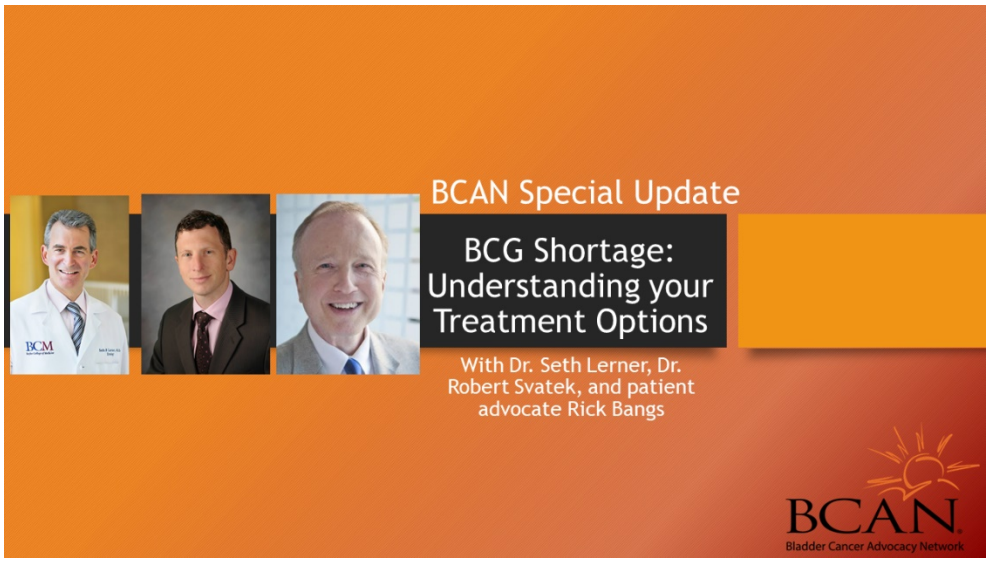
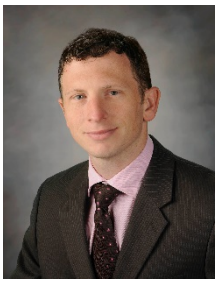


Meet our Presenters

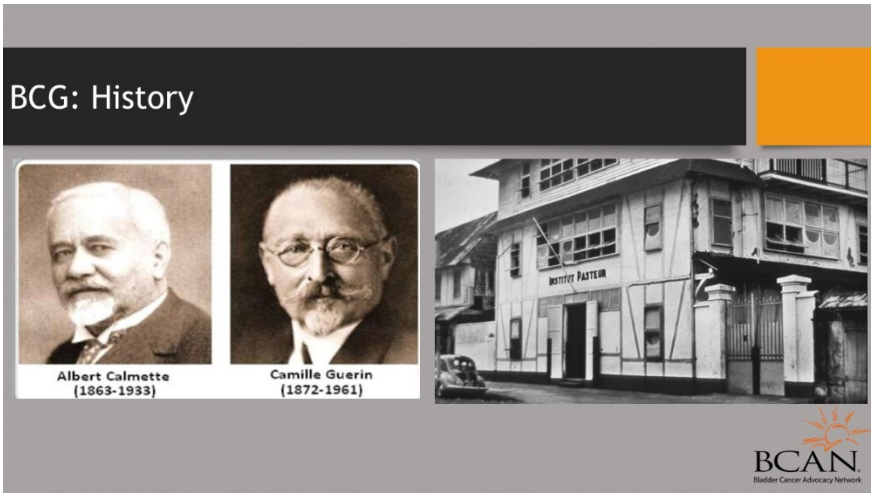
Dr. Seth Lerner is Professor of Urology and holds the Beth and Dave Swalm Chair in Urologic Oncology in the Scott Department of Urology at Baylor College of Medicine. He's co-chair of the National Cancer Institute's Bladder Cancer Task Force and Bladder Cancer Disease Working Group for the Cancer Genome Atlas Project. He chairs the local bladder cancer committee of SWOG and serves on the Board of Directors for the Bladder Cancer Advocacy Network.



