How Does HIV Persist and What Can We Do About It?

John W. Mellors, MD
October 17, 2018
Why Try To Cure HIV?

Which would you rather take?

- No drug toxicity or resistance
- No transmission!
- Life-long ART not required
A Short History of HIV Cure Research
1996-7: HIV Cure Possible?

- **Initiate ART**
- **Phase I** $t_{1/2} = 1.5$ days
- **Phase II** $t_{1/2} = 28$ days

**Clinical LOD (50 copies/mL)**

**Eradication?**

**Years on ART**

**Plasma HIV-1 RNA (copies/mL)**

- $10^{-1}$
- $10^{0}$
- $10^{1}$
- $10^{2}$
- $10^{3}$
- $10^{4}$
- $10^{5}$
- $10^{6}$
- $10^{7}$
HIV Cure “Impossible”: 1997-2009

SCIENCE VOL. 278 * 14 NOVEMBER 1997

Identification of a Reservoir for HIV-1 in Patients on Highly Active Antiretroviral Therapy
Diana Finzi, Monika Hermankova, Theodore Pierson, Lucy M. Carruth, Christopher Buck, Richard E. Chaissen, Thomas C. Quinn, Karen Chadwick, Joseph Margolick, Ronald Brookmeyer, Joel Gallant, Martin Markowitz, David D. Ho, Douglas D. Richman, Robert F. Siliciano

Recovery of Replication-Competent HIV Despite Prolonged Suppression of Plasma Viremia
Joseph K. Wong, Marjan Hezareh, Huldrych F. Günthard, Diane V. Havlir, Caroline C. Ignacio, Celsa A. Spina, Douglas D. Richman

Presence of an inducible HIV-1 latent reservoir during highly active antiretroviral therapy
Tae-Wook Chun, Lieven Stuyver, Stephanie B. Mizell, Linda A. Ehler, Jo Ann M. Mican, Michael Baseler, Alun L. Lloyd, Martin A. Nowak, and Anthony S. Fauci

Half-life of latent reservoir ~ 3.7 years (95% CI: 2.3-9.5)
Viremia Persists on ART – Proviruses Not All Latent

- **Initiate ART**
- **Phase I** $t_{1/2} = 1.5$ days
- **Phase II** $t_{1/2} = 28$ days
- **Phase III** $t_{1/2} = 273$ days
- **Phase IV** $t_{1/2} = 11.1$ years

Plasma HIV-1 RNA (copies/mL)

Clinical LOD (50 copies/mL)

- Perelson et al., Science 1996
- Maldarelli et al., PLoS Pathogens 2007
- Palmer et al., PNAS 2008
- Riddler et al., JID 2015
Viremia Rebounds Without ART

- **Initiate ART**
- **Phase I** $t_{1/2} = 1.5$ days
- **Phase II** $t_{1/2} = 28$ days
- **Phase III** $t_{1/2} = 273$ days
- **Phase IV** $t_{1/2} = 11.1$ years
- **Clinical LOD (50 copies/mL)**
- **Rebound in 2-4 weeks**

---

**Years on ART**

**Plasma HIV-1 RNA (copies/mL)**

- **Perelson et al., Science 1996**
- **Davey et al., PNAS 1999**
- **Maldarelli et al., PLoS Pathogens 2007**
- **Palmer et al., PNAS 2008**
- **Riddler et al., JID 2015**
Surprise!
Long-Term Control of HIV by CCR5 Delta32/Delta32 Stem-Cell Transplantation

Gero Hütter, M.D., Daniel Nowak, M.D., Maximilian Mossner, B.S., Susanne Ganepola, M.D., Arne Müßig, M.D., Kristina Allers, Ph.D., Thomas Schneider, M.D., Ph.D., Jörg Hofmann, Ph.D., Claudia Kücherer, M.D., Olga Blau, M.D., Igor W. Blau, M.D., Wolf K. Hofmann, M.D., and Eckhard Thiel, M.D.

