CODAGENIX

A Codon-Pair Deoptimized, Live-Attenuated Dengue Vaccine with Balanced Immunogenicity & Protection Across Preclinical Models

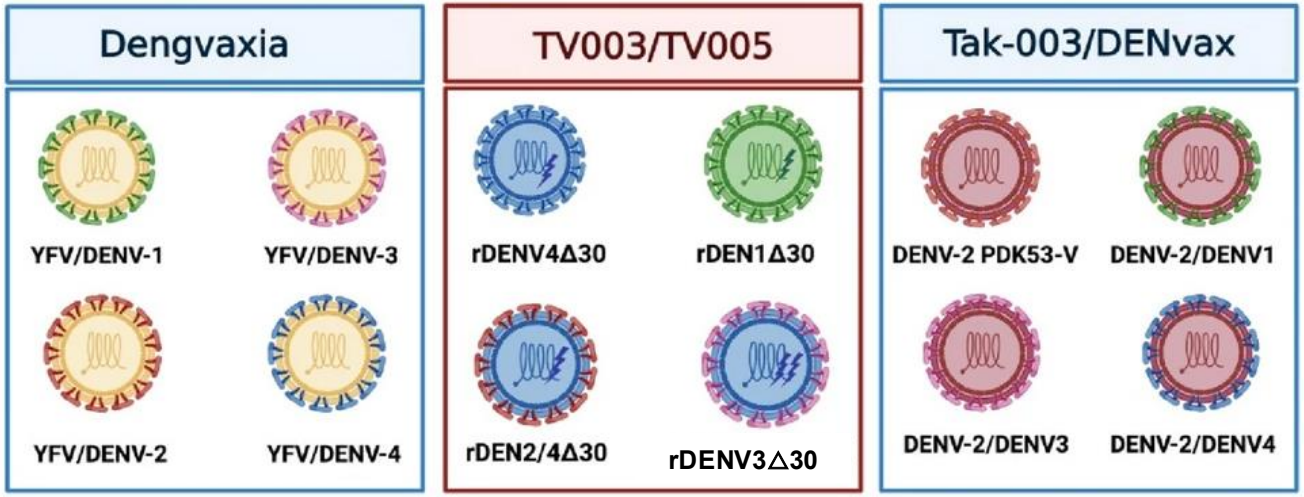
Steffen Mueller, Ph.D. (Founder & Chief Scientific Officer, Codagenix Inc.)

MHSRS 2026, August 4, Gaylord Palms Resort & Convention Center

Disclosures

- Steffen Mueller, PhD - Stock ownership: Codagenix, Inc.; Employment: Codagenix, Inc.

Licensed and Candidate Dengue vaccines are chimeric in some form



Dengvaxia (Sanofi) yellow fever backbone YFV prM and E replaced by homologous genes from each of DENV serotypes – DISCONTINUED (due to lack of efficacy & risk of Antibody Dependent Enhancement in naive individuals)

Tak-003/DENVax (Takeda) based on DENV2 strain (PDK-53-V) prM and E replaced by the homologous genes from each of DENV serotypes; all but DENV2 component are chimeras (DENV2 attenuated backbone) – US BLA withdrawn[1] while approved in EU, UK, Brazil, Argentina, Indonesia, and Thailand

TV003/TV005 (NIH/ Butantan/ Merck) deletion of 30 nt in TL2 stem-loop of 3′-UTR of DENV4 and DENV1 (rDEN4Δ30 and rDEN1Δ30), DENV2 strain chimerized with rDEN4Δ30 backbone – approved in Brazil, but temporarily suspended due to safety signal[2]

1. https://www.takeda.com/newsroom/statements/2023/takeda-announces-voluntary-withdrawal-of-US-biologics-license-application-for-dengue-vaccine-candidate-TAK-003/
2. Taylor L. *Dengue: Brazil suspends rollout of new vaccine after two deaths.* **BMJ.** 2026;393:e205610. doi:10.1136/bmj-2026-205610.

Global Health still needs a better DENV Vaccine

TAK-003 (Takeda)

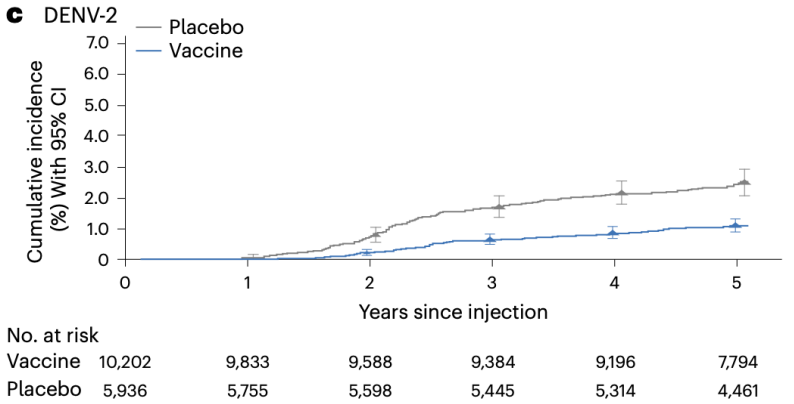
Takeda long-term Phase 3 study	Efficacy after 4.5 years[2] (w/o prior exposure)
DENV1	45.4% (26.1 to 59.7)
DENV2	88.1% (78.6 to 93.3)
DENV3	-15.5% (-108.2 to 35.9)
DENV4	-105.6% (-628.7 to 42.0)

1. https://www.takeda.com/newsroom/statements/2023/takeda-announces-voluntary-withdrawal-of-US-biologics-license-application-for-dengue-vaccine-candidate-TAK-003/
2. Tricou et al. Lancet Glob Health 2024;12:e257

Chimeric Vaccine Strains

TV003 (NIH/Butantan)

