

# [Modifying the non-muscle invasive bladder cancer immune microenvironment for opti...](https://assignbuster.com/modifying-the-non-muscle-invasive-bladder-cancer-immune-microenvironment-for-optimal-therapeutic-response/)

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## Introduction

In addition to malignant cells the TME is also made up of other non-transformed cells and secreted extracellular components. The interactions between the tumor cells and the tissue microenvironment are such that they regulate tumor progression but also determine cancer treatment responses. In particular, the tumor microenvironment often limits the infiltration and function of effector T cells into the tumor, recruiting myeloid derived suppressor cells (MDSCs), tumor associated macrophages (TAMs) and regulatory T cells (Tregs), providing an immunosuppressive niche to help cancer cells escape from immune surveillance ( [1](#B1) , [2](#B2) ). Understanding the complex interplay of the components that make up the tumor microenvironment can help inform on strategies to modulate the tumor microenvironment to be more immunogenic resulting in enhanced immune responses and improved therapeutic outcomes.

## The Gold Standard Immunomodulatory Approach to Treat NMIBC: Intravesical BCG

One of the oldest such immunomodulatory approaches and the gold standard treatment for non-muscle invasive bladder cancer is serial intravesical instillations with bacillus Calmette-Guerin (BCG) ( [3](#B3) , [4](#B4) ). Effective BCG therapy has been shown to prevent or delay tumor recurrence and progression and this has been attributed to its ability to induce a massive influx of inflammatory cells (Th1-polarized lymphocytes and neutrophils), the generation of classically activated resident tissue macrophages (M1), the production of Th1 cytokines (IFNγ, IL-12, and TNF-α) and the generation of anti-tumor targeted Th1-mediated cytotoxic responses ( [5](#B5) – [7](#B7) ). However, around 30% of patients are unresponsive to BCG therapy and increasing evidence points toward the pre-existing immune tumor microenvironment influencing the BCG response ( [8](#B8) ).

As is the case for many solid tumors, the tumor microenvironment of non-muscle invasive bladder cancer is characterized by the presence of pro-inflammatory cells (such as macrophages, myeloid-derived suppressor cells, regulatory T cells, dendritic cells, mast cells, neutrophils, and lymphocytes) and cytokines (such as tumor necrosis factor-α and interleukins) both in the supporting stroma and in tumor areas. Many of these cell types have been studied to investigate their influence on outcomes following BCG immunotherapy. Several published reports have provided evidence that a predominance of immunosuppressive cell types are associated with BCG immunotherapy failure. In particular, the presence of M2-like tumor associated macrophages (TAMs) has consistently been associated with shorter recurrence-free survival and thus a poor response to BCG ( [7](#B7) , [9](#B9) – [11](#B11) ). In NMIBC these TAMs are induced and maintained by Bone Morphogenetic Protein 4 (BMP4) secreted by the tumor cells ( [12](#B12) ). They are able to suppress adaptive immunity, support tumor growth and angiogenesis and aid cell migration, invasion and metastasis ( [13](#B13) ).

Whilst the TAMs are localized in the stroma-tumor margin of NMIBC, infiltrating the tumor area in high-grade tumors, another immunosuppressive cell type the Tregs localize in the stroma around the cancer lesion regardless of tumor stage and grade ( [9](#B9) ). High Treg counts were shown to be an independent predictor for recurrence following BCG treatment ( [7](#B7) , [9](#B9) ). Whilst the above studies focused on immunohistochemical analysis of the NMIBC tissue microenvironment, another study characterized immune cell populations in the urine of patients undergoing BCG instillations for the treatment of NMIBC as a surrogate for the bladder tumor microenvironment ( [14](#B14) ). They observed an infiltration of neutrophils, T cells, monocytic myeloid-derived suppressor cells (M-MDSCs) and group 2 innate lymphoid cells (ILC2), cells that have been shown to play a part in regulating tissue homeostasis during infection, chronic inflammation, metabolic disease and cancer ( [15](#B15) ). There was a lower recurrence-free survival in patients with a T cell-to-MDSC ratio of <1 than in patients in which the ratio was > 1. This difference between patient groups was even present before BCG therapy. Bladder tumor cells cultured *in vitro* with BCG could shift ILCs toward the ILC2 phenotype producing the Th-2 cytokine IL-13 which allowed the recruitment and immunosuppressive function of monocytic cells.

Amongst the robust immune response induced by BCG therapy, *in vitro* and *in vivo* studies have suggested a role for NK cells in BCG-induced cytotoxicity ( [16](#B16) – [18](#B18) ). Brandau et al. showed *in vitro* that BCG-activated killer (BAK) cells, of which NK cells were the major effector cell population, displayed substantial cytotoxicity against bladder tumor cells. Furthermore, using a syngeneic orthotopic murine bladder cancer model they demonstrated in NK-deficient beige mice and in mice treated with anti-NK1. 1 monoclonal antibody that BCG therapy was completely ineffective, suggesting a key role for NK cells during BCG immunotherapy ( [19](#B19) ).

As well as detecting a diverse infiltrate of innate and adaptive immune cells including the above mentioned cell types, another study reported a significant role for IL-17 positive mast cells in influencing the outcomes from BCG therapy ( [20](#B20) ). Patients with carcinoma *in situ* (CIS, high grade cancer cells that are only in the innermost layer of the bladder lining) with higher numbers of IL-17+ mast cells showed significantly longer event-free survival after intravesical BCG therapy than patients with less IL-17+ mast cells. This significant effect was only observed in patients who underwent intravesical BCG treatment suggesting that BCG amplifies the beneficial effects associated with increased numbers of IL-17+ mast cells.

Clearly the interactions between cancer and immunity are highly complex and multifactorial and in particular we still need to have a better understanding of the mechanisms hindering efficient constitutive and/or treatment-induced immune responses to tumors. Currently, in NMIBC, there are no reliable biomarkers which allow prediction of the efficacy of the BCG induced anti-tumor response despite many attempts to look at the immune response in bladder tissue before and after BCG treatment. This may be reflective of the fact that many of the studies to date looking at the immune response to BCG treatment have focused on individual cell types using traditional single immunohistochemical stains rather than performing a multiplex comprehensive analysis of both cellular and non-cellular immune components. With the introduction of new technologies that allow for a more global analysis of complex disease states a more comprehensive picture of the roles and interactions between these different components and their influence on therapies should be revealed. This will allow for more informed treatment strategies on how best to immunomodulate particular bladder cancer microenvironments to achieve the optimal therapeutic outcomes.

## The Urinary Microbiome: A Potential Emerging Factor in the Immunomodulation of NMIBC

Whilst urologists have been using BCG for over 40 years to manipulate the bladder microbiome to treat NMIBC, the patient's own pre-existing bladder microbiome may have a role not only in the development of bladder cancer but also in its response to immunotherapies ( [21](#B21) ). A greater understanding of the potential dysbiosis–the imbalance or alteration of bacterial composition of microbiota–in bladder cancer could lead to the bladder microbiome of patients being used as a modifiable way to optimize response to immunotherapy. Research to date suggests that the bladder microbiome may modulate the bladder microenvironment by various mechanisms. Firstly, bacterial strains have been shown to reduce mucosal inflammation due to inhibition of the NF-κB pathway, IL-6, and IL-8 ( [22](#B22) ). This action could affect immunotherapies e. g., BCG that rely on the initiation of a local inflammatory response. Furthermore, other studies have shown that certain bacterial species such as *Lactobacillus iners* , one of the prevalent genera detected in the human urinary microbiome ( [23](#B23) ), may be superior at binding fibronectin thus out-competing BCG whose activity relies on binding to urothelial fibronectin ( [24](#B24) ). To date, there have been few studies which have looked at the role of the urinary microbiome in bladder cancer. One of the first studies comparing the microbiome of urine specimens from healthy individuals ( *n* = 6) versus urothelial carcinoma patients ( *n* = 8) using 16S sequencing found that the abundance of the genus Streptococcus was most often significantly elevated in urothelial carcinoma patients ( [25](#B25) ). In contrast, Popovic et al. reported no significant differences in microbial diversity or overall microbiome composition in a study comparing the voided urine of 12 UCC patients to 11 controls using 16S sequencing, although did note that *Fusobacterium* , a genus associated with colorectal cancer, was enriched in the bladder cancer group ( [26](#B26) ). A third study, comparing 31 male UCC patients to 18 healthy controls using 16S sequencing of midstream voided urine showed an enrichment of some bacterial genera ( *Acinetobacter, Anaerococcus* , and *Sphingobacterium* ) and decrease of other bacterial genera ( *Serratia, Proteus* , and *Roseomonas* ) in the cancer group when compared to the non-cancer group. A further finding was the enrichment of *Herbaspirillum, Porphyrobacter* , and *Bacteroides* observed in cancer patients with high risk of recurrence and progression indicating that these genera may be potential biomarkers for risk stratification ( [27](#B27) ). Given the data on gut microbiota in modulating sensitivity to immune checkpoint inhibitors in advanced cancer patients ( [28](#B28) – [31](#B31) ) further studies investigating the influence of urinary microbiota on the bladder tumor response to anti-cancer therapy should be pursued. The studies performed to date whilst providing some preliminary interesting findings are limited due to the low numbers of samples studied and their use of voided urine which introduces contamination from microorganisms in the terminal portion of the urethra. Clearly larger scale future studies using catheterized urine need to be conducted to accurately evaluate the potentially important role of the bladder microbiome in both bladder cancer pathogenesis/progression and response to immunotherapy agents.

