Isabella Rosa Nanini

Mr. Speice

Independent Study and Mentorship II- 4A

8 September 2017

Research Assessment 1

Subject: Challenges Facing Pediatric Cardiothoracic Surgery

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Assessment:

To begin my ISM journey I had to begin to answer a question haunting me since the first day of school, what am I going to accomplish? Although a very broad question by researching problems within the field of pediatric cardiothoracic surgery possible project ideas or areas of interest may arise. I found two articles one on blood conservation in pediatric cardiac surgery a problem I witnessed in one of my observation days, and an article on tissue engineering a problem very prevalent in congenital heart repairs.

A moment that stuck with me from one of my first mentorship visits with Dr. Pirolli was a conversation we had on the unpredictability of postoperative complications and the importance of precautions intraoperatively. This article taught on the dangers of blood transfusions during

surgery, especially in pediatric cardiothoracic surgery. Many of these complications related to pediatric postoperative care, a topic I deeply researched for my original work project in ISM I, many of this complications are dealt with varying surgeon precautions like chest tubes and correct cannulation; these precautions are important to a student like me interested in pursuing this field; however, most precautions related to perfusionists and anaesthesiology. Approaches like Autologous Blood Donations, something I did not know existed, and invasive line precaution highlight the importance of how detail oriented the pediatric cardiothoracic surgical team have to be. Although this article specifically did not bring on new ideas for possible products, it enforced an important lesson brought by my mentor and allowed me to better understand the process of cannulation in surgery.

The second article on tissue engineering brought many ideas I had previously discussed with Dr. Robert Jaquiss, Chief of Pediatric Cardiothoracic Surgery at Children's Health Dallas. Tissue engineering is especially important in congenital heart defect repairs since "patching holes" is the most common repair with Ventricular Septal Defects and Atrial Septal Defects being the most common congenital heart defects. This article spoke of the intricate process of embryonic heart development and allowing me to better understand the congenital heart defects seen during my many observation dates. The limitations brought by the article where similar to what I had discussed with Dr. Jaquiss and brought back my interest in the decellularization/recellularization process. Other tissue engineering processes discussed on this article need to be more deeply research since I constantly find myself with a limited scientific knowledge to fully understand these intricate processes. However, I am very certain that my interests like with tissue engineering and this article allowed me to better understand that. With

my knowledge from my interview with Dr. Jaquiss and past research I feel ready to speak with my mentor and begin to prepare for my project.

There is still much more to learn and research before I can fully discover what I will achieve this year. However constant research and interviews with professionals involved in the pediatric cardiothoracic surgical team and my mentor will allow me narrow down this big question. There are endless problems in pediatric cardiothoracic surgery, it is a fairly new medical speciality career in high demand.

Strategies for blood conservation in pediatric cardiac surgery.

Sarvesh Singh. ***Annals of Cardiac Anaesthesia*****. Oct-Dec 2016 v19 i4 p705.**

Byline: Sarvesh. Singh

Cardiac surgery accounts for the majority of blood transfusions in a hospital. Blood transfusion has been associated with complications and major adverse events after **cardiac surgery**. Compared to adults it is more difficult to avoid blood transfusion in children after **cardiac surgery**. This article takes into account the challenges and emphasizes on the various strategies that could be implemented, to conserve blood during **pediatric cardiac surgery**.

Introduction

The number of children undergoing complex surgeries for congenital heart diseases is increasing day by day. In comparison to adults, children are at an increased risk of postoperative bleeding. The amount of blood loss and transfusion in children undergoing **cardiac surgery** is up to 15–110 and 155 ml/kg, respectively.[sup][1],[2] A study by Chambers et al . in 1996 documented that 98% of children who underwent **cardiac surgery** (with the aid of cardiopulmonary bypass [CPB]) received packed red blood cells (RBCs).[sup][3] A recent review reported that 38–74% of children who underwent **cardiac surgery** received a blood transfusion.[sup][4]

