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Pandemic Antiviral Discovery (PAD) Initiative: Catalyzing Antiviral Discovery and Development

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What is the PAD initiative?

- The Pandemic Antiviral Discovery (PAD) initiative is a consortium of funders (Novo Nordisk Foundation, Open Philanthropy, Bill & Melinda Gates Foundation) who have agreed to fund research leading to development of antivirals for pandemic preparedness
- Funding supports research focused on discovery and development of antivirals for coronaviruses, paramyxoviruses and orthomyxoviruses
- The PAD initiative manages a joint portfolio of programs, but funding mechanisms reside within each foundation who have agreed to a shared vision and global access goals.

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Virus Families of Pandemic Concern Supported by PAD

	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, India and Bangladesh
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) Remdesivir (RdRp), I.V.	Tamiflu (Neuraminidase) Xofluza (Exonuclease) Favipiravir (RdRp)	✘
Host Directed	IFN-λ; IFN-β (tbd)	IFN-λ, IFN-β (tbd)	IFN-λ, IFN-β (tbd.)

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R_0 measles = 15, smallpox = 3-6

New therapeutics are required to improve efficacy, safety, global access, and combat resistance emergence

Ideal Tools for Pandemic Preparedness and Resulting TPP

The ideal tool…

1. Has likely efficacy against any respiratory viral pathogen (family) of pandemic potential
2. Can be stockpiled, with immediate availability in case of the emergence a novel pathogen of concern
3. Is fit for PrEP, PEP, and early therapy use cases
4. Has utility in suppressing transmission
5. Has efficacy when vaccines fail (in those with compromised immune function; in the face of immune escape variants; before vaccine development, vaccine hesitant individuals)
6. Is affordable, deliverable, scalable, accessible

→ Small molecule drugs are highly suited to this role

Resulting Target Product Profile (optimistic)

Indication	Pre- and post-exposure prophylaxis and treatment for individuals at high risk of exposure
Target Population *(Global Access)*	Individuals > 6 years of age
Safety	Safety profile consistent with pre-exposure prophylactic use
Route of Administration / Duration	Oral capsule or tablet / once or twice per day dosing
Cost of Goods Sold	Affordable for LMICs
Stability / Shelf Life	Appropriate for stockpiling & LMICs

→ Holds for all 3 virus families

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The Problem of Drug Resistance

- Chronic infections (e.g., HIV, HCV) require combination antiviral therapies to reduce emergence of resistant variants that would **lead to treatment failures and loss of efficacy**
- For acute viral infections, treatment emergent resistance can reduce clinical efficacy and **introduce variants into the population** reducing effectiveness of antivirals in future outbreaks
  - Amantidine (M2 inhibitor): No longer used because most circulating influenza viruses are resistant
  - Tamiflu (neuraminidase inhibitor): In 2009 the predominant circulating flu strain contained a Tamiflu resistant allele suggesting that resistant strains are in the environment and could reemerge

Solution

- To reduce resistance risk and safeguard antivirals, active antiviral stewardship is required as outlined below:
  - Develop combination therapies to reduce resistance emergence and **provide commercial or policy incentives for their use**
  - Study resistance pathways to understand resistance risk and to monitor resistance in the clinic
  - Measure the fitness of resistant variants to understand impact on replication and pathogenesis
  - Study cross resistance to other antivirals within the same class and different class to inform future combination strategies

Creating Optimal Antivirals Takes Time

Typical approach over decades

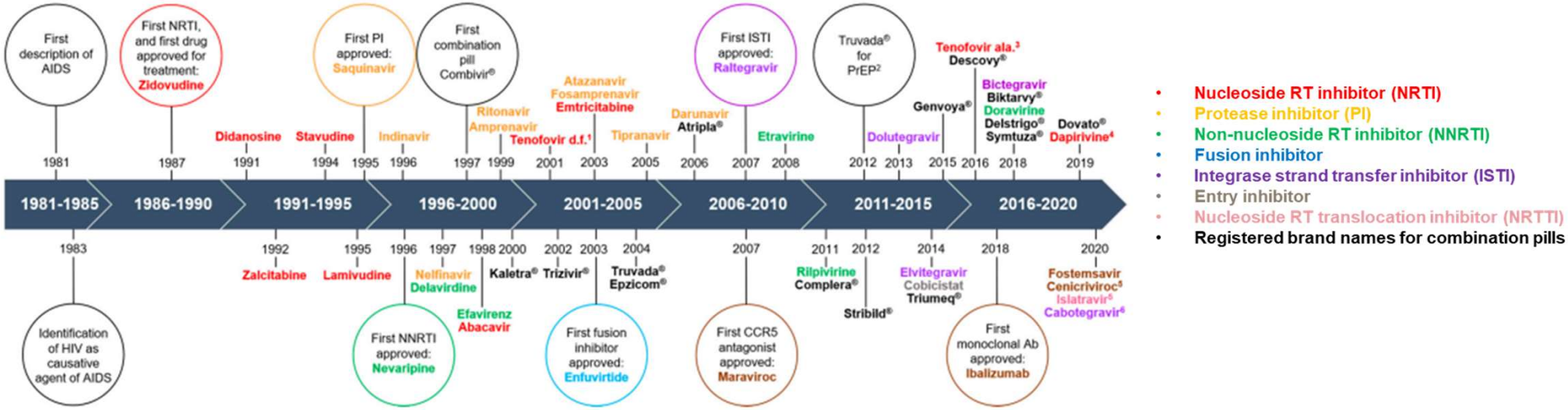
Single agent antiviral
- Minimal safety
- Resistance liabilities
- Minimal efficacy

