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Investigating Pediatric Disorders with Induced Pluripotent Stem Cells

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Abstract

The study of disease pathophysiology has long relied on model systems, including animal models and cultured cells. In 2006, Shinya Yamanaka achieved a breakthrough by reprogramming somatic cells into induced pluripotent stem cells (iPSCs). This revolutionary discovery provided new opportunities for disease modeling and therapeutic intervention. With established protocols, investigators can generate iPSC lines from patient blood, urine, and tissue samples. These iPSCs retain ability to differentiate into every human cell type. Advances in differentiation and organogenesis move cellular in vitro modeling to a multicellular model capable of recapitulating physiology and disease. Here, we discuss limitations of traditional animal and tissue culture models, as well as the application of iPSC models. We highlight various techniques, including reprogramming strategies, directed differentiation, tissue engineering, organoid developments, and genome editing. We extensively summarize current established iPSC disease models that utilize these techniques. Confluence of these technologies will advance our understanding of pediatric diseases and help usher in new personalized therapies for patients.

History of Disease Models

The optimal diagnosis and treatment of pediatric disease requires an understanding of physiology and pathophysiology. Throughout medical research history animal and cell culture models have been critical to this process. Mouse models, in particular, are extensively utilized because they are relatively convenient, and similar to humans at the chemical, molecular, cellular, and some anatomic levels. Furthermore, the use of transgenic mice allows for genetic manipulation to help elucidate molecular mechanisms. However,

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given that mice and humans diverged millions of years ago, there are critical physiological differences between the two species (1).

Human diseases often lack a mice ortholog. The equivalent disease in mice may be fatal or benign, and we cannot model some high level human organ functions or late onset diseases. Even non-human primates, despite being our closest ancestors, have important phenotypic differences (2). For example, because of these differences, it is particularly difficult to develop animal models for neurodegenerative or neurodevelopmental disorders. Differences in mouse cardiac morphogenesis have led difficulty modeling human congenital heart disease (3, 4). These limitations drive the need for human cell, tissue, and organ systems models.

Many human diseases involve terminally differentiated cell types, such as neurons and cardiomyocytes. These cell types are nearly impossible to sample, culture, and maintain. Even after generating primary cell lines from diseased tissues, ability to derive meaningful conclusions is often hampered by inconsistent replicability, dedifferentiation, and variability due to culture conditions. Tissues derived from human induced pluripotent stem cells (iPSCs) has the potential to overcome many inherent limitations of animal and cell culture models and provide an unprecedented new paradigm to model human diseases.

Pluripotent Stem Cells

During human embryogenesis, the ovum and spermatozoa fuse at fertilization, begin to divide, and differentiate into all cell lineages and tissue types in the human body. During development, these cells lose their pluripotency as they terminally differentiate into specific cell types. Embryonic stem cells (ESC) were first isolated from the blastocyst of developing mouse embryos in 1981, and from human embryos in 1998(5–7). These cells have the remarkable ability to retain pluripotency. The ESC discovery generated great excitement over their potential applicability in human disease modeling and regenerative therapies. However, limitations and controversies soon emerged.

The isolation of ESCs from human embryos is ethically controversial. Disease models utilizing ESC are limited to diseases identified through preimplantation genetic diagnosis (8). Genome editing ECSs provides an opportunity to generate particular mutations of interest, but technique remains largely limited to monogenic diseases. Recent breakthroughs in induced pluripotent stem cell (iPSC) technology circumvent many of these drawbacks.

Induced Pluripotent Stem Cells

In 2006, Shinya Yamanaka identified four transcription factors, (OCT4, SOX2, KLF4, and c-MYC), that were capable for reprogramming somatic mouse cells into a pluripotent state (9–11). This extraordinary feat was recapitulated one year later in human cells. These induced pluripotent stem cells (iPSCs) behave like ESCs with capability to differentiate to most other cell types, and circumvent the ethical controversy and sample limitations. As opposed to human embryos, iPSCs can be generated from readily accessible tissue samples, such as peripheral blood mononucleated cells (PBMCs). Patient samples can be reprogrammed to iPSCs, serving as an autologous, continuously renewing supply of pluripotent cells.

This has resulted in the dramatic expansion of the stem cell field, with development and improvements in reprogramming protocols and directed cellular differentiation. Patient-specific iPSCs can be generated from wide variety of patient samples, including PBMCs from blood samples, to dermal fibroblasts from punch biopsies, and epithelial cells from urine samples. iPSCs can then be differentiated to most other cell types including cardiomyocytes, neurons, and hepatocytes. Because the lines are patient-specific, they are expected to recapitulate features of many disease phenotypes, whether due to simple monogenic mutations or complex polygenic disease susceptibilities. The patient-specific iPSCs hold potential for disease modeling, predicting drug response and assessing environmental triggers of diseases. Thus, they provide great potential for research and clinical applications in personalized medicine.

Gene Editing iPSCs

Mouse models allow genetic alteration using transgenesis and gene knock-outs. Measuring the resulting phenotype is extremely valuable in the study of genetics and development. iPSCs allow us to utilize these same genetic approaches using human cell lines. The past decade has seen tremendous advances in gene editing technology, including ZFNs (zinc finger nucleases), TALENs (transcription activator like effector nucleases), and CRISPR–Cas9 (clustered regularly interspaced short palindromic repeat)(12–18). The common mechanism of these genomic editing approaches is that they create double stranded breaks (DSBs) at desired locations in the genome, which then can be repaired by either nonhomologous end-joining (NHEJ) that can result in insertion/deletions (indels) or homology directed repair (HDR), which results in precise gene modifications. Of these, the CRISPR-Cas9 technology, which appropriates the prokaryote defense mechanism, has quickly become dominant due to ease with which it can be adapted to precisely edit virtually any region in the host genome.

Genome editing, coupled with the iPSC technology, allow us to study disease mechanism like never before. These technologies allow us to precisely correct mutations and insert reporters under the endogenous regulatory control. They have also been used to demonstrate feasibility of genomic editing as a therapeutic modality (19, 20). Recently, a group corrected a pathogenic mutation in preimplantation human embryos, demonstrating the feasibility of gene correction therapy(21). While still a long way from clinical applications, many disease phenotypes have been corrected in cell culture. These studies show the potential of these powerful technologies for disease modeling, and for therapeutic genome engineering (Table 1).

