CELL & GENE THERAPY INSIGHTS

NEW HORIZONS IN CELLULAR IMMUNOTHERAPY: NEXT-GEN PLATFORMS & MODALITIES

SPOTLIGHT

COMMENTARY

Developing harmonized immune platforms: a must-have for realizing personalized therapies in solid tumors

David Morrow, Jan Langermans, Anton Ussi, Antonio L Andreu & Lucia Gabriele

The future of healthcare lies deeply in personalized medicine which we are all aware places the patient at the center of the therapies we develop. Advanced therapies are at the forefront of this strategy, but we are still not harnessing the true power of the data in immunology at our disposal that allow us to understand how our complex "individual' biological systems react to these novel therapies. The goal of CAR-T expansion into solid tumors remains elusive to our scientists with meta-analysis of solid tumor CAR-Ts tested in these tumors revealing only a mere 4.2 percent complete response, for example [1]. Understanding the interplay between a cell therapy, immune checkpoint inhibition, tumor environment, and host that has critical impact on immunotherapies is paramount for the developer and clinician. It demands an integrated, harmonized characterization strategy where innovative partnerships among clinical centers, academic institutions and research infrastructures represent a key strategy. Through the development of harmonized immune platforms comprising these inter-disciplinary teams for personalized therapies in solid tumours, we can provide the optimum innovation strategy and ensure reduction in the present failure rates. Done right, this can further advance the development of these must-have therapies to the clinic - for the right patients at the right time and at the right dose.

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THE LONG ROAD TO SUCCESS IN SOLID TUMORS

The impressive effectiveness of T-cells in oncology seen in patients is well established in the field [2–5]. Gene engineered T-cells are now non-exhaustively investigated for various cancer types, with the greatest success still falling in hematological cancers [3]. There are currently two gene modified T-cell therapies for B-cell malignancies - Kymriah and Yeskarta [4–6] - and one pending market approval. Of note, in 2019 there were over 800 clinical trials ongoing using CAR-T technology alone [7]. However, despite the promise and excitement of these therapies, little success has been seen in the last 3 years for these types of therapy in solid tumors. The road to success for CAR-Ts in solid tumors falls now into well-established research areas. These include amongst others:

1. CAR design with the type of co-stimulatory domain being central to the creation of next generation therapies,
2. Target antigen selection,
3. Delivery approaches,
4. Tumor microenvironment (TME)
5. Co-therapies including immunomodulatory reagents
6. Innovations in CAR-T trials [8–9].

This commentary piece however is not trying to highlight or discuss these well-established research questions. Instead, we aim here to discuss the pivotal need to develop platforms that harness the right technical expertise in immunomonitoring. Such platforms must be suitable to correlating response to CAR T therapy with TME or systemic immunologic dysfunctions determined by several variables, including immune cell balance, immune signature, and tumor lymphocyte function. Certainly, it is now well established that the responsiveness of patients to cell therapies and immune checkpoint inhibition relies on the immune status of the TME, which needs to be evaluated through immunoprofiling and immune signature. These both show great potential to be independent prognostic and predictive biomarkers. However, although they provide crucial insights into immune cell behavior, how they correlate with clinical outcome still requires a lot more investigation. Peripheral blood immune profiling, for example, has been investigated as a non-invasive method to predict response to immunotherapies [10]. In view of this, improving the capability to integrate and harmonize complementary sets of immune parameters across different tumors from different patients will allow us to stratify patients into responders versus non-responders, thereby having the effect of achieving greater success from a more personalized approach. This will result in the increased success of clinical trials where the failure rate currently stands at 80%, in addition to reducing relapse rates post treatment [7]. Furthermore, this can also help decrease the enormous, almost unaffordable price tags for these therapies due to the high clinical trial failure rate because of the unresolved technological challenges that such platforms could remedy.

WHAT SHOULD A PLATFORM CONSIST OF?

Nowadays, immuno-technologies for Precision and Personalized Medicine (PPM) are ever more present in research programs and have begun to be adopted in clinical medicine [11–12]. Their applications however need to be enhanced, implemented, and integrated with other platforms to have a real impact on human health, and to spur policy and economic actions. Technology platforms furthering a novel scientific agenda for diagnostic and prognostic screenings as well as for Prevention Medicine (PM) and/or PPM interventions is a priority. The right platform should have the necessary technologies and expertise in place that can discover

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and validate immune correlates to predict response and guide therapeutic decision-making for the individual patient. Central to this is standardized methodologies of measuring all immune parameters. Such platforms should bring together leading expertise and innovative technological approaches, thus meeting the needs of biotechnology companies, the pharmaceutical industry, and the academic research community. This is pivotal to the successful development of their novel cell therapies and immunotherapies including vaccines. Such an integrated and harmonized approach to immune correlation and prediction of therapeutic response and clinical outcome will improve the output of high utility, validated clinical tools.

