Molecules Against Novel (non-RBD) Targets

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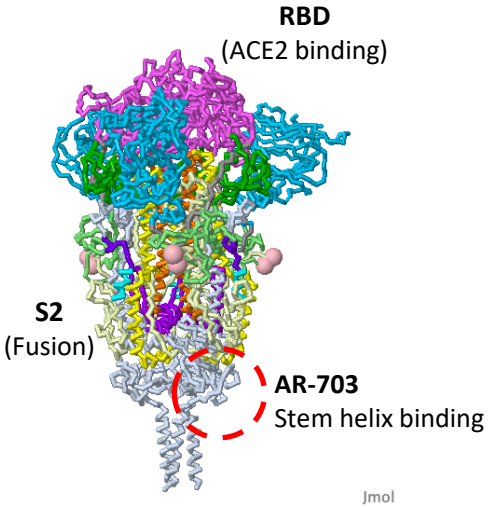
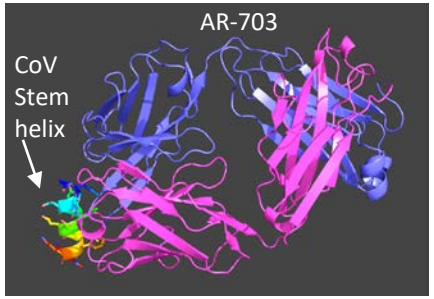
Sustaining mAb Efficacy Against Future Variants

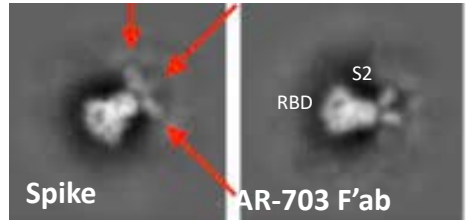
- Monoclonal antibodies have demonstrated efficacy and safety for both prophylaxis and treatment of SARS-CoV-2 infection
- Emergence of novel SARS-CoV-2 variants continues to pose challenges, requiring multiple strategies for developing new mAbs to keep pace with the new VOCs
  - New RBD mAbs targeting the new variants
  - Non-RBD mAbs targets
    - Different mechanism of action, e.g. viral fusion
    - Conserved epitope(s), enabling broader coverage of variants
    - Synergistic with RBD mAbs
    - Transmission blockage

Sustaining mAb Efficacy Against Future Variants

- Pan-coronavirus mAb targeting conserved Spike protein stem helix ('S2' domain)
  - New mechanism of action (viral fusion), critical for host entry
  - Conserved epitope, enable effectiveness against all VOC's, more future-proof against SARS-CoV-2 variants
  - Effective against SARS, MERS, seasonal human coronaviruses
- Synergistic with RBD mAbs
- Efficacious in ACE2, hamster, non-human primate (NHP) challenge models
- Long-acting, half-life extended for prophylaxis
- Inhaled formulation for treatment & transmission blockage

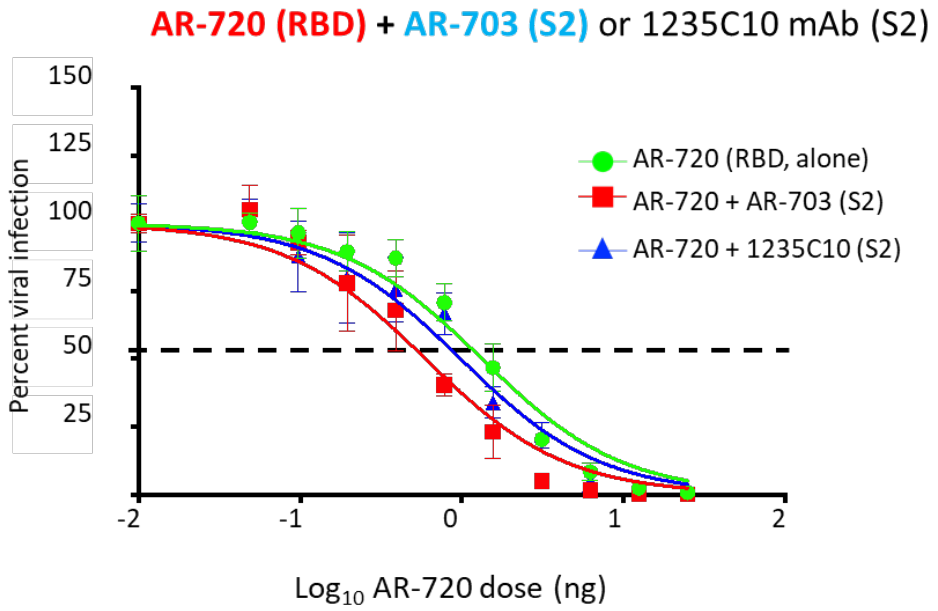






Piepenbrink, M et al. 2021 Cell Rep. Med. 16;2(3):100218:e1010691.

Synergy Observed when S2 mAb is Used with RBD mAb



	Individual mAbs (Wuhan)	Cocktail mixture (Wuhan)
(RBD)	NT_{50} AR-720 = 13.4 ng/mL	NT_{50} AR-720 **+** AR-703 = 5.9 ng/mL (AR-720)
(S2)	NT_{50} AR-703 = 406 ng/mL	= 240 ng/mL (AR-703)
(S2)	NT_{50} 1235C10 = 18,450 ng/mL)	NT_{50} AR-720 **+** 1235C10 = 9.8ng/mL (AR-720)
		= 1,970 ng/mL (1235C10)

Piepenbrink, M et al. 2022 PLoS Pathog. 21;18(7)

Novel Target Molecules: Challenges and Potential Solutions

- **Preclinical Tox Safety**
  - Number of animal species: Apply similar preclinical toxicology requirement of a single animal species for fully human mAbs not binding to a human host target, regardless of route of administration (systemic or inhaled)

- **Proof of efficacy**
  - For non-RBD targets, animal efficacy data (e.g. NHP) should be acceptable, as in-vitro neutralization titers may not be as predictive of in-vivo potency as for RBD directed mAbs
    - Prophylaxis: EC90 from animals as correlate of human efficacy and basis for human dose
    - Treatment: Animal (e.g. NHP) efficacy data
  - Human safety and PK study should be acceptable with animal efficacy data package

- **Combination Rule**
  - Non-RBD (and RBD) mAbs should not be subjected to combination rule with supportive preclinical data