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Psoralen +UVA (PUVA) Inactivation as an Agile Vaccine Platform for Multi-Pathogen Force Health Protection

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Disclaimer

All opinions expressed in this lecture are mine and do not necessarily reflect the opinions of Advocate Health, Wake Forest University School of Medicine, or the Veterans Administration.

THE PROBLEM

Why Platform Technologies Matter

Military infectious disease threats continue to evolve.

1. **Emerging pathogens**
   New threats appear faster than programs can be built
2. **Need rapid response**
   Timelines measured in months, not years
3. **Need scalable manufacturing**
   Shared, repeatable production workflows
4. **Need broad immune responses**
   Durable, protective, cross-reactive immunity

Whole-cell Inactivation is a proven concept. Can it be optimized for better effect?

MECHANISM

The PUVA Concept

Selectively destroy the genome while preserving native antigen structure.

1
Pathogen
Whole organism, intact

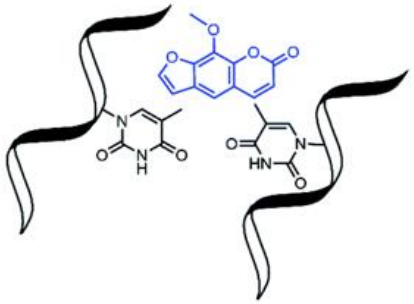
2
Psoralen intercalates nucleic acid
Small molecule slips between base pairs

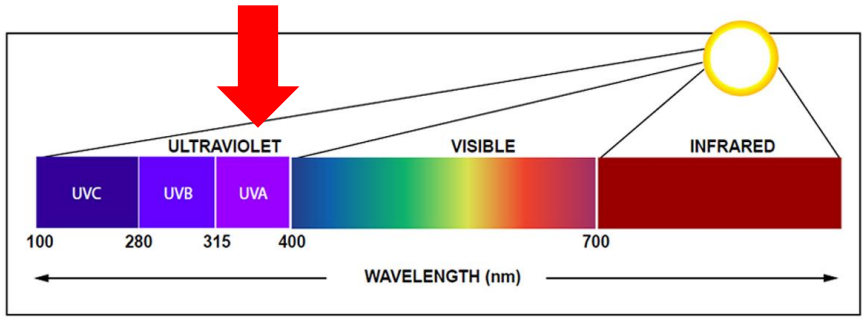
3
365-nm UVA
Long-wave illumination triggers the reaction

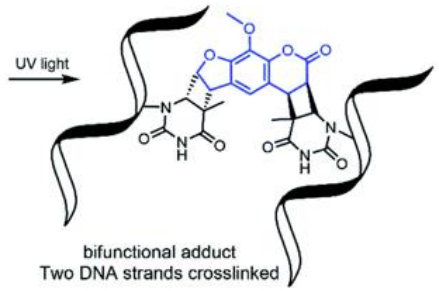
4
Permanent nucleic acid crosslinks
Covalent adducts lock the genome

5
Replication eliminated
No infectivity remains

6
Surface proteins remain structurally intact
Epitopes preserved







Selective nucleic acid damage. Native antigen preservation.

THE DIFFERENTIATOR

Why Preservation Matters

Traditional Inactivation

Heat / formalin / BPA

- ✕ Protein modification
- ✕ Conformational epitope loss

▼

Reduced neutralization

PUVA

Psoralen + 365-nm UVA

- ✓ Native conformation preserved
- ✓ Whole-pathogen antigen display

▼

Broad immune recognition

The objective is not simply inactivation — it is preservation of immunogenicity.

