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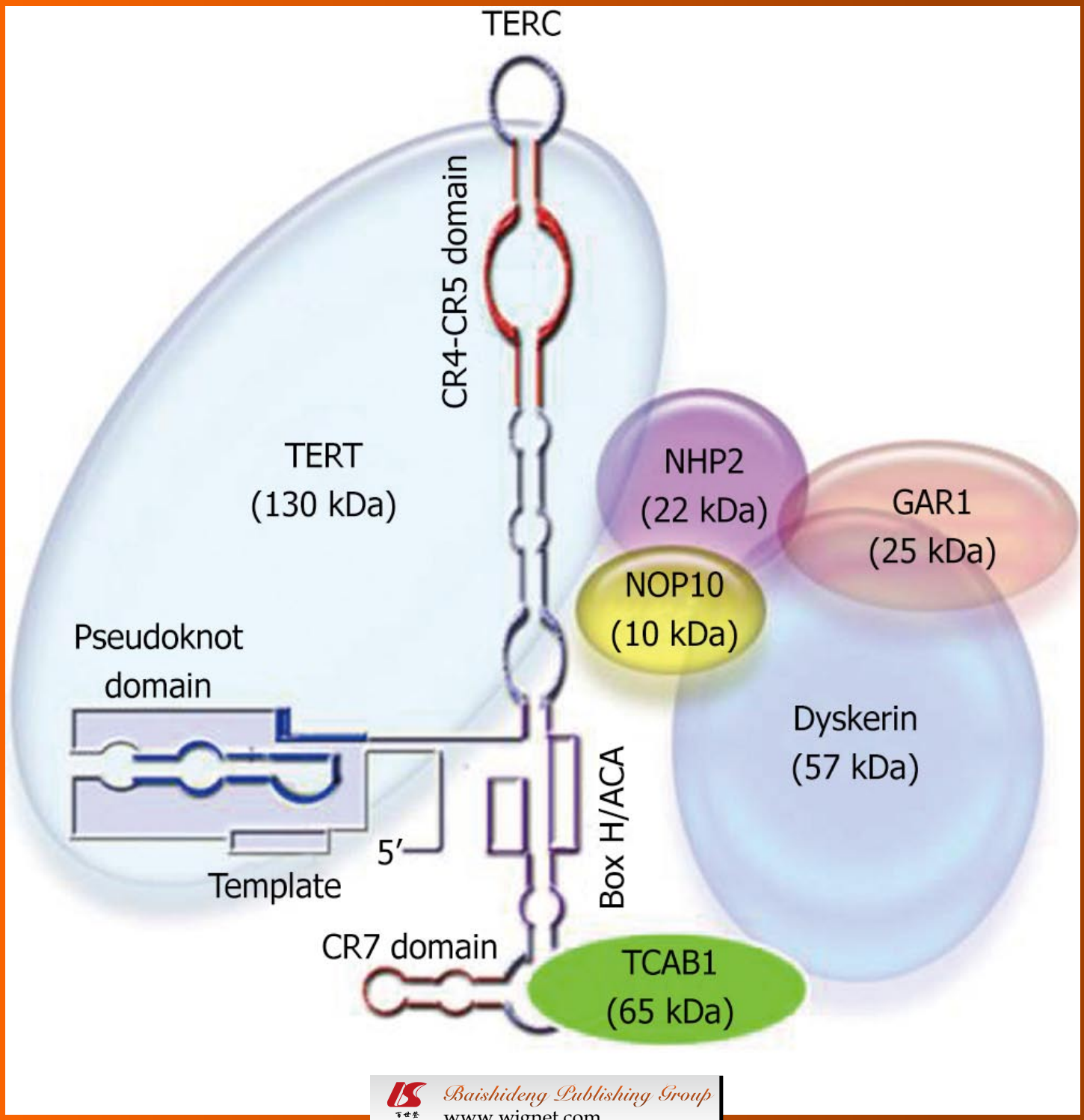

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EDITORIAL

Telomere dynamics in induced pluripotent stem cells: Potentials for human disease modeling

