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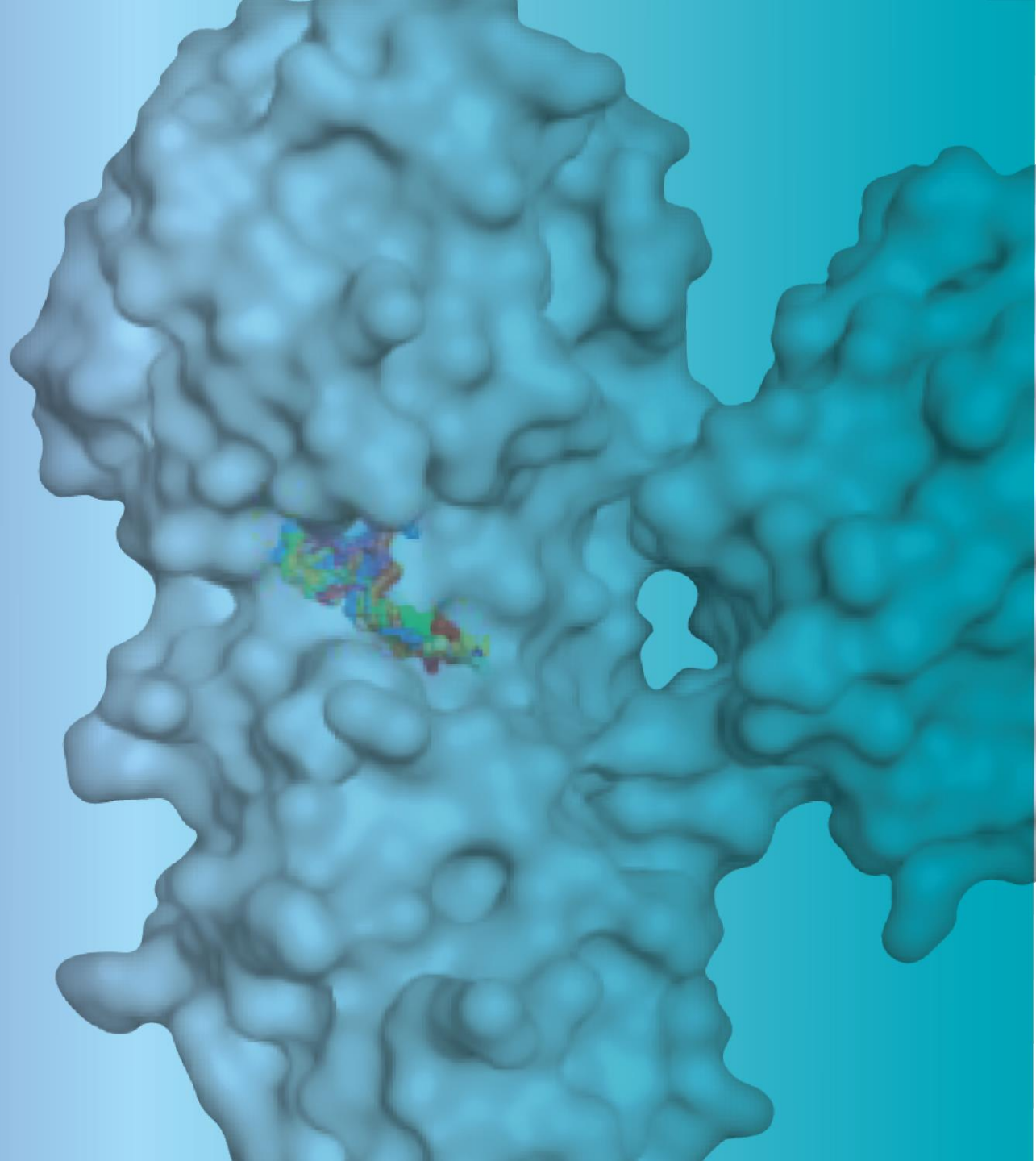
Potent antivirals to combat some of the most serious diseases facing humanity

Influenza A Oral PB2 Inhibitor CC-42344



2022 World Antiviral Congress
December 1, 2022

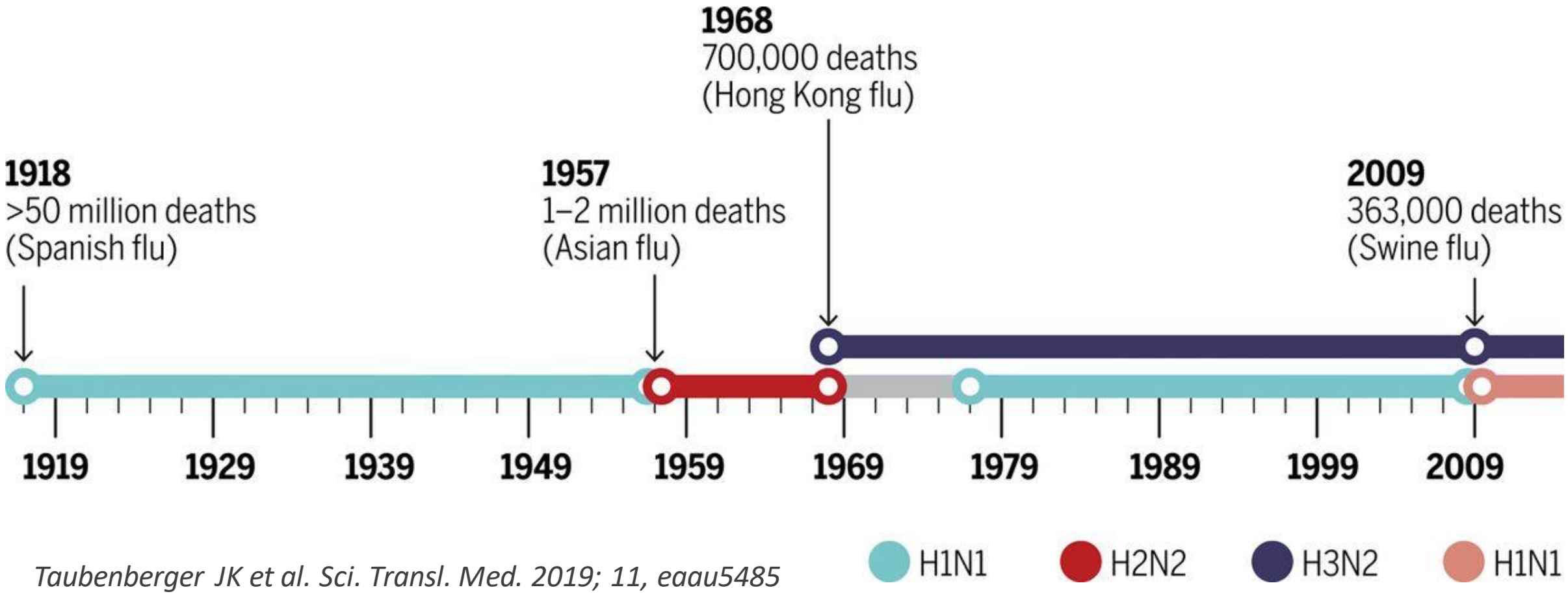
Forward-Looking Statements

This presentation contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995, including statements regarding the market opportunities for the treatment of acute and chronic viral diseases which are the focus of our programs; the development pipeline; our technology platform's ability to produce viable drug candidates at reduced development timelines and costs; the potential future payments and royalties in connection with the collaboration with Merck Sharp & Dohme Corp. ("Merck"); the expected future characteristics and progress in developing a compound for the effective treatment and prevention of COVID-19 infections and the anticipated timing of achieving the value-driving milestones, including the planned Phase 1 trial initiation in Q1 2023 for the COVID-19 CDI-988 oral protease inhibitor; the continuation of our second COVID-19 IND-enabling study; the planned Phase 2 clinical trial designs; the expected progress of our Influenza A program including expectation of obtaining Phase 1 results for our Influenza A CC-42344 oral PB2 inhibitor in 2022 and a Phase 2a study expected to begin in 2023; the expected progress of our norovirus program and the anticipated timing of achieving the value-driving milestones, including preclinical lead selection planned for the first half of 2023; and our expectations regarding future liquidity.

