



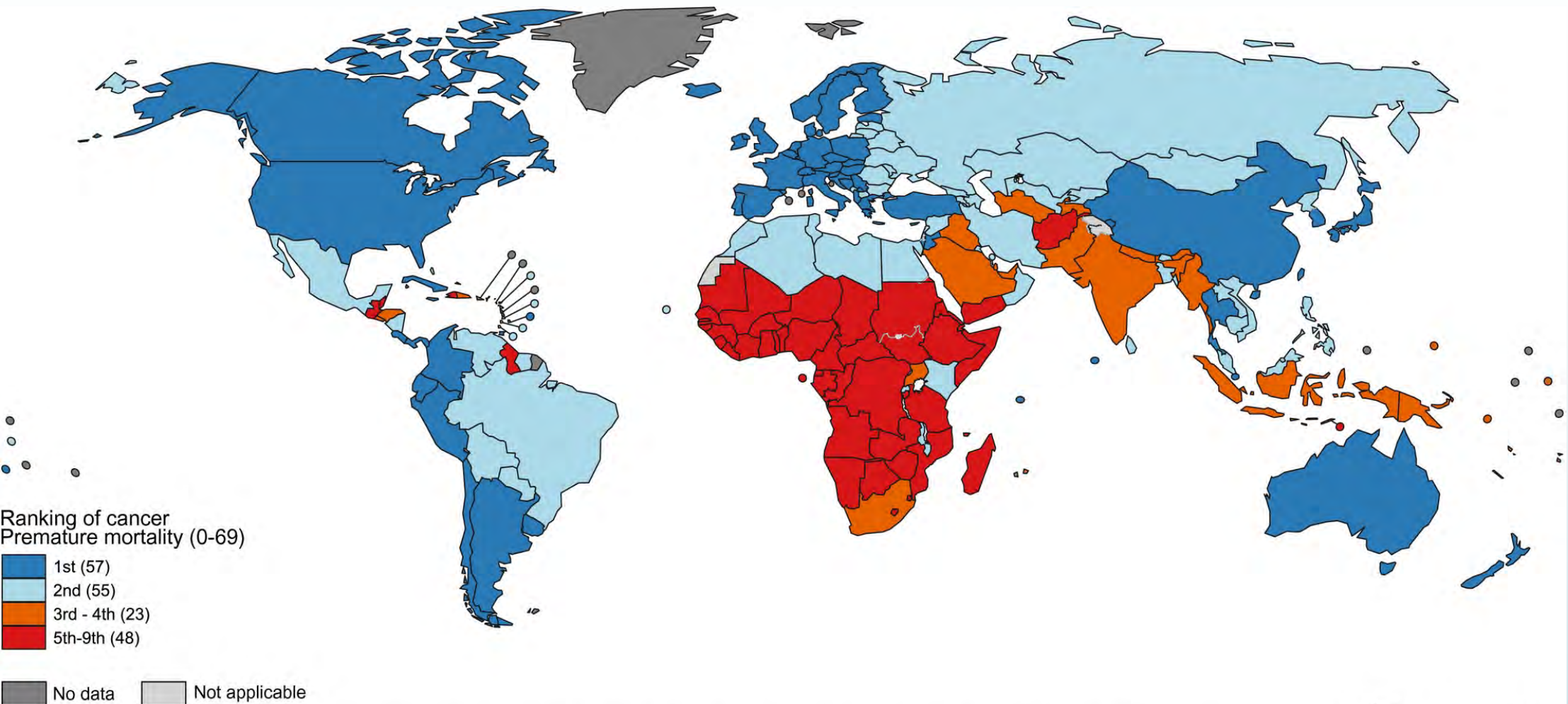
The Potential of Palm Phytochemicals in Cancer Management

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Wayne State University, Detroit, MI

2021

Rate of cancer Mortality



CA: A
cancer
Journal for
Clinicians
Feb 2021

The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

Data source: GHE 2020
Map production: CSU
World Health Organization

CANCER STATISTICS 2021

Estimated New Cases

			Males	Females			
Prostate	248,530	26%			Breast	281,550	30%
Lung & bronchus	119,100	12%			Lung & bronchus	116,660	13%
Colon & rectum	79,520	8%			Colon & rectum	69,980	8%
Urinary bladder	64,280	7%			Uterine corpus	66,570	7%
Melanoma of the skin	62,260	6%			Melanoma of the skin	43,850	5%
Kidney & renal pelvis	48,780	5%			Non-Hodgkin lymphoma	35,930	4%
Non-Hodgkin lymphoma	45,630	5%			Thyroid	32,130	3%
Oral cavity & pharynx	38,800	4%			Pancreas	28,480	3%
Leukemia	35,530	4%			Kidney & renal pelvis	27,300	3%
Pancreas	31,950	3%			Leukemia	25,560	3%
All Sites	970,250	100%			All Sites	927,910	100%

Estimated Deaths

			Males	Females			
Lung & bronchus	69,410	22%			Lung & bronchus	62,470	22%
Prostate	34,130	11%			Breast	43,600	15%
Colon & rectum	28,520	9%			Colon & rectum	24,460	8%
Pancreas	25,270	8%			Pancreas	22,950	8%
Liver & intrahepatic bile duct	20,300	6%			Ovary	22,950	5%
Leukemia	13,900	4%			Uterine corpus	12,940	4%
Esophagus	12,410	4%			Liver & intrahepatic bile duct	9,930	3%
Urinary bladder	12,260	4%			Leukemia	9,760	3%
Non-Hodgkin lymphoma	12,170	4%			Non-Hodgkin lymphoma	8,550	3%
Brain & other nervous system	10,500	3%			Brain & other nervous system	8,100	3%
All Sites	319,420	100%			All Sites	289,150	100%

Estimated New Cancer Cases and Deaths by Sex, USA, 2021

CA: A Cancer Journal for Clinicians, Volume: 71

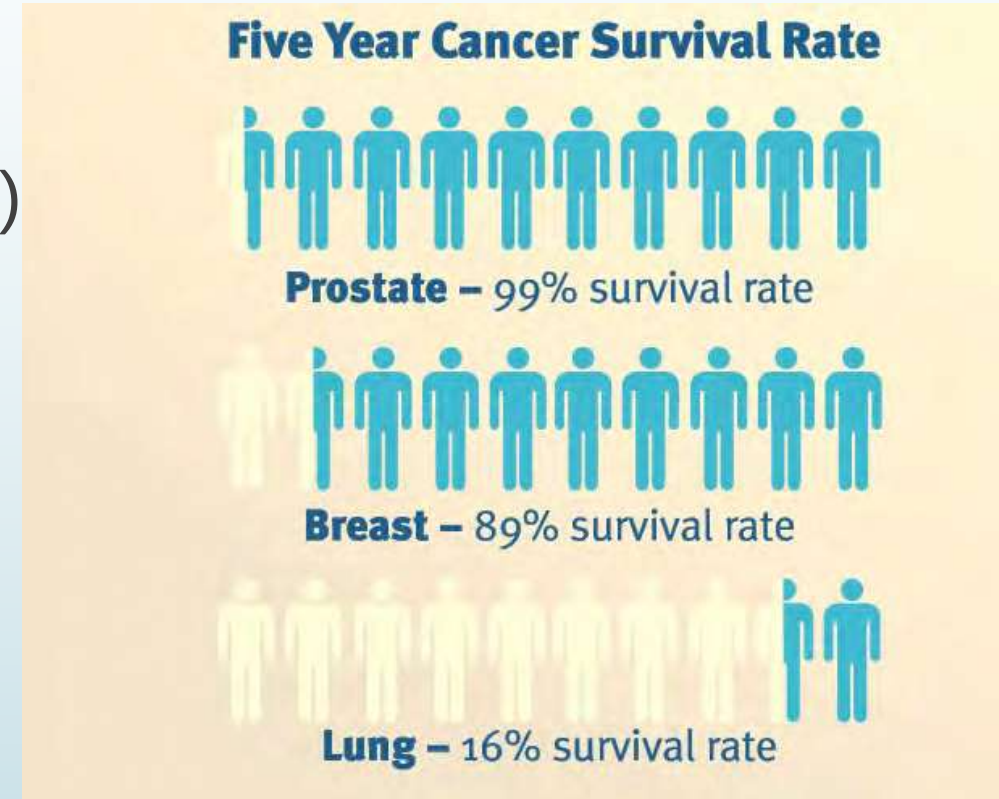


TYPES OF LUNG CANCER

Uncontrolled growth of abnormal lung cells, usually of the lining of air passages.

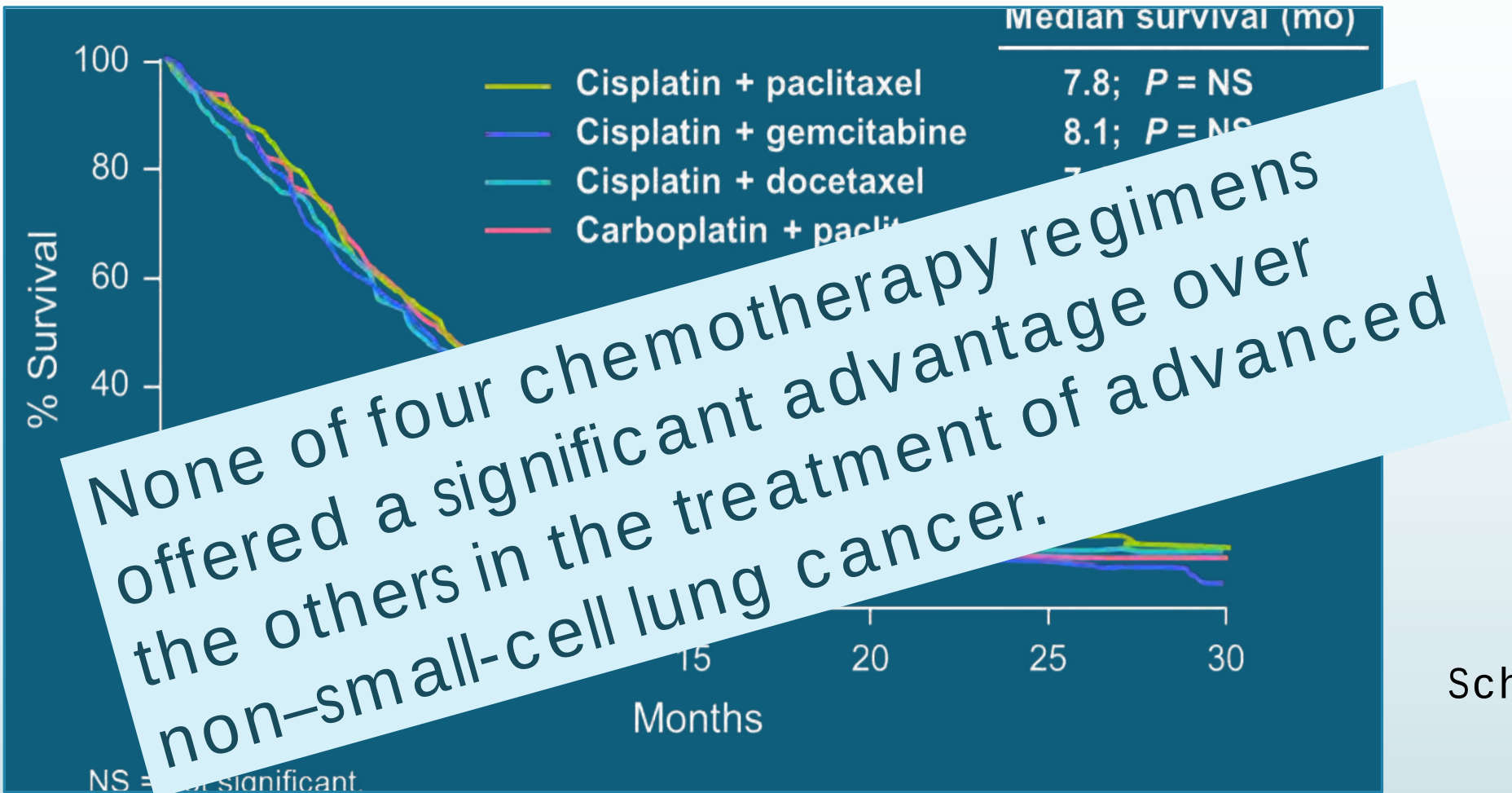
Categorized by cell type:

- Non-Small Cell – 87%
 - Adenocarcinoma (bronchoalveolar)
 - Squamous cell carcinoma
 - Large cell carcinoma
- Small Cell – 10-8%
- Lung Characinoid Tumor - 5%
- 5y survival rate ~ 16%



Source: The National Lung Screening Trial Research Team, NEJM, 2011, American Cancer Society.

