

Build a Smart Prosthesis that Will Grow with a Child (such as a Heart Valve or Cerebral Shunt, or a Self-Healing Prosthesis).

TASK GROUP DESCRIPTION

Pediatric cardiac valves

Background

The most common congenital valve problem in children is aortic stenosis (i.e., restricted aortic outflow). In the past, stenotic valves were commonly dilated with balloon catheters or surgically incised to increase the opening. Unfortunately, after balloon dilatation or surgery, valve integrity is compromised with significant leakage, which strains the left ventricle leading to dilation and dysfunction.

Replacement of an abnormal aortic valve in a small child is a unique challenge, particularly in sizing the new valve. There are no manufactured valves that perform well in very small children. The smallest successful artificial valve is roughly 17 millimeters in diameter, which infants with congenital aortic stenosis often cannot spatially accommodate. Enlargement of the aortic root can sometimes provide enough room to tolerate a 17 millimeter or 19 millimeter valve (using the Konno procedure) but not without consequence. Even with the Konno modification, implantation of a full adult-sized valve is impossible in very small children. Therefore, these patients will inevitably outgrow the implant and will require further surgery later in life.

In addition, mechanical valve substitutes also require lifelong protection against clotting with anticoagulant medications to prevent thrombus formation on the valve leaflets, which can cause strokes or lead to dysfunction of the valve. Implantations of animal tissue or xenograft valves avoid the need for anticoagulation but do not resolve this dilemma. Tissue valves are prone to premature calcification and degeneration in growing children. Even human homograft (cadaver) valves used in small infants tend to calcify before the patient reaches adulthood.

To overcome these significant problems with surgical treatment of congenital aortic valve disease, the Ross procedure was developed. In the Ross procedure the pulmonic valve is switched to the aortic position, where it continues to grow, and the pulmonic valve is replaced with a cadaveric homograft. This is the best long-term treatment for children with aortic valve and root abnormalities. The native tissue reconstruction provided by the Ross procedure also eliminates the burden and complications of anticoagulation. Moreover, the pulmonary autograft neither calcified nor degenerated over time in contradistinction to xenograft bioprosthesis.

A modified Ross autotransplant performed in concert with annular enlargement, the Konno-Ross, is performed by first harvesting additional muscle from the anterior right ventricular outflow tract as the autograft is procured. After removal of the diseased aortic valve, the aortic annulus is split open between the right and left coronary arteries. Then the pulmonic donor graft is sewn into this enlarged annulus, including the additional muscle skirt harvested with the autograft. The pulmonary homograft reconstruction of the right heart is purposely oversized to permit growth of the child and reduce the need for secondary operations. Although technically demanding, the use of the

Ross operation in pediatric patients with aortic valve disease is clearly a major step forward in the surgical management of these patients.

Initial Challenges to Consider

- Children who need a mitral valve replacement commonly receive a mechanical valve made of polymers or metals that are very durable. With a mechanical valve, anticoagulation is required chronically, and in a young child the valve would need replacement at least one time later in life as it becomes too small. Unlike the Ross procedure for the aortic valve, there are no similar procedures for the mitral valve.
- How can the atrial-ventricular valve be engineered to restore and maintain cardiac function? What will control the growth and development of the valve? Are there alternative ways in which the functional status of the valve can be monitored?

Vascular grafts

Background

The replacement or repair of diseased vessels with natural synthetic vascular grafts has become a routine treatment for certain types of intravascular disease. In coronary bypass surgery the autologous saphenous vein remains the graft of choice for its nonthrombogenic flow surface, ability to be healed by the host, as well as its strength and elasticity. Development of a synthetic small diameter vascular graft has been largely unsuccessful. Moreover, for the pediatric population these grafts are fixed and do not

conform to patient growth from childhood into adulthood. The unfortunate therapeutic strategy thus necessitates multiple surgeries.

Initial Challenges to Consider

Many laboratories are attempting to create an alternative to autologous veins for use in coronary artery bypass grafting and other shunt procedures. In general, researchers are either attempting to engineer nonthrombogenic synthetic materials for use as conduits or to tissue engineer living blood vessels from cells and scaffold.

One research tactic has been to create a three-dimensional construct from porous matrices (such as collagen, elastin, or polyglycolic acid), and seed them with cells. Some investigators recreate relevant biochemical and mechanical environments to allow endothelial smooth-muscle cells and fibroblasts to proliferate within an extracellular matrix under appropriate applied stresses. Another approach has been to create grafts from small intestine submucosa (SIS), which remodel into the tissue where they are implanted.

Can these or similar approaches be employed to create biologically compatible grafts that will not require lifelong anticoagulation and which will remodel to the demands of a growing patient? What approach would be best?

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TASK GROUP SUMMARY

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Summary

Human heart valves derived from the stem cells in a mother's amniotic fluid could be grown by scientists before a baby's birth, ready to repair heart defects when the child is born, reported scientists at November's American Heart Association meeting.¹

A recent study in chickens revealed that vertebrates—including humans—may possess the genetic signals needed to regenerate limbs the way salamanders do.

Researchers at the Salk Institute for Biological Studies stimulated the proper signals in a chick, inducing expression of the genes needed to grow back an amputated wing, according to an article published in *Genes and Development*.²

And *Outside Magazine* lists tissue engineering as number 70 on its December 2006 list of 100 of “the year’s most important people, ideas, trends, and gear”—right between a Pro pogo stick and a scenic waterfall in Peru.³

The field is decidedly hot, but building a “smart” prosthetic that can grow with a child—the aim of this task group—represents a formidable challenge. Development of these prosthetics represents a field rich with potential, one that might take great advantage of the advances mentioned above. Yet, many gaps in our knowledge remain on the road to clinical use of such technology. The potential benefits make the trip worth traveling, however, and this task group concentrated on identifying the areas where we lack knowledge and how we might begin to bridge these gaps in understanding.

