GEIG Meeting 2019

# Novel host-directed antivirals for influenza

**Dr. Andrés Pizzorno**

**Centre International de Recherche en Infectiologie (CIRI) – VirPath Team**
**Lyon (France)**

mario-andres.pizzorno@univ-lyon1.fr

# Potential COI disclosure

**Associate co-founder of Signia Therapeutics SAS:** French-based biotech dedicated to drug repurposing against respiratory infections and holding the license for the exploitation of diltiazem for pan-antimicrobial indications.

# Potential strategies for treating influenza

## VIRUS-DIRECTED

### Direct-acting antivirals

Target specific viral determinants: M2 inhibitors, NAIs, pol inhibitors…

### Immunotherapies

Passive humoral response vs. major antigens: immune plasma, hyper Ig, mAbs…

# Potential strategies for treating influenza

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Target specific viral determinants: M2 inhibitors, NAIs, **pol inhibitors**…

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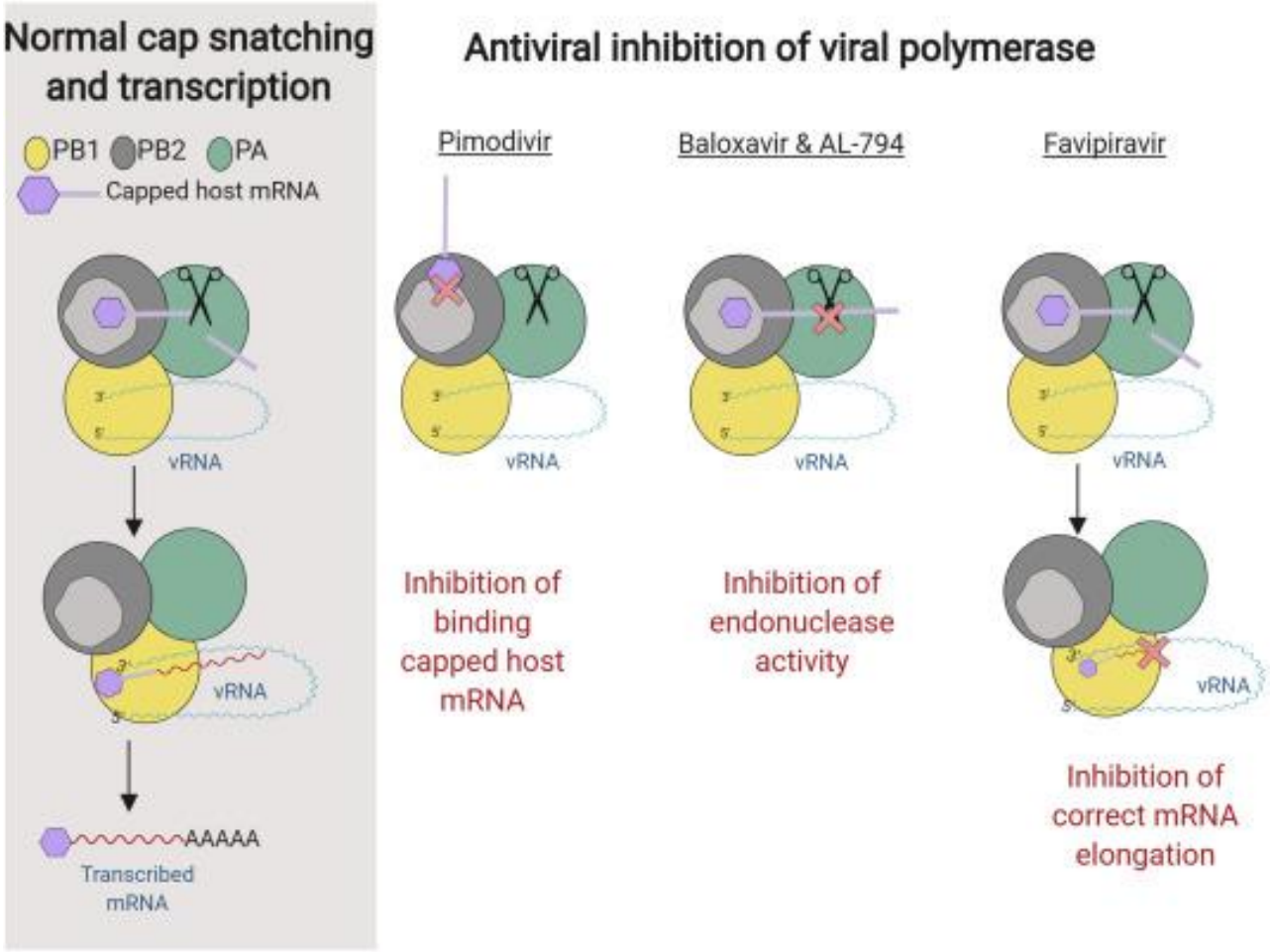
Passive humoral response vs. major antigens: immune plasma, hyper Ig, mAbs…




Mifsud EJ et al, Antiv Res 2019

# Potential strategies for treating influenza

## VIRUS-DIRECTED

### Direct-acting antivirals

Target specific viral determinants: M2 inhibitors, NAIs, pol inhibitors…

### Immunotherapies

Passive humoral response vs. major antigens: immune plasma, hyper Ig, mAbs…

## HOST-DIRECTED

### Immunomodulators

Enhance suboptimal or dampen harmful host immune responses to infection

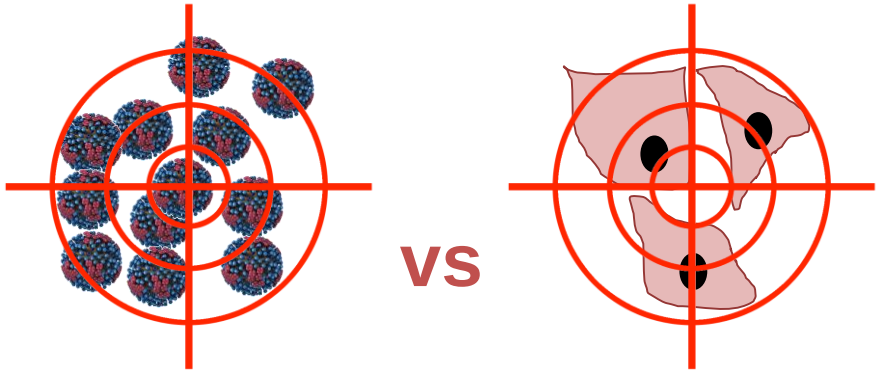
### With antiviral effects

Target host-virus interactions required for the viral replication cycle

# Why targeting the host instead of the virus?

## Cellular targets are more conserved than viral ones

- Independence of viral strain
- Antiviral resistance de-risking



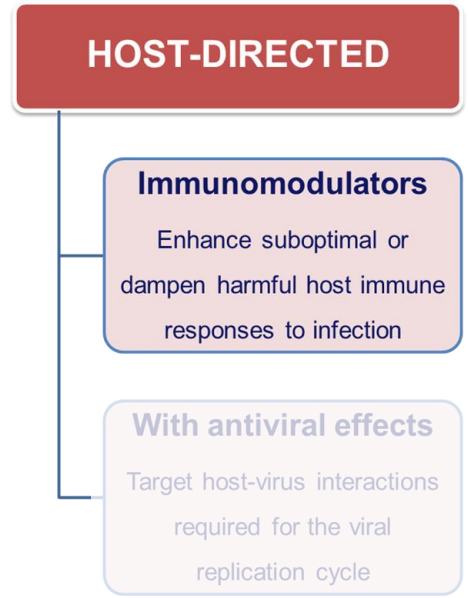

## Common host factors/pathways targeted by different viruses

- Potential broad spectrum antiviral effect

## Immunomodulatory effects

- Suitable for acute (short) infections
- Better adapted for severe cases

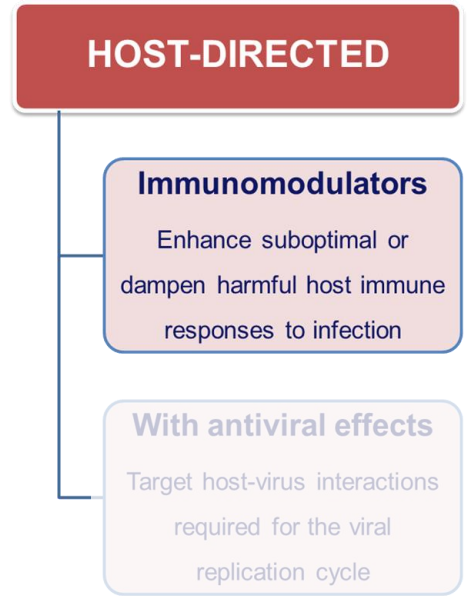
# Immunomodulators




## Rationale

- **Many disease manifestations due to the immune response rather than the virus**
- **Inflammatory response is a common factor among respiratory viruses**
- **Specific viral factors with proven immunomodulatory activity**
- **Patients show up late to the hospital** (severe cases)
- **By day 4-5 since symptom onset viral shedding is low** (utility of antivirals?)

