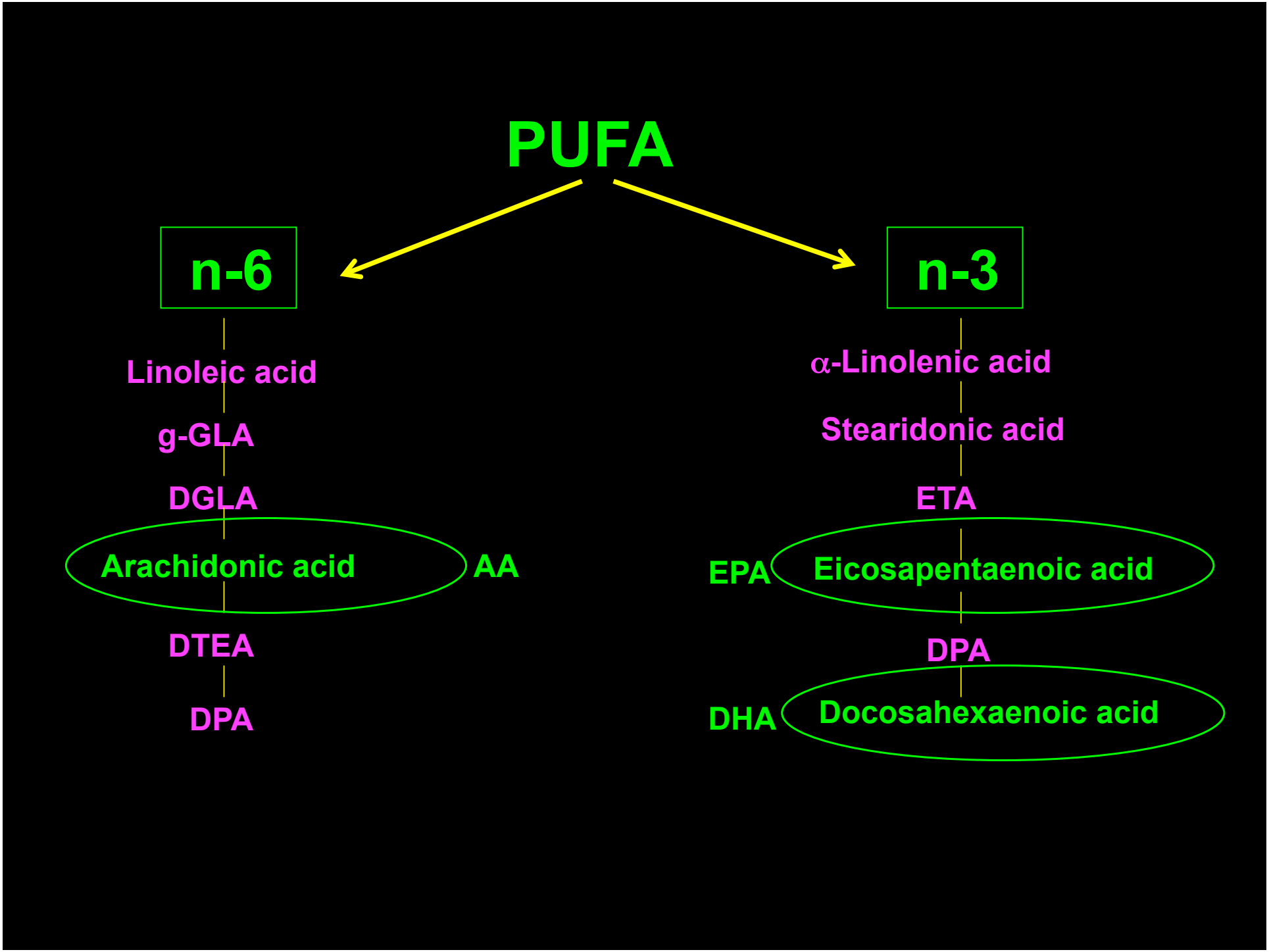
Effets des acides gras sur le système immunitaire : Modulation de la signalisation cellulaire

Naim Khan
UPRES EA 4183 “Lipides & Signalisation Cellulaire”
Université de Bourgogne, Dijon


PUFA
n-6
n-3
Linoleic acid
g-GLA
DGLA
Arachidonic acid
AA
DTEA
DPA
α-Linolenic acid
Stearidonic acid
ETA
EPA
Eicosapentaenoic acid
DPA
DHA
Docosahexaenoic acid

n-3 PUFA : “Pharmaconutrients”

- Lipid lowering effects (PPAR-α agonists)
- Antihypertensive (cardioprotectors)
- Anti-inflammatory actions

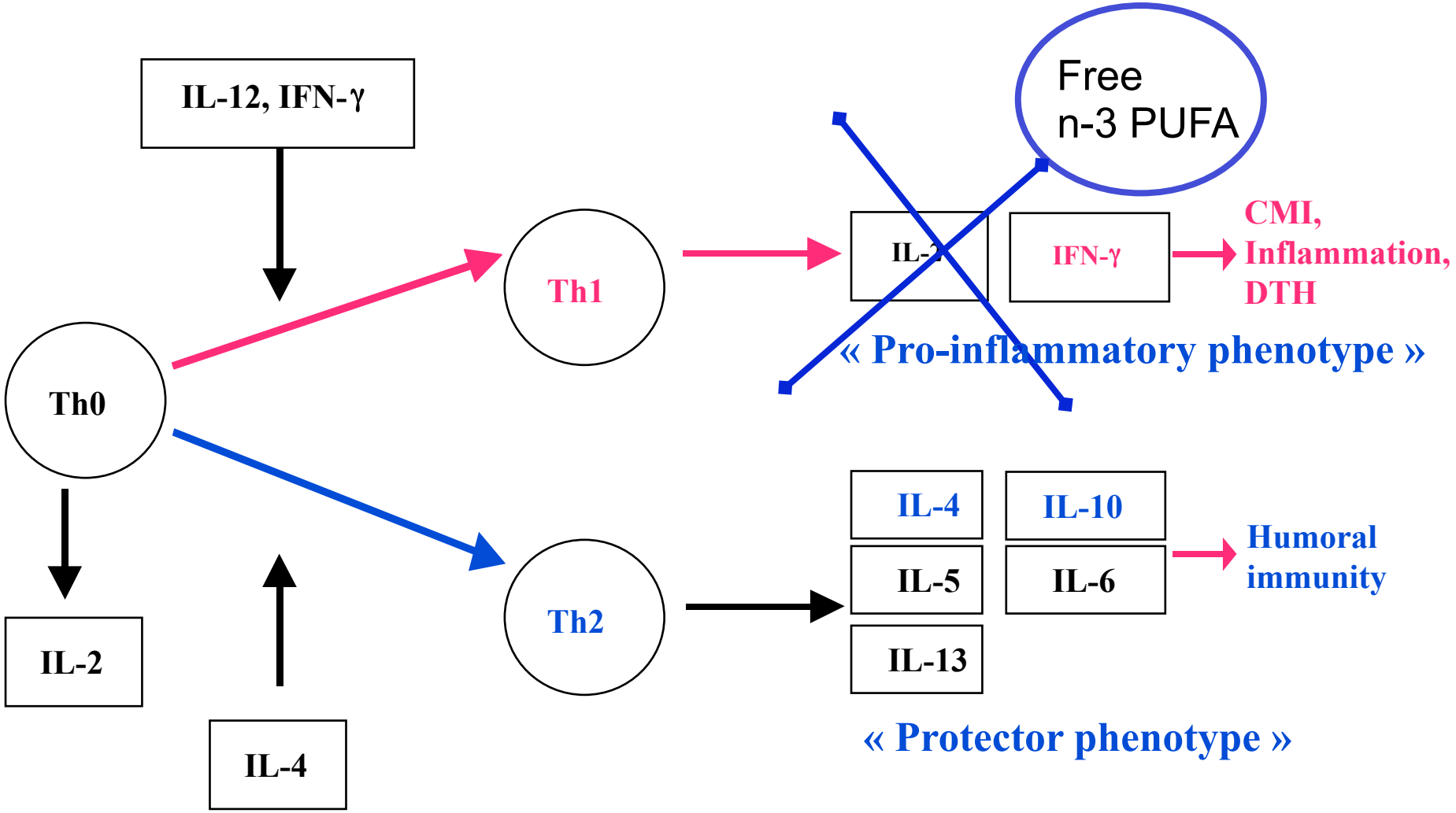
n-3 PUFA : “Immunosuppresseurs”

Eicosapentaenoic acid (EPA)

Docosahexaenoic acid (DHA)

- Psoriasis, Dermatitis,
- SLE, multiple sclerosis
- Rheumatoid Arthritis

Th1 & Th2 dichotomy

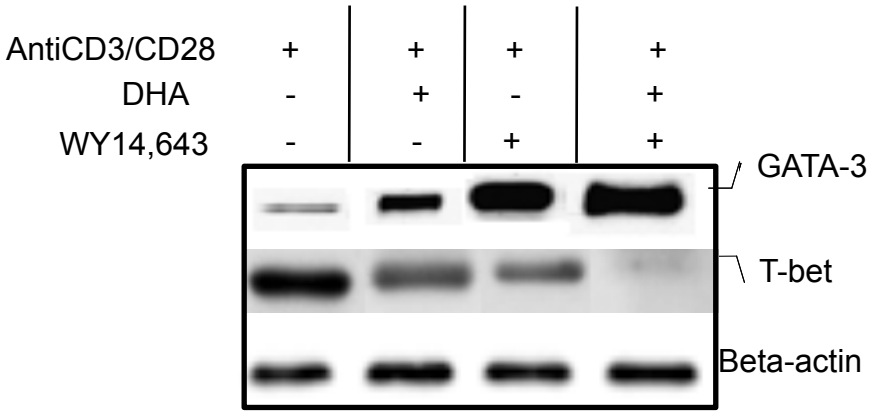


Ategbo *et al.* (2006). ***J Clin. Endocrinol Metab.*** 91:4137-43
Khan *et al.* (2006) ***J. Autoimm.*** 26:268-277

DHA modulates Th1/Th2 independently of PPAR-α activation

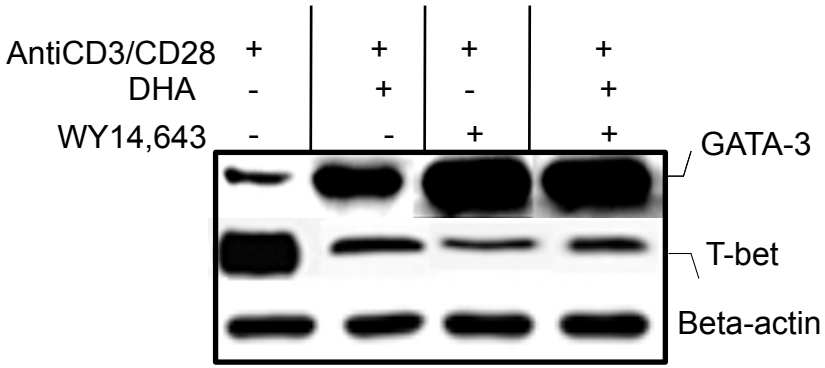
T-bet = Th1 differentiation
GATA-3 = Th2 differentiation

WT mice



Western blots

PPAR-α^{null} mice



Western blots

Mechanisms of action of n-3 PUFA as immunomodulators

Decrease in eicosanoids of n-6 family

Increase in eicosanoids of n-3 family (and resolvins & protectins)