Choice of a Disease

While a wide variety of human diseases are amenable to iPSC modeling. iPSCs are particularly attractive for diseases without a useful animal or cell culture model. The disease expression must be cell autonomous, preferably with clearly defined cell or tissue specific phenotypes. However, even in cases without a readily apparent disease phenotype, disease-specific iPSCs may be valuable for discovering gene networks and developmental programs altered in the disease state.

When a disease is thought to arise from a single causal gene mutation (i.e. monogenic), genomic editing would suffice to recapitulate disease phenotype. However, many diseases are complex, with polygenic and heterogeneous inheritance patterns. In such cases, generation of iPSCs from affected patients accurately replicates this complexity. For multifactorial disease we must consider disease penetrance and variable expressivity. In some instances, a disease may have both monogenic as well as polygenic etiology, and iPSCs may be a valuable tool. For example, iPSCs from Alzheimer's Disease patients have been valuable for modeling, and differentiating between, monogenic and polygenic etiologies (22). One must also consider the timing of disease onset. For congenital diseases, it may be informative to measure alternations in the development program during transition from the iPSC state to the terminal differentiated cell type. By contrast, diseases manifesting at a later age, or in adulthood, may require maturation techniques. Disease marked by disruption in a higher-level architecture may benefit from organoid models; three-dimensional multi-cell type organoids are available for most organs.

Cell Maturity and Epigenetic Considerations

Early efforts at directed differentiation of iPSCs resulted in cell types that resembled embryonic tissues; but accurate modeling of adult-onset diseases ideally requires generation of cells with mature, rather than embryonic, characteristics. Typically, long term culture following induction of iPSC differentiation leads to a more mature phenotype. This strategy produces iPSC-derived cardiomyocytes (iPSC-CMs) with increased expression of maturation-associated markers (23, 24). Alternative approaches to promote maturation of iPSC-CMs toward phenotypes that better resemble adult cardiomyocytes utilize novel culture methods such as enriched ECM (25–27). To age neuronal cells in vitro, Rotenone, which produces oxidative stress, has been used inducing telomere shortening and increase senescence markers (28). Similar aging-associated changes, such as telomere shortening and cellular senescence, are inducible using Progerin, a protein associated with premature aging in humans (28). The effects of "epigenetic memory" on directed differentiation of iPSCs are incompletely appreciated, but there is evidence that, after a successful reprogramming, iPSCs retain some epigenetic signature of the origin cell type. For instance, iPSCs reprogrammed from pancreatic tissue samples appear to be more readily differentiated to pancreatic beta cells than other tissue types (29). The impact of the epigenetic memory on the final phenotype of cells differentiated from iPSCs requires further investigation.

Derivation of iPSC Disease Models

The process of iPSC generation begins with somatic cells growing in tissue culture (Figure 1). A common source of somatic cells includes patient fibroblasts, obtained from skin punch biopsy, or postoperative tissue sample (11). More recent protocols derive iPSCs from patient samples obtained noninvasively, such as the peripheral blood mononuclear cells (PBMCs) in blood samples (30, 31) and squamous epithelial cells in urine samples (32, 33).

Somatic cells growing in tissue culture are first reprogrammed into iPSCs. This is accomplished through the transient, forced expression of transcription factors. Yamanaka's breakthrough came with discovery that forced expression of four transcription factors,

commonly expressed in pluripotent cells, sufficiently “reprogramed” differentiated cells back to pluripotency (10). These four factors (OCT4, SOX2, KLF4 and c-MYC,) are termed the Yamanaka factors. While Yamanaka and his colleagues initially utilized retroviral transduction of these reprogramming factors, various techniques were soon developed to increase reprogramming efficiency and minimize vector integration into the host genome. A number of reprogramming methods and commercially available reprogramming kits are now available (34). Latest methods differ in terms of number of reprogramming factors utilized (usually between 2 and 4), level of efficiency, factor exposure time, and level of integration into the host genome.

A popular method utilizes cellular transfection, often by electroporation, of a nonintegrating episomal plasmid containing the reprogramming factors(30, 31, 35). The nonintegrating reprogramming plasmid is undetectable after multiple passages. This method requires altered culture media, and reprogramming efficiency is often low. Another increasingly popular method utilizes a Sendai Virus for transfection into the cell cytoplasm(36). The genetic material of the RNA virus does not enter the nucleus, nor integrate into the host genome, thus leaving all traces of virus undetectable after multiple rounds of passaging. Adenovirus is another non-integrating virus presenting attractive an option, although its current reprogramming efficiency is low(37).

Transient expression of reprogramming factor mRNA is an excellent, completely integration free, strategy (38). However, this method is labor intensive, requiring multiple days of mRNA exposure, and efficiency is often low. An additional strategy utilizes expression of reprogramming factor proteins; but these proteins are difficult to synthesize and purify, and the structures are large and charged, limiting plasma membrane diffusion(39). Other methods involve transdifferentiating to desired cell types following transient passage through an iPSC – like stage, rather than via full reprogramming(40, 41). This method is useful only if one, terminally differentiated cell type is required.

Particular somatic cells types are particularly senescent, difficult to reprogram, and require more rigorous reprogramming methods, or alternative methods to increase efficiency. There are methods with higher efficiency utilizing integrative reprogramming. A Cre-Lox system or transposon can be utilized to excise the reprogramming factors at a later date, if needed(42). Alternate strategies to increase reprogramming efficiency include: adding valproic acid and sodium butyrate to inhibit histone deacetylase, adding vitamin C as an antioxidant, cell culture in hypoxic conditions, and adding small molecule inhibitors of transforming growth factor beta (TGF-B) or rho-associated protein kinase (ROCK) (43–48).

Reprogramming methods vary in duration of time to reprogram, reprogramming efficiency, level of integration, and the time to loss of the reprograming vector or plasmid. Integration free methods are vital if derived tissue will ever be utilized for therapy. Selection of a method requires consideration of the somatic cell type being utilized, including current published methods, and the ultimate goal of the experiment. With a combination of these methods, almost all somatic tissue types can be successfully reprogrammed to iPSCs.

