Published in final edited form as:

Regen Med. 2010 March ; 5(2): 279–288. doi:10.2217/rme.10.2.

Auto-bionics – a new paradigm in Regenerative Medicine and Surgery

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Summary

The concept of bionics represents the development of engineering and technology based on natural biological systems. Traditional applications of bionics in healthcare include artificial bionic organs which can be used to replace, mimic and even enhance biological function when compared to native organic equivalents (so-called 'Exo-bionics'). Recently there has been a new wave of bio-inspired treatments that act through the reorganisation of the existing biological organs in an individual to enhance physiology. Here the technology does not replace biological tissue, but augments function by tissue reorganization and modification – so-called 'Auto-bionics'. Examples include the Ross (Pulmonary Autograft) Procedure, Cardiomyoplasty, Skeletal-Muscle-Ventricles, Graciloplasty and Metabolic Gastric-Bypass (gastrointestinal rearrangement to modulate hormone release and treat diabetes). These procedures will have an increased role in reconstructive strategies and the treatment of obesity, diabetes, cardiovascular disease and cancer. Auto-bionics can enhance physiological function beyond normality in some cases and represents a new era in bio-inspired versatility.

Keywords

Bionics; Biomimicry; Ross Procedure; Cardiomyoplasty; Skeletal Muscle Ventricle; Graciloplasty; Bariatric; Gastric Bypass; Metabolic Surgery

Introduction

The development of tools to treat injury and disease has been one of mankind's earliest legacies. Luminaries such as Leonardo da Vinci ignited the development of engineering concepts that could be applied to the human body.[1, 2] In 1958, the air force physician Jack Steele first proposed the term *bionics* (also termed *biomimetics*)[3, 4] to represent the application of biological processes for the design of synthetically engineered objects. Many of these proposed bionic objects were anticipated to be functional aids for injured humans.

Advances in materials sciences, electrical engineering, biochemistry, enhanced biomaterials, robotics, tissue engineering and computing power have led to significant developments in medical bionics. As a result, this field is now recognised as an important component of modern biotechnological healthcare treatments (Figure 1).

Common examples of bionic therapies include mechanical limb prostheses, artificial muscles and hearts, retinal and cochlear implants.[4, 5] On occasion some of these bionic

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aids do not only act as ‘tissue replacements’, but rather out-perform their dynamic human equivalents. This includes the case of the athlete Oscar Pistorius who has no legs, yet can outperform other ‘normal bodied’ sprinters when utilising his carbon fibre leg prostheses.[6, 7]

The current lack of biological organs available for transplantation,[8] and the continued difficulties of immunosuppression[9] have led to our need for the increased development of bionic therapies. Many of these ‘conventional’ bionic therapies largely focus on electronic or artificially engineered treatment solutions. The use of these external synthetic therapies can therefore be considered as ‘Exo-bionic’ treatments (Greek exo - external). A converse paradigm however also exists. Here human treatment and enhancement can take place through the re-organisation and re-design of inherent organs and tissue within each individual – the process of Auto-bionics (Greek auto - self) (Table 1).

The application of Auto-bionic treatments is relatively new, and medical technology has only recently realised the benefits of such a concept. Some uses are static and include skin grafting, arterial and vein grafts for coronary operations and the use of muscle flaps in reconstructive surgery. However some auto-bionic therapies are active and result in dynamic or metabolic changes (Figure 2). Examples include heart and sphincter enhancement through dynamic myoplasty and metabolic pancreatic augmentation through metabolic surgery. Furthermore, just as in exo-bionics where an artificial prosthetic can hyper-augment normal function, some auto-bionic treatments can also lead to a supra-physiological functioning of organs. We herein describe some relevant examples of dynamic and metabolic auto-bionics in modern healthcare.

Cardiac Autobionics

Ross Procedure (replacing the aortic valve) - Synthetic exo-bionic cardiac valve replacement is fraught with long term anticoagulation problems, particularly in young patients. In order to overcome these difficulties, experimental models introduced the use of the pulmonary valve to replace the aortic valve.[10-12] Both valves were morphologically semilunar with three leaflets, and had similar function that permitted them to be considered as substitutes for each other.[13] Donald Ross performed the first pulmonary valve autograft to replace an aortic valve in a human in 1967,[14] a procedure that has since been named after him as the ‘*Ross Procedure*’. Here the pulmonary valve is placed at the site of the aortic valve, and a homograft valve is placed at the pulmonary position (Figure 3a).

