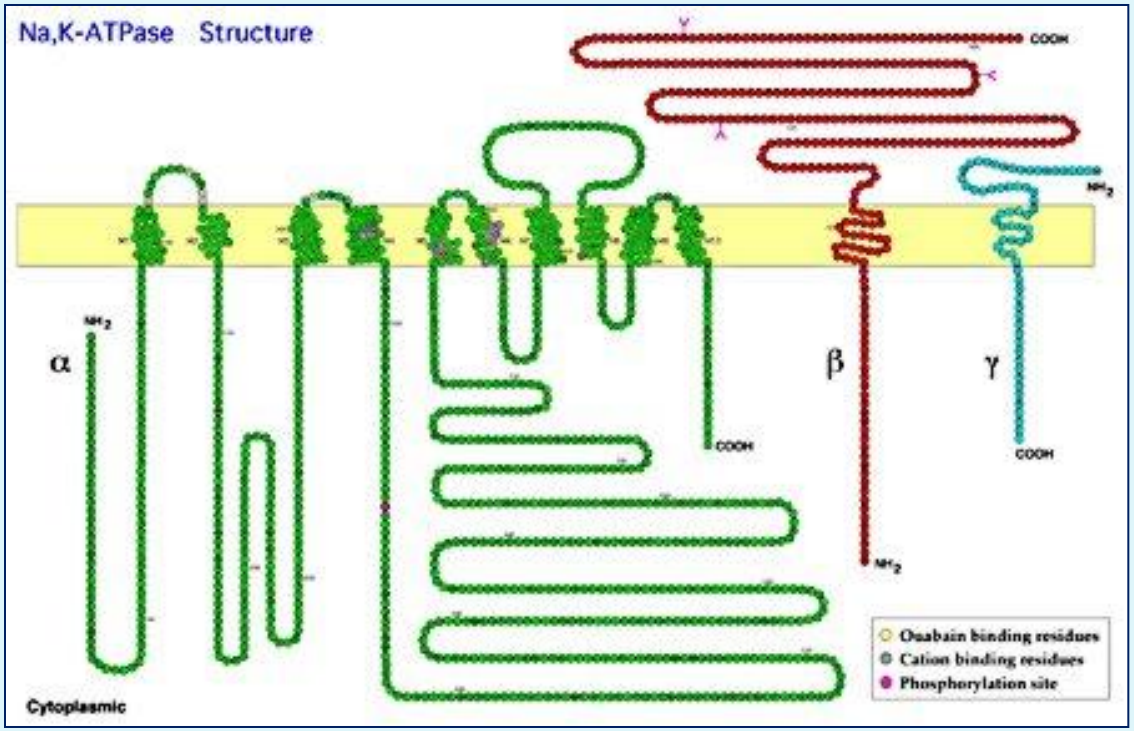
Na,K-ATPase



- Transmembrane protein
- Four isoforms of α subunits binding site for Na^+, ATP, and cardiac glycosides
- Three isoforms of β subunits
- One γ subunit
- Binding affinity of α subunits to cardiac glycosides

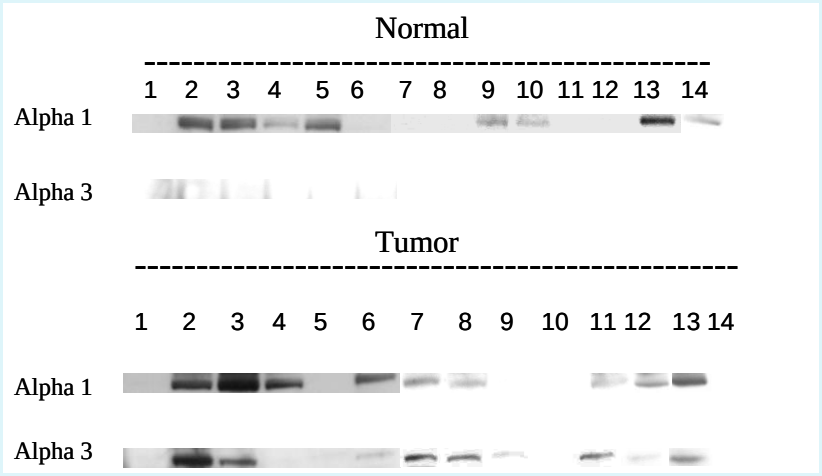
  α2 and α3 >> α1 (250 fold more sensitive to bind to CG)

Dysregulation of Na,K-ATPase α Subunit in Different Cancer Types

Cancer type	α 1	α 2	α 3	α 4	Assays	Function study
NSCLC	↑		↑		IHC	proliferation and migration
CCRCC	↑				IHC	Associated with poor survival
Glioblastoma	↑				IHC	
Melanoma	↑				IHC	
Colorectal cancer	↓		↑		IHC	
Medulloblastoma	↑		↑		IHC	
Bladder cancer	↓				IHC	

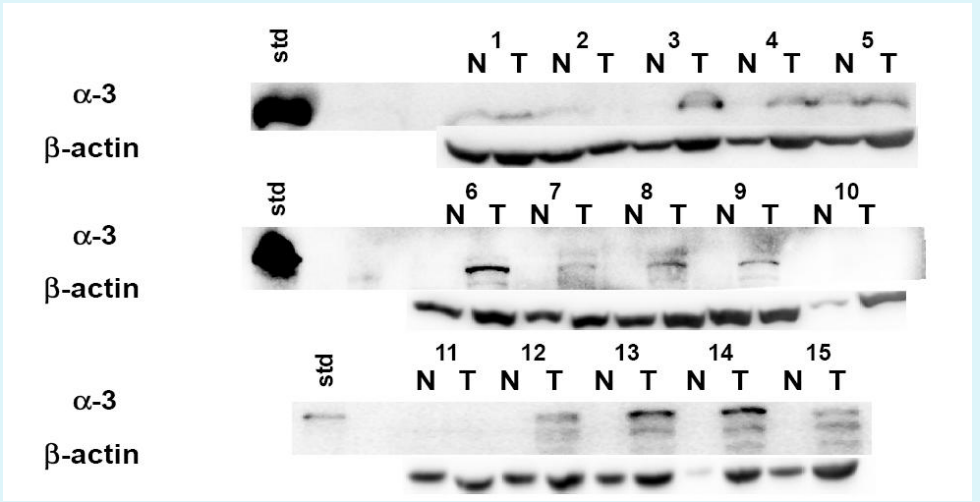
α3 expression is higher in human colon cancer compared to adjacent normal tissues

A.



MDACC

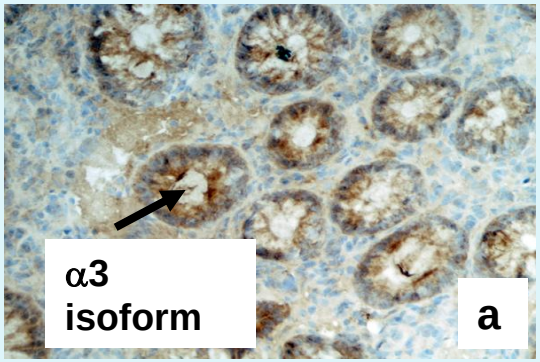
B.