## Oncolytic Virus Therapy: Converting “ Immunologically Cold” Tumors into Inflamed “ Hot” Tumors

One intervention capable of dramatically altering the TME immune landscape, is the use of oncolytic or “ cancer-killing” viruses (OVs) ( [32](#B32) ). OVs lead to improved anti-tumor immunity through the induction of both innate and adaptive immune responses, releasing the full range of tumor-associated antigens (TAAs) into an inflammatory environment via tumor lysis and the induction of immunogenic cell death, disrupting the immunosuppressive TME ( [33](#B33) – [36](#B36) ). Therefore, OVs are able to vaccinate against the entire range of TAAs and together with epitope spreading in the TME act as a personalized immunotherapeutic. Considerable evidence has shown that OVs are a very promising strategy to convert non-inflamed or “ cold” tumors into an inflamed or “ hot” phenotype to promote the priming of anti-tumor immune responses. To date, two studies have clearly shown the promise of this immunotherapeutic strategy to treat NMIBC. Firstly, preclinical work from our own group had indicated the sensitivity of bladder cancer cell lines to a novel oncolytic virus, Coxsackievirus A21 (CVA21) ( [37](#B37) ). CVA21 is able to target, infect and lyse cells expressing the CVA21 cellular receptors intercellular adhesion molecule-1 (ICAM-1) and decay-accelerating factor (DAF) ( [38](#B38) ). Infection of bladder cancer cell lines by CVA21 led to the induction of immunogenic cell death in CVA21-treated cell lines giving promise to the potential clinical translation of these results to generate long-lasting protective anti-tumor immunity in the bladder mucosa ( [37](#B37) ). These results provided the rationale for a Phase I/II clinical trial (CANON) to investigate the therapeutic potential of CVA21 as a new immunotherapy approach for the treatment of NMIBC ( [39](#B39) ). This trial determined safety, feasibility and immunomodulatory effects of CAVATAK in treatment naive tissue following escalating intravesical doses of a novel bio-selected formulation of CVA21 (CAVATAK) administered alone or in combination with mitomycin C (previously shown to up-regulate the viral entry receptor ICAM-1) ( [37](#B37) ) in 15 first-line NMIBC patients prior to TURBT surgery. Clinical activity of CAVATAK was highly tumor-selective and demonstrated the ability to induce tumor inflammation and hemorrhage following either single or multiple administrations of CAVATAK in several patients, and led to a complete resolution of tumor in one patient. Whether used alone or in combination with mitomycin C, CAVATAK caused marked inflammatory changes within NMIBC tissue biopsies by upregulating interferon-inducible genes including both Th1-associated chemokines and immune checkpoint inhibitory genes (PD-L1 and LAG3) supporting future combination studies with immune checkpoint inhibitors ( [40](#B40) – [42](#B42) ).

A second notable study in this field was the use of CG0070, a conditionally replicating oncolytic serotype 5 adenovirus (Ad5) designed to preferentially replicate in and kill retinoblastoma (Rb) pathway defective cells using the E2F-1 promotor ( [43](#B43) ). To enhance longlasting antitumor immunity, CG0070 encoded the cDNA for the human cytokine, granulocyte macrophage-colony stimulating factor (GM-CSF) which was selectively produced in Rb pathway–defective tumor cells due to the dependence of the E3 promoter that drives GM-CSF expression on transactivation by E1A. Preclinical *in vivo* studies with CG0070 demonstrated strong anti-tumor activity of the virus in bladder transitional cell carcinoma xenograft tumor models and showed significant anti-tumor synergy when combined with the chemotherapeutic agent docetaxel ( [43](#B43) ). In a phase 1 trial of 35 patients who had previously failed BCG therapy, CG0070 was administered intravesically in single or multiple doses at various levels ( [44](#B44) ). High levels of GM-CSF were identified in the urine of all patients after administration and no adverse events related to treatment were reported. The overall response rate to CG0070 was 48. 6% (17 of 35), which improved to 63. 6% (14 of 22) in the multi-dose group. Interim results from an ongoing phase 2 multicenter trial (NCT02365818) of intravesical instillation of CG0070 in 45 NMIBC patients who failed BCG therapy and had refused radical cystectomy showed an overall complete response of 47% (21/45) ( [45](#B45) ). Unfortunately, neither of the CG0070 clinical trials reported any immunohistochemical analysis of the tumor microenvironment to fully elucidate both the mechanism of action of CG0070 and potential immune activation. However, it is presumed that CG0070 works through direct tumor lysis by selective replication in Rb pathway-defective tumor cells and through immune-mediated killing resulting from immunogenic cell death and immune activation induced by the local GM-CSF production ( [45](#B45) ). Importantly, intravesical oncolytic virus therapy was extremely well-tolerated in all of the above clinical trials and thus may offer an alternative to the 40-year-old standard of care, BCG therapy, but without its limiting toxicities.

## Combination Approaches: Personalized Immunomodulation of a Patient's Tumor for Enhanced Therapeutic Outcome

Whilst the emergence of new immuno-oncology therapies has improved the survival rates of patients, particularly in hard to treat cancers, most cancer patients still either don't respond fully to immunotherapy agents or become resistant. This is in large part due to a lack of understanding of the tumor microenvironment of each patient's tumor to enable the correct immunotherapy approach to be targeted to the right tumor at the right time. It is becoming increasingly recognized that this will require the use of rational combination approaches so that more patients will respond and for longer. There are now a variety of rational combinations of immunotherapy and targeted agents which are also now being investigated in NMIBC. One such combination approach is the use of immune checkpoint inhibitors in combination with BCG. This is currently being evaluated in both a phase I study (NCT02324582) of pembrolizumab (antibody which targets and blocks PD-1) in combination with BCG for patients with high-risk NMIBC ( [46](#B46) ) and Atezolizumab (antibody against PD-L1) with or without BCG (NCT02792192). Inman et al. had already provided the evidence to support the rationale for such combination by demonstrating that PD-L1 expression is associated with high-grade tumors and intratumoral lymphocytic infiltration and was a key determinant of stage progression ( [47](#B47) ). In addition, PD-L1 expression was shown to be abundant in BCG induced bladder granulomata in 11/12 patients who failed BCG treatment, highly suggestive of a role for tumor PD-L1 in attenuating responses to BCG immunotherapy by inhibiting any anti-tumor T cells. More recently further preclinical work confirmed that PD-L1 expression was obviously upregulated in bladder cancer cells in response to BCG treatment both *in vitro* and *in vivo* ( [48](#B48) ). Wang et al. reported that treatment with a combination of BCG and anti-PD-L1 resulted in an enhanced anti-tumor effect in an orthotopic rat bladder cancer model by reducing tumor burden and prolonging survival. The antitumor immunity was attributed to an increase in the number and activity of tumor-infiltrating CD8+ T cells, as well as suppression of MDSCs in the TME ( [48](#B48) ).

Another promising immunotherapy agent currently being trialed in different immunotherapy combination strategies is an IL-15 superagonist, ALT-803, that has a proven potent ability to expand and functionally activate both NK cells and T-cells ( [49](#B49) ). This IL-15 superagonist has already shown significant anti-tumor activity as a monotherapy against various solid tumor models ( [50](#B50) , [51](#B51) ), however, used in combination with e. g., BCG has the potential to further augment the BCG-induced immune response. Indeed, in a bladder cancer rat model a 46% reduction in tumor burden in response to intravesical ALT-803 and BCG combination therapy (compared to 15% with BCG alone and 35% with ALT-803 alone) was linked to increased production and secretion of IL-1α, IL-1β, and RANTES, which in turn, induced the proliferation and activation of NK cells. This enhanced therapeutic index seen with BCG and ALT-803, administered subcutaneously or intravesically ( [52](#B52) , [53](#B53) ), provided a powerful justification for the ongoing current Phase Ib/II, multicenter study of intravesical BCG plus ALT-803 in high risk NMIBC (NCT02138734) ( [54](#B54) ).

The use of low-dose chemotherapy that elicits immune-potentiating effects by either inducing immunogenicity or relieving tumor-induced immunosuppression is another strategy being pursued to immunomodulate the tumor microenvironment. Certain chemotherapeutic agents not only have direct anti-tumor effects but have also been shown to play a role in depleting regulatory T cells ( [55](#B55) ), upregulating major histocompatibility complex class I expression and thus directly stimulating T cell function ( [56](#B56) ) as well as myeloid-derived suppressor cell (MDSC) depletion ( [57](#B57) ), increasing the level of type I interferons ( [58](#B58) ) and induction of immunogenic cell death ( [59](#B59) ). This “ chemo-immunotherapy” strategy was utilized to immunologically evaluate the efficacy of intravesical chemotherapeutic agents, mitomycin C (MMC) or Adriamycin (ADM) combined with BCG using an N-butyl-N-(4-hydroxybutyl) nitrosamine (BBN)-induced orthotopic bladder cancer model. Hori et al. showed that sequential treatment with BCG and chemotherapy inside the bladder was more effective than either agent alone ( [60](#B60) ). The synergy was mediated through direct cytotoxic effects and indirectly through changes to immune cells through recruitment of NK cells and inhibition of TAMS and Tregs in the TME. Therefore, intravesical chemotherapy was able to suppress protumoral immunity and enhance anti-tumoral immunity in turn increasing the efficiency of BCG and potentially being a novel treatment strategy for BCG-failure NMIBC.

