IMMUNO-ONCOLOGY INSIGHTS

ADDRESSING LINGERING SAFETY ISSUES FOR I-O PRODUCT CANDIDATES IN DEVELOPMENT

SPOTLIGHT

COMMENTARY

The rise of next-generation T-cell engagers with better safety and efficacy

Omid Vafa

The last decade has witnessed a gradual increase in the number of T-cell engagers (TCEs) entering the clinic for various oncology indications. The culmination of learnings from intensive research and development spanning the last thirty-five years in this space has yielded two TCE approvals: 1) catamuxamab (anti-EPCAMxCD3, Fresenius Biotech, Germany), a mouse-rat hybrid bispecific for malignant ascites that was approved by the EMA in 2009 and voluntarily withdrawn in 2017, and 2) blinatumomab (Micromet, Inc., Germany and Amgen, CA) comprising a mouse anti-CD19xCD3 dual single-chain variable fragment (scFv) that is administered intravenously (IV) for acute lymphoblastic leukemia (ALL, FDA approval in 2014). Blinatumomab remains the single approved and marketed TCE to date. Other first-generation TCEs have since suffered attrition in early development due to their toxicity or safety profiles as well as manufacturing complications. This review highlights key impediments to the clinical advance and the design limitations of first generation TCEs and discusses new approaches to overcome these hurdles. By addressing these fundamental shortcomings, next-generation TCEs have the potential to transform cancer treatment.

Immuno-Insights Insights 2020; 1(3), 169–176

DOI: 10.18609/ioi.2020.018

TCE BENEFIT–RISK PROFILES

TCEs are bi- or multi-specific engineered antibodies that can circumvent the T-cell receptor (TCR) and peptide-major histocompatibility (pMHC) complex recognition by bridging CD3 of the TCR with a

tumor-associated antigen (TAA) [1,2]. By doing so, TCEs form an immunological synapse between T-cells and cancer cells to elicit tumor cytotoxicity through the secretion of granzymes, perforins and pro-inflammatory cytokines, including TNFα, IL-6, IL-2 and IFNγ [3,4]. There are currently more than 75 such TCEs in clinical development (Paulina Szymanska, Beacon Target Therapies). Most recently, TCEs in early development have demonstrated clinical successes in hematological malignancies by targeting common plasma or B-cell antigens (e.g. CD19, BCMA, and CD20). There is also a growing trend towards targeting solid tumor antigens (e.g. HER2, PSMA, and CEA) to further address the 10x greater cancer patient population in need [4]. Several TCEs have shown promising overall response rates (ORRs) and complete responses (CRs) in early clinical trials and will soon enter Phase 2 and/or pivotal studies (e.g. glofitamab, epocritamab, REGN1979, REGN5458, CC-93269, JNJ-64007957, plamotamab; www.clinicaltrials.gov).

Earlier this year, Kampershroer *et al.* (2020) shared a summary of the "Preclinical safety and Translational Safety Assessment of CD3-based Bispecifics", a workshop that was sponsored and organized by the Health and Environmental Sciences Institute (HESI) Immuno-safety Technical Committee and the US Food and Drug Administration (FDA) Center for Drug Evaluation and Research (CDER) [5]. The article highlighted that the "key safety concerns with CD3 bispecifics are excessive release of cytokines, which translate to potentially life threatening cytokine release syndrome (CRS), target organ toxicity due to redirection of T-cells to normal tissues expressing the tumor-associated antigen (TAA) (off tumor/on-target toxicity) and in some cases neurotoxicity" [5]. To address these safety concerns related to CRS for blinatumomab, the only currently marketed CD3 bispecific to date, it was noted that step-up dosing (intra-patient dose escalation) and corticosteroid pre-treatment are standard protocol. This approach has since been commonly used for the numerous TCEs currently in clinical development. An important additional variable when considering dose escalation regimens is the level of tumor burden that can contribute to the onset of CRS [6]. Dose-reduced re-administration of blinatumomab after a grade 4 CRS adverse event was shown to be safe in a patient with relapsed acute lymphoblast leukemia [7]. Along with corticosteroids, tociluzimab (anti-IL-6 receptor) has also been used to manage grade 3 and 4 adverse events in the clinic [8]. While patient monitoring and management have improved for T-cell redirecting therapeutics, the safety concerns persist, and reports of adverse events from TCEs are well-documented in the public sector and in recent press releases.

