Will antibody-based anti-infective therapies save conventional treatment failures?

---Opportunities and challenges of development of antibody-based anti-infective therapies

2019 ASCPT Annual Meeting
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Why do We Need New Anti-infective Therapies?

• Emerging drug resistance
  • Carbapenem resistance
  • HIV drug resistance has increased from 11% to 29% since early 2000

• Absence of new antibiotics
  • Clinical failure in MDR (Multi-drug resistance)
  • Growing reliance on older and more toxic drugs (e.g. colistin)
  • No new class of Gram-negative small antibiotic has been produced in the last 50 years

• Two public workshops on non-traditional antibiotics held by DUKE university and the FDA in 2018

Apocalypse Pig: The Last Antibiotic Begins to Fail

McKenna, National Geographic 2015
Antibody-based Anti-infective Therapies is NOT New

**Challenges**
- Standardization
- Batch variability
- Patient safety
- Potential transmission of infectious hazards
- Supply
- Access

**Box 1: Indications for blood-derived antibodies for infectious diseases with a current American or European Union market authorization**
- Anthrax: treatment of Inhaled anthrax
- Botulism: treatment of botulism
- *Clostridium botulinum*: treatment of infant botulism caused by type A or B *C. botulinum* in patients < 1 year
- *Cytomegalovirus*: prophylaxis of cytomegalovirus disease associated with transplantation of kidney, lung, liver, pancreas and heart
- *Diphtheria*: treatment of diphtheria and rarely as prophylactic of diphtheria in asymptomatic, non-immunized individuals who have been exposed
- *Hepatitis A*: protection from hepatitis A in household and other close contacts
- *Hepatitis B*: prevention of Hepatitis B recurrence following liver transplantation; treatment of acute exposure to Hepatitis B-containing blood, sexual exposure to infected persons, infants born to infected mothers and household exposure to persons with acute infection
- *Hepatitis C*: Prevention of recurrent hepatitis C virus-induced liver disease in liver transplant recipients
- Measles: postexposure prophylaxis for suspected measles in unvaccinated persons
- Rabies: postexposure prophylaxis to rabies category III exposure (i.e. single or multiple transdermal bites or scratches, contamination of mucous membrane with saliva from licks, exposure to bat bites or scratches)
- *Rubella*: prophylaxis of rubella to exposed individuals in early pregnancy
- *Staphylococcus aureus*: treatment of *S. aureus* bacteraemia
- *Tetanus*: immediate prophylaxis after tetanus prone injuries in patients not adequately vaccinated, with unknown immunization status, severe deficiency in antibody production or vaccinated patients with high risk wounds
- *Vaccinia*: prevention or treatment of vaccinia/smallpox
- Treatment and/or modification of conditions which are complications resulting from smallpox vaccination
- *Varicella*: prophylaxis against varicella zoster virus infection in at-risk exposed patients

**Emil Adolf von Behring**
- The founder of serum therapy
- Discovery of diphtheria antitoxin serum in 1890 with Shibasaburo Kitasato
- First to be honored by the Nobel Prize for Medicine in 1901

https://www.nobelprize.org/prizes/medicine/1901/behring/facts/
Sparrow E et al., 2017
Monoclonal Antibody for Infectious Disease

- There are five mAbs approved for infectious indications by the FDA to date
- At least 38 mAb products in active clinical development for 14 infectious diseases

1975
The Birth of mAbs

1985
First US approvals

1990
OKT3 First approved mAb

1995
Palivizumab (RSV)

2000
Raxibacumab (anthrax)

2005
Obiltoxaximab (anthrax)
Bezlotoxumab (prevention of recurrence of C. diff infections)

2010
Ibalizumab (multidrug-resistant HIV-1)

2015

2020

1 as of November 2016, Sparrow E et al, 2017
Opportunities and Challenges for Monoclonal Antibodies for Infectious Diseases

Opportunities

• Could have a wide range of biological targets (membrane protein, toxin, immune modulator and etc.)
• New modalities (antibody-antibiotics conjugates, bispecific Abs and etc.)
• Mitigate resistance threat
  • Targeting highly conserved epitopes
  • Using antibody cocktails containing multiple mAbs
  • A single product to target multiple pathogens
• Long half-life for prophylaxis and/or more convenience dosing regime for treatment

Challenges

• PK of mAbs may be different in patients vs healthy subjects
• PD biomarkers to support dose selection in Phase 2/3 studies
• Technical barriers
  • Target/biomarker selection
  • Rapid point-of-care of diagnostics
  • Meaningful translation from preclinical to clinical
• Pathogen escape
• Alternative regulatory pathways
  • Novel clinical study design

Sparrow E et al., 2017; Pelferne E et al, 2019
Session Objectives

- Identify the opportunities and challenges in the development of antibody-based anti-infective therapies

- Initiate discussion about novel and feasible strategies to help solve the issues and accelerate the development process
Agenda

• Opening remark
  • Dr. Rong Deng (Genentech)
  • Dr. Yang He (Jaco Biopharmaceuticals)

• PK/PD challenges of developing Antibody-based anti-infective treatment
  • Dr. Joseph Balthasar (University at Buffalo – SUNY), 15 minutes

• A clinician’s perspective – The opportunity and challenges of development of antibody-based anti-infective treatment
  • Dr. Joshua Galanter (Genentech), 15 minutes

• Experiences with development of antibody-based anti-viral drugs
  • Dr. Qin Sun (FDA), 15 minutes

• Opportunities and challenges in the development of monoclonal antibodies as an integrated and layered medical countermeasure
  • Dr. Jeffrey Froude (Defense Threat Reduction Agency, 15 minutes)

• Panel discussion (25 minutes)
Questions for Panel Discussion

• Is the concept of PKPD, similar to the small molecules anti-infective, suitable to support dose selection in the development of antibody-based anti-infective? If not, what strategy should we use for dose selection?
  • Depending on MOA
  • Meaningful translation from preclinical to clinical
  • PK and /or PK/PD at site of action
  • PK in healthy volunteers vs patients

• Clinical study design
  • Patient population selection
  • Meaningful clinical endpoints

• Scientific, regulatory and economic barriers