*convertible*CAR™-T FAQ's and Answers

Xyphos' *convertible*CAR-T cell platform

1. Q: Are *convertible*CAR-T cells as efficacious as conventional scFvCD19 CAR-T cells in animal models?

   A: While such comparison does not leverage the unique advantages of *convertible*CAR-T cells, we performed several comparative studies and saw comparable efficacy between *convertible*CAR-T cells with CD20 MicAbody, conventional scFvCD19 CAR-T cells, and counterpart CD20scFv CAR-T cells in mouse models. Whereas conventional CAR-T cells are constitutively armed by the covalently attached scFv specific for just one antigen, the activity and targeting of *convertible*CAR-T cells is subject to control by MicAbody dose and target specificity. As expected, therefore, animal experiments have shown predictable relationships between efficacy and both *convertible*CAR-T cell numbers and how the MicAbody is administered. Crucially, we have been able to approach comparable efficacy to benchmark scFvCD19- and scFvCD20-CAR-T cells even in the absence of extensive dose-response optimization studies. For example, in a disseminated Raji leukemia study, the efficacy of 5 million scFvCD19 CAR-T cells was indistinguishable from that of 10 million *convertible*CAR-T cells plus MicAbody. Similarly, in solid Raji lymphoma studies, 35 million *convertible*CAR-T cells plus MicAbody were again at least as efficacious as 10 million scFvCD19 CAR-T cells (0.6% versus 3.7% of average masses of the tumors in the vehicle control cohorts, respectively). The opportunity for post-infusion control of CAR-T cell reactivity is one of the chief advantages of *convertible*CAR-T cells and the basis of our expectation that modifications to the CAR-T cell and MicAbody dosing regimens will afford further significant improvements in tumor control in the clinic.

   We understand and are pleased with the reasons for and opportunities created by needing more *convertible*CAR-T cells. All scFv Receptors on the conventional CAR-T cells are covalently bound to the scFv targeting motif. In contrast, and by design, MicAbody binding sites on the cell surface of *convertible*CAR-T cells are only partially saturated after rapid CAR-T cell expansion *in vivo*. The excess of unoccupied and inert CARs on the surface of *convertible*CAR-T cells provides for additional MicAbody-dose control of their activity, vacant CAR sites for multiplexed targeting, and privileged access for their bio-orthogonal ligands to deliver specifically to their cell surface other molecules such as cytokines, checkpoint antagonists, or ablating agents.

2. Q: Rather than developing a 2-component system to direct T cells to target cells, why not simply use a bispecific antibody that binds to CD3 on T-cells?

   A: The simple answer is that we designed the *convertible*CAR-T cell technology to combine the impressive efficacy of CAR-T's with the flexibility of bispecific antibodies. With Xyphos'

*convertible*CAR-T cells both the activity and targeting of *convertible*CAR-T cells can be precisely controlled by our proprietary bispecific antibody, the MicAbody.

Bispecific T cell engagers (BiTEs) and other bispecific T cell-engaging antibodies are designed to tether T cells to tumor cells. The tethering ultimately results in destruction of the tumor cells because the bispecific antibody delivers an activating signal to the recruited T cells. MicAbodies act in a related fashion because they too form an activating tether between T cells and tumor cells. Crucially, however, the MicAbodies only activate cells expressing the *convertible*CAR, whereas conventional bispecific antibodies are indiscriminate in which T cells they recruit and activate. Also, it is now well established that many tumors contain few tumor-infiltrating T-cells (so called "cold" tumors), and/or that those T-cells are exhausted. Both factors lead to a reduced response for T-cell engaging bispecific antibodies. In contrast, *convertible*CAR-T cells are expanded *in vitro* under defined conditions designed to reduce substantially heterogeneity of quality and quantity of patient's endogenous T cell cells. Reduced heterogeneity is expected to improve therapeutic reproducibility, reliability, and efficacy.

Furthermore, the history of CAR-T cell development reveals the importance of co-stimulatory components for the impressive efficacy of current CAR-T cells. First generation CAR-T cells that lacked co-stimulatory domains have now been replaced with second and third generation CAR's that possess co-stimulatory domains, such as CD28, 4-1BB, OX40, in order to provide the greater anti-tumor efficacy. Bispecific antibodies targeting CD3 do not activate co-stimulatory signals in T-cells and therefore are not so potent as current generation CAR-T cells or our *convertible*CAR cells that have the co-stimulatory domains integrated into the CAR. It is now well established – especially for CAR-T cell therapy – that durable complete T cell responses require costimulation. Our *convertible*CAR-T cells are therefore expected to demonstrate enhanced potency and long-term protection compared to bispecific antibodies.

3. Q: How complicated will the GLP toxicology and the Phase I study be with the 2-component *convertible*CAR-T cell and MicAbody system?

