Tissue Banking Innovation Practices

Research Summary

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RESEARCH SUMMARY

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Introduction

The Canadian Council for Donation and Transplantation (CCDT) initiated the following evaluation of current innovations in technology and surgical practice that utilize human tissue substitutes for their potential impact on tissue supply and demand in Canada. This study is also intended to assist the CCDT in the development of a framework for systematic and sustainable tissue banking services.

A literature review of current innovations and the development of innovation assessments were performed for the following areas:

- Artificial Cartilage,
- Corneal Tissue,
- Gene Therapy and Stem Cells in Orthopaedics,
- Hip Resurfacing,
- Artificial Skin and Wound Healing,
- Artificial Tendons, and
- Vascular and Pericardial Tissue: Bovine and Synthetic Options.

The literature review and innovation assessments were reviewed and commented on by individuals involved in tissue banking in Canada. The complete innovation assessments are located in the next section.

Assessment of Innovative Practices

Artificial Cartilage Assessment

Product and/or Procedure	Artificial Cartilage
Brief Description	Artificial cartilage products are currently focused on the development of hyaline articular knee cartilage. There are approved autologous-based cartilage replacements as well as fully synthetic products currently licensed for sale in North America.
Intended Impact on Patient Outcomes	Restoration or replacement of damaged articular cartilage. Largest area of focus is prevention of the need for total knee replacement and improved outcomes of small defect repair which combined accounts for over 500,000 surgical procedures per year in North America.
Current Access Pathway	Available for sale and also for clinical trial use.
Estimated Time to Market	A number of products for small defect repair using both autologous chondrocyte replacement and fully synthetic implants are available.
Impact on Tissue Availability: Demand	Demand for large allografts (e.g., such as large cadaver allografts) not effected by current synthetic approved products which are approved for small defect repair. Autologous chondrocyte products, however, may impact the demand for cadaver allografts if the product approvals are widened in the short term; currently these products are indicated for use where patients have not responded to arthroscopic or other surgical repair attempts. Expansion of the current indications for use is not likely in the near term (1 to 2 years) due to the numbers of adverse events reported with the use of products like Carticel® for current approved applications (see Wood et.al, 2006).
Impact on Tissue Availability: Supply	The development of products like autologous chondrocyte replacement or fully synthetic gels will not directly affect the supply of cadaver tissue.
Influence on Tissue Quality	None.
Influence on Tissue Safety	Artificial cartilage products would eliminate the potential risk of allograft disease transmission.
Accountability	Regulated as a biologic product or as a medical device. No accountability for tissue banks for these products.

Artificial Cornea Assessment

Product and/or Procedure	Artificial Cornea
Brief Description	Current non-biological artificial corneas are based on polymer intraocular lens technology similar to current minimally invasive cataract implants. Biological research is currently focused on biological tissue engineered innovations, in particular the development of collagen scaffolds that are capable of supporting cell infiltration of stromal cells. Amniotic membrane (AM) transplantation has shown potential for a tissue-based corneal alternative.
Intended Impact on Patient Outcomes	Current non-biological products are focused on restoring sight in high-risk patient groups that have had unsuccessful transplant attempts or are at high risk for transplant failure. Biological research is focused on the development of collagen-based cornea replacements; clinical trials will likely also occur with high-risk patient groups once a viable biologic product is developed.
Current Access Pathway	Prosthesis products through clinical trials or humanitarian device exemption. AM available commercially or through tissue banks.
Estimated Time to Market	Complications due to polymer implants must be mitigated prior to introduction of keratoprostheses in populations other than high-risk groups. Two companies have products in clinical trials. Expanded market development is not expected in the short term (<5 years); however, if polymer implant complications are mitigated, keratoprostheses may enter the market in the medium to long term (10 to 15 years). The market time frame for biological collagen corneas is also likely not to occur before 10 to 15 years because there is not yet a collagen-based product in human clinical trials. AM products currently available through tissue banks or private companies.
Impact on Tissue Availability: Demand	Current keratoprosthesis and AM products will only have an effect in failed or high-risk patient groups, or approximately 10-20% of all cornea transplants. Current products will not affect other patient groups in the short term (<5 years) and likely not until the 10- to 15-year horizon. Current AM products are focused on severe injury treatment or failed corneal transplants.
Impact on Tissue Availability: Supply	Greater adoption of current keratoprosthesis and AM products may have a slight effect in availability of corneas for patients outside of high-risk populations in the short term, i.e. there may be a supply alternative to cadaver allograft for high-risk patients. Positive results from long-term clinical trials are required in both areas for significant long-term reduction of the need for allograft cornea.

