Ring THERAPEUTICS

Anellovectors, a Gene Delivery Platform Based on Commensal Human Anelloviruses, Have the Potential to Evade the Immune System and Deliver DNA Payloads to a Broad Range of Tissues in a Redosable Manner

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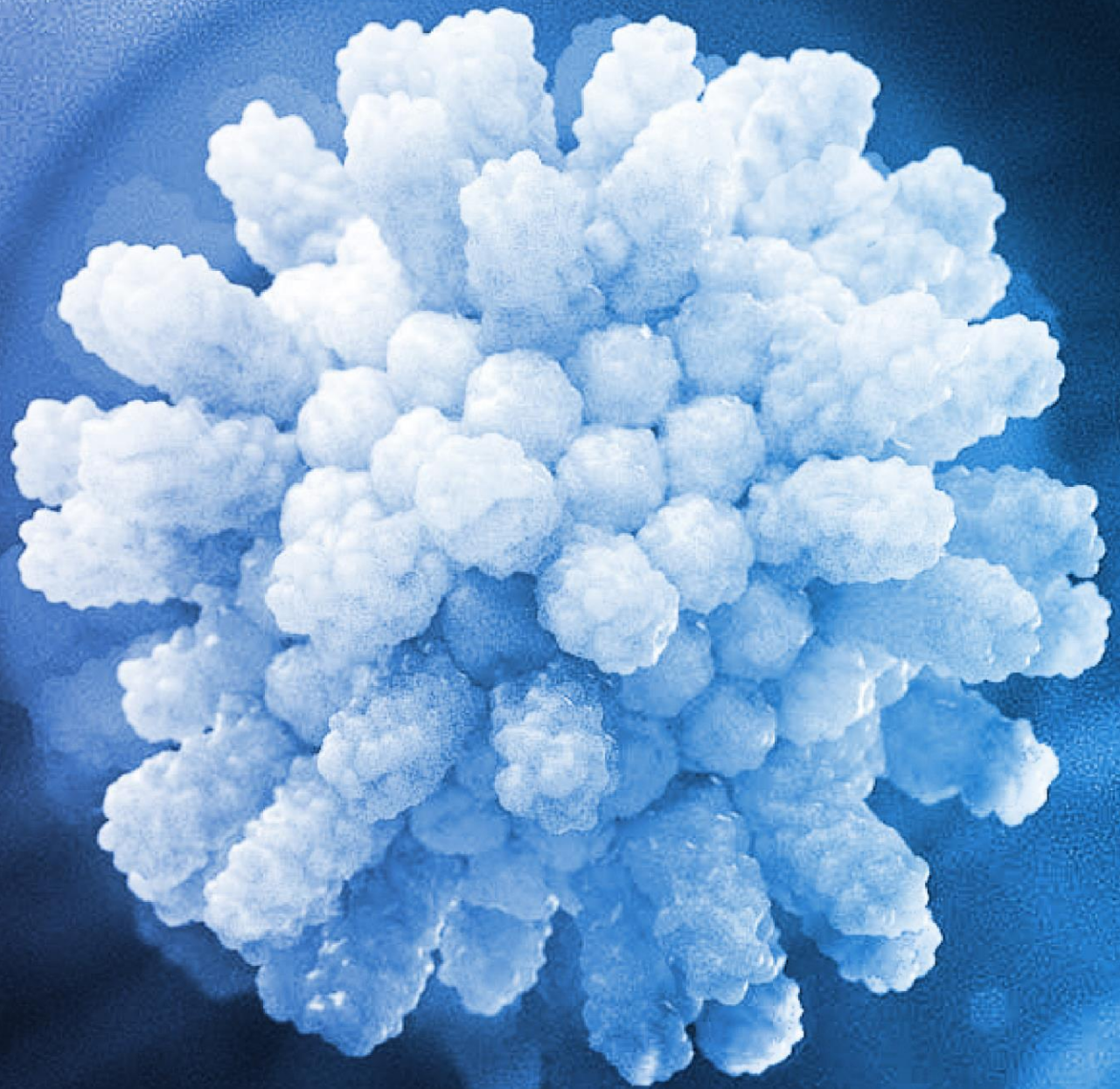
Chief Medical Officer

