Systematic Prediction of the Transcriptomic and Epigenetic Factors Driving Cell Identity and Cell Maintenance

MOGRIFY®
Transforming Cell Therapy

The Challenge

Leveraging stem cell derived cell types in the development of efficacious and scalable cell therapies.

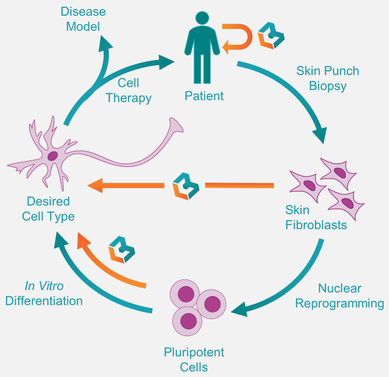
In 2007, a method for converting a mature human cell type into an induced pluripotent stem cell (iPSC) (Takahashi *et al*., Cell, 2007), a cell with proliferative and differentiative capabilities, was discovered and provided a way to address the challenges associated with the development and manufacture of cell therapies. However, the process of making iPSCs and then correctly differentiating them into the cells of interest is an inefficient and time-consuming process, requiring the development of complex differentiation protocols customized for every type of target cell.

These protocols usually require precise conditions, expensive reagents and excessive fine-tuning in methodology, often taking several years of trial-and-error and high in cost.

Therapeutic Applications

Transforming the development of *ex vivo* cell therapies and pioneering *in vivo* reprogramming therapies.

The MOGRIFY® and epiMOGRIFY technologies take a systematic approach to identify transcriptomic and epigenetic factors to affect and direct cell identity. By deploying next-generation sequencing, gene regulatory and epigenetic network data, this proprietary suite of platform technologies is capable of driving the speed, efficiency and maintenance of cellular reprogramming, and can be used to generate the scalable source of functional cell types required to address diseases with a high unmet clinical need.



Therapeutic Applications

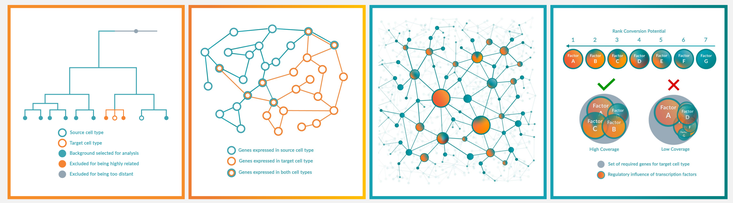
Autologous Therapies
Allogeneic Therapies
In vivo Therapies

MOGRIFY®

Watch MOGRIFY® Video

Systematically predict transcriptomic switches to drive cell conversion.

The MOGRIFY® technology (Rackham *et al*., Nature Genetics, 2016) was developed as a systematic means of identifying the key regulatory switches, such as an optimal combination of transcription factors, required to drive cell identity. The platform can be used to **enhance existing stem-cell forward reprogramming methods** or can bypass **development** pathways altogether, affecting a direct transdifferentiation between a mature cell type to another mature cell type.



Step 1 Calculation of contextual gene expression

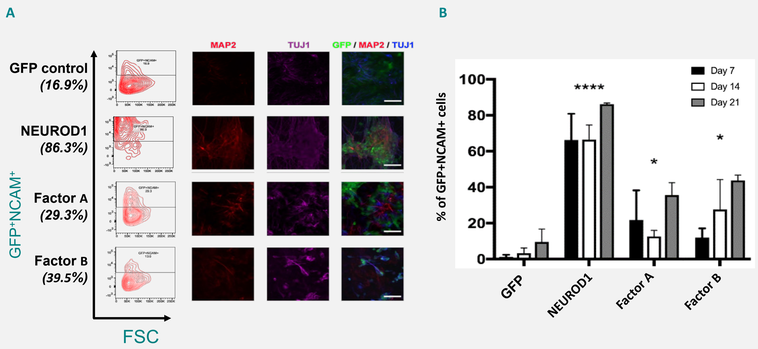
Step 2 Identification and scoring of genes that require change from source to target cell

Step 3 Building local regulatory network of influence around each transcription factor (TF)

Step 4 Scoring of the conversion potential of each TF and optimization of network coverage with combinations of TFs

Enhanced stem-cell forward reprogramming in the generation of neuronal cells

MOGRIFY® was used to predict factors to enhance the differentiation of pluripotent stem cells into cortical neurons. As expected, the top predicted factor was NEUROD1, a previously described strong inducer of neuronal fate. Two new TF never implicated in forward programming were identified, Factor A and B. Using NEUROD1 as positive control, and GFP as negative control for neuronal inductions, the predicted TFs were tested. (A) At day 14 post-transfection of the individual TFs, we observed a 3-fold increase in the amount of NCAM+ cells when the new TFs were used. (B) Results of NCAM+ expression at day 7, 14 and 21.



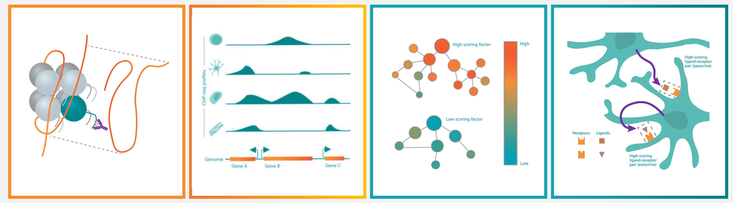
epiMOGRIFY

Explore epiMOGRIFY

Systematically predict the epigenetic switches required to drive and maintain cell identity.

The epiMOGRIFY technology (Kamaraj *et al*. Cell Systems 2020) combines gene-regulatory information with a model of a cell's epigenetic landscape and leverages changes in the level of DNA-histone methylation (H3K4me3 modifications). The platform utilizes data from more than 100 human cell/tissue types (available via the ENCODE and Epigenome Roadmap consortia) to accurately define culture conditions that can maintain the cell identity or induce cell conversion.

This can be applied in cGMP manufacture and enhances directed differentiation or cell conversion to support the development of scalable off-the-shelf therapies.



Step 1 H3K4me3 histone modification sequencing using ChIP-seq (chromatin-immunoprecipitation)

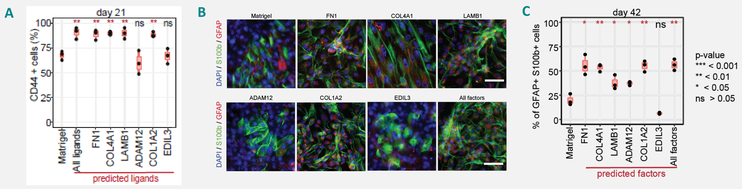
Step 2 Cell identity gene identification using ChIP-seq data (ENCODE)

Step 3 Key receptor identification, using the same "engine" as MOGRIFY® (considers both direct and indirect effects)

Step 4 Ligand identification for both paracrine & autocrine ligands

Novel Culture Conditions and Enhanced Differentiation of Astrocytes

epiMOGRIFY predicted 6 growth factors/substrates (FN1, COL4A1, LAMB1, ADAM12, COL1A2 and EDIL3) that are associated with astrocytes. The addition of these factor ligands to the culture in the differentiation process from H9 embryonic stem cells (ESCs) doubles differentiation efficiency (A), morphological maturity (B) and promotes the survival (C) of ESC-derived astrocytes.



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