The Landscape of Immune Responses Targeted by Phase I HIV Vaccine Candidates

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Global HIV Vaccine Enterprise

HIV Vaccine development challenge

Only a tiny fraction of candidates have a shot at being tested for efficacy

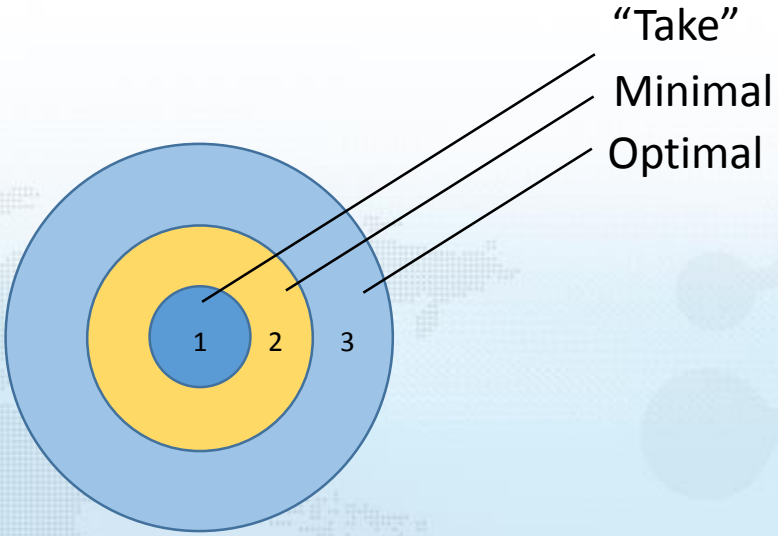
Animal models and Phase I/II trials are the only stages when optimization is possible

Lack of correlates of immune protection

What do you optimize for?

Questions we asked

1. Please list responses that may indicate “take” of the vaccine, but may not by themselves be critical for protection
2. What are the bare minimum immune responses that would indicate that the vaccine should be advanced to the next level of clinical development?
3. In addition to the responses listed above, are there desired/optimal immune responses that you expect to eventually generate with this candidate (or a version of it)?



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Process

- Not a multiple-choice list, questions are open-ended
  - Structured interviews/surveys
- Not actual go/no-go criteria, focus on what the goal/opinion is
  - Qualitative answers (not levels or % responding)
- Focus on research groups that have candidates in Phase I
  - Small sample size
  - Current candidates shaped by past events/ideas
- Reflect opinion on the mechanism of action and/or correlates of protection

People interviewed

• Tim Fouts	DNA/VSV; FLSC
• Barney Graham	DNA/Protein
• Tom Hanke	MVA/DNA/ChAd
• Bart Haynes	Sequential protein; peptide
• Sarah Joseph	DNA/MVA/protein
• Shan Lu	DNA/protein?
• Nelson Michael	Ad26/MVA +/- protein
• Harriet Robinson	DNA/MVA +/- protein
• Eric Sandstrom	DNA/MVA +/- protein
• Yiming Shao	DNA/Tiantan +/- protein

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Candidate G

Minimal

Polyclonal binding Ab
Tier 1 neutralization
CD4 T cell responses to Env
Durability

Optimal

Tier 2 neutralization
ADCC

Candidate H

Minimal

Optimal

Tier 2 neutralization

Durability

Candidate L

Minimal	Optimal
Polyclonal binding Ab	High IgG3 and low IgA
V1V2 binding Ab	In vitro viral inhibition
Any antiviral Ab activity	
Total T cell responses	
CD4 T cell responses to gag	
CD4 T cell responses to env	
CD8 T cell responses to gag	
CD8 T cell responses to env	
Durability	

