Arsenic is potent co-mutagen of ultraviolet light

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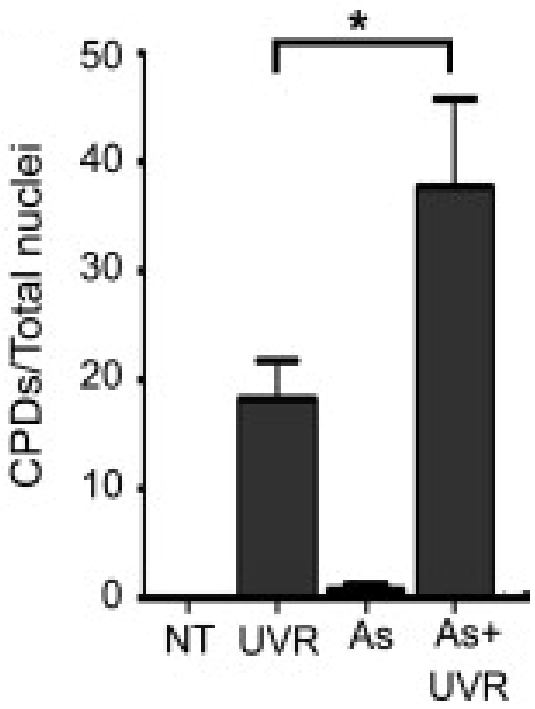
Environmental Co-exposure: Arsenic + UVR

UVR

Arsenic

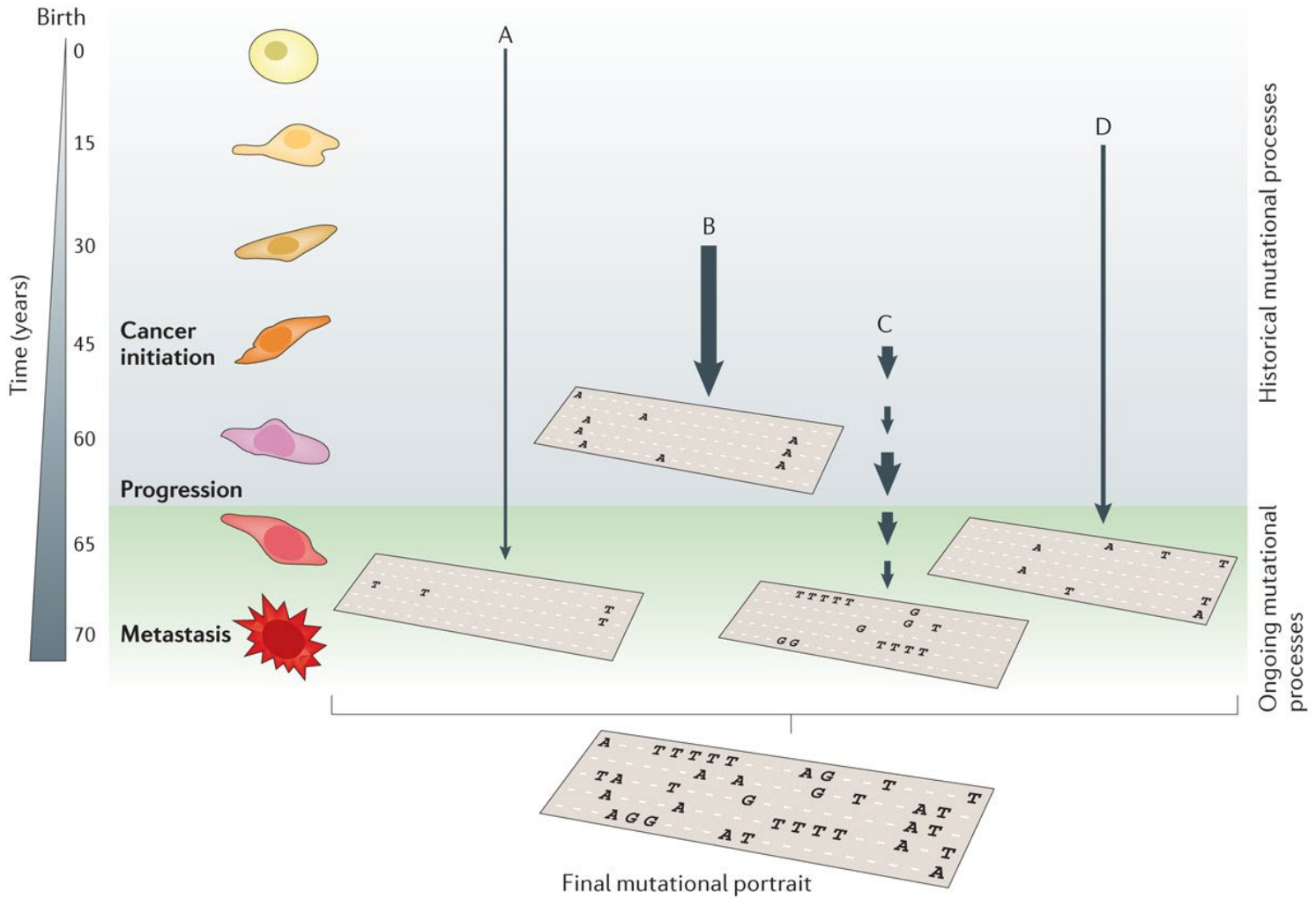
Arsenic Enhances UVR Carcinogenesis

DNA damage retention



Cooper et al., 2013. doi.org/10.1016/j.taap.2013.03.008
Rossman et al., 2001. doi:10.1006/taap.2001.927

