Center for Colon Cancer Research at the University of South Carolina

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WHY COLORECTAL CANCER?

**** **4th highest in cancer incidence and 2nd highest in mortality.**

**** **Diagnosed in ~150,000 Americans each year; kills ~50,000.**
→ 18 new cases per hour and 6 deaths.

**** **Diagnosed in ~2,200 South Carolinians each year; kills ~700.**
→ 6 new cases per day and 2 deaths.

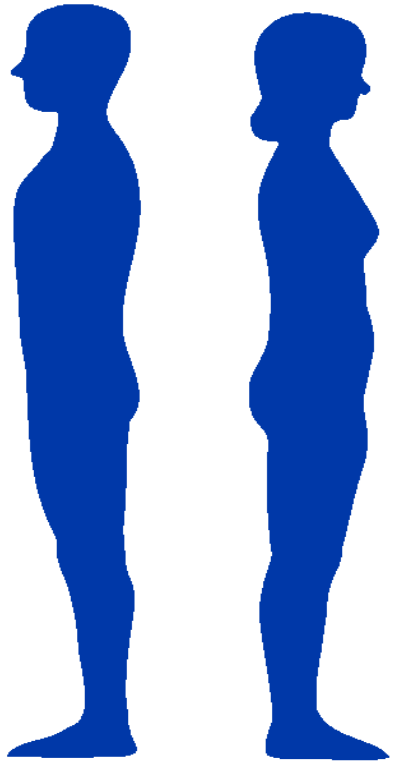
**** **Incidence and mortality higher in the African American community.**

**** **One of the most preventable of cancers.**
→ Each month, colorectal cancer kills the same number of people as 18 plane crashes?

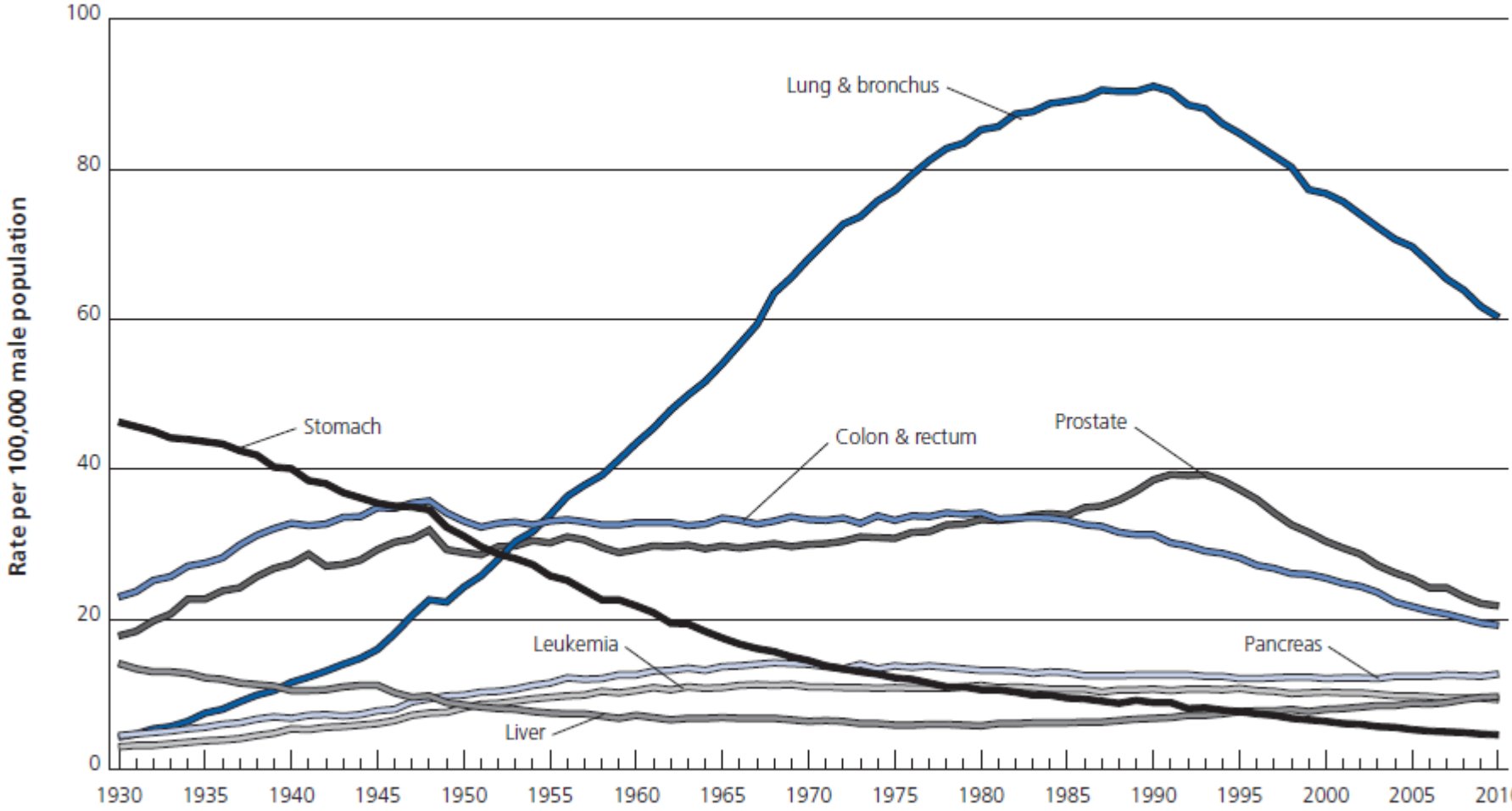
How many people died from cancer last year?

Estimated Cancer Deaths in the US in 2013

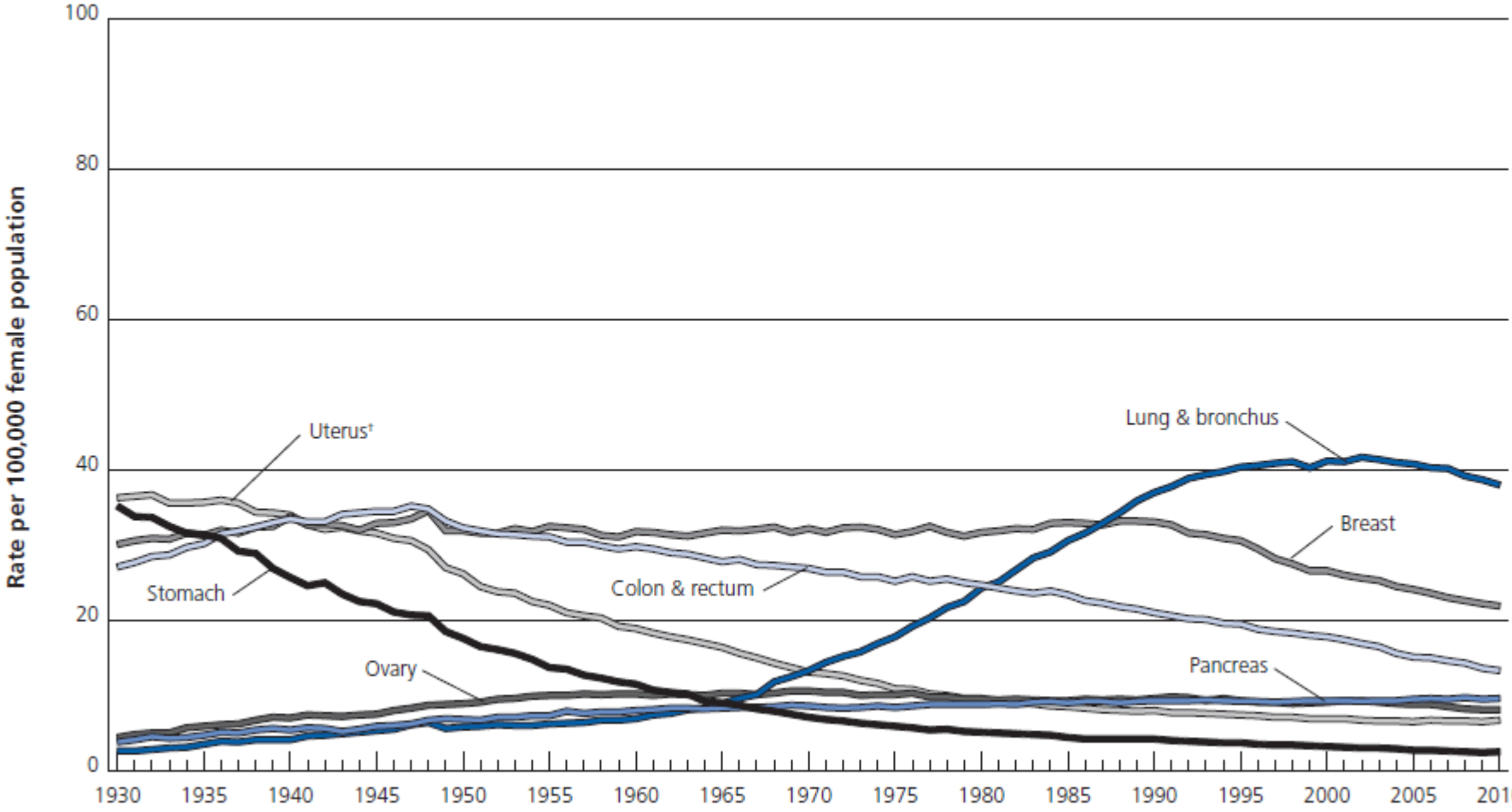
Men		Women	
Lung & bronchus	28%	26%	Lung & bronchus
Prostate	10%	14%	Breast
Colon & rectum	9%	9%	Colon & rectum
Pancreas	6%	7%	Pancreas
Liver & intrahepatic bile duct	5%	5%	Ovary
Leukemia	4%	4%	Leukemia
Esophagus	4%	3%	Non-Hodgkin lymphoma
Urinary bladder	4%	3%	Uterine corpus
Non-Hodgkin lymphoma	3%	2%	Liver & intrahepatic bile duct
Kidney & renal pelvis	3%	2%	Brain/other nervous system
All other sites	24%	25%	All other sites



