ProtaGene
Analytical Excellence

FACT SHEET

CGT Clinical Trials Safety
Integration Site Analysis (ISA)

Integration Site Analysis (ISA) is a key method for monitoring the safety of cell and gene therapy (CGT) vectors, essential for both integrating and non-integrating (low-integrating) therapies.

This safety assessment is critical for understanding the integration of genetic material, as required by regulators for long-term patient monitoring. Stably-integrating vectors permanently modify the genomes of targeted cells, and in rare but significant cases, integration events within or near proto-oncogenes have led to serious adverse events, such as leukemia [1].

Your Partner in Vector Integration Site Analysis

With over 20 years of experience in gene therapy and vector safety assessment, including over 130 peer-reviewed publications and participation in over 70 different trials supporting numerous BLA submissions, ProtaGene has been instrumental in the regulatory approval of groundbreaking new therapies. Our services have played a crucial role in various stages of preclinical development, clinical testing, and post-approval assessment for multiple gene therapy drugs using viral vectors. For examples on the data utilization, please refer to recent original publications [1-6].

To assess and understand potential risk(s) of delayed adverse events associated with integrating gene therapy vectors (e.g., lentiviral- or retroviral-based vectors or transposons), FDA recommend design of long term follow-up studies (LTFU observations), which are important to monitor long term safety of GT products.

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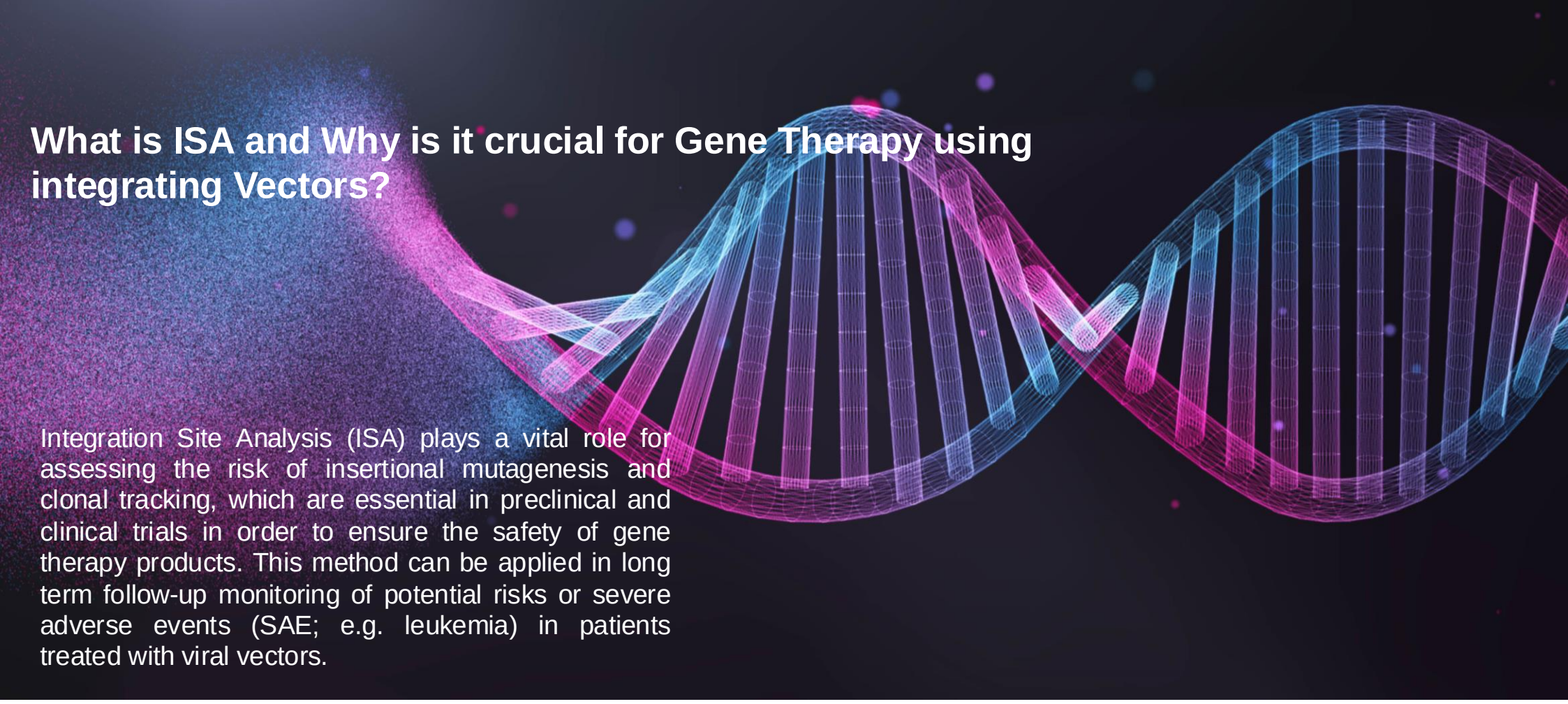
What is ISA and Why is it crucial for Gene Therapy using integrating Vectors?