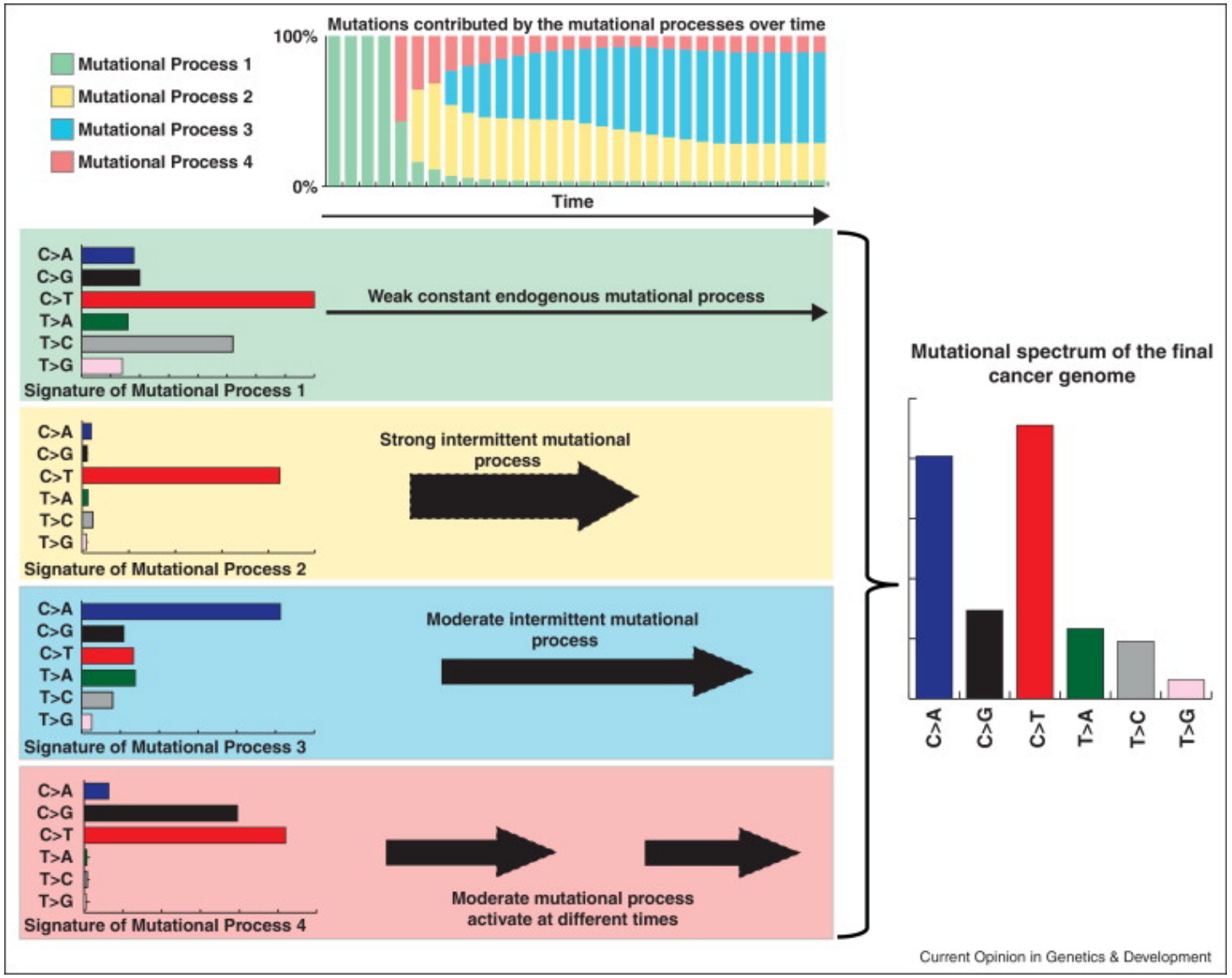
The genome as a record of environmental exposure



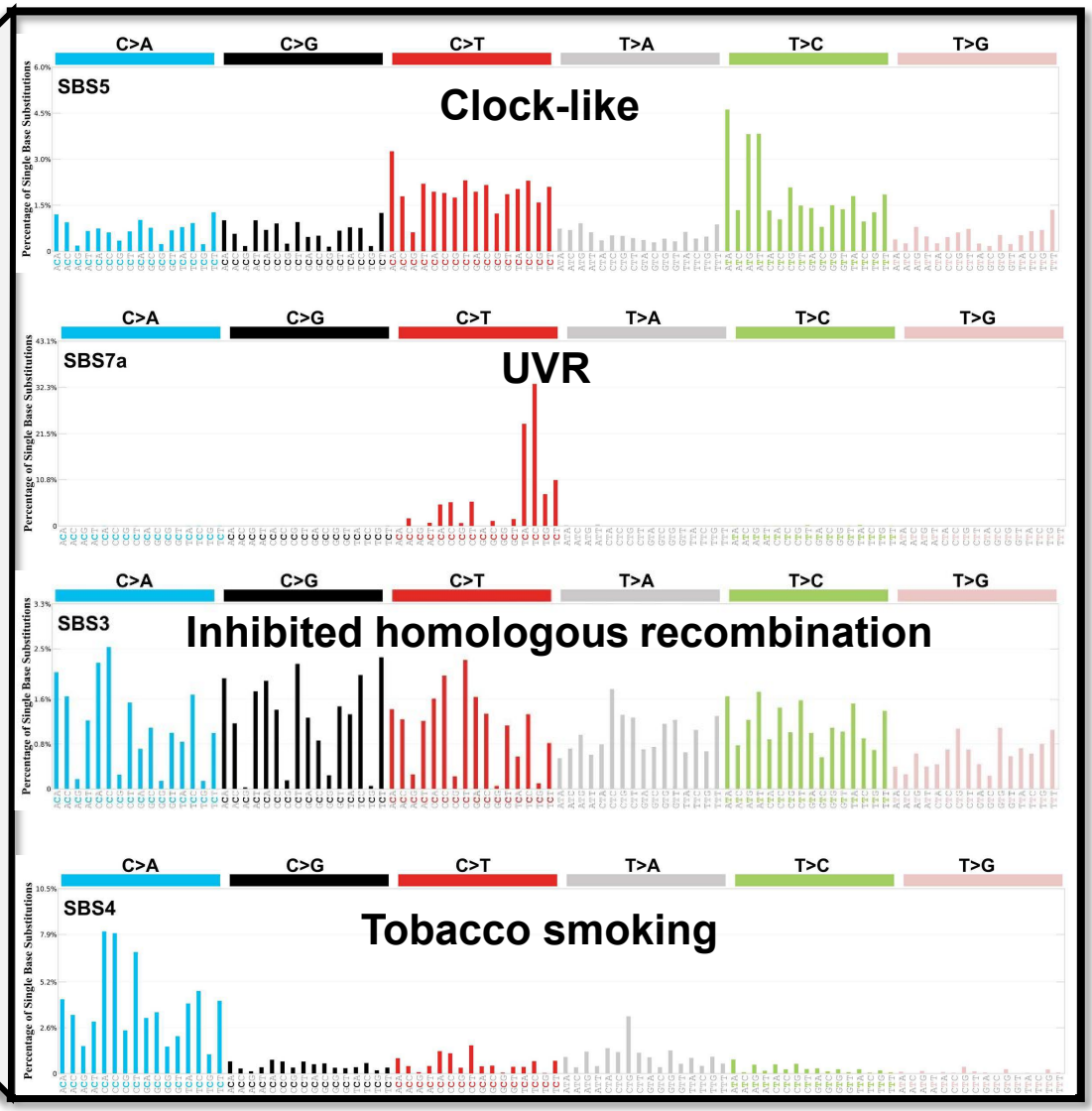
Nature Reviews | Genetics

Mutational Signatures Record Molecular Mechanisms of Carcinogenesis

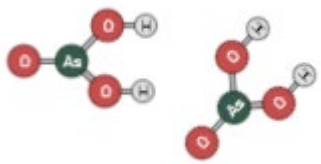
- Mutations arise from distinct mutational processes with variable strengths
- Processes may be operative at different times throughout life
- Each process has a unique signature