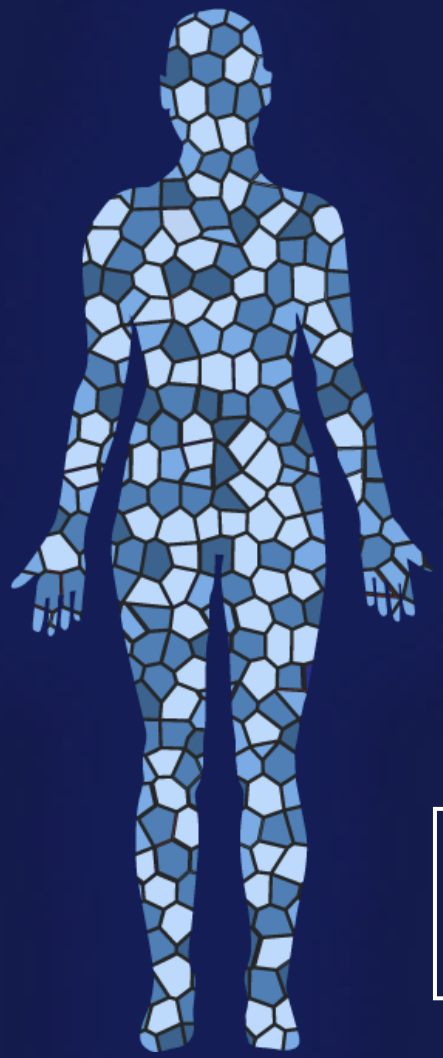
ASGCT 2024; ABSTRACT: 203



DISCLOSURES

- Work was performed at Ring Therapeutics by George S. Bounoutas, Riana Pozsgai, Isabella Gold, Alexander Auld, Parmi Thakker, Hiral Gujar, Erin Ozturk, Maitri Trivedi, Tuyen Ong, Ashley Mackey, Chris Wright
- Ring employees receive salary and equity-based compensation.

Delivering on the promise of genetic medicine



The Promise of Genetic Medicine
- Safe, potent and durable therapies for all

Genetic Medicine Today
- Approved products are improving lives of patients
- 2-3.5X more likely to get approval than other biologics[1]

But the full promise is not being delivered with AAV vectors…
- Pre-existing neutralizing antibodies
- No redosability due to immunogenicity
- Limited innate tropism
- Integration into genomic DNA

Ring Therapeutics differentiated approach has the potential to disrupt the field and deliver on the promise of genetic medicines

1. NEWDIGS Research Brief 2023F210v056 Success Rate Comparison. Are Cell and Gene Therapy programs a better bet?

Anelloviruses have evolved and lived in harmony with humans for millennia[1]

Anelloviruses intrinsic traits:

- Ubiquitous biodistribution
- Diversity leading to unique traits ideal for vector
- Natural immune evasion

97.7% ***Anelloviridae***[1]

2.3% **Other**[1]*

> Our data show the dynamics of the blood anellomes of two healthy subjects & demonstrate that **anelloviruses may persist in the host for over 30 years**.
>
> The **introductions of new lineages** and the clearance of **older lineages are rare**, and the **core, chronic anellome remains stable** and personal for many years.

—Kaczorowska et al.
J. Virol. 2022

1. Cebriá-Mendoza et al., 2021

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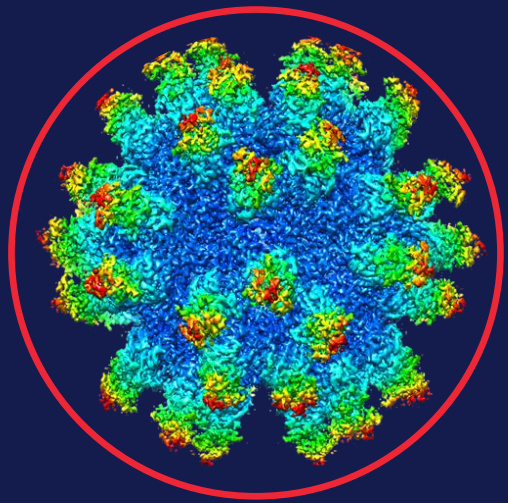
Ring is pioneering a new class of viral vector

Major Scientific Milestones :

- Produce WT virus in human cells from recombinant material (bioRxiv)
- Solve the structure of anelloviruses (bioRxiv)
- Comprehensively profile antibody response to the human anellome (Cell Reports)
- Characterize vast and dynamic anellovirus landscape (Cell Host and Microbe)
- Vectorize anelloviruses (ESGCT 2023)
- Demonstrate *in vivo* transduction with Anellovectors in mice and NHP (ESGCT 2023)



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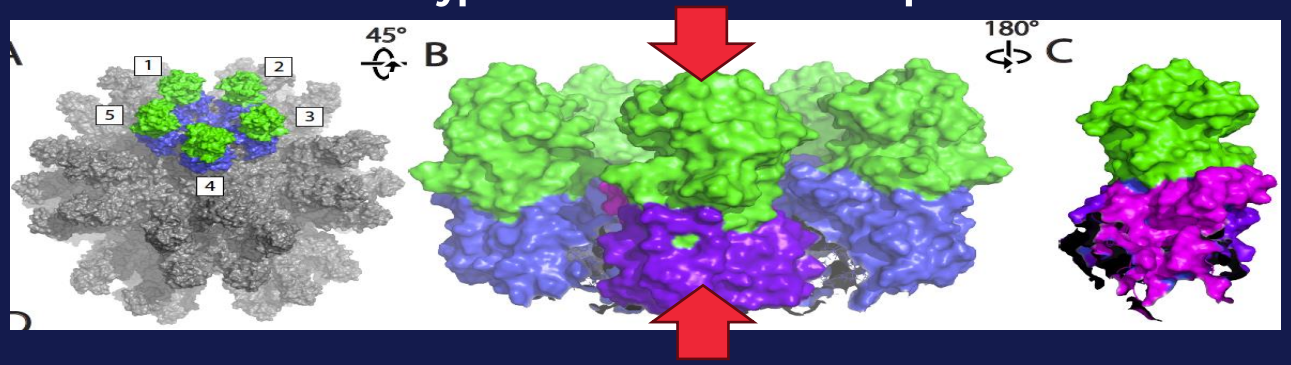
Anellovirus capsid structure suggests a mechanism for evading neutralizing antibody response

