MHC class I peptide libraries for the prevention & treatment of viral and bacterial infectious diseases by innovative multi-epitope T cell adaptive vaccines

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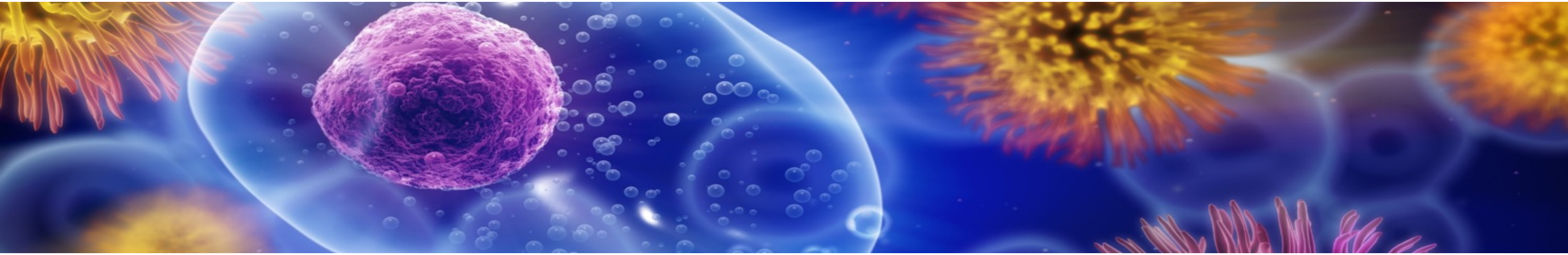

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Executive Summary

Emergex Vaccines Holding Limited ("Emergex")

Positively Impacting Human Health through the Development of Next Generation **T cell Adaptive Vaccines**

Emergex is a fully integrated, international **biopharmaceutical** company with in-house **R&D and GMP manufacturing** capabilities located in Abingdon, UK and Doylestown, PA

2016
Year established

US$58 bn
Core programs market opportunity

8+
Target indications

Manufacturing capability

37
Employees

2 Phase I Clinical Trials completed

Partnerships and Collaborations

CHUV · FIOCRUZ · NUS National University of Singapore · George Mason University · National Healthcare Group · ATCC · Duke-NUS Medical School · Instituto de Tecnologia em Imunobiológicos Bio-Manguinhos · UNIL | Université de Lausanne · Institute of Molecular and Cell Biology IMCB

Agenda

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- Background: Protective immunity and T cell adaptive vaccines
- Ligandome library platform
- Case study 1: Chikungunya virus vaccine
- Case study 2: Dengue virus vaccine
- Summary

Vaccines: Past, Today, and Tomorrow…

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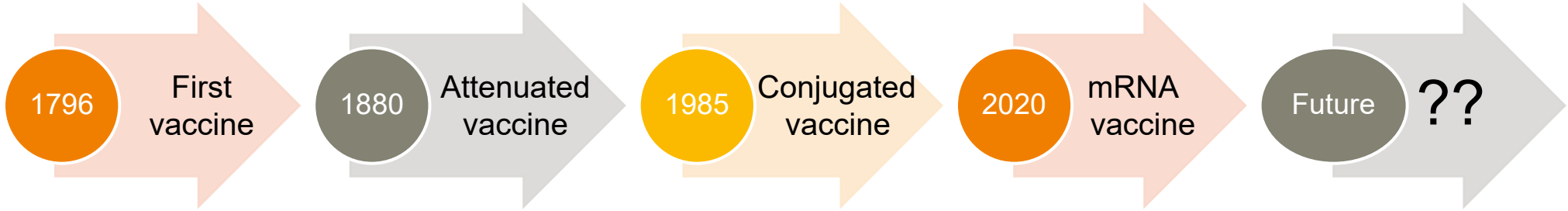

Ideal "next generation" vaccine candidate:

- Broad protection
- Durable immunity
- Rapid and cost-effective manufacture
- Favorable logistics

Overview of T cell adaptive vaccines

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Offers sterilising immunity

T cell priming vaccines can **provide sterilising immunity** and prevent intra-host and inter-host transmission as well as preventing virus-associated disease, unlike antibody-based vaccines

- This is due to T cell priming vaccines' generation of CD8+ T cells that **do not require productive infection** of cells or even de novo protein synthesis to recognize and eliminate infected cells
- T cell priming leads to development of circulating T cells with **tissue-homing potential** for frontline defence against pathogen

Cross-protection

T cell priming vaccines can be **cross-protective to a family of viruses** (e.g., coronaviridae, flaviviruses, etc.) in contrast to antibody-based vaccines that are serotype-specific