Survival of NSCLC Patients (n=1200) using different Chemotherapy Drugs



Schiller JH et al. N Engl J Med. 2002;346:92-98.

NOTCH/GAMMA- SECRETASE INHIBITORS

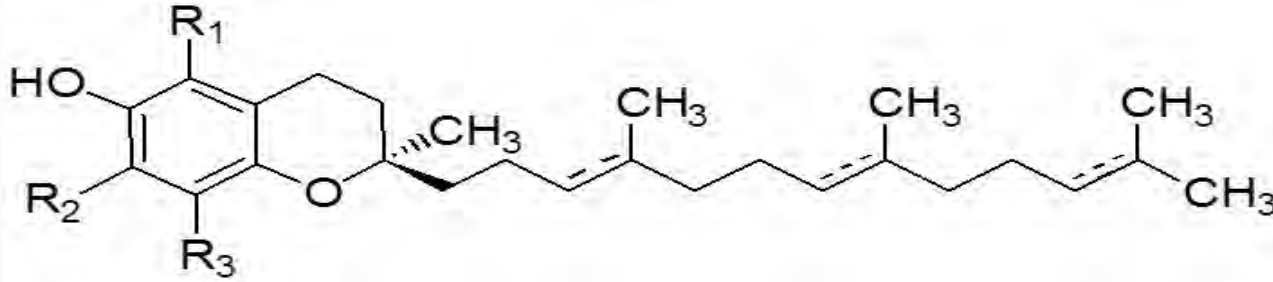
Agent (Manufacturer)	Mechanism	Phase in Development	Clinical Toxicities
LY451039 (Eli Lilly)	γ -secretase inhibitor	III	
MPC7689 (Genentech)	γ -secretase inhibitor	II	
RO4929097 (Roche)	γ -secretase inhibitor	I	Skin rash, N/V, fatigue
Tarenflurbil (Myriad Genetics)	γ -secretase inhibitor	III	Diarrhea, Constipation, nausea, abdominal cramping
			Skin rash, diarrhea, nausea, asthenia
			Fail

Minimally Toxic Inhibitors of Notch Signaling ?
 Dietary Bioactive Compounds ??
 Synergistic effects? Adjuvant Therapy?

Dietary Sources: Oil Palm Phytonutrients



TOCOTRIENOLS - ANTICANCER EFFECTS



- Breast
- Colon
- Melanoma
- Prostate

Isomer	R1	R2
α	CH3	CH3
β	CH3	H
γ	H	CH3
δ	H	H

Wali, V.B. and Sylvester, P.W. Lipids 43:1113-1123.

McAnally JA, et al. Cancer Lett 2003; 202: 181-92.;

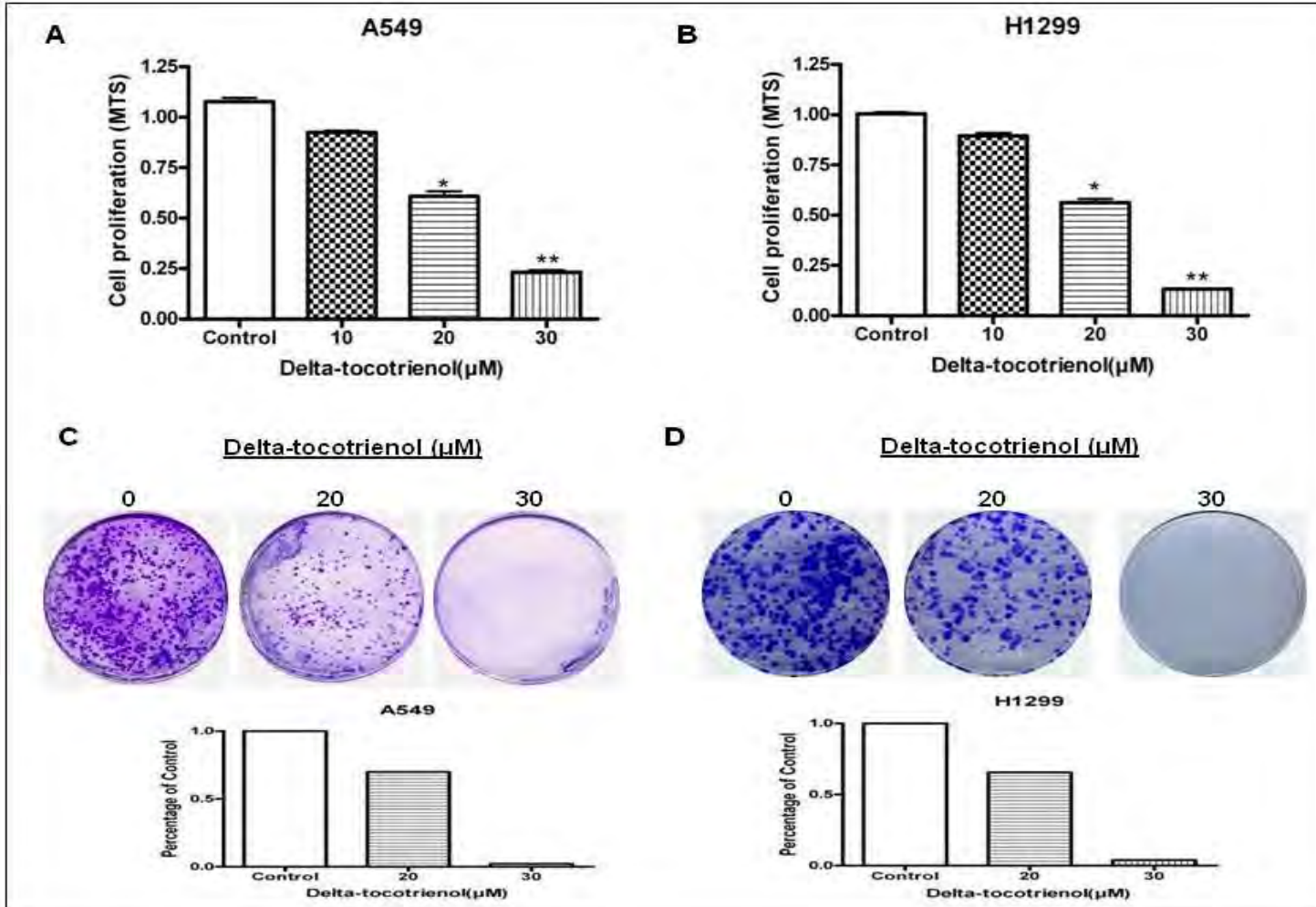
Nesaretnam, et al. Annals of the New York Acad Sci.1031: 143–157.

Central Hypothesis

Tocotrienols will behave as
preventative/therapeutic/adjuvant
micronutrients in
Non Small Cell Lung Cancer (NSCLC)



Tocotrienols inhibits cell proliferation of NSCLC adenocarcinoma cells (A549;



MTT assay;
72 h

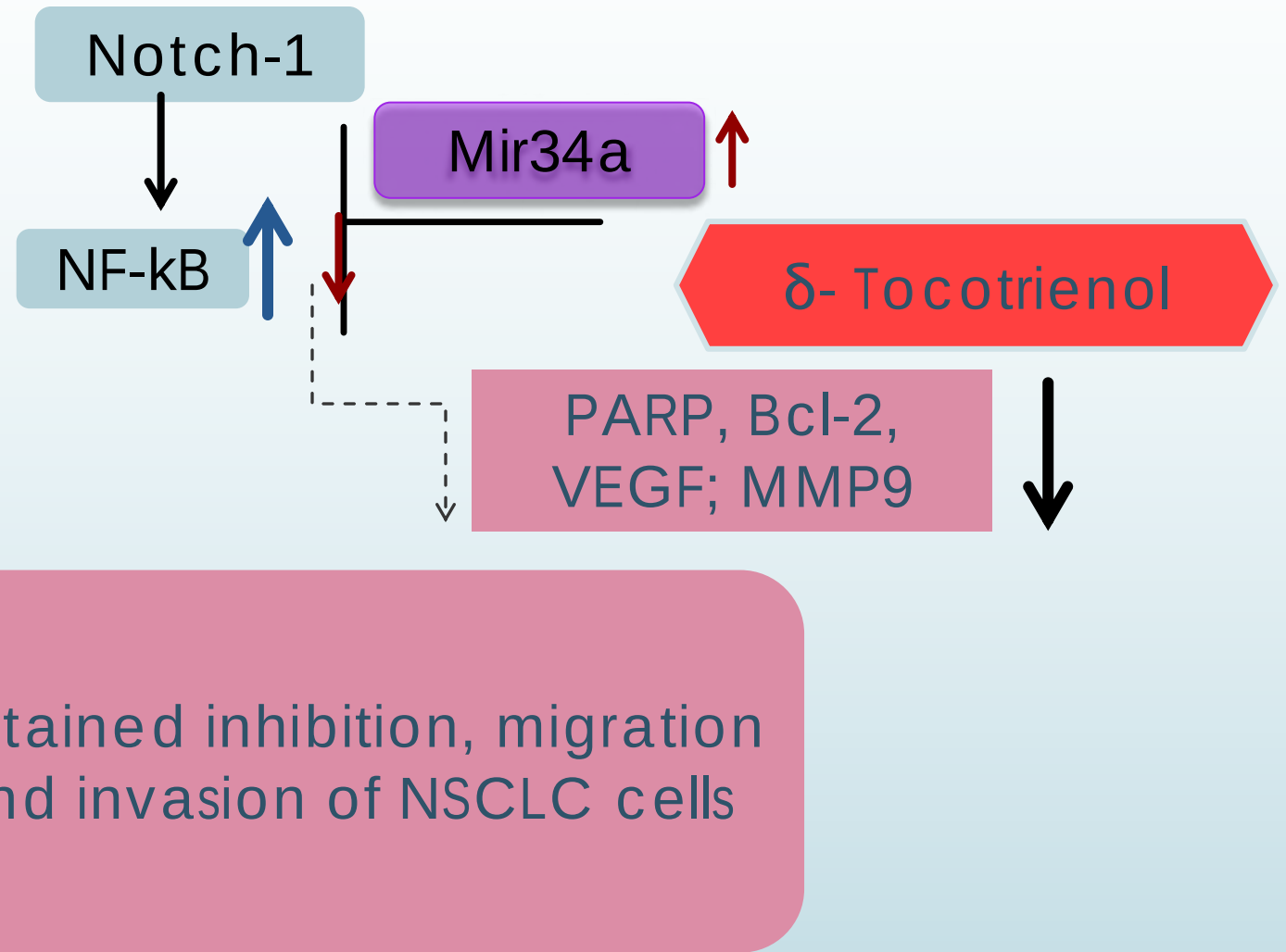
Clonogenic
Assay
21 days

Ji et al., J. Cell. Biochemistry. 2011

Tocotrienols modulates NOTCH signaling in NSCLC cells via up-regulation of the tumor suppressor, miRNA 34a

Delta-tocotrienol Suppresses Notch-1 Pathway by Up-regulating miR-34a in Non-small Cell Lung Cancer Cells. *International J. Cancer. 2012*

Tocotrienols rich mixture inhibits cell proliferation and induces apoptosis via down-regulation of the Notch-1/NF- κ B pathways in non-small cell lung cancer cells (NSCLC). *J. Nutrition and Dietary Supplements. 2017.*