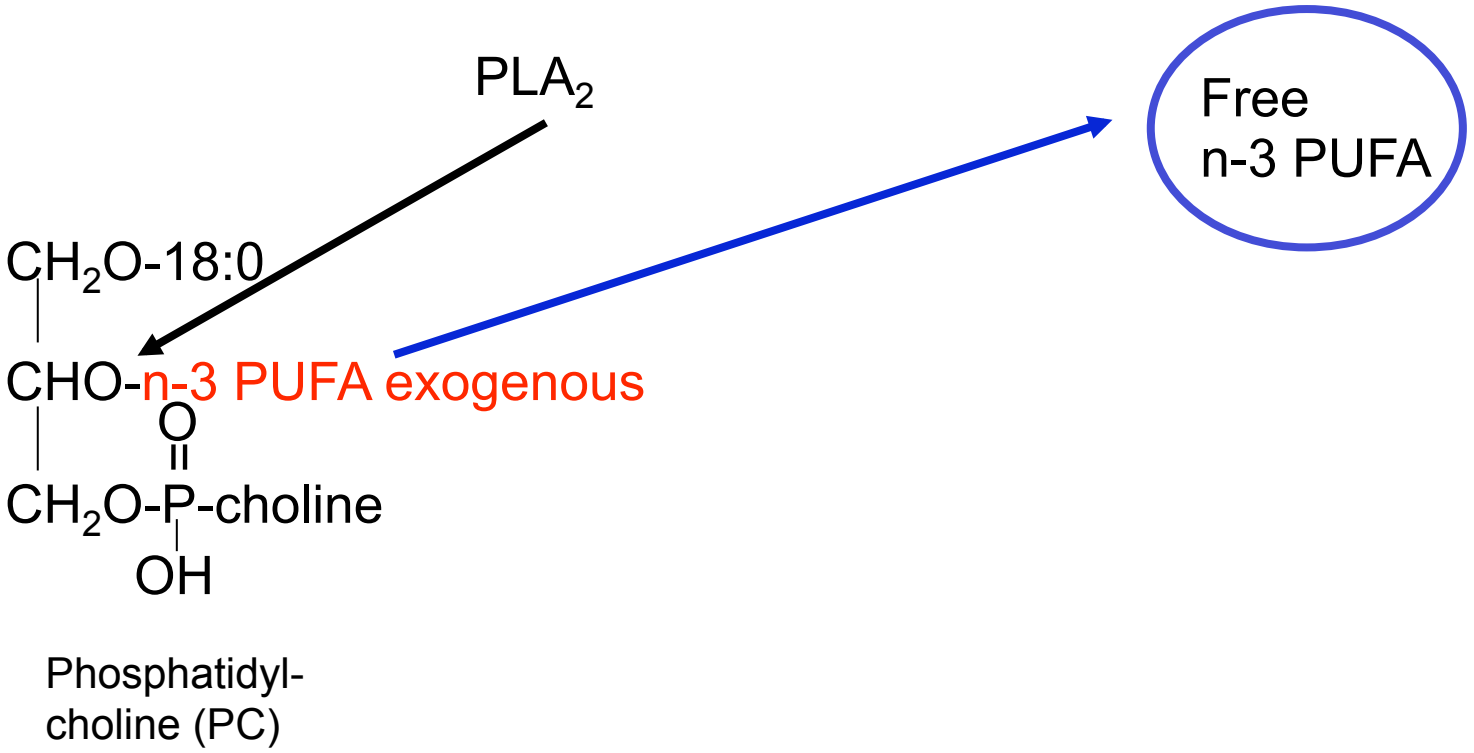
Decrease in activities of enzymes involved in metabolism of FA

Per se Actions ?

Our hypothesis : intervention with the second messengers

Jurkat T-cells

Phospholipids



Phosphatidyl-
choline (PC)

Phospholipase A_2

- Secretory

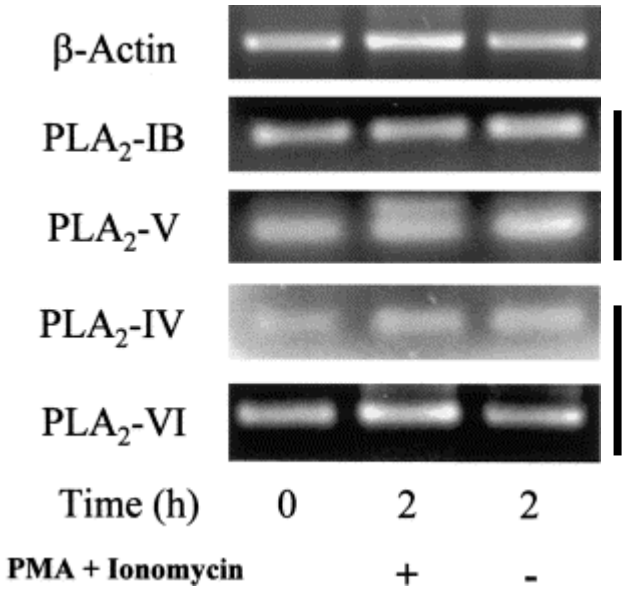
± 14 kDa, types - IB & V Ca^{2+} dep., $sPLA_2$

- Cytosolic

± 30-110 kDa -type - IV Ca^{2+} dep. $cPLA_2$

type - VI Ca^{2+} indep. $iPLA_2$

T-cells express $sPLA_2$ and $cPLA_2$



secreted PLA_2 (type IB and V)

Cytosolic PLA_2 (type IV Ca^{2+}-dependent and type VI Ca^{2+}-independent)

Release of ^{3}H-[arachidonic acid / EPA / DHA]

- **PLA_2 - type IB, V ($sPLA_2$) and type VI ($iPLA_2$) - release of arachidonic acid**

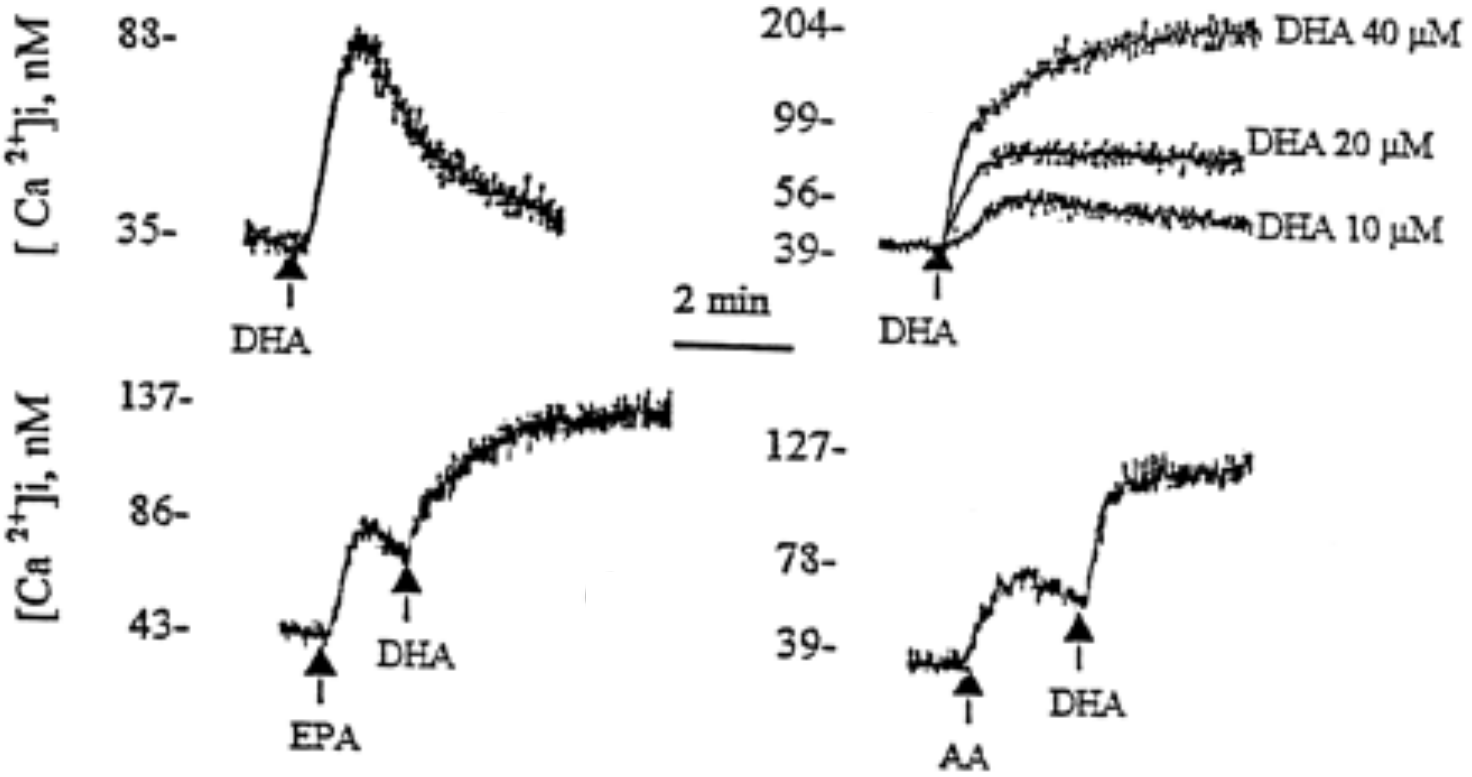
-**PLA_2 - type IV ($cPLA_2$) - release of DHA**

PLA_2 - type VI ($iPLA_2$) - release of EPA

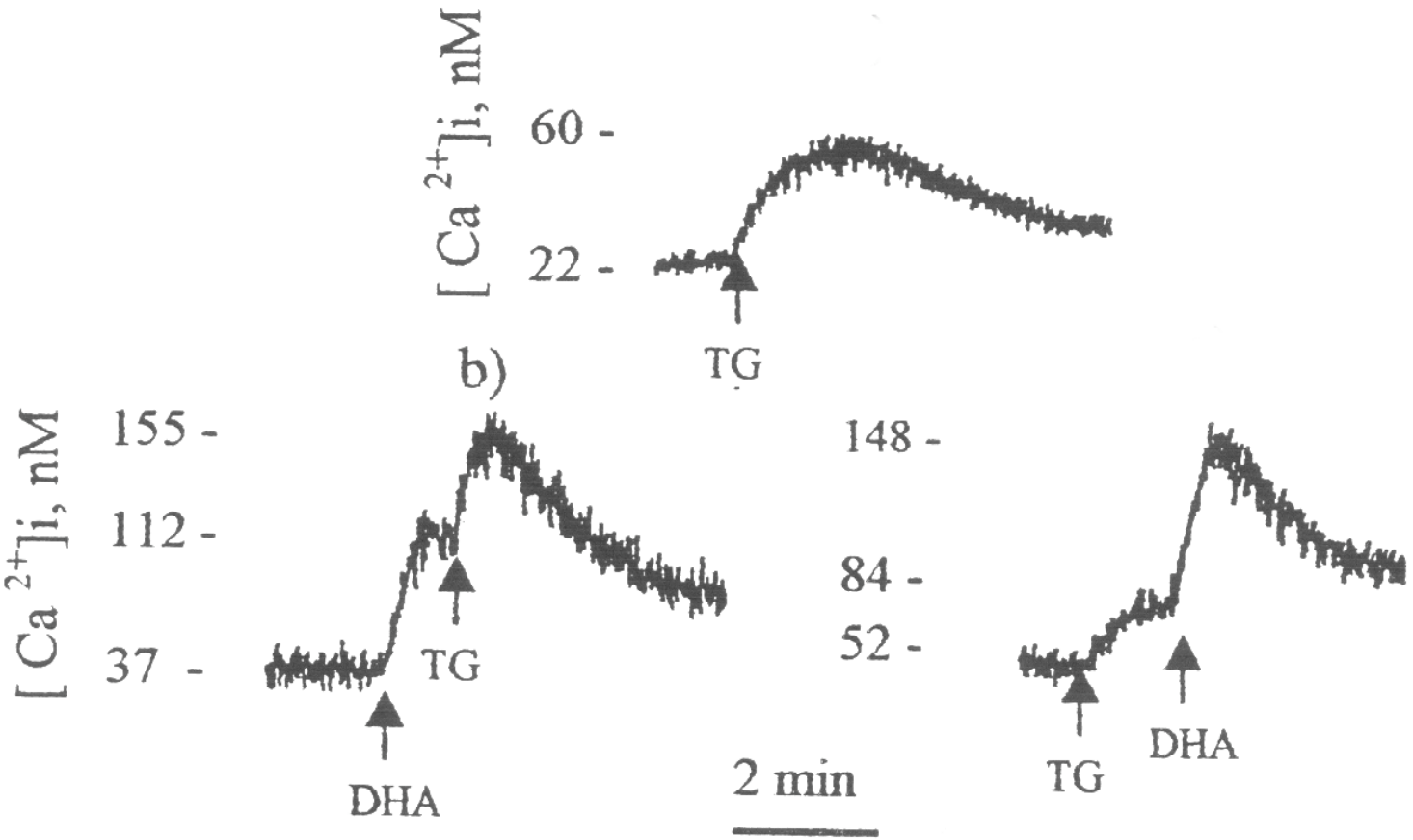
$sPLA_2$ are not involved in the release of DHA & EPA

Denys A. et al., 2005 J. Lipid Res. 46:752-8.