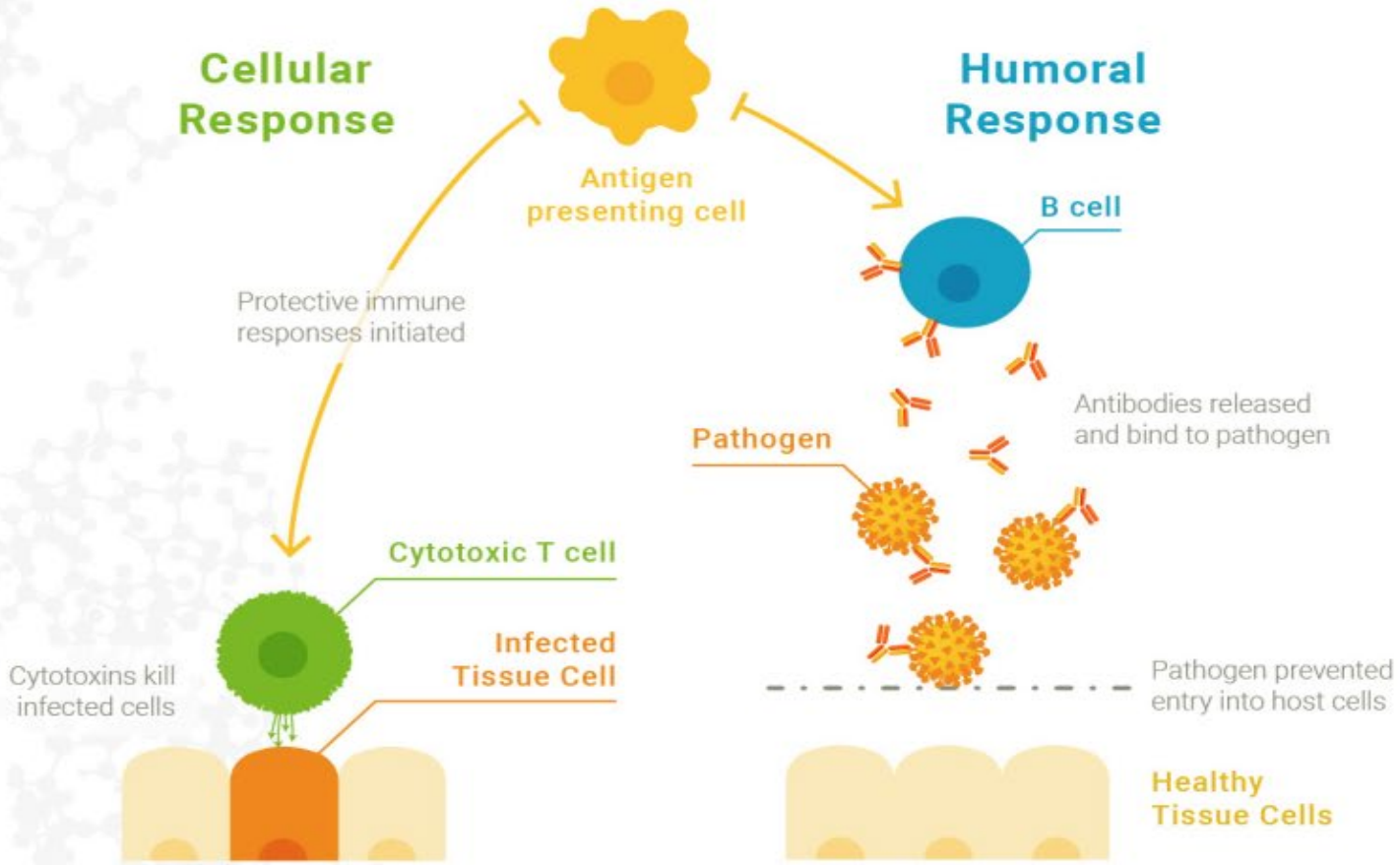
Efficacy against viral mutation

T cell priming vaccines are **mutation agnostic** due to the degeneracy of the class I epitope ligandome (i.e., repertoire of HLA class I-bound peptides expressed on infected cells)

