ANTIBODY THERAPEUTICS

Teneoboio’s Next Generation of Multispecific Antibody Therapeutics

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INTRODUCTION

Teneoboio has developed unique technologies, including a transgenic rat platform, UniRat®, expressing human heavy chain antibodies (UniAbs™) and a state-of-the-art sequence-based discovery engine to create novel multispecific antibodies for various therapeutic indications. In addition to therapeutic antibodies, UniAb binding domains can be successfully used as 1) antigen recognition domains on CAR T-cells, 2) targeting moieties for nanoparticles, 3) antibody drug-, toxin- or radiolabel-conjugates, and 4) viral payloads (eg, to modify the tumor microenvironment). Using this unique technology, Teneoboio has identified an unprecedented number of novel anti-CD3s, which in the context of bi- or multispecifics, enable maximal T-cell redirection for tumor cytotoxicity and minimal cytokine release. Teneoboio’s unique capabilities and anti-CD3 platform are being applied to develop a number of breakthrough multispecific therapeutic candidates to treat hematological and solid tumor cancers. Its lead multispecific therapeutic program, anti-BCMAxCD3, is in preclinical development for a planned IND submission in 2018.

ANTIBODY DISCOVERY

The past 30 years has seen a rapid evolution of therapeutic antibody technologies. A transformative milestone was the generation of transgenic human Ig rodent platforms, which enable the discovery of fully human antibodies with considerably less immunogenicity, overcoming the need to chimerize, humanize, and affinity mature mouse antibodies. A survey of more than 50 currently marketed antibody therapeutics further highlights the fidelity and success of rodent-derived antibodies compared to in vitro display approaches to antibody discovery. Not surprisingly, in vivo-derived antibodies have advantages conferred by physiological selection for critical quality attributes, including stability, solubility, and high affinity. In contrast, in vitro display methods lack these advantages. Hence, transgenic human Ig rodents have become a mainstay of therapeutic antibody discovery in the biopharmaceutical industry.

In the 90s, the engineering of antibodies extended beyond humanization and affinity maturation technologies to include the rational design of antibody Fvs through the selection of isotypes, the engineering for enhanced or silenced immune effector functions and the design for extended or reduced half-life. The generation and engineering of antibodies (eg, scFvs, llama VHs, human VHs) or alternative scaffolds (eg, DARPin, Centyirms, Fynomers) further afforded the ability to generate bi- and multispecific therapeutic candidates through the assembly of modular domains that were linked chemically or by amino acids. Additional technologies involved the “knobs-into-holes” Fc heterodimerization and variations thereof, to enable bispecific generation in the natural and structurally conserved antibody format. Through the years, an explosion of multispecific formats ensued, some of which progressed to clinical trials while others failed in development from challenges in manufacturability or limiting biology. With this backdrop, the next generation of transformational antibody therapeutics will reach beyond the monospecific, bivalent format toward physiologically compatible and developable human multispecific antibodies with improved or de novo biology, overcoming the therapeutic limitations of native human IgGs.
“The advents of immune-oncology checkpoint inhibitors and multispecific antibody technologies enable the redirection of the immune system for targeted killing of cancers of interest. The past decade has seen an exponential increase in such therapeutics, including CAR T-cell therapy, directed nanoparticles delivering payloads, antibody drug-, toxin-, and radiolabel-conjugates, etc. Teneobio’s UniRat and TeneoSeek platforms, combined with a toolkit of engineering capabilities afford the opportunity to rapidly and effectively identify antibody therapeutic leads as well as UniDabs for a variety of multispecifics and novel cellular and delivery technologies.”

Advances in molecular and high-throughput technologies are enabling innovative approaches to discovering and capturing antibody diversity, previously limited by clonal loss in traditional hybridoma generation. Specifically, next-generation sequencing has enabled comprehensive profiling of full antibody repertoires of immunized organisms. Furthermore, using advanced methods of gene assembly, one can synthesize thousands of unique antibody sequences to be expressed and screened in high-throughput format. Taken together, these technologies enable rapid screening and identification of affinity-matured functional antibody leads at unprecedented speeds. Using naturally derived human antibodies from transgenic rats and state-of-the-art sequence-based antibody discovery, Teneobio is developing the next generation of novel and manufacturable multispecific antibodies as therapeutics for oncology, immunology, and infectious diseases.

