Gene-Based Delivery of Broadly Neutralizing Antibodies for HIV Prevention

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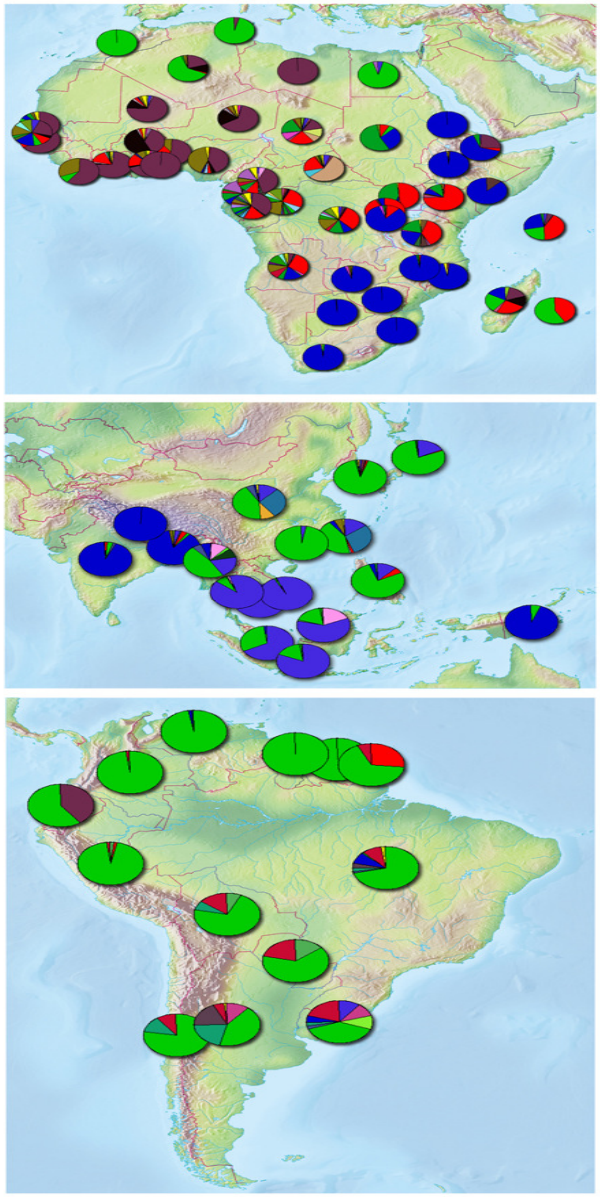
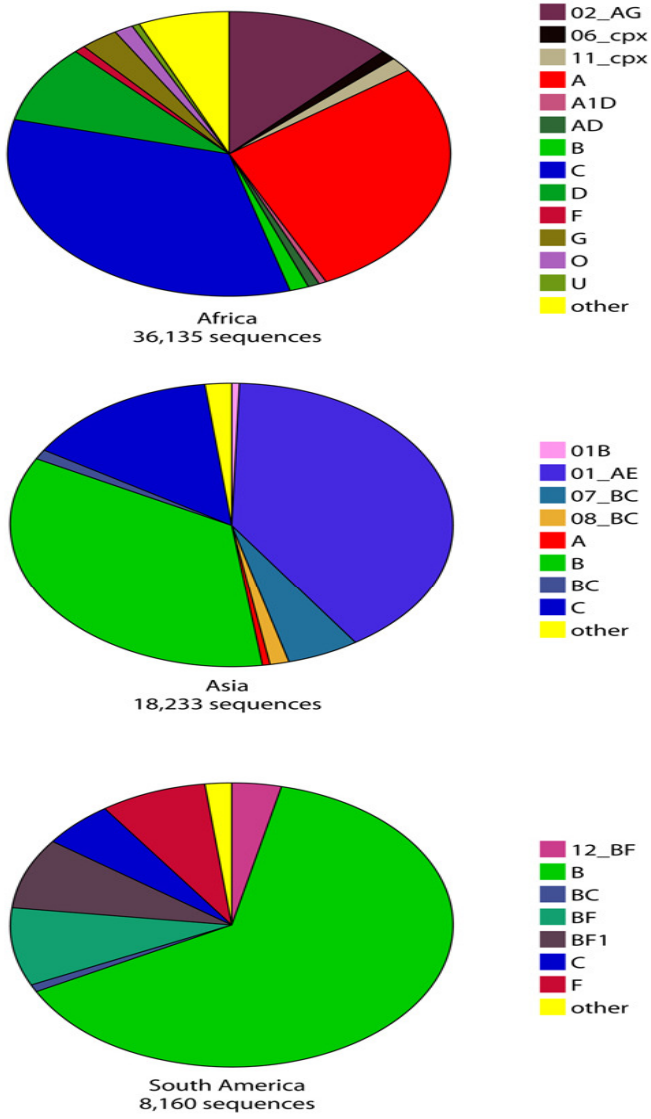
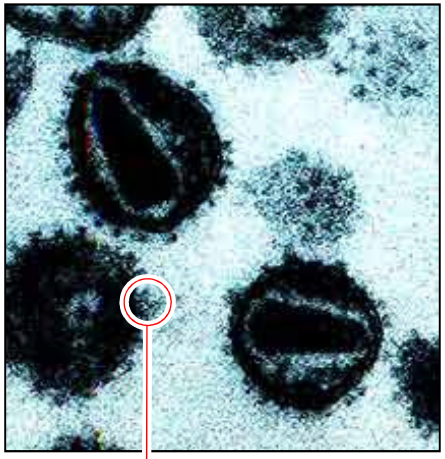
HIV is Hyper-Variable: Vaccine Needs to Elicit Broad and Durable Protective Immunity

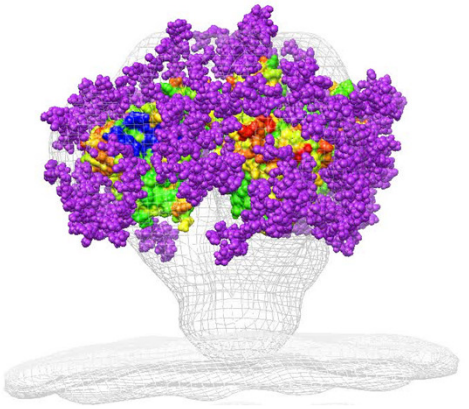




The HIV **broadly neutralizing antibody** problem for vaccine design remains unsolved

- Most licensed vaccines elicit neutralizing antibodies
- Neutralizing antibodies protect against SIV/HIV challenge in animal models
- Broadly neutralizing antibodies in humans against HIV exist (10-25% of HIV+), but it takes a long time (@3yrs)
- **No candidate vaccine in the pipeline elicits broadly neutralizing antibodies against HIV**





Plan B

….What if we can't develop a vaccine that induces bnAbs?