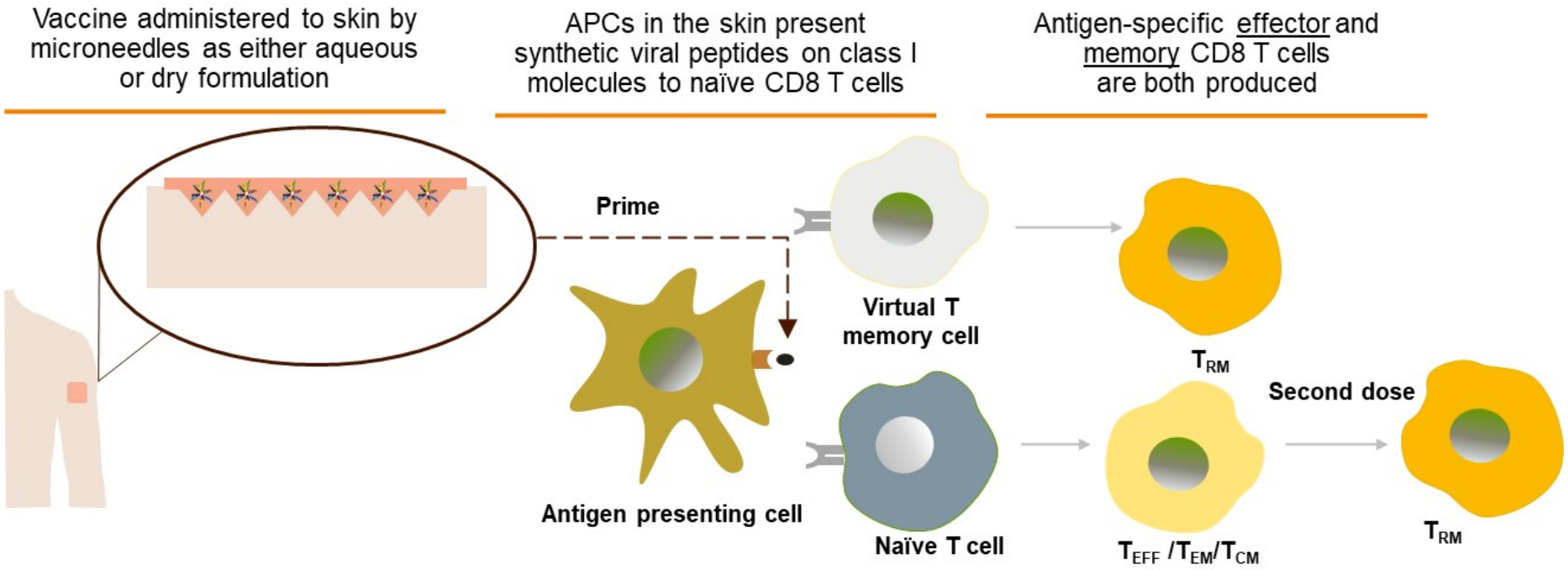
- Mutations in antibody-binding sites on surface antigens are under selective pressure, in contrast to T-cell peptide mutations which are stochastically generated

Protective immunity against infection involves humoral and cell-mediated immunity

- Antigen presenting cells 'prime' naïve CD8+ T cells to recognise specific non-self (viral) peptides expressed by infected cells – these become antigen-specific 'effector' T cells
- CD8+ T cells 'recognise' infected cells which express viral peptides ('signals' of infection) – no direct interaction with the virus and less likely to be impacted by viral mutation (conserved viral peptides are still presented on infected cell surfaces)
- CD8+ T cells interact with infected cells (the centres of viral replication) and kill the infected cells (apoptosis)



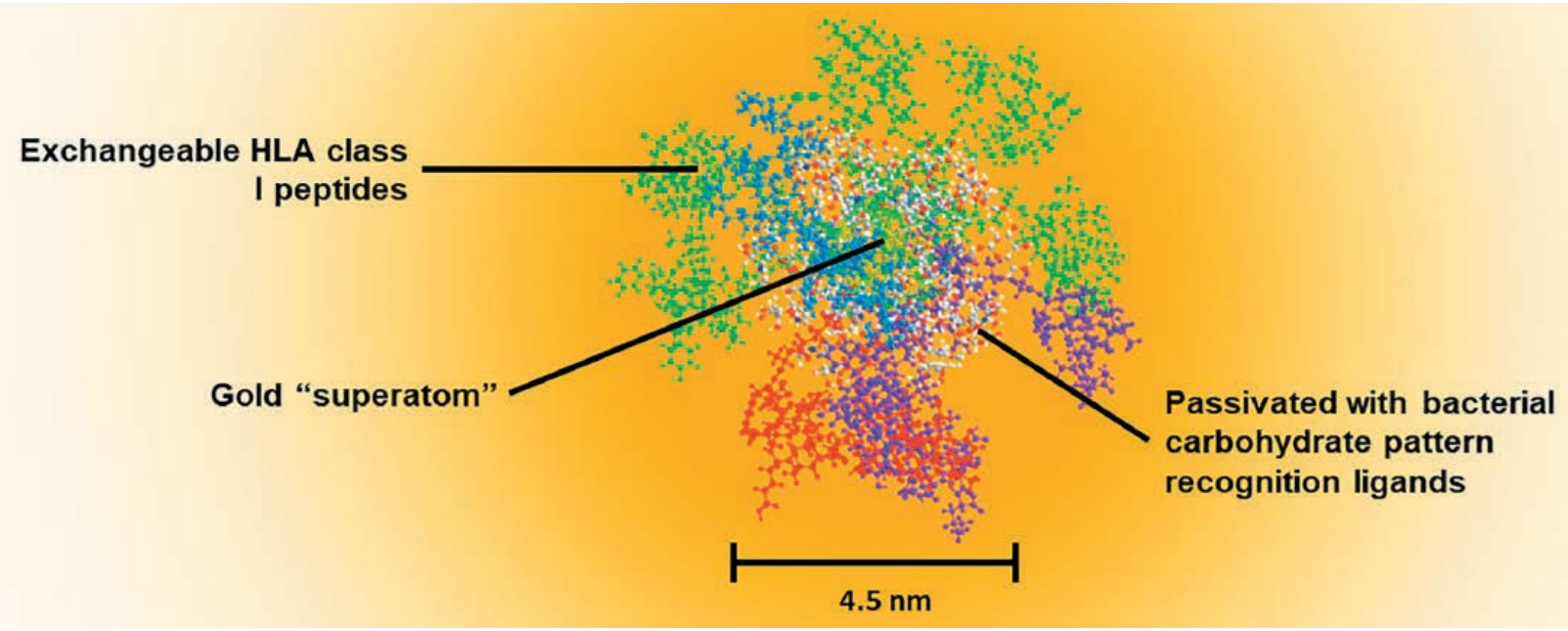
Next generation T cell adaptive vaccines