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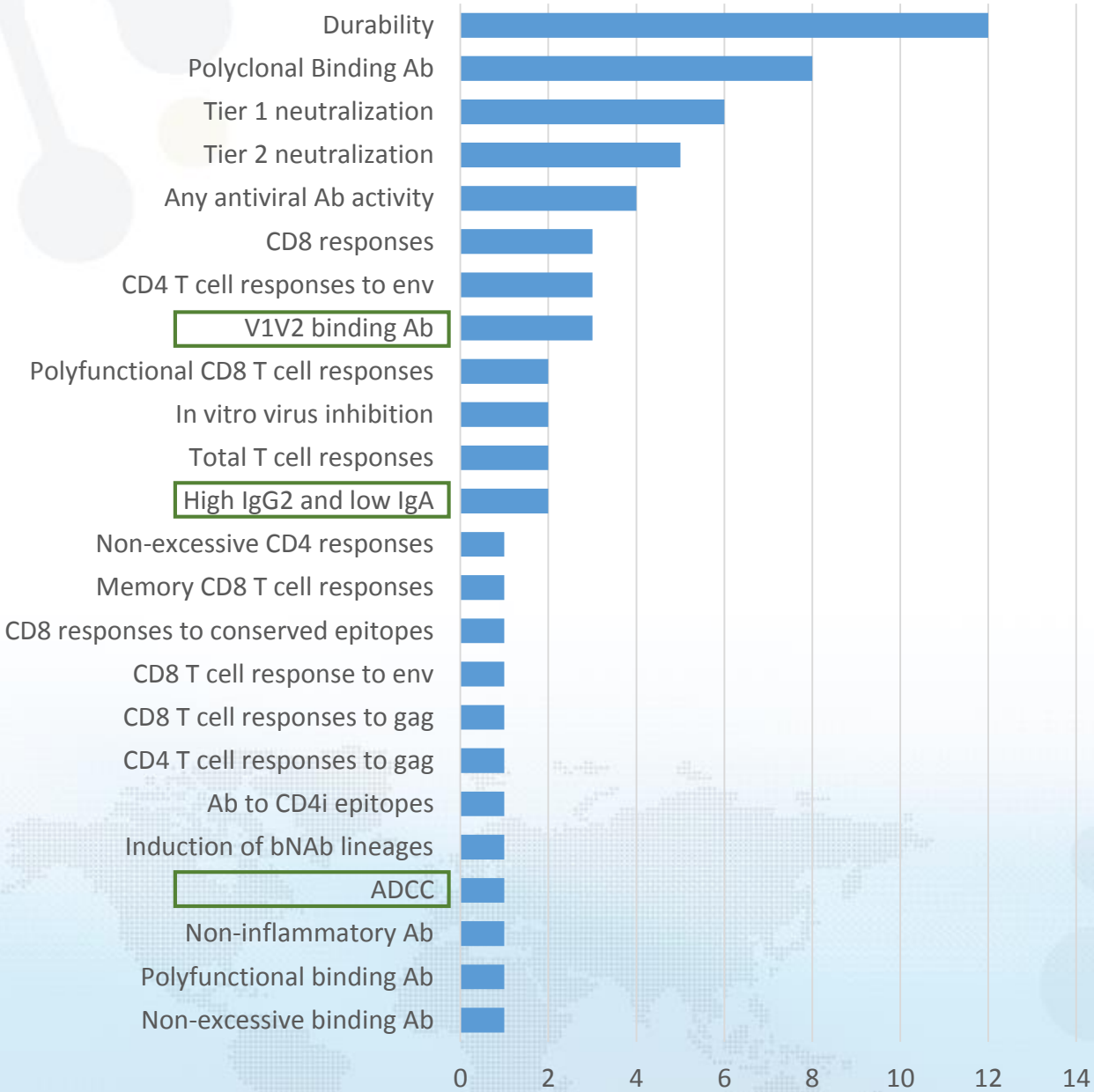
Popularity of Responses for Optimal Profile