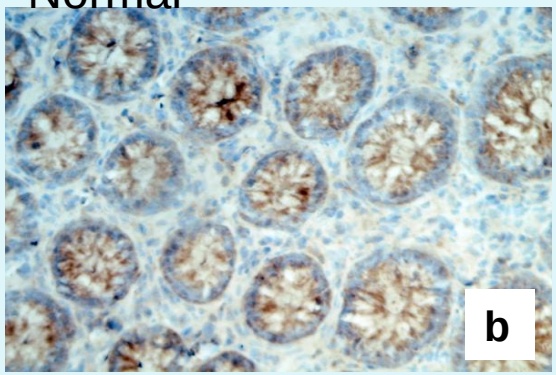
Cornell University

Na,K-ATPase α3 is translocated to perinuclear position in colon and lung tumor tissues

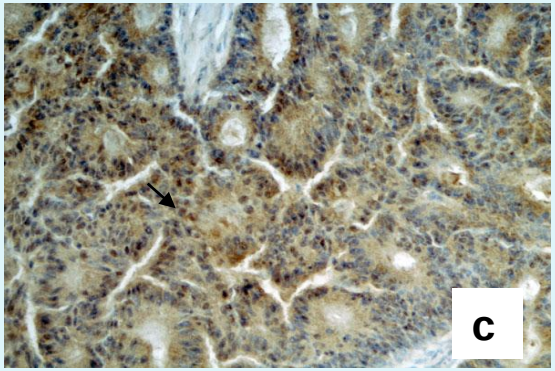
Normal



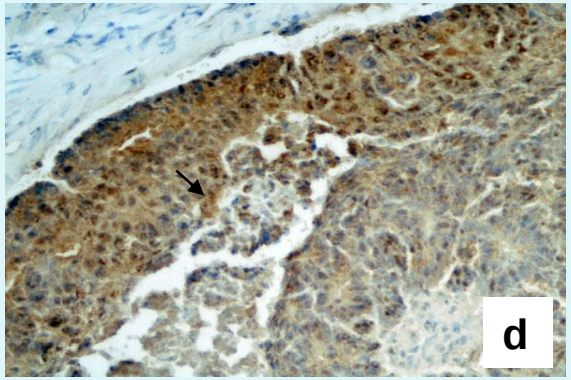
Normal

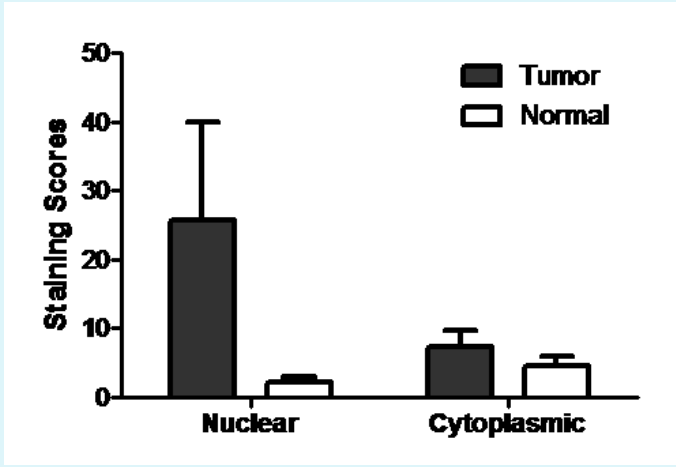


Cancer



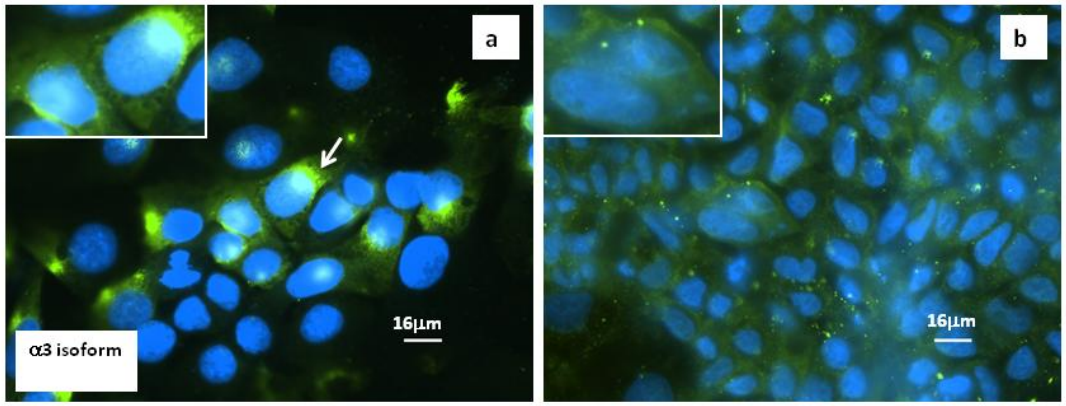
Cancer

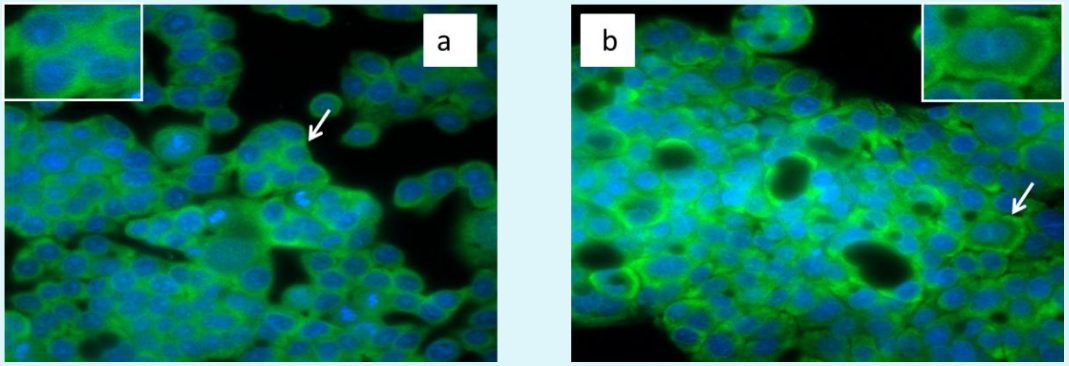


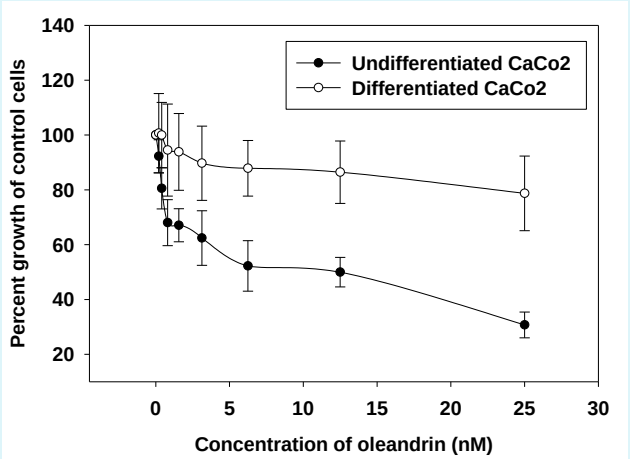


Yang P., Mol Carcinogenesis, 2014

Na,K-ATPase α3 subunit shifts from perinuclear position to plasma membrane in differentiated colon cancer cells