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



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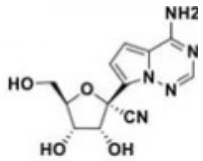
PAD funding will de-risk early assets making them more attractive for commercial investment for pandemic indications

COVID Antivirals: Discovery of Veklury and Paxlovid

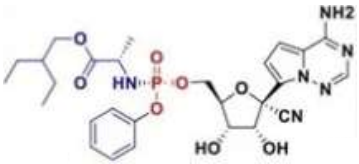
Veklury

Veklury parent (GS-441524) identified in 2012 for HCV with broad antiviral activity



GS-441524

Veklury – A prodrug based on Sofosbuvir for HCV developed for Ebola and COVID



Veklury (Remdesivir)

Preclinical RSV evaluation

Ebola preclinical program

Coronaviruses (MERS) preclinical program

Phase 1 completed

Phase 2 Ebola started

Phase 2/3 COVID started

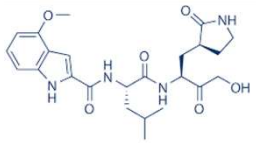
EUA COVID

2014 | 2015 | 2016 | 2017 | 2018 | 2019 | 2020 | 2021

Paxlovid

PF-00835231 identified in 2003 as a SARS-CoV-1 Mpro inhibitor

- I.V. dosing (not oral)
- Peptidomimetic with poor metabolism

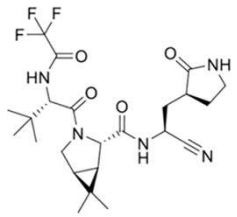


PF-00835231

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 (ritonavir)



Nirmatrelvir

Phase 1 completed

Phase 2/3 Completed EUA COVID

Paxlovid (Nirmatrelvir + Ritonavir)

- Orally active
- >85% reduction in hospitalization and death

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Repurposed (Veklury) vs New Chemical Entity (Paxlovid)

Pandemic Antiviral Discovery (PAD) Partnership

Value Proposition:

- A consortium of philanthropic funders (Novo Nordisk Foundation, Open Philanthropy, and the Bill and Melinda Gates foundation) to strengthen the pandemic preparedness ecosystem through support of basic research and development of antiviral programs that will increase "shots on goal" and tap into additional networks of expertise.
- Joint initiative has more impact than individual smaller programs: Stronger philanthropic voice. Shared mission and global access goals, but funding mechanisms remain with the individual organizations

Scope

- 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.**

Status

- Partnership publicly announced on March 14th, 2022
- Launched first joint RFP on March 21st, 2022 focused on henipavirus drug discovery
- Launched second joint RFP on **October 6, 2022 focused on influenza drug discovery**
- First PAD grants are expected to be announced early January 2023 on the PAD website
- We welcome inquiries from the scientific community seeking support for antiviral projects

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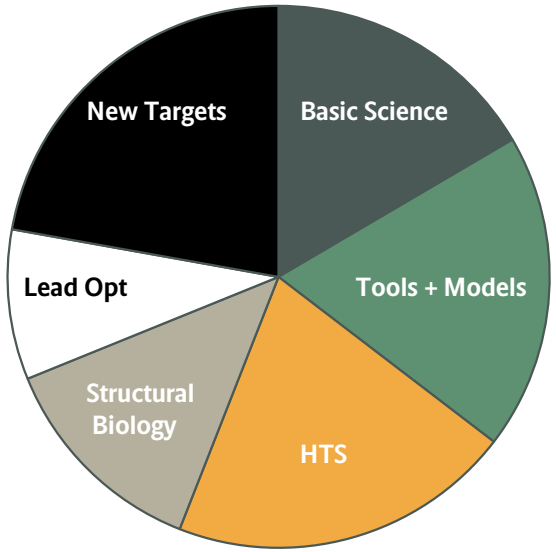
PAD expects to invest 30M in henipavirus research



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PAD Request for Proposals

‘Antivirals for Pandemic Influenza’

The deadline for submitting short concept notes is **14 December 2022**.

Researchers from around the world are encouraged to submit proposals

The RfP will support **discovery research and early development** designed to develop Phase-2 ready **novel small-molecule antivirals targeting pandemic influenza**.

Proposals should be consistent with at least one of these 4 areas:

- Direct acting antivirals with data demonstrating clear differentiation from currently marketed influenza antiviral products
- Host targeted therapies with data demonstrating clear benefit over currently marketed influenza virus therapeutics
- Compounds that target multiple pathways or mechanisms to reduce the likelihood of resistance emergence
- Compounds demonstrating activity against drug resistant influenza variants

Read more: padinitiative.com


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