CELL & GENE THERAPY INSIGHTS

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

SPOTLIGHT

EXPERT INSIGHT

Temferon™, an *ex-vivo* genetically modified cell therapy aiming to fill the gaps for solid tumor immunotherapy

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Despite significant advances, the clinical application of immunotherapy for cancer patients still has some challenges associated with safety and efficacy. Novel, cutting-edge therapeutic approaches, such as genetically modified cell-based therapies, are arousing interest thanks to their capability to effectively target tumors and/or immune cells of interest, reducing off-target effects and potentially providing a life-long effect. Genenta Science developed Temferon™, a novel *ex-vivo* genetically modified cell-based therapy for IFN-α local release into the tumor, achieved by bone marrow-derived myeloid cells characterized by Tie2 promoter activation (TEMs) leading to immunostimulatory reprogramming of the tumor microenvironment (TME). Temferon™ is being studied in both hematologic and solid tumors and could play a relevant role also in combination with current available therapies, overcoming issues related to off-target effects and limited long-term benefits for currently available immunotherapies.

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NEW FRONTIERS FOR CANCER TREATMENT

Immunotherapies, including chimeric antigen receptor T-cell (CAR-T), are increasingly recognized as important contributors to the therapeutic armamentarium in oncology and immune checkpoint inhibitors have rightfully gained an important role in the management of specific tumors [1,2]. Nevertheless, important obstacles persist in the effective use of these therapies. These include, among others, development of tumor resistance [3], poor response rates for many patients, lack of a durable response [4,5] and the inability to efficiently target many solid tumors. Immunotherapies were initially evaluated in hematological malignancies because in solid tumors physical and pharmacologic barriers for effective delivery exist, represented among others by complex tumor microenvironments (TME) [6] which also limit their biologic effects and clinical efficacy.

Very recently, cutting-edge technologies allow local and targeted delivery of immunotherapeutic payloads to the TME and these not only are viewed as the new frontier in cancer immunotherapy but are also renewing the interest for optimizing immunotherapies that showed efficacy, but had issues relating to tolerability when administered parenterally. Novel control mechanisms that potentially allow a life-long outcome, by targeting cellular delivery of immunotherapies to the TME with a toxicity minimization, provides an opportunity to fundamentally change the oncology treatment paradigm [7–11].

Interferon-α (IFN) was one of the first immunotherapy approaches to be brought into the oncology clinic and, thanks to its well-known effects on tumor growth [12,13] and immune system modulation [14], was considered a gold standard for certain types of cancer for many decades. It subsequently lost favor among clinicians due to systemic toxicity following parenteral administration as well as a lack of specific biomarkers to better define likely responders. We and others have been developing novel strategies using cell delivered IFN in order to effectively target tumors and/or immune cells of interest, reducing off-target effects and providing a long-term response. In this scenario, genetically modified cell therapies, that include a therapeutic payload such as IFN, might be able to enhance the efficacy of standard therapies, also contributing to broad T-cell penetration particularly in more difficult to manage tumors from an immunologic perspective, such as solid tumors with low mutational load or lacking dominant neo-antigens. Pre-clinical evidences show that IFN gene therapy counteracts the expansion of immunosuppressive myeloid cells and induces tumor growth inhibition [7–15] by triggering an immunostimulatory response in the TME that results in T-cell priming and effector function against multiple surrogate tumor-specific antigens [7].

TEMFERON™: A NOVEL PROMISING DELIVERY SYSTEM

Genenta Science has developed a genetically modified, hematopoietic stem and progenitor cell based platform that allows the specific and controlled targeting of immunotherapeutic payloads to the TME. This local delivery is achieved by *ex-vivo* engineering $CD34^+$ hematopoietic stem and progenitor cells (HSPCs) that, following *in-vivo* engraftment and differentiation into myeloid lineage cells, effectively become a local therapeutic payload reservoir. The transgene expression is fine-tuned to reach the therapeutic window thanks to a specific tumor-associated myeloid cell (Tie2-expressing monocytes – TEMs) promoter and a post-transcriptional regulation layer represented by a miRNA target sequence.