Long lasting memory T cells generated that are ready to respond to future infection

- CD8+ memory T cells become tissue-resident – ready to abort an infection prior to active viral replication
- Subsequent exposure to the pathogen results in a rapid cellular immune response; a natural humoral response follows, providing comprehensive immunologic protection
- CD8+ T memory cells have been shown to be active for decades (SARS-1 infection)

A Novel Vaccine Delivery Platform: Passivated gold nanoparticle



- **Central gold superatom** contributes to deactivation of enzymatic activity at the surface layer of the superatom
- **Bacterial mimetic carbohydrates** that are known pattern recognition elements and render the particle water-soluble
- **Exchangeable MHC Class I peptides**

Challenges for peptide discovery

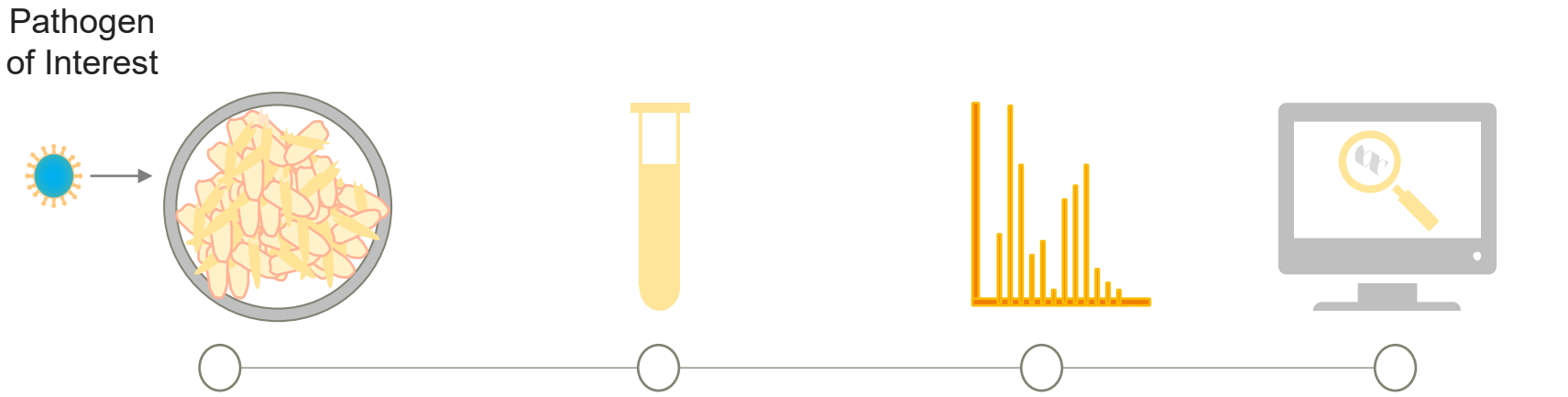
- Low abundance presenting on the cell surface
- Difficult to capture and enrich during pathogen intrusion
- A valid system to characterize peptide candidates
- Predictive algorithms often do not reflect natural infection

AND

The Emergex approach is……

Empirical generation of MHC Class I expression '**ligandome library**' of pathogen-derived protein fragments