DHA increases $[Ca^{2+}]i$

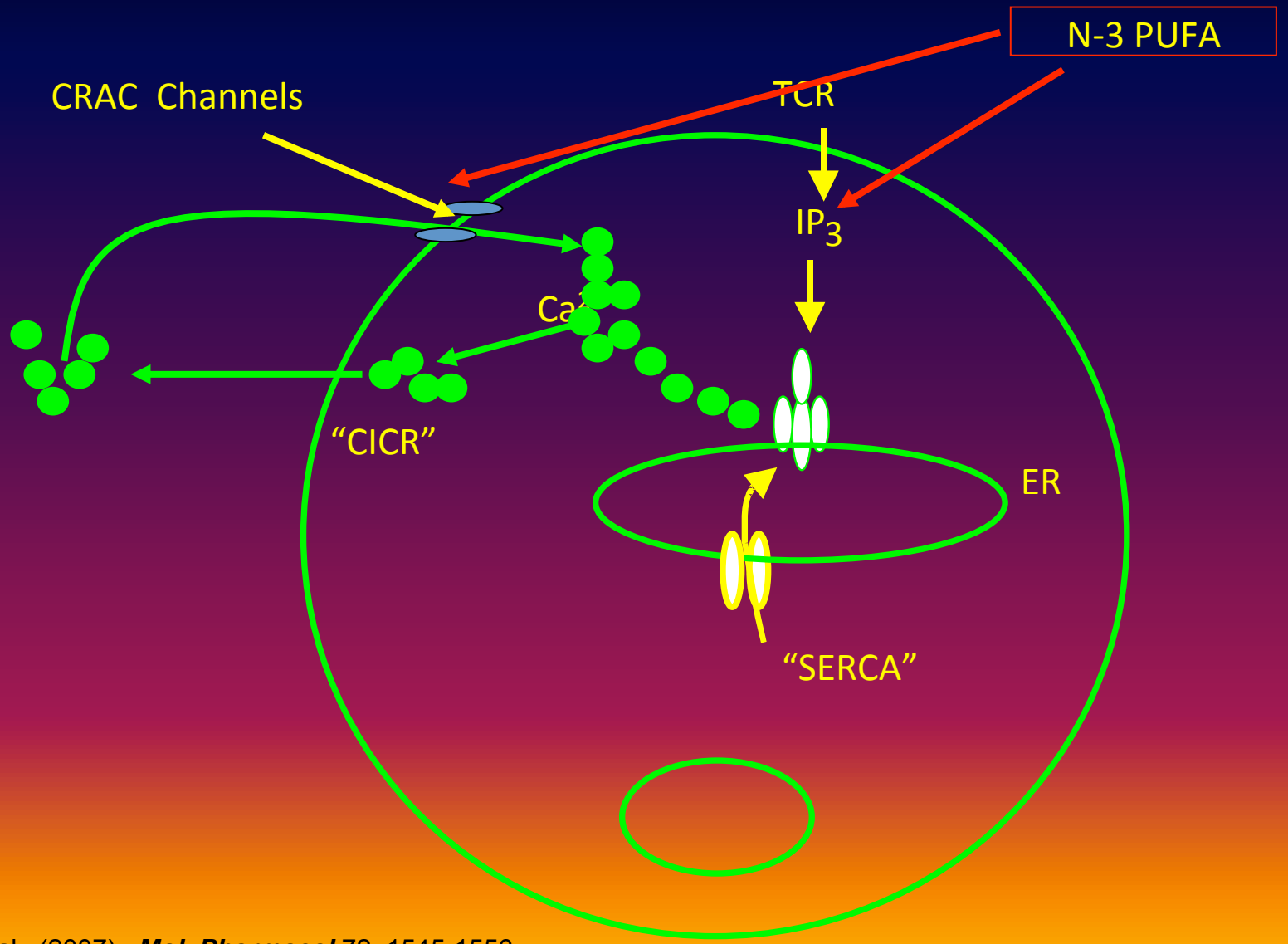


DHA does not act on SERCA



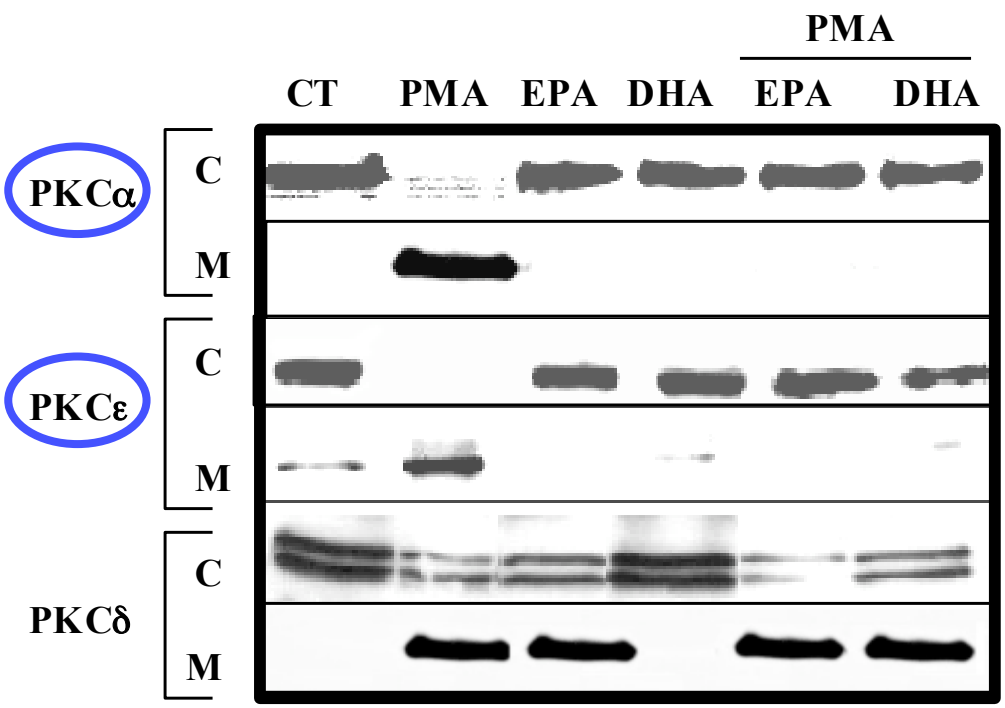
TG (thapsigargin) : SERCA inhibitor

"CAPACITATIVE MODEL OF $[Ca^{2+}]i$"



Aires V et al. (2007). ***Mol. Pharmacol*** 72: 1545-1556.
Khan N.A. (2010). ***Prost. Leuk. Ess. Fatty Acids.*** 82:179-187.

