**Supplementary information**

**Solar-simulated radiation and determination of MED**

We employed a 16S-300-003 SolarLight device equipped with a 300-watt xenon lamp, XPS300 power supply, and 0.5 meter liquid light guide with an 8-mm aperture (SolarLight, Glenside, PA) that emits both UVA and UVB, encompassing wavelengths from 290-400nm and weighted to mimic the solar spectrum. Minimal erythemal dose (MED) testing was initiated on the back using a disposable 6-holed adhesive pad (SolarLight), with doses ranging from approximately 20,000-100,000 J/m2. Emission was controlled by a shutter switch, and calibrated using a PMA2100 radiometer (SolarLight). The next day (approximately 24 hours later), the MED was determined from the lowest UV dose resulting in erythema that completely filled the 8-mm irradiated site (homogeneous erythema).

**RT-PCR reactions**

Each cDNA reaction utilized 250 ng RNA and the SuperScript III First-Strand Synthesis Super Mix (ThermoFisher Scientific) and accompanying reagents. Quantitative PCR reactions were each performed in 10 L using 1 L cDNA and reagents from a Rotor-gene SYBR Green PCR kit (ThermoFisher Scientific) according to the manufacturer’s instructions. The following primers (4 M final concentration, Integrated DNA Technologies Inc, Coralville, IA) were used for each respective gene: *Gclm*, 5’-TGGGCACAGGTAAAACCAA-3’ and 5’-CAGTCAAATCTGGTGGCATC-3’; *Gclc*, 5’-ATGCCATGGGATTTGGAAT and 5’-AGATATACTGCAGGCTTGGAATG-3’; *Slc1A4*, 5’-TTTGCGACAGCATTTGCTAC-3’ and 5’-TGTTCTCTTCAATGCACTTCATC-3’; *Slc7A11*, 5’-CAGAAGCTGCAGTTAGCCAAG-3’ and 5’-ATGAAGTCTCGCGCTCTTGT-3’; *RPLP0*, 5’-CCTCGTGGAAGTGACATCGT-3’ and 5’-ATCTGCTTGGAGCCCACATT-3’.

**Supplementary Table I.** Patient characteristics

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Placebo NAC p-value\*

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Number of subjects 50 50

Males/females (ratio) 33/17 (1.9) 28/22 (1.3) 0.41

Age, median (range) 46 (24-78) 42 (23-68) 0.30

Personal history of melanoma, number (%) 20 (40%) 15 (30%) 0.40

Family history of melanoma, number (%) 17 (34%) 19 (38%) 0.84

MC1R mutation#, number (%) 24 (48%) 26 (52%) 0.84

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\* A *t*-test was used for age. A Fisher’s exact test was used for all other comparisons.

# High-risk allele.

**Supplementary Table II.** Open-label post-trial study in 10 patients

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Variable Patients\* Percent 8-OG (mean, +SD) Univariate analysis

Control UV-irradiated P value#

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Treatment

Placebo 49 33.1 +24.2 96.2 +7.5

Drug 10 15.4 +18.4 95.4 +6.0 0.11

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Log (x100) TR-1 (mean, +SD) Univariate analysis

Control UV-irradiated Effect ratio┼ (95% CI), P value

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Treatment

Placebo 50 1.05 +0.76 1.26 +0.70 1.00

Drug 10 0.76 +0.79 0.93 +0.75 0.89 (0.69 – 1.15), 0.37

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Univariate analysis

CT║ *Gclm* (mean, +SD) Analysis of Covariance

Control UV-irradiated Expression ratio╫ (95% CI), P value

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Treatment

Placebo 50 9.74 +0.69 9.14 +0.75 1.00

Drug 10 9.35 +1.14 9.49 +1.08 0.69 (0.44 – 1.09), 0.12

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CT *Slc1A4* (mean, +SD)

Control UV-irradiated

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Treatment

Placebo 50 9.21+0.83 9.40 +1.06 1.00

Drug 10 8.50 +1.07 8.69 +0.67 1.22 (0.81-1.84), 0.34

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CT *Slc7A11* (mean, +SD)

Control UV-irradiated

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Treatment

Placebo 50 8.97 +1.04 9.03 +0.95 1.00

Drug 10 8.59 +1.99 8.86 +1.67 1.03 (0.65 – 1.64), 0.90

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\* 10 patients received drug 3 h after UV exposure. There were 50 patients in the placebo arm of the randomized trial, but one subject randomized to placebo was excluded from analysis of 8-OG because there was insufficient tissue.