Ligandome library generation



Case study:
Chikungunya (CHIKV) virus vaccine

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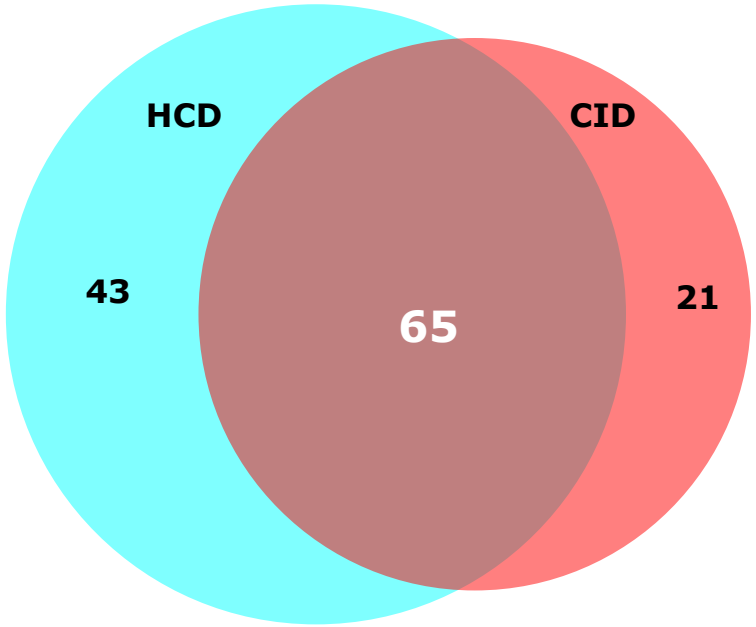
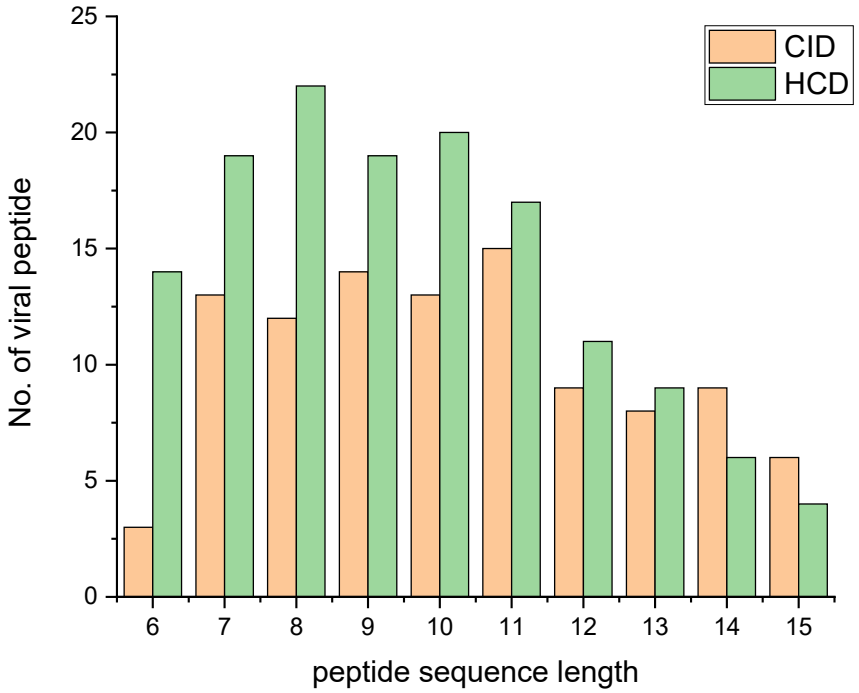
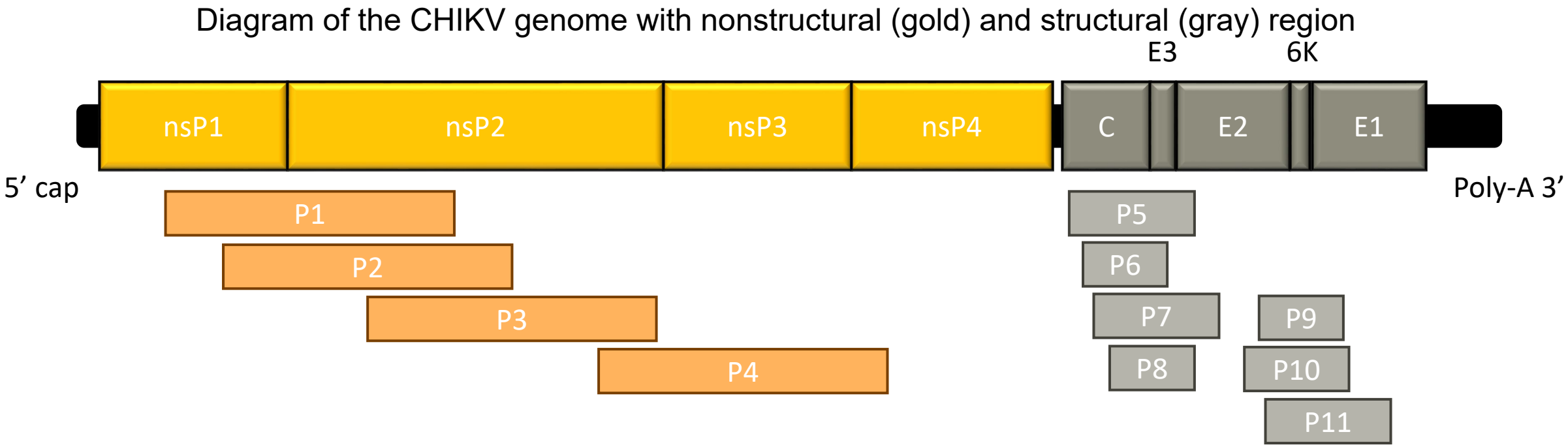


Summary of CHIKV specific peptides following viral infection using different fragmentation methods



