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**REGENERATIVE MEDICINE: AN INTRODUCTION**

Dr. Anthony Atala, M.D.\*

The idea of improving human life through engineering replacement organs is not new. Aviator Charles Lindburgh experimented with the concept in the 1920s in an effort to help his ailing sister-in-law. Today, the need is even greater. Every ninety minutes, a patient dies while on the waiting list for organ transplantation.<sup>1</sup> Since older organs are more prone to failure, the problem will only increase as modern medicine extends the human lifespan.

The ultimate goal of the field of regenerative medicine is to solve the critical shortage of donor organs and tissues available for transplantation. Scientists in this field use the principles of cell transplantation, materials science, and biomedical engineering to develop biological substitutes that can restore and maintain the normal function of damaged or lost tissues and organs. As its name implies, this science takes advantages of the body's natural healing powers.

The first attempt at engineering tissue involved the use of cells for skin coverage in 1981.<sup>2</sup> There were few advances over the next decade because of a host of challenges, including the difficulty of getting cells to multiply outside the body. Once that obstacle was overcome, there have been multiple advances in the field and, today, scientists around the world are working to apply the technology to help patients.

Regenerative medicine is not a single technology or technique.

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\* Anthony Atala, M.D., is the W.H. Boyce Professor and Director of the Wake Forest Institute for Regenerative Medicine, and Chair of the Department of Urology at the Wake Forest University School of Medicine. Dr. Atala is a surgeon in the area of pediatric urology and a researcher in the area of regenerative medicine and tissue engineering.

<sup>1</sup> Salley Satel, Op-Ed., *Death's Waiting List*, N.Y. TIMES, May 15, 2006, at A21.

<sup>2</sup> David A. Diamond & Anthony A. Caldamone, *Endoscopic Correction of Vesicoureteral Reflux in Children Using Autologous Chondrocytes: Preliminary Results*, 162 J. UROLOGY 1185, 1185 (1999).

For example, it can involve injecting functional cells into a damaged area of tissue to stimulate regeneration,<sup>3</sup> such as injecting muscle cells to treat urinary incontinence.<sup>4</sup> Or, natural or synthetic scaffolds can be used to provide a three-dimensional space for cells to form into new tissues with appropriate structure and function.<sup>5</sup> Some scaffolds are designed by nature. For example, a pig's heart valve that has been processed to remove all cells, leaving the support structure intact, can potentially serve as a scaffold for a patient's own cells -- creating a replacement valve that is a perfect match. Other scaffolds are made from "scratch" in the lab using materials such as collagen, the protein found in connective tissue.

One example of how scaffolds are used in tissue engineering is the implantation of laboratory-engineered organs<sup>6</sup> into humans.<sup>7</sup> The goal of this project was to find a better way to replace bladder tissue than the 100-year-old procedure to fashion a new bladder from the intestine. Because the intestine is designed to excrete, using it to hold urine can result in metabolic disorders<sup>8</sup> as well as an increased risk of cancer.<sup>9</sup> The technology to engineer a bladder begins with a small biopsy from the patient's own bladder. Cells that are programmed by nature to become bladder tissue are then extracted and multiplied in the lab. The next step is to place these cells on a bladder-shaped, porous, biodegradable scaffold, where they continue to multiply. The scaffold is then implanted in the patient's body. As the tissue continues to develop and integrates with the body, the scaffold degrades. In essence, the body serves as an incubator and completes the process that was begun in the lab.

The lessons learned through developing the bladder and other technologies are today being applied to a variety of projects. In our own laboratory, for example, scientists are working to grow more than

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<sup>3</sup> *Id.* at 1185.

<sup>4</sup> Alfred E. Bent et al., *Treatment of Intrinsic Sphincter Deficiency Using Autologous Ear Chondrocytes as a Bulking Agent*, 20 *NEUROLOGY & URODYNAMICS* 157, 158 (2001).

<sup>5</sup> Anthony Atala et al., *A Novel Inert Collagen Matrix for Hypospadias Repair*, 162 *J. UROLOGY* 1148, 1148 (1999); see also Abdel W. El-Kassaby et al., *Urethral Stricture Repair with an Off-the-Shelf Collagen Matrix*, 169 *J. UROLOGY* 170, 170 (2003).

<sup>6</sup> Frank Oberpenning et al., *De novo Reconstitution of a Functional Mammalian Urinary Bladder by Tissue Engineering*, 17 *NATURE BIOTECHNOLOGY* 149, 149 (1999).