DHA inhibits PKC translocation

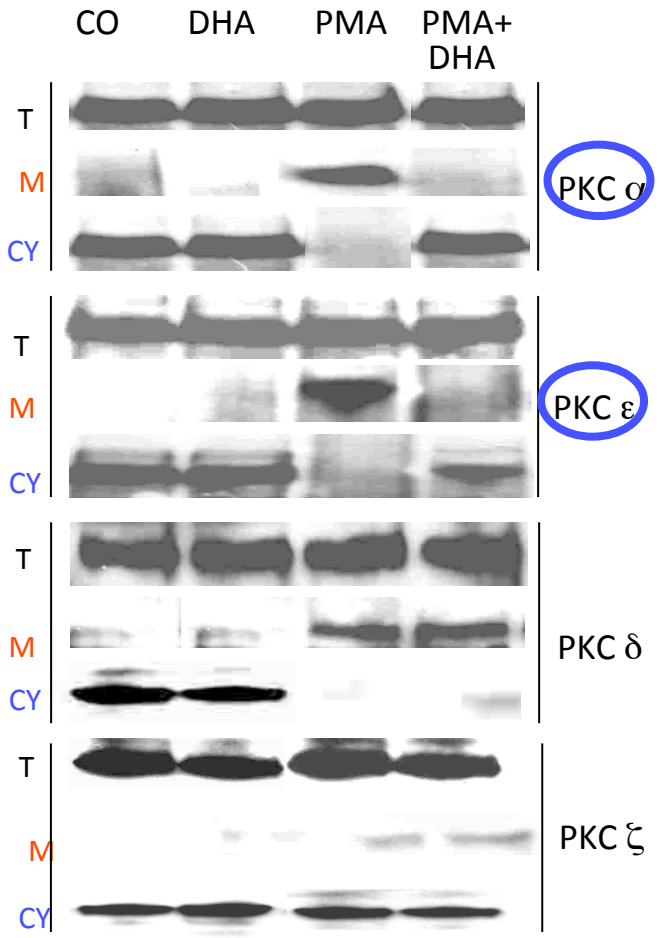


Jurkat T cells

Classic, cPKC = PKCα

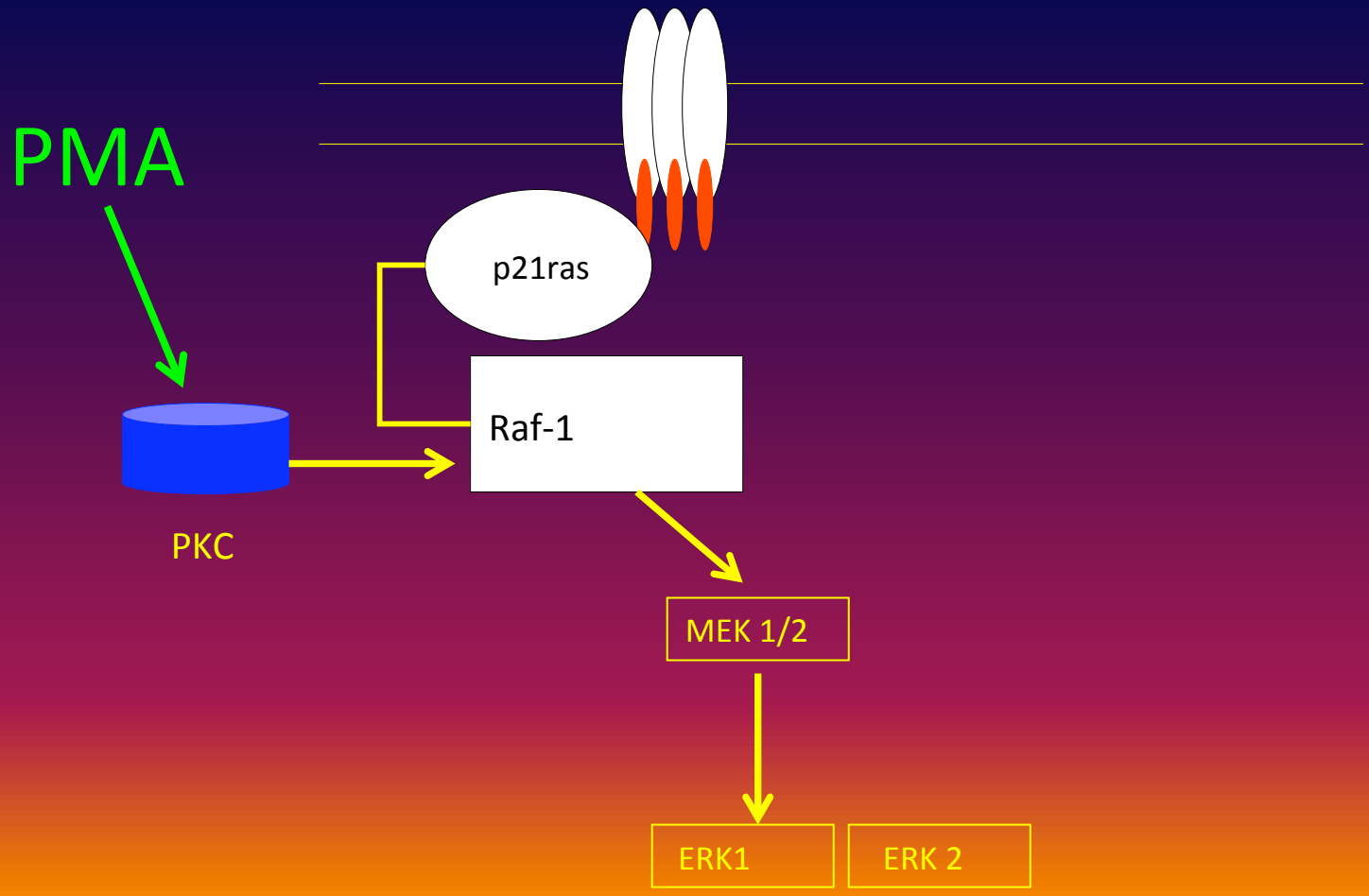
Novel , nPKC = PKCε

Atypic, aPKC = PKCδ or ζ

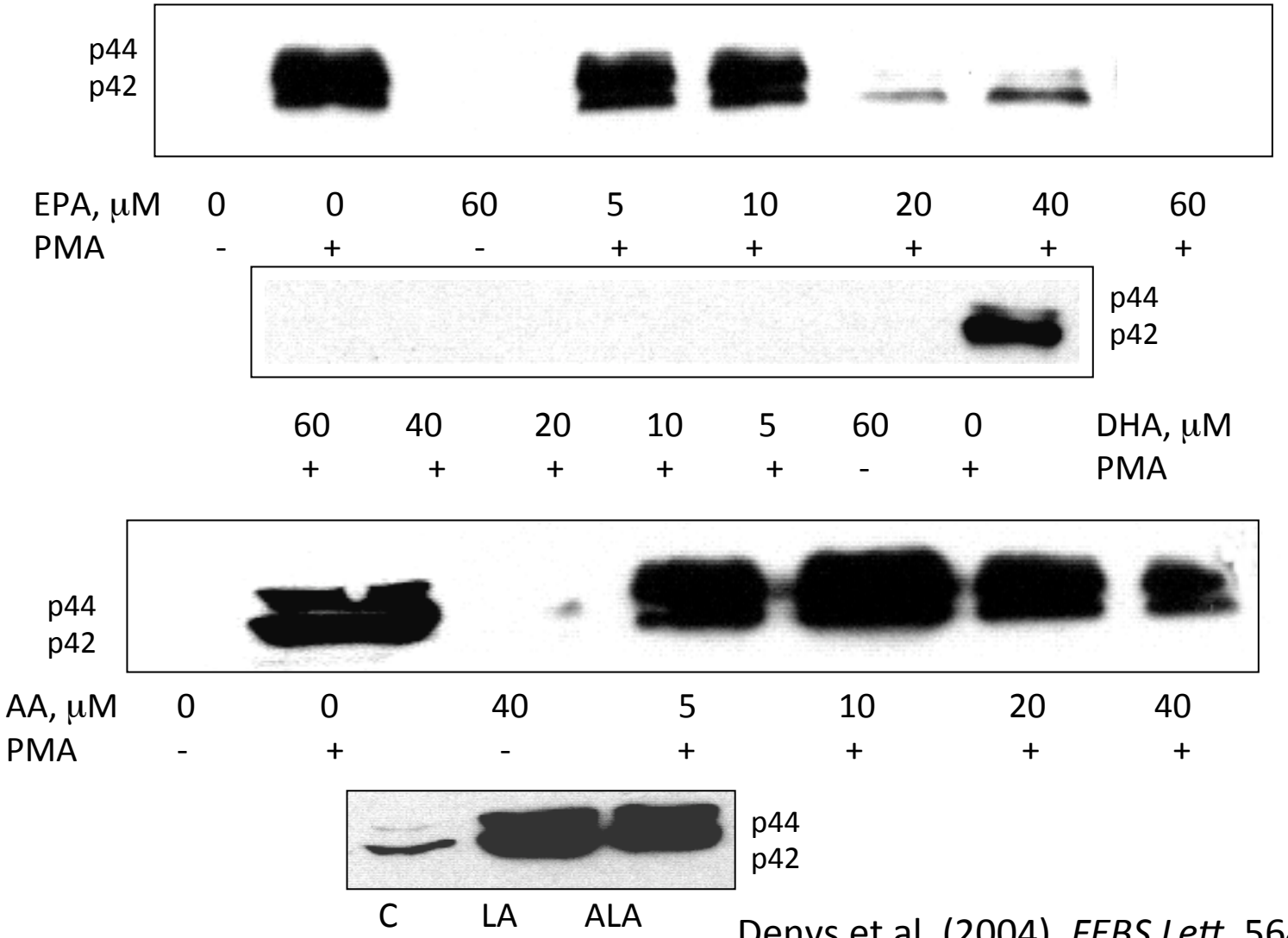


NIH / 3T3 cells

MAP Kinase signaling



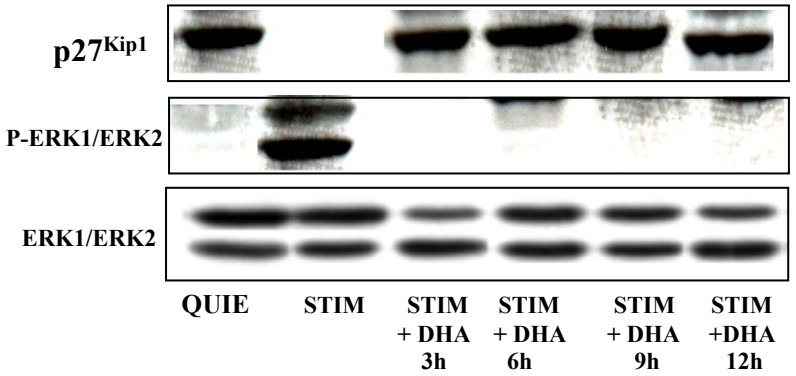
EPA and DHA diminish PMA-induced ERK1/ ERK2 phosphorylation



Denys et al. (2004). *FEBS Lett.* 564:177-1782.

DHA blocks cell cycle from late-G1 to S phase of cell cycle

DHA inhibits MAPK and could block cell cycle transition by preventing $p27^{Kip1}$ degradation

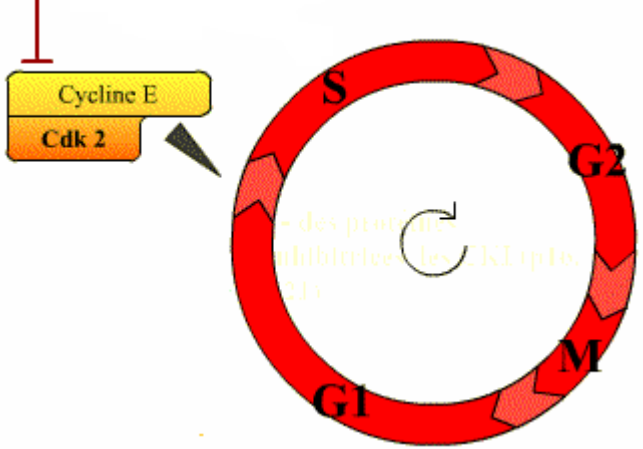


MAPK (ERK1/ERK2)

Proteasome Degradation

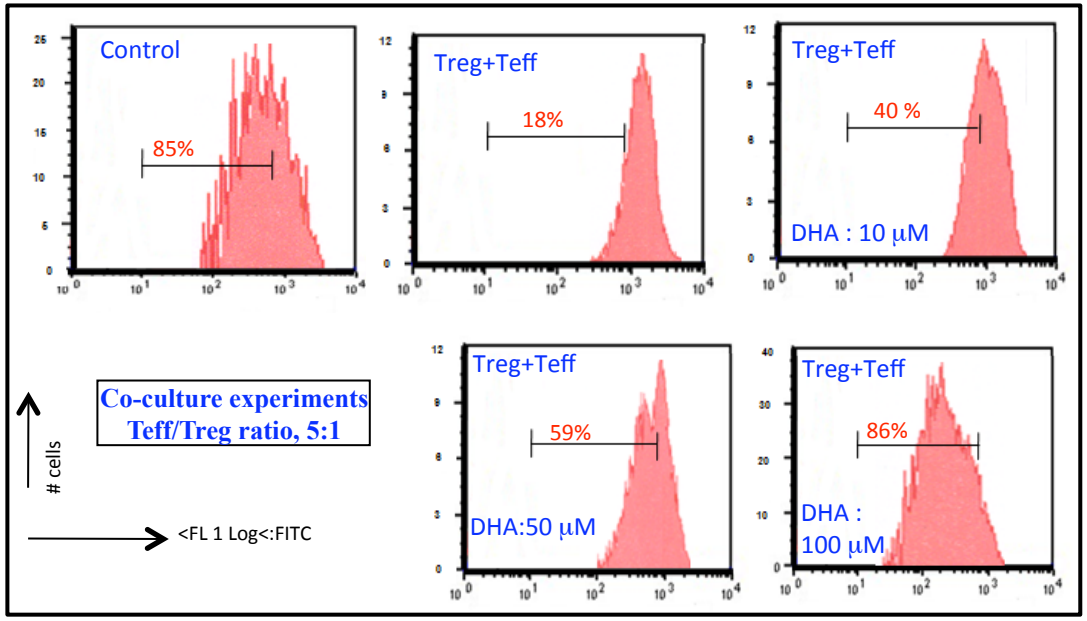
~~$p27^{Kip1}$~~

$p27^{Kip1}$

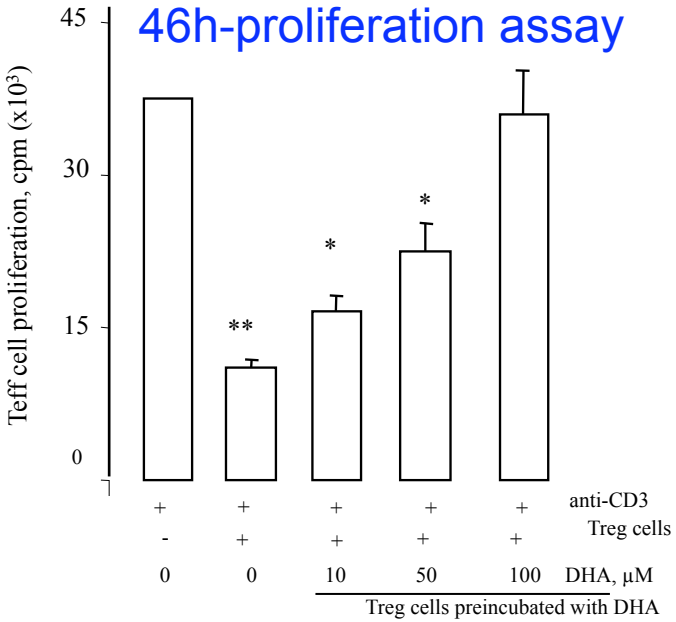


DHA curtails the suppressive capacity of Treg cells on Teff cell proliferation

In vitro and *ex-vivo* : (n-3 enriched diet containing EPAX7010 for 6 weeks)



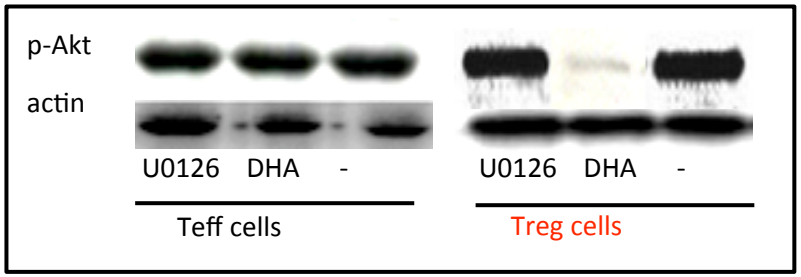
CFSE-labeled Teff cells



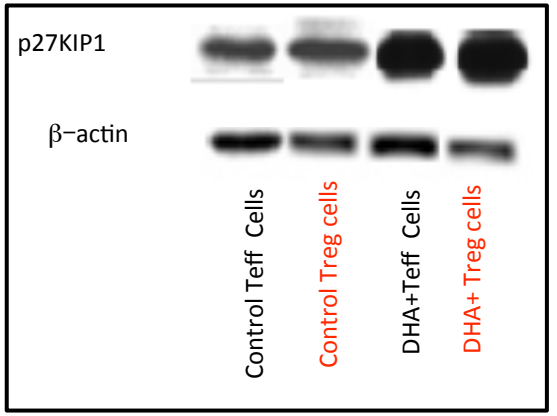
Yessoufou A. et al. (2009) *J. Lipid Res* 50:2377-2388.