# Immunomodulators

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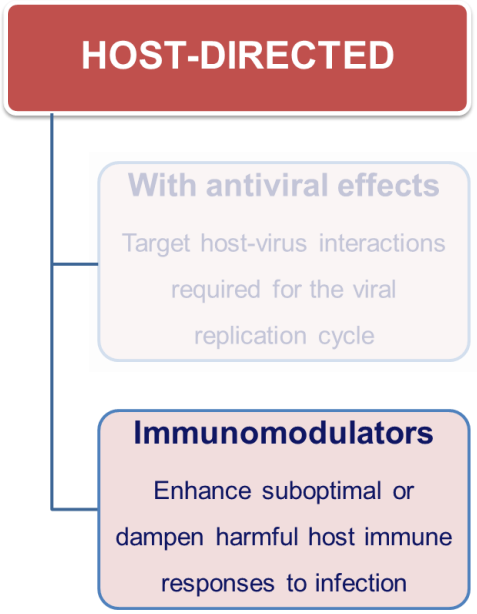
## Objectives

- **Shape specific facet(s) of the host's immune response to infection**
- **Enhance insufficient responses**
- **Control exaggerated responses** ("ck storms") **that lead to severe pathology**

# Immunomodulators




## Challenges

- **Ambivalence of the immune response** (inflammation vs tissue remodeling)
- **Delicate balance between protective vs negative effects**
- **Finely-tuned complex system** (timing, dose, pathway redundancy)
- **Organ/tissue microenvironment vs systemic effects**
- **Population-based differences** (age, co-morbidities, vaccination, etc…)

# Immunomodulators

**HOST-DIRECTED**

**With antiviral effects**

Target host-virus interactions required for the viral replication cycle

**Immunomodulators**

Enhance suboptimal or dampen harmful host immune responses to infection

## Challenges

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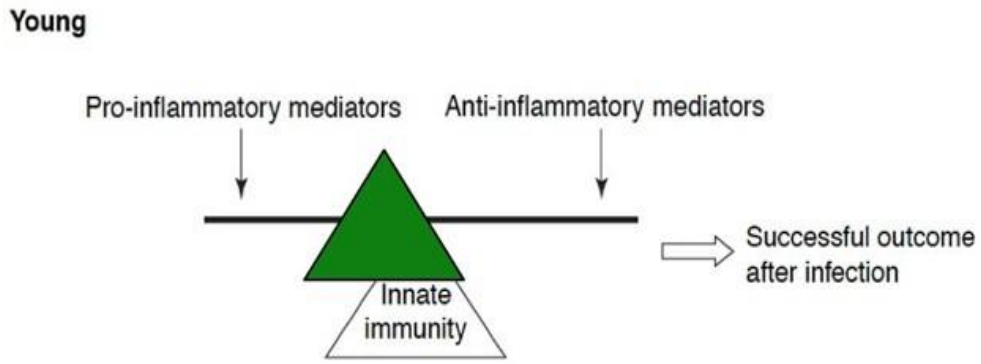


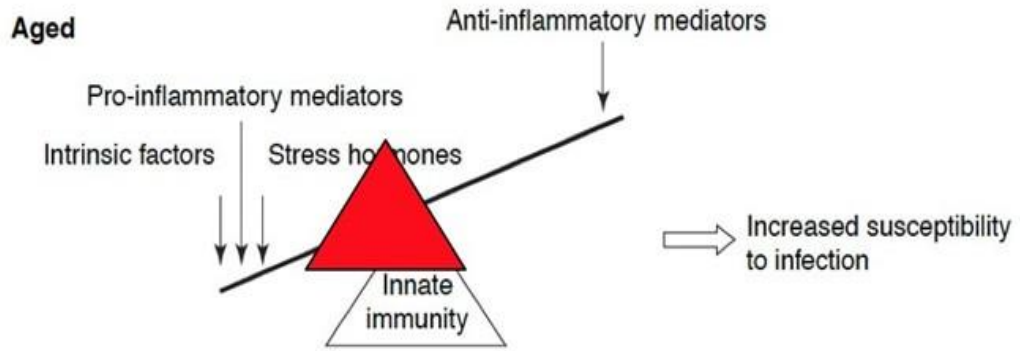

# Principal immunomodulators with positive clinical data

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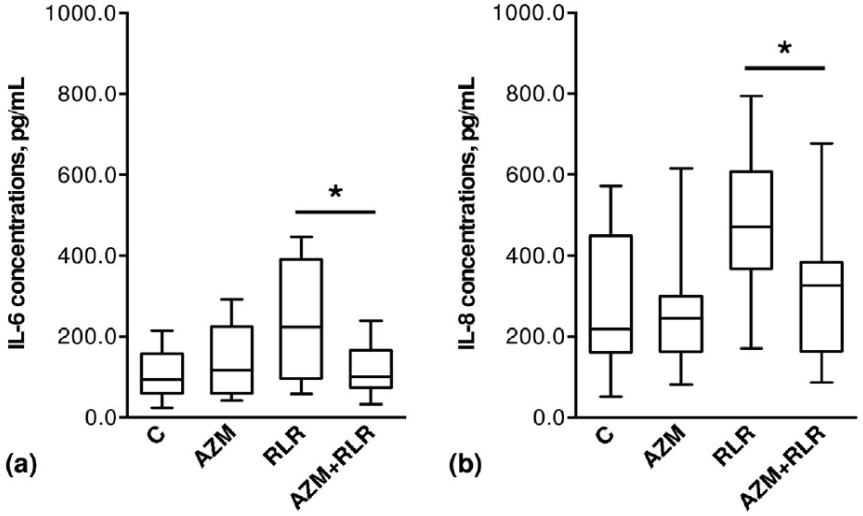
## **Macrolides** (e.g. Azithromycin, Clarithromycin)

- **Downregulate pro-inflammatory cytokines/chemokines, inhibit signal transduction and adhesion molecule expression, regulate inflammatory cell functions[1]**

- **NCT01779570: Phase 4, OSE vs OSE+AZM in severe influenza[2]**
  - **Significant anti-inflammatory effects of adjunctive AZM treatment**
  - **Virus control was unimpaired**
  - **Clinical benefits of a macrolide-containing regimen deserve further study**




[1] Hui DS et al, Antiv Res 2018 [2] Lee N et al, Antiv Res 2017

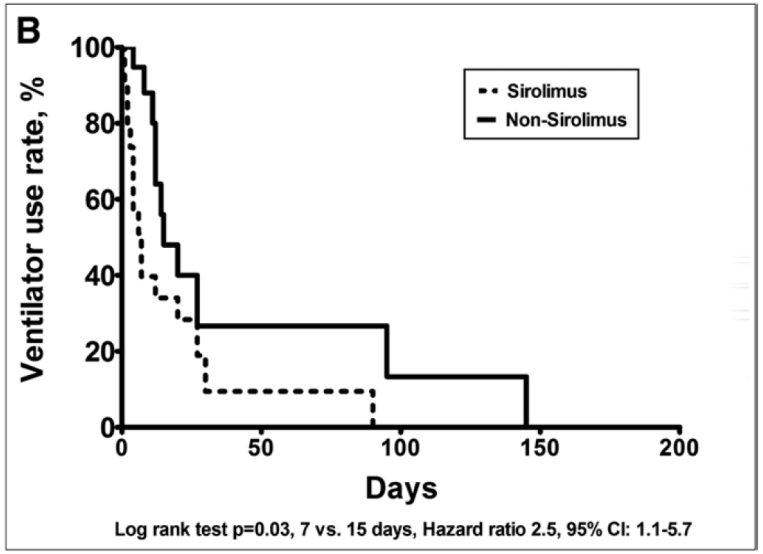
# Principal immunomodulators with positive clinical data