To date the use of vaccine therapy as a monotherapy in BCG-refractory NMIBC patients has shown disappointing clinical outcomes suggesting that this approach could be optimized by combining vaccination with local immunostimulation. One such approach to enhance a vaccine-induced immune response is through the use of Toll-like receptor (TLR) agonists that are able to modify the expression of selectins, integrins, chemokines, and chemokine receptors, thus enhancing T-cell attraction to the tumor site ( [61](#B61) , [62](#B62) ). Domingos-Pereira et al. used an orthotopic model expressing E7 as a prototype tumor antigen and a cognate E7 vaccine to explore the ability of either synthetic or bacterial intravesical instillation of synthetic toll-like receptor (TLR) agonists to increase CD8 T-cell recruitment to the bladder and improve bladder tumor regression ( [63](#B63) ). They showed that immunostimulation with Ty21a bacteria (attenuated *Salmonella enterica* typhi Ty21a live vaccine-strain against typhoid fever), but not CpG, after tumor antigen vaccination efficiently recruits vaccine-specific CD8 T cells to the bladder, resulting in tumor regression and 90% survival of the mice. Salmonella can provide TLR-4 ( [64](#B64) ) and TLR-9 agonists ( [65](#B65) ) and may engage TLR-5 through flagellin ( [66](#B66) ). In a more recent preclinical study the same authors demonstrated that whilst intravesical Ty21a induced tumor cell death and innate and adaptive immune responses in the same therapeutic line as BCG immunotherapy, Ty21a was more effective than BCG for bladder-tumor treatment and thus may be predictive of a higher efficacy in patients ( [67](#B67) ).

In a phase 1 clinical trial the activity of TMX-101, a liquid formulation of the toll-like receptor 7 agonist, imiquimod, was analyzed in low-grade NMIBC ( [68](#B68) ). Whilst the effective biologic dose in this phase 1 study could not be determined because no patient experienced a complete response, the safety of TMX-101 was confirmed. A phase 2 study using TMX-101 in patients with NMIBC containing carcinoma- *in-situ* reported results from 12 patients, of which half (6/12) had received ≥2 prior induction courses of BCG ( [69](#B69) ). TMX-101 was found to be safe and well-tolerated. Two patients demonstrated a negative cytology and biopsy result at 6 weeks following treatment. Following treatment there was a significant increase in urinary cytokines, including IL-6 and IL-18. It is clear given these encouraging results that further investigations with this agent are required. However, despite the immunostimulatory potential of TLR agonists their use in cancer has been decreasing ( [70](#B70) ). Perhaps in the future these agents can be combined with other immunotherapeutic treatments in a safe and efficient way in order to achieve enhanced anti-tumor responses in patients.

## Conclusions

The tumor microenvironment has a profound impact on the success or failure of treatments for NMIBC. There is a growing realization that remodeling the tumor microenvironment to achieve optimal therapeutic effects will require multiple complementary therapeutic approaches. At the core to achieving this is a critical understanding of the bladder tumor microenvironment including the influence of the bladder microbiome in NMIBC both during tumor progression and in response to treatment. Only with this knowledge can we optimally make use of novel emerging immunotherapies and how they can complement existing therapies to achieve alternative bladder-sparing options critically needed in patients with BCG unresponsive NMIBC.

## Author Contributions

NA wrote the main body of the text. GS contributed to the oncolytic virus section. HP reviewed and edited the manuscript.

## Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## References

1. Fridman WH, Pagès F, Sautès-Fridman C, Galon J. The immune contexture in human tumours: impact on clinical outcome. *Nat Rev Cancer* . (2012)12: 298–306. doi: 10. 1038/nrc3245

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=22419253) | [CrossRef Full Text](https://doi.org/10.1038/nrc3245) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=WH.+Fridman&author=F.+Pagès&author=C.+Sautès-Fridman&author=J.+Galon+&publication_year=2012&title=The+immune+contexture+in+human+tumours%3A+impact+on+clinical+outcome&journal=Nat+Rev+Cancer&volume=12&pages=298-306)

2. Wang D, DuBois RN. Immunosuppression associated with chronic inflammation in the tumor microenvironment. *Carcinogenesis* . (2015) 36: 1085–93. doi: 10. 1093/carcin/bgv123

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=26354776) | [CrossRef Full Text](https://doi.org/10.1093/carcin/bgv123) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=D.+Wang&author=RN.+DuBois+&publication_year=2015&title=Immunosuppression+associated+with+chronic+inflammation+in+the+tumor+microenvironment&journal=Carcinogenesis&volume=36&pages=1085-93)

3. Babjuk M, Böhle A, Burger M, Capoun O, Cohen D, Compérat EM, et al. EAU guidelines on non-muscle-invasive urothelial carcinoma of the bladder: update 2016. *Eur Urol* . (2017) 71: 447–61 doi: 10. 1016/j. eururo. 2016. 05. 041

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=27324428) | [CrossRef Full Text](https://doi.org/10.1016/j.eururo.2016.05.041) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=M.+Babjuk&author=A.+Böhle&author=M.+Burger&author=O.+Capoun&author=D.+Cohen&author=EM.+Compérat+&publication_year=2017&title=EAU+guidelines+on+non-muscle-invasive+urothelial+carcinoma+of+the+bladder%3A+update+2016&journal=Eur+Urol&volume=71&pages=447-61)

4. Herr HW, Morales A. History of bacillus Calmette-Guerin and bladder cancer: an immunotherapy success story. *J Urol* . (2008) 179: 53–6. doi: 10. 1016/j. juro. 2007. 08. 122

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=17997439) | [CrossRef Full Text](https://doi.org/10.1016/j.juro.2007.08.122) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=HW.+Herr&author=A.+Morales+&publication_year=2008&title=History+of+bacillus+Calmette-Guerin+and+bladder+cancer%3A+an+immunotherapy+success+story&journal=J+Urol&volume=179&pages=53-6)

5. Kitamura H, Tsukamoto T. Immunotherapy for urothelial carcinoma: current status and perspectives. *Cancers* . (2011) 3: 3055–72. doi: 10. 3390/cancers3033055

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=24212945) | [CrossRef Full Text](https://doi.org/10.3390/cancers3033055) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=H.+Kitamura&author=T.+Tsukamoto+&publication_year=2011&title=Immunotherapy+for+urothelial+carcinoma%3A+current+status+and+perspectives&journal=Cancers&volume=3&pages=3055-72)

6. Abebe F. Is interferon-gamma the right marker for bacille Calmette-Guérin-induced immune protection? The missing link in our understanding of tuberculosis immunology. *Clin Exp Immunol* . (2012) 169: 213–9. doi: 10. 1111/j. 1365-2249. 2012. 04614. x

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=22861360) | [CrossRef Full Text](https://doi.org/10.1111/j.1365-2249.2012.04614.x) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=F.+Abebe+&publication_year=2012&title=Is+interferon-gamma+the+right+marker+for+bacille+Calmette-Guérin-induced+immune+protection%3F&journal=Clin+Exp+Immunol&volume=169&pages=213-9)

7. Pichler R, Fritz J, Zavadil C, Schäfer G, Culig Z, Brunner A. Tumor-infiltrating immune cell subpopulations influence the oncologic outcome after intravesical Bacillus Calmette-Guérin therapy in bladder cancer. *Oncotarget* . (2016) 7: 39916–30. doi: 10. 18632/oncotarget. 9537

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=27221038) | [CrossRef Full Text](https://doi.org/10.18632/oncotarget.9537) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=R.+Pichler&author=J.+Fritz&author=C.+Zavadil&author=G.+Schäfer&author=Z.+Culig&author=A.+Brunner+&publication_year=2016&title=Tumor-infiltrating+immune+cell+subpopulations+influence+the+oncologic+outcome+after+intravesical+Bacillus+Calmette-Guérin+therapy+in+bladder+cancer&journal=Oncotarget&volume=7&pages=39916-30)

8. Nunez-Nateras R, Castle EP, Protheroe CA, Stanton ML, Ocal TI, Ferrigni EN, et al. Predicting response to bacillus Calmette-Guérin (BCG) in patients with carcinoma *in situ* of the bladder. *Urol Oncol* . (2014) 32: 45. e23–30. doi: 10. 1016/j. urolonc. 2013. 06. 008

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=24055426) | [CrossRef Full Text](https://doi.org/10.1016/j.urolonc.2013.06.008) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=R.+Nunez-Nateras&author=EP.+Castle&author=CA.+Protheroe&author=ML.+Stanton&author=TI.+Ocal&author=EN.+Ferrigni+&publication_year=2014&title=Predicting+response+to+bacillus+Calmette-Guérin+(BCG)+in+patients+with+carcinoma+in+situ+of+the+bladder&journal=Urol+Oncol&volume=32&pages=45)

9. Miyake M, Tatsumi Y, Gotoh D, Ohnishi S, Owari T, Iida K, et al. Regulatory T cells and tumor-associated macrophages in the tumor microenvironment in non-muscle invasive bladder cancer treated with intravesical Bacilli Calmette-Guérin: a long-term follow-up study of a Japanese cohort. *Int J Mol Sci* . (2017) 18: 2186. doi: 10. 3390/ijms18102186

[CrossRef Full Text](https://doi.org/10.3390/ijms18102186) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=M.+Miyake&author=Y.+Tatsumi&author=D.+Gotoh&author=S.+Ohnishi&author=T.+Owari&author=K.+Iida+&publication_year=2017&title=Regulatory+T+cells+and+tumor-associated+macrophages+in+the+tumor+microenvironment+in+non-muscle+invasive+bladder+cancer+treated+with+intravesical+Bacilli+Calmette-Guérin%3A+a+long-term+follow-up+study+of+a+Japanese+cohort&journal=Int+J+Mol+Sci&volume=18&pages=2186)

10. Lima L, Oliveira D, Tavares A, Amaro T, Cruz R, Oliveira MJ, et al. The predominance of M2-polarized macrophages in the stroma of low-hypoxic bladder tumors is associated with BCG immunotherapy failure. *Urol Oncol* . (2014) 32: 449–57. doi: 10. 1016/j. urolonc. 2013. 10. 012