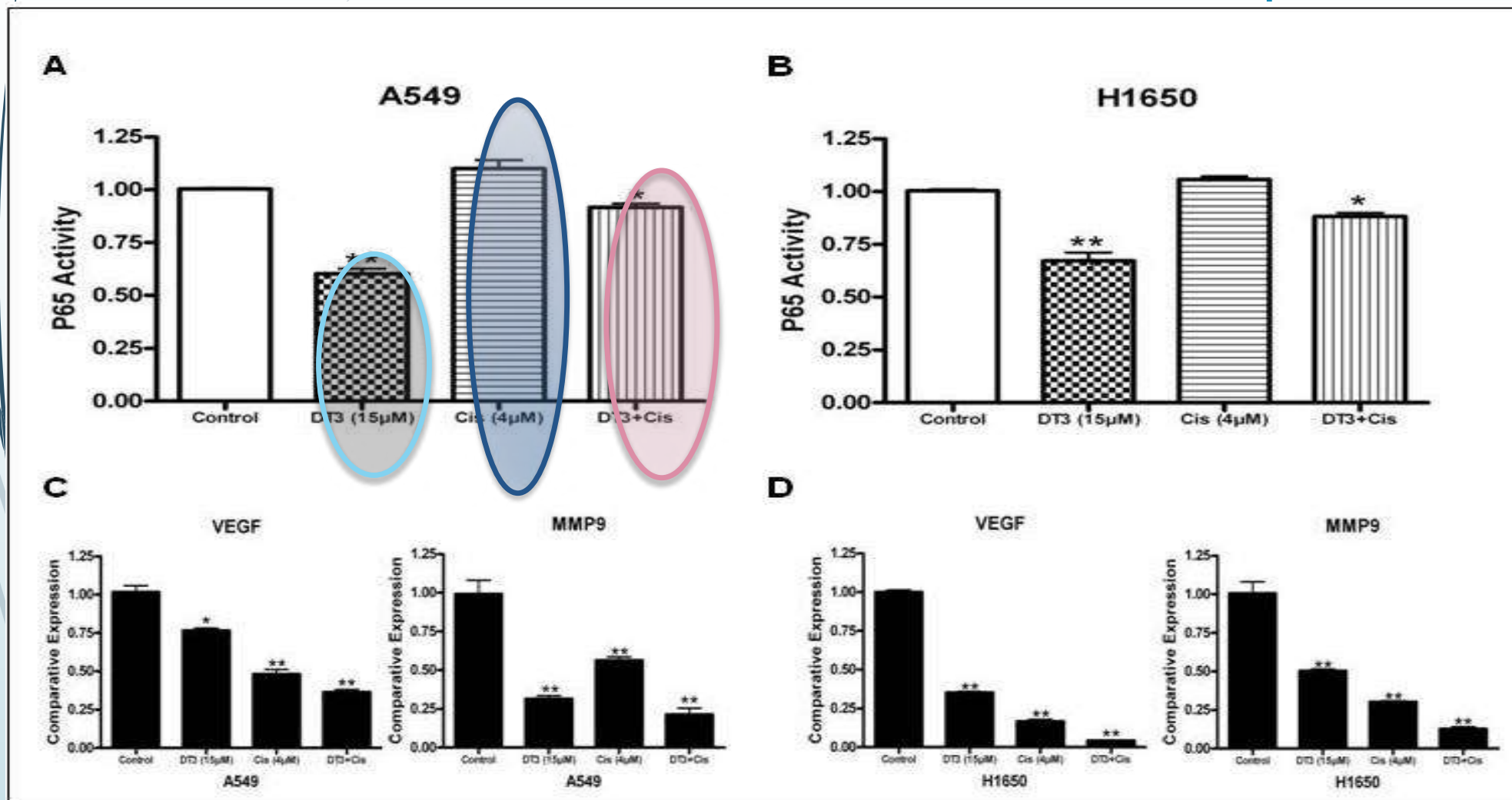


*Are there any Beneficial effects of using
Tocotrienols in conjunction with Cisplatin
on NSCLC cells?*



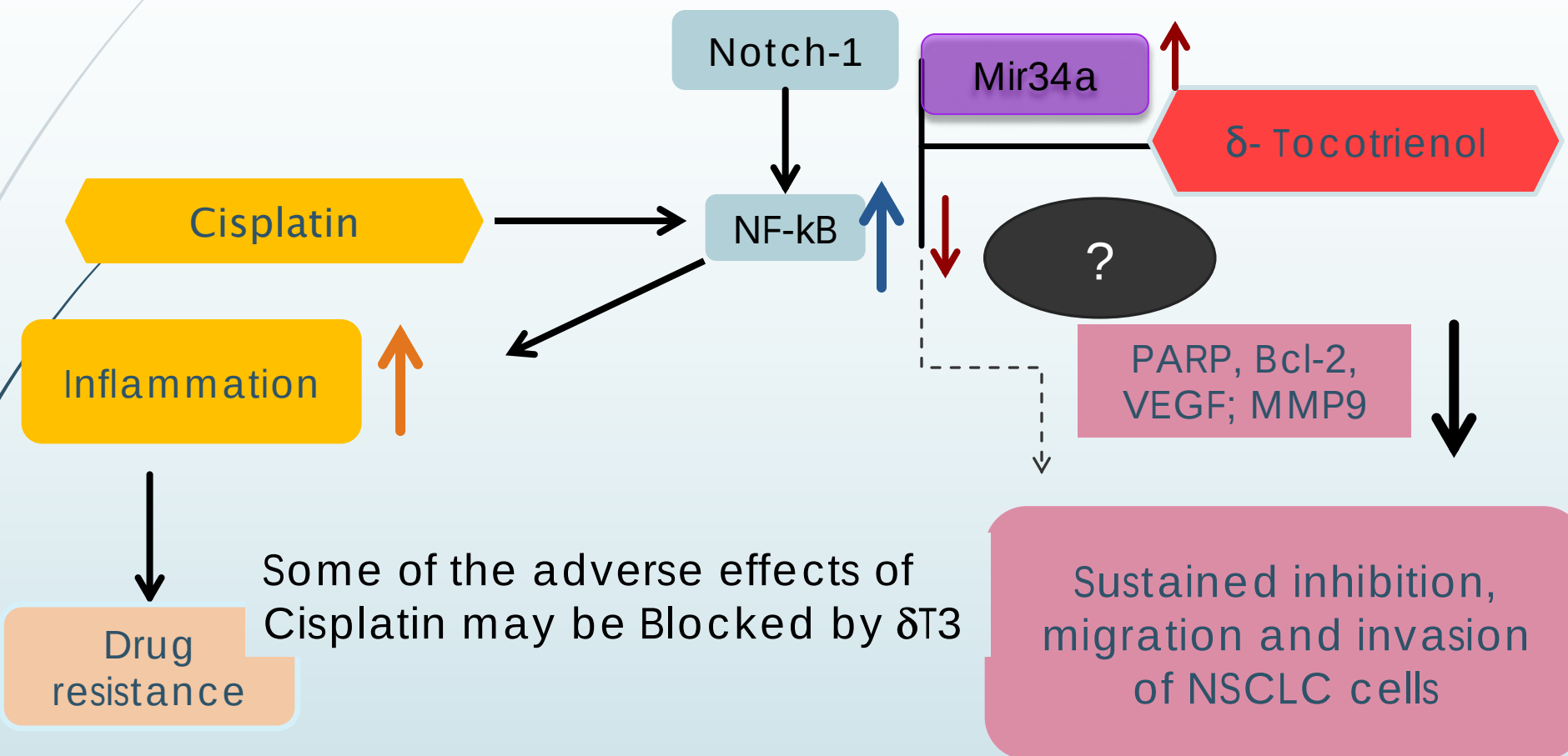
Ji X, Wang Z, Sarkar FH, Gupta SV.
Anticancer Res. 2012 Jul;32(7):2647-55.

Down-regulation of NF- κ B activity and its down-stream genes by Tocotrienols (δ T3) and the combination of δ T3 and cisplatin



Delta-tocotrienol augments cisplatin induced suppression of non-small cell lung cancer cells via inhibition of the Notch-1 pathway.

Anticancer Research 2012



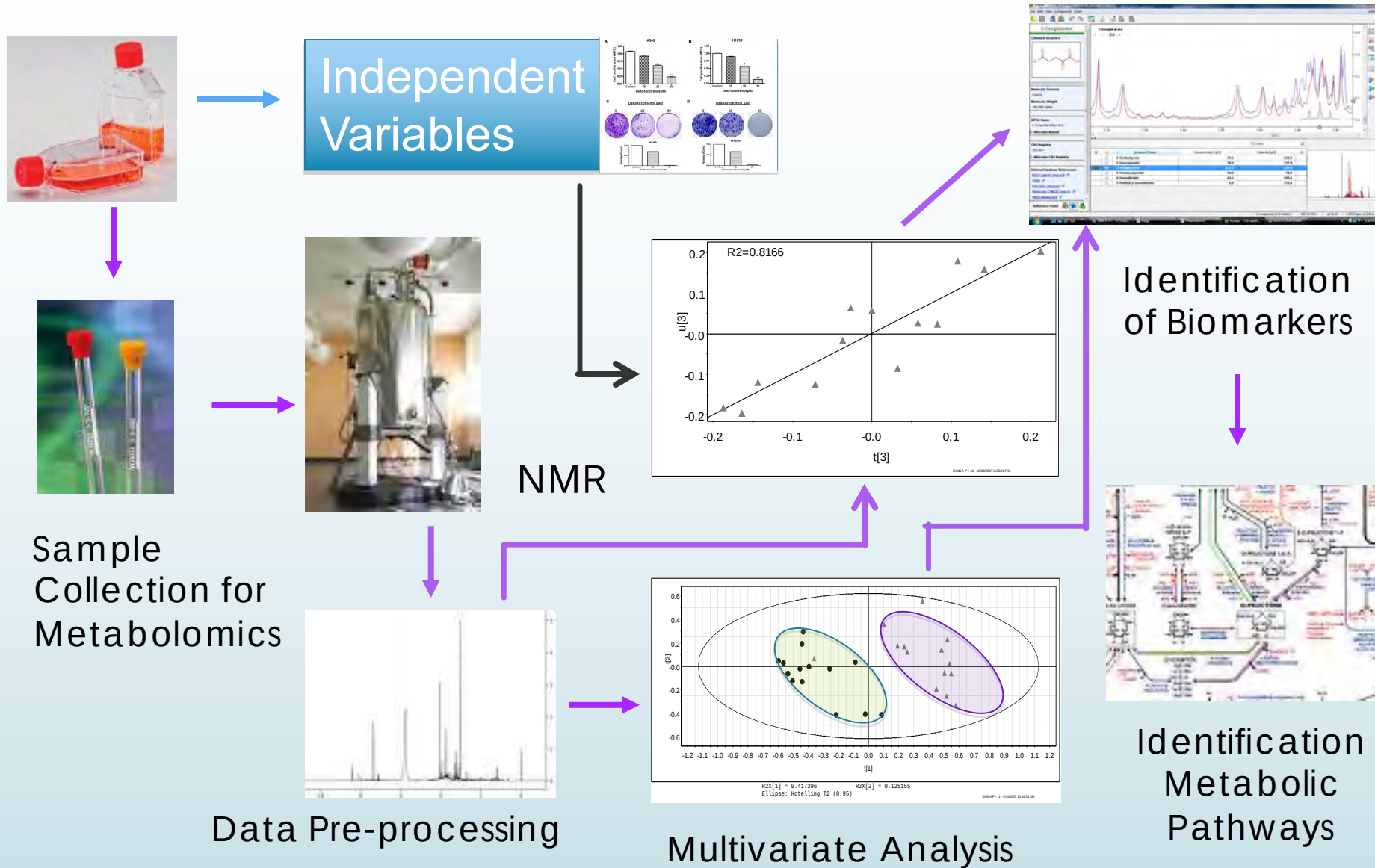
POTENTIAL Therapeutic Combination

Will Tocotrienols cause a change in the Metabolomic Profiles of NSCLC adenocarcinoma cells?

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What are the metabolites responsible for the change ??

