PANDEMIC PREPAREDNESS: ACCELERATING THE DISCOVERY OF NEW THERAPEUTICS

NASEM Webinar

January 10, 2023

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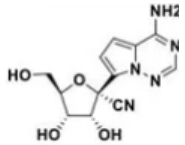
TOPICS TO BE COVERED

1. COVID-19: What did we learn?
2. Preparing for future pandemics: What tools do we need?
3. Defining the desired product
4. Multidisciplinary approach to drug discovery
5. Role of partnerships

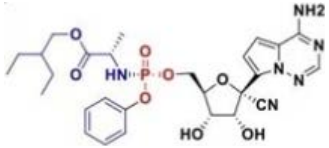
REPURPOSING FOR COVID: REMDESIVIR

Remdesivir parent (GS-441524) identified 2012 for HCV with broad antiviral activity[1]

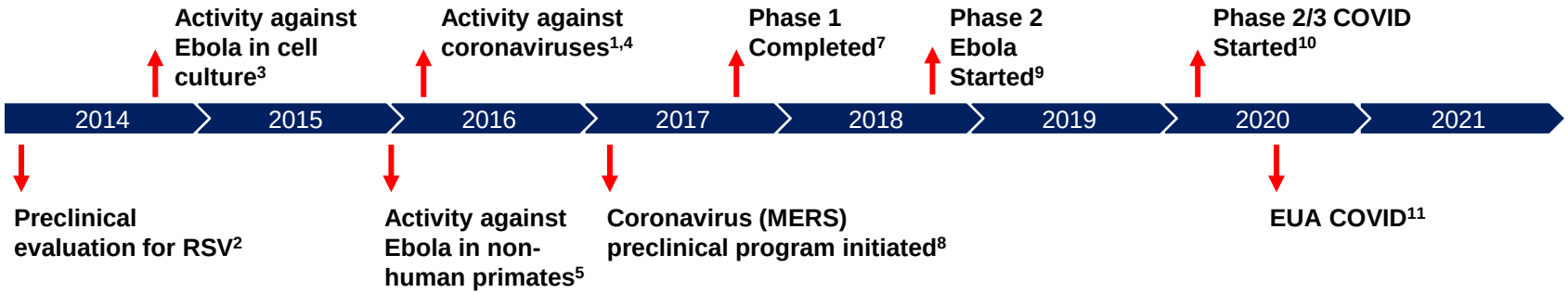


GS-441524

Remdesivir – A prodrug based on Sofosbuvir for HCV developed for Ebola and COVID[2,6]



Remdesivir



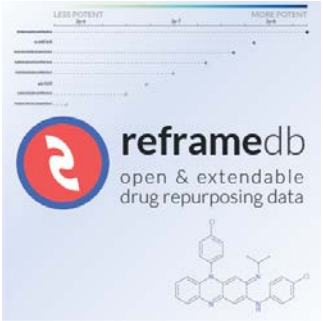
- Nucleoside analogs can have broad spectrum antiviral activity and a high barrier to resistance, however...
  - Poor metabolism to the active triphosphate in tissues requires prodrug strategies to improve pharmacokinetics and efficacy
  - Off-target inhibition of cellular enzymes raises potential safety liabilities
- Lack of efficacy for Ebola halted program but clinical data allowed for quick repurposing for SARS-CoV-2

[1]Cho et al., 2012, (PMID: 22446091); [2]Mackman RL, 2022, (PMID: 35291757); [3]Lo MK et al., 2017, (PMID: 2826269); [4]Sheahan TP et al., 2017 (PMID: 28659436); [5]Warren TK et al., 2016 (PMID: 26934220); [6]Seigel D et al., 2017 (PMID: 28124907); [7]Gilead press release; (7.1) Humeniuk R et al., 2020 (PMID: 32589775) Ph1 results; [8]de Wit E et al., 2020 (PMID: 32054787); [9]Mualngu S et al., 2019 (PMID: 31774950) [10]NCT04292730, NCT04292899; [11]https://www.fda.gov/media/137564/download

RESPONSE TO COVID-19

Could existing oral drugs be used to treat COVID-19?

