Review Article

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Novel therapeutic approaches: Rett syndrome and human induced pluripotent stem cell technology

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Abstract: Recent advances in induced pluripotent stem cell (iPSC) technology target screening and discovering of therapeutic agents for the possible cure of human diseases. Human induced pluripotent stem cells (hiPSC) are the right kind of platform for testing potency of specific active compounds. Ayurveda, the Indian traditional system of medicine developed between 2,500 and 500 BC, is a science involving the intelligent formulations of herbs and minerals. It can serve as a "goldmine" for novel neuroprotective agents used for centuries to treat neurological disorders. This review discusses limitations in screening drugs for neurological disorders and the advantages offered by hiPSC integrated with Indian traditional system of medicine. We begin by describing the current state of hiPSC technology in research on Rett syndrome (RTT) followed by the current controversies in RTT research combined with the emergence of patient-specific hiPSC that indicate an urgent need for researchers to understand the etiology and drug mechanism. We conclude by offering recommendations to reinforce the screening of active compounds present in the ayurvedic medicines using the human induced pluripotent neural model system for research involving drug discovery for RTT. This integrative approach will fill the current knowledge gap in the traditional medicines and drug discovery.

Keywords: Human induced pluripotent stem cells (hiPSC); Rett syndrome (RTT); neurodevelopmental disorder; ayurvedic medicines; drug discovery; active compounds; Indian Traditional Ayurvedic System

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Introduction

Human induced pluripotent stem cells (hiPSC)

Induced pluripotent stem cells (iPSC) provide a great platform for therapeutic (regenerative medicine, patient specific personalized medicine, cell replacement therapy) and non-therapeutic applications (disease modeling, drug discovery, pharmaceutical testing and toxicology). The discovery of iPSC from mouse skin fibroblasts using retroviral mediated reactivation of four pluripotent transcription factors (OCT4, SOX2, KLF4, c-MYC) by Takahashi and Yamanaka in 2006. Late in 2007, Thomson and Yu (University of Wisconsin-Madison, USA) and Yamanaka *et al.* (University of Kyoto, Japan) converted human fibroblasts into hiPSC and revealed the use of two alternative factors (Nanog and Lin 28) to facilitate the programming process using a lentiviral system (1). The unique properties of iPSC, self-renewal and differentiation of three germ layers similar to embryonic stem cells (ESC) are considered as novel cell sources for studying

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neurodegenerative diseases (2). hiPSCs are promised to develop novel patient-specific cell therapies and research models for inherited and acquired diseases. Neuronal model system differentiation from patient-specific hiPSC to mimic central nervous system (3) is a high-throughput screening platform for novel therapeutic targets and drugs.

An incurable neurological disorder—Rett syndrome (RTT)

RTT (OMIN # 312750), a rare and incurable postnatal neurological disorder predominantly affecting females with an incidence of 1 in 10,000 (4) is characterized by an apparently non- symptomatic phase for the first 6–18 months of age followed by apraxia, deceleration of head growth, gait abnormalities, stereotypic hand movements, and mental retardation. Classical RTT caused by *MeCP2* mutations occur predominantly as C > T transitions of CpG dinucleotides mostly on the paternal X chromosome (5). There are more than 300 different mutations found in the *MeCP2* gene in which 90% were classical patients. Most of these mutations are found in eight different "hot spots" such as missense or nonsense mutations within the MBD (R106W, R133C, T158M, and R168X) or TRD (R255X, R270X, R294X, and R306C) (6). Small C-terminal deletions, with one or both breakpoints located within the "deleted prone region" (DPR) of exon 4, account for 10% of the cases. Atypical RTT caused by mutations in either cyclin-dependent kinase-like 5 (*CDKL5*) and netrinG1 (*NTNG1*) or FOXG1/XBF-1 (7-9). However, at least 5% of typical forms and more other atypical forms are not linked to any of 4 genes known to be involved in the disease. Sudden unexpected death occurs in one-quarter of deaths caused by RTT (10). The course and severity of RTT are determined by the location, type, severity of mutation and X-inactivation. Therefore, two girls of the same age with the same mutation can appear quite different. We already detailed about the basic knowledge on RTT, *MeCP2*, and hiPSCs in our previous publication (11).

