



Newsletter No. 106

The recent Phase I clinical trial exploring pHIL12 plasmid intratumoral gene electrotransfer in basal cell carcinoma patients

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Recently we published in the European Journal of Surgical Oncology (Eur J Surg Oncol. 2025 Jan 6; 51(5):109574; <https://doi.org/10.1016/j.ejso.2025.109574>) the results of Phase I clinical trial of pHIL12 plasmid intratumoral gene electrotransfer, which represents another milestone of our project SmartGene.si (<https://www.smartgene.si/>), which was funded by Slovenian Ministry of Education Science and Sport and European Structural funds.

The study, performed in patients with basal cell carcinoma (BCC) of the head and neck region represents a promising advancement in cancer immunotherapy. This study harnessed the potential of gene electrotransfer (GET), a non-viral gene delivery method, to localize the production of interleukin-12 (IL-12) directly within tumors. IL-12 is a powerful immunostimulatory cytokine known to activate both innate and adaptive immune responses, primarily through the induction of interferon-gamma (IFN- γ). However, previous attempts at systemic recombinant protein IL-12 delivery have been hampered by significant toxicity, making localized delivery an attractive alternative. In this trial, we aimed to assess the safety, tolerability, and biological activity of the pHIL12 plasmid, which has been engineered without antibiotic resistance genes, thus aligning with European Medicine Agency regulatory preferences.

The study was designed as an open-label, single-arm, dose-escalation trial involving nine patients with operable BCC. Patients were divided into three cohorts, each receiving a different concentration of pHIL12 (0.5 mg/ml, 1 mg/ml, or 2 mg/ml). A single dose of pHIL12 was injected directly into the tumor, followed by application of electric pulses that transiently permeabilize cell membranes, thereby enhancing the uptake of the plasmid DNA into tumor cells. The rationale behind this approach was to induce local IL-12 expression, stimulate an immune response within the tumor microenvironment, and ultimately promote an antitumor effect while minimizing systemic exposure.

The primary objective of the trial was to assess safety and tolerability, while secondary goals included evaluating pharmacokinetics, pharmacodynamics, immune response, and preliminary tumor response. To ensure patient safety, a 30-day waiting period was implemented between gene therapy and tumor excision, allowing for the monitoring of potential acute and subacute toxicity.

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The results demonstrated that pHIL12 GET was well tolerated, with no serious adverse events reported. The majority of patients experienced minimal discomfort, with only mild pain or edema observed in a few cases. Blood parameters remained stable throughout the study, indicating no systemic toxicity. Furthermore, analysis of plasmid distribution showed that while the plasmid was present in the treated tumor immediately following the procedure, its copy number diminished over time, suggesting effective degradation and clearance—an additional marker of safety.

Analysis of tumor biopsies confirmed successful gene expression, with increased IL-12 and IFN- γ production observed in treated tumors. This suggests that the treatment effectively triggered a localized immune response. Additionally, histological analysis showed increased immune cell infiltration into the tumor microenvironment, further supporting the immunostimulatory effects of pHIL12 GET.

The clinical outcomes observed in the trial were also encouraging. Tumor response was evaluated using RECIST 1.1 criteria at one month, and while no complete responses were observed within the one month, three patients exhibited partial responses, and six patients had stable disease at the one-month follow-up. The highest plasmid concentration (2 mg/ml) demonstrated the strongest immune activation and the most pronounced tumor reduction.

In conclusion, the Phase I trial of pHIL12 plasmid intratumoral gene electrotransfer demonstrates that this novel approach is both feasible and safe for patients with BCC. The promising results regarding immune cell infiltration and partial tumor responses support the potential of pHIL12 GET as an immunotherapeutic strategy that could be combined with other tumor-ablative therapies such as electrochemotherapy or radiotherapy. Such combinations could enhance both local tumor control and systemic immune activation, potentially improving treatment outcomes for patients with more aggressive or advanced cancers. Furthermore, the study reinforces the importance of localized cytokine delivery as a means of reducing systemic toxicity while maintaining therapeutic efficacy.

Forthcoming events

8th Veterinary Workshop on Electroporation-Based Treatments

Ljubljana, April 15 – 16, 2025

<https://bit.ly/4hXqr5q>

11th COURSE: Advances in Electroporation-Based Therapy: From Principles to Clinical Applications

Erice, May 2 – 7, 2025

<http://www.eisbem.eu/index.php/2025-xi-course/>

17th International Bioelectrics Symposium (Bioelectrics 2025)

Eindhoven, September 14 – 17, 2025

<http://www.bioelectrics2025.nl/>

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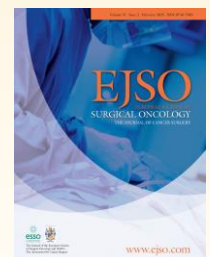
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