Lifelong Delivery of anti-HIV Monoclonal Antibodies from a Single Day of Vector Administration

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Neutralizing Antibodies to HIV

- The Neutralizing Antibody Response to HIV is Typically Strain Specific
- Some long-term infected individuals do make antibodies with potent neutralizing activity against a broad range of HIV isolates
- Such pbn-mAbs typically fall into five categories of recognition
- Monoclonal antibodies are the fastest growing segment of the pharmaceutical industry

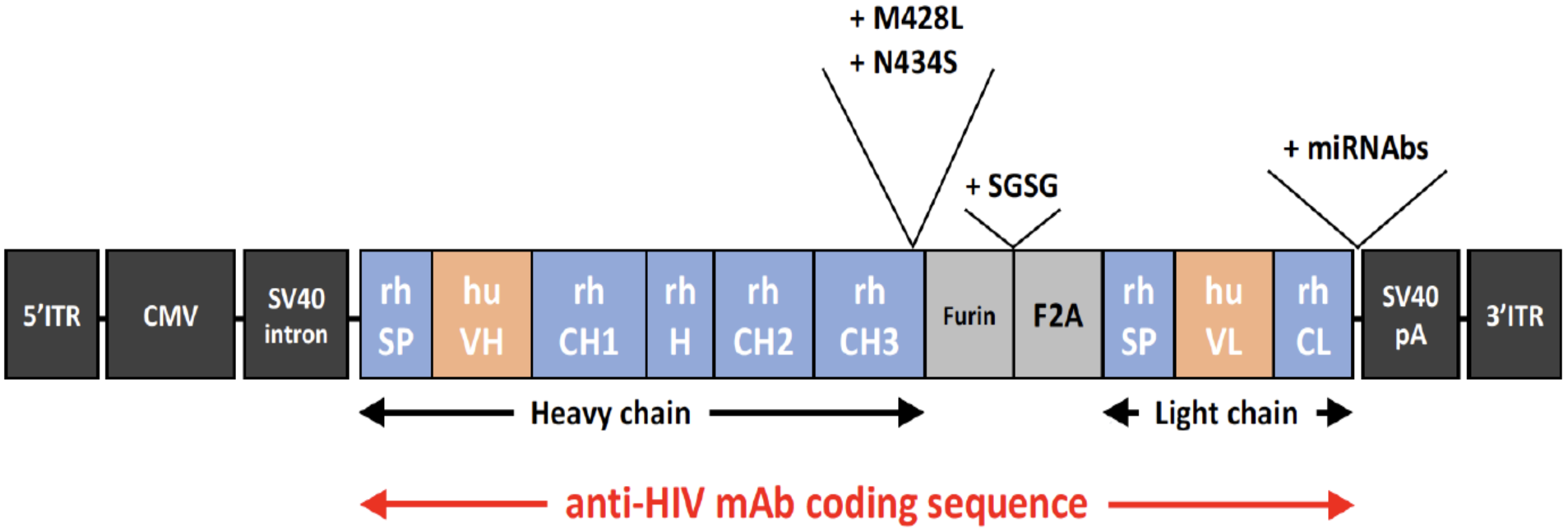
Considerable Drawbacks to Passive Administration

- Drawbacks of passive administration include:
  - extreme cost
  - need for repeated administrations month after month year after year
  - needle injection
  - compliance

- The Desrosiers laboratory has focused on long-term vector delivery of such pbn-mABs using AAV as vector

AAV as a long-term delivery vehicle - ideal in many respects

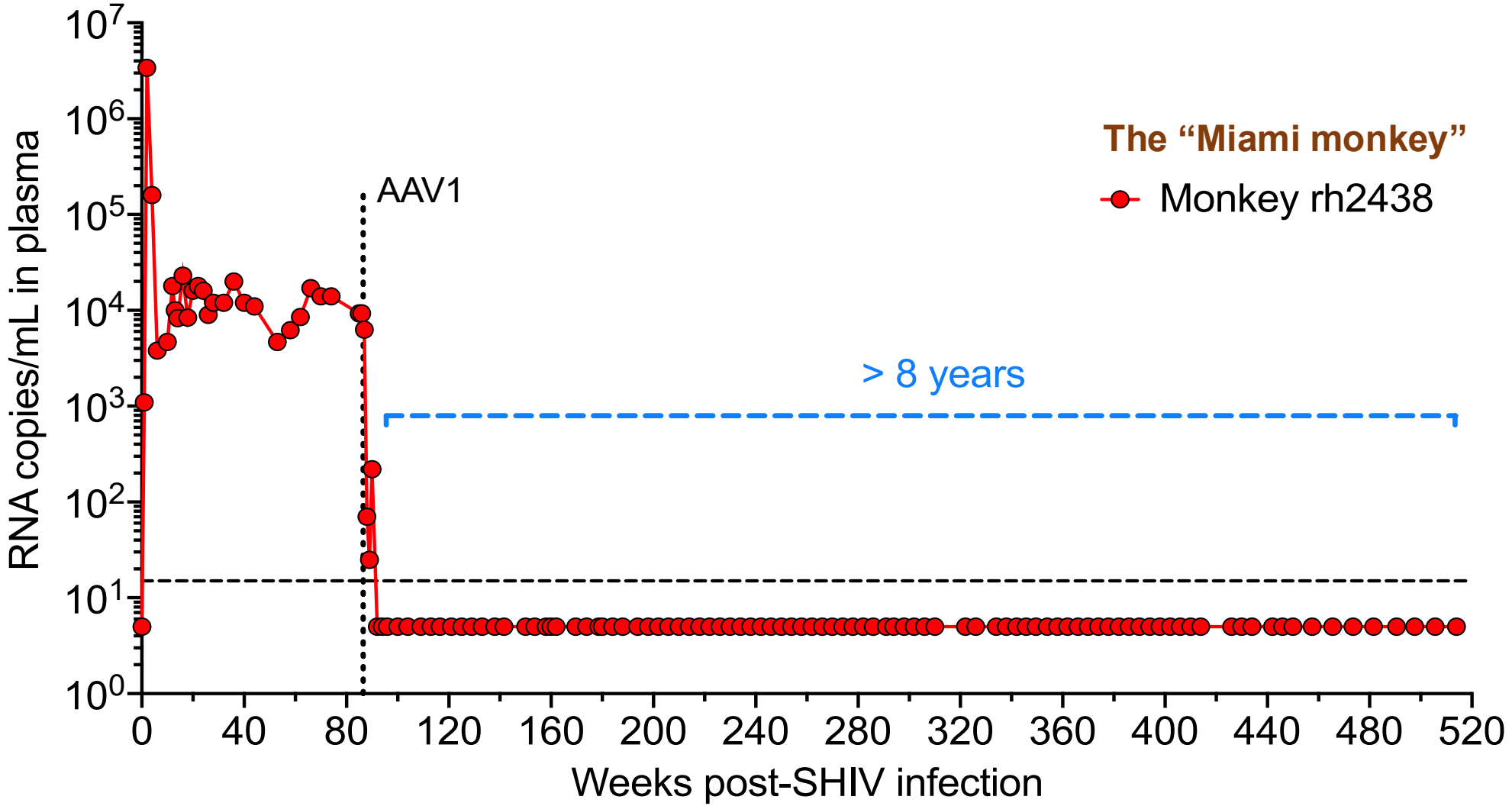
- The only protein expressed from AAV vector comes from the transgene put into it
- Proven ability to achieve long-term expression of the transgene product
- Outstanding safety record in human gene therapy trials (6 approved products in use)
- Little or no integration of AAV vector DNA into host genome sequences