Risks and Clinical Impact of Blood Transfusion

The most common complications of blood transfusion are leukocyte-related target organ damage (2–5%), febrile nonhemolytic transfusion reaction (1%), transfusion-related lung injury (0.05%), and bacterial infection (0.05%).[sup][5] Blood transfusion leads to increased incidence of infections (sepsis), respiratory complications (acute lung injury), **cardiac**complications (low **cardiac** output syndrome, increased inotropic usage), renal complications (acute kidney injury), duration of mechanical ventilation, Intensive Care Unit (ICU) and hospital length of stay, and cost of treatment and mortality.[sup][6],[7],[8],[9],[10],[11],[12] In **pediatric** patients undergoing heart transplant increasing amount of RBC transfusions are associated with increase length of ICU stay, inotropic scores, and major adverse events. Following modified Blalock–Taussig shunt procedures, blood transfusion >6 ml/kg is an independent risk factor for mortality.[sup][13] Larger volume blood transfusion correlates with longer intubation durations, ICU and hospital stays, higher peak C-reactive protein levels, and an increased blood urea nitrogen/creatinine ratio.[sup][14] Increased volume of packed blood cells when used in CPB prime and during CPB lead to excessive postoperative bleeding in **pediatric cardiac surgery**.[sup][15]

Challenges for Blood Conservation in **Pediatric** Age Group

Children pose a unique set of challenges pertaining to blood conservation due to their small blood volume; large priming volume of CPB circuits, requirements of higher hematocrit during CPB, presence of cyanosis in some children, immature coagulation system and hypothermia during CPB. Congenital deficiency of coagulation factor VII, VIII or von Willebrand factor further increases the risk of bleeding and therefore, blood transfusion.[sup][16],[17],[18] Furthemore, children with **cardiac** lesions involving systolic flow abnormalities are at increased risk of developing qualitative platelet dysfunction than those with diastolic flow abnormalities.[sup][19] The exposure to extracorporeal circuit also leads to the development of qualitative and quantitative platelet abnormalities, coagulation factor deficiencies, and hypofibrinogenemia.[sup][20]

Comment [1]: Something that always stuck with me from a mentor visit with Dr. Pirolli was that the postoperative recovery of a patient is unpredictable, anything could happen and as a surgeon you have to take precautions to ensure a hopefully easy recovery. Bleeding is one of those complications.

Comment [2]: Problems: Infection, respiratory complications, cardiac complications, renal complication, time on ventilator and CVICU. From my research on pediatric cardiac critical care during ISM I many of these postoperative problems are dealt with in different forms depending on the surgeon and different advanced approaches to ensure a shorter hospital stay

Comment [3]: Explains WHY blood transfusion leads to a more challenging postoperative healing

Comment [4]: Patient donates blood to themselves prior to surgery.

Comment [5]: Benefits: Prevents transfusion-transmitted disease.
Prevent red cell alloimmunization.
Decreases the number of banked allogeneic units needed.
Provides compatible blood for patients with alloantibodies.
Prevents some adverse transfusion reactions.
Provides reassurance to patients concerned about blood risks

Comment [6]: Disadvantages

Comment [7]: Use of ABD

Comment [8]: Ensures ABD success

Comment [9]: Precautions- avoiding excessive blood loss intraoperatively

Comment [10]: Limit- frequent flushing and sampling

Comment [11]: Does Children's Health Dallas use these precautions. Possible questions to Dr. Pirolli

Comment [12]: blood conservation technique that entails the removal of blood from a patient shortly after induction of anaesthesia

Comment [13]: Another alternative.

Comment [14]: Also wonder what circuit triggers Children's Health Dallas uses. I have not seen many CVICU patients suffering intense postoperative bleeding, wonder what precautions are taken to ensure this.

Comment [15]: Double benefit

Comment [16]: This article seems to predominantly focus on the anesthesiologist and the perfusionist running precautions rather than the surgeon...

Record Number: A467766542

Comment [17]: Focus of interest as of now.

