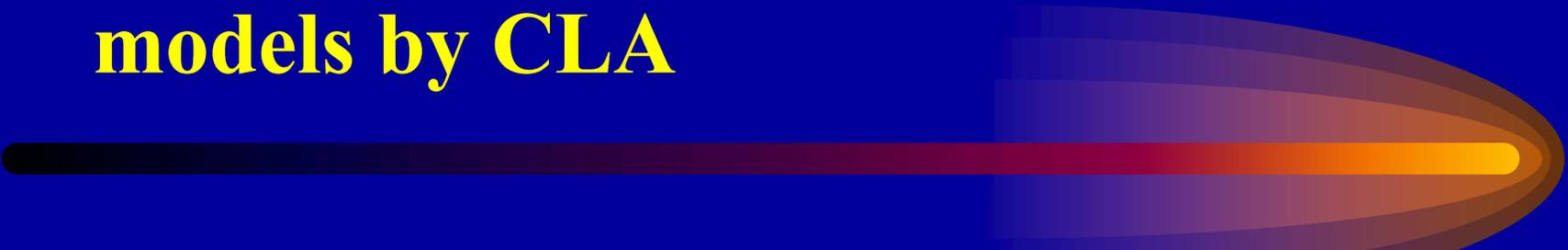




Recent Research on CLA and Mammary Cancer Prevention

**Clement Ip
Roswell Park Cancer Institute
Buffalo, New York**

Inhibition of tumorigenesis in animal models by CLA

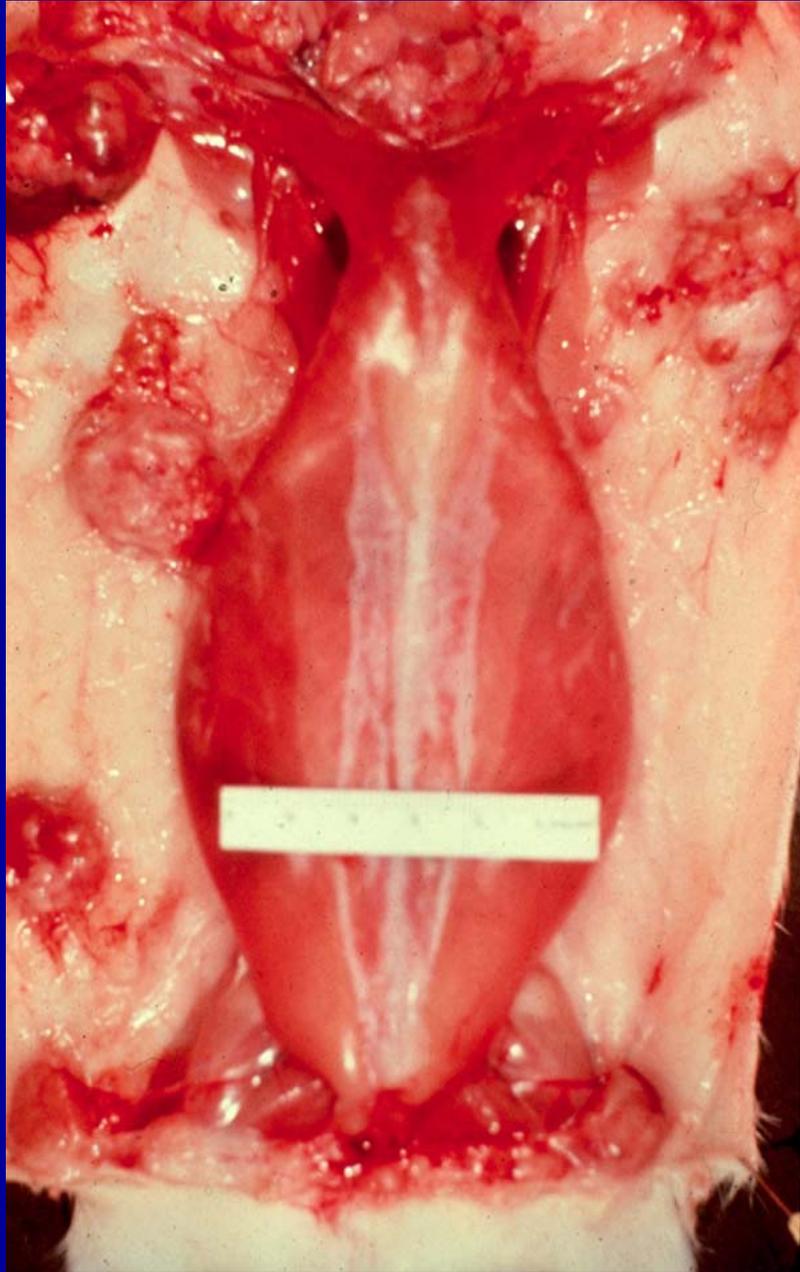


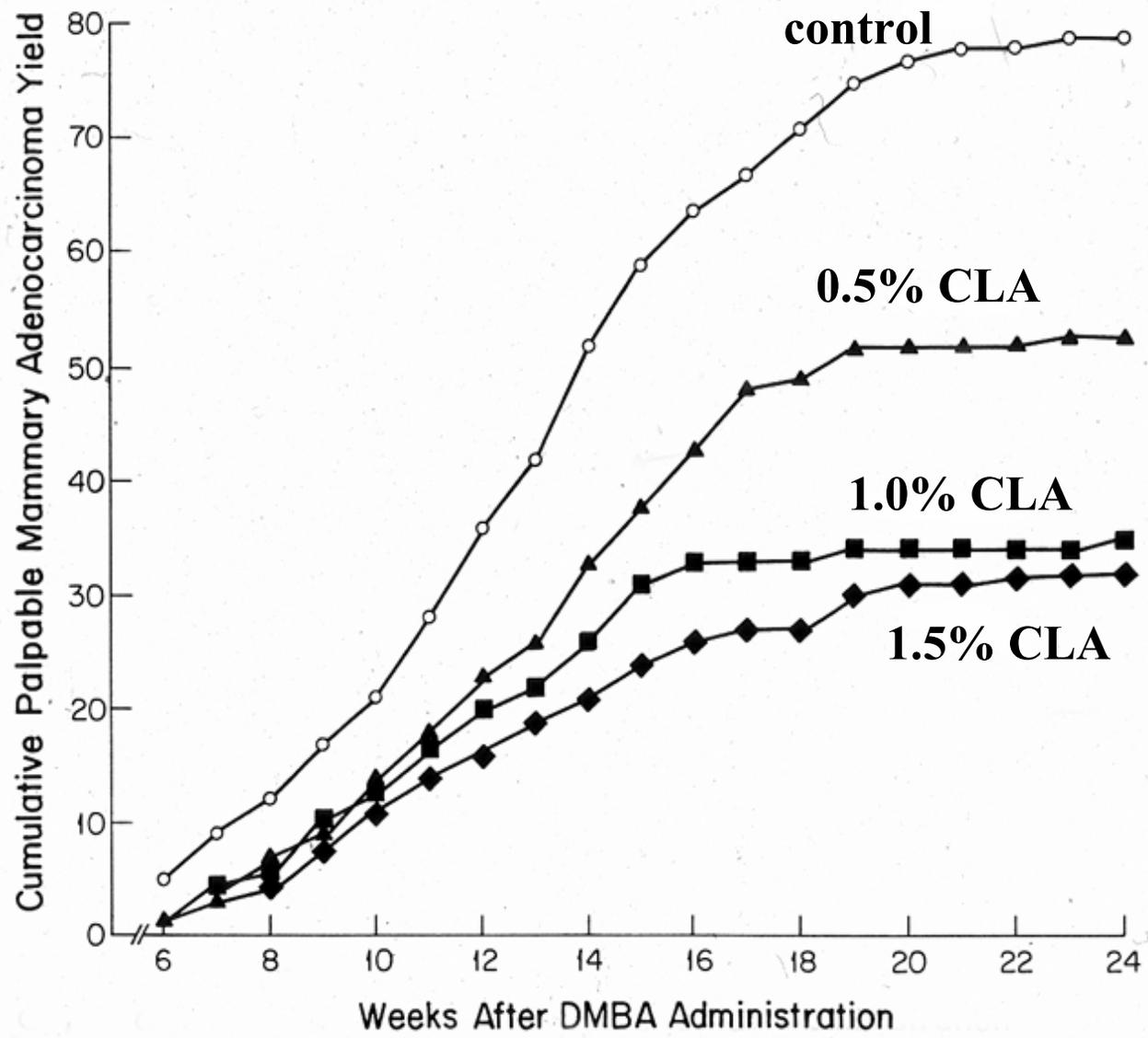
- **Chemical-induced mammary cancer, skin papillomas and colon aberrant crypt foci.**
