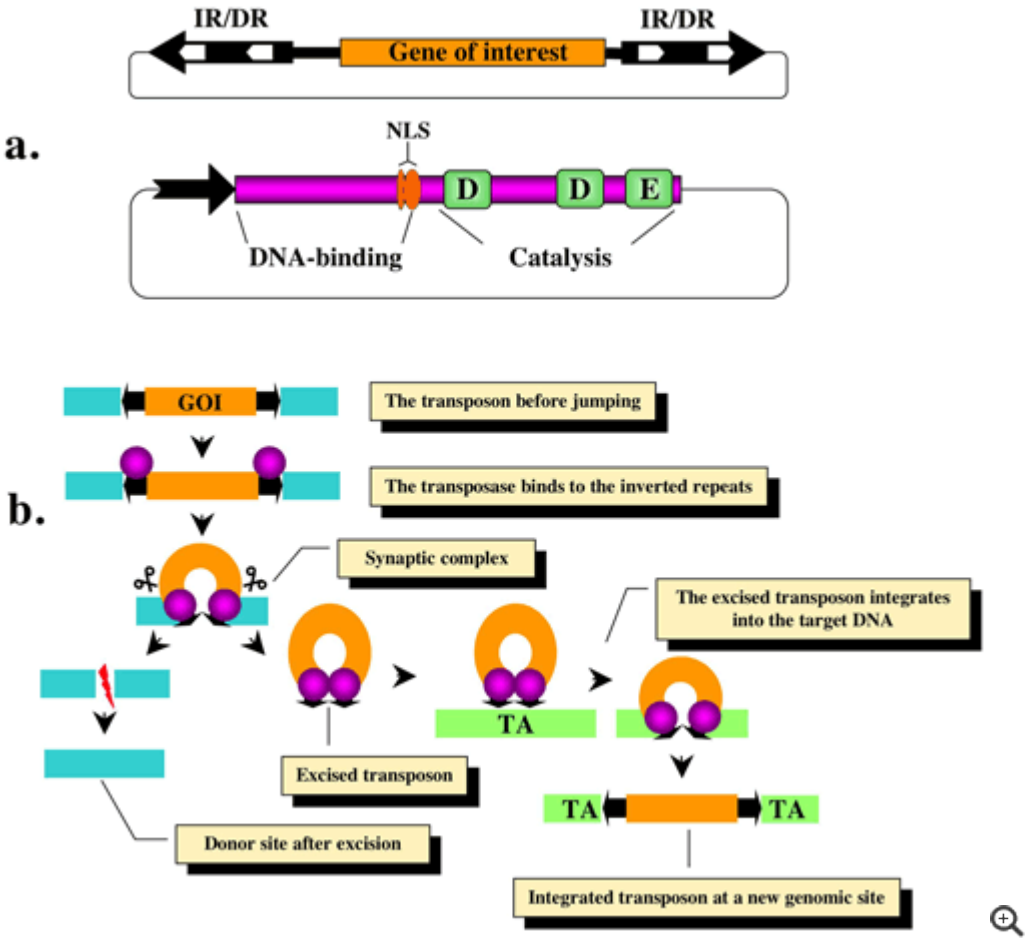
Transposons as non-viral vectors for gene therapeutic approaches

Research project summary

DNA-based transposons are natural gene delivery vehicles (Figure), and molecular reconstruction of the Sleeping Beauty (SB) transposon represents a cornerstone in applying transposition-mediated gene delivery in vertebrate species, including humans. Our recently developed 100-fold hyperactive SB system opened new avenues for gene therapeutic approaches, and we are currently developing preclinical animal models for gene therapy of monogenic diseases.



The Sleeping Beauty transposon system. Source: Zoltán Ivics

(a) Components and structure of a two-component gene transfer system based on Sleeping Beauty. A gene of interest (orange box) to be mobilized is cloned between the terminal inverted repeats (IR/DR, black arrows) that contain binding sites for the transposase (white arrows). The transposase gene (purple box) is physically separated from the IR/DRs, and is expressed in cells from a suitable promoter (black arrow). The transposase consists of an N-terminal DNA-binding domain, a nuclear localization signal (NLS) and a catalytic domain characterized by the DDE signature.

(b) Mechanism of Sleeping Beauty transposition. The transposable element carrying a gene of interest (GOI, orange box) is maintained and delivered as part of a DNA vector (blue DNA). The transposase (purple circle) binds to its sites within the transposon inverted repeats (black arrows). Excision takes place in a synaptic complex. Excision separates the transposon from the donor DNA, and the double-strand DNA breaks that are generated during this process are repaired by host factors. The excised element integrates into a TA site in the target DNA (green DNA) that will be duplicated and will be flanking the newly integrated transposon.