With respect to blinatumomab, neurotoxicity is also considered a dose-limiting adverse event and can occur independently of systemic CRS [6]. As such, Dr Hermann Einsele (University of Wurzburg, Germany) has purported that blinatumomab increases T-cell adhesiveness to vascular endothelium, thereby enhancing extravasation into the central nervous system (CNS). This results in targeting B-cells, causing localized cytokine release and subsequent migration of monocytes into the CNS that increases local inflammation and neurotoxicity [9]. Thus, beyond step-up dosing and dexamethasone use, Einsele has used a P-lectin antagonist, pentosan polysulfate to reduce T-cell adhesion to the endothelium and subsequent local cytokine release in the CNS. Most recently, Parker *et al.* identified CD19 expression in brain mural cells using single cell RNA sequencing data and confirmed protein expression by perivascular staining [10]. Hence, on target activity may also contribute to CAR T-cell and BiTE neurotoxicity, though this has not been formally demonstrated clinically. Together, the Einsele and Parker *et al.* data suggest that both extravasation and on target toxicity on mural cells may contribute to neurotoxicity with anti-CD19 T-cell redirection [11]. Curiously, a number of anti-CD20 TCEs that are currently in development and targeting the same B-cell population have not reported significant neurotoxicity in the clinic (e.g.

DOI: 10.18609/ioi.2020.018

mosenutuzmab and glofitumab, Roche; epocritamab, Genmab; odronextamab, Regeneron; plamotamab, Xencor). Whether these discrepancies in neurotoxicity are related to the specific target (CD19 versus CD20) or TCE format and whether subsequent inflammation in the CNS can be avoided with next-generation TCEs targeting CD19 are currently unknown. Recent pre-clinical studies of TNB-486 (Teneobio, CA), an anti-CD19 TCE that targets a novel conformational epitope on CD3 and possesses an extended half-life, show that it exhibits tumor cytotoxicity with minimal cytokine release [11]. This feature of the TCE may increase the benefit–risk ratio of targeting CD19 with the advantage of an extended half-life. The pending Phase 1 studies of TNB-486 in ALL and DLBCL will reveal the physiological relevance and potential increase in the therapeutic index, given its preclinical cytokine release profile. Moreover, epocritamab (anti-CD20x-CD3, Genmab), a subcutaneously administered bispecific DuoBody®, has demonstrated efficacy without severe neurotoxicity and is now undergoing further assessment in a dose expansion cohort (Genmab presentations at ASCO, 2020 and EHA 2020). Subcutaneously administered TCEs have reduced C_{max} and this may dampen cytokine release (Genmab presentation at EHA, 2019; [12]). Nevertheless, the general longer-term impact of this delivery route on anti-drug antibody responses (ADA), efficacy and toxicity remain to be established.

The FDA's recent retrospective study of 17 TCEs of different formats and related INDs involving Minimum Anticipated Biological Effect Level (MABEL) approaches in determining starting dose selection for First-in-Human (FIH) studies revealed that animal models are not ideal in predicting safe starting doses for FIH studies [13]. In general, non-human primates used for toxicological assessment of TCEs with conserved binding to TAA and CD3 better tolerate toxicities than patients. CRS and inflammatory responses were the most common adverse events along with neuro-, hepato- and gastrointestinal-toxicity and decreased lymphocytes [13]. Consistent with prior observations, lymphopenia was attributed to either direct depletion by the product or redistribution of B- and T-cells through endothelial attachment [14]. Moreover, neither receptor occupancy nor a non-severe toxic dose in animals were deemed appropriate for dose selection. Rather, a recommendation based on 30% or lower *in vitro* pharmacological activity (PA) was considered a better indicator of safe starting dose for FIH [13].