+ M428L
+ N434S
+ SGSG
+ miRNAbs
5'ITR
CMV
SV40 intron
rh SP
hu VH
rh CH1
rh H
rh CH2
rh CH3
Furin
F2A
rh SP
hu VL
rh CL
SV40 pA
3'ITR
Heavy chain
Light chain
anti-HIV mAb coding sequence

Immunity

50: 567-575, 2019

Viral loads (SHIV-AD8)



3BNC117

10-1074

10E8

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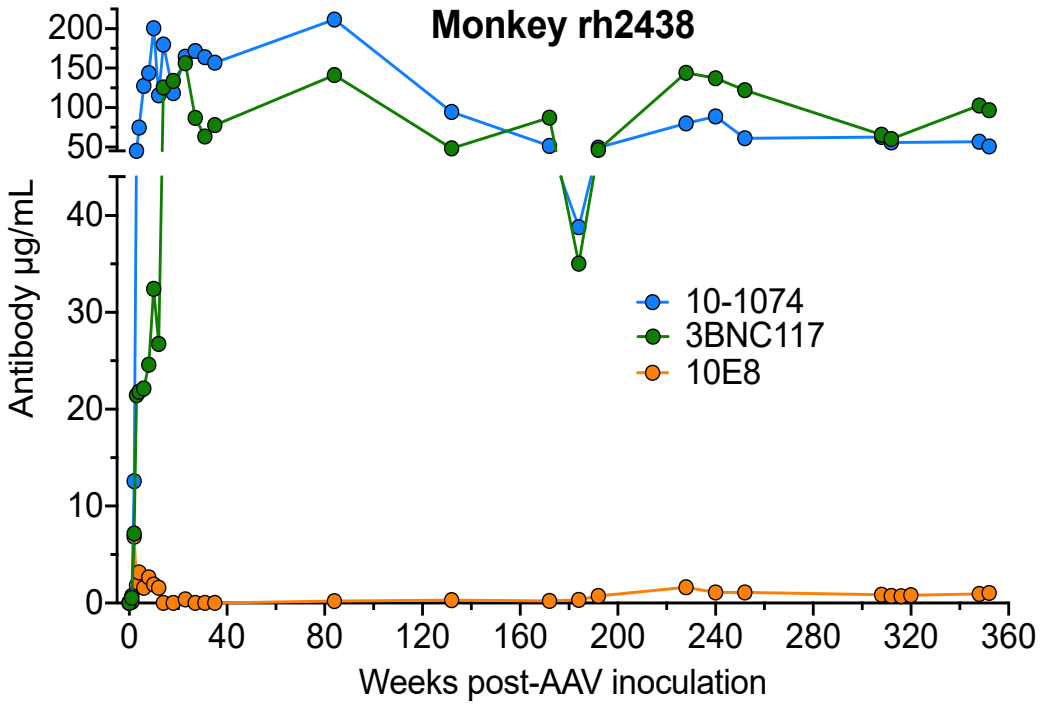
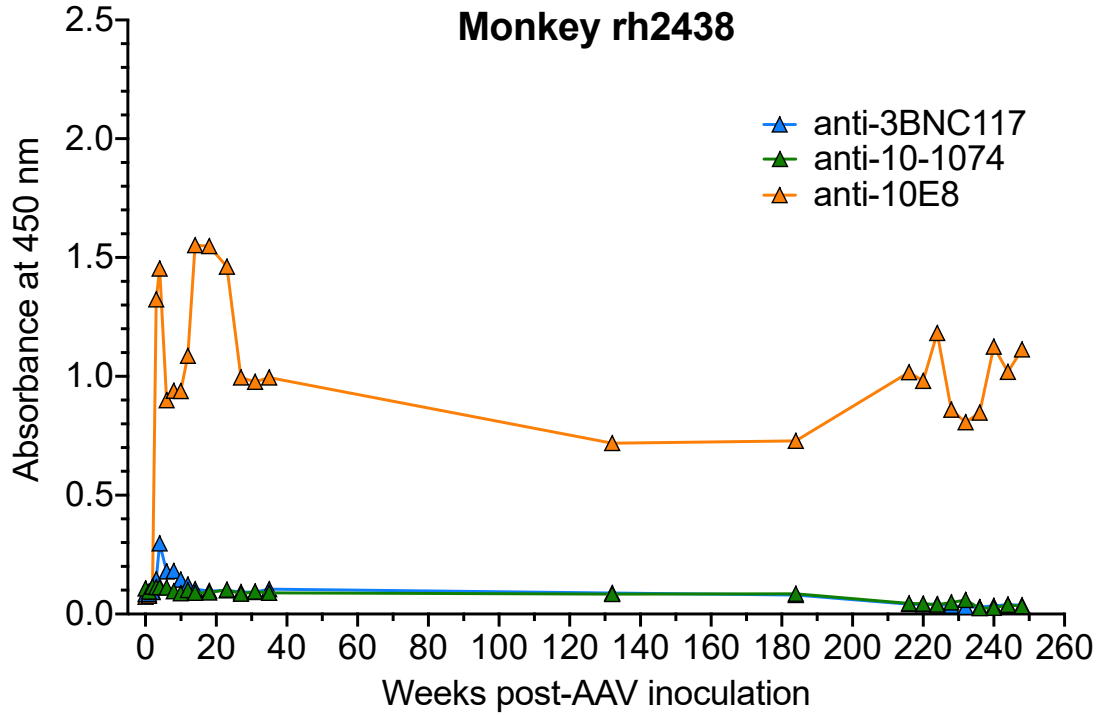
Measurements by Jeff Lifson

