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Annual General Meeting
22nd November 2019

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TWO PROJECTS:

1. **Primary Project**
   - Influenza Anti Virals
2. **Secondary Project**
   - Respiratory Anti-inflammatory
   - Chronic Obstructive Pulmonary Disease (COPD)

Additional Disease Targets
- Idiopathic Pulmonary Fibrosis (IPF)
- Allergic Airways Disease (Asthma)

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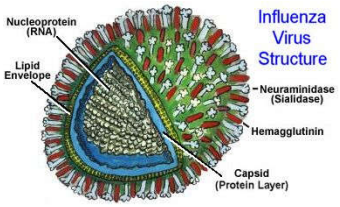
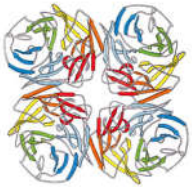
Science..
The Influenza Virus

RNA Core

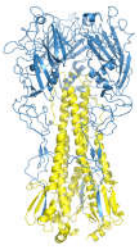
- 2 Surface glycoproteins
  - Haemaggluttinin (HA), Neuraminidase (N)
  - RNA coding these 2 glycoproteins
    - May rapidly mutate
    - H18 subtypes, N7 subtypes
    - Produces minor and also major changes to antigenic virus structure



Neuraminidase (NA)



Haemagglutinin (HA)



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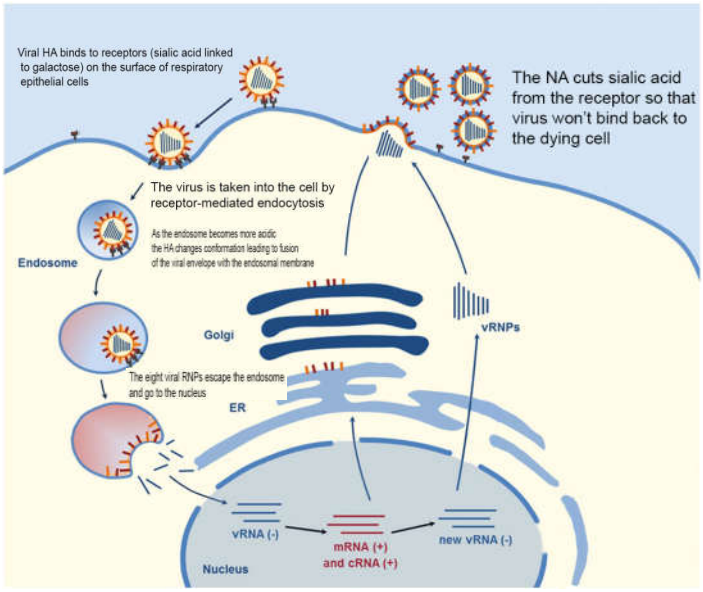
Replication cycle of influenza virus



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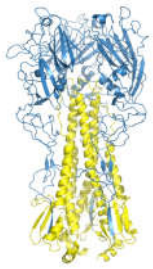
A target to stop infection is the HA



Haemagglutinin (HA)

Attempts to design a molecule to disable the HA using the lock and key approach to block the receptor-binding site have been unsuccessful

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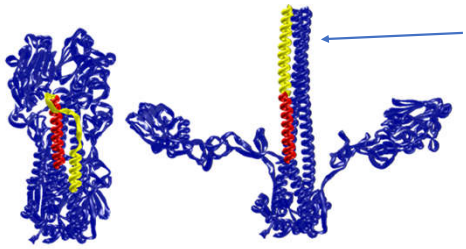
Mode of Action
Endosome escape requires a pH-dependent irreversible change in HA



A hydrophobic fusion region is revealed that can penetrate the endosomal membrane

pH 7 pH 5

We hypothesized that creating an acidic environment around the virus before it enters a cell would induce this conformational change prematurely, rendering the virus unable to bind to its receptor and infect cells