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Abstract

Recent advances in reprograming somatic cells from normal and diseased tissues into induced pluripotent stem cells (iPSCs) provide exciting possibilities for generating renewed tissues for disease modeling and therapy. However, questions remain on whether iPSCs still retain certain markers (e.g. aging) of the original somatic cells that could limit their replicative potential and utility. A reliable biological marker for measuring cellular aging is telomere length, which is maintained by a specialized form of cellular polymerase known as telomerase. Telomerase is composed of the cellular reverse transcriptase protein, its integral RNA component, and other cellular proteins (e.g. dyskerin). Mutations in any of these components of telomerase can lead to a severe form of marrow deficiency known as dyskeratosis congenita (DC). This review summarizes recent findings on the effect of cellular reprograming *via* iPS of normal or DC patient-derived tissues on telomerase function and consequently on telomere length maintenance and cellular aging. The potentials and challenges of using iPSCs in a clinical setting will also be discussed.

Key words: Induced pluripotent stem cells; Telomeres, Telomerase; Dyskeratosis congenita; Marrow failure

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BASIC BIOLOGY OF HUMAN TELOMERES AND TELOMERASE

Telomerase is a ribonucleoprotein complex whose main function is to elongate chromosomal 3' end sequences known as telomeres. The function of this unique enzyme in terminal DNA elongation is necessary in order to overcome the "end-replication problem" whereby conventional DNA polymerases cannot fully replicate linear DNAs[1,2]. Human telomerase is composed of a specialized reverse transcriptase protein (hTERT) and its intrinsic RNA template (hTERC), as well as the associated proteins dyskerin, NOP10, NHP2, GAR1, and TCAB1 (Figure 1). Telomere erosion (by 50-100 bp per cellular division) limits the replicative capacity of the majority of somatic cells, which do not express active telomerase[3,4]. Cells whose telomeres shorten to a "critical length" enter cellular crisis, which is characterized by replicative senescence or apoptosis, meaning cells either stop dividing or commit suicide[5,6]. Stem cells, germ cells, and certain types of somatic cells (e.g. lymphocytes) express the telomerase enzyme, allowing them to maintain telomere length and escape cellular crisis.

Human telomerase reverse transcriptase (hTERT) has been extensively characterized[7]. The protein is defined by the catalytic domain, which contains seven conserved

reverse transcriptase motifs essential for enzymatic activity. Functionally important regions have also been defined in the human RNA template (hTERC) (Figure 1)[8]. The template region is absolutely required for the hTERT protein to reverse transcribe it into telomeric DNA repeats. Other regions include the pseudoknot domain, required for hTERT binding and enzymatic activity, and the Box H/ACA domain, which is required for hTERC RNA processing and stability. Proper assembly and function of the telomerase complex also require other cellular proteins, such as dyskerin, NOP10, NHP2, and GAR1 (Figure 1).

DYSKERATOSIS CONGENITA

Dyskeratosis congenita (DC) is a rare inherited disorder characterized by mucosal leukoplakia, nail dystrophy, and abnormal skin pigmentation[9]. The majority of the cases occur in children, who, in addition to the aforementioned physical anomalies, suffer from bone-marrow failure syndromes and sometimes other symptoms indicative of premature aging, such as dental abnormalities, esophagostenosis, alopecia, and pulmonary disorders. Hematopoietic malignancies (e.g. MDS, Hodgkin's and acute myelogenous leukemias) and/or solid tumors of the GI tract, nasopharynx and skin have also been observed in some DC patients[10]. Since this disease affects rapidly renewing tissues, it has been speculated that DC is a telomerase disease. In support of this theory, most DC patients have short telomeres[11,12] and carry mutations in one of the three main components of the telomerase holoenzyme complex, dyskerin (DKC), hTERT protein, and hTERC RNA[13].