Dr. Robert Svatek is an Associate Professor and Chief of the Division of Urologic Oncology at the University of Texas Health, San Antonio. His practice is devoted to the care of bladder cancer patients, and he's built a center of excellence for invasive bladder cancer for patients from the South and Southwest Texas region. Dr. Svatek is actively involved in clinical trials for bladder cancer and runs an NIH funded Cancer Immunology lab. He focuses on the role of innate immunity in mediating cancer immune surveillance and cancer therapy.

Mr. Rick Bangs is bladder cancer and prostate cancer survivor and has worked as a patient advocate in a variety of roles, including research advocacy, government lobbying, educational support, support groups, one-on-one support and fundraising. As a research advocate, he serves as the member of the National Cancer Institute Council of Research Advocates, Co-Chair of the NCI Patient Advocate Steering Committee, one of two NCI genitourinary specific scientific steering committee patient advocates that ended up in the end of last year. And he's also served as NCI Cancer Care Direct Delivery, Scientific Steering Committee, Patient Advocate and Chair of the SWOG Patient Advocate Committee.

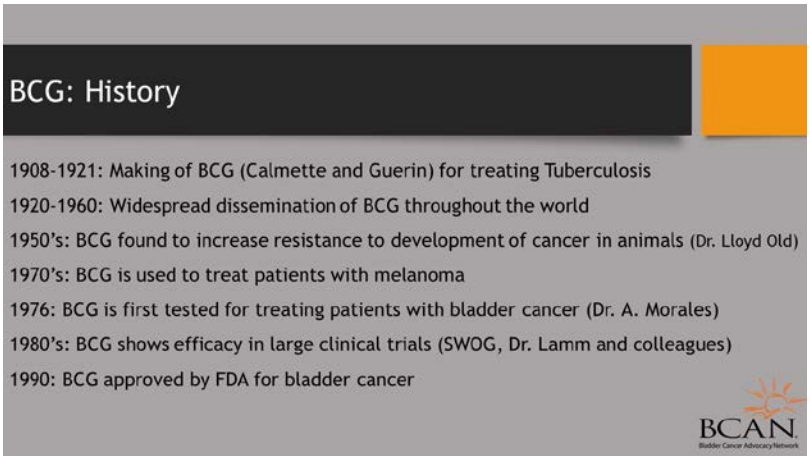
Stephanie C: We're excited to have all of you with us this evening. Thanks so much for joining us. I did want to provide a quick update as of March 25, 2019, on what BCAN has been doing and what we know about the BCG shortage. We have met, and will continue to meet with Merck to encourage quicker production of BCG to meet the needs of all BCG patients. We're meeting with the FDA Center for Biologic Evaluation and Research to encourage strains of BCG used in other countries to be allowed to be introduced into the United States. We're meeting with other pharmaceutical companies that want to introduce new strains and alternative immunotherapy treatments to fill the gap and meet patients' needs. BCAN has been asking the FDA to fast track the approval process to get those new strains into the United States market more quickly. Please watch for updates on our website, www.bcan.org\2019-bcg-shortage-bladder-cancer. We will keep you updated there. Now, I am going to turn this over to Dr. Svatek, who will introduce you a little bit to the background of BCG.



Robert Svatek: BCG was originally developed, not for bladder cancer, but for the vaccination against and prevention of tuberculosis. At the beginning of the 20th century, tuberculosis was rampant, and effective treatment such as the antibiotics that we have today were not available. What was clear though was that if a person was infected with tuberculosis and survived the infection, they would then be subsequently immune to any additional exposure. This is the idea behind vaccinating people prior to the exposure. This is the power of our immune system to form a type of memory towards particles that are foreign, including bugs such as tuberculosis. Dr. Albert Calmette and Dr. Camille Guerin worked tirelessly over two decades to develop a vaccine to treat tuberculosis. How did they do this, and what are the features of an effective vaccine? An effective vaccine requires two things. Number one, it must be a bacteria or an organism that is weakened enough so that it doesn't cause any illness when it's given, and number two is that it still must be intact enough to trigger a good immune response.