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Patent Overview

Invention

- **Compounds/drug candidates are designed to effect a conformational change of HA by converting the viral surface into a microacidic environment thus selectively interfering with viral lifecycle**
- **Compounds/drug candidates are composed**
  - **Have acidic groups which act to interfere with the binding of HA to the cell**
  - **Act extracellularly**
  - **Prevents Influenza infection of cell**
- **The antiviral efficacy of the compounds/drug candidates are proportional to the number of their acidic groups**

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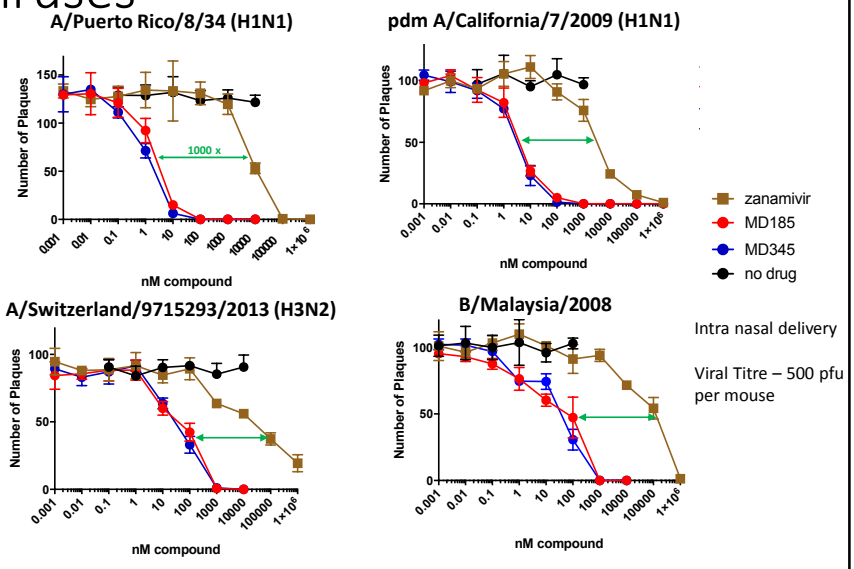
In vitro activity – Against 4 Flu Viruses



Aus Bio Drug Candidates 1000 x ZMR potency

Professor Lorena Brown, Global Virus Network Meeting. Melbourne 26 September 2017

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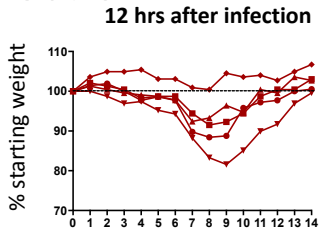
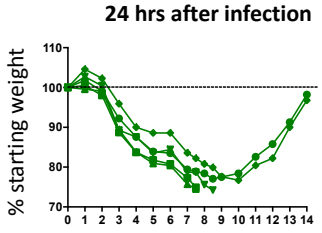
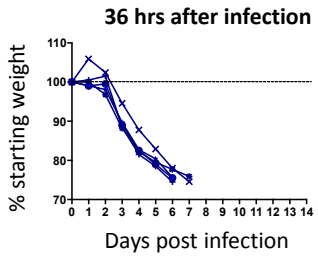
In vivo therapeutic effectiveness of zanamivir. A/PR/8/34/(H1N1) Infection







After a single treatment of 40 µg, zanamivir is only effective out to 12 hrs post infection

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Professor Lorena Brown, Global Virus Network Meeting. Melbourne 26 September 2017