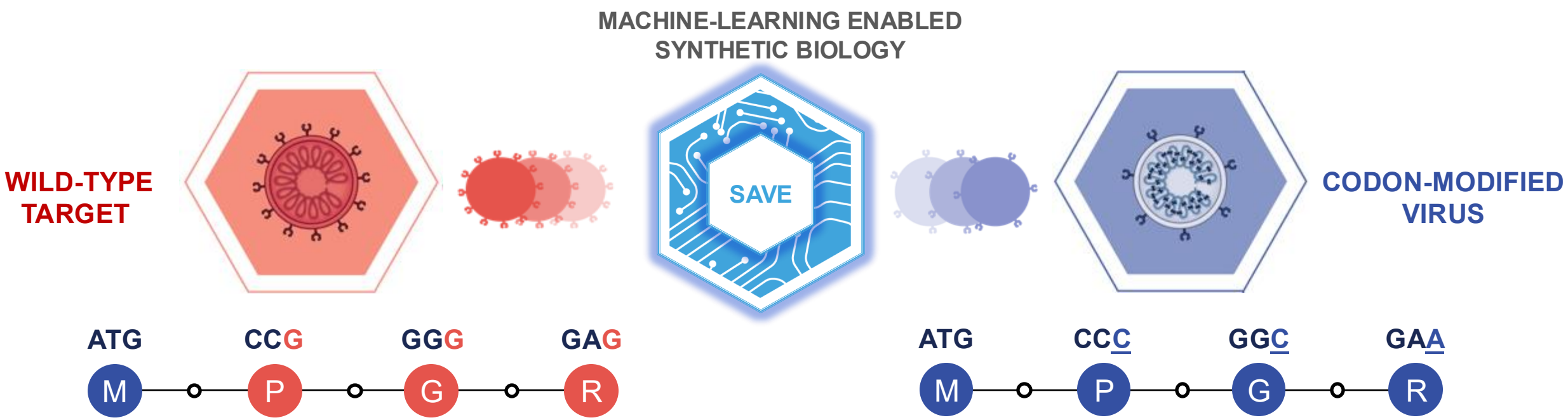
Butantan-DV Phase 3 study	Efficacy after 5 years [3] (w/o prior exposure)
DENV1	71.4% (60.5 to 79.3)
DENV2	36.7% (9.1 to 55.5)
DENV3	no data
DENV4	no data



- For both vaccines only the serotype component that is fully homologous provides good long-term efficacy (DENV1 for TAK-003, DENV2 for TV003)
- Humoral and cellular immune responses against the non-structural proteins (“backbone”) increasingly recognized as important drivers of protection

3. Kallas et al. Nature Medicine 32, 1393-1400 (2026)

Codagenix machine-learning enabled, rational viral LAV design platform[1,2]



Virus Genes Use "Fast" Human Codons/Codon Pairs

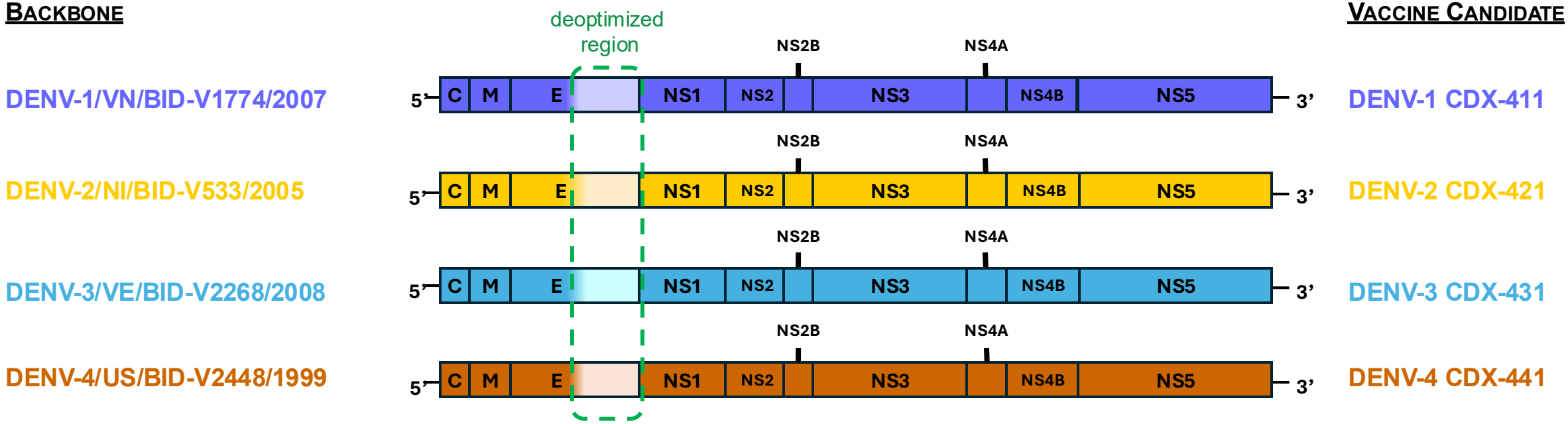
- Wild-type viruses optimized to replicate effectively in human cell
- Viruses use codons that are most efficiently translated by human or mammalian host cells
- Fast translation = Fast Replication, Rapid spread, cause disease

Re-designed with "Slow" Human Codons/Codon Pairs

- Attenuated but **same proteins** as wild type virus
- Results in a **less fit virus** to serve as vaccine or oncolytic therapy
- **Broad immune response**, akin to natural immunity, generating both antibody and T cell response[2]

[1] Coleman JR, et al. 2008. ***Science*** 320(5884):1784-7.
[2] Mueller S, et al., 2010. ***Nature Biotechnology.*** 28(7):723-6.

