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Translating early phase insights to the laboratory – improving the development of cancer prevention therapies

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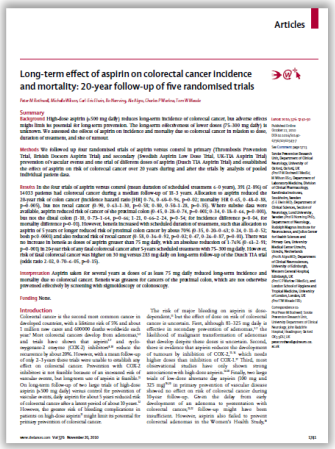
Leicester ECMC

ecmc Experimental Cancer Medicine Centres

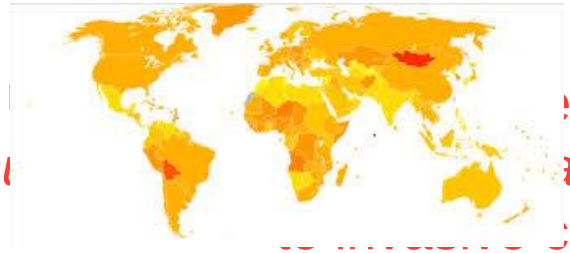
UK therapeutic cancer prevention network
collaborating to prevent cancer

Drug development backwards

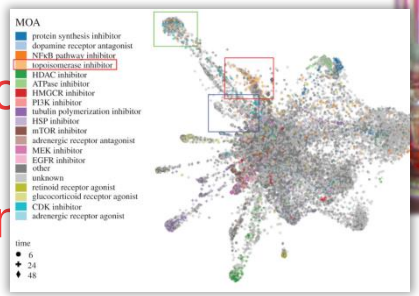

Articles

Long-term effect of aspirin on colorectal cancer incidence and mortality: 20-year follow-up of five randomised trials

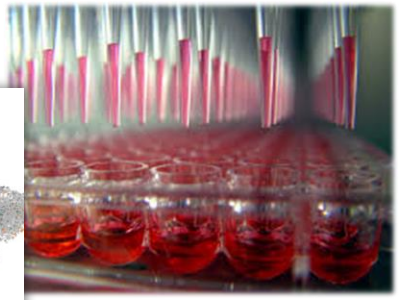
Trial data



Epidemiology



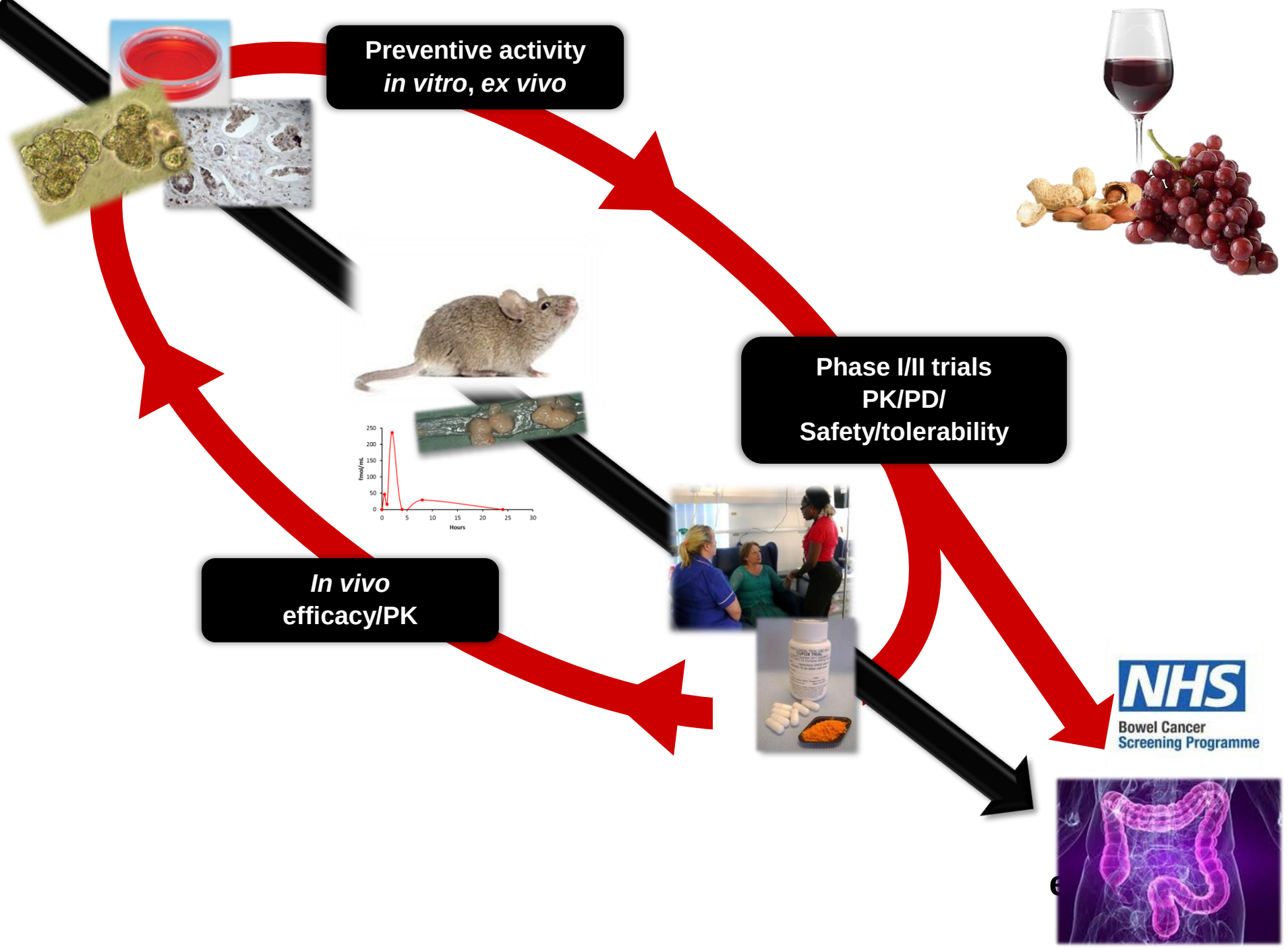
Signature mapping (AI)



