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Supplementary information

A call to adapt the regulation of HLA testing for T cell receptor-based therapeutics

In the format provided by the authors

Supplementary Material

Supplementary Figure 1:

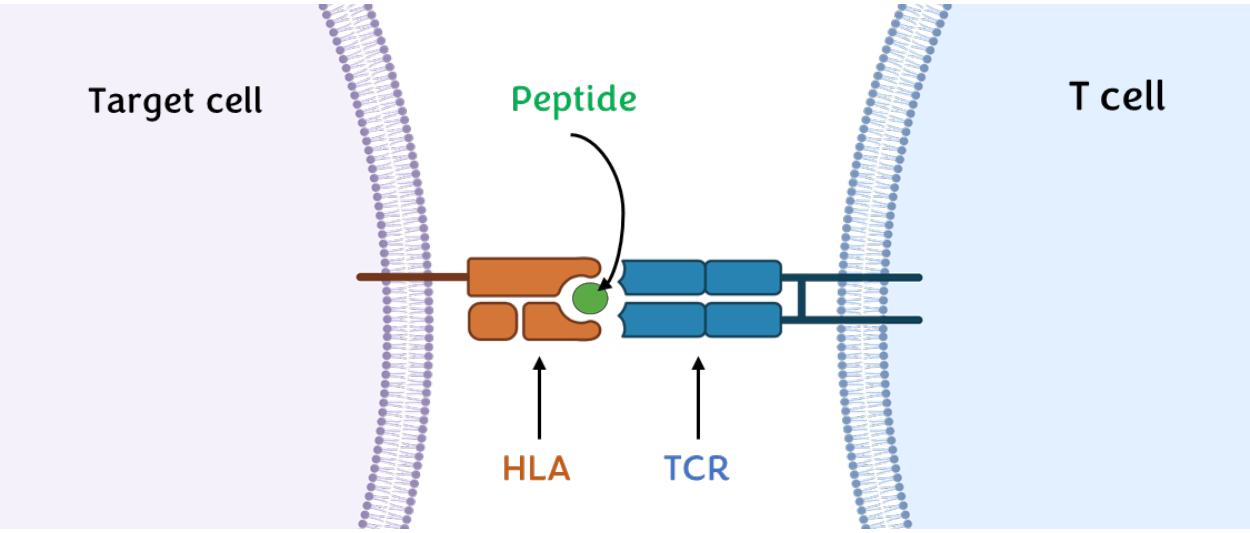

Figure 1. Antigen recognition by T-cell receptors (TCRs). αβ TCRs do not bind antigen directly but recognize short peptide fragments presented by human leukocyte antigen (HLA) molecules. The peptide fragments are derived from degradation of the endogenous cellular proteome which may contain foreign entities in case of infection, or from degradation of endocytosed cellular or microbial material. A given TCR typically displays high specificity toward a given peptide/HLA complex. Each HLA molecule can bind a variety of peptides that fit their unique peptide-binding groove. Each person expresses up to six different HLA class I (HLA-I) and about a dozen different HLA-II heterodimers which present peptides to CD8+ and CD4+ T cells. This system provides the host with the ability to present a wide spectrum of different peptides to T cells which can lead to broad T-cell based protection against pathogens and cancer. The HLA genotype of a person is determined in the germ line and does not change over a lifetime. Figure partially created with BioRender.

Supplementary Box 1: Further information on HLA genotyping
Differences in regulatory framework among world-regions

US regulatory framework:

In the US, HLA genotyping for TCR-mediated therapies is considered a companion diagnostic (CDx) categorized as class II, requiring de novo or 510(k) clearance for use with a specific ***commercial therapeutic*** *for each specific indication. This means that generally, TCR-mediated therapeutics can only be used together with a cleared CDx that includes the specific drug product and tumour indication in the label. FDA recently proposed the idea that minimum performance criteria could be defined that could enable the use of other (locally available) tests that meet those criteria and issued a guidance on a pilot program enabling this alternative pathway avoiding the one-drug-one-device scenario in certain cases (Food-and-Drug-Administration. Oncology Drug Products Used with Certain In Vitro Diagnostic Tests: Pilot Program. Guidance for Industry, Clinical Laboratories, and Food and Drug Administration Staff. 2023).*

A CDx-specific study is typically not required for HLA genotyping in clinical trials when the HLA genotyping test is used for investigational purposes. Instead, a risk-based approach can be applied to decide whether an Investigational Device Exemption (IDE) is required, or abbreviated IDE requirements must be met.