Plan B: Bypass adaptive immunity

- ✓ Select an antibody(s) or antibody-like molecule(s) of pre-determined specificity (broad, potent, etc.)
- ✓ Transfer the representative gene to the host (“vaccinee”)
- ✓ Endow with a protective “response”

Gene-Based Delivery of bnAbs

- **Selection of bnAbs**
- Gene-Based Delivery Systems
- Current Status and Future Directions

Broad and Potent Neutralizing Abs Are Found in Approximately 1% of HIV Infected Subjects

			Clade A	Clade B		Clade C		CRF01_AE
Rank	Score	Country	94UG103	92BR020	JRCSF	IAVI C22	93IN905	92TH021
1	3.67	Ivory Coast	900	900	2700	2700	2700	2700
2	3	Zambia	300	300	2700	300	2700	2700
5	2.83	Ivory Coast	300	300	900	300	2700	2700
5	2.83	Ivory Coast	300	900	2700	900	2700	100
5	2.83	Kenya	300	900	900	900	2700	300
5	2.83	South Africa	300	900	900	2700	2700	100
5	2.83	Rwanda	300	2700	900	2700	2700	<100
8	2.69	Zambia	345	345	1190	1190	1190	345
10	2.67	UK	300	900	900	2700	900	100
10	2.67	Zambia	900	900	900	300	2700	100
10	2.67	Uganda	900	900	900	2700	900	<100
15	2.5	Ivory Coast	300	900	300	900	900	300
15	2.5	South Africa	100	300	300	2700	900	900
15	2.5	South Africa	300	300	300	2700	2700	100
15	2.5	UK	300	900	300	900	900	300
15	2.5	South Africa	2700	100	300	2700	2700	<100
15	2.5	Uganda	900	900	900	900	900	<100
15	2.5	Zambia	300	<100	900	300	2700	2700

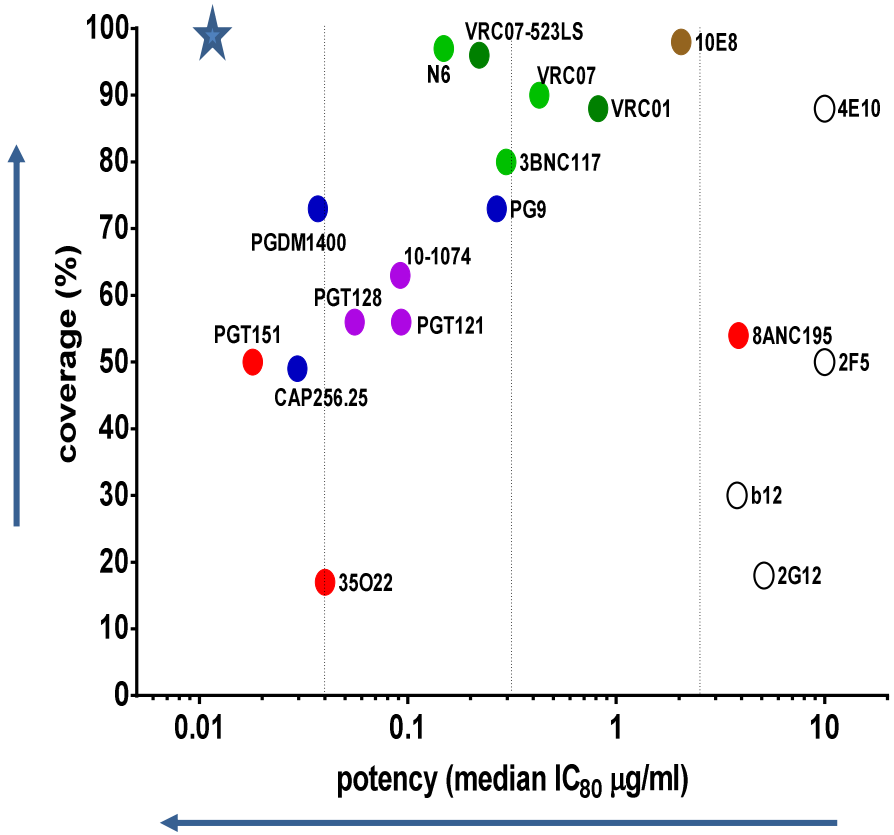
(Simek et.al, J Virology. 2009; **IAVI Protocol G**)

Broad and Potent Neutralizing Antibodies from an African Donor Reveal a New HIV-1 Vaccine Target

Laura M. Walker,[1]* Sanjay K. Phogat,[2]*‡ Po-Ying Chan-Hui,[3] Denise Wagner,[2] Pham Phung,[4] Julie L. Goss,[4] Terri Wrin,[4] Melissa D. Simek,[5] Steven Fling,[1] Jennifer L. Mitcham,[3] Jennifer K. Lehrman,[5] Frances H. Priddy,[5] Ole A. Olsen,[3] Steven M. Frey,[3] Phillip W. Hammond,[3] Protocol G Principal Investigators,† Stephen Kaminsky,[2] Timothy Zamb,[2] Matthew Moyle,[3] Wayne C. Koff,[5] Pascal Poignard,[1] Dennis R. Burton[1,6]‡

Clade	No. of viruses	Median IC_{50} (μg/ml) against viruses neutralized with an IC_{50} <50 μg/ml						
		b12	2G12	2F5	4E10	PG9	PG16	PGC14
A	27	6.98	17.10	5.70	6.20	0.16	0.11	41.59
B	31	0.80	0.82	2.41	5.22	0.43	0.70	21.88
C	27	6.46	2.93	31.51	2.97	0.22	0.25	11.97
D	25	1.47	7.71	3.17	4.60	0.10	0.02	38.57
CRF01_AE	10	21.53	>50	0.26	0.51	0.08	0.03	>50
CRF_AG	10	10.40	0.95	0.64	1.42	0.80	0.03	45.10
G	15	3.07	31.03	1.24	1.44	0.29	1.21	>50
F	15	>50	9.23	1.78	2.30	0.09	0.08	25.71
Total	162	2.82	2.43	2.30	3.24	0.22	0.15	25.99