## **Macrolides** (e.g. Sirolimus)

- mTOR pathway inhibitor, modulates protein synthesis and autophagy, reduces sensitivity of TCD4+/TCD8+ to IL2, lowers lung inflammation and inflitration[1]

- 100-2433C: Phase 2, OSE+PRED vs OSE+PRED+SIR in severe influenza with acute respiratory failure[2]
  - Small sample size: 38 patients
  - Higher liberation and shorted duration of mechanical ventilation
  - Increased % of negative viral PCR on day 7
  - Proinflammatory responses not measured

- NCT03901001: Phase 4, OSE vs OSE+SIR in severe influenza (ongoing)




[1] Hui DS et al, Antiv Res 2018 [2] Wang CH et al, Crit Care Med 2014

# Principal immunomodulators with positive clinical data

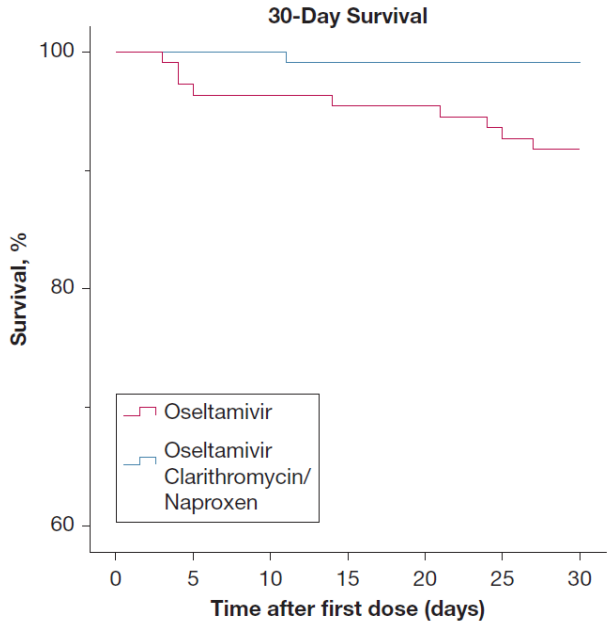
## **COX-2 inhibitor NSAIDs** (e.g. Naproxen, Mesalzine, Celecoxib)

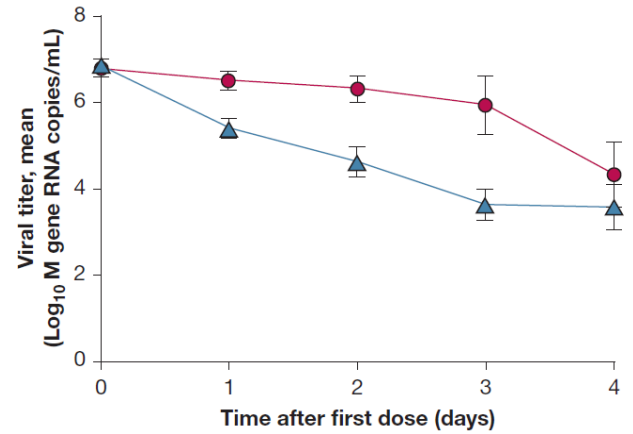
- **Downregulate pro-inflammatory cytokines/chemokines, reduce neutrophil activation and suppress H5N1 replication in macrophages**[1]

- **ISRCTN11273879: Phase 2b/3, OSE vs OSE+CLA+NPX* in severe influenza**[2]
  - **Combination reduced 30- and 90-day mortality, ICU and hospital stay**
  - **Reduced viral titers (days 1-3) and OSE-resistant variants**
  - **Proinflammatory responses not measured**

* Naproxen repurposed vs influenza for specifically binding of viral NP[3]

- **NCT02108366: Phase 3, OSE vs OSE+CEL in severe influenza (ongoing)**




[1] Hui DS et al, Antiv Res 2018 [2] Hung IF et al, Chest 2017 [3] Lejal N et al, AAC 2013

# Immunomodulators in preclinical or clinical evaluation

**Statins** (e.g. Atorvastatin, Simvastatin) Hui DS et al, Antiv Res 2018

**Corticosteroids** (e.g. Dexamethasone, Prednisolone) Rodrigo C et al, Cochr Dat Syst Revs 2016

**Type I IFNs** (e.g. Alferon) Liu Q et al, Expert Rev Anti Infect Ther 2014

**CK receptor agonists/antagonists** (e.g. IL33, IL7) Bian JR et al, Int J Clin Exp Med 2014

**PPAR agonists** (e.g. Gemfibrozil) Bauer CM et al, POne 2010

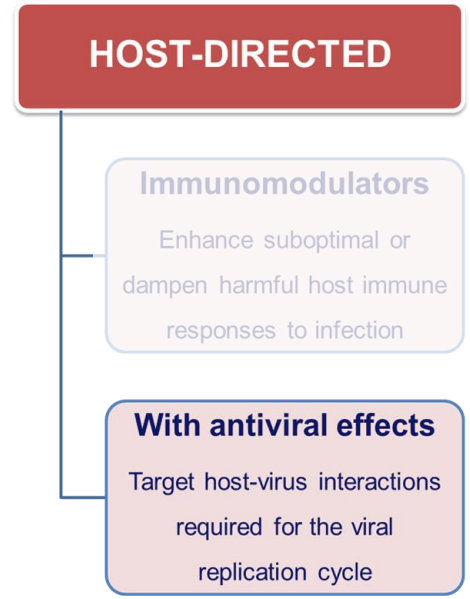
**TLR 4 ligands / antagonists** (e.g. Eritoran) Leiva-Juarez MM et al, Eur J Pharmacol 2018

**Eicosanoids / Leucotrienes** (e.g. GP1001, LTB4) Pernet E et al, Nat Microbiol 2019

**Iminosugars** (e.g. UV-4B) Tyrrell BE et al, Crit Rev Microb 2017

…

# Host-directed antivirals



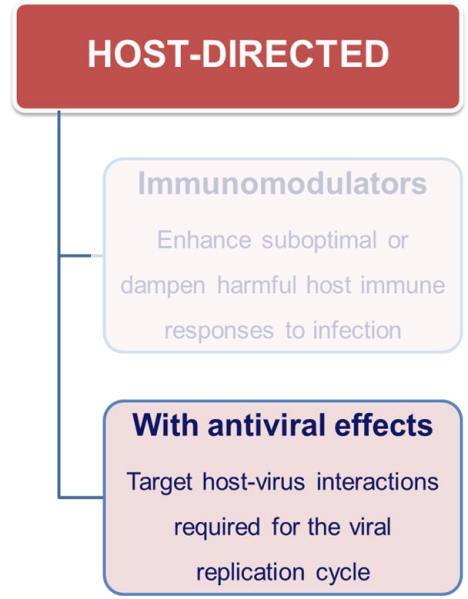

## Rationale

- Productive viral infection relies on the “hijacking” of key cellular processes

## Objectives

- Block or inhibit strategic cellular partners of the viral cycle
- Develop endogenous antiviral responses

# Host-directed antivirals




## Rationale

- **Productive viral infection relies on the “hijacking” of key cellular processes**

## Objectives

- **Block or inhibit strategic cellular partners of the viral cycle**
- **Develop endogenous antiviral responses**

## Challenges

- **Incomplete knowledge of complex host-virus interactions**
- **Target selection** (bottlenecks/checkpoints/pathways)
- **Pathway redundancy** (one target or multiple targets?)
- **Role of host-targets on other biological functions or pathologies** (potential unexpected effects)

# Host-directed antivirals under clinical evaluation

# Host-directed antivirals under clinical evaluation

## NITAZOXANIDE

- FDA-licensed against parasitic enteritis

- Interferes with N-glycosylation (HA) and intracellular trafficking

- Novel MoA: amplifies RIG-I and PKR-dependent IFN pathway in Ebola[1]

- Effective against various influenza A and B strains, including H275Y and avian

- Randomized Phase 2/3 trial in adults and adolescents with uncomplicated influenza:

  NCT01227421, +600 patients: oral 300mg NTZ bid x5, 2x300mg NTZ bid x5, placebo[2]

[1] Jasenosky LD et al, iScience 2019 [2] Haffizulla J et al, Lancet Inf Dis 2014

