BROAD-SPECTRUM THERAPEUTICS FOR VIRAL DISEASES: A MEDICAL COUNTERMEASURE PLATFORM FOR EMERGING THREATS

An Orthogonal Dual-interacting Nanotherapeutic Platform, Odin, For The Rapid Development Of Broadly Neutralizing Multi-specific Immunotherapeutics

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Monoclonal antibodies (mAbs) have proven transformative as antiviral therapeutics, but their development and use are hampered by their large size, complexity, and manufacturing cost. Consequently, the immunotherapeutics field has begun to explore alternatives to overcome these liabilities. Single-domain antibodies (sdAbs), including the camelid VHH or 'nanobody' are one such therapeutic alternative, with one nanobody having received FDA approval and several more in clinical trials. Although sdAbs embody the idea that good things—enhanced stability and solubility, rapid biodistribution, low-cost manufacturing—come in little packages, they also suffer key disadvantages relative to mAbs, including an exceptionally short half-life, no binding avidity, and the inability to induce Fc-mediated effector functions. Attempts to remedy these liabilities, such as nanobody-Fc fusions, erode the very advantages sought from the VHH platform. Biologics that combine broad anti-viral neutralization potency, rapid biodistribution with desirable pharmacokinetic profiles and/or the ability to recruit immune effector cells into a single molecule should outclass conventional mAbs in the clinic. This is exactly what Eitr Biologics, Inc. (Eitr) seeks to deliver.

Eitr's novel bispecific technology, the ODIN platform (Orthogonal Dual-Interacting Nanotherapeutic), structurally grafts camelid VHH single-domain antibodies together with bovine-derived ultralong CDR3 (UL-CDR3) 'stalk-and-knob' antibody structures into a small single-domain bispecific drug. UL-CDR3s can reach 50-70 amino acids and comprise a beta-hairpin stalk and a disulfide-rich knob domain, providing an even smaller (~6 kDa) autonomous antigen-binding structure that is ideally suited to binding cryptic antigenic sites not readily accessible to standard immunoglobins. Thus, ODIN molecules combine the unique functional properties of VHHs from immunized llamas (small, rapid biodistribution, high affinity and stability) with those of bovine UL-CDR3s from immunized cattle (small with a long reach) into a single well-folded single domain bispecific nanotherapeutic. These properties should allow ODINs to target small highly conserved epitopes on target viral antigens via either their VHH or UL-CDR3 component, making ODIN an ideal platform for the discovery of broad-spectrum anti-viral therapeutics. Additionally, the VHH or UL-CDR3 components of an ODIN can be utilized to manipulate their functional attributes in a 'plug-and-play' fashion, such as by targeting human serum albumin (HSA) to increase drug half-life or FcgRIII to recruit host immune factors. ODIN bispecifics can also be engineered to cross the blood brain barrier (BBB) and traffic to the central nervous system, where they can encephalitic viruses. This can be accomplished by pairing a BBB-targeting VHH with a broadly neutralizing UL-CDR3, or vice versa. The modularity of the ODIN can be further expanded to encompass single-chain ODIN-Fc fusions and multi-specific (i.e. tetraspecific) ODIN antibodies, circumventing manufacturing and chain-pairing issues associated with current multi-specific antibody technologies. Being aglycosylated, ODIN bispecific molecules allow for rapid manufacturing in cost-effective prokaryotic expression platforms, drastically reducing the cost of goods (COGs) and enabling accelerated production in response to an outbreak or biothreat.

A proof-of-concept ODIN, ODIN-1, successfully combined a broadly neutralizing SARS-CoV-2 spike-specific VHH with a broadly neutralizing HIV-1 UL-CDR3, binding and neutralizing multiple viral species. Eitr is currently expanding its pipeline across multiple priority pathogens, including ebolaviruses, marburgviruses, SARS-CoV-2, arenaviruses, and alphaviruses.