Delivering medicines for a global population

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Wednesday, August 21, 2024 | 4:00 p.m. PT

Outline

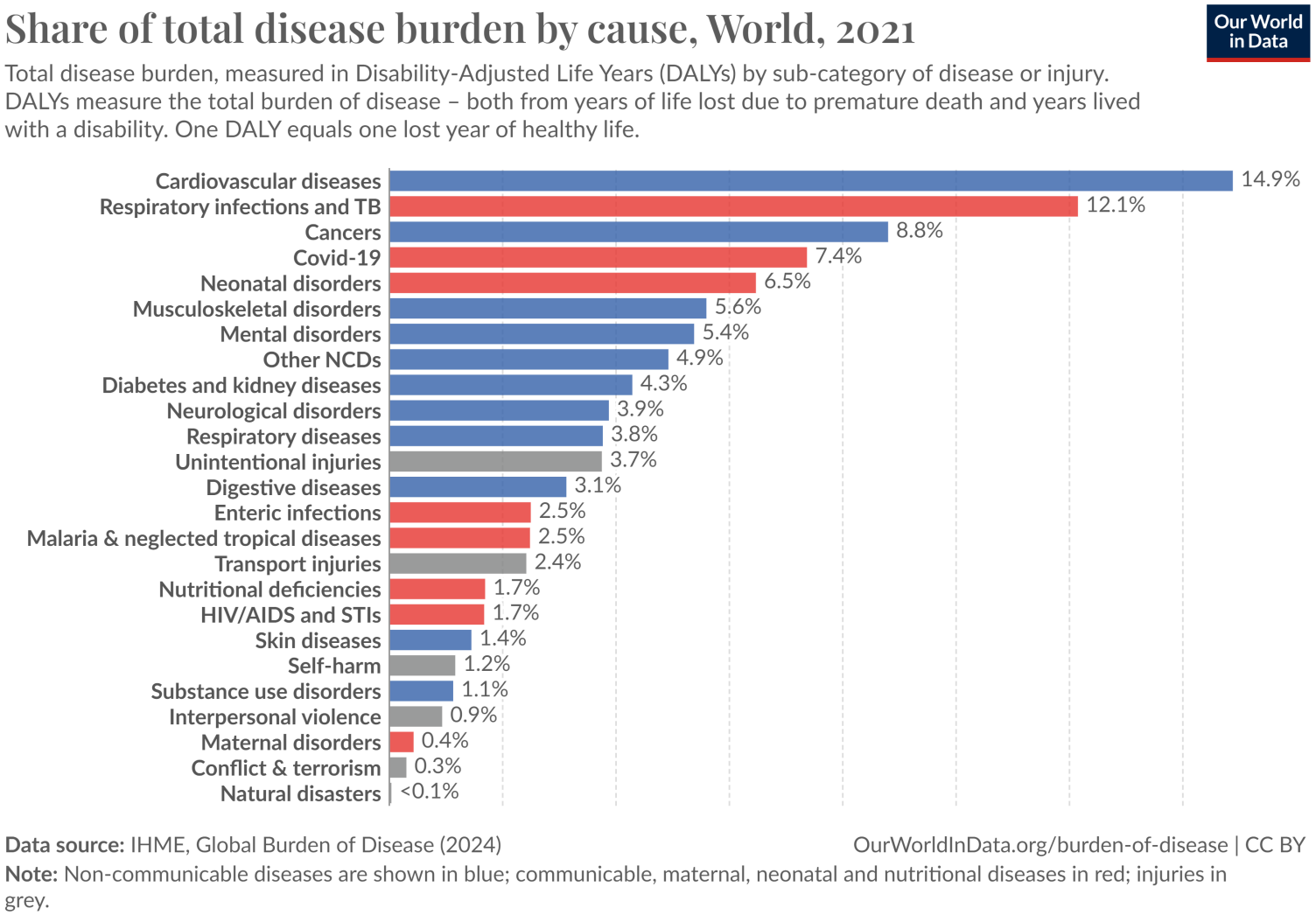
- What does a medicinal chemist exactly do?
- How do we improve our timeline to patients
  - Drug repurposing
  - Improved drug delivery
- Urgent need we can address as a non-profit – the next pandemic

My Journey at GNF and then onto Calibr-Skaggs

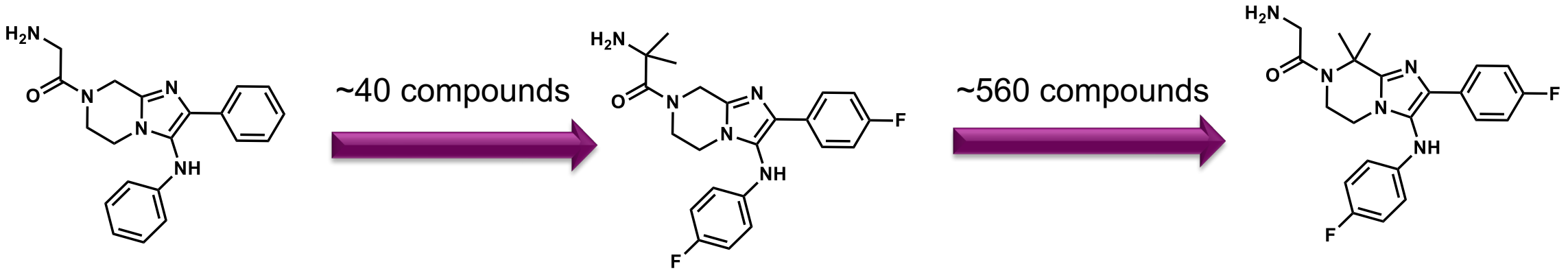
- Ran new chemical reactions in high school – inspired by discovery in chemistry
- Started off being inspired by Lyrica as an undergrad
- Took some time off in IT consulting to remind myself of my passion
- Learned about new reactions to help make compounds more easily in graduate school
- Decided to apply to drug discovery (Gilead or GNF)
- 2 chemists made a Phase 3 drug candidate in 18 months
- First lead 40 cmpds then 600 cmpds to a Phase 3 candidate

Why work on Global Health?

- All red on this graph effects poorer nations more but all countries
- Calibr-Skaggs work on all the others as well
- Biology can overlap between needs - key to work across basic biology



GNF Malaria Phase 3 Compound



- 3 chemical steps; novel chemistry application of a well-known reaction
- 7500 compound randomly made
- Commercially available compound collection since 1999

Kercher, et.al. *J Comb. Chem.* 2007, 1177

- Compound GNF776
  - *Pf* W2 (EC_{50}): 20 nM
  - Oral t½ = 6.2 h
  - PO $AUC_{0\text{-}inf}$ (D.N.) = 596.5 h*nM / (mg/kg)

Wu, et.al. *J. Med. Chem.* 2011, 5116.