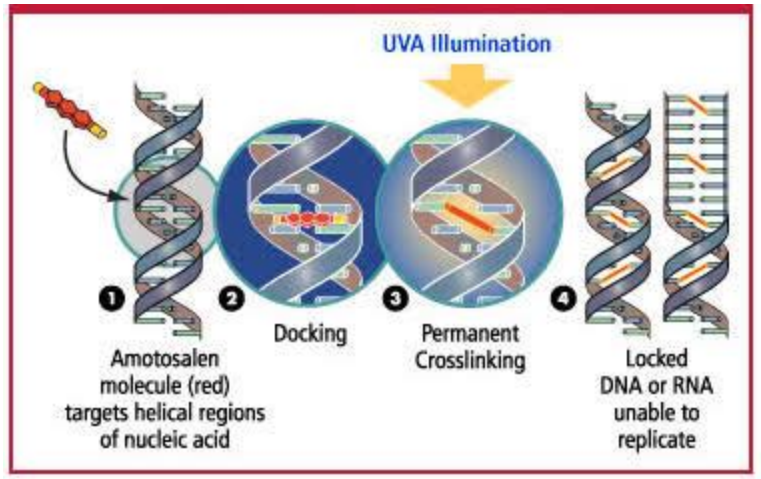
SAFETY HISTORY

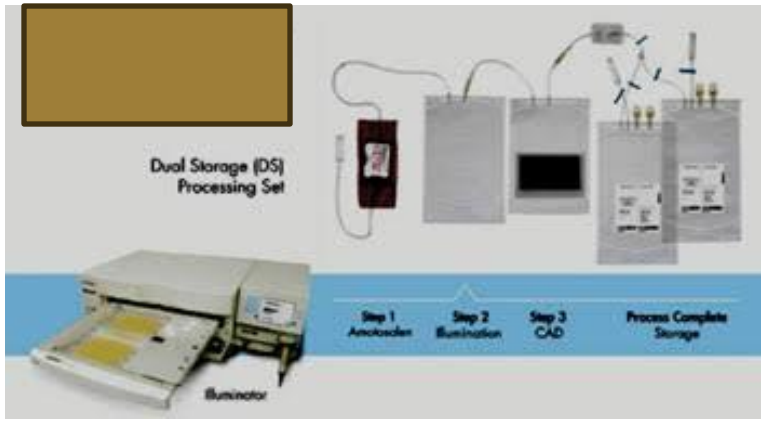
A Track Record Built in Blood Safety

a strong springboard for vaccines

From transfusion medicine to vaccine platform

- Amotosalen (psoralen) + UVA pathogen-reduction technology ("Helinx" / INTERCEPT) is used clinically to inactivate viruses, bacteria, and parasites in platelet and plasma units
- Selectively targets nucleic acids of contaminating pathogens and residual leukocytes while sparing the therapeutic function of the blood product.
- Decades of transfusion-medicine experience provide an established human safety profile
- Redfield et al. (1981):
  - HSV and influenza lost all measurable infectivity after psoralen-UVA
  - retained full antigenicity





The INTERCEPT Blood System for Platelets

Infect Immun. 1981 Jun;32(3):1216-26.

