Repurposing FDA-approved WNT Inhibiting Drugs for Treating Keloids

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INTRODUCTION

Problem: A keloid is a fibroproliferative skin disease that occurs due to an aberrant wound-healing process. Keloids occur primarily in people of color and cause issues like deep, unreachable itches, frequent pain, etc. They do not resolve spontaneously and need to be surgically removed. However, they have a recurrence rate of 100% following surgical removal alone and effective therapeutics are not available. To uncover new targets for keloid therapy and to better understand the molecular drivers of keloid disease, the Gunjan lab has performed unbiased transcriptomic analyses of keloid versus normal skin fibroblasts and found that the WNT signaling (Figure 1) was upregulated in keloid fibroblasts, suggesting that it could potentially be targeted for keloid therapy.

Hypothesis: Inhibition of the cyclooxygenase-2 (COX-2) enzyme destabilizes the β-catenin protein, which is an integral part of the canonical WNT pathway (Figure 1). COX-2 is known to contribute to inflammation responses because of its integral role in the arachidonic acid cascade. Food and Drug Administration (FDA) approved COX-2 inhibitors are commonly used as analgesics for pain relief and also because of their anti-inflammatory effects.

Possible Treatment Option: Varying concentrations of WNT inhibiting drugs and combinations were used in an *in vitro* cell viability assay to determine the best combinations for effective elimination of keloid cells. We envision using the WNT inhibiting drugs by administrating them locally in the keloid through intralesional injections that will inhibit the WNT pathway only in the affected area, while avoiding systemic effects of inhibiting WNT.

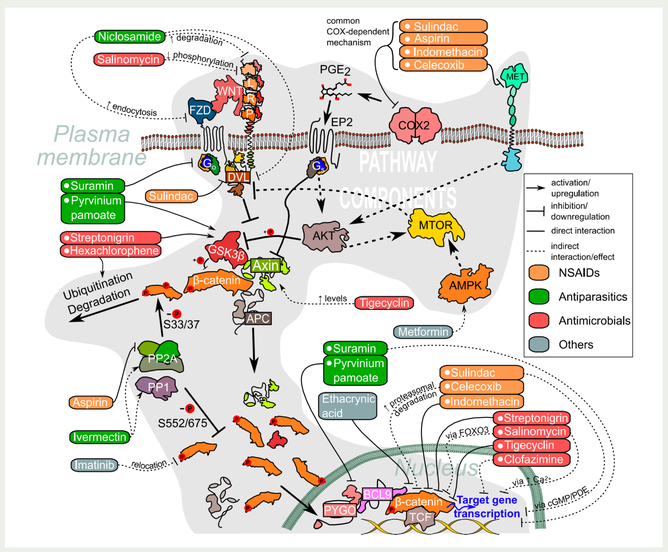

Figure 1. A simplified version of the WNT pathway in a cell is shown here. There are many points of inhibition. Sulindac and celecoxib target stabilization of β-catenin and salinomycin indirectly targets β-catenin and directly targets lipoprotein receptor-related protein (LRP) inhibition of the destruction complex (2).

METHODS

- Primary human dermal fibroblast cells from normal skin and keloids were used and grown in cell culture.
- A survival assay was performed.
- The assay included an untreated condition, and various drug combinations with and without radiation treatment.
- The assay data will be analyzed to find the best combination of drugs for keloid treatment.

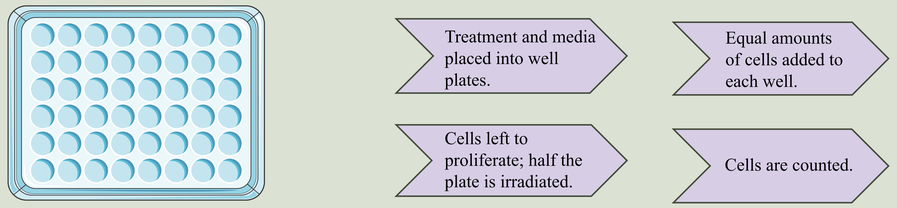

Figure 2. The figure contains a multi-well plate and a flowchart of the procedure we performed for the *in vitro* cell viability assay (1).