Integration Site Analysis (ISA) plays a vital role for assessing the risk of insertional mutagenesis and clonal tracking, which are essential in preclinical and clinical trials in order to ensure the safety of gene therapy products. This method can be applied in long term follow-up monitoring of potential risks or severe adverse events (SAE; e.g. leukemia) in patients treated with viral vectors.

Enabling Today's Therapeutics

Partnering for Pipeline Success

De-risking Regulatory Approvals

Advancing Gene Therapy Platforms

What is insertional mutagenesis?

There have been CGT clinical trials reports of serious adverse events, such as leukemia, attributed to integration events of the therapeutic vectors. While ISA results shed ligth onto the occurence of pre-dominant clones and intregration located within or near proto-oncogenes, early-stage insertional mutagenesis can be detected in patients.

Clonal dominance refers to the unexpected overrepresentation of cell clones with specific integration sites within a sample. This overrepresentation may result from vector integration near cancer-associated genes (insertional mutagenesis) altering the growth potential of cells. Longitudinal monitoring of patient samples can provide insights into clonal dynamics following gene therapy.

Working With Us

ProtaGene delivers a full service tailored and unique to the needs of each client, from receiving samples to report delivery, including sample QC, library preparation, next-generation sequencing (NGS), bioinformatics analysis, and comprehensive reporting.

We provide customer-focused solutions to support clients at every stage of the vector safety assessment process and aim to ensure biosafety of research participants or patients as well as the integrity of data and adhering to project compliance: according to GCP, GCLP, and GLP guidelines.

Our validated method, S-EPTS/LM-PCR, established for lentiviral vectors is the first validated method for ISA, and has supported several viral vector drugs from toxicology studies through to approval in both Europe and USA. This method was and can further be adapted to other vectors applied in cell and gene therapies.

Reference:

1. Duncan, C. N. "Hematologic cancer after gene therapy for cerebral adrenoleukodystrophy." New England Journal of Medicine (2024).
2. Kobbe, G., et al. "Aggressive lymphoma after CD19 CAR T-cell therapy." *New England Journal of Medicine* (2024)
3. Symington, E. "Long-term safety and efficacy outcomes of valoctocogene roxaparvovec gene transfer up to 6 years post-treatment." *Haemophilia* (2024)
4. Kanter, J. "Lovo-cel gene therapy for sickle cell disease: Treatment process evolution and outcomes in the initial groups of the HGB-206 study." *American journal of hematology* (2023)
5. Locatelli, F. "Betibeglogene autotemcel gene therapy for non–β0/β0 genotype β-thalassemia." *New England Journal of Medicine* (2022)
6. Schmidt, M. "Molecular evaluation and vector integration analysis of HCC complicating AAV gene therapy for hemophilia B." *Blood advances* 7.17 (2023).
7. FDA Workshop on Integration Site Analysis During Long Term Follow-Up for Gene Therapies with Integrating Viral Vectors – Zoom

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