Screening ReFRAME



Calibr
at Scripps Research

- 25 screens conducted by multiple research teams
- No antiviral candidates identified that met the desired Target Product Profile (oral agent)

www.reframedb.org

COVID-19 Therapeutics Accelerator

BILL & MELINDA GATES foundation

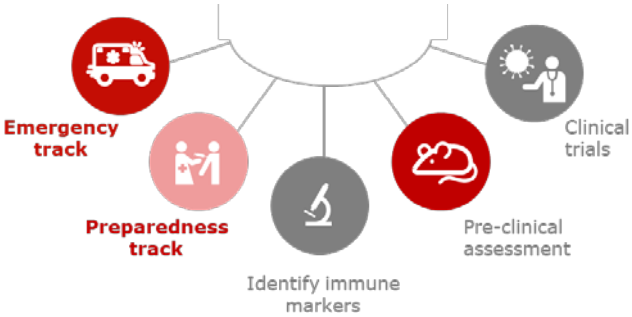
mastercard.

wellcome

- $298M from core funders + 16 additional donors
- Supporting efforts to research, develop and bring effective treatments against COVID-19 to market quickly and accessibly
  - ➢ Discovery, Clinical Trials, Real World Evidence, Manufacturing Capacity, Diagnostics

www.therapeuticsaccelerator.org

C A R E
CORONA ACCELERATED R&D IN EUROPE



- €78.5M over five years
- 37 research institutions and pharmaceutical companies

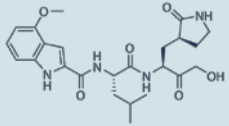
www.imi-care.eu

NEW DRUG DISCOVERY: NIRMATRELVIR

SARS-CoV-1 Mpro inhibitor PF-00835231 was identified in 2003

But:

1. Not absorbed and dosed IV
2. Peptidomimetic and highly metabolized by CYP3A4



Discovery program launched on March 13, 2020

Goal – quickly optimize PF-00835231 to deliver an oral drug by:

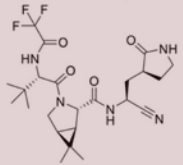
1. Reducing hydrogen bond donor from 5 to 3 to increase oral bioavailability
2. Addressing rapid metabolism in liver by combining with Cyp3A4 inhibitor

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

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-arrythmic)

Source: C&EN January 24th 2022, p16-18

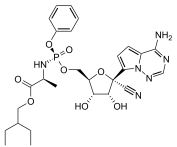
CURRENT SITUATION: REGISTERED COVID ANTIVIRALS

Encouraging progress but options remain limited and not well suited to low- and middle-income countries

Target: RNA-dependent RNA polymerase

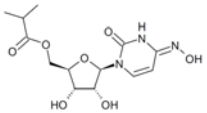
GILEAD

Veklury
(remdesivir)



MERCK RIDGEBACKBIO

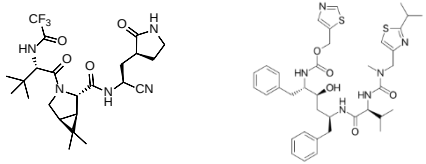
Lagevrio
(molnupiravir)



Target: Main protease

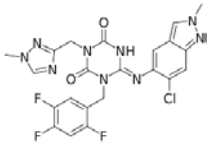
Pfizer

Paxlovid
(nirmatrelvir + ritonavir)



SHIONOGI

Xocova
(ensitrelvir)



