Curing HIV: time for a new direction

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Why do we even need a cure for HIV?

- Cost
- Accessibility
- Adherence
- Drug resistance
- Toxicities/side effects
- Persistent immune dysfunction


nature medicine

PERSPECTIVE

International AIDS Society global scientific strategy: towards an HIV cure 2016

Steven G Deeks[1,20], Sharon R Lewin[2,3,20], Anna Laura Ross[4], Jintanat Ananworanich[5,6], Monsef Benkirane[7], Paula Cannon[8], Nicolas Chomont[9], Daniel Douek[10], Jeffrey D Lifson[11], Ying-Ru Lo[12], Daniel Kuritzkes[13], David Margolis[14], John Mellors[15], Deborah Persaud[16], Joseph D Tucker[17], Françoise Barre-Sinoussi[18] & International AIDS Society Towards a Cure Working Group[19]

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HIV wholesale drug costs (US$)

- Australia: $27,000

- US: $40,000

- Global fund: $80

TDF/3TC/EFV
tenofovir/lamivudine/efavirenz

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How are drugs priced?

- ✓ Clinical value
- ✓ What the market can bear
- ✓ Patent environment
- ✓ Duration of treatment
- ✓ Route of administration
- ? R&D costs
- ✖ Costs of production

(hormone refractory prostate cancer)

(paroxysmal nocturnal hemoglobinuria)

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Ramifications for (1st-gen) HIV cure?

- ✓ Clinical value [cure]
- ✓ What the market can bear [HIC vs LMIC]
- ✓ Patent environment
- ✓ Duration of treatment [Short duration:adherence]
- ✓ Route of administration
- ? R&D costs
- ✖ Costs of production

➢ HOW MUCH DOES IT MATTER WHAT FORM IT TAKES?

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Take-home #1:

- too early to pick and choose
- scientists are not price-makers

➢ Let's pursue every avenue

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Why do we even need a cure for HIV?

- Stigma

"it's hard for someone like me to form a meaningful, lasting relationship"

"it eats silently on your self esteem"

"I want to get rid of HIV from my body completely"

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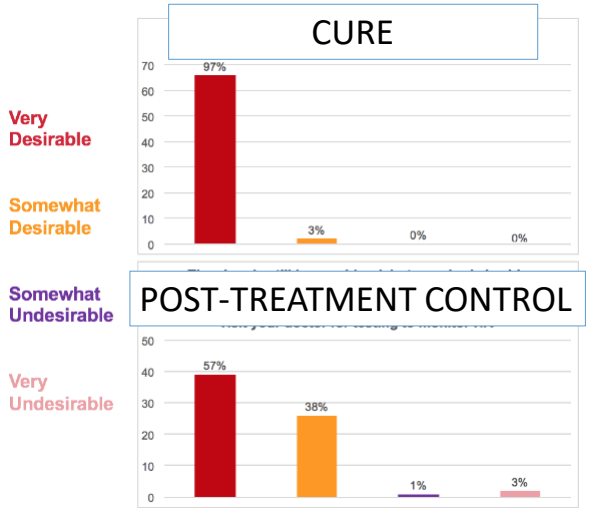
Experiences and expectations of cure trial participants



If PLWHIV want this….


James McMahon

why are scientists doing this?

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If we build it, they will come