Despite the technical intricacy of this operation, it has gained increased favour worldwide in view of its long term durability,[15-17] excellent cardiac haemodynamics and ventricular remodelling.[18] The current indication for the Ross procedure includes the treatment of aortic valve disease not subject to repair in patients with a life expectancy of over twenty years. This is particularly useful for women who wish to childbear after this operation.[19, 20] The operation has gained particular favour for the paediatric population in cases of critical aortic stenosis, as artificial biological prostheses show accelerated calcification and degeneration.[21, 22] The auto-bionic nature of this procedure was confirmed by a study by Gorczynski that although the pulmonary valve has evolved in vertebrates to sit in the low pressure pulmonary system, its tensile strength within this procedure is superior to that of the aortic valve.[23] The success of this operation has led to the use of the pulmonary valve at other sites in the heart including the mitral position (Ross II procedure).[24]

Cardiomyoplasty and aortomyoplasty (improving cardiac function) – As early as the 1930’s, pectoral skeletal muscle was successfully applied to repair damaged and post-ischemic cardiac tissue.[25, 26] These skeletal muscle grafts had the advantage of developing collateral blood flow to the cardiac epicardium.[27, 28] This early success led to the

mechanical application of diaphragmatic skeletal muscle to augment the pump function of failing hearts.[29-31] Just as in graciloplasty, the native skeletal muscle suffered from fatigue when used for continuous pump activity and was successfully overcome by transforming slow-twitch muscles by electrical stimulation.[32, 33] It was subsequently demonstrated that once the skeletal muscle was transformed, it could achieve 'cardiac-like function' continuously.[34]

Of the many skeletal muscles available for use in augmenting cardiac muscle, the latissimus dorsi was particularly applicable as an auto-bionic pump due to its proximity to the heart. This is because it could be harvested with its own native pedicle (blood supply), which would decrease any muscle ischaemia, and would naturally overcome any technical difficulties of finding alternative sources of oxygenated blood. In the mid 1980's a latissimus dorsi wrap around the heart was introduced for the treatment of congestive cardiac failure – this was known as the *Dynamic Cardiomyoplasty*. [35] In this operation, the left latissimus muscle is typically harvested and detached from the humerus. The thoracodorsal artery, vein and nerve are kept intact. It is then wrapped around the cardiac ventricles and is stimulated by electrodes linked to an electrical pacemaking device. Both the geometry and the pacing device allow the muscle graft to contract with the ventricles in synchrony to the heart during cardiac systole (Figure 3b). The operation demonstrated early success by dramatically improving symptoms, typically reducing patients New York Heart Association (NYHA) functional class by 1.5. Dynamic cardiomyoplasty results in increased myocardial contractility, reduced left ventricular wall stress and less oxygen demand. It improves effective ventricular wall thickness, reduces left ventricular volumes and can induce beneficial reverse ventricular remodelling.[36-43]

The proposed mechanisms of cardiac benefit after these procedures include a passive “girdling” effect and a dynamic “systolic squeezing effect”, [42] where controversially some have reported the muscle graft to contract up to four times stronger than inherent cardiac muscle.[44] However many studies cannot consistently confirm treatment effectiveness in terms of cardiac output and ejection fraction. As the patient group for cardiomyoplasty have such significant heart failure their inherent perioperative mortality can be as high. Mortality rates are lower in experienced centres, and vary from 2.6%-31%.[45, 46] Some of the experimental studies of cardiomyoplasty revealed that the beneficial effects of the procedure were due to the wall stress relief of the skeletal muscle wrap as opposed to its contractile function. This had led to the development of the exo-bionic cardiac wrap treatments such as the CorCap™ CSD mesh (Acorn Cardiovascular)[47] or the Myosplint® device.[48] The current uses of cardiomyoplasty however still includes the treatment of patients with congestive heart failure, chronically depressed right ventricular function, some individuals with ventricular tumours and as a bridge to transplantation.[49]

In order to provide further skeletal muscle options to increase the inherent cardiac muscle pump function, other auto-bionic procedures have been developed to address congestive cardiac failure. Of these *aortomyoplasty* resembles cardiomyoplasty in that it involved the wrapping of skeletal muscle around the ascending or descending thoracic aorta.[50, 51] This procedure has the advantage of increased technical ease although it has the possible disadvantages of dislodging atherosclerotic plaques or constricting the pulmonary vessels. It is currently still considered an experimental procedure, although early studies in a canine model demonstrate that it can offer provide haemodynamic support equivalent to that of an Intra Aortic Balloon Pump.[50]

