Experiences with development of antibody-based antiviral drugs

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- from molecule to patient
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Agenda

➢ **Background:** viral infections

➢ **Antiviral mAbs:**
  - approved
  - under development (*based on publicly available data and not a complete list*)

➢ **Clinical pharmacology related opportunities and challenges**
  - Fc-based \( t_{1/2} \) enhancing strategy: in vitro and in vivo
  - mAb PK in patients with organ impairment

➢ **Conclusions**
Background: viral infections

- **CMV** (cytomegalovirus): causes serious disease in immunocompromised patients; some anti-CMV small molecules (SMs) associated with neutropenia or nephrotoxicity

- **HBV** (hepatitis B virus): no functional cure; multiple SMs approved

- **HCV**: virologic cure after treatment with direct-acting antivirals for 8 to 12 weeks

- **HDV**: higher rate of progression than other hepatitis and only occurs in HBV co-infected patients; no approved drug

- **HIV-1** (human immunodeficiency virus-1): no functional cure; ibalizumab and SMs: NRTI (nucleoside reverse transcriptase inhibitor), NNRTI, PI (protease inhibitor), INI (integrase inhibitor), EI (entry inhibitor)
Background: viral infections

➢ **Influenza**: influenza A involved in pandemics; no approved drug for hospitalized patients with influenza infections

➢ **RSV** (respiratory syncytial virus): aerosolized ribavirin approved for treatment but not widely used; **palivizumab** for prevention of RSV in children at high risk

➢ **Others** (clinical efficacy studies challenging, not possible for Smallpox):
  - Ebola, Zika, Dengue, Smallpox, Rabies, etc.
  - If clinical efficacy studies are not ethical/feasible, approval may rely on animal efficacy models.
  - Guidance for Industry: Product Development Under the Animal Rule

*Note: not a complete list for all viral infections*
Antiviral mAbs: approved

- **Synagis® (palivizumab)**
  - Approval year: 1998
  - MOA (mechanism of action): RSV F protein inhibitor
  - Indication: prevention of RSV in pediatric patients at high risk
  - Dose regimen (intramuscular): 15 mg/kg monthly throughout the RSV season (5 doses)

- **Trogarzo® (ibalizumab)**
  - Approval year: 2018
  - MOA: CD4-directed post-attachment HIV-1 inhibitor
  - Indication: treatment of HIV-1 infection in adults with multidrug resistance, in combination with other antiretrovirals
  - Dose regimen (intravenous): a single loading dose of 2,000 mg followed by a maintenance dose of 800 mg every 2 weeks
# Antiviral mAbs: under development

- publicly available data and not a complete list
- does not include products discontinued from development

<table>
<thead>
<tr>
<th>Indication</th>
<th>mAb</th>
<th>MOA</th>
<th>Development Status</th>
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<tr>
<td>HIV-1</td>
<td>3BNC117/3BNC117LS</td>
<td>CD4 binding site of gp120</td>
<td>Phase II/Phase I</td>
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<td>VRC01/VRC01LS</td>
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<td>Phase II</td>
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<td>Phase I</td>
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<td>PGDM1400</td>
<td>V1V2 site of gp120</td>
<td>Phase I</td>
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<td>10-1074</td>
<td>V3 site of gp120</td>
<td>Phase I</td>
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<td></td>
<td>PGT121</td>
<td>V3 site of gp120</td>
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<td>10E8V/10E8VLS</td>
<td>membrane proximal external region (MPER) of gp120</td>
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<td>PRO140</td>
<td><strong>host</strong> CCR5 receptor</td>
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<td>10E8V2.0/iMab (bi-specific)</td>
<td><strong>MPER/host</strong> CD4 binding site</td>
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<tr>
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<td>SAR441236 (tri-specific)</td>
<td>CD4 binding site/MPER/V1V2 site of gp120</td>
<td>Phase I</td>
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Antiviral mAbs: under development

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<td>TCN-032</td>
<td>matrix 2 protein M2e</td>
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<td>RSV</td>
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<td>RSV F protein inhibitor</td>
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<td>ALX-0171 (nanobody, inhalation)</td>
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<td>Ebola</td>
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<td>RAB-1</td>
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<td>approved in India</td>
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Clinical pharmacology related opportunities and challenges

