Promising antibody therapeutics for SFTSV infection

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By targeting a previously unrecognized interdomain epitope, a study in *Vita* shows that a single-dose human antibody effectively neutralizes severe fever with thrombocytopenia syndrome virus (SFTSV) and provides strong protection in both mice and, for the first time, non-human primate SFTSV infection models.

Severe fever with thrombocytopenia syndrome (SFTS) is a life-threatening tick-borne viral hemorrhagic fever. Since its first identification in China in 2009, the disease has shown a marked upward trend across East and Southeast Asia. In China, the incidence has surged over 70-fold between 2010 and 2023, with more than 34,000 cumulative cases by 2024 and a case-fatality rate (CFR) of ~5%. In contrast, Japan and South Korea report lower incidence but persistently higher mortality; Japan reported a record high of 183 cases in 2025 with a stable CFR of ~27%, and South Korea saw its highest case count in five years with cohort CFRs of 17–27%[1]. Designated a priority pathogen by the World Health Organization (WHO) in 2017, SFTS currently lacks approved vaccines or specific antiviral therapies, leaving management reliant on supportive care. Although compounds such as ribavirin and favipiravir exhibit *in vitro* activity, their clinical utility is limited to early intervention and often proves ineffective in severe cases with high viral loads. Adjunctive immunomodulatory treatments and therapeutic plasmapheresis are employed to mitigate excessive inflammation and cytokine storm, with the latter's mechanism potentially involving neutralizing effect of the antibodies.

Neutralizing monoclonal antibodies (mAbs) have emerged as a promising therapeutic strategy for combating viral infections in recent years. In a study published in *Vita*, Bi *et al*. isolated and characterized broadly neutralizing mAbs with subnanomolar potency from survivors of severe fever with thrombocytopenia syndrome virus (SFTSV) infection (Fig. 1)[2]. Among eight characterized Gn-specific mAbs with half-maximal inhibitory concentration (IC_{50}) values below 1 μg/mL, several — including ZS1C5, ZS336, and ZS65 — were found to target a novel interdomain epitope spanning domains I and III of the viral Gn glycoprotein. These antibodies showed robust *in vitro* efficacy, and ZS1C5 displayed exceptionally high neutralizing efficacy against SFTSV, with an IC_{50} of 0.3 ng/mL. The interdomain epitope targeted is highly conserved across diverse SFTSV variants, supporting its potential as a broad-spectrum therapeutic target for SFTSV and underscoring the need for further preclinical development. Germline-encoded antibodies resembling ZS1C5 were identified through a structure-guided mining approach applied to human B cell repertoires, highlighting the capacity for swift immune recall.

Most importantly, extending beyond the murine models used in most existing pre-clinical studies for neutralizing antibody efficacy, Bi *et al*. evaluated protective efficacy in a non-human primate model, thereby providing critical evidence for further translation in a biological context closely resembling human physiology. The mAb ZS1C5 significantly reduced viremia, preserved platelet counts, and alleviated coagulation dysfunction in rhesus macaques, exhibiting remarkable safety and efficacy. Immediate next steps include standardized preclinical safety studies, dose optimization, antibody combination design, and preparation for clinical trials, paired with continuous antigenic surveillance.

The Gn glycoprotein is a principal target for neutralizing antibodies, mediating viral entry via binding to the C–C motif chemokine receptor 2 (CCR2). Although researchers have isolated various neutralizing mAbs against SFTSV Gn from convalescents or immunized animals, many exhibit suboptimal potency or breadth in subsequent validation experiments. Structural studies divide the Gn head into three domains (I, II, and III). MAbs targeting domain II often show weak neutralizing activity[3,4], whereas neutralization is normally associated with mAbs targeting domains I and III[5-7]. Recent deep mutational scanning analysis refined the functional mapping of the Gn head to eight more detailed epitopes, demonstrating that potent neutralizing antibodies mainly target epitopes IIIA and IA, followed by IIIB and ID[5]. Accordingly, domain I-targeting mAbs like BD70-4003, JK-2/JK-8, and SD4/SD22, as well as domain III-targeting mAbs like BD70-4008/BD70-4017 showed strong neutralization and robust protection against diverse SFTSV strains[5,8,9]. This aligns with findings that domain I is critical for receptor binding[10], a pattern also observed in related viruses such as Rift Valley fever virus (RVFV), where the structurally analogous domain A is a major antibody target. Notably, Bi *et al*. provide high-resolution insights into a novel, potent epitope bridging Gn domains I and III. The binding interface of antibody ZS1C5 and Gn spans 18 residues across the two domains, likely contributing to its superior neutralization potency.

Antibody-based therapeutics are a critical component of future antiviral strategies. The conserved interdomain epitope bridging Gn domains I and III represents a highly promising target for next-generation antiviral strategies, owing to its structural stability and broad conservation across SFTSV strains. Crucially, the implications of these findings extend beyond SFTSV. Some related high-consequence pathogens, including Guertu virus (GTV), Heartland virus (HRTV) and RVFV, also share structural homology in their Gn proteins, providing a rationale for developing broad-spectrum antibodies across the *Phenuiviridae* family. Together, Bi *et al*. not only establish mAb ZS1C5 as a potent candidate for SFTSV treatment but also successfully bridge the gap between

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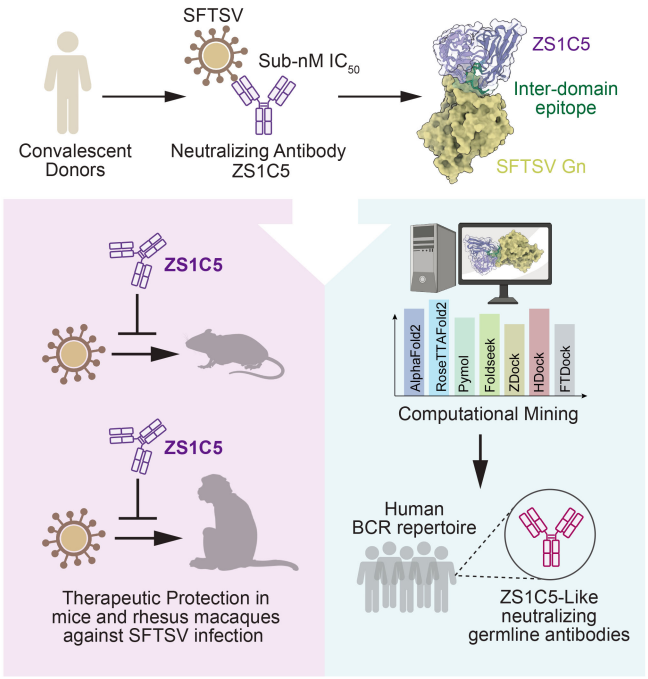

Fig. 1 ZS1C5 antibody isolation and BCR repertoire mining. Following the isolation of an ultrapotent SFTSV-neutralizing antibody ZS1C5 that targets a unique inter-domain epitope on Gn, Bi *et al.* conducted computational identification of ZS1C5-like neutralizing antibodies from the human BCR repertoire[2].

basic structural biology and urgent clinical needs, offering a transformative blueprint for next-generation therapeutics against these life-threatening viral hemorrhagic fevers.

COMPETING INTERESTS

The authors declare no competing interests.

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ADDITIONAL INFORMATION

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