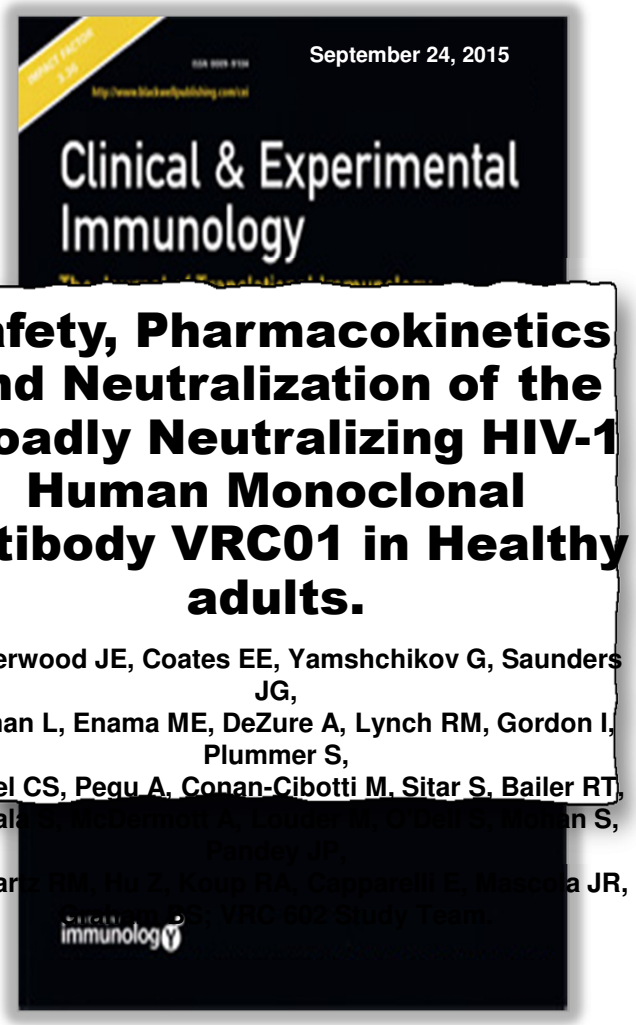
HIV-1 mAb Potency and Breadth
Panel of 208 diverse isolates



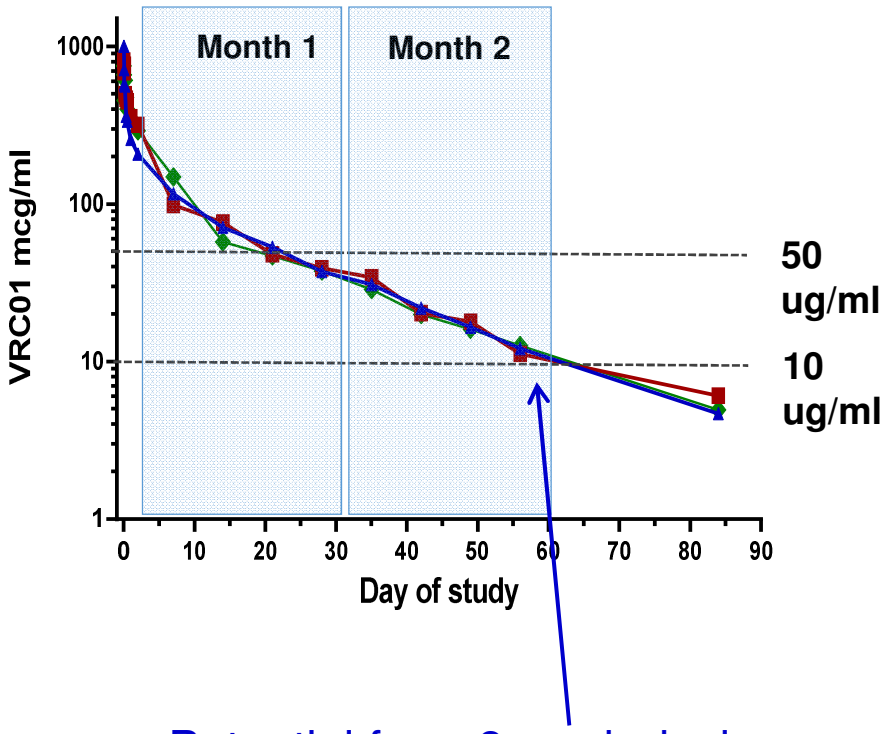
New antibodies 10 - 100 fold more potent

CAVD, VRC collaboration: Montefiori, Bailer, Louder et al.

VRC01 Phase I Study (Safety and PK)