DHA modulates ERK1/ERK2, Akt and P27kip1

Akt phosphorylation

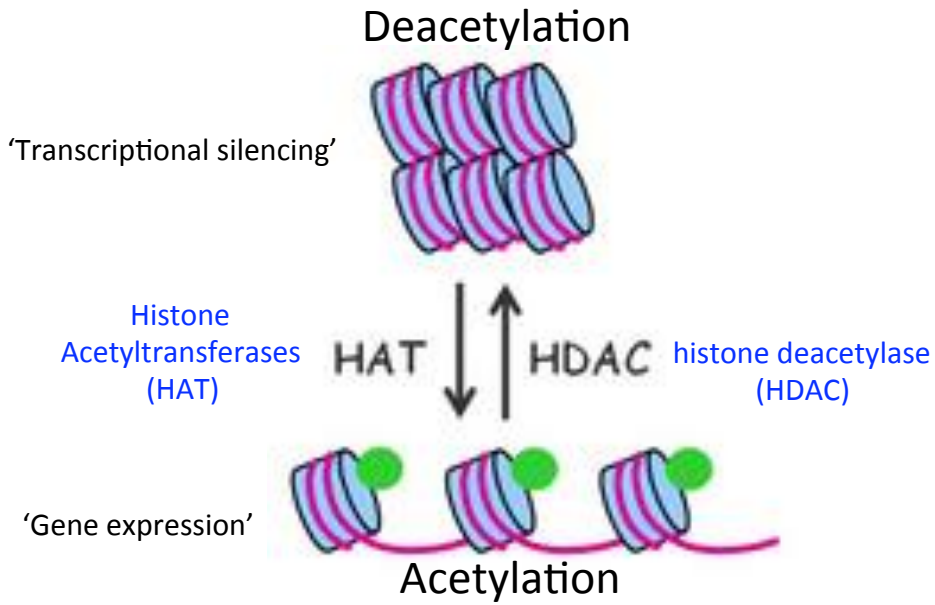


p27kip1

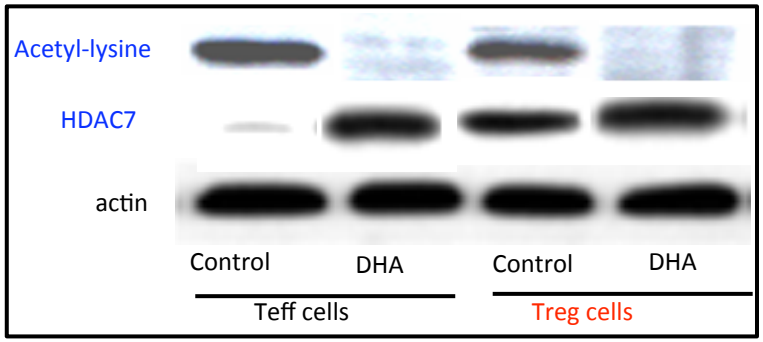


DHA modulates HDAC7

Epigenetic Control (chromatin remodeling)

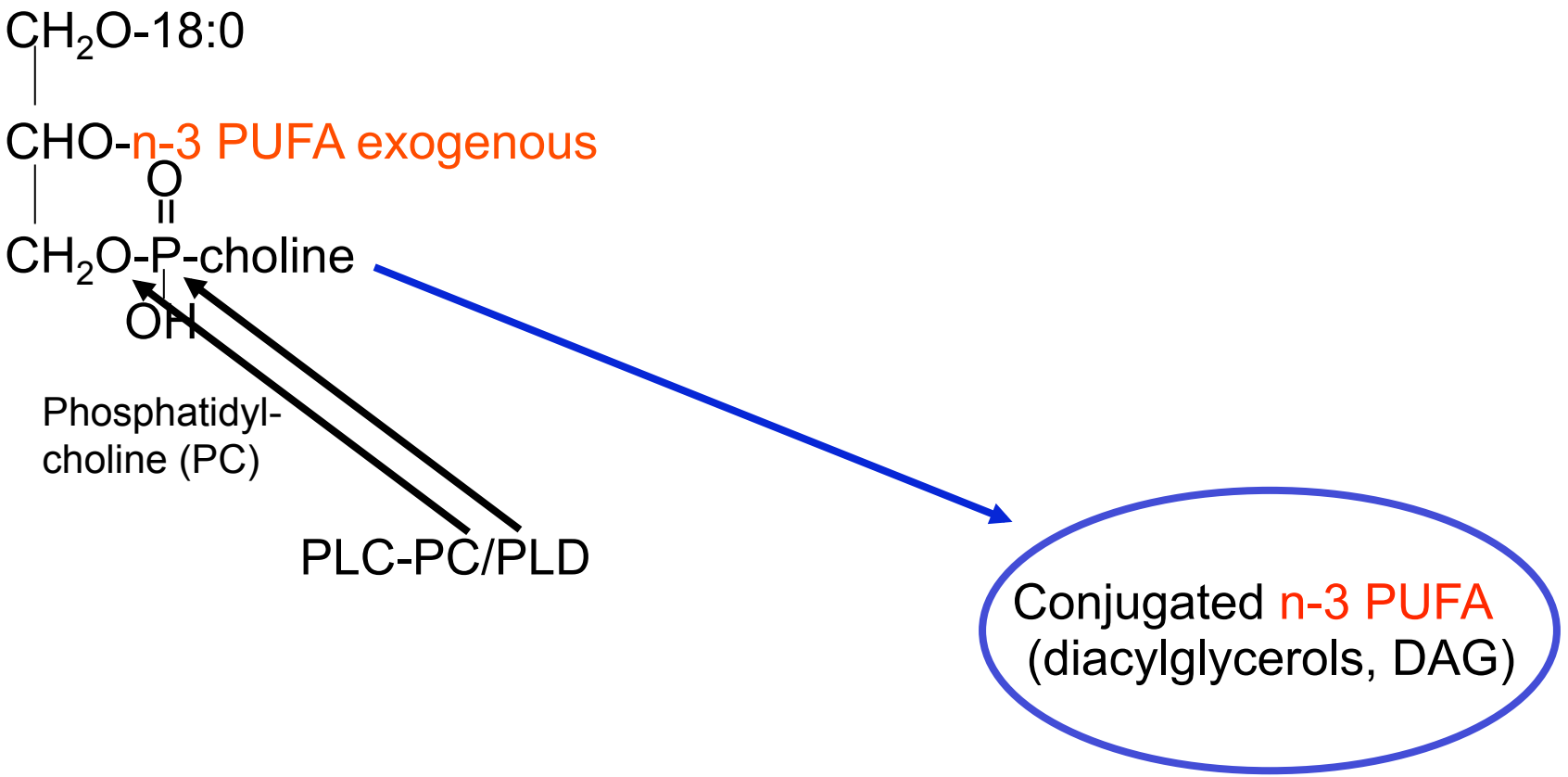


HDAC7

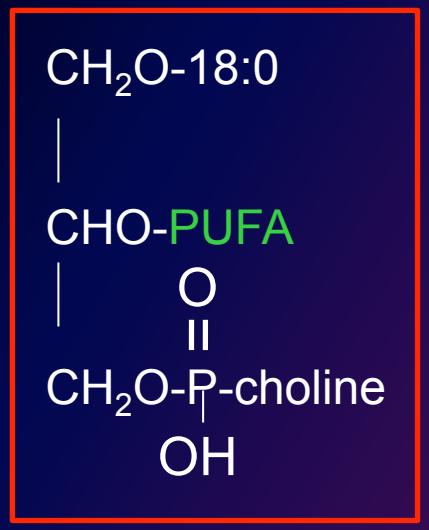


Foxp3-immunoprecipitation

Phospholipids



Activation of different isoformes of PKC by n-3 PUFA/DAG



SAG = 1-stearoyl-2 AA-*sn*-glycerol
SDG = 1-stearoyl-2 DHA-*sn*-glycerol
SEG = 1-stearoyl-2 EPA-*sn*-glycerol

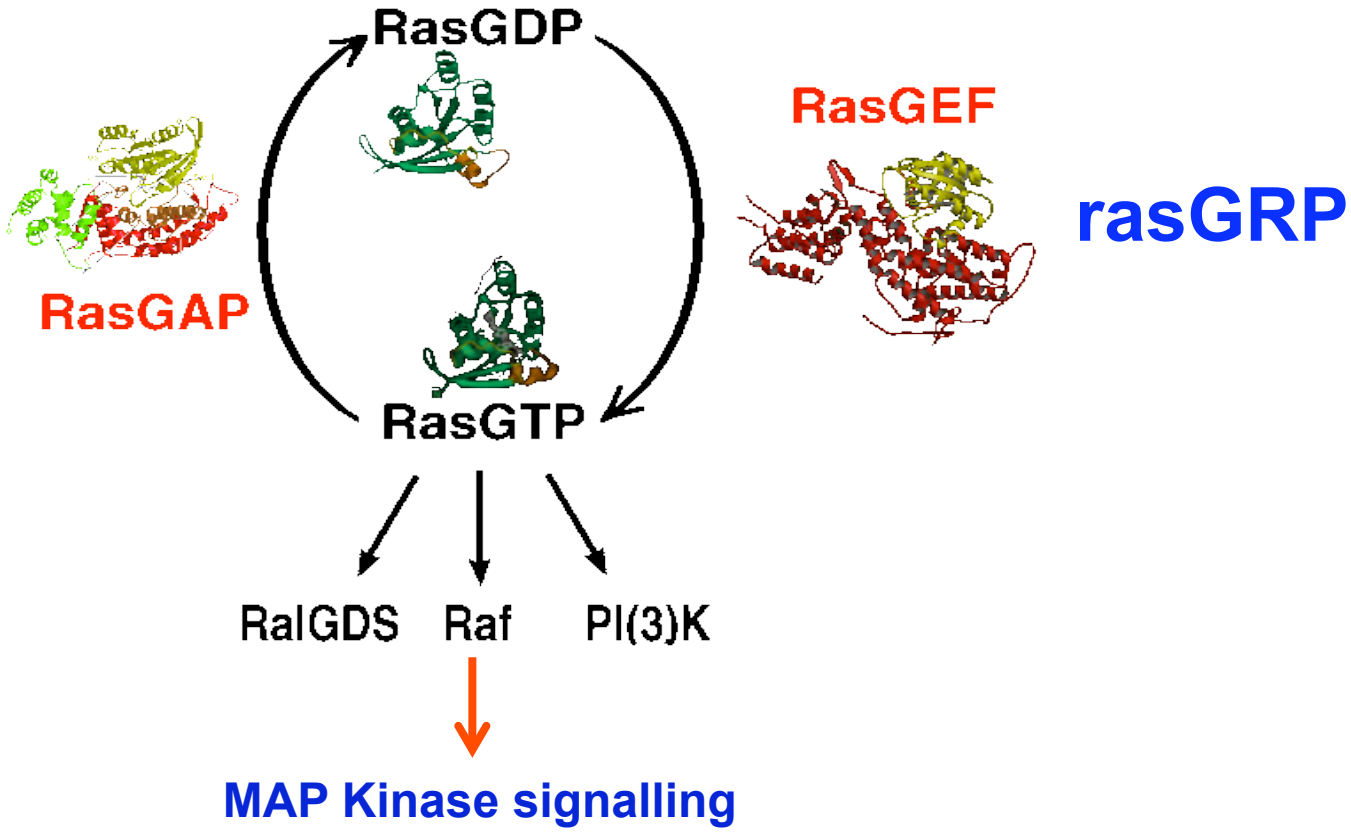
PKCα, PKCβ, PKCγ — ***cPKC*** — **Ca^{+2} - dependent**

PKCδ, PKCε — ***nPKC*** — **Ca^{+2} - independent**

Madani S. et al. (2001) *FASEB J.* 15:2595-2601.
Madani S. et al. (2004) *J. Biol Chem.* 279: 1176-1183.