There are three different patterns of DC disease inheritance: X-linked recessive, autosomal dominant, and autosomal recessive. The X-linked form of the disease is most severe and is caused by mutations in the *DKC1* gene on chromosome Xq28 that encodes dyskerin. Dyskerin is a nucleolar protein that is predicted to function in ribosomal RNA processing, in addition to a role in the biogenesis of the telomerase enzyme complex. Indeed, primary fibroblasts and lymphoblasts from X-linked DC patients have a lower level of hTERC RNA, which corresponds to lower levels of telomerase enzymatic activity and shorter telomere lengths than matched normal cells[14,15]. Interestingly, most *Dkc1* mutations are missense mutations and one contains a 3' deletion, indicating that frameshift and null mutations are possibly incompatible with life[16-26]. Indeed, a DKC1-null mouse is embryonic lethal[27]. In humans, one mutation (A353V) accounts for approximately 30% of all X-linked DC cases and is also seen quite frequently in a severe form of a disease known as Hoyeraal-Hreidarsson syndrome.

The autosomal dominant form of DC (AD-DC) is much less severe and less common than the X-linked form. Mutations in hTERT protein and hTERC RNA, as well as in the telomere binding protein TIN2, have been

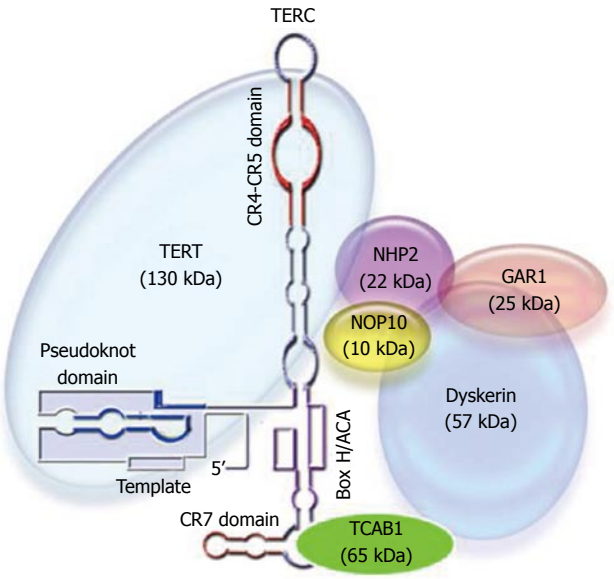

Figure 1 Telomerase enzyme. Simplified illustration of the telomerase enzyme showing its main components: hTERT, hTERC, Dyskerin, NOP10, NHP2, GAR1, and TCAB1. Functional regions of the hTERC RNA (template, pseudoknot, CR4-CR5, Box H/ACA, and CR7) are indicated. Mutations in hTERT, hTERC, TCAB1, NOP10 or Dyskerin have been shown to be associated with a severe form of human bone-marrow deficiency known as dyskeratosis congenita.

associated with AD-DC[28]. The vast majority of these mutations are heterozygous, resulting in a haploinsufficiency effect on telomerase function that accounts for the observed telomere shortening. In AD-DC families, the genetic lesion does not change, yet the onset of disease features occurs, on average, 20 years earlier in the children than in their parents. Telomere length appears to play a role in this accelerated disease presentation in later generations, as telomeres are significantly shorter in the later generations of affected families than in the earlier ones, leading to the "disease anticipation" idea based on telomere length measurement[29].

The causal gene(s) for the autosomal recessive form of DC remain somewhat elusive. A homozygous mutation (R34W) in the telomerase-associated NOP10 protein was found in all 3 affected members of a single family and appears to segregate with the disease, as unaffected family members are heterozygous. Patients and unaffected carriers do in fact have significantly shorter telomeres than controls. However, this mutation was not identified in any of the other 15 families screened, suggesting that it may be a very rare genetic risk factor[30]. A recent screen of another small cohort of DC patients identified two out of nine unrelated patients with unique compound heterozygous missense mutations in the TCAB1 locus (gene names WDR79 and WRAP53)[31]. TCAB1 is a WD40-repeat containing protein that binds the CAB box sequence within TERC[32]. It is a constituent of the active telomerase holoenzyme and inhibition of TCAB1 prevents telomerase from localizing to Cajal bodies where RNA-protein complexes are assembled and modified[33]. The proband from one of the families

has mutations in exon 2 (F164L) and exon 8 (R398W) of the gene, and the proband of the second family has mutations in exon 7 (H376Y) and exon 9 (G435R). They have classic DC symptoms and much shorter telomeres than healthy age-matched controls. The healthy parents and siblings of each proband carry only a single mutant TCAB1 allele, which is consistent with autosomal recessive inheritance. The mutations were not detected in 380 control individuals, again suggesting that these are rare mutations[31].