Skeletal Muscle Ventricles (improving cardiac function) are also still in their experimental phase as an auto-bionic therapy. In this procedure, the skeletal muscle from latissimus dorsi ventricles is applied to form an accessory cardiac pump (Figure 3c) as opposed to directly

augmenting the contractility of the heart or vessels as in cardiomyoplasty or aortomyoplasty. The concept of an accessory heart is well known in other biological systems,[52] and an added pumping chamber in series with the native heart is common in current exo-bionic hearts.[53]

The procedure involves mobilising the latissimus dorsi muscle and wrapping it concentrically around a mandrel in the shape of a conical spiral that approximates to the size of a subject's ventricle. This is left in the chest cavity and is electrically conditioned in order to transform the muscular wrap into a fatigue-resistant muscular cavity. After approximately six weeks, the mandrel is removed and the ventricular cavity can therefore act as an accessory cardiac pumping chamber.[34, 54] It is most commonly placed in continuity with the descending thoracic aorta to act as an aortic diastolic counterpulsator.

In order to decrease the rates of thromboembolism from the neo-ventricle, autologous pericardium is used to line the muscular cavity. This not only reduces thrombotic risk, but also adds structural integrity to the artificial chamber. Skeletal muscle ventricles therefore have an advantage over synthetic exo-bionic organs as, they do not add the complications of severe anti-coagulation and furthermore do not suffer from subsequent rupture.[55, 56]

These auto-bionic skeletal muscle ventricles have been demonstrated to function well in an animal model for over 4 years,[57] and have an added ability to permit the successful seeding of autogenous endothelial cells.[58] Haemodynamically, they can pump 464mL/min against an afterload of 80mmHg and a preload of 40-50mmHg, generating 194% of the left ventricular stroke work.[59, 60] After four hours, they can generate 0.68×10^6 erg of stroke work, approximately half that of the left ventricle.[61] Skeletal muscle ventricles can provide a cardiac assist contribution that is at least equal to that of the well established intra-aortic balloon pump (IABP),[62] and at 836 days they can still produce 19% diastolic augmentation.[63]

Other configurations for the skeletal muscle ventricle also exist. These include the pump placed between the left atrium and aorta which can produce a power output that corresponds to 22% of left ventricular power.[64] A left ventricular apex to aorta model also exists where the pump can produce 40-47% of the systemic output and increase the mean diastolic pressure by as much as 73%.[65]

These auto-bionic procedures therefore demonstrate significant potential, and are constantly evolving towards 'real-life' applications. Current developments include muscle conditioning through improved pacing systems and the use of vascular delay[46] that prepares a mobilised muscle in-vivo before final use as a pump.

Pelvic Autobionics

Graciloplasty (Creating a functional anal sphincter) - Gracilis is a muscle that lies medially in the adductor compartment of the thigh. Although it is large in all quadrupeds,[66] in hominids it is small and acts only as a weak adductor. Its role in human locomotion is therefore negligible, and it has been termed light-heartedly by some anatomists as the 'custodes virginittatis'.[67] As a result of this muscle's functional redundancy it has therefore been applied for various uses in reconstructive surgery.[68, 69]

In 1952, Pickrell and colleagues first described the use of applying the gracilis muscle to form a rectal neo-sphincter in the treatment of anal incontinence.[70] Although this had some success, a need for improved continence in patients with congenital and acquired anorectal dysfunction who had sphincter function too poor for the consideration of sphincteroplasty resulted in the development of dynamic graciloplasty (DGP).

In dynamic graciloplasty, the gracilis muscle is explanted and then transposed to encircle the anal canal. The aim of this procedure is to bring about changes in the fast-twitch fatigable (Type II) muscle fibres of gracilis to transform them into slow-twitch, fatigue-resistant (Type I) muscle fibres that more closely resemble the histological characteristics of the internal anal sphincter. The gracilis in its normal state only has 43% type I fibres as opposed to the anal sphincter which has 80% type I fibres.[71] The muscle is 'wrapped' around the anal canal forming either alpha, gamma (most common) or epsilon loops to reflect the patient's pelvic anatomy. An electric neurostimulator placed in the tissue of the lower abdominal wall, and communicates with the gracilis muscle via electrodes. The neurostimulator discharges a current that contracts the muscle (for the majority of the day), however when stimulation is turned off, the muscle relaxes and defecation occurs.