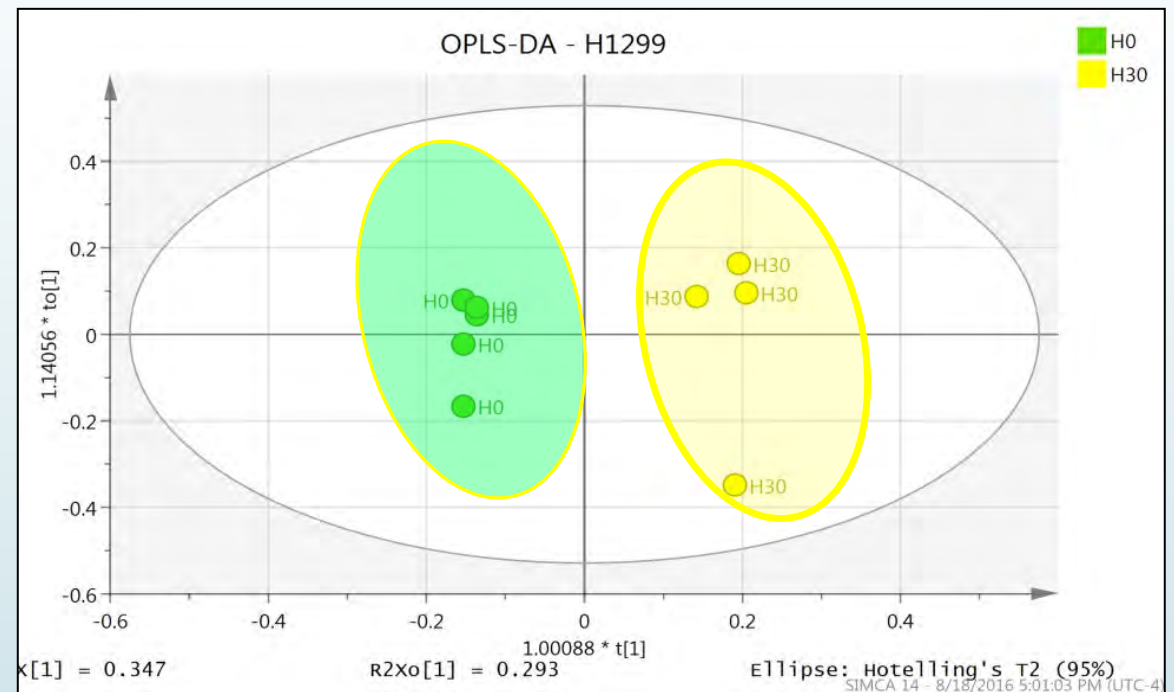
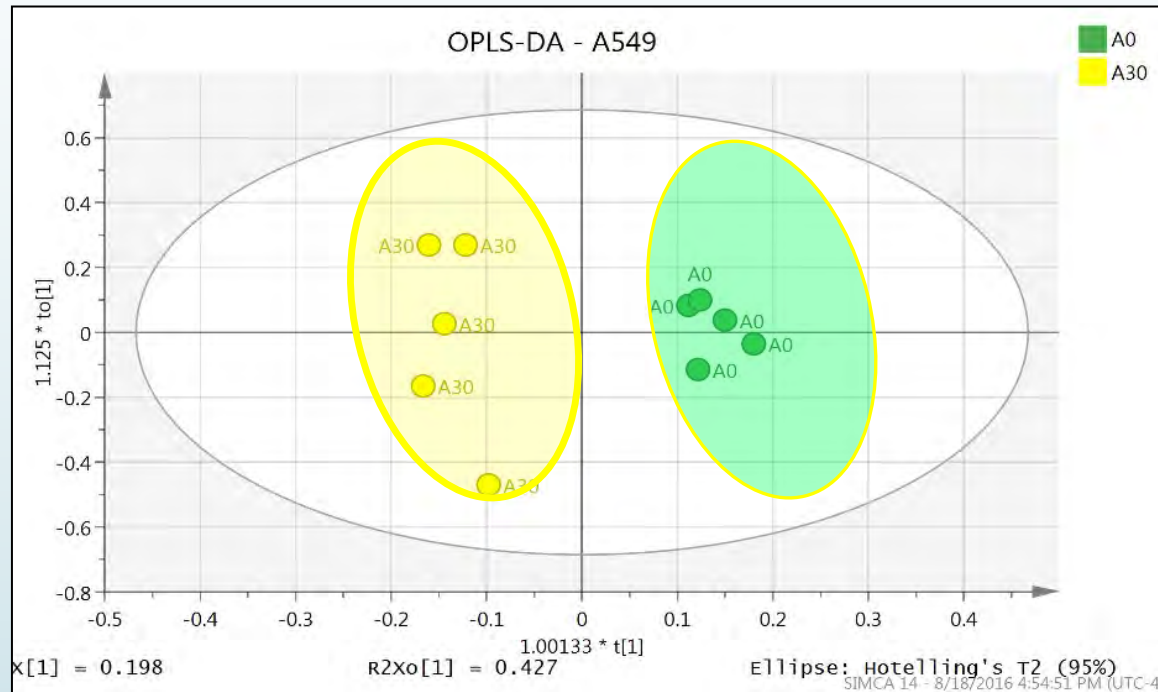
Metabolomics: Approach



Differences in the endo-Metabolome of untreated and Tocotrienol treated (30 μ M/72h) cells (^1H NMR 700MHz)

A549

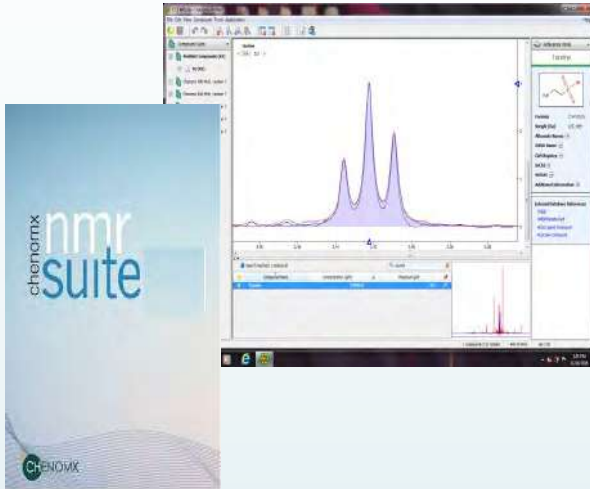
H1299



Metabolite Identification and Quantification

A549

Compound	p.value
Leucine	0.0031094
Asparagine	0.011165
Glutathione	0.01941
Glutamate	0.022502
Glycine	0.028151
Alanine	0.028325
Aspartate	0.031958
Lactate	0.036552
Glutamine	0.038622
2-Oxoglutarate	0.045169



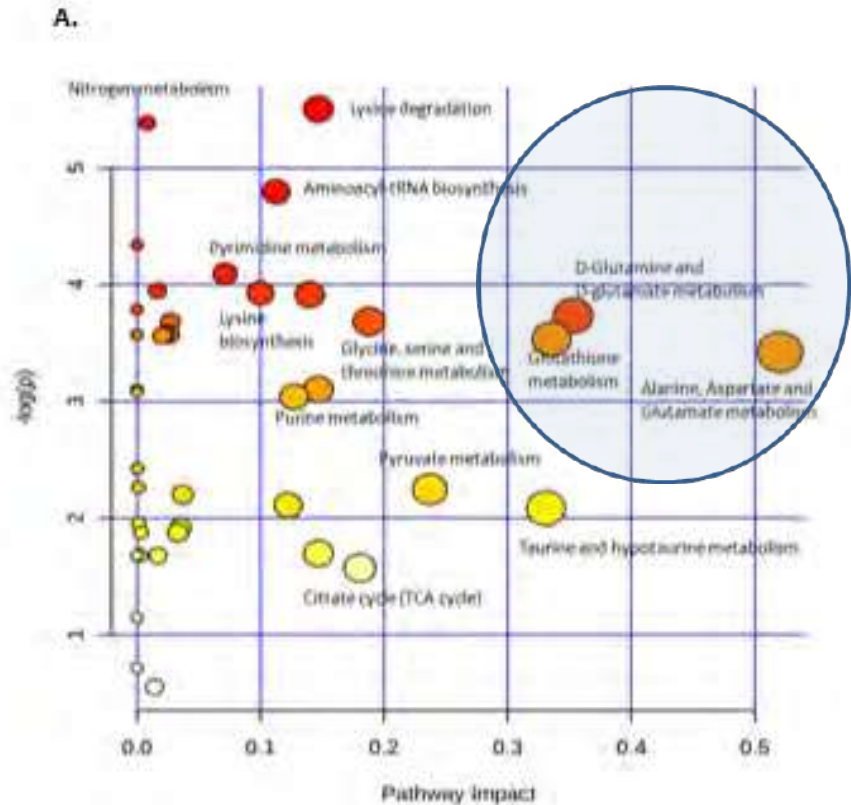
Chenomx NMR Suite

H1299

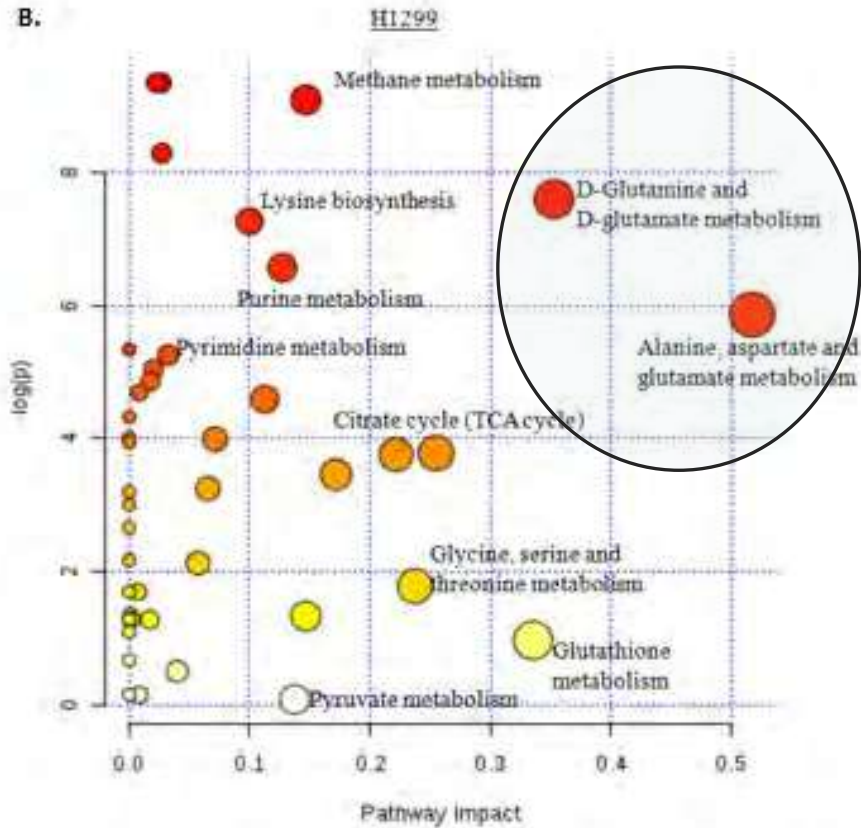
Compound	p.value
Leucine	9.76E-06
Dimethylamine	8.44E-05
AMP	0.0015987
Malate	0.0060782
Glutamate	0.006445
Aspartate	0.0085607
Alanine	0.01509
Histamine	0.027741
Glutamine	0.027915
Cystine	0.028024
Succinate	0.030707
Uracil	0.031634
Citrate	0.032505
Isoleucine	0.037876
2-Oxoglutarate	0.041127
ADP	0.04928
Arginine	0.049656