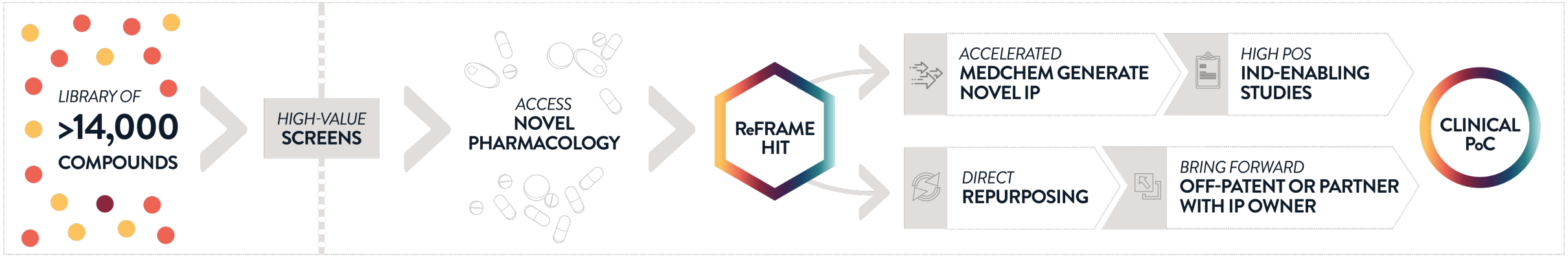
- KAF156 (Ganaplacide) – Expected approval 2026
  - *Pf* W2 (EC_{50}): 6 nM
  - CL = 21.92 mL/min/kg; V_{ss} = 11.8 L/kg
  - Oral t½ = 8.4 h
  - PO AUC_{inf} (D.N.) = 1035 hr*nM (mg/kg)
  - 12 chemical steps

Nagle, et. al. *J. Med. Chem.* 2012, 4244.
Meister, et. al. *Science* 2011, 1372.

Key challenge: How we expedite this long path to patients by taking advantage of chemistry and biology together?

Repurposing **F**ocused **R**escue and **A**ccelerated **ME**dchem (**ReFRAME**) Drug Repurposing Platform

THE FRONT ROW at Scripps Research | 100 YEARS | A Century of Science Changing Life



- FDA-approved drugs (39%)
- Investigational new drugs (58%)
- Preclinical compounds (< 3%)

Reframedb.org has all drug information and screening data

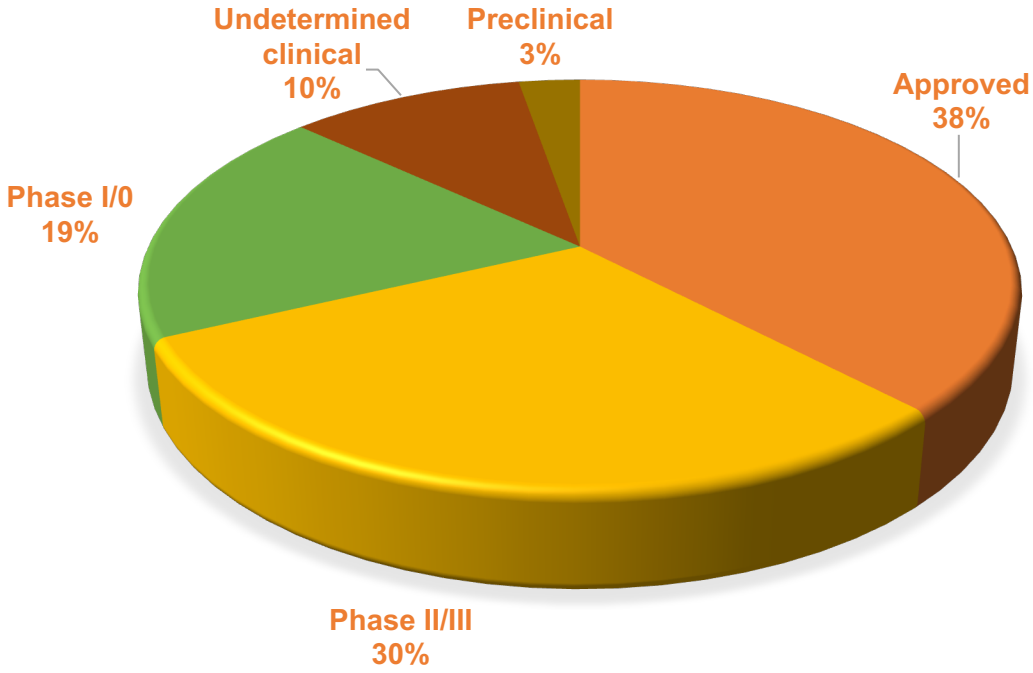
Calibr-Skaggs Institute for Innovative Medicines | Scripps Research

BILL & MELINDA GATES foundation

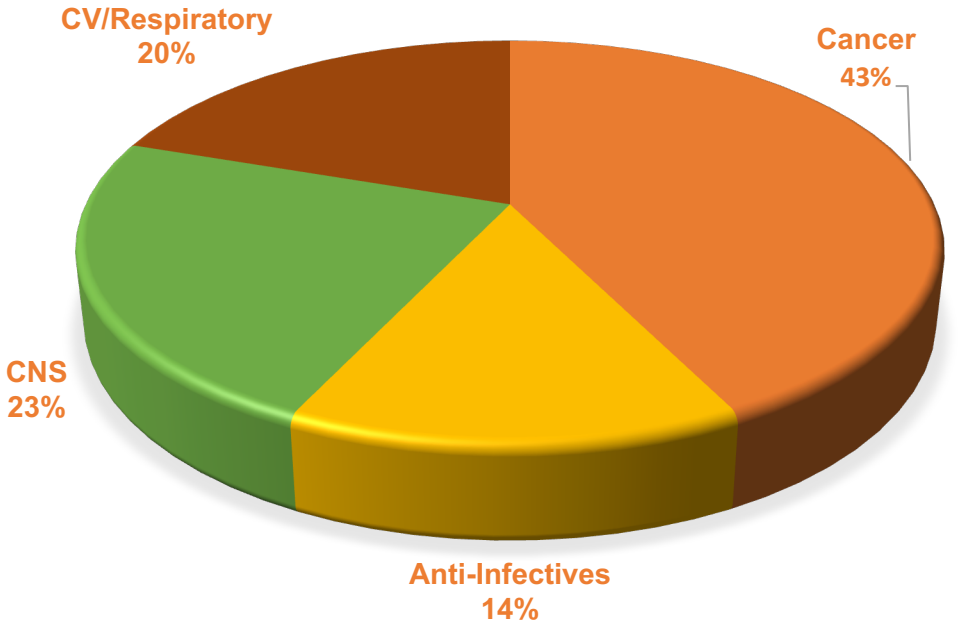
ReFRAME Collection: “Democratizing” Drug Discovery

