WHO GLOBAL CONSULTATION:

CAN REPURPOSED DRUGS REALLY HELP FIND OUTBREAK TREATMENTS FASTER?

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With contributions from colleagues Rob Jordan, Ken Duncan, Dan Hartman

DRUG REPURPOSING BENEFITS & CHALLENGES

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

LESSONS LEARNED FROM COVID-19 RESPONSE

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.

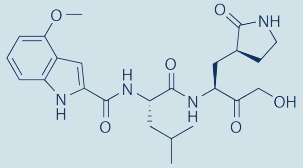
There's a need to also focus upstream in the disease course: Repurposed compounds are largely targeting disease process in moderate to severe patients, but there is a significant need for therapeutics that target mild to moderate patients (and even individuals pre/post-exposure)

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

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



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:

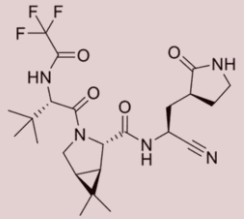
1. Reducing hydrogen bond donor from 5 to 3 to increase oral bioavailability
2. Addressing rapid metabolism in liver by combining with Cyp3A4 inhibitor

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-07321332 Nirmatrelvir synthesized on July 22, 2020

Favorable rat PK profile obtained with ritonavir boost



Phase 1 completed

Phase 2/3 completed

2003 | 1Q20 | 2Q20 | 3Q20 | 4Q20 | 1Q21 | 2Q21 | 3Q21 | 4Q21

PF-00835231 precursor to nirmatrelvir

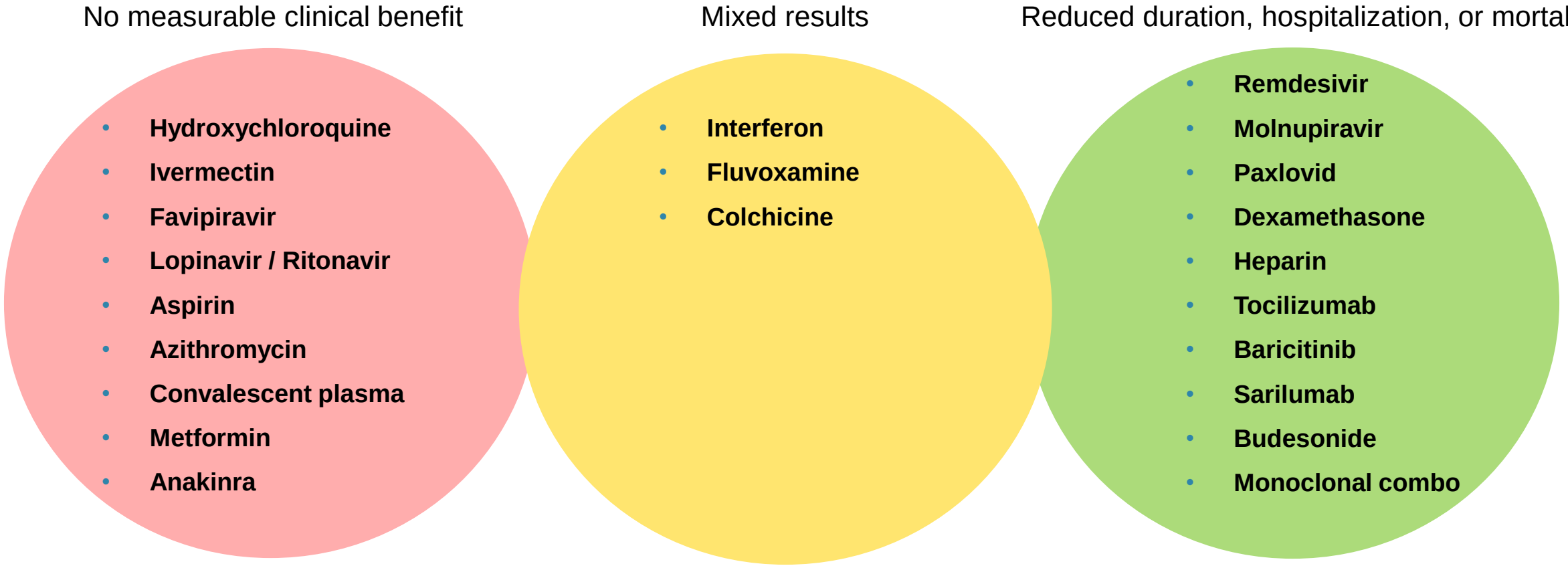
Antiviral Activity confirmed

1.4 Kg batch synthesized

EUA COVID

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-arrythmics)

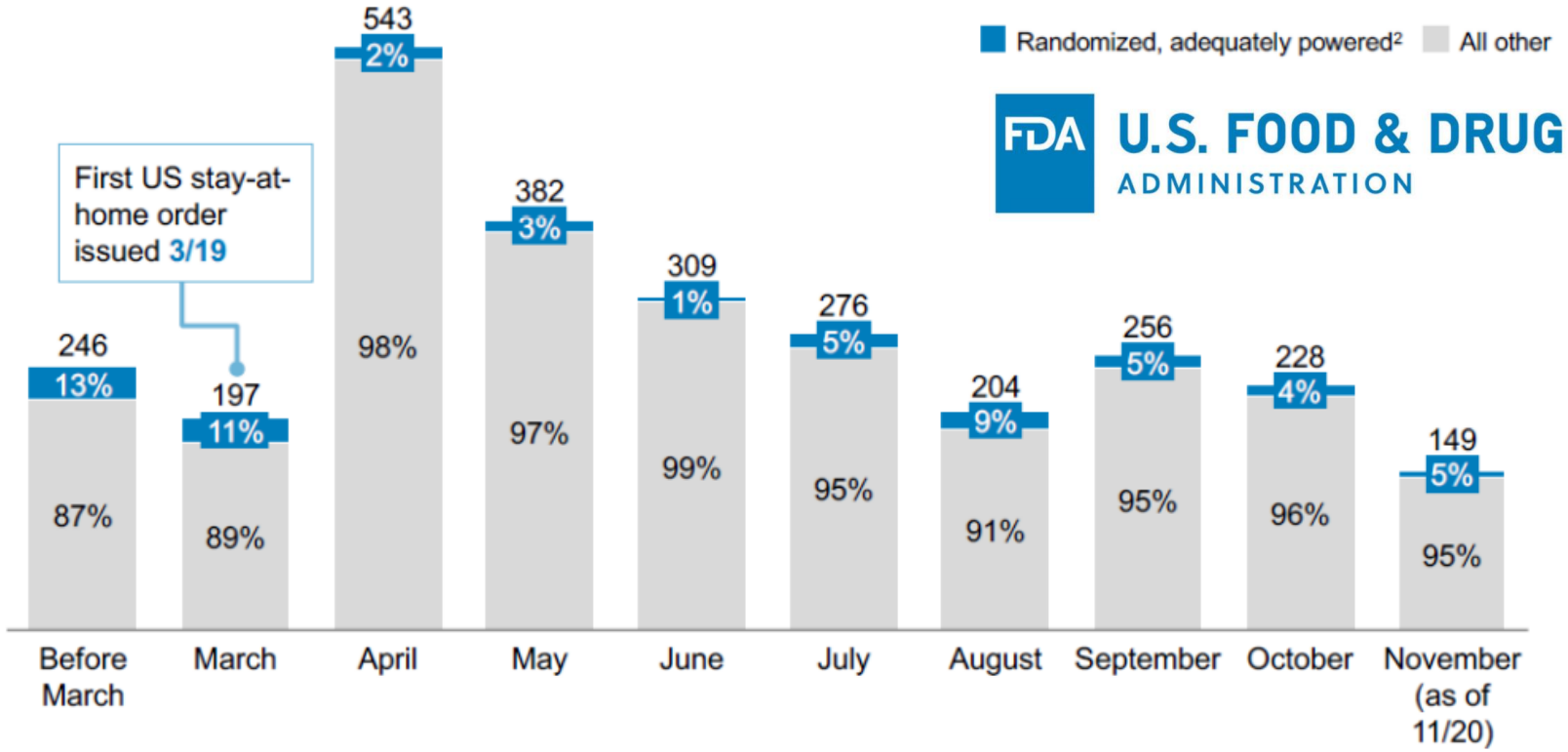
LARGE* RANDOMIZED CLINICAL TRIALS ARE CRITICAL