Hypervariable & solvent exposed



Less variable, near viral cavity, shielded from antibodies

AAV2

nAb A20 Fab

AAV receptor

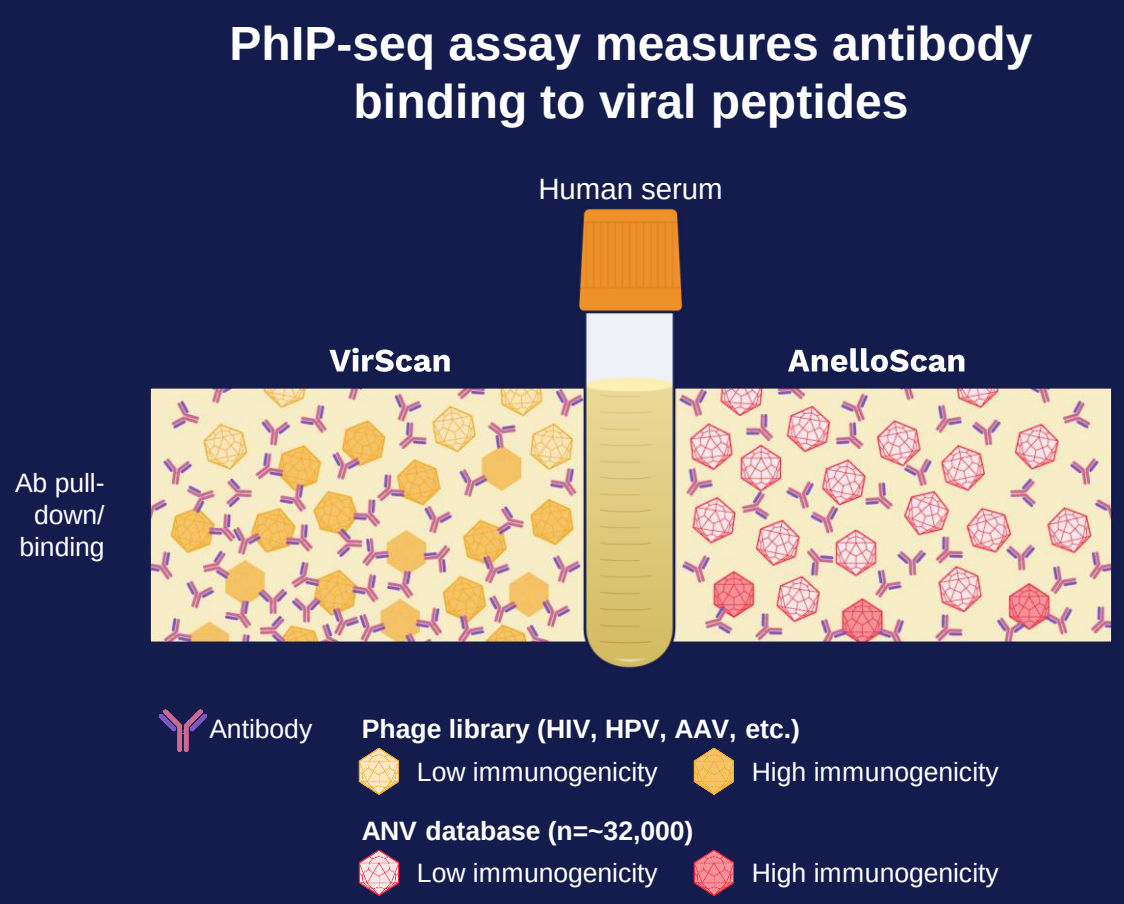
Neutralizing antibody binds AAV2 surface receptor
(McCraw et al., 2012; Zhang et. al., 2019)