RTT & hiPSC research in India

RTT, the second most common cause of intellectual disability in girls after Down syndrome in girls and women, was first recognized in the 1960s and the first report from India was in 1994 (12). Though RTT has a prevalence of 1 per 10,000 to 22,000 (13) in India, there are very few studies and case reports of RTT in India (14). Some of the studies were detection of two deletions of 44 bp (c.1157_1200del44 or p.L386fs) and 38 bp (c.1151_1188del38 or p.P384fs) in exon 4 or C-terminal segment (CTS) region of *MeCP2* in classical RTT patients of Indian origin (15); an unique family carrying non-identical *MeCP2* mutations in exon 2 wherein the proband with classical RTT was carrying a *de-novo* early truncating frameshift mutation while her asymptomatic mother was carrying a missense mutation were both predicted as pathogenic mutations (16); c.1160C > T (P387L) in exon 4 of the *MeCP2* gene homozygous mutation in Indian female patient was also reported recently (17). RTT is now recognized as one of the non-curable devastating neurodevelopmental disorders (18) that greatly affect society (19). Approximately, around 50 review articles were published about iPSC in India and a lesser number of research work done in hiPSC especially about characterization, differentiation and reprogramming factors.

There is a holistic therapy for curing the postnatal neurological disorders using the ancient medicinal systems like Siddha and Ayurveda in India. We further referred many recent in-depth reviews on hiPSC and the curative ayurvedic drugs for neurodegenerative disorders mainly for RTT.

Therapeutic target for treating RTT

The *MeCP2* gene is important for healthy brain activity. Mutations in *MeCP2* gene alter the level of MeCP2 and some downstream factors, which can cause neuronal defects in RTT.

MeCP2-Glutamatergic neurons

There are two types of neurons play a key role in RTT such as inhibitory and excitatory neurons. RTT affects every part of the brain. Generally, excitatory neurons are thought to carry information flow while inhibitory neurons are required for tuning the circuits. Restoring *MeCP2* gene expression only in glutamatergic neurons leads to complementary phenotypes of tremor, anxiety, and acoustic startle response (20).

MeCP2-GABAergic neurons

The inhibitory GABAergic neurons results in social problems and repetitive behaviors. Genetically restoring *MeCP2* expression only in GABAergic neurons of male *MeCP2* null mice enhanced inhibitory signaling, extended

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lifespan, rescued ataxia, apraxia, and social abnormalities but did not rescue tremor or anxiety. Restoring MeCP2 in neither excitatory nor inhibitory neurons alone is sufficient to fully rescue premature lethality, RTT-like symptoms, and RTT. Hence, modulating the excitatory/inhibitory balance through GABAergic neurons could prove a viable therapeutic option in RTT (21).

MeCP2 in cholinergic neurons

MeCP2 in cholinergic neurons is necessary and sufficient for autonomic cardiac control, thermoregulation, and survival. Targeting the overactive parasympathetic system may be a useful therapeutic strategy to prevent sudden unexpected death in RTT (10).

Downstream gene target

Loss of *MeCP2* function in RTT elevates PTP1B levels and thereby impairs insulin signaling and glucose metabolism. *PTPN1* encodes PTP1B which is a major metabolic regulator that inhibits insulin signaling by directly dephosphorylating the insulin receptor and IRS1. Therefore, inhibition of PTP1B is a direct target of *MeCP2*. Animal study by Krishnan *et al.* 2015 (22) revealed that the small- molecule inhibitors of PTP1B, the difluoromethyl phosphonic acid CPT157633 and the ursolic acid derivative UA0713 act as a potential downstream gene target for RTT **(**23).

MeCP2 reexpression

RTT shows a significant deficit in neuron-specific K^+-Cl^- cotransporter 2 (KCC2) expression, resulting in a delayed GABA functional switch from excitation to inhibition. Restoring KCC2 level rescues GABA functional deficits and therefore acts as a downstream gene target to treat RTT (18).

NF-κB pathway

Loss of *MeCP2* function leads to upregulation of *Irak1* gene, which is downstream of *MeCP2* resulting abnormal activation of NF-κB signaling. Macklis *et al.* in 2016 found the reduction of NF-κB signaling by genes can increase the dendritic complexity of cortical callosal projection neurons (CPN) and extends lifespan in RTT, indicating potential therapeutic strategies of RTT pathogenesis (24).