Product and/or Procedure	Artificial Cornea
Influence on Tissue Quality	None.
Influence on Tissue Safety	None.
Accountability for Tissue Banks	None. Current products regulated as a medical device. AM is regulated as other human-donated tissue.

Gene Therapy and Stem Cells in Orthopaedics Assessment

Product and/or Procedure	Gene Therapy and Stem Cell in Orthopaedics
Brief Description	Bone marrow-based mesenchymal stem cells are currently being used in products undergoing clinical trials in the U.S. for regeneration of meniscus tissue. Other products are combining bone matrix with mesenchymal stem cells. Gene therapy products, while showing promising laboratory results, are still in their infancy.
Intended Impact on Patient Outcomes	Intended as advanced tissue products capable of restoring damaged tissues rather than replacing tissues with grafts.
Current Access Pathway	Clinical trials for a small number of products.
Estimated Time to Market	Given that clinical trials have only begun within the last year, estimated time to market for mesenchymal stem cell products are not expected sooner than the mid-range time horizon (10 years). Gene therapy products have significant clinical hurdles and are not expected to develop commercially available product sooner than the 10- to 15-year horizon.
Impact on Tissue Availability: Demand	Neither mesenchymal stem cell nor gene therapy-based products is expected to impact the demand for bone tissue allografts prior to the 10- to 15-year horizon.
Impact on Tissue Availability: Supply	Neither mesenchymal stem cell nor gene therapy based products is expected to impact the supply for bone tissue allografts prior to the 10- to 15-year time horizon. If these products reach significant markets, they would be expected to reduce bone tissue supply requirements.
Influence on Tissue Quality	Gene therapy could potentially be used to modify tissues; however, specific applications are not known.

Influence on Tissue Safety	The combination of mesenchymal stem cells and gene components with tissue will require new safety protocols.
Accountability	The role of tissue banks with emerging mesenchymal stem cell or gene products is not known.

Hip Resurfacing Assessment

Product and/or Procedure	**Hip Resurfacing**
Brief Description	Available in clinical trials in a number of forms since the 1970s, the procedure and associated products are intended to replace total hip replacements with much smaller implants that only require partial removal of the surface of the femoral head. Older products had poor clinical outcomes. Current technology claims greatly improved clinical outcomes pending FDA approval in the U.S.
Intended Impact on Patient Outcomes	Hip resurfacing technology in its current form will not replace all total hip replacements and is currently only being indicated for patients typically under 50 who are likely candidates for both total hip replacement surgery and also eventual total hip revision surgery (http://www.fda.gov/fdac/features/2004/204_joints.html) There is currently no long-term data on the length of product life, and this data may not be available for approximately 10 years; widespread adoption of hip resurfacing as an option for total hip replacement will likely not occur until comparative long-term data is available.
Current Access Pathway	Through manufacturers for clinical studies only. Twelve clinical studies are currently recruiting patients or underway in the U.S. (see http://www.clinicaltrials.gov/ct/search;jsessionid=C6BECEDBC17C2F460641AB2FEEECFFF2?term=resurfacing). Current hip resurfacing technology is pending FDA approval in the U.S.
Estimated Time to Market	Currently hip resurfacing as an alternative to total hip replacement is in investigational studies in the U.S. The first market approvals are projected (from company literature) for late 2005/early 2006.
Impact on Tissue Availability: Demand	Hip resurfacing will only have a major impact on surgical bone supply when the technology is approved for use in older (>65) patients, who are the majority of total hip replacement candidates. Given that current clinical trials are not focusing on this patient group, the probability that bone demand will be affected by this technology in the next 10 to 20 years is low. If widely used in patients over 65, the effect would be lower use of bone void fillers (e.g., cancellous/cortical chips, substitutes) for hip replacements.

