**Repurposing Of Fda-Approved Drugs: *In Silico* Discovery And First-In-Human Dose Prediction Of Potential Broad-Spectrum Inhibitors Targeting The Envelope Protein Of Dengue Virus**

**Quynh Nguyen Nhu Le1**, Phuong Thuy Viet Nguyen1.

Department of Pharmaceutical Information Technology, School of Pharmacy – University of Medicine and Pharmacy at Ho chi Minh City1, Ho Chi Minh City, Vietnam

**Background and aims.** Dengue fever is a neglected vector-borne disease caused by the dengue virus (DENV), with no specific treatment currently available.1 Among current targets in dengue drug discovery, the envelope protein (E protein) is one of the most promising broad-spectrum targets due to its pivotal role in pathogenesis and approximately 40% sequence similarity across *Flavivirus* species.2 Given the time and cost of de novo anti-DENV drug development, drug repurposing has emerged as a practical and efficient alternative approach. The aim of this study was to identify potential broad-spectrum DENV inhibitors through *in silico* approaches, including virtual screening and prediction of effective starting dose, to accelerate early-stage development of anti-DENV candidates.

**Methods.** The study focused on the E protein of DENV-1, -2, -3, -4, and 1189 drugs retrieved from the DrugBank database. Initially, virtual screening was performed through molecular docking and molecular dynamics simulations (MDs) using Autodock vina 1.1.2 and Gromacs 2023.5, respectively. Subsequently, physiologically based pharmacokinetic (PBPK) models were developed using GastroPlus X and evaluated for the selected compound. The binding free energy obtained from MDs was then used to estimate IC50 and IC90 values. The optimal starting dose was predicted by integrating the estimated inhibitory potency and systemic exposure predicted by the PBPK model.

**Results.** Through *in silico* screening, A1062 (Rimegepant) was identified as the most promising broad-spectrum anti-DENV inhibitor. The constructed and validated PBPK modelsuccessfully reproduced the observed pharmacokinetic profile of Rimegepant. The absolute estimated IC50 and IC90 values were 377.65 ng/mL and 3776.5 ng/mL, respectively. By integrating these values with systemic exposure simulations from the PBPK model, the optimal starting dose was predicted to be 350 mg once daily.

**Conclusion/Discussion.** Rimegepant was identified as a potential broad-spectrum inhibitor targeting the E protein of DENV, with a predicted starting dose of 350 mg administered once daily.

**Acknowledgements**

We would like to thank the University of Medicine and Pharmacy at Ho Chi Minh City, Vietnam for supporting for this research.

**References:**

(1) World Health Organization. Dengue - Global situation. Updated 30/05/2024. Accessed 30/03, 2025. https://www.who.int/emergencies/disease-outbreak-news/item/2024-DON518

(2) Rey FA. Dengue virus envelope glycoprotein structure: new insight into its interactions during viral entry. Proc Natl Acad Sci U S A. Jun 10 2003;100(12):6899-901. doi:10.1073/pnas.1332695100