Pathway Analysis : MetaboAnalyst

A549



H1299



Key aberrant pathways

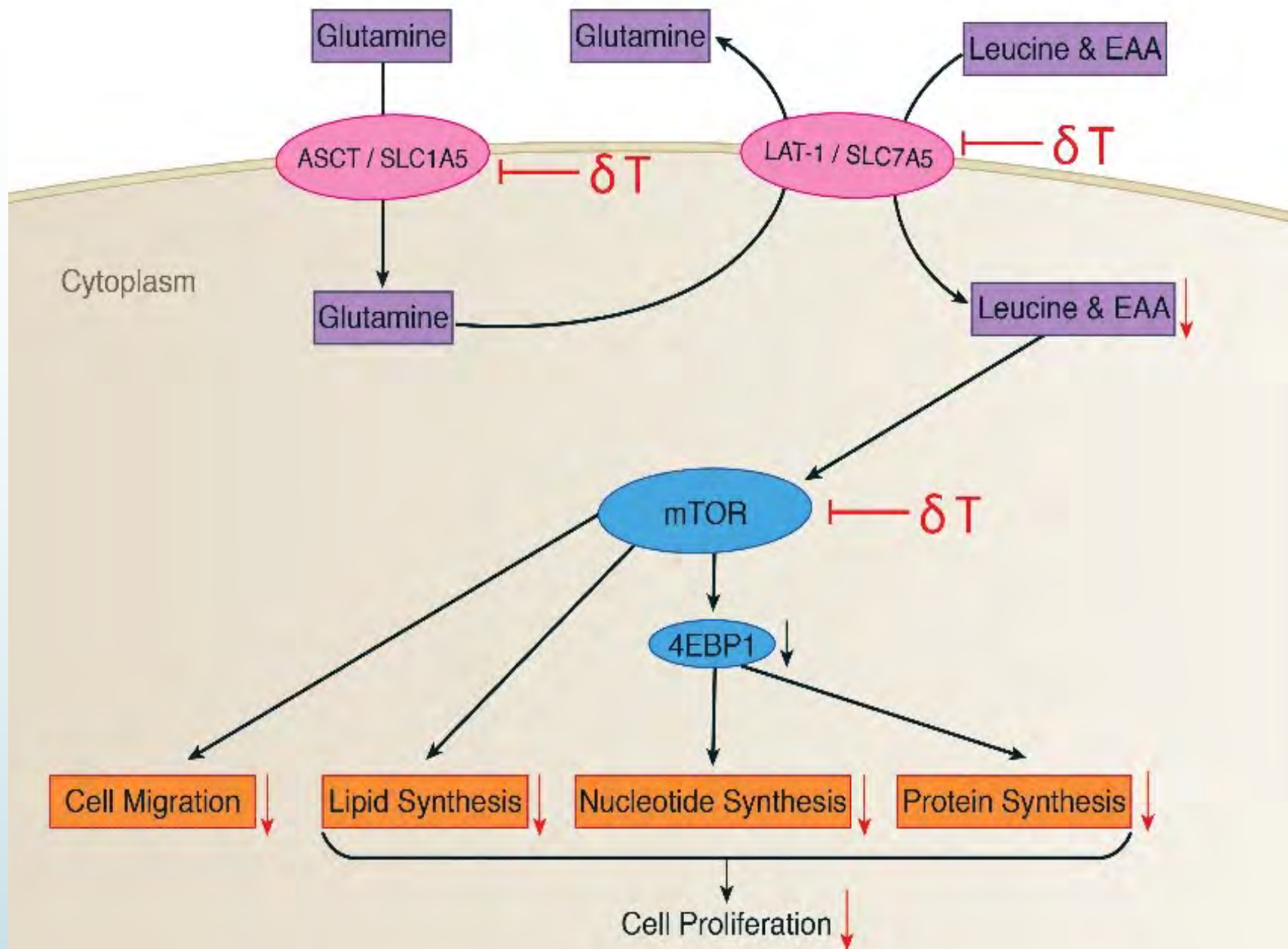
- D-glutamate and Glutamine
- Alanine, aspartate & Glutathione
- TCA cycle,

CONCLUSION

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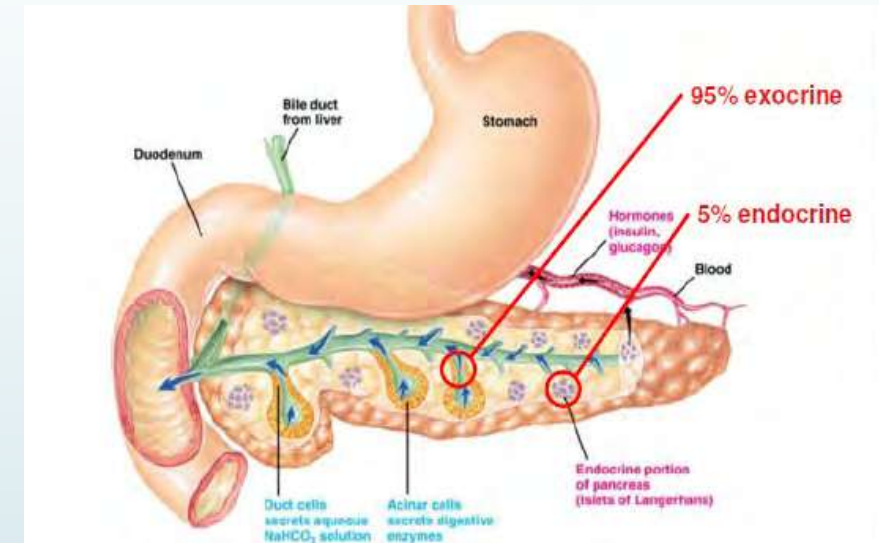
Delta Tocotrienol inhibits NSCLC cell proliferation by downregulation of mTOR via inhibition of glutamine receptors and decrease in Glutamine uptake

Rajasinghe, Hutchings & Gupta
Metabolites, 2019



Effect of OIL PALM PHENOLICS (OPP) in PANCREATIC CANCER

- Fourth leading cause of cancer-related mortality in the US.
- Poor Prognosis
 - 5 year survival rate < 5%.
 - Only 10% of patients are eligible for potentially curative surgery
 - Late diagnosis
 - Drug resistance
- Exocrine 95%



Pancreatic Cancer: Treatment Options

- Surgical resection
 - possible for 20% tumors—Pancreatico-duodenectomy (Whipple procedure)
- Radiation and Chemotherapy
 - Gemcitabine-drug of choice has only 10-15% response

Bioactive food components

- have shown promising results in treatment and even prolonging the survival time after diagnosis.



OIL Palm Phenolics (OPP)

Table 1. Concentrations of major phenolic components in oil palm phenolics (OPP)*

(Mean values, standard deviations and ranges)

Phenolic compounds	Concentration (mg/kg)		
	Mean	SD	Range
Protocatechuic acid	600	100	400–800
<i>p</i> -Hydroxybenzoic acid	7000	1000	5300–8600
Caffeoylshikimic acid (total of three isomers)	10 800	2400	7700–15 100
Total major phenolics	18 400	2900	13 800–24 300
Gallic acid equivalents	18 200	1700	15 700–21 300

* Values are on a dry weight basis (mg of each major phenolic component for every kg of freeze-dried OPP) and represent triplicate analyses of OPP samples processed from the aqueous by-products obtained from six different Malaysian palm oil mills according to the methods described by Sambanthamurthi *et al.*⁽¹⁴⁾.

Ravigadevi Sambanthamurthi
Kalyana Sundrum
Sayed Fairus
Leow Soon Soon
Sekaran, Sharmala

[Sambanthamurthi R1, Tan Y, Sundram K, Abeywardena M, Sambandan TG, Rha C, Sinskey AJ, Subramaniam K, Leow SS, Hayes KC, Wahid MB.](#)

Oil palm vegetation liquor: a new source of phenolic bioactives

British Journal of Nutrition (2011), 106, 1655–1663



Palm Phenolics and Pancreatic Cancer: Working Hypothesis

OPP will display anti-cancer properties in pancreatic cancer model.

Investigation of *In vitro* effects of OPP
BxPC3 ; Panc-1

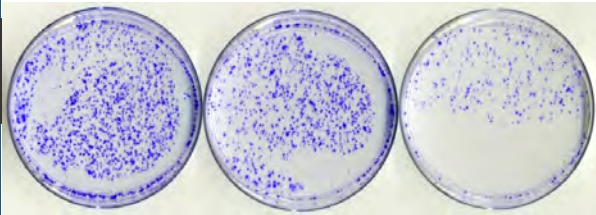
Gupta, SV, 2015 Anticancer Research 35: 97-106

PJ(μ l/ml)

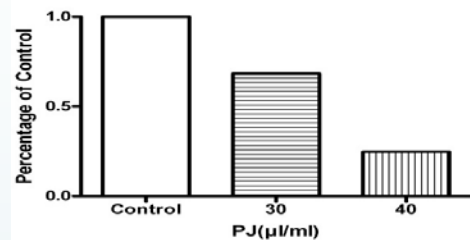
0

30

40



PANC-1



Oil Palm Phenolics

NF- κ B

VEGF,
MMP-9
Gene expression

Invasion,
Migration

Bcl- X_L ,
Survivin
cleaved Caspase 3,9

Cell Cycle Arrest in S phase
Cell Growth,
Apoptosis

Gupta, SV, 2015 Anticancer Research 35:
97-106



Investigation of *In vivo* effects of OPP in Pancreatic cancer transgenic mouse model

KPC: *Kras^{LSL.G12D/+}; p53^{R172H/+}; PdxCretg/+*

Clinically relevant model of Pancreatic Ductal carcinoma (PDA)



Study Design



Mice

KPC mice
(Kras^{LSL.G12D/+};
p53^{R172H/+};
PdxCre^{tg/+})

Control Mice
(Littermates without
mutation tg/+)

KC
Isocaloric control
diet/Saline
Nn8

KP
0.05% OPP diet / saline
n=8

KG
Control diet/ gemcitabine
n=8

KPG
OPP diet/gemcitabine
n=8

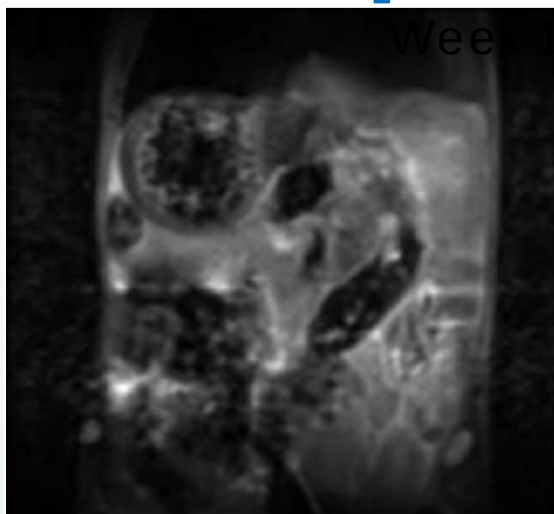
CC
Control diet/Saline
n=5

CP
OPP diet/saline
n=5

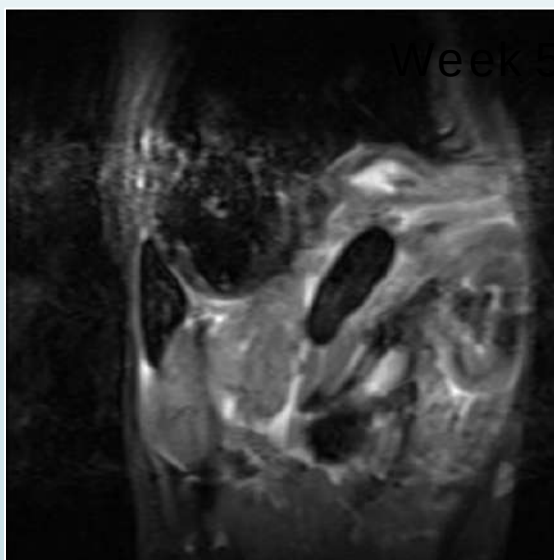
Effect of OPP on Tumor Volume (MRI)