Indications for this operation include congenital anal atresia or spina bifida, whilst acquired conditions include severe neural damage, or some patients who have already undergone abdominoperineal resection or total anorectal reconstruction for anorectal neoplasms. The mechanism of this auto-bionic transformation is that type I and II muscle fibres can be transformed interchangeably depending on the motor neurone supply they receive. Thus transposing a nerve for a type I muscle onto a type II, it will induce changes to adopt type I morphology. Similarly, electrical stimulation of the muscle externally can produce similar effects.[33, 72]

Results for this operation are quoted to deliver continence rates between 35-85%, with a preponderance of higher success rates attributed to centres with higher procedural volumes. Although this procedure can dramatically improve the quality of life of patients when successful, it does carry mortality rates ranging from 0-13%. This auto-bionic procedure does demonstrate some considerable success in the face of significant disease and has demonstrated cost-effectiveness,[73] it's direct competition is the exo-bionic procedure of implanting an artificial bowel sphincter (ABS). Both procedures have similar effectiveness in terms of continence, although the ABS demonstrates increased side effects in 82%-100% of patients compared to 74-82.8% for dynamic graciloplasty.[74, 75] It is clear that both procedures currently have unacceptably high complication rates, and the future of auto-bionic dynamic graciloplasty lies in further advances of muscle adaption (including the use of the Glutei and Sartorius). These auto-bionic neo-sphincters can then be applied in combination with other modalities such as biomaterials, gene therapy and stem cell therapy to augment treatment efficacy.

Pancreatic Autobionics

Roux-en-Y Gastric Bypass (improving insulin sensitivity and release) – The burgeoning pandemic of world obesity coupled with poor results of weight loss pharmacotherapy led to the development of 'so-called' weight loss or bariatric procedures to treat morbid obesity. It was soon realised however that these procedures did far more than simply weight loss. Pories and colleagues published on their series of gastric bypass in obese patients after a 14 year follow-up, reporting that in patients with type II diabetes mellitus, 83% achieved normal glucose level in the absence of medication.[76, 77] This was astounding at the time, as the improvement in glucose metabolism occurred within a few days of surgery before any noticeable weight loss. These findings were subsequently confirmed in numerous other studies. A large meta-analysis of 621 studies with 135,246 patients reported that in these bariatric operations, 78.1% of diabetic patients had complete resolution, and diabetes was improved or resolved in 86.6% of patients.[78] These operations have subsequently been termed as metabolic operations as they do not only deliver anatomical change but also induce metabolic benefits.[79]

The Roux-en-Y procedure (Figure 4) creates a small stomach pouch (<50ml) as a result of surgical partition of the upper part of the stomach. The remaining stomach accompanied by the duodenum and a segment of jejunum ('biliopancreatic limb') is then divided and anastomosed lower down the jejunum, with the segment distal to this forming a 'common limb'. The free segment of jejunum is now anastomosed to the small stomach pouch (gastroenterostomy stoma) to complete the 'Y' shape of the Roux-en-Y thus becoming the 'alimentary limb'. This rearrangement of alimentary organs allows processed food to 'bypass' the main portion of the stomach whilst maintaining the hormonal presence of the stomach within the alimentary tract and also preventing toxic biliary reflux.

These operations achieve weight loss by decreasing energy input (appetite and food intake) but also modulate energy expenditure (increasing metabolic rate) with only minimal impact on calorie absorption.[79-81] Their dramatic effect on diabetes has been proposed to ensue from two main schools. One considers ingested nutrients bypassing the stomach which subsequently releases an altered 'gut hormonal signal' in the lower gut (hindgut hypothesis). Alternatively a lack of nutrients in the main body of stomach may result in 'gut hormonal signals' released from the upper gastrointestinal system (foregut hypothesis). Other factors may also come into play as each operation actually results in five biological changes.[79] These include (1) Bile Flow alteration, (2) Restriction of stomach size, (3) Altered flow of nutrients, (4) Vagal manipulation and (5) Enteric gut and adipose hormone modulation. The so called 'BRAVE' effects.