 - **Transplantable human breast cancer cells or prostate cancer cells in SCID mice.**
-
- **No inhibitory effect with AOM-induced colon cancer in rats or intestinal cancer in Apc Min mice.**

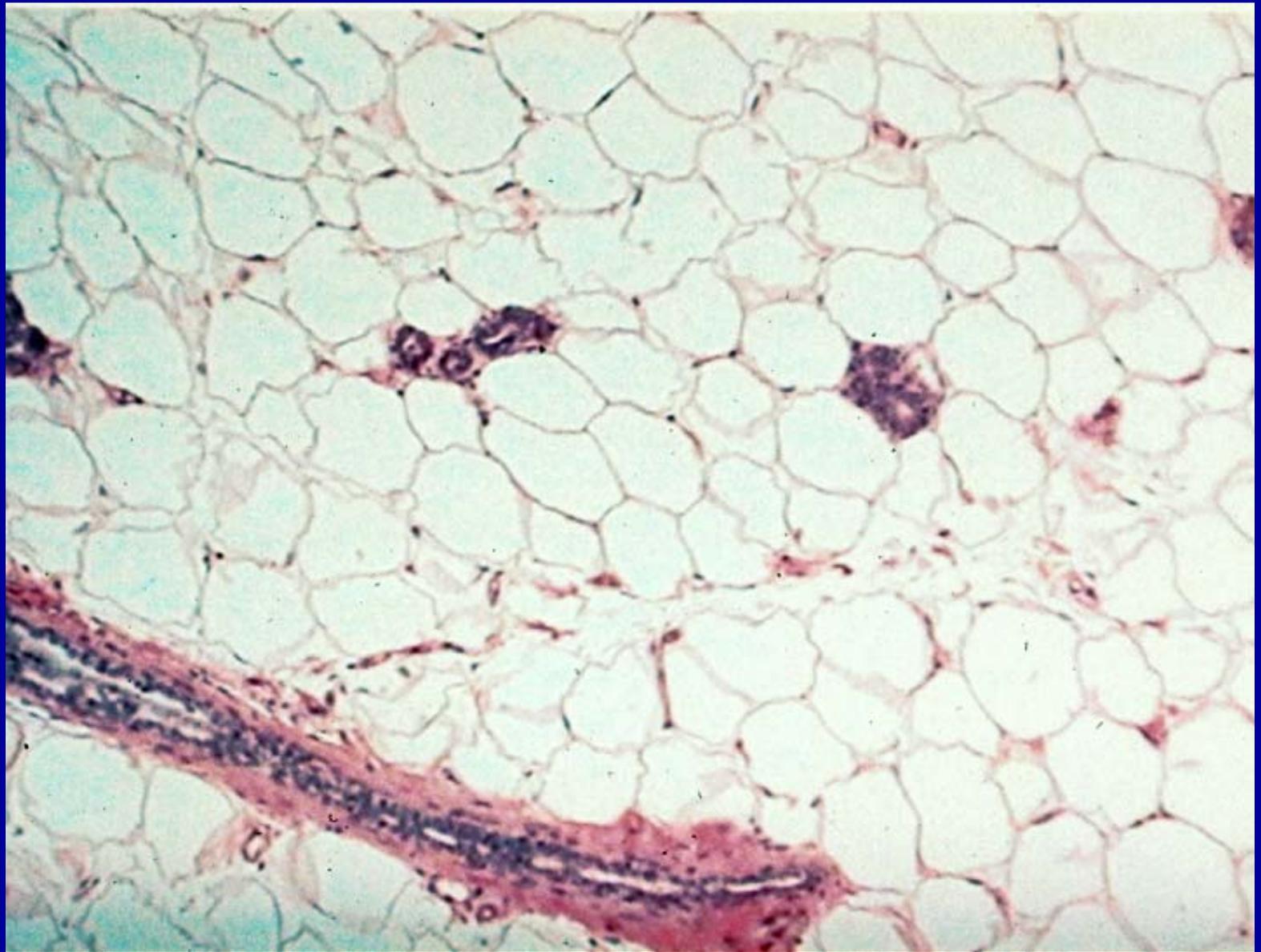
Inverse association between dietary and serum conjugated linoleic acid and risk of breast cancer in postmenopausal women