Clinical trials and drug discovery in RTT

Current therapeutic approaches aim to increase the expression of brain-derived neurotrophic factor (BDNF), a neurotrophin involved in brain development and plasticity to counteract the deficiency in *MeCP2*. BDNF does not cross the blood brain barrier (BBB), and therefore it has no immediate therapeutic application for RTT patients; however an alternative growth factor, insulin-like growth factor 1 (IGF1), crosses the BBB and shares similar properties and functions with BDNF. Animal research reveals that systemic administration of the active peptide of IGF1 improves physiological behavior and survival in *MeCP2* mutant mice suggesting that IGF1 can be a treatment in RTT patients (25). IGF1 can also rescue the impaired KCC2 level as a downstream gene target in RTT. Phase I clinical trials of recombinant IGF-1 treatment in patients with RTT have produced encouraging outcomes leads to ongoing Phase II trials. There are about 40 studies on RTT present in the clinicaltrial.gov, the drug based studies were listed in the below *Table 1*. There is no drug marketed for treating RTT till now.

Current trends in hiPSC technology

Recent advances in stem cell research, especially in the development of iPSC technology, provide a new paradigm for drug screening by permitting the use of human cells with the same genetic makeup as the patients without the typical quantity constraints associated with patient primary cells (26). The delivery of iPS cells treated with mitomycin C (MMC) loading with gold nanorods (AuNRs) for the targeted photothermal treatment of gastric cancer resulted in killing the tumor cells by the heat generated from the gold nanorods. This suggested that pre-treated iPS cells with MMC can be used as a novel and safe approach for targeted tumor therapy (27). Nanoplatform by the combination of Au nanorods, SiO_2, CXCR4 nanoparticles with hiPSC for the photothermal treatment paves a great promise for clinical translation in the near future (28). hiPSCs can be used as an autologous source for cell therapy. Transplantation of human iPSC-derived cells is a safe and efficient approach to promoting recovery after stroke and can be used to supply the injured brain with new neurons for replacement (29). Furthermore, the ability to simulate organ systems with hiPSCs may allow

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Table 1 List of clinical trials in Rett syndrome

Clinical trial ID	Trial title	Drug tested	Route	Phase	Status	Sponsor	Location
NCT02023424 (SHEBA-12-9855-BBZ-CTIL)	An open label, exploratory study to investigate the treatment effect of glatiramer acetate (Copaxone) on girls with Rett syndrome	Glatiramer acetate (Copaxone)	Sub cutaneous injection	I	Unknown	Sheba Medical Center	Israel
NCT02562820	Ketamine for the treatment of Rett syndrome: an exploratory trial	Ketamine	Intravenous infusion	I	Ongoing, but not recruiting participants	The Cleveland Clinic	United States
NCT02061137	A phase 1 clinical study to assess safety and efficacy of oral fingolimod (FTY720) in children with Rett syndrome	Fingolimod (FTY720); other name: Gilenya	Oral	I/II	Ongoing, but not recruiting participants	University Hospital, Basel, Switzerland; Novartis	Switzerland
NCT01253317	Pharmacological treatment of Rett syndrome by stimulation of synaptic maturation with IGF-1	rhIGF-1	Subcutaneous injection	I/II	Completed	Walter Kaufmann; International Rett Syndrome Foundation; Autism Speaks	United States
NCT00990691, 2007-006739-30, 2007-37	Pilot study of the effects of the desipramine on the neurovegetative parameters of the child with Rett syndrome	Desipramine	Oral	II	Completed	Assistance Publique Hopitaux De Marseille	France
NCT02153723; Rett syndrome Copaxone	Pharmacological treatment of Rett syndrome with glatiramer acetate (Copaxone)	Glatiramer acetate/ Copaxone	Subcutaneous injection	II	Ongoing, but not recruiting participants	Montefiore Medical Center Rett Syndrome Research Trust	United States
NCT01777542, IRB-P00005610	Pharmacological treatment of Rett syndrome by stimulation of synaptic maturation with recombinant human IGF-1 [Mecasermin (rDNA) injection]	Recombinant human insulin growth factor 1 (rhIGF-1); other names: Mecasermin (rDNA); Increlex	Subcutaneous injection	II	Completed	Boston Children's Hospital; International Rett Syndrome Foundation	United States

