Properties of eCD4-Ig relevant to a ‘functional cure’*

Mike Farzan, The Scripps Research Institute
Miami Winter Symposium, January 29, 2019

*more properly: a sustained drug-free state of virologic remission
Properties of eCD4-Ig relevant to a ‘functional cure’

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I am a stakeholder in Emmune Inc., which licenses eCD4-Ig from Scripps
What we are learning about bNAbs and a ‘functional cure’:

bNAbs can consistently reduce viral loads to undetectable in humans and NHP

Antibody effector functions likely contribute to this reduction

bNAbs can delay viral rebound, but the antibody must present to suppress the virus for any length of time

Even then, pre-existing viral resistance and viral escape are major hurdles to the therapeutic use of bNAbs

AAV-expressed bNAbs tend to raise anti-drug antibodies that interfere with their functions

In short, antibodies might establish a ‘functional cure’ in humans, but...

We need high and sustained levels of potent antibodies with maximum breadth, minimum immunogenicity, and efficient effector functions.
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We need: high and sustained levels of **potent** antibodies with **maximum breadth**, minimum immunogenicity, and efficient effector functions

**Breadth**
eCD4-Ig neutralized all 270 isolates tested with $\text{IC}_{80}$s < 9 µg/ml
This includes SIV and HIV-2 isolates
Percent of isolates with $\text{IC}_{80}$ < 20 µg/ml:
eCD4-Ig – 100%, 10-1074 – 61%, PGT121 – 60%
3BNC117 – 67%, PGDM1400 – 65%

**Potency**
Median $\text{IC}_{80}$ in clade C panel (µg/ml):
eCD4-Ig – 0.7, 10-1074 – 1.4, PGT121 – 3.7,
3BNC117 – 1.5, PGDM1400 – 1.2

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**New, more potent variants**

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Fetzer et al., JV, 2018
eCD4-Ig’s breadth corresponds to difficulty-of-escape

80 passages over 200 days in the presence of the IC_{95} s of NIH45-46, CD4-Ig and eCD4-Ig
We need: high and **sustained** levels of potent antibodies with maximum breadth, minimum immunogenicity, and efficient effector functions.

- 4 rhesus macaques for each study were inoculated with $2.5 \times 10^{13}$ AAV1 particles with 4:1 ratio of rh-eCD4-Ig to rh-TPST2.
- Macaques were challenged repeatedly with escalating doses of SHIV-AD8 or SIVmac239 until all controls were infected.
- Serum was analyzed for protein titers, viral loads, and immune response to rh-eCD4-Ig.
We need: **high** and **sustained** levels of potent antibodies with maximum breadth, minimum immunogenicity, and efficient effector functions.

Expression from 3 to 70 ug/ml. Sufficient for prophylaxis, but worse than bNAbs.
We need: high and **sustained** levels of **potent** antibodies with **maximum breadth**, minimum immunogenicity, and efficient effector functions.

Unlike other HIV/SIV vaccine studies in primates:
- All control animals were infected before any AAV-eCD4-Ig inoculated animals were.
- One-time inoculation. Protection lasts more than a year. Projected half-life > 5 years.
- Escalating IV doses, more rigorous than any other challenge schedule.
- Doesn’t rely on immune system: human variation, species differences are far less of a concern.
- No conventional (or unconventional) vaccine can protect against both viruses.
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*eCD4-Ig mediates efficient ADCC activity*

ADCC-inactive forms of eCD4-Ig, VRC01 and 10-1074 were mixed at 1 ug/ml with varying dilutions of patient sera with YU2-infected cells.

Davis-Gardner et al., PLoS Path, 2017

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But are we there yet?

6 SHIV-AD8-infected, ART-treated, rhesus macaques inoculated with:

\[ 2 \times 10^{12} \text{vg/kg AAV8- and AAV1-eCD4-Ig} \]

eCD4-Ig is rhesus eCD4-IgG2\textsuperscript{139N} with LS mutation

Basic protocol (with variations)
- SHIV-AD8 at week 0
- cART at week 12
- AAV8-eCD4-Ig at week 56
- AAV1-eCD4-Ig at week 70
- cART lifted at week 74
- Followed now for 50-70 weeks since cART lift (12/20/18)
- 4 control animals had viral loads from 1200-7000 copies/ml
Are we there yet? 6 (of 6) examples

Viral loads: <15 copies/ml
[eCD4-Ig]: 16.5 ug/ml
50 weeks since cART lift

Viral loads: 15 copies/ml
[eCD4-Ig]: 14.9 ug/ml
50 weeks since cART lift

SHIV-AD8 at week 0  cART at week 12  AAV8-eCD4-Ig at week 56  AAV1-eCD4-Ig at week 70  cART lifted at week 74
Are we there yet? 6 (of 6) examples

Viral loads: 6300 copies/ml  
[eCD4-Ig]: 12.3 ug/ml  
50 weeks since cART lift

Viral loads: <15 copies/ml  
[eCD4-Ig]: 19.6 ug/ml  
50 weeks since cART lift

SHIV-AD8 at week 0  
cART at week 12  
AAV8-eCD4-Ig at week 56  
AAV1-eCD4-Ig at week 70  
cART lifted at week 74
Are we there yet? 6 (of 6) examples

Viral loads: <15 copies/ml
[eCD4-Ig]: 19.0 ug/ml
70 weeks since cART lift

Viral loads: <15 copies/ml
[eCD4-Ig]: 4.6 ug/ml
70 weeks since cART lift
We need: high and sustained levels of potent antibodies with maximum breadth, minimum immunogenicity, and efficient effector functions

From here:
higher expression, repeat SHIV-AD8 with controls, try to control SIVmac239
Community slide and summary

Take home:

AAV-expressed eCD4-Ig has properties essential to establishing a functional cure in NHP

Some of these: 100% breadth, difficulty-of-escape, collaboration with serum antibodies, are unique to eCD4-Ig.

AAV-eCD4-Ig has established what looks like a functional cure of SHIV-AD8-infection in 4-5 of 6 macaques

We can make this approach more robust, and will attempt to establish a cure in SIVmac239-infected animals

Why this is important:

Positive persons may choose to control their virus with a single protein in serum rather than 3 compounds that enter nearly every cell in the body

A sustained expression of an ADCC-active inhibitor that can replace cART makes an excellent platform for LRA studies (kick-and-kill).

A functional cure of this sort is probably necessary as we attempt to implement imperfect eradication strategies. Otherwise continuous monitoring will be necessary.

Long-term expression of eCD4-Ig might by itself also change the rate of reservoir decline ('kill-and-kill'?).
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