**DISCOVERY PLATFORMS: UNIRAT & TENOSEEK**

Teneobio’s human Ig transgenic platform, the UniRat, is based on a triple knockout rat wherein the expressions of the native variable coding sequences and the heavy and light chain constant regions have been inactivated. The UniRat has been genetically modified to exclusively express the full human VDJ repertoire (all VH families), with transgenes of human heavy chain variable domains linked to a conserved rat Fc. Immunization of the UniRat elicits a normal antibody response that results in the expression of UniAbs, human heavy-chain-only antibodies of approximately 80 kDa, contrasting with the standard ~150-kDa human IgG. Importantly, heavy chain variable domains from the UniRat, UniDabs™, are the smallest antigen-binding units of a human IgG at approximately 12.5 kDa (~100 amino acids) and can be assembled as modular domains of multispecifics. Figure 1 illustrates a subset of such multispecific formats, enabling the generation of a plenitude of specificities against different epitopes on the same antigen or different specificities for different antigens. Heterodimerization of such heavy-chain-only multispecifics or their combination with standard heavy-light-chain formats is feasible, given that UniDabs (VH domains) do not interact with either kappa or lambda light chains in vitro or when co-expressed in cell lines.

Complementing Teneobio’s UniRat platform is a proprietary next-generation sequence-based discovery engine called TeneoSeek. The TeneoSeek discovery en-

**FIGURE 1**

Flexible and robust human multi-specific antibodies

UniRat™-derived multispecifics with flexible design and tuneable affinity and avidity.
The TeneoSeek discovery engine.

Unibody antibodies can then be rapidly assembled and further engineered for desired multispecificity and effector functions on human Fc backbones of interest. Of note, the highly manufacturable and stable UniDabs and their derived multispecifics, which have a melting temperature of ~60°C to 64°C, can be expressed at grams per liter and are easily manufactured in CHO cell lines. CHO cell supernatant yields of heterodimeric UniAb multispecifics are > 85% and can be purified using a single capture step process to 98% purity. The developability and expression profiles of UniAbs and their multispecific antibody derivatives are quite similar to that of standard antibodies and compatible with industry standard manufacturing platforms.

**UNIQUE T-CELL REDIRECTION PLATFORM FOR CANCER THERAPY**

Throughout the past decade, T-cell redirection using bispecific antibodies has provided favorable clinical outcomes in treatments of liquid tumors, including leukemia and lymphoma. Tenebio has used its technologies to provide unique solutions for T-cell redirecting therapies. The basis for the approach relies on the coupling of an anti-CD3 recognition domain with a targeting moiety as a fusion construct. In the past, a limitation to this approach has been partly target-related, given the difficulty of generating anti-CD3 antibodies, as well as CD3 biology. Specifically, limitations associated with the immunogenicity of CD3 epitopes and the industry's modification and/or humanization of less than a handful of known anti-CD3 antibodies (eg, OKT3 and SP34) have limited the application of this powerful approach to cancer therapy. To address these limitations, the TeneoSeek discovery platform was applied to identify > 100 unique anti-CD3 sequences spanning different target epitopes and covering a broad spectrum of affinities from low nM to pM affinities. Largely enabled by sequence and repertoire lineage analysis, leads from these efforts have yielded a diverse collection of novel anti-CD3 antibodies with unique and differentiated biology.

