VDA-1102: A NOVEL WELL-TOLERATED TREATMENT FOR ACTINIC KERATOSIS

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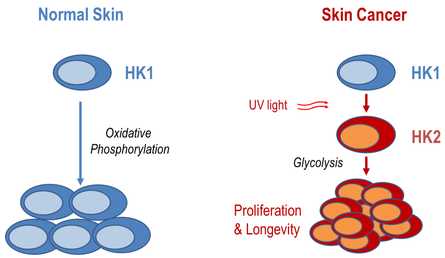
BACKGROUND

ACTINIC KERATOSIS

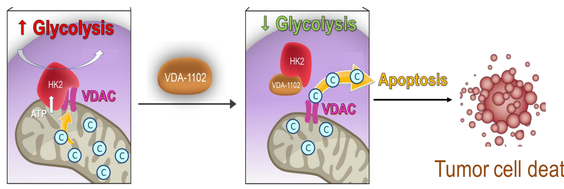
- Actinic Keratosis (AK) is a prevalent early-stage malignancy of the skin that can lead to cutaneous Squamous Cell Carcinoma (cSCC).
- Due to their mechanisms of action, current effective AK field treatments are irritating and painful, and cause unsightly skin eruptions.
- These side effects result in hesitancy by both patients and physicians to initiate therapy, patient compliance issues, and/or unwillingness to re-treat lesions in the same treatment field.
- Furthermore, large populations susceptible to multiple AKs (e.g. immunosuppressed, post-transplant, elderly patients) go untreated.
- Thus, an efficacious minimally-irritating topical treatment for AK is a pressing unmet medical need.

VDA-1102: MECHANISM OF ACTION

VDA-1102 is a novel small-molecule HK2-modulator that triggers apoptosis and blocks glycolysis in HK2-expressing malignant cells. Normal cells that do not express HK2 are unaffected by VDA-1102.



Hexokinase (HK) is the first enzyme in the glycolysis pathway. The HK1 isoenzyme is ubiquitously expressed in normal cells while levels of the HK2 isoenzyme are often increased in cancer cells.

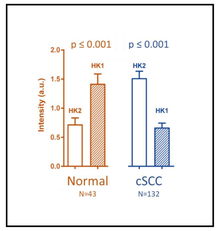


In cancer cells, HK2 attaches to the outer mitochondrial membrane via interaction with the VDAC1 channel. VDAC1/HK2 association results in apoptosis prevention (i.e., cell longevity) and a high rate of glycolysis that addresses the transformed cells' demand for energy and building blocks.

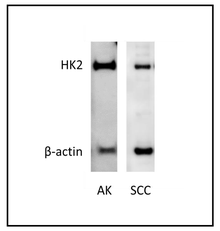
NON-CLINICAL DATA

HK2 IN ACTINIC KERATOSIS & SCC

High HK2 levels in skin SCC vs. Low HK2 levels in normal skin



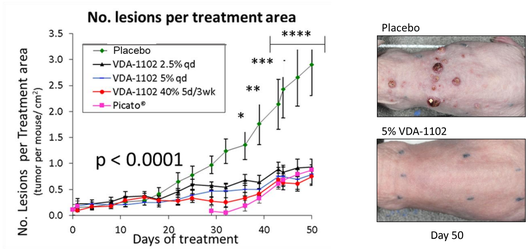
High HK2 levels in human AK and SCC cells



Left panel: Immunohistochemistry of SK208 and SK805 human tissue microarrays from US Biomax; **Right panel:** Western blot; HT 297.T human AK cells; A431 human skin SCC cells.

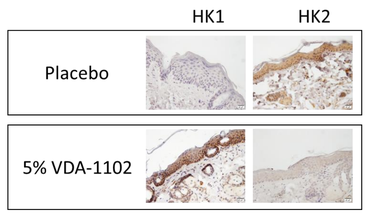
IN VIVO EFFICACY

Efficacy on UVB-damaged Skin of Hairless SKH-1 Mice



SKH-1 hairless female mice were chronically exposed to UVB radiation for 16 weeks (by which time >60% of mice developed at least one lesion) followed by a 50-day treatment phase (N=12 mice/group). p values compare the 40% treatment group to the vehicle-control. *p≤0.05, **p≤0.01, ***p≤0.001, ****p≤0.0001.