medicines patent pool

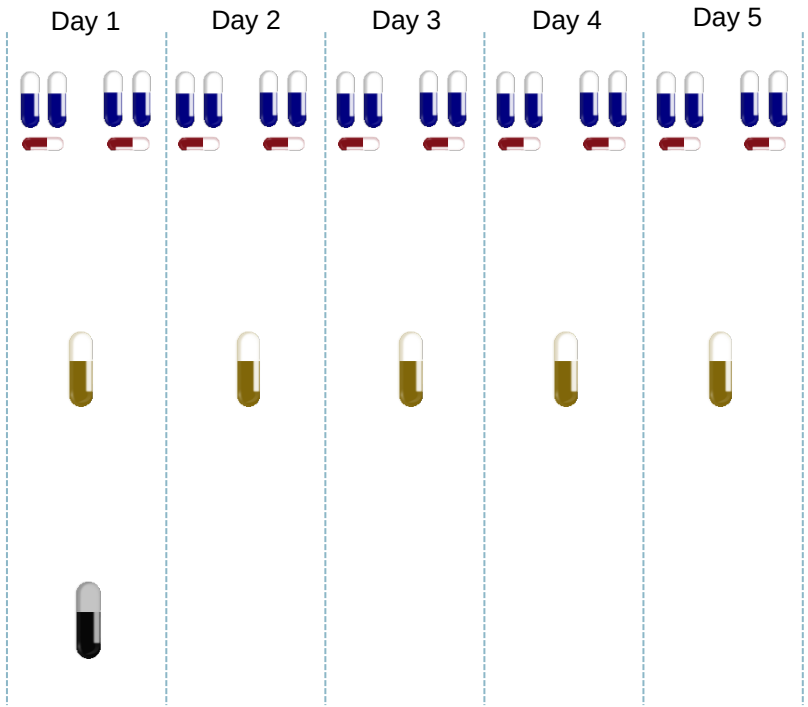
- United Nations-backed public health organization working to increase access to, and facilitate the development of, life-saving medicines for low- and middle-income countries.
- Molnupiravir, nirmatrelvir, and ensitrelvir have been licensed to MPP and sub-licenses issued to multiple generic manufacturers

ROOM FOR INNOVATION

Continuous innovation required to generate “ideal” drug

Today	**Twice daily** High pill burden Drug-drug interactions
Next Generation	**Once daily** More potent, fewer pills Combine mechanisms
Ideal	**Single pill** Improved pharmacokinetics or slow-release formulation

Five-day treatment



WHAT DID WE LEARN FROM COVID-19?

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 has had limited impact:

- Clinical trials of repurposed compounds have 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 the 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)

…and we must get ahead of these challenges before the next pandemic hits

RESPIRATORY VIRUS FAMILIES WITH POTENTIAL TO CAUSE NEXT PANDEMIC

	Coronaviruses	Orthomyxoviruses	Paramyxoviruses
Symptomatic disease with high (mortality)	Respiratory (1 to 10%)	Respiratory (1-2%)	Respiratory and neurologic disease (>40%)
Aerosol transmission	R_0 > 7 (omicron)	R_0 = 2	R_0 = 0.5 (limited transmission)
Seasonal strains circulate in humans	NL63, OC43	Seasonal influenza A and B	RSV, parainfluenza virus, metapneumovirus, measles
Caused pandemics or outbreaks	COVID-19, SARS-CoV-1, MERS	1918 H1N1 influenza	Outbreaks of Nipah virus in Malaysia and India
Animal reservoirs	Bats	Pigs, fowl, migratory birds, horses	Bats, pigs (Nipah) and horses (Hendra) are amplifying hosts

Available Antivirals	Direct Acting	Nirmatrelvir (Mpro) Molnupiravir (RdRp) I.V. Remdesivir (RdRp)	Tamiflu (Neuraminidase) Xofluza (Exonuclease) Favipiravir (RdRp)	✘
	Host Directed	IFN-λ; IFN-β (tbd)	IFN-λ, IFN-β (tbd)	IFN-λ, IFN-β (tbd.)

R_0 measles = 15, smallpox = 3-6

WHAT DO WE NEED TO DO TO BE BETTER PREPARED FOR THE NEXT PANDEMIC?

Address viral families with highest potential of causing the next pandemic…

Development of therapy pipeline for **coronavirus**, **orthomyxovirus** and **paramyxovirus** (specifically Nipah + Hendra) viral families

…with therapeutic modalities that can be widely accessed…

Focus on development of **small molecule antiviral therapeutics**

Therapeutics may inhibit either **viral or host targets,** if host targets are directly implicated in viral replication

Therapeutics may stimulate specific host antiviral responses that prevent infection

…through support of discovery and early clinical development

Activities required to identify, optimize, and bring a **new molecule through Phase 1** clinical trials

Investments in new **assays and models** that facilitate discovery and early development

WHY ARE SMALL MOLECULE DRUGS THE IDEAL TOOL FOR PANDEMIC PREPAREDNESS?