HOW TO REPROGRAM A SOMATIC NUCLEUS?

The successful cloning of an entirely new animal (e.g. Dolly the sheep) from a single cell *via* somatic cell nuclear transfer (SCNT) technology heralded humankind into a brave new era of genetic engineering[34]. For the first time, it is possible to reprogram a somatic cell to behave "young" again; to coax it into behaving like an embryonic stem cell that can then differentiate into cells of a variety of different lineages, which is the hallmark of pluripotency. By all measures, this is an intrepid undertaking with an outcome that is beyond anyone's expectations. SCNT technology involves transferring a somatic cell nucleus into an enucleated donor oocyte and stimulating this chimeric cell to divide and differentiate into cells of different lineages, the exact mechanisms of which are unknown[34]. Factors that can allow the cloned cell to achieve pluripotency remained largely unknown until a seminal discovery made by Takahashi and colleagues reported in 2006 that only four transcriptional factors (Sox2, c-Myc, Oct4, and Klf4) were needed to reprogram mouse fibroblasts to pluripotency[35]. In other words, it takes only four cellular factors to reprogram somatic cells to induced pluripotent stem cells (iPSCs), albeit at relatively low frequencies that vary by the age and tissue origin of the cells[35-39]. Other researchers have shown that different cellular factors (i.e., Nanog and Lin28) can also be used to achieve a similar outcome[40]. However, it was noted that many SCNT-transduced cells failed to divide and possibly entered a stage of cellular senescence or apoptosis[41], which might involve some of the known stress-activated senescence genes (e.g. p53, $p21^{WAF/CIP}$ and $p16^{INK4a}$) of the p53 and pRb stress response pathways[41-45].

EFFECTS OF CLONING ON TELOMERES AND TELOMERASE OF NORMAL CELLS

It was shown that telomeres of cells collected from the SCNT cloned sheep were shorter than those from age-matched control animals[46,47], raising a concern that the cloned cells might inherit telomeres of similar lengths as those from the donor nucleus. However, subsequent analysis of telomere lengths from other cloned animals (e.g. cattles) have shown that telomeres were elongated during the cloning process[48] due possibly to reactivation of telomerase in blastocyst stage embryos in the cloned nucleus[49].

It was demonstrated that iPSCs could not be generated from somatic cells from late generations (G3) of telomerase-null mice, possibly due to the high degrees of genomic instability as a result of telomere fusions, and that reintroduction of telomerase could restore the efficiency of generating iPSCs[50]. Interestingly, iPSCs derived from normal human and mouse cells show progressive telomere elongation with passaging in cultures, indicating that telomere elongation can occur post-programming[50-53]. Studies have also shown that telomerase enzymatic activity is significantly activated upon iPS manipulation[38-40,50,52,54] as a result of upregulated expression of the TERT protein and TERC RNA, as well as of the associated protein dyskerin[52,54]. The level of increase in TERT transcript and telomerase function, however, differs between human and mouse cells, about 100 fold in human iPSCs and a modest 2-3 fold in mouse iPSCs, possibly reflecting mechanistic differences in telomerase regulation in different organisms. During normal embryonic development, telomerase function is down regulated upon differentiation of iPSCs into different lineages, resulting in a telomere shorting effect. Several factors, including but not necessarily limited to chromatin structure, can influence the dynamics of telomere maintenance during and/or post-programming of the cells.