Impact on Tissue Availability: Supply	Greatest impact on surgical bone supply; i.e., a reduction in femoral head availability will directly reduce supply of surgical bone (for example, if hip resurfacing replaces total hip replacements, the supply of femoral heads may be greatly reduced or eliminated). Hip resurfacing is not a short-term (<5 year) threat to the supply of surgical bone; however, depending on the outcomes of clinical trials, it may impact the surgical bone supply in the long term (>10 year), and only if approved for use in patients older than 65.
Influence on Tissue Quality	None
Influence on Tissue Safety	None
Accountability for Tissue Banks	None. Regulated as a medical device and purchased outside of tissue banks.
Notes	Hip resurfacing as a replacement for total hip replacements should not be confused with another procedure called "hemisurfacing" which is a similar technology used to replace osteoarthritic and/or osteonecrotic tissue. Patients who are candidates for hemi-surfacing are not viable surgical bone donors, and this procedure does not affect the current surgical bone supply from total hip replacements.

Skin and Wound Healing Assessment

Product and/or Procedure	**Artificial Skin and Wound Healing**
Brief Description	Artificial skin substitutes have been available in a number of forms since the 1980s. Current products include both temporary and permanent grafts and are indicated for use for a variety of wound conditions including ulcers and deep burns. Despite recent advances, artificial skin products are not considered to surpass autografting and cadaver allografting for a number of clinical reasons and are also based on cost, in particular for burn patients.
Intended Impact on Patient Outcomes	Patient outcomes for artificial skin have been very successful for small-area treatments (e.g., DermaGraft use for foot ulcers) and have had limited success for burn patients (e.g., EpiCel). Vascularization of artificial skin is still poor compared with autografting.
Current Access Pathway	A large number of temporary and permanent artificial skin products are available for purchase.
Estimated Time to Market	Already on the market. Artificial skin that includes growth factors is expected to be in clinical trials in the next 5 years.

Impact on Tissue Availability: Demand	Currently, artificial skin products have been described as "underutilized" (Hrabchak et al. 2006). Current demand for human allograft skin is not expected to decrease until the next generation of artificial skin products are developed, in particular with the inclusion of growth factors and vascularization results approaching that of autografting is developed. Over the next 5 years the largest increase of artificial skin use will likely be in small defect products (e.g., for skin ulcers or small wound care).
Impact on Tissue Availability: Supply	Current cadaveric skin supply will likely not be affected by artificial skin products in the short term. If the inclusion of growth factors is successful in producing better vascularization and cell proliferation, skin banking could greatly reduce the supply requirements in the long term (10- to 15-year horizon).
Influence on Tissue Quality	The quality of skin grafts could potentially be standardized with the widespread adoption of a synthetic skin substitute.
Influence on Tissue Safety	Artificial skin products would eliminate the potential risk of allograft disease transmission; however, the use of xenograft tissue and other cell-based products carries other manufacturing and rejection risks that will also need to be mitigated.
Accountability	If tissue banks are not involved in the storage and distribution of substitutes, there will be no accountability for tissue banks in the use of substitutes.

