Poster 130

Broad and Potent In Vitro Neutralization of SARS-CoV-2 Variants by ADG20, a Half-Life–Extended Monoclonal Antibody in Development for the Prevention and Treatment of COVID-19

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INTRODUCTION

- ADG20 is a fully human IgG1 monoclonal antibody (mAb) that targets a highly conserved epitope on the receptor-binding domain (RBD) of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike protein[1]
- The Fc region of ADG20 has been modified to provide an extended half-life[1]
- ADG20 was derived from a survivor of the 2003 SARS-CoV epidemic and shows potent and broad in vitro neutralizing activity against SARS-CoV-2 and other human angiotensin-converting enzyme 2 (ACE2)–targeting SARS-like CoVs with pandemic potential[1-4]
- The spread of SARS-CoV-2 and continued emergence of variants represent ongoing global public health issues[5,6]
- Notably, some variants of concern (VOCs) exhibit enhanced transmissibility and/or evasion from neutralization by vaccine-elicited responses and some mAb therapies[2,3,5-9]
- There is an unmet need for additional prevention and treatment options that have the potential to maintain activity against emerging SARS-CoV-2 variants, as well as additional SARS-like viruses with outbreak potential
- Here, we report on the breadth of binding of ADG20 against a diverse panel of circulating SARS-CoV-2 variants, as well as additional SARS-like viruses
- In addition, we report on the in vitro neutralizing potency of ADG20 against a panel of circulating SARS-CoV-2 variants, including VOCs with reduced susceptibility to mAb products currently available under emergency use or in late-stage development

METHODS

In vitro binding affinity

- Binding affinities of ADG20 and other anti–SARS-CoV-2 mAbs were determined via flow cytometric analysis of antibody binding to yeast surface-expressed RBD[1]
  - 17 representative sarbecoviruses, grouped by phylogenetic lineages, were selected
  - Apparent binding affinity (K_D^{App}) values were determined following nonlinear regression fitting of binding titration curves
- mAbs were tested for binding to yeast-displayed RBD variants containing single mutations detected at high frequencies in the Global Initiative on Sharing All Influenza Data (GISAID) database in October 2020
  - Binding percentage was calculated relative to the wild-type (WT) SARS-CoV-2 RBD and assessed at the respective K_D^{App} concentration for the WT RBD

In vitro neutralizing activity

- Neutralizing activity against authentic SARS-CoV-2 virus variants, including Victoria (early Wuhan-like isolate), Alpha/B.1.1.7, Beta/B.1.351, Gamma/P.1, and Delta/B.1.617.2, was assessed in a focus reduction neutralization test using Vero cells[2,3]
  - Several mAbs, either available under emergency use authorization or in late-stage clinical development, were included as comparators
  - Half-maximal inhibitory concentration (IC_{50}) values were determined using nonlinear regression curve fitting
- Eighty-four SARS-CoV-2 variants containing single or double amino acid mutations in the spike protein and full sets of mutations observed in variants of interest and VOCs were assessed in a lentiviral pseudovirus assay[10]
  - D614G, an early variant of SARS-CoV-2, was used as a reference to calculate the IC_{50} fold change in neutralizing activity for ADG20

RESULTS

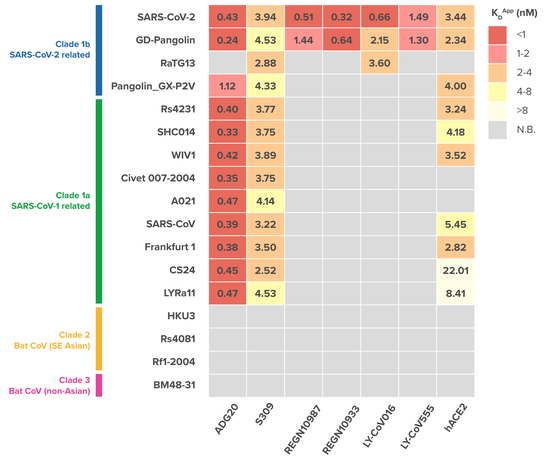
Binding affinity and breadth of ADG20

- ADG20 bound with high affinity to RBDs of 12/13 clade 1 SARS-like-CoVs, with K_D^{APP} values ranging from 0.24 to 1.12 nM (**Figure 1**)
- ADG20 maintained high binding affinity (>50% of WT RBD) to all circulating SARS-CoV-2 variants tested, including Alpha/B.1.1.7, Beta/B.1.351, and Gamma/P.1 (**Figure 2**)

In vitro neutralizing activity of ADG20

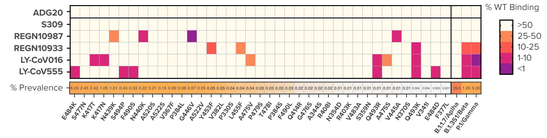
- ADG20 demonstrated potent activity in an authentic neutralization assay against all SARS-CoV-2 VOCs tested to date, including Alpha/B.1.1.7, Beta/B.1.351, Gamma/P.1, and Delta/B.1.617.2 (**Figure 3**)
  - IC_{50} values for ADG20 (ranging from 0.004 to 0.010) were comparable to or lower than those observed for other clinical-stage or emergency authorized antibodies
- ADG20 retained in vitro neutralizing activity within 0.4- to 5.1-fold relative to the reference D614G strain for all pseudovirus variants tested, including the newly emerging Delta plus/AY.1, Lambda/C.37, and Mu/B.1.621 variants (**Figure 4A**) and variants with single-/double-spike mutations (**Figure 4B**)

