WHO GLOBAL CONSULTATION:

CAN REPURPOSED DRUGS REALLY HELP FIND OUTBREAK TREATMENTS FASTER?

Aug 29-30, 2022

Presenter: Steven E. Kern, Ph.D.  Deputy Director Quantitative Sciences, Global Health
With contributions from colleagues Rob Jordan, Ken Duncan, Dan Hartman
**DEFINITION:** Drug repurposing is the use of existing preclinical and clinical candidate compounds to treat a primary disease condition outside of the candidate's initial clinical indication for use.

**BENEFITS:**
- Repurposed compounds have extensive safety, PK, and formulation data that *could* decrease development timelines and reduce cost for repurposing to a new indication which is predicated on:
  - Can be used at the same or lower drug exposure levels as the approved indication
  - No significant reformulation required for the repurposed indication
  - Dosage form is suitable for the new indication population

**CHALLENGES:**
- A candidate with a narrow therapeutic index may not be suitable for a disease with different risk/benefit profiles
- New formulations or routes of delivery often necessitates extensive preclinical safety and PK evaluations
- Repurposed compound's effect are often only partially active in the new indication, reducing clinical efficacy
Repurposing compounds didn’t really work: Despite many preclinical "hits", clinical trials of repurposed compounds demonstrated limited utility for addressing anti-viral activity against COVID-19. Immunomodulating agents did show benefit against secondary disease sequella.

We were unprepared: Lack of investment to learn lessons from previous PHEICs (Ebola, Zika) hampered the ability to efficiently assess repurposed compounds. Lack of investment in the development of antivirals—particularly those targeting readily-transmissible viral families—resulted in a very limited therapeutic arsenal for COVID-19.

There's a need to also focus upstream in the disease course: Repurposed compounds are largely targeting disease process in moderate to severe patients, but there is a significant need for therapeutics that target mild to moderate patients (and even individuals pre/post-exposure)

To get ahead of these challenges before the next pandemic hits, we need to have a large set of clinic-ready therapeutic candidates that can be readily deployed if an epidemic/pandemic were to emerge.
NIRMATRELVIR IS A RE-ACTIVATED SARS-1 DRUG

Discovery program launched on March 13, 2020, with unlimited human resources (200+ FTEs) and budget

Goal – quickly optimize PF-00835231 to deliver an oral drug by:
1. Reducing hydrogen bond donor from 5 to 3 to increase oral bioavailability
2. Addressing rapid metabolism in liver by combining with Cyp3A4 inhibitor

PF-00835231 was shelved in 2003 as a SARS-CoV-1 Mpro inh. But:
1. Not absorbed and dosed IV
2. Peptidomimetic and highly metabolized by CYP3A4

PF-07321332
Nirmatrelvir synthesized on July 22, 2020
Favorable rat PK profile obtained with ritonavir boost

Outcome – development of Paxlovid, a combination of nirmatrelvir and ritonavir
Ritonavir was originally developed as an anti-HIV drug. It has no activity against SARS-CoV-2 but is a potent inhibitor of human Cyp3A4. Thus ritonavir “boosts” the level of nirmatrelvir available to inhibit the virus without having to design a drug with reduced clearance.

PF-00835231 precursor to nirmatrelvir

2003
1Q20 ➔ 2Q20 ➔ 3Q20 ➔ 4Q20 ➔ 1Q21 ➔ 2Q21 ➔ 3Q21 ➔ 4Q21

Antiviral Activity confirmed
1.4 Kg batch synthesized

Phase 1 completed
Phase 2/3 completed

Paxlovid has major DDI (because of ritonavir) with more than 120 drugs where patients need a physician or pharmacist to make critical treatment decision (e.g., couldn’t be used with rifampicin and most anti-arrhythmics)
LARGE* RANDOMIZED CLINICAL TRIALS ARE CRITICAL

No measurable clinical benefit
- Hydroxychloroquine
- Ivermectin
- Favipiravir
- Lopinavir / Ritonavir
- Aspirin
- Azithromycin
- Convalescent plasma
- Metformin
- Anakinra

Mixed results
- Interferon
- Fluvoxamine
- Colchicine

Reduced duration, hospitalization, or mortality
- Remdesivir
- Molnupiravir
- Paxlovid
- Dexamethasone
- Heparin
- Tocilizumab
- Baricitinib
- Sarilumab
- Budesonide
- Monoclonal combo

Still under evaluation:
empagliflozin, low dose steroids, high dose steroids, sotrovimab, molnupiravir, paxlovid, artemesunate, infliximab, imatinib, interferon lambda, interferon beta

* with N > 1000 per arm in the trial
“...approximately 5% of the total COVID-19 trial arms in our assessment could be described as randomized and adequately powered.”

— Janet Woodcock Acting Commissioner of Food and Drugs Administration

Source: Clinicaltrials.gov accessed 11/20/2020 and WHO clinical trial registry accessed 11/20/2020

THIS TIME, LET'S NOT FORGET WHAT WE LEARNED

High-Throughput Screens

Validation

Primary Respiratory cells
(ali/hae)

Clinical Trials

Preclinical testing

Mechanism

PK/PD

COVID-19 Patients

Organoid & organ chip models
in development

Library: ReFRAME, others
Cell types attempted – Vero-E6, HeLa-ACE2, Calu3, A549-Ace2/TMPRSS2, Huh

Single point followed by dose response & Cytotoxicity

Counts <0.1 μM 0.1-1 μM 1-5 μM

Vero-E6 4 7 6
HeLa ACE2 7 19 23
Calu-3 36 68 15

Many actives identified (approved & investigational)
Small sub-set active in all systems

Air-liquid interface (ALI) culture system

Compound toxicity - TEER, CBF, LDH release
Antiviral effect - RT-qPCR, TCID50, IL-6.

