LIST OF SUPPLEMENTARY MATERIALS

SUPPLEMENTAL INFORMATION

RESULTS

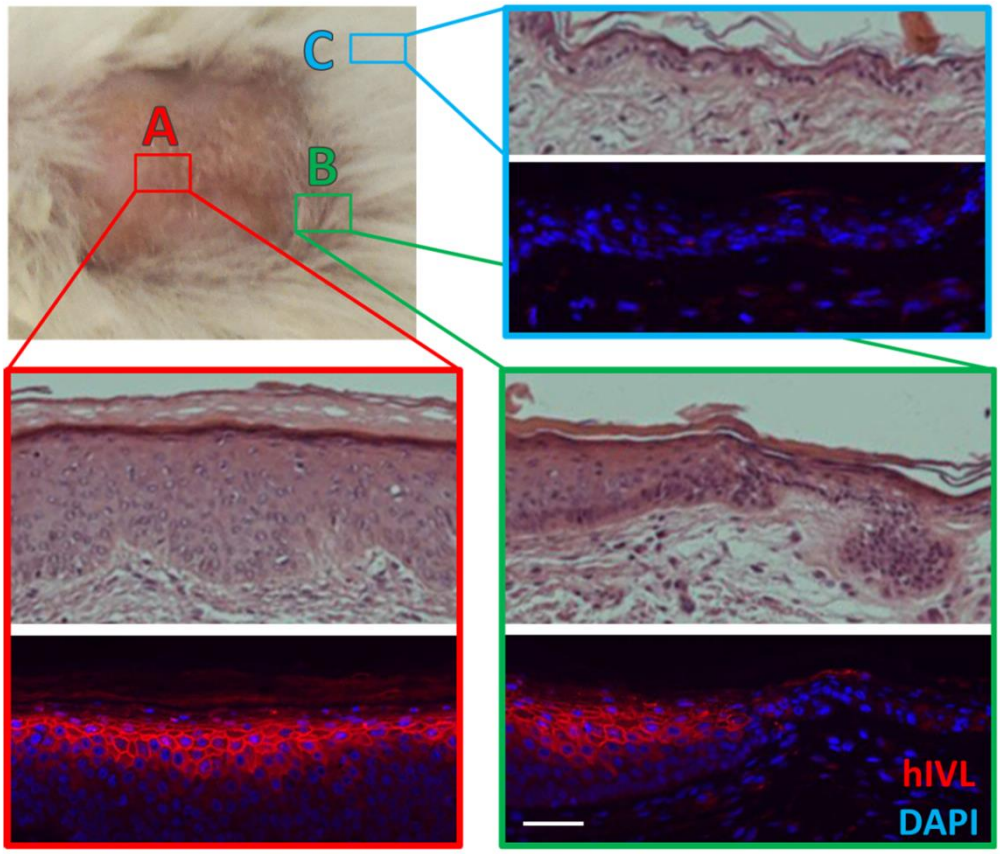

Figure S1. Validation of human skin xenografted onto immunodeficient mice. Human skin xenografts were treated as described in Figure 1. The upper right panel is a photograph of a xenograft at 12 weeks post-transplant. Boxed areas indicate regions shown in micrographs and immunofluorescent images. Within each box, the top panel has been stained with hematoxylin and eosin, while the bottom panel is stained with an antibody specific to human involucrin (red, hIVL; abcam #ab181980) and DAPI (indicating nuclei). **(A)**. The red box indicates the images were derived from totally within the human skin xenograft. Note the expression of human involucrin throughout the epidermis. **(B)**. The green box specifies the transition region between the human and mouse tissue. The junction point at which the human tissue abuts the mouse tissue is clearly demarcated by the loss of reactivity to human involucrin and the reduction in the thickness of the epidermis in the mouse skin **(C)**. The blue box represents mouse skin located outside of the xenograft. Observe the complete lack of reactivity to the human involucrin antibody. White scale bar = 100μm.