Cardiac Tissue Engineering: Implications for Pediatric Heart Surgery

Wolfram-Hubertus Zimmermann[1] and Robert Cesnjevar[2]

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Abstract

Children with severe congenital malformations, such as single-ventricle anomalies, have a daunting prognosis. Heart transplantation would be a therapeutic option but is restricted due to a lack of suitable donor organs and, even in case of successful heart transplantation, lifelong immune suppression would frequently be associated with a number of serious side effects. As an alternative to heart transplantation and classical cardiac reconstructive surgery, tissue-engineered myocardium might become available to augment hypomorphic hearts and/or provide new muscle material for complex myocardial reconstruction. These potential applications of tissue engineered myocardium will, however, impose major challenges to cardiac tissue engineers as well as heart surgeons. This review will provide an overview of available cardiac tissue-engineering technologies, discuss limitations, and speculate on a potential application of tissue-engineered heart muscle in pediatric heart surgery.

Comment [18]: In my interview with Dr. Jaquiss I learned of the many challenges behind tissue engineering. The perfect tissue engineered myocardium as of now does not exist, a tissue would have to imitate cardiac muscle, grow with a child, not be rejected, and it has to be thin yet strong. Bovine skin and the pericardium are often used at Children's Health Dallas; however there are many other alternatives to tissue engineering and I hope to learn more these different alternative in this article.

Keywords: Congenital heart disease, Tissue engineering, Myocardial repair, Regeneration, Stem cells

Go to:

Introduction

The heart is the first major organ that reaches functional competence in the developing embryo and subsequently enables blood flow through the pulmonary and systemic circulation. Its anlage can be distinguished morphologically as early as 7 days and 3 weeks after fertilization in mice and humans, respectively [32]. Heart function can be assessed by ultrasound shortly afterward [41, 48]. Embryonic heart development begins with the formation of the cardiac crescent; this structure will eventually fuse to establish the primitive heart tube; subsequent looping and septation will finally lead to the configuration of the four-chambered heart [32]. These complex processes are commonly disrupted, leading either to premature termination of pregnancy or congenital malformations [50]. Taken together, 4% of developing embryos are affected. Ultimately, structural myocardial defects are diagnosed in approximately 1% of all newborns, making heart malformations the most common pathological congenital condition.

Life-compatible defects, such as atrial and ventricular septum defects (ASDs and VSDs), are frequently associated with other cardiac and extracardiac malformations as well as chromosomal abnormalities (e.g., trisomies). More complex malformations are rare and include, for example, hypoplastic left heart syndrome (HLHS), double inlet left ventricle (DILV), double outlet right ventricle (DORV), tetralogy of Fallot (TOF), and transposition of the great arteries (TGA). Most of these congenital heart defects are generally not compatible with life and require comprehensive as well as early reconstructive surgeries such as a switch operation for TGA and staged Fontan palliation including the Norwood procedure in single-ventricle anomalies [15]. Especially in the latter pathology, surgical repair is generally palliative. Heart transplantation would be the ultimate therapeutic option but is limited by the scarcity of suitable donor organs. In addition, lifelong immune suppression often causes serious complications, including kidney failure and malignancies. Importantly, long-term outcome of the above-mentioned surgical interventions remains largely unknown and it would clearly be desirable to develop alternative strategies to repair hearts with severe congenital malformations.

One exciting but also highly controversial approach is intrauterine reconstructive surgery [40, 53]. The interested reader is referred to expert reviews in this field for detailed information on this intervention [14, 40]. Alternatively, biological repair using tissue-engineered myocardium might become an option. It will, however, require the generation of functionally competent heart muscle of sufficient size and with in vitro as well as in vivo growth potential.

Several tissue-engineering technologies are already available, enabling the generation of contractile heart muscle in the lab [58]. Moreover, proof-of-concept for an in vivo application of tissue-engineered myocardium to remuscularize a failing heart has already been provided in a rodent model of myocardial infarction [59]. It would, nevertheless, be pretentious to claim that cardiac muscle engineering is on the verge to clinical exploitation. Further refinements to eventually generate force-developing human heart muscle, to provide grafts of relevant size, and to control immunological issues will be necessary to advance the field. This review will discuss the state-of-the-art in myocardial tissue engineering, its limitations, and potential applications in pediatric heart surgery.