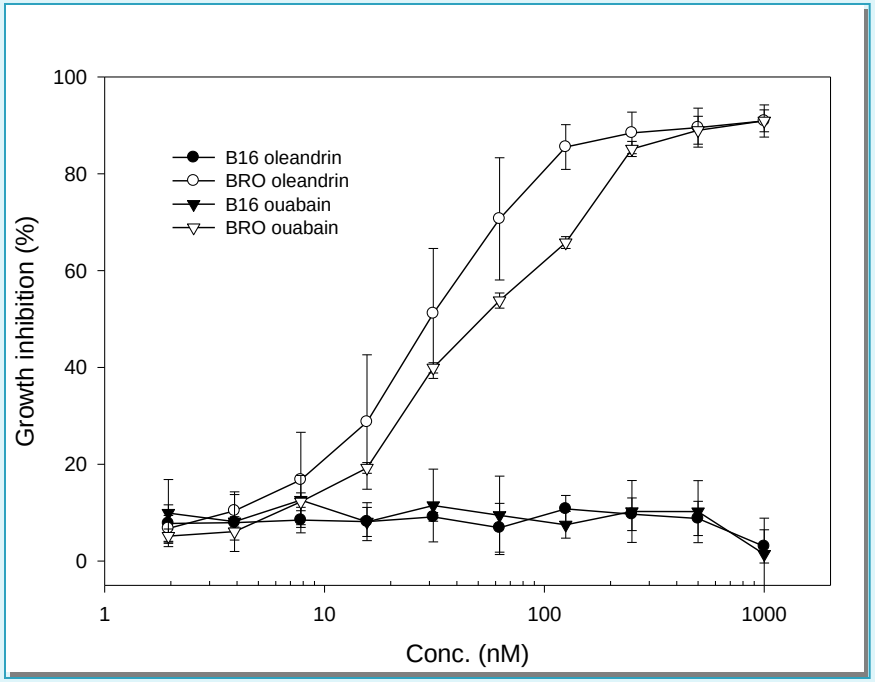


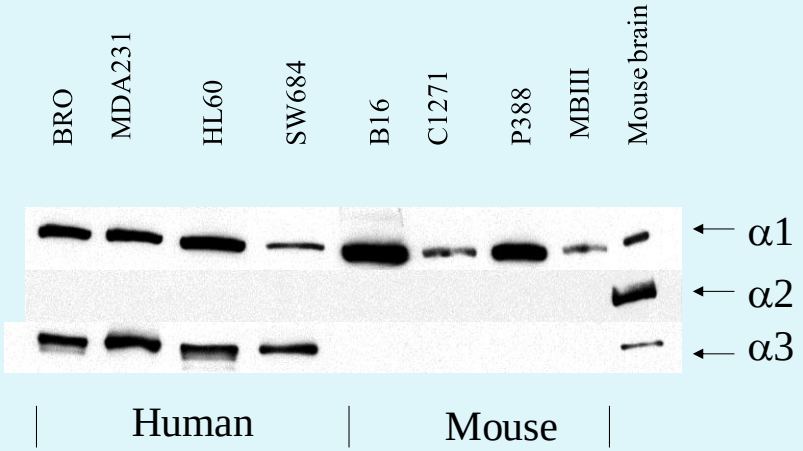




Yang P., Mol Carcinogenesis, 2014

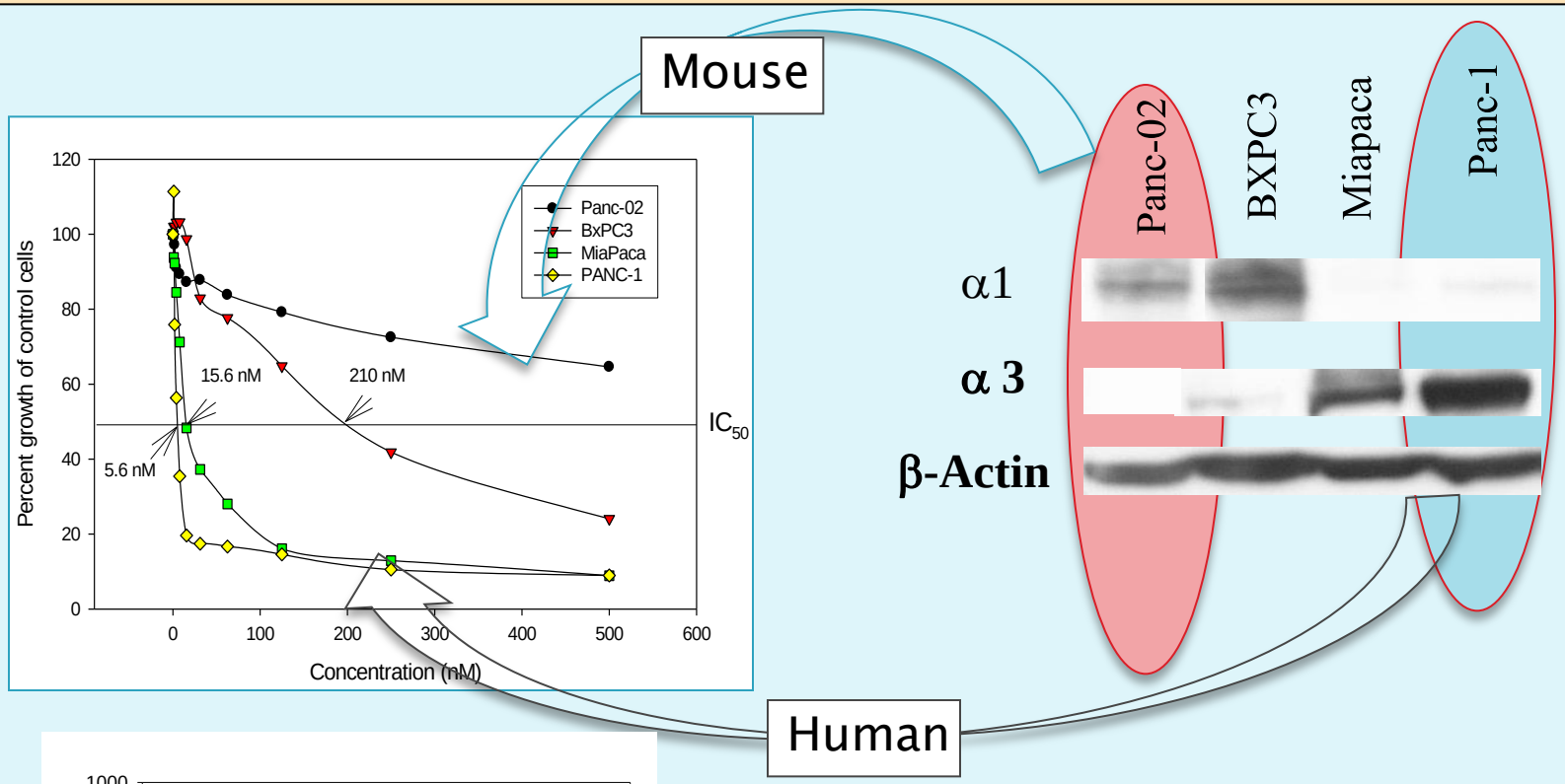
Role of Na,K-ATPase α-isoform in cardiac glycoside elicited anti-proliferative activity

