Reprogramming the Cardiac Field

Erik Willems, Mark Mercola

Pluripotent Stem Cells Induced From Mouse Somatic Cells by Small-Molecule Compounds
Hou et al

Reprogramming In Vivo Produces Teratomas and iPS Cells With Totipotency Features
Abad et al

Two recent reports show that it is possible to reprogram somatic cells to a stem cell state using only a chemical cocktail or by inducing genes in tissues of engineered mice. These studies herald a time when cellular plasticity can be manipulated directly in the body to regenerate damaged tissues and organs. How do we go from these milestones to therapeutic heart regeneration?

Induced pluripotent stem cells (iPSCs) have revolutionized the stem cell field ever since their introduction by Takahashi and Yamanaka in 2006, as reviewed in Robinton and Daley. iPSCs can be generated from a variety of mouse and human somatic cells through lentiviral-mediated overexpression of pluripotency-related genes such as Oct4, Sox2, Klf4, and cMyc (OSKM). Although phenotypically comparable with embryonic stem cells in that they can give rise to most cell types in the body, the fact that iPSCs are generated from adult patient tissues means that their differentiated derivatives can be used to model congenital disorders or even as autologous cells for transplantation.

Reprogramming somatic cells to a pluripotent state has involved gene transfer to transiently express key pluripotency genes such as OSKM. The potential safety risks of genome modification have engendered concern and, consequently, have driven the development of nonintegrating methods for expressing OSKM and similar reprogramming cocktails. More recently, several groups have succeeded in replacing OSKM and similar reprogramming cocktails or by inducing genes in tissues of engineered mice. These studies herald a time when cellular plasticity can be manipulated directly in the body to regenerate damaged tissues and organs. How do we go from these milestones to therapeutic heart regeneration?

Induced pluripotent stem cells (iPSCs) have revolutionized the stem cell field ever since their introduction by Takahashi and Yamanaka in 2006, as reviewed in Robinton and Daley. iPSCs can be generated from a variety of mouse and human somatic cells through lentiviral-mediated overexpression of pluripotency-related genes such as Oct4, Sox2, Klf4, and cMyc (OSKM). Although phenotypically comparable with embryonic stem cells in that they can give rise to most cell types in the body, the fact that iPSCs are generated from adult patient tissues means that their differentiated derivatives can be used to model congenital disorders or even as autologous cells for transplantation.

Reprogramming somatic cells to a pluripotent state has involved gene transfer to transiently express key pluripotency genes such as OSKM. The potential safety risks of genome modification have engendered concern and, consequently, have driven the development of nonintegrating methods for expressing OSKM and similar reprogramming cocktails. More recently, several groups have succeeded in replacing OSKM and similar reprogramming cocktails or by inducing genes in tissues of engineered mice. These studies herald a time when cellular plasticity can be manipulated directly in the body to regenerate damaged tissues and organs. How do we go from these milestones to therapeutic heart regeneration?

Induced pluripotent stem cells (iPSCs) have revolutionized the stem cell field ever since their introduction by Takahashi and Yamanaka in 2006, as reviewed in Robinton and Daley. iPSCs can be generated from a variety of mouse and human somatic cells through lentiviral-mediated overexpression of pluripotency-related genes such as Oct4, Sox2, Klf4, and cMyc (OSKM). Although phenotypically comparable with embryonic stem cells in that they can give rise to most cell types in the body, the fact that iPSCs are generated from adult patient tissues means that their differentiated derivatives can be used to model congenital disorders or even as autologous cells for transplantation.

Reprogramming somatic cells to a pluripotent state has involved gene transfer to transiently express key pluripotency genes such as OSKM. The potential safety risks of genome modification have engendered concern and, consequently, have driven the development of nonintegrating methods for expressing OSKM and similar reprogramming cocktails. More recently, several groups have succeeded in replacing OSKM and similar reprogramming cocktails or by inducing genes in tissues of engineered mice. These studies herald a time when cellular plasticity can be manipulated directly in the body to regenerate damaged tissues and organs. How do we go from these milestones to therapeutic heart regeneration?

Induced pluripotent stem cells (iPSCs) have revolutionized the stem cell field ever since their introduction by Takahashi and Yamanaka in 2006, as reviewed in Robinton and Daley. iPSCs can be generated from a variety of mouse and human somatic cells through lentiviral-mediated overexpression of pluripotency-related genes such as Oct4, Sox2, Klf4, and cMyc (OSKM). Although phenotypically comparable with embryonic stem cells in that they can give rise to most cell types in the body, the fact that iPSCs are generated from adult patient tissues means that their differentiated derivatives can be used to model congenital disorders or even as autologous cells for transplantation.

Reprogramming somatic cells to a pluripotent state has involved gene transfer to transiently express key pluripotency genes such as OSKM. The potential safety risks of genome modification have engendered concern and, consequently, have driven the development of nonintegrating methods for expressing OSKM and similar reprogramming cocktails. More recently, several groups have succeeded in replacing OSKM and similar reprogramming cocktails or by inducing genes in tissues of engineered mice. These studies herald a time when cellular plasticity can be manipulated directly in the body to regenerate damaged tissues and organs. How do we go from these milestones to therapeutic heart regeneration?
compounds, Valproic acid and DZNep, inhibit histone deacte-
lation and methylation, respectively.15,16 both of which might alter
chromatin to make the transcriptional landscape conducive
for pluripotency.17 Thus, probing the mechanisms for chromatin
remodeling and identifying the underlying genes at the target
loci might shed light on the network logic of reprogramming.