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=24252833) | [CrossRef Full Text](https://doi.org/10.1016/j.urolonc.2013.10.012) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=L.+Lima&author=D.+Oliveira&author=A.+Tavares&author=T.+Amaro&author=R.+Cruz&author=MJ.+Oliveira+&publication_year=2014&title=The+predominance+of+M2-polarized+macrophages+in+the+stroma+of+low-hypoxic+bladder+tumors+is+associated+with+BCG+immunotherapy+failure&journal=Urol+Oncol&volume=32&pages=449-57)

11. Takayama H, Nishimura K, Tsujimura A, Nakai Y, Nakayama M, Aozasa K, et al. Increased infiltration of tumor associated macrophages is associated with poor prognosis of bladder carcinoma in situ after intravesical bacillus Calmette-Guerin instillation. *J Urol* . (2009) 181: 1894–900. doi: 10. 2307/2955892

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=19237175) | [CrossRef Full Text](https://doi.org/10.2307/2955892) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=H.+Takayama&author=K.+Nishimura&author=A.+Tsujimura&author=Y.+Nakai&author=M.+Nakayama&author=K.+Aozasa+&publication_year=2009&title=Increased+infiltration+of+tumor+associated+macrophages+is+associated+with+poor+prognosis+of+bladder+carcinoma+in+situ+after+intravesical+bacillus+Calmette-Guerin+instillation&journal=J+Urol&volume=181&pages=1894-900)

12. Martínez VG, Rubio C, Martínez-Fernández M, Segovia C, López-Calderón F, Garín MI, et al. BMP4 induces M2 macrophage polarization and favors tumor progression in bladder cancer. *Clin Cancer Res* . (2017) 23: 7388–99. doi: 10. 1158/1078-0432. CCR-17-1004

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=28928159) | [CrossRef Full Text](https://doi.org/10.1158/1078-0432.CCR-17-1004) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=VG.+Martínez&author=C.+Rubio&author=M.+Martínez-Fernández&author=C.+Segovia&author=F.+López-Calderón&author=MI.+Garín+&publication_year=2017&title=BMP4+induces+M2+macrophage+polarization+and+favors+tumor+progression+in+bladder+cancer&journal=Clin+Cancer+Res&volume=23&pages=7388-99)

13. Rubio C, Munera-Maravilla E, Lodewijk I, Suarez-Cabrera C, Karaivanova V, RuizPalomares R, et al. Macrophage polarization as a novel weapon in conditioning tumor microenvironment for bladder cancer: can we turn demons into gods? *Clin Transl Oncol* . (2019) 21: 391–403. doi: 10. 1007/s12094-018-1952-y

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=30291519) | [CrossRef Full Text](https://doi.org/10.1007/s12094-018-1952-y) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=C.+Rubio&author=E.+Munera-Maravilla&author=I.+Lodewijk&author=C.+Suarez-Cabrera&author=V.+Karaivanova&author=R.+RuizPalomares+&publication_year=2019&title=Macrophage+polarization+as+a+novel+weapon+in+conditioning+tumor+microenvironment+for+bladder+cancer%3A+can+we+turn+demons+into+gods%3F&journal=Clin+Transl+Oncol&volume=21&pages=391-403)

14. Chevalier MF, Trabanelli S, Racle J, Salomé B, Cesson V, Gharbi D, et al. ILC2-modulated T cell-toMDSC balance is associated with bladder cancer recurrence. *J Clin Invest* . (2017) 127: 2916–29. doi: 10. 1172/JCI89717

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=28650339) | [CrossRef Full Text](https://doi.org/10.1172/JCI89717) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=MF.+Chevalier&author=S.+Trabanelli&author=J.+Racle&author=B.+Salomé&author=V.+Cesson&author=D.+Gharbi+&publication_year=2017&title=ILC2-modulated+T+cell-toMDSC+balance+is+associated+with+bladder+cancer+recurrence&journal=J+Clin+Invest&volume=127&pages=2916-29)

15. Artis D, Spits H. The biology of innate lymphoid cells. *Nature* . (2015) 517: 293–301. doi: 10. 1038/nature14189

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=25592534) | [CrossRef Full Text](https://doi.org/10.1038/nature14189) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=D.+Artis&author=H.+Spits+&publication_year=2015&title=The+biology+of+innate+lymphoid+cells&journal=Nature&volume=517&pages=293-301)

16. Suttmann H, Jacobsen M, Reiss K, Jocham D, Böhle A, Brandau S. Mechanisms of bacillus Calmette-Guerin mediated natural killer cell activation. *J Urol* . (2004) 172: 1490–5. doi: 10. 1097/01. ju. 0000131944. 52354. 63

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=15371877) | [CrossRef Full Text](https://doi.org/10.1097/01.ju.0000131944.52354.63) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=H.+Suttmann&author=M.+Jacobsen&author=K.+Reiss&author=D.+Jocham&author=A.+Böhle&author=S.+Brandau+&publication_year=2004&title=Mechanisms+of+bacillus+Calmette-Guerin+mediated+natural+killer+cell+activation&journal=J+Urol&volume=172&pages=1490-5)

17. Sonoda T, Sugimura K, Ikemoto S, Kawashima H, Nakatani T. Significance of target cell infection and natural killer cells in the anti-tumor effects of bacillus CalmetteGuerin in murine bladder cancer. *Oncol Rep* . (2007) 17: 1469–74. doi: 10. 3892/or. 17. 6. 1469

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=17487406) | [CrossRef Full Text](https://doi.org/10.3892/or.17.6.1469) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=T.+Sonoda&author=K.+Sugimura&author=S.+Ikemoto&author=H.+Kawashima&author=T.+Nakatani+&publication_year=2007&title=Significance+of+target+cell+infection+and+natural+killer+cells+in+the+anti-tumor+effects+of+bacillus+CalmetteGuerin+in+murine+bladder+cancer&journal=Oncol+Rep&volume=17&pages=1469-74)

18. García-Cuesta EM, López-Cobo S, Álvarez-Maestro M, Esteso G, Romera-Cárdenas G, Rey M, et al. NKG2D is a key receptor for recognition of bladder cancer cells by IL-2-activated NK cells and BCG promotes NK cell activation. *Front Immunol* . (2015) 6: 284. doi: 10. 3389/fimmu. 2015. 00284

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=26106390) | [CrossRef Full Text](https://doi.org/10.3389/fimmu.2015.00284) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=EM.+García-Cuesta&author=S.+López-Cobo&author=M.+Álvarez-Maestro&author=G.+Esteso&author=G.+Romera-Cárdenas&author=M.+Rey+&publication_year=2015&title=NKG2D+is+a+key+receptor+for+recognition+of+bladder+cancer+cells+by+IL-2-activated+NK+cells+and+BCG+promotes+NK+cell+activation&journal=Front+Immunol&volume=6&pages=284)

19. Brandau S, Riemensberger J, Jacobsen M, Kemp D, Zhao W, Zhao X, et al. NK cells are essential for effective BCG immunotherapy. *Int J Cancer* . (2001) 92: 697–702. doi: 10. 1002/1097-0215(20010601)92: 5 <697:: AID-IJC1245> 3. 0. CO; 2-Z

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=11340575) | [CrossRef Full Text](https://doi.org/10.1002/1097-0215%2820010601%2992%3A%205%20%3C697%3A%3A%20AID-IJC1245%3E%203.%200.%20CO; 2-Z) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=S.+Brandau&author=J.+Riemensberger&author=M.+Jacobsen&author=D.+Kemp&author=W.+Zhao&author=X.+Zhao+&publication_year=2001&title=NK+cells+are+essential+for+effective+BCG+immunotherapy&journal=Int+J+Cancer&volume=92&pages=697-702)

20. Dowell AC, Cobby E, Wen K, Devall AJ, During V, Anderson J, et al. Interleukin-17-positive mast cells influence outcomes from BCG for patients with CIS: data from a comprehensive characterisation of the immune microenvironment of urothelial bladder cancer. *PLoS ONE* . (2017) 12: e0184841. doi: 10. 1371/journal. pone. 0184841

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=28931051) | [CrossRef Full Text](https://doi.org/10.1371/journal.pone.0184841) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=AC.+Dowell&author=E.+Cobby&author=K.+Wen&author=AJ.+Devall&author=V.+During&author=J.+Anderson+&publication_year=2017&title=Interleukin-17-positive+mast+cells+influence+outcomes+from+BCG+for+patients+with+CIS%3A+data+from+a+comprehensive+characterisation+of+the+immune+microenvironment+of+urothelial+bladder+cancer&journal=PLoS+ONE&volume=12&pages=e0184841)

21. Bajic P, Wolfe AJ, Gupta GN. The urinary microbiome: implications in bladder cancer pathogenesis and therapeutics. *Urology* . (2019) 126: 10–15. doi: 10. 1016/j. urology. 2018. 12. 034

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=30615894) | [CrossRef Full Text](https://doi.org/10.1016/j.urology.2018.12.034) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=P.+Bajic&author=AJ.+Wolfe&author=GN.+Gupta+&publication_year=2019&title=The+urinary+microbiome%3A+implications+in+bladder+cancer+pathogenesis+and+therapeutics&journal=Urology&volume=126&pages=10-15)

22. Cosseau C, Devine DA, Dullaghan E, Gardy JL, Chikatamarla A, Gellatly S, et al. The commensal *Streptococcus salivarius* K12 downregulates the innate immune responses of human epithelial cells and promotes host-microbe homeostasis. *Infect Immun* . (2008) 76: 4163–75. doi: 10. 1128/IAI. 00188-08