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

* with N > 1000 per arm in the trial

AVOID UNINFORMATIVE SMALL TRIALS



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

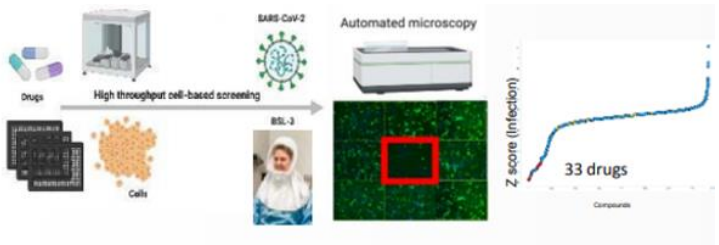
*"…approximately **5% of the total COVID-19 trial arms** in our assessment could be described as randomized and adequately powered."*

— Janet Woodcock Acting Commissioner of Food and Drugs Administration

Source: Nature. 2021 Feb BioBusiness Briefs. doi: https://doi.org/10.1038/d41573-021-00037-3

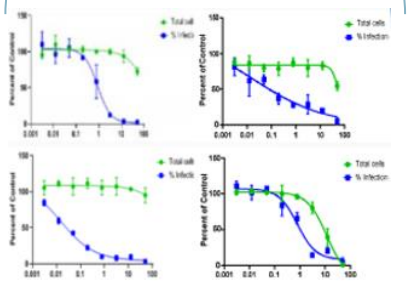
THIS TIME, LET'S NOT FORGET WHAT WE LEARNED

High-Throughput Screens



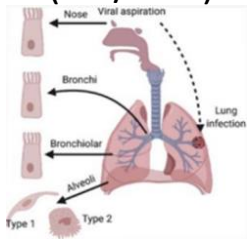
Library: ReFRAME, others
Cell types attempted – Vero-E6, HeLa-ACE2, Calu3, A549-Ace2/TMPRSS2, Huh

Validation

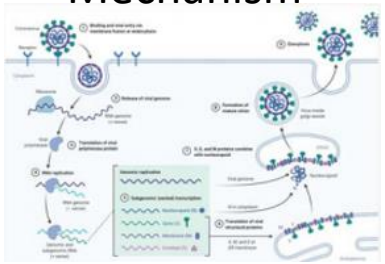


Single point followed by dose response & Cytotoxicity

Primary Respiratory cells (ALI/HAE)



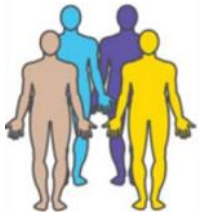
Mechanism



Clinical Trials

Preclinical testing

PK/PD



COVID-19 Patients

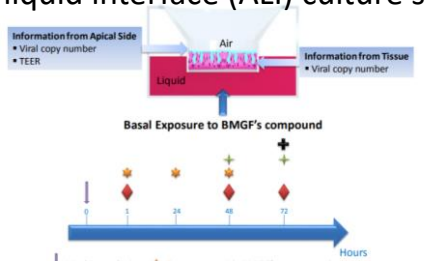
Organoid & organ chip models in development

ReFRAME screen - Compounds by E/IC50 (SI≥10)

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)

