VIS410, a Broad-Spectrum, Anti-Influenza A Monoclonal Antibody in Clinical Development Demonstrates Activity Against Recent Vaccine, Seasonal, and H7N9 Strains of Influenza

ARP0032

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ABSTRACT

Background: Seasonal influenza epidemics and periodic pandemics are a major global public health concern due to lack of effective therapies for the severely ill and the emergence of strains with high morbidity and mortality, including the avian influenza H7N9 strains. VIS410 is a monoclonal antibody that binds to the stem region of hemagglutinin (HA) and has shown broad spectrum activity against Group 1 and Group 2 influenza A viruses. VIS410 has demonstrated safety in Phase 1 and efficacy in Phase 2a human challenge studies, and is in development for the treatment of hospitalized patients. VIS410 was previously shown to bind H7N9 HAs from 2013 strains (including A/Anhui/01/2013) and demonstrated in vivo activity in lethal models of H7N9 infection. VIS410 antiviral activity was further assessed by binding, pseudovirus neutralization, and antibody dependent cellular cytotoxicity (ADCC) studies against HA from recent 2016/2017 H7N9 strains and microneutralization of current seasonal strains.

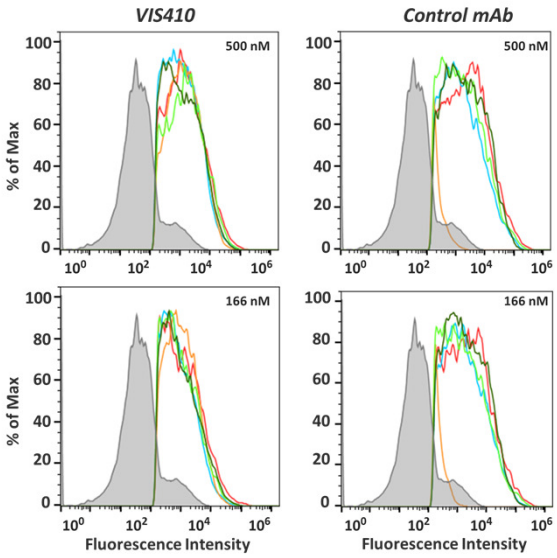
Methods: Full-length H7N9 HA sequences were obtained from the GISAID database and recombinantly expressed. For cell-based binding, HA constructs were transfected into Expi293 cells, and VIS410 binding was monitored by flow cytometry. For pseudovirus neutralization assays, lentiviral particles pseudotyped with H7 HA proteins were incubated with VIS410, and infection was measured based on reporter gene expression. ADCC activity of VIS410 was determined using a reporter bioassay with H7 HA-expressing 293T target cells. Microneutralization tests were performed with recent H1N1 and H3N2 seasonal influenza A strains against a range of VIS410 concentrations, and VIS410 EC50 values were determined.

Results: VIS410 bound HAs from 2016/2017 H7N9 viruses including representative HA from Yangtze River Delta and Pearl River Delta lineages. In addition, VIS410 directly neutralized pseudotyped lentiviruses expressing the novel H7 HA proteins. VIS410 elicited Fc-mediated ADCC against target cells expressing HA from 2013 and recent 2016/2017 H7N9 strains. VIS410 also demonstrated potent neutralization of recent circulating H1N1 and H3N2 viruses.

Conclusion: VIS410 demonstrated neutralizing activity against current circulating seasonal influenza A, and both binding and antiviral activity against newly emergent H7N9 strains. Previous studies in animal models have shown that VIS410 binding correlated with in vivo efficacy against 2013 H7N9 neuraminidase sensitive and resistant strains. These data support the potential of VIS410 for the treatment of seasonal influenza and emerging H7N9 viruses.