Table 1 (*continued*)

Table 1 (*continued*)

Clinical trial ID	Trial title	Drug tested	Route	Phase	Status	Sponsor	Location
NCT01703533, Neu-2566-RETT-001	A phase II randomized, double-blind, placebo-controlled, parallel-group, dose-escalation study of NNZ-2566 in Rett syndrome	Glycyl-L-2-Methylpropyl-L-GlutamicAcid (NNZ-2566); other name: Trofinetide	Injection	II	Completed	Neuren Pharmaceuticals Limited; Baylor College of Medicine; Texas Children's Hospital; International Rett Syndrome Foundation	United States
NCT02715115	A randomized double-blind, placebo-controlled, dose-ranging study of the safety and pharmacokinetics of oral NNZ-2566 in pediatric Rett syndrome	Glycyl-L-2-Methylpropyl-L-GlutamicAcid (NNZ-2566); other name: Trofinetide	Injection	II	Ongoing, but not recruiting participants	Neuren Pharmaceuticals Limited rettsyndrome.org	United States
NCT02563860	Pharmacological treatment of Rett syndrome with 3-Hydroxy-3 Methylglutaryl-coenzyme A reductase inhibitor-lovastatin (Mevacor)	Lovastatin; other name: Mevacor	-	II	Completed	Montefiore Medical Center; Rett Syndrome Research Trust	United States
NCT00593957; FD2408, FD-004247-01	Trial of Dextromethorphan in Rett Syndrome	Dextromethorphan; other name: Delsym	Oral syrup	II	Terminated	Hugo W. Moser Research Institute at Kennedy Krieger, Inc.	United States
NCT01520363 FD-004247-01	Placebo-controlled trial of dextromethorphan in Rett syndrome	Dextromethorphan	Oral	II	Open	Hugo W. Moser Research Institute at Kennedy Krieger, Inc.	United States
NCT01822249, OPBGC&RS_12_003, 2012-005021-76	A phase 2A randomized, placebo-controlled trial of EPI-743 in children with Rett syndrome	EPI-743	Oral	II	Completed	Edison Pharmaceuticals Inc.	Italy

Table 1 (*continued*)

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Table 1 (*continued*)

Clinical trial ID	Trial title	Drug tested	Route	Phase	Status	Sponsor	Location
2008-000787-16, C07-22	Open-label study of the effect of fluoxetine in patients aged 8-28 years with Rett syndrome typical	Fluoxetine; trade name: Prozac	Oral	II	Ongoing	Inserm	France
NCT02696044	Treatment of mitochondrial dysfunction in Rett syndrome with Triheptanoin: an open- label, 10-subject clinical trial of UX007 (Triheptanoin) in the treatment of mitochondrial dysfunction in participants with Rett syndrome, dyskinesia, and epilepsy	(UX007) Triheptanoin	Oral	II	Open	Emory University; Ultragenyx Pharmaceutical Inc.	United States
NCT02790034	A randomized, double-blind, placebo-controlled 6-month study to evaluate the efficacy, safety, and tolerability of sarizotan in patients with Rett syndrome with respiratory symptoms	Sarizotan; Other Names: sarizotan hydrochloride; EMD128130	Oral (Capsule)	II/III	Open	Newron	United States, India, Italy
NCT00069550, HD024448 5P01 HD024448	Pathogenesis of Rett syndrome: natural history and treatment	Dextrometh orphan drug: donepezil hydrochloride	–	III	Unknown	Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)	United States

Source: www.clinicaltrials.com; www.indianclinicaltrials.com; www.euctr.com.

for studying the effects of a drug's metabolites on target and non-target cell types. This is an important part of a drug's side effect profile that can currently be observed only in animal models or clinical trials. hiPSCs plays a larger role in studying the effects of polypharmacy, both in the general population and specific patient. Recently, "tissue chip" devices have become prominent because these cellular models are designed to recapitulate the structure and function of human organs, such as the lung, liver and heart; therefore, they are often called "organs-on-a-chip" or "human-on-a-chip" (30). Three-dimensional model systems are expected to be able to