EU regulatory framework:

In contrast to the US, the only ***approved*** *TCR-based therapy KIMMTRAK can be used based on HLA genotyping with any validated HLA genotyping assay from accredited laboratories. In the EPAR to KIMMTRAK, CHMP states that "HLA genotype is not an efficacy or safety biomarker for mUM [metastatic uveal melanoma] patients and it is a routine diagnostic test used in other high-risk clinical settings (e.g., in organ transplant)". Kimmtrak | European Medicines Agency (europa.eu). Our interpretation is that HLA genotyping is not considered a CDx in this context. The EU has recently implemented a new In Vitro Diagnostics (IVD) Regulation and this may change the requirements for HLA-typing assays for new TCR-mediated therapeutics to be approved in the future under the new regulation.*

Of note: To select patients for treatment with ***investigational therapeutics*** *in the EU, based on Medical Device Coordination Group (MDCG) 2022-10, a* ***CE-certified*** *assay that meets the intended use of the clinical trial is required. Alternatives are the use of an in-house test performed in a qualifying Health Institution or to conduct a clinical performance study. Requirements for investigational products are higher than for the first approved TCR-T therapy. However, in line with the argumentation outlined in this article, MDCG-2022-2 confirms that "*for markers that are not specific to a particular condition but are adequately defined by scientific validity to be relevant in multiple clinical settings, separate clinical studies for each clinical setting/indication would not be expected."

Great Britain and Northern Ireland

The United Kingdom is currently regulating IVDs through the 2002 Medical Device regulation. IVDR 2017/746 will not be adopted in Great Britain (GB) but will apply in Northern Ireland in line with the current treaty governing the UK leaving the EU (GB covers the UK excluding Northern Ireland). This is likely to be written in the next 12 months and complete review and approval in 2-3 years. Until then the current 2002 regulation will stand.

List of useful background information

- Guidance for Industry: In Vitro Companion Diagnostic Devices (July 2014) - *Defines in vitro companion diagnostic device and gives guidance to developers of therapeutic products and/or relevant IVD companion diagnostic devices on regulatory pathways to approval, labeling as well as investigational use.*
- Draft Guidance for Industry: Principles for Co-development of an In Vitro Companion Diagnostic Device with a Therapeutic Product (July 2016) – *Intents to assist sponsors in the co-development of a therapeutic product and an accompanying CDx from investigational phase through late stage development and contemporaneous marketing approval.*
- Guidance for Industry: Developing and Labeling In Vitro Companion Diagnostic Devices for a Specific Group of Oncology Therapeutic Products (fda.gov) (April 2020) *– Guidance on the prerequisites and process of introducing a broader labeling of companion diagnostics, covering the use with a specific group of oncology therapeutic products rather than with individual products.*
- Recommendations for Premarket Notification (510(k)) Submissions for Nucleic Acid-Based Human Leukocyte Antigen (HLA) Test Kits Used for Matching of Donors and Recipients in Transfusion and Transplantation | FDA - *Information on the types of studies FDA recommends for validation of HLA test kits submitted as 510(k)s and used for the matching of donors and recipients in transfusion and transplantation.*
- 21 CFR § 866.5960: Human leukocyte antigen typing companion diagnostic test – *US codification of the definition, the classifications classII and the special controls for HLA companion diagnostic test.*
- Fierce Biotech - FDA looks to bypass cancer drugs' companion diagnostics with new pilot program: Pazdur - Friends of Cancer Research (Nov 2022) – *Article gives an outlook on a pilot program at FDA, aiming at the definition of minimal performance criteria for diagnostic tests rather than mandating a one-drug-one-test situation for companion diagnostics. However, it is too early to say if this would facilitate development of and access to TCR-mediated therapeutics.*
- The European Union In Vitro Diagnostics Regulation 2017/746 (EU IVDR) (May 2022) - *New regulation for IVDs introducing the term Companion Diagnostic Device in the EU regulatory framework and aiming to provide harmonized classification rules and regulatory pathways for development and approval of IVDs, including companion diagnostics.*
- MDCG 2022-2 Guidance on general principles of clinical evidence for In Vitro Diagnostic medical devices (Jan 2022) – *Guidance on the process of performance evaluation for IVDs as set out in the IVDR. It acknowledges that based on IVDR Article 2 (39), "clinical performance may not be required for certain devices", and in particular that for "markers that are not specific to a particular condition but are adequately defined by scientific validity to be relevant in multiple clinical settings,*

separate clinical studies for each clinical setting/indication would not be expected" (Chapter 6.6.).

