Background on Rabies and Why Monoclonal Antibodies (mAbs) are Being Developed for Rabies PEP

Antimicrobial Drugs Advisory Committee Meeting
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Background on Rabies and Why Monoclonal Antibodies (mAbs) are Being Developed for Rabies PEP

Tanvir Bell, MD, FACP, FIDSA

1. Photos by Unsplash: racoon-Gary Bending, bat-Todd Cravens, fox-Zhang Zhang, and dog-Cam Bowers
– Describe the recommendations for and the components of rabies post-exposure prophylaxis (PEP)
– Describe characteristics of rabies pathogenesis
– Discuss advantages and disadvantages of mAbs for use in place of rabies immunoglobulin (RIG) as part of Rabies PEP
  • 2 Types of RIG
    – Human Rabies Immunoglobulin (HRIG)
    – Equine Rabies Immunoglobulin (ERIG)
– Describe the FDA public workshop on mAb as an alternative to RIG for rabies PEP
Rabies Therapies

• No established current treatment
  – clinical disease ~100% fatal
    • Very few case reports of people infected with rabies virus (or other lyssaviruses) survive
  – ~59,000 human deaths/year worldwide (95% Asia, Africa, Latin America)

• Post-exposure prophylaxis (PEP): ~100% effective
  – 17 million people/year globally; 23,000 people/year U.S.
  – Most rabies deaths due to no PEP or incorrect PEP

http://virology-online.com/viruses/Rhabdoviruses.htm
Global Deaths from Rabies

Countries shaded in grey are free from canine rabies

RIG as a Component of Rabies PEP

- **Advisory Committee on Immunization Practices (ACIP) by Animal Type**
  - Skunks, raccoons, fox, bats regarded as rabid unless (-) testing
  - Dogs, cats, ferrets can be watched for 10 days if not suspected rabid

- **World Health Organization (WHO) by Exposure**
  - **Category II**: Nibbling of uncovered skin, minor scratches or abrasions (without bleeding). *PEP recommendation does not include RIG.*
  - **Category III**: Single/multiple transdermal bites or scratches, licks on broken skin; contamination of mucous membranes with saliva; contacts with bats

- **Regimen**: Begin as soon as possible, though no time limitation for initiation

<table>
<thead>
<tr>
<th>Extensive wound cleansing</th>
<th>ACIP</th>
<th>WHO Category III Exposures</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 0</td>
<td>Day 0</td>
</tr>
<tr>
<td>RIG^+</td>
<td>HRIG Day 0*</td>
<td>HRIG or ERIG Day 0*</td>
</tr>
<tr>
<td>Rabies vaccine</td>
<td>IM Day 0, 3, 7, 14</td>
<td>IM if one site only Day 0,3,7, between 14-28 Additional 2 site IM and ID options</td>
</tr>
</tbody>
</table>

^As much as anatomically feasible should be infiltrated in area around/in wound
+RIG is not needed if received prior rabies vaccination
*Do not administer RIG after Day 7 of rabies vaccine (in cases where delayed RIG)

IM=Intramuscular; ID=Intradermal

Rabies Post Exposure Prophylaxis (PEP) in WHO Category III Exposures

1. Thorough wound washing
2. Prompt initiation of a rabies vaccination series
3. Prompt administration of rabies immunoglobulin (RIG) in and around the wound

Estimates - Effective for 99% of RABV exposures
1954 RIG Field Trial in Iran

18 Head/Face Bites: all wound washing and vaccine

13: +RIG
5: no RIG

1 death (8%)
3 deaths (60%)

11 without head bites ± RIG survived

Note: rabbit serum globulin and sheep brain derived vaccines used

Rabies Pathogenesis After Animal Exposure

Generally 20-60 days between bite and clinical disease (range 5 days to 6 years)

Rate of 15-100 mm/day

Role of PEP

Contribution of Passive Immunization to PEP Regimen

Adapted from CDC. Use of a Reduced (4-Dose) Vaccine Schedule for Postexposure Prophylaxis to Prevent Human Rabies: Recommendations of the Advisory Committee on Immunization Practices. MMWR 2010;59(No. RR-2).
RIG

