**Epidermodysplasia verruciformis** (EV) is a rare autosomal recessive skin disease that leads to a high susceptibility to dermal infection by human papillomavirus (HPV), specifically the β-strains.¹ These infections lead to persistent scaly wart-like lesions, macular lesions, a high risk of skin carcinoma, and possibly cutaneous horns.² Although the majority of the population has cell-mediated immunity to HPV, patients with EV lack this immunity.¹ EV is most commonly (75%) caused by a mutation in **TMC6** or TMC8.¹ **TMC6** and TMC8 code for transmembrane channel proteins which, among other things, form a complex with calcium- and integrin- binding protein-1 (CIB1).3 This complex acts as a restriction factor of HPVs in keratinocytes by possibly interacting with the two viral proteins E5 and E8, restricting HPV infection in normal individuals.3 **TMC6** and TMC8 most likely act to stabilize CIB1, which helps regulate CIB1 expression levels posttransciptionally.3 *It is unknown how this complex interacts specifically with β-HPVs to bypass infection and to what extent TMC6 plays a role in this.* This pathway, isolated or in combination with other possible TMC6 and TMC8 functions, explains typical EV.

The **long-term goal** of this project is to fully understand the role and to what extent TMC6 plays in the CIB1-TMC6-TMC8 complex, and how this leads to cell-mediated immunity to β-HPVs. This understanding could possibly lead to a novel therapeutic treatment option. The **primary goal** of this project is to understand the role TMC6 plays in stabilizing the complex, and whether or not TMC6 interacts directly with β-HPVs. Mus musculus will used as a **model** because it can be used to model skin carcinomas and has the components for a CIB1-TMC6-TMC8 complex4.My hypothesis is that mutations in specific regions or motifs of TMC6 decrease the stabilization of the CIB1-TMC6-TMC8 by not properly interacting with CIB1 domains.

**AIM 1: Determine if TMC6 interacts with CIB1 via specific regions**

**Approach:** I will first NCBI BLAST to identify mouse homologs of TMC6, and then Clustal Omega will be used to align homolog protein sequences in order to identify well-conserved amino acid regions and motifs on the TMC6 gene. I will cross-reference these regions and motifs with known EV causing mutations. Using CRISPR Cas9, I will mutate these regions in mice and will use RNA-seq to determine TMC6 and CIB1 expression levels at the age of sexual maturity. SMART will also be used to determine if TMC6 has known protein interactions with CIB1, or an intermediate to CIB1. **Hypothesis:** I hypothesize that the mutant mice will result in a decrease in CIB1 expression levels, but the TMC6-mutant protein will remain similar to TMC6 expression levels in controls. This is due to a decrease in CIB1 stabilization, reducing CIB1 expression posttransciptionally. **Rationale:**  By changing motifs in the TMC6 protein and measuring CIB1 levels I can see which regions are crucial for CIB1 stabilization. If TMC6 expression does change as well than that region is important for the stability of the TMC6 protein itself. These expression levels are important to understand the overall interaction between TMC6 regions and the CIB1-TMC6-TMC8 complex.

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