Forward-looking statements are prefaced by words such as "anticipate," "expect," "plan," "could," "may," "will," "should," "would," "intend," "seem," "potential," "appear," "continue," "future," believe," "estimate," "forecast," "project," and similar words. Forward-looking statements are based on our current expectations and assumptions regarding our business, the economy and other future conditions. Because forward-looking statements relate to the future, they are subject to inherent uncertainties, risks and changes in circumstances that are difficult to predict. We caution you, therefore, against relying on any of these forward-looking statements. Our actual results may differ materially from those contemplated by the forward-looking statements for a variety of reasons, including, without limitation, the risks arising from the impact of the COVID-19 pandemic, the Ukraine war, inflation and interest rate increases on the national and global economy, on our collaboration partners, clinical research organizations ("CROs"), Contract Manufacturing Organizations, and on our Company, including raw material and test animal shortages and other supply chain disruptions or labor shortages, the ability of our CROs to recruit volunteers for, and to proceed with, clinical trials, our and our collaboration partners' technology and software performing as expected, the results of future preclinical and clinical trials, general risks arising from clinical trials, receipt of regulatory approvals, regulatory changes, development of effective treatments and/or vaccines by competitors, including as part of the programs financed by the U.S. government, potential mutations in the virus which may result in variants that are resistant to a product candidate we develop, and our reliance on Merck for further development in the influenza A/B program under the license and collaboration agreement. Further information on the risk factors that could cause actual results to differ materially from those expressed or implied by forward-looking statements, is contained in our filings with the Securities and Exchange Commission, including our Annual Report on Form 10-K for the year ended December 31, 2021. Any forward-looking statement made by us in this presentation speaks only as of the date on which it is made. Factors or events that could cause our actual results to differ may emerge from time to time, and it is not possible for us to predict all of them. We undertake no obligation to publicly update any forward-looking statement, whether as a result of new information, future developments or otherwise, except as may be required by law.

The Influenza Pandemic: 100 Years, From 1918 Spanish Flu To 2009 Swine Flu

Influenza A is responsible for influenza pandemic and seasonal infections



Taubenberger JK et al. Sci. Transl. Med. 2019; 11, eaau5485

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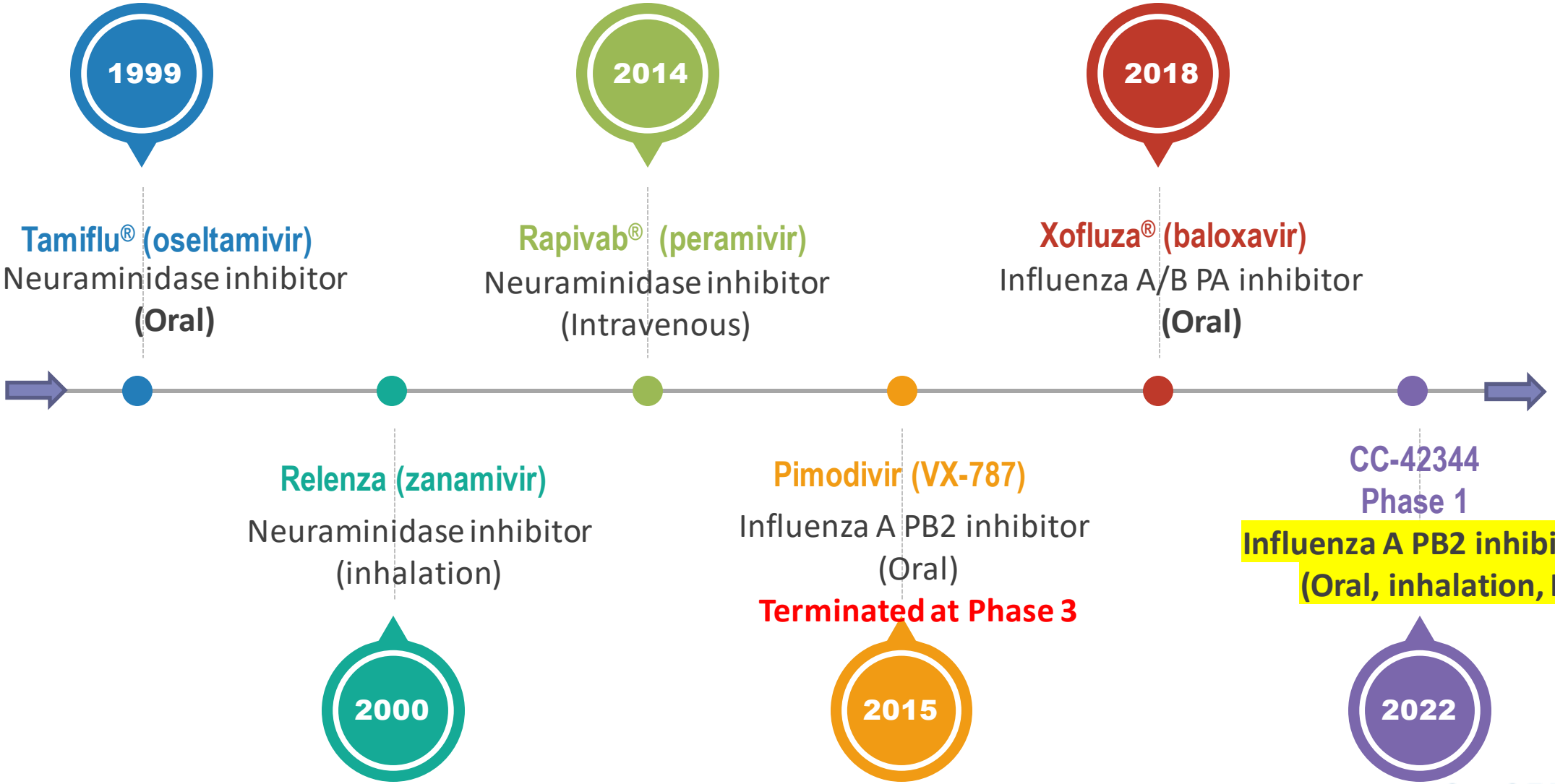
Influenza Antivirals: Emerging Pandemic Influenza and Drug Resistance Threats