For their discovery of BCG, they grew bacteria in their laboratory, actually on potato slices, and they used various animal models to test their vaccine. So the vaccine changed over years, and they would test it in different models until they developed the ideal conditions, which are again, that it's weak enough not to hurt the animal but strong enough to elicit an immune response. In 1921, they had finally succeeded in creating BCG, and they performed the first vaccination on an infant whose mother was severely afflicted with tuberculosis. The infant survived and soon this new vaccine, which was named Bacillus Calmette Guerin, or BCG, in recognition of these scientists, was then distributed all over the world.

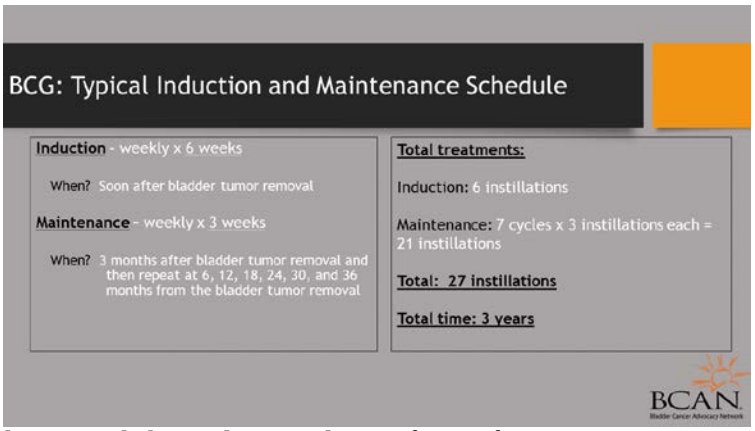
Sadly, Albert Calmette, who died in 1933, died without having had the satisfaction of knowing the widespread success of BCG in preventing tuberculosis, not to mention the enormous benefit that BCG would have for patients suffering from bladder cancer. At the time of his death, he was still defending the safety and the value of BCG.



From its origins in 1921, how did we get to using BCG for treating bladder cancer? As I mentioned, in 1921 BCG was widely distributed throughout the world to various physicians and scientists for use to prevent tuberculosis and for use to do research. This was sent to Russia, Japan, South America, North America, and its use to prevent tuberculosis was slowly and gradually adopted over the next century. Today in the United States, it's not used routinely, but in other parts of the world such as Africa and parts of Europe, it's still used to prevent tuberculosis, and infants are given the vaccine.

Robert Svatek: Important discoveries were made in the 1950's that led to experimentation with BCG. One important discovery was the idea or the fact that some animals that had been given BCG were found to be resistant to tumor growth and to subsequent tumor challenge. And these observations were later carried out and made in humans as well. The idea then is that if BCG can somehow enable the body to prevent tumor growth, then maybe we could use BCG to actually treat tumors.

The first tumor that was treated with BCG was a skin tumor, melanoma. And the BCG was actually injected directly into the melanoma tumors, and there are reports of spontaneous resolution or disappearance of melanoma skin tumors through BCG injection. BCG is no longer used to treat melanoma. There's different medications used now, but that early observation prompted investigations into other tumor types, including bladder cancer.