SUMMARY

Infection with the human immunodeficiency virus type 1 (HIV-1) requires the presence of a CD4 receptor and a chemokine receptor, principally chemokine receptor 5 (CCR5). Homozygosity for a 32-bp deletion in the CCR5 allele provides resistance against HIV-1 acquisition. We transplanted stem cells from a donor who was homozygous for CCR5 delta32 in a patient with acute myeloid leukemia and HIV-1 infection. The patient remained without viral rebound 20 months after transplantation and discontinuation of antiretroviral therapy. This outcome demonstrates the critical role CCR5 plays in maintaining HIV-1 infection.


Timothy Ray Brown, The American in ‘Berlin Patient’

No HIV Detectable After Many Years
How was Tim Brown Cured?

Stochastic Reversal of Latency

CCR5 -/−

No X4 Virus!

Mortality from Allogeneic BMT ~ 25%

Primarily inspirational!
REALITY CHECK AHEAD
### Boston Allotransplants (Henrich et al., Ann Intern Med 2014)

<table>
<thead>
<tr>
<th>HSCT/Patient Factor</th>
<th>Patient A</th>
<th>Patient B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mode of acquisition</td>
<td>Perinatal</td>
<td>Sexual (adult)</td>
</tr>
<tr>
<td>CCR5 genetics</td>
<td>Δ32 Heterozygous</td>
<td>Δ32 Heterozygous</td>
</tr>
<tr>
<td>Favorable HLA alleles?</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Pre-HSCT HIV-1 DNA</td>
<td>144 copies/10⁶ PBMC</td>
<td>96 copies/10⁶ PBMC</td>
</tr>
<tr>
<td>Type of Allogeneic HSCT</td>
<td>HLA C-mismatched unrelated; CCR5&lt;sup&gt;wt&lt;/sup&gt;/&lt;sup&gt;wt&lt;/sup&gt;</td>
<td>Matched related donor; CCR5&lt;sup&gt;wt&lt;/sup&gt;/&lt;sup&gt;wt&lt;/sup&gt;</td>
</tr>
<tr>
<td>HSCT Conditioning</td>
<td>Reduced intensity</td>
<td>Reduced intensity</td>
</tr>
<tr>
<td>GVHD</td>
<td>Chronic, mild (skin)</td>
<td>Chronic, mild (skin)</td>
</tr>
<tr>
<td>Length of ART post-HSCT</td>
<td>4.5 years</td>
<td>2.8 years</td>
</tr>
<tr>
<td>Blood Chimerism</td>
<td>&lt;0.001% host PBMC</td>
<td>&lt;0.001% host PBMC</td>
</tr>
<tr>
<td>Post-HSCT HIV-1 DNA</td>
<td>undetectable</td>
<td>undetectable</td>
</tr>
</tbody>
</table>
ATI: Patient A

Clinical symptoms
Restarts ART
Symptoms resolve

Days Post-ATI

Log$_{10}$ Plasma HIV-1 RNA

HIV-1 DNA
- - - - - +

0 14 28 42 56 70 84 98 112 126 140 154 168 182
ATI: Patient B

Plasma HIV-1 RNA not detected by SCA (<0.4 copies/ml)
HIV-1 DNA not detected (<0.07 copies/10^6 PBMCs)

Fevers, fatigue
ART
CSF RNA = 269 copies/ml
Symptoms resolve
Eradication Cure?

<table>
<thead>
<tr>
<th></th>
<th>Infected Cell Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre Transplant</td>
<td>$\sim 10^{-3}$</td>
</tr>
<tr>
<td>Post Transplant</td>
<td>$&lt;10^{-8}$</td>
</tr>
</tbody>
</table>
No other Cures from Allo-transplants with CCR5-/- donors