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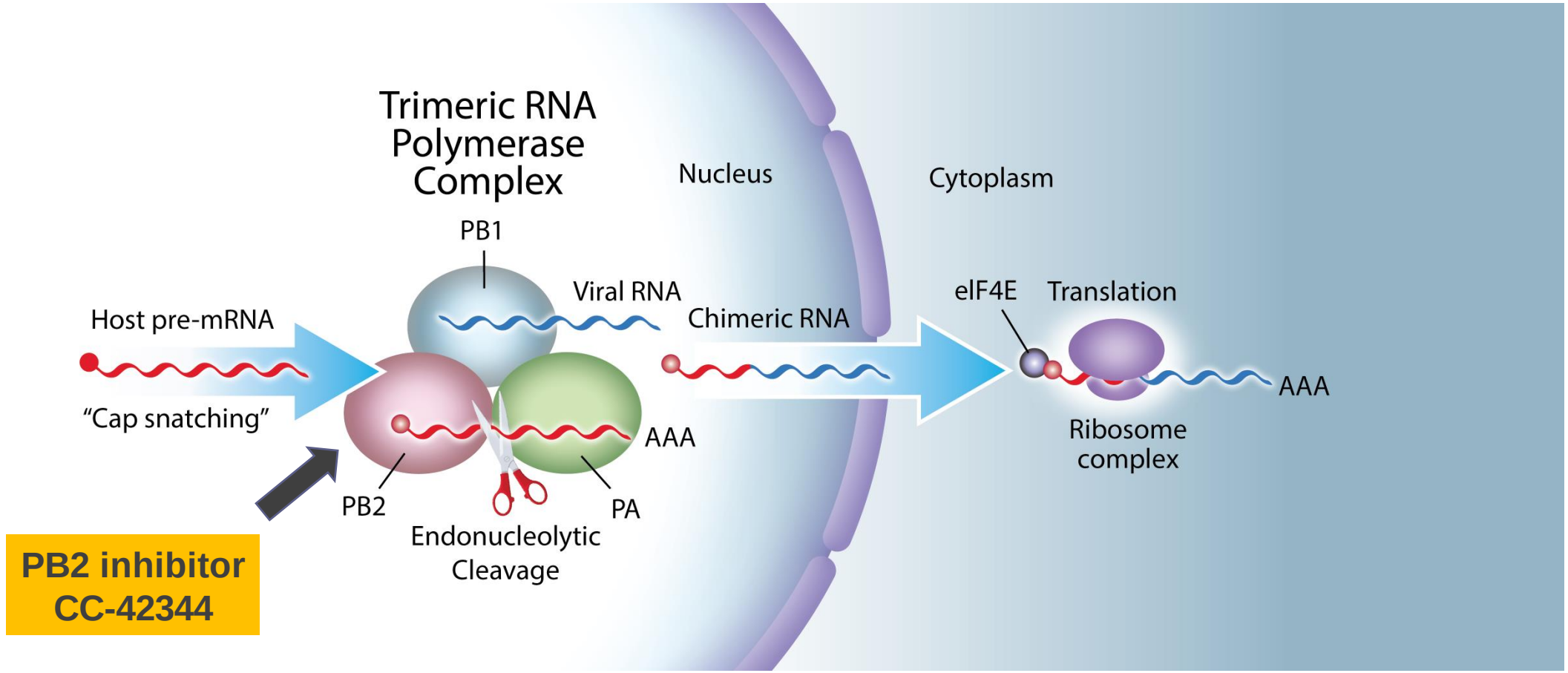
CC-42344 Inhibitor Targets PB2 of Influenza Polymerase Complex

Cap Binding (PB2), Endonuclease (PA), and Polymerase (PB1) are Essential for Influenza Viral Replication



Boivin S et al. J. Biol. Chem. 2010;285:28411-28417

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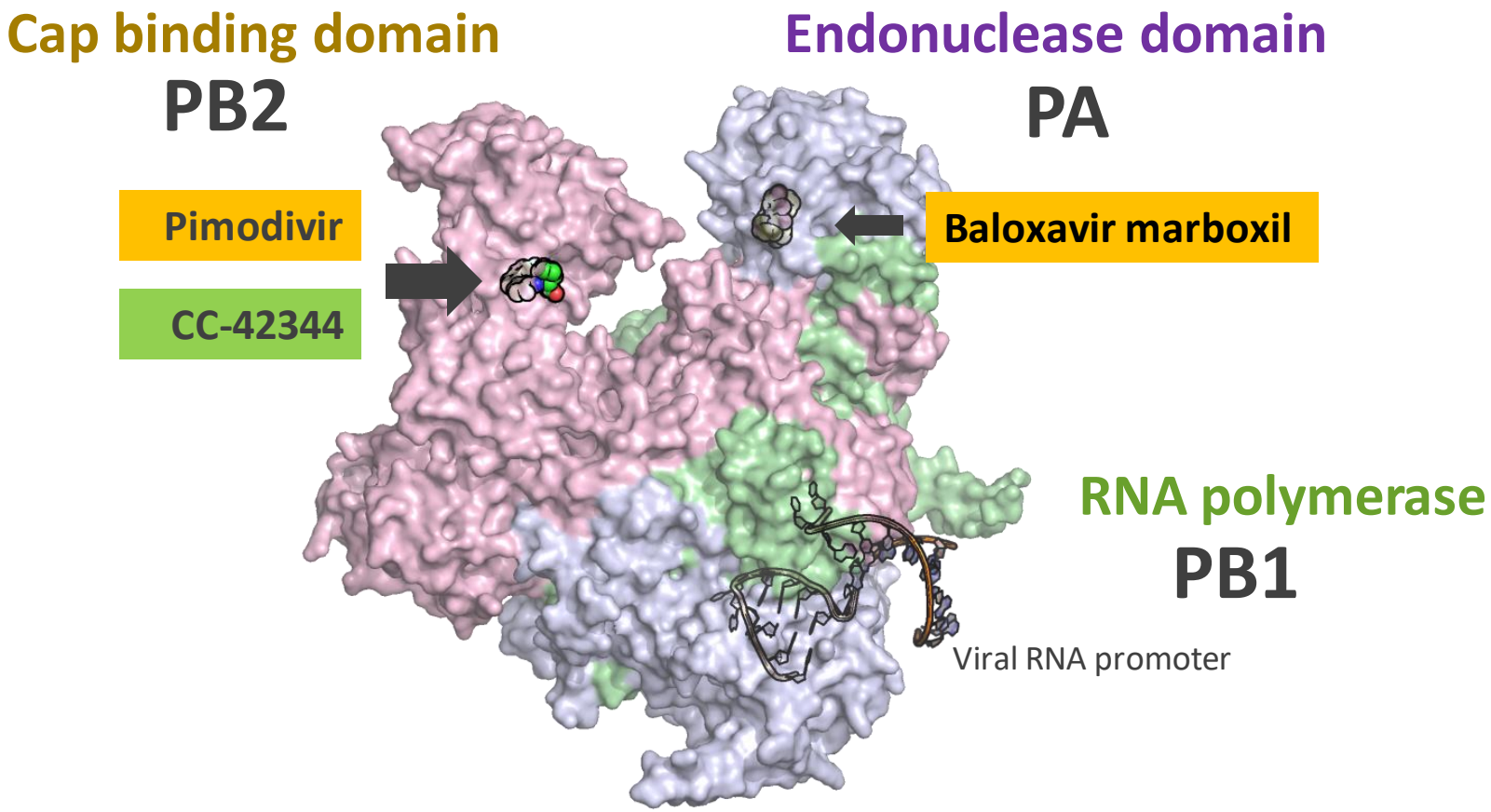
Influenza Virus Polymerase Complex (PA:PB1:PB2)

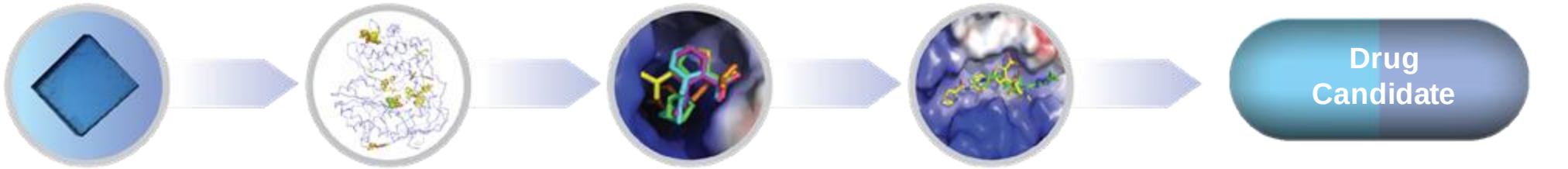


Reich *et al.* (2014) ***Nature*** – PDB id 4WSB

Equipped With A Proprietary Drug Discovery Platform

Leveraging X-ray crystallographic insights of target-inhibitor complexes to generate unique insights:

- Novel chemistry to overcome drug resistance
- Interrogate multiple binding pockets
- Rapid iterative structure-based drug discover platform



