**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 the **EVER1** and/or EVER2 genes, coding for **TMC6** and TMC8 respectively.¹ TMC6 codes for a transmembrane channel protein which forms a complex with zinc transporter protein (ZnT-1), which regulates cytoplasmic and nucleic zinc concentrations in keratinocytes.³ *It is unknown how TMC6 interacts with ZnT-1 to regulate zinc concentrations, and how this leads to cell-mediated immunity to HPV. It is also unknown if TMC6 stimulates tumor necrosis factor-alpha (TNF-α),* which is critical to induce apoptosis and prevent the persistence of HPV infection.³ Both of these pathways could contribute in isolation, or combination, to produce EV disease states.

The **long-term goal** of this project is to understand the underlying physiological properties that makeup cell-mediated immunity to β-HPV, and use these findings to produce a treatment option, other than surgical removal of warts, for patients with EV. The **primary goal** of this project is to understand the role TMC6 plays in regulating intracellular zinc concentrations via the TMC6/ZnT-1 complex, and to understand if TMC6 has a role in stimulating TNF-α. Mus muscalis will used as a **model** to assess the intraorganellar regulation of zinc in keratinocytes. In addition, transgenic mice with induced HPV5 and with or without knockout of EVER1 will be used to determine the correlation between TMC6 and TNF-α.4 My hypothesis is that TMC6 modulates ZnT-1 by either increasing or decreasing its activity, and that TMC6 stimulates TNF-α in tumor cells.

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