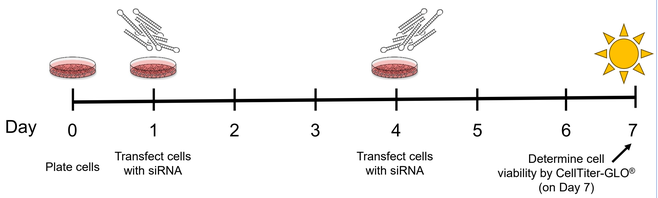
siRNAs targeting CD320 and LRP2 selectively kill squamous skin cancer cells while leaving normal skin cells unharmed

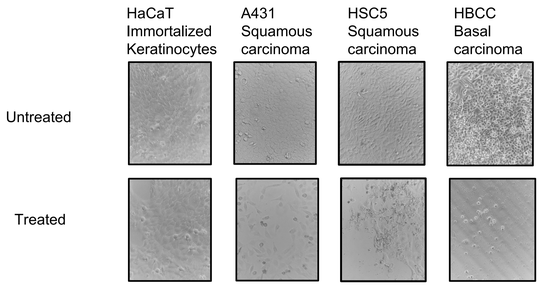
David J. Elzi[1], Reggie Jacob[1], and William Bauta[1]

Background

- CD320 and LRP2 are transmembrane receptors which transport Vitamin B12 (cobalamin) into the cell (1-2).
- We have previously shown that simultaneous silencing of CD320 and LRP2 receptors by siRNAs is toxic to cancer cells, including breast, prostate, lung, brain and melanoma cancers, but leaves normal cells unharmed (3).
- There is interest in developing as topical therapeutics for various inflammatory skin conditions, such as alopecia areata (4).
- Cutaneous squamous and basal cell carcinomas are common cancers treated with surgery. However, in many cases squamous cell carcinomas require additional therapy because surgery alone results in incomplete resection and high risk of recurrence (5-6).
- We are developing combinations of self delivering siRNAs targeting CD320 and LRP2 as topical treatments for squamous and basal cell carcinoma.

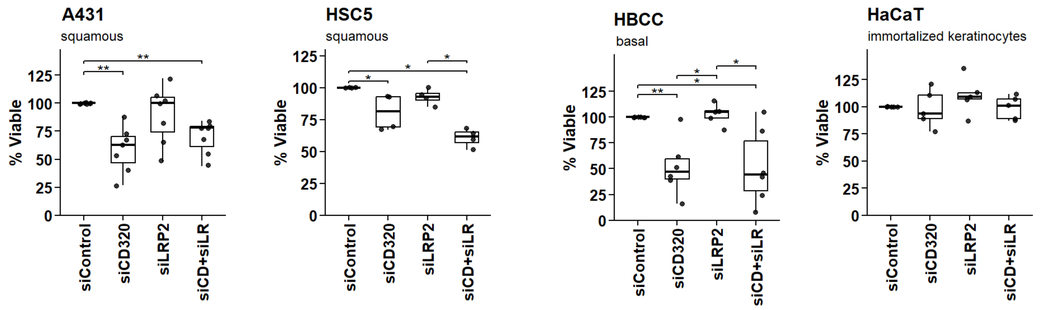
siRNAs to CD320 and LRP2 are toxic to skin cancer cells





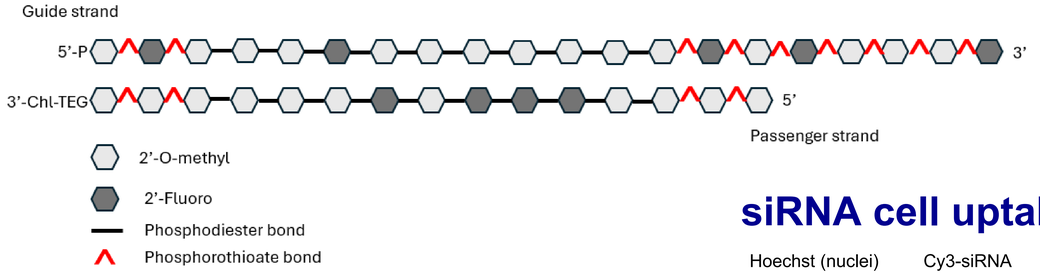
Cells are transfected with siRNAs and are harvested for the Cell-Titer-GLO® assay, which measures ATP production as an indication of viability.

Squamous and basal skin cancers are affected by CD320 and LRP2 knockdown



Box plots show median, interquartile range (25th–75th percentiles), and whiskers to 1.5× IQR. Individual replicates shown as dots. Pairwise Wilcoxon tests; *p < 0.05, **p < 0.01

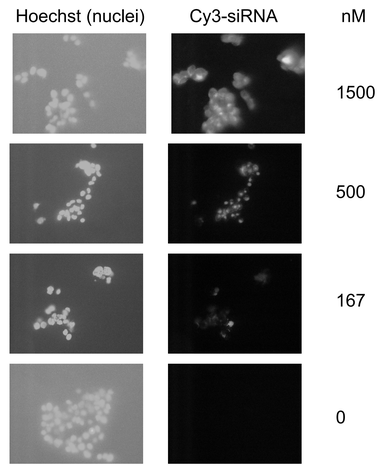
Self delivering and stabilized siRNAs



Advantages

- Increased stability
- Increased specificity
- Increased duration of effect
- Used in siRNA treatment development for skin inflammation (7)

siRNA cell uptake

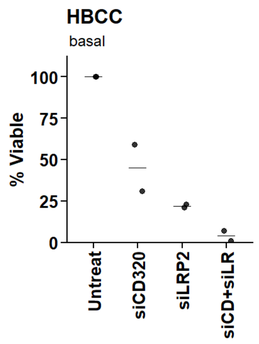


A431 cells were treated 24 hours with siRNAs and visualized.

Toxicity of self-delivering siRNAs squamous and basal skin cancers

Cell	Untreated*	siCD320/ siLRP2*
HaCat (keratinocytes)	100	107
A431 (squamous)	100	82
HSC5 (squamous)	100	68
HBCC (basal)	100	7

* % viability to untreated



Conclusions and future directions

- CD320 and LRP2 knockdown is toxic to squamous and basal cutaneous carcinoma, while leaving non-cancerous cutaneous cells unharmed
- Self-delivering, stabilized, siRNAs can enter cutaneous cancer cells.
- Self-delivering, stabilized siRNAs show efficacy in squamous and basal carcinoma cells in preliminary studies
- Optimization of the dosing regimen of the stabilized siRNAs is ongoing.

References

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