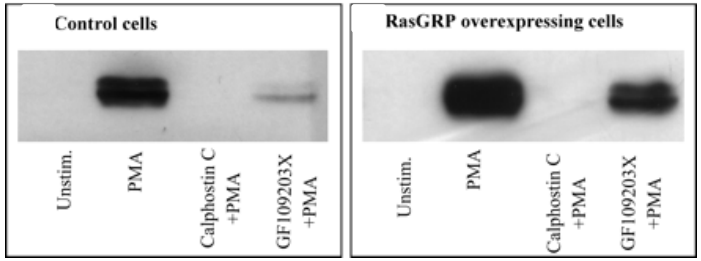
……n-3 PUFA/DAG ——————

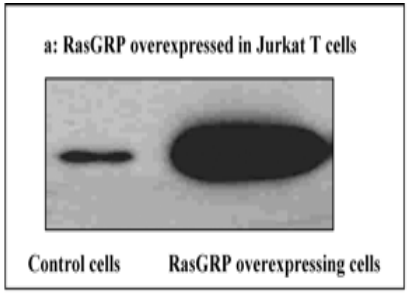
HNFQEMTYLKPTFCEHCAGFLWGI I KQGYKCKDCGANOHKQCKDLLVLAC	rasGRP
HKFK I HTYGSPTFCDHCGSLLYGL I HQGMKCDTCDMNVHKQCV INVPSLC	PKC



……n-3 PUFA/DAG

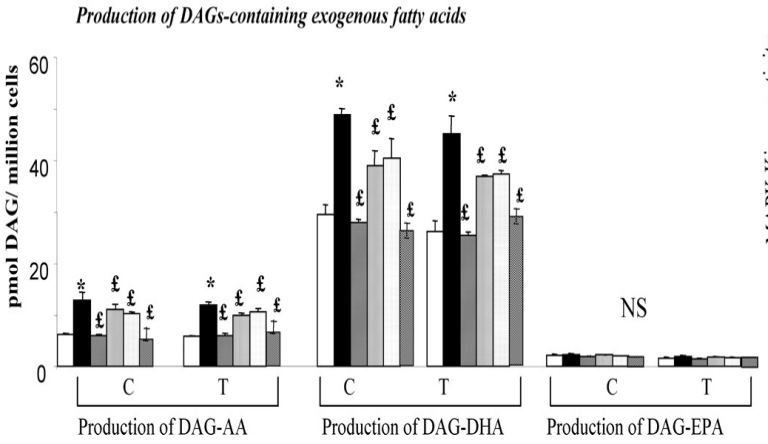
MAP Kinase signalling

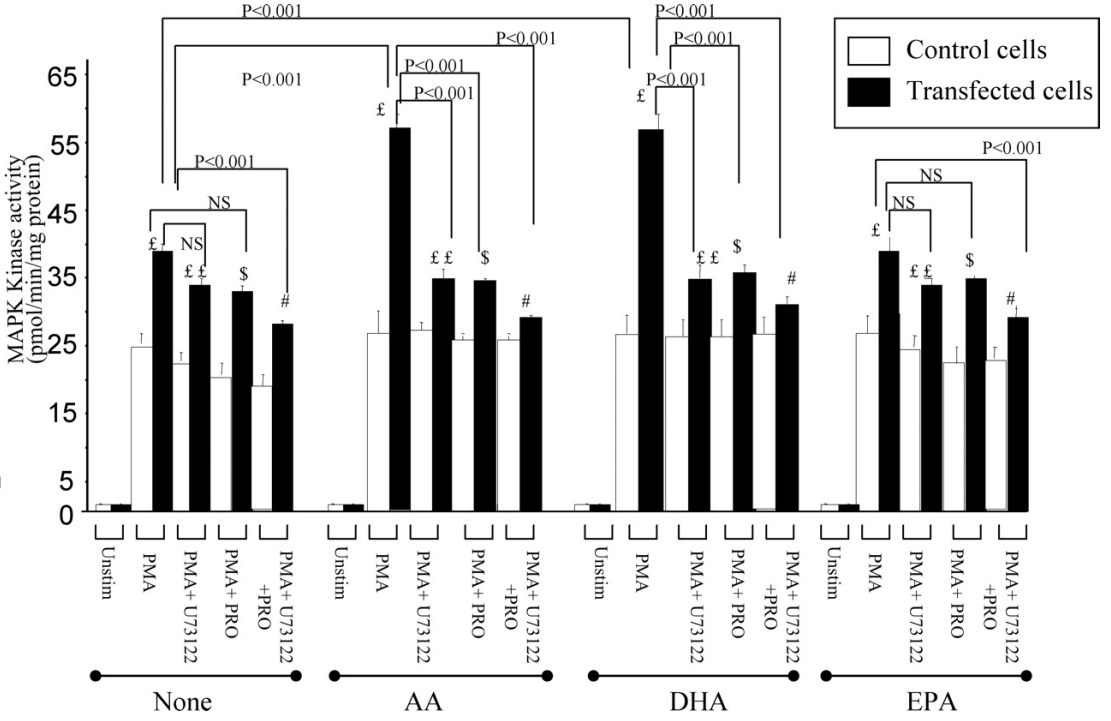




Binding of 3H-Pdbu to RasGRP

Competitor	*nH*	IC_{50} (μM)	*Ki* (μM)
SAG	0.79 ± 0.02	4.52 ± 0.09	4.49 ± 0.01
SDG	1.03 ± 0.05	8.41 ± 1.01	8.37 ± 1.02
SEG	0.87 ± 0.07	5.00 ± 1.02	4.97 ± 1.04

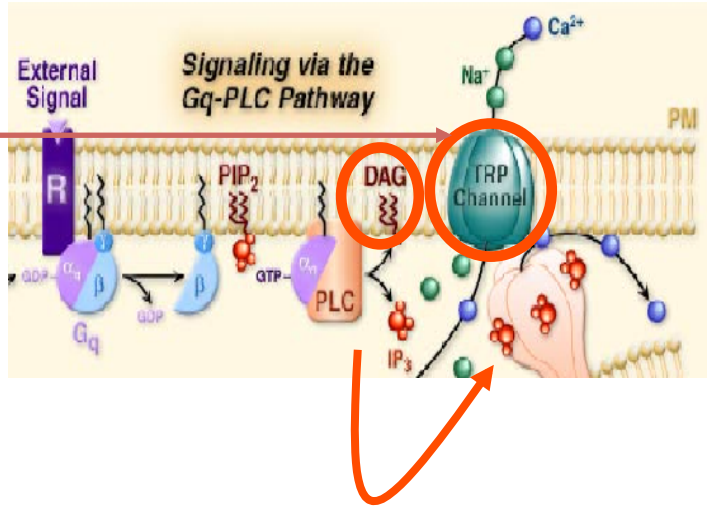


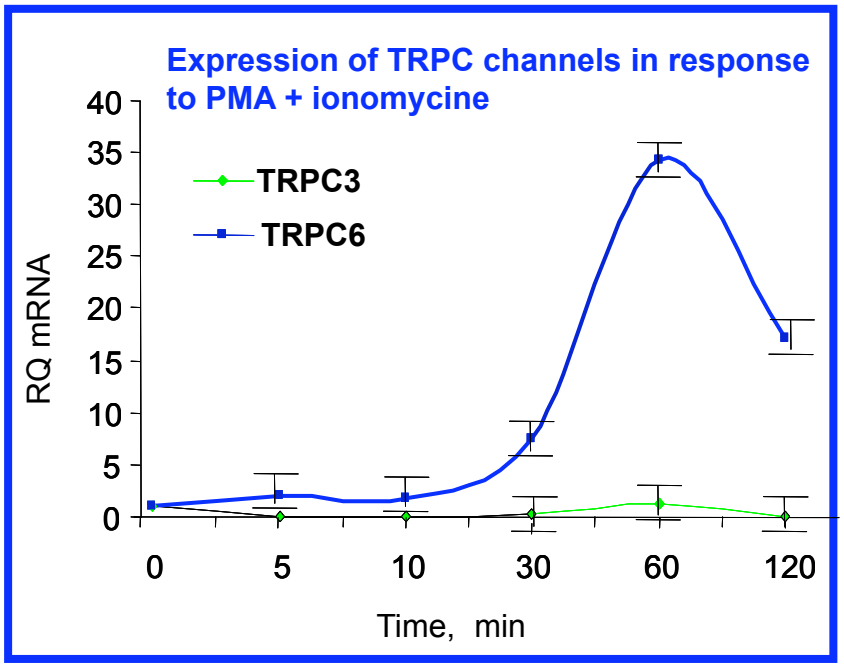


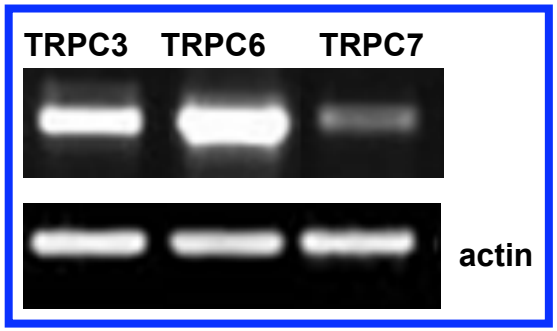
n-3 PUFA/DAG modulate calcium influx via TRPC6 channels

TRPC3, 6 and 7

(70% homology)

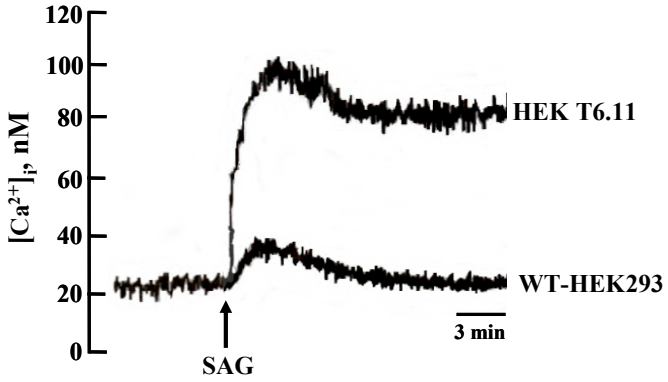


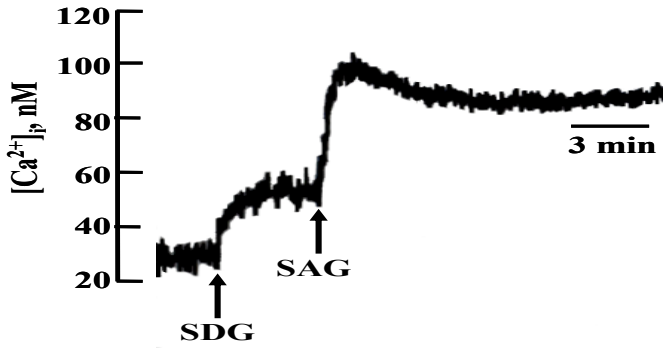


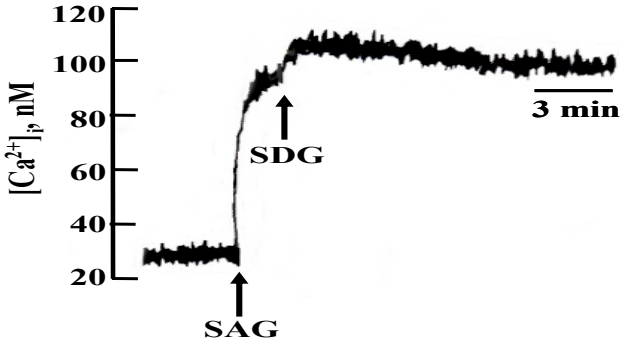


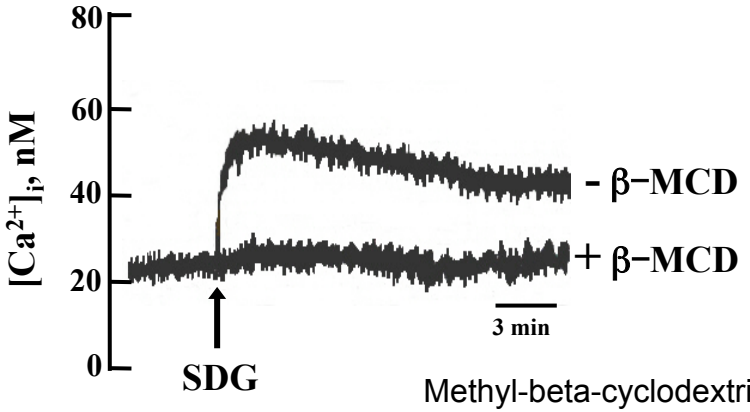
Aires V. et al. (2007). *Biochimie.* 89:926-937