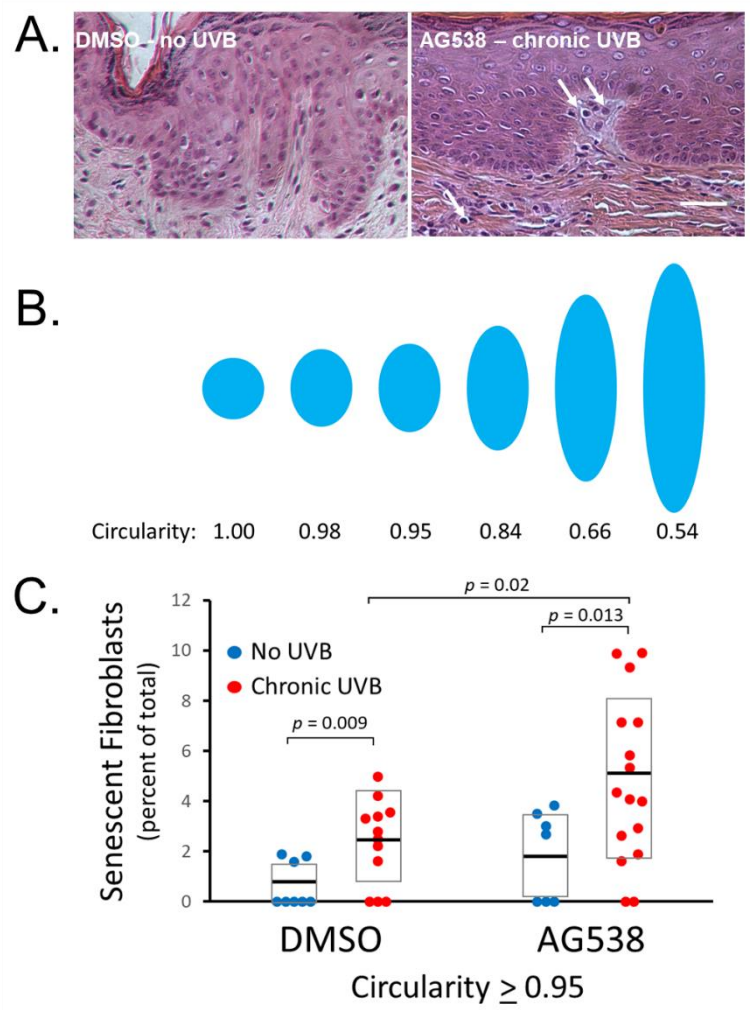

Figure S2. Chronic UVB exposure to human skin increases the proportion of senescent fibroblasts in the papillary dermis. Human skin xenografts were treated as described in Figure 1. Previously, we have validated the use of measuring fibroblast nuclei circularity as a method of determining the proportion of senescent fibroblasts contained within the dermis, due to the decrease in elongation accompanying the advent of senescence (9,10). (**(A)**. Representative H&E stained sections of human skin xenografts. White arrows indicate fibroblast nuclei that meet the criteria of circularity greater than 0.95. **(B)**. Examples of the shapes of ellipses having specific degrees of circularity. **(C)**. Number of senescent fibroblasts within the papillary dermis as determined by the circularity of their nucleus using Nikon Elements imaging software. *p*-values derived from student t-test. If no relationship is indicated on the graph, there was no statistically significant difference between the pairs. Scale bar = 100μm.

