A novel Sleeping Beauty transposase system for development of gene therapies

EMBLEM TECHNOLOGY TRANSFER

Challenge

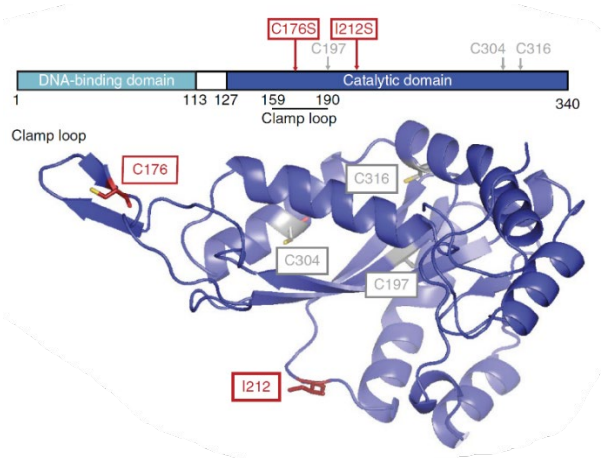
- Gene therapy has gained major interest in research and development, especially in the field of cancer immunotherapy. Non-viral vectors such as the Sleeping Beauty (SB) transposon promise a higher biosafety and lower immunotoxicity in comparison to viral vectors.
- However, delivery of the SB gene increases risks of DNA-mediated geno- and cytotoxicity and provides limited control of transgenesis, hampering safe clinical application.

Solution

- We present a novel SB protein which overcomes these risks and provides a safer tool for the development of gene therapies, for example CAR T cells.

Technology

SBprotAct: High solubility SB (hsSB) transposase protein variant



- Enhanced solubility
- Enhanced stability
- (-80°C to 95°C)
- Suitable for large scale, low-cost, high yield recombinant production (yield: 6 mg per 1L culture; purity 99.9%)
- Safe & effective: Direct delivery of SBprotAct into a variety of mammalian cell lines and primary cells
- Dose-dependent transgene integration for tight control of inserted transgene copy number
- Hit-and-run fashion (max. 2 days time window) to minimize the risk of undesired transposition events and genotoxicity
- Efficient delivery of large transgenes (>10kb)

Domain composition of the SB protein and crystal structure of the SB100X transposase catalytic domain (PDB 5CR4) with the hsSB substitutions marked (red). Structurally buried cysteines (gray) were mutated as a control.

Internal EMBLEM Reference

2017-052, 2019-017

Key Inventors

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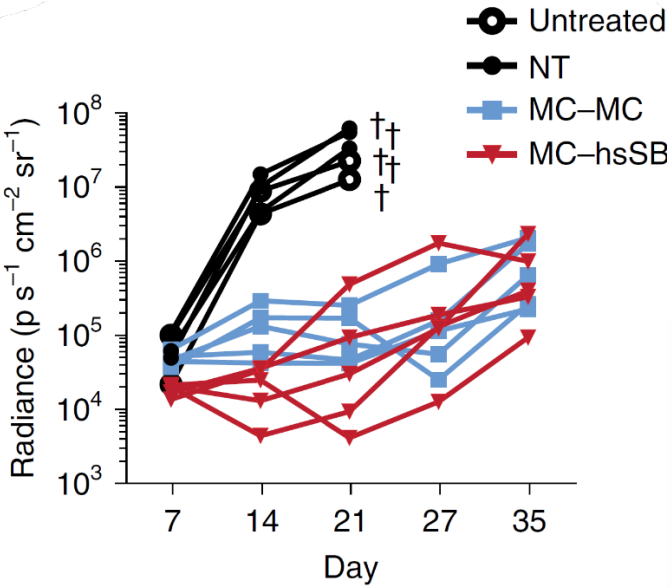
Applications

- Stable & efficient mammalian cell engineering
- Functional genomics, cancer gene discovery, transgenesis
- Gene therapy with ex vivo cell manipulation
- Pharmaceutical industry (SBprotAct has high transgenesis rates in CHO cells, which constitute the main manufacturing platform for protein therapeutics & biologics such as therapeutic antibodies)
- Therapeutic cell manufacturing (e.g. CAR T) in point-of-cares (hospitals and clinics), supporting increased accessibility of gene and immunotherapies.



CD19 CAR T cell generation by SBprotAct and functional analysis of the cell product: NSG mice received intravenous injections of 5 × 10^5 Raji lymphoma cells expressing ffLuc (day 0). Seven days later, mice were treated with 5 × 10^6 CD19 CAR T cells or non-transfected control T cells and imaged at the indicated time points. A summary of luminescence signals.

Intellectual Property

WO2019038197, WO2020169673

Commercial Opportunity

The technology was demonstrated in human cell lines (HeLa), mouse embryonic stem cells (mESC), hematopoietic stem cells and primary T-cells.
We offer licensing opportunities as well as a technology evaluation program.

Further Reading

Querques et al. 2019, Nature Biotechnology, “A highly soluble Sleeping Beauty transposase improves control of gene insertion”.

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