Focus on induced pluripotency and cellular reprogramming

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Reflecting on the opportunities that ‘induced pluripotency’ offers for basic research and clinical translation, the 2015 Focus of *The EMBO Journal* highlights some of the most challenging biological questions studied using advanced iPSC-based technologies.

The concept of ‘induced pluripotency’ stems from research showing that embryonic and differentiated cells are genetically identical and that a handful of transcription factors are sufficient to revert the fate of any given cell. The Nobel Prize-winning discovery of transcription factor-based ‘reprogramming’ inspired many laboratories to define conditions for the derivation, expansion, and differentiation of induced pluripotent stem cells (iPSCs) into every imaginable cell type. Combined with genome editing tools, scientists and clinicians are now equipped to model complex human diseases and to explore the potential of iPSCs for therapeutic and regenerative applications.

The progress of iPSC-based research is breathtaking, and the first clinical trials are encouraging. *The EMBO Journal* has invited leading experts to discuss recent progress and challenges in delivering on the translational promise of iPSC-based treatments.

Cellular hierarchies emerge very early in the *hematopoietic system* and initial attempts to manipulate lineage commitments revealed transcription factor (TF) networks that govern distinct cellular identities. Based on this conceptual premise, *Derrick Rossi & Wataru Ebina* discuss advances in direct cell fate conversion for the generation of transplantable human hematopoietic stem cells (HSCs). The authors arrive at a ‘roadmap’

toward the clinical translation of induced human HSCs that integrates new mechanistic insights into the control of HSC identity.

Petra Hajkova & colleagues emphasize the role of *chromatin* during TF-based reprogramming. This additional level of regulation offers new therapeutic opportunities arising from chromatin-remodeling enzymes to influence histone deposition or histone and DNA modifications.

Jeffrey Karp & colleagues introduce the broad range and unique features of *biomaterials* that could further unleash the regenerative capacity of iPSCs. These include nanoparticles to ease drug delivery, cargos for spatio-temporal control of reprogramming factors, and platforms for efficient reprogramming and iPSCs expansion. Biomaterial scaffolds for tissue regeneration, *ex vivo* disease modeling or substrates for bio-printing may address safety, scalability, and immunogenic challenges.

The successful reprogramming of fibroblasts into functional neurons opened the door for the generation of mature neurons in the ‘dish’, particularly from patients carrying neurological disorders. *Kristin Baldwin & Rachel Tsunemoto* and *Evangelos Kiskinis & Justin Ichida* review technological advances in the generation/maturation of neuronal subtypes for disease modeling. They also discuss the combination of iPSCs with genome editing to gain insights into previously inaccessible neurological disorders.

The existence of adult stem cells and their re-activation for *cardiac* regeneration are still debated. *Kenneth Chien & colleagues* revisit the principles of cardiac programming and the regenerative potential from an evolutionary perspective. They discuss

transplantation of iPSC-derived cells and direct *in vivo* conversion/trans-differentiation to achieve cardiac regeneration.

Cellular reprogramming has also reignited attempts to generate *pancreatic beta cells* for autologous cell therapies of diabetes. *Dieter Egli & colleagues* reflect on the generation of functional mono-hormonal beta cells *in vitro*. They highlight the value of patient-derived cells and propose that immune system modifications may have to be engineered into pancreatic grafts to prevent autoimmune responses.

Much remains to be learned about the intestine in infection, cancer, inflammation, malnutrition, and intrinsic pathologies. *James Wells & Katie Sinagoga* summarize efforts to directly differentiate pluripotent stem cells into human intestinal organoids (HIO) to model disease and offer easy access to genetic manipulations.

Finally, *Kenneth Zaret & Jungsun Kim* introduce reprogramming of *human cancer* cells to recapitulate tumor initiation. The concept that ‘pluripotency dominates over cancer phenotype’ may complement genetic animal models for biomarker discovery, mechanisms of disease progression, and the assessment of treatment efficacy.

While these reviews can only offer vignettes of the diversity of stem cell research, we hope that this *EMBO Journal Focus* will serve as a reference and inspiration for new experiments and therapeutic discoveries.

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