Tendon and Ligament Assessment

Product and/or Procedure	**Artificial Tendon**
Brief Description	Early attempts at artificial tendon products based on braided fabrics had poor results and no biological activity. Recent product advancements have included greater mechanical properties as well as biological activity including improved in-growth and vascularization. Future product developments are being developed for "seeded" artificial ligaments that have improved adhesion and biological activity through the use of stem cells and platelet-rich fibrin combinations.
Intended Impact on Patient Outcomes	Restoration of full activity, particularly for younger patients. Intended improvement in strength over processed cadaver tissue.
Current Access Pathway	Several products currently on the market and in clinical trials.
Estimated Time to Market	Advanced products already on the market (e.g., WMT's GraftJacket®).

Impact on Tissue Availability: Demand	Demand for ligament grafts has a number of factors: 1) Demand for ligament tissues will increase with the aging population. 2) Change in current demand from cadaver ligament tissue will depend on the ability of tissue banks to provide allograft tissue, surgeon preference and improvements in synthetic products. 3) The majority of demand for stronger synthetic products will likely occur among high-demand patients (i.e., highly physically active), whereas lower-demand patients may continue to receive allograft or autograft procedures. Given the complexity of products like GraftJacket® and continued development of platelet and stem cell products, demand for human-derived allografts is expected to decrease in the medium to long term (10 to 15 years).
Impact on Tissue Availability: Supply	Increased development of products like the LARS ® system and GraftJacket® will reduce pressure on the supply of human-derived allograft.
Influence on Tissue Quality	Increased function and performance over cadaver allografts, in particular due to processing requirements of human allograft tissue.
Influence on Tissue Safety	Reduced potential for disease transmission.
Accountability	None. Products are regulated as a medical device and are purchased outside of tissue bank operations.

Bovine and Synthetic Cardiac and Vascular Tissue Assessment

Product and/or Procedure	**Cardiac and Vascular Tissue**
Brief Description	Bovine tissues have been in use since the 1970s as pericardial patches and continue to be in use today. A number of bovine graft products are currently available on the market. Paediatric tissues are in clinical trials for ventricular reconstruction and are showing similar results to homografts. Synthetic grafts have been in development since the 1970s and are commonly used, e.g., Gore-Tex®. Future applications may include collagen or hyrogel-based technology seeded with endothelial cells and other biologically active components.

Intended Impact on Patient Outcomes	Common uses of bovine graft include pericardial augmentation during open-heart surgery and paediatric ventricular reconstruction. Bovine grafts are intended to offer a wider range of options for viable graft, particularly in paediatric applications where availability and graft size may be a significant issue. At least one long-term clinical trial with bovine jugular xenografts has shown over 90% survivability after 4 years, and the study authors recommend the xenograft as an alternative to homografts (see Breymann et al. 2005).
Current Access Pathway	A wide range of vascular and pericardial tissue products are currently on the market. Bovine products for use in paediatric ventricular reconstruction are currently in clinical trials.
Estimated Time to Market	Bovine products for use in paediatric ventricular reconstruction have been in clinical trials for over 5 years. If clinical trials continue to show outcomes comparable to allografting, product licensing could potentially occur in the medium time horizon (5 to 10 years). Products based on hydrogel or collagen technology are still in exploratory or bench tests and would not be expected to be licensed for market before the long-term time horizon (>15 years).
Impact on Tissue Availability: Demand	If products like Contegra® are licensed for use outside of clinical trials, the demand for tissue for paediatric tissue in particular could be significantly lowered. Demand for adult vascular and cardiac tissues will likely not be affected by current product development efforts before the long-term horizon (<15 years).
Impact on Tissue Availability: Supply	Supply options for allograft vascular and cardiac grafts will likely be increased, in particular for paediatric patients, if products like Contegra® are licensed for use outside of clinical trials. Any increase in the use of bovine or synthetic grafts will improve access to the supply of human-derived allograft materials; however, an effect on the supply for adult patients will likely not be on the market before the long-term time horizon (>15 years).
Influence on Tissue Quality	Tissue quality could potentially be standardized, particularly in the choice of size range options.
Influence on Tissue Safety	Artificial skin products would eliminate the potential risk of allograft disease transmission; however, the use of xenograft tissue and other cell-based products carries other manufacturing and rejection risks that will also need to be mitigated.
Accountability	If tissue banks are not involved in the storage and distribution of substitutes, there will be no accountability for tissue banks. Tissue banks may be involved if current management of, e.g., heart valves is extended to xenograft and synthetic products.