Age-adjusted Cancer Death Rates*, Males by Site, US, 1930-2010



Age-adjusted Cancer Death Rates*, Females by Site, US, 1930-2010



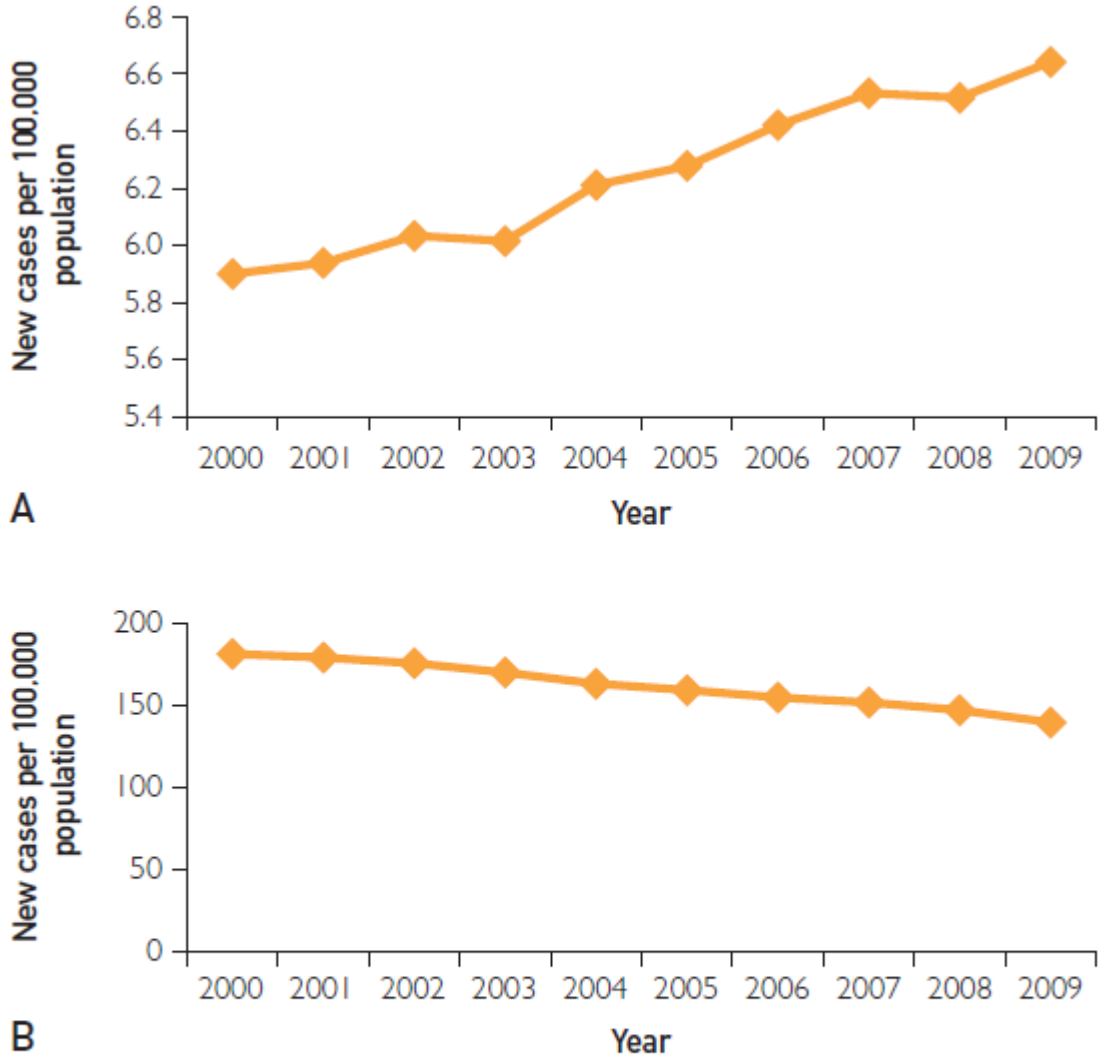
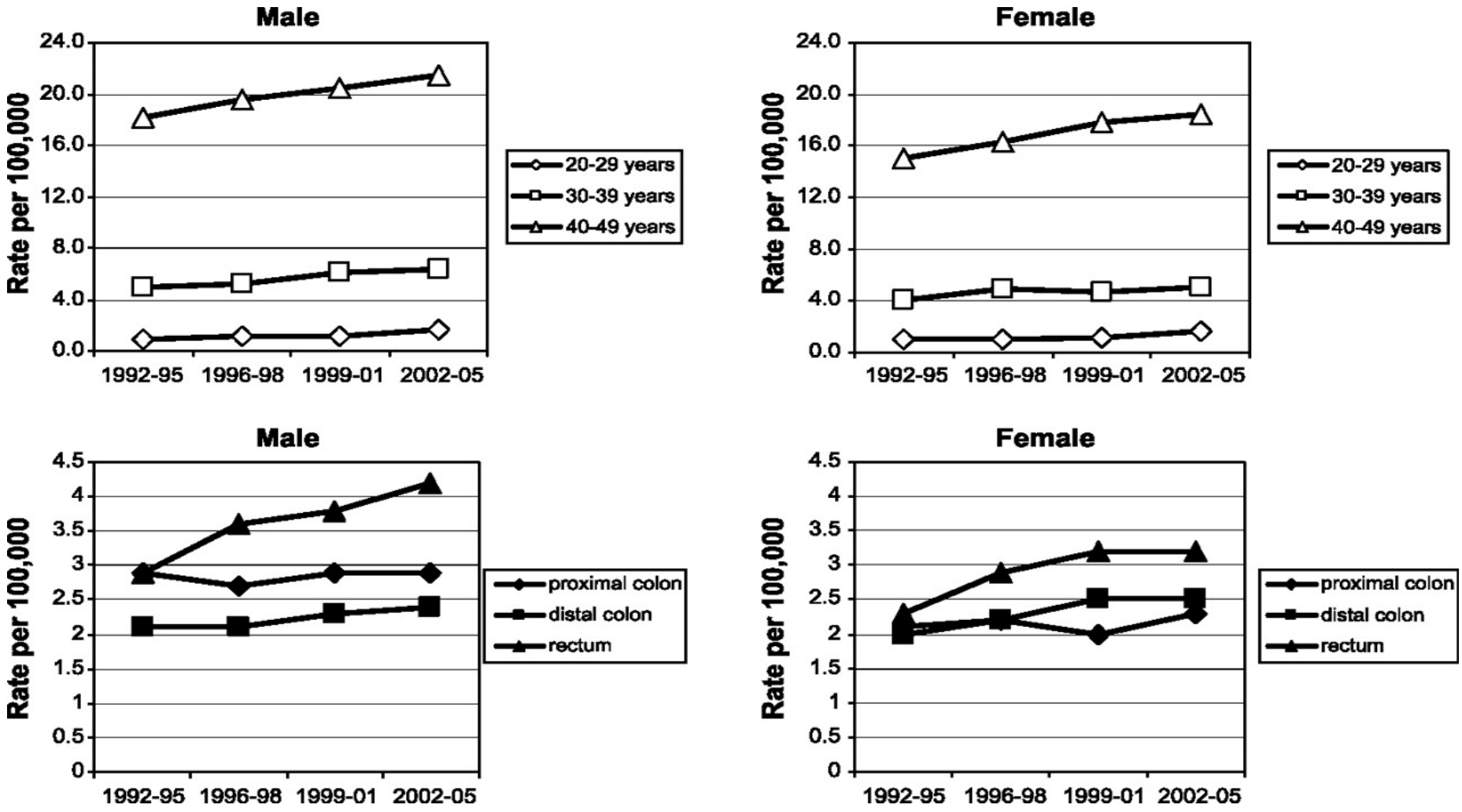


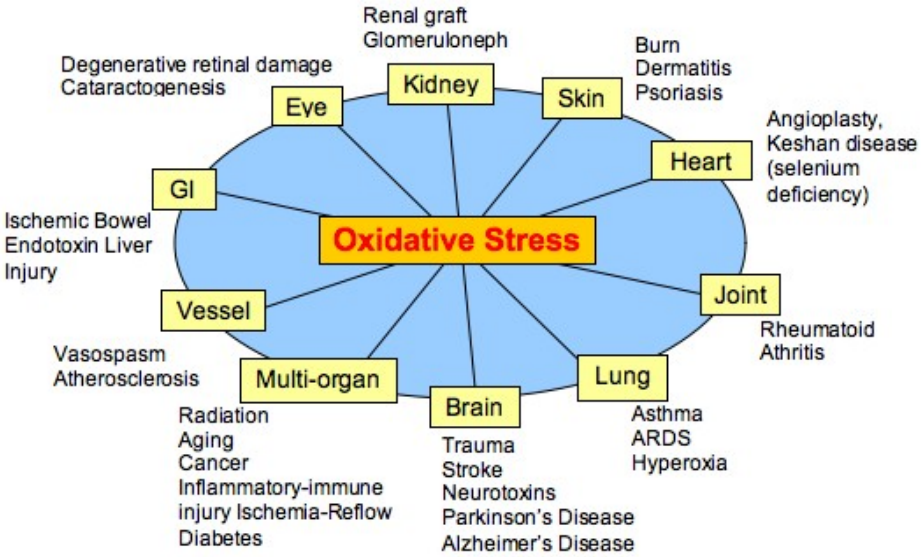
FIGURE 1. Surveillance, Epidemiology, and End Results age-adjusted colorectal cancer incidence per 100,000 individuals in those younger than 50 years (A) and those 50 years or older (B).