Delivery and ADAs





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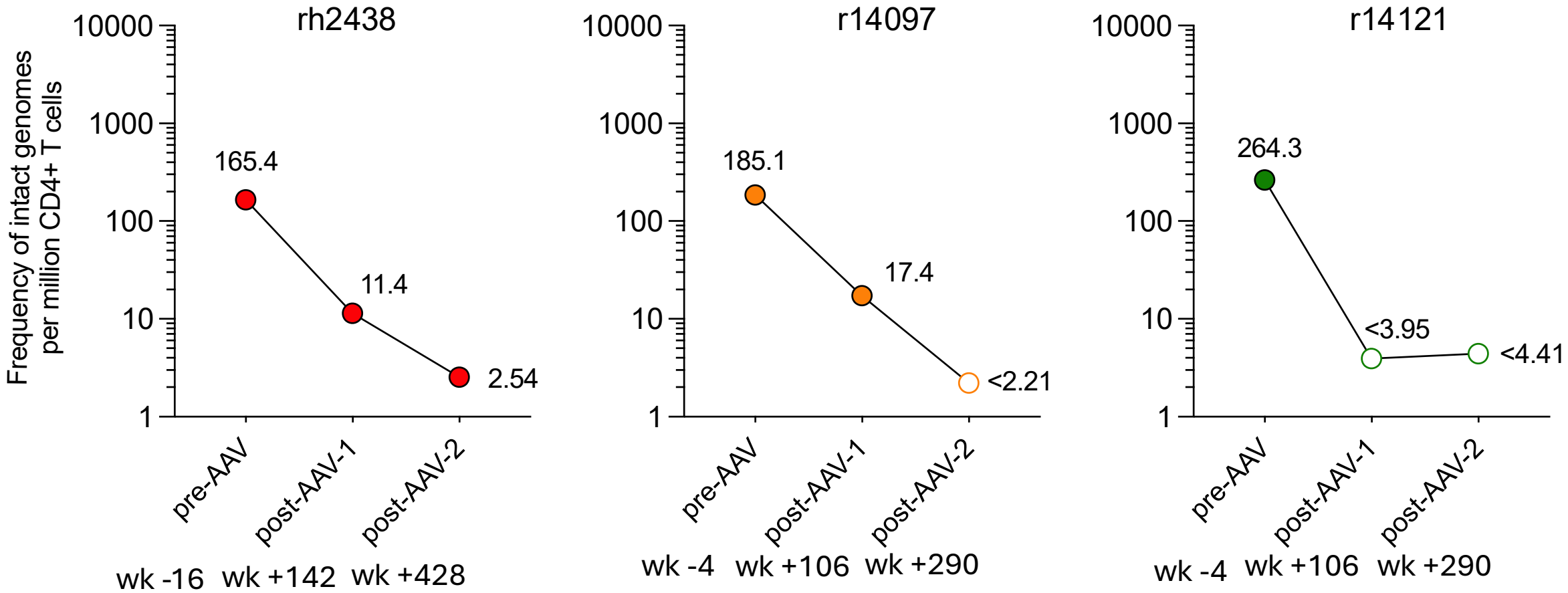
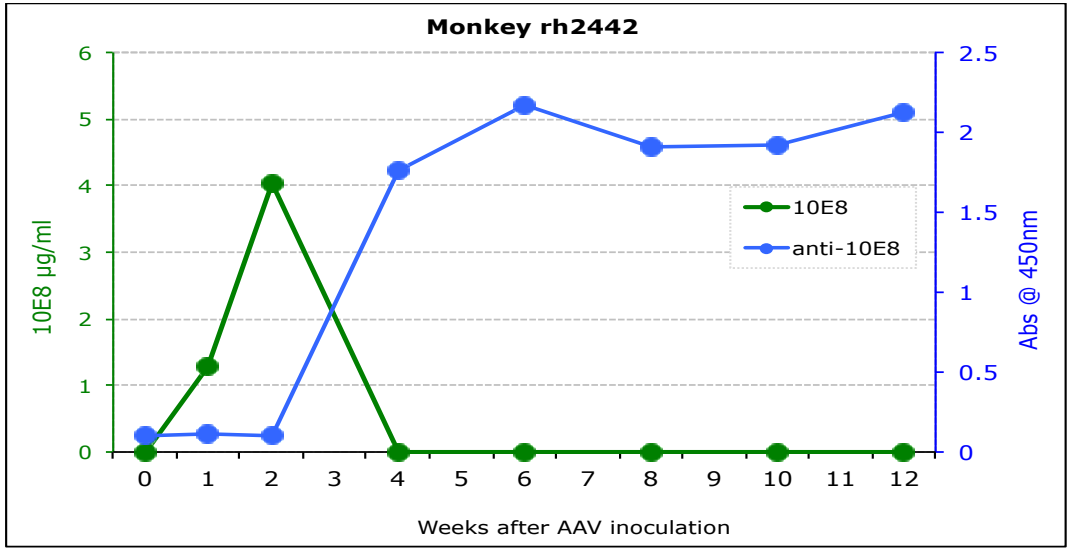
Reservoir Size