<table>
<thead>
<tr>
<th>Location of Transplantation</th>
<th>Age of Patient</th>
<th>Type of Cancer</th>
<th>Type of Graft</th>
<th>Outcome after Transplantation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Berlin†</td>
<td>40</td>
<td>Acute myeloid leukemia</td>
<td>HLA-matched unrelated</td>
<td>Alive after 7 yr, no viral rebound, no ART</td>
</tr>
<tr>
<td>Utrecht, the Netherlands‡</td>
<td>33</td>
<td>Myelodysplastic syndrome</td>
<td>Combined haploidentical bridge with umbilical-cord blood</td>
<td>Died from relapse of the myelodysplastic syndrome and pneumonia after 2 mo</td>
</tr>
<tr>
<td>Münster, Germany§</td>
<td>51</td>
<td>Non-Hodgkin’s lymphoma</td>
<td>HLA-mismatched unrelated</td>
<td>Died from infection after 4 mo</td>
</tr>
<tr>
<td>Essen, Germany¶</td>
<td>30</td>
<td>Non-Hodgkin’s lymphoma</td>
<td>HLA-matched unrelated</td>
<td>Died from relapse of non-Hodgkin’s lymphoma after 12 mo</td>
</tr>
<tr>
<td>Minneapolis§</td>
<td>12</td>
<td>Acute lymphoblastic leukemia</td>
<td>Umbilical-cord blood</td>
<td>Died from GVHD after 3 mo</td>
</tr>
<tr>
<td>Santiago, Chile§</td>
<td>46</td>
<td>Non-Hodgkin’s lymphoma</td>
<td>HLA-matched related</td>
<td>Died from pneumonia shortly afterward</td>
</tr>
<tr>
<td>Barcelona§</td>
<td>37</td>
<td>Non-Hodgkin’s lymphoma</td>
<td>Combined haploidentical bridge with umbilical-cord blood</td>
<td>Died from relapse of non-Hodgkin’s lymphoma after 3 mo</td>
</tr>
</tbody>
</table>

100% Mortality

Hütter, NEJM 2015
Early ART Is Not Early Enough
RV411: Time to VL Rebound in Fiebig I Treated Individuals

7 men and 1 woman
median age 29 yrs
ART in Fiebig I for median of 2.8 yrs
VL < 20, no blips
Median CD4 577 cells/mm³

ATI for up to 24 weeks
(VL q 3-7 days)
ART resumed with VL > 1000

Time to viral load rebound >20 copies/ml
Median 26 days
Range 13 to 48 days

Colby, Ananworanich, et al, Nat Med 2018
Therapeutic Approaches
Which Cure Strategy?

**Host Modification**
Confer resistance of susceptible cells to HIV

**Kick, Kill and Control**
Reactive latent proviruses, kill HIV expressing cells & increase immune control without ART
Which Cure Strategy?

Host Modification
Confer resistance of susceptible cells to HIV
Stochastic Reversal of Latency

Host cell modification

KO: CCR5 (Sangamo)
KI: sh5/C46 (Calimmune)

Chronically producing cell
CCR5-modified CD4 T cells at 1 week post infusion constituted 13.9% of circulating CD4 T cells.

Modified cells had an estimated mean half-life of 48 weeks.

After ART interruption, decline in circulating CCR5-modified cells (−1.81 cells per day) was significantly less than the decline in unmodified cells (−7.25 cells per day) (P = 0.02).

HIV RNA became undetectable in one of four patients who could be evaluated.
Challenges moving forward:
- Is cytoreductive therapy needed? Acceptable?
- Is there X4 escape?
- Scalability? Cost?
Which Cure Strategy?

Kick, Kill and Control
Reduce reservoirs & improve immune control without ART
“Kick, Kill & Control” HIV Cure Strategy

“KICK”
Spontaneous or Induced HIV Expression

Stimulate & recruit CD8+ CTLs, NKs, Monocytes
“Kill & Control”

Effector molecules targeted to cells expressing HIV envelope
“Kill & Control”

Elimination of expressing cells

Prevent Infection of CD4+T-cells
“KICK” Candidates (LRAs)

- PKC agonists
  - most potent activators but toxicity of concern
- Brd4 inhibitors
  - JQ1 and analogs
- TLR agonists
  - TLR-4, 7
- Cytkokines
  - IL-15
- SMAC mimetics (non-canonical NFkB)
  - AZD5582
- HDACi
  - Vorinostat, panobinostat, **romidepsin**
ACTG A5315:
A Phase I/II Study of Romidepsin in HIV-Infected Adults with Suppressed Viremia on Antiretroviral Therapy to Assess Safety, Tolerability, and Activation of HIV-1 Expression

Deborah McMahon, MD, for the A5315 Team
University of Pittsburgh
RMD Activates Intracellular HIV Expression Ex Vivo at Concentrations Expected from Doses of 2 and 5 mg/m²

Ex vivo HIV-1 induction from resting CD4 cells from donors on ART

A5315 Study Design

- **Study intervention**: Participants randomized 4:1 to receive i.v. RMD (12 participants/cohorts) or **placebo** (0.9% saline) (3 participants/cohorts).