KC : ↑

Week 1

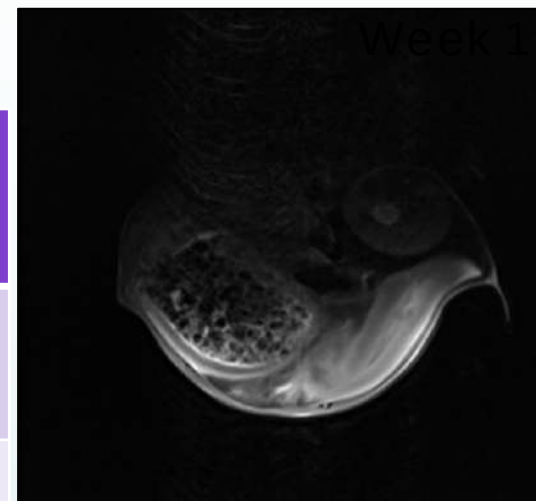


Week 5

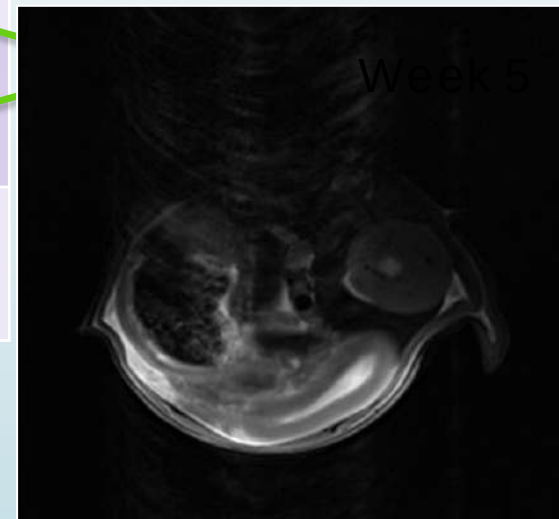


KP : ↓

Week 1

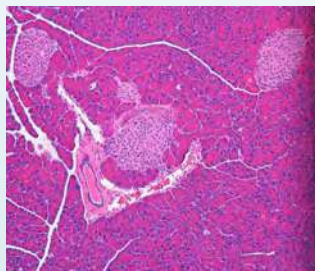
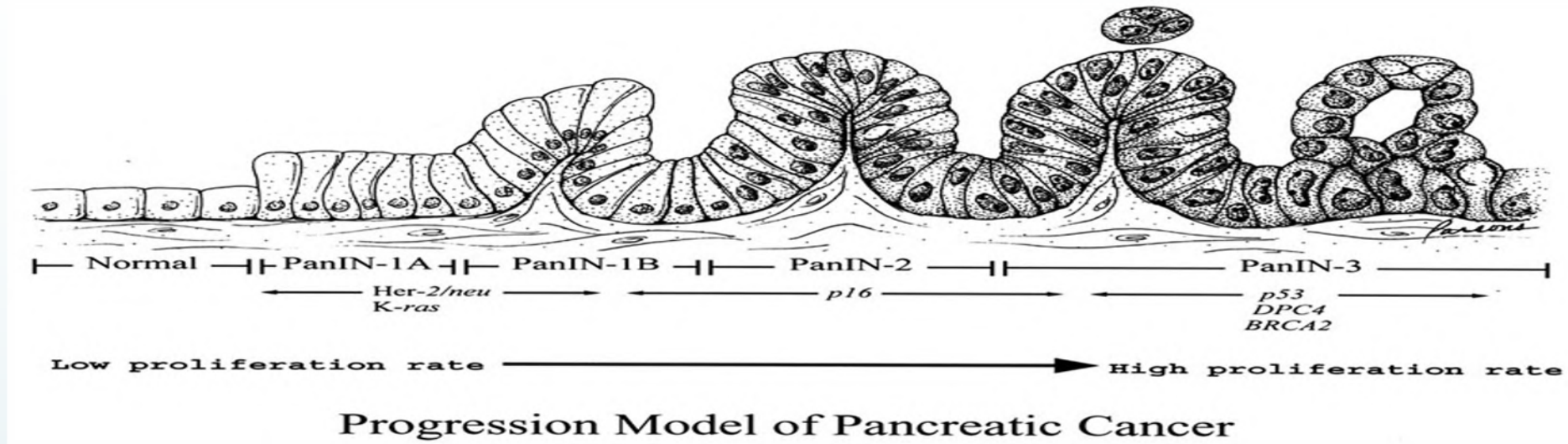


Week 5

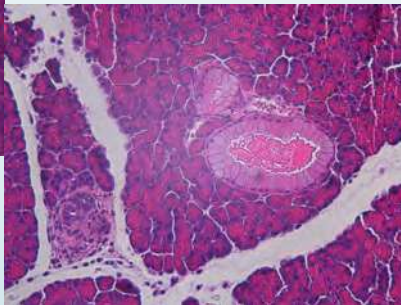


Group	Total # of Tumors	Size Increase	Size Decrease
KC	10	7	-
KGm	10	4	1
KP	10	4	6
KPG	7	3	2

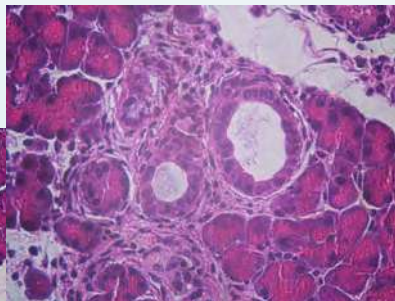
Histology: PaCa Progression Model



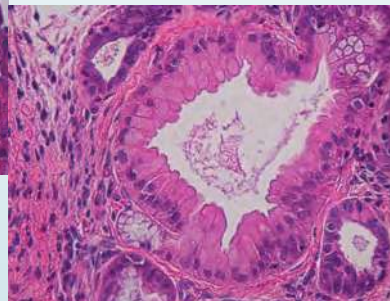
Normal



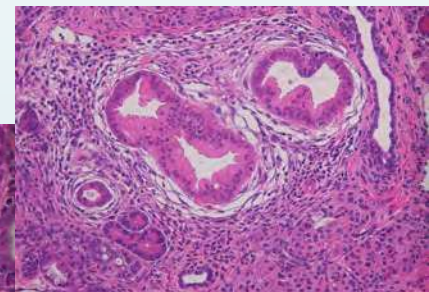
PanIN-1



PanIN-2



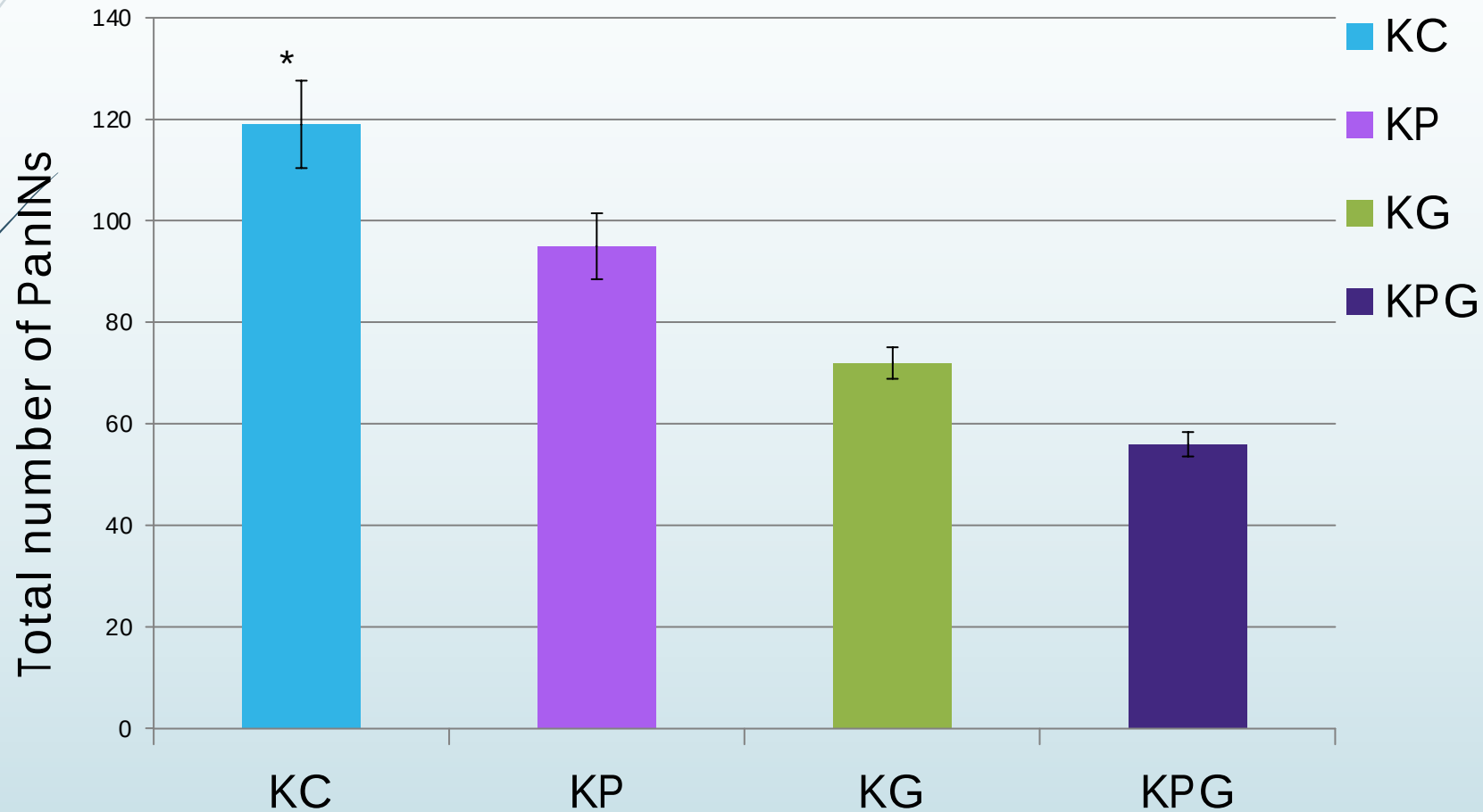
PanIN-3



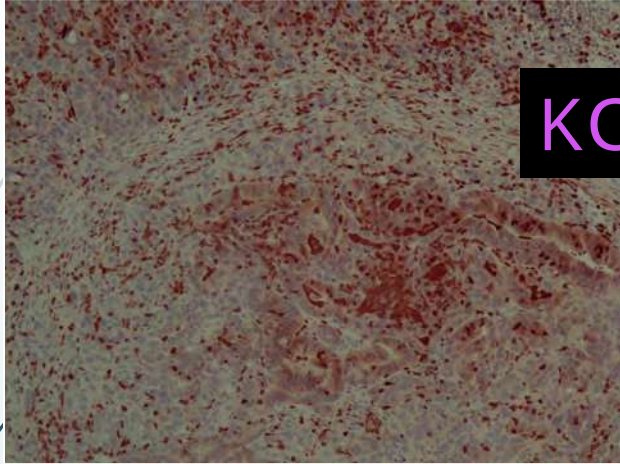
Adeno
Carcinoma

Hruban, et al "Cancer Research 66.1 (2006): 95-106.