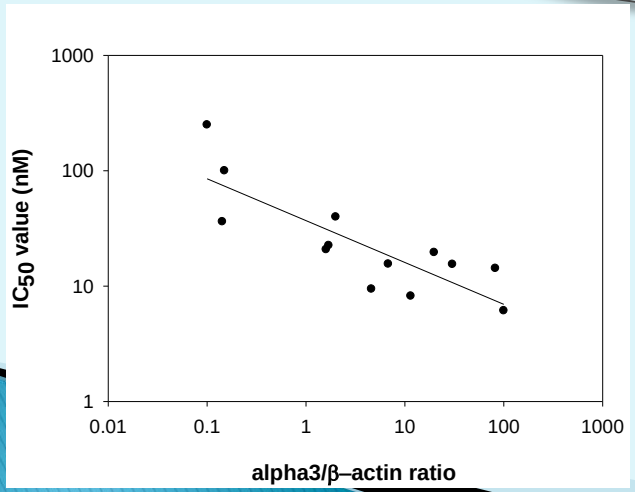




Lin Y., J. Exp Therap, 2010

Role of Na,K-ATPase α3 in Cardiac Glycoside Elicited Anti-proliferative Activity

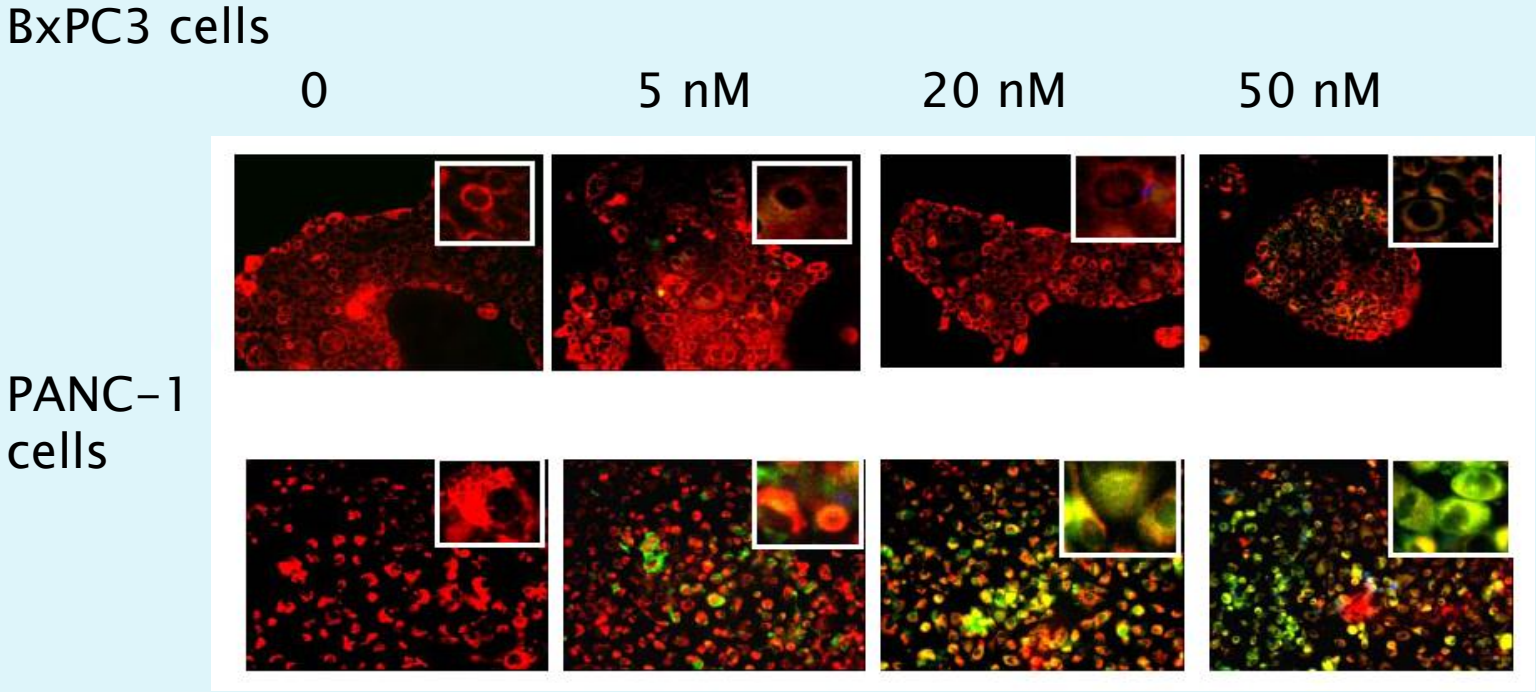




Cell lines	α3/β-actin
Panc-1	71
MiaPaca	32
BxPC3	3.8
Panc-02	0

Yang, P., et al., Mol. Cancer Ther. 2009

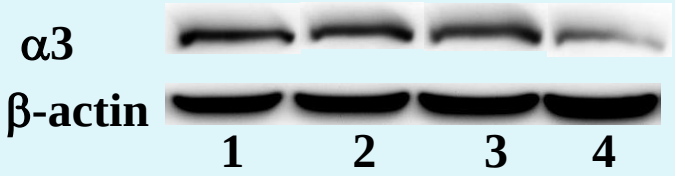
Expression of α3 Affects the Uptake of Oleandrin in Human Pancreatic Cancer Cells

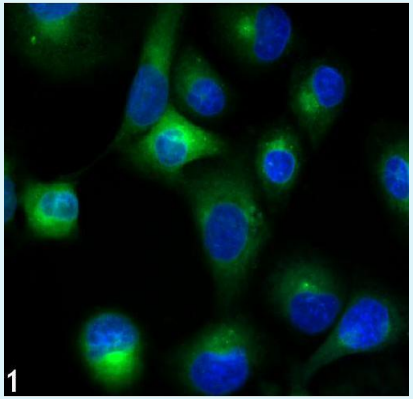


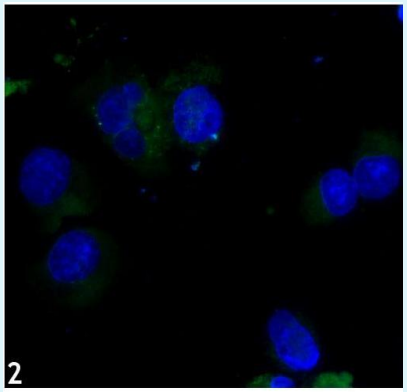
Oleandrin bound to BODIPY dye presents as green.