A. Aro et al. Nutr. Cancer 38: 151-157, 2000

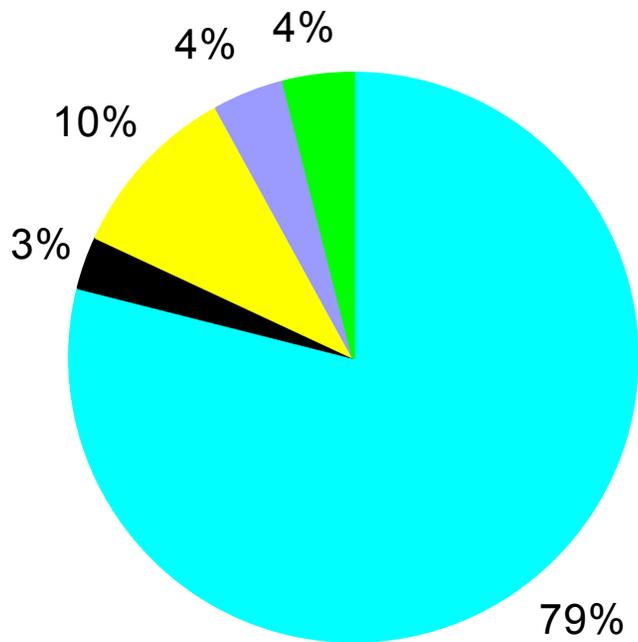
- **68 premenopausal & 127 postmenopausal women diagnosed with breast cancer, matched with 75 premenopausal & 133 postmenopausal women from the general population.**
- **In postmenopausal women, dietary/serum CLA significantly lower in cases than in controls, RR = 0.4 in the highest quintile.**