Beyond safety concerns associated with drug potency, additional variables may limit and negatively impact TCE efficacy. Highly potent TCEs may induce T-cell exhaustion or anergy through overstimulation and possibly induce cell death. Moreover, in some patients the native T-cell population maybe insufficient or too low for significant efficacy. Hence, the biological design of the next generation of TCEs should consider a number of structural and quality attributes to elicit the desired patient biology that may not be captured by the first generation of CD3 bispecific formats that were optimized for *in vitro* potency and not for long-term efficacy. Important to this end, it would be beneficial to have continuous exposure and durable response of an active but non-toxic dose where T-cell exhaustion or anergy will not occur. Chronic T-cell stimulation from greater TCE exposure and target antigen engagement can extend the effector phase of T-cell activation and elicit T-cell exhaustion and the loss of memory T-cells [15]. Moreover, it was established that PD-1 upregulation is one of the mechanisms of resistance to blinatumomab, and combination treatment with pembrolizumab enhanced T-cell function and induced an anti-leukemic response [16]. Hence, many are now considering combinations (e.g. with checkpoint inhibitors) and multispecific platforms that can engage T-cell co-stimulatory molecules (e.g. CD28) to overcome such T-cell exhaustion and maximize effector activity. Nevertheless, these approaches would need to be carefully balanced in consideration of potential risks for adverse events, including

CRS. TCE-induced CRS detected in the clinic generally occurs after the initial dose, and subsequent doses are less problematic. Thus, it will be important to assess the upregulation of T-cell exhaustion markers with greater exposures that can reduce efficacy in subsequent dosing during continuous or periodic IV infusions. Blinatumomab, in light of its short half-life and toxicity profile, requires both step dosing and continuous IV delivery by infusion pump at microgram quantities over 4–8 weeks (e.g. 9 mcg/day for the first week, followed by 28 mcg/day for the remaining 3 weeks) [17]. Arguably, while blinatumomab's short half-life poses a delivery inconvenience, it also enables controlled administration to quickly stop infusion at signs of toxicity (e.g. pro-inflammatory cytokine increase associated with CRS or neurotoxicity). Hence, the increase in half-life of any TCE should be weighed against the potential increases in toxicities or T-cell exhaustion and anergy posed by improved pharmacokinetic and pharmacodynamic (PK/PD) profiles.

Unlike blinatumomab, next-generation TCEs possessing "silent" Fc (muted effector function) or other half-life extending moieties (e.g. anti-albumin or albumin fusion constructs) will enable a more convenient intermittent dosing schedule on a weekly or biweekly basis [4]. Several strategies have been developed to maximize therapeutic indices while mitigating toxicity profiles of highly potent TCEs, including:

i. Using an infusion pump to continuously deliver TCEs in a tight range below dose limiting toxicity;

ii. Introducing metalloprotease cleavage sites in pro-drug forms of TCEs that are activated site-specifically at the tumor site;

iii. Localized viral delivery of TCEs to tumors;

iv. Subcutaneous delivery of TCEs to minimize C_{max} and enable gradual systemic exposure;

v. Step-up dosing regimens and vi) next-generation TCEs that can decouple tumor cytotoxicity from cytokine release. Additionally;

vi. The measure of safety and efficacy through relevant biomarkers that monitor T-cell activation, proinflammatory cytokines, CRS and tumor cell killing can inform better dosing regimens and reduce the CRS without compromising efficacy.