- MDCG 2022-10: Q&A on the interface between Regulation (EU) 536/2014 on clinical trials for medicinal products for human use (CTR) and Regulation (EU) 2017/746 on in vitro diagnostic medical devices (IVDR) (May 2022) – *Developed by clinical trials experts from Clinical Trials Facilitation and Coordination Group (CTFG) and in vitro diagnostics experts from the IVD sub-group of the MDCG, this Q&A document intents to clarify the interface between the two new EU regulations and how IVDs can be used in the context of drug clinical trials. Based on this guidance, an IVD used in a clinical trial needs to be either CE marked for the intended purpose, or be used as in-house IVD based on Article 5(5) IVDR, or be assessed as device for performance study.*
- New European legislation designed to protect patients is delaying clinical trials for thousands of people with cancer and rare diseases (efpia.eu)) – *Article describes how introduction of IVDR leads to delays in clinical trials and launch of innovative treatments in Europe. Delays arise from the need for an IVD to undergo an assessment process when the test result influences patient medical management. Recommendations to alleviate those barriers are provided.*
- UK Medical Devices Regulation 2002: Medical Device regulation and safety - *Currently regulating In vitro Diagnostics in the UK.*

Supplementary Box 2. Ethic declarations

Competing interest

Author name	Employed by a company working in the field of TCR therapeutics?	If so, which company?	If so, which?	Holds stock/options in a pharmaceutical company	Acts as a consultant ?	If so, which?2	Any other potential conflict of interest
Miriam Meyer	Yes	Immatics Biotechnologies	Immatics Biotechnologies GmbH	Yes	No		None
Andrea Mahr	Yes	Immatics Biotechnologies	Immatics Biotechnologies GmbH	Yes	No		None
Anders Wennborg	Yes	Miltenyi Biomedicine		No	No		None
Axel Roers	No			No	No		None
Cassian Yee	No		Immatics Biotechnologies GmbH	Yes	Yes	Immatics, T-Cypher Bio, Achilles Therapeutics	None
Dennis Williams	Yes	Adaptimmune	Adaptimmune	Yes	No		None
Dirk Nagorsen	Yes	Affini-T Therapeutics	Affini-T Therapeutics, Amgen Inc.	Yes	No		None
Dolores J. Schendel	Yes	Medigene Immunotherapies GmbH/AG	Medigene AG	Yes	No		None
Eric Tran	No			No	Yes	AstraZeneca	Scientific Advisory Board member for Turnstone Biologics.
Gavin MacBeath	Yes	TScan Therapeutics	TScan Therapeutics	Yes	No		None
Ian Johnston	Yes	Miltenyi Biotec B.V & Co KG		No	No		None
Joanna E. Brewer	Yes	Adaptimmune	Adaptimmune	Yes	No		None
Justine Dell'Aringa	Yes	Bristol Myers Squibb	Bristol Myers Squibb	Yes	No		None
Koustubh Ranade	Yes	Immunocore	Immunocore	Yes	No		None
Leanne Peiser	Yes	Bristol Myers Squibb	Bristol Myers Squibb	Yes	No		None
Luise U. Weigand	Yes	Zelluna Immunotherapy AS	Immunotherapy AS	Yes	No		None
Mark Moyer	Yes	Immunocore	Immunocore	Yes	No		None
Michael Loveridge	Yes	T-knife Therapeutics	T-knife, BMS	Yes	No		None
Özlem Türeci	Yes	BioNTech SE	BioNTech SE	Yes	No		None
Pallavur Sivakumar	Yes	Bristol Myers Squibb	Bristol Myers Squibb	Yes	No		None
Pamela Larson	Yes	Medigene AG		No	No		None
Anthony Goldstone	No			No	No		None
Ruben Rizzi	Yes	BioNTech SE	BioNTech SE	Yes	No		None
Sarah Hersey	Yes	Bristol Myers Squibb	BMS, Novartis, Johnson and Johnson	Yes	No		Member of the Personalized Medicine Coalition board, board member of Sampled, Board Observer for Precede Biosciences
Sophie Papa	Yes	Enara Bio	Enara Bio	Yes	Yes	Zelluna	None
Volker Daniel	No			No	No		None
Cedrik M Britten	Yes	Immatics Biotechnologies	Immatics Biotechnologies	Yes	No		None