Summary of Results

None of the emerging technologies reviewed in this study are going to displace traditional tissue banking in the next 10 years. Tissue banks are going to remain a vital component of the Canadian health care system well into the future as a number of the technologies currently under development are complementary to tissue banking.

Tissue banks could also have a significant role in the development of the emerging technologies reviewed in this report, in particular with technologies based on autologous cell donation, allograft skin, adult bone marrow and amniotic membrane.

Of the emerging products/technologies reviewed, there are a number of innovations currently on the market or in clinical trials, including:

- Hip resurfacing technology,
- Artificial cornea and corneal alternatives (amniotic membrane; synthetic keratoprosthesis),
- Synthetic cartilage and tendon, and
- Synthetic and xenograft vascular grafts.

All other innovation areas are either in animal trial or bench testing and will not emerge as products for at least 10 to 15 years.

None of the technologies reviewed on the market or in clinical trial, in their current form, have the potential to fully displace the need for human allograft tissue.

Innovations that may become available in the next 5 to 15 years include:

- Artificial cornea (keratoprostheses in the general transplant population),
- Autologous chondrocyte cartilage transplantation,
- Permanent artificial skin (collagen scaffold based), and
- Mesenchymal stem cells for knee cartilage repair.

These technologies do have the potential to impact current tissue bank supply and demand; however, deceased allograft will continue to be required for the majority of ocular, skin and musculoskeletal grafting procedures.

Groundbreaking or potentially disruptive innovations that could change the need for traditional allografts are in development, including:

- Artificial cornea utilizing collagen scaffolds,
- Vascular grafts from collagen scaffolds, and
- Genetic therapy innovations in orthopaedics.

These innovations are all in bench or animal testing and will likely not emerge on the market within 15 years.

Recommended Areas for Further Research

Based on the emerging product innovations described above, tissue banks may want to explore the following areas for further research.

Bone Marrow Banking for Mesenchymal Stem Cell Production

Tissue banks may want to explore the possibility of starting or increasing bone marrow collection and banking. A shortage of human donated bone marrow has been identified as a major barrier to orthopaedic stem cell product development and production. Tissue banks could procure adult bone marrow from organ donors (or potentially deceased donors if donation could occur in a short time frame) for use in stem cell products. Adult bone marrow has similar storage characteristics to bone, in that it can be stored cryogenically for up to three years. Commercial partnerships, similar to those with demineralized bone matrix manufacturers, could be explored for stem cell product development.

Cell Autobanking

Autologous tissue procurement is a major component of autologous chondrocyte cartilage products. Tissue banks may want to explore the potential of providing autobanking services for this product area. Private companies are currently providing similar services (e.g. storage of umbilical cord blood); however, there may be other areas where tissue banks could perform similar services, e.g. knee biopsies could be kept and banked for potential cell growth in autologous chondrocyte growth. Potential may also exist for collection of cells for use in genetic therapies.

Amniotic Membrane Banking

If not doing so already, tissue banks may want to explore collection and banking of amniotic membrane for ocular procedures and for potential commercial partnerships for the development of artificial cornea tissue.

Skin Banking for Use in Artificial Tendon Products

Allograft skin is being used in at least one product currently on the market for use in the development of artificial tendon (Graftjacket®). Tissue banks that have not done so already may want to explore the potential of expanding traditional skin donation for use in other product areas like artificial tendon or other collagen scaffold products. Medical device licensing implications would need to be evaluated.