# Host-directed antivirals under clinical evaluation

## NITAZOXANIDE

**Positive *in vitro* and *in vivo* results for the NTZ+OSE combination**

**NCT01227421:**

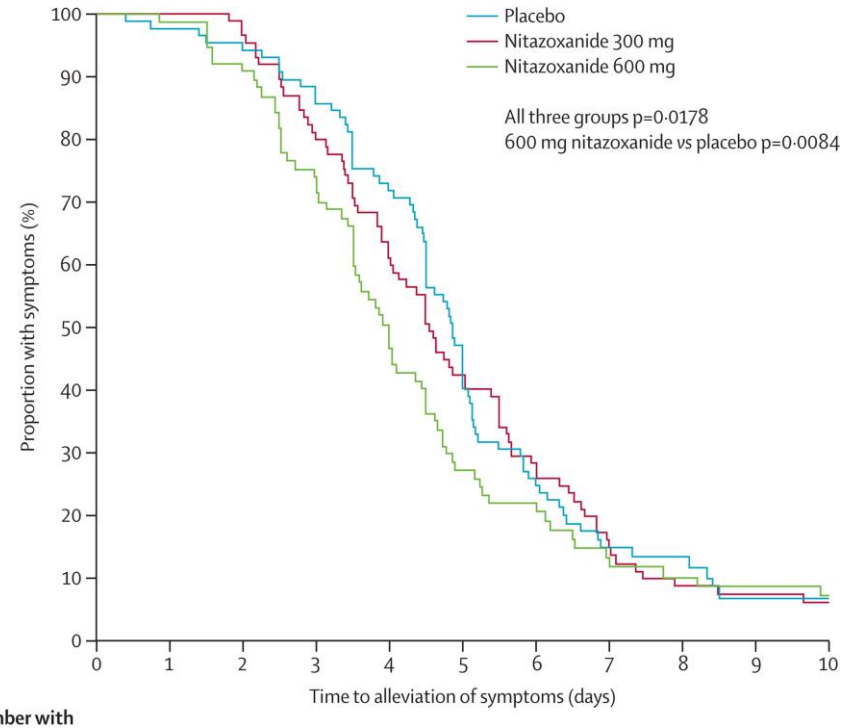
**-1 day symptom resolution**

**-1 log viral titer on day 3**

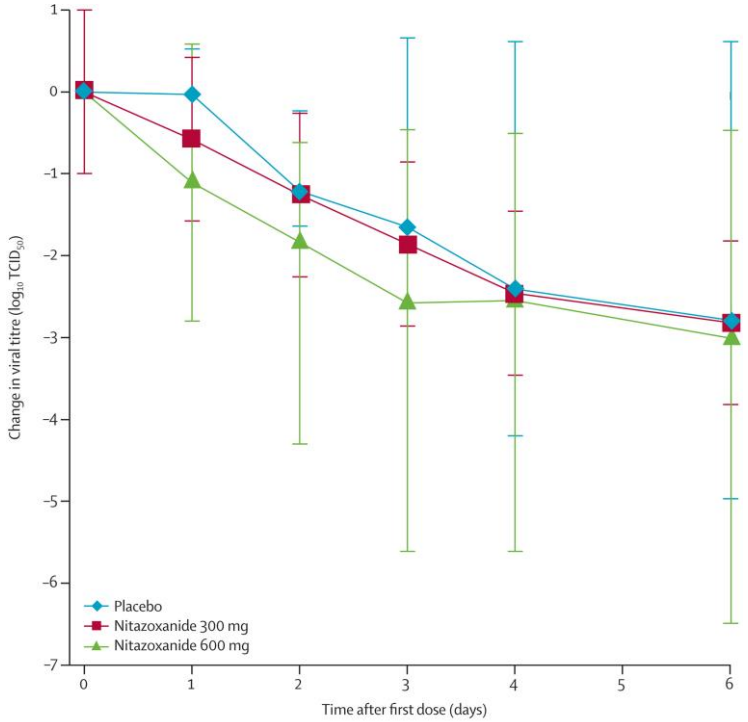
**Increased adverse events in both treated groups**

**NCT01610245, NCT02612922 and NCT03336619:**

**Phase 3, results not yet disclosed**




| Number with symptoms (at risk) at each timepoint | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Placebo | 87 | 83 | 81 | 74 | 61 | 38 | 21 | 11 | 8 | 4 | 4 |
| Nitazoxanide 300 mg | 89 | 87 | 83 | 68 | 52 | 36 | 24 | 12 | 7 | 6 | 5 |
| Nitazoxanide 600 mg | 79 | 76 | 70 | 55 | 36 | 21 | 14 | 8 | 7 | 6 | 5 |




| Days after 1st dose | Mean change (95% CI) in viral titre | | |
|---|---|---|---|
| | Placebo (n=41) | Nitazoxanide 300 mg (n=41) | Nitazoxanide 600 mg (n=39) |
| Day 1 | −0·03 (−0·61 to 0·55) | −0·58 (−1·10 to −0·07) | −1·11 (−1·69 to −0·52) |
| Day 2 | −1·21 (−0·98 to −0·43) | −1·26 (−1·96 to −0·56) | −1·84 (−2·46 to −1·22) |
| Day 3 | −1·65 (−2·31 to −1·00) | −1·86 (−2·58 to −1·15) | −2·58 (−3·03 to −2·12) |
| Day 4 | −2·41 (−3·02 to −1·79) | −2·46 (−3·15 to −1·77) | −2·55 (−3·06 to −2·04) |
| Day 6 | −2·79 (−3·40 to −2·18) | −2·82 (−3·41 to −2·18) | −3·01 (−3·48 to −2·54) |

# Host-directed antivirals under clinical evaluation

## **DAS181** (Fludase)

- **Recombinant cell-surface anchored sialidase**

- **Inhibits virus attachment to respiratory cells by removing SA residues**

- **Initially developed vs influenza, now also validated vs PIV** (FDA Fast Track designation)

- **Effective against various influenza A and B strains, including H275Y and avian**

- **Randomized Phase 2 trial in influenza-infected adults:**

  **NCT01037205, 177 patients: inhaled 10mg DAS once, 1x10mg DAS d x3, placebo[1]**

[1] Moss RB et al, J Inf Dis 2012

# Host-directed antivirals under clinical evaluation

## DAS181 (Fludase)

**NCT01037205:**

**Reduced viral loads between days 1 and 2 for both DAS181**

**Sustained viral load reduction only for multi-dose DAS181**

**Increased adverse events in both treated groups**

**NCT01740063:**

**Phase 2b, F02 and F04 formulations, results not yet disclosed**

**Table 2. Summary of Log-Transformed Influenza Viral Load by Polymerase Chain Reaction from Pharyngeal Wash: Baseline (Day 1) to Day 2, Day 1 to Day 3, and Day 1 to Day 5 (Modified Intent to Treat Population)**

| Study Visit/ Value | Multiple Dose DAS181 (N = 56) | Single Dose DAS181 (N = 69) | Placebo (N = 52) |
|---|---|---|---|
| Baseline (Day 1) | | | |
| N | 56 | 67 | 52 |
| Mean (SD) | 5.35 (1.417) | 4.85 (1.196) | 4.69 (1.468) |
| Median | 5.35 | 4.87 | 4.96 |
| Minimum, maximum | 2.4, 8.9 | 2.4, 7.3 | 2.4, 8.1 |
| Change from day 1 to day 2 | | | |
| N | 56 | 65 | 51 |
| Mean (SD) | −1.06 (1.458) | −0.90 (1.285) | −0.25 (1.144) |
| Median | −1.01 | −0.79 | −0.34 |
| Minimum, Maximum | −6.2, 2.3 | −4.3, 1.6 | −2.5, 2.3 |
| *t* test[a] | | | |
| *P* value | .002 | .006 | |
| Change from day 1 to day 3 | | | |
| N | 52 | 64 | 50 |
| Mean (SD) | −1.46 (1.582) | −1.18 (1.272) | −0.73 (1.183) |
| Median | −1.46 | −1.19 | −0.69 |
| Minimum, Maximum | −5.9, 1.5 | −4.3, 1.4 | −3.7, 1.8 |
| *t* test[a] | | | |
| *P* value | .009 | .054 | |
| Change from day 1 to day 5 | | | |
| N | 54 | 62 | 49 |
| Mean (SD) | −2.38 (1.359) | −1.78 (1.533) | −1.64 (1.417) |
| Median | −2.45 | −1.96 | −1.54 |
| Minimum, maximum | −5.0, 1.3 | −4.9, 4.4 | −5.7, 1.7 |
| *t* test[a] | | | |
| *P* value | .008 | .645 | |

$Log_{10}$-transformed viral load data. Undetectable values or those reported as being <500 copies/mL were assumed to be 250 copies/mL.