Once iPSC culture is established, differentiation to almost any cell or tissue is possible. Differentiation usually involves initial differentiation to one of the three germ layers, ectoderm, mesoderm or endoderm, followed by further differentiation into a specific cell type. Differentiating iPSCs into terminally differentiated, clinically relevant cell types, utilizes protocols that often mimic the developmental pathways operant during embryogenesis. We highlight some of the major steps towards differentiation, whereas each particular cell type requires specific cell culture conditions, timing, and small molecule exposure (49, 50)(Figure 1).

Organoids

Sometimes a simple, two-dimensional iPSC-derived tissue culture model cannot fully recapitulate complex organ systems involving three-dimensional (3D) architecture; such cases necessitate organoid modeling. In vitro organogenesis, the exciting new frontier in in vitro disease modeling, aims to organize iPSCs into 3D structures that better recapitulate in vivo physiology (Table 2)(51, 52). Previous attempts at organoid modeling utilized primary tissue cells, but primary cells are difficult to obtain and often fails to propagate in vitro. In principle, iPSCs are an ideal cell source to make tissue organoids. The most comprehensive organoid model to date involves a fully vascularized and functional human liver (53). A 3D gastric organoid was created that progresses through developmental stages adopts similar architecture to the stomach (54). This organoid provided valuable insights into the gut development, as well as H. Pylori infection (55). Human iPSCs were grown also on rat intestinal matrix, to engineer a humanized intestinal graft for nutrient absorption in patients with short bowel syndrome (21). The established protocol for generating 3D cerebral organoids from iPSCs, replicates brain developmental stages. The organoid reproduces a variety of brain structures, including the cerebral cortex, ventral telencephalon, choroid plexus and retina (56). Manipulating specific developmental signaling pathways in ventral-anterior foregut spheroids recently generated an iPSC-based human lung model (47). Lastly, an iPSC-based human kidney organoid model was recently developed displaying glomerulus-like structures and renal tubules (57). Future *in vitro* organogenesis effort must address the need for chemically defined synthetic extracellular matrices (ECMs), and incorporation of support cell types such as interspersed neurons, immune cells, and other regulatory cells. While the regenerative medicine field is still in infancy, transplantation of functional tissues derived from patient's own cells could profoundly improve the health of patients with end-organ failure.

Large Scale Biorepositories

With the rapid development of iPSC disease models around the world, there are now multiple large-scale efforts to establish well-characterized biorepositories of disease specific iPSCs lines. The largest involved the New York Stem Cell Foundation (NYSCF), California Institute for Regenerative Medicine (CIRM), Human Induced Pluripotent Stem Cells Initiative (HipSci) and Stem cells for Biological Assays of Novel drugs and prediCtive toxiCology (StemBANCC)(58–61). These biorepositories are meant to increase collaboration and accelerate progress.

Disease Models

Human iPSC disease models have been developed in nearly every organ system. Numerous diseases have been modeled utilizing iPSCs from mice, but we focus on human derived models. A number of excellent review articles have summarized iPSC disease modeling(62–76); here we focus on common pediatric disorders and adult disorders with congenital and genetic etiology. We highlight some of the established disease models in each organ system and provide a more comprehensive list of disease models (Table 1).

Cardiac disease

Some of the earliest iPSC disease models were for cardiovascular disorders. Cardiac disease modeling with iPSC-derived cardiomyocytes has been highly successful; this is because iPSCs easily differentiate to cardiomyocytes, and many disease states result from altered cardiomyocyte function. Cardiac diseases, such as cardiomyopathies, mitochondriopathies, and channelopathies have been successfully modeled; whereas congenital heart diseases involving structural malformations require further refinement.

Congenital Long QT Syndrome (LQTS) was one of the first diseases modeled using patient-derived iPSCs (77–79). (66–68). Congenital LQTS is an inherited condition, marked by aberrant repolarization and resultant cardiac arrhythmias. iPSC models of both type 1 and 2 LQTS, due to KCNQ1 and KCNH2 gene mutations respectively, successfully recapitulate the prolonged repolarization phenotype. Pharmacotherapy, including nifedipine and pinacidil, reversed phenotype. Gene therapy has been utilized to generate a LQTS models (80), and to correct the mutation and restore electrophysiology in an iPSC-CM model of Brugada Syndrome (personal communication).

In addition, iPSC-CMs models have been developed for multiple inherited cardiomyopathies, including, familial dilated cardiomyopathy (DCM), hypertrophic cardiomyopathy (HCM), mitochondrial cardiomyopathy and arrhythmogenic right ventricular cardiomyopathy (ARVC) (80–83). In many familial dilated cardiomyopathy (DCM), specific sarcomere defects in cardiomyocytes lead to ventricular dilation and impaired contractile function; whereas in HCM, a different set of defects in the same sarcomere components lead to ventricular thickening and impaired relaxation. The iPSC-CM based models of DCM and HCM have provided valuable insight into how specific mutations in the sarcomere genes result in structural and functional defects observed in patients. Moreover, gene editing techniques have been used in iPSC-CM models to correct causal mutations and reverse cardiomyopathy (84). Beyond structural diseases, an iPSC-based model of viral cardiomyopathy due to Coxsackivurs infection was used to evaluate antiviral therapies (85). Other iPSC-based cardiac disease models include Pompe’s disease, Fabry disease, catecholaminergic polymorphic ventricular tachycardia, Timothy Syndrome, Leopard Syndrome, and Noonan Syndrome (86–90).

Hematologic Disease

In principle, hematologic disorders are well suited for modeling with iPSCs, given involvement of one cell type, easily derived from iPSCs, and unaffected by secondary

structure or organ architecture. Sickle Cell Disease (SCD) is a group of inherited blood disorders that cause great misery worldwide. The disease results from a single point mutation to the β-globin gene. This single mutation results in a truncated hemoglobin protein S with diminished oxygen carrying capacity and propensity to aggregate, causing pain and end organ damage. The NIH funded a large, comprehensive, and ethnically diverse library of SCD iPSCs lines for detailed in vitro study. In iPSC disease models, the SCD mutation has been corrected (91, 92). (80, 81).