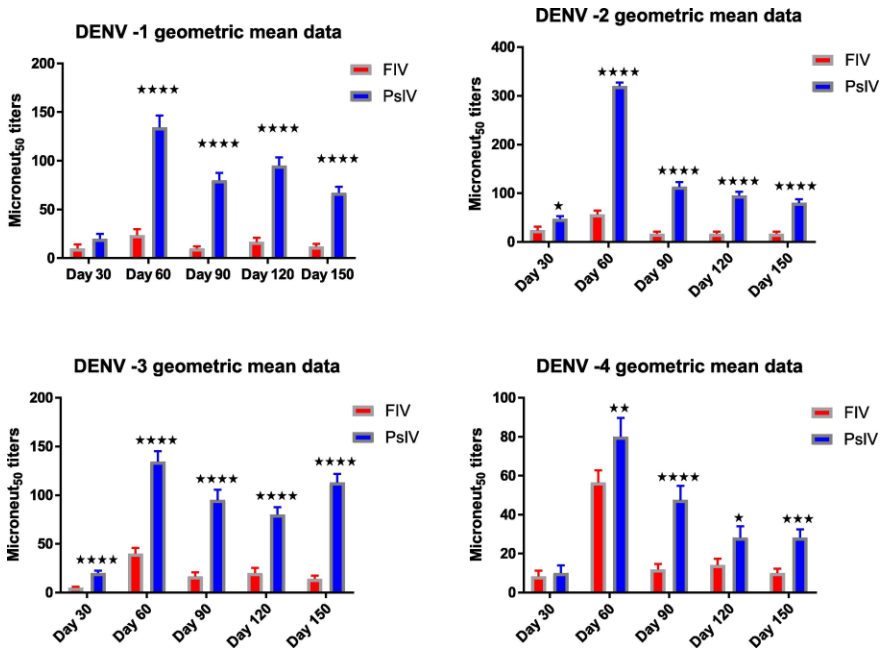
EVIDENCE

Validation in Dengue

- Preparation of vaccine
  - Immunogenic in mice (Clin Vaccine Immunol. 2009 Dec 9;17(2):304–306)
  - Immunogenic and decreased viremia in NHP (Vaccine 2011 March 24; 29(15):2691-2696)
- Monovalent and Tetravalent vaccines compared with formalin
  - Equal or more immunogenic in mice and NHP (Vaccine. 2020 April 9; 38(17):3313-3320)

Equivalent or higher
neutralizing antibodies vs. formalin

Superior responses
in nonhuman primates



Proof of concept that antigen preservation results in improved immune response

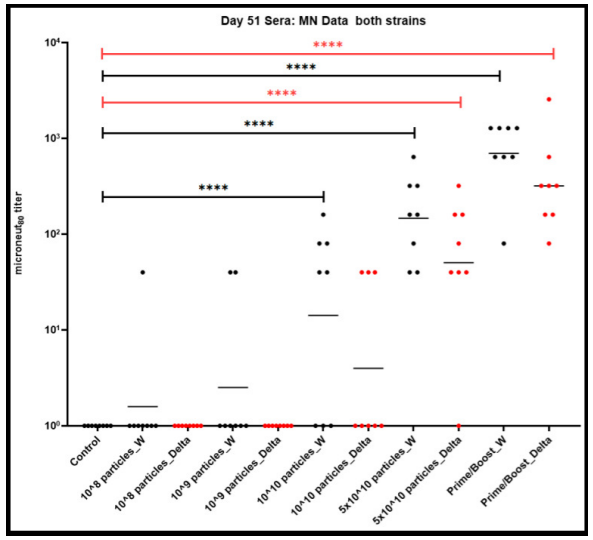
EVIDENCE

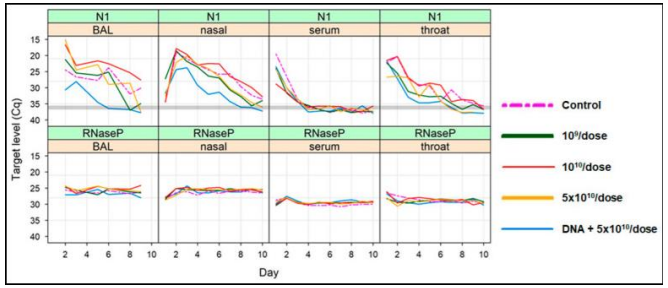
Validation in SARS-CoV-2

- Immunogenic in mice (Pathogens. 2021 May 19;10(5):626.)
- Evaluated in NHP with Advax-CpG adjuvant and as a booster following DNA vaccination (Vaccines. 2024 Apr 24;12(5):451)
  - Induced dose-dependent neutralizing antibody responses against both the SARS-CoV-2 Washington strain and Delta variant.
  - DNA prime + PsIV boost strategy generated the strongest antibody.
  - Boosted animals rapidly cleared Delta variant infection following intranasal viral challenge.
  - Supports Advax-CpG-adjuvanted PsIV as both a standalone vaccine and booster with potential protection against emerging SARS-CoV-2 variants.