Screening

Safety is param
Novel agents are not

Cancer subtype
Mutational drivers
UNKNOWN


Preventive activity
in vitro, *ex vivo*
Phase I/II trials
PK/PD/
Safety/tolerability
In vivo
efficacy/PK
fmol/mL
Hours
NHS
Bowel Cancer
Screening Programme

Safe & well-tolerated at doses up to 1g

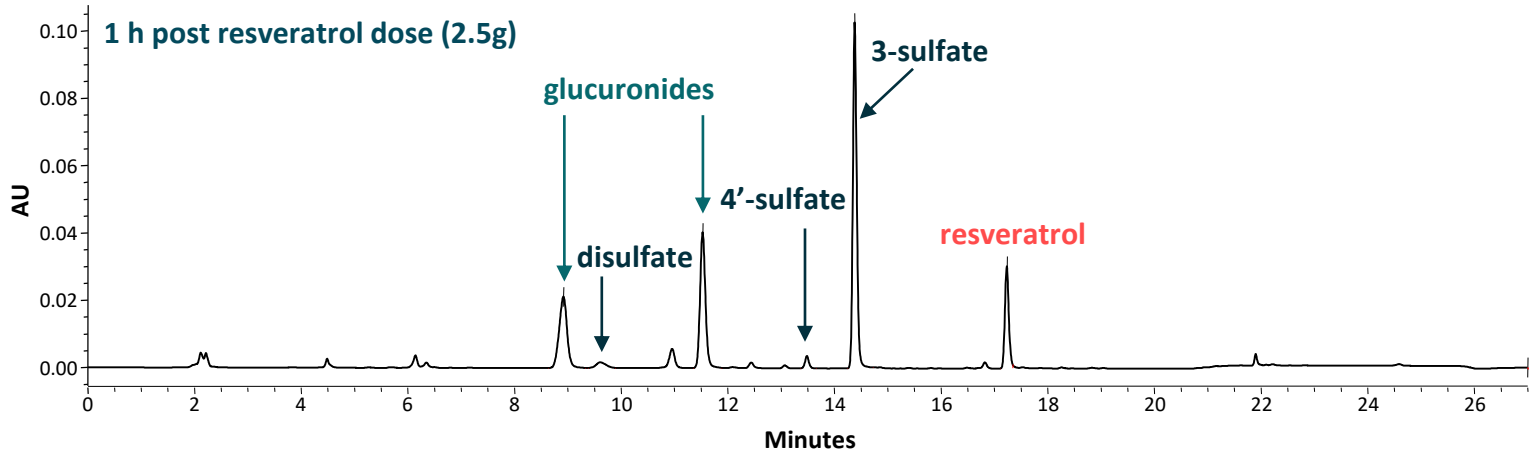
Symptom		Number of volunteers			
		0.5 g	1.0 g	2.5 g	5.0 g
Raised blood bilirubin:	Total	1	1		
	Conjugated		2		
	Unconjugated		2		
Skin discolouration			1		
Cystitis			1		
Acne				1	
Abdominal pain				4	3
Cramp				1	
Diarrhoea				2 ([2]1)	7 ([2]2,[3]1)
Discomfort on passing fa				1	
Flatulence				1	2
Nausea				2	3
Fatigue				1	
Pruritis				1	
Chest pain					1
Dizziness					1
Dry mouth					1
Red/itchy eyes					1
Urine colour change					1

Long term use of doses >1.0g not recommended for prevention purposes

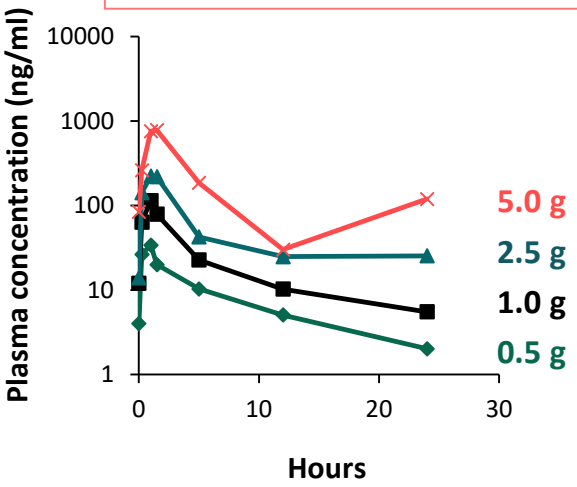
NCI Common Terminology Criteria for Adverse Events v 4.0