Chronic Granulomatous Disease (CGD) is a genetically heterogeneous immunodeficiency marked by impaired neutrophil function and consequent susceptibility to certain bacterial and fungal infections. Various iPSC disease models accurately recapitulate the CGD phenotype. Further, a mutation was corrected in an CGD iPSC model resulting in recovery of neutrophil function (93, 94). Severe Combined Immunodeficiency (SCID) is another genetically heterogeneous immunodeficiency marked by defective differentiation of functional T cells and B cells. One form of SCID, caused by a mutation in Janus family kinase JAK3 gene was successfully modeled in vitro, when iPSCs demonstrated defective T cell differentiation.

The defect was subsequently corrected using CRISPR-Cas9 (22).

Hemophilia A and B are bleeding disorders caused by factor VIII deficiency. They have been effectively modeled with iPSCs and corrected in iPSC in vitro (95–98). Thalassemia and Fanconi Anemia have been modeled with iPSCs, and the Thalassemia in vitro phenotype has been reversed with the gene editing (99–101)These models open the door to new therapies, including an unlimited source of healthy, gene corrected, iPSC-derived, hematopoietic cells.

Neurologic Diseases

Historically, human neurologic diseases have been difficult to model in vitro given the inherent complexity of neural networks, and the inability to sample human brain and nervous tissues. Therefore iPSC-based models offer tremendous potential. Neurologic diseases result from defects in multiple nervous system cell types including neurons, astrocytes, and glial cells. Most of these relevant cell types can be generated using current iPSC differentiation protocols. Advances in tissue engineering may soon provide organoid models of the complex cell networks comprising the brain, spinal cord and peripheral nervous system.

Parkinson’s disease (PD) is a devastating illness marked by progressive deterioration of the dopaminergic neurons, leading to motor and cognitive declines. PD is caused by complex interaction between inherited genetic susceptibility and environmental exposures. Dopaminergic neurons derived from PD patients retain this complex genetic background, and successfully recapitulate the disease phenotype (102, 103). iPSC lines are helping to advance understanding of inherited and sporadic disease pathogenesis (104). In iPSC lines harboring different familial mutations implicated in PD, pharmacologic interrogation provided insight into the convergent cellular pathways involved in pathogenesis (105). Gene

correction of the mutations in diseased iPSCs reverses the abnormal dopaminergic neuronal phenotype (106).

Amyotrophic Lateral Sclerosis (ALS) is a condition marked by progressive deterioration of upper and lower motor neurons in the brain and spinal cord. Motor neurons derived from affected patient iPSCs effectively model ALS phenotype. The model has provided insight into disease pathogenesis, and proven useful for screening drug candidates (107–113). Spinal Muscular Atrophy (SMA) is an autosomal recessive disorder affecting voluntary skeletal muscles. SMA was one of the first genetic disorders successfully modeled using iPSCs (114–118), which replicate SMA's affect on the neuromuscular junction (115). Lastly, Alzheimer's Disease (AD) is a neurodegenerative disorder marked by progressive cognitive decline in later life. Etiology of this condition is multifactorial, involving both complex genetic inheritance, and environmental influences. Patient-derived iPSC lines have been used to differentiate between inherited and sporadic cases. They will play an important role in elucidating the myriad of contributors to AD (22, 119, 120).

Psychiatric disorders, including schizophrenia and bipolar disorder, have been modeled utilizing iPSCs. Schizophrenia is a complex and devastating psychiatric disease marked by development of psychosis in early adulthood. Etiology is likely multifactorial, resulting from genetic susceptibility as well as environmental influences. The disease affects neurobehavioral function at the highest levels, and its complex genetic influences make development of a valid animal model very challenging, if not impossible. In the context of this critical knowledge gap, schizophrenia patient iPSC-derived neurons have provided insight into disease pathogenesis, identifying genetic risk factors and altered signaling pathways (121–126). Interestingly, specific phenotypic markers, such as decreased neuronal connectivity and lower glutamate expression, were reversed in iPSC models of schizophrenia upon exposure to antipsychotic pharmacotherapy(127). In addition, an iPSC model of bipolar disorder demonstrated altered neurogenesis and neuroplasticity, and the phenotype recovered with pharmacologic rescue (128). Another bipolar model showed differential response to the commonly prescribed bipolar medication, lithium (129). Both bipolar iPSC findings may be valuable for developing new therapies and tailoring existing therapies.

Rett Syndrome is a severe neurodevelopmental disorder caused by mutations in the MECP2 gene. iPSC neurons derived from affected patients exhibited phenotypic differences such as smaller soma size, fewer synapses, and abnormal signaling in comparison to controls (119, 120). Pharmacological intervention rescued the synaptic abnormalities and identified a potential developmental window for therapeutic response.

Ongoing advances in iPSC-derived brain organoids more accurately model complex brain architecture. They will have profound impact on the study of human neurodevelopmental disorders, including microcephaly and autism(56).

Digestive and Pulmonary System

iPSC-derived tissues have been developed to model a number of gastrointestinal (GI) and pulmonary diseases. For example, Wilson's disease is a copper transport disorder affecting the liver and other organs. Copper accumulation leads to end organ damage. iPSC-derived hepatocytes from a patient with Wilson's disease exhibited the pathognomonic copper transport defect, and the phenotype reversed with expression of the wild-type protein (130). Alpha-1 antitrypsin (A1AT) deficiency is a condition of defective α-1 antitrypsin function, leading to pulmonary deterioration and liver cirrhosis. iPSC-derived hepatocytes from a A1AT deficiency patient recapitulated many of the cellular features of the A1AT deficiency; these affects were also reversed by gene correction (131). Patient iPSC-derived hepatocytes have been used to model a number of other disorders, including various familial hypercholesterolemia and glycogen storage diseases (132). An iPSC-derived endodermal cell model recently provided insight into the familial pulmonary hypertension (133). In addition to these cellular disease models, iPSC-derived organoids hold great promise for the study of GI and pulmonary diseases.