~80 compounds profiled; small subset active

In vivo Models (Intranasal)

Compound information ~30
SARS-CoV-2 infected hamster model

Compound information ~11
Mouse adapted SARS-CoV-2 infected mouse model

Library:
- ReFRAME
- Others

Cell types attempted:
- Vero-E6
- HeLa-ACE2
- Calu3
- A549-Ace2/TMPRSS2
- Huh

Counts:
- <0.1 μM
- 0.1-1 μM
- 1-5 μM

Vero-E6: 4, 7, 6
HeLa ACE2: 7, 19, 23
Calu-3: 36, 68, 15

Many actives identified (approved & investigational)
Small sub-set active in all systems

Antiviral effect:
- RT-qPCR
- TCID50
- IL-6

~80 compounds profiled; small subset active
Mechanisms for Calu-3 ReFRAME hits
- Cell Cycle
- Channel
- EGFR Signaling
- Electron Transport
- TMPRSS2
- Metabolism
- Nucleosides and Nucleotide Metabolism
- Signaling
- Other
- Unknown

Validating mechanisms will support rational design of effective combinations targeting different phases of viral lifecycle

Remdesivir & PF-0835231 shows additive effect in HAE

Viral Replication Machinery (RdRp, Nsp12)
- Remdesivir (Nucleotide prodrug)
- Molnupiravir/EIDD-2801/NHC (Nucleoside prodrug)
- Favipiravir (Nucleoside)
- AT-527 (Nucleotide prodrug)
- Galidesivir (Nucleoside)

Potential targets - Endonuclease (nsp15), Methyltransferases (nsp14/10, nsp16/10), RdRp (nsp12/nsp7/msp8), Helicase (nsp13)

Viral Proteases,
3CL protease (PF-0835231), Papain-like protease

Host Proteases
TMPRSS2 inhibitors (Camostat, Nafamostat)
Furin
Cathepsin K

DHODH inhibitors (Brequinar)

EGFR Signaling
EGFR receptor inhibitors
PI3K inhibitor
mTOR1/2 inhibitors
Cyclophilin (Alisporivir)

THERE IS STILL MUCH WE NEED TO KNOW

Remdesivir & PF-0835231 shows additive effect in HAE
Exploring Real-World Data is an option for quickly assessing repurposing potential of common therapeutics.

- Propensity matching or similar techniques are crucial for reducing (not eliminating) bias.
- Access to large EMR derived patient level data that is properly formatted for analysis is not trivial.
- Analysis of response covariates could help define enrichment criteria for prospective trials.

(RWS= real world study  RCT=randomized control trial)

https://icoda-research.org/project/dp1-efct/

Jaap Mandema (Certara), Hugh Montgomery (UCL), Shuai Fu (Certara), Estelle Russek-Cohen (ERCStatLLC), Christina Bromley, (Analytika, Inc.), Samer Mouksassi (Certara), Amy Lalonde (Lilly), Aaron Springford (Cytel), Larry Tsai (Genentech), Phil Amberry (AstraZeneca), Doug McNair, (BMGF), Nawab Qizilbash (OXON/London School of Hygiene and Tropical Medicine), Stuart Pocock (London School of Hygiene and Tropical Medicine), Névine Zariffa (NMD Group)
Learnings

We were unprepared: Lack of investment in development of antivirals—particularly those targeting readily-transmissible viral families—resulted in a very limited therapeutic arsenal for COVID-19

Repurposing compounds didn’t really work: Clinical trials of repurposed compounds demonstrated limited utility for addressing COVID-19; waiting until the next pandemic to pursue novel R&D will be too late

There’s a need to focus upstream in course of disease: Repurposed compounds are largely targeting disease process in moderate to severe patients, but there is a significant need for therapeutics that target mild to moderate patients (and even individuals pre/post-exposure)

What the world needs to do and where the scientific community must be synergistic

Address viral families with highest potential of causing the next pandemic (coronavirus, orthomyxovirus and paramyxovirus (specifically Nipah + Hendra) with therapeutic modalities that can be widely accessed

• Development of orally-active small molecule antivirals
  • Inhibit either viral or host targets, if these host targets are directly implicated in viral replication
  • Stimulate specific host antiviral responses that prevent infection
  • Explore “Programmable” antivirals (siRNA, CRISPR, etc.)

Program design elements:

• Early science and preclinical tools – available to all
• Experienced drug discovery (Pharma, Biotech, Non-profits, CROs)
• Properly designed clinical trials for robust assessment of impact
• Commitment to data sharing and access
• Funding partnerships – collaborate with government, academic, commercial, and philanthropic funders
CREATING OPTIMAL ANTIVIRALS TAKES EFFORT & TIME

Typical approach over decades

Single agent antiviral
- Minimal safety
- Resistance liabilities
- Minimal efficacy

Incremental improvement and combination
- DDI with other agents
- Less resistance
- Improved efficacy
- High pill burden / low compliance

Single Tablet Combination
- Safe
- Less resistance
- High efficacy
- Low pill burden / high compliance

PrEP / PEP
- Disease prevention
- Reduced transmission

Evolution of HIV drugs: Time and Innovation

Current status, relevant viruses:
- Influenza, coronaviruses – single agents
- Paramyxoviruses – currently no treatment options