- Using multiple drug databases allows us to capture more early-stage clinical candidates for biologists to screen
- Half of the collection synthesized by Calibr-Skaggs to enable biologists to access compounds they would not be able to get otherwise
- Compound distribution as expected given historical therapeutic areas of commercial areas of interest but these allow us to use human drug classes to pathogen drug classes

Distribution based on Development Stage



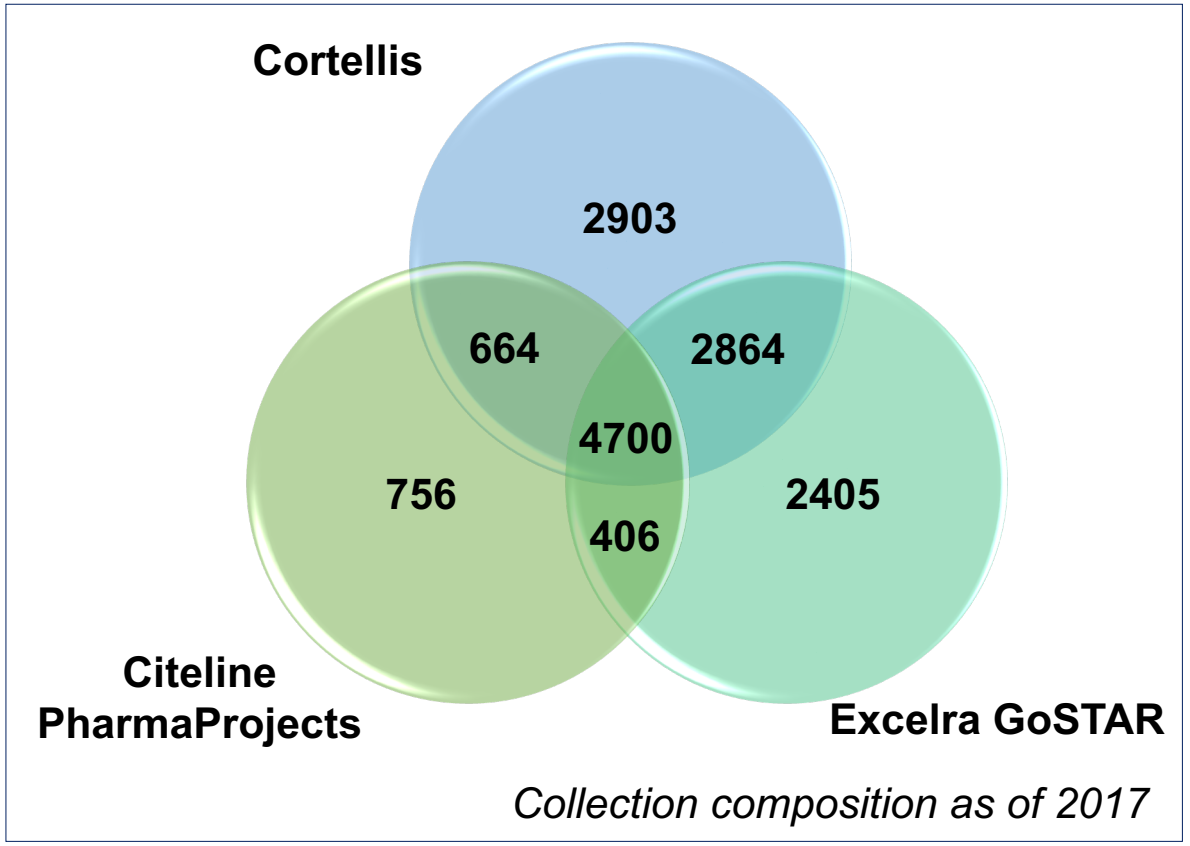
Top Disease Indications Most Frequently Annotated



ReFRAME Collection: Data Vendor Summary

RESULTS

- A total of four data vendors were used due to geographic editorialization but three we considered essential
- Data vendors chosen primarily based on pharma usage
- Total of ~18 K entries in the collection with defined chemical structure
- ~1K entries based on “best guess” approach for early clinical candidates
- Only 6K are off the shelf – we made 6K in 2015
- **Additional drug database updates since 2015 incorporated to add ~3000 more entries to include in the collection**
- **Nearly 1M data points of open access for AI models**



Collection composition as of 2017

COMPARISON TO OTHER REPURPOSING SETS

- Only set to make compounds not off the shelf
- Wikipedia 5K drug entries are included in this set
- 92% of the structures are in NIH PubChem collection

FUTURE POTENTIAL WORK

- Source 6K compounds not in the collection – really only interrogating two-thirds of all compounds available
- Additional informatics profiling to annotate safe plasma levels in humans and animals, free fraction, EC_{50} in safety assays
- Creating subsets for smaller screens based on mechanism of action or drug class (like β-lactam antibiotics)

What has been done in ReFRAME in 6 Years?

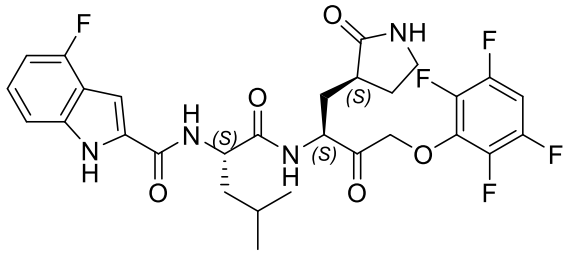
Enumerating the Value of ReFRAME

ReFRAME has led to 14 PCC, PCD and clinical stage programs accelerated through repurposing

- 256 ReFRAME screens in queue
- 188 ReFRAME screens completed (dose response)
- 177 ReFRAME dose response data sets uploaded to ReFRAMEdb.org
- 105 ReFRAME primary data sets uploaded to ReFRAMEdb.org