Endocrine System

In principle, iPSC technology can be utilized to model every organ of the endocrine system, but here we focus on the pancreas and thyroid. Diabetes is characterized by elevated blood glucose due to absolute and relative deficiency of the hormone insulin. Diabetes leads to significant long-term sequelae and is a current global health epidemic. Normally, the pancreatic islet cells respond to elevated blood glucose levels with insulin production and release, tightly maintaining glucose homeostasis. While insulin therapy has been transformative, it has been difficult to accomplish the exquisite regulation of blood glucose achieved by the pancreas. Islet cell transplantation from deceased human donors have shown potential for tighter glucose control, but these cells are difficult to access and maintain (134, 135). These limitations motivate efforts to develop functioning islets from iPSCs (29).

The thyroid gland follicular cells produces thyroid hormone, which affects almost every system in the body. Functional thyroid follicles have been generated from embryonic stem cells, and work is under way using patient-derived iPSCs (136). iPSC-derived thyroid progenitor cells were generated from individuals with hypothyroidism, as well as healthy controls, providing insight into thyroid development and dysfunction (137).

Renal System and Multisystem Disorders

The kidney has an essential role in electrolyte and fluid balance, waste removal and acid-base status. These functions are sustained by the kidney's complex structure, comprised of multiple cell types. While dialysis and transplantation can be life-saving in end-stage kidney failure, these treatment modalities require tremendous resources, and have significant inherent limitations. Human iPSC-derived kidney cells (iPSC-KCs) have significant potential for disease modeling and regeneration. While it is currently unknown whether iPSC-KCs can reconstitute all of kidney physiology in vitro, studies indicate that these cells can self-organize into kidney organoids containing cell populations with characteristics of

proximal tubules, podocytes and endothelium. The kidney organoids functionally recapitulate various aspects of renal epithelial physiology, and various kidney disease phenotypes. For instance, CRISPR-Cas9-mediated disruption of podocalyxin, a major constituent of the glycocalyx of the glomerular podocytes, leads to junctional defects in podocyte-like cells (115). In addition, disruption of the polycystic kidney disease genes PKD1 and PKD2 lead to pathognomonic cyst formation (138).

iPSC models have also been utilized to recapitulate multiorgan system disease. The multisystem disorder Trisomy 21, or Down Syndrome (DS), is one of the most common genetic disorders treated by Pediatricians. Trisomy 21 iPSC-derived neurons were found to have reduced synaptic activity, consistent with the DS physiology. These cell lines were utilized to highlight the role of astroglia in DS pathogenesis (139–141). In addition, Trisomy 21 iPSCs exhibited abnormalities of the hematopoetic precursor-like cells (142). Recent studies demonstrated Hutchinson-Gilford Progeria (HGP) patient-derived iPSCs displayed differences in Progerin expression, and showed premature aging. These disease lines provided insight into HGP etiology (143, 144). By generating iPSCs from syndromic patients, and deriving multiple cell types, there is great potential for disease modeling and therapy in these complex multisystem disorders.

Limitations and Future Directions

In the short time since Yamanaka's discovery and Nobel Prize, cellular reprogramming and iPSC technology have provided great insight into disease pathogenesis, and hope for regenerative therapies. Nonetheless, there remain a number of important limitations to the technology that necessitate further research and development. For instance, tissue sampling is particularly difficult in Pediatric patients, and future innovation should focus on non-invasive tissue acquisition; this includes ever smaller amounts of blood samples and skin biopsies as well as improvement in reprogramming of epithelial cells from urine samples. Further improvements are needed in iPCS reprogramming efficiency, non-integrative reprogramming methods and patient safety. Efficiently generating mature and functional cells will require a better understanding of embryonic development and of intermediate cell types. Organoid or organs-on-a-chip technologies should be further developed to overcome extant limitations of two-dimensional cell culture models. Moreover, we need to further explore the impact reprogramming and tissue derivation on the epigenome. With continued advancements, iPSC technology holds great potential for regenerative medicine, tissue engineering, personalized therapies, disease modeling, toxicity monitoring and drug testing.

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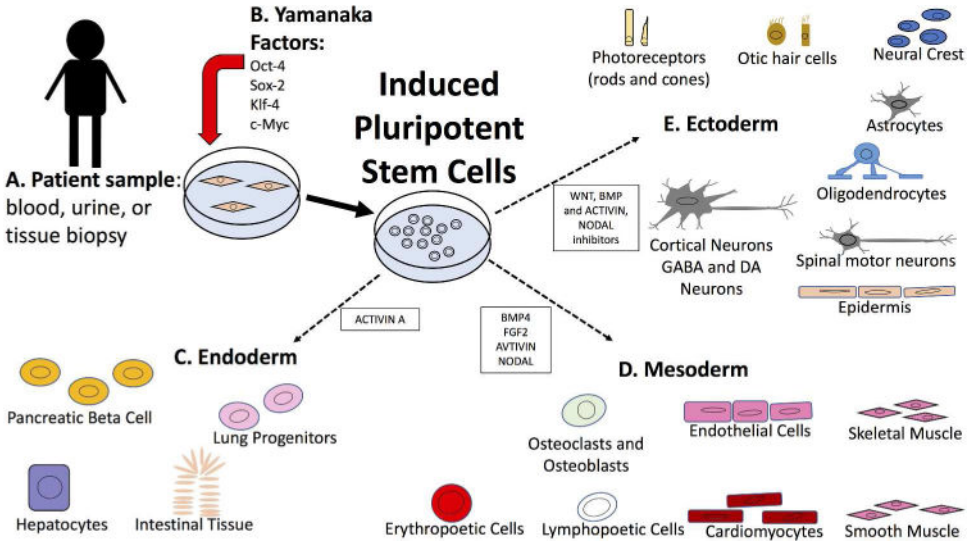

Figure 1.

A) To generate somatic tissue cultures, established protocols allow tissue sampling from skin fibroblasts, peripheral blood samples and urine sample. B) Reprogramming methods involve transient, forced expression of the four Yaminaka factors, Oct-4, Sox-2, Klf-4, c-Myc, C) ActivinA differentiates iPSCs to definitive and multipotent endoderm progenitors. Endoderm derivatives include anterior endoderm, multipotent lung progenitors, hindgut endoderm, intestinal tissue, hepatocytes, and pancreatic beta cells. D) iPSC induction with BMP4, FGF2 and ActivinA drives mesoderm derivatives including a primitive streak mesoderm, erythropoietic as well as lymphoid progenitors, osteoclasts, chondrogenic cells, adipogenic cells, smooth muscle cells, skeletal muscle cells, endothelial cells and cardiomyocytes. E) Neural progenitors become astrocytes, oligodendrocytes, cortical neurons, neural crest stem cells, spinal motor neurons, GABA neurons and DA neurons. Exposure to ascorbic acid and BMP4 differentiates iPSCs to keratinocytes then to epidermis. Nicotinamide induces retinal pigment epithelium and 3D culture of the cells creates an optic cup including a neural retinaiPSC are inducible to primordial germ cell-like cells, and further to oocyte-like cells, follicle-like cells, and spermatozoa.