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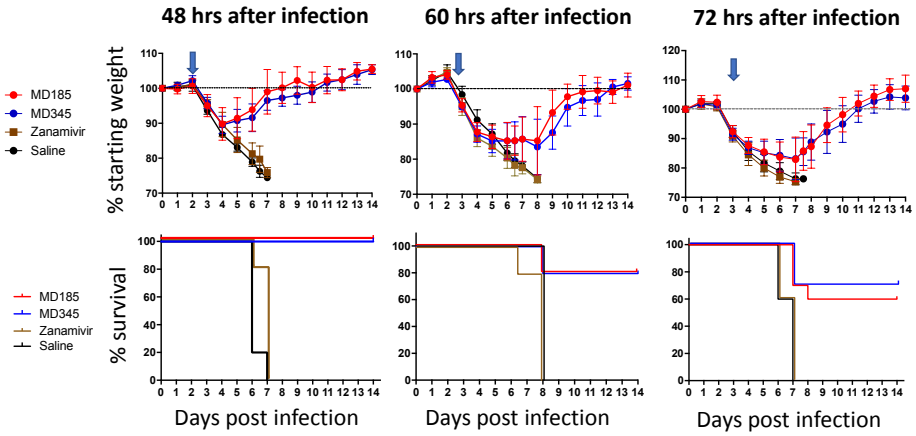
In vivo therapeutic effectiveness



A single 40 µg dose of an AB drug candidate at 48 hours prevented all deaths and single dosing at 60 – 72 hours significantly reduced mortality in all cases. In all cases the AB candidates significantly outperformed Zanamivir.

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Professor Lorena Brown, Global Virus Network Meeting. Melbourne 26 September 2017

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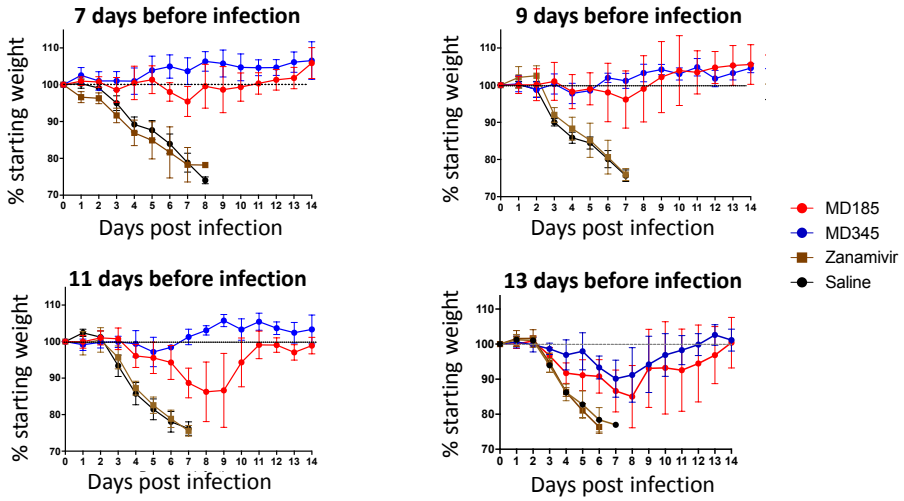
In vivo prophylactic effectiveness



When given up to 13 days before infection, one 5 µg dose of an AB Drug Candidate is fully protective against death.

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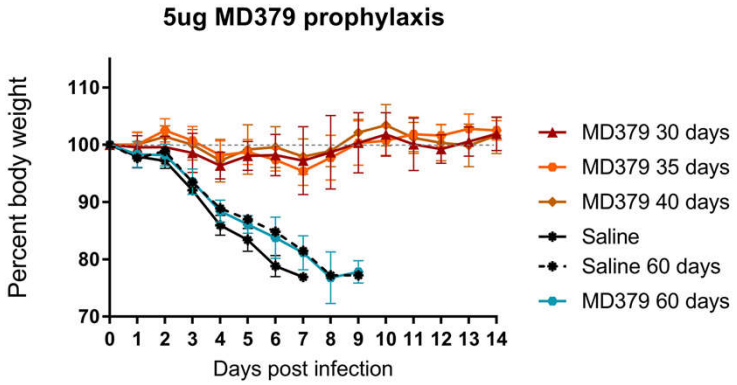
What is the duration of the protective effect?