1. Can be developed for any respiratory viral pathogen (family) of pandemic potential
2. Can be stockpiled, with immediate availability in case of the emergence of a novel pathogen of concern (before vaccine development)
3. Fit for post-exposure prophylaxis and early therapy use cases
4. Utility in suppressing transmission
5. Efficacy when vaccines fail (in those with compromised immune function; in the face of immune escape variants)
6. Affordable, deliverable, scalable, accessible

Consideration: Use Case and Target Product Profile (TPP)

USE CASE

Critical to define how a drug will be used

Disease progression	Pre-exposure	Post-exposure incubation	Mild disease	Severe disease
Interventions	**Pre-exposure prophylaxis (PrEP)** • Outbreak response • Protect vulnerable populations (health care workers, first responders, pregnant women)	**Post-exposure prophylaxis (PEP)** • Outbreak response • Contacts	**Treatment** • Prevent progression to severe disease in high-risk patients	**Treatment** • Control over-active immune response, other symptoms
Considerations	• Safety profile – any side effects will not be tolerated • Regulatory	• Safety profile – minimal side effects • Regulatory	• Peak viral load • High likelihood of compliance • Patients will likely tolerate some side-effects or inconvenience	• Antivirals unlikely to be effective – need to target host processes rather than the virus
	Target virus			**Target host**

TARGET PRODUCT PROFILE

Defines the characteristics of the product (as on the drug label), based on the Use Case

Special considerations for global use:

- No requirement for monitoring ➡
- No drug-drug interactions ➡
- Minimal ➡
- Oral ➡
- No specialized formulation ➡
- Heat stable ➡
- Very low ➡
- No cold chain ➡
- Global strategy, WHO PQ ➡

Attribute	Minimal acceptable	Ideal	Annotations
Indication	This describes the criteria to be achieved for a product to be of use clinically	This describes the “best case” scenario	Can be used to capture information relevant to the attribute
Target population			
Target countries			
Efficacy			
Safety			
Coadministration			
Contraindications			
Route of administration			
Dosage form/schedule			
Shelf-life			
Cost of goods			
Storage			
Regulatory path			

Most products fall between these characteristics

TARGET CANDIDATE PROFILE

Defines the characteristics of the candidate... many factors to consider

Efficacy

Activity against pathogen
Enzyme activity
Selectivity
Frequency of resistance
Animal model
etc.

DMPK

in vitro
Solubility
Permeability
Efflux ratio
Microsomal turnover
Cyp inhibition/induction
Metabolite id
etc.

in vivo
Oral bioavailability
Elimination half-life
Volume of distribution
Dose linearity
Tissue distribution
etc.

Toxicity

in vitro
Micronucleus test
Ames test
hERG assay
CEREP panel
etc.

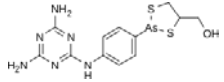
in vivo
Maximum tolerated dose
Dose-limiting toxicology
Therapeutic index
Dose for IND-enabling studies
etc.

Chemistry/ Pharm. Dev.

Synthetic route
IP status
Preclinical formulation
Salt selection
Polymorph screening
Stability
Human dose prediction
etc.

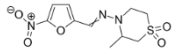
A SUCCESS STORY: HUMAN AFRICAN TRYPANOSOMIASIS

1949 **Melarsoprol**

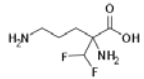


2009 **NECT**[1,2]

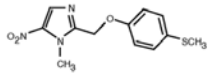
Nifurtimox



Eflornithine

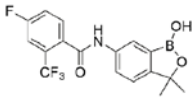


2018 **Fexinidazole**[3]



2023? **Acoziborole**[4]

(Pending approval)