Telomere chromatin structure has been shown to be altered during the reprogramming process. High levels of trimethylation of histone at lysine 9 (H3K9) and of histone H4 at lysine 20 (H4K20) are normally observed at telomeric regions, whereas lower levels, as in embryonic stem cells, are detected upon cellular reprograming[50]. The subtelomeric DNA regions in human iPSCs have also been shown to be hypermethylated, as compared to those in the original somatic cells, and to contain high degrees of heterogeneity in their methylation patterns[51]. In contrast to human iPSCs, no obvious changes were observed in the subtelomeric regions of mouse fibroblasts upon reprogramming[50]. It is possible that the reprogramming-induced changes in methylation at or near the subtelomeric regions may alter the expression of genes in the vicinity. For example, it has recently been shown that mouse and human iPSCs upregulate the expression of TERRA RNA[50,51], which is known to regulate both telomere length and its chromatin structure[55]. Deng and colleagues have shown that the association of TERRA RNA with a telomeric DNA binding protein TRF2 can facilitate heterochromatin structural formation *via* its association with the histone HP1α and trimethylated H3K9[56]. While heterogeneity in levels of telomere-specific gene expression may exist in human *vs* mouse iPSCs, a general consensus is that the chromatin structures at subtelomeric and/or telomeric regions can change upon reprogramming and can revert back as in the original somatic cells[57-59].

EFFECTS OF iPS MANIPULATION ON TELOMERES AND TELOMERASE OF DC PATIENT-DERIVED CELLS

Recent studies (described above) suggest that reprogramming of somatic cells *via* iPS technology can hold great promise for correcting defects in telomerase function and/or telomere attrition observed in patients with DC, a disease with short telomeres leading to limited bone-marrow stem cell reserve and renewal capacity[60]. The question is whether iPS reprogramming of somatic cells collected from DC patients can reactivate telomerase enzymatic activity to elongate telomeres. To address this question, Agarwal and colleagues[54] attempted to reprogram fibroblasts collected from either an X-linked DC patient with the del37L mutation in the dyskerin gene[14,26] or an autosomal dominant DC patient who is heterozygous for a truncated form of the hTERC gene (del378-451) due to an 821 bp deletion on chromosome 3q26.2-3[60]. In both cases, the mutations greatly reduced the levels of hTERC RNA expression in the cells[15,60]. The patients' primary fibroblasts were retrovirally transduced with Oct4, Sox2, Klf4, and c-Myc genes, the pluripotent phenotype of the iPSCs was monitored by conventional iPSC assays[61], and the mean telomere lengths were measured by Southern blot. Significant upregulation of telomerase activity was observed in DC patient cells-derived iPSCs, which correspondingly showed telomere elongation upon cellular passaging. More importantly, differentiated cells showed down-regulated telomerase activity and accelerated telomere attrition. Given that the hTERC gene expression in the original fibroblast cells has been shown to be suboptimal[15,60], it is quite unexpected that telomere lengths in their iPSCs can be elongated to a degree similar to control fibroblasts. A possible explanation is that the hTERC gene expression in the iPSCs was found to be significantly upregulated (by 3-8 fold); this the authors attributed to a unique feature of pluripotency as several of the telomerase-associated genes could be targeted by pluripotency-associated transcription factors[54].

PROMISES, OBSTACLES AND CHALLENGES OF iPS TECHNOLOGY

One exciting potential of iPSCs is to use them to model the pathogenesis of human disease *in vitro*. Toward this end, Batista *et al*[62] have recently derived iPSCs from fibroblasts collected from: autosomal dominant DC patients with mutations in hTERT (P704S and R979); X-linked DC patients with dyskerin mutations (L54V and del37L); and autosomal recessive DC patient with the recently identified disease-associated mutations in TCAB1 gene (H376Y/G435R)[31], using either retrovirus or lentivirus expressing the four required transcription factors (Sox2, c-Myc, Klf4 and Oct4). The authors found that, even in the undifferentiated state, iPSCs derived from these DC patients exhibit the precise features of each form of the disease. Unlike an earlier study[54], profound defects in telomere maintenance were observed[62]; the reasons for the discrepancy between the studies are unclear but is likely due to possible differences in experimental conditions or statistical variations among the iPS clones[63]. In the Batista study[62], iPSCs derived from the hTERT-mutated cells with telomerase haploinsufficiency exhibited blunted telomere elongation effect during reprogramming. In iPSCs from X-linked DC patients, dyskerin mutations severely impaired telomerase assembly and function, and hence disrupted telomere synthesis during reprogramming. In iPSCs derived from cells with the TCAB1 mutations, which led to the mis-localization of the telomerase enzyme from Cajal bodies to nucleoli, proper telomere synthesis was abrogated during reprogramming. Prolonged passaging of some of the undifferentiated iPSC cultures could lead to progressive telomere attrition and eventual loss of self-renewal capacity of the cultures, closely mimicking processes that might occur to the tissue stem cells of the patients. These findings suggest that iPSCs can serve as a good cell-culture-based system for disease modeling and for developing therapeutic strategies (e.g. drug screening).