EVIDENCE

Validation in SARS-CoV-2





Dose-dependent immunity

Titers scaled with antigen dose

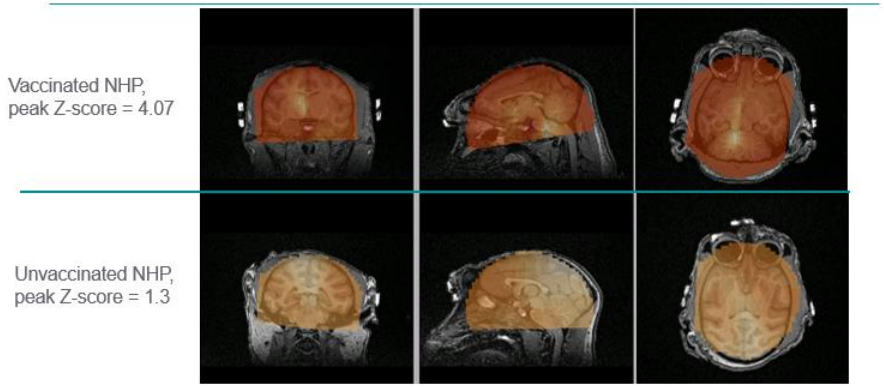
DNA prime enhanced responses

Prime-boost outperformed either alone

Rapid viral clearance

Vaccinated animals cleared virus after challenge

NHP Resting State MEG Maps



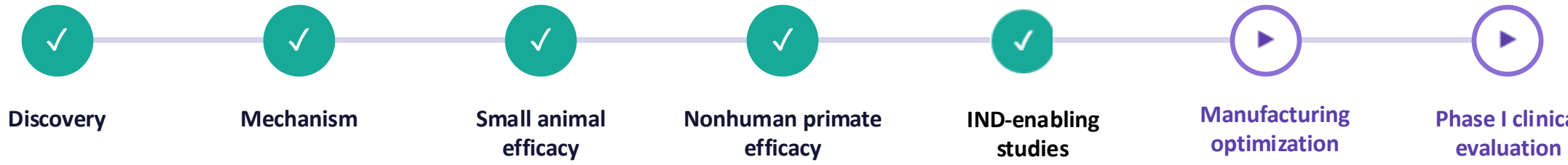
Relative values shown for illustration — replace with study figure.

Protection extended beyond immunogenicity to challenge studies.

Vaccines. 2024 Apr 24;12(5):451

WHERE WE STAND

Technology Readiness



COMPLETE

IN PROGRESS / PLANNED

DoD investment has advanced the platform from concept toward clinical translation.