Figure 1. ADG20 binds with high affinity to SARS-like-CoV RBDs



S309, the parent antibody of VIR-7831 (sotrovimab); REGN10987 (imdevimab); REGN10933 (casirivimab); LY-CoV016 (etesevimab); LY-CoV555 (bamlanivimab).
hACE2, human ACE2; N.B., non-binding.

Figure 2. ADG20 maintains binding activity against commonly circulating SARS-CoV-2 variants



S309, the parent antibody of VIR-7831 (sotrovimab); REGN10987 (imdevimab); REGN10933 (casirivimab); LY-CoV016 (etesevimab); LY-CoV555 (bamlanivimab).
% Prevalence: SARS-CoV-2 variant frequencies (percentage of total sequences) as of August 17, 2021 in the GISAID database.

Figure 3. ADG20 potently neutralizes authentic SARS-CoV-2 VOCs

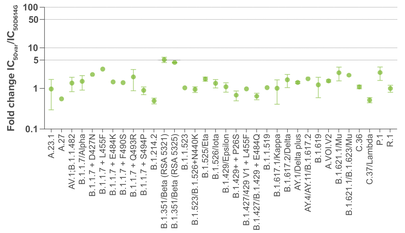
	Victoria	Alpha/ B.1.1.7	Beta/ B.1.351	Gamma/ P.1	Delta/ B.1.617.2
ADG20	0.004	0.006	0.010	0.009	0.006
S309	0.040	0.078	0.082	0.076	0.113
REGN10933	0.004	0.014	3.284	6.177	0.003
REGN10987	0.032	0.028	0.007	0.013	0.017
LY-CoV555	0.006	0.009	>10	>10	8.311
LY-CoV016	0.034	3.225	>10	>10	0.012
AZD1061	0.013	0.012	0.014	0.007	0.038
AZD8895	0.005	0.011	0.046	0.046	0.003

IC_{50} (μg/mL)
<0.02
0.02-0.2
0.2-1
1-10
>10

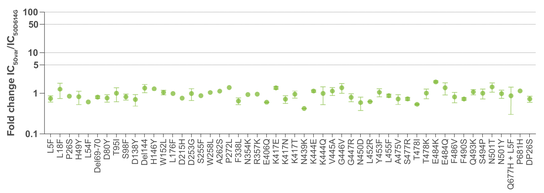
S309, the parent antibody of VIR-7831 (sotrovimab); REGN10933 (casirivimab); REGN10987 (imdevimab); LY-CoV555 (bamlanivimab); LY-CoV016 (etesevimab); AZD1061 (cilgavimab); AZD8895 (tixagevimab).

Figure 4. ADG20 maintains neutralizing activity against (A) circulating SARS-CoV-2 variants and (B) variants with single-/double-spike mutations in a pseudovirus assay

A. Neutralizing activity against circulating SARS-CoV-2 variants



B. Neutralizing activity against SARS-CoV-2 variants with single-/double-spike mutations



Adagio Therapeutics, Inc. utilized the non-clinical and pre-clinical services program offered by the National Institute of Allergy and Infectious Diseases (NIAID) to generate the pseudovirus data.

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DISCLOSURES

CIK is an employee of Adimab LLC. LMW is an employee of Adagio Therapeutics, Inc. and an inventor on a patent application submitted by Adagio Therapeutics, Inc., describing the engineered SARS-CoV-2 antibody. Adagio Therapeutics, Inc. utilized the non-clinical and pre-clinical services program offered by the National Institute of Allergy and Infectious Diseases (NIAID) to generate the pseudovirus data.

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KEY FINDINGS

ADG20 retained binding to RBDs from all ACE2-binding sarbecoviruses and SARS-CoV-2 variants tested

ADG20 maintained potent in vitro neutralizing activity against all SARS-CoV-2 variants tested

By targeting an epitope conserved across SARS-related viruses, ADG20 demonstrated broad neutralization coverage of circulating SARS-CoV-2 variants, suggesting a low likelihood of encountering circulating escape variants

CONCLUSIONS

- ADG20 demonstrated broad binding activity against a diverse panel of circulating SARS-CoV-2 variants, as well as additional SARS-like viruses
- In addition, ADG20 demonstrated potent in vitro neutralizing activity against all SARS-CoV-2 variants tested, including VOCs and newly emerging Delta plus/AY, Lambda/C.37, and Mu/B.1.621 variants
- These data support further clinical investigation of ADG20 not only for COVID-19 but also for potential utility in future outbreaks caused by other SARS-like viruses
- Ongoing clinical trials are evaluating ADG20 for both the prevention (EVADE, NCT04859517) and treatment (STAMP, NCT04805671) of COVID-19