Monoclonal Antibodies for Influenza Prevention, Therapy, or Vaccine Antigen Design

2018 Global Vaccine and Immunization Research Forum (GVIRF)

Workshop 9 – Antibody Mediated Prevention

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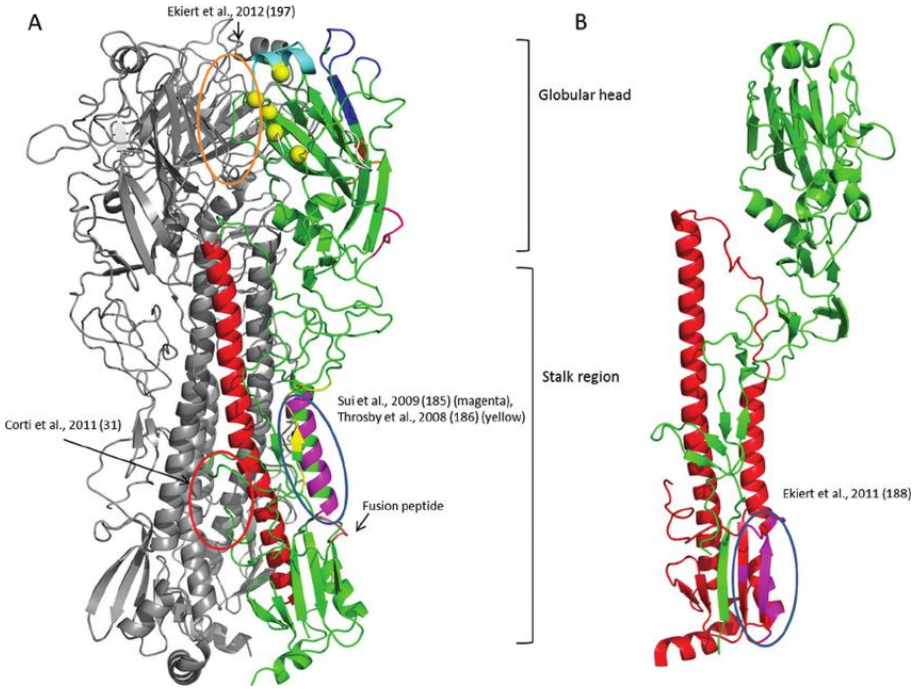
Outline

- Mechanisms of antibody-mediated protection against influenza
- Potential antigen targets
- Utility of mAbs → potential indications
- The pipeline
- Advancing development → controlled human challenge studies
- Delivery to the respiratory tract by inhalation

Mechanisms of Antibody-Mediated Protection and Targets

- Upper vs lower respiratory tract immunoglobulin
- Virus neutralization by inhibition of virus entry (binding or fusion)
- Reduction of virus spread by inhibition of virus release
- Acceleration of recovery by reduction of virus load via FcR-mediated cytolysis (ADCC) or phagocytosis (ADCP)

- Broadly conserved targets expressed on influenza viruses type A and/or type B
  - Virus glycoprotein HA (stalk domain): group 1, group 2, or pan-A
  - Virus glycoprotein NA
  - Virus matrix protein 2 ectodomain (m2e)



Utility of Broadly Protective mAbs

- Therapy of severe influenza alone or in combination with an antiviral
- Prophylaxis if cost is reduced and half-life is extended
  - Particularly when vaccination is infeasible or ineffective, such as during an advancing pandemic, for health-care workers or others at high risk
- For vaccine antigen discovery
  - Pre-clinical studies
  - Human challenge studies if there is an appropriate model