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=18625732) | [CrossRef Full Text](https://doi.org/10.1128/IAI.00188-08) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=C.+Cosseau&author=DA.+Devine&author=E.+Dullaghan&author=JL.+Gardy&author=A.+Chikatamarla&author=S.+Gellatly+&publication_year=2008&title=The+commensal+Streptococcus+salivarius+K12+downregulates+the+innate+immune+responses+of+human+epithelial+cells+and+promotes+host-microbe+homeostasis&journal=Infect+Immun&volume=76&pages=4163-75)

23. Sidddiqui H, Nederbragt AJ, Lagesen K, Jeansson SL, Jakobsen KS. Assessing diversity of the female urine microbiota by high throughput sequencing of 16S rDNA amplicons. *BMC Microbiol* . (2011) 11: 244. doi: 10. 1186/1471-2180-11-244

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=22047020) | [CrossRef Full Text](https://doi.org/10.1186/1471-2180-11-244) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=H.+Sidddiqui&author=AJ.+Nederbragt&author=K.+Lagesen&author=SL.+Jeansson&author=KS.+Jakobsen+&publication_year=2011&title=Assessing+diversity+of+the+female+urine+microbiota+by+high+throughput+sequencing+of+16S+rDNA+amplicons&journal=BMC+Microbiol&volume=11&pages=244)

24. McMillan A, Macklaim JM, Burton JP, Reid G. Adhesion of *Lactobacillus iners* AB-1 to human fibronectin: a key mediator for persistence in the vagina? *Reprod Sci* . (2013) 20: 791–6. doi: 10. 1177/1933719112466306

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=23202727) | [CrossRef Full Text](https://doi.org/10.1177/1933719112466306) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=A.+McMillan&author=JM.+Macklaim&author=JP.+Burton&author=G.+Reid+&publication_year=2013&title=Adhesion+of+Lactobacillus+iners+AB-1+to+human+fibronectin%3A+a+key+mediator+for+persistence+in+the+vagina%3F&journal=Reprod+Sci&volume=20&pages=791-6)

25. Xu W, Yang L, Lee P, Huang WC, Nossa C, Ma Y, et al. Mini-review: perspective of the microbiome in the pathogenesis of urothelial carcinoma. *Am J Clin Exp Urol* . (2014) 2: 57–61.

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=25126590) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=W.+Xu&author=L.+Yang&author=P.+Lee&author=WC.+Huang&author=C.+Nossa&author=Y.+Ma+&publication_year=2014&title=Mini-review%3A+perspective+of+the+microbiome+in+the+pathogenesis+of+urothelial+carcinoma&journal=Am+J+Clin+Exp+Urol&volume=2&pages=57-61)

26. Bučević Popović V, Šitum M, Chow CT, Chan LS, Roje B, Terzić J. The urinary microbiome associated with bladder cancer. *Sci Rep* . (2018) 8: 12157. doi: 10. 1038/s41598-018-29054-w

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=30108246) | [CrossRef Full Text](https://doi.org/10.1038/s41598-018-29054-w) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=V.+Bučević+Popović&author=M.+Šitum&author=CT.+Chow&author=LS.+Chan&author=B.+Roje&author=J.+Terzić+&publication_year=2018&title=The+urinary+microbiome+associated+with+bladder+cancer&journal=Sci+Rep&volume=8&pages=12157)

27. Wu P, Zhang G, Zhao J, Chen J, Chen Y, Huang W, et al. Profiling the urinary microbiota in male patients with bladder cancer in China. *Front Cell Infect Microbiol* . (2018) 8: 167. doi: 10. 3389/fcimb. 2018. 00429

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=29904624) | [CrossRef Full Text](https://doi.org/10.3389/fcimb.2018.00429) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=P.+Wu&author=G.+Zhang&author=J.+Zhao&author=J.+Chen&author=Y.+Chen&author=W.+Huang+&publication_year=2018&title=Profiling+the+urinary+microbiota+in+male+patients+with+bladder+cancer+in+China&journal=Front+Cell+Infect+Microbiol&volume=8&pages=167)

28. Roy S, Trinchieri G. Microbiota: a key orchestrator of cancer therapy. *Nat Rev Cancer* . (2017) 17: 271–85. doi: 10. 1038/nrc. 2017. 13

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=28303904) | [CrossRef Full Text](https://doi.org/10.1038/nrc.2017.13) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=S.+Roy&author=G.+Trinchieri+&publication_year=2017&title=Microbiota%3A+a+key+orchestrator+of+cancer+therapy&journal=Nat+Rev+Cancer&volume=17&pages=271-85)

29. Vétizou M, Pitt JM, Daillère R, Lepage P, Waldschmitt N, Flament C, et al. Anticancer immunotherapy by CTLA-4 blockade relies on the gut microbiota. *Science* . (2015) 350: 1079–84. doi: 10. 1126/science. aad1329

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=26541610) | [CrossRef Full Text](https://doi.org/10.1126/science.aad1329) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=M.+Vétizou&author=JM.+Pitt&author=R.+Daillère&author=P.+Lepage&author=N.+Waldschmitt&author=C.+Flament+&publication_year=2015&title=Anticancer+immunotherapy+by+CTLA-4+blockade+relies+on+the+gut+microbiota&journal=Science&volume=350&pages=1079-84)

30. Gopalakrishnan V, Spencer CN, Nezi L, Reuben A, Andrews MC, Karpinets TV, et al. Gut microbiome modulates response to anti-PD-1 immunotherapy in melanoma patients. *Science* . (2018) 359: 97–103. doi: 10. 1126/science. aan4236

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=29097493) | [CrossRef Full Text](https://doi.org/10.1126/science.aan4236) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=V.+Gopalakrishnan&author=CN.+Spencer&author=L.+Nezi&author=A.+Reuben&author=MC.+Andrews&author=TV.+Karpinets+&publication_year=2018&title=Gut+microbiome+modulates+response+to+anti-PD-1+immunotherapy+in+melanoma+patients&journal=Science&volume=359&pages=97-103)

31. Routy B, Le Chatelier E, Derosa L, Duong CPM, Alou MT, Daillère R, et al. Gut microbiome influences efficacy of PD-1-based immunotherapy against epithelial tumors. *Science* . (2018) 359: 91–7. doi: 10. 1126/science. aan3706

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=29097494) | [CrossRef Full Text](https://doi.org/10.1126/science.aan3706) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=B.+Routy&author=ChatelierE.+Le&author=L.+Derosa&author=CPM.+Duong&author=MT.+Alou&author=R.+Daillère+&publication_year=2018&title=Gut+microbiome+influences+efficacy+of+PD-1-based+immunotherapy+against+epithelial+tumors&journal=Science&volume=359&pages=91-7)

32. Achard C, Surendran A, Wedge ME, Ungerechts G, Bell J, Ilkow CS. Lighting a fire in the tumor microenvironment using oncolytic immunotherapy. *EBioMedicine* . (2018) 31: 17–24. doi: 10. 1016/j. ebiom. 2018. 04. 020

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=29724655) | [CrossRef Full Text](https://doi.org/10.1016/j.ebiom.2018.04.020) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=C.+Achard&author=A.+Surendran&author=ME.+Wedge&author=G.+Ungerechts&author=J.+Bell&author=CS.+Ilkow+&publication_year=2018&title=Lighting+a+fire+in+the+tumor+microenvironment+using+oncolytic+immunotherapy&journal=EBioMedicine&volume=31&pages=17-24)

33. Guo ZS, Liu Z, Bartlett DL. Oncolytic immunotherapy: dying the right way is a key to eliciting potent antitumor immunity. *Front Oncol* . (2014) 4: 74. doi: 10. 3389/fonc. 2014. 00074

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=24782985) | [CrossRef Full Text](https://doi.org/10.3389/fonc.2014.00074) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=ZS.+Guo&author=Z.+Liu&author=DL.+Bartlett+&publication_year=2014&title=Oncolytic+immunotherapy%3A+dying+the+right+way+is+a+key+to+eliciting+potent+antitumor+immunity&journal=Front+Oncol&volume=4&pages=74)

34. Donnelly OG, Errington-Mais F, Steele L, Hadac E, Jennings V, Scott K, et al. Measles virus causes immunogenic cell death in human melanoma. *Gene Ther* . (2013) 20: 7–15. doi: 10. 1038/gt. 2011. 205

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=22170342) | [CrossRef Full Text](https://doi.org/10.1038/gt.2011.205) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=OG.+Donnelly&author=F.+Errington-Mais&author=L.+Steele&author=E.+Hadac&author=V.+Jennings&author=K.+Scott+&publication_year=2013&title=Measles+virus+causes+immunogenic+cell+death+in+human+melanoma&journal=Gene+Ther&volume=20&pages=7-15)

35. Takasu A, Masui A, Hamada M, Imai T, Iwai S, Yura Y. Immunogenic cell death by oncolytic herpes simplex virus type 1 in squamous cell carcinoma cells. *Cancer Gene Ther* . (2016) 23: 107–13 doi: 10. 1038/cgt. 2016. 8

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=26987291) | [CrossRef Full Text](https://doi.org/10.1038/cgt.2016.8) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=A.+Takasu&author=A.+Masui&author=M.+Hamada&author=T.+Imai&author=S.+Iwai&author=Y.+Yura+&publication_year=2016&title=Immunogenic+cell+death+by+oncolytic+herpes+simplex+virus+type+1+in+squamous+cell+carcinoma+cells&journal=Cancer+Gene+Ther&volume=23&pages=107-13)