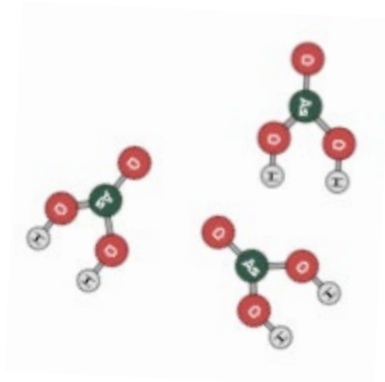


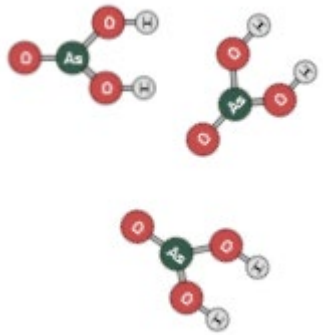
Proposed Aetiology of Mutational Signatures



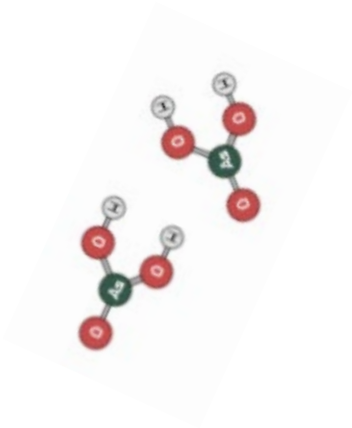
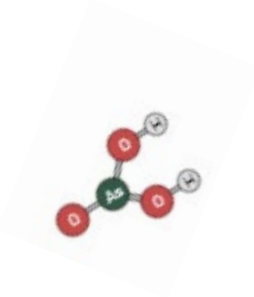
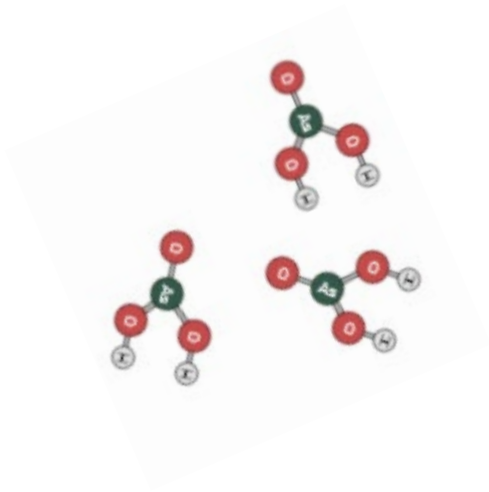
https://software.broadinstitute.org/cancer/cga/msp

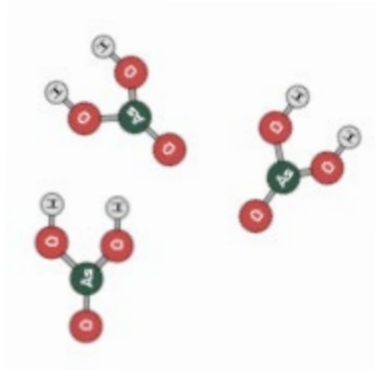




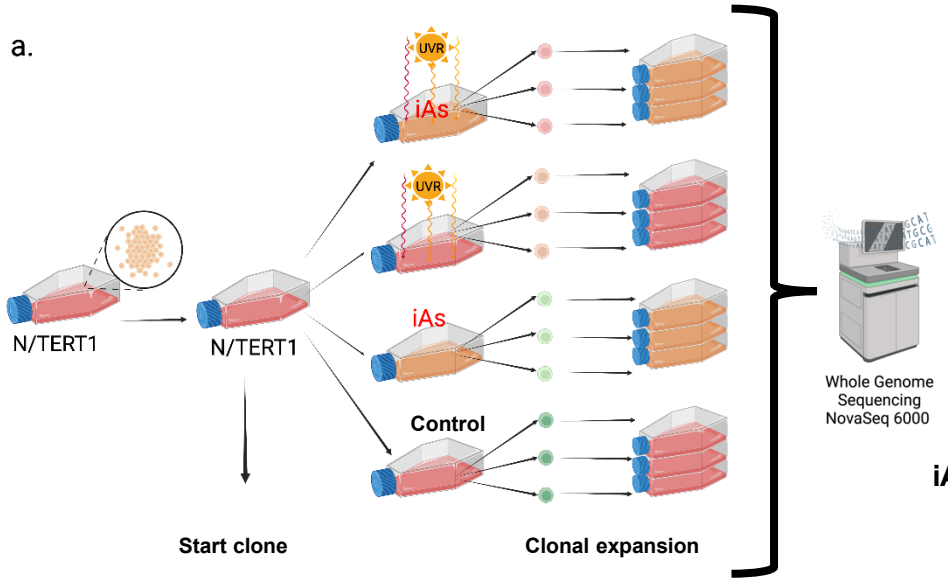


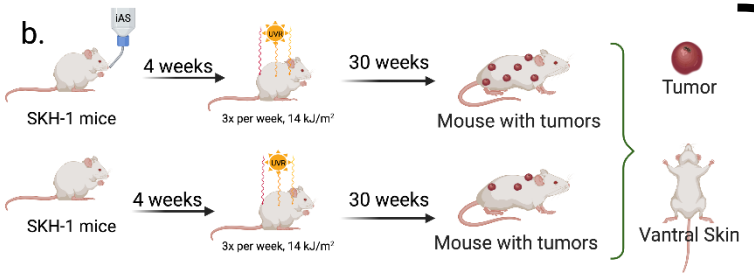
What can we learn about Arsenic-UV co-carcinogenesis using mutational signature analysis?