  - Cohort 1: 12 participants (0.5 mg/m² RMD in 0.9% saline) - completed
  - Cohort 2: 12 participants (2.0 mg/m² RMD in 0.9% saline) - completed
  - Cohort 3: 12 participants (5.0 mg/m² RMD in 0.9% saline) - completed

**Ongoing, fully enrolled, not presented today:**

- Cohort 4: 12 participants (5.0 mg/m² RMD in 0.9% saline q14d x 4 doses)
## Dose-Dependent Romidepsin Concentrations (ng/mL) Median (Q1,Q3)

<table>
<thead>
<tr>
<th>Time Post-Infusion</th>
<th>Romidepsin Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.5 mg/m²</td>
</tr>
<tr>
<td>Hour 4</td>
<td>12 (6.6, 16.7)</td>
</tr>
<tr>
<td>Hour 6</td>
<td>3.2 (-,-)*</td>
</tr>
</tbody>
</table>

*N=1 detectable; Q1,Q3 not available
Plasma Viremia by SCA Cohorts 1-3

Figure 10.2: Median (Q1, Q3) SCA (copies/mL) over time (by dose)

Median (Q1,Q3)
CA-HIV RNA Cohorts 1-3
Copies/10^6 resting CD4+ cells

Median (Q1,Q3)
CA-HIV DNA Cohorts 1-3
Copies/10^6 resting CD4+ cells

Median (Q1,Q3)
### Dose-Dependent Increase in CD4+ T-cell Activation

<table>
<thead>
<tr>
<th>Time point</th>
<th>Romidepsin Dose</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.5 mg/m²</td>
<td>2 mg/m²</td>
</tr>
<tr>
<td>Day 2</td>
<td>0.3%</td>
<td>0.5%</td>
</tr>
<tr>
<td>Day 7</td>
<td>-0.1%</td>
<td>1.6%</td>
</tr>
<tr>
<td>Day 28</td>
<td>0.4%</td>
<td>0.9%</td>
</tr>
</tbody>
</table>

*Jonckheere-Terpstra Test for trend
Summary

• Single dose RMD was safe and generally well-tolerated
  ▪ Administered at doses below the MTD
• RMD exposures were dose-dependent
  ▪ At levels a/w with proviral activation ex vivo in infected donor cells
• No increase in viremia post-infusion by SCA or Abbott M2000
  ▪ At 24 and 48 hours or at day 7
• No change in HIV CA-RNA or CA-DNA in resting CD4+ cells pre-infusion to 24 hours post-infection
  ▪ Disconnect between ex vivo and in vivo responses
• Multi-dose study completed (4 x 5 mg/M²); CROI 2019
Spontaneous or Induced HIV Expression

Effector molecules targeted to cells expressing HIV envelope

Elimination of expressing cells

Prevent Infection of CD4+ T-cells

"Kill and Control"

VRC-01 (A5342)
bnMAb Binding Sites

N332 Glycan Supersite:
PGT128, DH542,
PGT121, 10-1074

gp41 MPER:
2F5, 4E10, 10e8

V1V2 Glycan:
PG9, PG16
PGT141-145
CAP256-VRC26.25
PGDM1400

CD4 Binding Site:
PG04, CH31, 12A12, VRC13,
VRC01, VRC01LS,
VRC07-523LS, 3BNC117, N6

GP/41 interface
8ANC195
PGT151
35022
Antibody Potency/Breadth

Panel of 206 HIV Env pseudoviruses from all major clades

Breadth: % of Envs neutralized

More potent

Virus IC<sub>80</sub> titer (μg/ml)