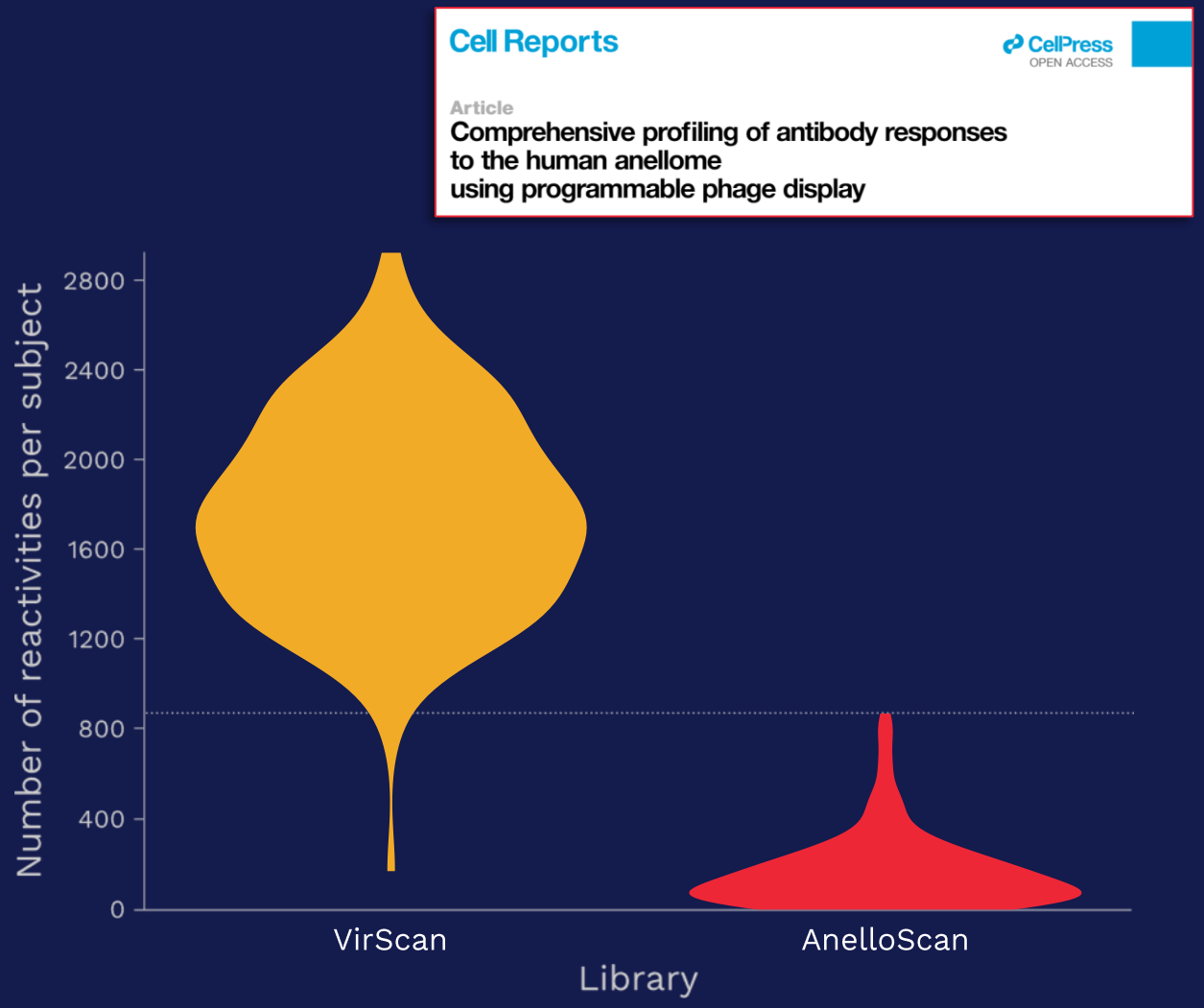
ANV10

Fab

HVR protects antibody binding of surface receptor

Very few ANV antibodies are found in human serum compared to other viruses





Abbreviations: Ab, antibody, AAV, adeno-associated virus; ANV, anellovirus; HIV, human