While recent studies have shown great potential for iPSCs in disease modeling, several obstacles still exist before contemplating the clinical application of iPSCs to treat human diseases. First and foremost, since most successful iPS studies involve the use of retroviral or lentiviral transduction, safety is a principle and valid concern. Several non-viral techniques to deliver the transgenes have recently been developed that should lessen the concern of possible turmorigenesis[64]. Despite recent advances in iPS technology development, the efficiency of reprogramming somatic cells still remains an issue. Recent observations have also indicated that the epigenetic changes at telomeres and elsewhere in the genome of iPSCs are not necessarily identical to those found in embryonic stem cells[65]. This line of investigation clearly deserves more attention as any aberrance in chromatin structure and function potentially renders the iPSCs useless, or worst yet, prone to chromosome instability.This would lead to acquisition of undesired mutations[66] and/or increase in chromosome copy number variations[67-69] that cause enhanced susceptibility to cellular transformation. It is not entirely clear either how to differentiate iPSCs into various cellular lineages in order to generate tissue-specific stem cells for clinical utility.

While the therapeutic usage of iPSCs in clinics appears to be beyond the reach of current technologies[70], several recent studies have provided exciting proof of concepts. A number of human and mouse fibroblast-derived iPSCs have been successfully differentiated into a variety of tissue/cell types, such as cardiomyocytes[71,72], hematopoietic cells[73,74], endothelial-like cells[75], insulin-secreting islet-like cells[76], retinal pigment epithelial cells[77,78], and neurons[79,80]. Using a humanized mouse model of sickle cell anemia, Hanna and colleagues have

successfully used genetically engineered skin-derived iPSCs to correct a genetic defect caused by the FANCA gene[73]. It is also possible to introduce the iPSC-differentiated endothelial progenitor cells into the livers of genetically defective hemophilic mice in order to cure bleeding disorder[81]. These studies offer exciting potential and optimism for advancing iPS technology for possible future clinical use in humans.

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Events Calendar 2011

March 26, 2011
Stem Cell Agency Governance Subcommittee Meeting, Crowne Plaza SFO, 1177 Airport Blvd, Burlingame, CA, United States

January 29-February 2, 2011
LabAutomation2011, Palm Springs, CA, United States

February 4, 2011
7th annual Swiss Stem Cell Network meeting, Swiss Federal Institute of Technology in Lausanne, Switzerland

March 1, 2011
The 6th Annual Stem Cell Summit, 11 Fulton Street, New York City, NY, United States

March 22, 2011
StemCONN 2011, Farmington, CT, United States

March 27-31, 2011
SBS 17th Annual Conference and Exhibition, Orlando, FL, United States

April 6-8, 2011
EMBO Conference-Advances in Stem Cell Research: Development, Regeneration and Disease, Institut Pasteur, Paris, France

April 7-10, 2011
2011 CSHL Meeting on Stem Cell Engineering & Cell Therapy, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, United States

April 25-26, 2011
International Conference on Stem Cell Research, Hotel Equatorial Penang, Malaysia

April 27, 2011
6th Annual Wisconsin Stem Cell Symposium, BioPharmaceutical Technology Center, Madison, WI, United States

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The World Stem Cells and Regenerative Medicine Congress 2011, Victoria Park Plaza, London, United Kingdom

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The 4th Annual Israeli Stem Cell Meeting, Beit Sourasky, Chaim Sheba Medical Center, Israel

May 26-27, 2011
7th annual Stem Cell Research & Therapeutics Conference, Boston, MA, United States

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2011 CSHL Meeting on Stem Cell Biology, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, United States

October 2011
3rd Annual World Stem Cells & Regenerative Medicine Congress Asia 2011, Seoul, South Korea

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Patent (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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