Predictive modeling that integrates such measures has been applied to assess dosing regimens in the clinic for mosunetuzumab (anti-CD20xCD3, Roche) using mechanistic quantitative systems pharmacology (QSP) modeling [18]. Such modeling, combined with preclinical *in vivo* non-human primate and human clinical studies have further demonstrated that step fractionated dosing regimens can mitigate the risk of high systemic cytokine (e.g. IL-6) peaks in non-Hodgkin's lymphoma (NHL) patients without compromising anti-tumor efficacy [18]. Cytokine levels were shown to be highest after the first dose of mosunetuzumab when B-cells were present in peripheral blood and lymphoid-tissue compartments. For the subsequent doses, IL-6 secretion from peripheral blood was negligible after initial depletion of circulating B-cells, and the bulk of the IL-6 was secreted within tissues [18]. Undoubtedly, systems modeling approaches will be extended to other B-cell malignancies to identify better protocols for improved therapeutic indices in the future. Still, these approaches are of afterthoughts to address and optimize regimens for already existing potent molecules. What about designing the next generation of molecules for better therapeutics windows?

The clinical safety and toxicity of TCEs are also determined by their humanicity (relative level of human peptide sequences) developability and manufacturability profiles. The first two are the most critical, given that a) an ADA response to non-human peptides can potentially cross-link the TCE and b) physiologically unstable CD3 bispecifics can aggregate. Both can negatively impact TCE pharmacokinetics (PK) and potentially trigger CRS by prematurely activating T-cells in the absence

DOI: 10.18609/ioi.2020.018

of tumor target engagement. Such liabilities could also significantly impact the distribution and exposure of the TCE in circulation, restricting it to lymphatic tissues, increasing the likelihood of immunogenicity or an ADA response that may compromise safety and efficacy. Attention to these potential liabilities will be most critical for the scientists and physicians who are focused on discovering and developing novel bi- or multi-valent antibody formats, including asymmetric, symmetric and scFv- and variable heavy chain-based or alternative scaffold fusion constructs (reviewed by [1,4,19]). The clinical successes or failures of these various formats will inform future structure and function-related design considerations for optimal PK/PD, including the appropriate TCE affinities, valencies, epitopes on the TAA and CD3 as well as understanding optimal half-life.

NEXT-GENERATION TCES FOR BETTER SAFETY & EFFICACY

Moving forward with next-generation TCEs, a holistic approach to design and format warrants careful consideration. The complexity and interdependency of the various binding domains can impact the overall safety-efficacy profile of the therapeutic. To this end, a number of newly engineered TCE formats comprise the next generation of CD3 bispecifics that are entering the clinic. Some of these efforts involve the fine-tuning of TAA binding domains and CD3 affinity and epitopes to minimize CRS while retaining efficacy with half-life, culminating in a better therapeutic index. For example, companies like Macrogenics and Xencor have sought to engineer CD3 affinity for reduced cytokine release [1,2]. Others, like Teneobio, have identified novel anti-CD3 binders to a novel conformational CD3 epitope that capture a "sweet spot" of activity, where TCEs can elicit tumor cytotoxicity with minimal cytokine release [20]. These approaches, and the biology enabling this window of engagement within such a "sweet spot" were reviewed recently [4]. There are ongoing efforts [Teneobio unpublished data] to further elucidate the signal transduction pathways that differentiate these novel TCEs from the previous generation of high-affinity potent bispecifics engaging the epsilon chain of CD3.

Teneobio's CD3-bispecific platform was discovered and characterized in light of observations of dual threshold activation that triggers cytotoxicity versus cytokine release. This dual threshold was previously characterized for TCR-pMHC interactions and immune synapse formation [21,22]. Of import, beyond the characteristic decoupling of cytotoxicity from cytokine release, Teneobio's TCEs have demonstrated an increased therapeutic index in animal models, with reduced upregulation of inhibitory checkpoints associated with T-cell exhaustion (e.g. PD1 and CTLA-4) and preferential activation of cytotoxic T-cells over regulatory T-cells (Tregs) [4,20]. The clinical benefit-risk ratio of such novel TCEs will be revealed in the near future, as many of these assets are now in the clinic (e.g. TNB-383B, anti-BCMAxCD3) or soon entering the clinic (TNB-486, anti-CD19xCD3; TNB-585, anti-PSMAxCD3, IND filings Q3/Q4 2020).

