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Research Idea: *I propose the use of computational methods to determine a skin permeability model in order to investigate the permeation rates and constants of various substances. Furthermore, I will use this model to understand and apply to skin parameter functions.*

Intellectual Merit: Despite years of trial and computation, researchers still struggle to create an extremely accurate skin model to predict skin permeability.[1]I will begin with creating an improved model of skin permeability using QSPR (quantitative structure permeability relationship) modeling. The model will correlate certain descriptors (codified structural and physicochemical characteristics of a compound) to the property of interest (Kp) through an equation. The equation used to predict the thermophysical property of the permeation coefficient, Kp, will be based on Fick's first law for diffusion of a substance through a given material[2]:

$$Kp = \frac{Km \cdot D}{h}$$

Km is the partition coefficient, D is average diffusion coefficient, and h the thickness of the material of interest (skin). These QSPR models have proven to be the most effective in predicting, even with simple models such as the model of Potts and Guy.[3] Potts and Guy were originally successful with linking the permeability of a compound with its partition coefficient between water and octanol and molecular size.[1] Other models have used that model as a foundation with similar levels of success. However, there is room for improvement. Previous data and models have suffered from poor choices in descriptors, delivery vehicles for the molecule of interest (surfactants), and not considering various skin parameters that would affect absorption.[1] In my model, the descriptors to be factored in at the very least would include: molecular weight, solute size, lipophilicity. But it would also descriptors of the skin being treated: trans-epidermal water loss (TEWL) for skin barrier function, hydration content, sebum content, and elasticity. These are often left out and likely contribute to flawed models. In order to validate the success of the model, goodness of fit would be checked using R^2; predictiveness and robustness would checked with QLMO2 (leave-many-out) or bootstrap methods as cross-validation.[1] In conjunction with my *in silico* research, I would like to apply the concept to *in vitro*, and *in vivo* experimentation. I will use *in vitro* skin to test compounds with various delivery vehicles (creams, ointments, lotions, gels, patches, etc.) and their interactions with certain skin parameters such TEWL, hydration content, sebum content, and elasticity. The *in vivo* portion will evaluate the same skin parameters using human subjects treated with in-active forms of the topical delivery vehicles, as to eliminate unnecessary drug exposure. These experiments can be used to correct for any affects the delivery vehicle used to administer an active ingredient can have on the permeability of said active.

Resources: In order to carry out the computational portion, I will need information from databases such as ZINC for compounds of interest and a license to a QSPR building software such as BioPPSy.[4,5] BioPPsy will provide a dataset of common descriptors and will perform accurate regressions for validation. For *in vitro* applications, I will need a representative brick and mortar skin model (Figure 1); porcine skin, for example is widely used for human skin comparisons.[1] Access to a clinical lab facility with human subjects willing to have their skin tested with various non-invasive instruments and treated with various topical inactive vehicle formulations. I have over 4 years of experience of clinical lab experience involving instrumental

skin analysis of human subjects and am knowledgeable in the use and comprehension of topical products and the following instruments. Instruments required for the in-vivo clinical would be a Novameter for skin hydration content, Evaporimeter for TEWL (barrier function), Sebumeter for skin sebum content, and a Cutometer for skin elasticity.[6,7,8,9]

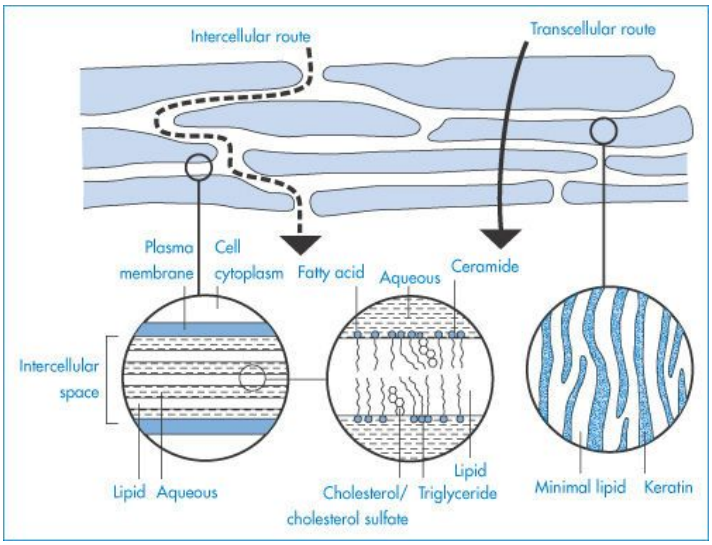

Figure 1: Brick and mortar model and the potential drug pathways of the stratum corneum. [10]

Broader Impacts: The understanding of skin permeability is essential to the success of cosmetic and pharmaceutical industries, which has financial and convenience benefits, but there are also more humanitarian applications. Certain pharmaceuticals and drugs are delivered via topical products which must permeate the skin to act and treat. Being able to predict the permeability of a drug computationally prior to expensive *in vitro* methods will be efficient, safer, and cost effective. Overall, creating an accurate skin permeability model has widespread and significant current applications and future potentials.

References: [1] Pecoraro, Beatrice, et al. "Predicting Skin Permeability by Means of Computational Approaches: Reliability and Caveats in Pharmaceutical Studies." Journal of Chemical Information and Modeling, vol. 59, no. 5, 2019, pp. 1759–1771.. [2]Neely, Brian J, et al. *Journal of Pharmaceutical Sciences*, U.S. National Library of Medicine, 2009, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2762392/. [3] Lian, Guoping, et al. "An Evaluation of Mathematical Models for Predicting Skin Permeability." Journal of Pharmaceutical Sciences, U.S. National Library of Medicine, Jan. 2008, https://www.ncbi.nlm.nih.gov/pubmed/17722002. [4] "ZINC15." ZINC, http://zinc.docking.org/. [5] Enciso, Marta, et al. "BioPPSy: An Open-Source Platform for QSAR/QSPR Analysis." PloS One, Public Library of Science, 10 Nov. 2016, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5104412/.[6]Nova® Dermal Phase Meter, Model DPM 9003 (NOVA Technology Corp., Gloucester, MA.) [7] cyberDERM RG1 Evaporimeter (cyberDERM, Broomall, PA.) [8] Sebumeter® SM 815 (Courage + Khazaka electronic GmbH, Köln, Germany) [9] Cutometer® MPA 580 (Courage + Khazaka electronic GmbH, Köln, Germany) [10] Themes, UFO. "Parenteral Routes of Drug Administration." Basicmedical Key, 14 Aug. 2016, https://basicmedicalkey.com/parenteral-routes-of-drug-administration/.