DNDi
Drugs for Neglected Diseases *initiative*

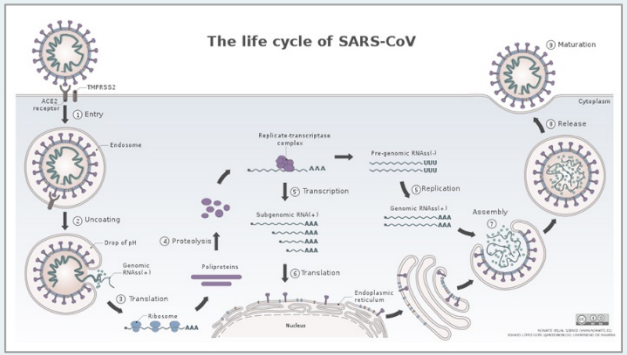
[1]https://doi.org/10.1016/S0140-6736(09)61117-X
[2]https://doi.org/10.1371/journal.pntd.0000720
[3]https://doi.org/10.1016/S0140-6736(17)32758-7; [4]https://doi.org/10.1016/S1473-3099(22)00660-0
[4]https://doi.org/10.1016/S1473-3099(22)00660-0

VIRUS LIFECYCLE AND POINTS OF INTERVENTION

Viruses are diverse and propagate in human cells in different ways

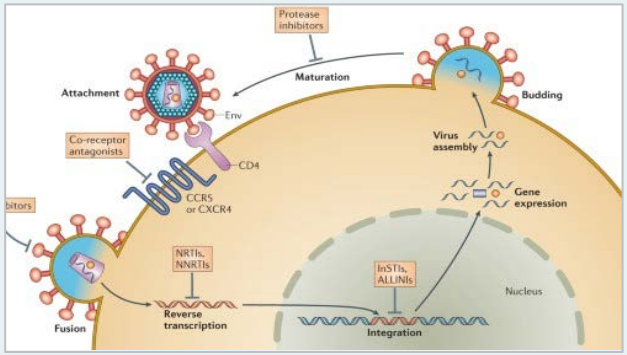
e.g.

SARS



American Society for Microbiology

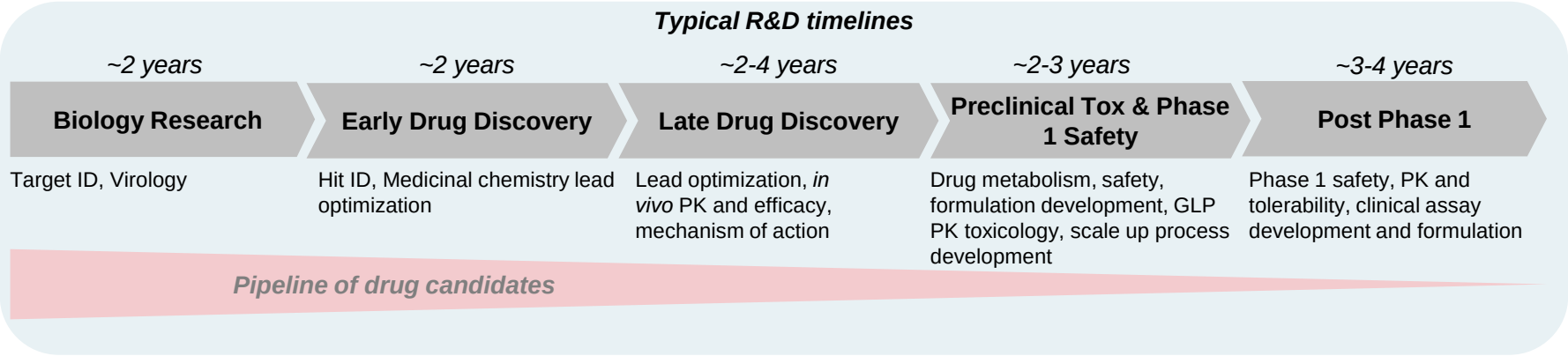
HIV



Laskey, S., Siliciano, R. *Nat Rev Microbiol* **12,** 772–780 (2014).