Current Vaccine Candidates use the more current clinical isolates for the backbone and maintained 50% deoptimization in E segment



- Facilitated by fully synthetic test tube-based reverse genetics system developed in-house (no more plasmids!)
- Homologous backbones thought to improve serotype specific immunogenicity
  - NS1 blocking antibodies
  - Cellular immune responses against non-structural proteins

High Titer Growth of CDX Strains under Animal Origin Free Conditions

	pre MVS (FFU/mL)	cGMP MVS (FFU/mL)
CDX-411 (DENV1)	9.2×10^7	6.4×10^7
CDX-421 (DENV2)	9.9×10^6	9.4×10^6
CDX-431 (DENV3)	5.7×10^7	7.9×10^7
CDX-441 (DENV4)	4.4×10^7	1.5×10^7

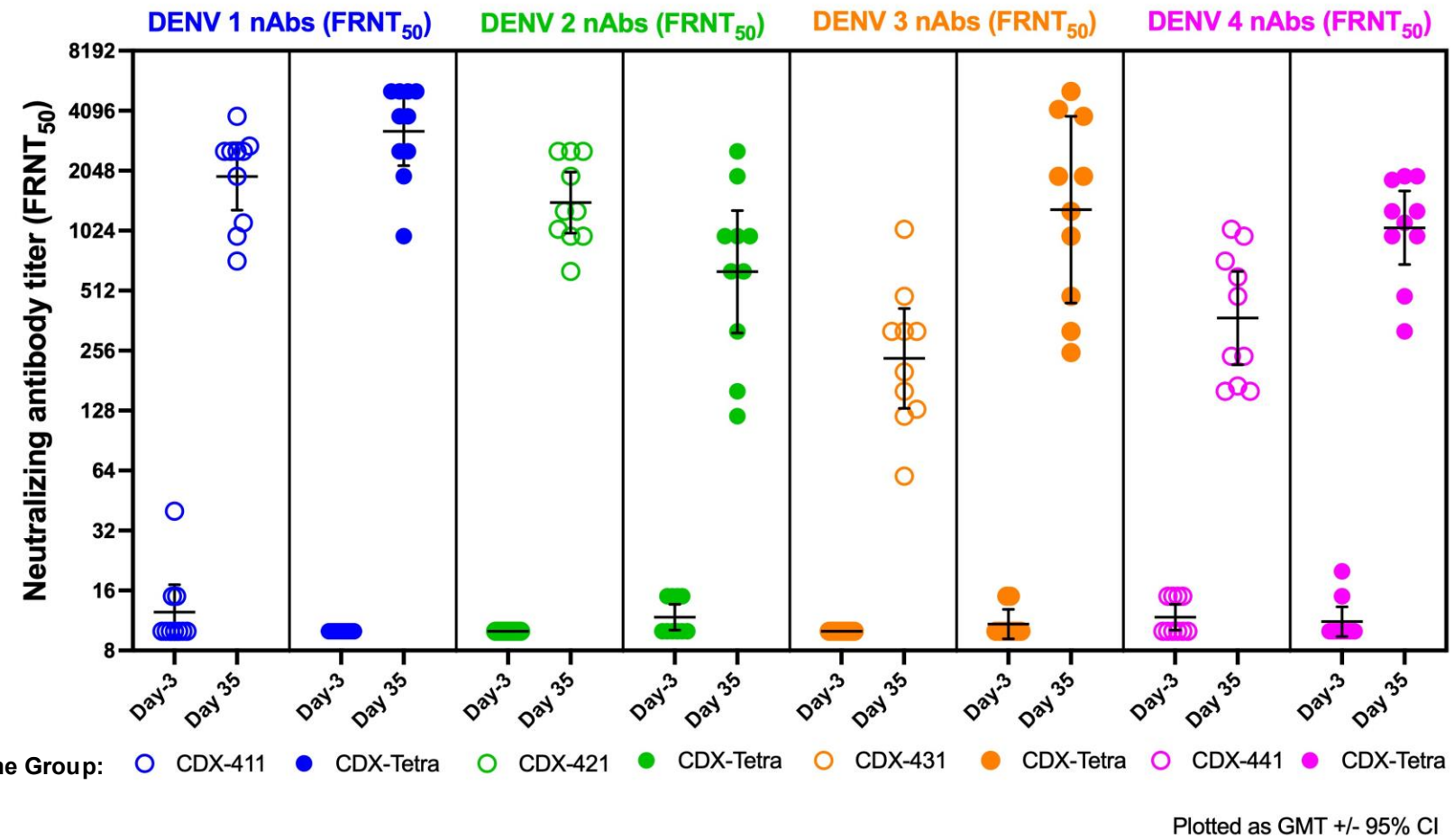
- WHO Vero 10-87, serum free, animal origin free Master Cell Bank (cGMP)
- Serum free, animal origin free infection conditions
- Simplified purification scheme to produce injection grade drug product (under development)

Tetravalent balanced Immunogenicity without Evidence of Interference

- **Interferon α/γ receptor -/- mice (IFNagr-/-)**
- N=10 each monovalent or tetravalent
- 10^6 FFU vaccinated day 0 & day 21
- Day 35 neutralizing antibodies by $FRNT_{50}$

- Similar homotypic nAb responses after monovalent or tetravalent vaccination – no apparent interference between vaccine strains

Neutralizing Antibody Responses after Vaccination with 2 Doses (d0 / d21) of monovalent or tetravalent CDX-DENV Vaccine Candidates (Study CY70)