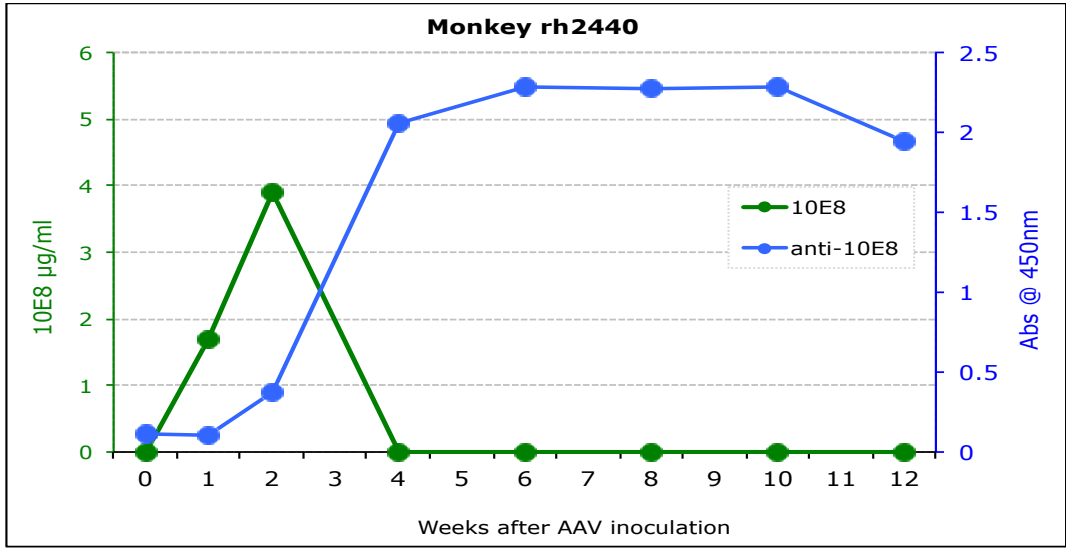
a

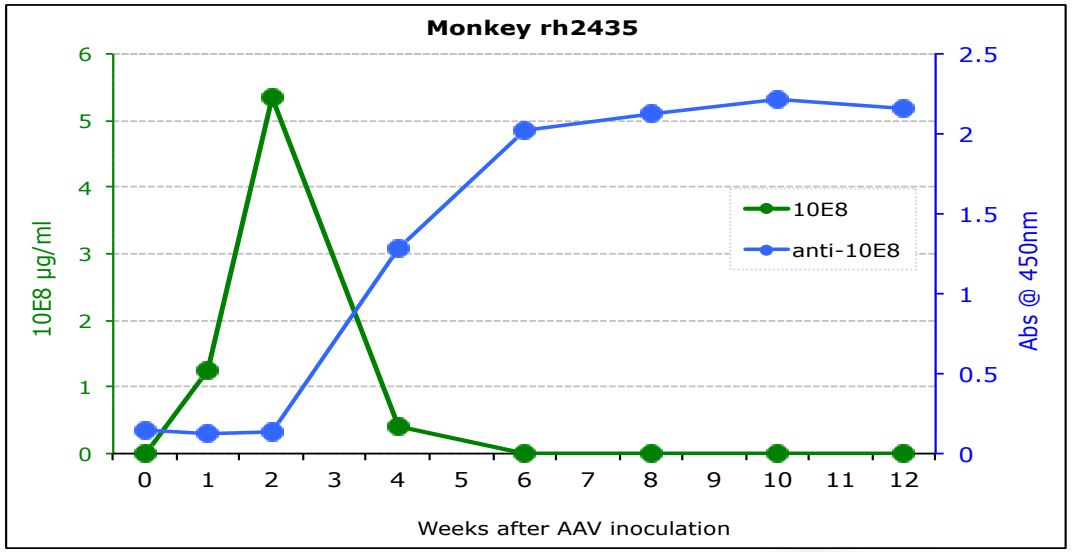


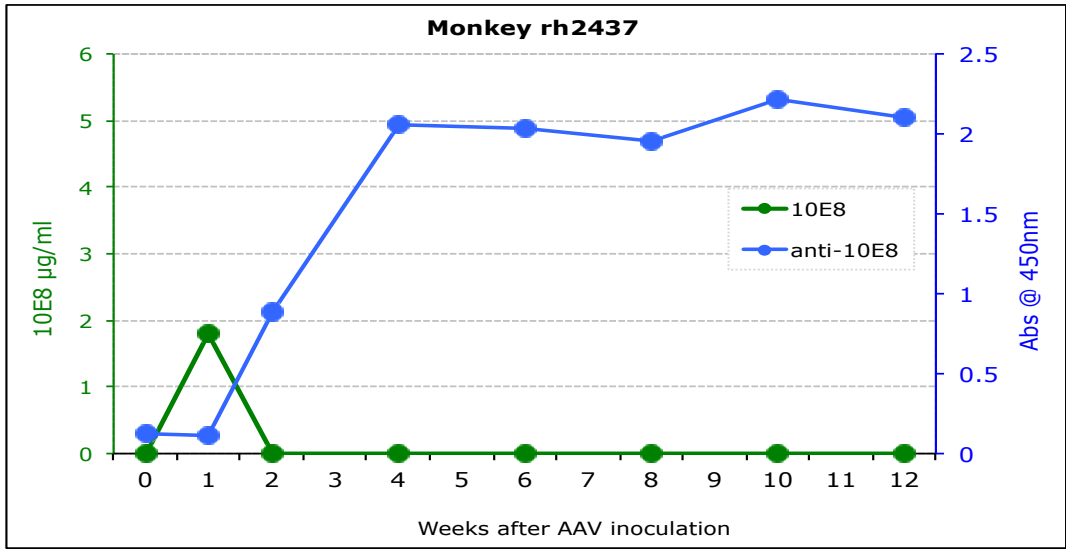
Assays by Robert Siliciano lab

ADAs - The Problem









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Molecular Therapy
25: 76-86 2016