Recent clinical utility and the therapeutic application of bispecific anti-CD3 antibodies have been complicated by adverse events, including cytokine release syndrome and neurotoxicity. In contrast to these first-generation anti-CD3 molecules, Tenebio’s unique anti-CD3 platform is based on the access to a diverse set of anti-CD3s with different binding and T-cell activation profiles, decoupling tumor-specific cytotoxicity from cytokine release. A comprehensive analysis of a subset of these leads has yielded variants that can differentially kill cancer cells with minimal proinflammatory cytokine release, potentially increasing the therapeutic window. This would be particularly advantageous for anti-CD3 bispecifics with longer in vivo half-lives. The ability to tailor anti-CD3-based bispecifics for targets of interest offers prospects of a next generation of safer and improved therapies using clinically validated cancer cell targets. These safety
profiles are currently being assessed in vivo, and studies to date indicate that multispecifics derived from the UniAb platform exhibit mouse and monkey half-lives that are consistent with that of standard antibodies. Additional in vivo studies have validated the anti-CD3 platform, demonstrating the efficacy of the bispecifics in weekly dosing of mouse models. With a planned IND filing for 2018, the clinical validation of Tenebio’s anti-CD3 platform and lead therapeutic candidate, anti-BCMAxCD3 (bivalent for BCMA, monovalent for CD3) for the treatment of multiple myeloma, may open new opportunities to address challenges related to efficacy and adverse events associated with T-cell targeting of liquid and solid tumors. To this end, Tenebio is applying its T-cell redirection platform in additional therapeutic discovery programs, including anti-CD22xCD3 and anti-CD19xCD22xCD3 for lymphoma and ALL as well as anti-PSMAxPSCAxCD3 for prostate cancer.

NEXT-GENERATION MULTISPECIFIC UNIAB-BASED THERAPEUTICS

The advents of immune-oncology checkpoint inhibitors and multispecific antibody technologies enable the redirection of the immune system for targeted killing of cancers of interest. The past decade has seen an exponential increase in such therapeutics, including CAR T-cell therapy, directed nanoparticles delivering payloads, antibody drug-, toxin-, and radiolabel-conjugates, etc. Tenebio’s UniRat and TeneoSeek platforms, combined with a tool kit of engineering capabilities afford the opportunity to rapidly and effectively identify antibody therapeutic leads as well as UniDabs for a variety of multispecifics and novel cellular and delivery technologies. The ease of assembling multispecifics with modular binding domains enables the exploration of synergies to activate and redirect the immune system to cancer cells. Multispecific UniAbs and UniDabs can be assembled for improved affinity through increased avidity against targets of interest (eg, a bivalent heavy chain only anti-BCMA can competitively block APRIL ligand binding to BCMA). Additionally, UniAbs can be optimized for tissue specificity and selectivity through avidity for different antigens co-expressed on tissue targets of interest. Bi- or multiparapatic multispecifics can elicit gain-of-function or de novo activities, otherwise absent in monospecific antibodies or with their combinations. Biological activation or redirection of T-cells can be further explored to assess multispecific combinations that offer the best efficacy and safety profiles. Moreover, the application of UniDabs as extra-cellular domains for CAR T-cells has been validated and shown to be superior to the use of scFvs in some settings. The applications of UniDabs as antibody-drug/radiolabel conjugates, targeting moi eties on nanoparticles, viral payloads to modify the tumor microenvironment, or imaging tools (given their relatively small size and tumor penetration) offer endless possibilities to exploit these human variable domains for therapeutic benefit. Tenebio’s unique platforms and antibody drug discovery capabilities are poised to deliver on these goals for a variety of indications, including oncology, immune disorders, and infectious diseases.

REFERENCES


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BIOGRAPHY

Dr. Omid Vafa is the Chief Business Officer at Tenebio, Inc. He has more than 15 years of global business and scientific experience in biotechnology and biopharmaceutical drug discovery, asset evaluation, transactions, and licensing. Prior to joining Tenebio, he was the Director of Strategy and Scientific Partnerships at Janssen Pharmaceutical Companies of Johnson and Johnson and the Biotechnology and Oncology Lead at the London Innovation Center of B&J. He earned his PhD at Georgetown University, his MBA from the Villanova University School of Business, and his BS from the University of California at Irvine. He completed his postdoctoral fellowships at The Scripps Research Institute (TSRI) and the Salk Institute for Biological Studies in La Jolla, California. He can be contacted at ovafa@tenebio.com.