From a translational perspective, there does not seem to be
a pressing basic scientific need to optimize iPSC generation
further; commercial vendors already provide custom-made
iPSCs and a limited range of differentiated derivatives. In addi-
tion, in situ iPSC generation is compromised by the predict-
able consequence of teratomas. Nevertheless, the Abad and
Hou articles together herald a future for cardiology in which
therapeutic reprogramming might be achieved directly in pa-
tient tissues, perhaps by bypassing pluripotency and proceed-
ing directly to cardigenic cell types.

Recent articles from Islas et al.18 Ieda et al.19 Qian et al.20
and Song et al21 have shown that it is feasible to generate
cardiomyocytes and cardiomyogenic progenitors in vitro by
directly reprogramming mouse and human fibroblasts with
transcription factors such as Gata4, Tbx5, Mef2c, Mesp1,
Myocardin, Ets2, and Hand2. Although these studies were
inspired by Yamanaka’s discovery, direct reprogramming is a
concept first introduced in the late 1980s when Taccott et al22
identified MyoD as a single gene that could convert fibroblasts
to skeletal myoblasts. Introduction of ≥1 lineage-specific
transcription factor into fibroblasts thus converts somatic
cells from diverse lineages directly into the lineage of choice,
which has now also been attained for several other cell types,
including neurons and pancreatic β-cells.23,24 An exciting ap-
application of the direct reprogramming approach is its trans-
lation to the in vivo context. Although teratoma induction in
the Abad article clearly illustrated that reprogramming in vivo
is more efficient than in vitro, it also demonstrated remark-
able plasticity of adult organs in response to reprogramming.
Furthermore, initial reports indicate that it is possible to take
the next step and directly reprogram cells in vivo to facilitate
endogenous repair. In the pancreas, for instance, functional
β-cells can be generated in vivo from exocrine cells by deliv-
er of Ngn3, Pdx1, and Mafa, 3
β-cell–specific transcription factors.25,26 Similarly, a degree of myocardial restoration after
infarction in the mouse was achieved by directly reprogram-
ning resident fibroblasts into cardiomyocytes.20,21

Clearly, direct reprogramming has exciting benefits and may
surpass iPSC generation as a routine tool to study car-
diac biology and disease in patient-specific cells, and may
even be adapted for therapeutic regeneration. Cardiac direct
reprogramming is, however, still in its infancy, and the under-
lying biology is far from understood. We think that following
a chemical biology approach may expose how direct re-
programming works and may reveal why reprogramming differs
in mice versus humans. For example, in human cells, cardiac
genes can be induced, yet spontaneous action potentials are
rare and no contraction is observed.25-28 Interestingly, initial
findings in the mouse suggest that cardiomyocytes made by
direct reprogramming can show considerably more mature
electrophysiological properties than their iPSC-derived coun-
terparts, as demonstrated by action potential measurements;29
however, it is not clear how or why such a mature state is
attained nor why it is not achieved with human cells, at least
in vitro.25,26 Nevertheless, although it is at an early stage of
development and we need a deeper theoretical understanding
of the phenomenon, direct reprogramming to cardiomyocytes
seems to have a promising future. Thus, iPSC technology
continues to humanize cardiac disease research, not only by
making it possible to recapitulate congenital disease in a cell
culture dish but also by suggesting that therapeutic regener-
ation might be enhanced by direct conversion of nonmyocytes
directly in the heart of the patient.

Sources of Funding
This work was supported by the National Institutes of Health
grants (R01HL113601 and R01HL108176), the California Institute
for Regenerative Medicine Grant (TG2-01162), and the Fondation
Ledoux.

Disclosures
None.

References
1. Takahashi K, Yamanaka S. Induction of pluripotent stem cells from
mouse embryonic and adult fibroblast cultures by defined factors. Cell.
2006;126:663–676.
2. Robinton DA, Daily QG. The promise of induced pluripotent stem cells in
3. Mercola M, Colas A, Willims E. Induced pluripotent stem cells in cardio-
to pluripotency and directed differentiation of human cells with synthetic
DA. Induction of pluripotent stem cells by defined factors is greatly im-
AC, Di Giorgio FP, Koszka K, Huangfu D, Akutsu H, Liu DR, Rubin LL,
Eggan K. A small-molecule inhibitor of tgf-beta signaling represses sox2
Ding S. Reprogramming of human primary somatic cells by OCT4 and
K, Ge J, Xu J, Zhang Q, Zhao Y, Deng H. Pluripotent stem cell induced
from mouse somatic cells by small-molecule compounds. Science.
10. Abad M, Mosteiro L, Pantaja C, Cañamero M, Rayon T, Ors I, Graña O,
Megías D, Domínguez O, Martínez D, Manzanares M, Ortega S, Serrano
M. Reprogramming in vivo produces teratomas and iPSC cells with audio-
LC. Transcriptomic signature of trophoblast differentiation in a human
12. Giakoumopoulou M, Golos TG. Embryonic stem cell-derived trophoblast
differentiation: a comparative review of the biology, function, and signal-
15. Miranda TB, Cortez CC, Yoo CB, Liang G, Abe M, Kelly TK, Marquez
VE, Jones PA. DZNep is a global histone methylation inhibitor that reacti-
ves developmental genes not silenced by DNA methylation. Mol Cancer
16. Marchion DC, Bicaku E, Daud AI, Sullivan DM, Munster PN. Valproic acid
alters chromatin structure by regulation of chromatin modulation pro-


Reprogramming the Cardiac Field
Erik Willems and Mark Mercola

Circ Res. 2014;114:409-411
doi: 10.1161/CIRCRESAHA.113.302946
Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2014 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/114/3/409

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation Research can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation Research is online at:
http://circres.ahajournals.org/subscriptions/