[a] Treatment vs placebo.

**Table 4. Log Rank Test of Time to Sustained Decreasing Shedding of Influenza Virus (Pharyngeal Wash) as Defined by Time to 1 Log or Greater Decrease from Day 1 (Modified Intent to Treat)**

| | Multiple Dose DAS181 (N = 56) | Single Dose DAS181 (N = 69) | Placebo (N = 52) |
|---|---|---|---|
| Time to ≥1 log drop sustained (days) | | | |
| Event[b]/censored[c] | 49/7 | 56/12 | 39/13 |
| Median time | 2 | 4 | 4 |
| 95% confidence interval | (1, 4) | (2, 4) | (4, 5) |
| Log-rank test[a] | | | |
| *P* value | .007 | .164 | |

Undetectable values or those reported as being <500 copies/mL were assumed to be 250 copies/mL.

[a] Treatment vs placebo.

[b] Number of participants who reached sustained 1 log drop at certain date during the study.

[c] Number of participants who did not reach sustained 1 log drop during the study and were censored at the date of last follow-up visit.

# Host-directed antivirals under clinical evaluation

## LASAG

- L-Lys acetylsalicylate-glycine

- Interferes with vRNP transport by inhibiting the NF-kB activating kinase IkkB[1]

- Retains anti-inflammatory activity of ASA

- Effective against various influenza A and B strains

- Randomized Phase 2a trial in adults with severe influenza:

  EudraCT2012-004072-19, 115 patients: inhaled 800mg LASAG tid x5, placebo (soc: OSE)[2]

[1] Mazur I et al, Cell Microbiol 2007 [2] Scheuch G et al, Emerg Micr Infect 2018

# Host-directed antivirals under clinical evaluation

## LASAG

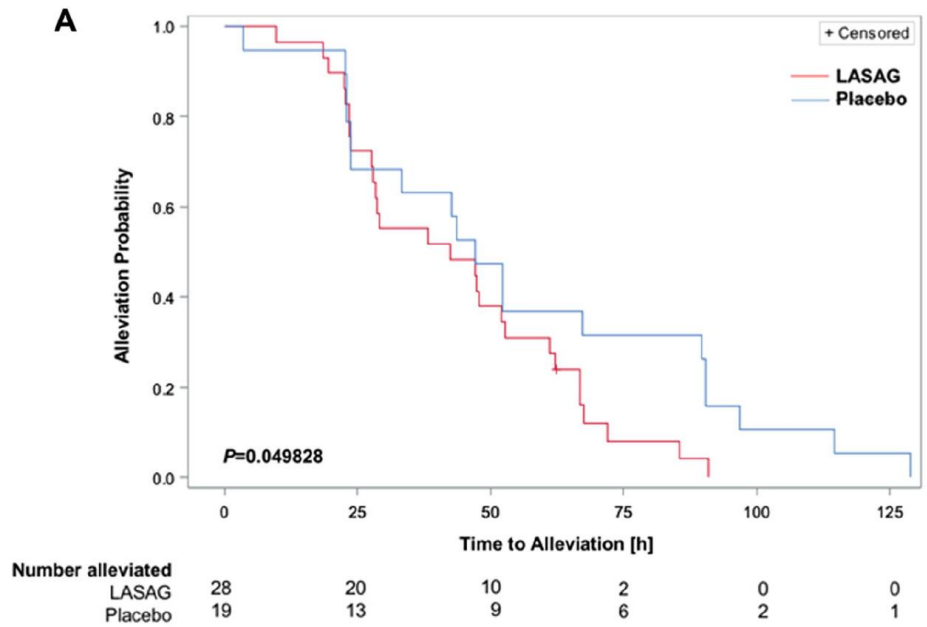
**EudraCT2012-004072-19:**

**Low statistical power of the study**

**-0.5/1 day symptom resolution**

**No difference in viral titer**

**Moderately increased adverse events in LASAG group**



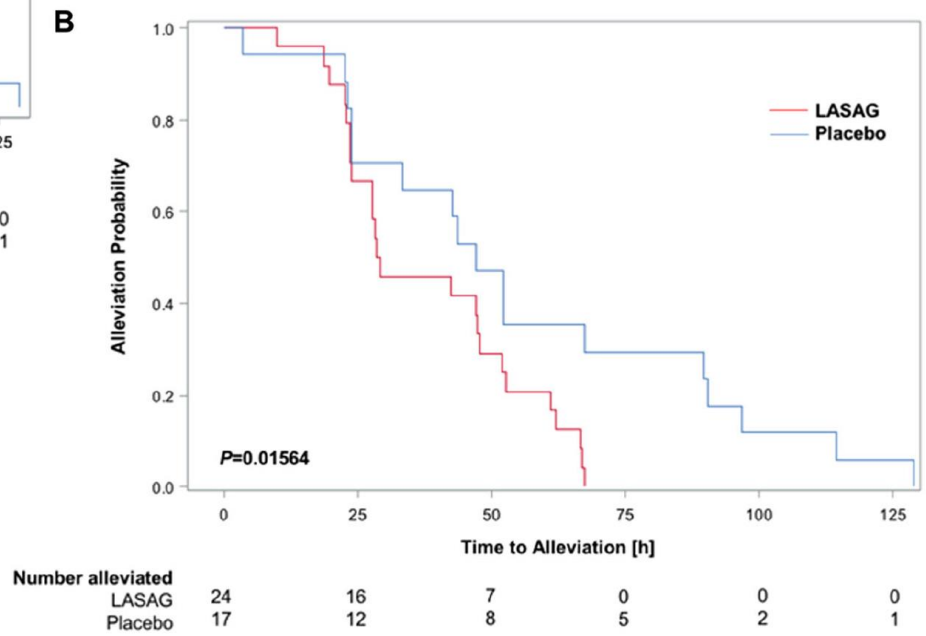




**Fig. 4 Kaplan-Meier estimation of time to clinical symptom alleviation. a** The MITT subset consisted of patients with RT-PCR-confirmed influenza and CSS ≥ 14. As censoring occurred within the population, Kaplan–Meier estimates and the log rank test were used for primary hypothesis testing. The *P*-value obtained with the log-rank test was $P = 0.049828$ (in favor of LASAG) **b** Per protocol analysis of patients with RT-PCR confirmed influenza and CSS ≥ 14. The difference was statistically significant based on a log rank test with $P = 0.01564$ (in favor of LASAG)

# Host-directed antivirals under clinical evaluation

## DILTIAZEM

- FDA-licensed Ca2+ channel inhibitor for chronic hypertension

- Ca2+ modulation putative role in virus entry inhibition[1]

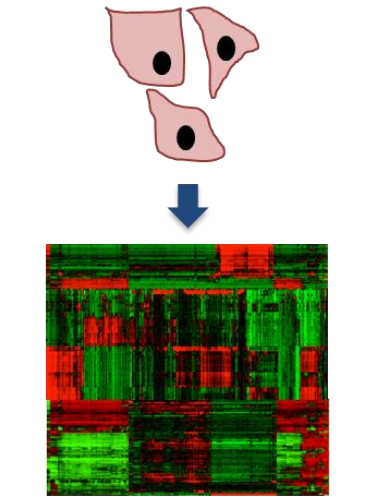
- Novel MoA: reverses the “transcriptomic signature of infection”, induces IFN-III antiviral response in the respiratory epithelium[2]

[1] Fujioka Y et al, Cell Host Micr 2018 [2] Pizzorno A and Terrier O et al, Front Immunol 2019

# Host-directed antivirals under clinical evaluation

## DILTIAZEM

- The global gene expression profile as a signature of a specific cellular state[1]