Extending PUVA to Bacterial Pathogens

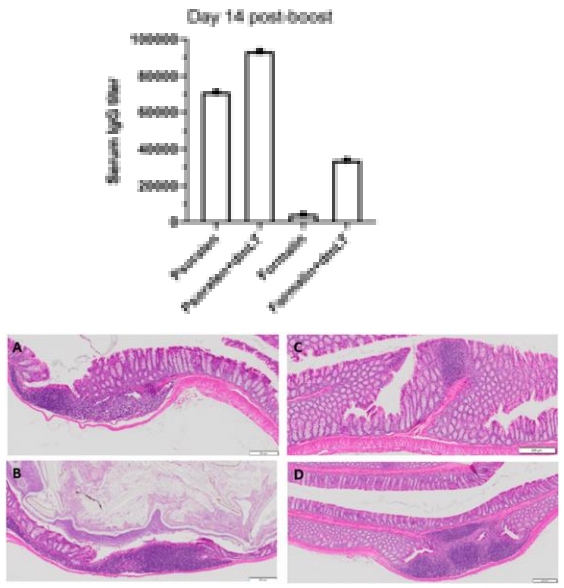
Same chemistry, new target

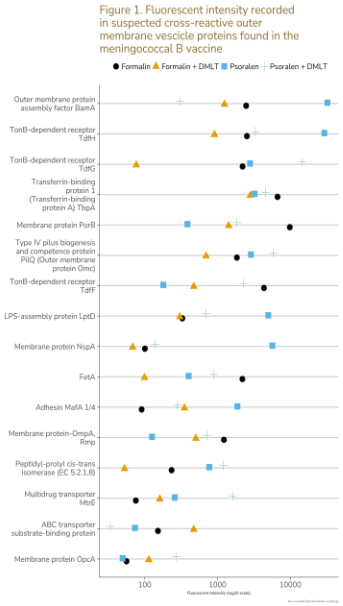
Psoralen intercalates and crosslinks bacterial DNA on UVA exposure just as it does with viral genomes — blocking replication while leaving cell-surface antigens structurally intact.

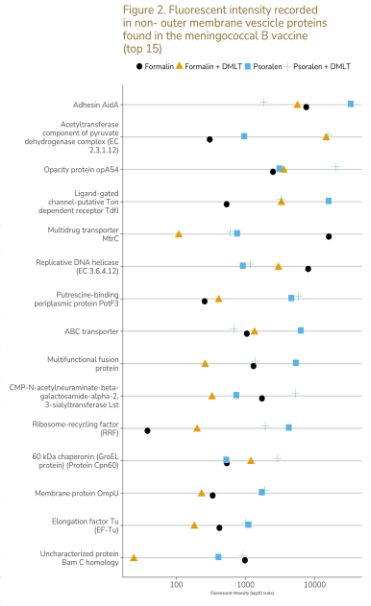
“Killed but Metabolically Active” (KBMA)

With optimized dosing, organisms are rendered fully non-replicating and non-pathogenic yet retain enough metabolic activity to be more immunostimulatory than heat- or formalin-killed bacterins.

- <u>Pathogens inactivated</u>
  - ETEC, UPEC
  - Campylobacter
  - Shigella
  - Neisseria
- All equal or better immunogenicity compared with formalin in mice and NHP







Beyond Vaccines: KBMA Probiotics for Wound Protection

A therapeutic extension of the same inactivation chemistry

1

Select protective strain

A probiotic bacterial strain with antimicrobial / wound-healing activity is chosen as the chassis.

2

PUVA-inactivate

The strain is rendered non-replicating by psoralen-UVA — metabolic and antimicrobial activity is preserved.

3

Apply at the wound

Delivered locally to compete with and inhibit pathogens without the infection risk of a live organism.

4

Protect against infection

Goal: reduce wound-infection rates in at-risk patients

Why PUVA fits: it removes replicative/infective risk from a live bacterial therapeutic while leaving the very metabolic machinery responsible for its protective activity functionally intact.

THE BIG PICTURE

1 Viral Vaccines

Dengue, SARS-CoV-2, and other viruses – a pipeline built on a shared purification-and-inactivation workflow.

2 Bacterial Vaccines

Whole-cell KBMA vaccines against enteric and other bacterial threats, preserving multi-antigen, native-conformation immunogens.

3 Optimized Antigen Presentation

PUVA-inactivated pathogens as immunogens for generating high-quality polyclonal antibodies against native surface targets.

4 KBMA Probiotics

Non-replicating, metabolically active probiotic strains for localized protection against wound infection.

SUMMARY

1. Decades-proven human safety in blood-product pathogen reduction
2. Nucleic-acid-selective mechanism preserves native, conformational epitopes
3. Demonstrated superiority to formalin inactivation in dengue and SARS-CoV-2 NHP studies
4. Extends naturally from viruses to bacteria to probiotic therapeutics

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PATENTS

Psoralen-inactivated viral vaccine and method of preparation — Porter

Psoralen-inactivated Coronavirus Vaccine and Method of Preparation — NMRC provisional, filed 1 Dec 2020

Gonorrhea vaccine - Wake Forest provisional

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