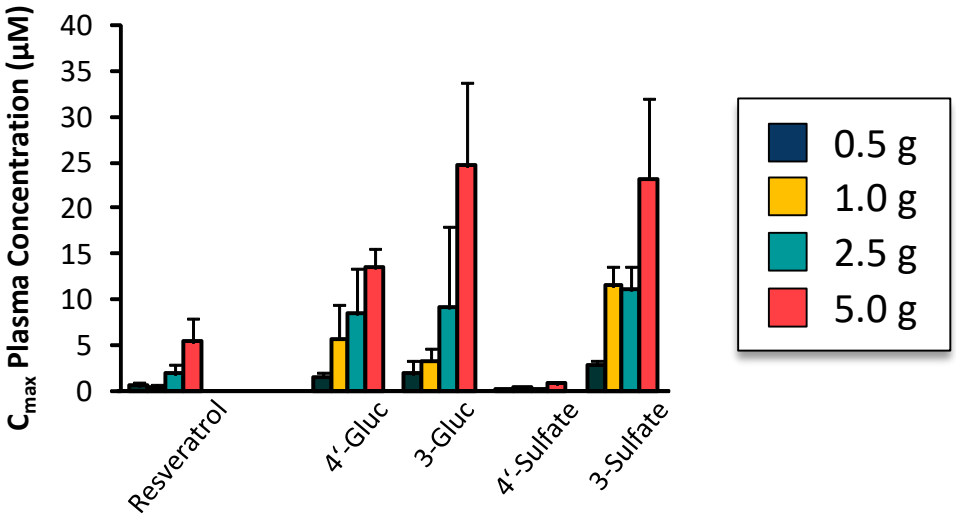
Brown *et al*. (**2010**) *Cancer Res*.

Phase I repeat dose study of resveratrol in volunteers



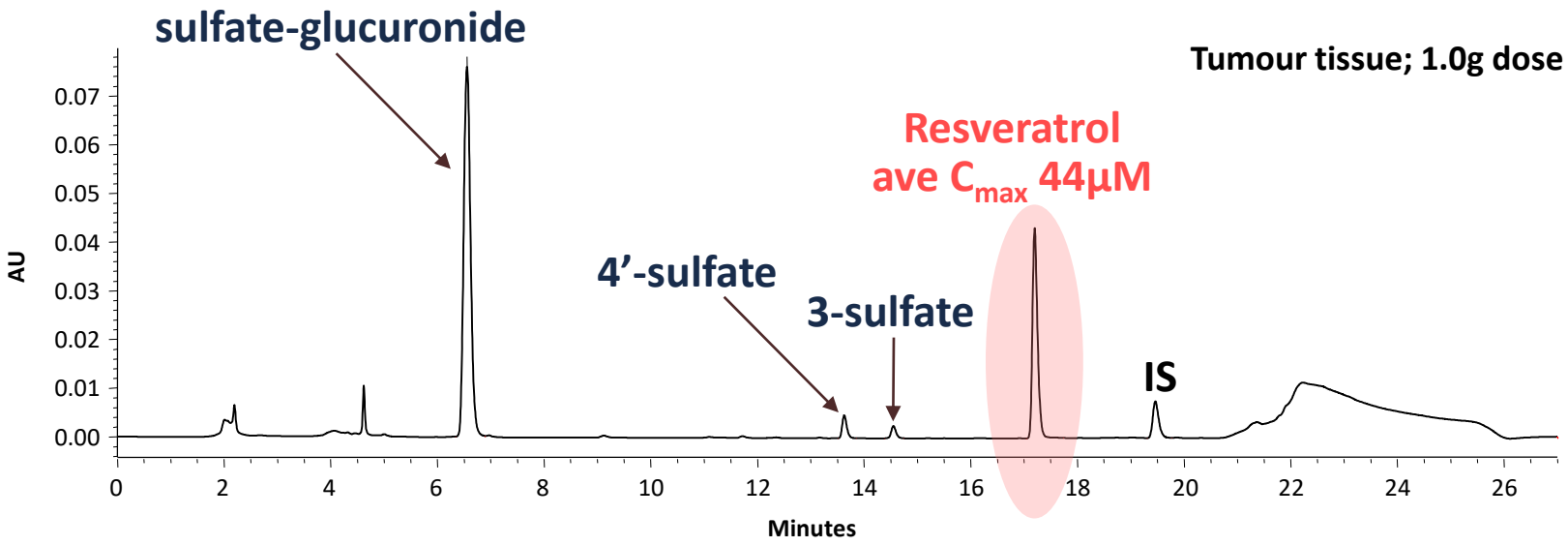
Resveratrol average C_{max} ~0.2-4.2 µM
C_{ave} ~0.04-0.6 µM





Brown *et al*. (**2010**) *Cancer Res*.

High concentrations of resveratrol in colorectal tissue after repeat dosing

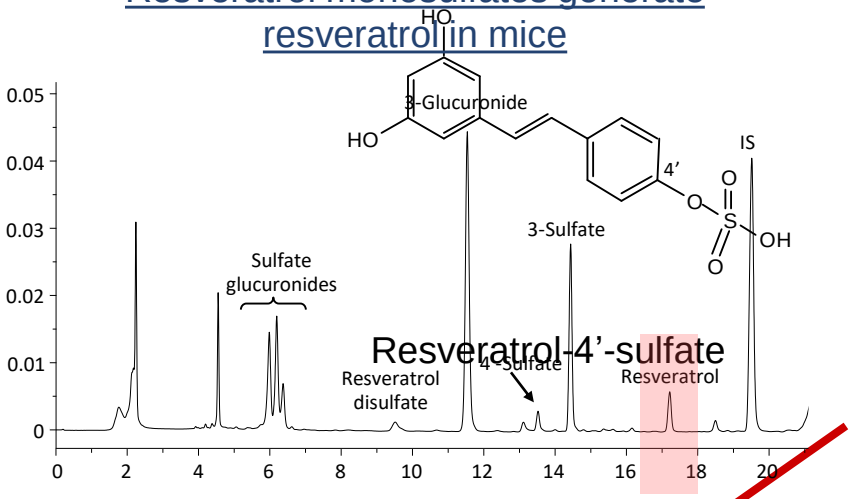


- Average resveratrol tissue concentrations are ~70-fold higher than plasma C_{max}
- Sulfate and glucuronide metabolites also present at high concentrations