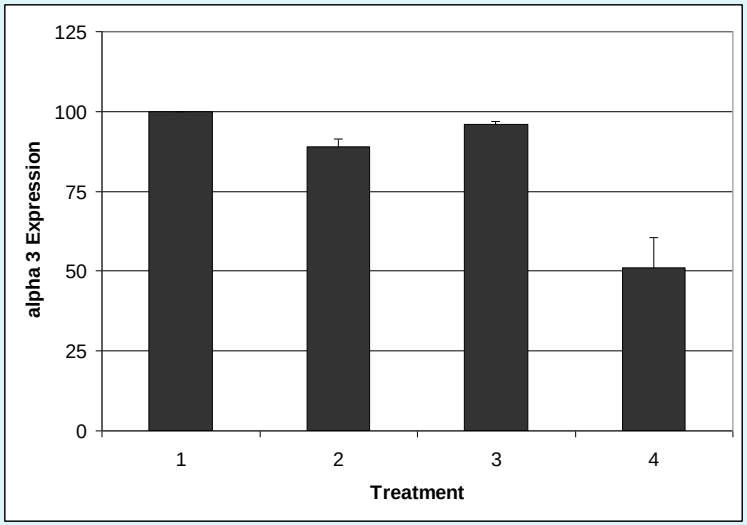
Yang, P., et al., Mol. Cancer Ther. 2009

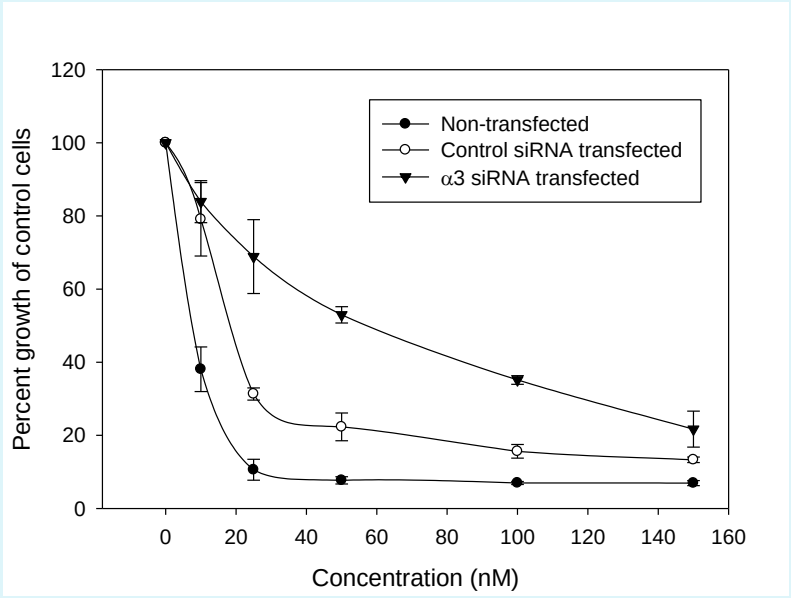
siRNA-mediated Reduction of α3 Alters Oleandrin Uptake and Oleandrin Induced Growth Suppression

