Paving the Way for Bladder Bioengineering
By Stefania Ana

You're in class and all of a sudden you've had an accident on yourself. Your face gets red due to the embarrassment, but in reality the social embarrassment is nothing compared to the real issue. Children with disorders that arise prior to birth, such as spina bifida, and those with spinal cord injury often suffer the consequence of bladder dysfunction. Children with bladder dysfunction may exhibit frequency, urgency, retention, and lack of control over urination. This is caused when the bladder is unable to stretch properly, which prevents it from expanding as it fills with urine and leads to loss of bladder control.. This not only causes social embarrassment but also results in the misery of infection, bladder stones, and renal injury [1,2].

The standard treatment for children with bladder dysfunction is bladder augmentation. Bladder augmentation is a surgical procedure that makes the bladder larger and more elastic [3]. During a bladder augmentation surgery a cut is made along the bladder and sections of the intestines are used to cover the cut when enlarging (augmenting) the bladder (Fig. 1). However, there are short-and-long-term complications with bladder augmentation. Short-term complications can include recurrent urinary tract infection and bladder stone formation, which may cause painful and frequent urination or completely block any urine from leaving the body [4]. A potential long-term complication is adenocarcinoma, which is a cancerous and often lethal tumor that can appear 10 years after bladder augmentation surgery [5].

So what can be done to help alleviate the thousands of children suffering from bladder dysfunction and to sidestep the negative consequences of bladder augmentation? In the past couple of decades, researchers have been trying to find the solution to this question through bioengineering. The idea is to create a bladder graft (piece of living tissue) that can contract like a bladder and look like a bladder (have the right cell types) by using a patient's very own cells! Bioengineered bladder grafts (BBGs) have been created and tested on small animal models, such as mice; the BBGs instead of intestines were very successful in these experiments.. The quick success of BBGs in mice led Atala et al. to perform a clinical trial on 10 children in 2006. Sadly, the trial was a total disappointment—after 3 years, 4 of the 10 children started to experience urine leakage. Thankfully, none of the children died or suffered serious injury [6]. While it is a huge relief that inserting a BBG doesn't kill humans, it also did not get rid of the bladder dysfunction in any of the children tested.

How could this up-and-coming BBG lead to complete failure? The experiments done on mice beforehand held promising results, which paved the way to the creation of human bladder grafts made from patients' own cells. What was missing? Vascularization. Vascularization is the development of blood vessels. These new BBGs had everything except blood vessels. In large human BBGs, the ingrowth of blood vessels from the native bladder is not fast enough for timely vascularization of the graft. Without a blood supply, BBGs do not become nourished fast enough and become ischemic and contracted. Ergo, a failed BBG in human clinical trials.

This is where we at Dr. Eric Kurzrock's lab step in. We believe that if a BBG has pre-existing blood vessels, then maybe those engineered vessels in BBGs will be able to connect to those of the native bladder and nourish the graft soon after transplant. So how do we do it?

Our lab is currently using stem cells to revascularize (and eventually restore blood circulation to) bioengineered bladder tissue. Stem cells are cells that can self-renew and become any cell in the body when given certain signals. Everyone has stem cells throughout their body

and it is our intention to use endothelial stem cells to create blood vessels within BBGs. Once the BBG has pre-existing vessels, it will be implanted into the bladder to see if and how quickly the pre-existing vessels in the BBG can fuse with the host bladder vessels to provide a timely blood supply to the graft.

Altogether, our lab has already shown that this process works on mice. Therefore, we do know that having pre-existing vessels in the BBG will allow for a better blood supply; thus, creating a more functional and safe bladder graft. Pre-existing vessels in BBGs could be the key for bladder bioengineering. For this reason, our lab will proceed with larger animal models (pigs). If all goes well, the possibility of human clinical trials for treating children with spina bifida or spinal cord injury is on the near horizon.