immunodeficiency virus; HPV, human papillomavirus

Arze *et al*, 2021

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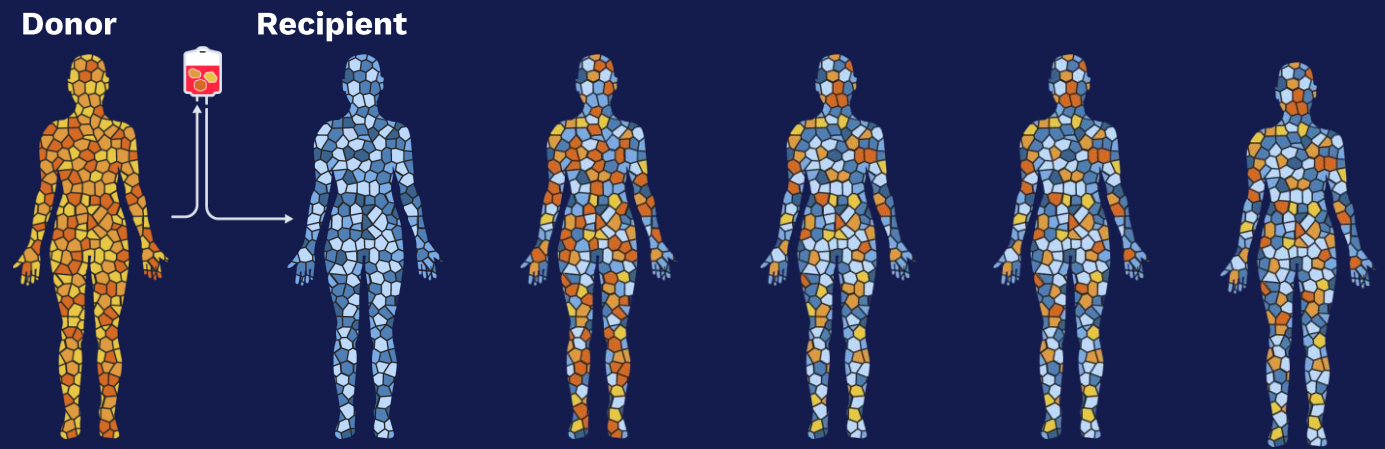
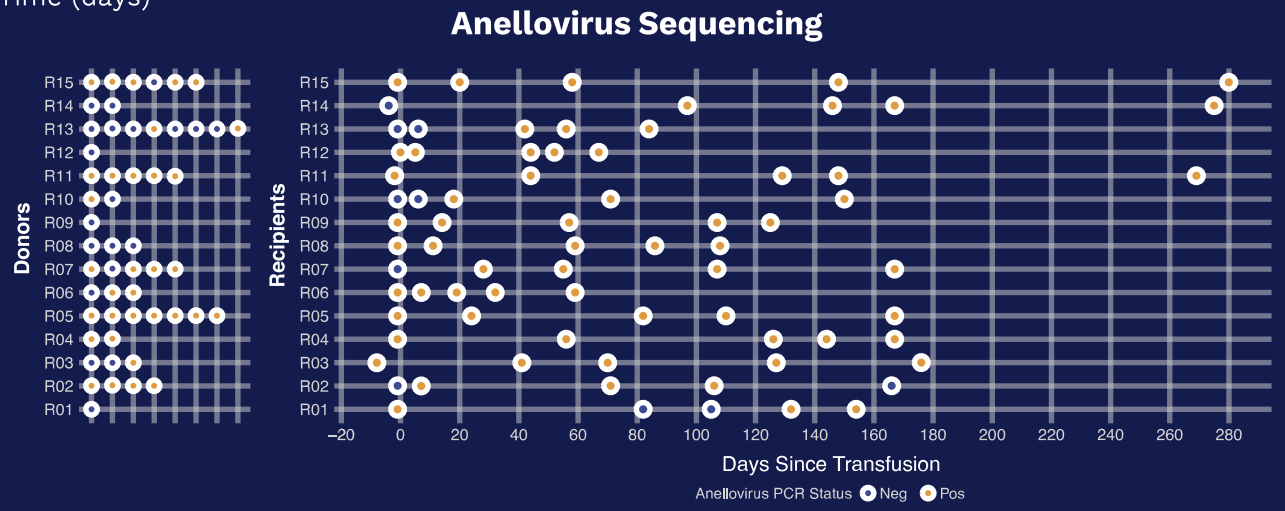
Real world experience demonstrates Anellovirus' immune tolerance and persistence