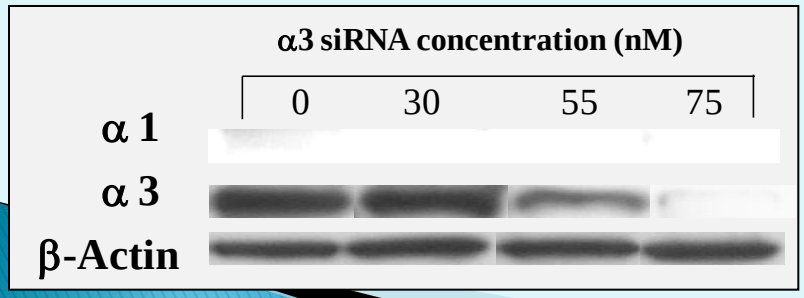






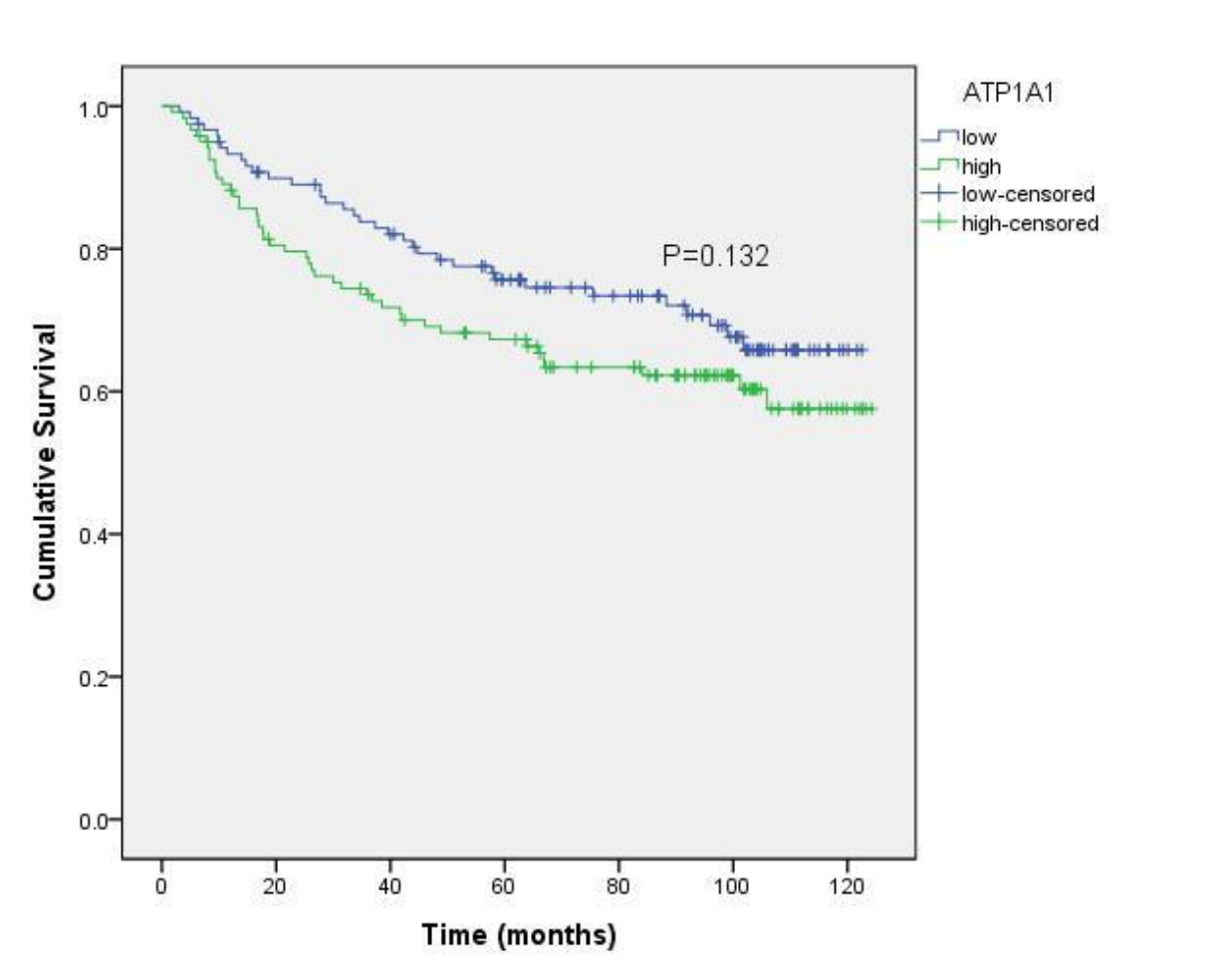




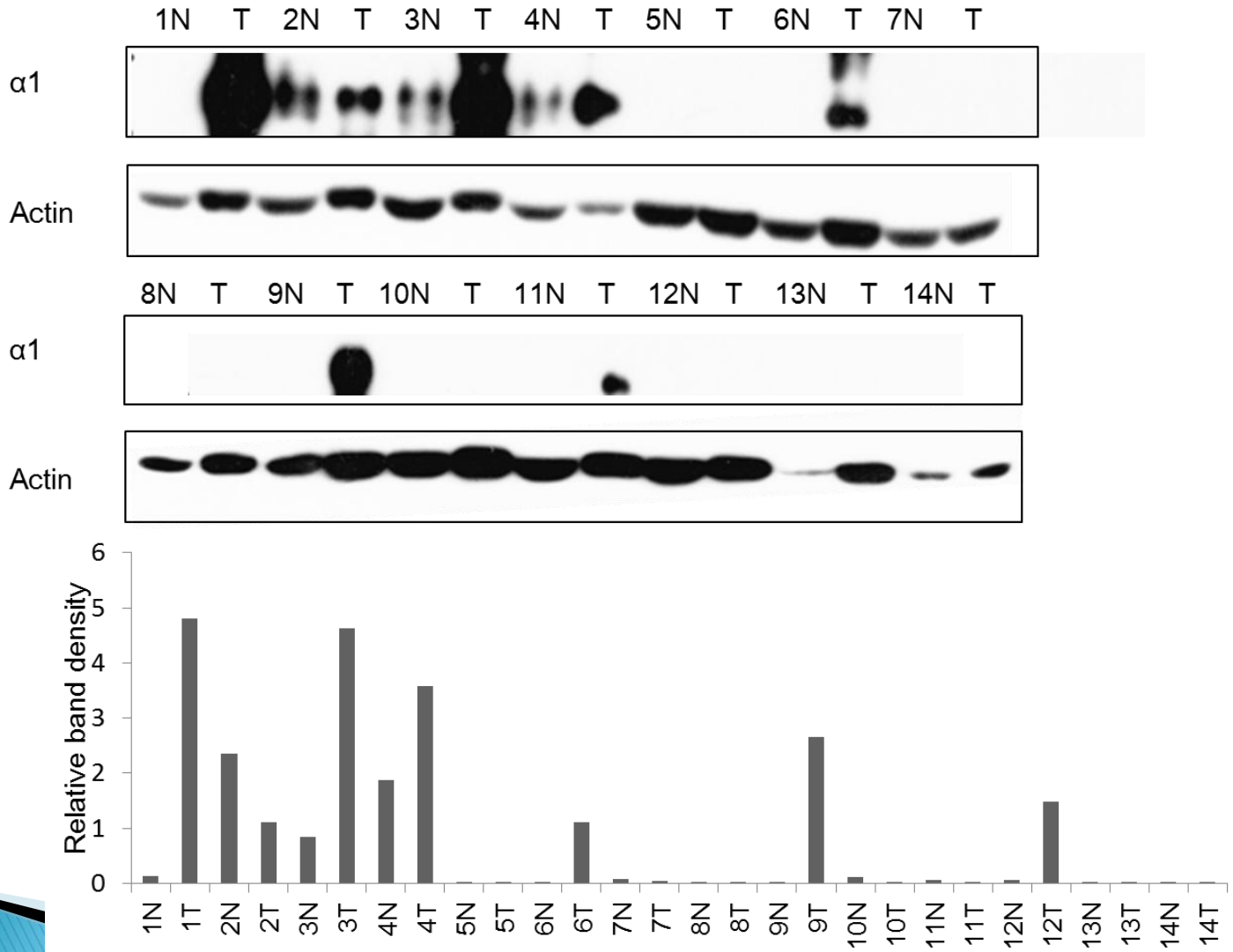


Yang, P., et al., Mol. Cancer Ther. 2009

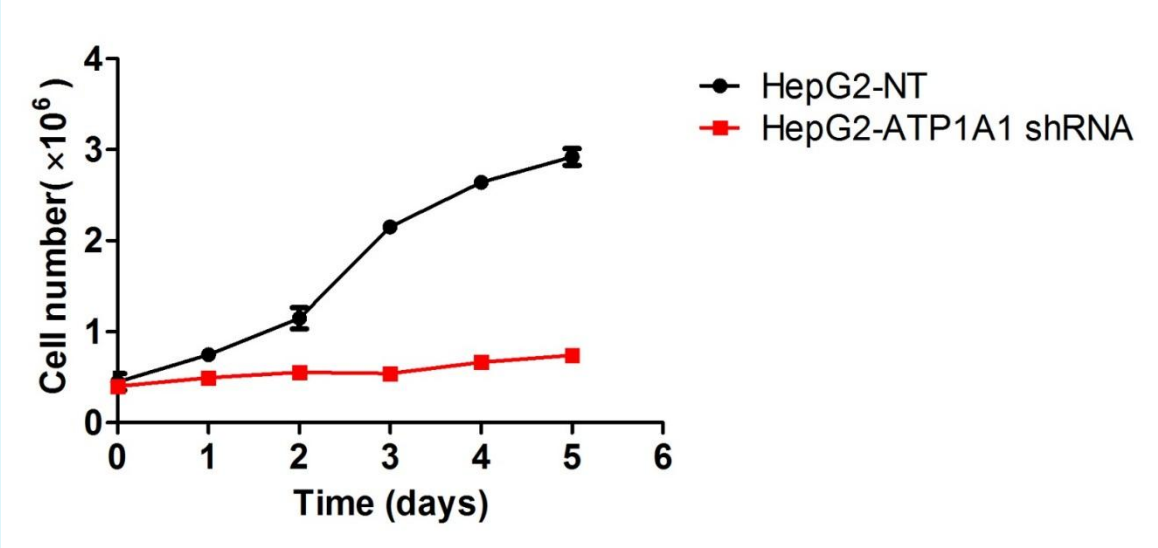
Higher Na,K-ATPase α1 Expression Was Associated with Poor Prognosis in Patients with HCC