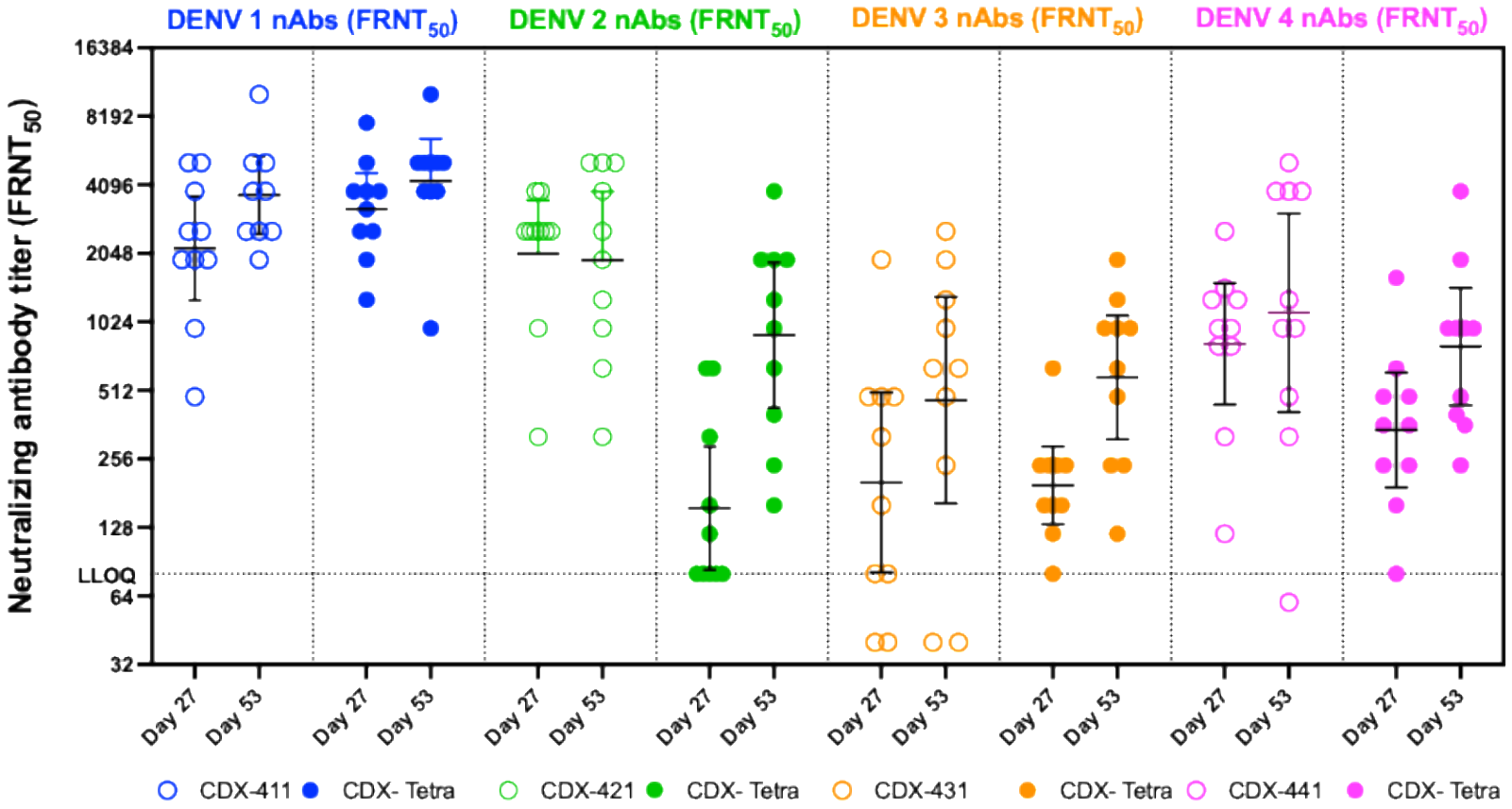
Plotted as GMT +/- 95% CI

Immunogenicity in IFNar1 -/- mice

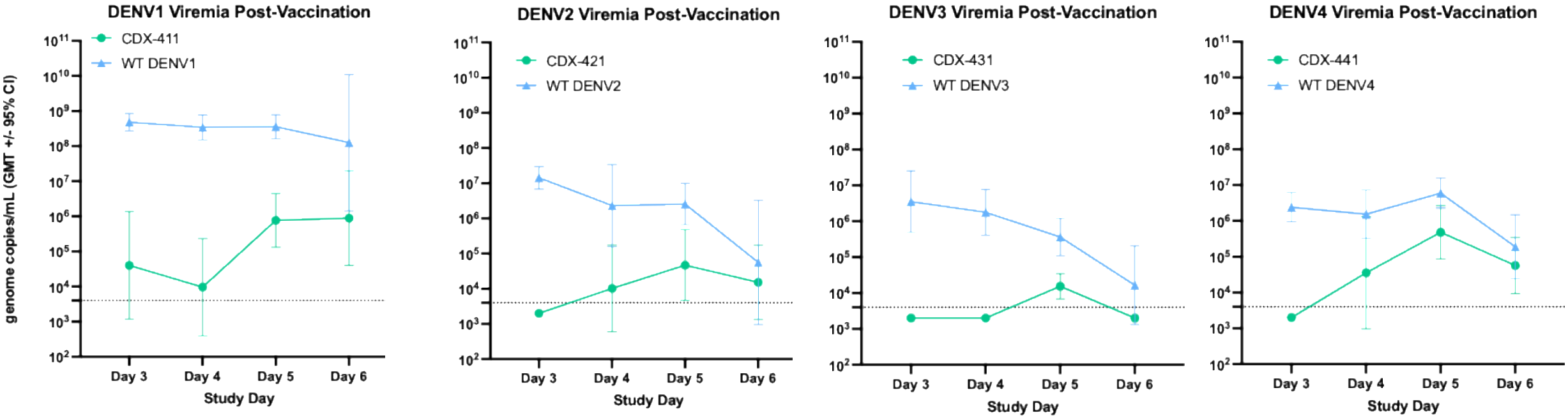
- **<u>Interferon α receptor -/- mice (IFNar-/-)</u>**
- N=10 each monovalent or tetravalent
- 10^5 FFU vaccinated day 0 & day 29
- Day 27, 53 neutralizing antibodies by $FRNT_{50}$

- Similar homotypic nAb responses after monovalent or tetravalent vaccination – no apparent interference between vaccine strains

Neutralizing Antibody Response after Vaccination with 2 Doses (d0/d29) of monovalent or tetravalent CDX-DENV Vaccine Candidates (Study E3268)



