TCR Engineered T-Cell Therapy 2018:

an industry analysis of technologies, pipelines, stakeholders & deals

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HLA-bound **TUMAPs** are identified and quantified using the XPRESIDENT technology directly from primary human tumor and normal tissue samples by liquid chromatography tandem mass spectrometry (LC-MS/MS). Over-presentation on peptide level is confirmed by over-expression using RNAseq. Candidate TUMAPs may be suitable targets for TCR-based immunotherapies. Furthermore, healthy tissue analyses help to predict potential on- and off-target toxicities for the identified targets and compound TCRs.

TUMAP pHLA target restricted **TCRs** are identified in high throughput from primary human peripheral blood mononuclear cell (PBMC) samples, possible for several targets in parallel. TCRs are re-expressed and qualified as clinical candidates for further development, adoptive cellular therapies (or TCR bispecific approach).

TCR identification requires cutting-edge technologies to differentiate target-specific TCRs from the natural repertoire. The criteria that define clinical candidate TCRs, are affinity and specificity. Immatics combines different technologies to apply maximal stringency already during TCR identification. TUMAP-restricted T cells are isolated directly from the natural repertoire or after in vitro T cell priming. 2D multimer staining allows for highest sensitivity and specificity during analysis and single cell isolation via FACS. Finally, highly sensitive and robust, high throughput-adopted 5' RACE on single cell level allows for TCR coding sequence identification. Usually,150 TCRs per target are collected from ~25 healthy donors. The identified TCRs are conducted to TCR qualification for further characterization and validation.

For TCR characterization, isolated TCRs are re-expressed in primary T cells via electroporation of in vitro transcribed mRNA. First step during characterization is to classify all identified TCRs according to functional avidity and initial specificity. The functional avidity is determined by target peptide-titration. Initial specificity characterization covers a number of peptide-sequence based similar peptides, that are detected by mass-spectrometry on normal tissues. Clinical candidate TCRs differentiate similar peptides from TUMAP targets and thus pass an important step in safety profiling. Positional scanning, like alanine-scanning, provides insight into TCR-individual binding characteristics and enable the first search for TCR motif based similar peptides in Immatics' XPRESIDENT database.

TCR qualification addresses 3 questions: TCR efficacy, safety and specificity. This includes the analysis of TCR-mediated responses towards target-positive and -negative cells. First, efficacy is

expressed in 50% of esophageal squamous cell carcinomas and is broadly expressed in various other tumors.

Takara's proprietary **siTCR gene therapy** involves the use of the siTCR vector technique to silence endogenous TCR creation. This technique minimizes the involvement of endogenous TCRs and allows for obtaining more lymphocytes that express the target TCR, thereby reducing the risk of side effects and improving effectiveness.

In a joint project with Mie University, an exploratory investigator-initiated phase I clinical trial of TBI-1201 to treat esophageal cancer in HLA-A*24:02 positive patients with confirmed MAGE-A4 expression (ClinicalTrials.gov NCT02096614) is ongoing. The study began in March 2014. Doses of $5x10^8$ and $5x10^9$ cells are being evaluated with different pretreatment protocols in 12 patients. Following pre-treatment with cyclophosphamide alone or in combination with fludarabine, MAGE-A4-specific TCR gene transduced T lymphocytes are transferred to HLA-A*24:02 positive patients with solid tumors which are 1) unresectable, refractory to standard therapy (chemotherapy, radiotherapy, etc), metastatic or recurrent, and 2) MAGE-A4-expressing. The primary objective is to evaluate the safety and in vivo kinetics, and the secondary is to evaluate clinical effect.

To generate TBI-1201, scientists at Mie University established a cytotoxic T-lymphocyte (CTL) clone that recognizes the MAGE-A4143-151 peptide in an HLA-A*24:02-restricted fashion. Using receptor engineering, they constructed a retrovirus vector, MS-bPa, for transduction of T cells with the TCR-alpha and -beta chains derived from the MAGE-A4143-151-specific T-cell clone. They developed retroviral vectors encoding both small interfering RNA (siRNA) constructs that specifically downregulate endogenous TCR and a codon-optimized, siRNA-resistant TCR specific for MAGE-A4.