A: The GLP pharm-toxicology study urged by the FDA in our pre-pre-IND meeting is a single species study mimicking our proposed first-in-human study. The safety assessments of the CAR-T cells and the MicAbody can be temporally conducted in parallel, and as soon as the NOAEL for the prearmed CAR-T cells has been established, the NOAEL for the MicAbody in combination with CAR-T cells can follow. The FDA currently has extensive familiarity and experience with GLP toxicology of CAR-T cells.

Our proposed first-in-human study will be in patients who have failed standard of care therapies. As a result, the study must, for ethical reasons, provide some potential benefit to each volunteering patient. The *convertible*CAR-T cell alone and the MicAbody alone are inert and could provide no potential for benefit to the patient. Accordingly, our proposed "3+3" protocol is to treat each subsequent cohort with an increased number of pre-armed

*convertible*CAR-T cells, and two to three weeks later in the absence of grade 3 or 4 adverse events, within each cohort add as controlled by the treating physician, a nested single-dose escalation of free MicAbody to titrate the rearming of the *convertible*CAR-T cells.

4. Q: How does *convertible*CAR technology improve CAR-T cell persistence *in vivo*?
   A: First, a significant impediment to the persistence of current CAR therapies is the use of mouse-derived scFv receptors, which can elicit robust anti-drug antibody (ADA) responses in immunocompetent patients . The *convertible*CAR components are derived from human proteins and are designed to avoid ADA responses, thereby improving efficacy and persistence.

   Additionally, expression of scFv CARs (due to their unnatural configuration) has a functional consequence on the T cell, including tonic signaling which can lead to their premature exhaustion. Our *convertible*CAR is based upon a minimally modified naturally occurring surface-expressed protein (iNKG2D), which leads to enhanced stability on the surface of our *convertible*CAR-T cells. Furthermore, we can demonstrate that even in the presence of saturating levels of MicAbody (and in the *absence* of a tumor target), there is no activation of the cells and thus, the absence of tonic signaling.

   Finally, *privileged partnering* between iNKG2D and its orthogonal ligand can provide selective and local delivery of cytokines to promote the persistence of *convertible*CAR cells as well as drive their expansion as needed, without activation.

5. Q: Aren't MicAbodies going to be immunogenic since they are modified human proteins?
   A: Possibly some patients, depending on their MHC genotypes and immune status, will generate an immune response against MicAbodies. The modified, non-natural iNKG2D-binding domain of the MicAbodies contain nine or fewer substitutions, far fewer mutations than typical CDRs of therapeutic antibodies. Further, we have generated MicAbodies based on different natural ligands of NKG2D so as to be able to by-pass an immune response to a particular MicAbody by simply switching the MicAbody – with or without changing the targeting domain. For the MicAbody binding domain on *convertible*CAR-T cells, only one amino acid change was made to generate the non-natural, inert NKG2D receptors of *convertible*CAR cells. Supporting our protein design choices, *in silico* immunogenicity analyses of both the inert NKG2D and orthogonal ligands predict no more risk of immunogenicity than do their respective wild type alleles. Overall, we anticipate MicAbodies and the non-natural, inert NKG2D receptors will be significantly less immunogenic than the CAR-T cells based on scFv's derived from mouse antibodies and currently in the clinic .

6. Q: Why do you expect MicAbodies will access solid tumors and be efficacious when typical monoclonal antibodies are ineffective because they don't penetrate solid tumors?

A: Naked monoclonal antibodies and Antibody-Drug Conjugates (ADCs) are efficacious in numerous different solid tumors, e.g. trastuzumab, cetuximab, anti-mesothelin. Since MicAbodies, are very similar to therapeutic antibodies, we expect them to be able to access the tumor microenvironment as well as their monoclonal counterparts. The *convertible*CAR-T cells should respond to inflammatory signals emitted from solid tumors as do natural T cell populations. Recent successes with monoclonal antibodies that relieve T cell checkpoints show that T cells can have remarkable efficacy against a range of solid tumors. *convertible*CAR-T cells have similar potential to be efficacious depending on how they are deployed.

Bystander T-cells are frequently present in solid epithelial tumors, and when unarmed, *convertibe*CAR-T cells are effectively bystander (inert) T-cells. Once the inert CAR-T cells are present in the tumor, MicAbody targeting the cancer cells can be administered, potentially enter the tumor, bridge the cancer cells and the otherwise inert CAR-T cells, and effect target cell cytolysis. Furthermore, a MicAbody targeting immune-suppressor cells within the tumor can be multiplexed with the cancer cell-targeted MicAbody or even administered prior to the latter in order to reduce the hostile tumor environment and enable more effective cytolysis.