Distribution of CHIKV specific peptides using different fragmentation methods

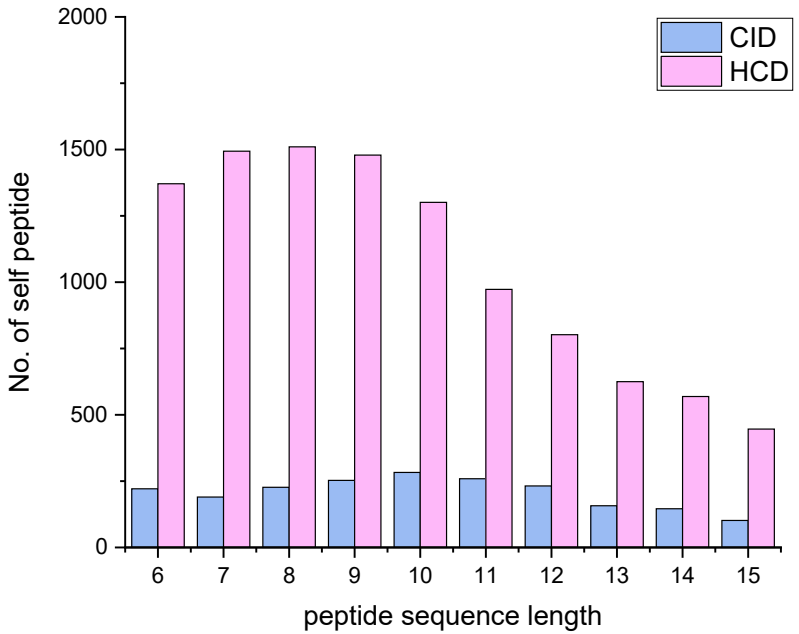
MHC class I viral peptides



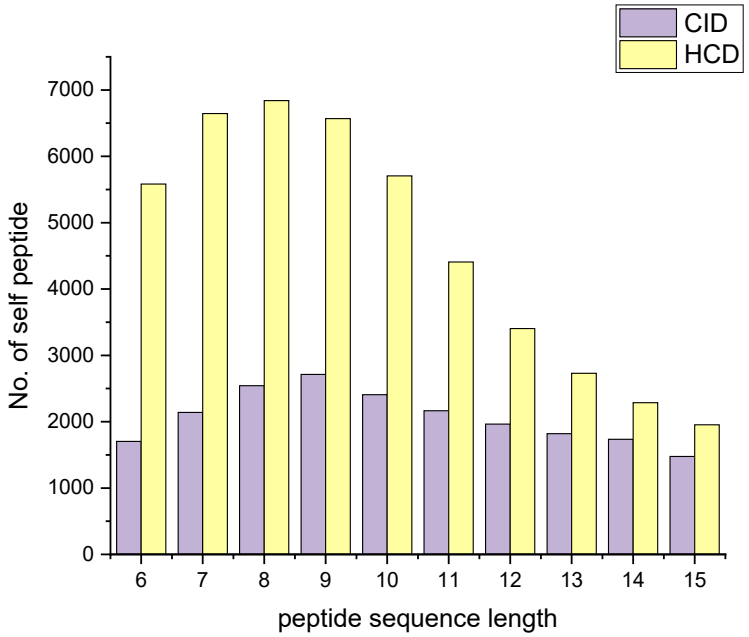
- Viral peptides have been identified in both non-structural and structural protein regions
- Hotspot regions are observed in structural protein peptide pool

Figure inspiration: Natrajan MS, Rojas A, Waggoner JJ. Beyond Fever and Pain: Diagnostic Methods for Chikungunya Virus. J Clin Microbiol. 2019 May 24;57(6):e00350-19. doi: 10.1128/JCM.00350-19. PMID: 30995993; PMCID: PMC6535601.

Self peptides: host immunity changes



Un-infected group



Infection group

Distribution of self peptide sequence length between un-infected and infected samples

Host cell proteome

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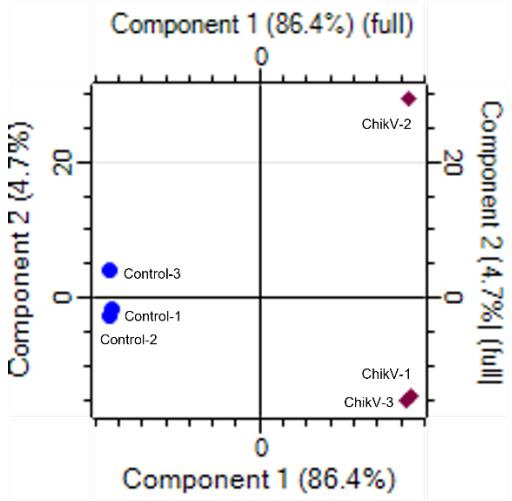
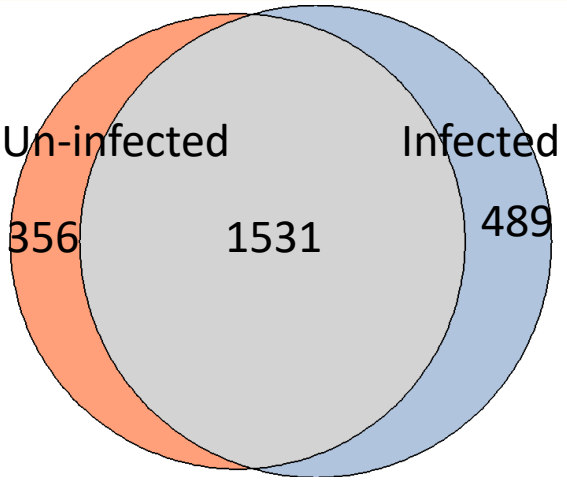
Scree plot from the principal component analysis (PCA) between un-infected and infected samples

a.