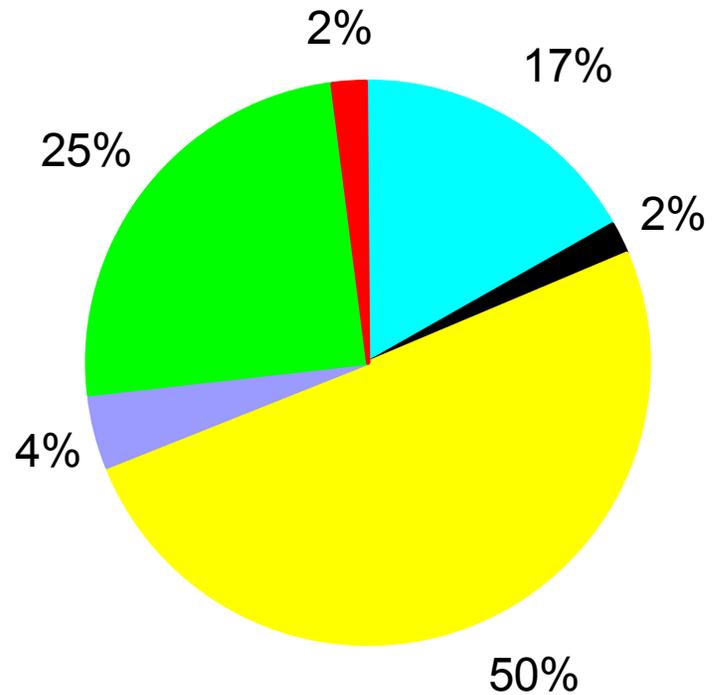




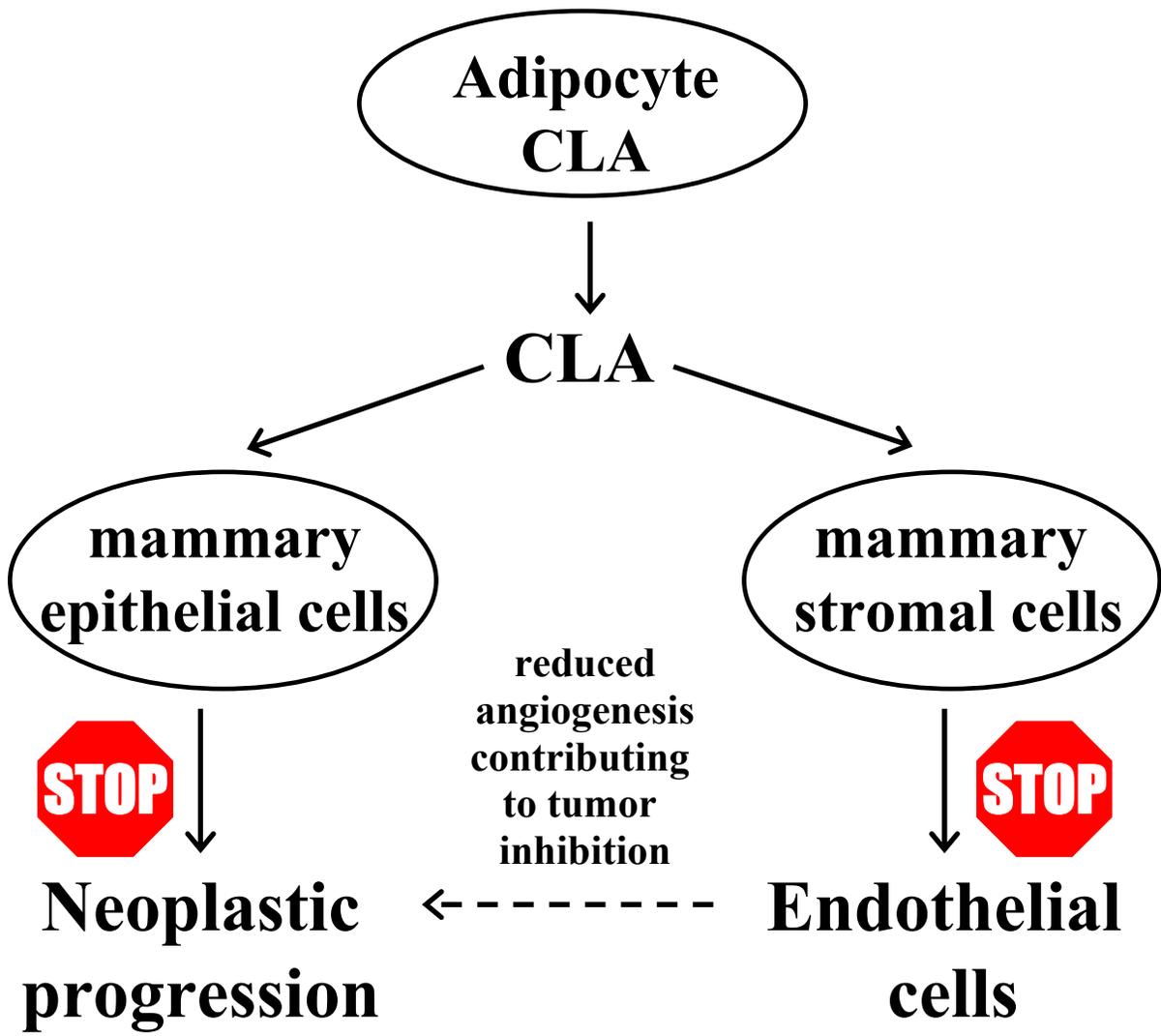
Incorporation of CLA and LA into different lipid fractions