7. Q: Why target CD20 when those medical needs are already satisfied by monoclonal antibodies and approved CD-19 targeted CAR-T cells?

A: Today, conventional CD19-targeted CAR-T cells have induced very impressive, high rates of responses in patients with refractory B-cell hematologic malignancies. However, long-term disease-free survival is not complete. The malignant cells of many relapsed patients lack CD19, and may be better treated with a CD20-targeting approach, either sequentially or simultaneously with *convertible*CAR-T cells plus CD20 MicAbody. In clinical studies, conventional CD20-targeted scFvCAR-T cells have not shown the same efficacy as have CD19-targeted CAR-T cells, apparently because of the instability of the CD20-based scFv CAR resulting in "exhaustion" of the T-cell. In contrast, CD20-targeting MicAbodies are as stable *in vitro* and *in vivo* as Rituximab. Therefore, Xyphos will develop its CD20-targeted *convertible*CAR-T cell for treatment of patients with relapsing, CD19-negative B-cell malignancies.

Targeting CD20-positive B-cell malignancies also leverages a validated target for which there is valuable knowledge of likely adverse events and their management as well as efficacy endpoints.

8. Q: When will the first *convertible*CAR-T cell and MicAbody system be in the clinic?

A: We can anticipate entering the clinic in late 2019, early 2020.

9. Q: What are the pharmacokinetic and pharmacodynamics properties of MicAbodies in humans?

A: Those properties will be determined during first-in-human clinical studies. In mice MicAbodies have properties typical of human IgG1 antibodies.

Differentiation and IP of platform

10. Q: Why is a *convertible*CAR-T cell safer than the typical pre-targeted CAR-T cell?
A: In the absence of a targeting and activating MicAbody, *convertible*CAR-T cells are incapable of engaging antigens and are therefore inert. MicAbodies are also inert in the absence of *convertible*CAR-T cells and their target. *convertible*CAR-T cells are selectively activated only in the presence of a MicAbody and a tumor cell displaying the antigen to which the MicAbody binds. By contrast, conventional CAR-T cells are fully functional when infused in a patient and only require antigen encounter to be activated, without offering any activity control. In summary, clinicians can control the activity of *convertible*CAR-T cells by changing MicAbody dosage, but they have no such means to control conventional CAR-T cells except to kill them.

11. Q: Next generation CAR-T cells entering preclinical and clinical stages contain effective on/off/kill switches, so why use a complicated two-component system of *convertible*CAR-T cells plus MicAbody to control activity by dosing?
A: On-off switches in CARs are examples of elegant cell engineering in conventional CAR-T cells targeting a single tumor antigen. However, they complicate the intracellular machinery, and this added operational complexity increases the risk of failure or unanticipated effects. Furthermore, on-off switch CARs still require dosing with another drug component in order to exert control. By contrast, MicAbodies offer the ability to implement on/off/kill switches deploying privileged partnering *and* to switch or multiplex targets within the same molecule class and without producing multiple CAR cells. This flexibility of targeting and multiplexing is not provided by conventional CAR technologies.

12. Q: What are the advantages of the *convertible*CAR-T cell and MicAbody system over UNUM?
A: A unique safety liability of UNUM's high affinity CD16 receptor CAR is that the CAR-cell will be activated by and attack any off-target cell that is opsonized by any normal CD16-binding IgG. The inert NKG2D of the *convertible*CAR, due to its privileged partnering with the orthogonal MicAbody, cannot bind any natural ligands and thus is without an analogous safety liability in the presence of even an excess of natural ligands, soluble or cell surface displayed. Furthermore, in contrast to our *convertible*CAR-T platform, the CD16 CAR of UNUM's CAR-T cell cannot be deployed to deliver functional domains (like cytokines, checkpoint inhibitors or modulators) selectively and exclusively to their CAR-T cells, since there is no privileged partnering between UNUM's CAR and any ligand.

13. Q: How is the *convertible*CAR-T platform different from that of CALIBR's "switch" platform?
A: There are two important aspects shared by the two platforms. First, each can provide via an adapter a dose-dependent activation of their respective CAR-T cells. Second, each provides a

means of converting or switching the targeting of the CAR-T cells without starting over with CAR-T cell engineering and production. But there are differences on several fronts.