RESULTS

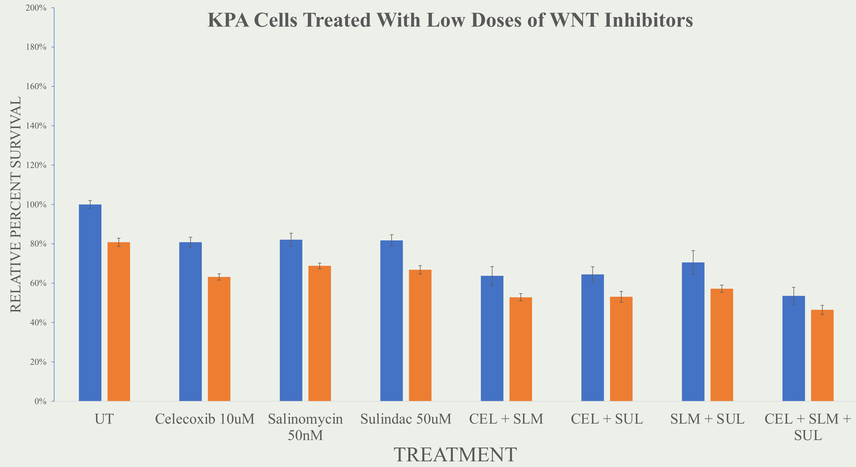

Figure 3. Relative survival of fibroblasts upon treatment with different WNT inhibitors, either with (orange bars) or without (blue bars) radiation. Error bars indicate standard deviation obtained from 3 independent measurements. UT = Untreated, CEL = Celecoxib, SUL = Sulindac and SLM = Salinomycin.

CONCLUSIONS

- A combination of all three WNT inhibiting drugs celecoxib, salinomycin, and sulindac appears to be the most effective at killing keloid fibroblasts, suggesting synergy in their actions.
- Radiation synergized with the drugs in killing keloid fibroblasts
- The individual treatments with celecoxib, salinomycin or sulindac alone decreased proliferation to a similar degree at the drug concentrations used.
- The best two drug combinations were celecoxib with salinomycin, and celecoxib and sulindac. The salinomycin plus sulindac combination was not as effective as the other two drug combinations with celecoxib.
- Combinations of these WNT inhibitor used at higher concentrations may be useful in killing keloid fibroblasts with or without radiation.
- The p-value, being less than 0.005, signifies that the observed combinations are statistically significant with a confidence level exceeding 99.5%. This result strongly suggests that the observed effects are not due to random chance.

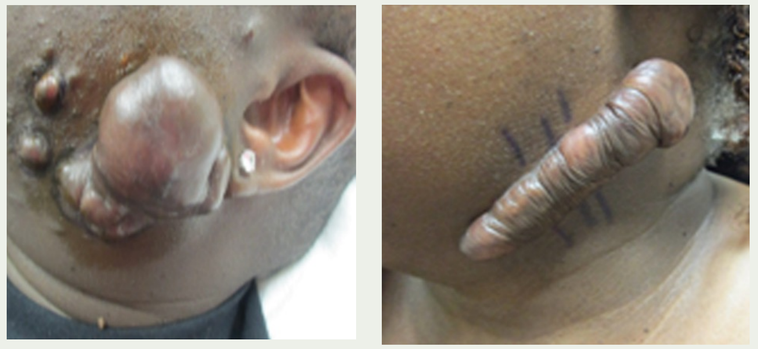

Figure 4. Examples of different keloids are shown above. The size of keloids vary greatly and substantially affects the quality of life of the patient when keloids are located in a very visible spot (3).

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