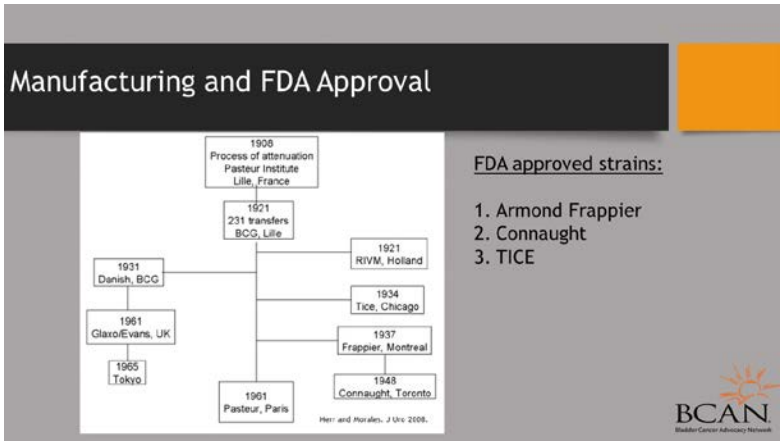
What BCG needs to work, is it needs close contact with the tumor. In bladder, we have this remarkable ability to administer agents directly to the bladder mucosa or directly to bladder tumors through a catheter. In the 1970's, Dr. Morales from Canada performed the first human trial using BCG installation and had some remarkable observations of efficacy. Subsequently, large clinical trials were conducted, including a large important trial by the Southwest Oncology Group, which showed efficacy of BCG and initiated the widespread use of BCG for preventing bladder cancer and for treating certain types of bladder cancer. In 1990, the FDA approved BCG for treatment of bladder cancer. Now, we can talk about how BCG is given and why that's done. The BCG is often lumped, the treatment is lumped into two different courses. The induction and the maintenance. Induction is the initial treatment phase. It's a six-week treatment phase. BCG is given, as I said, through a catheter. A Foley catheter is placed into the bladder and it's instilled in a solution of water and allowed to just rest there in the bladder for a period of two hours. And then the Foley catheter is removed, the BCG is discarded after two hours. And this is given

weekly for six weeks as the initial induction course. That is often done relatively soon after the initial diagnosis. The bladder tumor is removed by a resection, endoscopic resection. We often call it transurethal resection, and then enough time is allowed for the bladder to heal. That can be anywhere from two to six weeks, and BCG is then started and the installation is performed in the clinic once a week for six weeks.

Maintenance treatments are given once a week for three weeks. And they're roughly given every six months, although we add an additional one at three months following the tumor removal. The scheme there is that the maintenance treatments are given at three months and then six months from tumor removal and then every six months for three years.

Robert Svatek: Why give so much BCG? Is that really necessary? There's clear evidence that giving maintenance BCG, this three years of treatment, can significantly and substantially decrease the likelihood of tumor relapse. That was shown in another large SWOG trial looking at the benefit of maintenance therapy. Even though it's sometimes onerous to give that amount of BCG and sometimes it takes a lot of effort on both the patient and the physician to do so, there's clear level one evidence that this is effective.

The question I ask is so are all BCG vaccines the same? And why do we have more than one BCG vaccine? As early as 1921, the cultures of BCG were distributed by the Pasteur Institute to laboratories around the world. Implementation of BCG varied from country to country.



There are several fascinating histories that have been written about these specific strains and how they revolutionized tuberculosis in the country. But because BCG was a live vaccine, it's a live bacteria, it was necessary to culture this in fresh media every few weeks. Despite efforts to standardize the growth and the preparation of the media, there were lots of different conditions that were used in these different production facilities throughout the world. What happened was that changes in the BCG bacteria took place in different countries throughout the world. These genetic changes stayed with the bacteria, and as a result of decades and decades of change, we now have bacteria that are very different.

In the 1960s, the system was then converted to where there was a standardization and what we call using seed lots, so that 1961, the changing or the genetic nuances and changes of the BCG stopped. But before that time, all the changes took place. Strains that are currently used today, such as Tokyo strain and TICE strain, they're different because of these evolutionary changes that took place in different labs. Next slide.

Why are there shortages? Supply does not meet the demand. The supply and demand is one potential reason for a shortage. Previously, another strain was made by a company out of Canada, the Connaught strain, and that company no longer makes Connaught. There was also another company a longer time back that made another strain called the Armond Frappier. That company no longer makes that strain.

In the United States, patients are limited to one manufacturer, Merck, that makes the TICE BCG strain. And now Merck is supplying TICE BCG for many countries throughout the world, and it's just a matter of the supply not meeting the demand.

Growing BCG and propagating it is difficult. It takes expertise in this area. As you can imagine with a live bacteria, if there's any contamination, that could have serious consequences to the production. Contamination and factory problems such as that have led to partial shutdown of factories that has then resulted in manufacturing problems. Also, because of the prior scare in experience in dealing with shortages, there's been hoarding. Big hospitals can acquire large amounts of BCG and store it, which can result in temporary shortages.