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mimic human physiology more accurately than traditional two-dimensional cultures, among which "organ-on-a-chip" and "body-on-a-chip" are advanced formats of "tissue-on-a-chip" devices (31). Once "tissue-on-a-chip" devices are developed and accepted as a standard part of the preclinical drug development process, they can be used to predict whether a drug candidate is safe or toxic to humans in the safety of the laboratory setting (32). This is an increasingly important aspect of drug development, taking into account the commonality of multiple medication regimens and a patient population that will likely increase the number of medications as they age (33). A total of 1,500 compounds were tested on wild-type hiPSC-derived neural progenitor cells for their effect on the Wnt/β-catenin signaling pathway for identifying a potential novel neuropsychiatric drug (34).

Limitations associated with drug screening for RTT

Drug screening for neurological disorders is a tedious process and it is insignificant to confirm the efficacy of the respective drug dosage. The main issue is the difference between the mice and human neurons activity against the drug. Drug treatment using hiPSC derived neuron model system is more successful for neurodevelopmental disorders than late-onset neurodegenerative disorders, likely because of the foetal-like properties of the cells (35). It is difficult to correlate the drug pharmacodynamics in the neurodegenerative disorder animal models. There are also some limitations associated with drug screening even in hiPSC such as genetic aberration and teratoma formation by retroviral or lentiviral systems of gene incorporation in the generation of iPSCs. Five oncogenes were found to overexpress in iPSCs whereas the oncogene RAB25 was found to express in cells derived from iPSCs (36). Apart from these limitations, generation of patient specific or mutation specific hiPSC model system is a great challenge and cost effective but ultimately it can be the immortal modal system as compared with animal models. It is unlikely that hiPSC technology will successfully model for all disorders (37).

Indian traditional ayurvedic system: curative drugs for neurological disorders

Ayurveda is a science of life and science of longevity to health and personalized medicine. India is known for its traditional medicinal systems—Ayurveda, Siddha, and Unani. Ayurveda has an extensive pharmacopeia, predominantly herbs and minerals. The Ayurvedic concept appeared and developed between 2,500 and 500 BC in India, which is the largest producer of medicinal plants. There are currently about 20,000 medicinal plants have been recorded. Clinical trials are ongoing in more than 100 natural product derived drugs and at least 100 molecules/compounds are in the preclinical development stage (38). In the Indian system of medicine, the following medicinal plants have shown promising activity in neuropsychopharmacology: *Allium sativum*, *Bacopamonnierae*, *Centellaasiatica*, *Celastruspaniculatus*, *Nicotianatabaccum*, *Withaniasomnifera*, *Ricinuscommunis*, *Salvia officinalis*, *Ginkgo biloba*, *Huperizaserrata*, *Angelica sinensis*, *Uncariatomentosa*, *Hypericumperforatum*, *Physostigmavenosum*, *Acorus Calamus*, *Curcuma longa*, *Terminaliachebula*, *Crocus sativus*, *Enhydrafluctuans*, *Valerianawallichii*, *Glycyrrhizaglabra* etc. (39). The Medhya Rasayanas are group of medicinal plants described in Ayurveda, known to improve mental health, intellect ability, immunity and hence longevity. Medha means intellect/retention and Rasayana means therapeutic procedure. *Medhya Rasayana* is a group of 4 medicinal plants that can be used singly or in combinations.

(I) Mandukaparni (*Centella asiatica*). Useful in treating mental retardation (improvement in performance IQ), Social Quotient, immediate memory span.
(II) Yashtimadhu (*Glycyrrhiza glabra*). Spatial learning, preliminary free radical scavenging, cerebral ischemia and antioxidant capacity towards LDL oxidation. It increases the circulation into the CNS system, improves learning and memory on scopolamine-induced dementia.
(III) Guduchi (*Tinospora cordifolia*). Strong free radical scavenging properties against reactive oxygen and nitrogen species. It is useful for treatment of improving behavior disorders, mental deficit and IQ levels.
(IV) Shankhpushpi (*Convolvulus pluricaulis*). Anxiolytic and memory enhancing, mood elevating, retard brain aging (40).

