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Editorial overview: Cell reprogramming: Carpe diem

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Jianlong Wang obtained his BS at Nankai University in Tianjin, China, his MS at the Institute of Microbiology (Chinese Academy of Sciences) in Beijing, China, and received his PhD at University of Massachusetts at Amherst studying plant RNA viruses and host–virus interactions in symptom modulation. He studied pluripotency networks in embryonic stem cells as a postdoctoral fellow at the Children's Hospital Boston in Harvard Medical School. He started his lab at the Department of Cell, Developmental and Regenerative Biology at Ichan School of Medicine at Mount Sinai in

The pace of research in cell reprogramming after the breakthrough by Takahashi and Yamanaka [1] has been tremendous, and we can now convert somatic cells into induced pluripotent stem cells (iPSCs) with exogenous factors *in vivo*, or *in vitro* entirely with chemical compounds [2]. The discovery of iPSCs has also stimulated the development of parallel disciplines of cell reprogramming. Disciplines such as the generation of mouse and human pluripotent stem cells with different potency and characteristics or transdifferentiation [3], which can be achieved using different target cell types *in vivo*, or *in vitro* by means of chemical compounds. This issue of *Current Opinion in Genetics and Development* highlights the most recent progress in the field of cell reprogramming.

After just over a decade the pressure is growing, perhaps too quickly, to translate basic iPSC research into clinical applications, and in fact the first clinical trials with iPSCs have started in Japan, whilst others are in preparation in different countries. Yet, despite the surrounding excitement, a series of challenges remain for widespread clinical application, including the clonal variation between iPSC lines (reviewed by Ortmann/Vallier and Lin/Xiao), which severely influences differentiation efficiency and the functionality of the derived progeny. Defining the standards for comparing human iPSCs is, however, complicated by multiple reprogramming methods and culture conditions used in different laboratories, and the fact that human embryonic stem cell (ESC) lines are also highly heterogeneous. A major reason for this clonal variation is the appearance during somatic cell reprogramming of aberrations in DNA methylation, which is controlled by the balance between DNA methyltransferases (DNMTs) and DNA demethylases (TETs) (reviewed by Bogdanovic/Lister and Scott-Browne *et al.*). Currently, it is unclear whether this abnormal DNA methylation is caused by the lack of a phase of complete DNA demethylation, whose presence is essential for early embryonic development, or by specific signaling pathways activated during reprogramming. The choice and dosage of the exogenous factors are critical determinants of cell reprogramming quality, and Julian *et al.* review the role of SOX transcription factors in different cell fate conversions. Besides clinical application, clonal variation might also be a problem for *in vitro* modeling of complex genetic diseases, such as Parkinson's disease (reviewed by Calatayud *et al.*), reinforcing the need to handle large number of iPSC clones that can only be generated through consortia.

Human naïve culture conditions (reviewed by Bates and Silva) aim to mimic the extrinsic and intrinsic signaling responses of mouse pluripotent cells (reviewed by Zhao and Jin), which could result in less cell-line dependent heterogeneity of the differentiated cell types. However, multiple human

New York City in 2009. His lab studies the biochemical basis and molecular mechanisms governing stem cell pluripotency and somatic cell reprogramming, with a focus on transcriptional, posttranscriptional, posttranslational, and epigenetic regulatory mechanisms.

naïve cell culture variants have been reported, suggesting the existence of not a single defined state but rather a spectrum. Deeper understanding of early lineage specification, including trophoectoderm formation, in the developing embryo (reviewed by Jaber *et al.*) will be important to improve human naïve culture protocols and for generating cells with increased developmental potential. A relevant parameter that should be considered during the transition between pluripotent states is metabolic switching (reviewed by Cliff and Dalton). Producing iPSCs or transdifferentiated cells only with chemicals (reviewed by Xie *et al.*) might also result in reduced experimental variability. However, chemical somatic cell reprogramming has only been achieved in the mouse setting, and a problem of transdifferentiation is that the cells need to be prepared every time and the obtained cell number is limited, though this can be bypassed by producing progenitors rather than terminally differentiated cells.

A driving force to improve cell-reprogramming methodologies has been to unveil the underlying mechanisms. In this sense, despite so much recent progress, a coherent comprehensive theory of chromatin changes and 3D-nuclear reorganization in reprogramming is still elusive (reviewed by Guo and Morris), in particular in the human context. Cheloufi and Hochedlinger review the role of the chromatin assembly complex CAF-1, a histone chaperone, in enhancing both mouse somatic cell reprogramming and transdifferentiation, which occurs at least in part through increasing chromatin accessibility. Because of the potently accelerated kinetics and very high reprogramming efficiency, this and other similar approaches should prove invaluable for producing high-resolution epigenetic and transcriptional maps of cell reprogramming processes (reviewed by Firas/Polo, Habibi/Stunnenberg, and Wang *et al*), including single-cell maps (reviewed by Natarajan *et al.*). The corresponding transcriptional maps should also include non-coding RNA species, not only microRNAs but also long non-coding RNAs (reviewed by Hao *et al.* and Yan *et al.*), and endogenous retroviruses (reviewed by Gautam *et al.*), as they participate in a growing number of cellular processes. The integration of these mega data into computer networks such as *CellNet* or *Mogrify*, and their comparison to other cell types of interest, will help to measure the quality of cell fate conversions and design approaches that enhance them (reviewed by Guo/Morris and Firas/Polo). Importantly, in addition to the epigenetic and transcriptomic information, these computer networks should include the analysis of post-transcriptional (reviewed by Chen and Hu) and post-translational modifications. Regarding the former, RNA can undergo over 100 modifications, among which the deposition of m^6A (reviewed by Aguilo and Walsh) is receiving increasing attention due to its critical role in controlling pluripotency exit during differentiation through the regulation of pluripotency gene mRNA stability. As for the post-translational modifications, new developments in proteomics techniques (reviewed by Abazova and Krijgsveld) make quantification more accurate from a reduced number of cells. It would also be interesting to apply a wide variety of novel proteomics techniques to cell reprogramming, including those useful for profiling RNA-protein interactions. Ultra-quick and efficient cell reprogramming will similarly facilitate the study of chromatin changes using advanced microscopy methods and super resolution imaging (reviewed by Ricci *et al.*). Magnified imaging of chromatin might also help differentiate iPSC lines with different epigenetic characteristics.

Thanks to the above-mentioned advances and many more discoveries in the pipeline, the field of cell reprogramming is bursting with possibilities, and so

designing and engineering any cell fate is progressively becoming a reality. Moreover, the frontiers between stem cells and other disciplines are now converging, and for example findings like somatic cell reprogramming *in vivo* (reviewed by Taguchi and Yamada) link cell reprogramming with both aging and cancer. Although many uncertainties regarding the quality and safety of the reprogrammed cells need to be solved, we should enjoy and foster this exciting moment in science where impossible seems nothing and nothing seems impossible.

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