- Viruses have relatively small genomes and therefore not many proteins or enzymes to target
- Targets may have same function but differ in gene sequence and protein structure from family to family or even within the same family
  - e.g., Proteases differ mechanistically (HIV has aspartyl, SARS-CoV-2 has cysteinyl) and in substrate specificity
  - Drug designed against one virus unlikely to be effective against another (with some exceptions)
- Viruses mutate quickly and can escape target inhibition
- There has been limited success in targeting host factors essential for viral replication
  - Small magnitude of effect, potential for toxicity

ANTIVIRAL DRUG DISCOVERY



Challenges with antiviral drug discovery and development

1. Access to virology laboratories with BSL2, BSL3, and BSL4 containment
2. Obtaining drug exposure at C_{min} above IC_{90} for inhibition of virus replication with dosing schedules that inhibit virus replication until the host immune response controls infection
3. Lack of animal models of virus replication to establish preclinical PK/PD relationships

Pay attention to drug resistance

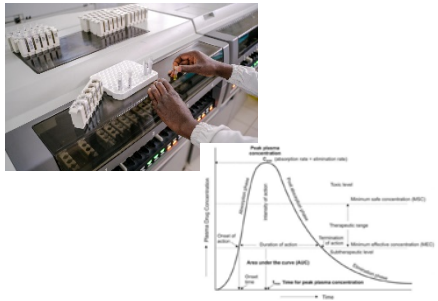
Problem

- Chronic infections (e.g., HIV, HCV) require combination therapy to reduce emergence of resistant variants
- For acute viral infections, treatment emergent resistance can reduce clinical efficacy and introduce variants into the population

Solution

- Develop combination therapies to reduce resistance emergence
- Study resistance pathways to understand resistance risk
- Measure the fitness of resistant variants to understand impact on replication and pathogenesis
- Study cross resistance

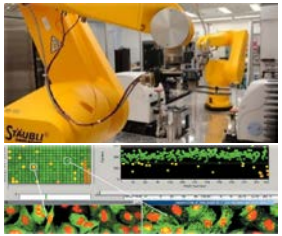
INTEGRATED DRUG DISCOVERY



Hit-to-Lead:
Establish SAR
Limited profiling

Lead optimization:
Bring all required properties together

Target → Hit → Lead → Candidate



Multiple tools:
Library screening
Virtual design
Fragment-based
DNA-encoded libraries
etc.

WHAT WILL BE THE IMPACT OF AI IN DRUG DISCOVERY?

Insilico Medicine

Insilico Medicine Announces Novel 3CL Protease Inhibitor Preclinical Candidate for COVID-19 Treatment

USA - English

NEWS PROVIDED BY
Insilico Medicine →
May 24, 2022, 09:00 ET

SHARE THIS ARTICLE

- Insilico's candidate demonstrated a favorable profile with good *in vivo* efficacy at low doses, efficient synthesis, and no need for co-administration with Ritonavir.
- The candidate is intended to be used for the treatment of SARS-CoV-2 and its variants, along with other coronaviruses. Insilico's candidate has a novel structure that can be synthesized efficiently, designed by its propriety AI-driven small molecule generation platform, Chemistry42.

Source: https://insilico.com/news/

PostEra

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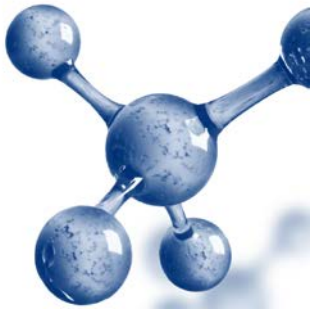


CASE STUDIES

COVID Moonshot: PostEra's machine learning platform in real world drug discovery

PostEra's machine learning drove the prioritization of crowdsourced ideas

Moonshot crowdsourced antiviral ideas, inspired by a fragment screen, from over 400 scientists around the world. PostEra's machine learning drove the prioritization of these ideas and designed the synthesis of all 2000 compounds made as part of COVID Moonshot as well as using our ML technology to develop new chemotypes.

In 18 months, the project progressed from a fragment screen to the nomination of Development Candidates ready for IND-enabling studies.

