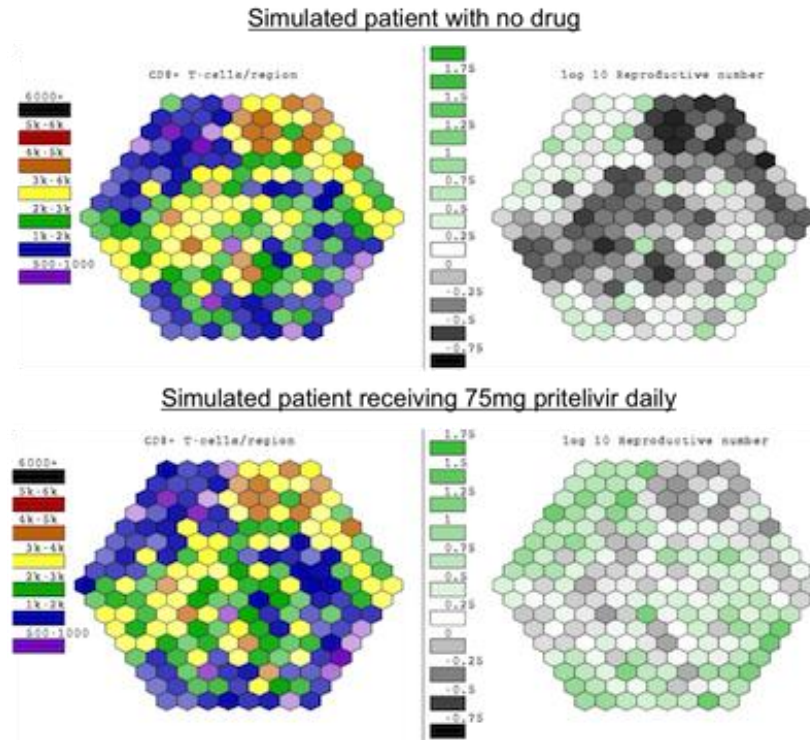# Finding the goldilocks dose for new antivirals

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J Herman

The left panels demonstrate heterogeneity of CD8 T cell densities in 200 genital tract micro regions in our mathematical model. Each region is intended to approximate a 5 mm diameter of tissue. The right panels demonstrate the reproductive number, which is inversely correlated with CD8+ T cell density. There is no potential for virus to spread extensively in grey or black regions, whereas green regions are not immunologically protected and virus has the potential to expand more extensively leading to lesions. The top two panels represent a simulated patient on no drug. The bottom two panels demonstrate a simulated patient on high dose pritelivir (75mg daily). While, there is an equivalent spatial distribution of CD8 T cell densities across the genital tract, the overall growth potential for virus is lower on high dose treatment: a higher percentage of regions are grey or black meaning that HSV reactivation would result in rapid viral elimination.

Image provided by Dr. Joshua Schiffer.

An often unappreciated facet of developing new therapeutics is the design and execution of clinical trials. Recently, predictive therapeutic biomarkers have become commonplace for trial design. By understanding the molecular drivers of disease researchers have developed drugs that target these molecular pathologies. Drugs like vemurafenib (for mutant BRAF in melanoma) are only beneficial to patients affected by specific genetic and molecular lesions. Identifying and enriching the clinical trial population for likely 'responders' results in a clear representation of drug efficacy. However, even with the best patient groups doctors must still identify optimal doses for a trial to demonstrate

efficacy. Often these are estimated from results of human cultured cells and mouse models of disease. Doctors must understand the lifespan of the compound in the human body, but also the drug concentration required to achieve the desired activity. When doses are too high they can cause unnecessary adverse effects, when doses are too low therapies are not efficacious. Dr. Joshua Schiffer and other Fred Hutch researchers in the Clinical Research and Vaccine and Infectious Disease Divisions are using mathematical models to identify optimum patient dosing for antiviral therapies. In a recent *Science Translational Medicine* article, researchers developed a mathematical model of herpes simplex virus (HSV2) suppression using the novel helicase inhibitor, pritelivir.

The model consists of three major sets of equations for the following: pharmacodynamics (PD), pharmacokinetics (PK), and viral kinetics in the absence of drug. PD equations represent the concentration dependent inhibition of pritelivir on HSV2 shedding, while PK equations model the distribution and serum lifespan of pritelivir. The FDA requires PK and PD data for licensure of all new therapeutics; however, in modeling and understanding HSV2 suppression, researchers found these equations alone could not explain results seen in clinical trials. "We identify that standard pharmacodynamics models do not accurately capture the true potency of antiviral drugs. To compute this potency in a dose response fashion requires synthesizing these models with equations that capture the natural features of infection," said Dr. Schiffer. A key component to modeling HSV2 infection was to include equations representing the infectious cycle of the virus. In an infected individual, a herpes outbreak occurs when virus is released from a neuronal pool and infects the genital tract. As virus incubates in this initial site of genital infection, it can then spread locally ultimately becoming a lesion. Researchers modeled this using 200 'micro regions' where virus could spread depending on the location and T cell activity of each micro region.

To validate this model, researchers compared its predictions to patient data from an in-depth phase II trial using pritelivir. In that trial patients were placed on four different pritelivir doses, then patients swabbed commonly infected areas every day for the one month trial. From these samples researchers measured HSV copy numbers and found that higher daily doses of pritelivir decreased viral shedding. The mathematical model was used to simulate over 100 trials that consistently predicted equivalent shedding rates to real patients at all four doses. The model also demonstrated that pritelivir decreased HSV shedding rates by indirectly decreasing viral cell-to-cell transmission. Upon a new outbreak there is a lag in the immune response required to clear the virus, if neighboring cells are infected during this lag time they will still be cleared, but if a spatially distant seeding occurs this will prolong the episode length. Thus by decreasing cell-to-cell transmission overall, pritelivir dramatically reduces these secondary ulcers and overall outbreak length.

In generating this mathematical model researchers also identified important new measures for choosing doses in clinical trials. Most doses are estimated from EC_{50} measures established with cultured human cells that may not fully represent in vivo activity. Researchers identified an 'in vivo EC_{50}' by testing many EC_{50} values (drug concentration in serum) in their model ranging from 0-100 ng/mL and comparing the results to the patient shedding numbers. It was found that pritelivir doses from 50-70 ng/mL best matched patient data, importantly these values range from 2-15 fold higher than in vitro studies. The model also revealed that pritelivir levels are very stable in patients, which translates to understanding patient response even with missed doses, "a surprising finding was that total cumulative weekly dose is highly predictive of shedding rate in a clinical trial population. Therefore, if we knew the number of missed doses, we could extrapolate the predictive shedding rate" said Dr. Schiffer.

While this model is specific to HSV2 and pritelivir, this approach can be adapted to other infectious diseases, as long as the viral kinetics are well understood. A model specific to one disease and drug combination would function very much like a therapeutic biomarker, and could increase the efficiency of clinical trials. "I am hopeful that our approach will allow the field to more accurately assess drug potency in vivo and therefore select dosing regimens more strategically. This could potentially lower expenditures on drug trials and also increase the likelihood of demonstrating therapeutic efficacy" said Dr. Schiffer.

Schiffer JT, Swan DA, Magaret A, Corey L, Wald A, Ossig J, Ruebsamen-Schaeff H, Stoelben S, Timmler B, Zimmermann H, Melhem MR, Van Wart SA, Rubino CM, Birkmann A. 2016. Mathematical modeling of herpes simplex virus-2 suppression with pritelivir predicts trial outcomes. *Sci Transl Med.* 8(324): 324ra15. Doi: 10.1126/scitranslmed.aad6654.