Comment [19]: I have never deeply studied embryonic heart development, unless I was researching the main idea behind a couple of congenital heart diseases I got to see be surgically treated by Dr. Pirolli

Comment [20]: Cardiac crescent- primitive heart tube- four chambered heart

Comment [21]: Important explains why congenital heart defects exists

Comment [22]: Shows the impact and need of pediatric cardiothoracic surgeons and pediatric cardiologists

Comment [23]: These are the most common congenital heart defects and have a positive prognosis after surgery

Comment [24]: I have seen this surgical repair

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State-of-the-Art in Cardiac Tissue Engineering

The ultimate goal in therapeutic cardiac tissue engineering is to generate biocompatible, nonimmunogenic heart muscle with morphological and functional properties of natural myocardium. To this end, at least four distinguishable tissue engineering modalities have been established over the past 15 years (reviewed in [11, 58]; Fig. 1). These include the following: (1) the *bioengineering approach*, involving seeding of heart cells on preformed biocompatible scaffolds [4, 5, 27, 29]; (2) the *biological assembly approach*, utilizing hydrogels to entrap heart cells and support their intrinsic capacity to organize into a cardiac syncytium [10, 56, 57]; (3) the *cell sheet approach*, using a unique technique to detach and serially stack monolayer cell cultures to form contractile heart tissue sandwiches [46]; (4) the *decellularization–recellularization approach*, taking advantage of the ability to strip tissues of all cellular components but at the same time retain their extracellular matrix structure to be used as a reseeding substrate for heart or cardiogenic stem cells [39]. In addition to the mentioned techniques, other modalities, such as the microtissue approach [21], have been developed and might indeed provide therapeutic tissue structures. This review will, however, focus only on tissue-engineering modalities enabling the generation of force-generating heart muscle on a macroscopic scale:

1. The *bioengineering approach* utilizes preformed scaffolds, which are either chemically engineered, such as polylactic acid (PLA), polyglycolic acid (PGA), and polyglycerol sebacate (PGS) [4, 5, 9], or derived from biological sources, such as collagen/gelatin from tendon, alginates from seaweed, and silk from silkworms or spiders [27, 30, 42], and subsequently processed to generate sponges or meshes with various pore sizes. Cells are eventually seeded onto these scaffolds and cultured in a three-dimensional (3D) format. Importantly, most of the above-mentioned materials, with collagen and silk being exceptions, do not support cardiomyocyte attachment or growth in an optimal way. In addition, limited diffusion and, thus, oxygen and nutrient supply have been main caveats of the *bioengineering approach*. Moreover, synthetic polymers commonly have unfavorable degradation properties (e.g., the acidification of surrounding tissue in the case of PLA and PGA) and cause inflammatory responses [52]. This is acceptable or even desirable if the above-mentioned materials are used as suture material, but it is unacceptable if the materials are used as tissue scaffolds in vivo. To overcome this limitation, one might opt to degrade the respective materials before implantation. From the engineering and regulatory point of view, the above-mentioned (bio-)materials would be advantageous because its components are fully chemically defined and have already been approved (e.g., PLA, PGA, alginate, collagen/gelatin sponges) by the US Food and Drug Administration (FDA).

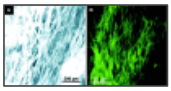
Comment [25]: Biocompatible scaffolds is what I was mostly interested in last year

Comment [26]: Have not heard of biological assembly approach

Comment [27]: What I learned about at the AP Biology genetics conference

Comment [28]: More readily available and more easily produced. I believe bioengineered tissue is the most common used engineered tissue in pediatric cardiothoracic surgery