Protection against death and weight loss due to 500 pfu PR8 can last longer than 40 days after a single 5 µg dose

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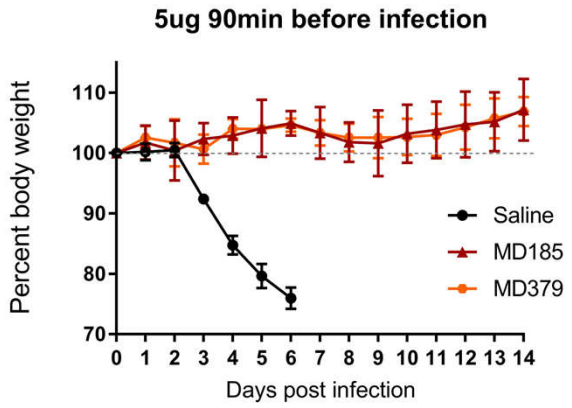
These drug candidates work promptly.



PR8 Virus – 500 pfu per mouse

Short and long acting prophylaxis now demonstrated

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Resistance Studies

Summary University of Melbourne

- Development of anti viral resistance is a significant concern for influenza anti viral drug development
- Sensitivity to AB compounds unaffected by H274Y substitution conferring Oseltamivir resistance
- Resistance to the E119G mutant was > 10 fold less than zanamivir
- Mutants with decreased sensitivity were selected but they were unfit
- Escape mutants reported to have occurred in up to 23% of Baloxavir Marboxil treated patients
- We do not expect resistance to be a significant factor in the clinical development of the Aus Bio anti virals – due to the dual mode of action of these drug candidates

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Key Pre Clinical Features of Aus Bio's Influenza Anti Virals

To date (November 2019)

- **Improved Therapeutic Performance –** Pre and Post Infection Murine Models – 1 dose only. Preventative and therapeutic indications anticipated. Possible once only oral inhalation dose.
- **Pan Strain Anti-Viral Activity –** "Pan Strain Efficacy". Flu A and B strains Oseltamivir resistant high path strains (Avian flu strains H7N9 H5N1) (NIAID/NIH support continues)
- **Extended Duration of Efficacy –** Supported by preclinical data. Long duration of activity greatly enhances the feasibility of prophylaxis – critical in pandemic context*
- **Low Propensity for Drug Resistance –** Anticipated low drug resistance to MOA.
  - dual MOA

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Summary – Target Product Profile
Dose 20mg "10mg x 2" inhalations on one occasion.
1. Highest Potency of known Influenza Anti Virals
2. Pan influenza strain specificity
3. Anticipated high therapeutic index with wide therapeutic window
4. Unique extracellular MoA
5. Low propensity for resistance – due to MoA
6. Immediate and long lasting anti viral efficacy and prophylaxis - Suitable for treatment and prevention of any influenza viral infection.

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MD990 : Respiratory Anti Inflammatory Project

Targets

1. Chronic Obstructive Pulmonary Disease (COPD)
2. Additional Targets
   a). Idiopathic Pulmonary Fibrosis (IPF)
   b). Allergic Airways Disease (Asthma)

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MD990 – Respiratory Anti Inflammatory Project

COPD – Some Facts

- Major cause of Chronic Morbidity and Mortality World Wide
- 3rd Leading Cause of Death
- Common Preventable Disease
- Enhanced Chronic Inflammatory response to particles or gases eg. cigarette smoke
- Persistent Airflow Obstruction
- Limitation of Airflow (Airways Obstruction)
- Destructive Chronic Inflammatory Process

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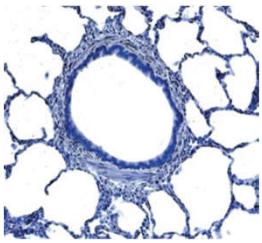
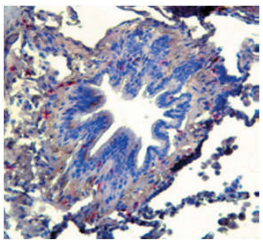
MD990 : Some Pathological Consequences of Cigarette Smoke