Specifically, we have developed Temferon™, an *ex-vivo* genetically modified cell-based therapy for the selective and local tumor targeting of IFN-α using TEMs. Patient-derived HSPCs are genetically modified with a third-generation lentiviral vector, encoding for the human IFN-α2 protein and carrying

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miRNA target sequences for stringent expression control [7–11,16–18]. Lentiviral vectors are particularly attractive for clinical applications due to their ability to efficiently transduce non-proliferating or slowly proliferating cells, such as $CD34^+$ stem cells, allowing a persistent gene transfer in transduced cells [8,19]. Possible off-target and systemic effects are minimized by adding in the design of the lentiviral vector the recognition target sequence of miRNA-126. Indeed, miRNA-126 is highly expressed in HSPCs and down-regulated in the differentiated progeny, and this allows the suppression of IFN-α expression specifically in the primitive HSPC compartment (Figure 1) [16,20].

Therefore, Temferon™ represents a unique opportunity to overcome tolerability issues associated with systemic administration of IFN. Furthermore, IFN deployed locally in TME may allow full exploitation of its pleiotropic anti-tumor activities while limiting systemic adaptation to chronic IFN stimulation and immunoparalysis possibly associated with this phenomenon [7,8,14,20]. Most importantly, Temferon™ does not require *'a priori'* knowledge about the antigen to be targeted and induces the simultaneous targeting of multiple tumor specific antigens thus diminishing the risk of immune evasion [7]. Taking this into consideration, Temferon™ is literally an 'agnostic' immunotherapy that could be successfully applied to several cancers and immune contexts. Moreover, thanks to the selected cellular carrier, the Tie2-expressing monocytes that are spontaneously and actively recruited by growing tumors, Temferon™ represents a unique opportunity for the local delivery of therapeutic payloads. Furthermore, as Temferon™ is based on the administration of engineered HSPCs, there is the potential to reach a life-long durability of response. All the above cited features may overcome the current limitations of immunotherapy. Our technology, thanks to the transcriptional and post-transcriptional miRNA-mediated control of transgene expression, opens future possibilities to employ genes other than IFN-α as a payload, expanding therapeutic opportunities for many forms of cancer [8,16,21,22].

BREAKING IMMUNE TOLERANCE WITH IFN

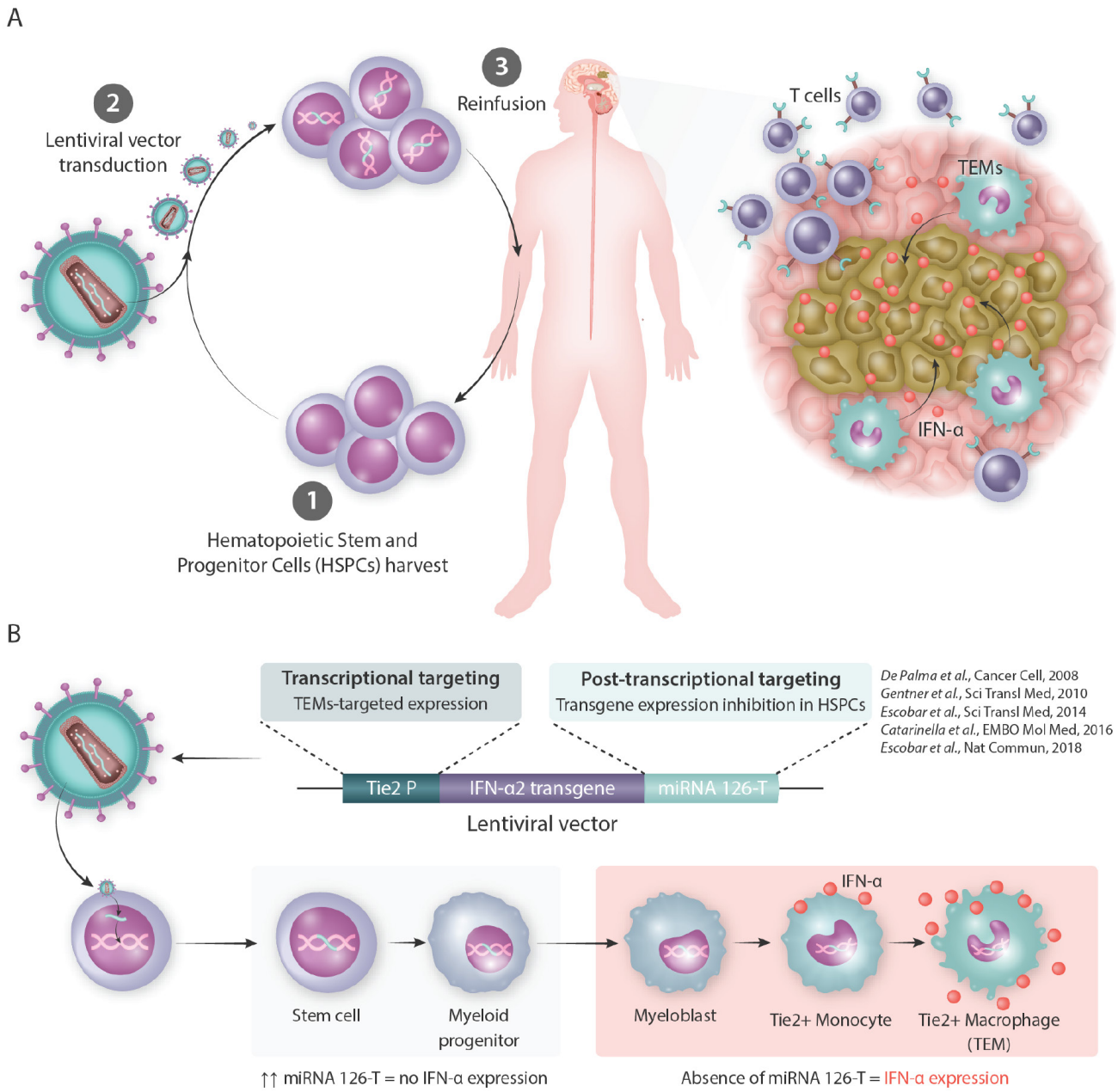
The induction and long-term maintenance of an effective immune surveillance is essential for the success of innovative cancer immunotherapies. Understanding the mechanisms contributing to localized immune suppression within the TME is fundamental to improve the efficacy of current and well-established therapies as well as to achieve a better targeting to break established immune evasion or tolerance in the era of novel and personalized therapies. In this regard, IFN could be envisioned as a key player to accomplish this purpose.