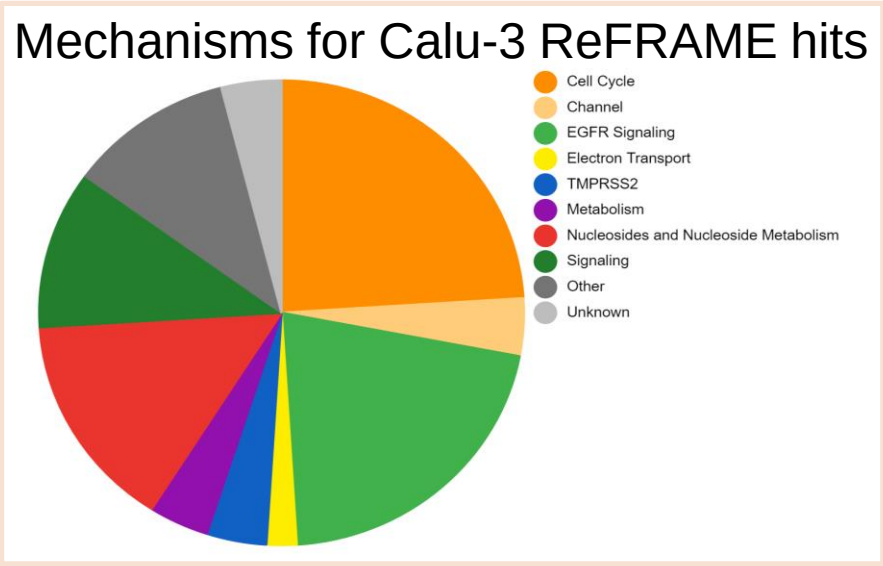
Compound information ~30

SARS-CoV-2 infected hamster model

Compound information ~11

Mouse adapted SARS-CoV-2 infected mouse model

THERE IS STILL MUCH WE NEED TO KNOW



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 (Nucleobase)*
- *AT-527 (Nucleotide prodrug)*
- *Galidesivir (Nucleoside)*

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

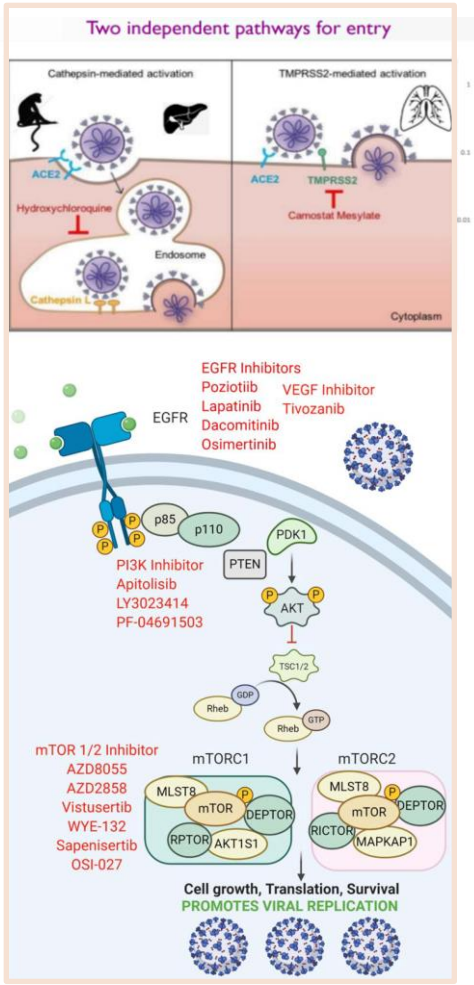
Viral Proteases,
3CL protease (*PF-0835231*), Papain-like protease

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

DHODH inhibitors (*Brequinar*)

EFGR Signaling
EGFR receptor inhibitors
PI3K inhibitor
mTOR1/2 inhibitors

Cyclophilin (Alisporivir)