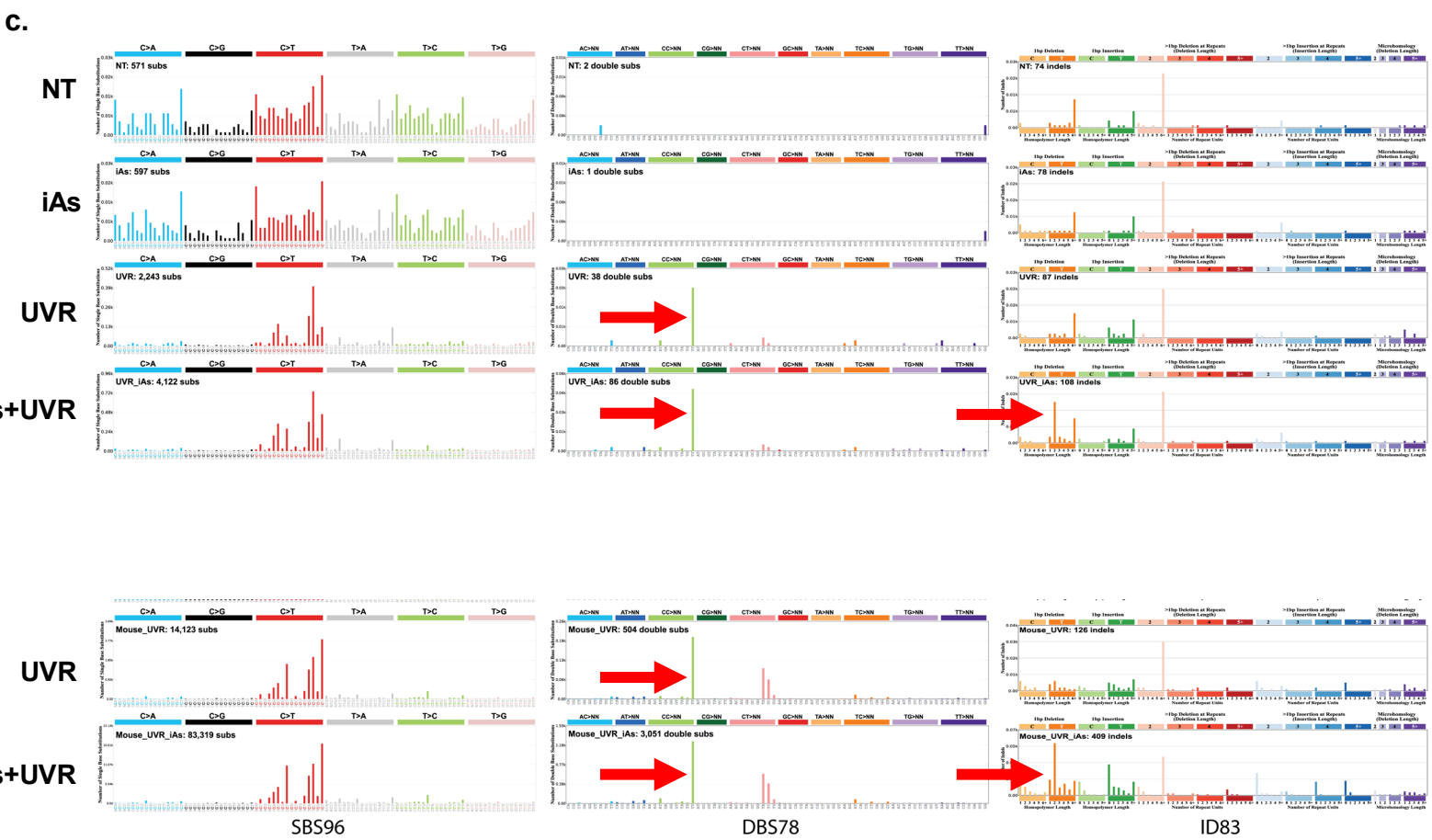






Mutational Signatures Experimental Design



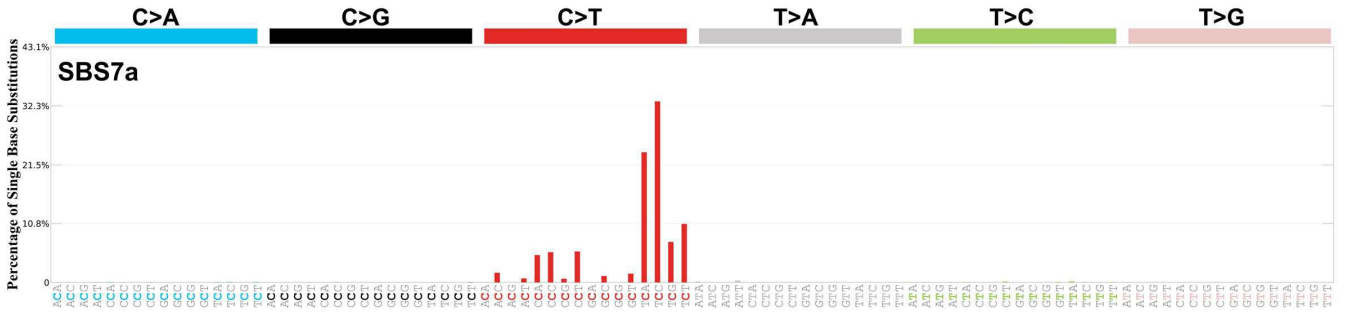




Classes of Mutations

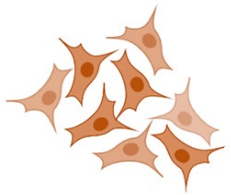
Single base substitutions

(SBS)



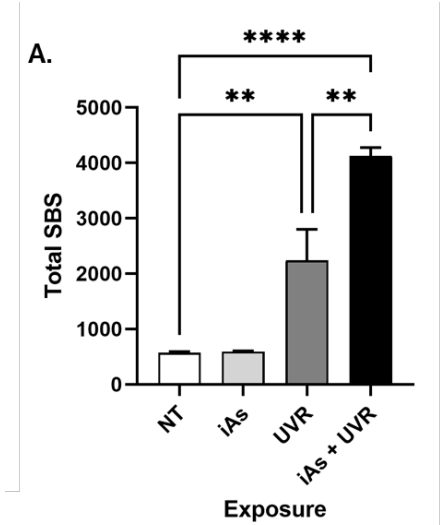
Arsenic Enhances the Mutational Burden of UVR Exposure