36. Koks CA, Garg AD, Ehrhardt M, Riva M, Vandenberk L, Boon L, et al. Newcastle disease virotherapy induces longterm survival and tumor-specific immune memory in orthotopic glioma through the induction of immunogenic cell death. *Int J Cancer* . (2015) 136: E313–25. doi: 10. 1002/ijc. 29202

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=25208916) | [CrossRef Full Text](https://doi.org/10.1002/ijc.29202) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=CA.+Koks&author=AD.+Garg&author=M.+Ehrhardt&author=M.+Riva&author=L.+Vandenberk&author=L.+Boon+&publication_year=2015&title=Newcastle+disease+virotherapy+induces+longterm+survival+and+tumor-specific+immune+memory+in+orthotopic+glioma+through+the+induction+of+immunogenic+cell+death&journal=Int+J+Cancer&volume=136&pages=E313-25)

37. Annels NE, Arif M, Simpson GR, Denyer M, Moller-Levet C, Mansfield D, et al. Oncolytic immunotherapy for bladder cancer using coxsackie A21 virus. *Mol Ther Oncolytics* . (2018) 9: 1–12. doi: 10. 1016/j. omto. 2018. 02. 001

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=29989024) | [CrossRef Full Text](https://doi.org/10.1016/j.omto.2018.02.001) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=NE.+Annels&author=M.+Arif&author=GR.+Simpson&author=M.+Denyer&author=C.+Moller-Levet&author=D.+Mansfield+&publication_year=2018&title=Oncolytic+immunotherapy+for+bladder+cancer+using+coxsackie+A21+virus&journal=Mol+Ther+Oncolytics&volume=9&pages=1-12)

38. Shafren DR, Dorahy DJ, Ingham RA, Burns GF, Barry RD. Coxsackievirus A21 binds to decay-accelerating factor but requires intercellular adhesion molecule 1 for cell entry. *J Virol* . (1997) 71: 4736–43. doi: 10. 1128/JVI. 71. 6. 4736-4743. 1997

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=9151867) | [CrossRef Full Text](https://doi.org/10.1128/JVI.71.6.4736-4743.1997) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=DR.+Shafren&author=DJ.+Dorahy&author=RA.+Ingham&author=GF.+Burns&author=RD.+Barry+&publication_year=1997&title=Coxsackievirus+A21+binds+to+decay-accelerating+factor+but+requires+intercellular+adhesion+molecule+1+for+cell+entry&journal=J+Virol&volume=71&pages=4736-43)

39. Annels NE, Mansfield D, Arif M, Ballesteros-Merino C, Simpson GR, Denyer M, et al. Viral targeting of non-muscle invasive bladder cancer and priming of anti-tumour immunity following intravesical Coxsackievirus A21. *Clin Cancer Res* . (2019) 25: 5818–5831. doi: 10. 1158/1078-0432. CCR-18-4022

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=31273010) | [CrossRef Full Text](https://doi.org/10.1158/1078-0432.CCR-18-4022) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=NE.+Annels&author=D.+Mansfield&author=M.+Arif&author=C.+Ballesteros-Merino&author=GR.+Simpson&author=M.+Denyer+&publication_year=2019&title=Viral+targeting+of+non-muscle+invasive+bladder+cancer+and+priming+of+anti-tumour+immunity+following+intravesical+Coxsackievirus+A21&journal=Clin+Cancer+Res&volume=25&pages=5818-5831)

40. Ribas A, Dummer R, Puzanov I, VanderWalde A, Andtbacka RHI, Michielin O, et al. Oncolytic Virotherapy Promotes Intratumoral T Cell Infiltration and Improves AntiPD-1 Immunotherapy. *Cell* . (2018) 174: 1031–2. doi: 10. 1016/j. cell. 2018. 07. 035

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=30096300) | [CrossRef Full Text](https://doi.org/10.1016/j.cell.2018.07.035) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=A.+Ribas&author=R.+Dummer&author=I.+Puzanov&author=A.+VanderWalde&author=RHI.+Andtbacka&author=O.+Michielin+&publication_year=2018&title=Oncolytic+Virotherapy+Promotes+Intratumoral+T+Cell+Infiltration+and+Improves+AntiPD-1+Immunotherapy&journal=Cell&volume=174&pages=1031-2)

41. Samson A, Scott KJ, Taggart D, West EJ, Wilson E, Nuovo GJ, et al. Intravenous delivery of oncolytic reovirus to brain tumor patients immunologically primes for subsequent checkpoint blockade. *Sci Transl Med* . (2018) 10: eaam7577. doi: 10. 1126/scitranslmed. aam7577

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=29298869) | [CrossRef Full Text](https://doi.org/10.1126/scitranslmed.aam7577) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=A.+Samson&author=KJ.+Scott&author=D.+Taggart&author=EJ.+West&author=E.+Wilson&author=GJ.+Nuovo+&publication_year=2018&title=Intravenous+delivery+of+oncolytic+reovirus+to+brain+tumor+patients+immunologically+primes+for+subsequent+checkpoint+blockade&journal=Sci+Transl+Med&volume=10&pages=eaam7577)

42. Sivanandam V, LaRocca CJ, Chen NG, Fong Y, Warner SG. Oncolytic viruses and immune checkpoint inhibition: the best of both worlds. *Mol Ther Oncolytics* . (2019) 13: 93–106. doi: 10. 1016/j. omto. 2019. 04. 003

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=31080879) | [CrossRef Full Text](https://doi.org/10.1016/j.omto.2019.04.003) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=V.+Sivanandam&author=CJ.+LaRocca&author=NG.+Chen&author=Y.+Fong&author=SG.+Warner+&publication_year=2019&title=Oncolytic+viruses+and+immune+checkpoint+inhibition%3A+the+best+of+both+worlds&journal=Mol+Ther+Oncolytics&volume=13&pages=93-106)

43. Ramesh N, Ge Y, Ennist DL, Zhu M, Mina M, Ganesh S, et al. CG0070, a conditionally replicating granulocyte macrophage colony-stimulating factor–armed oncolytic adenovirus for the treatment of bladder cancer. *Clin Cancer Res* . (2006) 12: 305–13. doi: 10. 1158/1078-0432. CCR-05-1059

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=16397056) | [CrossRef Full Text](https://doi.org/10.1158/1078-0432.CCR-05-1059) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=N.+Ramesh&author=Y.+Ge&author=DL.+Ennist&author=M.+Zhu&author=M.+Mina&author=S.+Ganesh+&publication_year=2006&title=CG0070,+a+conditionally+replicating+granulocyte+macrophage+colony-stimulating+factor–armed+oncolytic+adenovirus+for+the+treatment+of+bladder+cancer&journal=Clin+Cancer+Res&volume=12&pages=305-13)

44. Burke JM, Lamm DL, Meng MV, Nemunaitis JJ, Stephenson JJ, Arseneau JC, et al. A first in human phase 1 study of CG0070, a GM-CSF expressing oncolytic adenovirus, for the treatment of nonmuscle invasive bladder cancer. *J Urol* . (2012) 188: 2391–7. doi: 10. 1016/j. juro. 2012. 07. 097

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=23088985) | [CrossRef Full Text](https://doi.org/10.1016/j.juro.2012.07.097) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=JM.+Burke&author=DL.+Lamm&author=MV.+Meng&author=JJ.+Nemunaitis&author=JJ.+Stephenson&author=JC.+Arseneau+&publication_year=2012&title=A+first+in+human+phase+1+study+of+CG0070,+a+GM-CSF+expressing+oncolytic+adenovirus,+for+the+treatment+of+nonmuscle+invasive+bladder+cancer&journal=J+Urol&volume=188&pages=2391-7)

45. Packiam VT, Lamm DL, Barocas DA, Trainer A, Fand B, Davis RL 3rd, et al. An open label, single-arm, phase II multicenter study of the safety and efficacy of CG0070 oncolytic vector regimen in patients with BCGunresponsive non-muscle-invasive bladder cancer: interim results. *Urol Oncol* . (2018) 36: 440–7. doi: 10. 1016/j. urolonc. 2017. 07. 005

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=28755959) | [CrossRef Full Text](https://doi.org/10.1016/j.urolonc.2017.07.005) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=VT.+Packiam&author=DL.+Lamm&author=DA.+Barocas&author=A.+Trainer&author=B.+Fand&author=RL3rd.+Davis+&publication_year=2018&title=An+open+label,+single-arm,+phase+II+multicenter+study+of+the+safety+and+efficacy+of+CG0070+oncolytic+vector+regimen+in+patients+with+BCGunresponsive+non-muscle-invasive+bladder+cancer%3A+interim+results&journal=Urol+Oncol&volume=36&pages=440-7)

46. Jamil ML, Deebajah M, Sood A, Robinson K, Rao K, Sana S, et al. Protocol for phase I study of pembrolizumab in combination with Bacillus Calmette-Guérin for patients with high-risk non-muscle invasive bladder cancer. *BMJ Open* . (2019) 9: e028287. doi: 10. 1136/bmjopen-2018-028287

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=31320352) | [CrossRef Full Text](https://doi.org/10.1136/bmjopen-2018-028287) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=ML.+Jamil&author=M.+Deebajah&author=A.+Sood&author=K.+Robinson&author=K.+Rao&author=S.+Sana+&publication_year=2019&title=Protocol+for+phase+I+study+of+pembrolizumab+in+combination+with+Bacillus+Calmette-Guérin+for+patients+with+high-risk+non-muscle+invasive+bladder+cancer&journal=BMJ+Open&volume=9&pages=e028287)