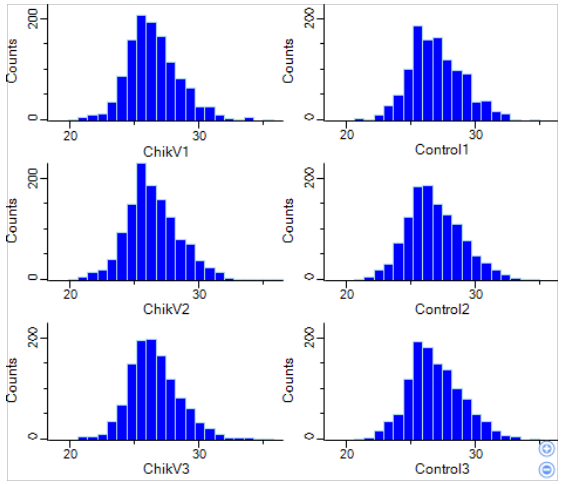
b.



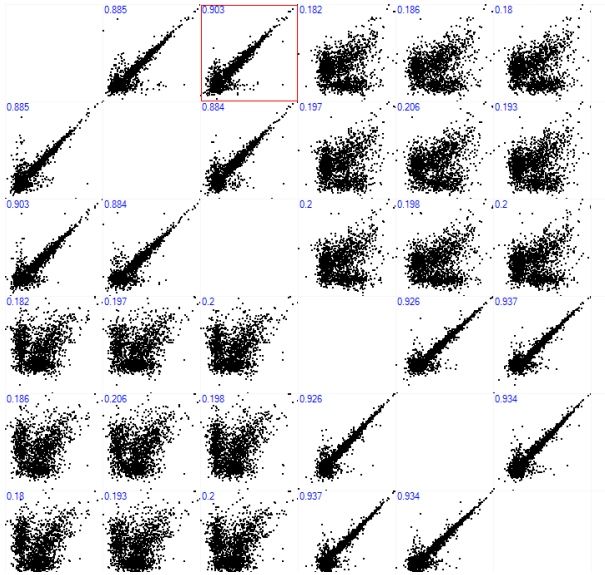
Venn diagram showing the overlap and unique number of protein identifications in un-infected and infected samples

Histogram of intensities of the proteins identified in un-infected and infected samples

c.



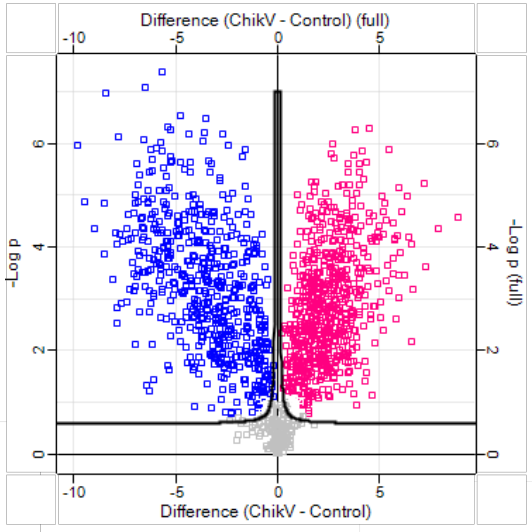
d.



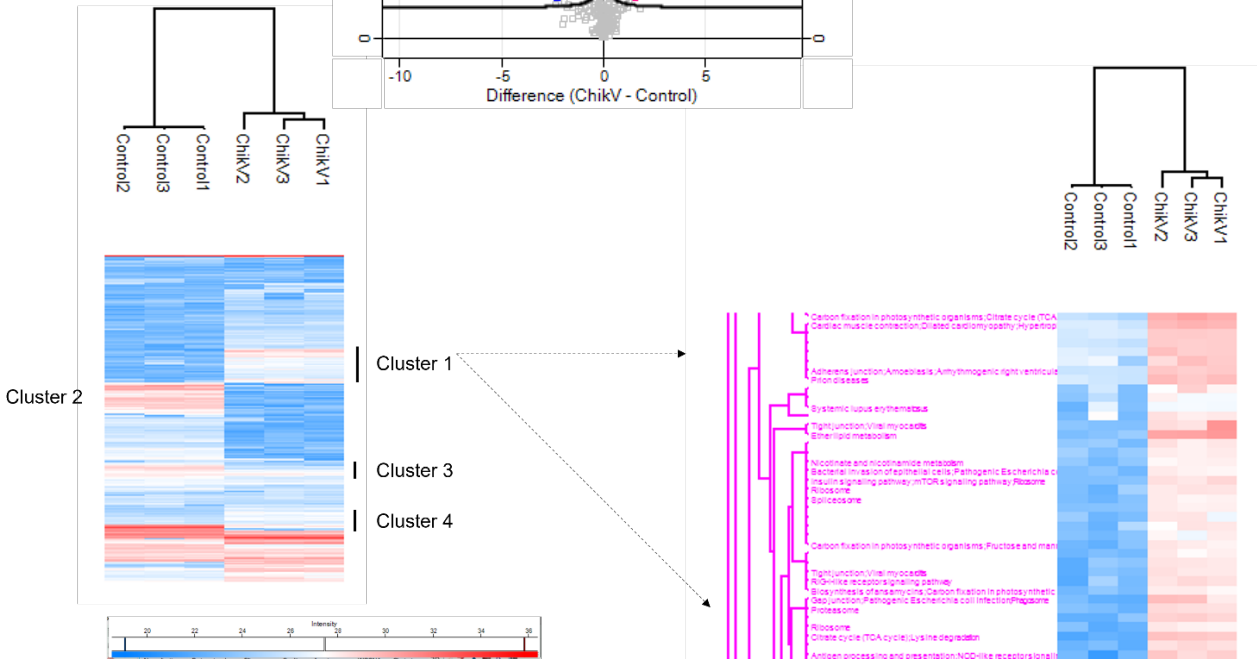
Pearson correlation coefficient analysis between un-infected and infected samples