Grow drug target x-ray crystals → Select drug binding pocket → Hit-to-lead process → Lead optimization → **Direct-Acting Antiviral**

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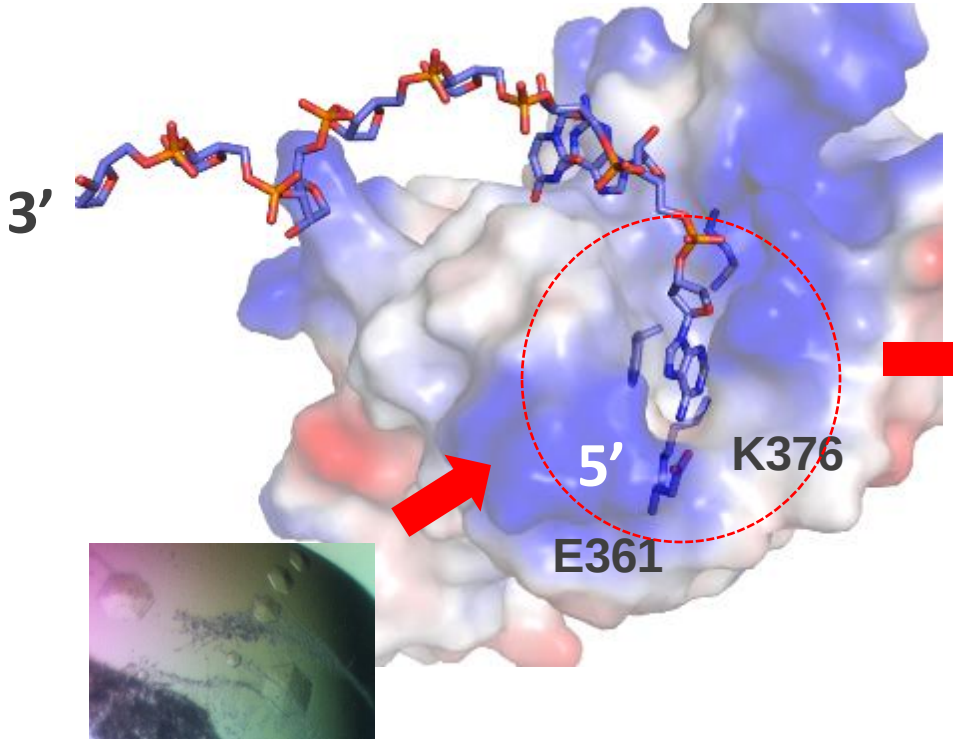
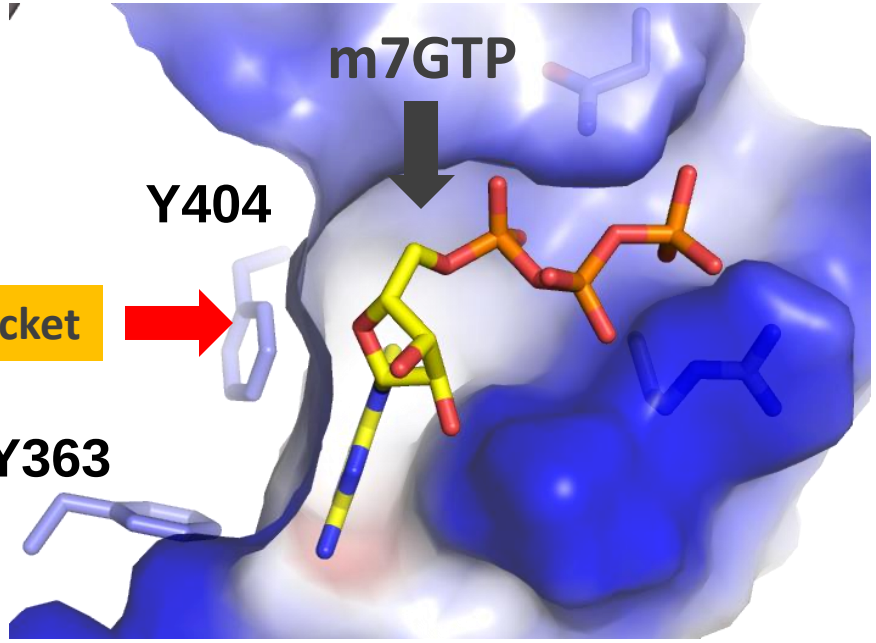
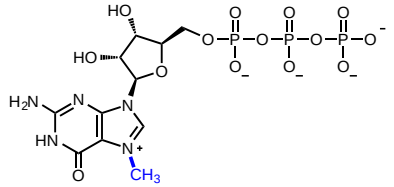
Essential Role of PB2 Protein In Viral Transcription and Replication

(A) Crystal structures of PB2:ssRNA complex



(B) Crystal structures of PB2:m7GTP complex





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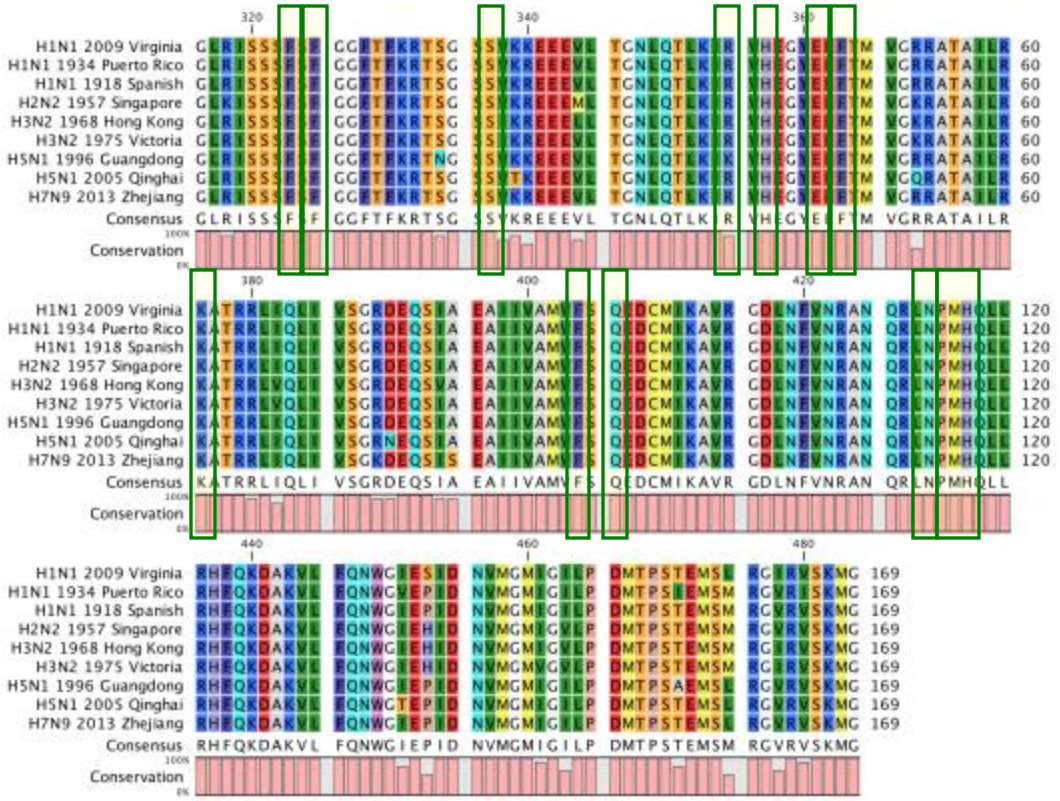
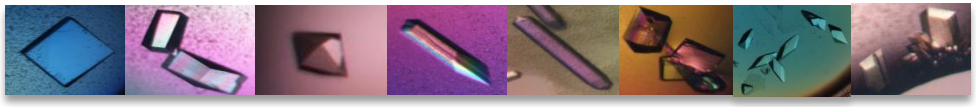
PB2 m7GTP Binding Site is Highly Conserved