Different targets have been identified within the IFN signaling cascade that may play an important role in breaking immune tolerance in cancer. Activation of the stimulator of IFN genes (STING) pathway and IFN production stimulation are critical for the endogenous anticancer immune response. Emerging evidence suggests that STING also regulates anticancer immunity in an IFN-independent manner. STING activation, not only induces cell death, but also enhances cancer antigen presentation, contributes to T-cells priming and activation, facilitates the trafficking and infiltration of T-cells into tumors and promotes the recognition and killing of cancer cells by T-cells [23].

Data suggest that IFN may synergize from an efficacy perspective not only with chemotherapy, but also with radiotherapy by multiple mechanisms, acting on apoptosis, immunogenic cell death and immune cells [24,25]. Preliminary data also indicate that targeting tumor-inherent IFN signaling could offer an opportunity to overcome primary or acquired resistance to immune checkpoint inhibitors. Notwithstanding these encouraging observations, patient specific factors also need to be addressed to make this a realistic clinical option. IFN plays a role in the control of cancer

FIGURE 1

Overview of Temferon™ manufacturing process and mechanism of action (A) and transgene transcriptional and post-transcriptional controls (B).



stem cell (CSC) growth and low-dose exogenous IFN administration has been shown to favor differentiation over self-renewal of CSC and activates immune responses against CSC [26]. IFN may also have a role in potentiating antigen presentation effects and have direct action on dendritic cells with a potential role in optimizing the efficacy of oncology vaccines [12].

Several well-established clinical approaches rely on the triggering of IFN endogenous expression (e.g. radiotherapy, immunomodulatory drugs such as lenalidomide, etc.) [27,28] and novel experimental agents are designed with the purpose of either activating downstream players of IFN pathway [29,30] or, for IFN-α local delivery directly into the tumor, avoiding systemic toxicities [31–33]. These

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includes gene therapy-based approaches such as Temferon™ for use in both hematological and solid tumors.

IFN-α: AN ATTRACTIVE TARGET FOR CLINICAL ONCOLOGY RESEARCH

As of August 2020, 41 were the active clinical trials (CTs; https://clinicaltrials.gov [34]) investigating different IFN-α forms, used either in combination with conventional agents or as monotherapies, in hematological or solid tumor indications (Table 1).