Comment [29]: disadvantage

2. The *biological assembly approach* takes advantage of the intrinsic propensity of cardiomyocytes to generate “cardiac microtissues” if cultured at a high cell density in suspension [1, 21, 22, 34]. Suspending cells in casting molds containing mixtures of extracellular matrix material, such as collagen, laminin, and fibronectin [10, 36, 56, 57], or naturally occurring products from blood, such as fibrin [19], supports self-aggregation in a defined 3D environment. Exposing the developing tissues to biophysical stimuli, such as mechanical strain and electrical stimulation [12, 42], can further be used to guide cardiac tissue formation and will eventually yield strongly contracting heart tissue equivalents [57, 59]. In contrast to the *bioengineering approach*, the shape and size of forming tissues are not governed by the matrix material itself, but by the casting molds utilized for initial tissue reconstitution. Although diffusion is also a limitation of the *biological assembly approach*, it appears that hydrogels enable better oxygen and nutrient transport as compared to preformed matrixes. This might be the reason why tissue formation in, for example, engineered heart tissue (EHT) is not restricted to outer layers of the collagen hydrogel-culture format [57]. Instead, muscle within EHTs forms a delicate 3D network, composed of 20–200-μm-thick muscle bundles (Fig. 2). Importantly, single-muscle units generated by the *biological assembly approach* might be fused to form large tissue constructs [36]. This property might in principle even be exploited to generate clinical-scale tissue constructs of various geometries.
3. 
4. Fig. 2
5. Muscle formation in EHT. Actin staining (white in [**a**], green in [**b**]) denotes the formation of a dense network of muscle strands, which might in some cases reach a diameter of up to 200 μm. Images from [57] (**a**) and [36] (**b**). (Color figure **...**
6. The *cell sheet approach* is based on temperature-controlled release of cell monolayers from PIPAAm (polyisopropylacrylamide)-coated culture dishes [38]. PIPAAm has unique hydrophobic or hydrophilic properties depending on the environmental temperature. Physiological temperatures (37°C) facilitate cell attachment, whereas low temperatures (20°C) render the polymeric surface hydrophilic and consequently lead to rapid detachment of cell monolayers. Importantly, this detachment procedure does not disturb cell–cell contacts within the monolayer and apparently maintains all cell surface structures. This might explain why cell sheets can rapidly attach and establish electrical contacts to each other [18, 47] as well as to underlying myocardium if applied in vivo [31]. Yet, the *cell sheet approach* is also diffusion limited. This becomes apparent at a monolayer-stack diameter of ~100 μm (four to six layers) [46]. Employing sequential grafting of thin layers on top of each other can, however, be exploited to generate compact vascularized tissues with a diameter of at least 1 mm in vivo [47].
7. The *decellularization-recellularization approach* employs tenside (SDS: sodium dodecyl sulfate) and DNase treatment to dispose of all potentially immunogeneic structures of the

Comment [30]: advantage

Comment [31]: disadvantage

Comment [32]: advantage

Comment [33]: disadvantage

heart and subsequent reseeding of the remaining extracellular matrix (ECM) with cells either by direct injection into the “naked” ECM or transfusion through spared vascular channels [39]. The latter approach appears better suited to reestablish a homogenous musculature in the heart but would require that cells migrate into the heart’s ECM and form a continuous functional syncytium. Future studies will have to provide evidence that this can indeed be achieved and that the resulting hearts can be transplanted and perform as desired in vivo. To this end, first short-term data from a heterotopic heart transplantation model are encouraging [39].

Comment [34]: still very new

Fig. 1

Tissue engineering modalities enabling the generation of large macroscopically contracting tissue constructs: (1) *bioengineering approach* [27, 42], (2) *biological assembly approach* [36, 57], (3) *cell sheet approach* [19, 46], and (4) *decellularization–recellularization* **...**

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Limitations

Myocardial tissue engineering still has to go a long way in order to be translated into a clinically exploitable treatment modality, and it is difficult to predict when or even whether it will ever reach its proposed potential. Yet, important recent clinical studies have demonstrated that tissue-engineered products might indeed be applicable to offer mechanical and/or paracrine support to failing hearts ([7]; Sawa et al., personal communication). These studies could clearly be considered pivotal because they describe a first-in-man application of the *bioengineering* [7] and *cell sheet approach* (Sawa et al., personal communication). Yet, the patient number in both of these studies was minimal; therefore, carefully designed follow-up studies need to be conducted to identify the potential of tissue-engineered products in heart repair. However, unearthing the ultimate potential of myocardial tissue engineering will likely require the utilization of contractile muscle elements to remuscularize a failing heart and thereby also functionally compensate for a loss of cardiac muscle. Force-generating myocardium will have to be engineered in vitro and seamlessly integrated in diseased hearts to achieve this goal. Importantly, the potential of electrical and structural integration of heart cells into an allogeneic recipient has already been demonstrated by multiple groups [13, 44, 59] and it is likely that electrical integration will not be an issue if demarcation of implants by scar formation can be controlled [43]. Hence, the most pertinent limitations include (1) the applicability of human heart cells in