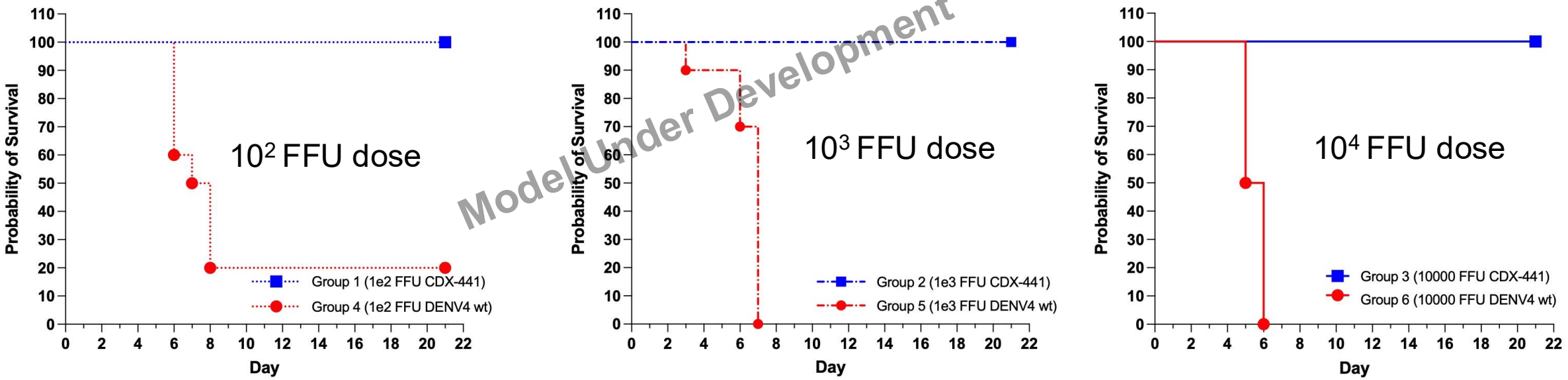
Attenuation – Reduced viremia relative to wildtype strains (IFNar1 -/- mice)



- **<u>Interferon α receptor -/- mice (IFNar-/-)</u>**
- N=10 each monovalent or tetravalent
- 10^5 FFU monovalent vaccine strains or corresponding parent wildtype strain
- Detection of circulating virus in blood by RT-qPCR
- Slower replication kinetics of vaccine within host (allows immune response more time to “react”)
- Reduced peak viremia of vaccine strains compared to corresponding wildtype parental strain

Attenuation in Lethal Neuro-tox Model: I.C. Injection of adult IFNaR -/- Mice

Survival of adult IFNaR -/- Mice after Intracranial Injection with CDX-441 or DENV4 WT parent



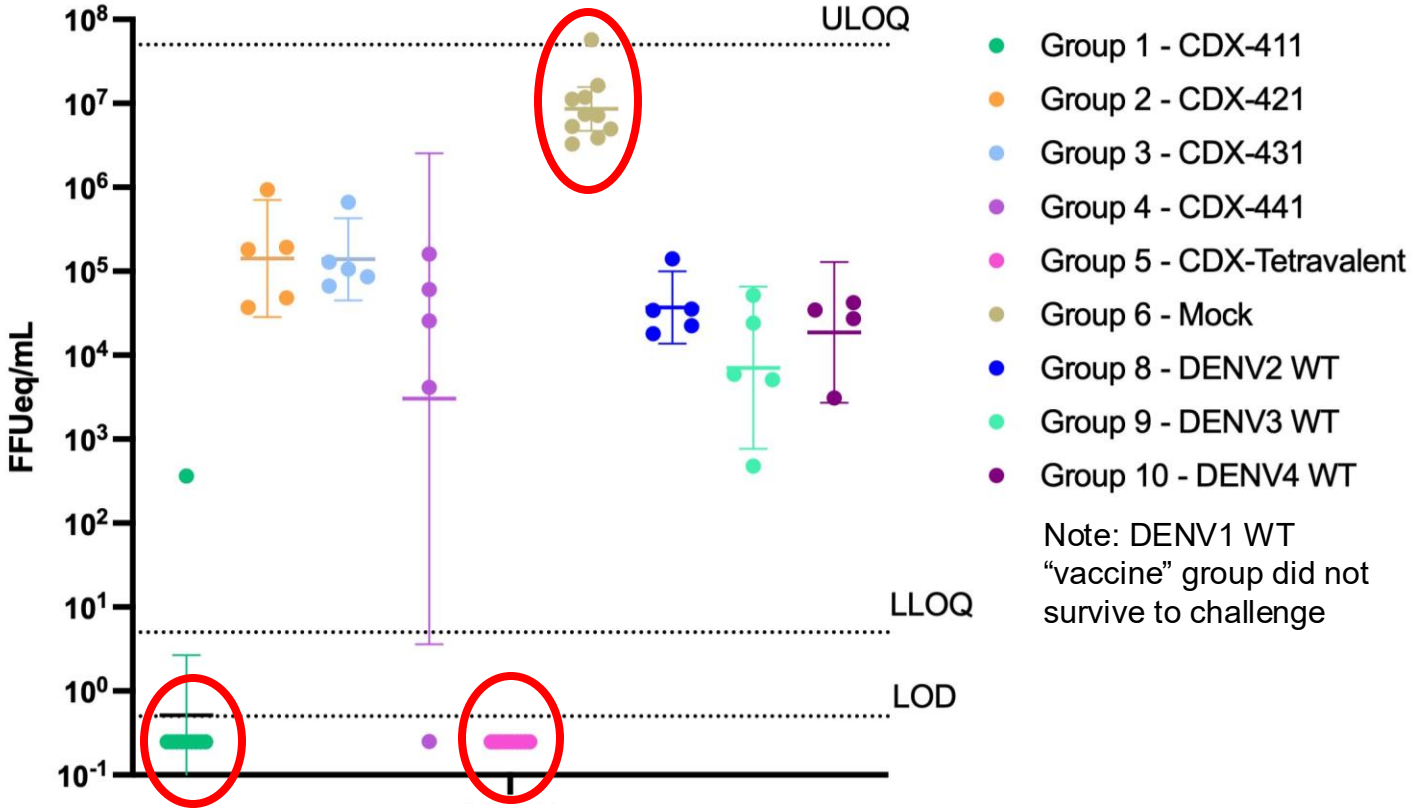
- 3–4-month-old interferon α receptor -/- mice (IFNaR-/-)
- 10^2 FFU, 10^3 FFU, 10^4 FFU intracranial injection of CDX-441 vaccine strain or parental DENV4 WT (N=10)
- monitor death & moribundity

- **CDX-441 > 300-fold attenuated compared to parental DENV4 WT strain**

Potent Protection from DENV1 WT Challenge

- Protection from challenge
- All monovalent, tetravalent, and WT vaccinated groups challenged with DENV1 WT
- Day 3 RNAemia by serotype specific RT-qPCR
- Partial heterotypic protection
- Complete protection requires homotypic vaccine component

DENV1 WT Day 3 Post Challenge RNAemia (Study CY70)