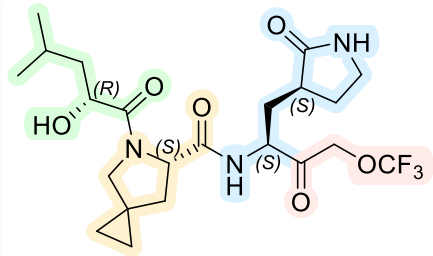
LO Initiated	PCC Declared	IND-Enabling	Clinical Trials
mCIU795 PI^{pro}-CoV-2 - *Calibr*			
kBNC350 (Apilimod) Ebola - *Calibr*			
kCBE897, Artelinic Acid MDS - *Calibr*	**kCAT546** SARS-CoV-2 - *Univ of Maryland*		
Mavatrep Sickle Cell - *NIH*			
kCBK404 Cryptosporidiosis - *Calibr / Univ of Houston*			
mCNW330 CoV-2 Nucleoside – *Calibr / AViDD*		**BMF164** Fibrosis - *Calibr*	**CMX990** SARS-CoV-2 M^{pro} Inhibitor
mCNV741 SARS-CoV-2 M^{pro} - *Calibr*	**kAAC984** Osteoarthritis - *Scripps / Calibr*		
Mavacoxib Schistosomiasis - *UCSD*			
kCBN952, VB-201 Cryptosporidiosis - *Calibr*			**Auranofin (kAAD326)** Tuberculosis
mCOT466 Dengue - *Calibr*			
kCNV945 SARS-CoV-2 - *Scripps*			
CMQ069 Malaria - *Calibr*			
CBK323 Elastase Inhibitor - *Calibr*			
CMR316 AEC2 Proliferation, Idiopathic Pulmonary Fibrosis			
Itraconazole Fibrosis / Keloids			
Rifabutin (kAAF041) MDR Acinetobacter baumannii			
Clofazimine (kAAE089) Cryptosporidiosis in HIV Patients			

COVID-19 | Optimization of Reframe Hit to Human Trials



1 (Emricasan warhead)
HeLa-ACE2 EC_{90} = 72 ± 14 nM
HLM-CI(int) = 147.7 µL/min/mg
hPPB = 99.3%

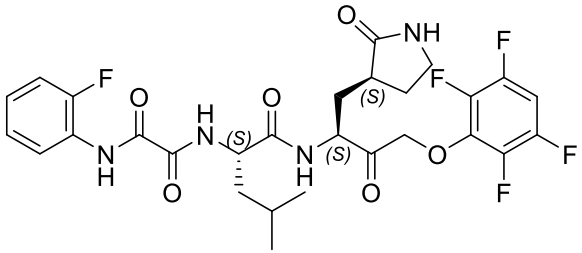
ReFRAME Screen to human safety in 18 months (July 2020 – March 2022)



CMX990 (clin. candidate)
(Leucic acid P2-cap)
HeLa-ACE2 EC_{90} = 90 ± 26 nM
HLM-CI(int) = 7.5 µL/min/mg
hPPB = 56.3%

Discovery to Ph1 (oral-unboosted BID) in ~10 months
J. Med. Chem. **2024**, *67*, 4, 2369–2378

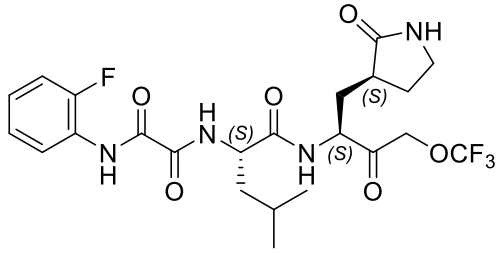
Aniline removal (~300 cmpd P3 SAR)



2 (Oxamide P2-cap)
HeLa-ACE2 EC_{90} = 54 ± 1 nM
HLM-CI(int) = 1109 µL/min/mg
hPPB = 93.4%

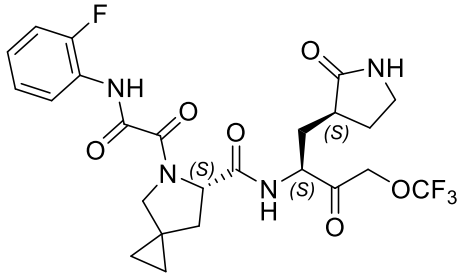
Cys Warhead development

~70 cmpds made to date



3 (**Novel warhead** discovered)
HeLa-ACE2 EC_{90} = 17 ± 11 nM
HLM-CI(int) = 29.6 µL/min/mg
hPPB = 72.8%

P2 modifications for cathepsin selectivity



4 (early lead-1, **Proline P2**)
HeLa-ACE2 EC_{90} = 23 ± 9 nM
HLM-CI(int) = 53.7 µL/min/mg
hPPB = 63.6%

Key next step: Cover more viruses using the same protease mechanism than Paxlovid

Long-Acting Injectables (LAI) to Reduce Drug Cost

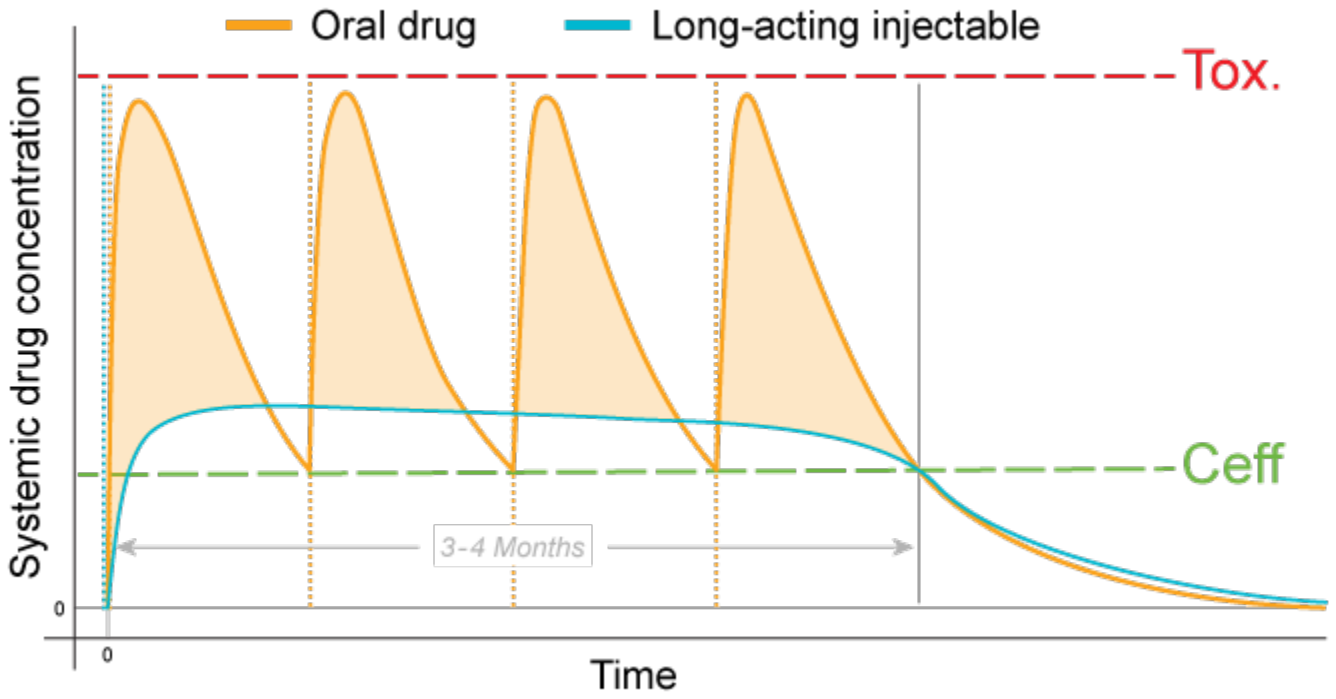
Impact a series of acute and chronic conditions through development of long-acting injectables