Regulatory Considerations

Most of the innovations reviewed for this project will classify as medical devices. If an innovation classifies as a medical device and contains human tissue, it is automatically a Class IV device. Manufacturers of Class IV devices must hold a medical device license for all devices imported, sold or advertised for sale in Canada. As part of the application for a medical device license, the efficacy and safety of the device must be confirmed. Proposed

medical device research with humans is evaluated according to the Investigational Authorization program.

Timing of Innovation Development and Marketing

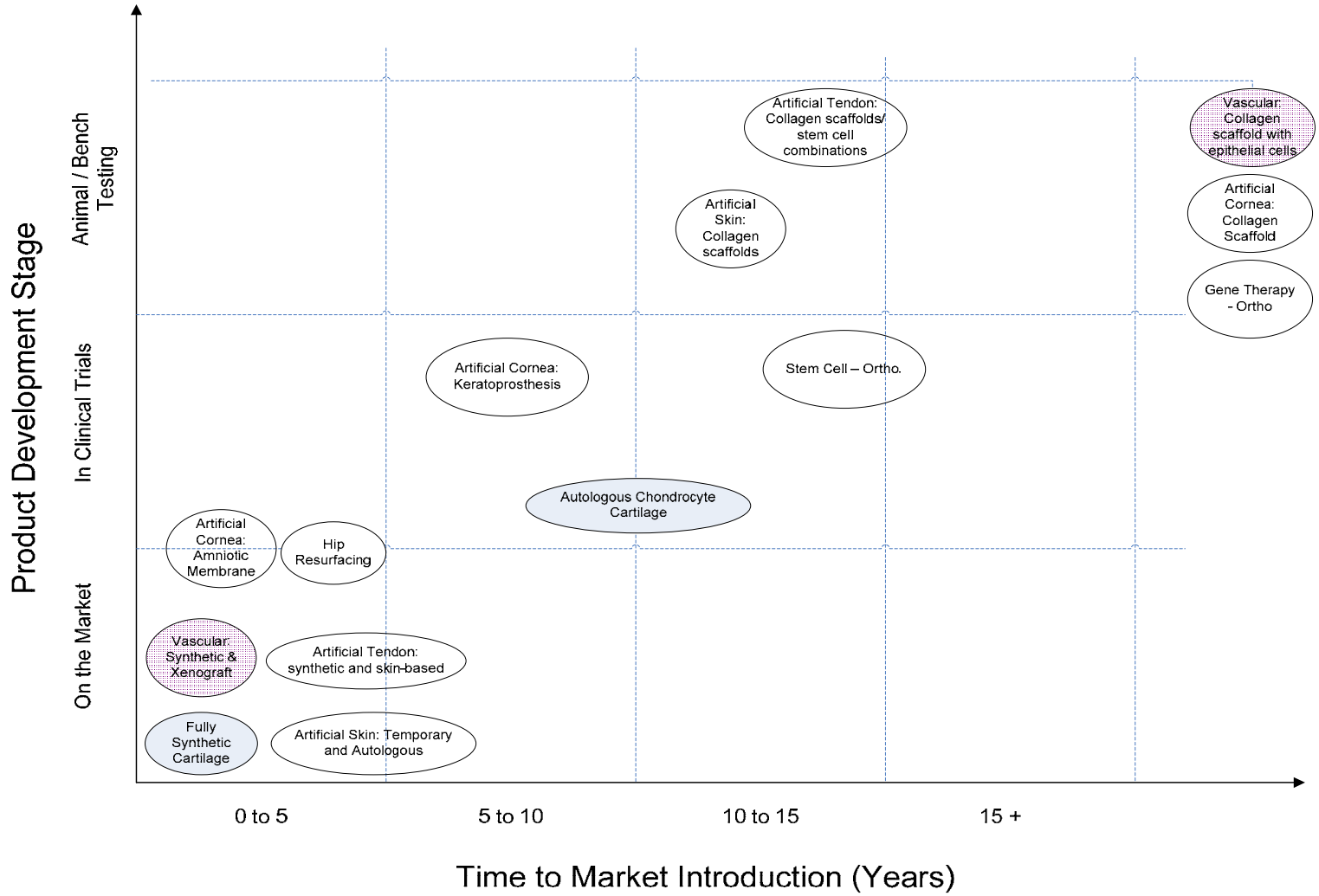
The introduction of new tissue products is highly dependent on the outcomes of long-term clinical trials. Along with clinical benefits, the new technologies will also be required to show economic benefits in order to obtain reimbursement for the new products. These are significant hurdles to overcome and are the main factors in getting a medical product from the lab to widespread use in surgical procedures. It is assumed that a new tissue product will not impact current tissue banking practice until the new product has been released to market.