Anelloviruses are transferred during transfusion from donor to recipient safely





Immune Evasion

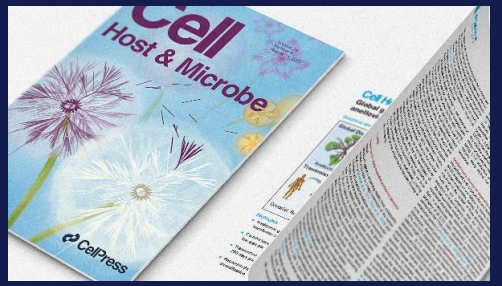
Anelloviruses can be transmitted with minimal immune response

Safety

Anelloviruses can be transmitted safely

Persistence

Multiple donor anellovirus strains detected in recipient subset @ 260+ days



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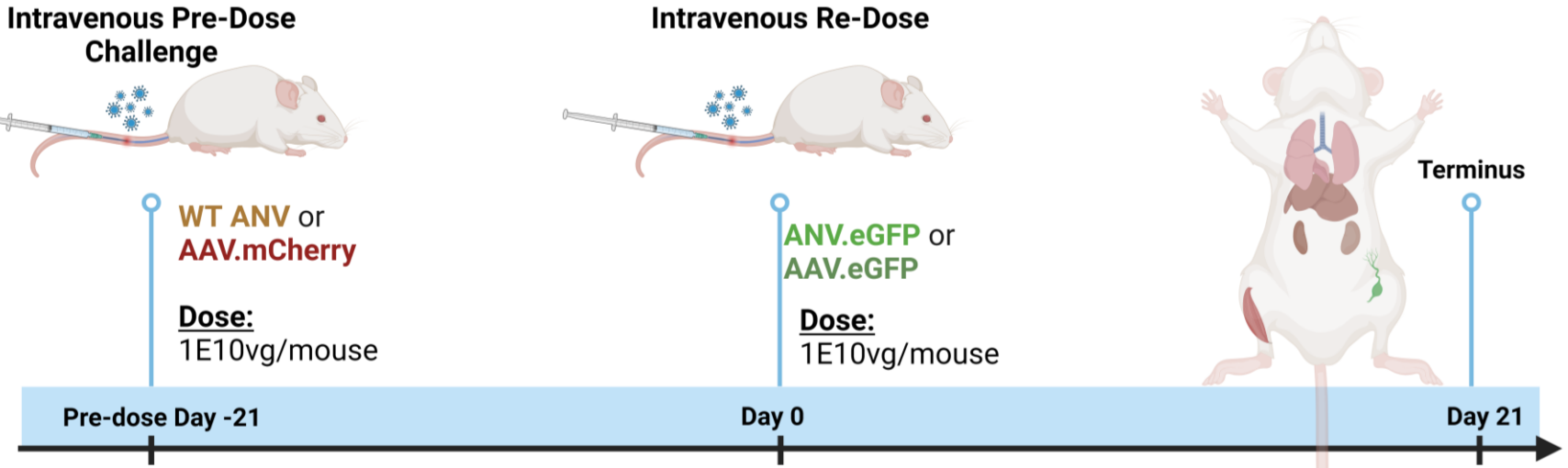
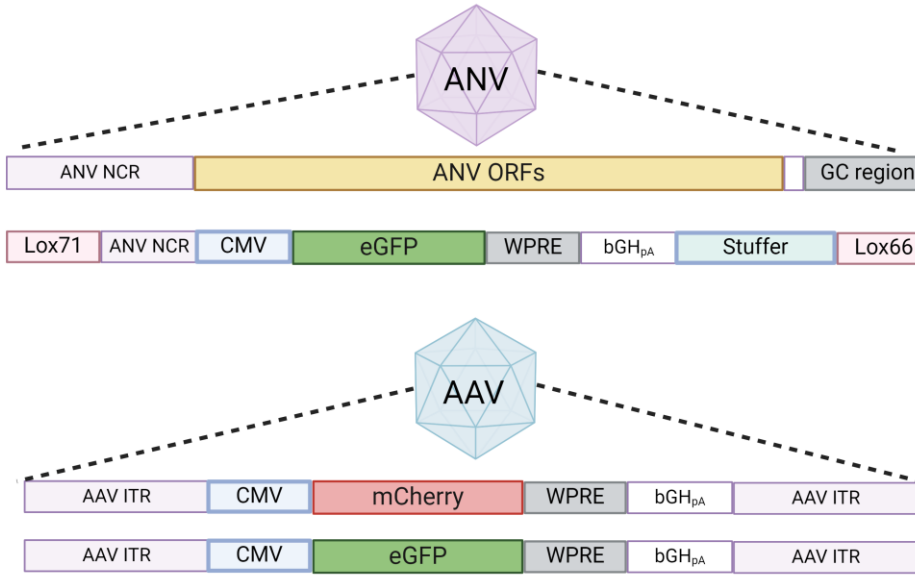
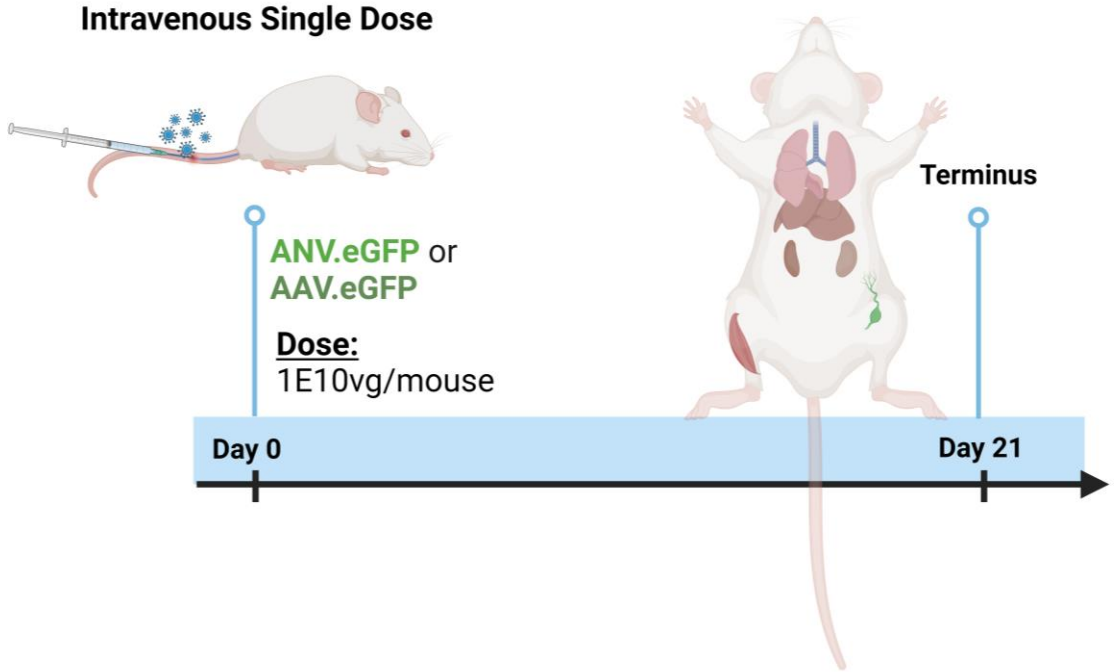
Systemic Redosing Study Design