VIS410 BINDS HEMAGGLUTININ (HA) FROM RECENT H7N9 VIRUSES

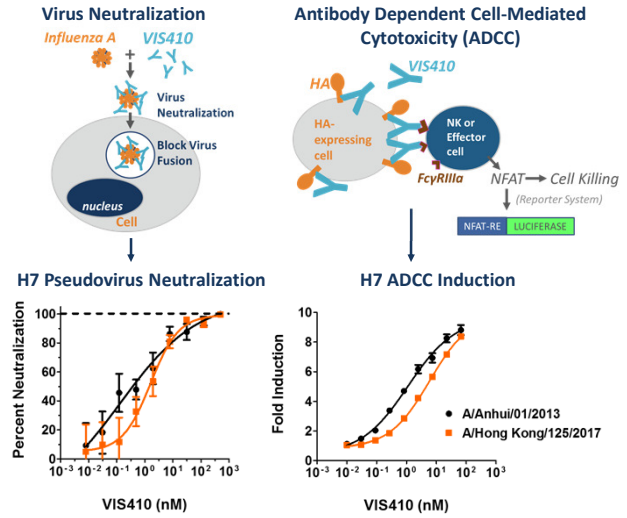
- **VIS410 previously demonstrated HA binding and in vivo activity in lethal models of H7N9 infection with 2013 *NA-sensitive* and *resistant* strains.**
- **Recent 2016/2017 H7N9 viruses evolved from 2013 strains to form two new lineages: Yangtze River Delta (YRD) and Pearl River Delta (PRD) lineages – *VIS410 binds PRD and YRD H7 HAs similarly to A/Anhui/01/2013.***
- **Recent strains contain prevalent HA polymorphism in VIS410 contact residue (HA2 E57A) – *VIS410 binds A/Anhui/01/2013 HA containing E57A, demonstrating VIS410 tolerates this polymorphism in its epitope.***



*** PRD Candidate Vaccine Virus***

H7 HA genes were synthesized and cloned into a mammalian expression vector. HA constructs were transfected into Expi293 cells. Binding of VIS410 or a control HA-stem targeting antibody (mAb) to H7 HA-expressing cells was assessed using flow cytometry. All lineages – 2013, YRD, and PRD – HAs bind to VIS410. A/Jiangsu/60457/2016 binds poorly to the control mAb – which also targets HA stem but is not as broadly-reactive as VIS410.

TWO MECHANISMS OF VIS410 ANTIVIRAL ACTIVITY AGAINST H7N9



- **VIS410 directly neutralizes pseudotyped lentiviruses expressing H7 HA A/Hong Kong/125/2017 and A/Anhui/01/2013.**
- **VIS410 elicits potent Fc-mediated antibody dependent cellular cytotoxicity (ADCC) against H7N9 HA.**

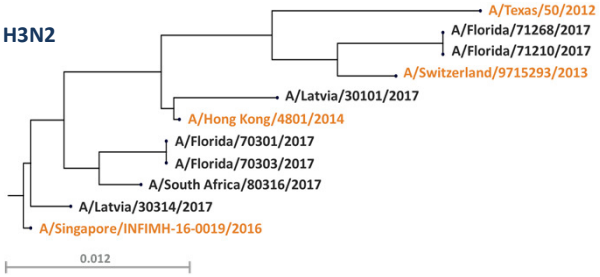
VIS410 NEUTRALIZES DIVERSE RECENT SEASONAL STRAINS

Influenza Virus Sensitivity to VIS410 Using Microneutralization Assay

Influenza Strain	Vaccine/ Seasonal	Subtype	EC50 (µg/mL)
A/Texas/50/2012	VACCINE	H3N2	22
A/Switzerland/9715293/2013	VACCINE	H3N2	5.5
A/Hong Kong/4801/2014	VACCINE	H3N2	2.5
A/Latvia/30101/2017	SEASONAL	H3N2	0.28
A/Latvia/30314/2017	SEASONAL	H3N2	1.0
A/Florida/70303/2017	SEASONAL	H3N2	0.34
A/Florida/71210/2017	SEASONAL	H3N2	0.97
A/Florida/71268/2017	SEASONAL	H3N2	3.1
A/South Africa/80316/2017	SEASONAL	H3N2	0.57
A/California/7/2009	VACCINE	H1N1	0.50
A/Michigan/45/2015	VACCINE	H1N1	0.67
A/Florida/70702/2017	SEASONAL	H1N1	0.41
A/South Africa/80811/2017	SEASONAL	H1N1	0.38

EC_{50} = 50% effective antiviral concentration

VIS410 is Potent Against Diverse Recent Circulating and Vaccine Flu A Strains



Genetic relationship of HA sequences from recent H3N2 vaccine strains (orange) and circulating seasonal isolates from a clinical study (dark blue) was determined. Scale bar represents the frequency of amino acid variations within the specified distance. Phylogenetic trees were constructed using the Neighbor-Joining Method with Jukes-Cantor protein distance measurement.

SUMMARY

- **VIS410 binds HA from recent H7N9 viruses from YRD and PRD lineages.**
- **VIS410 demonstrates two mechanisms of antiviral activity against H7 HA: direct neutralization and ADCC activity.**
- **VIS410 potently neutralizes recent vaccine strains and circulating isolates.**
- **VIS410 is currently being evaluated in a Phase 2b clinical study with hospitalized influenza A patients.**

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