Figure 1 below shows the expected timing of the market release of each tissue product area based on the reported timing of clinical trials. It is assumed that reimbursement has been obtained for the tissue product. Figure 1 is intended to provide tissue banks with a sense of when the innovations described above may begin to affect tissue supply and demand. Timing of the potential impact is described in periods of 0 to 5, 5 to 10, 10 to 15 and greater than 15 years before tissue banks are affected by introduction of the tissue product to market.

Artificial or alternative cartilage products that are fully synthetic are currently on the market, but it is not clear if there is a clinical benefit. Autologous technologies will likely gain wider use over the next 5 to 10 years. Genetic therapy potential is being explored in animal trials, and they are at least 15 years from market introduction.

Corneal alternative products are currently on the market in the form of amniotic membrane available from some tissue banks and at least one company. Artificial cornea keratoprostheses are currently in clinical trials (AlphaCor®) for patients that have rejected allograft cornea transplants. Collagen scaffolds combined with stem cell or genetic therapies are being explored in bench and animal tests.

Figure 1: Innovation Time to Market



Stem cell-based products in orthopaedics are currently in small clinical trials; however, there is not any stem cell or genetic products currently on the market. Stem cell products intended for knee cartilage repair may be on the market within 10 years if the current clinical trials show a clinical benefit. Genetic therapy applications in orthopaedics have been described as being in their infancy and are at a minimum 15 years from product licensing.

Hip resurfacing products are available for sale and through clinical trials; however, they will likely not have an impact on surgical bone banking within the next 15 years.

Skin and wound healing products are currently available on the market for temporary wound and burn coverage, and one permanent skin graft product is also available that is cultured from the patient's own cells (EpiCel®). Developments in collagen scaffolds are expected to continue and may emerge within 10 years. Allograft skin is still considered the gold standard, particularly for burn patients.

Artificial tendon and ligament products are currently on the market (e.g., LARS ligament system; GraftJacket®). Clinical improvements on these products are expected in 10 to 15 years, particularly for products that utilize stem cell technologies; however, allograft tendon continues to be the gold standard.

Synthetic and xenograft vascular products are currently available on the market. Collagen scaffolds seeded with epithelial cells are being explored in animal and bench testing.

Conclusion

None of the emerging technologies described above are going to displace traditional tissue banking in the next 10 years. Tissue banks are going to remain a vital component of the Canadian health care system well into the future as a number of the technologies currently under development are complementary to tissue banking. Tissue banks could also have a significant role in the development of the emerging technologies (discussed below).

None of the technologies on the market, in their current form, have the potential to fully displace the need for human allograft tissue.

Innovations that may become available in the next 5 to 15 years have the potential to impact current tissue bank supply and demand; however, allograft will continue to be required for corneal, skin and bone grafting procedures.

Tissue banks may want to explore the potential of providing services and/or developing commercial partnerships in the following areas:

- Amniotic Membrane Banking,
- Bone Marrow Banking for Mesenchymal Stem Cell Production,
- Cell Autobanking, and
- Skin Banking for Use in Artificial Tendon Products.

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