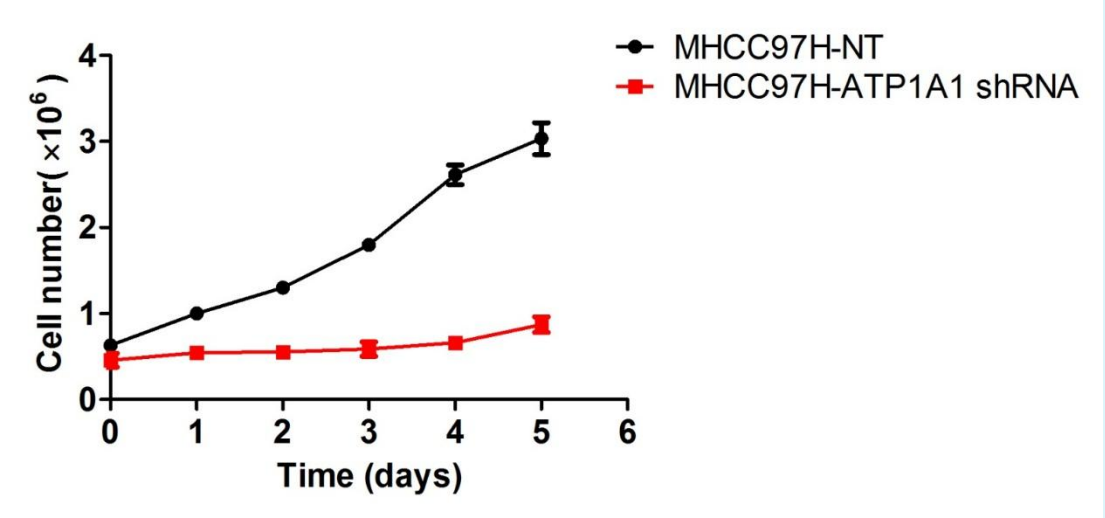


Na,K-ATPase α1 Overexpresses in HCC Tumor Compared to Normal Liver Tissues



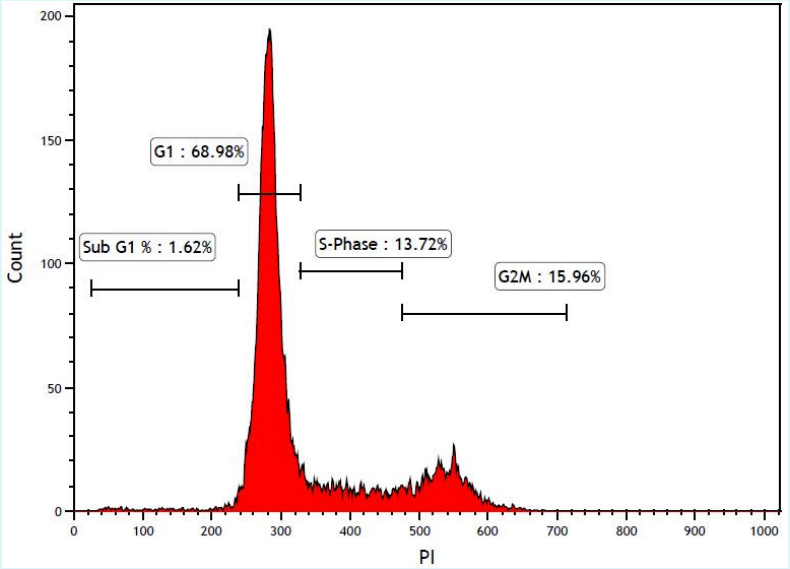
Knocking Down Na,K-ATPase α1 Slows Down the Growth of Human HCC Cells



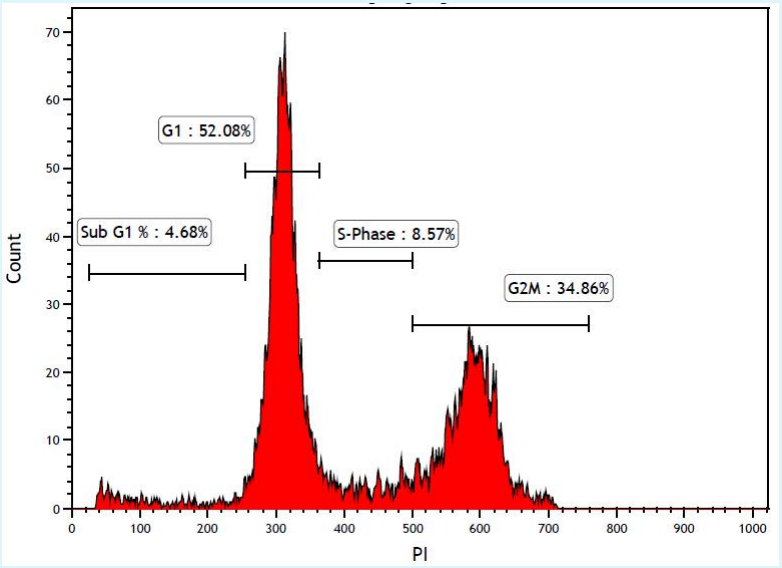


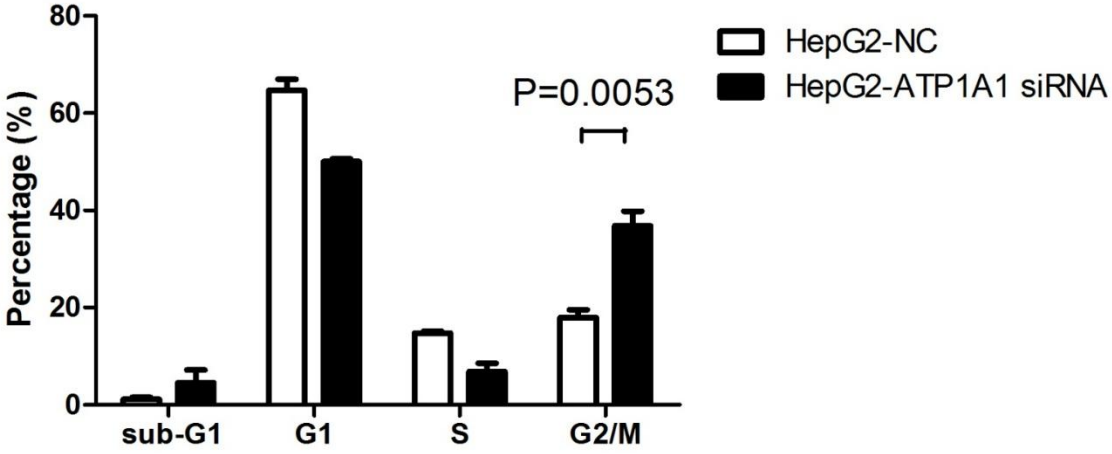
Knocking Down Na,K-ATPase α1 Causes G2/M Phase Arrest in HepG2 Cells