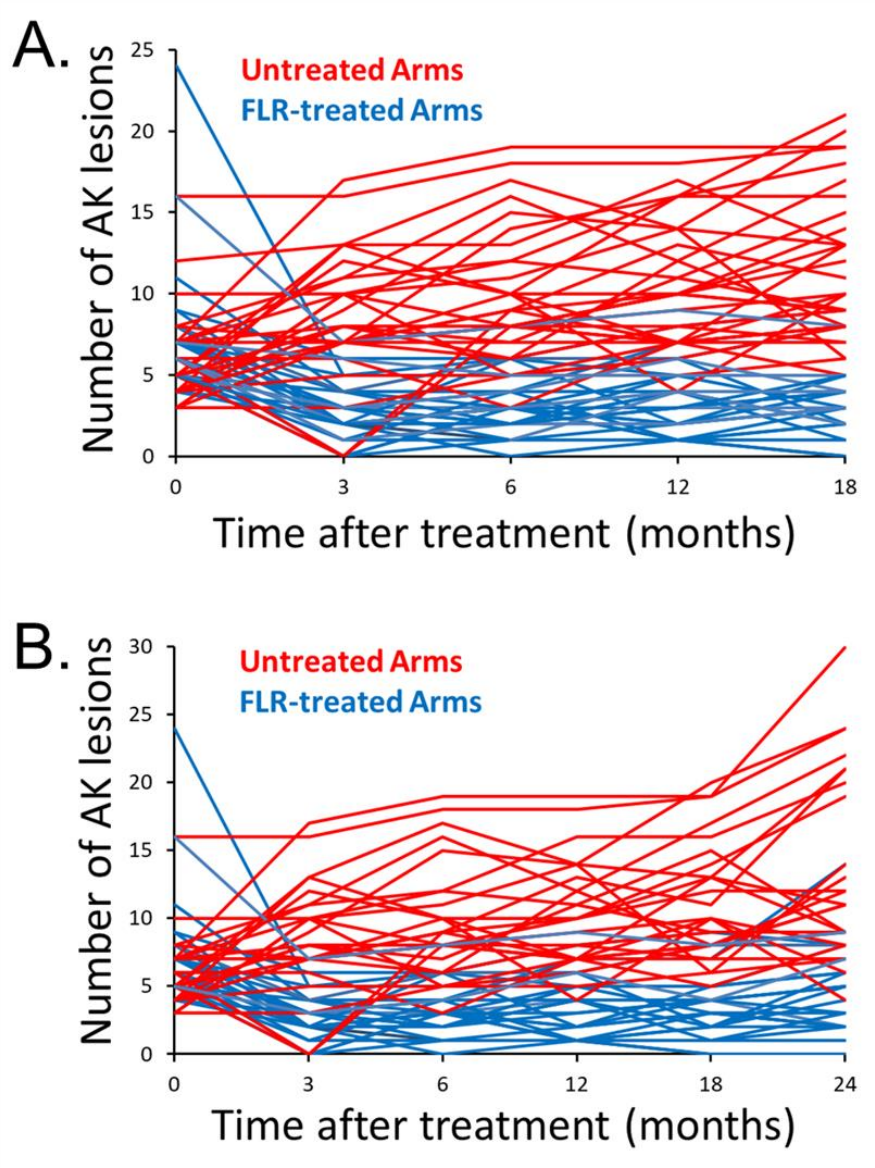

Figure S3. FLR-treatment prevents the occurrence of new AK lesions. The number of AKs observed on both the FLR-treated (blue) and untreated (red) arm over 18 months (**A**; 42 subjects) and 24 months (**B**; 33 subjects).