- Two types of RIG
  - Human (HRIG): used in US
    - HyperRAB® (1974)
    - Imogam® (1984)
    - KEDRAB™ (2017)
  - Equine (ERIG)

- Limitations
  - High Cost
    - <2% utilization world-wide
  - Cold storage
  - Potential shortages
  - Potential blood borne pathogens
    - Virus inactivation steps required

Rabies mAb cocktails

WHO: >2 mAbs that target non-overlapping antigenic sites on the rabies virus outer G protein

Potential Advantages

- ↑ consistency
- more rapid production capability
- no blood-borne pathogen transmission risk

Potential Challenges

- Narrower spectrum of rabies virus coverage
- Potential for greater Vaccine interference

Picture: https://www.who-rabies-bulletin.org/site-page/virus-structure
Issues in Assessing Activity of Rabies mAbs as a Component of the PEP Regimen

- Neutralizing activity vs diverse rabies virus strains
- Proof of concept/selection of mAb dose for initial clinical evaluations
- Passive protection during first few days of PEP
- Effects on rabies vaccine response
- Non-rabies-exposed population
- Suspected rabies-exposed population

https://www.cdc.gov/rabies/specific_groups/doctors/serology.html
Objective: Discuss the challenges and identify additional scientific work needed to advance development of monoclonal antibodies (mAb) targeting rabies virus for use in a post-exposure prophylaxis (PEP) regimen, to be used in conjunction with licensed rabies vaccine.

• Public workshop to facilitate sharing of the available data and complexities in the field of rabies PEP
• Forum for discussion and for identifying research gaps relevant to regulatory and public health issues
• Additional information perhaps not fully covered today
  – WHO, Industry, and experiences from physicians/trialists at rabies treatment centers
  – Ethical considerations in rabies mAb trial designs

https://www.fda.gov/Drugs/NewsEvents/ucm540832.htm
Some Take Away Points from 2017 Workshop

• Hamster model most established
• Limitations of rabies virus neutralizing antibody (RVNA) tests as a surrogate for efficacy
• Correlation of RVNA from passively administered RIG with mortality is unknown
• Need for mAbs expressed by WHO and providers (international)
• Logistical issues-wound injection, confirmation of rabid animal
• mAb status – Industry
  – 2 years for 200 patient trial in India
• RIG controlled trials vs placebo controlled trials

https://www.fda.gov/Drugs/NewsEvents/ucm540832.htm
Acknowledgements

- Jeff Murray, Sarah Connelly, Chris Ellis, Hengrui Sun, Mario Sampson, and multiple other contributors from DAVP/OAP, OB, and OCP
- Robin Levis and Dorothy Scott (from CBER)
- Rabies experts from the 2017 Rabies Workshop

DAVP=Division of Antiviral Products
OAP=Office of Antimicrobial Products
OB=Office of Biostatistics
OCP=Office of Clinical Pharmacology
CBER=Center for Biologics Evaluation and Research
Neutralizing Activity of Anti-Rabies Virus Antibodies in Cell Culture

Antimicrobial Drugs Advisory Committee Meeting
April 25, 2019

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Neutralizing Activity of Anti-Rabies Virus Antibodies in Cell Culture

Damon Deming, PhD
Senior Virologist
Division of Antiviral Products
April 25, 2019

www.fda.gov

Micrograph from F. A. Murphy, UTMB
Rabies Virus G Diversity

Benedictis et al. 2016  https://doi.org/10.15252/emmm.201505986
Photographs from Pixabay.com
Rabies Virus G Protein

Antigenic Sites:

II  I  IV  III  a

Extracellular domain amino acid 1-439
Transmembrane domain 440-461

mAb = monoclonal antibody
RIG = anti-rabies virus immunoglobulin

Rabies Virus G Protein

**Extracellular domain**
- amino acid 1-439

**Transmembrane domain**
- 440-461

**Antigenic Sites:**
- I
- II
- III
- IV
- III a

**mAb cocktail:**

**mAb = monoclonal antibody**

**RIG = anti-rabies virus immunoglobulin**

Rabies Virus G Protein

Antigenic Sites:

II  I  IV  III  a

mAb cocktail:

Polyclonal RIG:

mAb = monoclonal antibody
RIG = anti-rabies virus immunoglobulin

Rabies Virus G Protein

Antigenic Sites:
- mAb cocktail:
- Polyclonal RIG:

mAb = monoclonal antibody
RIG = anti-rabies virus immunoglobulin

Rabies Virus G Protein

Antigenic Sites:

mAb cocktail:

Polyclonal RIG:

mAb = monoclonal antibody
RIG = anti-rabies virus immunoglobulin

Neutralization Assays

• Used for measuring rabies virus neutralizing activity (RVNA) of antibodies
• Validated for use as clinical and veterinary assays
  – Rapid Fluorescent Focus Inhibition Test (RFFIT)\(^1\)
  – Fluorescent Antibody Virus Neutralization (FAVN) test\(^2\)
  – evaluating response to vaccination
  – RIG production
  – comparing neutralizing activity and breadth

\(^1\) Smith, Yager, Baer. Bull World Health Organ. 1973 May;48(5)535-41
Image of 96-well Tissue Culture plate from MatTek.com (P96GC-1.5-5.F)
Example: Quantification

Antibody + Virus

Serial dilution of antibody

Same amount of virus in each well

1:2 → 50 TCID$_{50}$
1:4 → (50% Tissue Culture Infectious Dose)
1:8 →
1:16 →
1:32 →
1:64 →
1:128 →
1:256 →
Example: Quantification

Antibody + Virus

Serial dilution of antibody

Same amount of virus in each well

1:2 → 1:4 → 1:8 → 1:16 → 1:32 → 1:64 → 1:128 → 1:256

Virus +

50 TCID$_{50}$
Example: Quantification

Antibody + Virus

Serial dilution of antibody

Same amount of virus in each well

1:2
1:4
1:8
1:16
1:32
1:64
1:128
1:256

Activity

- 50% endpoint dilution / 50% effective concentration (EC₅₀)
  - starting protein concentration known (micrograms/milliliter [μg/mL])
  - compared to reference antibody (International Units/milliliter [IU/mL])

Example: Quantification
Example: Quantification

Antibody + Virus

mAb
Starting concentration: 1 μg/mL

Serial dilution of antibody

Same amount of virus in each well

1:2 1:4 1:8 1:16 1:32 1:64 1:128 1:256

EC₅₀ Value

- Starting concentration: 1 μg/mL
- 50% endpoint titer: 1:32
- EC₅₀ value = 31 ng/mL
Example: Quantification

Antibody + Virus

Polyclonal
Starting concentration: ?

Serial dilution of antibody

Same amount of virus in each well

1:2 → 1:4 → 1:8 → 1:16 → 1:32 → 1:64 → 1:128 → 1:256

50 TCID₅₀
Example: Quantification

Antibody + Virus

Polyclonal
Starting concentration: ?

Serial dilution of antibody

Same amount of virus in each well

Reference Antibody

<table>
<thead>
<tr>
<th>Serial Dilution</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1:2</td>
<td></td>
</tr>
<tr>
<td>1:4</td>
<td></td>
</tr>
<tr>
<td>1:8</td>
<td></td>
</tr>
<tr>
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<td></td>
</tr>
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<td>1:32</td>
<td></td>
</tr>
<tr>
<td>1:64</td>
<td></td>
</tr>
<tr>
<td>1:128</td>
<td></td>
</tr>
<tr>
<td>1:256</td>
<td></td>
</tr>
</tbody>
</table>

Example: Quantification
Example: Quantification

Antibody + Virus

Polyclonal
Starting concentration: ?

Serial dilution of antibody

1:2
1:4
1:8
1:16
1:32
1:64
1:128
1:256

Reference
Antibody

Same amount of virus in each well

Activity

Reference: 2 IU/mL
– 50% endpoint titer:
  • 1:32 for sample
  • 1:128 for reference
  • EC<sub>50</sub> value = (32/128) × 2 IU/mL = 0.5 IU/mL

Example: Quantification
Comparing Activity and Breadth

• In vivo neutralizing activity estimated using antibody concentration from the most relevant tissue
  