CRC incidence trends among young non-Hispanic White adults (20-49 y) by age and anatomic subsite, 1992 to 2005.

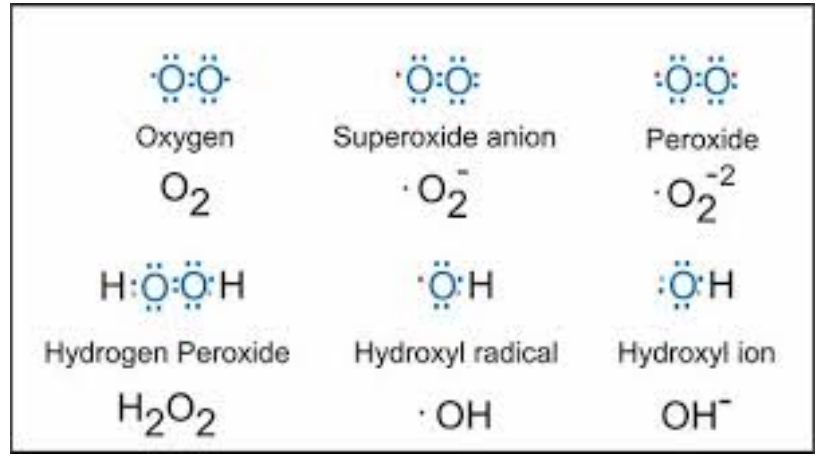


Siegel R L et al. Cancer Epidemiol Biomarkers Prev 2009;18:1695-1698

Cancer Epidemiology, Biomarkers & Prevention



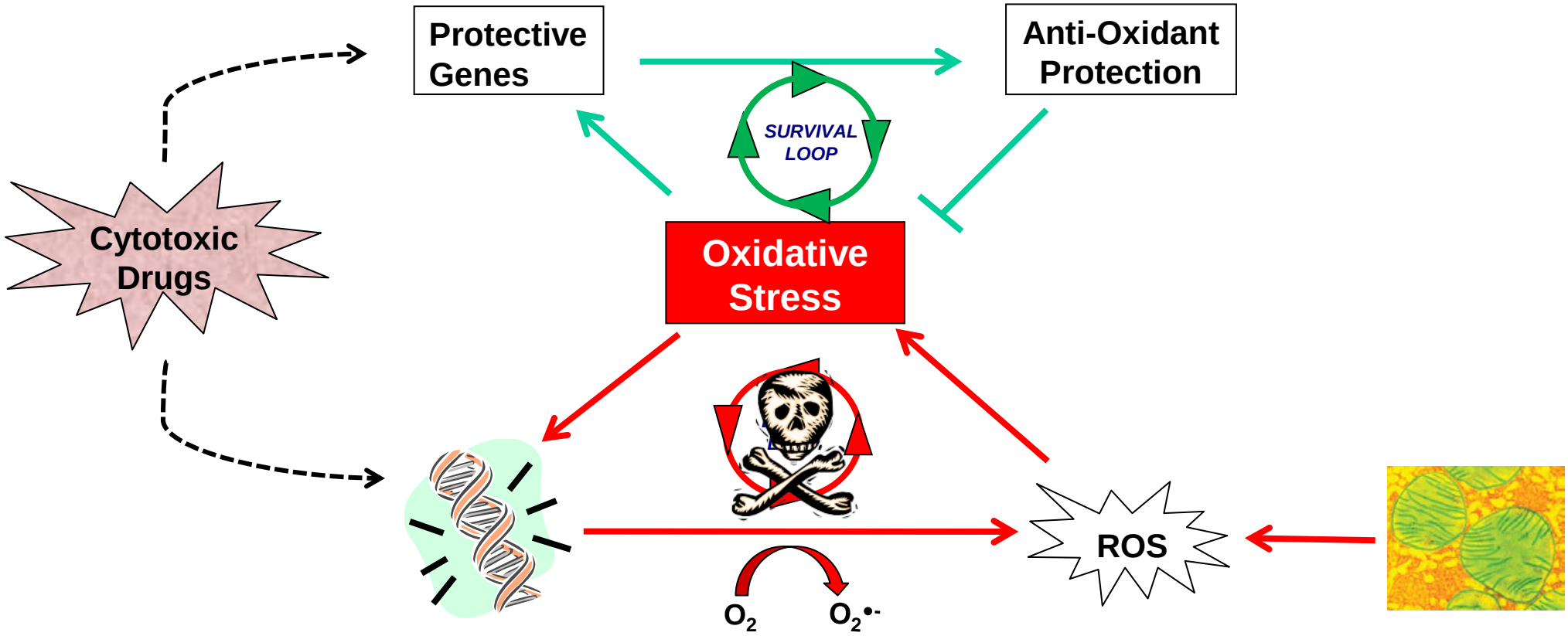
Reactive Oxygen Species (ROS)



Are there situations where oxidative stress is of value?

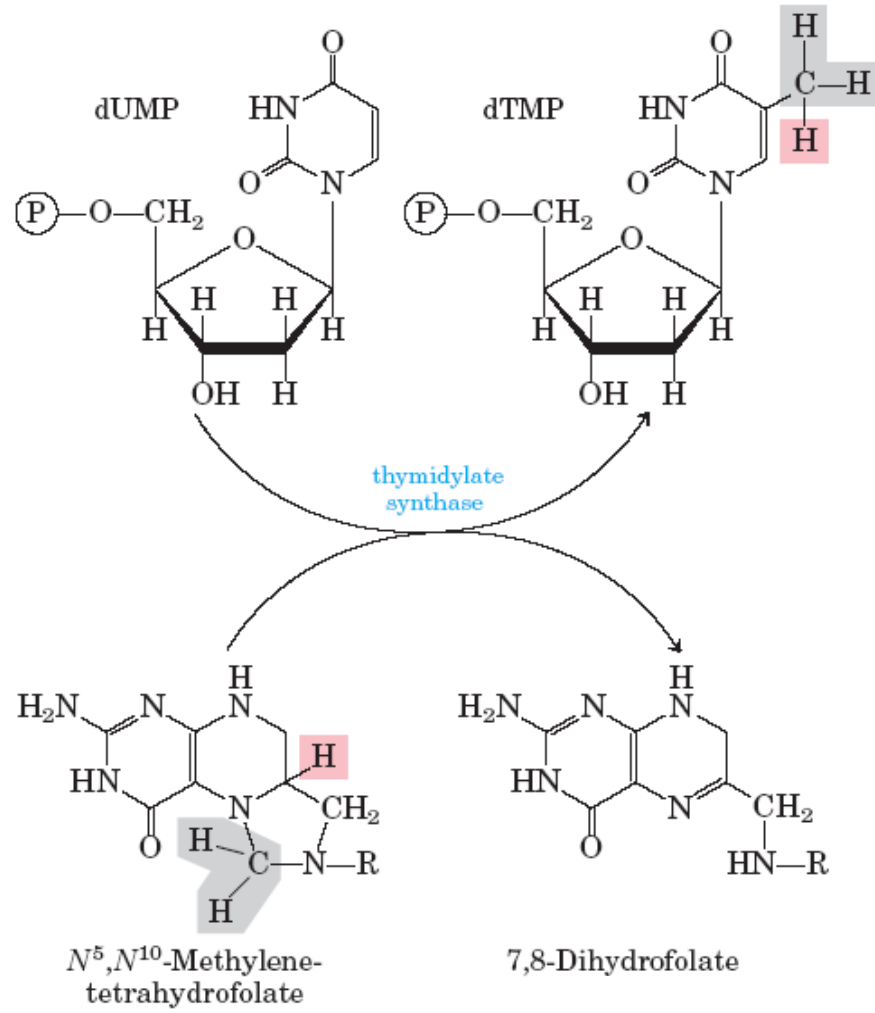
*Efficacy of colon cancer chemotherapy is linked to **oxidative stress** mediated by drug-induced **ROS***