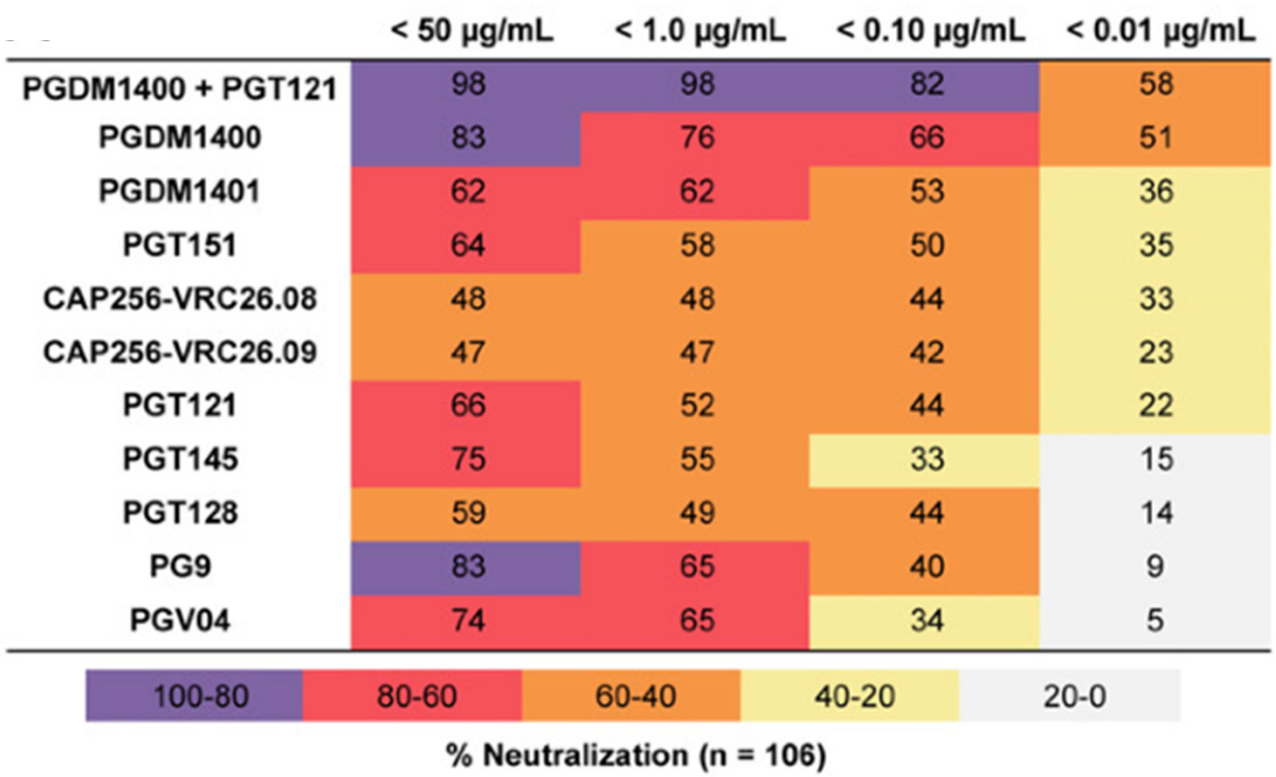


Serum levels of VRC01 (20 mg/kg)



- Potential for q 8 week dosing
- Phase 2b test of concept to begin 2Q 2016 (AMP trial).

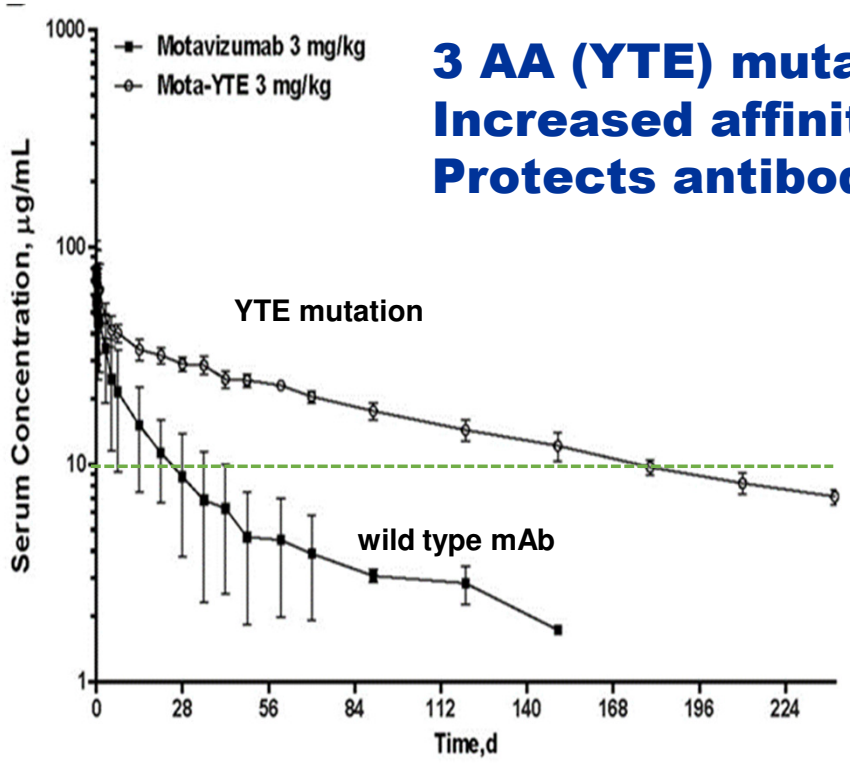
Combinations of bnAbs are better



	< 50 µg/mL	< 1.0 µg/mL	< 0.10 µg/mL	< 0.01 µg/mL
PGDM1400 + PGT121	98	98	82	58
PGDM1400	83	76	66	51
PGDM1401	62	62	53	36
PGT151	64	58	50	35
CAP256-VRC26.08	48	48	44	33
CAP256-VRC26.09	47	47	42	23
PGT121	66	52	44	22
PGT145	75	55	33	15
PGT128	59	49	44	14
PG9	83	65	40	9
PGV04	74	65	34	5

Sok, D etal, Proc Natl Acad Sci U S A. 2014 Dec 9;111(49):17624-9.

Extending half-life in humans



Days

3 AA (YTE) mutation in Fc region
Increased affinity for FcRn
Protects antibody from catabolic pathway

➡ **Maintain > 10 ug/ml for ~ 6 months**

Gene vector Ab delivery

- **AAV**
- **DNA, mRNA**

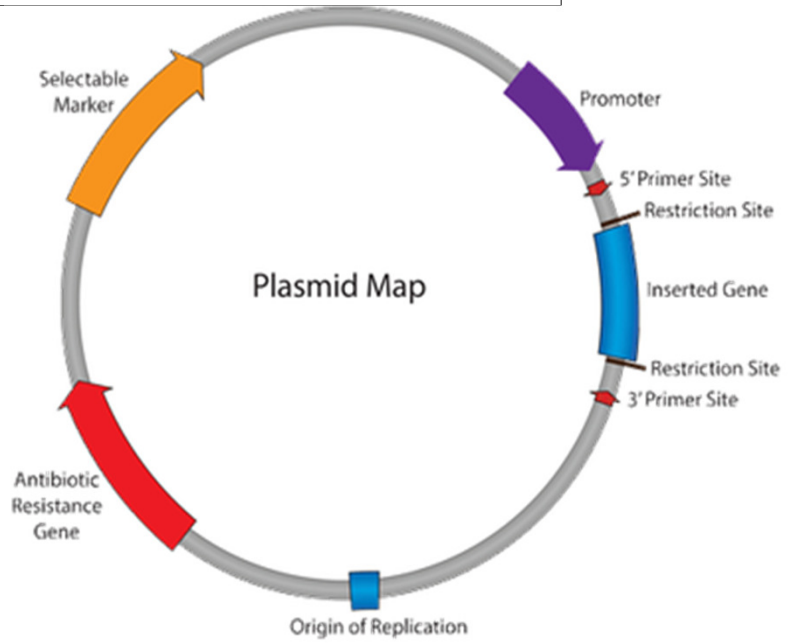
Robbie G J et al.
Antimicrob. Agents Chemother. 2013;57:6147-6153