mAb Pipeline – Clinical Stage Candidates

mAb	Binding to	Company	Trials (latest stage)	NCT (clinicaltrials.gov) – active clinical programs
CR6162	Group 1 HA stalk	Janssen	Ph 2 (H1N1 challenge)	NCT02371668 recruiting (N=200 RCT for 1D post challenge Rx with 50 mg/Kg)
CR8020	Group 2 HA stalk	Janssen	Ph 2 (H3N2 challenge)	NCT01756950 completed (N=22 RCT, pre-challenge infusion 15mg/Kg →NoGo)
MHAA4549A	Influenza A stalk	Genentech	Ph 2 (H3N2 challenge)	NCT01980966 completed (N=100 RCT, infusion of 400-3600mg iv 24-36h post-challenge)
MEDI8852	Influenza A stalk	MedImmune	Ph 2 (safety, disease sx, virus shedding)	NCT 02603952 completed (N=375 RCT for RX ± oseltamivir of influenza A ≤5 days of sx)
VIS410	Influenza A stalk	Visterra	Ph2	NCT02989194 completed (N=150 RCT for Rx [low, hi dose] of uncomplicated influenza A ≤3 days of sx) NCT03040141 recruiting (N=390 RCT for RX ± oseltamivir of hospitalized influenza A)
CT-P27	Influenza A stalk	Celltrion	Ph 2 (challenge)	NCT02071914 unknown status since 2014
TCN-032	M2e	Theraclone	Ph 2 (H3N2 challenge)	NCT01719874 completed

MHAA4549A Treatment of H3N2 Infection (Human Challenge Model)

- N=100 healthy adults challenged with A/Wisconsin/67/2005 (H3N2)
- Treated 24-36h later with:
  - mAb 400mg or mAb 1200mg or 3600mg, or placebo, or oseltamivir
- Results
  - mAb 3600mg significantly reduced the viral burden relative to placebo, by the area under the curve (AUC) of nasopharyngeal virus infection, quantified using quantitative PCR (98%) and 50% tissue culture infective dose (TCID50) (100%) assays
  - Treatment also reduced peak viral load, duration of viral shedding, influenza symptom scores, mucus weight, and inflammatory biomarkers
  - Serum PK was linear, half-life of ~23 days.
  - No subjects developed anti-drug antibodies; mAb was well-tolerated
- Status – asset not one of 46 mAbs listed on Genentech clinical stage pipeline

Mcbride, Antimicrob Agents Chemother. 2017 doi: 10.1128/AAC.01154-17. Print 2017 Nov

VIS410 Treatment of Uncomplicated Influenza A

- Prior study confirmed administration of mAb 24h post-challenge with H1N1pdm09 virus reduced NP-shedding by 92 % (AUC) and peak NP-virus load by 2.2 log (both by $TCID_{50}$)
- Ph 2a study start: Dec 2016, study supported by a contract with BARDA
- Adults (18-65) at 54 sites (US, Europe, S Africa) with ≤3 days of illness
- Randomized:
  - mAb (single low dose)
  - mAb (single high dose)
  - Placebo
- Outcome measures
  - 1◦ - safety
  - 2◦ - Influenza PROs (incidence, severity, duration), virus in NP (AUC), peak virus load in NP, duration of virus shedding in NP
- Completed Nov 2017→ results not public but apparently supportive of beginning a Ph 2b study in Jan 2018

VIS410 Treatment ± Oseltamivir of Hospitalized Influenza A Requiring O_2

- Ph 2b study start: Jan 2018
- Adults at 68 hospitals (US, Canada, Europe, S Africa) with ≤5 days of illness
- Randomized:
  - mAb (single low dose) + oseltamivir
  - mAb (single high dose) + oseltamivir
  - Oseltamivir
- Efficacy measures
  - 1◦ - time to cessation of O_2 support, i.e. PsO_2 >92% on room air x8h
  - 2◦ - peak virus load in NP, duration of virus shedding in NP, time to normalization of 4/5 vital signs, time to cessation of ventilator support, time to resumption of nl activities, time to alleviation of influenza sx, % with influenza complications
- Visterra granted Fast Track status for VIS410 by FDA in 2017

TCN-032 Treatment of H3N2 Infection (Human Challenge Model)