CLA



LA

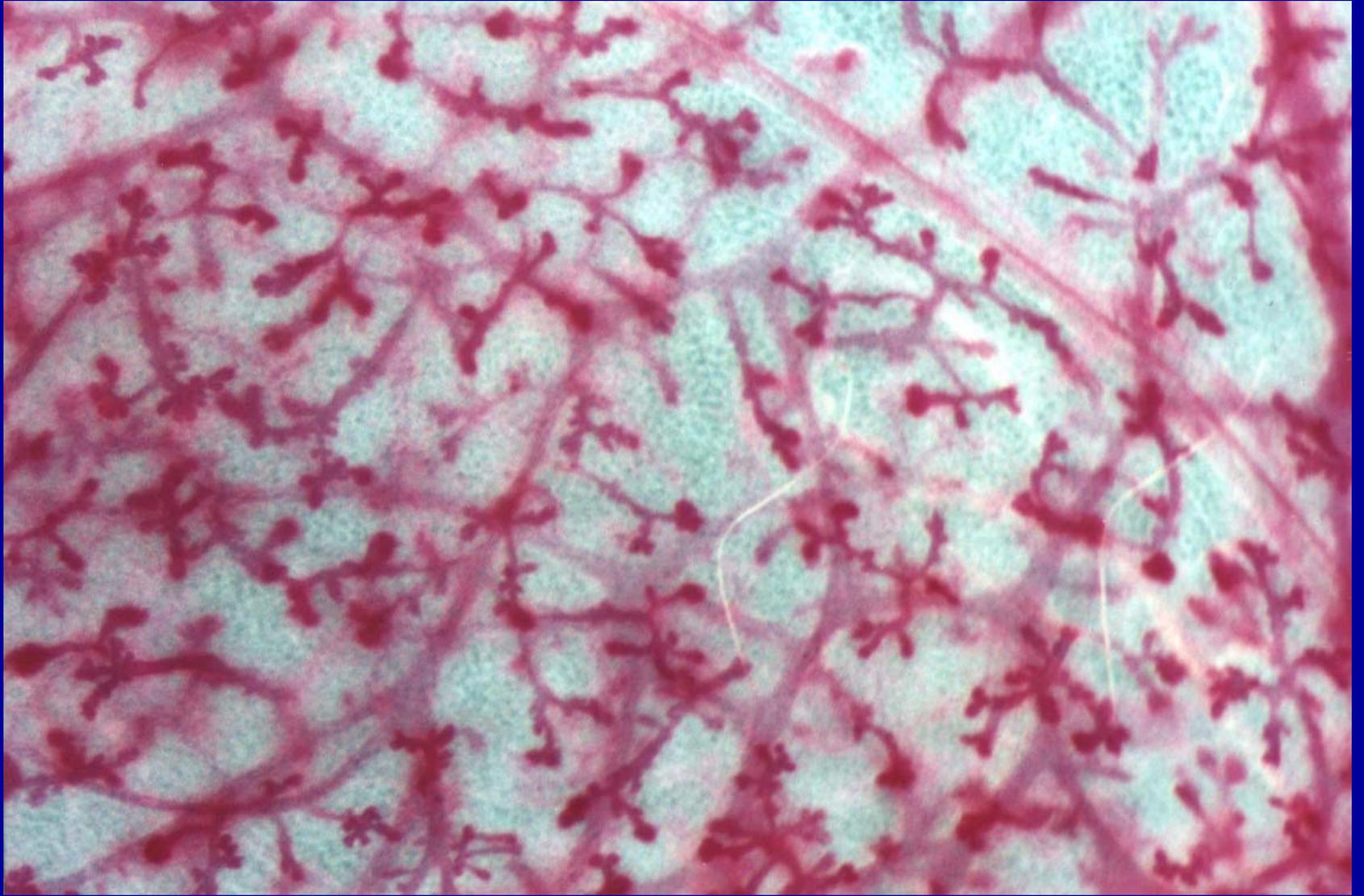


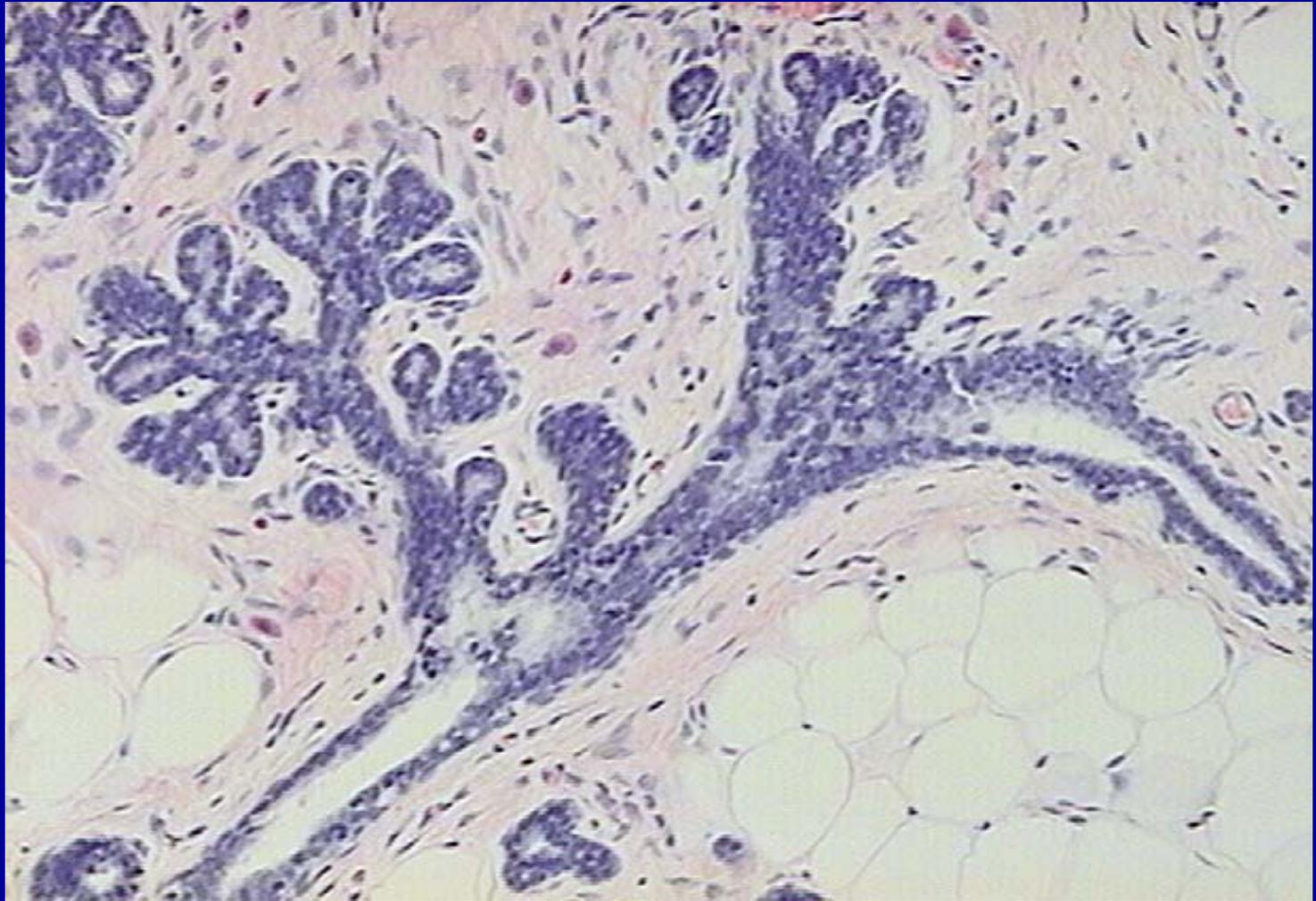


The hallmark of chemoprevention is the ability to block clonal expansion of transformed lesions, and if CLA is a good anticancer agent, there should be evidence suggestive of this attribute.