- Chronic indications require daily dosing of therapy, making treatment adherence a major obstacle
  - Viral infections (e.g. HIV, HBV, HCV), where missed doses could lead to increased viral reservoir
  - Neuroscience disorders, where missed doses could exacerbate the condition
- Progression or relapse in many diseases can be attributed to patients not adhering to treatment regimen as prescribed by their physician

- **Opportunity:** Leverage Calibr-Skaggs' long-acting injectable platform technology to develop therapies with enhanced pharmacokinetic properties and infrequent dosing regimens, providing a new paradigm for medicines that treat chronic diseases. Two product development pathways exist:
  - Develop prodrugs or enhanced formulations of existing chemical matter, and in some cases enabling accelerated registration via the FDA 505(b)(2) regulatory pathways
  - Generate novel chemical matter, obtaining patent protection and freedom to operate (FTO) through combination of formulations and novel chemical structures

LAI: Scientific rationale to Improve Drug Safety

Unmet medical need: *To improve adherence, there is a need to develop infrequent dosing regimens to improve drug efficiency*



The shaded section represents **wasted drug** that (1) ***isn't required for efficacy***, (2) ***leads to higher costs and increased environmental impact***, and (3) ***could lead to tolerability issues***.

Calibr-Skaggs | LAI Discovery Platform

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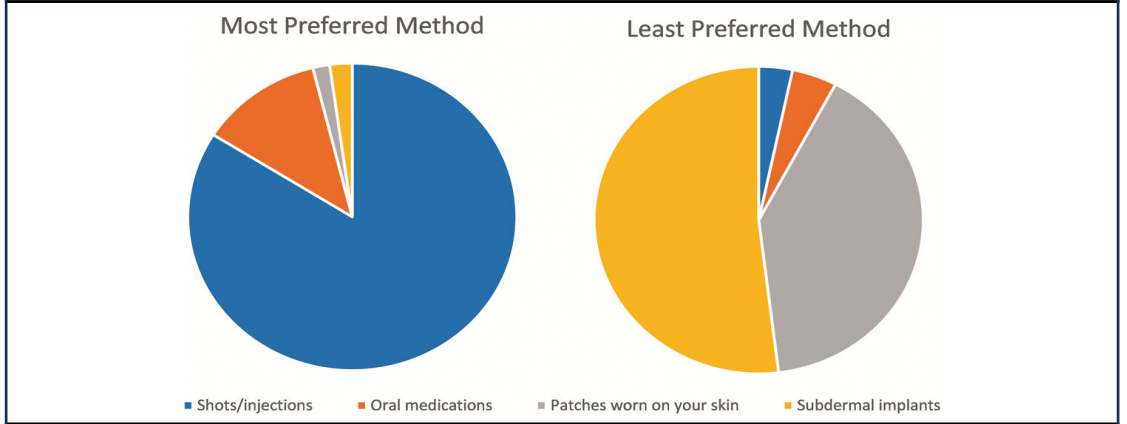
Addressing the need for long-acting treatment to improve patient compliance and safety margins

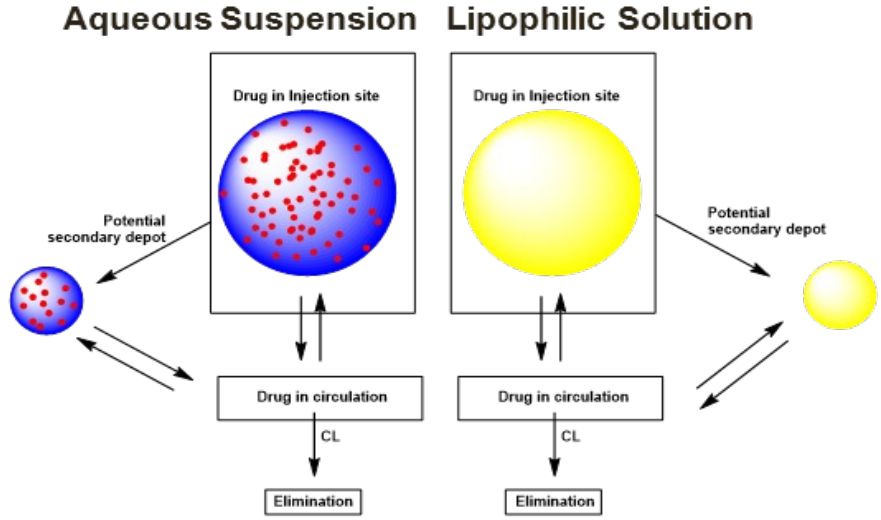
Rationale and Strategy for Long-acting Injectables:

- Long-acting injectables (LAIs) have become a significant platform technology at Calibr over the last 5 years
- LAIs have proven to be an effective route to improve compliance in high-risk populations for HIV treatment, e.g., CABENUVA (cabotegravir + rilpivirine); a similar approach is ideal for prevention
- Drug efficacy has been improved with LAI approaches for diseases like HIV, where minimal effective drug concentrations are maintained and where a high C_{max} from an oral formulation can lead to maximal concentration-related toxicities and waste drug
- User-friendly sub-cutaneous or intramuscular injections can be self-administered
- Market research from MMV and others indicate a strong preference for LAI over daily or weekly oral treatment, or even vaccines that require multiple boosts
- Calibr-Skaggs seeks to combine our expertise in LAI prodrug chemistry and with formulations to improve safety margins and further flatten exposure curves

Patient Preferences for Routes of Drug Administration in LMIC



Depot Prodrug/Formulation Strategies



Malaria | Long-Acting Atovaquone (MMV371) for Prophylaxis

A first-in-class LAI for malaria chemoprevention

Objective: To deliver a low cost, long-acting intervention to further increase the impact of Seasonal Malaria Chemoprevention (SMC) for malaria control and elimination

Rationale/Strategy:

- No approved LAI for malaria chemoprevention
- Atovaquone/proguanil (Malarone) is a daily oral pill widely used for malaria prophylaxis with a long history of being safe
- Low intrinsic clearance of atovaquone (ATO) is ideal for a long-acting injectable and the hydroxyl group offers a convenient handle for prodrug modification

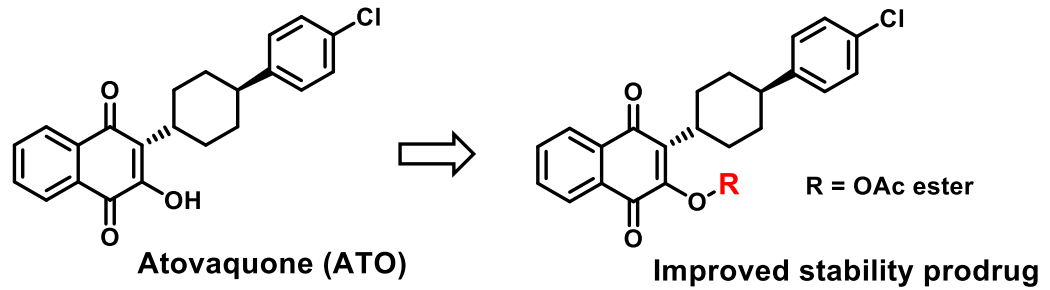
Key Results:

- Single-step synthesis to generate the prodrug minimizes the cost of goods; **the ester has improved shelf-stability compared to oral atovaquone**
- Intramuscular injection of MMV371 in an aqueous suspension gives a flatter exposure profile with lower burst / dose dumping as compared to ATO suspension
- Exposure over the target concentration (136 nM) was maintained for 55-70 days in rats; potential for 3 months in humans
- No injection site reactions were observed and very well tolerated in toxicology studies
- Human injection volume was estimated to be ~630 µL (≤ 1 mL is ideal) and remained syringable through a 27-guage needle (ideal); both factors will reduce needle pain

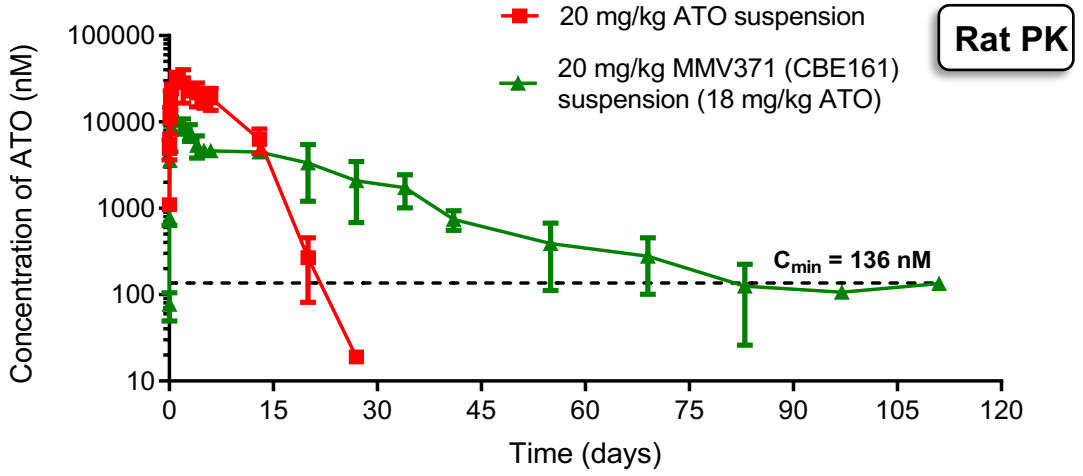
Outlook:

- Licensed to MMV in 2018 for clinical development
- FIH studies expected to start in Q3 2024

Utilizing the Hydroxyl Group on ATO to Add Chemical Handles that Modulate Properties and Depot Release



Controlled Release of an Aqueous Suspension with a Prodrug that is Rapidly Converted into Parent ATO in Blood



Using These Tools to Address Pandemic Influenza

Direct-acting and host-directed inhibitors needed for now influenza combinations to improve efficacy and reduce resistance

Objective: Discover novel small-molecule, broad-spectrum oral antivirals targeting viral proteins of influenza virus A and B with innovative mode of action to prepare for next pandemic but can also be used for seasonal flu treatment as well

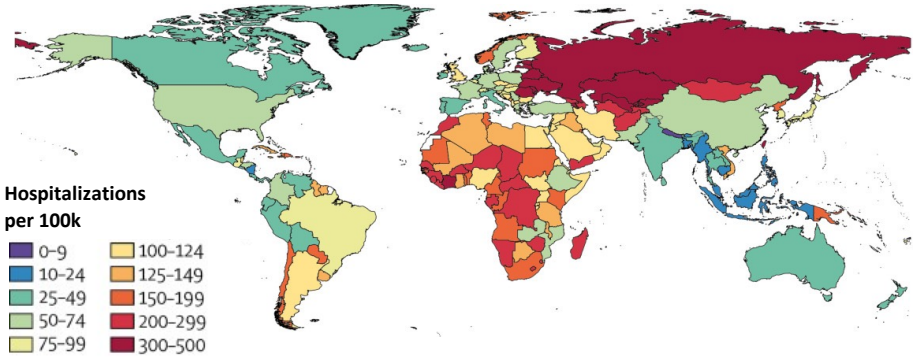
Strategies / Current Status

1. Identify 'single pill' first-in-class combination of existing or improved flu drugs with novel compounds to overcome fast known resistance - *novel baloxavir analog mCOX956 to combine with off-patent Tamiflu for first-in-class as preclinical candidate in 12 months*

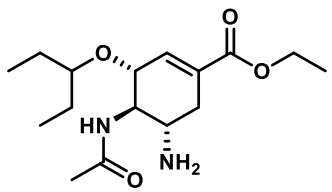
2. Screen for inhibitors of Influenza in mouse model to account for host-directed targets such as in vivo flu models – *20 cmpds out of 200 have potent activity for dose response testing*

3. Cell-based M1 oligomerization inhibition assay and biochemical M1 binding assay as novel first-in-class modality - *early lead M1 inhibitors for in vivo efficacy that are as potent as Tamiflu in vitro and similar in vivo clearance*

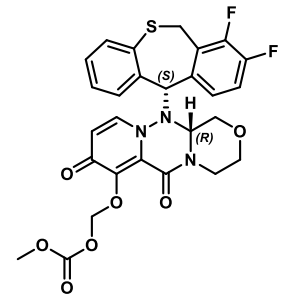
Global Burden of Influenza



Improving existing influenza drugs to be used in combinations



Oseltamivir (Tamiflu – off patent)



Baloxavir (off patent 2036)