Diacylglycerol-containing fatty acids induce increases in $[Ca^{2+}]i$ *via* TRPC3/6 channels

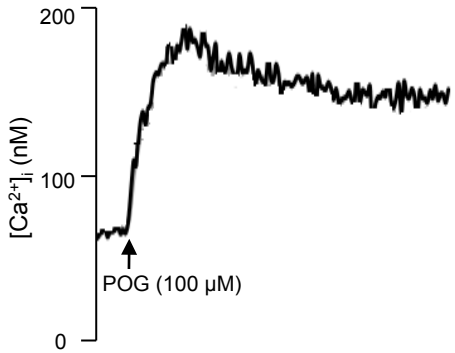


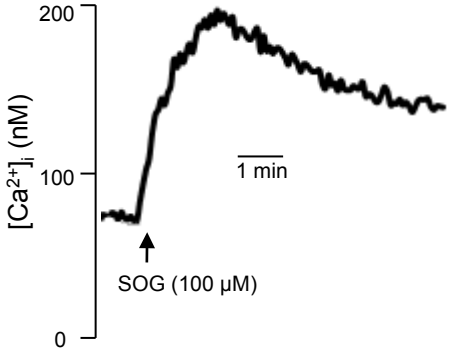


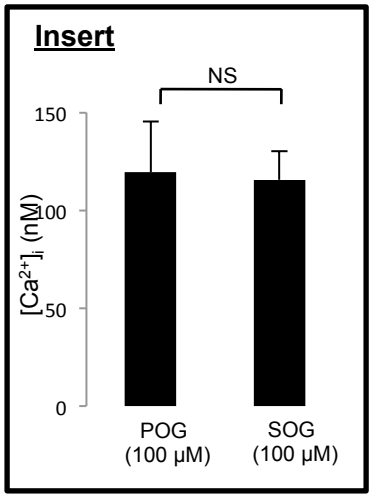




Methyl-beta-cyclodextrin (MCD)



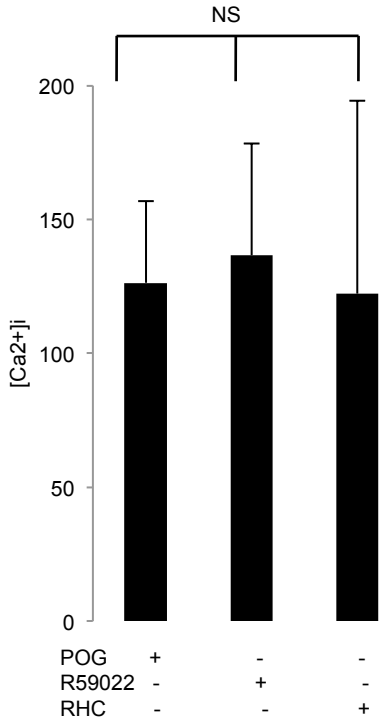




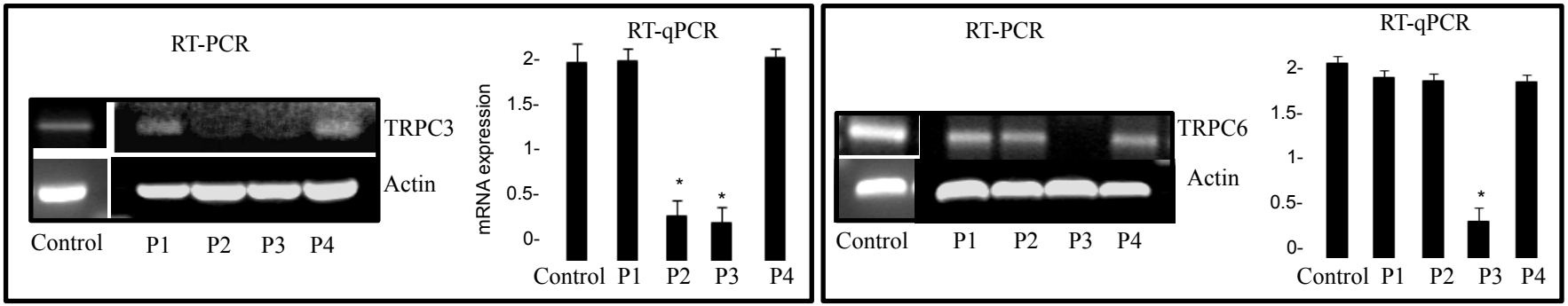
1-palmitoyl-2-oleyl-*sn*-glycerol (POG)

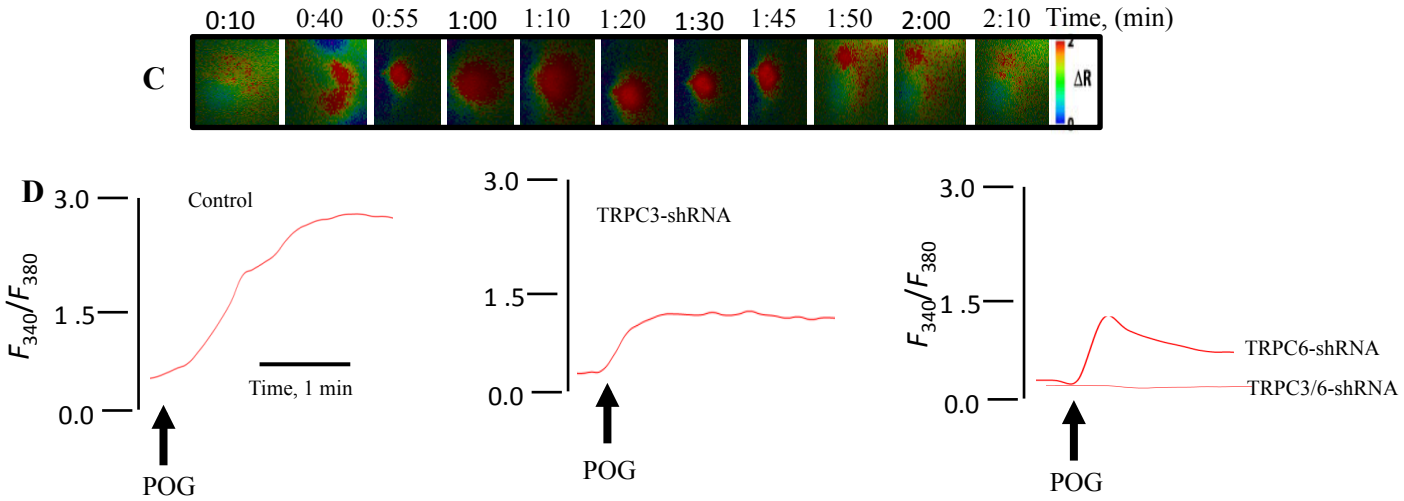
1-stearoly-2-oleyl-*sn*-glycerol (SOG)