Phytochemical based antioxidants may have neuroprotective (preventing apoptosis) and neuroregenerative roles, by reducing or reversing cellular damage and by slowing progression of neuronal cell loss. There is ample scientific and empirical evidence supporting the use of antioxidants for the control of neurological disorders. As the focus of medicine shifts from the treatment of manifest disease to prevention, herbal medicine is coming into consideration, being a

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Mutation in RTT	iPSC-derived cell types	Drugs tested for treatment	Outcomes	Ref	Projected ayurvedic drugs	Mode of action	Ref
MeCP2 T158M, MeCP2 Q244X, MeCP2 1155DEL32, MeCP2 R306C	Neural progenitor cells	IGF1	Increased glutamatergic synapse number	(3)	Mandukaparni *(Centella asiatica)*	Neuronal dendritic growth stimulator, increasing anti-oxidant status, improve the altered levels of neurotransmitters such as 5HT, acetylcholine, epinephrine, nor-epinephrine, GABA (gamma-aminobutyric acid) and Glutamate, improve the mental ability and fatigability	(40)
	Glutamatergic neurons	Gentamicin	Increased MeCP2 protein levels and glutamatergic synapse numbers		Shankhpushpi (*Convolvulus pluricaulis*)	Regeneration of brain cells reverses social isolation and increased total motor activity	(44)
					Bramhi(*Bacopa monnieri*)	Effect on cholinergic system, Memory enhancement, cognitive function	(45-47)
					Withanolide & Ashwagandha (*Withania somnifera*)	Neurotic regeneration, synaptic reconstruction, axon extension dendrite extension synaptogenesis memory improvement and GABA-like activity	(48)

Figure 1 Outcomes of the drugs screened in hiPSC-RTT neuronal system and the mode of action ofprojected ayurvedic drugs (40,44-48).

renaissance of age-old human tradition (41).

Projected curative drugs for RTT: Ayurveda with hiPSC technology

Medhya Rasayana will cure the symptoms of RTT. The treatment is cost effective and devoid of side effects. As so far the drugs tested for RTT using hiPSC neuronal modal system were having action on synapse number, spine number and soma size. The role of 'Medhya drugs' in neuronal stem cells differentiation is also described earlier (42). Earlier reports indicate that 'Rasayan drugs' could be used in stem cell therapy based on the regeneration and cell renewal properties. A tablet prepared from four Medhya Rasayana herbs aid in yielding concentrated medicament with the same efficacy as per the classically proposed drug dosage at lower dose (43). The active compounds in Medhya drugs will reverse neurological disorders and psychomotor activities (40). Hence, these active compounds pave a way to cure the RTT symptoms like repetitive hand movements and mental impairment. *Figure 1* depicts the drugs tested and projected Madhya drugs need to test in the hiPSC-RTT neuronal model system.

Way forward and conclusions

Comprehensive research on the discovery of novel neuroprotective drug candidates has proven that natural products, such as plant extracts and their bioactive compounds, can have tremendous potential as lead neuroprotective candidates. A source of herb-based drugs severely compromises proper understanding of Ayurveda, which insists on restoring balance to doshas and dhatus, and preventing a repetition of their vitiation, as the first priority. Identification and characterization of new medicinal plants to cure neurological diseases and brain injuries are the major and increasing scientific interest in recent years. There are more than 120 traditional medicines that are being used for the therapy of central nervous system (CNS) disorders in Asian countries (49). Solely using herbal drugs is against the ethos of Ayurveda. Sadly, even in India, current research and practice of Ayurveda are moving on the lines of allopathy where drugs take center stage. Unfortunately, modern medicine based psychoactive drugs have met with limited success in the treatment of various neurological and psychiatric disorders due to multi-factorial nature of these diseases. The world is trying to move towards holistic and integrative approaches, which represent the core of Ayurveda. Using hiPSCs in phase I clinical trials may provide a more sensitive assay for a candidate drug's toxicity and safety compared with conventional clinical trial phases. Hence, in future the integrative approach of novel drug discovery from Ayurveda using hiPSC will pave the wave for drugging the undruggable diseases.

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Footnote

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