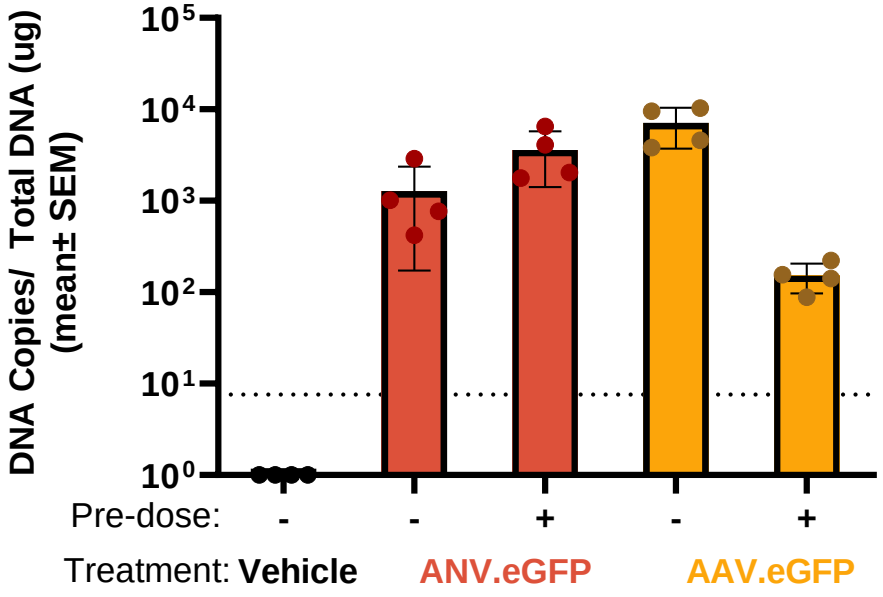


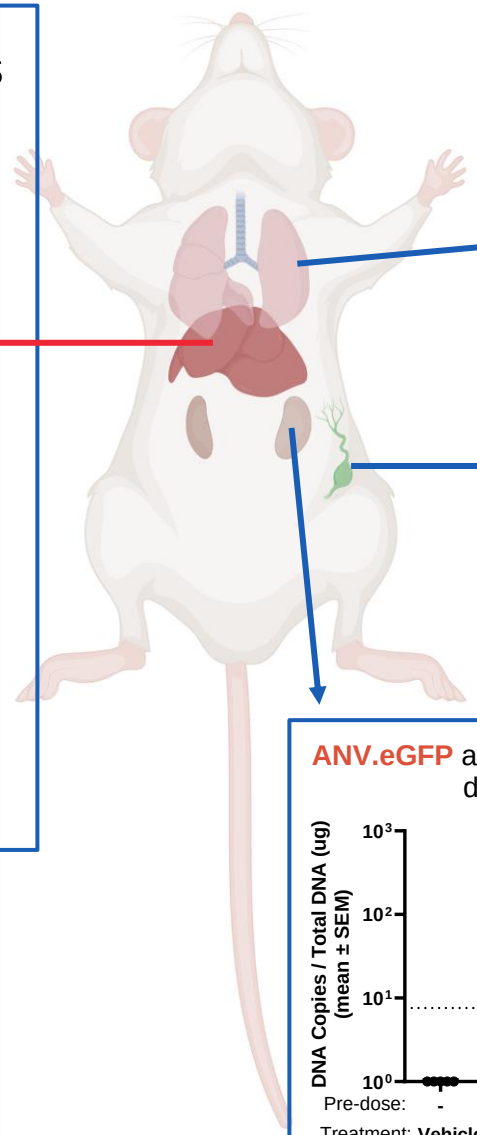




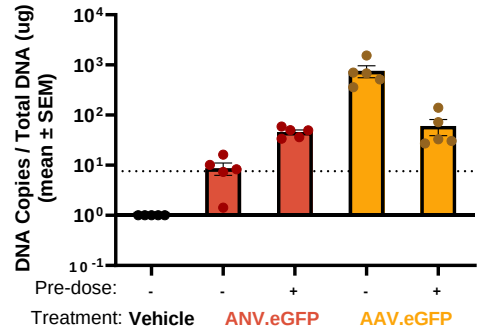
With systemic redosing in mice, greater DNA delivery was observed with ANV (vs AAV)

ANV.eGFP and AAV.eGFP genome copies detected in **Liver**

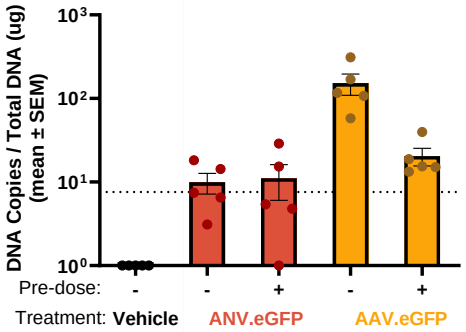




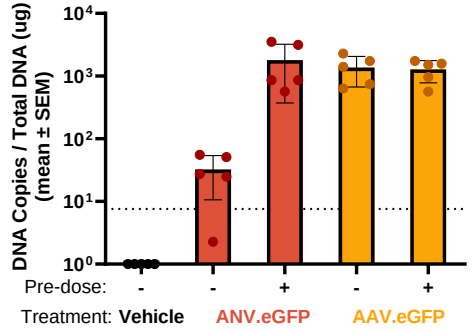
ANV.eGFP and AAV.eGFP genome copies detected in **Lungs**