Broad and potent

Less broad but 500x more potent

Very broad, very potent

87 80 96 97

54 62 73 48

98 98
A5342/VRC01 Study

- Double-blind, randomized, placebo-controlled, Phase I study
- 40 participants (20 per arm)
- VRC01 40 mg/kg IV at Day 0 & 21 (Arm A) or Day 42 & 63 (Arm B)
## Summary of Virologic Outcomes

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Arm A Median (Q1, Q3)</th>
<th>Arm B Median (Q1, Q3)</th>
<th>p-value*</th>
<th>Arms A and B Combined</th>
<th>Change from Pre- to Post-VRC01</th>
<th>p-value**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change from baseline to Week 6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cell-associated HIV RNA/DNA ratio^</td>
<td>1.12 (0.92, 2.15)</td>
<td>0.83 (0.57, 2.37)</td>
<td>0.16</td>
<td>0.04 (0.02, 0.08)</td>
<td>0.05 (0.02, 0.08)</td>
<td>1.24 (0.61, 2.15)</td>
</tr>
<tr>
<td>Cell-associated HIV RNA (log_{10} cps/10^6 CD4 cells)</td>
<td>0.08 (-0.23, 0.32)</td>
<td>-0.08 (-0.26, 0.29)</td>
<td>0.39</td>
<td>1.55 (0.99, 1.99)</td>
<td>1.48 (0.99, 2.10)</td>
<td>0.09 (0.23, 0.32)</td>
</tr>
<tr>
<td>Cell-associated HIV DNA (log_{10} cps/10^6 CD4 cells)</td>
<td>-0.06 (-0.13, 0.06)</td>
<td>-0.01 (-0.08, 0.13)</td>
<td>0.30</td>
<td>2.93 (2.43, 3.15)</td>
<td>2.92 (2.51, 3.11)</td>
<td>-0.05 (-0.12, 0.06)</td>
</tr>
<tr>
<td>Stimulated Virus Production from total CD4+T-cells (log_{10} cps/ml)</td>
<td>-0.13 (-0.51, 0.92)</td>
<td>0.12 (-0.52, 0.30)</td>
<td>0.91</td>
<td>2.99 (2.06, 3.37)</td>
<td>2.66 (2.28, 3.41)</td>
<td>-0.10 (-0.51, 0.44)</td>
</tr>
<tr>
<td>Week 6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p-value***</td>
<td>1.0</td>
<td></td>
<td></td>
<td>16/38 (42%)</td>
<td>14/38 (37%)</td>
<td></td>
</tr>
<tr>
<td>Plasma HIV RNA ≥1 cp/ml by single copy assay (%)</td>
<td>8/19 (42%)</td>
<td>7/19 (37%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*p-value*

**p-value**

***p-value***

****p-value****
Conclusions

• In individuals with chronic ART-suppressed HIV infection, VRC01 infusions were safe and well tolerated.

• Two high-dose infusions of VRC01 did **not** affect virologic outcomes including:
  ▪ Residual plasma viremia
  ▪ Cell-associated HIV RNA/DNA levels
  ▪ Total stimulated virus production from CD4+T-cells

• Potential mechanisms being evaluated to explain the lack of response include
  ▪ viral envelope resistance to VRC01
  ▪ inherent inability of VRC01 to clear virus particles or env-expressing cells
  ▪ poor penetration of VRC01 to sites of virus expression
Other “Kill & Control” Candidates

- **Immune Checkpoint Blocking Antibodies (ICBs)**
  - Anti-PD-1/PD-L1, LAG-3, 2B4, CD160, TIM-3, others
  - ACTG 5370: anti-PD-1
  - Safety concerns

- **Cellular therapies**
  - CD8+T-cells with chimeric antigen receptors (CARs)
  - Activated NK cells

- **Therapeutic Vaccines**
  - Multiple approaches
  - CMV vector; VSV vector; Ad26/MVA vectors; Dendritic cell
  - Conserved antigens