Other drug developers have engineered proteolytic sites in CD3-bispecific pro-drugs that are activated in the tumor microenvironment by local proteases [23]. In doing so, T-cell activation and tumor targeting is relatively restricted in space and time, potentially minimizing systemic exposure and cytokine release for a better therapeutic index. These approaches are in preclinical stages and will soon enter the clinic (Cytomx, Maverick, Harpoon, Amunix). Still others have explored site specific tumor delivery of TCEs as payloads using vaccinia, oncolytic adenovirus, and in oncolytic measles viruses [24–26]. Efficacy with such viral payloads was shown in both xenograft and syngeneic models without toxicity [26]. In the near future, the outcomes of these more complex engineered formats and viral delivery approaches will be determined by their clinical validation for localized tumor persistence, their immunogenicity and ease of manufacturing and their stability. Additional efforts to target solid tumors involve format plays, where

preferential dual-antigen targeting of tumors is favored by multivalency and avidity relative to single-target antigens on normal tissues [27]. Alternatively, low-affinity bivalency against specific TAAs has been shown to enable improved targeting of antigens that are expressed at higher levels on tumors than on normal tissues and may reduce off-tumor, on-target toxicities in the clinic [28]. Importantly, these advantages will need to be carefully weighed for each TAA considered, given that some TAAs when cross-linked by bivalent TCEs can rapidly internalize and reduce surface copy number required for robust and redirected T-cell mediated tumor toxicity.

Increasing the therapeutic index through the various aforementioned approaches will likely provide opportunities to further assess synergistic benefits of combination therapies. A major impediment to addressing solid tumors has been the immunosuppressive tumor microenvironment (TME) and the physical barrier to penetration known as the stroma [29]. Various strategies are being explored to turn the immune deprived "cold tumors" into inflamed "hot tumors" that comprise T-cell infiltrating lymphocytes [30]. These strategies include targeted depletion of immune suppressive cells, including macrophages, Tregs, myeloid-derived suppressor cells (MDSCs) by using checkpoint inhibitors, introducing proinflammatory cytokines, and localizing costimulatory molecules to the tumor among other approaches. Additional approaches focus on disrupting the extracellular matrix/basement membrane, and fibroblasts [31,32]. Undoubtedly, future combination studies with these many disruptive approaches will further enhance anti-tumor access and boost the anti-tumor immune response of TCEs with better safety and efficacy profiles.

CONCLUSION

Looking to the future, there is much optimism that next-generation TCEs will transform the treatment of liquid and solid tumors. As the operations researcher, Russell L Ackoff, once famously said, "A problem never exists in isolation; it is surrounded by other problems in space and time. The more of the context of a problem that a scientist can comprehend, the greater are his chances of finding a truly adequate solution." To that end, iterative learnings from the clinical outcomes of the next wave of multispecific therapeutics will further inform the creation of TCEs with better benefit–risk profiles. With innovative dosing regimens (e.g. step-up dosing), alternative delivery routes (e.g. localized or subcutaneously), and novel drug combinations, next-generation TCEs are on the trajectory to providing meaningful solutions to unmet cancer patient needs.