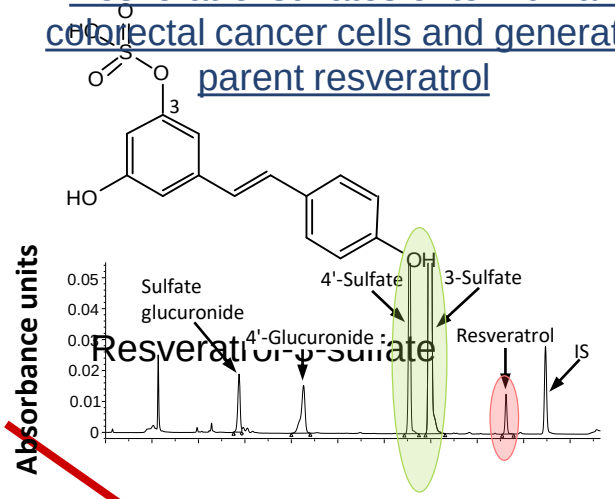
Patel *et al*. (**2010**) *Cancer Res*.

Do resveratrol metabolites contribute to activity?

Resveratrol monosulfates generate resveratrol in mice

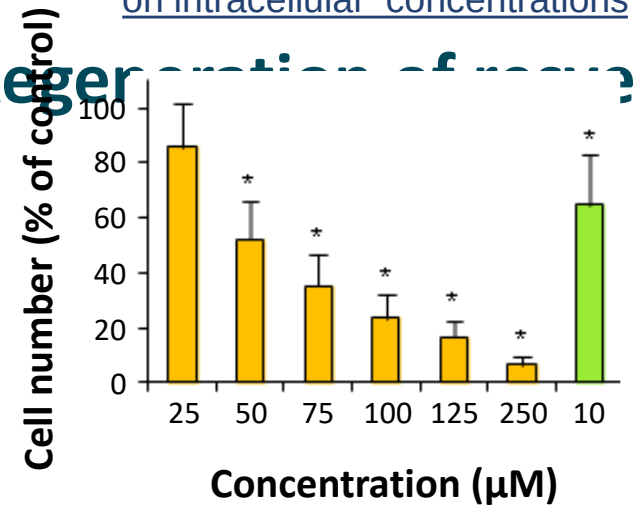


Resveratrol sulfates enter human colorectal cancer cells and generate parent resveratrol



Resveratrol sulfates inhibit the proliferation of cancer cells, but not normal cells – dependent on intracellular concentrations

Regeneration of resveratrol?



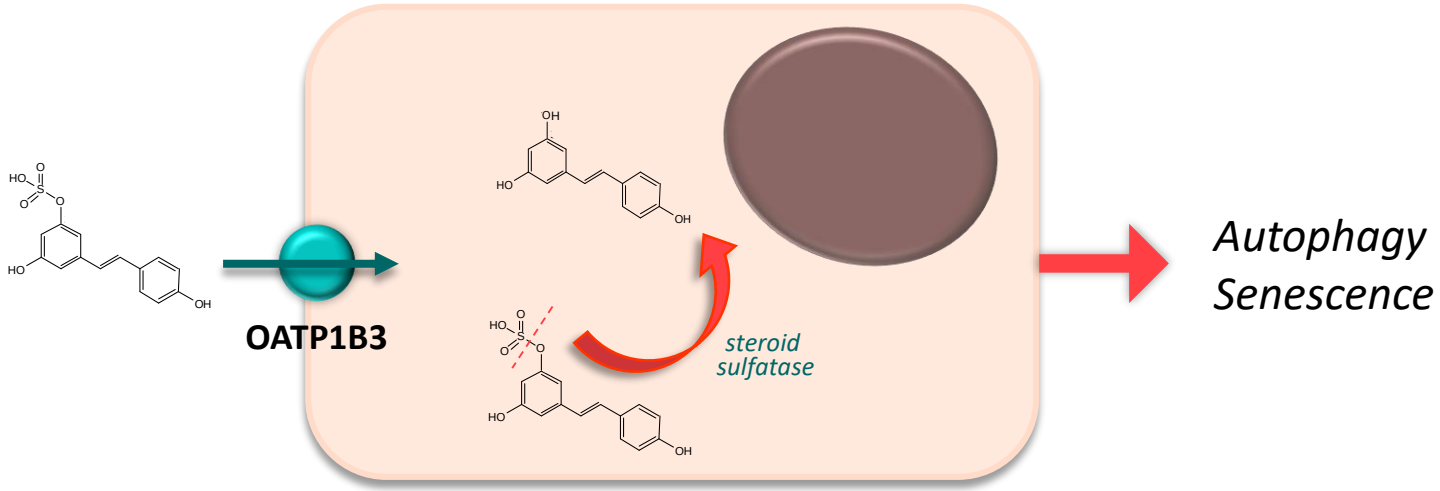
Intrinsic activity?

