Temporal encoding and manipulation of vertebrate cell histories with a new CRISPR/Cas9 system

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Defining the cellular origins and interactions regulating the assembly of functional tissues and organs requires genetic labelling, manipulation and cell-lineage reconstruction strategies. Current imaging-based techniques for cell labelling and manipulation in complex vertebrate organisms lack temporal resolution. Here we present TEMPO (*T*emporal *E*ncoding and *M*anipulation in a *P*redefined Order), a new tool based on CRISPR/Cas9 and transgene frame switches driven by an ordered gRNA cascade. The system allows *in vivo* labelling and manipulation of cells in a predefined order, preserving both spatial and temporal information. In zebrafish and mouse, we demonstrate that TEMPO recapitulates known developmental sequences of neuron formation. By introducing temporal perturbations in cell cycle regulators in mouse cortex progenitors, we show that TEMPO can be used to manipulate the proportion and distribution of neurons and glia of a given cell generation and reveal their interactions with other cell generations in a single sample. Thus, TEMPO provides a powerful resource to manipulate temporal factors required for cell-type specification and study their influence on vertebrate tissue and organ morphogenesis.