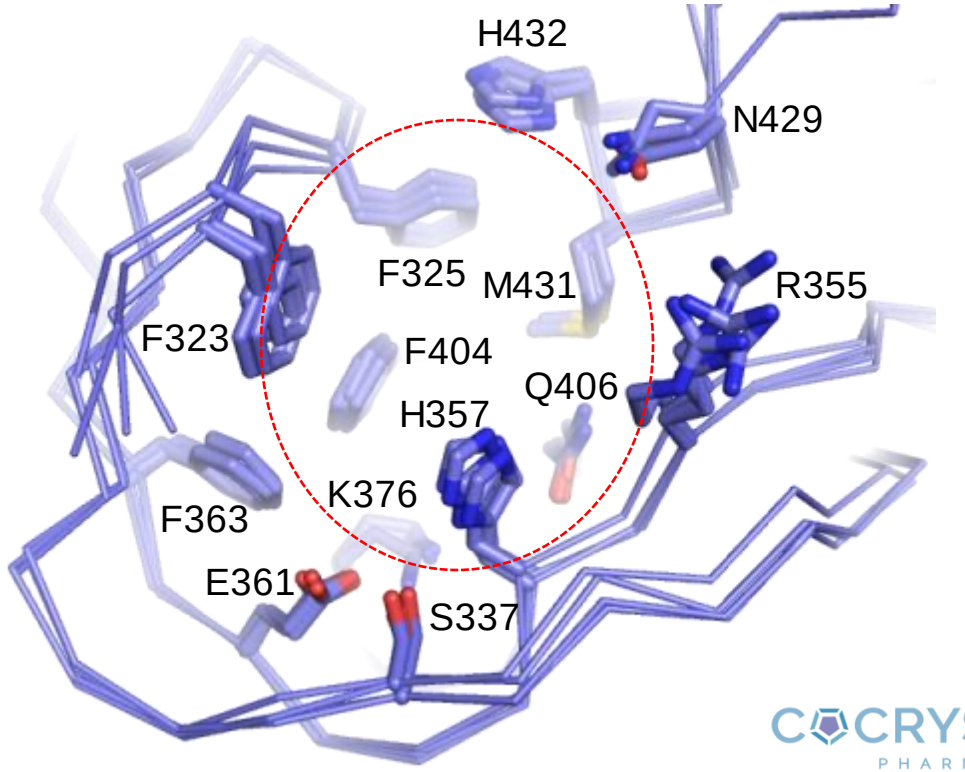
(A) Pandemic and seasonal influenza A PB2 H1N1, H2N2, H3N2, H5N1, and H7N9



H1N1 H2N2 H3N2 H5N1 H7N9 PB2 crystals



(B) Overlayed m7GTP binding pockets



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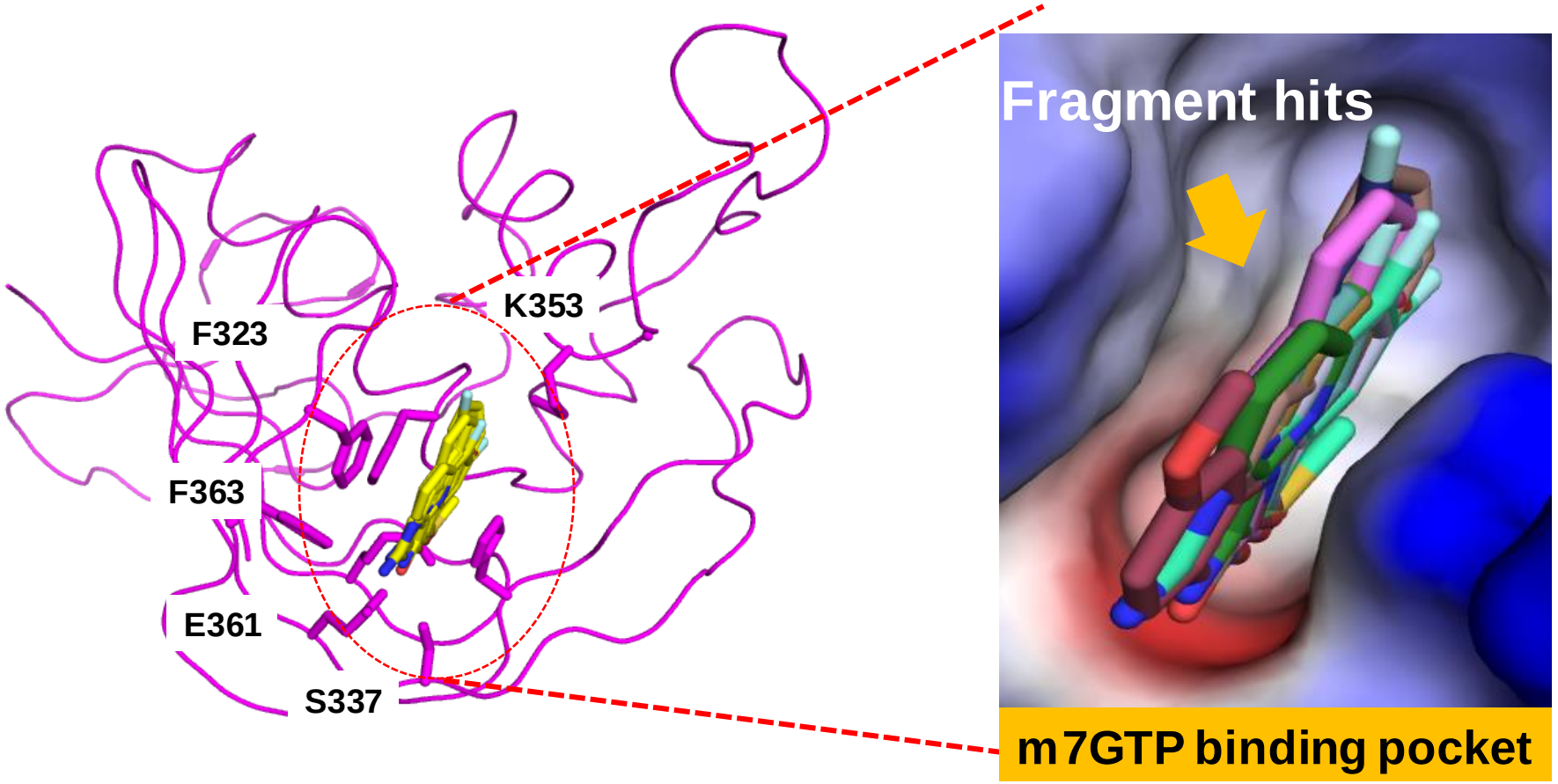
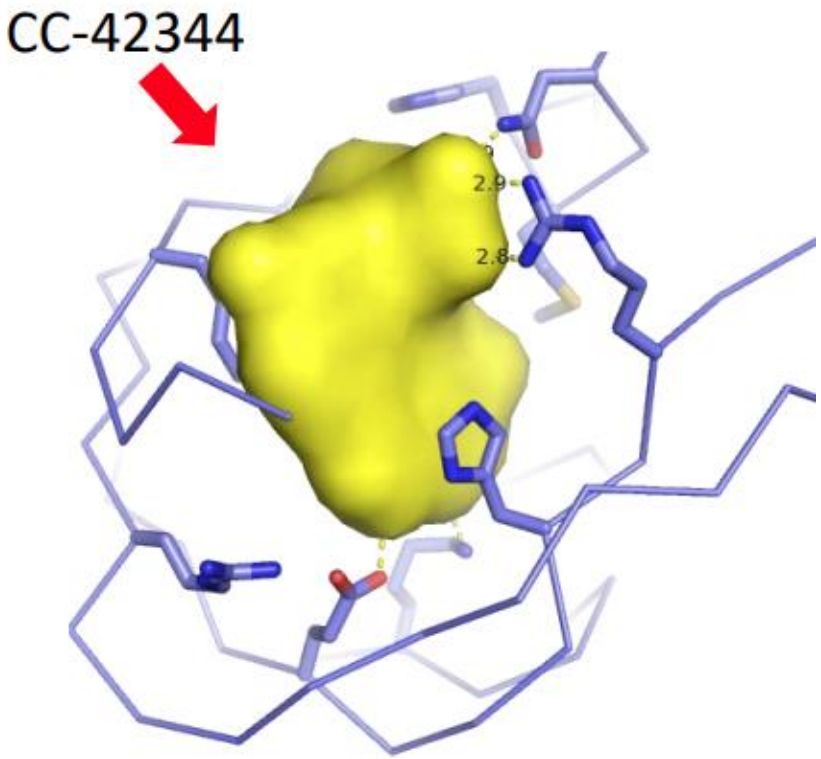
Structural Insight Into Broad-spectrum PB2 Inhibitor Design