Recently, genetically modified cell-based therapies as a modality for delivering targeted IFN therapy to tumors, are viewed as an attractive development for potentially improving clinical outcomes. One strategy relies on *in-vivo* delivery of the therapeutic gene using a viral vector such as adeno-associated virus. Such an approach may result in non-specific off-target effects due to the wide distribution of the viral vector, difficulties in transgene dose tuning and it may be limited by the possible presence of pre-existing antibodies to AAV serotypes in patients.

Specifically, the role of adenovirus vector-based (AAV) gene therapy delivering IFN was investigated in both non-muscle invasive bladder cancer [32] and malignant mesothelioma [33,35]. FerGene developed an AAV gene therapy containing IFN-alfa-2b. Every three months, AAV was administered into the bladder and, after integrating in bladder wall cells, these started to release IFN-alfa-2b. By this novel approach, the patient's own bladder was turned into a reservoir for IFN release that was able to enhance the body's natural defenses against cancer. However, its clinical application has some restrictions for not easily reachable tumors and due to the limited durability of response. An analogous approach has been taken by Trizell with the administration of an AAV for IFN-alfa-2b

TABLE 1

Characteristics of recruiting or active interventional clinical trials with IFN-α.

Conditions	N° of CTs (total n= 41)
Solid tumors	27
Hematologic malignancies	14

Interventions with IFN-α* different form (N° of trials) and conditions

Native biological IFN-α (n=12)	DC vaccine + IFN-α (n=1)	Pegylated or recombinant (n=24)	Gene therapy§ (n=4)
▶ Neuroendocrine tumors	▶ Malignant melanoma	▶ Neuroendocrine tumor	▶ Glioblastoma multiforme
▶ Breast cancer		▶ Polycythemia vera	▶ Multiple myeloma
▶ Ovarian cancer		▶ Squamous cell carcinoma of skin	▶ Malignant pleural mesothelioma
▶ T-cell leukemia-lymphoma		▶ T-cell leukemia-lymphoma	▶ Epithelial tumor/ metastatic cancer
▶ Melanoma		▶ Renal cell carcinoma	
▶ Leukemia		▶ Chronic myeloid leukemia	
▶ Lymphoproliferative disorder		▶ Fallopian tube cancer/ovarian cancer/peritoneal cancer	
▶ Polycythemia vera		▶ Melanoma	
▶ Lymphomatoid granulomatosis		▶ Breast cancer	
		▶ Colorectal cancer	
		▶ Prostate cancer	
		▶ Hematological neoplasms	

*One CT included both native biological and pegylated IFN-α.
§Two trials with Temferon™.

delivery into the pleural cavity in patients with mesothelioma.

A replication-defective adenoviral vector containing the human IFN-alfa-2b gene was studied in a Phase 2 study in patients with malignant pleural mesothelioma with concomitant celecoxib followed by chemotherapy. Results suggested that this approach was feasible, safe and well-tolerated and showed an overall disease control rate of 87.5% and an almost doubling of median survival time compared to historical study controls (17 months vs 9 months) with approximately 25% of patients living at least 2 years and approximately 20% surviving to at least 3 years [33]. These data provided to Trizell the rationale to move to a Phase 3 pivotal study. Moreover, combination approaches including IFN delivered by gene therapy together with chemotherapy and systemic checkpoint inhibitors or other immuno-modulators may provide a suitable treatment approach in non-muscle invasive bladder cancer and perhaps other indications [36,37].

These recent experiences based on IFN-α suggest that the therapeutic potential of this cytokine has not been fully achieved and that new delivery strategies designed to establish effective local tissue concentrations of IFN-α may represent new clinical options for several cancers. In this scenario, Temferon™ provides a more refined and targeted therapy compared to *in-vivo* gene therapy approaches as it relies on *ex-vivo* transduction of HSPCs with lentiviral vector carrying the therapeutic gene under the control of TEMs promoter and micro-RNA target sequences.