Reduction in cell numbers is due to autophagy and senescence

Patel *et al*. *Sci. Transl. Med* 2013

Potential role of sulfate metabolites

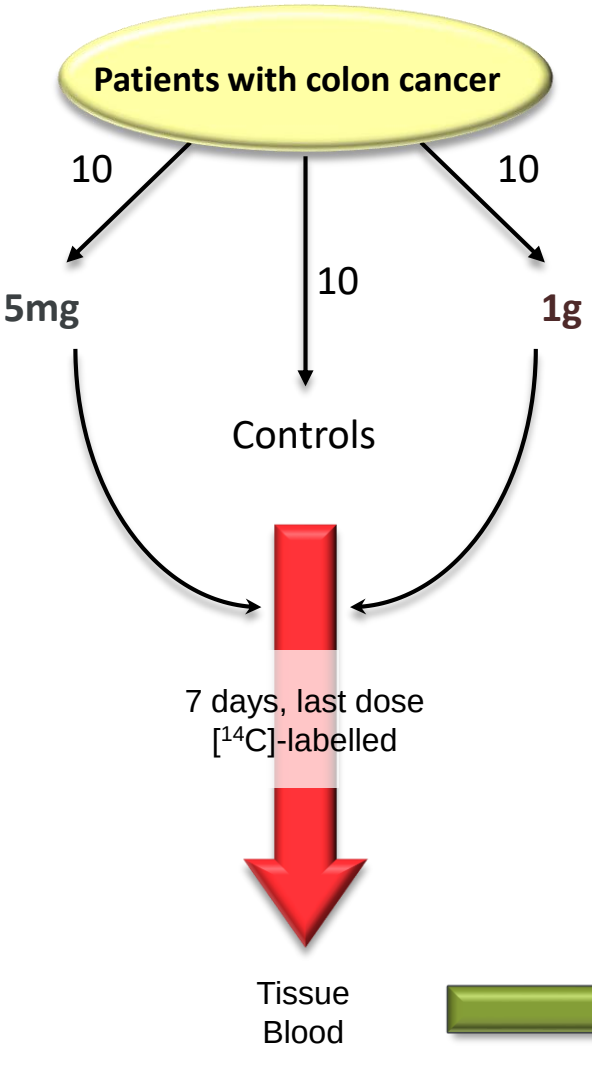
- Clinically achievable concentrations of resveratrol sulfates cause autophagy & senescence
- Effects due to resveratrol formation
- Effects are cell specific – dependent on uptake and presence of certain transporters – could provide selectivity
- Sulfates present at higher systemic concentrations – reservoir for long term resveratrol exposure - more important for activity



- Encouraging for the continued development of resveratrol for systemic diseases or internal target tissues

Andreadi *et al*. *Autophagy* 2014

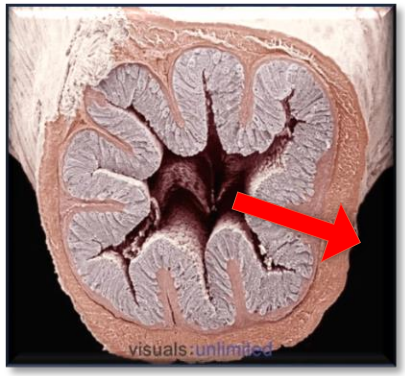
What doses should be used - Is more always better?