*Apologies, too many references to cite!*
“Kick, Kill & Control” Strategy: Promising Macaque Studies

- Spontaneous or Induced HIV Expression
- Stimulate & recruit CD8+ CTLs, NKs, Monocytes
- Effector molecules targeted to cells expressing HIV envelope
- Eliminate expressing cells
- Prevent Infection of CD4+ T-cells

TLR-7 Agonist GS-9620

TLR-7 Agonist GS-9620 + PGT-121

Borducchi EN...Barouch DH. Nature 2018
SHIV RNA Following ART Discontinuation

- **Sham**: 11/11 Rebound (100%)
- **TLR7**: 10/11 Rebound (91%)
- **PGT121**: 9/11 Rebound (82%)
- **PGT121+TLR7**: 6/11 Rebound (55%)
3BNC117 plus 10-1074 Combination ATI Study

Inclusion:
- On ART > 24 months, with HIV-1 VL < 50 copies/ml x 18 months and < 20 copies/ml at screen
- Current CD4 count > 500 cells/ul
- CD4 count nadir > 200/ul

Mendoza P...Nussenzweig MC. Nature 2018
• Median time to rebound was 21 weeks of 15 weeks after last mAb infusion

• Viral rebound only occurred after 3BNC117 levels declined to < 10 µg/ml, which was followed by a period of 10-1074 monotherapy.

Mendoza P…Nussenzweig MC. Nature 2018
Post-treatment Controllers

Initial Viral Load 860,000
IUPM 12 weeks $= 0.68/10^6$
HLA A*01, A*29, B*38, B*44
No ART detected in blood

Initial Viral Load 85,000
IUPM 12 weeks $= 1.4/10^6$
HLA-A*03, A*25, HLA-B*18, B*44
No ART detected in blood

Mendoza P…Nussenzweig MC. Nature 2018
Key Upcoming Human Studies

• Higher dose cohorts of GS-9620 TLR-7 agonist in HIV-1 infection
  ▪ 8, 10, 12 mg doses q2wks
• bnMAb with greater potency, longer-half life, better effector function
  ▪ Combinations: PGT121 or 10-1074 (V3) + VRC07-523LS or 3NC117 or N6 (CD4bs)
  ▪ Do they affect the reservoir? Time to Rebound?

• Human Therapeutic Vaccines:
  ▪ RV405: Ad26/MVA vaccination in F1-4
  ▪ DC-03: Dendritic cell, HIV conserved peptide in F1-2
  ▪ DC-04: Dendritic cell, HIV conserved peptide vs. whole virus in F6
  ▪ PennVax: HIV gag/pol or gag/pol/env with IL-12 DNA vaccine
  ▪ A5369: HIV gag conserved element DNA vaccine

• “Kitchen Sink”
  ▪ Vaccine + TLR + 2 or 3 bnMAb
How does the future look for HIV cure?

There are always unrealistic optimists and skeptics

*Remember, 1 pill a day to treat HIV was a once fantasy!*
Lab Collaborators

- Leah Brand
- Joe Brooker
- John Bui
- Joshua Cyktor
- Nathan Enick
- Elias Halvas
- Jana Jacobs

- Kevin Joseph
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- Asma Naqvi
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- Xiaolin Wu

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- David Wells
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The Ohio State University
Penn Therapeutics
The Ponce de Leon Center
UCLA Care Center
UCLA
Univ Colorado Hospital
Univ Pittsburgh
Univ Rochester
Univ Washington

Study Participants

Industry Partners

Romas Geleziunas
Jim Rooney

Joe Camardo

Others
CRS Blood Center Staff
CRS Lab Staff
Pitt ISL Staff
Pitt VSL Staff
Curtis Dobrowolski (Karn Lab, CWRU)

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Questions?
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Lu Zheng

**MHRP**
Denise Hsu
Merlin Robb
Jintanat Ananworanich
Nelson Michael

**Thai Red Cross**
Eugene Kroon
Nittaya Phanuphak
Praphan Phanuphak

**Scripps Institute**
Dennis Burton

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What’s Ahead?

TRAPPIST-1 System

b  c  d  e  f  g

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