REFERENCES

1. Ellerman D. Bispecific T-cell engagers: Towards understanding variables influencing the in vitro potency and tumor selectivity and their modulation to enhance their efficacy and safety. *Methods* 2019; 154: 102–17.
2. Clynes RA, Desjarlais JR. Redirected T Cell Cytotoxicity in Cancer Therapy. *Annu. Rev. Med.* 2019; 70: 437–50.
3. Goyette J, Nieves DJ, Ma Y, Gaus K. How does T cell receptor clustering impact on signal transduction?. *J. Cell Sci.* 2019; 132(4): jcs226423.
4. Vafa O, Trinklein ND. Perspective: Designing T-Cell Engagers With Better Therapeutic Windows. *Front. Oncol.* 2020; 10: 446.
5. Kamperschroer C, Shenton J, Lebrec H, Leighton JK, Moore PA, Thomas O. Summary of a workshop on preclinical and translational safety assessment of CD3 bispecifics. *J. Immunotoxicol.* 2020; 17(1): 67–85.
6. Shimabukuro-Vornhagen A, Gödel P, Subklewe M *et al.* Cytokine release syndrome. *J. Immunother. Cancer* 2018; 6(1): 56.
7. Marini BL, Sun Y, Burke PW, Perissinotti AJ. Successful reintroduction of blinatumomab in a patient with relapsed/refractory acute lymphoblastic leukemia following grade 4 cytokine release syndrome. *J. Oncol. Pharm. Pract.* 2018; 24(1): 67–73.
8. Maude SL, Barrett D, Teachey DT, Grupp SA. Managing cytokine release syndrome associated with novel T

DOI: 10.18609/ioi.2020.018

cell-engaging therapies. *Cancer J.* 2014; 20(2):v119–22.

9. Helwick C. ASCO Post, April, 10, 2020: https://ascopost.com/issues/april-10-2020/bispecific-antibodies-successes-and-challenges/

10. Parker KR, Migliorini D, Perkey E *et al.* Single-Cell Analyses Identify Brain Mural Cells Expressing CD19 as Potential Off-Tumor Targets for CAR-T Immunotherapies. *Cell* 2020; 183(1): 126–142. e17.

11. Malik H, Buelow B, Rangaswamy U *et al.* TNB-486, a Novel Fully Human Bispecific CD19 x CD3 Antibody That Kills CD19-Positive Tumor Cells with Minimal Cytokine Secretion. *Blood* 2019; 134 (Supplement_1): 4070.

12. Engelberts PJ, Hiemstra IH, de Jong B *et al.* DuoBody-CD3xCD20 induces potent T-cell-mediated killing of malignant B cells in preclinical models and provides opportunities for subcutaneous dosing. *EBioMedicine* 2020; 52: 102625.

13. Saber H, Del Valle P, Ricks TK, Leighton JK. An FDA oncology analysis of CD3 bispecific constructs and first-in-human dose selection. *Regul. Toxicol. Pharmacol.* 2017; 90: 144–52.

14. Molema G, Kroesen BJ, Helfrich W, Meijer DK, de Leij LF. The use of bispecific antibodies in tumor cell and tumor vasculature directed immunotherapy. *J. Control Rel.* 2000; 64(1-3): 229–39.

15. Lejeune M, Köse MC, Duray E, Einsele H, Beguin Y, Caers J. Bispecific, T-Cell-Recruiting Antibodies in B-Cell Malignancies. *Front. Immunol.* 2020; 11: 762.

16. Feucht J, Kayser S, Gorodezki D *et al.* T-cell responses against CD19+ pediatric acute lymphoblastic leukemia mediated by bispecific T-cell engager (BiTE) are regulated contrarily by PD-L1 and CD80/CD86 on leukemic blasts. *Oncotarget.* 2016; 7(47): 76902–76919.

17. Kantarjian H, Jabbour E, Topp MS. Blinatumomab for Acute Lymphoblastic Leukemia. *N. Engl. J. Med.* 2017; 376(23): e49.

18. Hosseini I, Gadkar K, Stefanich E *et al.* Mitigating the risk of cytokine release syndrome in a Phase I trial of CD20/CD3 bispecific antibody mosunetuzumab in NHL: impact of translational system modeling. *NPJ Syst. Biol. Appl.* 2020; 6(1): 28.