  – concentration in tissue approximated using inoculated concentration
  
  – any dilution should be consistent between antibody-based products
  
  – in vivo neutralizing potential = concentration mAb ÷ EC$_{50}$ value

Syringe icon made by Freepik from www.flaticon.com
Comparing Activity and Breadth

Hypothetical data

RIG (150 IU/mL)
Comparing Activity and Breadth

Hypothetical data
Comparing Activity and Breadth

- CVS-11
- ERA
- coyote (TX)
- dog (BR)
- dog (Ph)
- fox (AL)
- fox (AZ)
- mongoose (PR)
- raccoon dog (LT)
- raccoon (FL)
- skunk (AR)
- skunk (KS)
- big brown
- canyon
- common vampire
- Eastern red
- fringed myotis
- hoary
- Mexican free-tailed
- Seminole
- silver-haired
- tricolored

Log_{10} (Antibody Concentration/EC_{50} value)

- mAb 1 (2.5 mg/mL)
- mAb 2 (2.5 mg/mL)
- RIG (150 IU/mL)

Hypothetical data
Comparing Activity and Breadth

**Hypothetical data**

- mAb 1 (2.5 mg/mL)
- mAb 2 (2.5 mg/mL)
- mAb Mix (5 mg/mL)
- RIG (150 IU/mL)

Log$_{10}$ (Antibody Concentration/EC$_{50}$ value)

- CVS-11
- ERA
- coyote (TX)
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- tricolored

lab terrestrial bats
Conclusions

• Neutralization assays can be used to:
  – evaluate the activity and breadth of the neutralizing activity of mAbs and mAb cocktails
  – compare to approved RIG or other mAbs

• Develop (and maintain) a standardized assay
  – several rabies virus strains reflecting the antigenic diversity of circulating strains
  – consideration given to viruses most likely to be exposed to humans
  – strains with polymorphisms at sites known to affect neutralization of a given mAb(s)
  – determining best practices for interpreting assay results will be an ongoing effort
Clinical Trials to Evaluate Rabies mAb Cocktails as a Component of Post-Exposure Prophylaxis & A Proposed Development Pathway

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Stephanie Troy, MD
Medical Officer
DAVP, OND, CDER, FDA
Clinical Trials to Evaluate Rabies mAb Cocktails as a Component of Post-Exposure Prophylaxis & A Proposed Development Pathway

Stephanie Troy, MD
Medical Officer, DAVP
April 25, 2019
Content

• Clinical Trial Issues
  – Strengths and weaknesses of surrogate endpoints
  – Logistic constraints with a mortality endpoint

• Possible Development Pathway
  – Information Needed Prior to Clinical Trials in Rabies Virus (RABV)-Exposed Subjects
  – Information Needed from Clinical Trials in RABV-Exposed Subjects

References for statements made are included in the backgrounder.
Possible Data from Clinical Trials

Healthy Subjects

- Safety
- Pharmacokinetics (PK)
- Serologic endpoints (Rabies Virus Neutralizing Antibodies, or RVNA)

RABV-Exposed Subjects

- Safety
- Confirmation of PK (with administration in and around a wound)
- Confirmation of serologic endpoints
- Lack of rabies mortality
Possible Data from Clinical Trials

Healthy Subjects
- Safety
- PK
- Serologic endpoints

RABV-Exposed Subjects
- Safety
- Confirmation of PK (with administration in and around a wound)
- Confirmation of serologic endpoints
- Lack of rabies mortality

Endpoints that might be used to evaluate efficacy
Serologic Assays (RVNA): 2 sources

• Passive Immunization (mAb cocktail)

• Active Immunization (Immune response to the inactivated rabies vaccine)

Serologic Measures

PEP = post-exposure prophylaxis; HRIG = human rabies immunoglobulin; mAb = monoclonal antibody

Hypothetical Example
Serologic Measures

Early RVNA Levels (up to Day 7)
- No established protective threshold
- Indirect measure (serum, not tissue)

Hypothetical Example
Serologic Measures

Late RVNA Levels (Day 14 on)
- Measure of vaccine interference, not mAb/RIG efficacy

RIG = rabies immunoglobulin

Hypothetical Example
Serologic Measures: Summary

When complete PEP (vaccine + wound washing + RIG/mAb cocktail) is given:

<table>
<thead>
<tr>
<th>Component</th>
<th>Contribution</th>
<th>Limitations</th>
</tr>
</thead>
</table>
| Early RVNA levels (≤ Day 7)| -measure of mAb cocktail’s RVNA contribution | -indirect measure (serum versus tissue)  
- no established protective threshold  
- does not measure breadth of activity |
| Late RVNA levels (≥ Day 14)| -measure of vaccine interference     | -creative methods needed if RVNA levels from mAb cocktail alone exceed 0.5 IU/mL                                                              |
Clinical Trials in RABV-Exposed Subjects

Gold standard would be randomized controlled trials demonstrating the contribution of the mAb cocktail towards ↓ in rabies mortality.

Percent Rabies-Free Survival

- Wound washing + vaccine: ~99%
- Wound washing + vaccine + RIG: ~99.9%

UNCERTAINTY
- Rabies status of animal
- Viral inoculum in saliva
- Bite location
- Bite severity
- Exposure-to-PEP interval
- Type of vaccine and RIG used
- Host factors
Clinical Trials in RABV-Exposed Subjects

Adequately powered Randomized Controlled Trials with a mortality endpoint:

- Placebo-controlled trials (versus vaccine and wound washing alone) \( \rightarrow \) not acceptable
- Noninferiority trial versus HRIG \( \rightarrow \) not feasible (too many subjects required)

Alternative: Demonstration of an acceptable survival rate for PEP including the mAb cocktail

What is an acceptable survival rate?
Data on Efficacy of PEP with RIG

• Pooled field trials of PEP including RIG
  – ~99.86% survival for any location bite after WHO category III exposures in rabies endemic countries
  – Limitations: Studies used various vaccines, schedules, intervals before dosing...

• Observational Data
  – Philippines large bite treatment center: PEP + RIG failure rate of ~0.01%
  – Reported U.S. rabies cases: none in PEP recipients
  – Limitations: Not all rabies cases may be diagnosed and captured

WHO= World Health Organization
## Survival Rate Assurances

<table>
<thead>
<tr>
<th>Sample Size (Patients Receiving mAb cocktail after Possible Rabies Exposure)</th>
<th>Upper Bound 95% Confidence Interval for Mortality Rate (using the Clopper-Pearson method)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>With 0 rabies deaths</td>
</tr>
<tr>
<td>500</td>
<td>0.74%</td>
</tr>
<tr>
<td>750</td>
<td>0.49%</td>
</tr>
<tr>
<td>1000</td>
<td>0.37%</td>
</tr>
<tr>
<td>1500</td>
<td>0.25%</td>
</tr>
<tr>
<td>2000</td>
<td>0.18%</td>
</tr>
</tbody>
</table>

No rabies deaths out of 750 RABV-exposed PEP + mAb recipients indicates survival rate is >99.5% (using the 95% confidence interval)
## Sample Sizes for >80% Power

<table>
<thead>
<tr>
<th>Clinically Acceptable Mortality Boundary</th>
<th>Assumed PEP with mAb Mortality Rate</th>
<th>Sample Size</th>
<th>Power</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.05%</td>
<td>0.01%</td>
<td>14500</td>
<td>82%</td>
</tr>
<tr>
<td>0.10%</td>
<td>0.01%</td>
<td>6000</td>
<td>88%</td>
</tr>
<tr>
<td>0.15%</td>
<td>0.01%</td>
<td>4000</td>
<td>94%</td>
</tr>
<tr>
<td>0.20%</td>
<td>0.01%</td>
<td>2000</td>
<td>82%</td>
</tr>
<tr>
<td>0.30%</td>
<td>0.01%</td>
<td>1500</td>
<td>86%</td>
</tr>
<tr>
<td>0.40%</td>
<td>0.01%</td>
<td>1000</td>
<td>91%</td>
</tr>
</tbody>
</table>

These are based on the assumption that the true rabies mortality rate with PEP including RIG is 0.01%. The sample size would be higher if the true mortality rate is assumed to be >0.01%.
Data Regarding Feasibility: Ease of Enrollment

• Eligible subjects have to be treated quickly and could be spread over large area (referral to distant clinical trial center may not be feasible)

• The large centralized bite centers that treat thousands of WHO category III exposures annually provide RIG (some free of charge)

• A rabies mAb trial in India took >2 years to enroll 200 subjects
  – However, a study with 4000 subjects is reportedly planned.
Key Question for Clinical Trials

How much confidence that survival is not compromised by the use of a mAb cocktail in place of RIG is enough confidence?

