Antiviral therapy, a lot has been achieved, yet far to go

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University of Leuven, Belgium
www.antivirals.be & www.facebook.com/NeytsLab
What do we have today ....

Herpesvirus

HIV

HBV

HCV

What do we not have today …?

Antivirals against paramyxovirus, enterovirus/rhinovirus, arenavirus, bunyaviridae, coronavirus, flavivirus, alphavirus, norovirus, rabies virus, filovirus, hepatitis E virus....
The Neyts-lab of Virology, Antiviral Drug & Vaccine Research

Our Mission: The development of (i) antiviral strategies against a range of (RNA) viruses and (ii) a game-changing novel vaccine technology platform.
Using cell based/phenotypic antiviral screens

** the needle = a promising hit
# the haystack = the infected cell
Caps-It a robotized lab-in-a-box...

... and a human-out-of-the-box system

Biosafe handling and full containment at all times
Caps-It an automated platform in a BSL3+ environment
Video see www.antivirals.be
Safe import, export and handling of materials containing live pathogens

Chlorine dioxide decontamination

Video see www.antivirals.be
Dengue

Second-most prevalent mosquito-borne infection after malaria.
~360 million infections and ~96 million cases/year.
~ 2/5th of the world's population at risk [WHO]
One hospitalization every minute around the globe

LAHORE: Dengue outbreak in Lahore is taking a serious turn, as cases are pouring in at such an overwhelming rate that hospitals are forced to lay three patients on one bed, Geo News reported.
Potent NS4b targeting pan-serotype inhibitors

DENV-2 hit
Med Chem

Pan-serotype Low nM to pM activity Clinical isolates

DENV NS4B
No human homologue – no homologue of HCV NS4B

97% conserved intra-serotype, 78% conserved inter-serotype

Critical for viral replication
Potent pan-serotype DENV activity
KU Leuven, the Wellcome Trust and Janssen are together joining the fight against Dengue fever (breakbone fever).

Report to the Community 2013

Economic Sustainability

Collaboration in the fight against Dengue fever
Need for pan-flaviviruses antivirals

Japanese encephalitis

~ 50,000 cases/year (30% mortality)

Yellow fever

200,000 cases/year, 30,000 deaths

Zika virus
Chikungunya

www.paho.org  www.who.org
A novel class of CHIKV inhibitors ....

MADTP

<table>
<thead>
<tr>
<th>Virus (Strain)</th>
<th>EC&lt;sub&gt;50&lt;/sub&gt; (µM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>899 (lab)</td>
<td>2.6</td>
</tr>
<tr>
<td>Venturini (Italy 2008)</td>
<td>1.4</td>
</tr>
<tr>
<td>Congo 95 (2011)</td>
<td>0.75</td>
</tr>
<tr>
<td>St Martin (2013)</td>
<td>4.3</td>
</tr>
<tr>
<td>VEEV</td>
<td>6.2</td>
</tr>
</tbody>
</table>

Delang et al., Sci Reports 2016
.... that target viral capping

Resistant CHIKV clones: P34S mutation in NS1
Introduction in WT background confirms resistant phenotype

Decroly et al, Nature Reviews Microbiology 2012

Block formation of m7Gppp-nsP1 and thus capping

Delang et al., Sci Reports 2016
Favipiravir (T-705) protects against CHIKV

Flu inhibitor also active against flavi-, arena-, bunya-, filoviruses

KU LEUVEN
Rhino & enteroviruses

Exacerbations of asthma and COPD
I think I need antibiotics for my col...

IT'S A VIRUS!
ANTIVIRALS

Exploring the role of antiviral drugs before and after eradication

- treatment of immunodeficient people who are excreting poliovirus;
- preventative treatment for people exposed to poliovirus, for example through unintentional laboratory exposure;
- use in communities exposed to circulating vaccine-derived poliovirus (cVDPV) outbreaks in the post-eradication era (likely in conjunction with inactivated polio vaccine).
Entero/rhinovirus capsid binders

Pocapavir (V-073), originally discovered @ Schering-Plough; licensed by ViroDefense Inc.