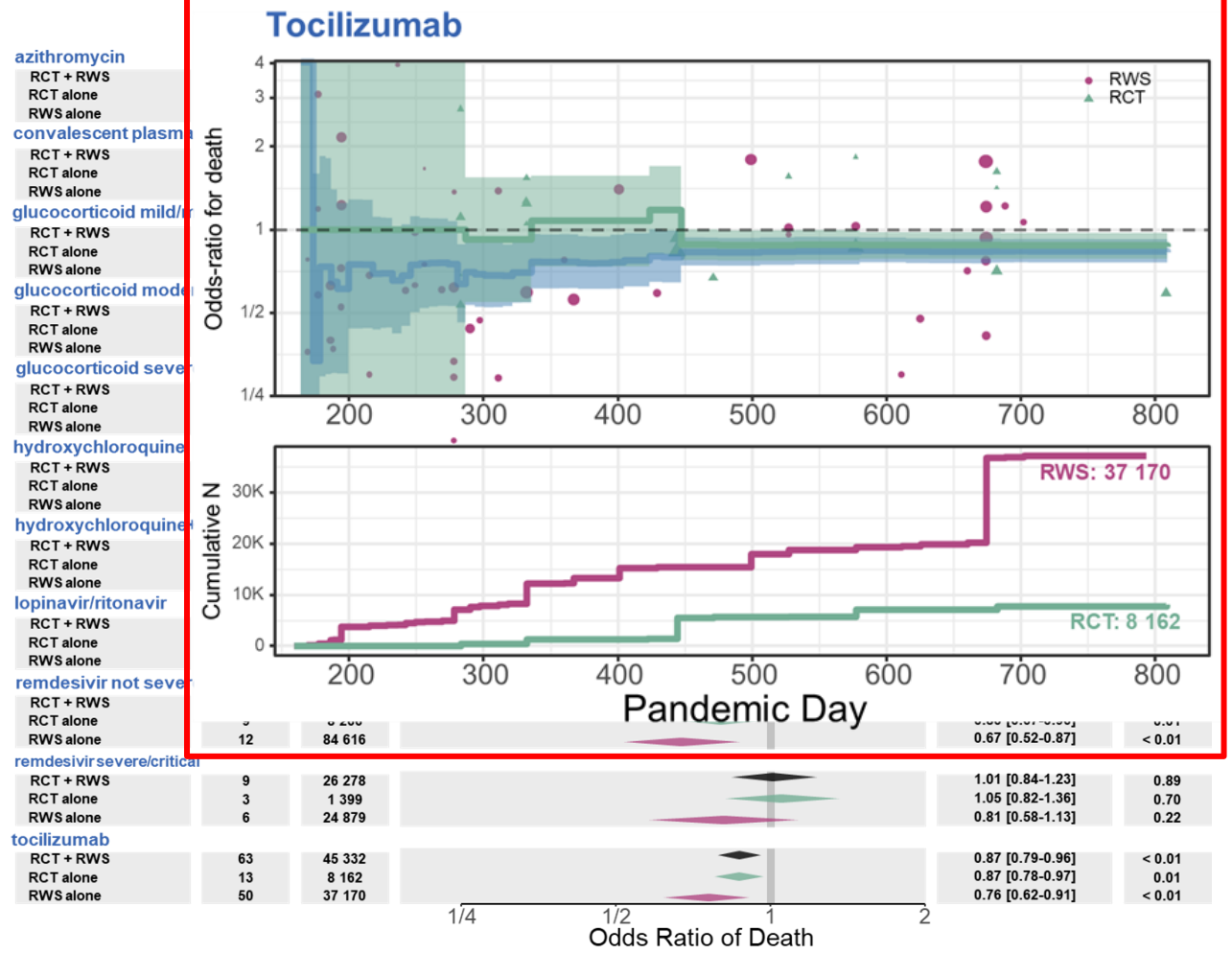


FINDING TREATMENTS FASTER

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 coviates could help define enrichment criteria for prospective trials.