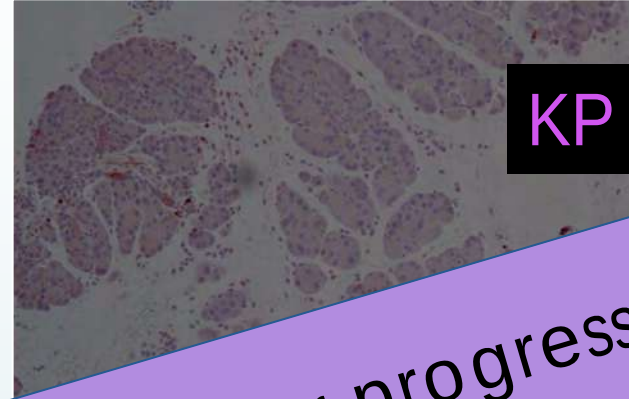
Total Number of Pancreatic Lesions were significantly ↓ in the treated groups as compared to Control animals



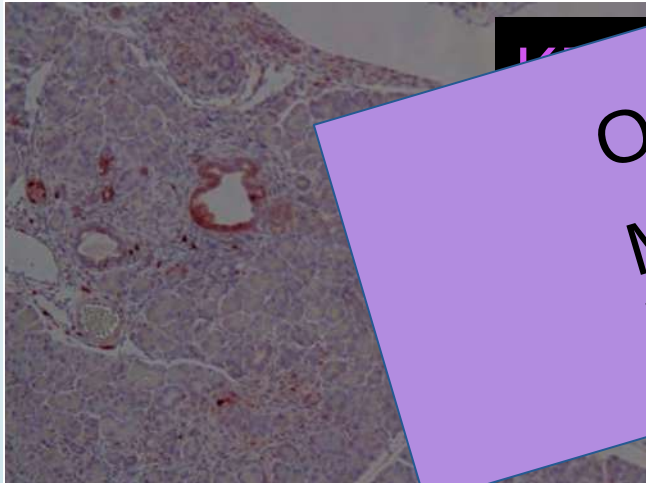
Confirmation of Cancer Reduction in Treated Groups by Immunohistochemistry with S100P (10X)



KC 6



KP 3

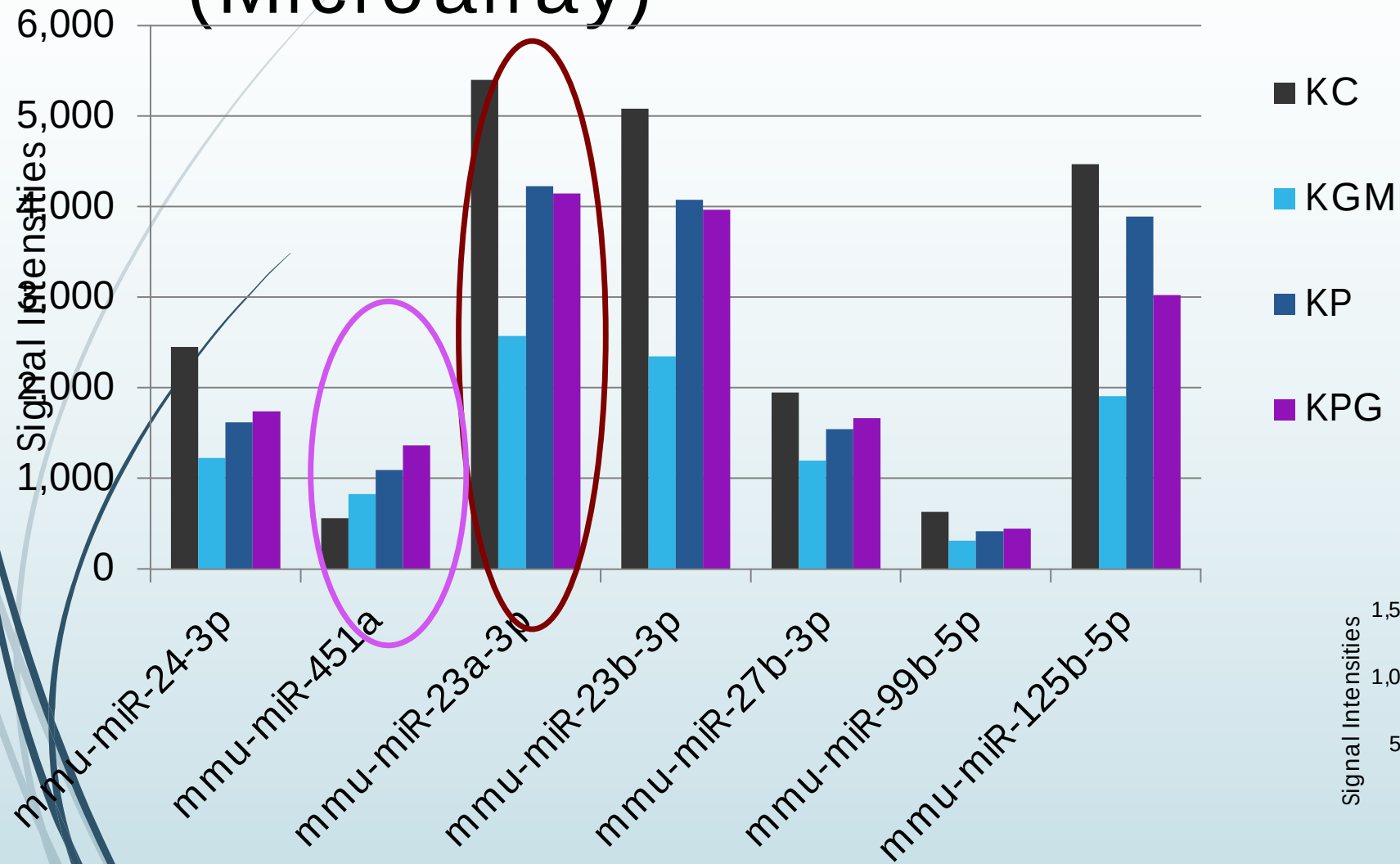


KP 6

OPP reduced tumor progression
MRI; Histology;
Immunohistochemistry

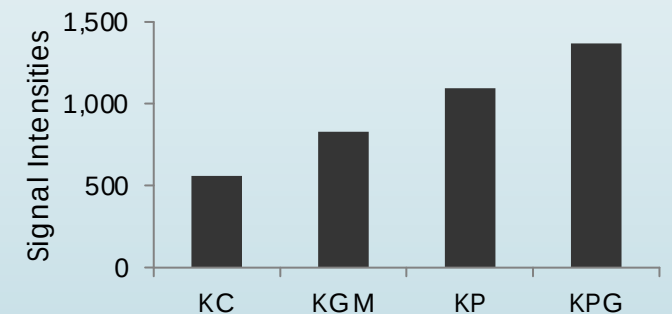
Mechanism??

Cancer Related miRNA were Significantly Regulated with Treatment (Microarray)