Websource: ViralZone


Pocapavir (others pleconaril, pirodavir, vapendavir…)

Websource: ViralZone
A novel enterovirus inhibitor with different binding pocket than capsid binders

Pleconaril

CP17

Pleconaril binding pocket

CP17 binding pocket
Tryptophan dendrimers as highly potent inhibitors of EV-A71

Sun et al., submitted
# Novel enterovirus/rhinovirus inhibitors

![KRICT Logo](image)

Korean Research Institute for Chemical Technology

<table>
<thead>
<tr>
<th>Compound</th>
<th>EV71</th>
<th>CVB3</th>
<th>PV1</th>
<th>HRV-2 (A)</th>
<th>HRV-14 (B)</th>
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</thead>
<tbody>
<tr>
<td># 1 (hit)</td>
<td>0.9</td>
<td>0.2</td>
<td>4</td>
<td>&gt;100</td>
<td>&gt;100</td>
</tr>
<tr>
<td># 56</td>
<td>0.01</td>
<td>0.02</td>
<td>0.7</td>
<td>&gt;100</td>
<td>&gt;100</td>
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<tr>
<td># 438</td>
<td>0.008</td>
<td>0.001</td>
<td>0.05</td>
<td>4.3</td>
<td>0.05</td>
</tr>
</tbody>
</table>

EC$_{50}$ in µM

<table>
<thead>
<tr>
<th>Compound # 696</th>
</tr>
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<tbody>
<tr>
<td>HRV-A (19 isolates)</td>
</tr>
<tr>
<td>HRV-B (5 isolates)</td>
</tr>
</tbody>
</table>

EC$_{50}$ in µM
High barrier to resistance and 2C as target

Resistance selection > 20 passages
At least 4 mutations in 2C
Reverse genetics: multiple mutations needed for resistance
No effect on 2C NTPase

Hexameric model of the 2C protein of Echovirus 30

Xia et al., PLoS Pathogens 2015
Highly effective in enterovirus infected mice

**CVB4 Pancreatitis model**

**Histopathology Markers**

- Edema
- Inflammation
- Necrosis

**Viral load**

- Log$_{10}$CCID$_{50}$

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**Lethal CVB4 model in SCID**

- Percent survival
- Days post infection

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**Pancreas**

- CVB4 (TCID$_{50}$/100 mg tissue)
- Days of treatment

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**KU LEUVEN**
(VIRAL) DIARRHEA

4 min flow of the Niagara Falls

~ 4 billion cases of diarrhea worldwide/year (www.who.int)
3 days with each 4 “events” of 200 ml = 9,600,000,000 liter
Antiviral treatment of mouse norovirus infection

**Fecal consistency**

Rocha-Pereira et al., J. Virol, 2013

2′C methylcytidine (2CMC)
Transmission of mouse norovirus

5 infected animals
+
5 non infected sentinels

Survival

Group A (non treated)

Infected mice

Sentinel mice

MDD : 4 d pi

MDD : 8.4 ± 0.5 d pi

Rocha-Pereira et al., J. Antimicrob Chemother (2014)
Prophylaxis with 2CMC prevents transmission

5 infected animals + 5 sentinels (non infected)

Survival

100% survive past 18 d pi

Bedding was replaced at 4 d pi

huNoV replicates in zebrafish larvae
160 people die of rabies every day, says major new study

17 April 2015
A global study on canine rabies, published today (16 April 2015), has found that 160 people die every single day from the disease. The report is the first study to consider the impact in terms of deaths and the economic costs of rabies across all countries. Even though the disease is preventable, the study says that around 59,000 people die every year of rabies transmitted by dogs.
Hepatitis E virus

- Gt 1-2: exclusively human
- Gt 3-4: zoonosis
  - pig, deer,… (worldwide)

Chronic infections [gt 3 (gt 4)]
A mutation in the HEV RdRp of transplant patients “resistant” to ribavirin

G1634R mutation detected in HEV RdRp of several patients after long term ribavirin treatment
The HCV drug sofosbuvir inhibits HEV

Gouttenoire et al., Gastroenterol (2015)
Conclusion

Antivirals still needed against many viral infections

Excellent molecular targets to be further explored such as
- flavivirus NS4B
- enterovirus 2C
- alphavirus nsP1

Broad-spectrum RNA virus inhibitors needed
- pan-genus
- pan-family
- multi-family
  - e.g. PI of picorna & noroviruses
  - T-705-like?
  - nucleoside analogues

Off-label use (e.g. Sofosbuvir against HEV)
THANK YOU

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www.antivirals.be
Join us in Baltimore for the 32nd ICAR!

The 32nd International Conference on Antiviral Research (ICAR), hosted by the International Society for Antiviral Research (ISAR), will take place at the Hyatt Regency, Baltimore, USA. The conference will begin on Sunday, May 12, 2019, and will conclude on Wednesday, May 15, 2019. Check here for the list of invited speakers and their bios.