A chief difference between the two systems is the nature of ectodomain of the chimeric antigen receptor: CALIBR uses an scFv as its binding moiety, while the *convertible*CAR employs a minimally mutated variant of a natural human cell surface receptor, NKG2D. The clinical utility of scFv's can be complicated by anti-drug antibody (ADA) responses; CARs based on scFv's are also sometimes prone to self-aggregation resulting in deleterious tonic signaling that causes T cell exhaustion. These complications are not relevant to the *convertible*CAR because of the near-natural form of its ectodomain. In a similar fashion, the protein neo-epitope that is targeted by the CALIBR CAR is derived from yeast, and though *in silico* modeling studies suggest this peptide foreign to humans is not likely to initiate ADAs, this remains to be established in the clinic. The *convertible*CAR binds mutated versions of natural human proteins fused to antibody chains (as part of MicAbodies); ADAs are not expected to be a problem with MicAbodies because of the small number of changes introduced into the NKG2D ligand; but if one arises, it can be readily overcome simply by switching to an alternative MicAbody format (employing an available, distinctly different orthogonal iNKG2D ligand). By contrast, the CALIBR scFv-based CAR has mono-specificity and presents no such opportunities for an alternative receptor.

14. Q: Does Xyphos have any intellectual property protection of MicAbodies and *convertible*CAR-T cells?
A: U.S. and PCT patent applications were published in February 2017. See WO/2017/024131.

15. Q: Won't the antibody portions of the MicAbodies infringe existing composition of matter patents?
A: As Xyphos is initially focusing on validated tumor targets, numerous mAbs against those targets have not been patented or are now off-patent. Further, as Xyphos is broadening its pipeline, many of the issued patents claiming mAbs are sequence-specific and not target-specific, thereby leaving opportunities for generating novel antibodies, e.g. generated by phage- or yeast-display technologies. Finally, we also intend to obtain access to novel mAbs through strategic partnerships or licensing.

16. Q: Does the Xyphos have access to or freedom to operate in the CAR-cell space?
A: The key patent in the field, commonly known as Eshhar "465" (US 7,741,465), has 2 independent claims each limited to an scFv CAR on a cell. Given our unique construct not based on scFv, we apparently do not infringe the patent.

Concerning other CAR components: Years after many journal publications and the filings of now expired patents, hundreds of patents have been filed and tens of U.S. patents issued, all claiming CARs and CAR-cells with the same unnatural component parts, e.g. TCR CD3 zeta, CD28, 4-1BB, in spite of the obvious prior art. Clearly, there must be freedom-to-operate

deploying such component parts to create CARs with variations in the targeting domains, connectors, transmembrane components, etc. Adding to the complexity, there are several *inter partes* reviews and litigation underway, but those appear to be the result of companies in pivotal clinical trials directly using another's claimed sequences of extracellular domains of CARs. We are closely monitoring the IP landscape together with our external IP counsel.

Manufacturing considerations

17. Q: Can the Xyphos manufacture autologous and allogeneic *convertible*CAR-T cells?
A: We plan to partner with entities with that capability or contract with established CDMO's capable of eventual commercial scale cGMP production of CAR-Ts.

18. Q: How does MicAbody manufacturing compare to therapeutic antibody production??
A: Production is comparable to typical monoclonal antibodies at laboratory scale by transient expression in HEK293 or CHO cells or in stable CHO cells.

19. Q: Doesn't manufacturing both cGMP CAR-T cells and cGMP MicAbodies double the cost and make the product not viable commercially? Wouldn't it be easier and more cost-effective to simply generate new CAR-T cells for each desired target?
A: The cost and time to manufacture and QC release a GMP MicAbody™ protein with a new targeting domain (new V_H and V_L variable domains while keeping the IgG C_{H1}-C_{H3}, C_L, and *convertible*CAR-engaging ligand the same) will be significantly less than manufacturing and QC releasing a new transducing vector plus a new CAR-T cell, either autologous or allogeneic, with a new targeting domain. In addition, a portfolio of individual MicAbodies with frequently indicated targets could be manufactured and approved, and then the desired MicAbody would be selected from the portfolio of approved MicAbodies for use in multiple patients without changing or even retreating with the patients' *convertible*CAR-T cells.

20. Q: Won't administering more *convertibe*CAR-T cells and MicAbodies cost more than fewer scFvCAR-T cells?
A: Note that the proposed pricings of the 2 approved CAR-T cell therapies are not based on numbers of cells administered. In fact, in pivotal studies of adults the dose ranges were quite broad, as much as 5-fold different. Effectively, the cost of goods for different numbers of cells administered is marginal.

The MicAbody component of the *convertible*CAR-T treatment will add cost to the therapy, but the predicted dose levels of MicAbodies are only a small fraction of the typical dose of an anticancer monoclonal antibody. The big economic and clinical advantage of *convertible*CAR-T therapy will be the ability to control CAR-T cell activity by MicAbody dosing and to change targeting by adding sequentially or simultaneously more than a single

targeting MicAbody to treat or prevent tumor escape without having the patient endure the morbidity, delay and expense of generating a new scFvCAR-T cell population.

21. Q: Are MicAbodies stable at ambient temperatures; can they be lyophilized for commercial purposes?

A: They are stable at ambient and 4°C as well as frozen, typical of a monoclonal antibody.