RV144 correlates



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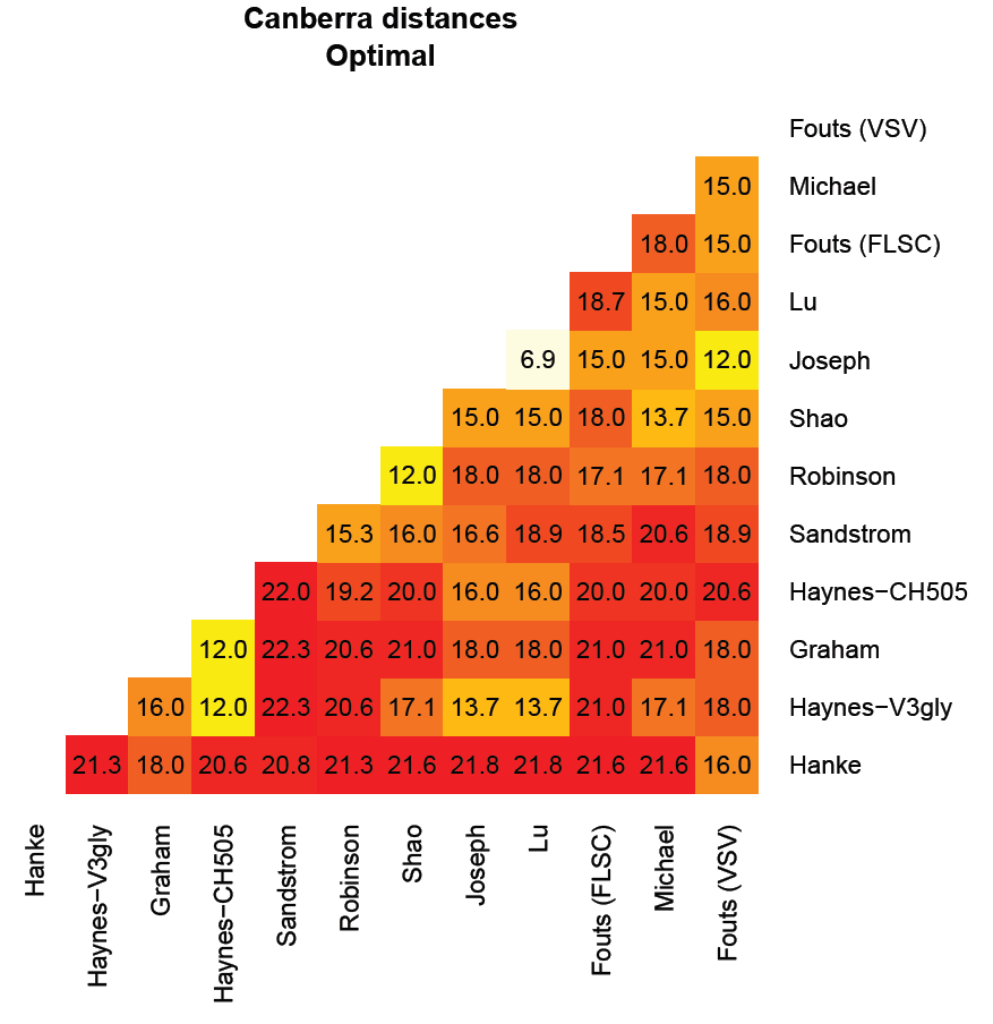
Create pairwise distances based on similarity of chosen immune responses