Gene-Based Delivery of bnAbs

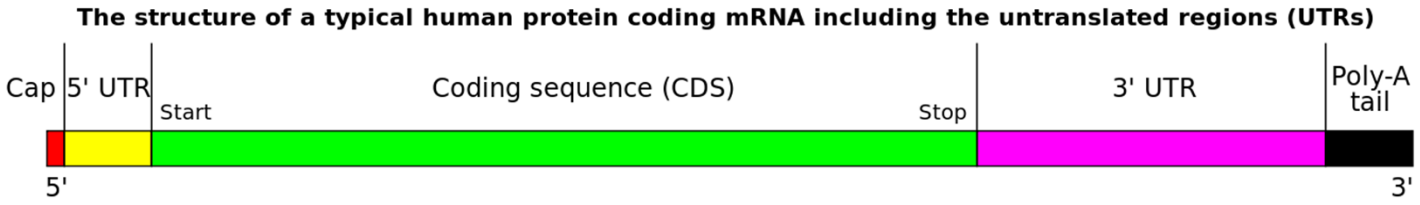
- Selection of bnAbs
  - Potency; Breadth; Half-Life; Fc Functionality
- **Gene-Based Delivery Systems**
- Current Status and Future Directions

Nucleic Acid Delivery of bnAbs

Plasmid DNA



mRNA

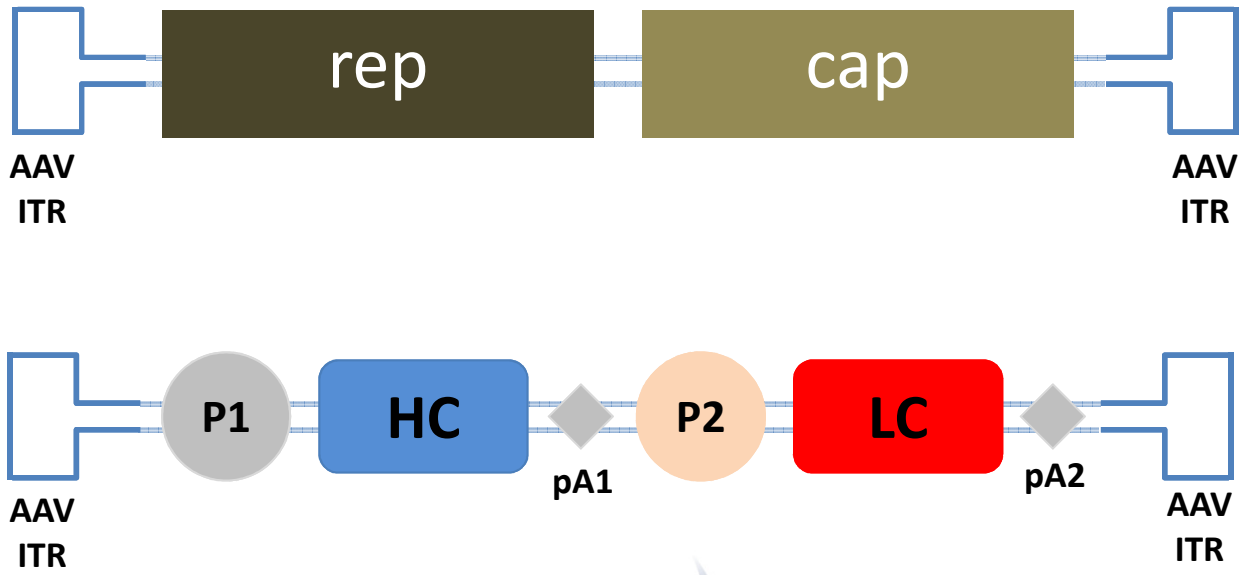


The structure of a mature eukaryotic mRNA. A fully processed mRNA includes a 5’ cap, 5’ UTR, coding region, 3' UTR, and poly(A) tail.

Nucleic Acid Delivery of bnAbs

- Great potential; early in development
  - Ease of manufacturing; speed
- DNA
  - Adjuvants
  - Delivery systems
  - Electroporation
  - Multiple companies working in this space
- mRNA
  - Adjuvants
  - Self amplification
  - Multiple companies working in this space

Adeno-associated virus (AAV)