- Male condom *might not*
- Female condom
- Microbicides
- PrEP
- Fuzeon

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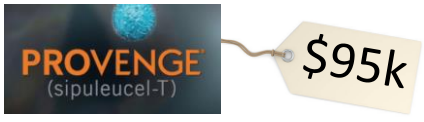
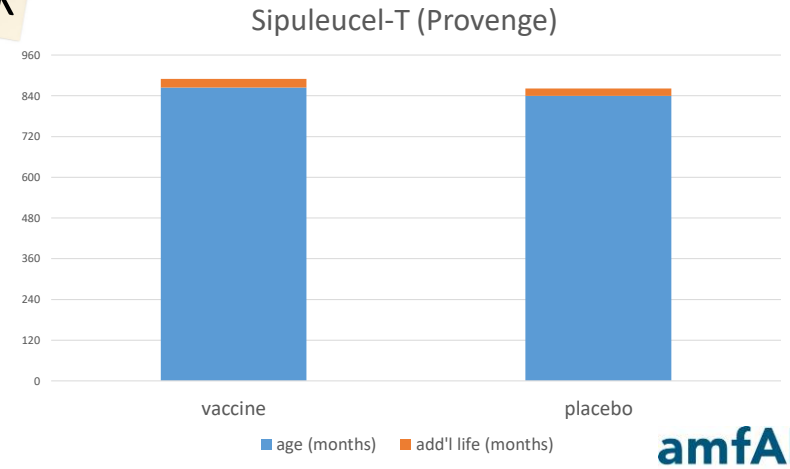
PTC is “easier” – therapeutic vaccine should do the trick





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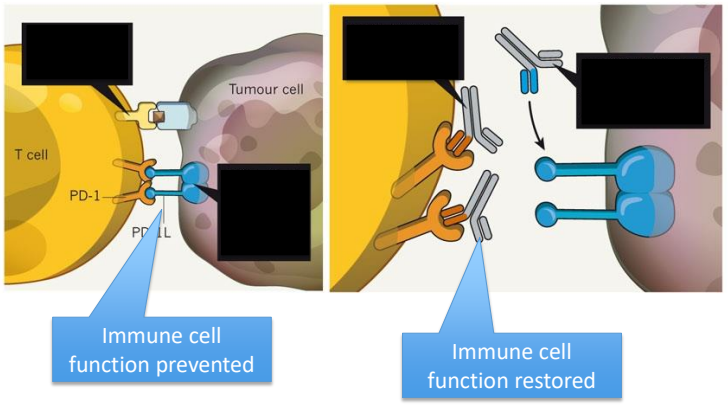
PTC is easier –we can learn from cancer

WAKING UP THE BODY'S DEFENCES

Tumour cells can inhibit the body's immune response by binding to proteins, such as PD-1, on the surface of T cells. Antibody therapies that block this binding reactivate the immune response.



HIV?

- Mutational escape
- Ag presentation

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Non-immune control mechanisms?

- Enhanced epigenetic silencing

J Virol. 2012 Dec;86(23):13081-4. doi: 10.1128/JVI.01741-12. Epub 2012 Sep 12.

Long-term nonprogressor and elite controller patients who control viremia have a higher percentage of methylation in their HIV-1 proviral promoters than aviremic patients receiving highly active antiretroviral therapy.

Palacios JA[1], Pérez-Piñar T, Toro C, Sanz-Minguela B, Moreno V, Valencia E, Gómez-Hernando C, Rodés B.

- Gut microbiome

Science. 2017 Nov 2. pii: eaan3706. doi: 10.1126/science.aan3706. [Epub ahead of print]

Gut microbiome influences efficacy of PD-1-based immunotherapy against epithelial tumors.

Routy B[1,2,3], Le Chatelier E[4], Derosa L[1,2,3], Duong CPM[1,2,5], Alou MT[1,2,3], Daillère R[1,2,3], Fluckiger A[1,2,5], Messaoudene M[1,2], Rauber C[1,2,3], Roberti MP[1,2,5], Fidelle M[1,3,5], Flament C[1,2,5], Poirier-Colame V[1,2,5], Opolon P[6], Klein C[7], Iribarren K[8,9,10,11,12], Mondragón L[8,9,10,11,12], Jacquelot N[1,2,3], Qu B[1,2,3], Ferrere G[1,2,3], Clémenson C[1,13], Mezquita L[1,14], Masip JR[1,14], Naltet C[15], Brosseau S[15], Kaderbhai C[16], Richard C[16], Rizvi H[17], Levenez F[4], Galleron N[4], Quinquis B[4], Pons N[4], Ryffel B[18], Minard-Colin V[1,19], Gonin P[1,20], Soria JC[1,14], Deutsch E[1,13], Loriot Y[1,3,14], Ghiringhelli F[16], Zalcman G[15], Goldwasser F[9,21,22], Escudier B[1,14,23], Hellmann MD[24,25], Eggermont A[1,2,14], Raoult D[26], Albiges L[1,3,14], Kroemer G[27,9,10,11,12,28,29], Zitvogel L[30,2,3,5].