N/TERT1 cells

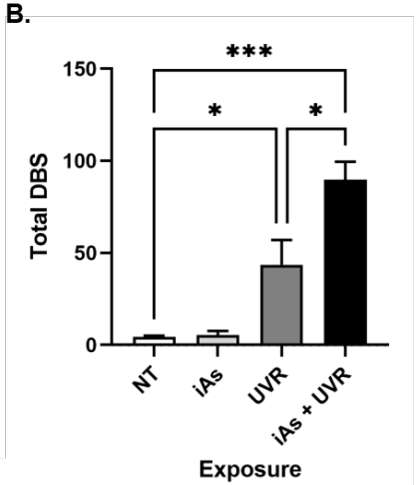


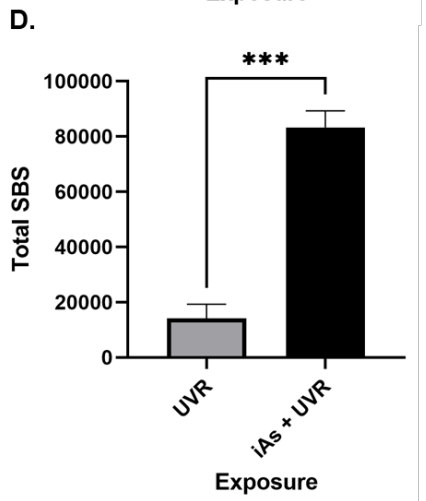
SKH-1 mice

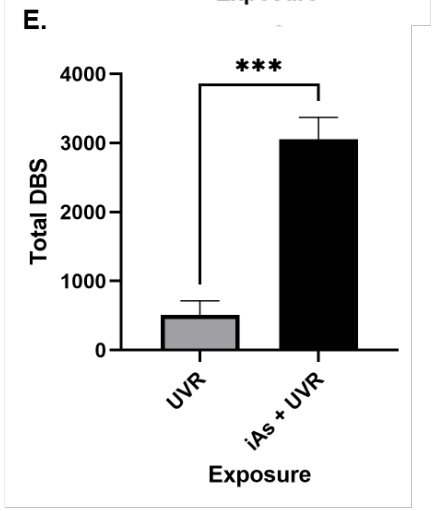
Single base substitutions



Doublet base substitutions

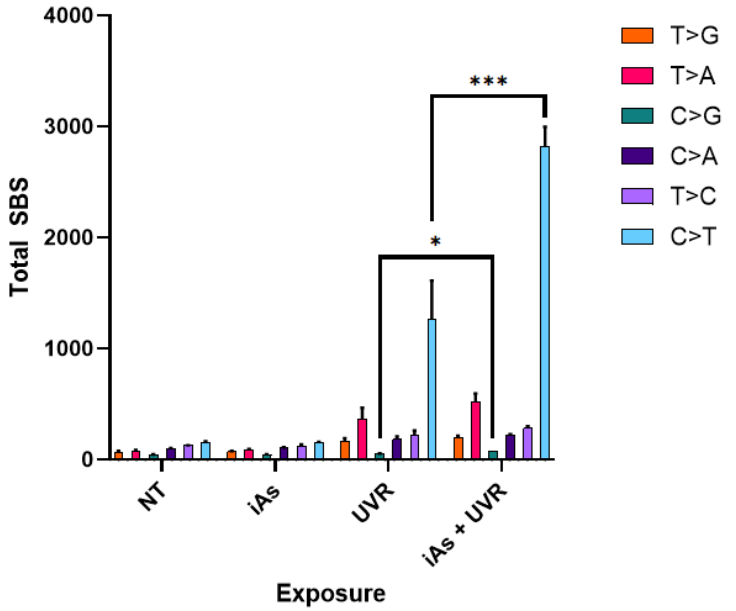




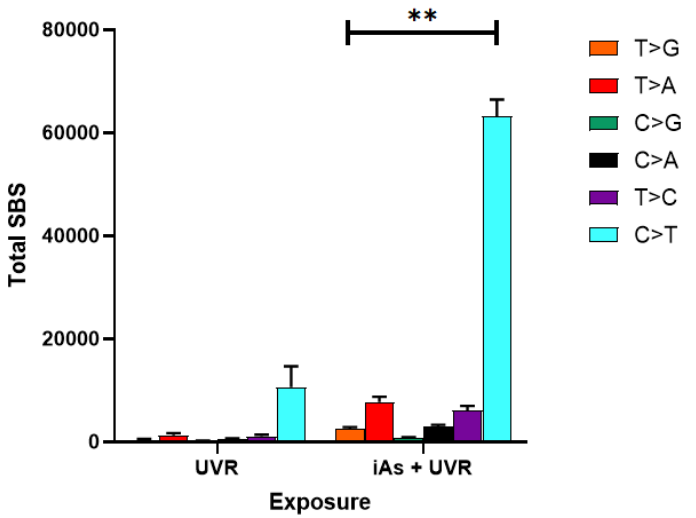


Arsenic Increases Select UVR Mutations

N/TERT1 cells



SKH-1 mice

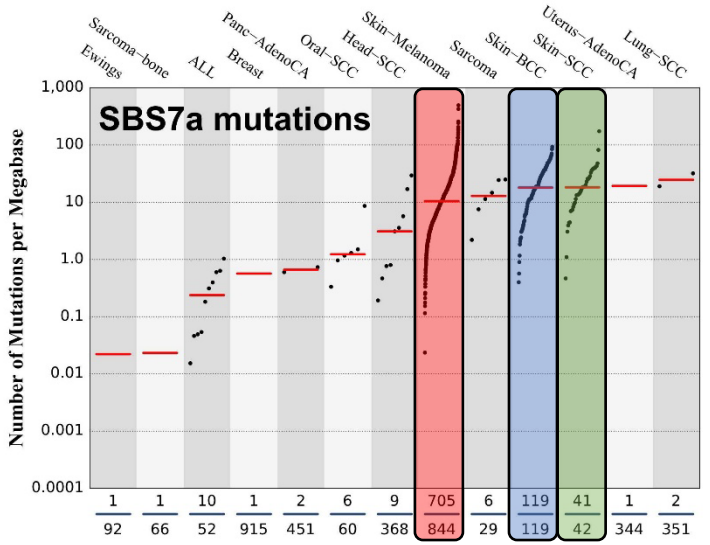


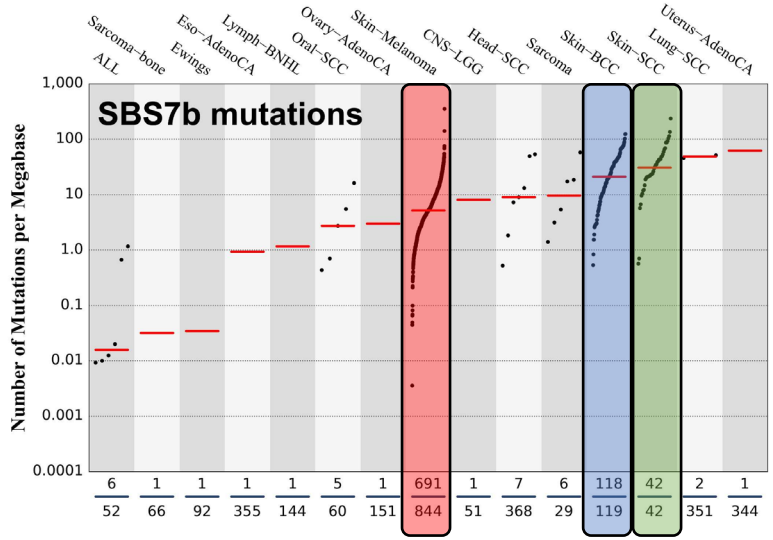
Arsenic selectively enhances C>T and C>G mutations