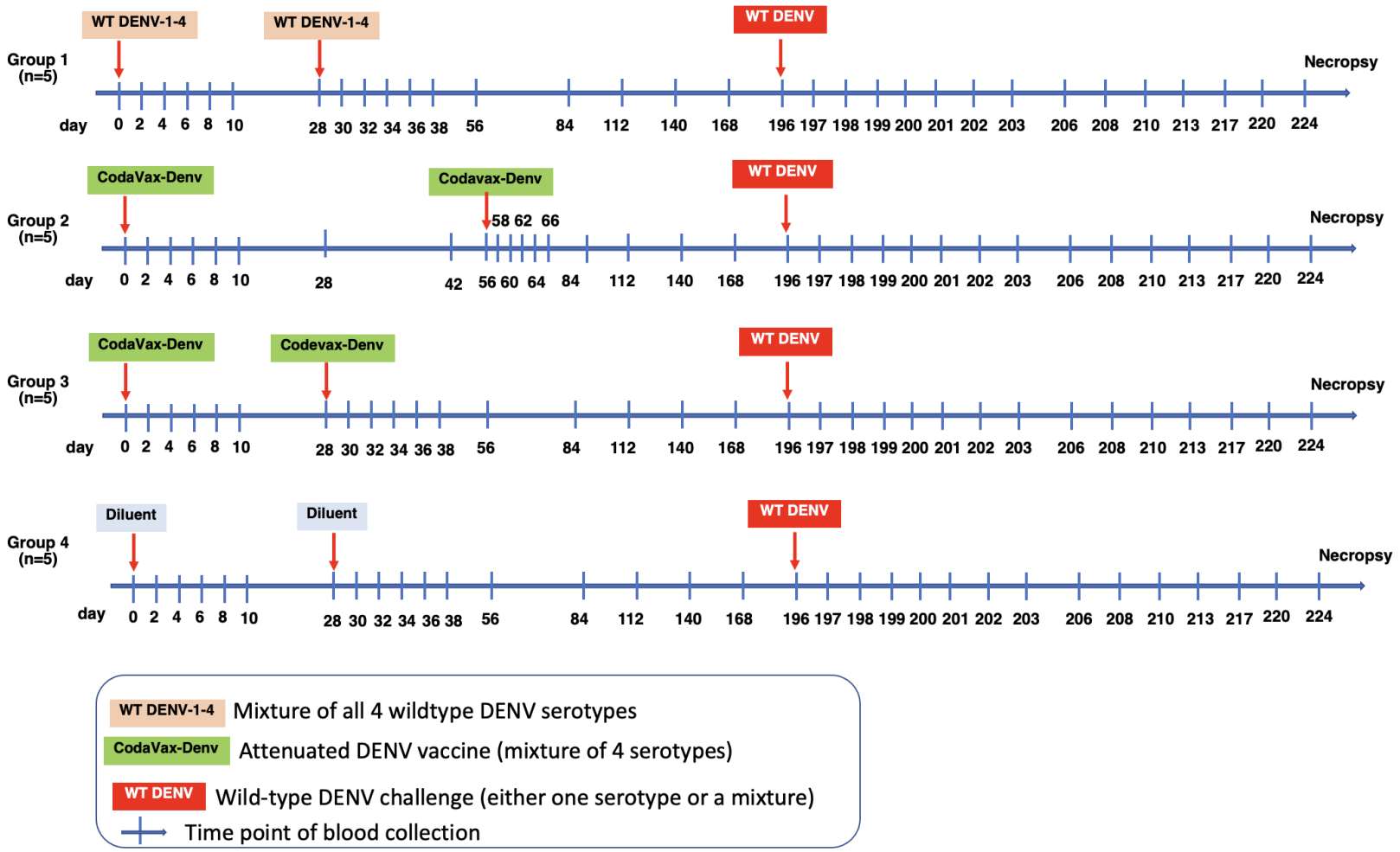


Note: DENV1 WT "vaccine" group did not survive to challenge

CY70

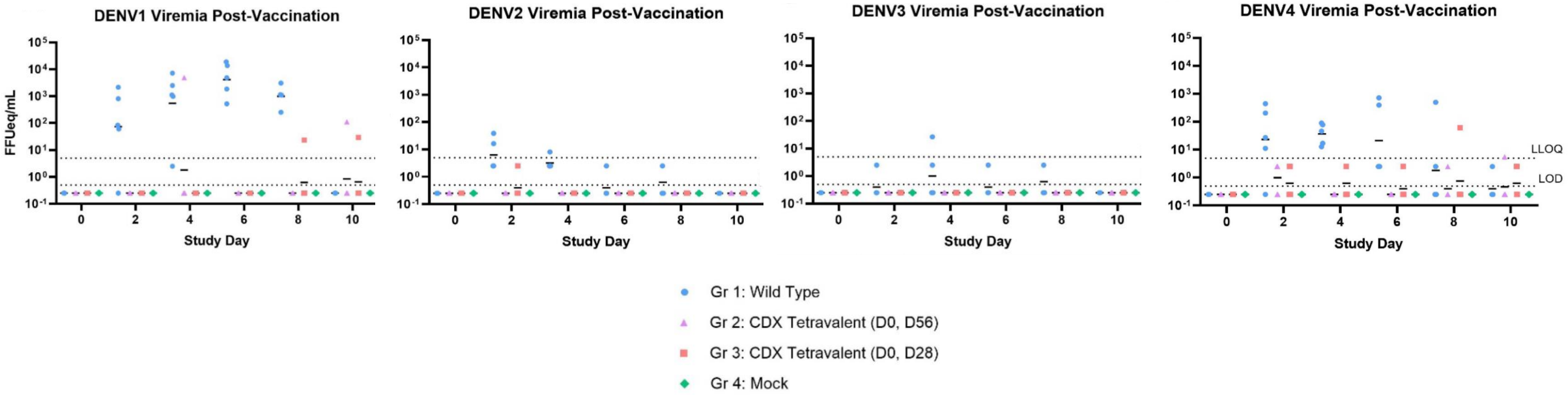
CodaVax-DENV Non-Human Primate Study for Safety and Efficacy