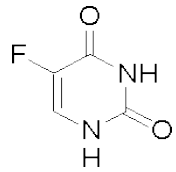
Balance between ROS-mediated cell death vs. activation of survival mechanisms determines response to cancer therapy



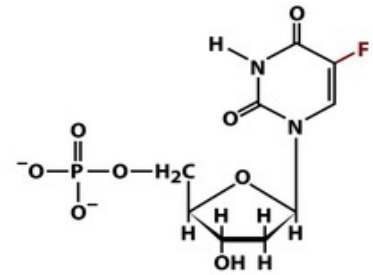
Therapeutic agents directed at Thymidylate Synthase were among the first targeted drugs for treatment of cancer

Thymidylate synthase (TS) catalyzes the reductive methylation of dUMP to form dTMP that is required for DNA replication and repair

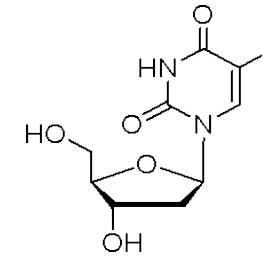




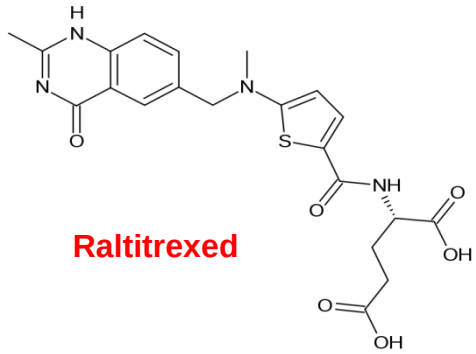
5-fluorouracil



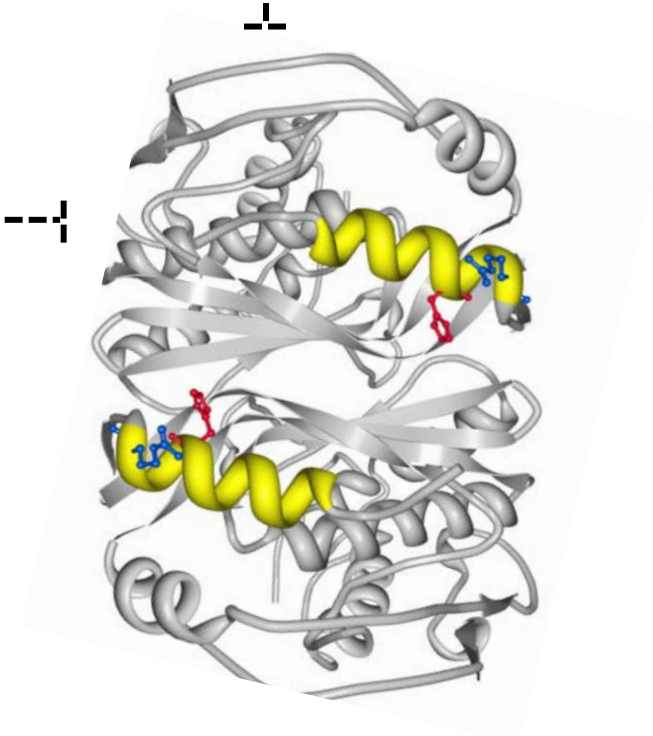
5-Fluorodeoxyuridylate (FdUMP)