Table 1

iPSC Disease Models

Disease	Organ System	Derived Cell Type	Leading Reference	Gene Editing for Model or Correction
Long QT Synrome	**Cardiovascular**	**Cardiomyocyte**	Itzhaki, Ilanlt, et al. "Modelling the long QT syndrome with induced pluripotent stem cells." *Nature* 471.7337 (2011): 225–229.	Wang, Yongming, et al. "Genome editing of isogenic human induced pluripotent stem cells recapitulates long QT phenotype for drug testing." Journal of the American College of Cardiology 64.5 (2014): 451–459.
Familial Dilated Cardiomyopathy	**Cardiovascular**	**Cardiomyocyte**	Sun, Ning, et al. "Patient-specific induced pluripotent stem cells as a model for familial dilated cardiomyopathy." *Science translational medicine* 4.130 (2012): 130ra47–130ra47. 1395–1403.	Karakikes, Ioannis, et al. "Correction of human phospholamban R14del mutation associated with cardiomyopathy using targeted nucleases and combination therapy." Nature communications 6 (2015).
Arrhythmogenic right ventricular cardiomyopathy (ARVC)	**Cardiovascular**	**Cardiomyocyte**	Kim, Changsung, et al. "Studying arrhythmogenic right ventricular dysplasia with patient-specific iPSCs." *Nature* 494.7435 (2013): 105–110. ehs226.	
Catecholaminergic polymorphic ventricular tachycardia (CPVT)	**Cardiovascular**	**Cardiomyocyte**	Jung, Christian B., et al. "Dantrolene rescues arrhythmogenic RYR2 defect in a patient-specific stem cell model of catecholaminergic polymorphic ventricular tachycardia." *EMBO molecular medicine* 4.3 (2012): 180–191. Novak, Atara, et al. " Cardiomyocytes generated from CPVTD307H patients are arrhythmogenic in response to β-adrenergic stimulation." *Journal of cellular and molecular medicine* 16.3 (2012): 468–482.	
LEOPARD syndrome (lentigines, electrocardiographic abnormalities, ocular hypertelorism, pulmonary valve stenosis, abnormal genitalia, retardation of growth and deafness)	**Cardiovascular**	**Cardiomyocytes**	Carvajal-Vergara, Xonia, et al. "Patient-specific induced pluripotent stem-cell-derived models of LEOPARD syndrome." *Nature* 465.7299 (2010): 808–812.	

Disease	Organ System	Derived Cell Type	Leading Reference	Gene Editing for Model or Correction
Timothy Syndrome (Long QT)	**Cardiovascular**	**Cardiomyocytes**	Yazawa, Masayuki, et al. "Using induced pluripotent stem cells to investigate cardiac phenotypes in Timothy syndrome." *Nature* 471.7337 (2011): 230–234.	
Hypertrophic Cardiomyopathy	**Cardiovascular**	**Cardiomyocytes**	Lan, Feng, et al. "Abnormal calcium handling properties underlie familial hypertrophic cardiomyopathy pathology in patient-specific induced pluripotent stem cells." *Cell stem cell* 12.1 (2013): 101–113.	Sheng, Calvin C., et al. "Cellular and Cardiac Microtissue Assays of iPSC-derived Myocytes With the Hypertrophic Cardiomyopathy Mutation in MYH7-Val606Met." (2015): A12532–A12532.
Cardiac Na+ channel mutations	**Cardiovascular**	**Cardiomyocytes**	Davis, Richard P., et al. "Cardiomyocytes derived from pluripotent stem cells recapitulate electrophysiological characteristics of an overlap syndrome of cardiac sodium channel disease." *Circulation* (2012): CIRCULATIONAHA-111.	
Mitochondrial Cardiomyopathy - Barth Syndrome	**Cardiovascular**	**Cardiomyocytes**	Wang, Gang, et al. "Modeling the mitochondrial cardiomyopathy of Barth syndrome with induced pluripotent stem cell and heart-on-chip technologies." *Nature medicine* 20.6 (2014): 616–623.	
Pompe Disease	**Cardiovascular**	**Cardiomyocytes**	Huang, Hsiang-Po, et al. "Human Pompe disease induced pluripotent stem cells for pathogenesis modeling, drug testing and disease marker identification." *Human molecular genetics* (2011): ddr424.	
Fanconi Anemia	**Blood**	**Hematopoietic Cells**	Raya, Ángel, et al. "Disease-corrected haematopoietic progenitors from Fanconi anaemia induced pluripotent stem cells." *Nature* 460.7251 (2009): 53–59.	
Sickle Cell Disease	**Blood**	**Hematopoietic Cells**	Ye, Lin, et al. "Induced pluripotent stem cells offer new approach to therapy in thalassemia and sickle cell anemia	Zou, Jizhong, et al. "Site-specific gene correction of a point mutation in human iPS cells