- Multiple hits bound to the highly conserved m7GTP binding pocket



CC-42344: Oral Pandemic and Seasonal Influenza A Therapeutic

Pandemic and seasonal influenza A PB2 crystals (H1N1, H2N2, H3N2, H5N1, and H7N9)



Cocrystal structure of CC-42344 (1.47 Å)

- Potent anti-influenza structure-based inhibitor
- Binds a highly conserved region of influenza A PB2 of polymerase complex (PA:PB1:PB2)
- Broad-spectrum activity against pandemic and seasonal influenza strains (EC_{50}, 0.12 – 5 nM)
- Active against oseltamivir and baloxavir resistant strains (EC_{50}, 0.5 – 9 nM)
- Exhibits high barrier to drug resistance
- Shows strong in vitro synergistic effects with oseltamivir, baloxavir, and favipiravir

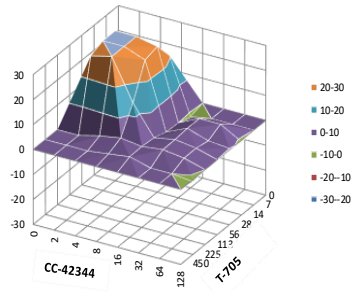
CC-42344 Shows Broad-spectrum Antiviral Activity Against Pandemic and Seasonal Influenza A Strains

Influenza serotype	Strain	CC-42344, EC_{50} nM
H1N1	A/PR/8/34	**1**
H1N1	A1/Denver/1/57	**3**
H1N1	A/Fort Monmouth/1/47	**2**
H1N1	A/NY/18/09	**5**
H3N2	A/AICHI/2/68	**0.2**
H5N1	Duck/MN/1524/81	**<3.2**
H5N1	Hong Kong/213/2003	**4.5**
H5N1	Thailand/16/2004	**<3.2**
H7N7	Netherlands/219/2013	**5.6**
H7N9	Anhui/1/2013	**<3.2**
H1N1- Oseltamivir resistant	A/HK/2369/09 H274Y	**9**
H3N2-Oseltamivir resistant	A/Wuhan/395/95	**0.5**
H1N1- Baloxavir resistant (I38T)	A/PR/8/34 I38T	**0.5**

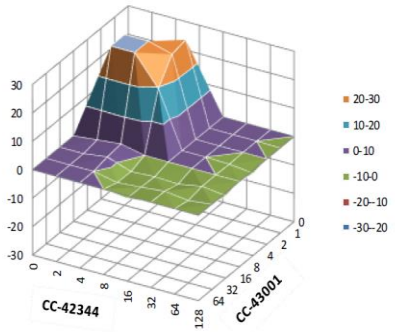
CC-42344 Shows Strong Synergistic Effects With Approved Influenza Antivirals

Polymerase inhibitor

Favipiravir



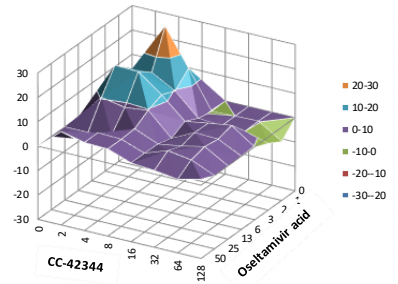
Cocrystal 42344



Baloxavir

PA inhibitor

Oseltamivir



Neuraminidase inhibitor

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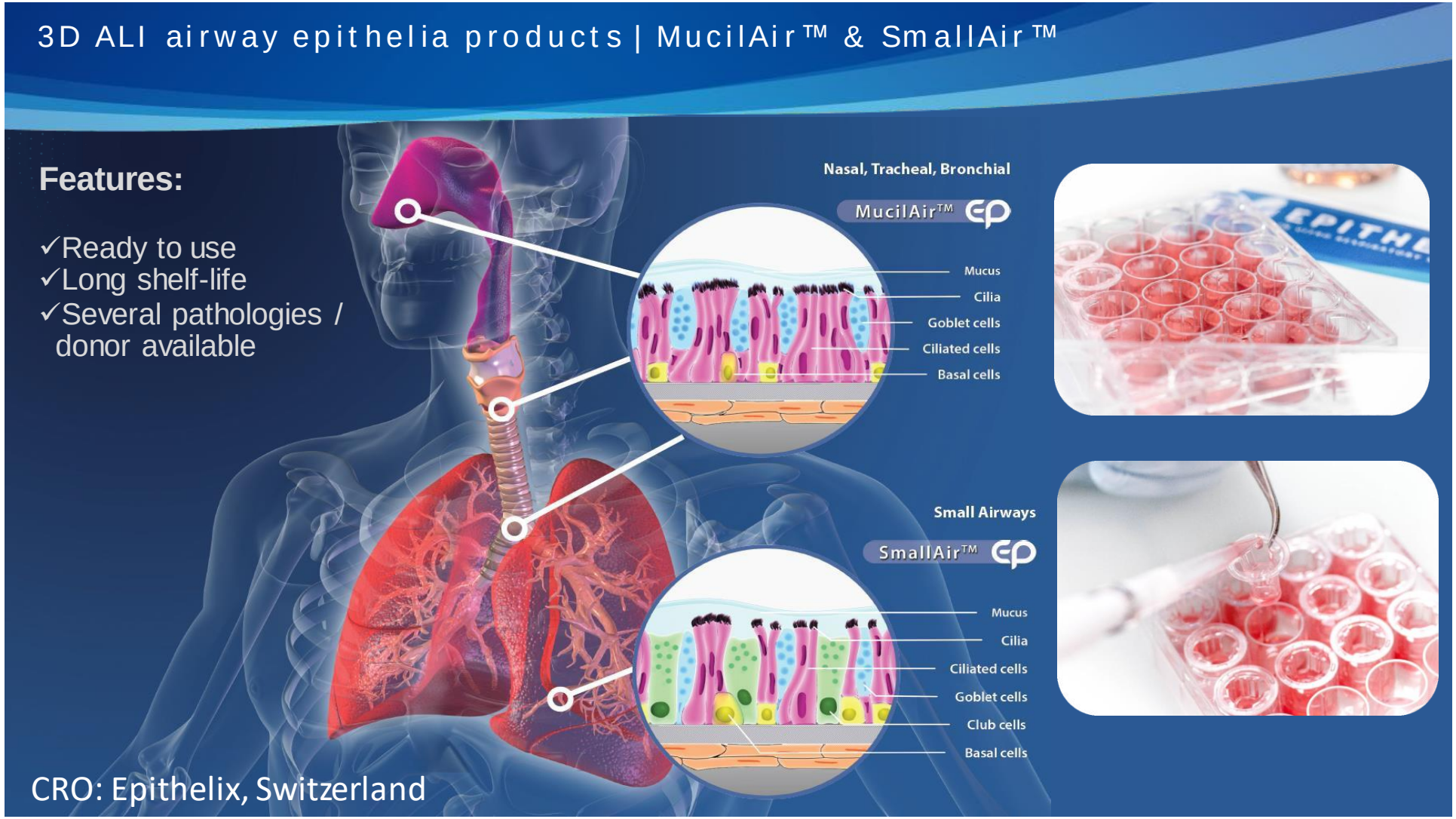
CC-42344 vs Pimodivir (VX-787): Key Differentiators

