Animal-Free Testing Strategy for Measuring Antivenom Potency

New Approach Methodology for Immediate Adoption

Traditionally, antivenom potency testing is done using mice; the gold standard method requires up to 300 mice per batch testing. **Transcell-Quantiphi's Digital Animal Replacement Technology (DART),** an *in vitro* New Approach Methodology (NAM) that leverages AI and ML-like *in silico* tools and utilizes human MicroPhysiological Systems (hMPS) model in the place of mice. Additionally, the AI-powered prediction model, complemented with Robotic Process Automation, publishes potency data obtained from the *in vitro* neutralization performed on the relevant hMPS platform. **It is an animal-free technology that delivers human-relevant potency values for clinical correlation and extra benefits to antivenom producers to reduce time, effort, and resources on batch releases.**

Preface

Preclinical research significantly influences the design of first-in-human studies, as the majority of drug candidates face failure during clinical trials and approval processes. In particular, phase 1 clinical trials experiences over 90% of these failures and it is believed that a robust preclinical program can mitigate last-minute unexpected debacles. Clinical trial data from 2010 to 2017 identified four primary reasons for the high failure rate: lack of clinical efficacy (40%-50%), unmanageable toxicity (30%), poor drug-like properties (10%-15%), and inadequate strategic planning, commercial viability (10%) (1). Despite extensive preclinical studies, greater percentages of drug candidates show unfavourable outcomes in the clinical trials eg., Recombinant VIIa for treating stroke exhibited no clinical benefits and increased thromboembolic events, while Aliskiren drug proposed to treat CHF (congestive heart failure) failed to reduce cardiovascular-related deaths. Such setbacks are observed across drugs, vaccines, biologics, and medical devices (2). Hence testings on animal models extrapolated to humans has become less reliable. The pharmaceutical sector needed a solution to assess the safety and efficacy of the goods intended for human consumption, hence it is imperative to adopt human-relevant research methodologies and technologies.

To address these growing concerns over animal testings and its relevance to human inferences, various organizations and regulatory bodies proposed alternatives during the discovery and developmental processes with ***special recommendations given by WHO like bodies to relook into the routine testings undertaken for batch releases****. The EU Commission advocates a 3Rs strategy (replacement, reduction, refinement) for animal testings (3). The FDA Modernization Act 2.0 integrates computer models and in silico technologies into drug development (4) and has coined the term New Approach Methodologies (NAMs), an alternative to traditional animal-based assays. Canada passed Bill C-47, Budget Implementation Act, 2023, banning cosmetic animal testings and encouraging non-animal methods in drug research (5). The Indian Government has also amended the New Drugs and Clinical Trial Rules (2023) to encourage advanced computational techniques and replace*

animal testing (6). **We are of the opinion that prioritizing NAMs has the potential to enhance regulatory decisions that safeguard human health, as they can mimic human biology and offer mechanistic insights into toxicity risks**.

Transcell-Quantiphi and Digital Animal Replacement Technology

Transcell-Quantiphi's Digital Animal Replacement Technology (DART) is a **revolutionary approach** that combines human MicroPhysiological Systems (hMPS), that provide and support relevant information of definite organ or tissue and Artificial Intelligence (AI)/Machine Learning (ML) tools to create a non-animal assay system for assessing safety risks and efficacy measurements of the pharma/biological products. Here, the DART application eases the problem of routine animal-based testings in the antivenom industry for their batch releases into the market. Antivenom potency is an intrinsic value that is dependent on the immunoglobulin content as well as the capacity of the dose that neutralizes the venom activity, hence its potency value changes. Despite these challenges, antivenom testings are required before the product can be released into the market given that the potency varies for each batch. As this is a mandatory exercise for the antivenom industry enabling healthcare providers and drug regulatory agencies to determine the clinical dose for envenomation, DART can be a viable and intelligent option for adoption ensuring a animal free assessment throughout the process.

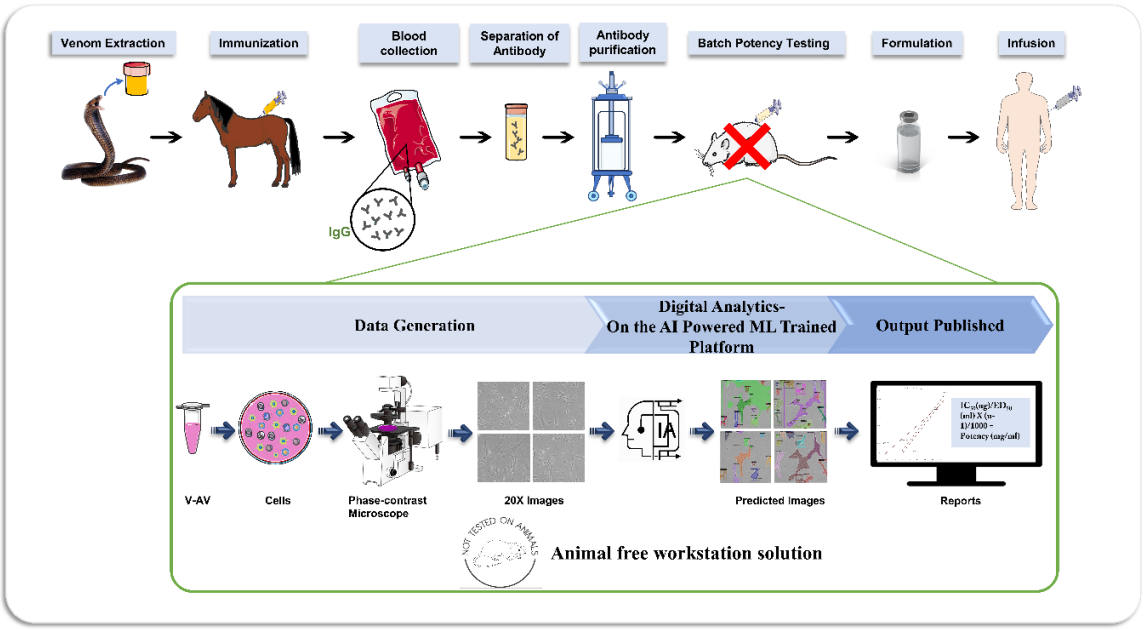

Figure: Intervention of DART in the Antivenom industry. V-AV: Venom-Antivenom mixture

Authored By: Vasanthi Dasari, Praveen Parkali, Swati Shukla - Transcell

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