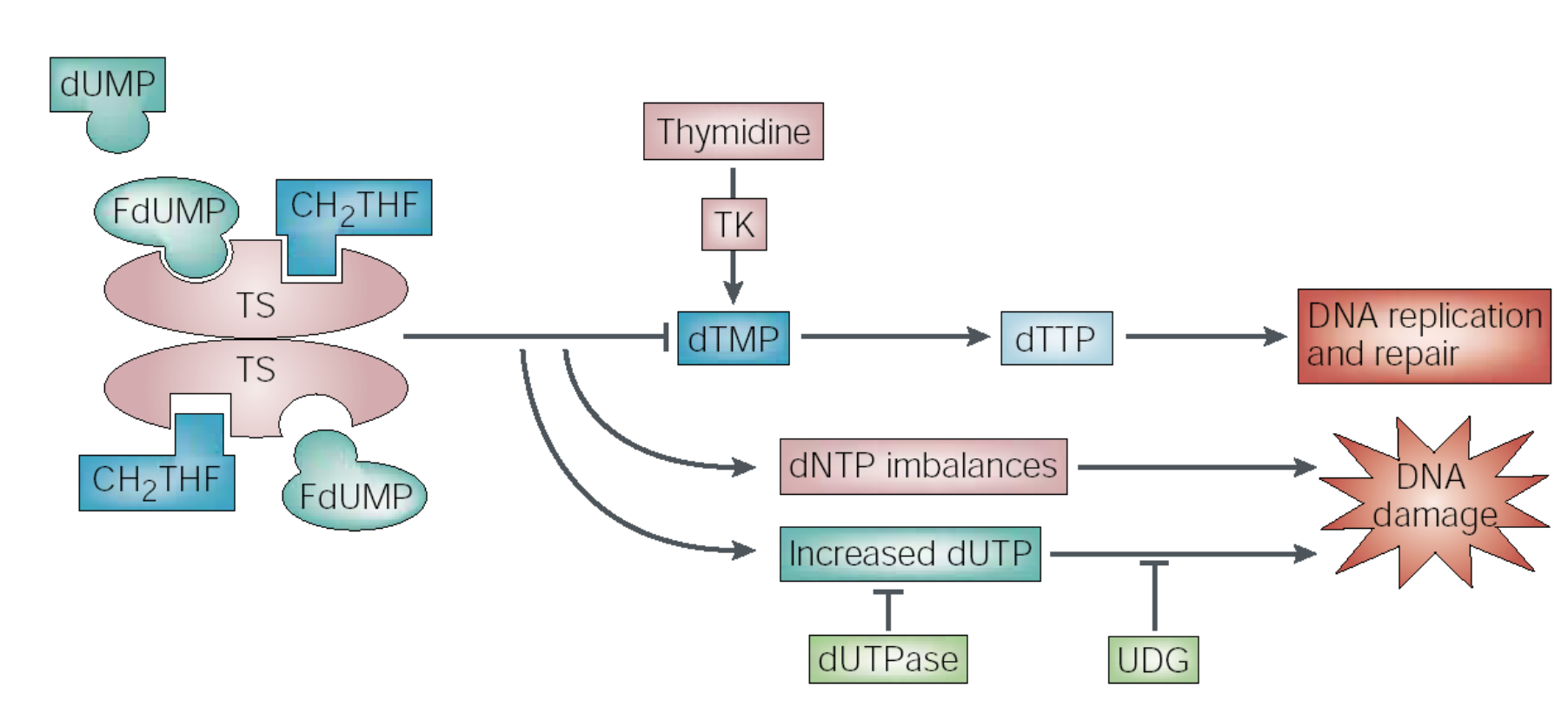


5-fluoro-2'-deoxyuridine



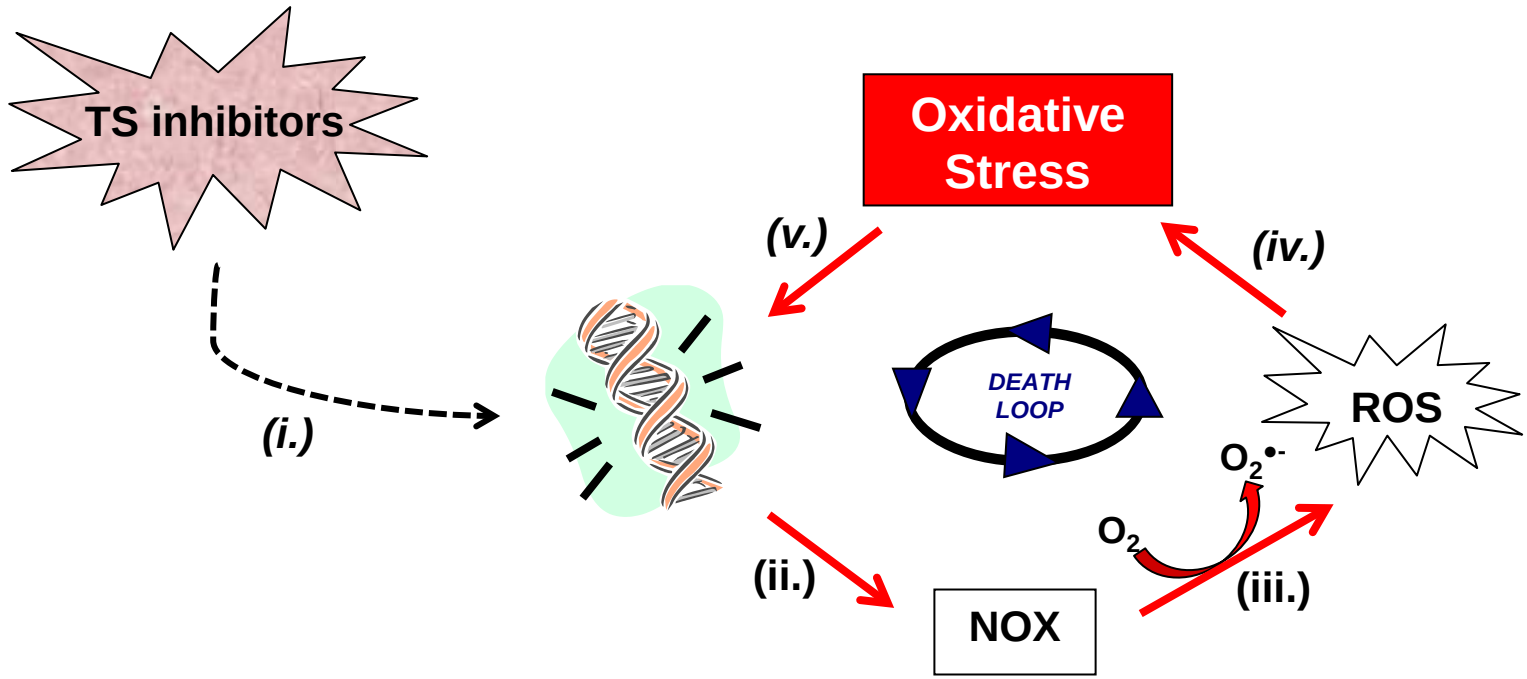
Raltitrexed

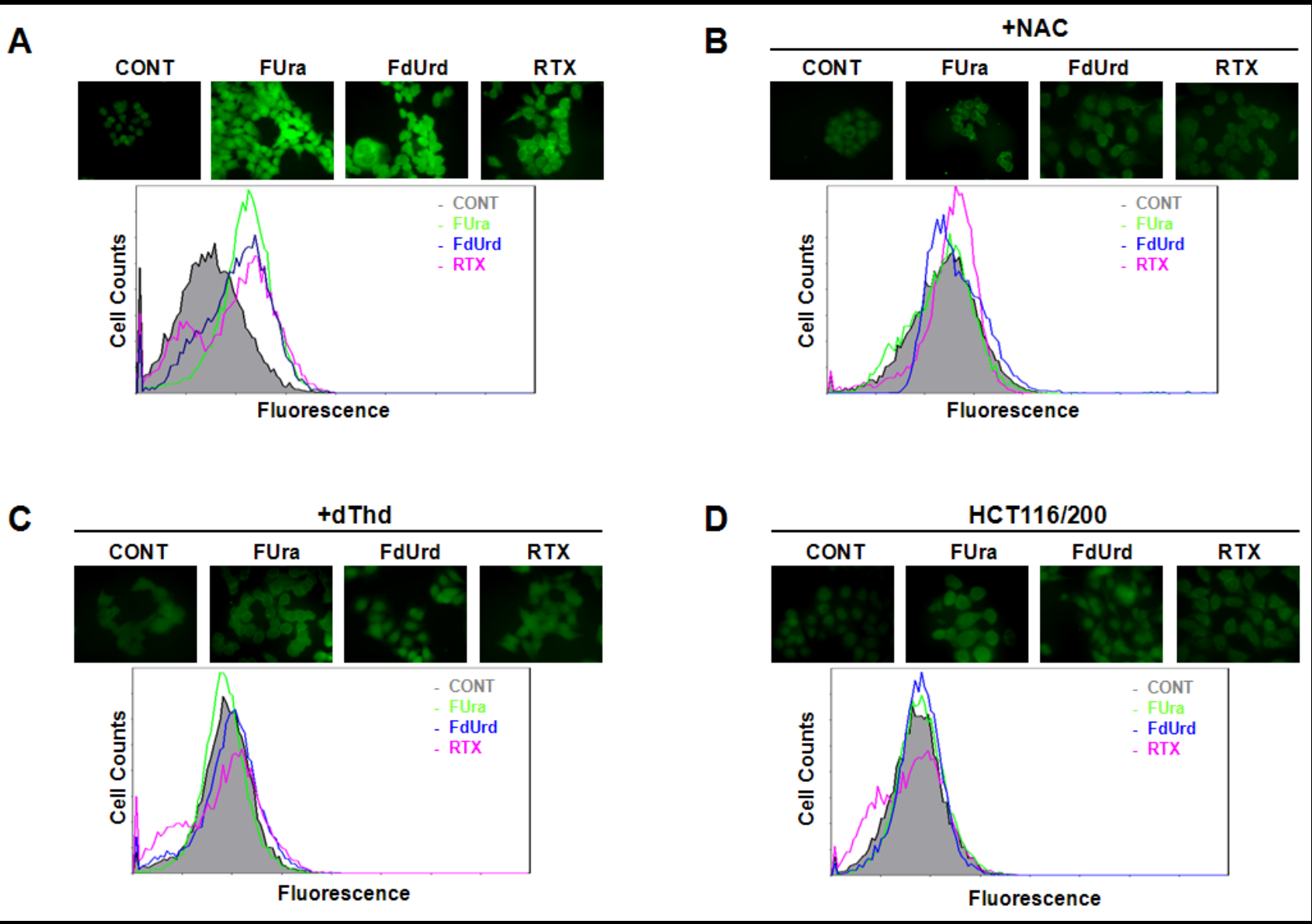




Longley *et al. Nature Reviews Cancer* 3:330 (2003)

TS inhibitors induce a redox-mediated death loop




A
CONT
FUra
FdUrd
RTX
Cell Counts
Fluorescence
CONT
FUra
FdUrd
RTX
B
+NAC
CONT
FUra
FdUrd
RTX
Cell Counts
Fluorescence
CONT
FUra
FdUrd
RTX
C
+dThd
CONT
FUra
FdUrd
RTX
Cell Counts
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HCT116/200
CONT
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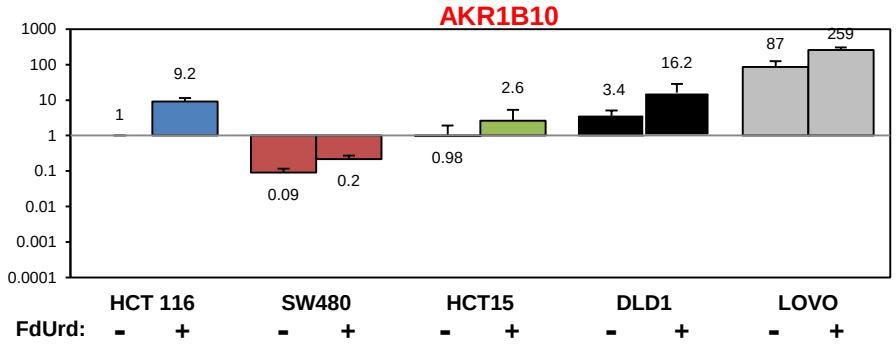
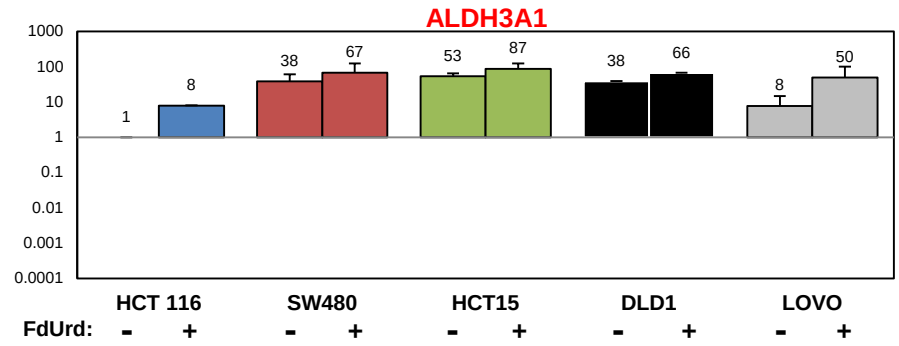
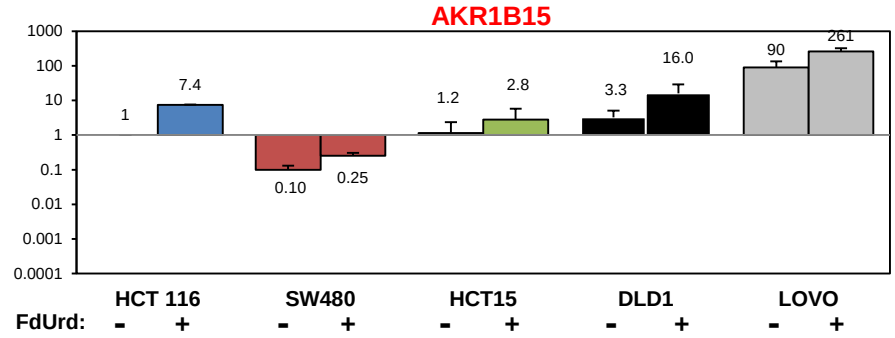
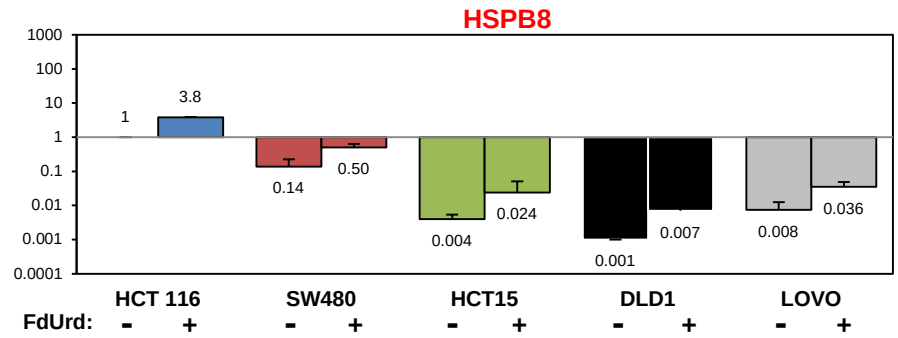
RTX