An Arduous Route to Finding Tolerance

- Inclusion of miRNAbs sequences
- Use of CpG-depleted vectors to lower innate immunity
- Oral administration of mAb prior to AAV administration
- GMO commensal bacteria
- Liver-directed AAV-antibody delivery
- Co-injection of AAV and IDO-Gal3 to reduce local inflammation
- RBC targeting using bi-specific mAbs or mAb-peptide conjugates
- Nucleoside-modified mRNA-LNP immunomodulation

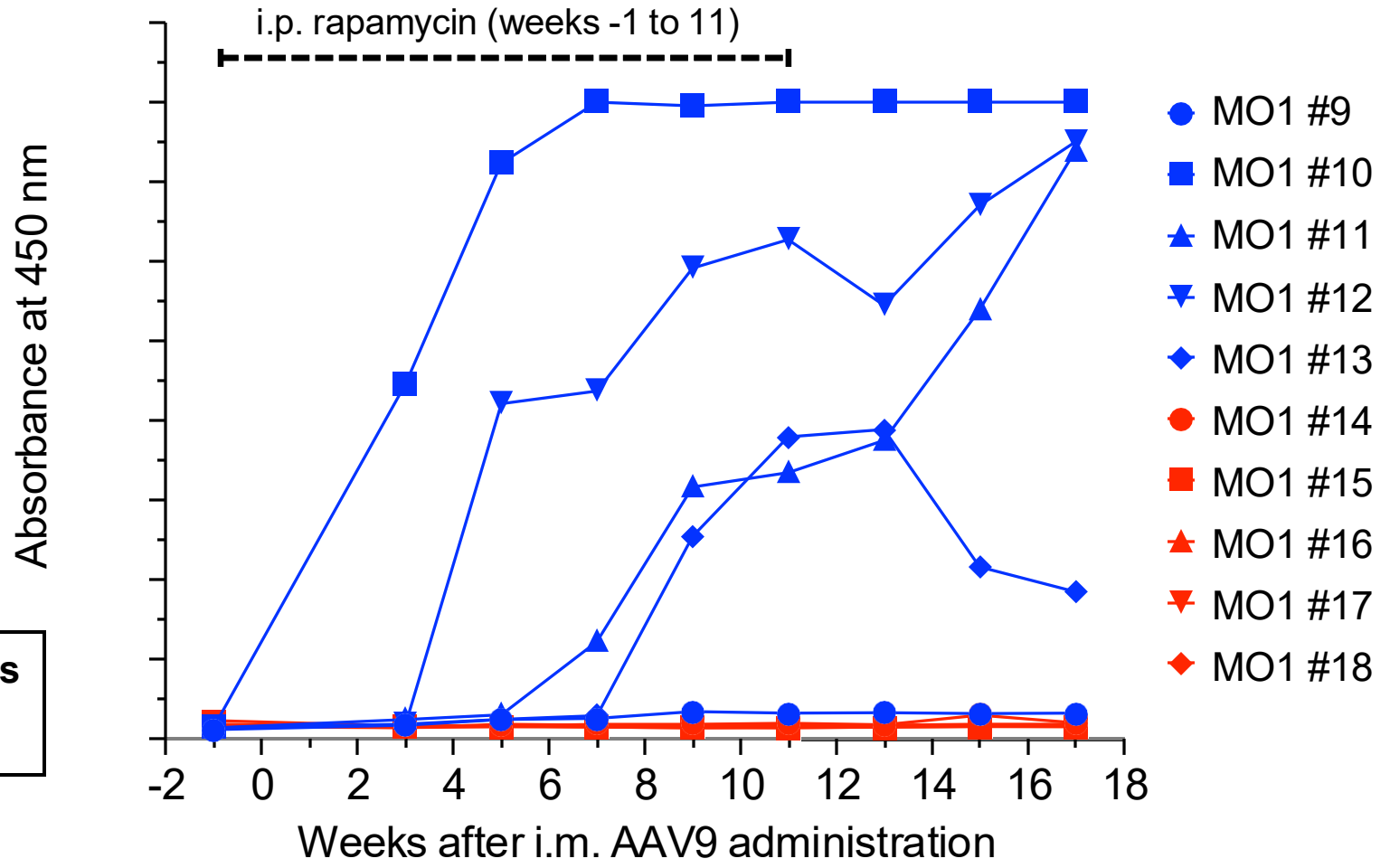
Rapamycin

- Considered an immunomodulatory drug
- Inhibits mTOR
- FDA approved
- Used in transplants to prevent organ rejection
- Long-term use has been shown to increase longevity
- Shown to be safe in HIV-infected people

  with Kaposi Sarcoma: J Acq Immdef Syn 2012: 59: 447-454

  in kidney transplants: Am J Transplant 2014: 14: 1136-1141

Transient Use of the Immunomodulatory Agent Rapamycin Solves the problem



Nature Communications

16: 8906 2025

Blue - no rapamycin

Red = rapamycin (starting week -1; 3x per week)