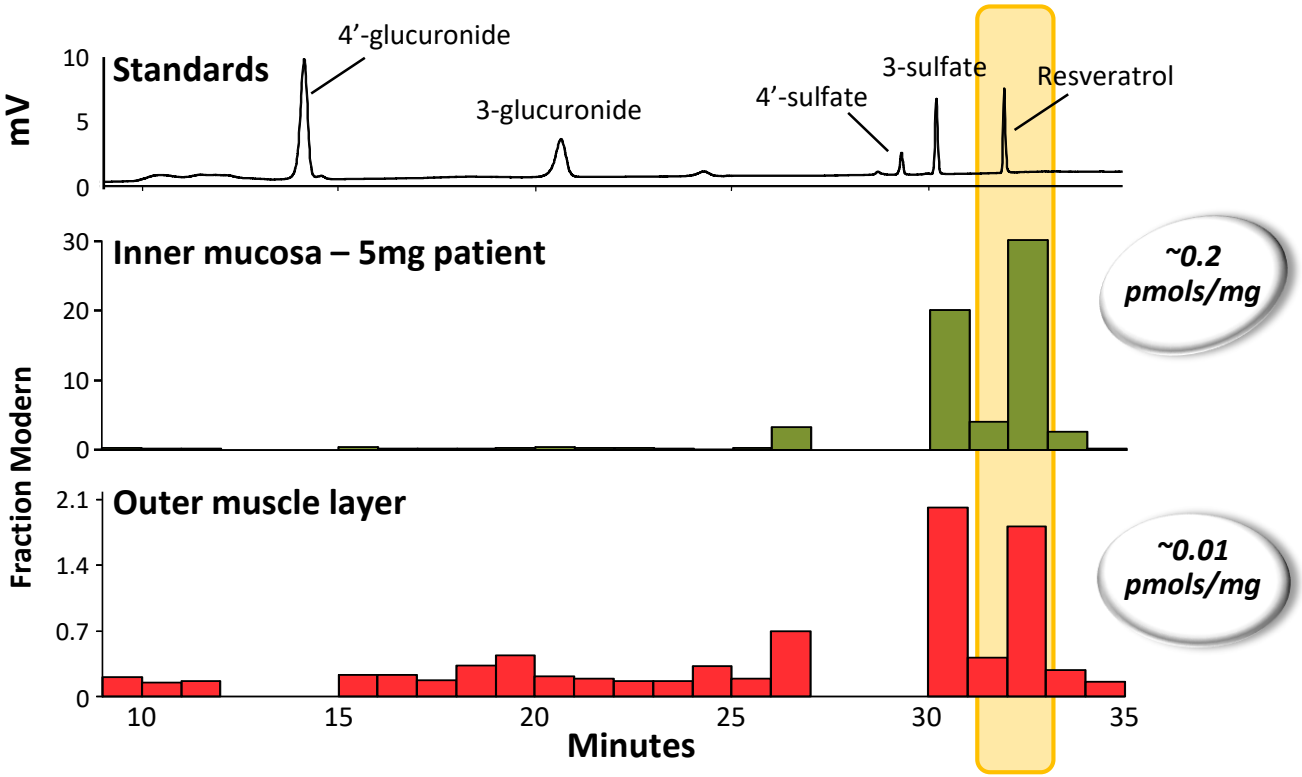
[^{14}C]-resveratrol

AMS and HPLC-AMS analysis

Levels of [^{14}C]-resveratrol equivalents in colon tissue

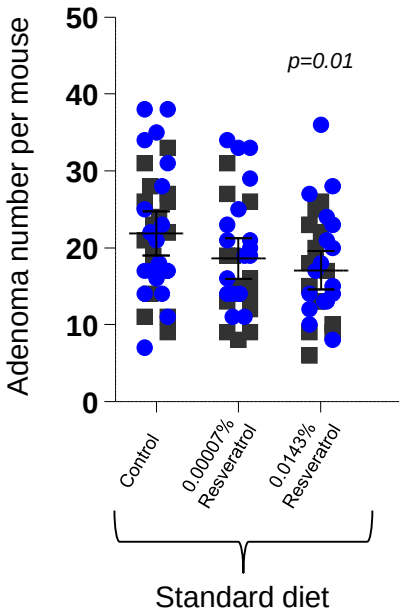


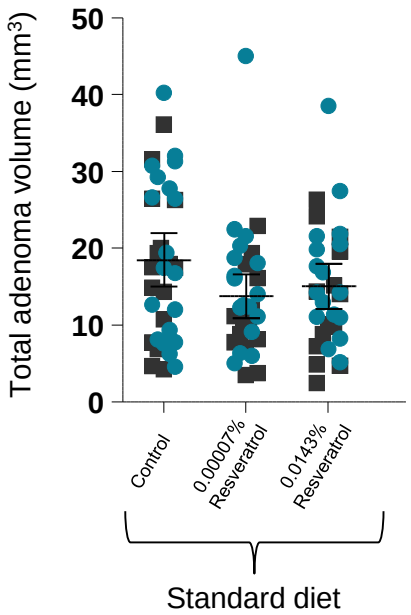
Concentration dependent on: **Dose**
Time



Cai *et al*. *Sci. Transl. Med.* **2015**

Dietary doses inhibit colorectal carcinogenesis in *Apc*^{Min} mice

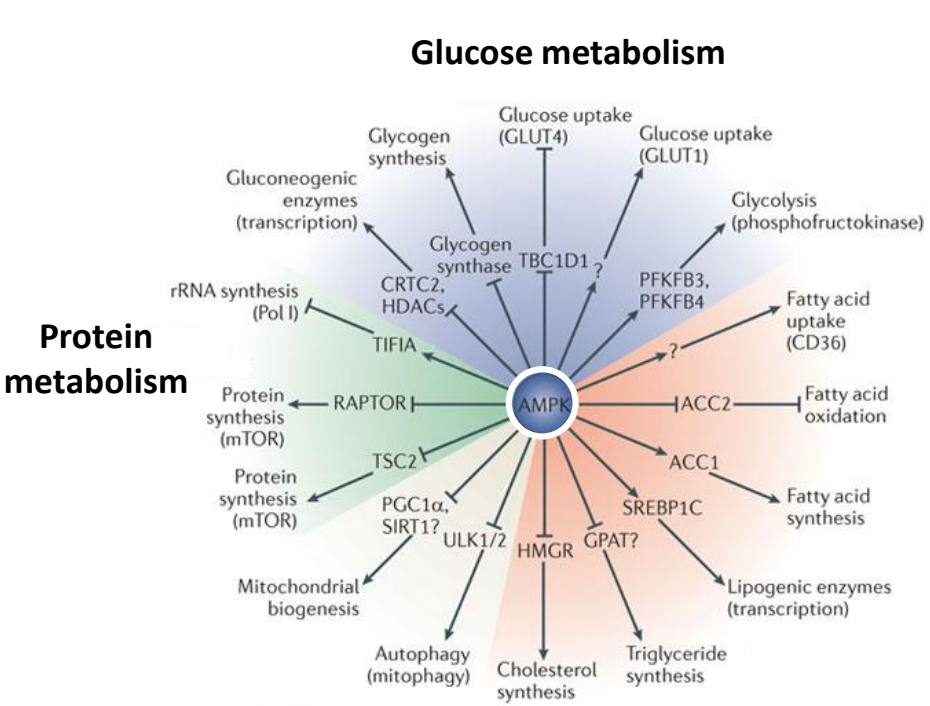




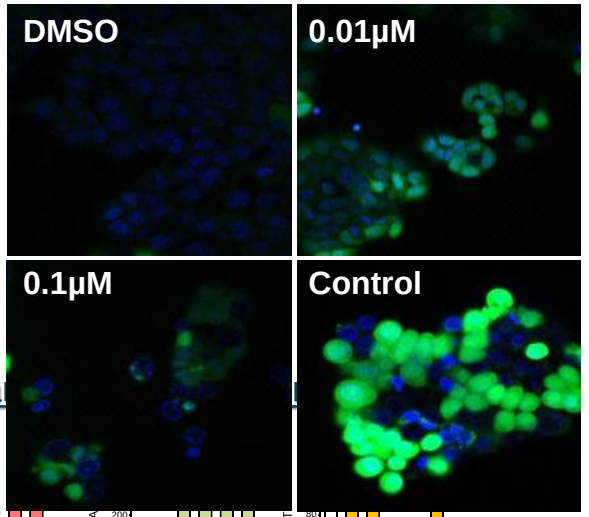
Resveratrol protects against the tumour-promoting effects of a high fat diet and inhibits cell proliferation in adenomas