Wild-type genome

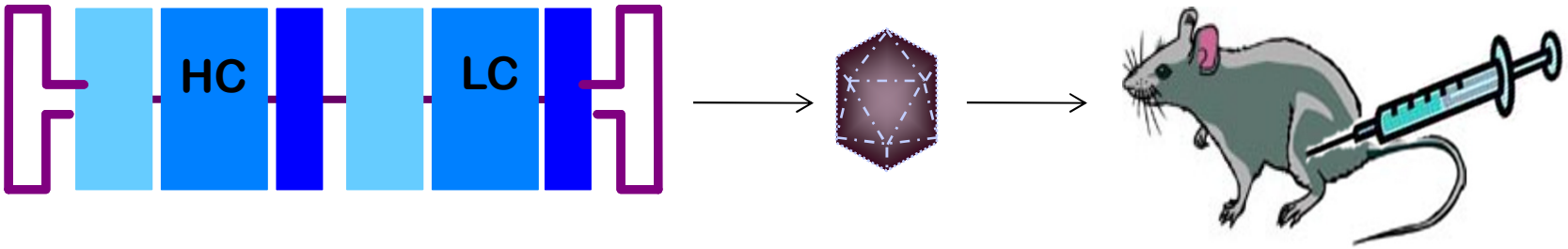
Recombinant genome

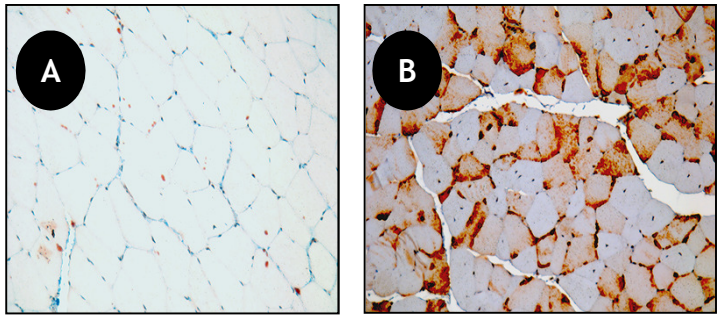
Packaging reaction

rAAV vector with antibody gene

Phil Johnson

Human bnAb gene transfer in mice





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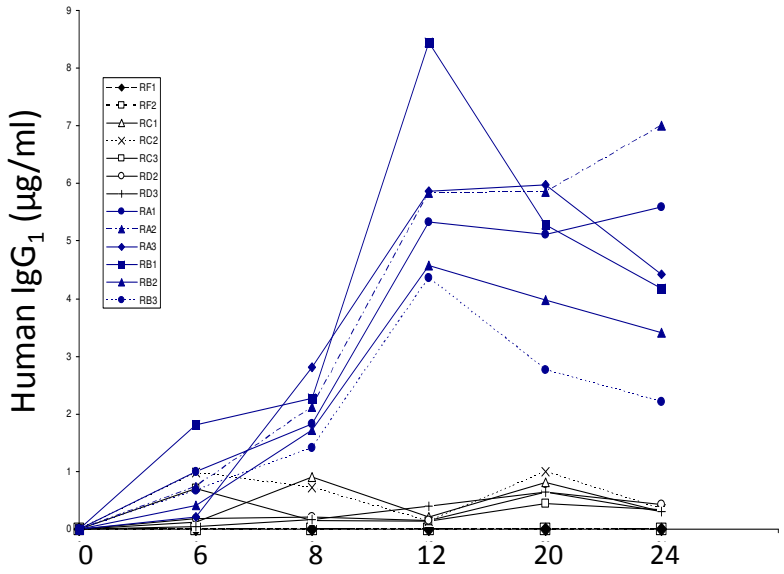


Lewis et al (2002) J Virol 76:8769-8775

Proof of concept in monkeys:2009

nature medicine

Vector-mediated gene transfer engenders long-lived neutralizing activity and protection against SIV infection in monkeys

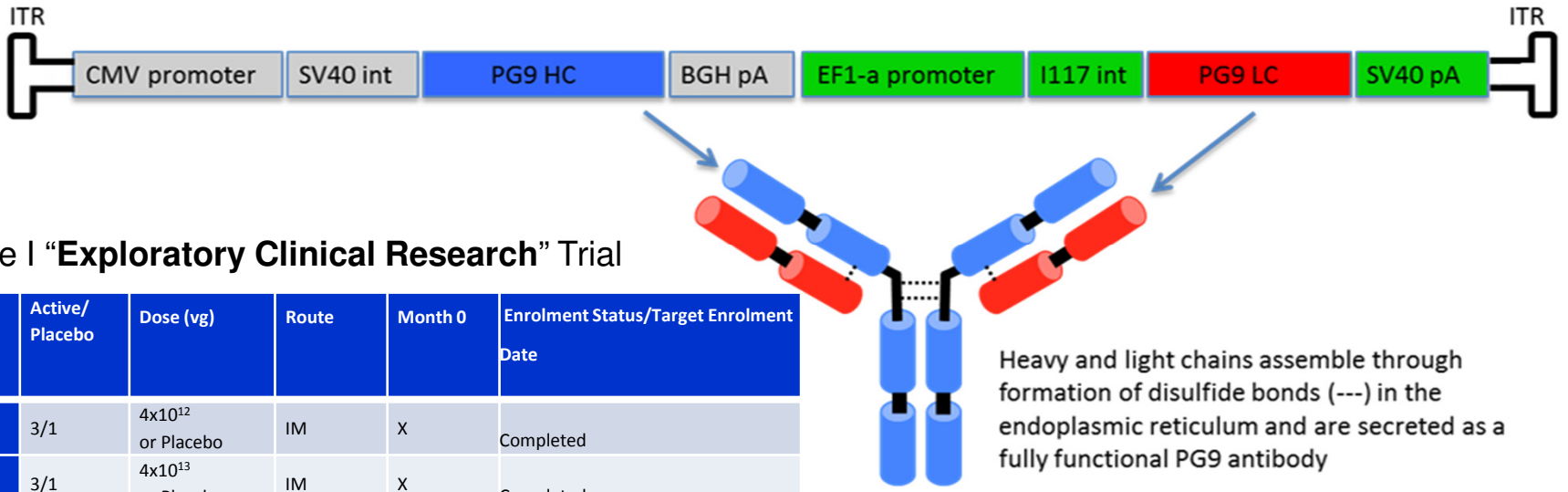
Philip R Johnson[1], Bruce C Schnepp[1], Jianchao Zhang[2], Mary J Connell[1], Sean M Greene[1], Eloisa Yuste[3], Ronald C Desrosiers[3] & K Reed Clark[2]

The key to an effective HIV vaccine is development of an immunogen that elicits persisting antibodies with broad neutralizing activity against field strains of the virus. Unfortunately, very little progress has been made in finding or designing such immunogens. Using the simian immunodeficiency virus (SIV) model, we have taken a markedly different approach: delivery to muscle of an adeno-associated virus gene transfer vector expressing antibodies or antibody-like immunoadhesins having predetermined SIV specificity. With this approach, SIV-specific molecules are endogenously synthesized in myofibers and passively distributed to the circulatory system. Using such an approach in monkeys, we have now generated long-lasting neutralizing activity in serum and have observed complete protection against intravenous challenge with virulent SIV. In essence, this strategy bypasses the adaptive immune system and holds considerable promise as a unique approach to an effective HIV vaccine.

NATURE MEDICINE VOLUME 15 | NUMBER 8 | AUGUST 2009

Vector Mediated Gene Delivery of Broadly Neutralizing Antibodies AAV1-PG9 Prototype

PG9 Antibody Expressed in rAAV-vector with Dual Promoter ("PG9-DP")



Phase I "**Exploratory Clinical Research**" Trial

Group	Active/ Placebo	Dose (vg)	Route	Month 0	Enrolment Status/Target Enrolment Date
A	3/1	$4x10^{12}$ or Placebo	IM	X	Completed
B	3/1	$4x10^{13}$ or Placebo	IM	X	Completed
C*	3/1	$8x10^{13}$ or Placebo	IM	X	Completed
SRB review to determine progression to either C1, or D and D1					September 2015
C1	9/3	$8x10^{13}$ or Placebo	IM	X	
Total Number of Volunteers: 24 (18/6)					
OR					
D	3/1	$1.2x10^{14}$ or Placebo	IM	X	January 2016
D1	3/1	$1.2x10^{14}$ or Placebo	IM	X	April 2016
Total Number of Volunteers: 20 (15/5)					December 2015

*Group C enrollment delay due to study pause and subsequent recruitment challenges