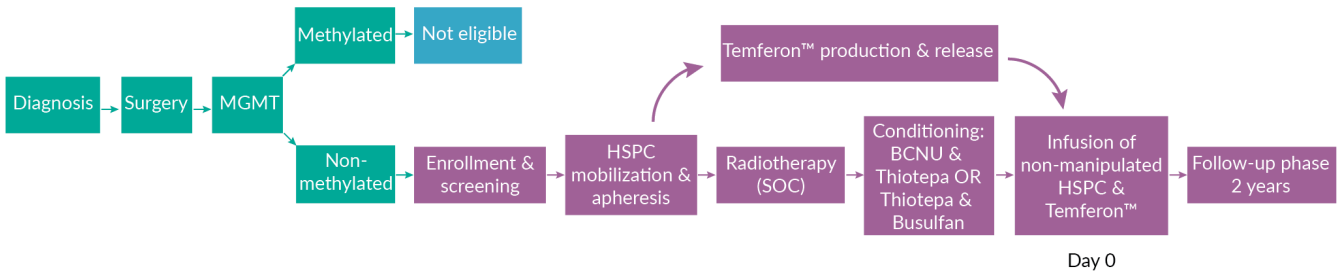
Temferon™ is therefore an attractive alternative as it can sustainably supply a targeted immune modulating cytokine for a long period, overcoming systemic toxicity related to traditionally administered IFN-α treatments.

Temferon™ from bench to bedside

Two Phase 1/2a clinical studies are currently ongoing in Italy, evaluating the safety and biological effects of Temferon™ in patients with rapidly progressing multiple myeloma (TEM-MM-101, NCT 03875495) and in patients with newly diagnosed glioblastoma multiforme (GBM) and unmethylated O-6-methylguanine-DNA methyltransferase (MGMT) promoter (TEM-GBM-001, NCT03866109) who have limited benefit from treatment with temozolomide. The TEM-GBM-001 study is a dose escalation study recruiting up to 21 patients. The study design is shown in Figure 2. Potentially eligible patients are identified immediately after GBM surgical resection, once MGMT promoter methylation status is known. In Part A of the study, the safety and tolerability of 3 escalating doses of Temferon™ including 2 different conditioning regimens, are investigated in up to 15 patients. In Part B, additional 6 patients will be evaluated using a conditioning regimen and a single dose of

FIGURE 2

TEM-GBM-001 study design.



MGMT: o6-methylguanine-DNA methyltransferase; HSPC: hemopoietic stem and progenitor cell; SOC: Standard of care; BCNU: Carmustine; Temferon™ production and release: advanced medicinal product manufacturing process by an authorized contract manufacturing organization followed by its characterization and release by a Qualified Person for clinical use.

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Temferon™ selected from Part A. Exploratory endpoints will evaluate Temferon™ biological effects relating to changes in novel brain imaging parameters, immunological responses, IFN signaling and TME. The first 2 cohorts completed recruitment and Temferon™ dosing in June 2020.

Preliminary clinical data are very encouraging. Thanks to the robust control mechanisms built into Temferon™, patients treated so far had a rapid hematologic engraftment and recovery with no dose limiting toxicities identified. Notably, transduced myeloid cells in peripheral blood were observed on average within 14 days after Temferon™ administration and still persist for up to 1 year post treatment. Dose escalation continues in Cohort 3 [17,18].

GENE THERAPY & IFN-α IN CANCER TREATMENT: FUTURE PERSPECTIVES?

A 'one size fits all' approach for cancer management is no longer viewed as an appropriate approach to the development of new and innovative medicines. An important lesson should be learnt by strategies implemented to better target tumors that are likely to respond in terms of immune-modulation and reversal of immune tolerance. An improvement in cancer therapies efficacy will involve a more personalized and multimodal approach. It is essential to understand how conventional and new therapies might be used; indeed, the characteristics of a therapy designed to 'debulk' tumor are likely to be very different from those specific to IFN therapy used to maintain patients in remission by enhancing immune surveillance. Characterization of biomarkers specific to the TME and immunological responses, which are expected to vary according to the immunotherapy utilized, should be studied to better identify the patients who are more prone to respond and how changes in these parameters translate into clinical benefit. Novel methods, such as Temferon™, conceived to maximize anti-tumor efficacy by an immunostimulatory action towards multiple antigens, while minimizing safety concerns due to off-target effects, are facilitated in solid tumor homing and ensure durable response and their development is encouraged. The technology platform on which Temferon™ is based on can also be applied to a multitude of potentially therapeutic payloads.

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AUTHORSHIP & CONFLICT OF INTEREST

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