Augmenting Repurposing Efforts with NCE Development

Repurposing

- ReFRAME: no direct repurposing opportunities immediately identified; key recommendation for future pandemic preparedness is to screen focused direct-acting antiviral set, and then larger ReFRAME collection
- Completion of recent expansion of antiviral subset (~500 compounds) completed in 2023 with Gates Foundation

Other Recommendations:

- Expand antivirals further for future pandemic preparedness to include synthesis of ~600 antivirals not currently funded
- Establish validated panel of viral assays with viruses that use different coronavirus entry mechanisms (DPP4 receptor – MERS vs ACE2 in SARS and CoV-2) and profile against ReFRAME for future pandemic preparedness

NCEs

- Effective antivirals are needed to treat patients, combat spread in areas lacking vaccines, and address variants/resistant mutants, and future pandemic threats
- Polymerase and protease inhibitor repurposing has performed relatively poorly to date against SARS-CoV-2

Other Recommendations:

- Need focused optimization for to create pan-coronavirus antiviral combinations (of polymerase and protease inhibitors) effective against variants and that can overcome target resistance emergence
- Although oral route is preferred, multiple routes of administration should be explored to meet global needs and optimize efficacy including LAIs as “chemical vaccines”
- Multiple candidates need to be advanced through Phase 1 clinical studies – this is where protease inhibitors failed (e.g., Pfizer IV compound; PF-835231)

Novel Drugs Influenza, Coronavirus, HRV/RSV for Pandemic Prep

Novel first-in-class pan-viral novel protease inhibitor mCMX579 and novel nucleoside mCOT466

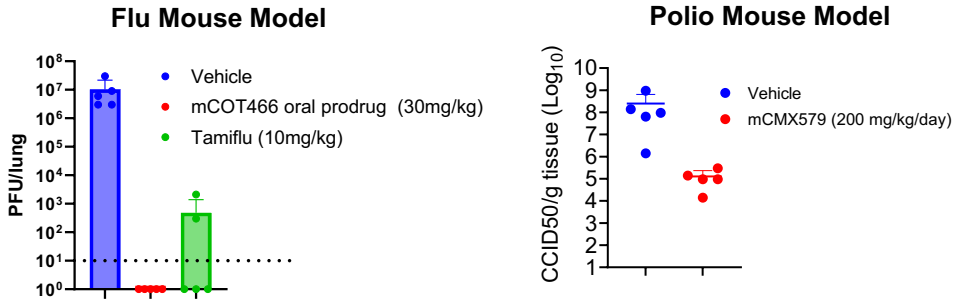
Objective: Develop a first-in-class daily oral nucleoside and protease that addresses multiple respiratory viruses of pandemic potential with a focus on flu and coronaviruses, but are also active on rhinovirus and RSV

Rationale/Strategy: There is a need for novel oral pan-antivirals to treat a range of respiratory viruses in advance of another pandemic like flu/SARS/HRV. Calibr-Skaggs aims to develop pan-viral 2-drug combinations (e.g., polymerase and protease inhibitors) to circumvent resistance and limit total dose (analogous to HCV cure treatment)

Recent Progress:

- Identified novel first-in-class nucleoside, mCOT466, against RSV with > 30-fold improvement in cytotoxicity (CC_{50} = 4 µM) and similar EC_{90} (130 nM) to tubercidin (whose EC_{90} = CC_{50}) against RSV
  - mCOT466 also has excellent activity on flu, SARS-CoV-2, MERS and HRV with EC_{90} < 100 nM
  - Demonstrated potent broad spectrum of antiviral activities against various RNA viruses (Flu, DENV, ZIKA, YFV, SARS-CoV-2, MEV, COXV-B3, Polio and CHIKV) *in vitro* with on-target biochemical selectivity (20x) to human polymerase
  - Potent *in vivo* activity demonstrated in flu mouse model when administered orally BID, with no detectable virus at 30 mg/kg *vs.* Tamiflu at 10 mg/kg
- Identified lead first-in-class protease inhibitor mCMX579 with demonstrated >10x potency on MERS, polio and rhinovirus when compared to approved nirmatrelvir and ensiltrelvir
  - mCMX579 demonstrated polio mouse efficacy at doses as low as 200 mg/kg/day
  - mCMX579 demonstrated first-in-class pharmacological demonstration of activity across respiratory viral families expressing 3C protease including patient strains resistant to approved drugs
- Excellent PK in dogs to enable safety profiling currently ongoing for both compounds

In vivo Activity of mCOT466 and mCMX579



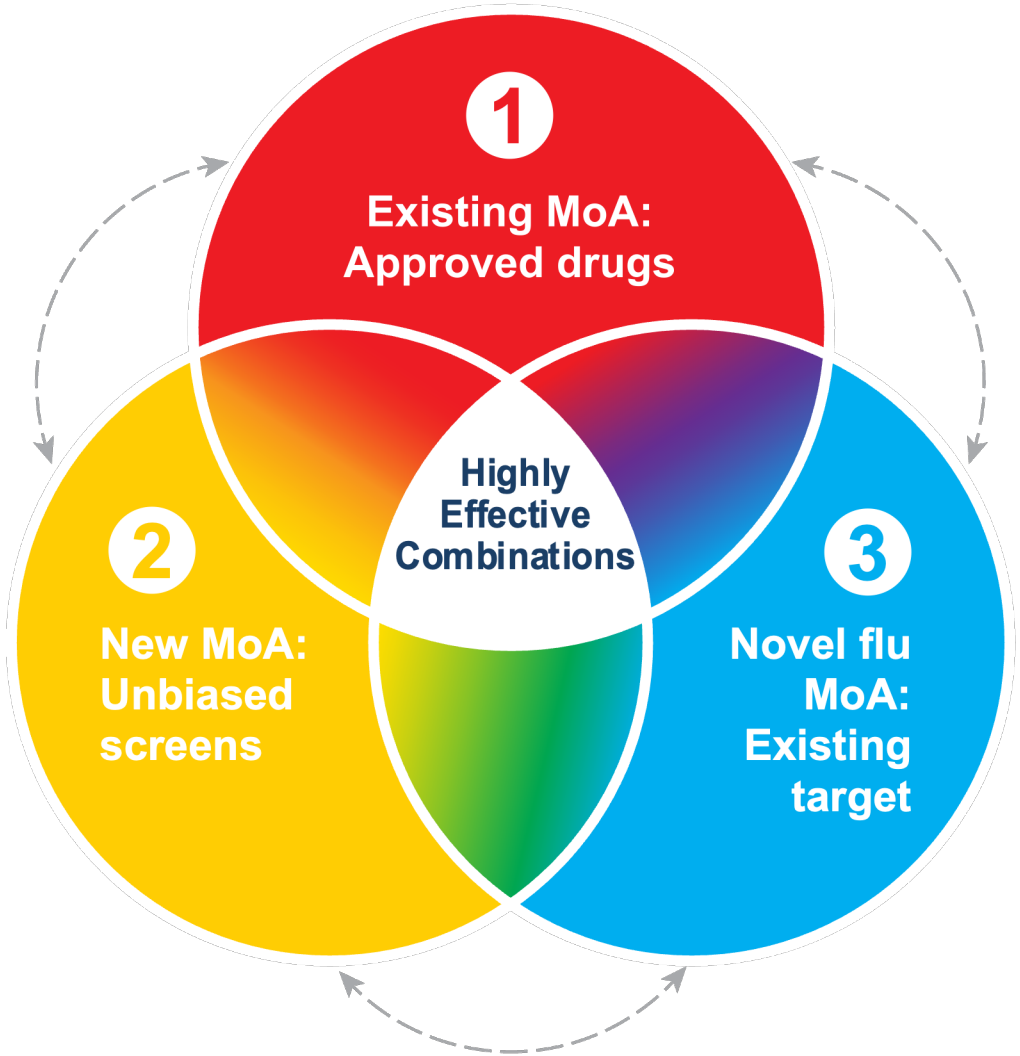
Broad-Spectrum Profiling of mCMX579 Activity Against Drug-Resistant Coronavirus Proteins