- *Ref: Cosio MG et al. NEJM 2009;360: 2445-54.*
- **Airway remodelling is a feature of COPD. No current treatments alleviate remodelling.**

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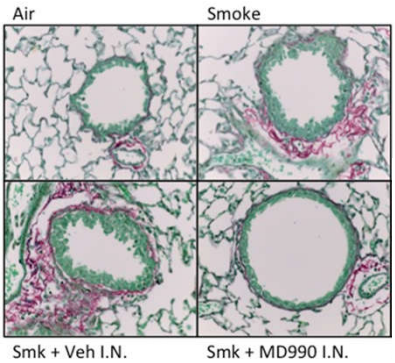
Histology – First Mouse Smoking Study

Results

Representative slides – Airway Remodelling



Note

Small airway remodeling is a cardinal feature of early COPD and no current treatment is able to suppress this.

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MD990 -Respiratory Anti-Inflammatory 4 Murine Smoking Studies Complete

Smoke Exposure -

12 Cigarettes, 75 minutes bd, 5days/week, 8 to 10 weeks smoke exposure

Varying Protocols – aids lead candidate selection

a) AB Compounds given throughout 8 weeks
- Smoke exposure – 1 study

b) AB Compounds given for 4 to 6 weeks
- post 8 to 10 weeks smoke exposure – 3 studies

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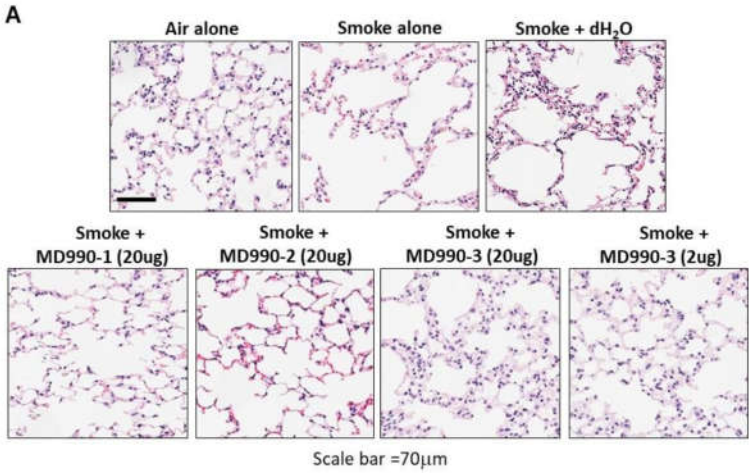
vii) Emphysema score



A) Representative photomicrographs of H&E-stained lung sections from each of the 7 groups studied show the extent emphysema within the lungs. Bar = 70µm.

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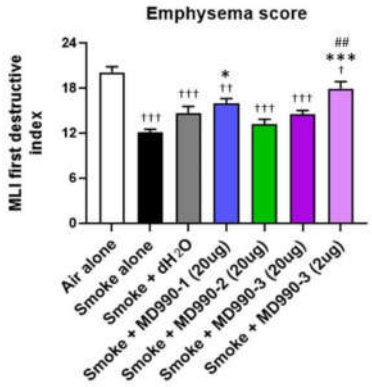

B) *Also shown is the mean ± SEM emphysema score (based on the MLI first destructive index) from 5 fields/mouse, n =7-8 mice/group. †p<0.05, ††p<0.01, †††p<0.001 vs air alone group; *p<0.05, ***p<0.001 vs smoke alone group; ##p<0.01 vs smoke+dH2O group.*

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Reproducible Results –

a) Inflammation Suppressed
b) Airway remodeling prevented or suppressed

"Encouraging results – MD990 -3 was shown to provide optimal safe and broad overall protection against COPD pathology in the model studied"

PI- Monash University

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Fifth Mouse Smoking Experiment

Results anticipated Feb/March 2020

- Up to 10 weeks smoke exposure
- 6 active treatment groups
  - Additional compounds evaluated

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Thank you from all at Aus Bio

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