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PTC ↔ cure continuum

- >30 years elite control, viral clearance = 0
- > 10 years post-treatment control, viral clearance = 0

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Take-home #2:

- People living with HIV want a cure
- PTC may not be easier
- PTC may not be stepping stone to cure

➢ Let's make cure our goal

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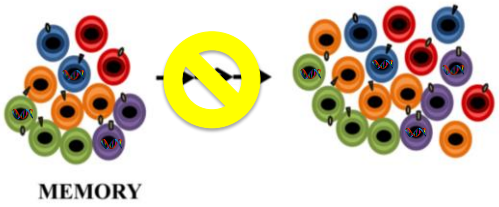
3 ways to cure HIV:



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How to target reservoir cells

- Use targeting moiety
- Use immune system

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Using the immune system

- Boost/redirect immunity
  - Exhausted
  - Dysfunctional
  - Off-target
- Bypass immune system
  - e.g. CAR T cells

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CAR T development timelines

1987: first CAR T cell (phosphorylcholine)

Cancer	HIV
• 1997: first anti-CD19	• 1994: first construct
• 2010: first anti-CD19 clinical trial	• 2000: first clinical trial

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CAR T cells

- First CAR T cell - 1987

30 years

FDA News Release

FDA approval brings first gene therap
United States

CAR T-cell therapy approved to treat certain children and young adults with l
leukemia

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For Immediate Release August 30, 2017

FDA News Release

FDA approves CAR-T cell therapy to treat adults with certain types of large B-cell lymphoma

Yescarta is the second gene therapy product approved in the U.S.

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For Immediate Release October 18, 2017

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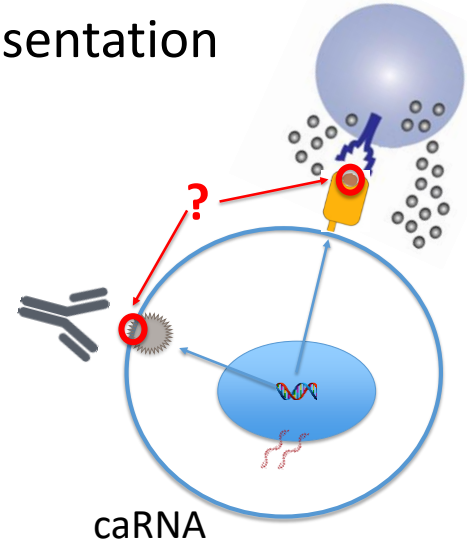
LRAs to induce targetable antigen

- Induce peptide presentation
- Induce protein



caRNA

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How to target provirus

MEMORY

Gene therapy

- Nucleases
- Target sequence
- In vivo delivery

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Can gene therapy be delivered?

A $150,000 instrument being tested in gene-therapy studies of cancer. It automatically adds a new gene to a person's blood cells.

Rewriting Life

This Lab-in-a-Box Could Make Gene Therapy Less Elitist

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Putting it all together

- Let's pursue *every* avenue
- Let's make *cure* our goal
- *Look* at cure challenges, *see* something different

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Thanks to…

Conference organizers

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Annette Sohn
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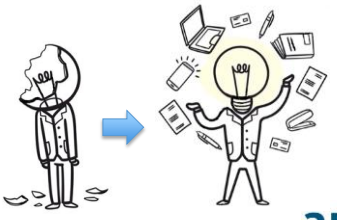
Damian Purcell
Jon Karn
Bob Siliciano
Marcella Flores



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