Cai *et al*. *Sci. Transl. Med.* **2015**

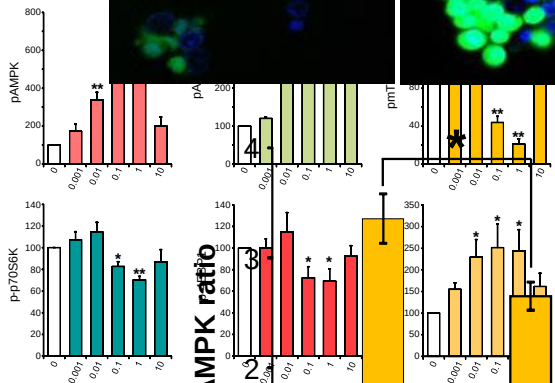
Resveratrol activates AMPK

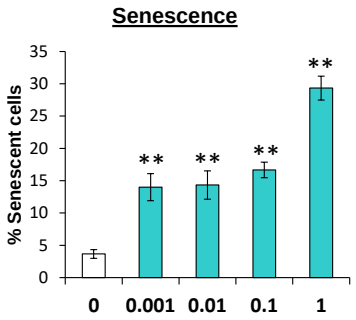


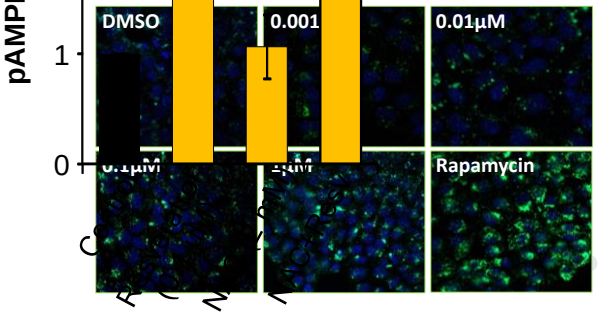
A role for oxidative stress?