Disease	Organ System	Derived Cell Type	Leading Reference	Gene Editing for Model or Correction
			and option in prenatal diagnosis in genetic diseases." *Proceedings of the National Academy of Sciences* 106.24 (2009): 9826–9830.	derived from an adult patient with sickle cell disease." *Blood* 118.17 (2011): 4599–4608. Sebastiano, Vittorio, et al. "In situ genetic correction of the sickle cell anemia mutation in human induced pluripotent stem cells using engineered zinc finger nucleases." Stem cells 29.11 (2011): 1717–1726.
Thalassemia	**Blood**	**Hematopoietic Cells**	Ye, Lin, et al. "Induced pluripotent stem cells offer new approach to therapy in thalassemia and sickle cell anemia and option in prenatal diagnosis in genetic diseases." *Proceedings of the National Academy of Sciences* 106.24 (2009): 9826–9830.	Xie, Fei, et al. "Seamless gene correction of β-thalassemia mutations in patient-specific iPSCs using CRISPR/Cas9 and piggyBac." *Genome research* 24.9 (2014): 1526–1533.
Type 1 Diabetes	**Endocrine**	**islet beta cells**	Bar-Nur, Ori, et al. "Epigenetic memory and preferential lineage-specific differentiation in induced pluripotent stem cells derived from human pancreatic islet beta cells." *Cell stem cell* 9.1 (2011): 17–23.	Ramiya, Vijayakumar K., et al. "Reversal of insulin-dependent diabetes using islets generated in vitro from pancreatic stem cells." *Nature medicine* 6.3 (2000): 278–282.
Hemophilia A	**Blood**	**Modeling and gene correction**	Park, Chul-Yong, et al. "Functional correction of large factor VIII gene chromosomal inversions in hemophilia A patient-derived iPSCs using CRISPR-Cas9." *Cell Stem Cell* 17.2 (2015): 213-220.	
Amyotrophic Lateral Sclerosis	**Nervous**	**Motor Neurons**	Dimos, John T., et al. "Induced pluripotent stem cells generated from patients with ALS can be differentiated into motor neurons." *science* 321.5893 (2008): 1218–1221.	
Chronic granulomatous disease	**Blood**	**Neutrophils**	Dowey, Linzhao Cheng, and Harry L. Malech. "Oxidase deficient neutrophils from X-linked chronic granulomatous." (2011).	Zou, Jizhong, et al. "Oxidase-deficient neutrophils from X-linked chronic granulomatous disease iPS cells: functional

Disease	Organ System	Derived Cell Type	Leading Reference	Gene Editing for Model or Correction
				correction by zinc finger nuclease-mediated safe harbor targeting." Blood 117.21 (2011): 5561–5572.
Familial Dysautonoimia	**Nervous**	**Peripheral Neurons**	Lee, Gabsang, et al. "Modelling pathogenesis and treatment of familial dysautonomia using patient-specific iPSCs." *nature* 461.7262 (2009): 402–406.	
Spinal Muscle Atrophy	**Nervous**	**Motor neurons**	Ebert, Allison D., et al. "Induced pluripotent stem cells from a spinal muscular atrophy patient." *Nature* 457.7227 (2009): 277–280.	
Schozophrenia	**Nervous**	**Neurons Brain Organoid**	Brennand, Kristen J., et al. "Modelling schizophrenia using human induced pluripotent stem cells." *Nature* 473.7346 (2011): 221–225.	
Alzheimer's disease	**Nervous**	**Neurons**	Israel, Mason A., et al. "Probing sporadic and familial Alzheimer/'s disease using induced pluripotent stem cells." *Nature* 482.7384 (2012): 216–220. Yagi, Takuya, et al. "Modeling familial Alzheimer's disease with induced pluripotent stem cells." *Human molecular genetics* 20.23 (2011): 4530–4539. Kondo, Takayuki, et al. "Modeling Alzheimer's disease with iPSCs reveals stress phenotypes associated with intracellular Aβ and differential drug responsiveness." *Cell stem cell* 12.4 (2013): 487–496.	
Parkinson's disease	**Nervous**	**Dopaminergic neurons**	Sánchez-Danés, Adriana, et al. "Disease-specific phenotypes in dopamine neurons from human iPS-based models of genetic and sporadic Parkinson's disease." *EMBO molecular medicine* 4.5 (2012): 380–395.41ra90.	Sanders, Laurie H., et al. "LRRK2 mutations cause mitochondrial DNA damage in iPSC-derived neural cells from Parkinson's disease patients: reversal by gene correction." Neurobiology of disease 62 (2014): 381–386.
Rett Syndrome	**Nervous**	**Neurons**	Marchetto, Maria CN, et al. "A model for neural	

Disease	Organ System	Derived Cell Type	Leading Reference	Gene Editing for Model or Correction
			development and treatment of Rett syndrome using human induced pluripotent stem cells." *Cell* 143.4 (2010): 527–539.	
Autism Spectrum Disorder	**Nervous**	**Neurons**	Prilutsky, Daria, et al. "iPSC-derived neurons as a higher-throughput readout for autism: promises and pitfalls." *Trends in molecular medicine* 20.2 (2014): 91–104.	
Microcephaly	**Nervous**	**Brain organoid**	Lancaster, Madeline A., et al. "Cerebral organoids model human brain development and microcephaly." *Nature* 501.7467 (2013): 373–379.	
Helicobacter Pylori	**Digestive**	**Gastric organoid**	McCracken, Kyle W., et al. "Modelling human development and disease in pluripotent stem-cell-derived gastric organoids." *Nature* 516.7531 (2014): 400–404.	
Laminopathies	**Multi-organ**	**iPSCs**	Liu, Guang-Hui, et al. "iPSC Disease Modeling of Laminopathies." *Human iPS Cells in Disease Modelling*. Springer Japan, 2016. 53–67.	Liu, Guang-Hui, et al. "Targeted gene correction of laminopathy-associated LMNA mutations in patient-specific iPSCs." Cell stem cell 8.6 (2011): 688–694.
Hutchinson-Gilford progeria	**Multi-organ**	**neural progenitors endothelial cells fibroblasts VSMCs mesenchymal stem cells**	Liu, Guang-Hui, et al. "Recapitulation of premature ageing with iPSCs from Hutchinson-Gilford progeria syndrome." *Nature* 472.7342 (2011): 221–225.	
Gyrate Atrophy	**Nervous**	**iPSCs**	Howden, Sara E., et al. "Genetic correction and analysis of induced pluripotent stem cells from a patient with gyrate atrophy." Proceedings of the National Academy of Sciences 108.16 (2011): 6537–6542.	Howden, Sara E., et al. "Genetic correction and analysis of induced pluripotent stem cells from a patient with gyrate atrophy." Proceedings of the National Academy of Sciences 108.16 (2011): 6537–6542.
Duchenne muscular dystrophy (DMD)	**Nervous**	**Skeletal Muscles**	Salani, Sabrina, et al. "Generation of skeletal muscle cells from embryonic and induced pluripotent stem cells as	Li, Hongmei Lisa, et al. "Precise correction of the dystrophin gene in duchenne