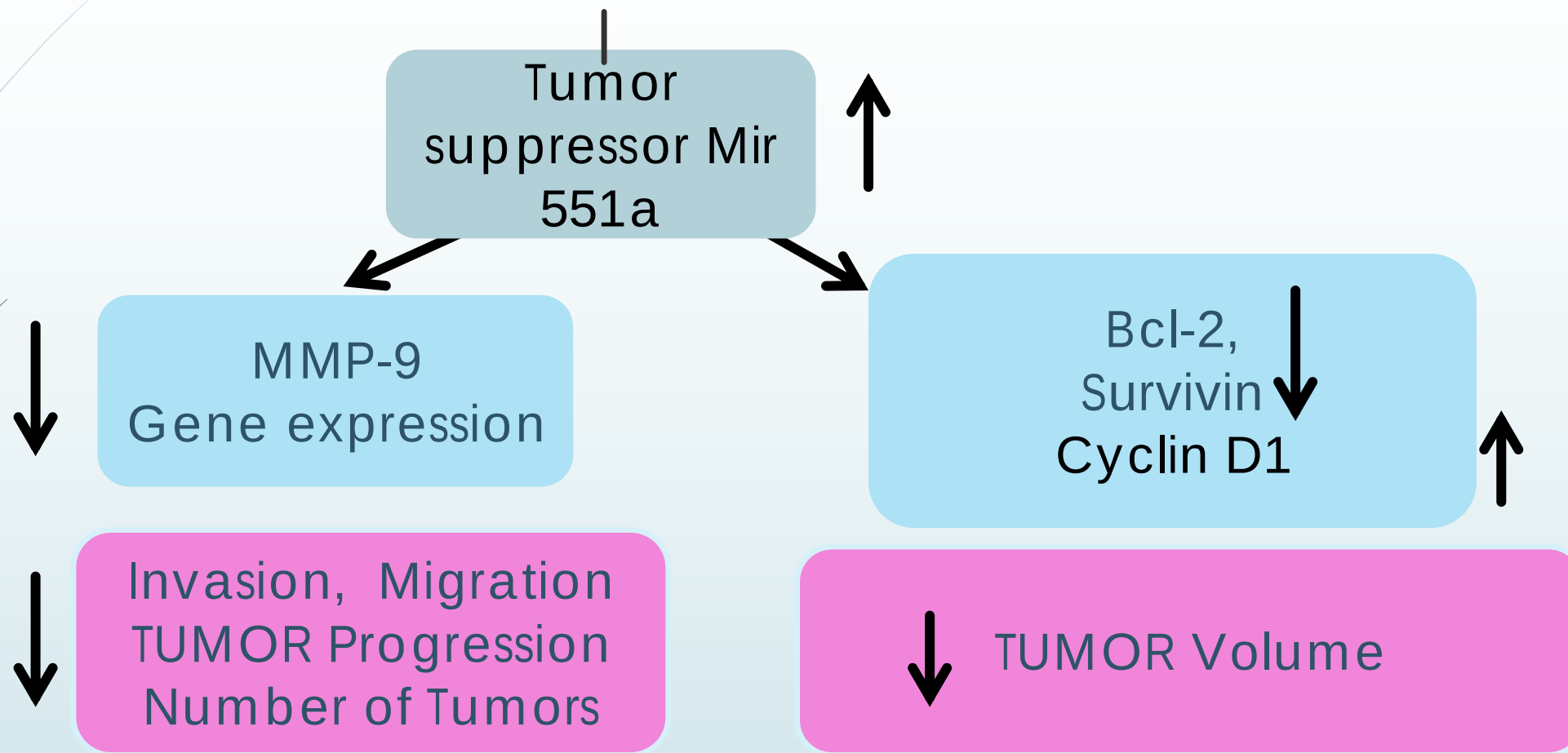


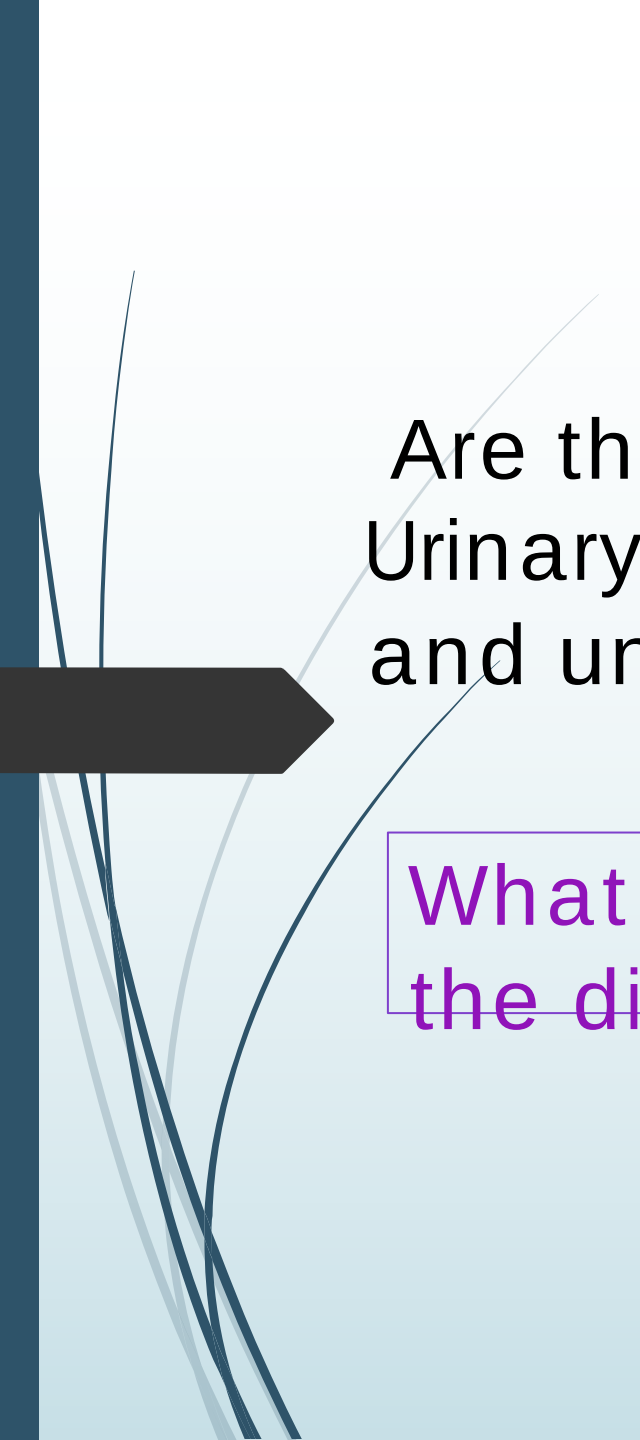
Validated by
RT-PCR

mmu-miR-451a



Oil Palm Phenolics

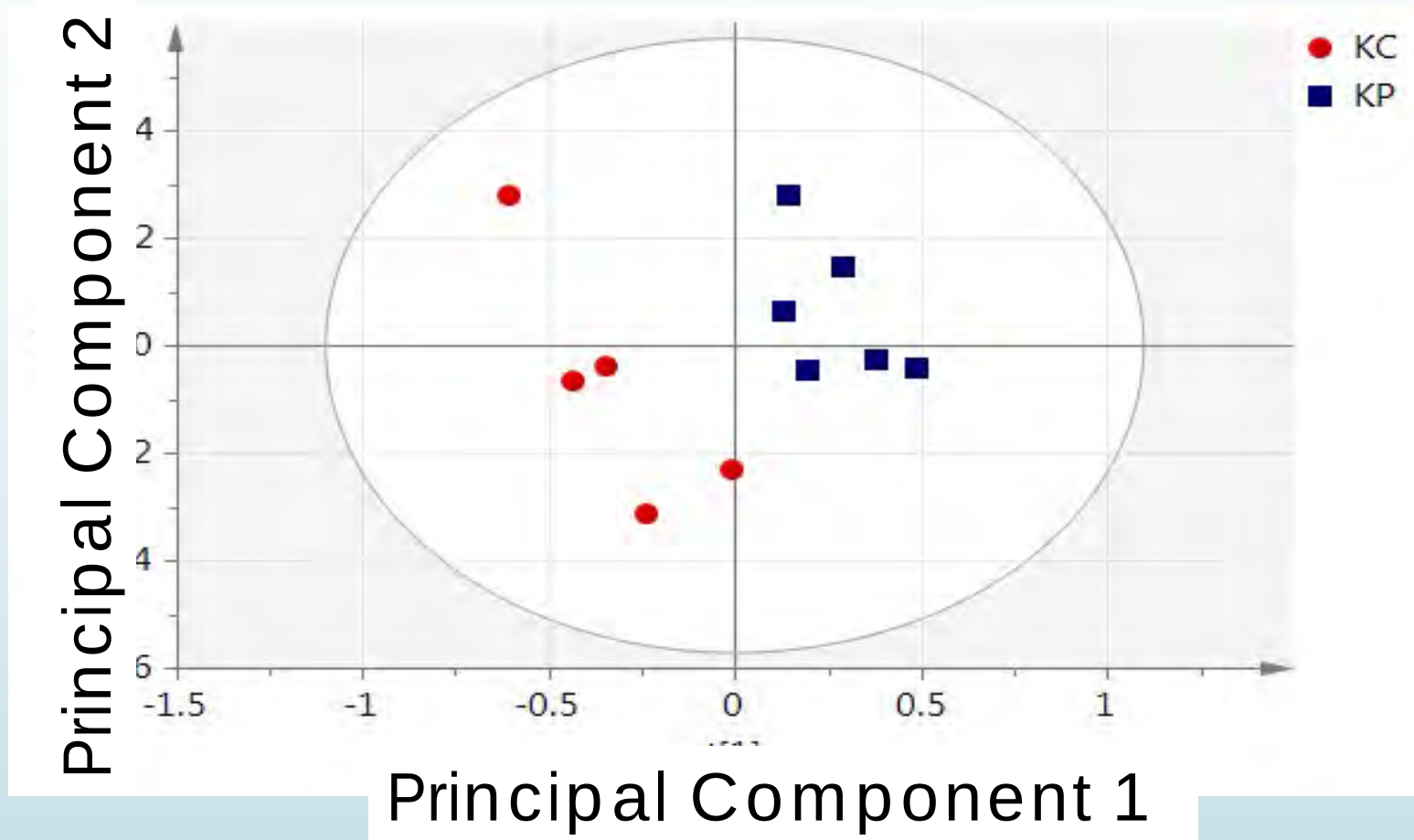




Are there any differences in the ^1H NMR
Urinary Metabolomic Profiles of OPP treated
and untreated cancer mice?

What are the “metabolites” responsible for
the difference?

Differences in Urinary Metabolomic profiles of Cancer (KC) and OPP fed (KP) groups at Week 6



Metabolites Found to be Significantly Different
between the **Control** and **OPP fed** groups

Citrate

Propylene glycol

Dimethylamine

Pyruvate

Ethylene glycol

Succinylacetone

Guanidoacetate

Tartrate

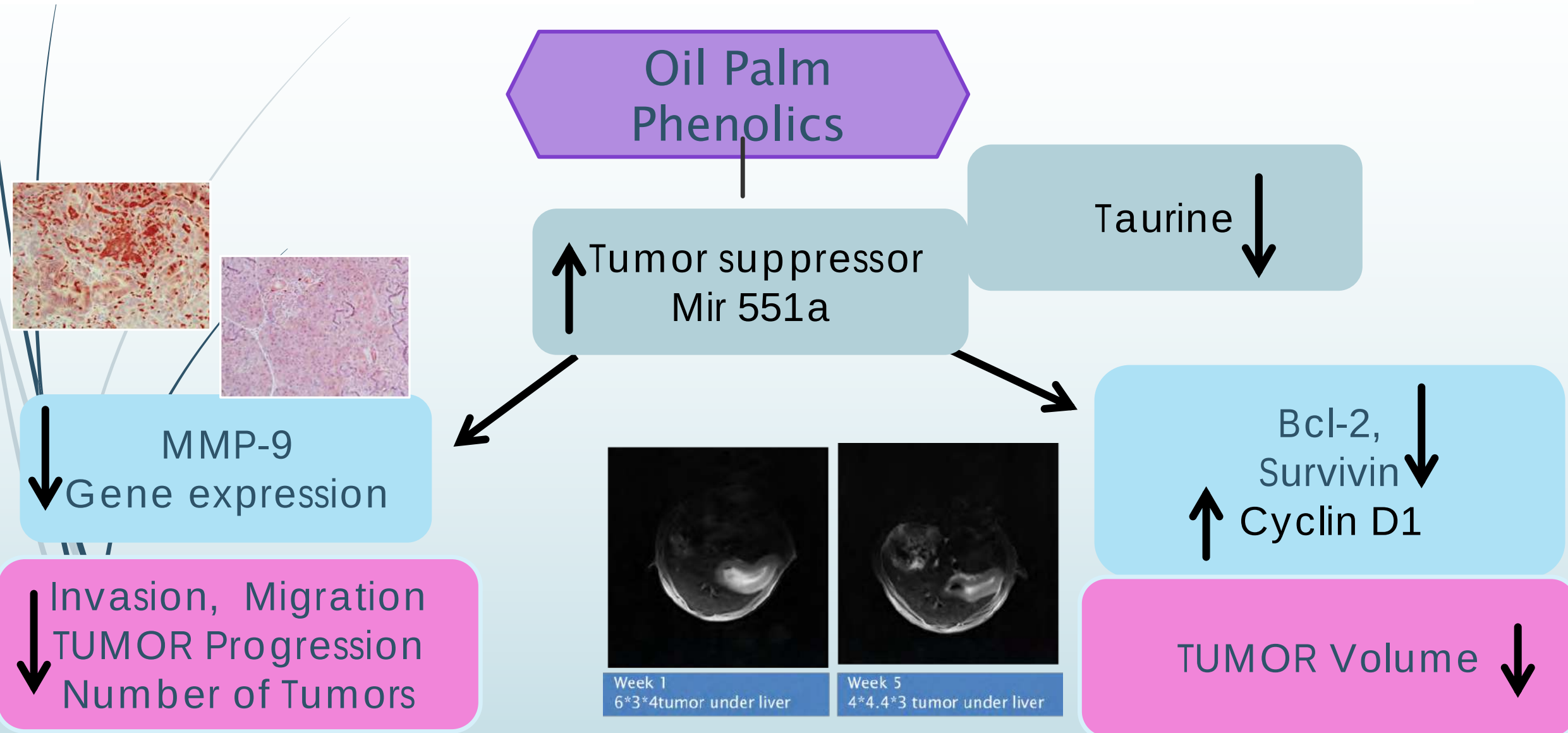
Malonate

Taurine

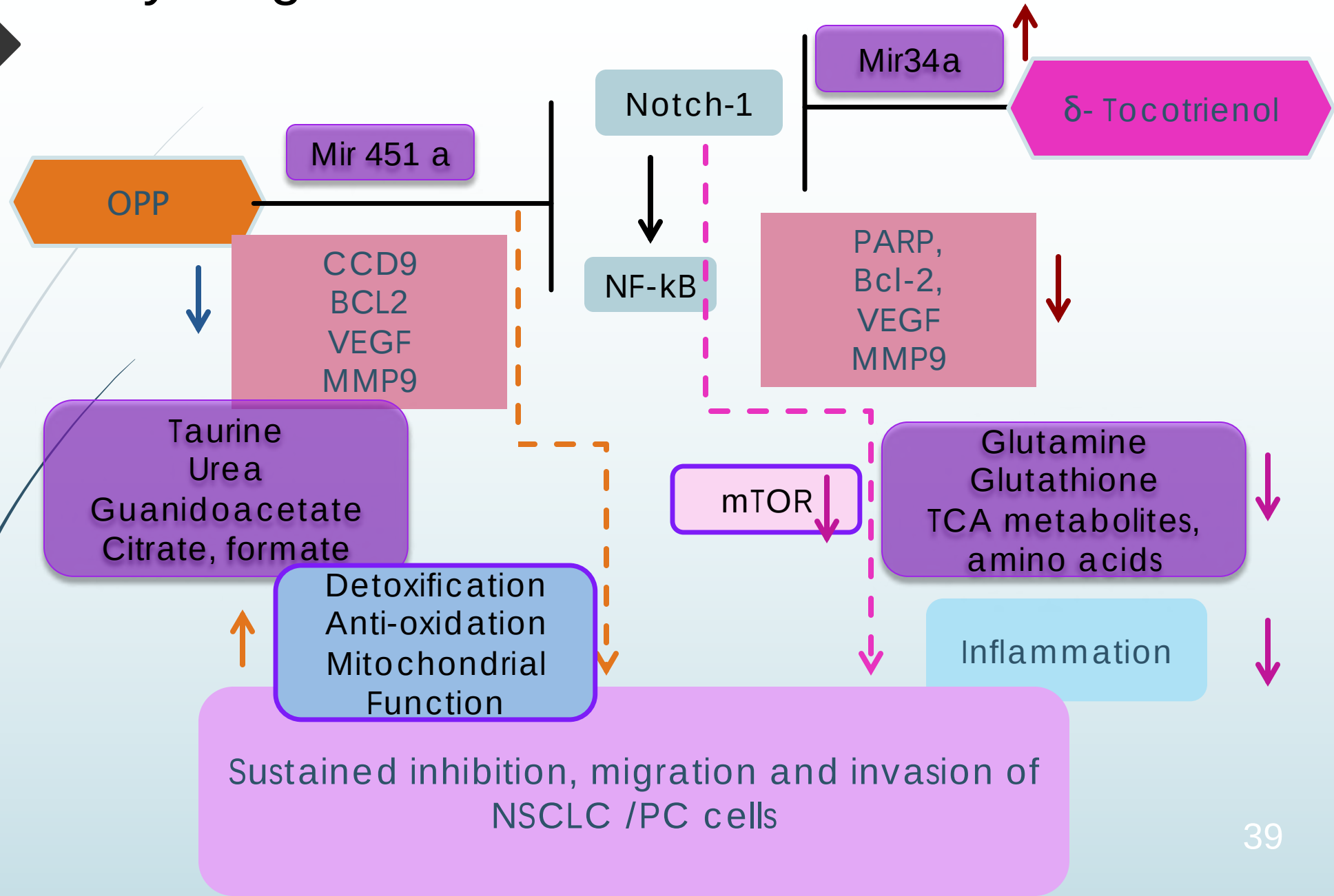
N-Carbamoyl- β -
alanine

Urea

Conclusion: Dietary Oil Palm Phenolics arrested the growth of Pancreatic Cancer in KPC transgenic mice



Possible Synergism of OPP and Tocotrienol??



Thank you!!



Ming Ji

Arvind Goja

Nadia Saadat

Lichachavi Raj



National Institutes
of Health



American
River Labs