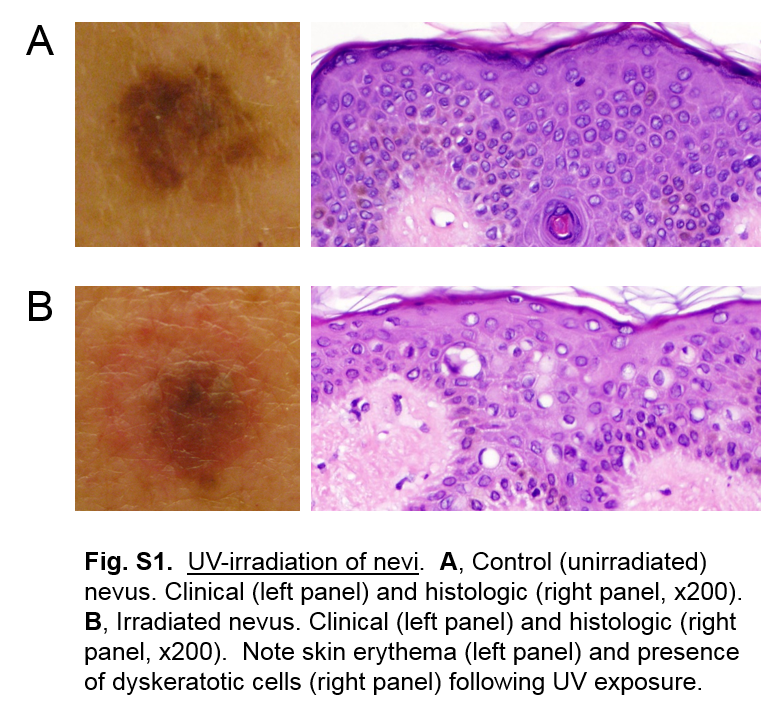
# Wilcoxon test was used to assess significance of differences in the median percent nevus melanocytes with 8-OG expression in the UV-irradiated nevus compared to that in the control (unirradiated) nevus.

┼ The effect ratio is the ratio of log TR-1 expression in nevus melanocytes in the UV-irradiated nevus compared to that in the control (unirradiated) nevus.

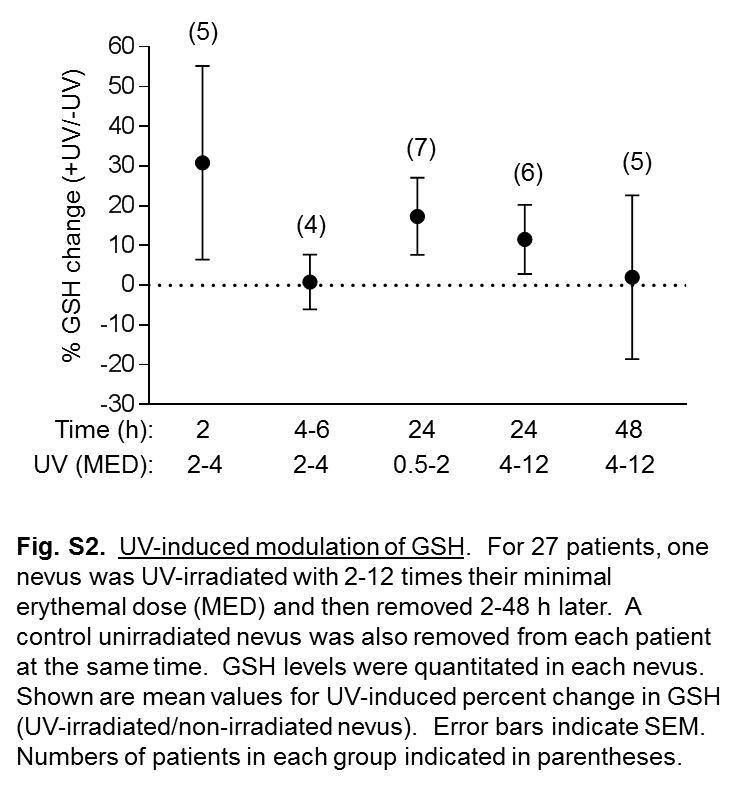
║ ΔCT is the difference in CT between the gene of interest and RPLP0.

╫ Analysis of covariance was used to examine the relationship between individual categorical variables and the change in ΔCT, with categorical variable and ΔCT in the un-irradiated nevus as predictors and ΔCT in the irradiated nevus as response. The expression ratio is estimated as 2-ΔCT.

**Supplementary Figure S1**

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**Supplementary Figure S2**

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