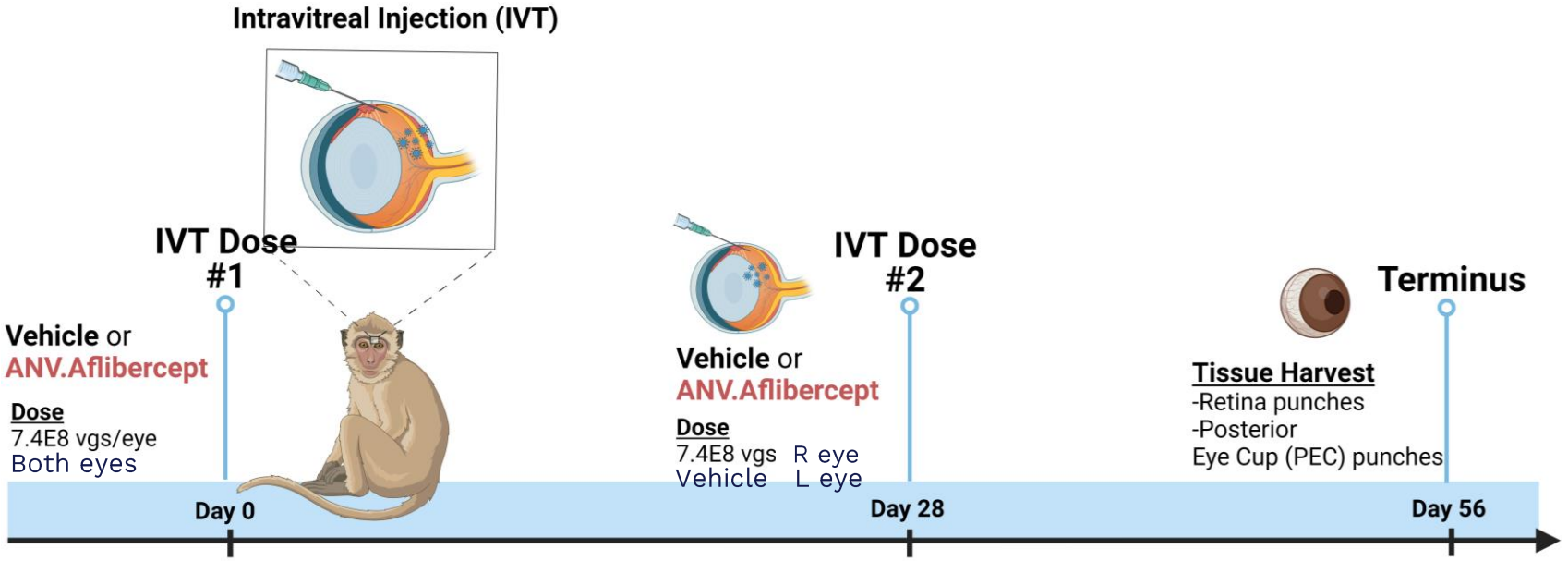
ANV.eGFP and AAV.eGFP genome copies detected in **Kidney**



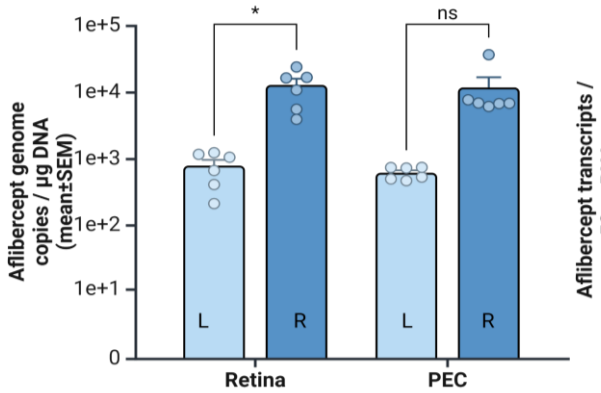
ANV.eGFP and AAV.eGFP genome copies detected in **Lymph nodes**



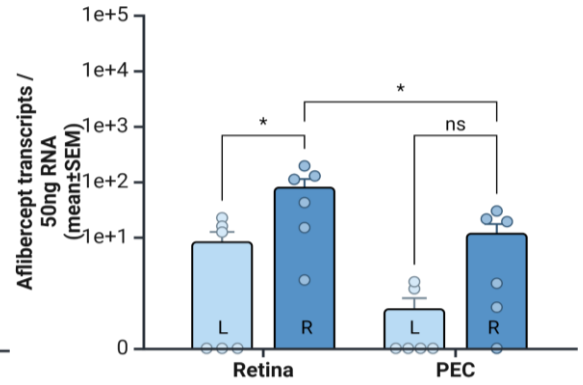
ANV.Aflibercept IVT redosing safely increases transduction in NHP



ANV.Aflibercept genome copies detected in NHP **PEC** & **Retina**



ANV.Aflibercept mRNA copies detected in NHP **PEC** & **Retina**



ns indicates no statistical significance
* indicates p<0.039

ANV.Aflibercept ANV.Aflibercept redose

Conclusions

- Anellovirus is a naturally immune evasive commensal
  - Capsid structure suggests immune evasion mechanism
  - Levels of capsid antibody very low
  - Safely persists in transfusion recipients
- Systemic redosing of ANV demonstrates similar or greater infectivity with the second dose, redosing AAV has the reverse effect
- A similar pattern for ANV redosing observed in NHP with IVT injection, including both DNA and RNA, supporting the potential for redosing in eye diseases (e.g. wet & dry AMD)
- Leverage redosing data to advance pipeline and optimize clinical programs

Acknowledgements

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Thank you

RingTx.com
Flagshippioneering.com