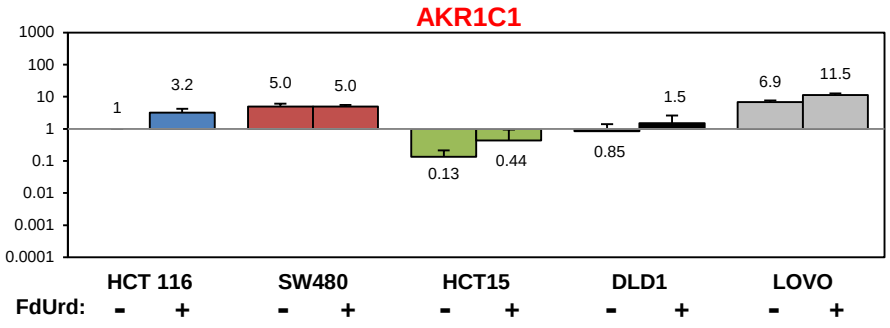
Gene expression profiling indicated that a number of genes regulated by transcription factor Nrf2 are induced in cells exposed to TS inhibitors.

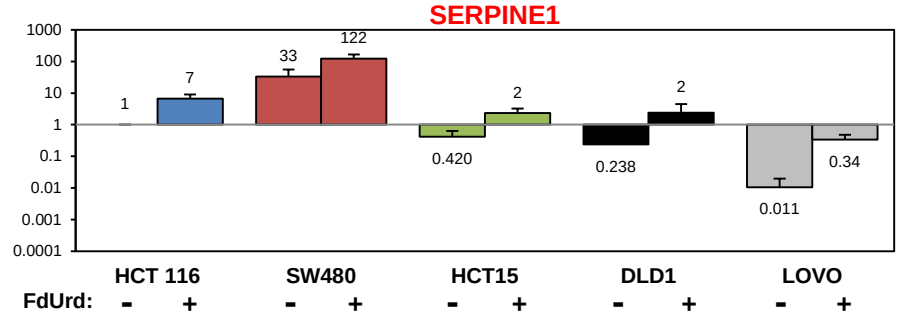












Nrf2 is a transcription factor that activates genes involved in protection against oxidative and electrophilic stress.

Its induction by a wide variety of synthetic and naturally-occuring chemical agents reduces the impact of chronic and degenerative disorders such as cancer, heart disease, diabetes, kidney dysfunction, etc.

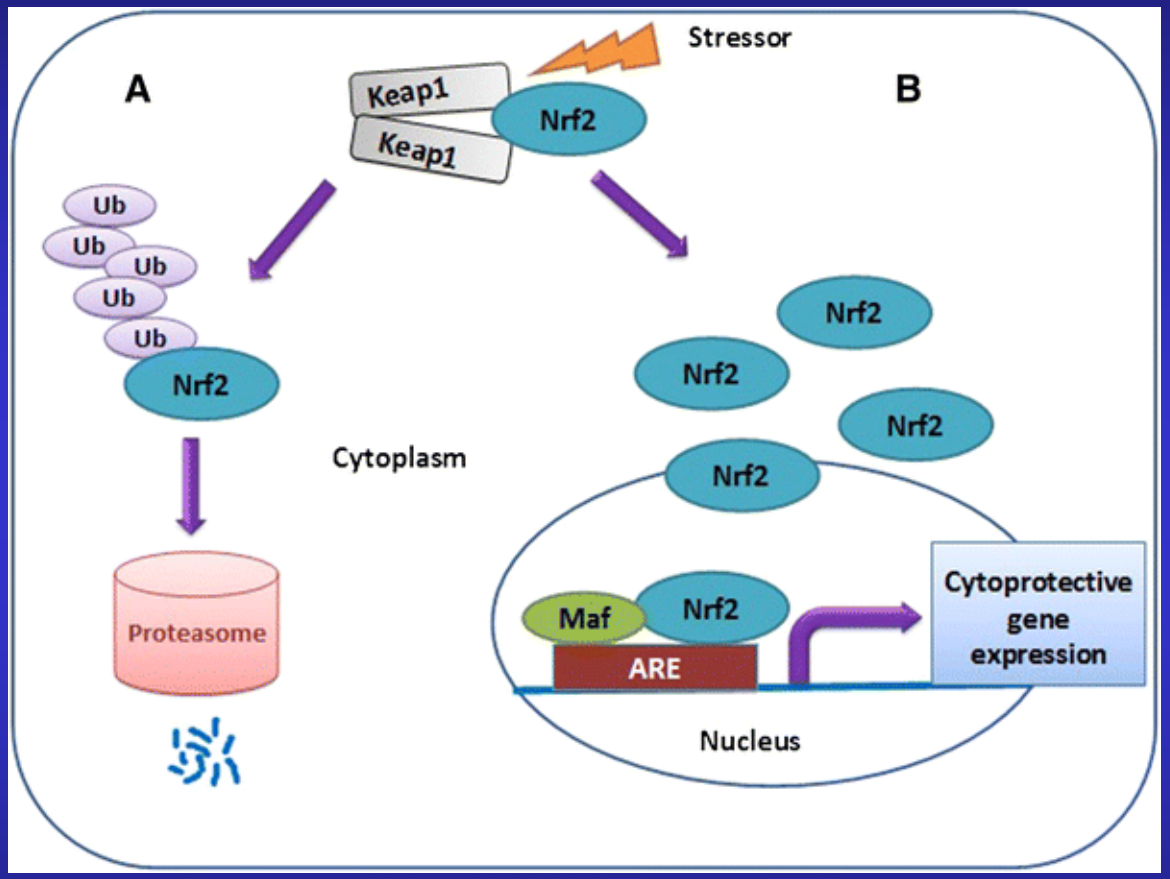
Double-edged sword:

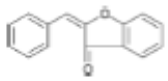
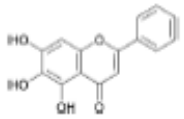
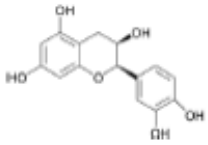
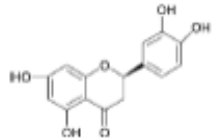
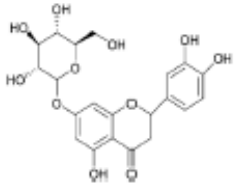
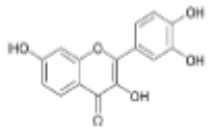
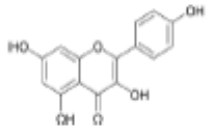
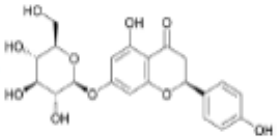
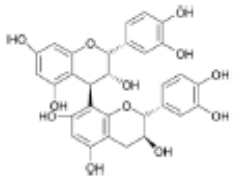
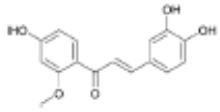
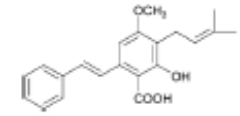
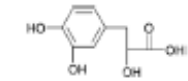
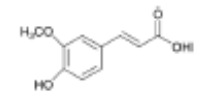
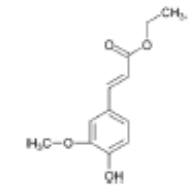
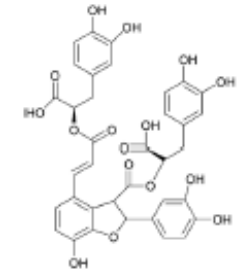
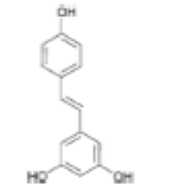
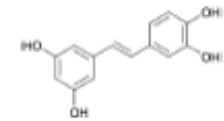
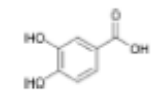
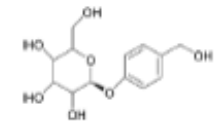
Anti-oxidative/anti-carcinogenic action protects against cancer initiation…

but also protects established tumors against excessive stress, thereby promoting progression and therapeutic resistance

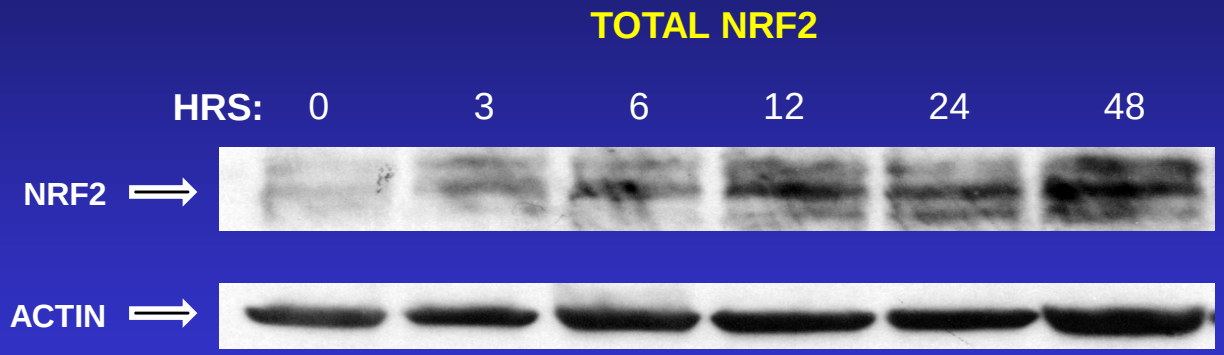
Allows cancer cells to flourish in an oxidative environment