HepG2 NC



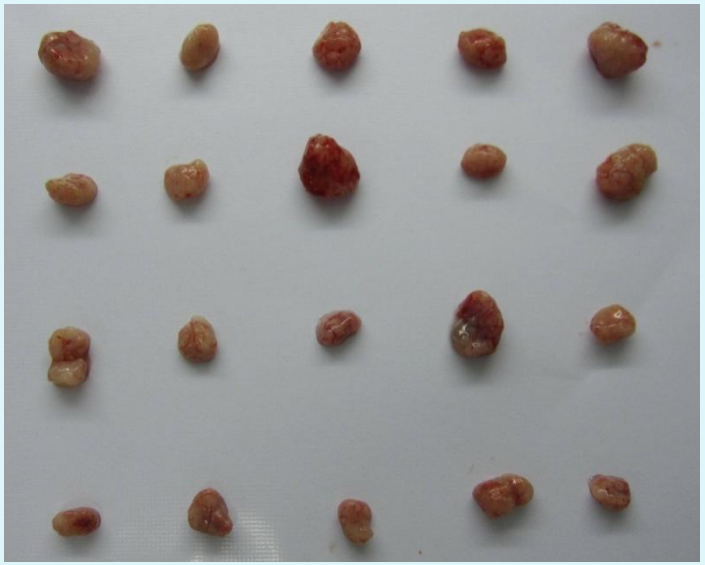
HepG2 ATP1A1 siRNA



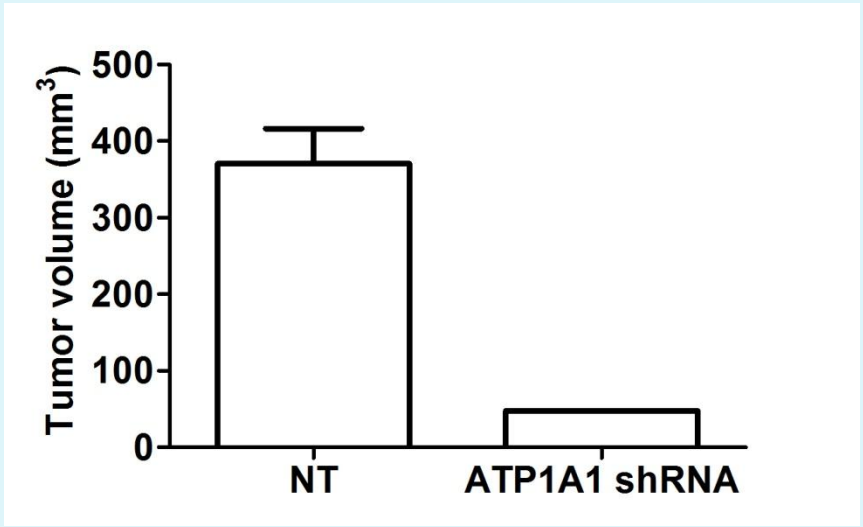


knocking Down α1 Substantially Reduced HCC Tumorigenesis

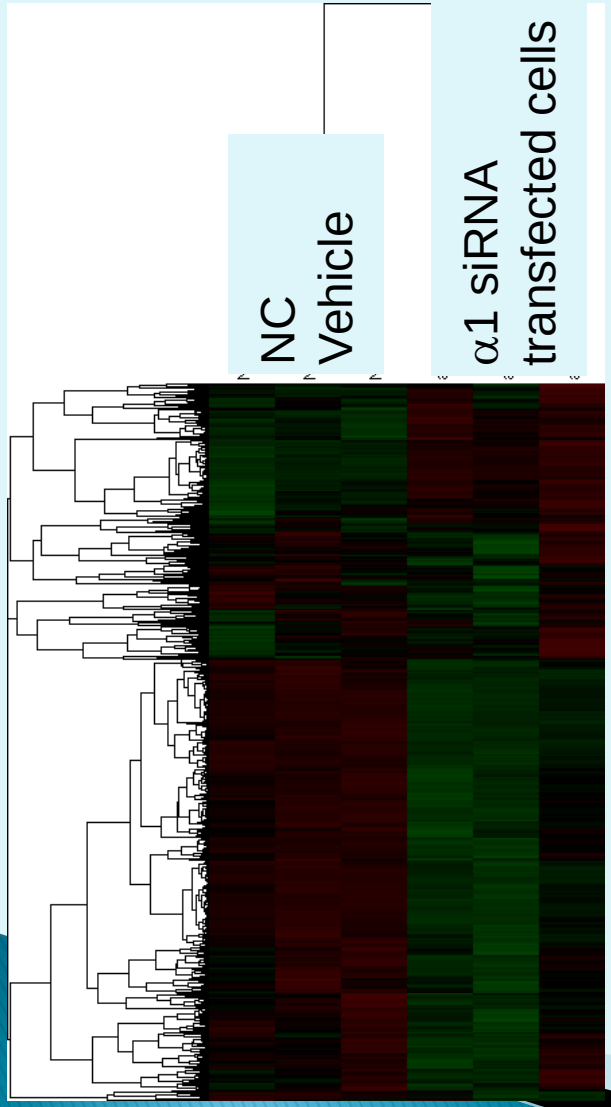
MHCC97H-NT



MHCC97H-ATP1A1 shRNA



Knockdown α1 in HepG2 Cells Markedly Altered Gene Expressions



Reactome pathway	Branches	FDR
Cell cycle	Cell cycle checkpoints (G2/M checkpoints)	<1.111e-04
	Cell cycle, mitotic	<3.333e-04
	Chromosome maintenance	<5.882e-05
Cellular responses to stress	Cellular senescence	8.99e-05
DNA repair	Nucleotide excision repair	2.632e-04
DNA replication	M/G1 transition	<2.632e-05
	Synthesis of DNA	<5.000e-05
Metabolism	Metabolism of lipids and lipoproteins	<3.704e-05
	The citric acid (TCA) cycle and respiratory electron transport	<2.564e-05
	Metabolism of nucleotides	<2.439e-05
	Metabolism of vitamins and cofactors	<1.316e-05
	Metabolism of amino acids and derivatives	<9.091e-05
	Biological oxidations	<2.381e-05

Summary

- **The expression and distribution of Na,K-ATPase α subunits, especially α1 and α3, are differentially regulated in tumor cells compared to that of normal cells.**
- **Na,K-ATPase α1 and α3 subunits are differentially regulated in human colon, pancreatic and hepatocellular carcinoma.**
- **The relative expression of Na,K-ATPase subunits appears to affect the bioavailability and cytotoxicity of cardiac glycoside in pancreatic cancer cells.**
- **Na,K-ATPase α1 may function as a signaling protein in HCC and could be a new target for HCC treatment.**

Acknowledgements

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- Dr Liping Zhuang

Phoenix Biotechnology

- Crandall Addington