- Neutralization at 6 months go/no-go data expected 2Q 2016
- **If successful, AAV1-PGT121 and AAV1-PGDM1400 would potentially be combined as a candidate to advance thru test of concept (2b) trial**

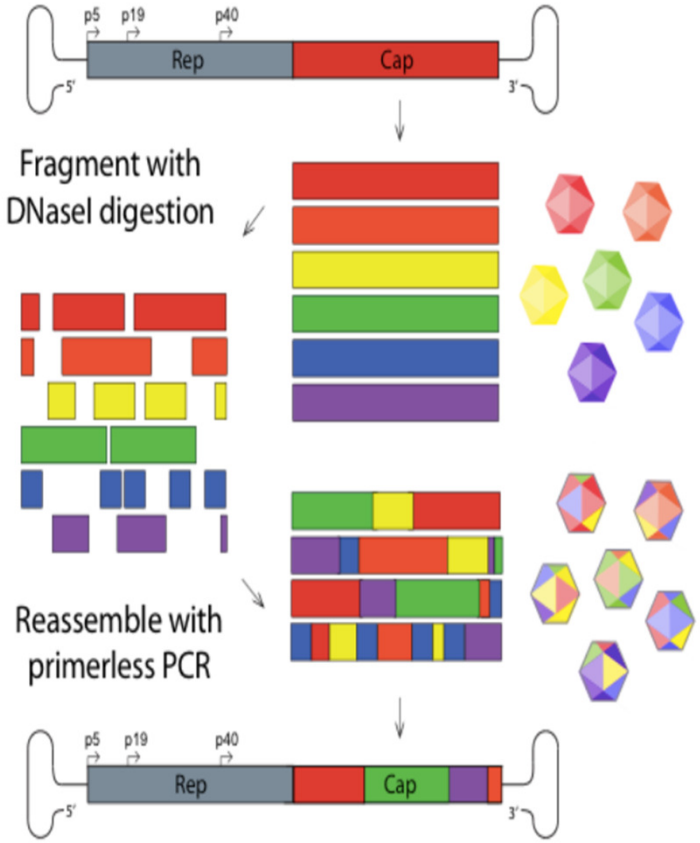
AAV Delivery of bnAbs: Future Directions

- **Selection of Antibodies**: Combinations
  - PGT 121 + PGDM 1400
  - Other combinations

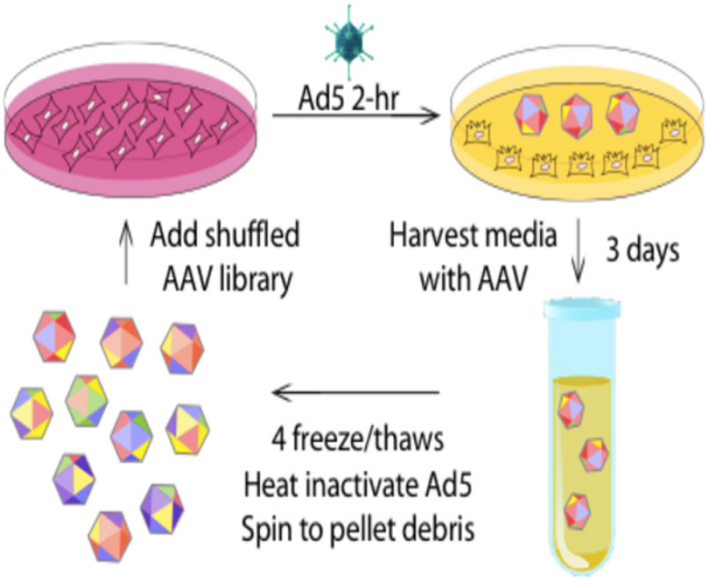
- **Selection of AAV Vector**
  - Synthetic Capsids Improve Transduction in muscle (Mark Kay, Stanford)

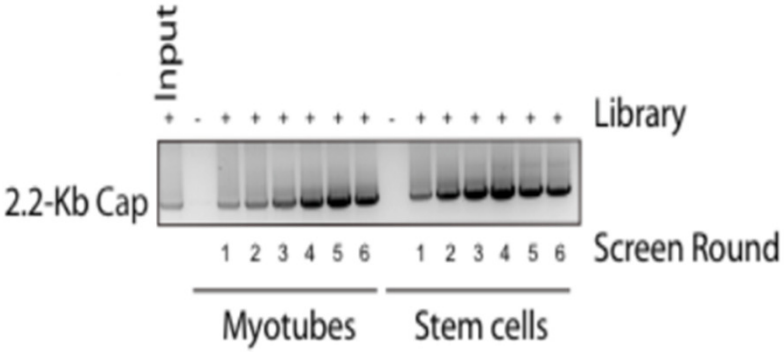
Synthetic AAV Capsids Increase Transduction in Muscle