			mCMX579	Nirmatrelvir (Paxlovid)	Ensitrelvir (Xocova)	AG-7404 (Ph1)
Beta Coronaviruses	SARS-CoV-2	WT	1.6%	12.7%	38.3%	70.7%
		S144A	1.5%	47.6%	80.8%	84.3%
		P132H (Omicron)	1.2%	32.7%	60.7%	>100%
		L50F+E166V	< 1%	>100%	50.5%	78.3%
	Other Hu β-CoV	**SARS-CoV-1**	< 1%	23.2%	53.9%	89.6%
		MERS-CoV	7.3%	47.8%	>100%	>100%
		HKU1	1.3%	54.7%	>100%	>100%
		OC43	3.0%	79.5%	>100%	>100%
Alpha CoV		229E	4.3%	68.5%	>100%	>100%
		NL63	6.2%	89.0%	72.6%	>100%
Neg Controls		ZIKV	>100%	>100%	>100%	99.5%
		GFP	98.9%	94.4%	61.6%	>100%

Developing Novel Combinations Influenza

Novel first-in-class combination of approved flu MoA that can be moved forward due to novel IP

1. In vivo mouse flu screen of Reframe compounds has found anti-inflammatory compounds and other anti-virals not active in vitro
2. Viral fusion mechanism of action with mCQE962 with EC90 < 50 nM and good clearance



Novel Baloxavir analog mCOW956 (endonuclease) and generic Tamiflu active in mouse flu model; next step is safety studies

Novel nucleoside mCOT466 (polymerase) active in mouse flu model with oral dosing; next step is

Strategy for H5N1 Pandemic Preparedness

Strategy

- Repurposing requires having all clinical and late-stage preclinical antiviral compounds in the collection as a focused set for screening - this work is ongoing at Calibr-Skaggs
- Focus efforts on generating Phase 1-ready assets with conserved mechanisms (protease/polymerase inhibitors and viral entry mechanisms), and evaluate for best combination partners (“next gen Tamiflu”)
- Make 6000 compound that have been in clinic but not in ReFRAME yet

Approach

- Create collection of polymerase inhibitors as pan-coronavirus countermeasures
- Polymerase inhibitors require screening against specific viral pathogens given general lack of potent cross-reactive compounds; an additional ~100 nucleoside analogs have been generated for virus screening
- Continue to leverage and expand nucleoside prodrug platform for oral and long-acting injectable drugs
- Focus on shared entry mechanism targets (e.g., TMPRSS2)

Beyond COVID-19

- Focused on influenza but other respiratory viruses of pandemic potential
- In vivo / whole organism screening of Reframe collection
- Explore ML and complex animal models / organoids to identify effective host targeted drugs to combine with antivirals
- Address Vector-born pathogens where we can address both the vector (mosquitoes, ticks) and the virus (like Dengue)

Calibr-Skaggs | Global Health Pipeline

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	Discovery Stage	Hit-to-Lead	Lead Optimization	IND-Enabling	Phase 1
Malaria	PfAC-b screen (TropIQ) GTP-CH1 biochemical screen Serine Hydrolase inhibitor platform	SuFEx platform cFRS & cIRS inhibitor Blood-stage active hits (MMV) Liver-stage active hits (UCSD)	LAI Ivermectin LAI MMV533	Single-dose cure/1-month prophylaxis (CMQ069) (IND targeted 4Q24)	LAI ATO (CBE161) (FIH targeted 2H24; *MMV)*
Tuberculosis	150K Screen (cholesterol media)	Intramacrophage hits; 4 series Rv1625c agonist (073 back-up)	LAI / Oral Teixobactin LAI Rv1625c agonist (CLB073; Gates MRI)	Rv1625c agonist (CLB073) (IND targeted 3Q24; Gates MRI) Pks13 AT (CMX410 & CMZ523) (PCD targeted 3Q24; Gates MRI)	
Adjuvants	Novel TLR7/8, TLR9 agonists Novel STING and NOD2 agonists Novel NLRP3 agonist		STING agonist TLR8 agonist TLR7 agonist NOD2 agonist		
Antivirals	HCMV* – Screening Calibr nucs Influenza – ReFRAME in vivo screen Influenza direct-acting – potentiation scrn	Influenza direct-acting – oral combo Influenza – M1 modulators	Influenza – host-directed M85		HIV LAI (CLZ629) *(GILEAD/MERCK)*
Pandemic Preparedness (NIH AViDD)	CoV-2 – helicase, ion channel screens Dengue/Zika/YFV – RdRp, NSP1 Ebola – RdRp, VP35 Lassa – RdRp, vRNP HPV/RSV (cross-profiling)	CoV-2 – non-covalent M^{pro}, RdRp, PL^{pro} Lassa – Nucleocapsid inhibitor	CoV-2 – covalent M^{pro} Poliovirus – covalent M^{pro} (acrylates and ketones)		
Neglected Tropical Diseases (Wellcome Trust)	Chagas Disease Schistosomiasis - ReFRAME DENV uHTS Leishmaniasis Crypto novel series		Chagas – Nitrothiophenes DENV – RdRp (nuc) Crypto Aminothiazoles Crypto PheRS inhibitors Crypto Azaquinolines		

Preclinical PoC Achieved
Paused Program
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