Comment [35]: This is a problem that has a lot of place for research

Comment [36]: proved successful

Comment [37]: These are all possible product ideas that could shape my ISM year

Comment [38]: I don't think I have enough scientifical knowledge to understand electrical integration

cardiac tissue engineering, (2) overcoming size limitations, and (3) providing fully biocompatible tissue-engineered muscle. The following list provides a discussion of these issues:

1. Human heart cells can be isolated from biopsy and autopsy material. These cells will, however, not be suitable for myocardial tissue engineering given their limited number, lack of cell cycle activity, and inability to reestablish a functional syncytium once they have been dispersed into single-cell suspensions. Consequently, cardiogenic stem cells will have to be exploited. Adult stem cells from the bone marrow do not harbor the capacity to generate the substantial amount of myocytes needed for complex myocardial reconstitution [3, 35, 37]. In contrast, embryonic stem cells can, in principle, provide cardiomyocytes in adequate numbers [55]. In addition, embryonic stem-cell-derived myocytes are still capable of developing into complex functional syncytia [20] and, only recently, the use of embryonic stem-cell-derived cardiomyocytes was demonstrated in myocardial tissue engineering [6, 17]. Collectively, these data provide strong evidence that embryonic stem cells might be an appropriate cell source for clinical-scale myocardial tissue engineering. However, cardiomyocyte yield from embryonic stem cells is generally low (1–5%; [23]) and scalability will, consequently, be an important issue to generate relevant cardiomyocyte numbers and eventually "force-generating" human myocardium. The later goal has, despite two recent reports using embryonic stem-cell-derived myocytes in a 3D culture format [6, 45], not been achieved, but it is likely that hydrogel-cultures will be instrumental to generate such tissues [60]. Similarly, nonembryonic pluripotent stem cells, including induced pluripotent stem cells [49], spermatogonial stem cells [16], and parthenogenetic stem cells [51], will be exploitable in cardiac tissue engineering. These cell types will, on the one hand, not require cell harvest from an early embryo and might, in addition, be suitable for the generation of autologous cells; however, other ethically controversial issues remain, including the need for genetic manipulations in the induced pluripotent stem-cell-based technology and the risk of in vitro mutagenesis and teratoma formation after an in vivo application.
2. It will be essential to generate and implant thick muscle tissues to achieve meaningful contractile support in the setting of heart failure, to adequately replace scarred heart tissue in individuals with myocardial infarction, or to repair tissue deficiencies in pediatric hearts. The need for continuous oxygen and nutrient supply to metabolically highly active myocardium is a key issue for all tissue-engineering technologies. Although myocardium can already be reconstituted in vivo with a diameter of up to 1 mm [47, 59], this would likely be insufficient to impart a clinically relevant effect. In vivo physiological muscle diameters of at least 10 mm need to be matched. To achieve this goal, "in vitro vascularization" might be a prerequisite. It is unlikely that this will be achieved by simply adding endothelial cells or smooth muscle cells to a tissue reconstitution mixture, although it has been clearly documented that nonmyocytes will have beneficial effects, which include the formation of primitive capillary structures in tissue-engineered heart muscle [28, 36, 57]. This will, however, not likely be sufficient to provide immediate

Comment [39]: IMPORTANT

Comment [40]: What I could possibly be solving in my final product

Comment [41]: the way to go

Comment [42]: also researched this last year at the AP Biology genetics conference

circulatory support to large engineered tissue grafts in vivo. To overcome this limitation, vascularized myocardial tissues could be generated in vivo either by seeding cardiogenic cells in prevascularized chambers [33] or by introducing a macrovasculature with defined inflow and outflow to enable surgical anastomoses to, for example, the coronary arteries [24].