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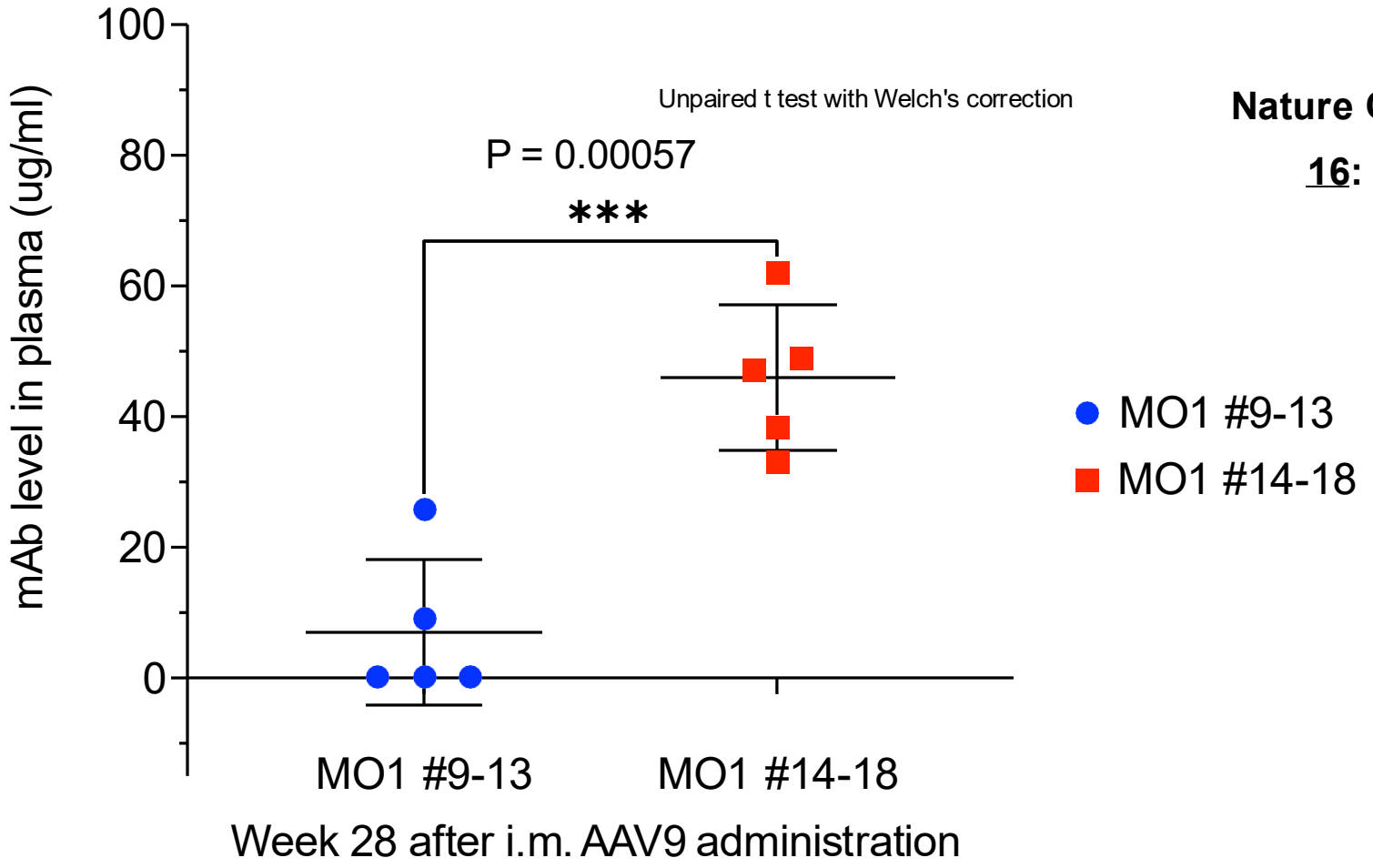
C-rh 3BNC117 levels in immunocompetent B6/129J mice



