

Alvaro Morales, Kingston, Canada

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March 2023 marked the 50th year from the first intravesical Bacillus Calmette–Guérin (BCG) instillation in a patient with bladder cancer, and this was celebrated at the 4th Annual Bladder Cancer Forum, held in Kingston, Canada. A major highlight of this meeting was a special lecture (<https://www.cua.org/program/16937>) by Dr Alvaro Morales in which he shared his personal perspectives on the 50 years of BCG in bladder cancer with scientists, trainees, and urologists from across North America.

BCG immunotherapy remains the gold standard treatment for non-muscle invasive bladder cancer (NMIBC). This groundbreaking treatment strategy was introduced to the treatment of patients with NMIBC by Dr Alvaro Morales, a urologist at the Kingston General Hospital, Queen's University. Following the initial successes and failures of BCG immunotherapy in large, randomized clinical trials across multiple cancer types, Alvaro Morales, was enthusiastic about bringing this treatment approach for patients with NMIBC in early 1970s.

Alvaro was born and raised in Colombia. After obtaining his undergraduate medical training from the Javeriana University in Bogota, he moved to the United States and undertook post-graduate training in surgery in Washington DC and Boston. He continued with further training in Toronto, Kingston, and Aberdeen, and then completed a fellowship at the Laboratory of Immunodiagnosis at the National Cancer Institute in Bethesda MD. It was during his training in the United States that Alvaro became interested in the anti-tumor effects of BCG.

In 1972, Alvaro was appointed as a faculty member in the Department of Urology at the Kingston General Hospital, Queen's University, by Andrew Bruce. Alvaro's inspiration for bringing BCG to bladder cancer treatment was the 5 principles underlying the anti-tumor efficacy of BCG established by Zbar and colleagues in the late 1960s[1-3]: (1) limited size of the tumor, (2) the ability to mount an immune response to mycobacterial antigens, (3) presence of sufficient number of viable bacteria in the preparation, (4) contact between



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BCG bacteria and cancer cells, and (5) development of immune response against tumor-associated antigens. According to Alvaro, each of these 5 features perfectly aligned with the desirable local environment present in the bladder of intermediate and high-risk patients with NMIBC.

BCG was brought to Canada in 1925 by Armand Frappier, at the University of Montreal, to conduct research on tuberculosis[4]. Alvaro was aware of the population-based observational study by Frappier's group in which children receiving BCG vaccine experienced 50% reduction in leukemia incidence[5]. This study prompted Alvaro to access lyophilized BCG from the Frappier Institute for a clinical trial that he initiated in 1973 at the Kingston General Hospital, Canada, in which 9 patients were enrolled. He developed a BCG treatment schedule primarily based on immunological principles as well as the initial packaging of the vaccine vials by Frappier Institute. These 9 patients did not experience recurrence after receiving treatment with 6 intravesical weekly doses of BCG. Following the first

publication by Alvaro Morales on the success of BCG immunotherapy in 1976[6], this treatment approach was validated in 2 large, randomized trials sponsored by the American National Cancer Institute[7], approved by the FDA for treatment of carcinoma in situ, and adopted by urologists across the world. Of note, Alvaro faced a few initial challenges in securing funding to initiate this first BCG trial in patients with NMIBC. His application to obtain funding support from the Medical Research Council of Canada was rejected with feedback that this treatment approach is a “throwback to the stone age of immunology.” The first BCG trial was later supported by the Cancer Institute of New York. This success was followed by additional funding from the Ontario Cancer Treatment and Research Foundation for the subsequent remarkably efficacious trial on patients with carcinoma in situ, for which no other treatment besides cystectomy was then available[6].

Donald Lamm with investigators from the South West Oncology Group, further developed the 3-week maintenance schedule that was added to the initially established induction schedule of 6 weekly doses[8]. After close to 5 decades of continuous success, BCG remains to be matched or surpassed by any novel therapeutic. In a recent publication, in addition to highlighting the major milestones in improving response to BCG, Alvaro shared the letter written to him by the daughter of Professor Camille Guérin, thanking him for developing this treatment for bladder cancer after she had received 24 instillations for her own treatment of NMIBC[9].

In 1982, Alvaro Morales became the head of the department of urology and continued in this position until 1997. He served as the president of the Canadian Urological Association in 1993–1994. Following retirement from clinical practice Alvaro established the Center for Applied Urologic Research at Queen’s University in 2004.

For his seminal contributions in the field of urology, he received several awards including the CUA *Lifetime Achievement award* in 1999, *Yamanouchi* (renamed the *Mostafa Elhilali*) award from the Société Internationale d’Urologie (2002), *the William B Coley medal from the*

Cancer Research Institute of New York (1992), *the Hugh Hampton Young award of the AUA and the Colombian Order of Merit*. In 2011, Alvaro Morales was appointed to the Order of Canada, the highest accolade for Canadians who make extraordinary contributions to the nation. Eventually he developed other related interests that included endocrinological aspects of male aging and the effect of androgens in prostate cancer. Alvaro has published over 340 papers and 2 books on his areas of interest. Alvaro’s peers and colleagues describe him as a humble leader and a role model for several of his trainees and surgeon scientists. Undoubtedly, this Giant in Urology has made one of the most significant contributions in the treatment of patients with bladder cancer.

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