<sup>7</sup> Anthony Atala et al., *Tissue-engineered Autologous Bladders for Patients Needing Cystoplasty*, 367 *LANCET* 1241, 1242 (2006).

<sup>8</sup> Martin Kaefer et al., *Continent Urinary Diversion: The Children's Hospital Experience*, 157 *J. UROLOGY* 1394, 1395, 1396 (1997).

<sup>9</sup> Trevor M. Soergel et al., *Transitional Cell Carcinoma of the Bladder Following Augmentation Cystoplasty for the Neuropathic Bladder*, 172 *J. UROLOGY* 1649, 1649 (2004).

twenty tissues and organs, including the heart, lungs, blood vessels, heart valves and pancreas. Tissues are at different stages of development, with some already being used clinically, a few in preclinical trials, and some in the discovery stage.

Recent advances in the field of regenerative medicine include an international team's success implanting a section of engineered trachea, created with stem cells from the patient's bone marrow, in a woman with tuberculosis.<sup>10</sup> This advance is exciting because it illustrates the potential for using stem cells in tissue engineering and of using donor tissue as scaffolds. In this case, the trachea scaffold was made by removing cells from a section of trachea from a deceased donor. Of course, as with any new technology, we must be cautious. This has been applied to only one patient and the follow up period was relatively short.

Just last month, Canadian scientists reported success growing new blood vessels in laboratory animals.<sup>11</sup> To generate the tissue, the scientists injected a collagen-based material that attracts new cells. This injectable material is essentially a "smart scaffold" in that it attracts particular cells in the blood that can form the lining of blood vessel walls. Once the cells are there, the material helps keep them alive and prompts them to become blood vessels.

All of these examples point out the vital role that cells play in regenerative medicine. It is ideal to use a patient's own cells because the resulting organ/tissue is a perfect match and patients don't need powerful anti-rejection medications. For patients with extensive end-stage organ failure, however, a tissue biopsy may not yield enough normal cells for expansion and transplantation. Additionally, for organs such as the heart and pancreas, scientists have not yet learned how to expand these cells outside the body. In these situations, stem cells are envisioned as being an alternative source of cells. True stem cells exhibit two remarkable properties: the ability to self-renew and the ability to differentiate into many specialized cell types.<sup>12</sup> According to the Centers for Disease Control ("CDC"), an estimated three thousand Americans die every day of diseases that could have been treated with stem-cell-derived tissues.<sup>13</sup>

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<sup>10</sup> Toshihiko Sato & Tatsuo Nakamura, *Tissue-engineered Airway Replacement*, 372 LANCET 2003, 2003 (2008).

<sup>11</sup> Erik J. Suuronen et al., *An Acellular Matrix-bound Ligand Enhances the Mobilization, Recruitment and Therapeutic Effects of Circulating Progenitor Cells in a Hindlimb Ischemia Model*, 23 FASEB J. 1447, 1454 (2009).

<sup>12</sup> Ali H. Brivanlou et al., *Setting Standards for Human Embryonic Stem Cells*, 300 SCIENCE 913, 913 (2003).

<sup>13</sup> Robert P. Lanza et. al., Letters, *The Ethical Reasons for Stem Cell Research*, 292 SCIENCE 1299, 1299 (2001), Robert P. Lanza, et al., *Generation of Histocompatible Tissues Using Nuclear Transplantation*, 20 NATURE BIOTECHNOLOGY 689, 689

Stem cells can be derived from discarded human embryos (human embryonic stem cells) and from adult sources (bone marrow, fat, skin). In addition, a new type of stem cell has been identified in placenta and amniotic fluid that is believed to represent a developmental stage between embryonic and adult stem cells.<sup>14</sup> These amnion cells are distinct from human embryonic stem cells, but resemble them in two important ways. They can be easily expanded in the laboratory and can be induced to differentiate into multiple specialized cell types. However, unlike embryonic stem cells, the amnion cells do not form tumors when they are transplanted. Also, since they are easily obtained from afterbirth, they are non-controversial.