Non-linea

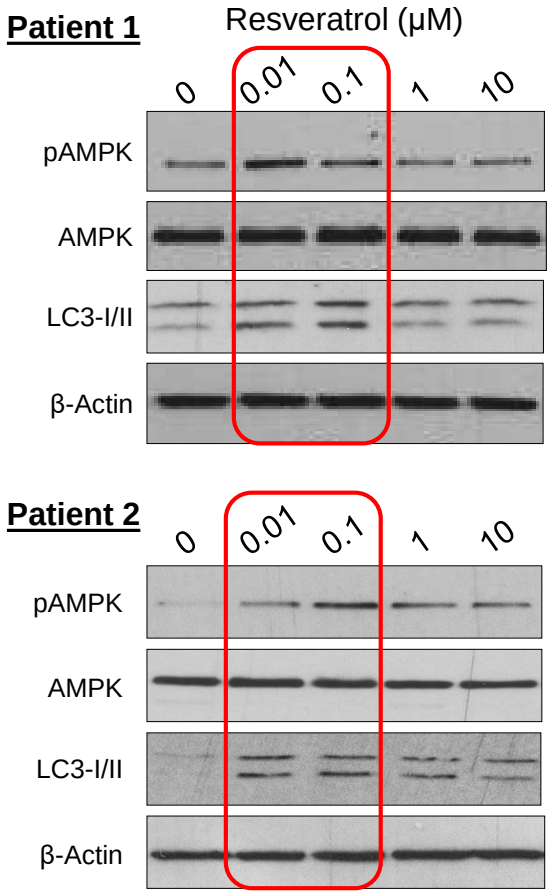


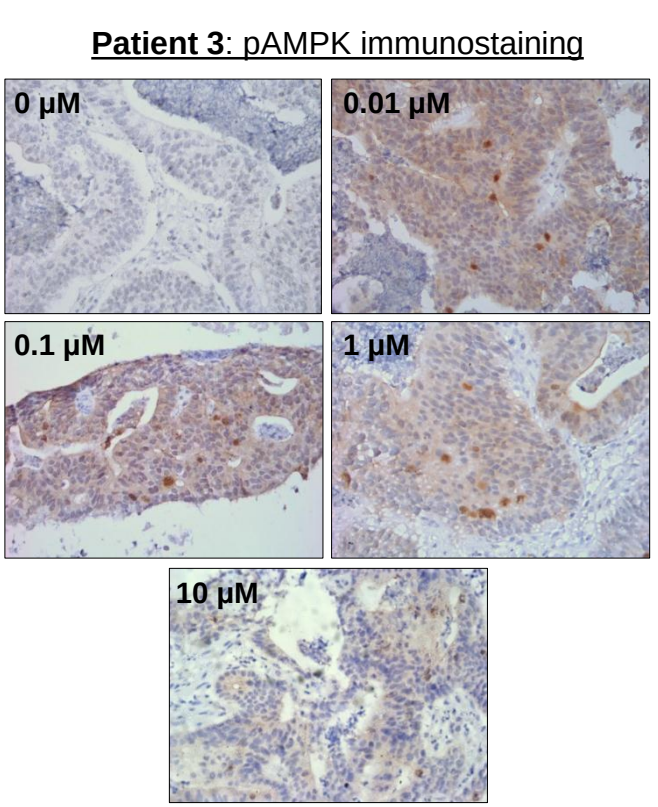




Cai *et al*. *Sci. Transl. Med.* **2015**

Anticancer effects of resveratrol translate to human tissues

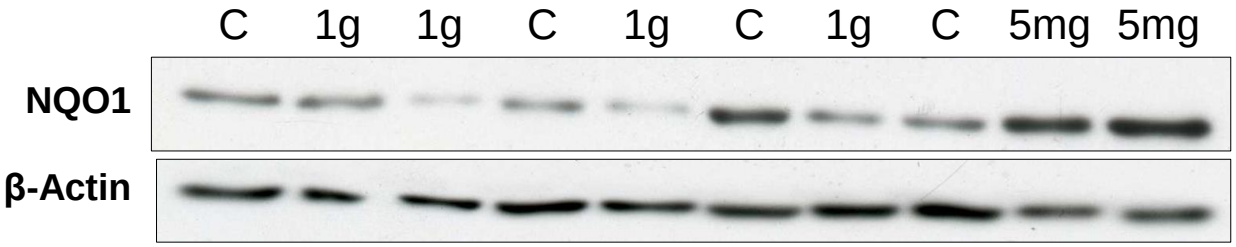


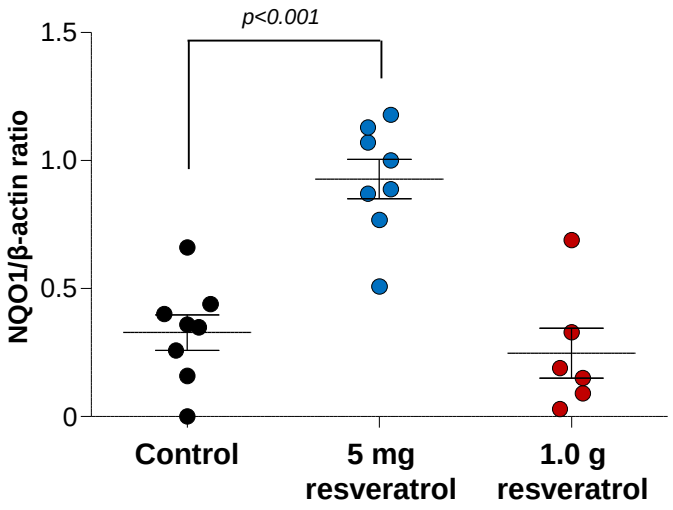


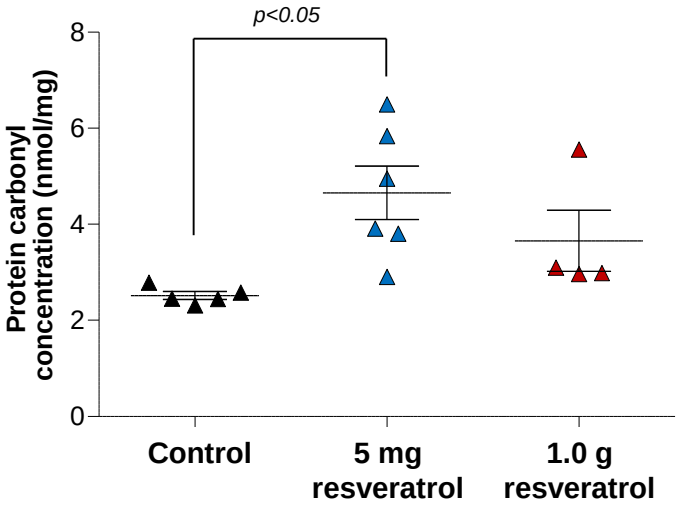
Activation of AMPK signalling and increased autophagy at low, clinically achievable concentrations – mimicking effects seen in mice and cultured adenoma cells.

Cai *et al*. *Sci. Transl. Med.* **2015**

Low dose resveratrol modulates markers of oxidative stress in colorectal mucosa of treated patients







Cai *et al*. *Sci. Transl. Med.* **2015**

Lessons and conclusions

- Integration of clinical PK data is essential - clinically achievable concentrations (and metabolites) must be used for preclinical work
- Importance of delineating dose-response relationships and including dietary-achievable exposures in development strategies – doses need to be optimised before undertaking large scale clinical prevention trials
- Both doses warrant further testing
- Inter-individual differences (lifestyle, diet, health status) and tumour-specific features may influence response to resveratrol

Where next?

COLO-PREVENT (Phase III)

Total sample size in two trials = 1,458

INCLUSION CRITERIA

Patients identified from English BCSP across 60 centres

Polyps removed

Patient classified as **high-risk** for recurrence or cancer (according to new criteria)

Current aspirin or metformin use?
N= 4400

Predict 30% uptake

Not currently taking aspirin or metformin and able to tolerate aspirin

(Expect ~75%)

Screen ~ 3200

Seeking a 30%↓ 80% power

Consent/randomisation (1:1)
N= 862

Aspirin 300mg or 75mg OD based on BW
N=431

Aspirin plus **Metformin** (500mg BD)
N=431

Colonoscopy at **3 years** (per new BCSP guidelines) for primary outcome – mean adenoma number per person (MAP)

Assume 15% drop out
&
3% crossover in each arm

COLO-PREVENT-SS (Phase II)

Signal-seeking sub-trial

Predict 50% uptake

Already taking aspirin/metformin.
Unable to tolerate aspirin.
Don't want to take aspirin/metformin

(Expect ~25%)

Screen ~ 1200

Seeking a 35%↓ 80% power

Consent/randomisation stratified by aspirin/metformin use (1:1:1)
N= 596

Placebo
N=199

Resveratrol 5mg OD
N=199

Resveratrol 1g OD
N=199

Colonoscopy at **1 year** to use as interim analysis of MAP for stop/go decision for each dose

Assume 10% drop out

Transfer most effective dose to main trial
(subject to additional future funding)

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Andy Gescher
Will Steward

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HOPE AGAINST CANCER
Where there's Hope there's Life

NHS National Institute for Health Research

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