- Safety, immunogenicity and efficacy of CodaVax-DENV at UC Davis, CA
- 20 rhesus macaques in 4 groups (n=5)
- Comparing attenuation (vaccine viremia) and immunogenicity compared to matched tetravalent wildtype “vaccination”
- Comparing 4 week vs. 8 week booster
- Duration of protection (WT challenge after 6 months)



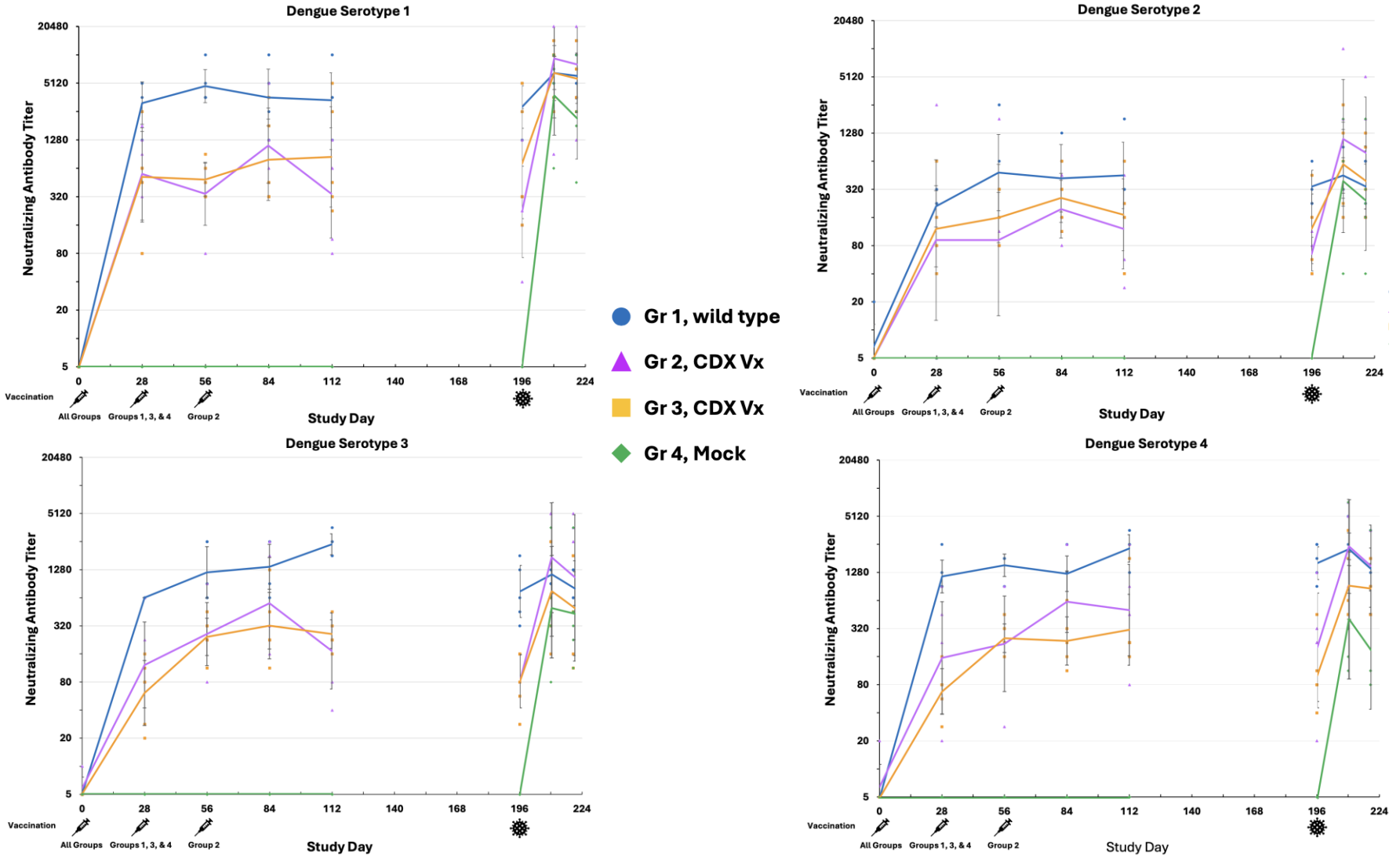
Conducted at UC Davis

Attenuated Viremia of CodaVax-DENV in Rhesus Macaques



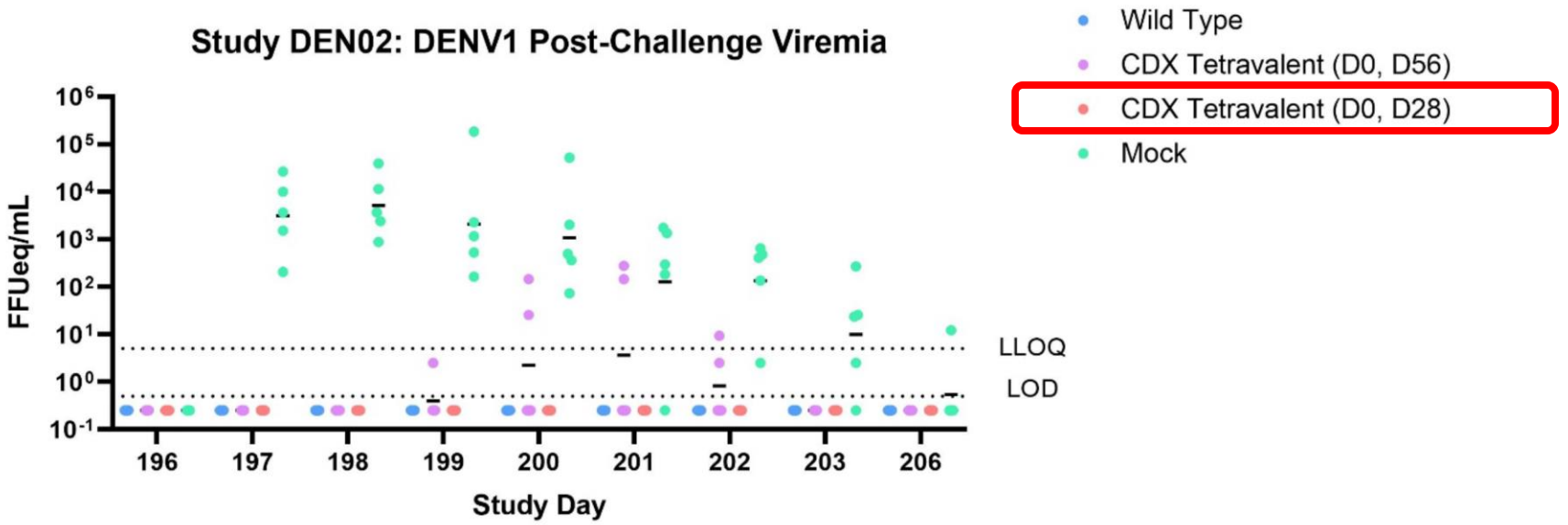
- Groups of 5 rhesus macaques were inoculated by SC route with tetravalent CodaVax-DENV (1e6 FFU each strain) or tetravalent WT (1e6 FFU each strain)
- Serum viremia of each vaccine or WT strain was assessed by serotype-specific RT-qPCR during the first 10 days following dose 1
- Reduced or undetectable viremia (RT-qPCR) of CodaVax-DENV vaccine strains relative to their corresponding WT parental strain (DENV1 & DENV4)
- Direct viremia comparison for DENV2 & DENV3 is difficult since WT DENV2 and DENV3 also don't produce much viremia in our NHP model