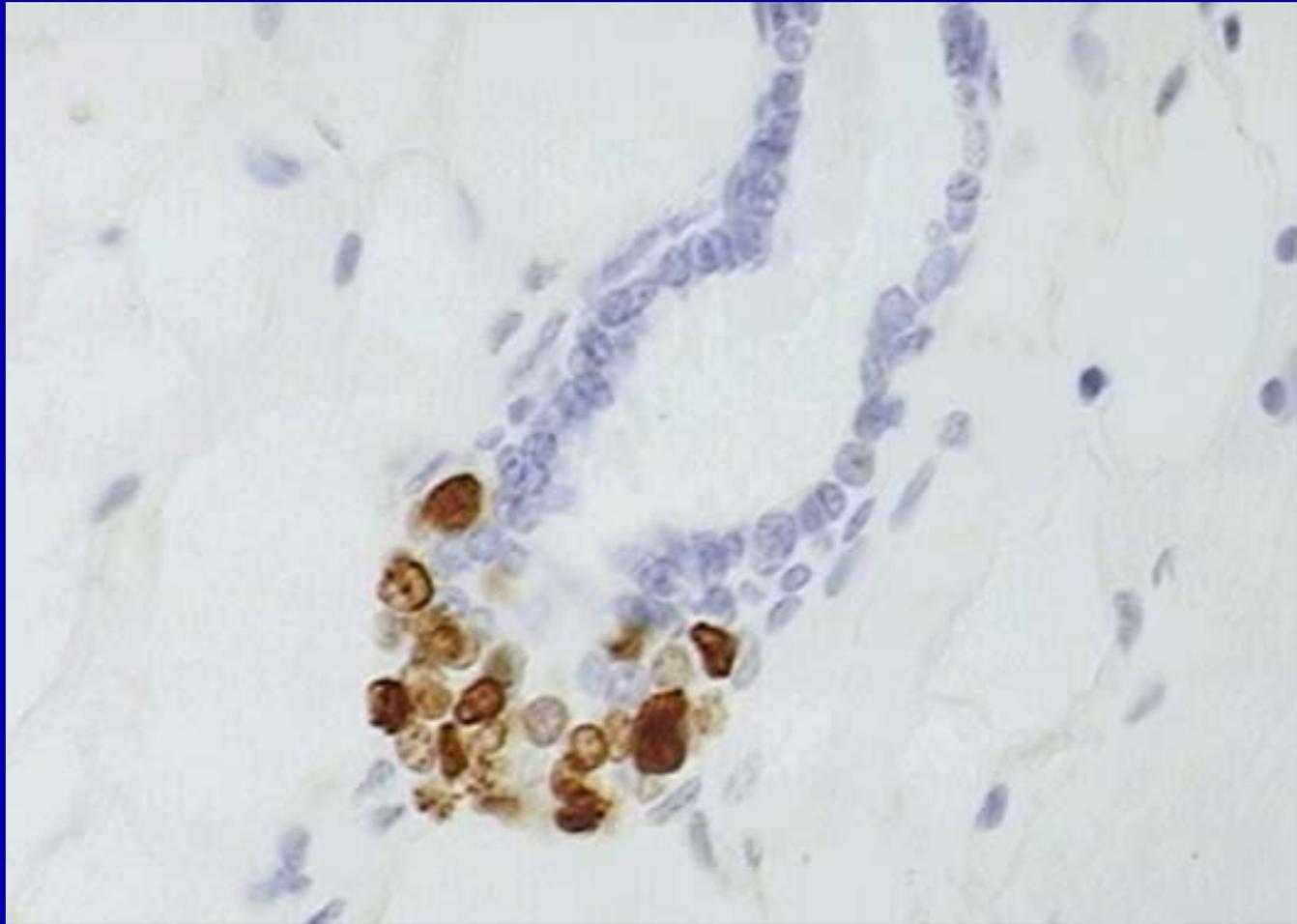


**How early in the carcinogenesis
process can the inhibitory effect
of CLA be detected?**

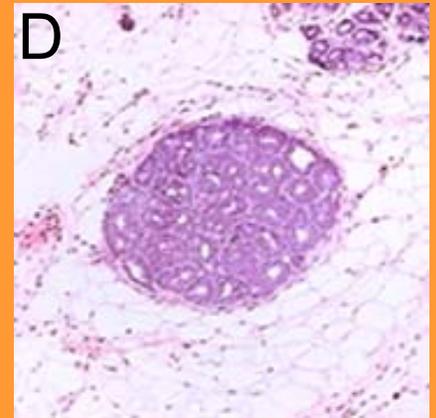
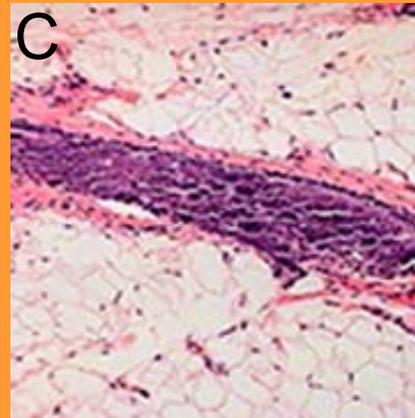
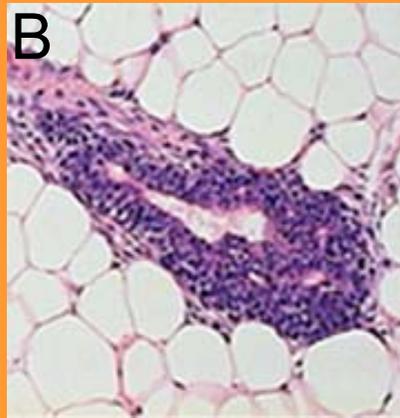
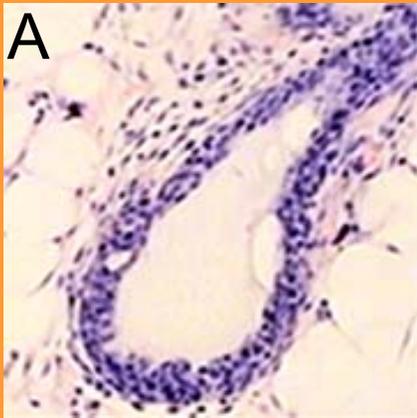