3. Tissue-engineered myocardium would ideally be generated from biocompatible and autologous material. Biocompatible matrix materials are commonly available (e.g., collagen). Unfortunately, autologous cardiogeneic cells are not readily available. Adult stem cells from the blood or bone marrow would be logistically ideal but do not have the intrinsic capacity to give rise to cardiomyocytes of sufficient quality and quantity [2]. In contrast, embryonic stem cells can give rise to *bona fide* cardiomyocytes [8, 20, 54], which would, however, elicit an immune response in an allogenic recipient [25]. Alternatively, induced pluripotent [49], spermatogonial [16], and parthenogenetic [51] stem cells could be applied autologously. These cell types appear to have the most characteristics of embryonic stem cells, including the capacity to give rise to cardiomyocytes. This makes them an attractive source for cardiac-muscle-engineering and other tissue-engineering applications. Finally, the necessity for an autologous application needs to be carefully considered, given the time needed to generate a therapeutic autologous cell pool (weeks to months) and, subsequently, an autologous tissue (takes roughly 7 days when embryonic stem cells are used to generate EHTs; our own unpublished data). Having this in mind, it might be worthwhile to consider cell banking for tissue-engineering applications. In this scenario, cells with defined immunological features would be banked to be matched with an allogeneic recipient. Under these circumstances, it would be likely that induction of differentiation followed by cardiac muscle engineering could be achieved within 2–3 weeks. This time frame appears clinically acceptable. In addition, palliative procedures could bridge the gap until tissue-engineered products would be ready for a clinical application. Time-frame concerns for early postnatal heart surgery might also be irrelevant if immune-matched heart tissue could be generated to be available at birth.

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Application of Tissue-Engineered Myocardium in Pediatric Heart Surgery

Comment [43]: Different

Tissue-engineered-based myocardial repair has been mainly discussed for adult patients, being affected either by global heart failure or localized myocardial damage (e.g., after a myocardial infarct) [58]. Minimal myocardial reconstruction, as sometimes required in isolated ASDs and VSDs, might not be ideal conditions for biological repair with tissue-engineered myocardium. However, children with hypomorphic ventricles as observed in HLHS or DILV could potentially

benefit from an augmentation of the affected ventricle or septation of a single ventricle with a fully biological contractile patch (Fig. 3). These procedures would likely require further inflow and outflow track reconstruction as well as seamless electrical and structural integration of the biological graft into the recipient heart. It would, in addition, be likely that such an intervention would have to be paralleled by electrical synchronization of the implant and the recipient heart. Given the prognosis of children with single-ventricle anomalies and the lack of organ donations for heart transplantation, this additional intervention might be acceptable. Another issue will be to perform the appropriate preclinical and clinical studies to assess safety and feasibility as well as efficacy of such an intervention. Major safety concerns will also depend on the utilized cell type. Especially in the case of embryonic stem cells or non-embryonic pluripotent stem cells and derivatives, teratoma formation cannot be ruled out [26]. This issue has, however, not stopped the FDA from granting approval to a first-in-human trial with embryonic stem-cell-derived oligodendrocytes in spinal cord injury repair (GRNOPC1, Geron Corp.).

Comment [44]: most recently seen

Comment [45]: why challlenging

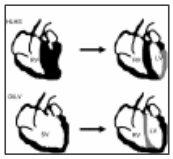

Fig. 3

Schematic drawings of potential applications of tissue-engineered myocardium (*gray*) for left ventricular augmentation (*top*) or single-ventricle septation (*bottom*) in children with HLHS or DILV, respectively. RV: right ventricle; LV: left ventricle; SV: **...**

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Conclusions

Organ repair strategies utilizing cell products are rapidly evolving. Adult stem cells from the bone marrow will be tested shortly in a pivotal phase III trial for efficacy (TOPCARE-AMI). Results from this study are expected in 2011 (Zeiher et al., personal communication). Derivatives from embryonic stem cells will enter a first clinical trial shortly. The outcome of the latter will be of paramount importance not only for cell implantation studies but also for the tissue engineering field. In particular, cardiac tissue engineering will depend crucially on the availability of stem cells capable of providing cardiomyocytes in large numbers. To this end, embryonic stem cells or nonembryonic pluripotent stem cells, including induced pluripotent stem cells, spermatogonial stem cells, and parthenogenetic stem cells, appear to be instrumental. If safety can be demonstrated for embryonic stem cell derivatives in spinal cord injury, it will be logical to also

advance tissue-engineering technologies that utilize embryonic stem cells or nonembryonic alternatives into large animals and subsequently human trials.

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Acknowledgments

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