Draft TPP and overview of CCHF candidate therapeutics

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Virus structure

- **Order** *Bunyavirales*
- **Family** *Nairoviridae*
- **Lipid bilayer envelope**
- **Genome:** 3 negative sense ssRNA segments
  - **S** (nucleocapsid protein)
  - **M** (structural glycoproteins $G_N$ and $G_C$)
  - **L** (RNA dependent RNA polymerase)

CCHFV: replication cycle

1. Attachment to unknown receptor
2. CME (CCHFV), other endosomal route
3. pH dependent fusion EE or LE
4. Primary transcription
5. Translation
6. Replication
7. Assembly
8. Egress

CCHFV: replication cycle

Aura Garrison, Ph.D. USAMRIID
Identification and development of antivirals targeting CCHF and host components

<table>
<thead>
<tr>
<th>Viral Lifecycle Stages</th>
<th>Host machinery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cell Attachment (receptor binding)</td>
<td>Cell-surface molecules</td>
</tr>
<tr>
<td>Internalization</td>
<td>Endocytosis</td>
</tr>
<tr>
<td>pH dependent fusion EE or LE</td>
<td>Late endosome / lysosomal factors</td>
</tr>
<tr>
<td>Transcription/ translation</td>
<td>mRNA, ribosomal machinery</td>
</tr>
<tr>
<td>Polyprotein processing</td>
<td>Cellular proteases</td>
</tr>
<tr>
<td>Replication</td>
<td>NTPs, primers, ?</td>
</tr>
<tr>
<td>Assembly and trafficking</td>
<td>Membrane trafficking proteins</td>
</tr>
<tr>
<td>Release</td>
<td>Budding machinery</td>
</tr>
</tbody>
</table>
Potential CCHF Therapeutics

Direct Antivirals

Host-response modifiers
Potential CCHF Therapeutics

Direct Antivirals

- Synthetic
  - NA-based
  - Small Molecule Nucs
  - Small Molecule non-Nucs

Biologics

- Blood product
- mAbs
  - IFNαβ
Potential CCHF Therapeutics

Host-response modifiers

1) Such as coagulopathy agents or agents that dampens consequence of CCHF infection (recombinant NAPc2).

2) Small molecules targeting host.
   Examples: Kinase inhibitors, fusion-like inhibitors

3) anti-cytokines and chemokines

...when to administer these products?
...PK:PD relationship?
Ideal therapeutics for CCHF infections

1) Easy to access, easy to store, and widely available
2) Inexpensive
3) Safety/safety/safety
4) Easy to administer
5) Long-shelf life
6) Clear uncomplicated regulatory path for approval
7) Broad activity against all strains of CCHF
8) Treat/intervene at any stages of infection
9) Can be added to other treatment options
10) Well distributed to multiple tissues based on the infection pattern
**Immunotherapeutic**

1) CCHF-bulin 3–9 mL, 1–5 d or longer IM humans >60(human)
   antibody targets unidentified
   human convalescent plasma

2) CCHF-venin 30 mL combined with 30 mL of CCHF-Bulin
   IV humans Y 100(human)
   antibody targets unidentified
   human convalescent plasma

3) mAb-13G8 1 mg/dose, two doses SC, IP
   IFNAR−/−, mAb 5A3 treated C57BL/6 mice
   GP38 may involve complement
Synthetic Small Molecules: Direct antiviral targeting CCHF RNA synthesis

Ribavirin: 500 mg (oral), 30 mg/kg–7.5 mg/kg IV
oral, SC, IV, IP
2gm followed by 1gm daily.
humans, mice (STAT-1 and IFNAR−/−)

Favipiravir: 300 mg/kg IP IFNAR−/−mice EC50: 10-20uM EC90: 30uM

Remdesvir: In vitro data, EC50 probably too high to be useful
### Essential Data Elements to support non-clinical data