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



ICODA
International COVID-19 Data Alliance

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

Jaap Mandema (Certara), Hugh Montgomery (UCL), Louis Dron (Cytel), Shuai Fu (Certara), Estelle Russek-Cohen (ERCStatLLC), Christina Bromley, (Analytika, Inc.), Samer Mouksassi (Certara), Amy Lalonde (Lilly), Aaron Springford (Cytel), Larry Tsai (Genentech), Phil Ambery (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)

PANDEMIC PREPAREDNESS AND OUR ROLE

What did we learn from Covid-19 drug discovery and how can we be better prepared in future?

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)

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

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

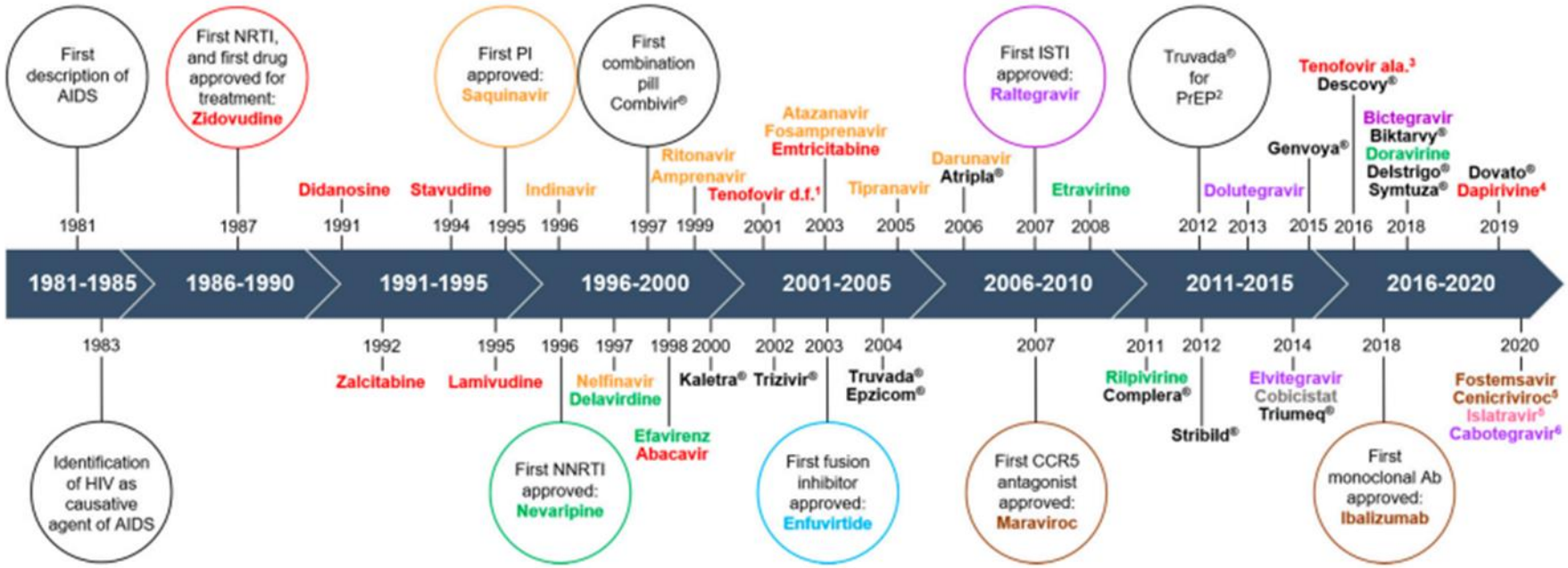
Single agent antiviral
- Minimal safety
- Resistance liabilities
- Minimal efficacy

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



- Nucleoside RT inhibitor (NRTI)
- Protease inhibitor (PI)
- Non-nucleoside RT inhibitor (NNRTI)
- Fusion inhibitor
- Integrase strand transfer inhibitor (ISTI)
- Entry inhibitor
- Nucleoside RT translocation inhibitor (NRTTI)
- Registered brand names for combination pills

Current status, relevant viruses:

Influenza, coronaviruses – single agents

Paramyxoviruses – currently no treatment options

