Commentary: Searching for the golden fleece—How do you repair damaged myocardium?

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The idea that stem cell transplantation may be able to repair or replace damaged myocardium is the “golden
fleece” that has intrigued investigators for more than 30 years. This interest started with mouse embryos and ul-
timately led to the discovery, in 1998, of a method to derive stem cells from human embryos and to grow the
cells in the laboratory. These cells are called human em-
brovonic stem cells and have served as a source of stem
cells for research for at least 20 years. More recently, re-
searchers identified conditions that allow some specialized
adult cells to be “reprogrammed” genetically to assume a
stem cell–like state. The Nobel prize was awarded to Gur-
don and Yamanaka in 2012 for their work in the discovery
that mature human cells can be reprogrammed into human
pluripotent stem cells (hiPSCs). There are many potential
applications that could use hiPSCs (Figure 1). One partic-
ularly attractive possibility for hiPSCs is their use in re-
generating injured myocardium or replacing myocardial
damage that consists of nonfunctioning postinfarct scar.

Like many ideas in medicine and surgery, the concept that hiPSCs can simply be injected into damaged myocardium to
fix the problem of postinfarct injury is clear, simple, and
wrong.1 In this issue of the Journal, Aoyama and coauthors2
lay out the expanded picture of what is necessary for hiPSCs to
provide reparative properties to injured or nonfunctioning
myocardial cells. Aoyama and coauthors2 answer the ques-
tion of how you define mature cardiomyocytes in culture.
They point out that electrophysiologic, genetic, and func-
tional analyses are necessary to evaluate maturation. Many
studies have investigated the efficiency of generating and
characterizing hiPSC-derived cardiomyocytes. These gener-
ated cells are often immature with regard to biochemical,
physiologic, and morphologic properties and consist of arte-
rual, ventricular, and nodal cells. Consequently, these cells
beat asynchronously in various directions, resembling em-
brovonic cardiomyocytes, and tend to be arrhythmogenic.
Maturation is an essential element for hiPSCs to transform
into functioning myocardial cells. The key element in this
process is to define mature functioning cardiomyocytes. In

Concise terms, that is exactly what the Aoyama and coau-
thors did. I confess that the experimental details are elusive
at best, and confusing or obscure at worst, to most cardiotho-
racic surgeons, me included. Suffice it to say that this study
provided the basis for generation of functional cardiomyo-
cyes that contract synchronously and set the stage for future
studies that include delivery systems that use biomaterials for
transplantation into animals and eventually into humans.

It is worth speculating how the mature myocardial cells
created and characterized by Aoyama and coauthors2 might
be introduced into damaged or destroyed myocardium. Cre-
atation of a viable functioning myocardial cell is the initial
and essential first step. A subsequent step includes delivery
of mature myocardial cells into the target (damaged or de-
stroyed myocardium). The list of delivery methods is vast
and includes such exotic things as microporous iron oxide
scaffolds,3,4 electrospun nanofibers,5 and antibody-armed
platelets to direct stem cells to injured myocardium.6
Further, it may be helpful to speculate on the optimal source
of hiPSCs. Some authors suggest that spermatogonial stem
cells provide some optimal characteristics that are ideal for
regenerative purposes.7 It is likely that other delivery
methods, alternative sources of stem cells, and optimal
stem cell maturation characteristics will provide ideal cir-
cumstances for regeneration of damaged myocardium.

Clearly, more work needs to be done, but future studies
and applications offer very attractive possibilities for treat-
ments of damaged myocardium.
References