Balanced Immunogenicity of CodaVax-DENV in Rhesus Macaques



- Relatively balanced immunity against all four serotypes
- Vaccine GMTs ~512 ± 3-fold
- Disproportionally higher GMTs against DENV1 seen in this rhesus model not seen in African green monkeys or mice (see earlier slides) – could it be an artifact of rhesus model?
- Day 28 vs. Day 56 boosting schedules performed similarly (D28 boosting perhaps slightly better)
- Individual serotype specific GMTs of the tetravalent vaccine similarly “attenuated” compared to corresponding WT (4x, 3x, 9x, 7x reduction for DENV-1, -2, -3, -4 respectively)
- Immunogenicity analysis performed at US Navy Medical Research Command (NMRC)

Long-term protection against DENV1 WT challenge in Rhesus Macaques



- Groups of 5 rhesus macaques were inoculated by SC route with tetravalent CodaVax-DENV (1e6 FFU each strain) or tetravalent WT (1e6 FFU each strain)
- 6 months post vaccination (SD 196) were challenge with DENV1 WT; DENV1 challenge virus in blood was monitored for 10 days by RTqPCR

- Complete protection from challenge after D0/D28 vaccination regime

Conducted at UC Davis

Next Steps

Manufacturing cGMP drug substances (in process)

Developing Phase 1 study design

CODAGENIX

Summary

- Created tetravalent DENV LAV based on Codagenix Codon Pair Deoptimization Technology
- Each serotype vaccine component in its cognate (homologous) backbone
- Apparent well-balanced immunogenicity vs. attenuation @ ~ 50% deoptimization of E-glycoprotein ORF
  (more and less attenuated backup strains available, if needed)
- No indication of strain interference (similar immunogenicity of monovalent vs. tetravalent vaccination)
- Lead candidate strains CDX-411, -421, -431, -441 cGMP MVS manufactured, clinical Drug Substance manufacturing ongoing
- Dengue program open to partnering

Thank You

- Codagenix Dengue Group
  - Chen Yang, Ph.D.
  - Ying Wang, Ph.D.
  - Keri Wyllie, M.P.A.
  - Katie Pfeffer, M.S.
  - Kimber Poffenberger, Ph.D.
  - Diana Noah, Ph.D.
  - Linda Maldonado, M.S.
  - Keith Inman, Ph.D.
  - Maddie Fisher, M.S.
- Naval Medical Research Command (NMRC)
  - Kalyan Sundaram, Ph.D.
  - Daniel Ewing
- UC Davis (National Primate Research Center)
  - Koen van Rompay, Ph.D., DVM

Thank You @ USG

NIH:

- 5R01AI075219-05 (Wimmer 2008-12)
- 5R01AI110792-04 (Wimmer 2015-18)
- 1R43AI116035-01 (2014-15)

NIH NCEAs (@UTMB):

- HHSN27200009 / A71 Base D1 (2015)
- HHSN27200009 / A71 Option 4a (2017)
- HHSN27200009 / A71 Option 4b (2017)
- HHSN27200009 / A04 Base C2 (2019)
- HHSN27200006 / A04 Base C1 (2019)
- HHSN272201000040I A63 Option 1 Study C1 (2023)
- HHSN272201000040I A63 Option 2 Study C2 (2024)

DOD:

- SBIR W81XWH18C0046 (2017-18)
- SBIR W81XWH19C0051 (2019-21)
- JWMRP W81XWH2220026 (2022 -)
- USAMRDC HT94252320048 (2023 -)

Wild-type reference prM + E sequences or genomes of other DENV vaccines are very dated from their time of original viral circulation

		DENV-1	DENV-2	DENV-3	DENV-4
Dengvaxia (Sanofi) prM + E YFV 17D backbone	Year isolated	**1980**	**1980**	**1988**	**1978**
	wt strain	PUO-359/TVP-1140 Thai	PUO-218 Thai	PaH881/88	1228 (TVP-980)
Qdenga (Takeda) prM + E chimeric DENV2 backbone	Year isolated	**1964**	**1964**	**1964**	**1976**
	wt strain	16007/PDK-13 Thailand	16681/PDK-53 Thailand	16562 TC-7/DGMK30 Philippines	1036 Indonesia
TV003 (Butantan, Merck) chimeric rDENV2/4Δ30	Year isolated	**1974**	**1974**	**1978**	**1981**
	wt strain	Western Pacific/74	Tonga/74 New Guinea C, NGC	Sleman/78	Dominica/81

1. Guy et al. Vaccine 2011;29:7229
2. Velasco et al. PLOS Neglected Tropical Diseases 2024;18(12):e0012697
3. Silva et al. Exp Biol Med (Maywood) 2023;247(24):2201