19. Spiess C, Zhai Q, Carter PJ. Alternative molecular formats and therapeutic applications for bispecific antibodies. *Mol. Immunol.* 2015; 67(2 Pt A):95–106.

20. Trinklein ND, Pham D, Schellenberger U *et al.* Efficient tumor killing and minimal cytokine release with novel T-cell agonist bispecific antibodies. *MAbs* 2019; 11(4): 639–52.

21. Faroudi M, Utzny C, Salio M *et al.* Lytic versus stimulatory synapse in cytotoxic T lymphocyte/target cell interaction: manifestation of a dual activation threshold. *Proc. Natl Acad. Sci. USA* 2003; 100: 14145–50.

22. Purbhoo MA, Irvine DJ, Huppa JB, Davis MM. T cell killing does not require the formation of a stable mature immunological synapse. *Nat. Immunol.* 2004; 5: 524–30.

23. Kavanaugh WM. Antibody prodrugs for cancer. *Expert Opin. Biol. Ther.* 2020; 20(2): 163–71.

24. Yu F, Wang X, Guo ZS, Bartlett DL, Gottschalk SM, Song XT. T-cell engager-armed oncolytic vaccinia virus significantly enhances antitumor therapy. *Mol. Ther.* 2014; 22(1): 102–11.

25. Fajardo CA, Guedan S, Rojas LA *et al.* Oncolytic Adenoviral Delivery of an EGFR-Targeting T-cell Engager Improves Antitumor Efficacy. *Cancer Res.* 2017; 77(8): 2052–63.

26. Speck T, Heidbuechel JPW, Veinalde R *et al.* Targeted BiTE Expression by an Oncolytic Vector Augments Therapeutic Efficacy Against Solid Tumors. *Clin. Cancer Res.* 2018; 24(9): 2128–37.

27. Mazor Y, Sachsenmeier KF, Yang C *et al.* Enhanced tumor-targeting selectivity by modulating bispecific antibody binding affinity and format valence. *Sci. Rep.* 2017; 7: 40098.

28. Bacac M, Klein C, Umana P. CEA TCB: A novel head-to-tail 2:1 T cell bispecific antibody for treatment of CEA-positive solid tumors. *Oncoimmunology* 2016; 5(8): e1203498.

29. Valkenburg KC, de Groot AE, Pienta KJ. Targeting the tumour stroma to improve cancer therapy. *Nat. Rev. Clin. Oncol.* 2018; 15(6): 366–381.

30. Hegde PS, Chen DS. Top 10 Challenges in Cancer Immunotherapy. *Immunity* 2020; 52(1): 17–35.

31. Watabe T, Liu Y, Kaneda-Nakashima K *et al.* Theranostics Targeting Fibroblast Activation Protein in the Tumor Stroma: 64Cu- and 225Ac-Labeled FAPI-04 in Pancreatic Cancer Xenograft Mouse Models. *J. Nucl. Med.* 2020; 61(4): 563–9.

32. Thomas D, Radhakrishnan P. Tumor-stromal crosstalk in pancreatic cancer and tissue fibrosis. *Mol. Cancer* 2019; 18(1): 14.

AFFILIATION

Omid Vafa

Teneobio, Inc., 7999 Gateway Blvd, Newark, CA 94560, USA

AUTHORSHIP & CONFLICT OF INTEREST

Contributions: *All named authors take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.*

Acknowledgements: *Special thanks to Hugh Davis and Tony Lubiniecki for their critical reviews of the manuscript.*

Disclosure and potential conflicts of interest: *Dr Vafa is an employee of Teneobio, Inc. with equity interests.*

Funding declaration: *The authors received no financial support for the research, authorship and/or publication of this article.*

ARTICLE & COPYRIGHT INFORMATION

Article source: *Invited; externally peer reviewed.*

Submitted for peer review: *Sep 15 2020;* ***Revised manuscript received:*** *Nov 6 2020;* ***Publication date:*** *Dec 4 2020.*