In addition to providing scientists a ready source of stem cells for research, a national bank of amnion cells -- with approximately 100,000 specimens -- could theoretically provide up to ninety-nine percent of the population with a perfect genetic match for transplantation. As science moves forward, the cells can potentially be used to engineer tissues or organs specifically for each patient

Beyond the options discussed above, there are yet other ways to obtain stem cells. In fact, science has advanced to the point that the debate over whether it is appropriate to use embryonic cells has become almost obsolete. For example, a recent, exciting advance is the successful transformation of adult cells into stem cells through a type of genetic "reprogramming."<sup>15</sup> This technique, which causes a normal cell to become de-specialized and revert back to being a stem cell, does not involve the use of embryos. Stem cells generated by reprogramming would be genetically identical to the original cell and would not be rejected. It has recently been shown that reprogramming of human cells is possible.<sup>16</sup> Although this is an exciting phenomenon, we have limited understanding of the mechanism.

Another source of stem cells is therapeutic cloning, which is also called nuclear transplantation and nuclear transfer. Most scien-

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<sup>14</sup> Paolo De Coppi et al., *Isolation of Amniotic Stem Cell Lines With Potential for Therapy*, 25 NATURE BIOTECHNOLOGY 100, 100 (2007); Paolo De Coppi, et al., *Amniotic Fluid and Bone Marrow Derived Mesenchymal Stem Cells can be Converted to Smooth Muscle Cells in the Cryo-Injured Rat Bladder and Prevent Compensatory Hypertrophy of Surviving Smooth Muscle Cells*, 177 J. UROLOGY 369, 374 (2007).

<sup>15</sup> See Kazutoshi Takahashi & Shinya Yamanaka, *Induction of Pluripotent Stem Cells from Mouse Embryonic and Adult Fibroblast Cultures by Defined Factors*, 126 CELL 663, 663 (2006); Marius Wernig et al., *In Vitro Reprogramming of Fibroblasts into a Pluripotent ES-cell-like State*, 448 NATURE 318, 318 (2007); Kazutoshi Takahashi et al., *Induction of Pluripotent Stem Cells from Adult Human Fibroblasts by Defined Factors*, 131 CELL 861, 861 (2007); Junying Yu et al., *Induced Pluripotent Stem Cell Lines Derived from Human Somatic Cells*, 318 SCIENCE 1917, 1917 (2007).

<sup>16</sup> Wernig et al., *supra* note 15, at 318.

tists agree that the cloning of individuals -- known as reproductive cloning -- is off-limits. The goal of therapeutic cloning, on the other hand, is not to create a new individual, but to create a line of stem cells that can be used in therapy. The process involves the introduction of a nucleus from a donor cell into an egg cell with the nucleus removed. The egg is prompted to divide, generating an early-stage embryo with a genetic makeup identical to that of the donor.<sup>17</sup>

These early stage embryos are used to produce embryonic stem cell lines whose genetic material is identical to that of its source. These cells have the potential to become almost any type of cell in the adult body, and thus would be useful in tissue and organ replacement applications.<sup>18</sup> While promising, nuclear transfer technology has certain limitations that require further improvements before it can be widely applied. Currently, for example, the efficiency of the overall cloning process is low.

The variety of stem cell types and sources illustrates an important point about the future of regenerative medicine. Just as it is likely that all types of stem cells will play a role in regenerative medicine, it is likely that no one regenerative medicine technology is going to be best for all patients. One day, there may be a boutique of technologies that physicians and scientists can select from based on a patient's needs. For example, it is difficult to predict which form of regenerative medicine will eventually be used to help patients with damaged heart muscle. Will it be best to inject stem cells that will find their way to the damaged tissue? Or will we create patches of tissue in the lab that can be used to mend a poorly functioning organ? As we are pursuing solutions for patients, we should keep in mind that in many cases, we will not need an entire new organ to dramatically improve the patient's life. Our interest should not be specifically to build a human heart, or any organ for that matter, but to make patients better -- no matter what strategy is used.

As the field moves forward and advances happen more rapidly, one of our biggest challenges will be to strike a balance between getting therapies to patients quickly, while at the same time ensuring that these new treatments are safe. There is nothing worse for a physician than to have a patient who is out of options. On the other hand, our professional oath obligates us to "do no harm." This is a delicate balance, and the future of the field depends on us getting it right. In our striving to help patients, we must never compromise safety and risk tainting our field and the promise it holds.

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<sup>17</sup> Lanza et al., *supra* note 13 at 689.

<sup>18</sup> Konrad Hochedlinger & Rudolf Jaenisch, *Nuclear Transplantation, Embryonic Stem Cells and the Potential for Cell Therapy*, 349 NEW ENG. J. MED. 275, 275 (2003).