DAG-Oleic acid



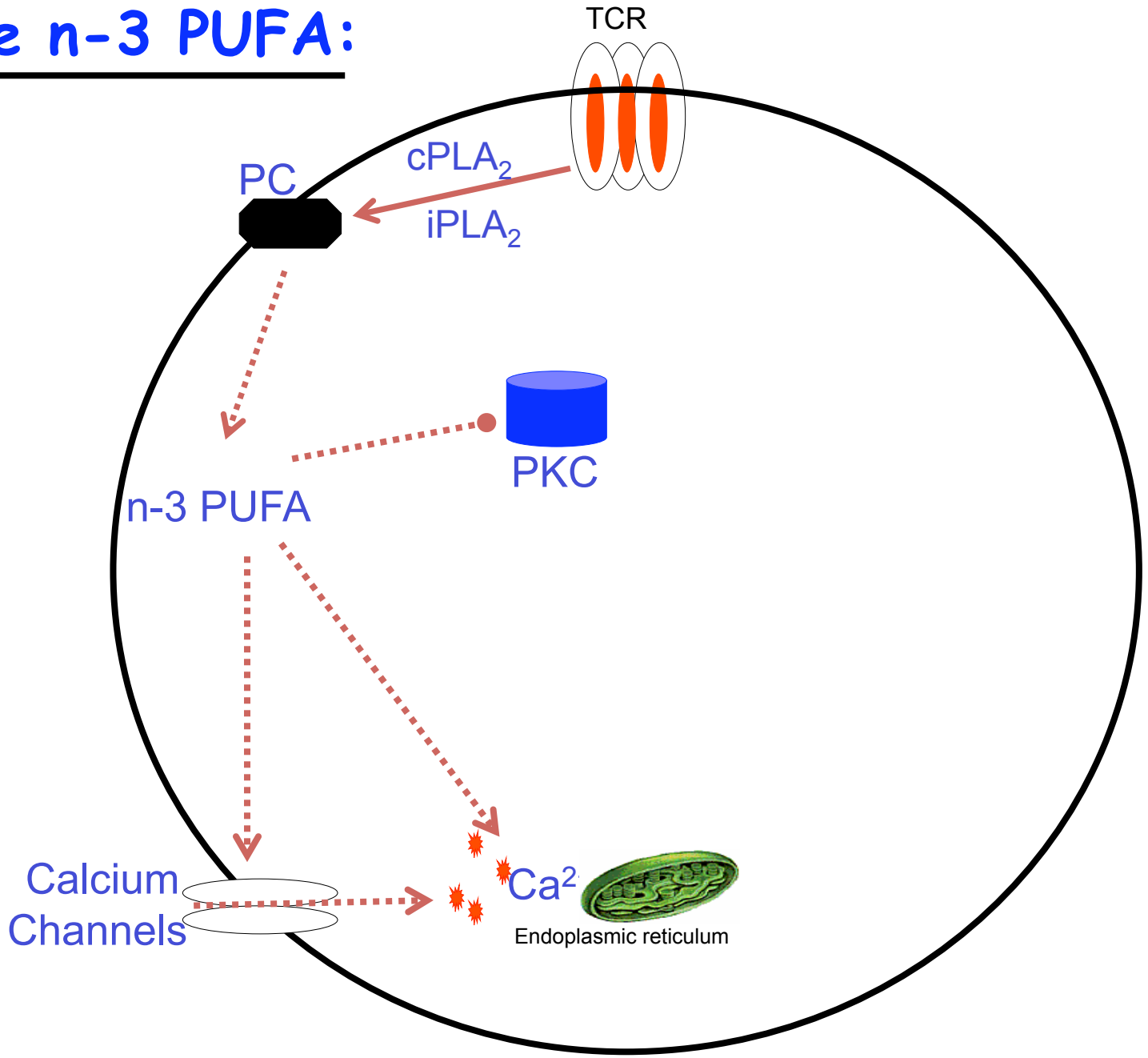
silencing of TRPC3 & TRPC6 by shRNA





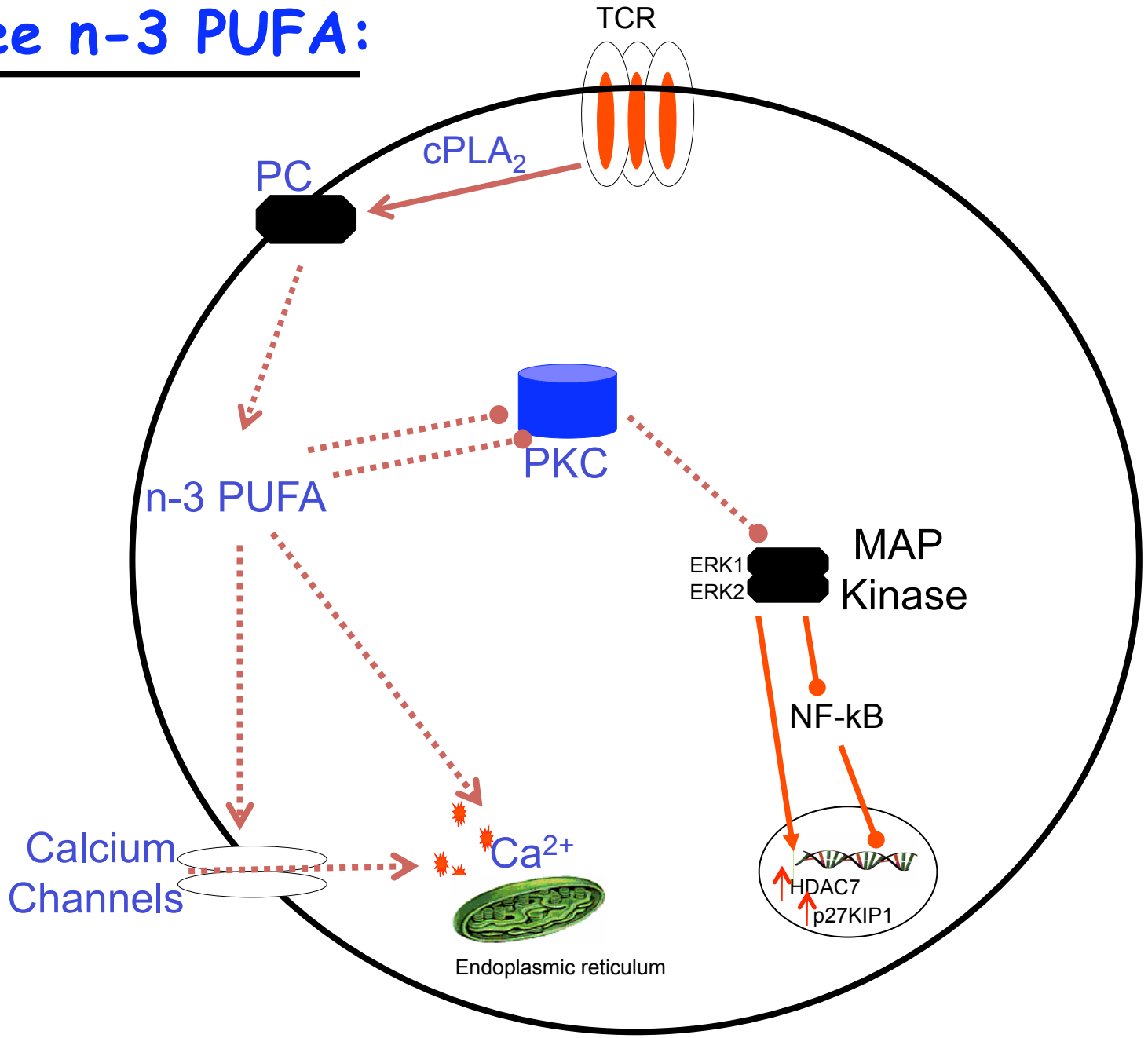
DAG-Oleic acid : single cell experiments

Free n-3 PUFA:



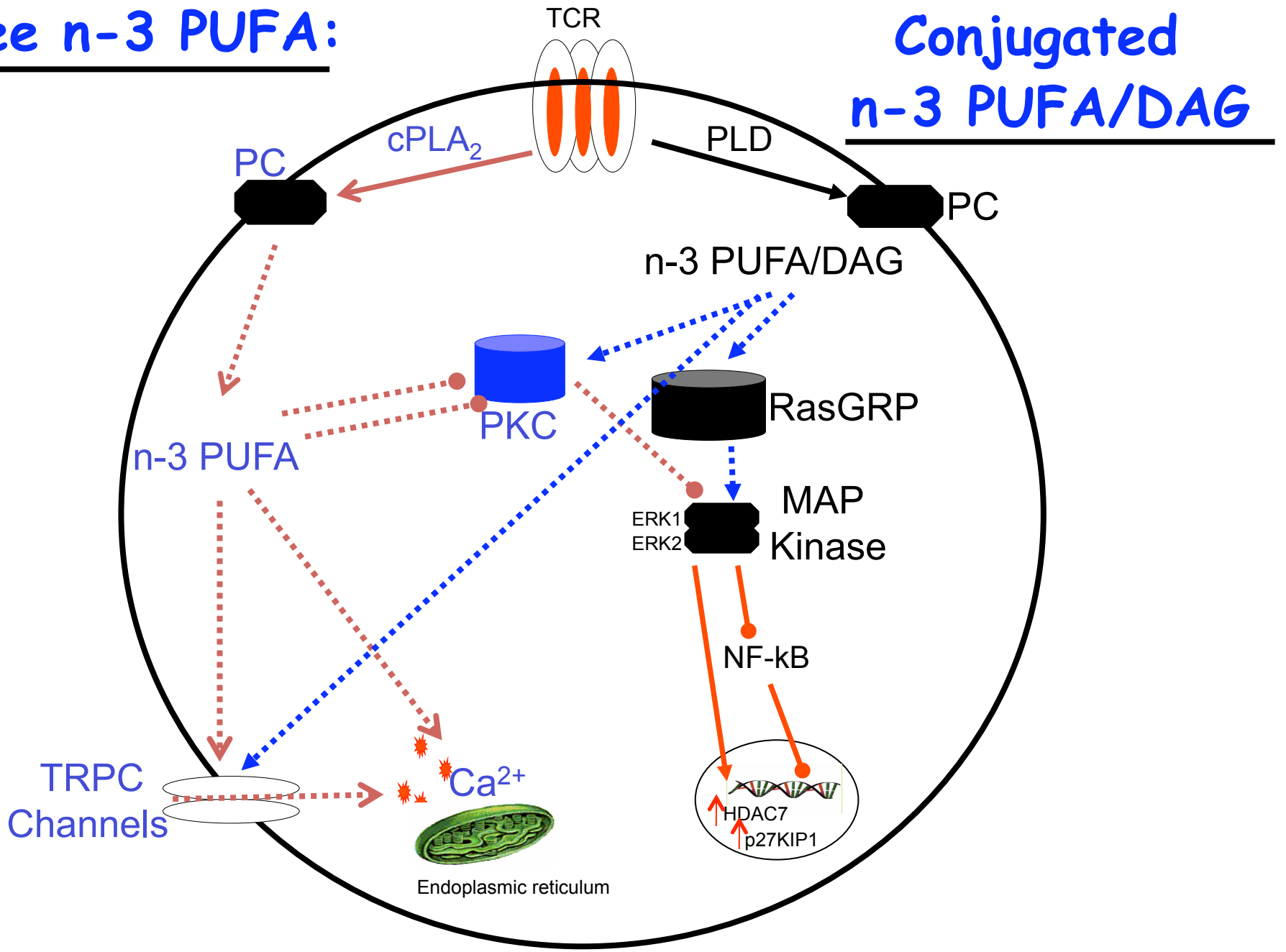
Kim *et al.* (2010). *Prog Lipid Res.* 49:250-61.

Free n-3 PUFA:



Kim *et al.* (2010). *Prog Lipid Res.* 49:250-61.

Free n-3 PUFA:



Conjugated n-3 PUFA/DAG

Kim *et al.* (2010). *Prog Lipid Res.* 49:250-61.

COLLABORATIONS

- K. Moutairou (Cotonou)
- H. Merzouk (Tlemsen)
- E. Elboustani (Marrakech)
- G. Bouley (Sherbrooke)
- J. Stone (Montreal)

N. A. KHAN

A. HICHAMI

J. PROST

A. M. SIMONIN

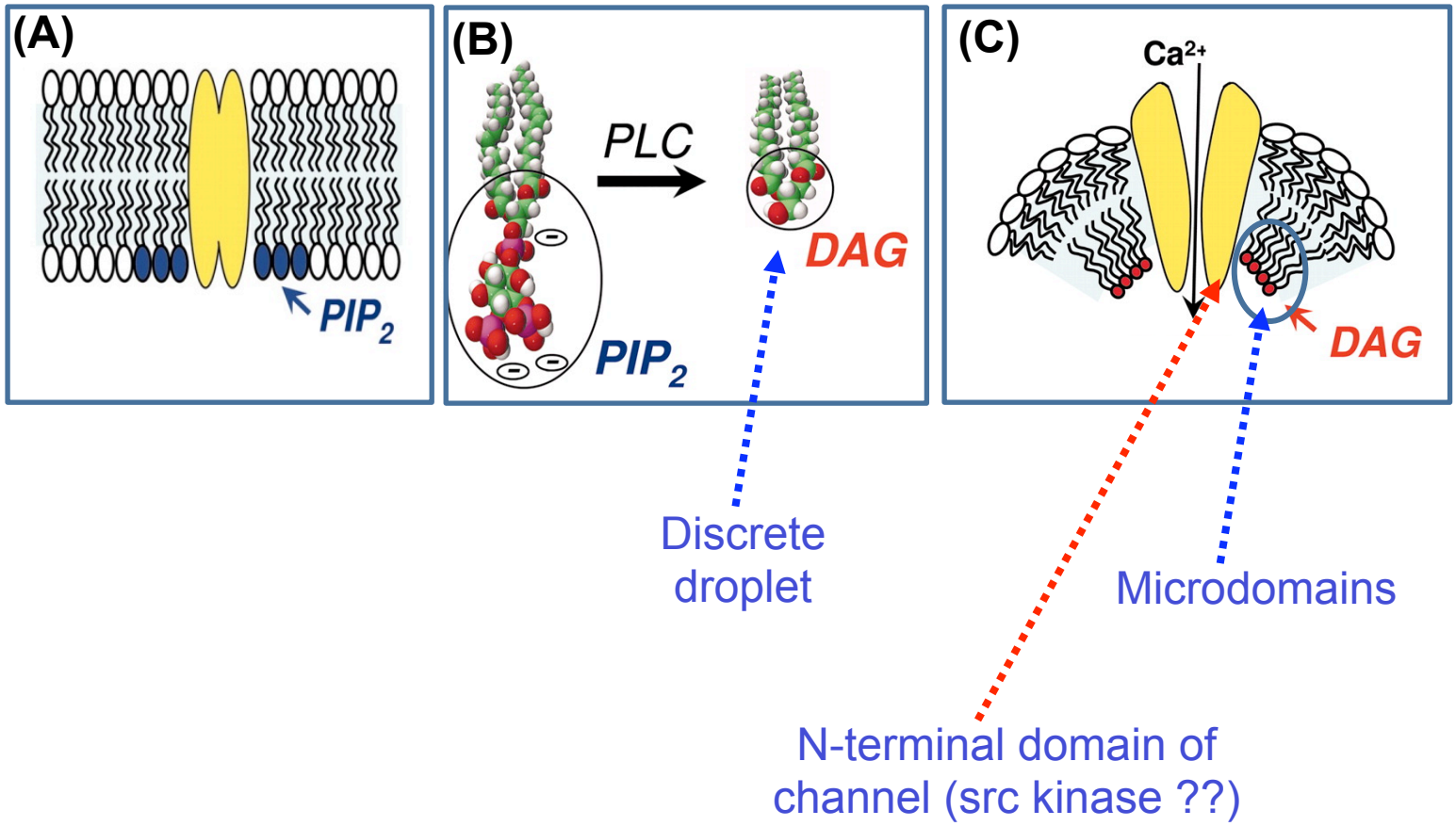
C. TESSIER

S. MADANI

C. TRIBOULOT

A. DENYS

V. AIRES


(A)
PIP2
(B)
PLC
DAG
PIP2
(C)
Ca2+
DAG
Discrete droplet
Microdomains
N-terminal domain of channel (src kinase ??)