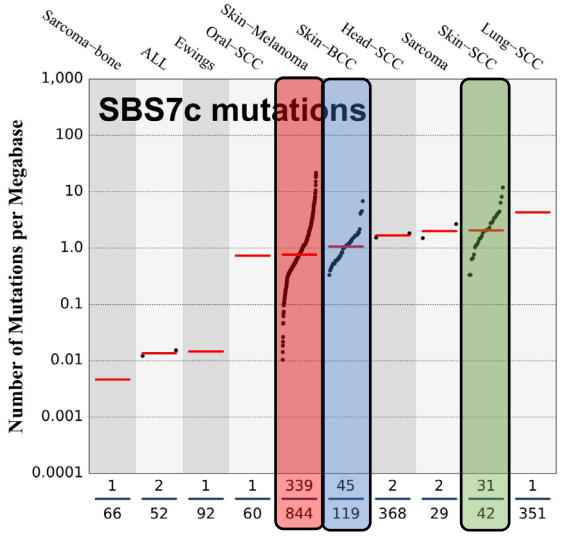
Distribution of UVR Signatures Across Human Cancers

Percent of human cancers with UVR signatures

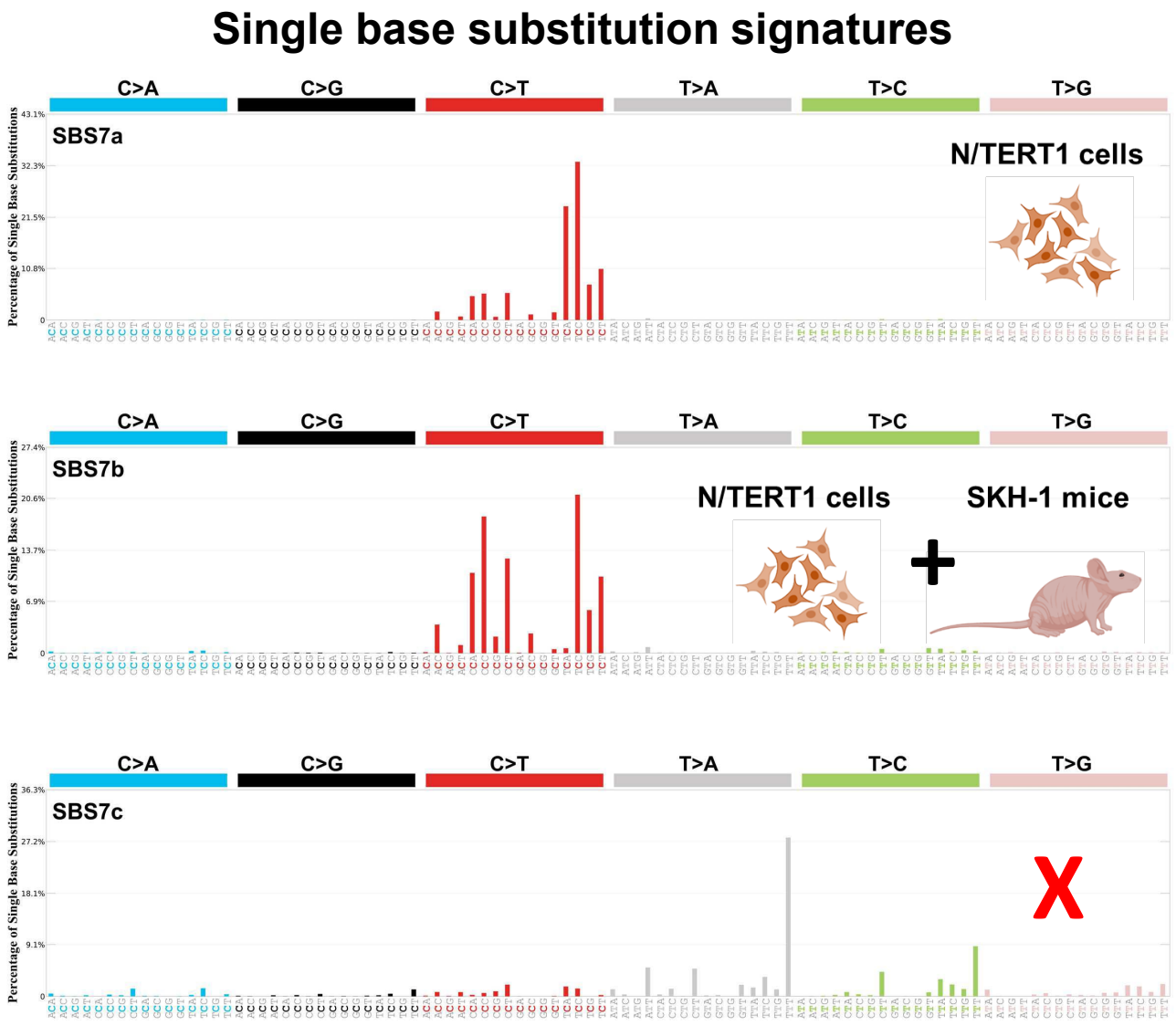
Cancer Type	SBS7a	SBS7b	SBS7c
Melanoma	84	82	40
Skin-BCC	100	99	38
Skin-SCC	98	100	74
Sarcoma	21	21	7
Head-SCC	2	2	1
Oral-SCC	10	8	2
Lung-SCC	1	1	<1