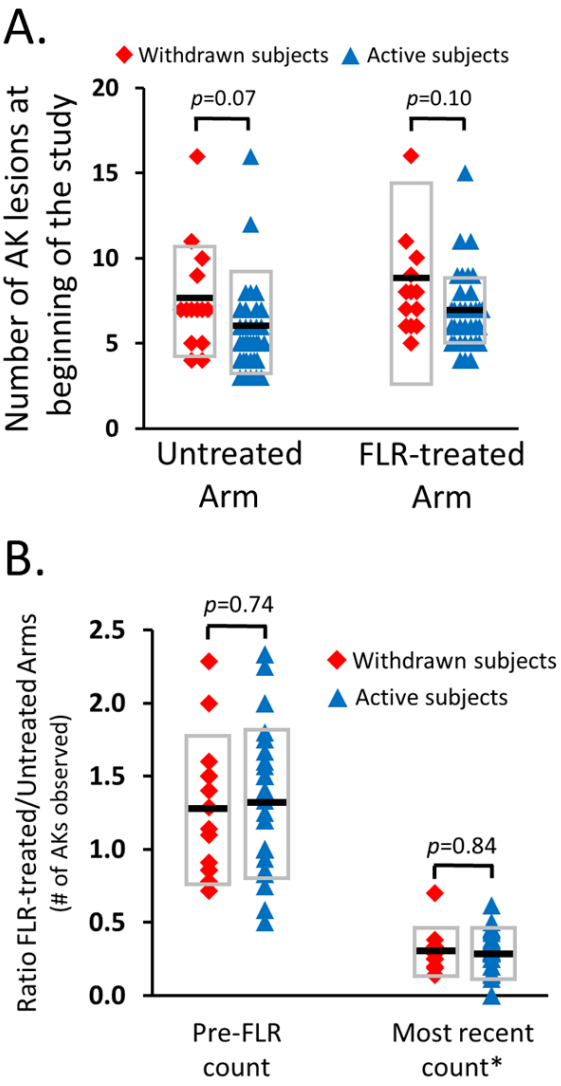

Figure S4. The prevention of AK lesions following FLR-treatment occurs irrespective of inherent photodamage. For the safety of the subjects, if ≥20 AKs occur on a single arm the subject was withdrawn from the study and given field therapy of topical 5-fluorouracil cream or topical photodynamic therapy. To date, fourteen subjects have reached the threshold of 20 AKs, all were on their untreated arms. **(A)**. Comparing the initial numbers of AKs from the 14 subjects that were withdrawn to the 34 subjects still active in the study, there were no differences in the initial photodamage assessed at the beginning of the study (*p* values > 0.05, two-tailed student t-test). **(B)**. Subjects that accumulated ≥20 AKs on their untreated arms had an equivalent decrease in AKs on their FLR-treated arms when compared to subjects still active in the study (*p* values > 0.05, two-tailed student t-test). *For subjects withdrawn from the study, the data are presented for their last observation; for active subjects, the data are indicated from their last measurement.

Table S1 Demographic characteristics of subjects in Clinical Study #1.

	AGE AT TIME OF TREATMENT	GENDER	SIDE TREATED	ANATOMICAL LOCATION TREATED	Included in Ki67:TD staining	IGF-1 mRNA
1 year						
	66	MALE	LEFT	SUN-EXPOSED	Y	Y
	77	FEMALE	RIGHT	SUN-PROTECTED	Y	N
	71	MALE	RIGHT	SUN-EXPOSED	WITHDREW	
	84	MALE	LEFT	SUN-EXPOSED	Y	Y
	80	MALE	RIGHT	SUN-EXPOSED	Y	Y
	84	MALE	LEFT	SUN-PROTECTED	Y	Y
	67	MALE	LEFT	SUN-EXPOSED	Y	Y
	65	MALE	LEFT	SUN-EXPOSED	Y	Y
	81	MALE	LEFT	SUN-PROTECTED	Y	Y
	75	MALE	RIGHT	SUN-EXPOSED	Y	Y
	80	MALE	RIGHT	SUN-EXPOSED	Y	Y
	81	FEMALE	LEFT	SUN-EXPOSED	N	Y
	78	MALE	LEFT	SUN-PROTECTED	N	Y
AVERAGE	76.1	2 FEMALE	5 RIGHT	9 SUN-EXPOSED	12 COMPLETED	
RANGE	(65-84)	11 MALE	8 LEFT	4 SUN-PROTECTED	1 WITHDREW	
2 year						
	68	FEMALE	RIGHT	SUN-EXPOSED	BIOPSY UNUSABLE	
	67	MALE	RIGHT	SUN-EXPOSED	Y	N
	69	MALE	LEFT	SUN-EXPOSED	WITHDREW	
	74	MALE	RIGHT	SUN-EXPOSED	Y	Y
	78	MALE	LEFT	SUN-EXPOSED	Y	Y
	67	FEMALE	RIGHT	SUN-EXPOSED	Y	Y
	68	FEMALE	LEFT	SUN-EXPOSED	DECEASED	
	85	MALE	LEFT	SUN-EXPOSED	Y	Y
	82	FEMALE	RIGHT	SUN-EXPOSED	Y	Y
	68	MALE	LEFT	SUN-PROTECTED	Y	Y
	79	MALE	RIGHT	SUN-PROTECTED	Y	Y
	69	MALE	LEFT	SUN-EXPOSED	Y	Y
	66	MALE	RIGHT	SUN-EXPOSED	Y	Y
AVERAGE	72.3	4 FEMALE	7 RIGHT	11 SUN-EXPOSED	10 COMPLETED	
RANGE	(66-85)	9 MALE	6 LEFT	2 SUN-PROTECTED	3 WITHDREW	