Disease	Organ System	Derived Cell Type	Leading Reference	Gene Editing for Model or Correction
			an in vitro model and for therapy of muscular dystrophies." Journal of cellular and molecular medicine 16.7 (2012): 1353–1364.	muscular dystrophy patient induced pluripotent stem cells by TALEN and CRISPR-Cas9." Stem cell reports 4.1 (2015): 143–154.
Hypothyroidism	**Endocrine**	**Human thyroid progenitors**	Kurmann, Anita A., et al. "Regeneration of thyroid function by transplantation of differentiated pluripotent stem cells." Cell stem cell 17.5 (2015): 527–542.	
Gaucher Disease	**Neurvous**	**Neurons**	Awad, Ola, et al. "Altered TFEB-mediated lysosomal biogenesis in Gaucher disease iPSC-derived neuronal cells." Human molecular genetics 24.20 (2015): 5775–5788.	
Classical lissencephaly	**Nervous**	**Cerebral Organoids**	Bershteyn, Marina, et al. "Human iPSC-Derived Cerebral Organoids Model Cellular Features of Lissencephaly and Reveal Prolonged Mitosis of Outer Radial Glia." Cell Stem Cell (2017).	
Noonan Syndrome Hypertrophic Cardiomyopathy	**Cardiovascular**	**Cardiomyocytes**	Jaffré, Fabrice, et al. "Generation of Raf1 Mutant and Crispr-cas9 Corrected Isogenic iPSC-derived Cardiomyocytes to Model Hypertrophic Cardiomyopathy in Noonan Syndrome." (2015): A397–A397.	Jaffré, Fabrice, et al. "Generation of Raf1 Mutant and Crispr-cas9 Corrected Isogenic iPSC-derived Cardiomyocytes to Model Hypertrophic Cardiomyopathy in Noonan Syndrome." (2015): A397–A397.
Hereditary spastic paraplegia	**Nervous**	**Neurons**	Denton, Kyle R., et al. "Loss of spastin function results in disease-specific axonal defects in human pluripotent stem cell-based models of hereditary spastic paraplegia." Stem cells 32.2 (2014): 414–423.	
Mitochondrial Metabolic Disorders	**Nervous**	**neural progenitor cells**	Lorenz, Carmen, et al. "Human iPSC-derived neural progenitors are an effective drug discovery model for neurological mtDNA disorders." Cell Stem Cell (2017).	
Fragile X Syndrome	**Multi-organ**	**FX-iPSCs Neurons**	Urbach, Achia, et al. "Differential modeling of Fragile X syndrome by human embryonic stem	

Disease	Organ System	Derived Cell Type	Leading Reference	Gene Editing for Model or Correction
			cells and induced-pluripotent stem cells." Cell stem cell 6.5 (2010): 407.	
α1-antitrypsin deficiency	**Digestive**	**Hepatocyte like cells**	Tafaleng, Edgar N., et al. "Induced pluripotent stem cells model personalized variations in liver disease resulting from α1-antitrypsin deficiency." Hepatology 62.1 (2015): 147–157.	Yusa, Kosuke, et al. "Targeted gene correction of [agr] 1-antitrypsin deficiency in induced pluripotent stem cells." Nature 478.7369 (2011): 391–394.
Wilson's Disease	**Multi-organ**	**Hepatocytes Neurons**	Zhang, Shiqiang, et al. "Rescue of ATP7B function in hepatocyte-like cells from Wilson's disease induced pluripotent stem cells using gene therapy or the chaperone drug curcumin." Human molecular genetics 20.16 (2011): 3176–3187.	Zhang, Shiqiang, et al. "Rescue of ATP7B function in hepatocyte-like cells from Wilson's disease induced pluripotent stem cells using gene therapy or the chaperone drug curcumin." Human molecular genetics 20.16 (2011): 3176–3187.
Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS)	**Nervous**	**iPSCs**	Yahata, Naoki, et al. "TALEN-mediated shift of mitochondrial DNA heteroplasmy in MELAS-iPSCs with m. 13513G> A mutation." Scientific Reports 7.1 (2017): 15557.	Yahata, Naoki, et al. "TALEN-mediated shift of mitochondrial DNA heteroplasmy in MELAS-iPSCs with m. 13513G> A mutation." Scientific Reports 7.1 (2017): 15557.
Tuberous sclerosis	**Nervous**	**iPSCs**	Armstrong, Laura C., et al. "Heterozygous loss of TSC2 alters p53 signaling and human stem cell reprogramming." H uman Molecular Genetics 26.23 (2017): 4629–4641.	

Table 2

Major Human Organoid Models

Organ System	Disease Models	Reference
Liver	Alagille Syndrome Cystic Fibrosis	Takebe, Takanori, et al. "Vascularized and functional human liver from an iPSC-derived organ bud transplant." Nature 499.7459 (2013): 481–484.
Brain - Cerebrum Cerebellum Hippocampus	Microcephaly Autism Schizophrenia	Lancaster, Madeline A., et al. "Cerebral organoids model human brain development and microcephaly." Nature 501.7467 (2013): 373-379.
Intestine	Cancer Cystic Fibrosis Short Bowel Syndrome	Watson, Carey L., et al. "An in vivo model of human small intestine using pluripotent stem cells." Nature medicine 20.11 (2014): 1310–1314. Kitano, Kentaro, et al. "Bioengineering of functional human induced pluripotent stem cell-derived intestinal grafts." Nature Communications 8.1 (2017): 765.
Kidney		Takasato, Minoru, et al. "Kidney organoids from human iPS cells contain multiple lineages and model human nephrogenesis." Nature 526.7574 (2015): 564–568.
Stomach	H. Pylori Peptic Ulcer Cancer	McCracken, Kyle W., et al. "Modelling human development and disease in pluripotent stem-cell-derived gastric organoids." Nature 516.7531 (2014): 400-404.
Lungs	Cystic Fibrosis Bronchopulmonary Dyplasia	Dye, Briana R., et al. "In vitro generation of human pluripotent stem cell derived lung organoids." Elife 4 (2015): e05098.