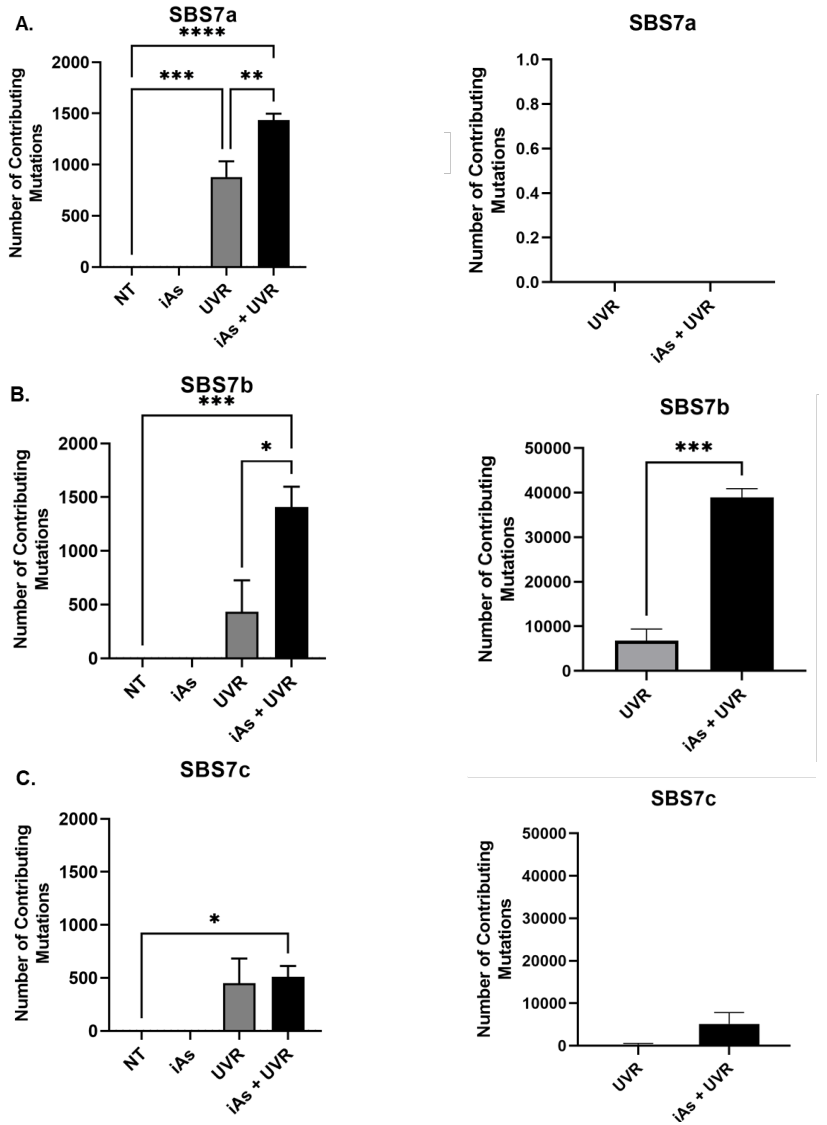






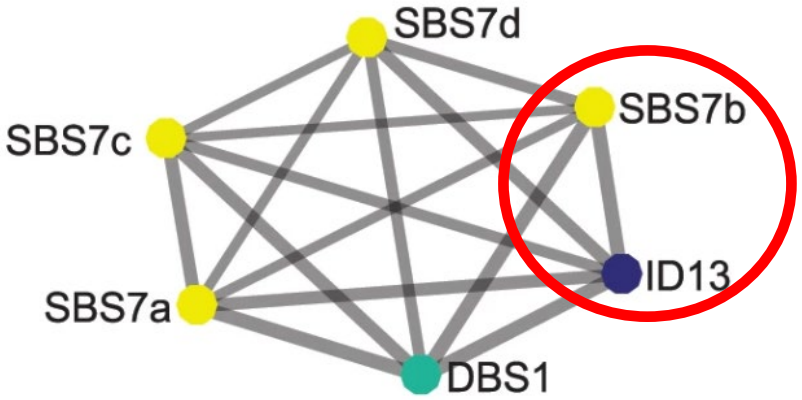
Select UVR Signatures are Enhanced by Arsenic