Host cell proteome

a. Volcano plot showing the up- or down-regulated proteins upon viral infection (P<0.05)



b. Heat map showing the hierarchical cluster analysis of the whole cell proteome



Case study:
Dengue virus vaccine (clinical trial)

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Intradermal delivery of a T Cell Adaptive Vaccine using a microneedle device

Design

- Phase I, double-blind, randomized, vehicle-controlled, dose-finding
- Stage 1 of a 2-stage adaptive clinical trial

Objectives

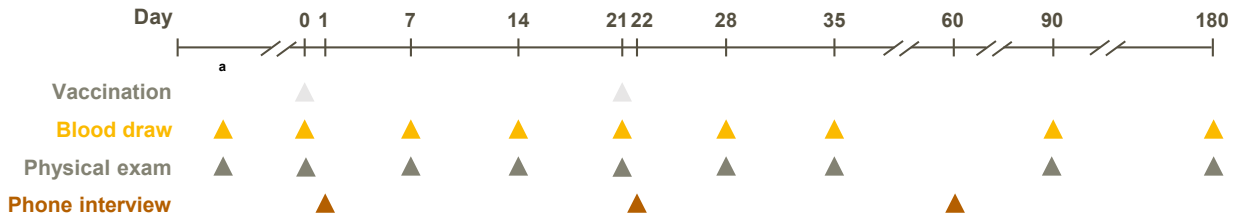
- **Primary**: Evaluate the safety and reactogenicity of two intradermal injections of two different doses of PepGNP-Dengue administered to healthy volunteers*
- **Secondary**: (1) Assess evidence of a CD8 T-Cell-mediated immune response as a 'surrogate of protection' against severe Dengue disease. (2) Check the *absence* of an antibody-mediated response

Treatment Arms

Heathy adults (18–45 years)

- LD vaccine
- LD vehicle
- HD vaccine
- HD vehicle

Trial Schedule†



[a]Screening period from day -60 to day -1

Positive Results From Phase I Clinical Trial

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- The vaccine was **well tolerated**, with no serious adverse events reported
- The vaccine was immunogenic, and capable of eliciting **vaccine-specific effector and memory CD8+ T-Cells** against dengue virus
- **Proof-of-concept** in a clinical setting, a vaccine comprising specific peptides attached to a nanoparticle carrier can successfully induce virus-specific CD8+ T-Cell responses

Why the Results of This Clinical Trial Are Important

Memory T-Cell Presence is Crucial for Protection vs Disease

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- Following encounter with APC presenting MHC Class I-peptide, asymmetric division of activated CD8 T-Cells gives rise to effector T-Cells and memory T-Cells

- Memory CD8 T-Cells confer host protection against future infection
  - Whilst effector cells undergo robust contraction, memory cells persist long-term and are capable of vigorous proliferation following antigen re-encounter
  - Compared to naïve cells of the same antigen-specificity, memory CD8 T-Cells persist in greater numbers, can populate peripheral organs, are poised to immediately proliferate, will execute cytotoxic functions, and secrete effector cytokines upon antigen re-encounter

- The memory T-Cell pool consists of a heterogenous population of cells, with different memory cell subsets defined by their phenotype, function and anatomical location/trafficking

Martin MD, Badovinac VP. Front Immunol 2018;9:2692

Conclusions

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- Viral- and bacterial-derived ligandomes may provide a new approach to address rapidly mutating or even potentially unknown pathogens by specifically targeting broadly protective T cell responses.
- Peptide libraries from a diversity of viral and bacterial pathogens have been generated including Flavivirus (Dengue, Yellow Fever, Zika), Betacoronavirus (SARS-CoV-1, SARS-CoV-2), Alphavirus (Chikungunya), Enterovirus (Hand, foot, and mouth disease), Influenza A, and Francisella tularensis.
- Libraries contain several hundred to several thousand peptides ranging in size from 8 to 15mers with variation observed in infectious titer and post-infection timeframe.
- T cell adaptive vaccines naNO-Dengue and naNO-COVID have completed phase I clinical trials with positive results.
- The core ligandome technology can be applied to develop innovative and sustainable medical countermeasures for priority biothreat and biodefense pathogens.

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Please also visit Emergex's

Poster #115

Thank you!