- Anti-m2e mAb binds to virus-infected host cells, can reduce virus replication by interfering with virus budding, by complement-dependent cytotoxicity, by antibody-dependent cell-mediated cytotoxicity (ADCC), or by FcR mediated phagocytosis of ab-coated free virus
- N=61 healthy adults challenged with A/Wisconsin/67/2005 (H3N2)
- Treated 24h later with:
  - mAb 40mg/Kg or placebo
- Results of mAb treatment:
  - Did not meet 1◦ obj to reduce the proportion of subjects developing any grade ≥2 influenza symptom or fever (35% vs 48%, P=0.14)
  - 35% reduction (P = .047) in median total symptom area under the curve (days 1–7) and 2.2 log reduction in median viral load area under the curve (days 2–7) by quantitative polymerase chain reaction (P = .09) compared with placebo-treated subjects
- Status: As of 2014, seeking a development partner
  - (http://www.theraclone-sciences.com/pdf/Theraclone-Corporate-Overview_2014-05-04.pdf)

Ramos, J Infect Disease 2015 doi.org/10.1093.infdis/jiu539

Anti-Neuraminidase, a New Target

- 5 anti-NA mAbs (mouse) that demonstrate broad binding, neuraminidase inhibition, and ADCC *in vitro* [1]
- All protect mice against lethal infection when administered 24 or 48h post challenge with influenza B viruses belonging to both HA lineages and spanning >70 years of antigenic drift
- In the mouse model, one dose of antibody 1F2 was more protective than the current standard of treatment, oseltamivir, given twice daily for six days
- No anti-NAs are listed as being in clinical development → a promising target for therapeutic indication, as anti-NA is correlated with reduction of sx severity in natural and experimental infection[2]

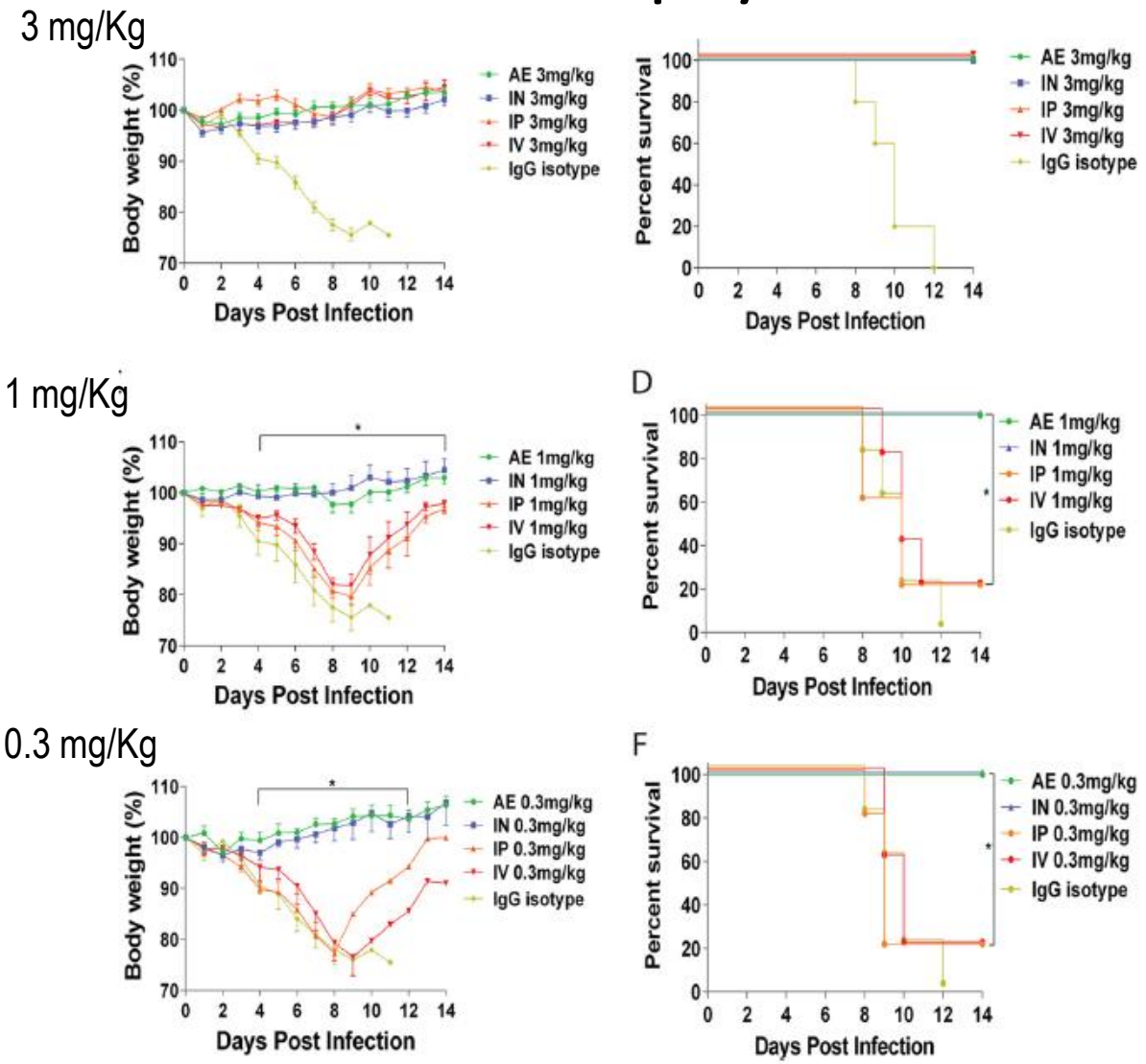
[1] Wohlbold, Nat Microbiol 2017 doi: 10.1038/s41564-017-0011-8