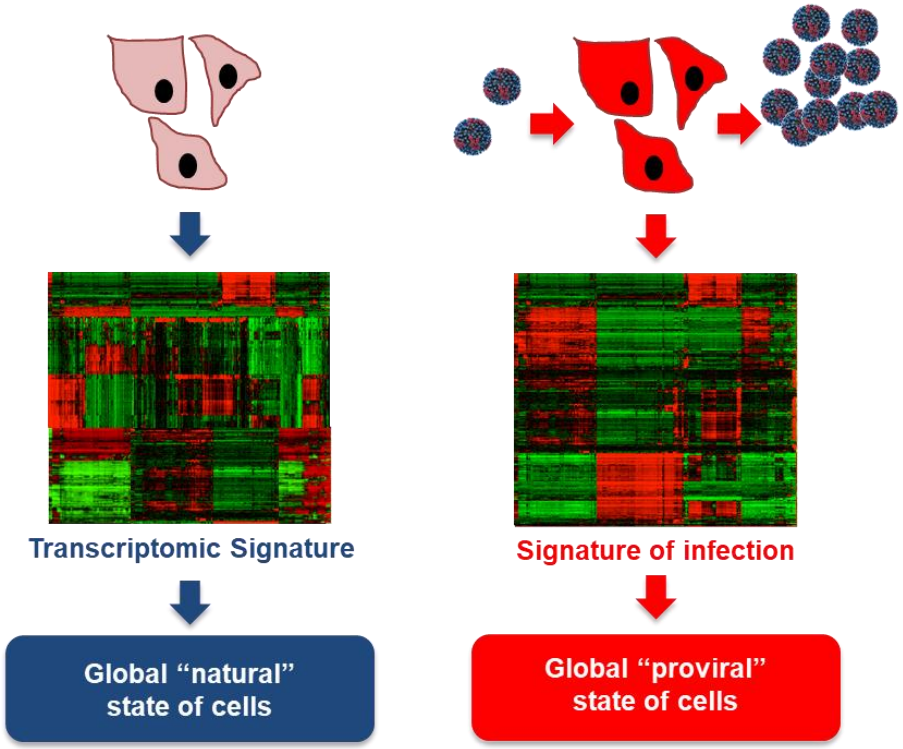



[1] Josset et al., PLoS One 2010 / Terrier et al., J Gen Virol 2013 / Pizzorno A and Terrier O et al, Front Immunol 2019

# Host-directed antivirals under clinical evaluation

## DILTIAZEM

- The global gene expression profile as a signature of a specific cellular state, including infection[1]

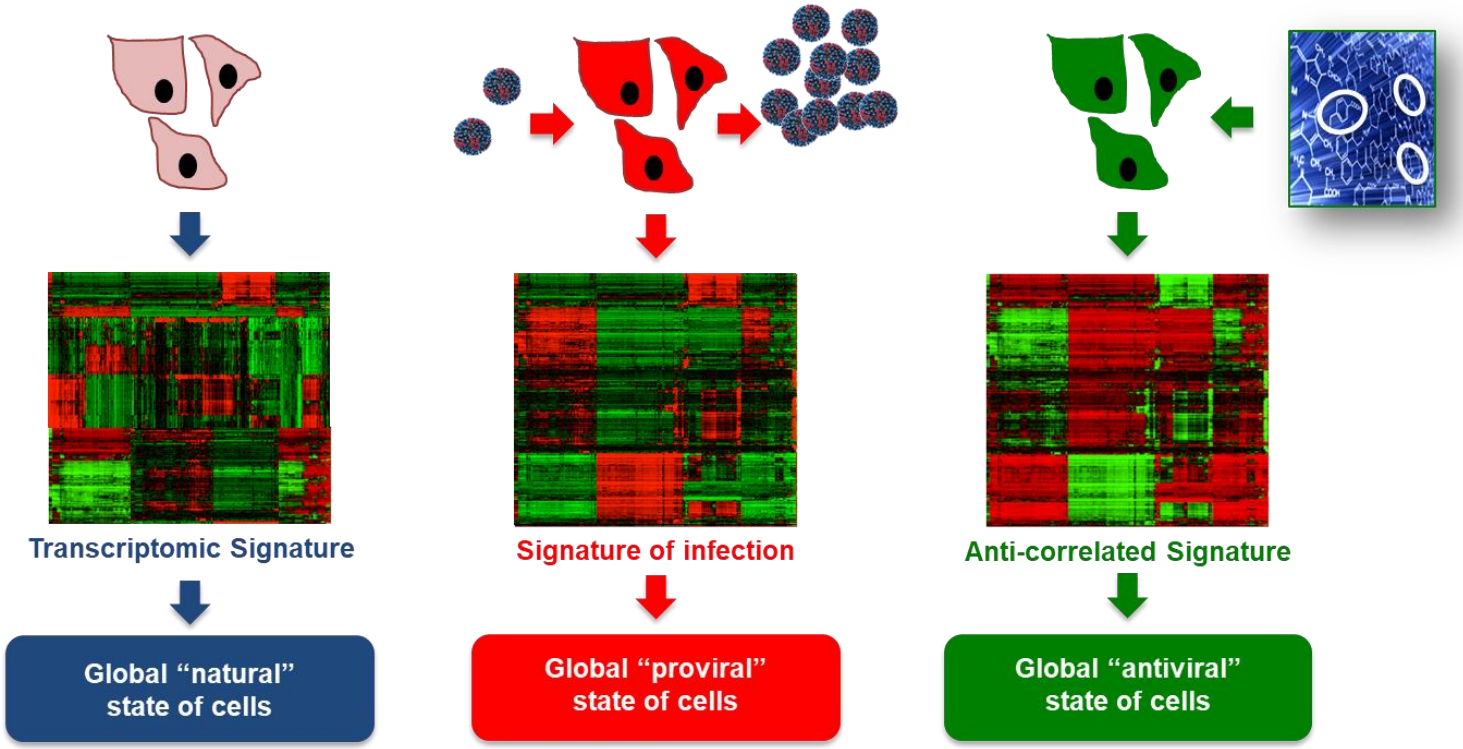



[1] Josset et al., PLoS One 2010 / Terrier et al., J Gen Virol 2013 / Pizzorno A and Terrier O et al, Front Immunol 2019

# Host-directed antivirals under clinical evaluation

## DILTIAZEM

- Drugs with anti-correlated signatures as potential antiviral candidates

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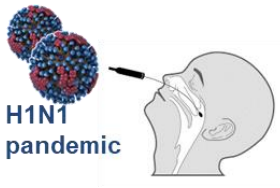
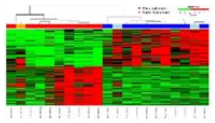
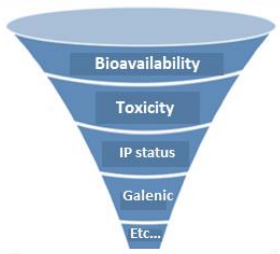
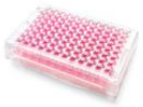
# Host-directed antivirals under clinical evaluation

## DILTIAZEM



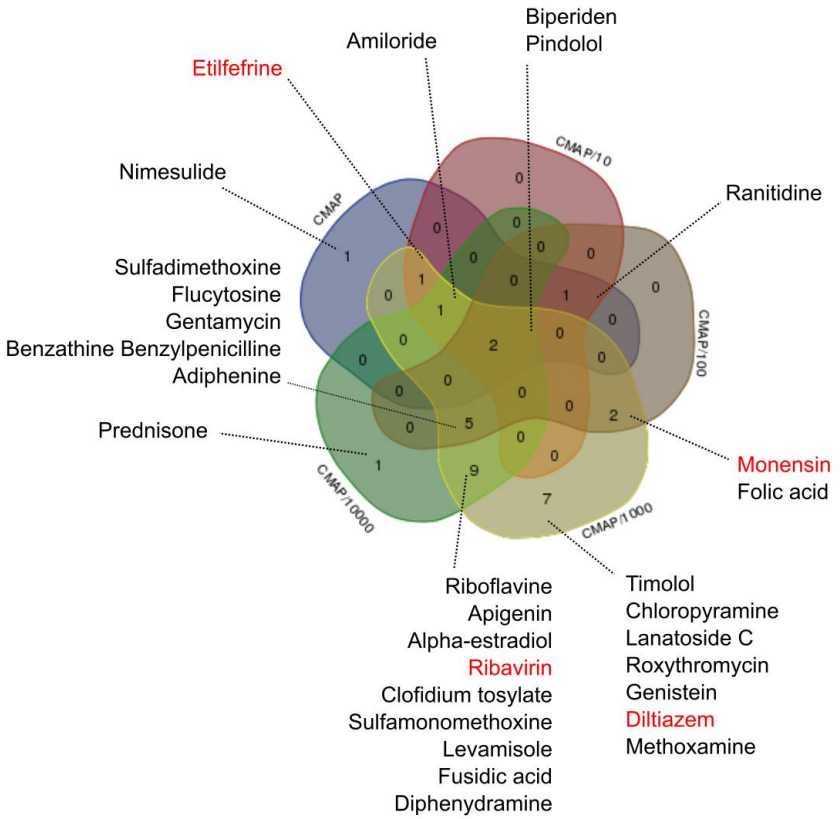
**Clinical samples**
*Paired nasal washes*