47. Inman BA, Sebo TJ, Frigola X, Dong H, Bergstralh EJ, Frank I, et al. PD-L1 (B7-H1) expression by urothelial carcinoma of the bladder and BCG-induced granulomata: associations with localized stage progression. *Cancer* . (2007) 109: 1499–505. doi: 10. 1002/cncr. 22588

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=17340590) | [CrossRef Full Text](https://doi.org/10.1002/cncr.22588) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=BA.+Inman&author=TJ.+Sebo&author=X.+Frigola&author=H.+Dong&author=EJ.+Bergstralh&author=I.+Frank+&publication_year=2007&title=PD-L1+(B7-H1)+expression+by+urothelial+carcinoma+of+the+bladder+and+BCG-induced+granulomata%3A+associations+with+localized+stage+progression&journal=Cancer&volume=109&pages=1499-505)

48. Wang Y, Liu J, Yang X, Liu Y, Liu Y, Li Y, et al. Bacillus Calmette-Guérin and anti-PD-L1 combination therapy boosts immune response against bladder cancer. *Onco Targets Ther* . (2018) 11: 2891–9. doi: 10. 2147/OTT. S165840

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=29844686) | [CrossRef Full Text](https://doi.org/10.2147/OTT.S165840) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=Y.+Wang&author=J.+Liu&author=X.+Yang&author=Y.+Liu&author=Y.+Liu&author=Y.+Li+&publication_year=2018&title=Bacillus+Calmette-Guérin+and+anti-PD-L1+combination+therapy+boosts+immune+response+against+bladder+cancer&journal=Onco+Targets+Ther&volume=11&pages=2891-9)

49. Rhode PR, Egan JO, Xu W, Hong H, Webb GM, Chen X et al. Comparison of the Superagonist complex ALT-803, to IL15 as cancer immunotherapeutics in animal models. *Cancer Immunol Res* . (2016) 4: 49–60. doi: 10. 1158/2326-6066. CIR-15-0093-T

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=26511282) | [CrossRef Full Text](https://doi.org/10.1158/2326-6066.CIR-15-0093-T) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=PR.+Rhode&author=JO.+Egan&author=W.+Xu&author=H.+Hong&author=GM.+Webb&author=Xetal.+Chen+&publication_year=2016&title=Comparison+of+the+Superagonist+complex+ALT-803,+to+IL15+as+cancer+immunotherapeutics+in+animal+models&journal=Cancer+Immunol+Res&volume=4&pages=49-60)

50. Kim PS, Kwilas AR, Xu W, Alter S, Jeng EK, Wong HC et al. IL- 15superagonist/IL15RalphaSushi-fc fusion complex (IL-15SA/IL-15RalphaSu-fc; ALT-803) markedly enhances specific subpopulations of NK and memory CD8+T cells, and mediates potent anti-tumor activity against murine breast and colon carcinomas. *Oncotarget* . (2016) 7: 16130–45. doi: 10. 18632/oncotarget. 7470

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=26910920) | [CrossRef Full Text](https://doi.org/10.18632/oncotarget.7470) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=PS.+Kim&author=AR.+Kwilas&author=W.+Xu&author=S.+Alter&author=EK.+Jeng&author=HCetal.+Wong+&publication_year=2016&title=IL-+15superagonist%2FIL15RalphaSushi-fc+fusion+complex+(IL-15SA%2FIL-15RalphaSu-fc;+ALT-803)+markedly+enhances+specific+subpopulations+of+NK+and+memory+CD8+T+cells,+and+mediates+potent+anti-tumor+activity+against+murine+breast+and+colon+carcinomas&journal=Oncotarget&volume=7&pages=16130-45)

51. Liu B, Jones M, Kong L, Noel T, Jeng EK, Shi S, et al. Evaluation of the biological activities of the IL-15 superagonist complex, ALT-803, following intravenous versus subcutaneous administration in murine models. *Cytokine* . (2018) 107: 105–12. doi: 10. 1016/j. cyto. 2017. 12. 003

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=29452720) | [CrossRef Full Text](https://doi.org/10.1016/j.cyto.2017.12.003) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=B.+Liu&author=M.+Jones&author=L.+Kong&author=T.+Noel&author=EK.+Jeng&author=S.+Shi+&publication_year=2018&title=Evaluation+of+the+biological+activities+of+the+IL-15+superagonist+complex,+ALT-803,+following+intravenous+versus+subcutaneous+administration+in+murine+models&journal=Cytokine&volume=107&pages=105-12)

52. Gomes-Giacoia E, Miyake M, Goodison S, Sriharan A, Zhang G, You L, et al. Intravesical ALT-803 and BCG treatment reduces tumor burden in a carcinogen induced bladder cancer rat model; a role for cytokine production and NK cell expansion. *PLoS ONE* . (2014) 9: e96705. doi: 10. 1371/journal. pone. 0096705

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=24896845) | [CrossRef Full Text](https://doi.org/10.1371/journal.pone.0096705) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=E.+Gomes-Giacoia&author=M.+Miyake&author=S.+Goodison&author=A.+Sriharan&author=G.+Zhang&author=L.+You+&publication_year=2014&title=Intravesical+ALT-803+and+BCG+treatment+reduces+tumor+burden+in+a+carcinogen+induced+bladder+cancer+rat+model;+a+role+for+cytokine+production+and+NK+cell+expansion&journal=PLoS+ONE&volume=9&pages=e96705)

53. Furuya H, Chan OTM, Pagano I, Zhu C, Kim N, Peres R, et al. Effectiveness of two different dose administration regimens of an IL-15 superagonist complex (ALT-803) in an orthotopic bladder cancer mouse model. *J Transl Med* . (2019) 17: 29. doi: 10. 1186/s12967-019-1778-6

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=30654801) | [CrossRef Full Text](https://doi.org/10.1186/s12967-019-1778-6) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=H.+Furuya&author=OTM.+Chan&author=I.+Pagano&author=C.+Zhu&author=N.+Kim&author=R.+Peres+&publication_year=2019&title=Effectiveness+of+two+different+dose+administration+regimens+of+an+IL-15+superagonist+complex+(ALT-803)+in+an+orthotopic+bladder+cancer+mouse+model&journal=J+Transl+Med&volume=17&pages=29)

54. Huang J, Shiao SL, Furuya H, Rosser CJ. Immunogenomic analysis of exceptional responder to ALT-803 (IL-15 Analogue) in BCG unresponsive nonmuscle invasive bladder cancer: a case series and review of the literature. *J Immunother* . (2019) 42: 354–8. doi: 10. 1097/CJI. 0000000000000269

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=31107371) | [CrossRef Full Text](https://doi.org/10.1097/CJI.0000000000000269) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=J.+Huang&author=SL.+Shiao&author=H.+Furuya&author=CJ.+Rosser+&publication_year=2019&title=Immunogenomic+analysis+of+exceptional+responder+to+ALT-803+(IL-15+Analogue)+in+BCG+unresponsive+nonmuscle+invasive+bladder+cancer%3A+a+case+series+and+review+of+the+literature&journal=J+Immunother&volume=42&pages=354-8)

55. Scurr M, Pembroke T, Bloom A, Roberts D, Thomson A, Smart K, et al. Low-dose cyclophosphamide induces antitumor T-cell responses, which associate with survival in metastatic colorectal cancer. *Clin Cancer Res* . (2017) 23: 6771–80. doi: 10. 1158/1078-0432. CCR-17-0895

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=28855352) | [CrossRef Full Text](https://doi.org/10.1158/1078-0432.CCR-17-0895) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=M.+Scurr&author=T.+Pembroke&author=A.+Bloom&author=D.+Roberts&author=A.+Thomson&author=K.+Smart+&publication_year=2017&title=Low-dose+cyclophosphamide+induces+antitumor+T-cell+responses,+which+associate+with+survival+in+metastatic+colorectal+cancer&journal=Clin+Cancer+Res&volume=23&pages=6771-80)

56. Wan S, Pestka S, Jubin RG, Lyu YL, Tsai YC, Liu LF. Chemotherapeutics and radiation stimulate MHC class I expression through elevated interferon-beta signaling in breast cancer cells. *PLoS ONE* . (2012) 7: e32542. doi: 10. 1371/journal. pone. 0032542

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=22396773) | [CrossRef Full Text](https://doi.org/10.1371/journal.pone.0032542) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=S.+Wan&author=S.+Pestka&author=RG.+Jubin&author=YL.+Lyu&author=YC.+Tsai&author=LF.+Liu+&publication_year=2012&title=Chemotherapeutics+and+radiation+stimulate+MHC+class+I+expression+through+elevated+interferon-beta+signaling+in+breast+cancer+cells&journal=PLoS+ONE&volume=7&pages=e32542)

57. Wu K, Tan MY, Jiang JT, Mu XY, Wang JR, Zhou WJ, et al. Cisplatin inhibits the progression of bladder cancer by selectively depleting GMDSCs: a novel chemoimmunomodulating strategy. *Clin Immunol* . (2018) 193: 60–9. doi: 10. 1016/j. clim. 2018. 01. 012

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=29410331) | [CrossRef Full Text](https://doi.org/10.1016/j.clim.2018.01.012) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=K.+Wu&author=MY.+Tan&author=JT.+Jiang&author=XY.+Mu&author=JR.+Wang&author=WJ.+Zhou+&publication_year=2018&title=Cisplatin+inhibits+the+progression+of+bladder+cancer+by+selectively+depleting+GMDSCs%3A+a+novel+chemoimmunomodulating+strategy&journal=Clin+Immunol&volume=193&pages=60-9)