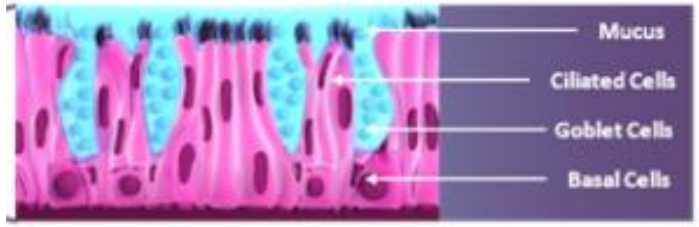
Property	Pimodivir (VX-787)	Cocrystal CC-42344
Hit identification	**Anti-influenza hits** **From influenza cell-based screening**	**PB2 structural hits** **From Cocrystal drug discovery platform**
Drug binding pocket	PB2 m7GTP	PB2 m7GTP
Broad-spectrum activity	Single digit nanomolar EC50 Seasonal and pandemic influenza A strains	Single digit nanomolar EC50 Seasonal and pandemic influenza A strains
Drug resistance	**Six major resistance variants on PB2** **Q306H, S324I, S324N, S324R, F404Y, N510T*** **(EC_{50} fold shift, 63-257)**	**No resistance variant** (one mutation, **F363L**, detected by deep sequencing from resistance screening)
Mechanism of inhibition	**Single MOI** Target m7GTP pocket of free PB2	**Multiple MOIs** Targets free PB2, pre-mRNA bound PB2, and trimeric polymerase complex (PB2:PA:PB1)
Route of Administration	Oral (Combination regimen) **(600 mg Pimodivir,BID + 75 mg Oseltamivir, BID)**	**(1) Oral** (Monotherapy, QD or BID) **(2) Inhalation** **(3) Injectable**
Status of clinical trials	**Phase III halted**	**Phase 1, near completion**

**: Byrn RA, et al. Antimicrob Agents Chemother 2015; 59, 1569-1582*

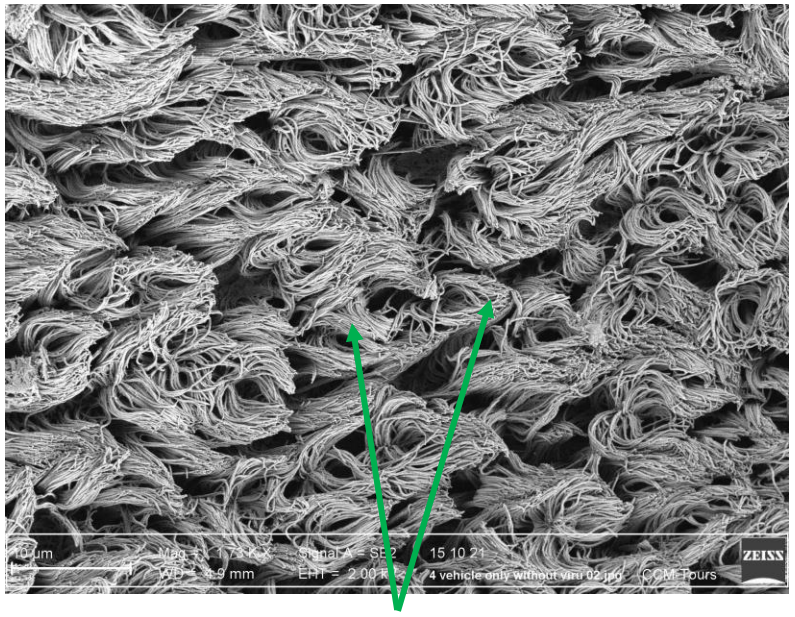
CC-42344 Showed No Lung Toxicity in Human Nasal and Bronchial Airway Epithelia (HAE)