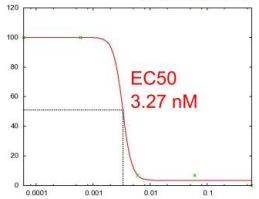
**Physiological signatures of infection**
*1500 modulated genes*

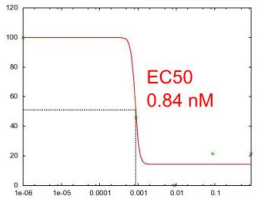
**In silico screening**
*1300 FDA approved drugs*
*7000 expression profiles*

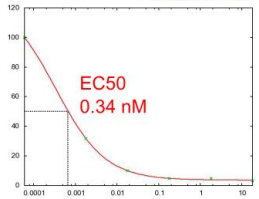
**In silico selection**
*35 compound candidates*

**In vitro validation**
*31/35 compounds*



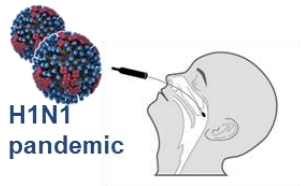



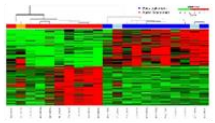



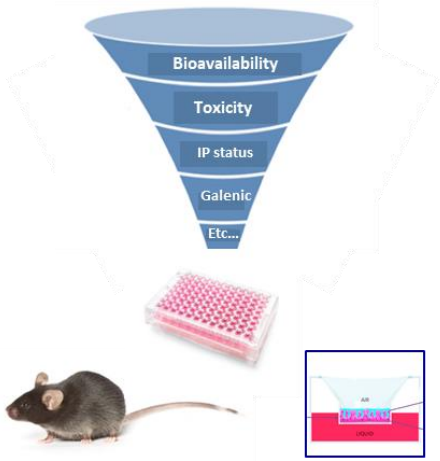

Pizzorno A and Terrier O et al, Front Immunol 2019

# Host-directed antivirals under clinical evaluation

## DILTIAZEM




**Clinical samples**
*Paired nasal washes*

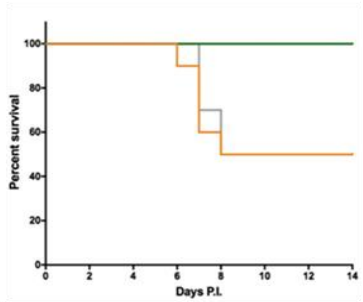
**Physiological signatures of infection**
*1500 modulated genes*

**In silico screening**
*1300 FDA approved drugs*
*7000 expression profiles*

**In silico selection**
*35 compound candidates*

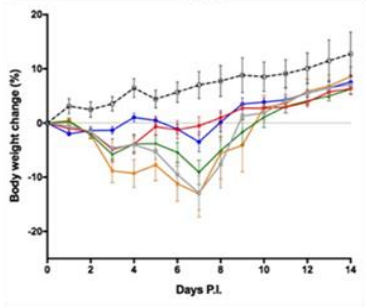
**In vitro validation**
*31/35 compounds*

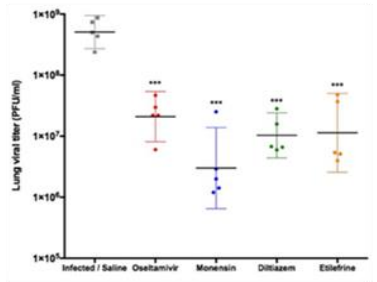
**In vivo and ex-vivo validation**
*2 high potential compounds*
*Synergistic drug combination*

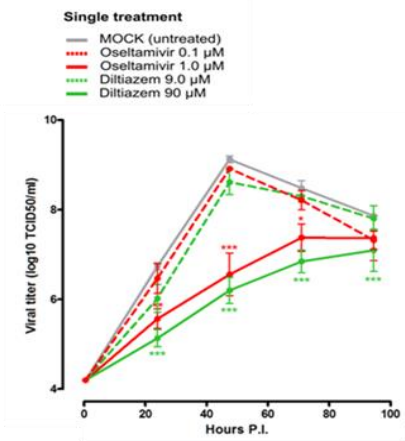


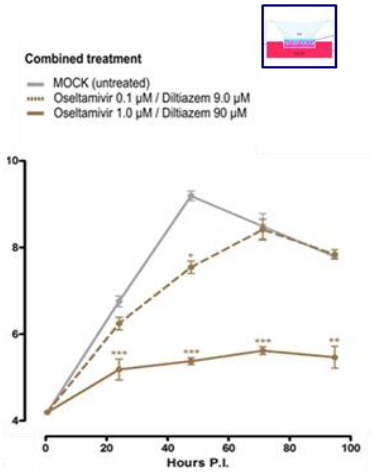







Pizzorno A and Terrier O et al, Front Immunol 2019

# Host-directed antivirals under clinical evaluation

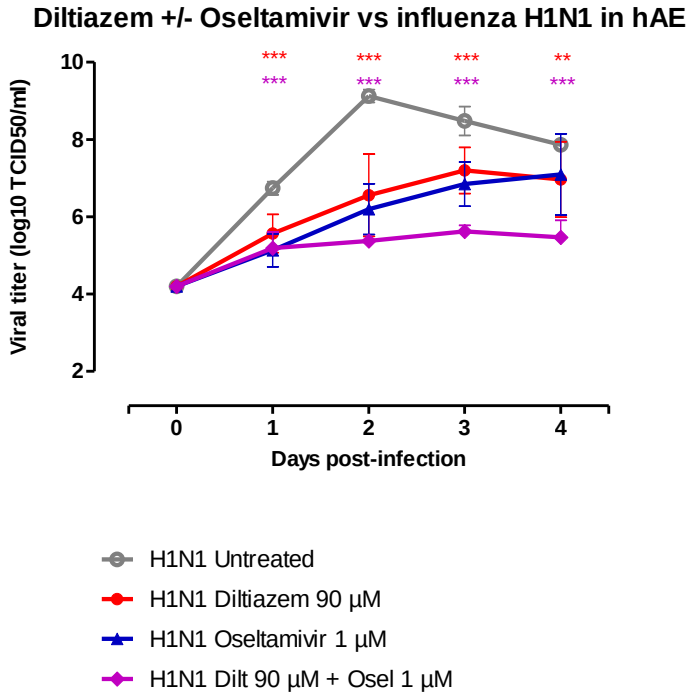
## DILTIAZEM

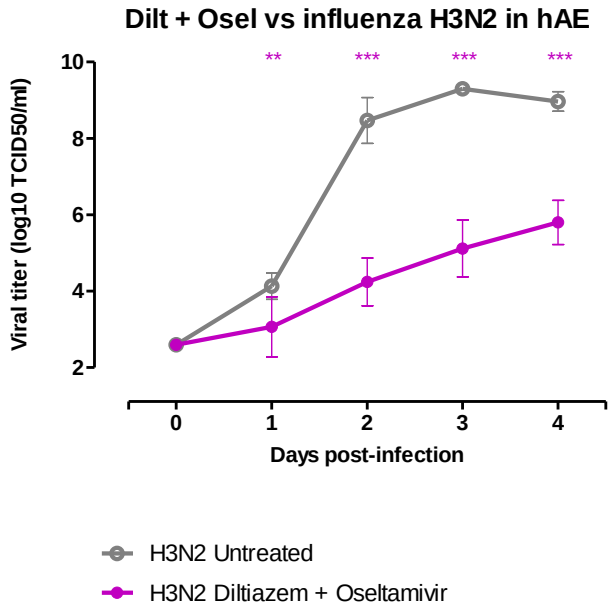
### Efficacy of DIL in hAE:

**Effective against drug-sensitive and drug-resistant influenza A strains**

**2 log reduction in viral titers**

**3-5 log reduction in combination with OSE**



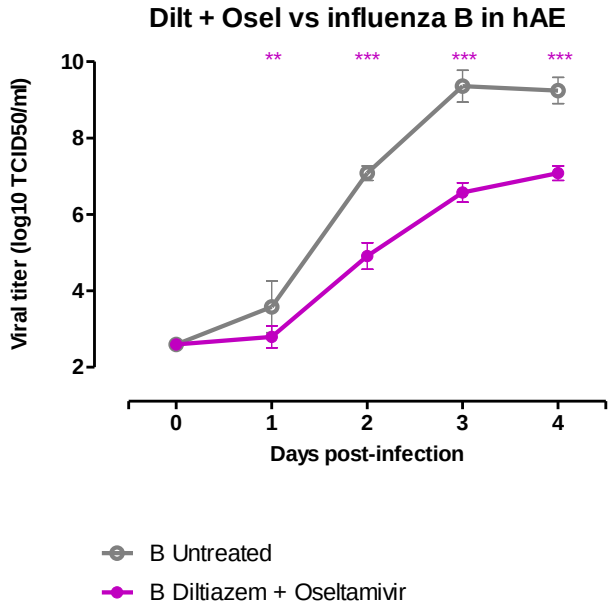




### NCT03212716:

**Randomized Phase 2b trial in adults with severe influenza**

**180 patients: oral 150mg OSE bid x10, 150mg OSE bid x10 + 60mg DIL tid x10**

**Ongoing, results expected Q2 2020**




[1] Pizzorno A and Terrier O et al, Front Immunol 2019 and unpublished data

# Other host-directed antivirals in pre-clinical development

# Other host-directed antivirals in pre-clinical development[1]

**Arbidol:** bioavailable dynamin-2 (host or viral?) entry inhibitor, broad spectrum antiviral activity in animal models and in the clinic (day 4). Approved in Russia and China. Blaising J et al, Antiviral Res 2013

**Verdinexor:** bioavailable selective inhibitor of Exportin 1 (XPO1), effective against different IAV strains in mice and ferrets even after delayed treatment (day 4). Currently in Phase I. Perwitasari O et al, POne 2016

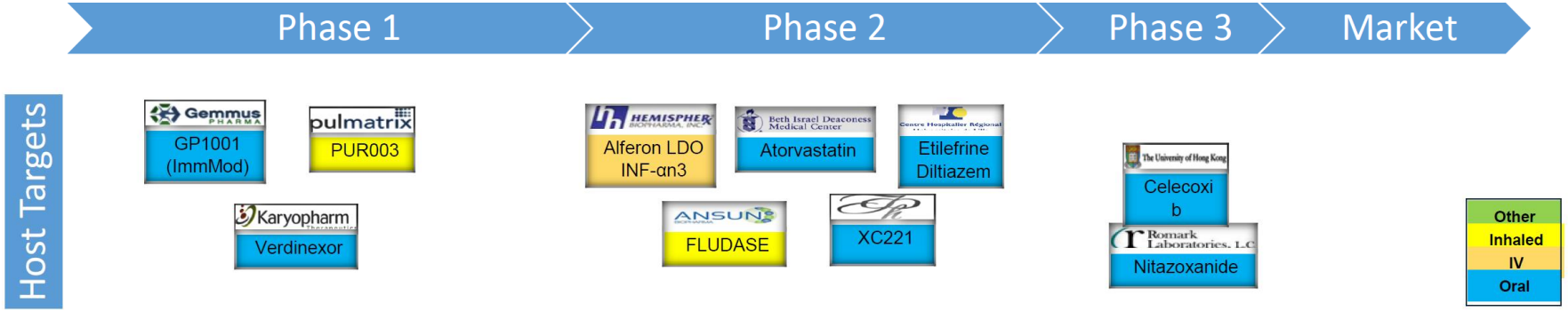
**CI-1040:** orally bioavailable MEK inhibitor, administration 48 hpi protected 60% of IAV-infected mice compared to 0% in the OSE-treated group. Haasbach E et al, Antiviral Res 2017

**Protectin D1:** endogenous lipid of the respiratory tract, administration reduces IAV mRNA cytoplasmic translocation, LVTs and improves survival in mice. Morita M et al, Cell 2013

**SP600125:** bioavailable inhibitor of JNK1/JNK2, reduced viral titers and proinflammatory ck in mice infected with highly-pathogenic IAV. Nacken W et al, Biol Chem 2012

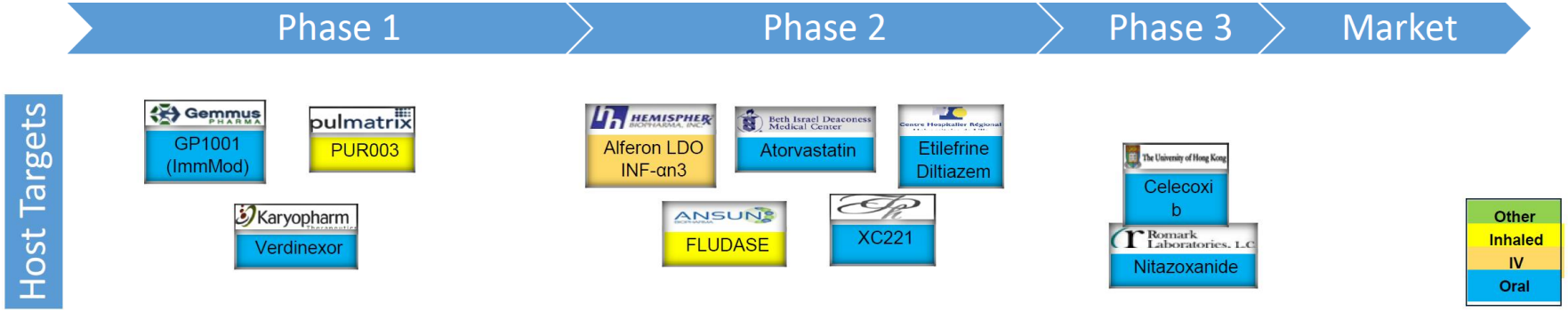
[1] Mostly reviewed in: Yip TF et al, Front Immunol 2018

# Conclusions




Adapted from R. Johnson (BARDA)

# Conclusions




Adapted from R. Johnson (BARDA)

- **Immunomodulators:**
  - **Lower potential as "go-to" treatments than host-directed antivirals**
  - **Interesting option for severe cases** (adjunctive therapies)
  - **Tailored treatments for specific age groups and underlying conditions**

- **Host-directed antivirals:**
  - **Promising option as standalone therapies and in combination with virus-directed approaches**
  - **Focusing on a single host target probably challenging** (redundancy/toxicity)
  - **Interesting repurposed candidates with antiviral & immunoprotective activity** (nitazoxanide, LASAG, diltiazem)

# Moving forward: main R&D challenges yet to be addressed

- **Candidates with solid pre-clinical data but more efficacy data in humans is underscored**
- **Close knowledge gap on the complexity of host-virus interactions and viral pathogenesis**
- **Classic pre-clinical models do not exactly reflect human host-responses** (hAE, lung-on-chip, dirty mice, humanized mice, ferrets, human controlled infections…)
- **Exploit epidemiological/observational data** (hospital admissions, length of stay, mortality…) **for potential repurposing avenues**
- **Improve the design of clinical trials to account for other clinically relevant outcomes/endpoints than viral load**[4]

# Take home message

## Virus-directed vs Host-directed antivirals

# Take home message

## Virus-directed vs Host-directed antivirals: why not both?

| | VIRUS-DIRECTED | HOST-DIRECTED | COMBINATION |
|---|---|---|---|
| Treatment window | *short (0 - 48h)* | *moderate (0 - 96h)* | *moderate (0 - 96h)* |
| Treatment dose | ***low*** | *moderate - high* | ***low - very low*** |
| Potential secondary effects | ***very low*** | *low - moderate* | ***very low - low*** |
| Resistance threshold | *low - moderate* | ***high*** | ***very high*** |
| Broad spectrum potential | *no* | ***yes*** | ***yes*** |
| Potential vs severe cases | *low* | *moderate* | ***moderate - high*** |
| Potential vs emerging strains | *uncertain* | *possible* | *possible* |

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