Source: https://postera.ai/moonshot/

COOPERATION

Investments in early science & preclinical tools

Develop resources that **could be used by all partners**, e.g., disease models, implicated pathways, targets, in vitro assays, animal models

Data sharing and access commitments

Responsible pricing for low- and middle-income countries + open access publication, data sharing for pre-competitive activities

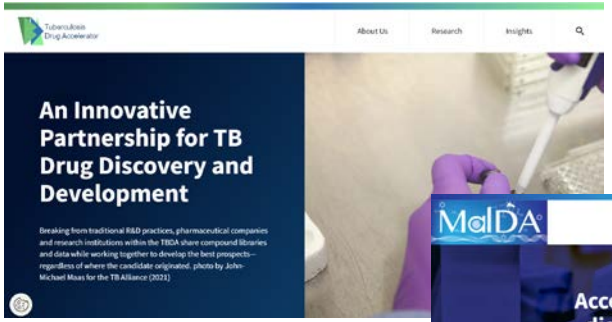
Professional drug discovery

Engagement of **Pharma, Biotech, Non-profit** and **CROs**

Funding Partnerships

Align with **public sector/philanthropic** funders and **governments:** Leverage additional capacity & support for infrastructure & translational development

EXAMPLES OF COOPERATIVE PROGRAMS



tbdrugaccelerator.org

Drug candidates to form part of a regimen that is:

Pan-TB – All *M. tuberculosis* strains

Shorter – 2 months or less

Safer – No baseline safety monitoring

Simpler – Oral, once-daily dosing

Affordable – < 150/course

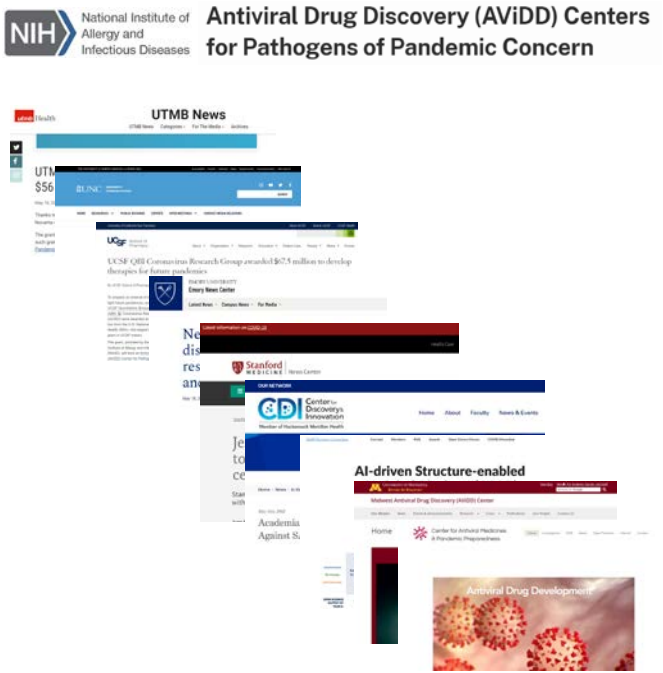
malariada.org

Drug candidates that contribute to:

Tackling drug resistance – Target new mechanisms; find agents that do not generate resistance

Improving compliance – Single exposure radical cure

Driving towards elimination and eradication – Ability to block transmission



PARTNERSHIP

novo nordisk fonden
Benefiting people and society

Open Philanthropy

BILL & MELINDA GATES foundation

https://padinitiative.com/

The primary mission is to **catalyze discovery and early development of a panel of antivirals for treatment of pandemic threat viruses** that include coronaviruses, orthomyxoviruses and paramyxoviruses

The antivirals must meet a target product profile **suitable for global deployment**

Commitment to **global access principles** and global engagement to increase impact

Initial combined investment of up to $90M

SUMMARY

Pandemic preparedness: Accelerating the discovery of new therapeutics

1. Learn from past failures and develop countermeasures now against viral threats
2. Ensure innovation results in antiviral developments suitable for global deployment
3. Multi-disciplinary teams are key to success
4. Coordinate and integrate – as with the PAD initiative – to increase efficiency
5. Ensure equitable access to new products – key to stopping an emerging pathogen