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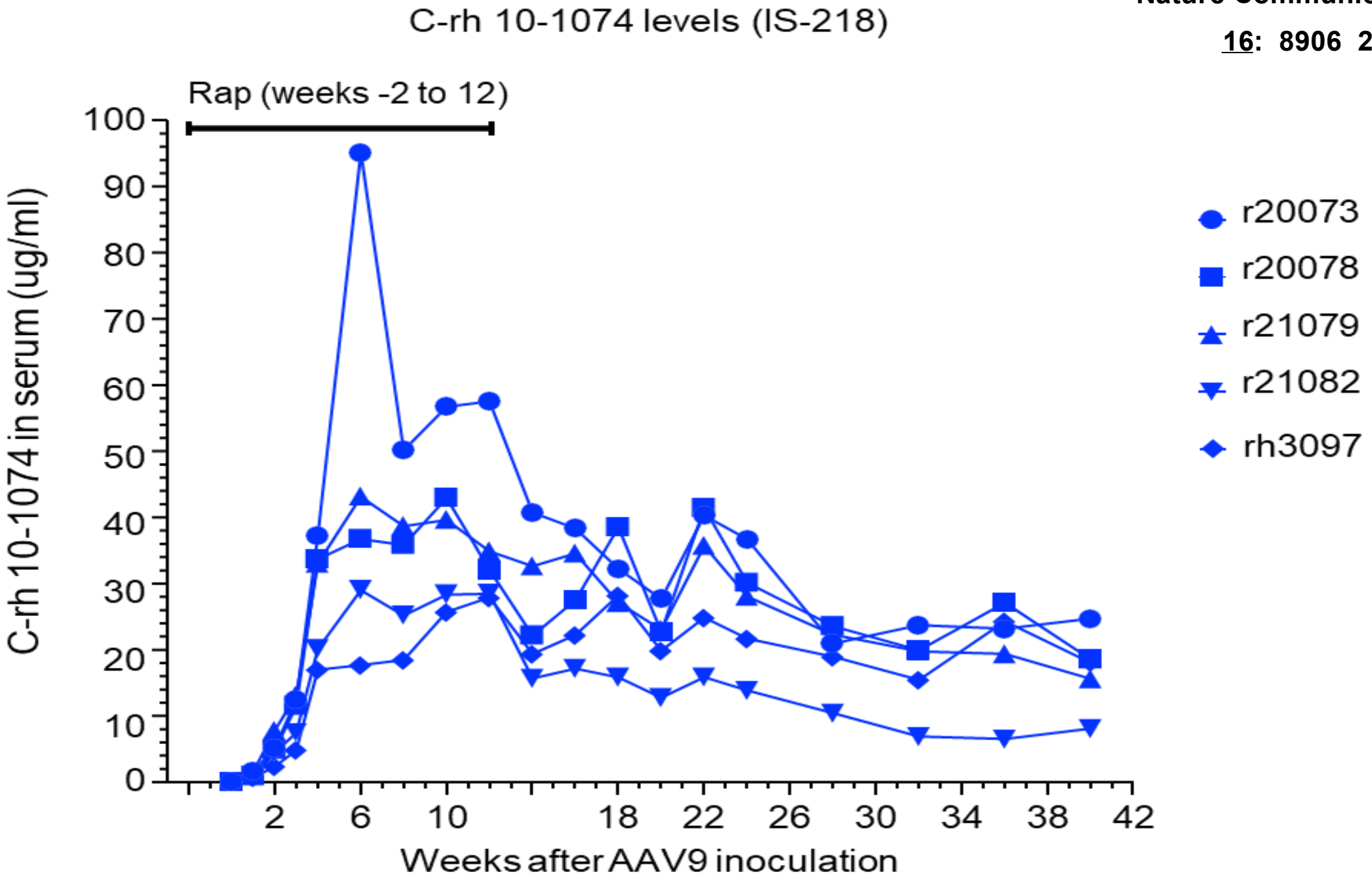
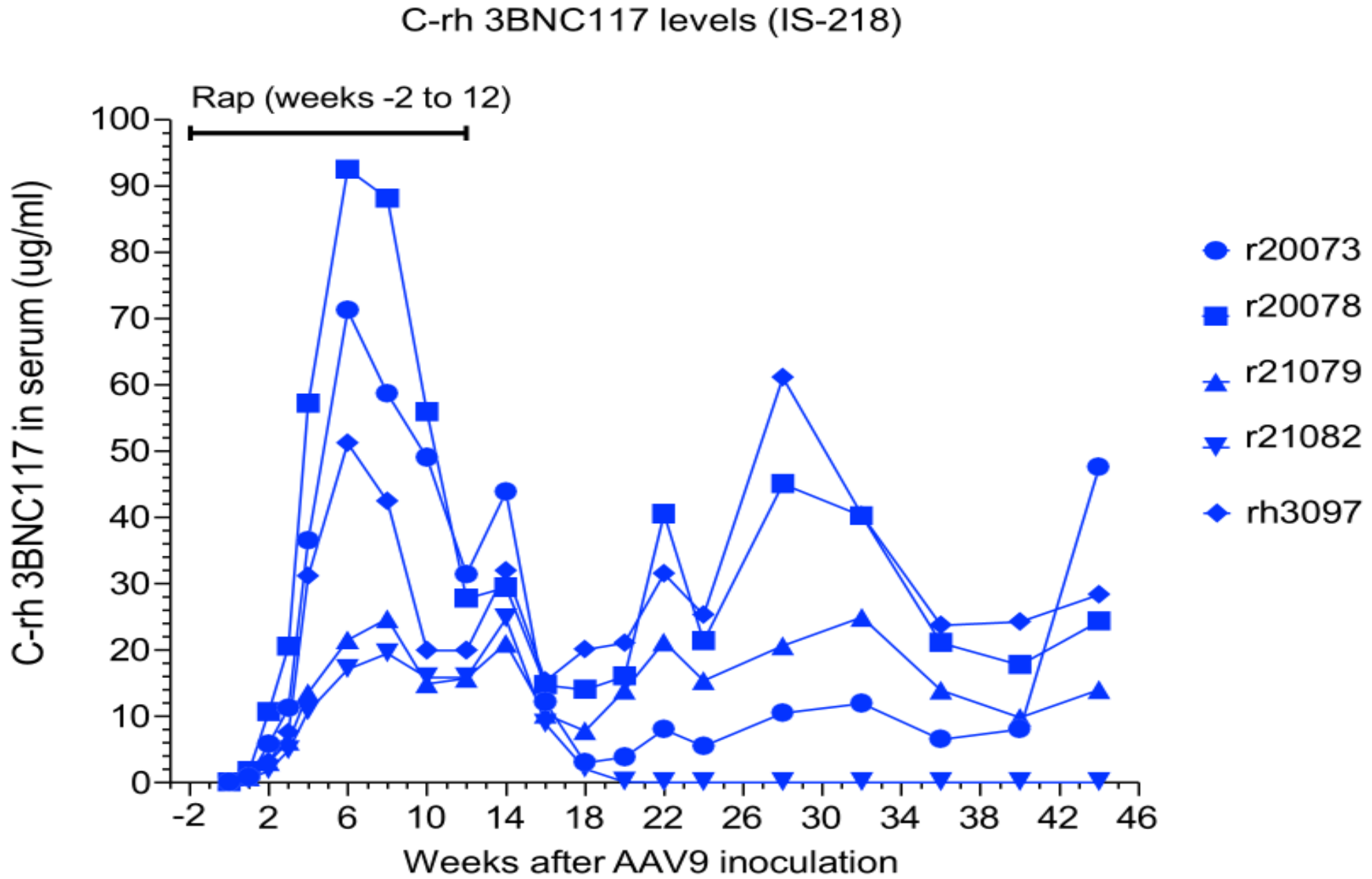
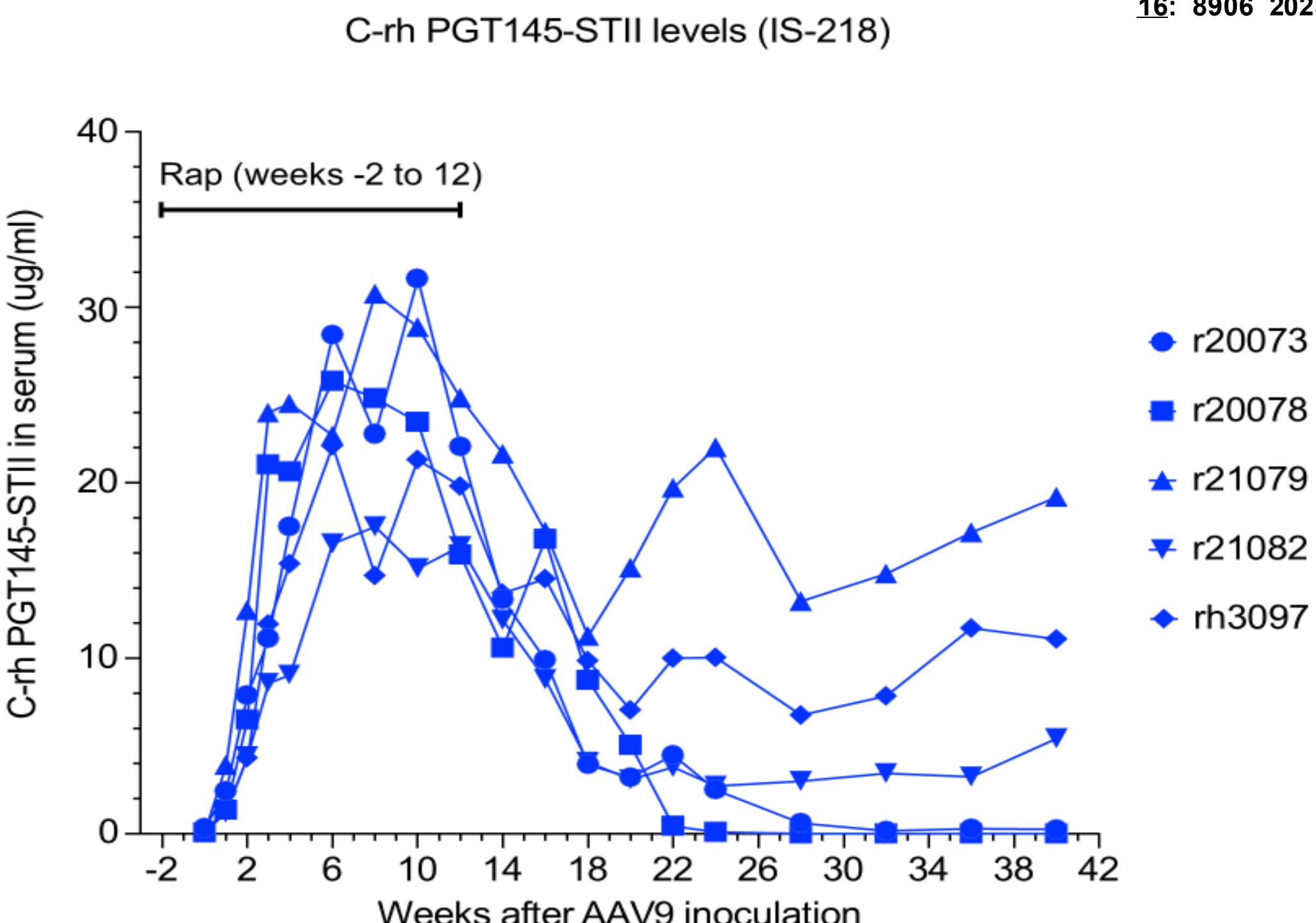
A Monkey Trial to Confirm the Mouse Results