**Fc-based t$_{1/2}$ enhancing strategy: in vitro and in vivo**

- **Fc-based t$_{1/2}$ enhancing strategy:**
  
  A (N434A), AAA (T307A/E380A/N434A), LS (M428L/N434S), QL (T250Q/M428L), YTE (M252Y/S254T/T256E)

- **MEDI8897:**
  
  - Indication: prevention of RSV for all infants (IM, Phase II)
  
  - t$_{1/2}$ enhancing strategy: YTE modification
  
  - **In vivo:**
    
    t$_{1/2}$: 85-117 days in adults; 63-73 days in preterm infants once-per-RSV-season dose

  - **In vitro:**
    
    enhanced neonatal Fc receptor (FcRn) binding at pH 6.0

Clinical pharmacology related opportunities and challenges

**Fc-based $t_{1/2}$ enhancing strategy: in vitro and in vivo**

- Some Fc variants with improved FcRn binding at pH 6.0 in vitro do not exhibit increased $t_{1/2}$ in vivo.

- The $t_{1/2}$ enhancing effect depends on both increased FcRn binding at pH 6.0 and minimal effect on FcRn binding at pH 7.4:
  - underestimation of binding effect at pH 7.4
  - affinity threshold (KD: 860 nM) at pH 7.4 determining IgG recycling efficiency
  - increased FcRn binding at pH 7.4 beyond the threshold offsetting the benefits of increased binding at pH 6.0

*Ref: J Biol Chem. 2015, 13, 290, 4282*
Clinical pharmacology related opportunities and challenges

mAb PK in patients with organ impairment

- Renal impairment:
  FDA guidance: the clearance of therapeutic proteins (TPs) with MW<69 kDa may be affected by renal impairment (mAb MW: ~ 150 kDa)

- Hepatic impairment (HI):
  - FDA or EMA guidance: no information for biologics
  - 2013 paper by FDA researchers – Are HI studies necessary for TPs?
    7 TPs (only 3 mAbs) with HI information
    Results inconclusive due to limited data
    Ref: Clin Ther. 2013, 35, 1444

  - New research – Does HI affect PK of mAbs? (TPs with HI data after 2013)
    Almost no data for severe HI (n=0 or 1 for all)
    Limited data for moderate HI (4 mAbs/2 antibody-drug conjugates [ADCs] with n≥5)
    Sufficient data for mild HI (≈ 20 mAbs with n=tens to hundreds)
    Research team: Qin Sun, Shirley Seo, Simbarashe Zvada, Chao Liu, Kellie Reynolds
Clinical pharmacology related opportunities and challenges

mAb PK in patients with organ impairment

- **Hepatic impairment (HI):**
  - Significant exposure decrease for several mAbs or ADCs (mAb part):
    - *Ado-trastuzumab emtansine ADC*: ↓40%/70% in mild/moderate HI
    - *Evolocumab*: ↓40%/50% in mild/moderate HI
    - *Brentuximab vedotin ADC*: ↓35% in moderate HI (n=1 for mild/severe HI)
  - Trend for AUC decrease/lower albumin level associated with lower exposure for additional mAbs
  - Potential mechanisms:
    - factors affecting FcRn binding (endogenous IgG level), target-mediated drug disposition (TMDD), FcγR binding, etc.
  - HI may impact the disposition of mAbs (or ADCs [mAb part])
  - Additional data are needed, particularly for moderate/severe HI
Conclusions

➤ Antiviral mAbs:
  generally safe, long half-life (up to 3 to 4 months), less frequent dosing, good neutralization potency/breadth, increased resistance barrier (bi-, tri-, or multi-domain mAbs), minimal DDI concern

➤ Multiple clinical pharmacology related challenges:

- Fc-based t_{1/2} enhancing:
  balance FcRn binding at both pH 6.0 and 7.4
  no compromised efficacy and no increased immunogenicity

- mAb dose selection:
  Specific population: patients with hepatic impairment; pediatric patients; patients with different levels of viral load/target expression or immune deficiency

  Dose level/ratio for combination therapy (e.g., anti-HIV mAbs)

  Inhaled mAbs (e.g., anti-flu or anti-RSV) with minimal systemic exposure (PK/PD correlation challenging/infeasible)
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