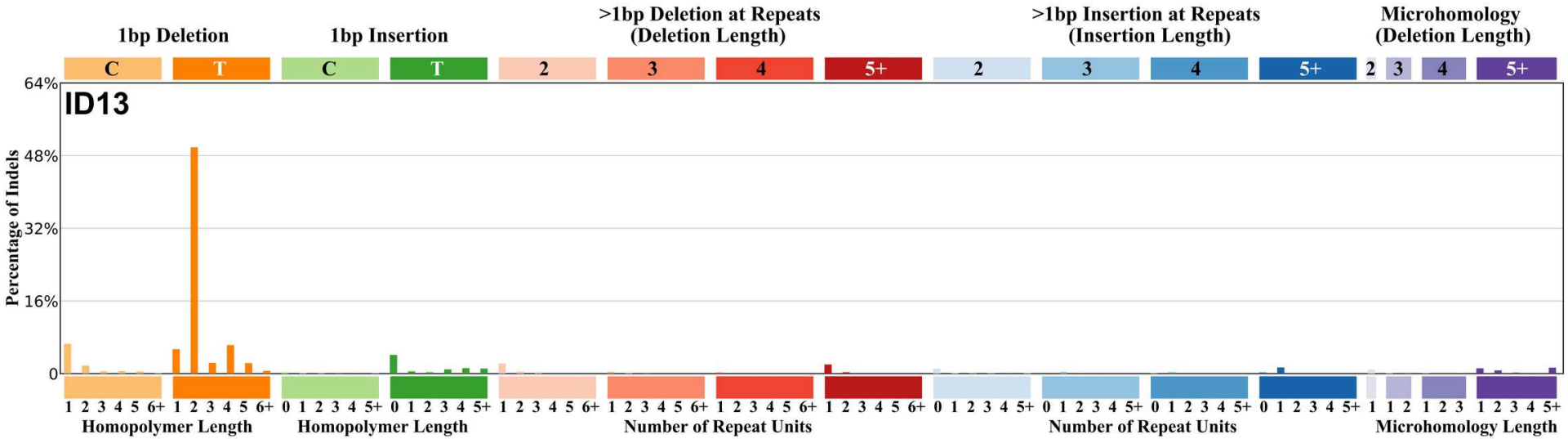




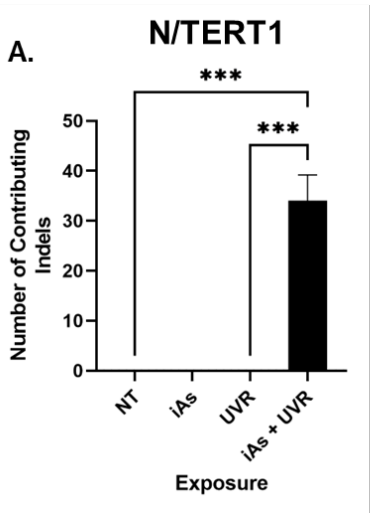
Indel Signature ID13

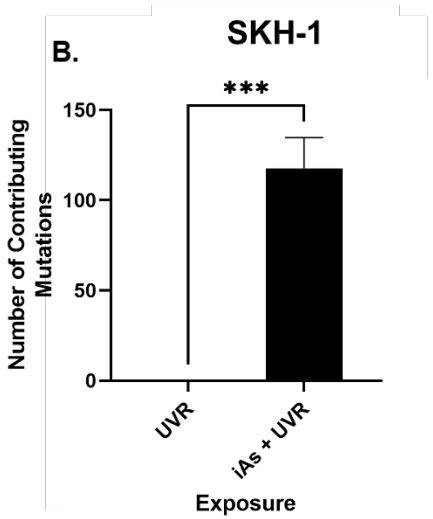
Characterized by deletions of thymine at thymine–thymine dinucleotides



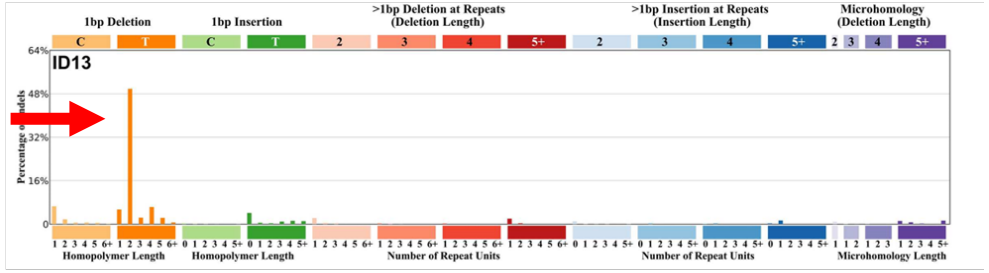


Indel ID13 is a Result of Combined Arsenic and UVR Exposure





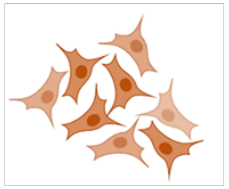
C.



UVR alone

iAs + UVR

N/TERT1 cells



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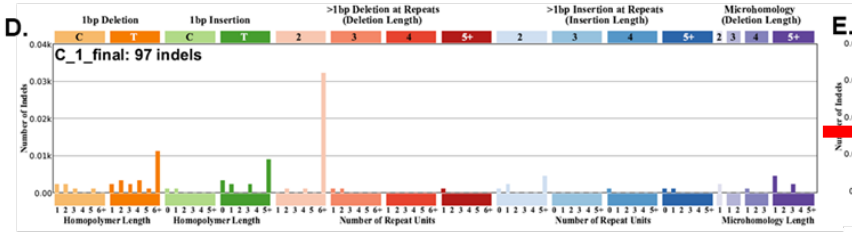
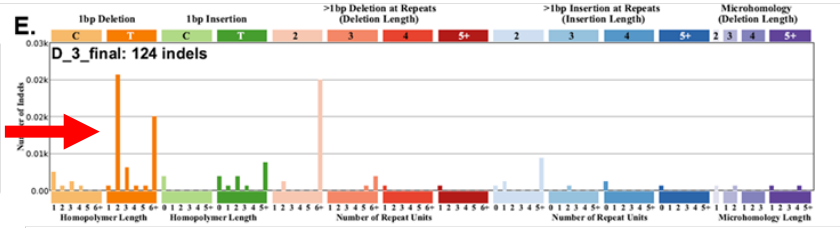


E.



SKH-1 mice

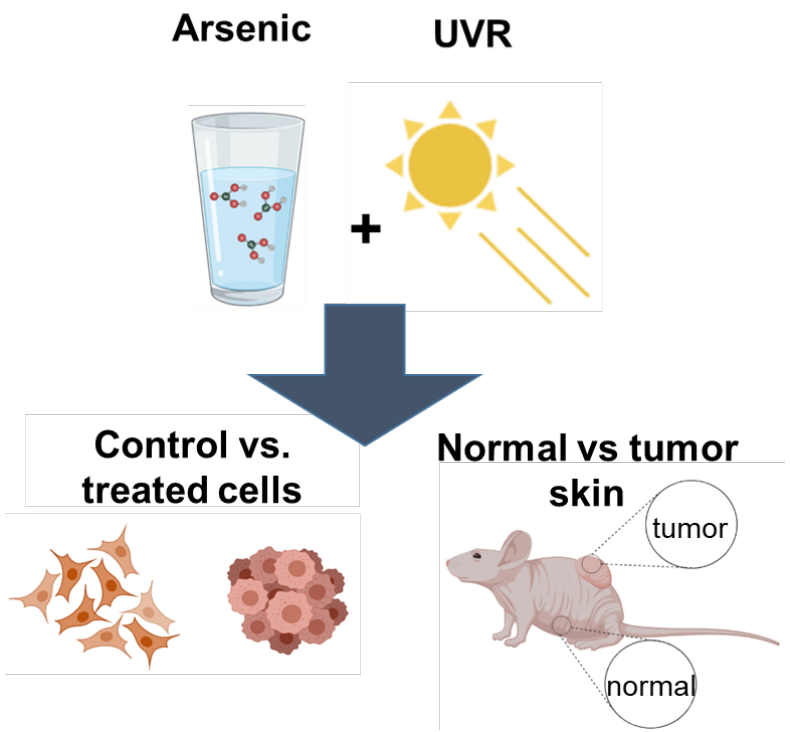
F.

G.

Indel Signature ID13 is found in a subset of human BCC tumors

Percent of BCC tumors with signature								
	UVR-associated signatures				Clock-like	Clock-like	DSB repair	Tobacco smoking
	SBS7a	SBS7b	DBS1	ID13	SBS1	SBS5	ID3	ID8
ID13+ (58 total BCC)	90	97	95	100	98	55	10	17
ID13- (244 total BCC)	88	97	90	0	93	48	27	36

Summary



- Arsenic enhances UVR mutational burden
- Specific mutations and UVR mutational signatures are enhanced by arsenic co-exposure
- We propose ID13 represents arsenic-UVR co-exposure serving as an indicator

Future work: Investigate mechanisms of arsenic-targeted UVR mutational signatures and identify arsenic-enhanced UVR driver mutations.

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