– 6000 versus 750 subjects needed to demonstrate >99.9% survival versus >99.5% survival
– Is extra assurance worth it given the uncertainties and the added cost for development?
– Is assurance of >99.9% survival even enough?

Photo by Adi Goldstein on Unsplash
Proposed Approach

- Animal Challenge Studies
  - Show survival benefit
- Cell Culture Data
  - Show breadth of coverage
- Clinical Studies (Healthy Subjects)
  - Acceptable $t_{1/2}$, early RVNA levels and vaccine interference
- Clinical Studies (RABV-Exposed Subjects)
  - Confirm RVNA levels in bite setting & support survival benefit
Data Prior to Trials in RABV-Exposed

1. Comparable breadth of activity against the diversity of rabies strains in cell culture studies for the mAb cocktail versus HRIG

Hypothetical Example
2. Comparable survival in animal rabies challenge studies for the mAb cocktail versus HRIG

Hypothetical Example
Data Prior to Trials in RABV-Exposed

3. Comparable half-life, early RVNA levels, and levels of vaccine interference for the mAb cocktail versus HRIG in clinical trials in healthy subjects
First Topic for Discussion

The types of data needed to allow initiation of PEP with mAb cocktail trials in rabies virus-exposed subjects

Are the three described components enough?
Trials in RABV-Exposed Subjects

Randomized, controlled trials of mAb cocktail versus HRIG, each in combination with thorough wound washing and rabies vaccine series, in subjects with WHO category III rabies exposure (predominantly in rabies endemic countries)

Map from https://www.who.int/rabies/epidemiology/en/ accessed 2/25/19
Trials in RABV-Exposed Subjects

- Start with lower risk WHO category III exposures in adults
- Expand to include higher risk exposures (head, neck, multiple bites) and pediatric subjects
- Assess whether PEP was administered promptly and correctly at time PEP is given
- Follow subjects for rabies deaths for at least one year
Trials in RABV-Exposed Subjects

Endpoints:

• Confirmation of the following (with administration in and around a wound)
  – Comparable early RVNA levels to HRIG
  – Comparable vaccine interference to HRIG

• Comparable safety to HRIG

• Lack of rabies mortality
Trials in RABV-Exposed Subjects

Proposal for Initial Submission for mAb cocktail Approval

• ≥ 1000 subjects receive the mAb cocktail in total for safety evaluation (healthy subjects can be included)
• ≥750 subjects with WHO category III exposures in rabies endemic countries randomized to the mAb cocktail arm

- No rabies death would indicate >99.5% survival with use of PEP including the mAb cocktail
- Sufficient to detect safety signals with rates ≥0.3%
Trials in RABV-Exposed Subjects

Proposal for Initial Submission for mAb cocktail Approval

- ≥ 1000 subjects receive the mAb cocktail in total for safety evaluation (healthy subjects can be included)
- ≥750 subjects with WHO category III exposures in rabies endemic countries randomized to the mAb cocktail arm

Proposal for a Post-Marketing Requirement

- 6000 total subjects with WHO category III rabies exposure in rabies endemic countries who have received mAb cocktail as part of PEP (subjects from pre-marketing studies can be included in this total).

Provides >80% power to demonstrate >99.9% survival with use of PEP including the mAb cocktail (assuming the true survival rate is 99.99%)
Second Topic for Discussion

The types of data needed to support a Biologics License Application (BLA) of a rabies mAb cocktail for use in PEP

How much assurance that survival is not compromised by use of the mAb cocktail in place of HRIG is needed for:

1. Initial approval?
2. Recommendation as a first line PEP component

How much data should be collected pre- versus post-approval?
Acknowledgments

• Jeff Murray, Tanvir Bell, Damon Deming, Sarah Connelly, Chris Ellis, Hengrui Sun, Mario Sampson, and multiple other contributors from DAVP/OAP, OB, and OCP

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