BrdU-labeled TEB



Progression of mammary gland premalignant lesion (IDP)



Activity of 9,11-CLA versus 10,12-CLA in inhibiting the formation of IDPs and carcinomas in the rat mammary gland

<u>Treatment</u>	<u>IDP Expt.</u>		<u>Carcinoma Expt.</u>	
	<u>No. of rats</u>	<u>Total yield</u>	<u>No. of rats</u>	<u>Total yield</u>
control	6	72	30	84
9,11-CLA	6	46	30	51
10,12-CLA	6	48	30	55

CLA content in mammary gland



<u>CLA in diet</u>	<u>Tissue conc. (nmol/mg lipid)</u>	
	<u>9,11-CLA</u>	<u>10,12-CLA</u>
9,11-CLA	84.2 ± 8.3	—
10,12-CLA	—	51.8 ± 6.2



Net growth = Cell proliferation minus Cell death

CLA ↓ proliferation & ↑ cell death



**Cancer Prevention by
Dairy Product Enriched
in 9,11-CLA**

Ip et al.

J. Nutr. 129: 2135-2142, 1999

Rumen

Linoleic acid
(*c9,c12*-C18:2)



CLA
(*c9,t11*-C18:2)



Vaccenic acid
(*t11*-C18:1)



Stearic acid
(C18:0)

Tissue

CLA
(*c9,t11*-C18:2)



$\Delta 9$ desaturase

Vaccenic acid
(*t11*-C18:1)



Vaccenic acid and CLA content in butter fat

**regular
butter** **high CLA
butter**
(g/100 g total fatty acid)

Vaccenic acid

1

12

CLA

0.5

4



Can VA substitute for CLA as an anticancer agent?

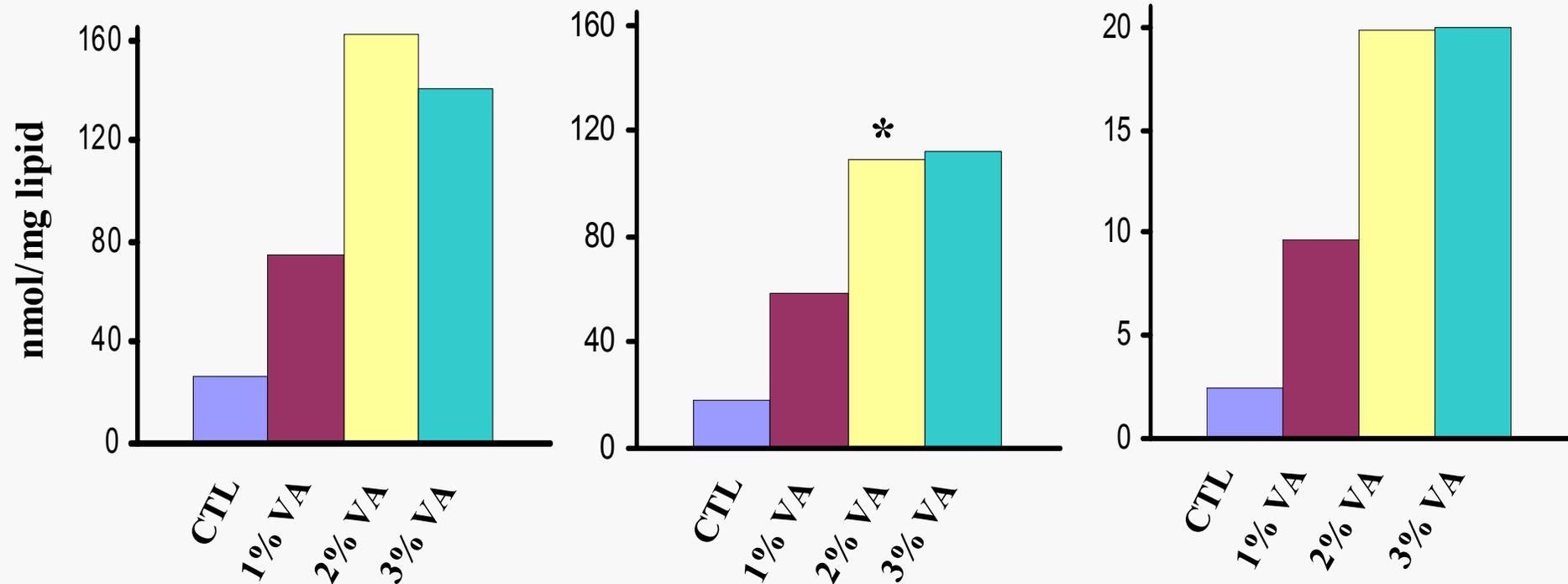
Step 1: To find a dose of VA that will produce a tissue level of CLA known historically to be associated with mammary cancer prevention.

