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SCON – AN ARTIFICIAL INTRON DEVOID OF HYPOMORPHIC TARGET GENE EFFECTS - FOR ONE-STEP GENERATION OF CONDITIONAL ANIMAL MODELS

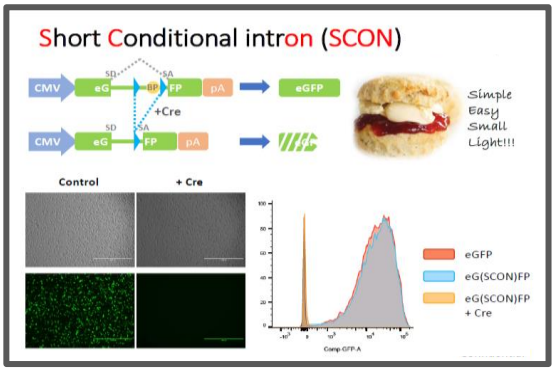
Keywords: SCON, conditional gene knockout, artificial intron, CRISPR, animal model

INVENTION NOVELTY

"SCONs" are artificial "Short COnditional INtrons" that do not change natural gene function or expression level upon genomic introduction within an exon sequence. A conditional gene knockout is induced via a recombinase-based event which partially removes the artificial intron, resulting in a lack of a functional gene product.

VALUE PROPOSITION

Gene knockouts (KO) in cells or animals have made substantial contributions to understanding the molecular functions of genes. For essential or developmentally active genes, a conditional knockout (cKO) strategy is often required to elucidate their functions. To prevent potential developmental or other unwanted physiological effects, the expression level of such targeted genes needs to be unaffected. This remains a major, unresolved challenge even in the CRISPR era.



a) Scheme of SCON integration into the eGFP sequence and removal by Cre-recombinase; b) eGFP expression analysis [Source: Scheme provided by IMBA]

TECHNOLOGY DESCRIPTION

"SCONs" were developed to overcome these limitations by analysing the minimum requirements for a functional, artificial, conditional intron. The SCON methodology is based on genomic integration of the conditional intron within an exon sequence. Resulting from the proprietary SCON architecture, no hypomorphic effects are detectable which have been observed for currently known "artificial intron" strategies, such as DECAI (DEgradation based on Cre-regulated- Artificial Intron).

Upon transcription of the targeted gene an additional splice event takes place which removes the inserted SCON, reconstituting the original mRNA sequence of the targeted gene. The conditional gene knockout is induced by a recombinase-based genomic event which partially removes the artificial intron and destroys the introduced splice sites resulting in compromised mRNA splicing and a lack of a functional gene product.

COMMERCIAL OPPORTUNITY

The technology is available for licensing or further co-development.

DEVELOPMENT STATUS

The SCON technology has been validated in HEK293T cells, zebrafish and Xenopus laevis embryos, mouse ES cells and mouse intestinal organoids. Proof of concept experiments for generation of mouse models by targeted integration of SCON elements were performed for developmentally essential genes, such as Ctnnb1 (beta-catenin) and Sox2 via direct injection of commercially synthesized single-stranded deoxynucleotides into one or two cell mouse embryos. About 8% of the offspring carried the precise heterozygous SCON integration and homozygous mice developed normally.

PATENT SITUATION

A priority establishing European patent application was filed in May 2021 (EP21172761) followed by a PCT application (WO2022/234086A1), entitled "Controlled gene expression methods and means".

FURTHER READING

Wu et al. (2022) Nature Experimental & Molecular Medicine, Vol. 54, p. 2188–2199; https://doi.org/10.1038/s12276-022-00891-0

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