compared to electrotransport of cytochrome c (Cyt c) and ribonuclease A (RNase A) under similar conditions (923.0 ± 496.1 and 170.71 ± 92.13 μg/cm^2, respectively)—despite its having a higher electrophoretic mobility. The focus of the study then became to understand and explain the causes of its poor iontophoretic transport. Lowering formulation pH to 5 increased histidine protonation in the protein and decreased the ionization of fixed negative charges in the skin (pI ~4.5) and resulted in a small but statistically significant increase in permeation. Co-iontophoresis of acetaminophen revealed a significant inhibition of electroosmosis; inhibition factors of 12–16 were indicative of strong lysozyme binding to skin. Intriguingly, lidocaine electrotransport, which is due almost exclusively to electromigration, was also decreased (approximately 2.7-fold) following skin pretreatment by lysozyme iontophoresis (cf. iontophoresis of buffer solution)—suggesting that lysozyme was also able to influence subsequent cation electromigration. In order to elucidate the site of skin binding, different porcine skin models were tested (dermatomed skin with thicknesses of 250 and 750 μm, tape-stripped skin and heat-separated dermis). Although no difference was seen between permeation across 250 and 750 μm dermatomed skin (13.57 ± 12.20 and 5.37 ± 3.46 μg/cm^2, respectively), there was a statistically significant increase across tape-stripped skin and heat-separated dermis (36.86 ± 7.48 and 43.42 ± 13.11 μg/cm^2, respectively)—although transport was still much less than that seen across intact skin for Cyt c or RNase A. Furthermore, electroosmotic inhibition factors fell to 2.2 and 1.0 for tape-stripped skin and heat-separated dermis—indicating that lysozyme affected convective solvent flow through interactions with the epidermis and predominantly the stratum corneum. Finally, cation exchange and hydrophobic interaction chromatography confirmed that although lysozyme had greater positive charge than Cyt c or RNase A under the conditions used for iontophoresis, it also possessed the highest surface hydrophobicity, which may have facilitated the interactions with the transport pathways and encouraged aggregation in the skin microenvironment. Thus, high charge and electrophoretic mobility seem to be inadequate descriptors to predict the transdermal iontophoretic transport of proteins whose complex three-dimensional structures can facilitate interactions with cutaneous transport pathways.

Feturi, F. G. et al. (2018). "Mycophenolic acid for topical immunosuppression in vascularized composite allotransplantation: Optimizing formulation and preliminary evaluation of bioavailability and pharmacokinetics." *Front Surg* 5:20.

Mycophenolic acid (MPA), is the active form of the ester prodrug mycophenolate mofetil (MMF). MMF is an FDA approved immunosuppressive drug that has been successfully used in systemic therapy in combination with other agents for the prevention of acute rejection (AR) following solid organ transplantation (SOT) as well as in vascularized composite allotransplantation (VCA). Systemic use of MMF is associated with GI adverse effects. Topical delivery of the prodrug could thus provide graft-targeted immunosuppression while minimizing systemic drug exposure. Our goal was to develop a topical formulation of MPA with optimal in vitro/in vivo characteristics such as release, permeation, and tissue bioavailability to enable safety and efficacy evaluation in clinical VCA. Permeation studies were performed with a solution of MPA (10 mg/mL). In vitro release and permeation studies were performed for different semisolid formulations (Aladerm, Lipoderm, emollient, and VersaBase) of MPA (1% w/w) using a Franz Diffusion Cell System (FDCS). In vivo pharmacokinetic characterization of MPA release from Lipoderm was performed in rats.