The acceleration of the research required to implement such processes for immunomonitoring of patients requires a high level of knowledge and coordination, as well as the application of standards and quality to reduce uncertainty and ascertain the immunotherapy pipeline for solid tumours [13–14]. This can be made possible through effective interaction between private-public networks. In Europe, this collaboration is facilitated by research infrastructures such as EATRIS, which is the European research infrastructure for translational medicine [15–17]. EATRIS has developed a dedicated platform that consists of a dynamic flow of knowledge and resources among 110 world class Institutions across 13 EU countries that integrate and harmonize innovative technologies to monitor immune parameters across different solid tumour types. This enables the identification of patients that can benefit from novel cell therapies and immunological strategies for the treatment of cancer.

High-end, validated analytical technologies are central to a deep and appropriate immune monitoring for pre-clinical and clinical studies aimed at a comprehensive elucidation of the underlying bases of immune responses following the administration of a given therapeutic. These innovative tools range from high-throughput analyses of the transcriptomes and proteomes of single immune cells and integrated mass cytometry immunophenotyping, to imaging immune strategies and standardized immune functional tests, pioneering the use of non-invasive technologies to explore and track the dynamics of the immune system. For example, clinical use of the innovative imaging technology constitutes an unprecedented advance beyond the state of the art, allowing the tracking of the fate of cells after its use in cell therapy in human beings [18–20]. Multimodal imaging approaches in its right form can complement the immunomonitoring tests of any such platform by acting potentially as an early prognostic indicator of therapy success by evaluating proliferation of T-cells, localization and subsequent change in tumor sizes. It is noteworthy that with so many new therapies being assessed on the initial response of the patient, robust, standardized, and validated capabilities to monitor immune responses are essential. This will result in the correct evaluation for shaping interactions between immune cells in tumours leading to better outcomes in preclinical and, translational projects, and clinical trials.

Building such a platform with standardized analytical procedures across different institutions is paramount towards producing new scientific knowledge in the field. The EATRIS Vaccine, Inflammation and Immunomonitoring Platform is one example of a research resource that offers a complete array of expertise and innovative tools allowing high-quality translational research capacity in the immunology field to the developers of immunotherapies.

The key to success of such innovative technological offerings relies primarily in the ability to bring different expertise together in the same workflow. Immunotherapy developers, researchers, immunologists, multimodal imaging specialists, clinicians, regulators, and patients must all be part of such harmonised platforms to address the multifactorial research questions and hurdles in answering them [Figure 1]. Only with a concerted approach, utilizing the right technologies, can the long road to achieving the success of cell

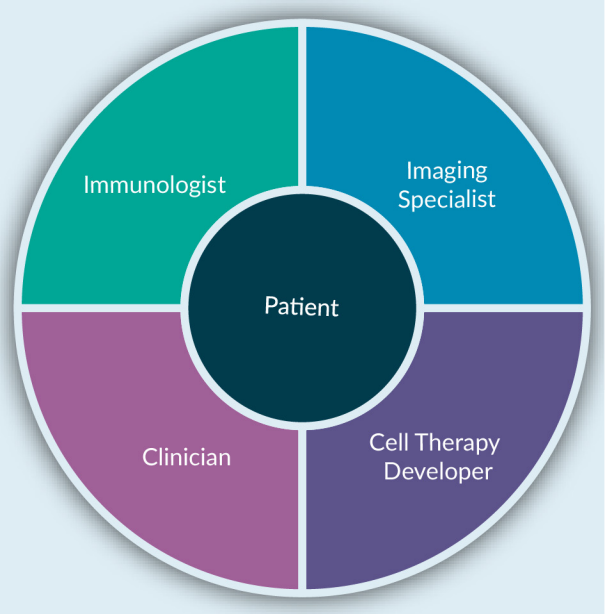
therapies and different immunotherapies in solid tumours be a clinical reality.

CONCLUSION

Despite the initial success of CAR T cell therapy in hematologic cancers, realizing the same degree of benefit in solid tumors still seems a very long way away. Similarly, although revolutionary therapeutic benefit for immune checkpoint inhibitors was predicted and hoped for, response rates range are still only between 10% to 40% [21]. Both therapeutic strategies still come with significant toxicity and high costs for healthcare systems across the globe, with many countries simply not able to make these therapies available. Hence, there exists an urgent and unmet medical need for reliable predictors of response for patient selection. In this regard, the research landscape lacks faithful models and strategies to standardize methods of analysis and there is still a lack of coordination between all stakeholders in the field of developing new innovative therapies for solid tumors. This commentary piece calls for the utilization of innovative platforms such as the EATRIS Vaccine, Inflammation and Immunomonitoring Platform and similar standardized technology platforms that overcome these bottlenecks through harmonized approaches. These platforms must be validated across European and global laboratories, and proficient in integrating immune correlates that predict patient outcome and therapeutic decisions. Achieving this goal will facilitate faster and more efficient cell and immunotherapy development and as a result, lower health costs making these therapies a reality for patients.

FIGURE 1

Key stakeholders of harmonized immune platforms for personalized cell and immunotherapy development for solid tumors



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AFFILIATION

David Morrow
EATRIS, European Research infrastructure for Translational Medicine

Jan Langermans
EATRIS, European Research infrastructure for Translational Medicine

Anton Ussi
EATRIS, European Research infrastructure for Translational Medicine

Antonio L Andreu
EATRIS, European Research infrastructure for Translational Medicine

Lucia Gabriele
EATRIS, European Research infrastructure for Translational Medicine

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