The additional issue of growth raises the degree of difficulty in creating prostheses for children, in addition to the scientific and technological challenges inherent in building any prosthesis—such as compatibility with the host, integration with host tissues, and control of the prosthesis. Growth, as the task group defined it, includes changes in size, performance of the prosthetic, rate of growth, and complexity—in terms of the child’s changing cognitive, emotional and hormonal, behavioral, and biological state.

Charge to Task Group

The task of building a smart prosthesis to grow with a child encompasses a diverse array of scenarios—from heart valves to bones to blood vessels or bladders. Some examples of prostheses that grow with children already exist: An artificial femur can lengthen within a child’s leg to keep pace with growth, expanding every one to two years via noninvasive stimulation controlled by a doctor.⁴ Several children recently received laboratory-grown bladders built from their own cells.⁵ Though, as these children grow no one can yet be certain how the bladders will grow and adjust within their changing bodies.

So many possibilities exist that the task group started to get a handle on the problem by categorizing examples of prosthetics that need to grow with children according to the degree of difficulty associated with developing them. The relatively easier end of the spectrum included bones and shunts to drain cerebrospinal fluid. Growing an entire limb or creating a device that requires an interface between brain and machine that must incorporate an element of cognitive development pose the most challenging problems. As the challenge increases, the group noted, so too does the need for interdisciplinary collaboration to address it. An orthopedic surgeon might develop an artificial bone that grows, but creating a prosthetic that interacts with a child’s changing brain will require input from neurologists, neurosurgeons, engineers, materials scientists, and developmental psychologists. This stratification by difficulty of each task helped to identify the scope of challenges to address, and allowed the group to clearly see what thematic concerns spread across all of these specific cases.

Knowing what we don't know can be the key to heading in the right direction for the answer. The group focused much of its time on developing a taxonomy to use in thinking about how to develop a smart prosthetic to grow with a child.

Strategy

Making a prosthetic that can grow with a child requires many decisions. First, in the taxonomy developed by the task group a primary choice must be made between two general strategies: building the prosthetic using tissue engineering and regenerative medicine or using synthetic systems. Tissue engineering, such as that used to create the bladders already in use, might use a child's own cells to grow an organ outside of the body. A synthetic system could allow for preparation of a tissue—such as a heart valve—from artificial materials to be placed in the body during an emergency situation, when doctors and researchers do not have the time to grow one from a patient's own cells.

The next decision involves making control of the prosthetic active or passive. On the passive end of this continuum, the prosthetic would require no regulation by the child. The device's adaptation and growth with the child would be autoregulated. On the other end an active device would require a child to learn how to use it over time. A tertiary decision, control of the device, would require doctors and researchers to decide where the prosthetic's instructions came from. It might be controlled internally—carrying its roadmap for growth with it inside the body—perhaps in the timed release of certain growth factors. Or it might require a doctor to exert external control, such as radio frequency signals, to tell a prosthetic bone to lengthen a few centimeters every year or two, during a child's visit to the office.

Future Challenges

Researchers, doctors, and engineers must address several gaps in our knowledge to develop prosthetics that are smarter, more durable, and more accurate replications of natural tissues and organs. The task group identified several areas, including longevity, growth boundaries, and exploiting developmental biology, that presents challenges unique to prosthetics intended for growing children.

The longevity of prosthetics in children must exceed that of any available to date. Adult patients receiving hip replacements today often outlive these artificial joints. A child's prosthetic must survive nearly a lifetime—70, 80, or over 90 years.

The growth boundaries on a child's prosthetic warrant thoughtful consideration: It must grow to the correct size while maintaining function and keeping pace with the child's growth but must also cease growth and segue into a "dynamic endstate"—a state, perhaps no longer physically growing but continuing to respond, adapt, and communicate with the body around it.

The ability of a prosthetic to work with a child's own developing brain or limbs might offer a meaningful advantage. Though creating a prosthetic for a child presents unique challenges, it also provides the opportunity to capitalize on the unique complement of growth factors and plasticity within a child's cells and tissues. But prosthetics can take advantage of this natural milieu only if the most advantageous window of time is precisely identified.

Bioethical, economic, and regulatory concerns also represent overarching issues that will infuse the decisions made in the course of developing these prosthetics for children.

Task Group Recommendations

Considering these gaps in current knowledge and the highly interdisciplinary nature of the work required to develop smart prosthetics to grow with a child, this task group recommended a future workshop with three general goals: building an initial plan for the immediate next steps required for research to move forward; establishing a calendar of attainable goals—which prosthetics for children are likely to be achievable within five years, ten years; and building of interdisciplinary teams amongst those at the forefront—those in fields such as prosthetic research, developmental biology, tissue engineering, electrical engineering, surgery, and clinical medicine. The workshop, suggested this task group, might be most productive if organized into working groups based on specific prosthetic projects, such as heart valves, bladders, or legs.

One member of the group, Jeremy Gilbert of the Biomedical and Chemical Engineering Department at Syracuse University, said, “Clearly nature has worked out these mechanisms in exquisite detail.” Now it’s our turn to figure them out.

Notes

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