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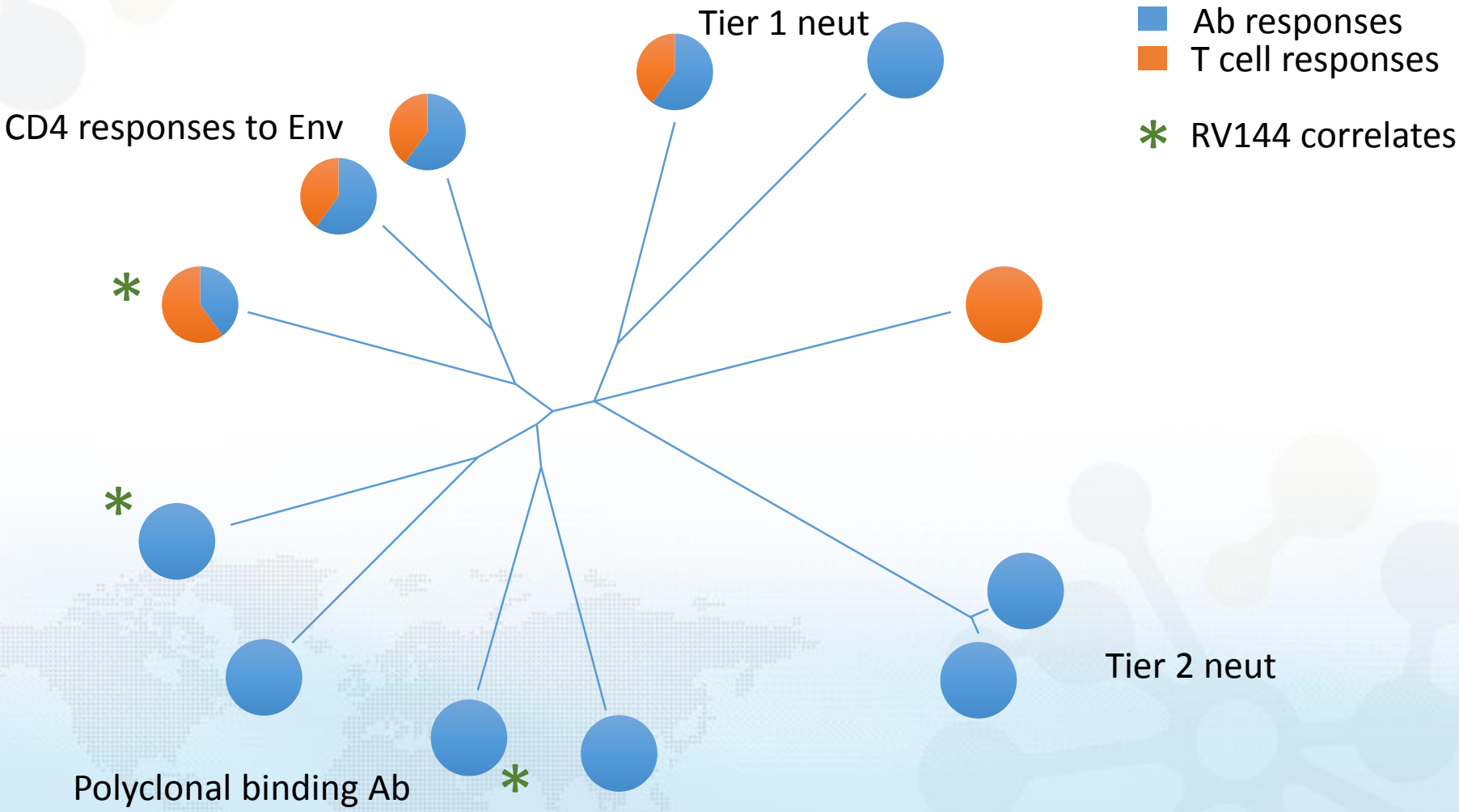
Neighbor-joining tree of candidates by minimal responses