58. Sistigu A, Yamazaki T, Vacchelli E, Chaba K, Enot DP, Adam J, et al. Cancer cell-autonomous contribution of type I interferon signaling to the efficacy of chemotherapy. *Nat Med* . (2014) 20: 1301–9. doi: 10. 1038/nm. 3708

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=25344738) | [CrossRef Full Text](https://doi.org/10.1038/nm.3708) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=A.+Sistigu&author=T.+Yamazaki&author=E.+Vacchelli&author=K.+Chaba&author=DP.+Enot&author=J.+Adam+&publication_year=2014&title=Cancer+cell-autonomous+contribution+of+type+I+interferon+signaling+to+the+efficacy+of+chemotherapy&journal=Nat+Med&volume=20&pages=1301-9)

59. Wang YJ, Fletcher R, Yu J, Zhang L. Immunogenic effects of chemotherapy-induced tumor cell death. *Genes Dis* . (2018) 5: 194–203. doi: 10. 1016/j. gendis. 2018. 05. 003

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=30320184) | [CrossRef Full Text](https://doi.org/10.1016/j.gendis.2018.05.003) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=YJ.+Wang&author=R.+Fletcher&author=J.+Yu&author=L.+Zhang+&publication_year=2018&title=Immunogenic+effects+of+chemotherapy-induced+tumor+cell+death&journal=Genes+Dis&volume=5&pages=194-203)

60. Hori S, Miyake M, Tatsumi Y, Morizawa Y, Nakai Y, Onishi S, et al. Intravesical treatment of chemotherapeutic agents sensitizes bacillus Calmette-Guerin by the modulation of the tumor immune environment. *Oncol Rep* . (2019) 41: 1863–74. doi: 10. 3892/or. 2019. 6965

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=30628699) | [CrossRef Full Text](https://doi.org/10.3892/or.2019.6965) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=S.+Hori&author=M.+Miyake&author=Y.+Tatsumi&author=Y.+Morizawa&author=Y.+Nakai&author=S.+Onishi+&publication_year=2019&title=Intravesical+treatment+of+chemotherapeutic+agents+sensitizes+bacillus+Calmette-Guerin+by+the+modulation+of+the+tumor+immune+environment&journal=Oncol+Rep&volume=41&pages=1863-74)

61. Rakoff-Nahoum S, Medzhitov R. Toll-like receptors and cancer. *Nat Rev Cancer* . (2009) 9: 57–63. doi: 10. 1038/nrc2541

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=19052556) | [CrossRef Full Text](https://doi.org/10.1038/nrc2541) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=S.+Rakoff-Nahoum&author=R.+Medzhitov+&publication_year=2009&title=Toll-like+receptors+and+cancer&journal=Nat+Rev+Cancer&volume=9&pages=57-63)

62. Jinushi M. The role of innate immune signals in antitumor immunity. *Oncoimmunology* . (2012) 1: 189–94. doi: 10. 4161/onci. 1. 2. 18495

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=22720240) | [CrossRef Full Text](https://doi.org/10.4161/onci.1.2.18495) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=M.+Jinushi+&publication_year=2012&title=The+role+of+innate+immune+signals+in+antitumor+immunity&journal=Oncoimmunology&volume=1&pages=189-94)

63. Domingos-Pereira S, Hojeij R, Reggi E, Derré L, Chevalier MF, Romero P, et al. Local Salmonella immunostimulation recruits vaccinespecific CD8 T cells and increases regression of bladder tumor. *Oncoimmunology* . (2015) 4: e1016697. doi: 10. 1080/2162402X. 2015. 1016697

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=26140240) | [CrossRef Full Text](https://doi.org/10.1080/2162402X.2015.1016697) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=S.+Domingos-Pereira&author=R.+Hojeij&author=E.+Reggi&author=L.+Derré&author=MF.+Chevalier&author=P.+Romero+&publication_year=2015&title=Local+Salmonella+immunostimulation+recruits+vaccinespecific+CD8+T+cells+and+increases+regression+of+bladder+tumor&journal=Oncoimmunology&volume=4&pages=e1016697)

64. Li Q, Cherayil BJ. Role of Toll-like receptor 4 in macrophage activation and tolerance during Salmonella enterica serovar Typhimurium infection. *Infect Immun* . (2003) 71: 4873–82. doi: 10. 1128/IAI. 71. 9. 4873-4882. 2003

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=12933828) | [CrossRef Full Text](https://doi.org/10.1128/IAI.71.9.4873-4882.2003) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=Q.+Li&author=BJ.+Cherayil+&publication_year=2003&title=Role+of+Toll-like+receptor+4+in+macrophage+activation+and+tolerance+during+Salmonella+enterica+serovar+Typhimurium+infection&journal=Infect+Immun&volume=71&pages=4873-82)

65. Magnusson M, Tobes R, Sancho J, Pareja E. Cutting edge: natural DNA repetitive extragenic sequences from gram-negative pathogens strongly stimulate TLR9. *J Immunol* . (2007) 179: 31–5. doi: 10. 4049/jimmunol. 179. 1. 31

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=17579017) | [CrossRef Full Text](https://doi.org/10.4049/jimmunol.179.1.31) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=M.+Magnusson&author=R.+Tobes&author=J.+Sancho&author=E.+Pareja+&publication_year=2007&title=Cutting+edge%3A+natural+DNA+repetitive+extragenic+sequences+from+gram-negative+pathogens+strongly+stimulate+TLR9&journal=J+Immunol&volume=179&pages=31-5)

66. Gewirtz AT, Navas TA, Lyons S, Godowski PJ, Madara JL. Cutting edge: bacterial flagellin activates basolaterally expressed TLR5 to induce epithelial proinflammatory gene expression. *J Immunol* . (2001) 167: 1882–5. doi: 10. 4049/jimmunol. 167. 4. 1882

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=11489966) | [CrossRef Full Text](https://doi.org/10.4049/jimmunol.167.4.1882) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=AT.+Gewirtz&author=TA.+Navas&author=S.+Lyons&author=PJ.+Godowski&author=JL.+Madara+&publication_year=2001&title=Cutting+edge%3A+bacterial+flagellin+activates+basolaterally+expressed+TLR5+to+induce+epithelial+proinflammatory+gene+expression&journal=J+Immunol&volume=167&pages=1882-5)

67. Domingos-Pereira S, Cesson V, Chevalier MF, Derré L, Jichlinski P, Nardelli Haefliger D. Preclinical efficacy and safety of the Ty21a vaccine strain for intravesical immunotherapy of non-muscle-invasive bladder cancer. *Oncoimmunology* . (2016) 6: e1265720. doi: 10. 1080/2162402X. 2016. 1265720

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=28197393) | [CrossRef Full Text](https://doi.org/10.1080/2162402X.2016.1265720) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=S.+Domingos-Pereira&author=V.+Cesson&author=MF.+Chevalier&author=L.+Derré&author=P.+Jichlinski&author=HaefligerD.+Nardelli+&publication_year=2016&title=Preclinical+efficacy+and+safety+of+the+Ty21a+vaccine+strain+for+intravesical+immunotherapy+of+non-muscle-invasive+bladder+cancer&journal=Oncoimmunology&volume=6&pages=e1265720)

68. Arends TJ, Lammers RJ, Falke J, van der Heijden AG, Rustighini I, Pozzi R, et al. Pharmacokinetic, pharmacodynamic, and activity evaluation of TMX-101 in a multicenter phase 1 study in patients with papillary non-muscle-invasive bladder cancer. *Clin Genitourin Cancer* . (2015) 13: 204–9. doi: 10. 1016/j. clgc. 2014. 12. 010

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=25660383) | [CrossRef Full Text](https://doi.org/10.1016/j.clgc.2014.12.010) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=TJ.+Arends&author=RJ.+Lammers&author=J.+Falke&author=AG.+van+der+Heijden&author=I.+Rustighini&author=R.+Pozzi+&publication_year=2015&title=Pharmacokinetic,+pharmacodynamic,+and+activity+evaluation+of+TMX-101+in+a+multicenter+phase+1+study+in+patients+with+papillary+non-muscle-invasive+bladder+cancer&journal=Clin+Genitourin+Cancer&volume=13&pages=204-9)

69. Donin NM, Chamie K, Lenis AT, Pantuck AJ, Reddy M, Kivlin D, et al. A phase 2 study of TMX-101, intravesical imiquimod, for the treatment of carcinoma in situ bladder cancer. *Urol Oncol* . (2017) 35: 39. e1–39. doi: 10. 1016/j. urolonc. 2016. 09. 006

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=28341495) | [CrossRef Full Text](https://doi.org/10.1016/j.urolonc.2016.09.006) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=NM.+Donin&author=K.+Chamie&author=AT.+Lenis&author=AJ.+Pantuck&author=M.+Reddy&author=D.+Kivlin+&publication_year=2017&title=A+phase+2+study+of+TMX-101,+intravesical+imiquimod,+for+the+treatment+of+carcinoma+in+situ+bladder+cancer&journal=Urol+Oncol&volume=35&pages=39)

70. Aranda F, Vacchelli E, Obrist F, Eggermont A, Galon J, Sautès-Fridman C, et al. Trial Watch: toll-like receptor agonists in oncological indications. *Oncoimmunology* . (2014) 3: e29179. doi: 10. 4161/onci. 29179

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=25083332) | [CrossRef Full Text](https://doi.org/10.4161/onci.29179) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=F.+Aranda&author=E.+Vacchelli&author=F.+Obrist&author=A.+Eggermont&author=J.+Galon&author=C.+Sautès-Fridman+&publication_year=2014&title=Trial+Watch%3A+toll-like+receptor+agonists+in+oncological+indications&journal=Oncoimmunology&volume=3&pages=e29179)