Nrf2 regulation by Keap1:

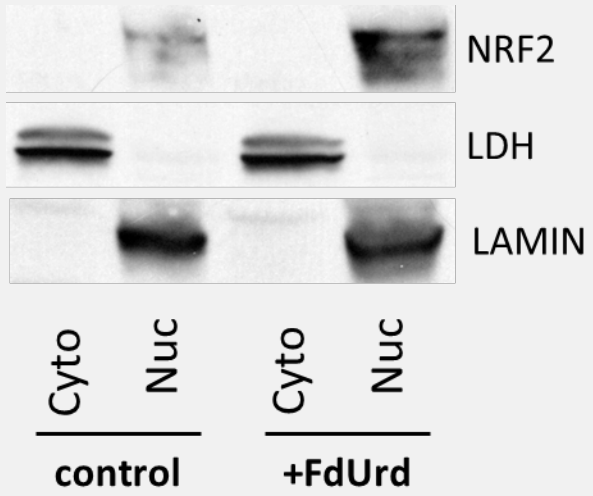


	Aurones	Flavonoid	*Dipteryx odorata*
	Baicalein	Flavonoid	*Scutellaria baicalensis*
	Epicatechin	Flavonoid	Cocoa and tea
	Eriodictyol	Flavonoid	*Dracocephalum rupestre*
	Eriodictyol-7-*O*-glucoside	Flavonoid	*D. rupestre*
	Fisetin	Flavonoid	Fruits and vegetables
	Kaempferol	Flavonoid	Green tea, broccoli, apple and berries
	Naringenin-7-*O*-glucoside	Flavonoid	*D. rupestre*
	Procyanidin B2	Flavonoid	Cocoa, red wine and grape juice
	Sappanchalcone	Flavonoid	*Caesalpinia sappan*
	Cajaninstilbene acid	Polyphenol	*Cajanus cajan*
	Danshensu	Polyphenol	*Salvia miltiorrhiza*
	Ferulic acid	Polyphenol	
	Ethyl ferulate	Polyphenol	Fruits and vegetables such as tomatoes, sweetcorn and rice
	Lithospermic acid B	Polyphenol	*S. miltiorrhiza*
	Resveratrol	Polyphenol	Peanuts, grapes and red wines
	Piceatannol	Polyphenol	*Euphorbia lagascae*
	Protocatechuic acid	Polyphenol	Green tea
	Gastrodin	Polyphenol	*Gastrodia elata*

NRF2 expression is induced by TS inhibitors:

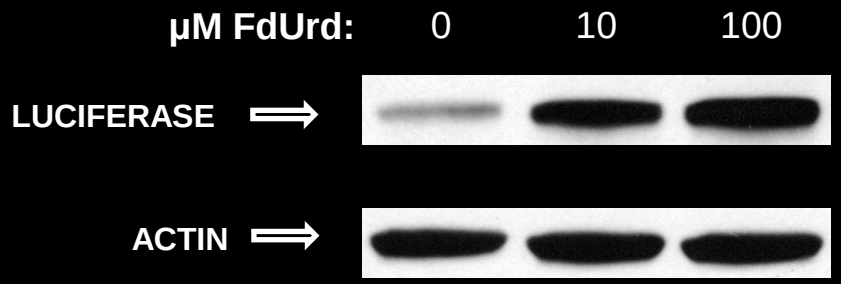


NRF2 is constitutively activated and induced in the nucleus by TS inhibitors:

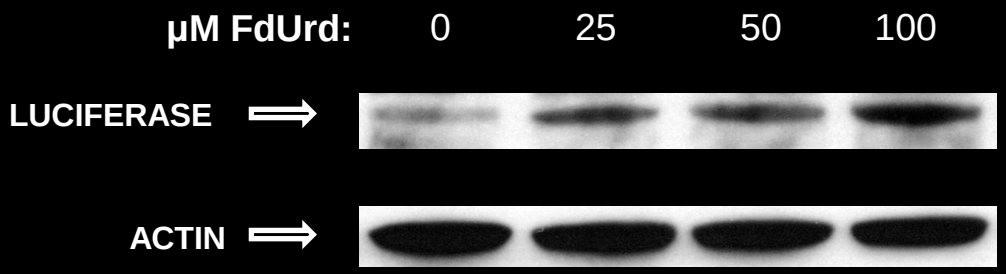


TS inhibitors induce gene expression via the Antioxidant Response Element (ARE)

Transiently-transfected ARE-LUC Reporter:

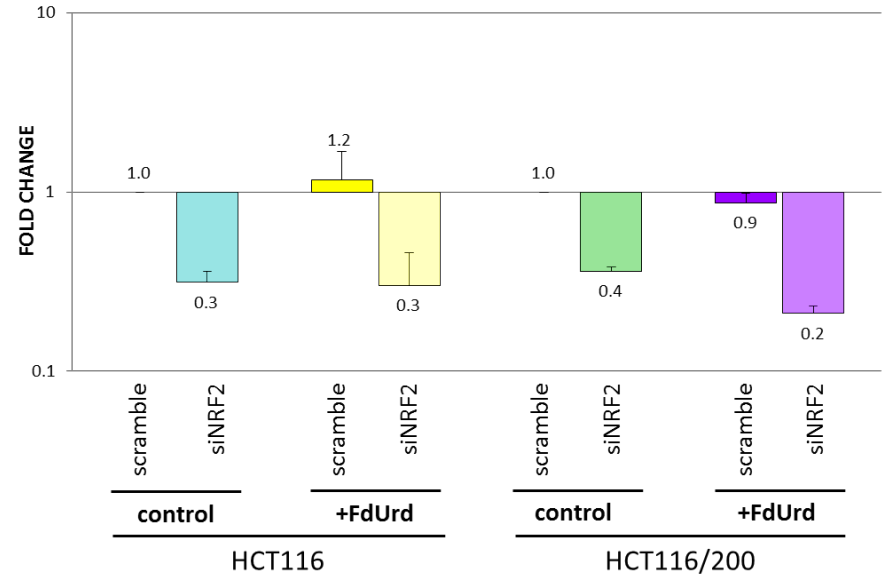


Stably transfected ARE_7-LUC:

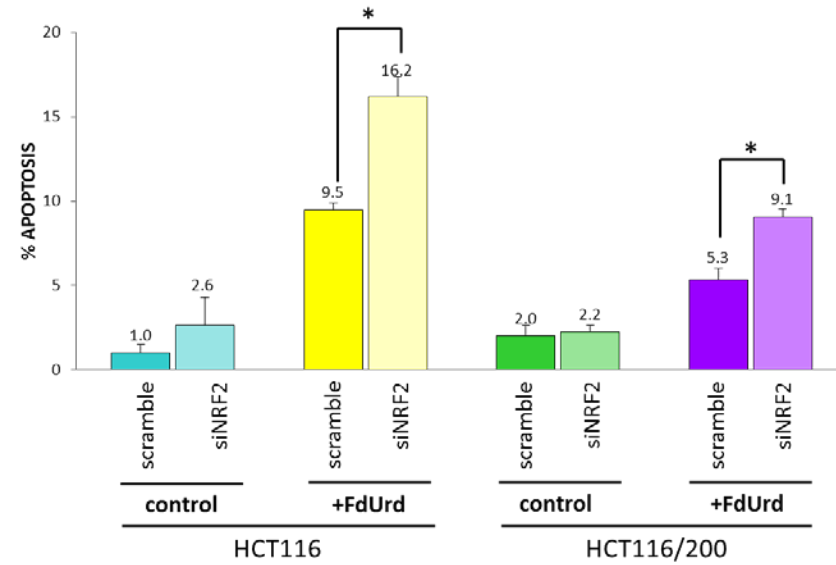


“Knock-down” of NRF2 increases sensitivity to TS inhibitors:

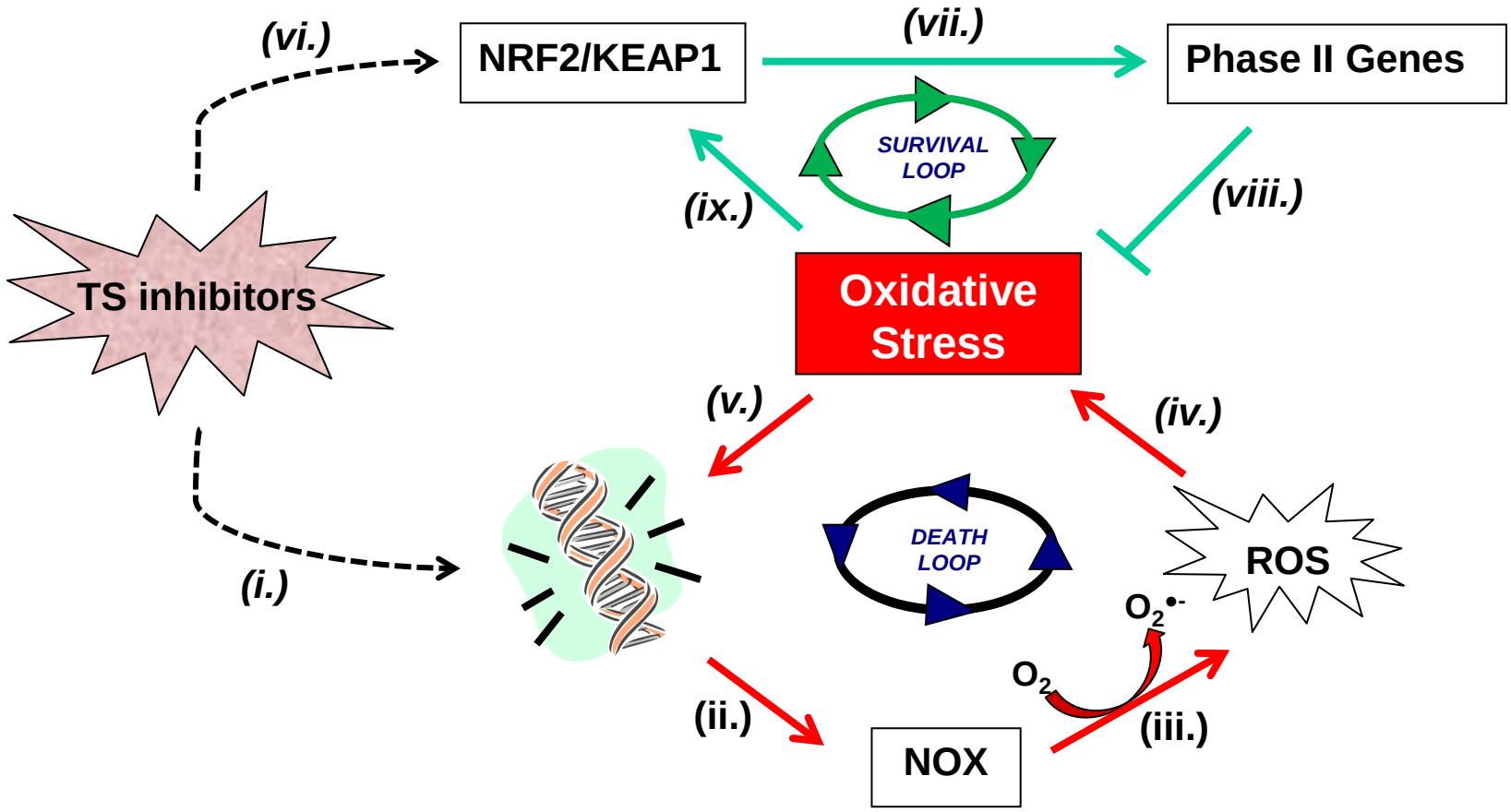
NRF2 expression



Apoptotic index



In addition to a redox-mediated death loop, TS inhibitors induce a Nrf2-mediated survival loop

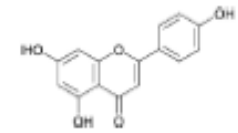
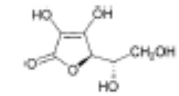
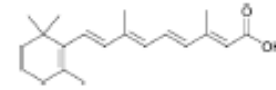
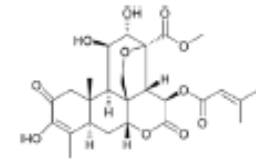
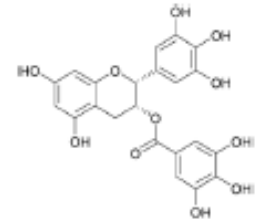
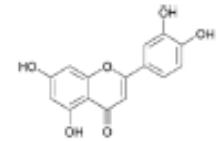
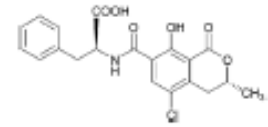


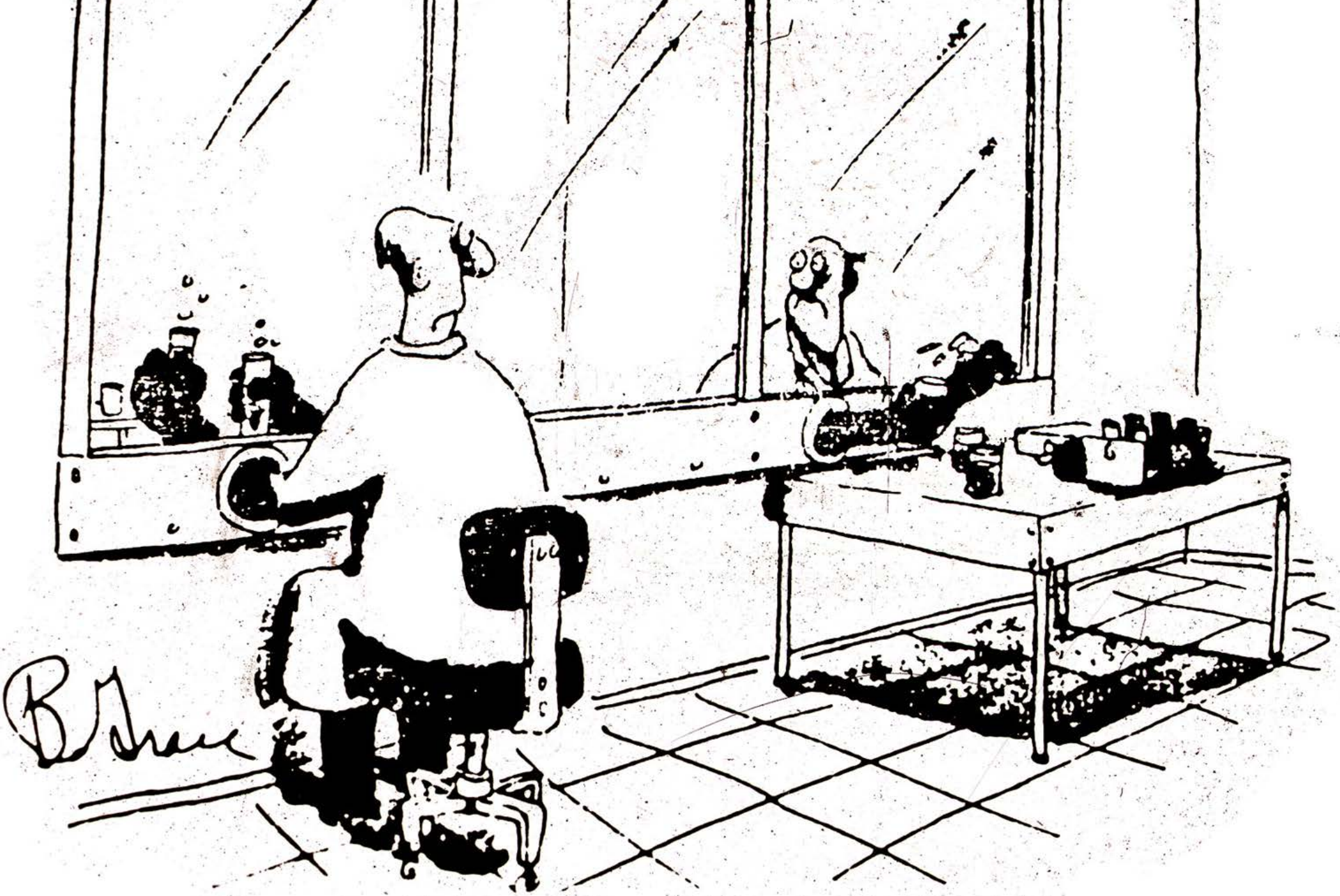
Can we reduce the protective effect of Nrf2, so as to enhance therapeutic efficacy?

(1.) Gene therapy approach

(2.) Natural product-derived inhibitors of Nrf2 activation

A dietary strategy to reduce the impact of Nrf2 activation and promote response to chemotherapy?

	Apigenin	Flavonoid	Fruits and vegetables
	Ascorbic acid	Vitamin C	Citrus fruits
	All-*trans* retinoic acid	Vitamin A	From dietary β-carotene
	Brusatol	Quassinoid	*Brucea javanica*
	EGCG	Polyphenol	Green tea
	Luteolin	Flavonoid	Celery, green pepper, parsley, perilla leaf, and chamomile tea
	Ochratoxin A	Mycotoxin	*Aspergillus* and *Penicillium* subspecies
	Trigonelline	Alkaloid	Fenugreek seeds



WORDS OF WISDOM

(1.) “There are questions in search of technology, and technology in search of questions; the former is good science, while the latter is dead-end science.”
---John Knopf, 1978

(2.) “One thing I can say with reasonable assurance: the probability of getting a grant is very low if you do not submit an application.”
---Ken Paigen, 1982

(3.) “It is better to keep your mouth shut and be thought a fool, than to open it and remove all doubt.”
---Anonymous