<table>
<thead>
<tr>
<th>Challenge strain</th>
<th>Challenge Stock</th>
<th>Animals</th>
<th>Animal Model</th>
<th>Assays</th>
</tr>
</thead>
</table>
| - Viral isolate from a lethal human infection in an outbreak with high mortality | - Titer by plaque assay  
- Particle: PFU ratio  
- Sterility  
- Mycoplasma  
- Endotoxin analysis  
- Genotypic / phenotypic analysis | - Species  
- Sex  
- Weight  
- Age  
- Country of origin  
- Pre-screened for specific Ab | - Challenge Dose  
- Challenge Route  
- Time to onset of disease  
- Disease time course  
- Clinical Signs  
- Laboratory parameters  
- Euthanasia criteria  
- Gross Pathology  
- Histopathology  
- Lethality | - Challenge Dose  
- Viremia  
- ELISA  
- PRNT  
- RT-PCR  
- Chem Panel  
- Hematology |
<table>
<thead>
<tr>
<th></th>
<th>Challenge Materials</th>
<th>Assays and reagents</th>
<th>Animal Models</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CCHF</strong></td>
<td>No characterized stocks</td>
<td>Bench level</td>
<td>NHP (Cyno), IFN KO mice</td>
</tr>
<tr>
<td></td>
<td>Need strain selection</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Nipah</strong></td>
<td>No characterized stocks</td>
<td>Bench Level</td>
<td>Hamster, ferret and AGM potential models</td>
</tr>
<tr>
<td></td>
<td>Need strain selection</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Lassa Fever</strong></td>
<td>No characterized stocks</td>
<td>Bench Level</td>
<td>Guinea pigs, Macaques</td>
</tr>
<tr>
<td></td>
<td>Need strain selection</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ebola</strong></td>
<td>Characterized Stocks variant selected and standardized</td>
<td>Validated plaque assay for challenge material only</td>
<td>Macaques – rhesus and cyno fairly well characterized</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GP ELISAs RT-PCR</td>
<td>Natural history is established</td>
</tr>
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for WHO use only
## Characteristics of the Target Product Profile

The desired R&D outcome for each disease is defined as the target product profile (TPP). Each R&D project in the portfolio is selected, progressed, and managed according to well-defined decision matrices based on these TPPs.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Questions</th>
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</thead>
<tbody>
<tr>
<td><strong>Indications:</strong></td>
<td>Which diseases?</td>
</tr>
<tr>
<td><strong>Population:</strong></td>
<td>Who are the patients and where?</td>
</tr>
<tr>
<td><strong>Clinical Efficacy:</strong></td>
<td>How does it impact the disease?</td>
</tr>
<tr>
<td><strong>Safety and Tolerability:</strong></td>
<td>Deep understanding of adverse events</td>
</tr>
<tr>
<td><strong>Stability:</strong></td>
<td>How long can it be stored in the field?</td>
</tr>
<tr>
<td><strong>Route of Administration:</strong></td>
<td>How and when is it given to patients?</td>
</tr>
<tr>
<td><strong>Dosing Frequency:</strong></td>
<td>How often and how long must it be given?</td>
</tr>
<tr>
<td><strong>Cost:</strong></td>
<td>Will it be affordable to target population?</td>
</tr>
<tr>
<td><strong>Time to Availability:</strong></td>
<td>How long will it take to develop?</td>
</tr>
</tbody>
</table>

### Draft Target Product Profile for CCHF Therapeutic

<table>
<thead>
<tr>
<th>Category</th>
<th>Objective</th>
</tr>
</thead>
</table>
| **Safety**                                    | ^28 day – 3 mo: rat, dog, or NHP safety toxicology (minimum NHP)  
Human safety evaluated: NHVs/patients (<50 subjects)  

| **Tolerability**                              | No critical or severe adverse events; tolerable AEs acceptable (eg: injection site reaction, rash, vomiting, GI)                                                                                           |
| **Efficacy**                                  | Optimal: 100% survival reduce viral titer to undetectable in 4-6 days after treatment initiation.                                                                                                           |
| **Route of Administration/Ad Mix**           | Optimal Parenteral (IV) and Oral. Must be able to administered with multiple other supportive treatment.                                                                                                   |
| **Frequency of Dosing**                       | Oral: Threshold: capsule/pill/elixir; U/BID  
Optimal: elixir; multiple/day  
Parenteral: Threshold: U/BID bolus to short infusion  
Optimal: continuous infusion                                                                                                      |
| **Duration of Treatment**                     | 4-10 days                                                                                                                                                                                              |
| **Storage Conditions**                        | Ambient/accommodating locale (no frozen product)                                                                                                                                                        |
| **Clearance-dependence (liver/kidney)**       | Consider metabolic route of elimination (biochemical test/clinical evidence [physical exam, jaundice]). No known liver or kidney liabilities.                                                               |
| **Manufacturing**                             | *Efficient, high yield synthesis/expression                                                                                                                                                            |
| **Cost of Goods**                             | Optimal: global deployment opportunity  
Minimal: affordable in limited healthcare systems                                                                                                                                                    |

^ not applicable for repurposed, FDA approved therapeutics and candidates with completed clinical development  
* eg: 20,000 treatment regimens within 1 month
Ways forward for successful therapeutic identification and development for CCHF

Standardized, validated reagents and tools

Enhance Proteomics (viral interactomes) and detail genomics

Genome: 3 negative sense ssRNA segments
  - S (nucleocapsid protein)
  - M (structural glycoproteins G_N and G_C)
  - L (RNA dependent RNA polymerase)

Lack of multiple lead therapeutics: Screening technologies, various Abs/best combinations??, well-annotated libraries

Well-defined TPP