The gut hormones that are significantly increased by these operations include Glucagon-like peptide-1 (GLP-1) and Peptide YY (PYY). GLP-1 may have an important role in the resolution of diabetes as it protects against pancreatic Beta-Cells Against Apoptosis,[82] and also stimulates cAMP-dependent insulin exocytosis.[83, 84] Furthermore it acts on other systems such as the heart where it can act as an inotrope and may contribute to the beneficial reverse remodelling seen in the heart after these operations.[85] The auto-bionic nature of this metabolic procedure is further demonstrated in a rare group of patients who develop post-operative hyperinsulinaemic hypoglycaemia (nesidioblastosis).[86, 87] In these patients, the pancreas has augmented supra-physiological insulin release, to the extent that some patients need to go on to undergo a partial pancreatectomy so as to maintain normal insulin levels.

Conclusion

The concept of auto-bionics – where the body is enhanced through the application of biological design in re-designing or rearranging inherent body tissue is expanding. Dynamic Graciloplasty, the Ross procedure, Dynamic Cardiomyoplasty, Skeletal Muscle Ventricles and Roux-en-Y gastric bypass are only some contemporaneous examples. These procedures can lead to novel treatments and physiological enhancements not only limiting our need for organ transplantation but also competing successfully against traditional exo-bionic therapies (such as artificial prostheses). The future of this field lies with continued research into inherent body physiology coupled with increased application of this novel area of bionics alongside other therapeutic modalities including genetic modification and stem cell therapy.

Auto-bionics will have an increased role in reconstructive strategies and the treatment of obesity, diabetes, cardiovascular disease and cancer. It has been known since the time of Hippocrates[88] that the nature of getting well is inherent within each individual. The concept of auto-bionics clarifies that the future of mankind's healthcare is not only dependent on external technological advances, but also on how we can apply novel biological principles to transform our body systems using increasingly innovative methods.

Future Perspective

Auto-bionic procedures are likely to increase in volume and variety. The lack of organs available for transplantation and the continuing improvements necessary for conventional exo-bionic procedures will lead to further requirements, adoption and development of auto-bionic concepts. These procedures can be augmented through the use of other regenerative medical technologies including developments in stem cell therapy. Ultimately this will allow the introduction of novel treatment strategies that can be purely auto-bionic or alternatively combination therapies. Specific uses will include the treatment of type II diabetes associated with the worldwide epidemic of obesity, but also for management of diabetic patients at lower weight categories. Auto-bionics will also play an increased role in cardiovascular treatments, cancer and reconstructive strategies.

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Executive Summary

Concept

- Auto-bionics is the application of biological principles to augment or replace physiological functions by manipulation of inherent body tissue/organs.
- Conventional bionics or biomimicry represents Exo-bionics: the application of biological principles to augment or replace physiological functions by electronic or electromechanical components.
- Auto-bionic and exo-bionic therapies can be dynamic or static.
- Auto-bionic therapies can include Tissue Replacement, System Reorganization and Tissue Redesignation.

Examples

- The Ross procedure is auto-bionic as it applies a semi-lunar valve from one location in the heart to another, this offers improved haemodynamics and tensile strength.
- Dynamic Cardiomyoplasty and skeletal muscle ventricles provide auto-bionic cardiac pumping using inherent skeletal muscles.
- Dynamic Graciloplasty can use inherent skeletal muscles to transform their function to provide auto-bionic sphincter activity.
- Metabolic Gastric Bypass offers the auto-bionic resolution of type II diabetes and may hyper-augment insulin release in some cases.

Future

- Auto-bionic procedures can be augmented through the use of other regenerative medical technologies including developments in stem cell therapy.
- Auto-bionics will have an increased role in reconstructive strategies and the treatment of obesity, diabetes, cardiovascular disease and cancer.

Figure 1. Regenerative medicine and surgery

Figure 2. Auto-bionics and Exo-bionics

Figure 3. Cardiac Auto-bionics. (a) Ross Procedure, (b) Dynamic Cardiomyoplasty (c) Skeletal Muscle Ventricle

Figure 4. Pancreatic Auto-bionics

Table 1
Definitions of Auto-bionic and Exo-bionic

Treatment	Definition
Bionics or Biomimicry (conventional)	Application of biological principles to augment or replace physiological functions by electronic or electromechanical components – can be considered as ' Exo-bionics '
Auto-bionics	Application of biological principles to augment or replace physiological functions by manipulation of inherent body tissue/organs