4.3 Profiles of NY-ESO-1 Specific TCR T-Cells

4.3.1 GSK3377794; NY-ESO SPEAR T-cell therapy; NY-ESO-1^{c259}T

In September 2017, GlaxoSmithKline (GSK) exercised its option under a collaboration and license agreement with Adaptimmune Therapeutics signed in 2014 to exclusively license the right to research, develop, and commercialize Adaptimmune's NY-ESO SPEAR (Specific

In August 2016, Cell Medica entered into a research collaboration with UCL (University College London) aiming to utilize UCL's novel T cell receptor (TCR) technology (Press Release Aug 24, 2016). The collaboration also provides Cell Medica with an exclusive worldwide option and license agreement for these technologies as well as TCR gene sequences for the development and commercialization of specific products. The UCL TCR technology has the potential to produce strong expression of TCRs by the engineered T cells which is expected to improve their efficacy in fighting tumors.

UCL will conduct the preclinical and early clinical research under the guidance of a Joint Steering Committee. Cell Medica will support the product development work with its substantial experience in manufacturing clinical-grade cell therapies and establishing robust production processes suitable for industrial scale-up. Following completion of successful first-in-man studies, the products will transfer to Cell Medica for later-stage clinical development and commercialization.

Cell Medica has entered into an exclusive license and option agreement with UCL Business, the technology commercialisation company of UCL, for the dominant TCR platform patent and two target antigens. As part of this agreement, both parties can bring targets or platform technologies to the collaboration, aiming to generate leading-edge modified TCR products.

Acquisition of Catapult Therapy TCR

In June 2017, Cell Medica acquired Catapult Therapy TCR Limited, a subsidiary of Cell and Gene Therapy Catapult (CGT Catapult), and initiated a collaboration to establish cell therapy manufacturing for Cell Medica at CGT Catapult's GMP manufacturing facility in Stevenage, UK (Press Release June 20, 2017). Catapult Therapy TCR was a special purpose company set up by CGT Catapult, UCL Business and Imperial Innovations, and managed by CGT Catapult, for the development of the WT1 T cell receptor (TCR) cell therapy discovered through research at UCL and Imperial College London. CGT Catapult has been developing the WT1-TCR cell therapy for the treatment of acute myeloid leukaemia and myelodysplastic syndrome. Early development work, including initiation of a Phase I trial, was conducted at UCL and Imperial College London with funding from the UK charity Bloodwise. CGT Catapult advanced the product to a larger Phase I/II clinical trial and developed an improved manufacturing process. Having completed the

Table 29: Financing Sources of Selected Diversified Companies with TCR-T Activities

Company	Technologies	Source / Year	Amount (US$)
Adicet Bio	TCR-like antibodies γδT-cells for CAR & TCR	Series A / 2016	51
		Partnering / 2016	25
Cell Medica	CTLs, TCR-T, NKTs	2007/2009	13 mln
		CPRIT grant / 2012	26.5 mln
		Series B / 2014	69.7 mln
		Series C / 2017	83.7 mln
Eureka Therapeutics	CAR- and TCRL-T ARTEMIS technology	Series B / 2008	8 mln
		Series C / 2014	21 mln
		Series D / 2018	60 mln
Medigene	Target & TCR discovery, TCR-T, vaccines	PO / 2015	54.6 mln
		Sale of stock / 2016	7 mln
		Divestment / 2016	3.4 mln
		Partnering / 2016	15 + 8 mln
		DO / 2017	24.4 mln
Tmunity Therapeutics	Next gen CAR-T, TCR-T, allogeneic, Treg	Equity / 2016	10 mln
		Series A / 2018	135 mln