Human Nasal Epithelia Destruction Upon Influenza Infection



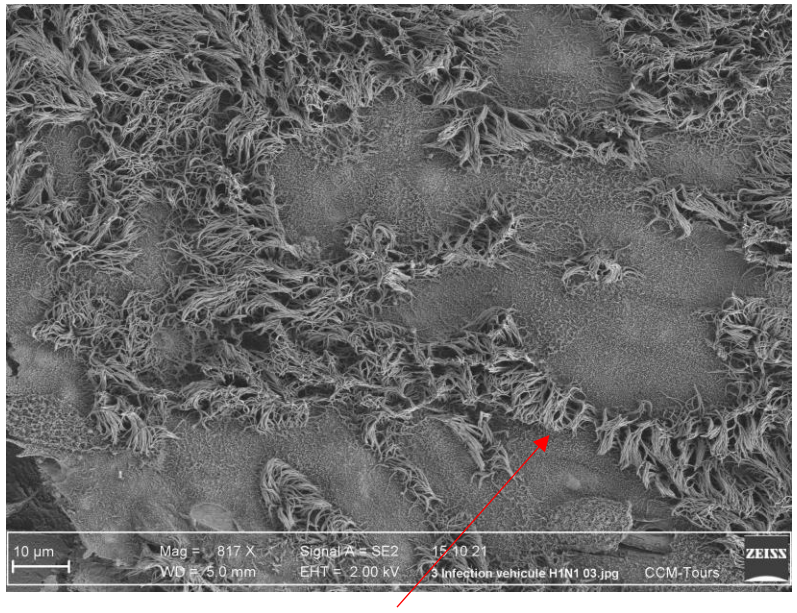
Uninfected human respiratory epithelia



- Layer of intact cells with numerous cilia visible

H1N1

Infected human respiratory epithelia



- Cells are killed by H1N1 virus, and most cilia are destroyed

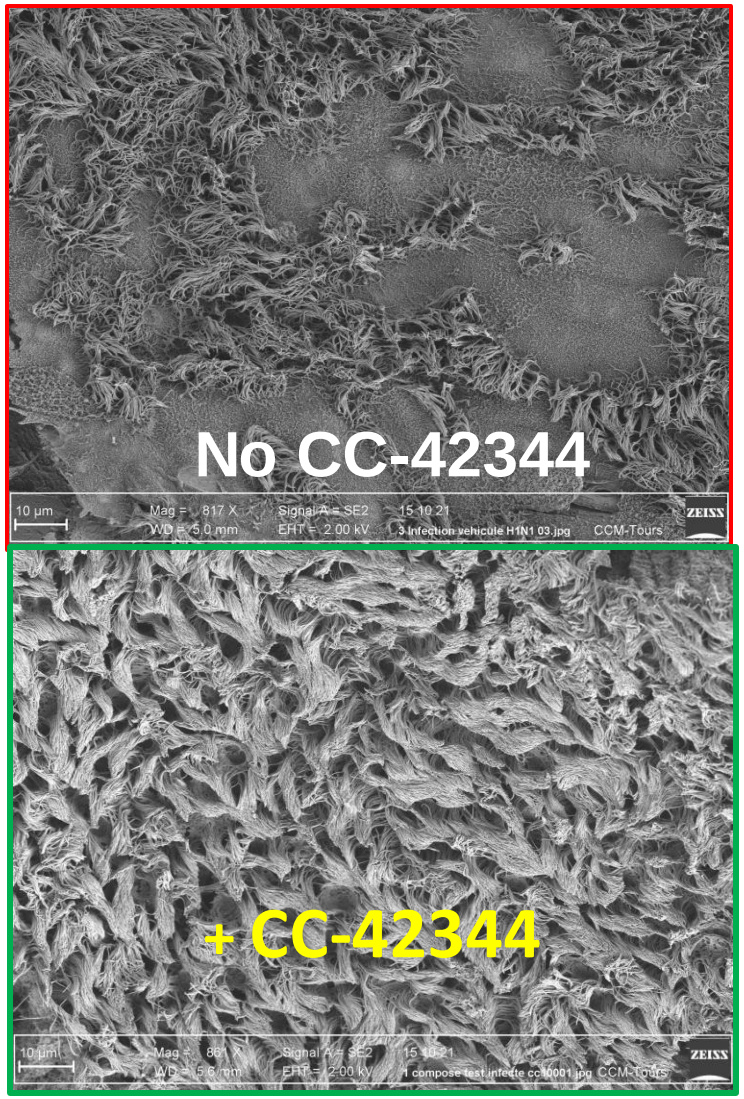
16

Excellent Antiviral Activity of CC-42344 in H1N1-Infected Human Bronchial Epithelia

Normal human respiratory epithelia

No treatment

With CC-42344



17

A Phase 1 Study in Healthy Participants to Evaluate the Safety, Tolerability, and PK of the Oral Influenza A PB2 Inhibitor CC-42344

Phase 1 CC-42344 Study Completed: Database Lock Pending

Phase 1 trial site: Linear Clinical Research-Harry Perkins Research Institute , Perth, Australia

Participants:

- Single-center, randomized, double-blind, placebo-controlled
- Single dose, multiple dose; 7-day nontreatment follow-up period
- Healthy adult volunteers
- Each cohort comprised of 8 subjects; 6, CC-42344 and 2, placebo
- N = 56; 32, SAD; 24, MAD

Single-ascending dose (SAD) →

100 mg	200 mg	400 mg	800 mg
4 cohorts of 8 participants each (24 active; 8 placebo) 1 cohort (400 mg) assessed food effects			

Multiple-ascending dose (MAD) →

50 mg	100 mg	200 mg
3 cohorts of 8 participants each (18 active; 6 placebo) Once daily x 14 days		

Endpoints

- Safety: adverse events (AEs) and laboratory abnormalities
- Food effect

19

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Key Entry Criteria

- Healthy males and females ≥ 18 and ≤ 55 years
- Body weight ≥ 50 kg
- Body mass index ≥ 18 and ≤ 32 kg/m^2
- Non-pregnant, non-lactating
- Must abstain from alcohol or caffeine from 48 hours before study confinement through study
- Must not have taken prescribed medication in 14 days before dosing, or OTC drugs and herbal remedies within 7 days before dosing (except vitamins, minerals, paracetamol, HRT)
- Other routine screening criteria to include exclusion concurrent illness and clinical laboratory values or history

CC-42344 Oral PB2 Inhibitor
Phase 1 SAD Study Summary and Next Steps

- Phase 1 study healthy volunteer study completed: Database lock pending
  - **No serious AEs reported**
- Phase 2a human challenge study planned in 2H of 2023
  - CRO: hVIVO, Queen Mary's Bioenterprise Centre, London, UK
  - Study design: randomized, double-blind, placebo-controlled in healthy volunteers treated after inoculation with an influenza strain

Best-in-Class Influenza A PB2 Inhibitor CC-42344

✓	Broad-spectrum activity	Activity against pandemic and seasonal influenza A strains and drug resistant strains
✓	Potency and resistance	Single digit nanomolar potency with high barrier to resistance
✓	Mechanism of Action	Novel inhibition mechanism
✓	Combination regimen	Strong synergistic effects with approved influenza antivirals and no DDI issues
✓	Safety profile	Clean safety profile (F% = 80%) Phase 1 – SAD and MAD completed

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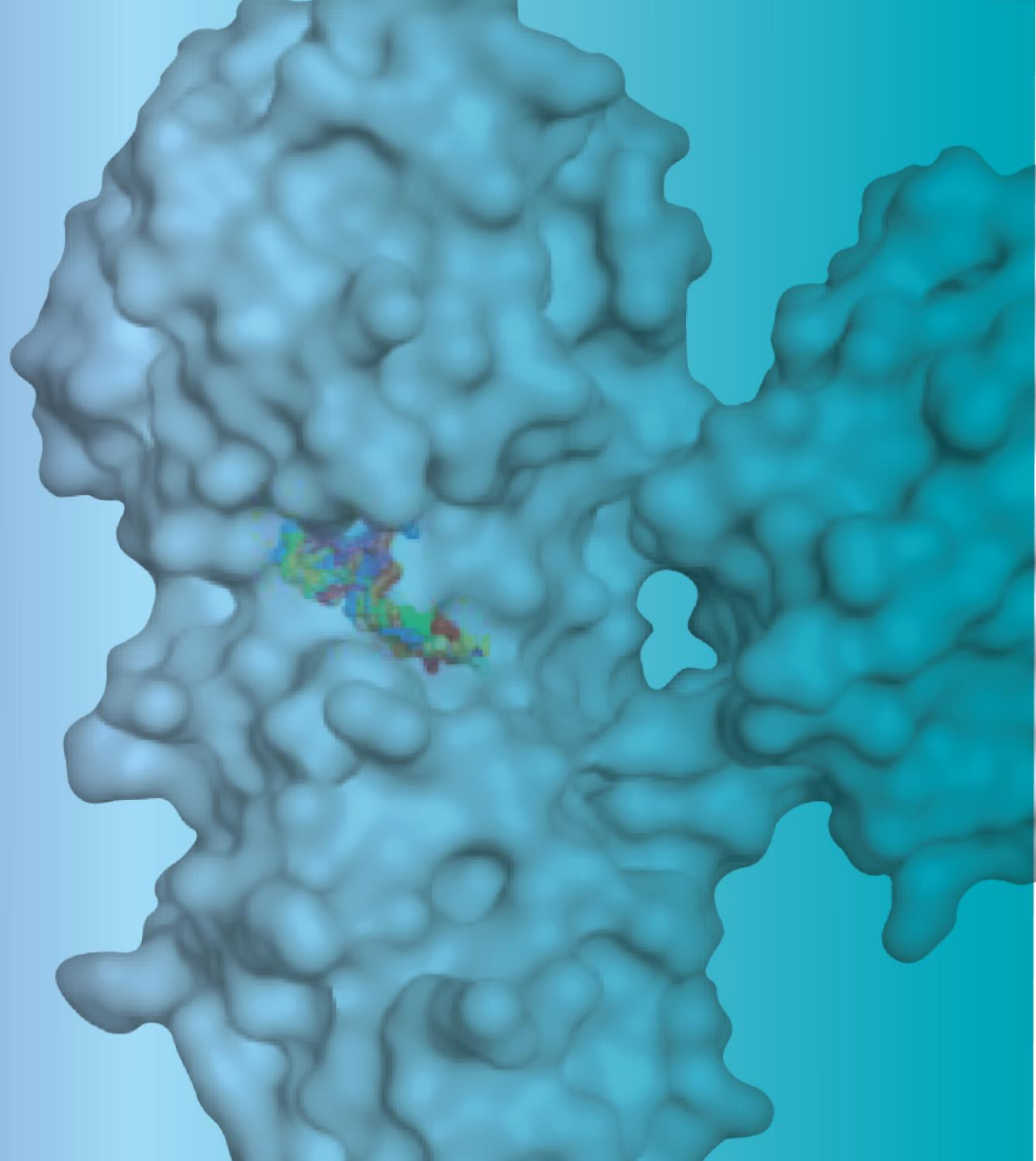
Influenza A Oral Inhibitor
CC-42344



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