Ten parental serotypes



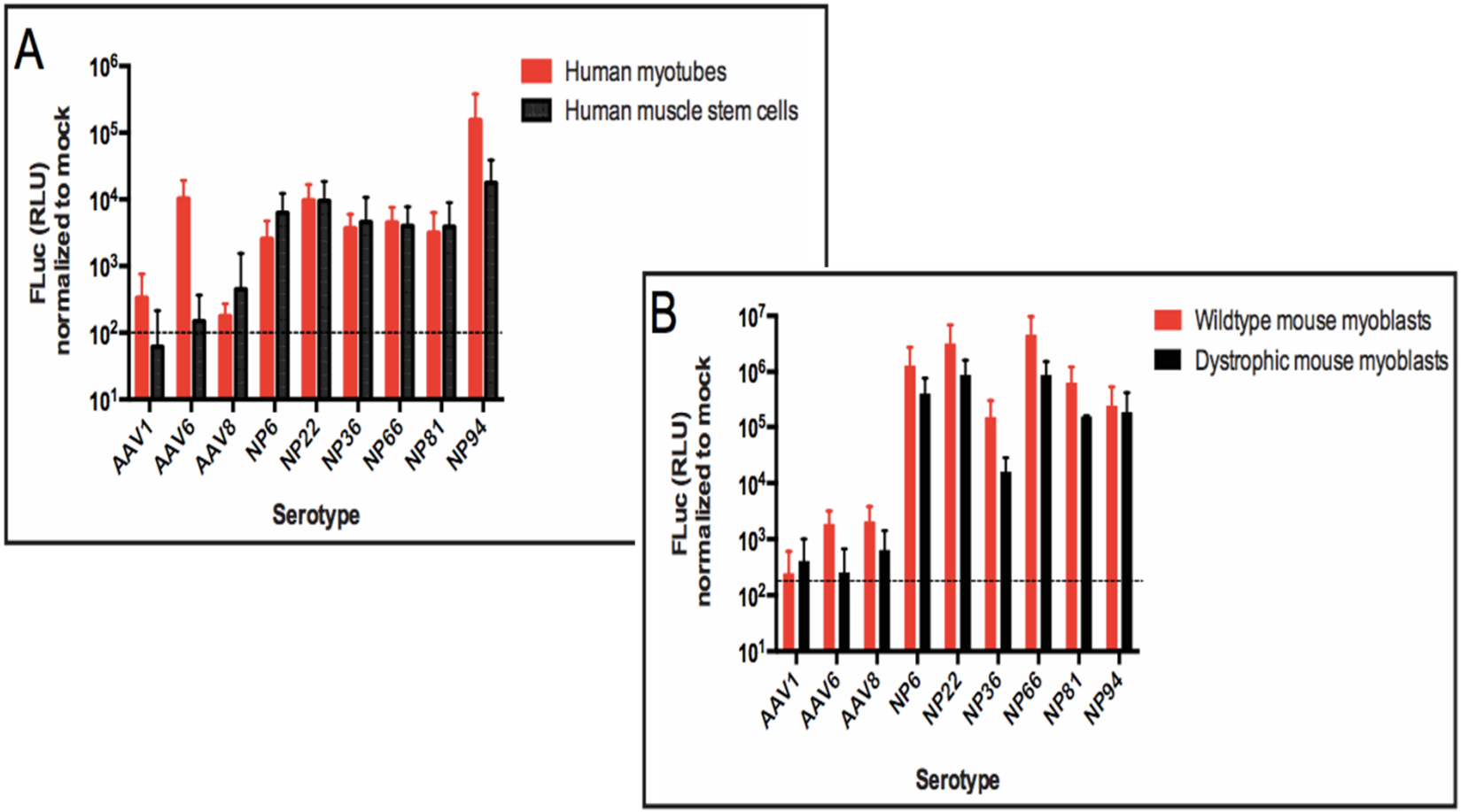
Selection screen





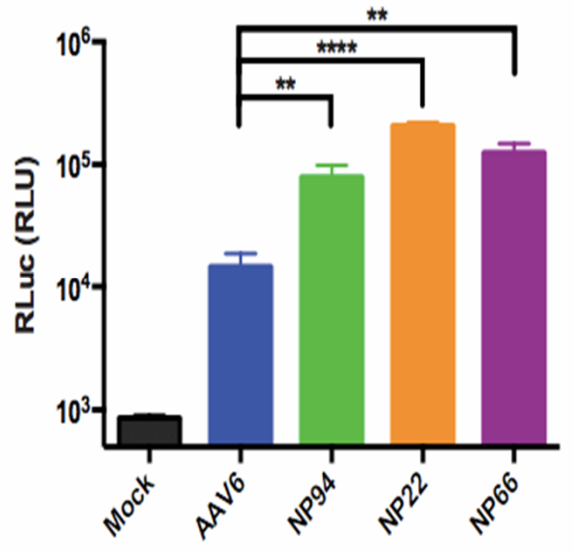
(Courtesy of Mark Kay and Nicole Paulk, Stanford)

Transduction of cultured muscle cells

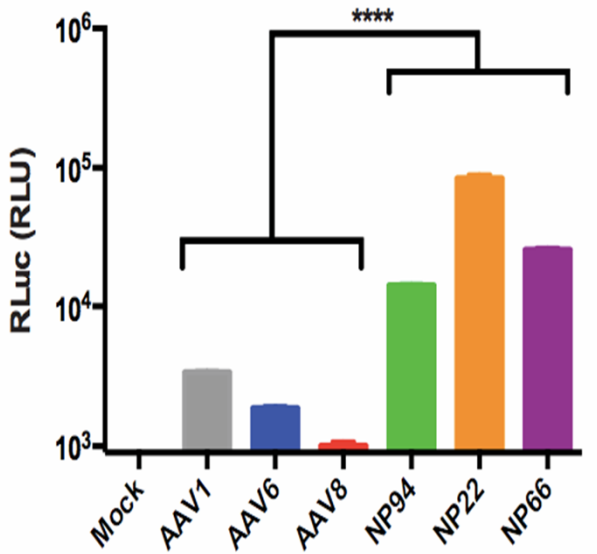


(Courtesy of Mark Kay and Nicole Paulk, Stanford)

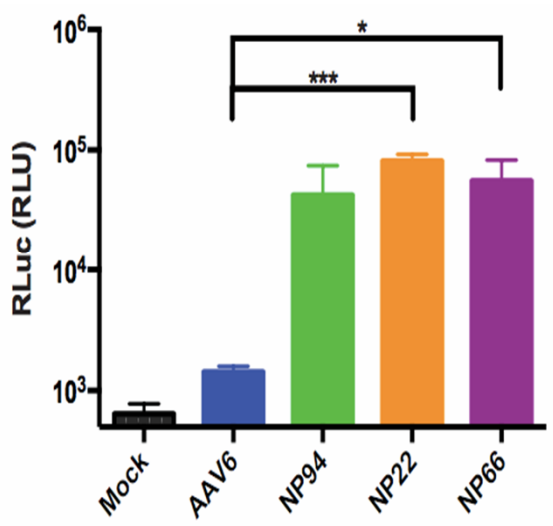
Transduction of muscle explants



***Pectoralis major* fibers (human)**



***Latissimus dorsi* fibers (human)**



***Biceps femoris* fibers (rhesus**

(Courtesy of Mark Kay and Nicole Paulk, Stanford)

Summary and Future Directions

- Broadly neutralizing antibodies have been identified vs. HIV, and may have utility in HIV prevention
  - VRCO1 test of concept trial 2Q, 2016
- Genetic delivery of bnAbs offers the potential to safely administer bnAbs, with significant potential for long-lived expression
- Future directions
  - Combination of bnAbs
  - mRNA; epDNA; Viral vectors (e.g. AAV)
  - Designer transgenes and capsids

Phil Johnson Lab

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Mary Connell
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Amy Smith
Ryan Jensen
Sean Greene
Katharina Scholz
Jianchao Zhang
Anne Lewis

CHOP Vector Core

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John Mascola

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