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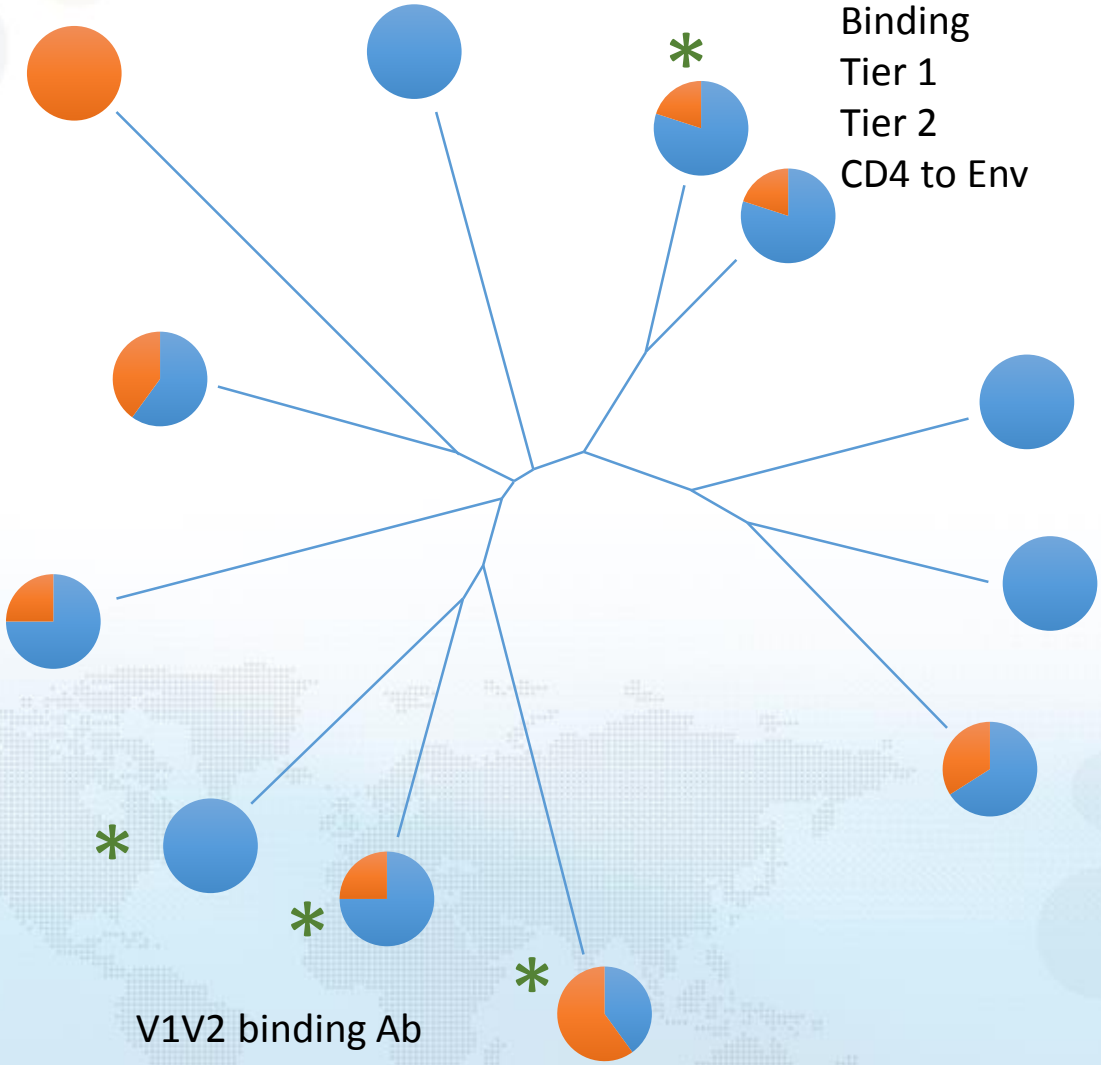
Neighbor-joining tree of candidates by optimal responses



Ab responses
T cell responses

* RV144 correlates

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Conclusions

- There are no prominent “camps” or closely-related clusters
- A large number of sought-after immune responses are singletons
  - Bad thing: No agreement on what the correlates of protection are
  - Good thing: The field is exploring a wide diversity of hypotheses
- The majority of vaccine candidates target both humoral and cellular responses
- RV144 correlates are targeted, but only by a minority of candidates

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