Letter to the editor: Checking the pulse of adoptive cell therapy for solid tumors. Thoughts from the abstracts submitted to the 35th Annual Meeting of the Society for the Immunotherapy of Cancer (SITC 2020)

Martina Markovska,¹ Francesco Marincola²

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ABSTRACT

Adoptive cell therapy (ACT) for the treatment of solid malignancies has not met yet the success of hematological malignancies. This is due to additional roadblocks peculiar to its deployment for the former application. While T-cell fitness stands as a prerequisite for all purposes of ACT, selection of optimal tumor-specific antigens, efficient trafficking to neoplastic tissues, and overcoming immune exclusion and/or suppression are challenges pertaining predominantly to solid malignancies. To gain insights about the current interest on the subject in both academia and industry, we surveyed a snapshot of topical activities and checked the pulse of the field by reviewing content extracted from 94 abstracts submitted, under the subject “cellular therapies”, to the 35th Anniversary Annual Meeting of the Society for the Immunotherapy of Cancer.

Adoptive cell therapy (ACT) particularly adopting engineered T-cell receptors (TCRs) or chimeric antigen receptors (CARs) for the treatment of solid malignancies has not met yet the success of hematological malignancies.¹ This is due to additional roadblocks peculiar to its deployment for the former application. While T-cell fitness, the impact of ACT on endogenous immune responses, and the durability of cell therapy activity stand as a prerequisite for all purposes of ACT, selection of optimal tumor-specific antigens, efficient trafficking to neoplastic tissues, and overcoming immune exclusion and/or suppression are challenges pertaining predominantly to solid malignancies.² We recently summarized the sequence of conditions that gage the therapeutic index for ACT, emphasizing the need to enhance T-cell performance with an integrated approach that covers simultaneously all components of T-cell physiology relevant to their successful deployment.²

To gain insights about the current interest in both academia and industry, we surveyed a snapshot of topical activities and checked the pulse of the field. We conflated in an image (figure 1) content extracted from 94 abstracts submitted, under the subject “cellular therapies”, to the 35th Anniversary Annual Meeting of the Society for the Immunotherapy of Cancer.³ Invited talks were excluded to focus on spontaneous submissions independent of potential selection biases. We included abstracts pertaining or potentially relevant to the development of therapeutic products. Since our interest was on solid cancers, we excluded reports on hematological malignancies. We weeded abstracts dedicated to analytical assessments, biomarker, and/or target discovery. These important topics may influence ACT effectiveness in the long term but do not represent looming drug-gable solutions. Finally, we omitted reports on diseases other than cancer or veterinarian applications.

We observed that current trends revolve around fine tuning of product development by tweaking T-cell expansion methods and other aspects of process development. In addition, a large proportion of abstracts focused on development of off-the-shelf products to streamline production, distribution, and consistency. Beyond such “practical” studies, the general impression was that most research focuses on rationalizing the use of an antigenic target over another and fine tune CAR or TCR interactions with their respective target expressed by cancer cells. This is done by optimizing affinity/specificity and activation requirements through engineering CAR or TCR structures that include

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¹Immunology, Radboud Universiteit, Nijmegen, Gelderland, The Netherlands
²Science, Refuge Biotechnologies, Menlo Park, California, USA

Correspondence to

Dr Francesco Marincola;
fmarincola@gmail.com

Figure 1 Trends in the ACT product development for the treatment of solid malignancies based on abstracts spontaneously submitted to the 35th Annual Meeting of the Society for the Immunotherapy of Cancer (SITC 2020) divided according to broad categories. (+) marks the number of abstracts in a given subcategory. Abstracts are referenced according to their number as published in the *Journal for the Immunotherapy of Cancer*³; in bold are abstracts including a commercial entity among the author list while solely academic reports are in light gray. Abbreviations: DN, dominant negative; KO, knockout; LOH, loss of function; MSC, myeloid suppressor cell; TA, tumor antigen; Abstract # in bold, industry. For other abbreviations, we refer to the text or to the individual numbered abstracts.

multiple antigen specificities corresponding to distinct requirements for T-cell activation that follow alternate Boolean logic permutations. Moreover, a few studies proposed enhancements of individual components of engineered CARs and TCRs. However, such efforts were mostly directed toward technical improvements rather than addressing with a holistic approach the convolutedness of T-cell homeostasis. Few studies aimed at upstream regulatory pathways regulating overall T-cell differentiation and function such as preservation of stem cell-like properties as suggested, for instance, by Lynn *et al.*⁴

Consider that two anti-cancer immunotherapy modalities succeeded in the last decade: ACT for hematological malignancies and checkpoint blockade in solid tumors. While it may be challenging to dramatically improve over the success experienced in the treatment of B-cell

malignancies, much can be done in the context of solid tumors since checkpoint blockade either as a monotherapy or in combination can address only one or few among several immune suppressive mechanisms.⁵ By combining ACT with intrinsic blockade of checkpoint expression in adoptively transferred T cells, it is possible to improve their persistence and function following transfer.^{6,7} This may be further enhanced by educating ex vivo T cells to deploy functions that are not a natural part of the repertoire of resident T cells such as production of IL-12 or maintenance of stemness. This is the true power of adoptive transfer that allows for ex vivo “re-education” of a naturally occurring entity. Yet, most interest seems to reside in practical improvements rather than conceptual advances. We hope that things will change and that next year abstracts will reflect more diverse and broader

trends in ACT development encompassing an integrated enhancement of physiological T-cell effector functions.

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