HK1 & HK2 Levels in UBV-damaged Mouse Skin

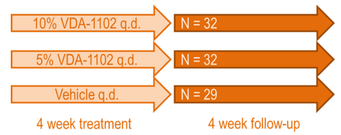


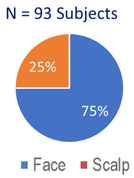
Immunohistochemistry of skin biopsies from UVB damaged SKH-1 hairless mice treated with placebo (for 2 days) or 5% VDA-1102 (for 50 days).

CLINICAL PHASE 2A DATA

EFFICACY

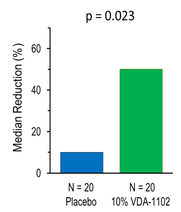
Study Design



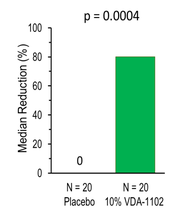


4-8 AK lesions (Grades 1-2) in a 25cm² area on face or scalp

Facial AK Lesions



Facial Grade 2 AK Lesions



SAFETY

Category	Treatment		
	Placebo (N = 29)	VDA-1102 5% (N = 32)	VDA-1102 10% (N = 32)
Any TEAE	7 (24%)	10 (31%)	13 (41%)
Any TEAE Related to Treatment	1 (3%)	2 (6%)	0
Any SAE	0	1 (3%)	1 (3%)
Any SAE Related to Treatment	0	0	0
Study Withdrawals	2 (6%)	0	0
Dose Adjustments	1 (3%)	1 (3%)	1 (3%)

TEAE = Treatment Emergent Adverse Event, DAE = Serious Adverse Events (SAE), ITT Population

PHARMACOKINETICS

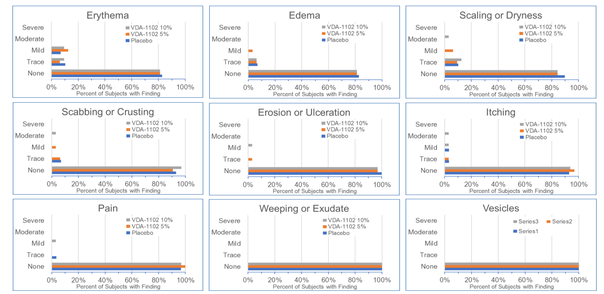
Pharmacokinetic analysis for the parent compound (VDA-1102) and for its major metabolite demonstrated no systemic exposure of either.

	Placebo	5% VDA-1102	10% VDA-1102
Parent (VDA-1102)	BLQ	BLQ	BLQ
Major metabolite	BLQ	BLQ	BLQ

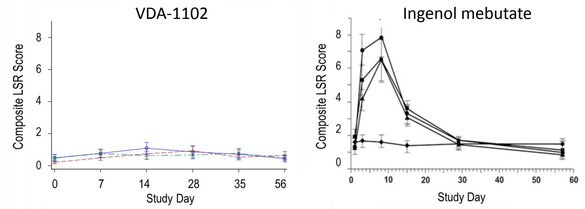
BLQ = Below Lowest Level of Quantitation: 1 ng/ml for VDA-1102 and 20 ng/ml for major metabolite; N=4/group.

LOCAL SKIN REACTION

Local Skin Reactions



Composite Local Skin Reaction Score



Anderson et al, J Am Acad Derm 60:934 (2009)

The means of the composite LSR scores from all 3 cohorts were indistinguishable (left panel)

CONCLUSIONS

- VDA-1102 is a selective HK2-modulator that triggers apoptosis in HK2-expressing malignant cells such as AK and cSCC, without effecting the surrounding normal tissue.
- In a proof-of-concept Phase 2a clinical trial, VDA-1102 ointment (applied once-daily for 28 days) reduced the number of AK lesions on the face and scalp of adult subjects, while being very well-tolerated both locally (skin) and systemically.
- A Phase 2b dose-ranging trial with VDA-1102 ointment (applied for 3 months) is currently ongoing.

Reference: V. Behar et al, "A Hexokinase 2 Modulator for Field-Directed Treatment of Experimental Actinic Keratoses", *Journal of Investigative Dermatology* (2018).