Dose response of vaccenic acid (VA) on the accumulation of vaccenic acid, CLA and CLA metabolites (CD 18:3 + CD 20:3 + CD 20:4) in mammary fat pad

vaccenic acid

CLA

CLA metabolites

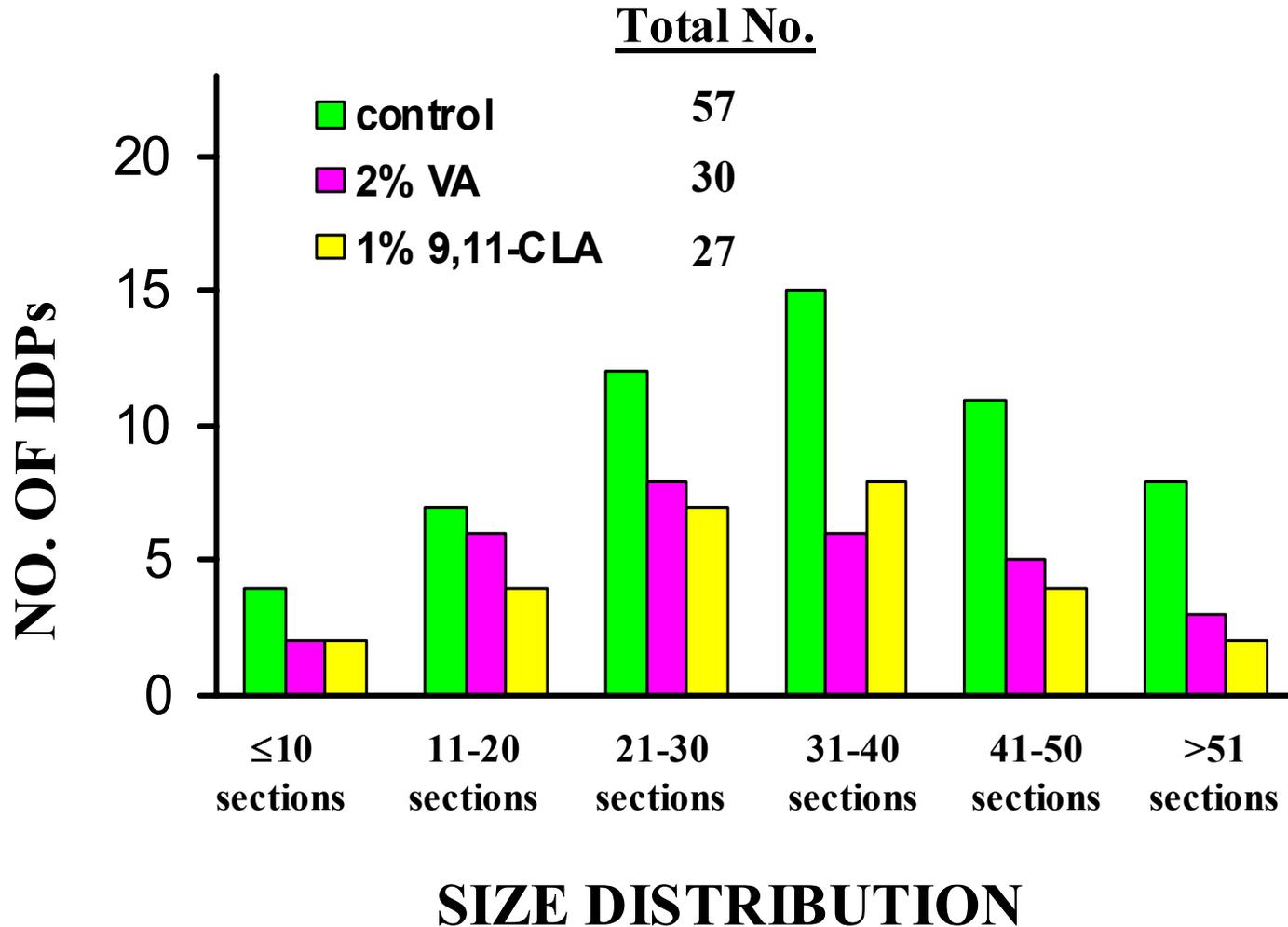




Can VA substitute for CLA as an anticancer agent?

Step 2: To find an appropriate endpoint in order to evaluate the efficacy of VA.

Reduction of IDPs by VA or CLA



CLA

conjugated diene – 18:2



conjugated diene – 18:3



conjugated diene – 20:3



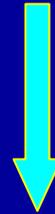
conjugated diene – 20:4

desaturase

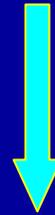
elongase

desaturase

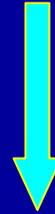
linoleic acid (18:2)



γ-linolenic acid (18:3)



dihomo-γ-linolenic acid (20:3)



arachidonic acid (20:4)

Arguments against the significance of CLA metabolism in the anticancer effect of CLA

Empirical observations on CLA metabolism	Interpretation
Conjugated AA is found only when dietary level of LA is low	Conjugated AA not important because anticancer effect of CLA is independent of LA in the diet
Even if formed, tissue conjugated AA conc. is very low. Phospholipid distribution profile of conjugated AA is very different from that of AA	Unlikely that conjugated AA will diminish the availability of phospholipid-AA which is the precursor for eicosanoid biosynthesis

Future Research Directions

Area	Questions
Field effect of CLA	<ul style="list-style-type: none">• Role of stromal stem cell differentiation?• Interaction between adipocytes and epithelial cells?
Signal transduction	<ul style="list-style-type: none">• Receptors for CLA – PPAR, SREBP or others?• Transcriptional control of activated receptors?
Gene expression	<ul style="list-style-type: none">• What are the critical genes?• Functional significance of CLA-responsive genes?