- Five AAV-negative monkeys enrolled
- Naïve not SHIV-infected
- Rapamycin week -2 to 12
- AAV-9 week 0
- Three antibodies
  - 3BNC117
  - 10-0174
  - PGT-145

Nature Communications
16: 8906 2025




C-rh 3BNC117 levels (IS-218)
Rap (weeks -2 to 12)
C-rh 3BNC117 in serum (ug/ml)
100
90
80
70
60
50
40
30
20
10
0
-2
2
6
10
14
18
22
26
30
34
38
42
46
Weeks after AAV9 inoculation
r20073
r20078
r21079
r21082
rh3097


C-rh PGT145-STII levels (IS-218)
Rap (weeks -2 to 12)
C-rh PGT145-STII in serum (ug/ml)
0
10
20
30
40
-2
2
6
10
14
18
22
26
30
34
38
42
Weeks after AAV9 inoculation
r20073
r20078
r21079
r21082
rh3097

Rapamycin Levels (ng/ml)

Week	r20078	r21082	rh3097	r21079	r20073
0	39	45	60	28	55
1	18	21	44	27	14
2	14	3	27	13	4
3	51	54	44	40	>60
4	21	27	30	26	28
5	18	16	30	8	17
6	20	17	22	17	19
8	12	12	15	12	11
12	13	19	39	15	17

Nature Communications

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Conclusions

- Consistent long-term delivery was achieved in 12 of 15 delivery attempts with AAV as vector
- All five monkeys achieved consistent long-term AAV delivery of 2/3 or 3/3 mAbs
- We have improved upon our consistency of Rapamycin delivery in our monkey trials

What about SHIV-infected monkeys?

It is proving much more difficult to achieve the needed antigen-specific tolerance in SHIV-infected monkeys than in naïve monkeys

It is a work in progress, But we are getting there

❖ **Remember** . . . can be used for **prevention** as well as treatment

- **It has been 40+ years since the discovery of HIV and there is *still* no vaccine**
- **There have been 11 vaccine efficacy trials to date and all have failed miserably**
- **The approach described here could be used for vaccine-like prevention of infection in humans**
- **There are good reasons to believe that this approach will be efficacious in humans**

Disclosure

I am a part of the start up company “Marguron”

Acknowledgements

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  -- veterinarians
  -- scientists
- Johns Hopkins
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Thank you!

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