[2] Memoli, mBio 2016 doi: 10.1128/mBio.00417-16.

Improving Human Challenge Studies for Influenza Countermeasures

- Current models administer virus intra-nasally at high dose to subjects screened to have low or absent HI antibodies to the challenge virus
  - Low rates of susceptibility
  - Infection is limited to upper respiratory tract unlike in natural disease
  - Despite large doses, disease signs are minimal, fever is rare, and resp function is unaffected
- The 1◦ effects of mAb treatment are assessed by measures of virus shedding → not fully predictive of clinical benefit
- BMGF is convening a meeting at the end of May to discuss the path forward to improving the influenza challenge model
  - To invigorate development of universal influenza vaccines
  - A by-product could be an improved model to evaluate anti-influenza mAbs

mAb Delivery to the Respiratory Tract by Inhalation More Effective for Prophylaxis than Parenteral Route



- 10-fold reduction of 6F1 (anti-HA stalk group 1 mAb) was effective in preventing weight loss and death in mice treated with mAb by aerosol or i.n. and then challenged 2h with $5LD_{50}$ of H1N1pdm09
- Could be a dose-sparing (lower cost) approach to provide protection or interrupt transmission w/ a broadly reactive extended half-life anti-influenza A mAb
  - For HCWs in an advancing pandemic?
  - For LMIC if a low cost battery-operated nebulizer can be manufactured

Leyva-Grada et al, Antimicrob Agents Chemo 2015

Summary

- Broadly protective mAbs binding to the HA stalk are candidate countermeasures for therapy and prophylaxis of influenza
- Several are in active clinical development: most advanced is VIS410
  - Further development plans for Genentech's MHAA4549A and MedImmune's MEDI8852 are uncertain (not disclosed)
- All of these mAbs have been evaluated in human challenge models with a confirmed effect on virus NP shedding when administered h post-challenge
- The clinical relevance of reduced virus shedding 24h post-treatment remains uncertain → an improved human challenge system that accurately modeled human disease would invigorate the field
- Anti-NA mAbs also have the potential to be broadly protective → a combo of broadly protective anti-HA and anti-NA mAb may be more effective for therapy and prophylaxis
- Intravenous delivery is inefficient for delivery of a mAb to the respiratory epithelium → there may be advantages in aerosol delivery via inhalation