

# Hopes and challenges: translational medical research in bladder cancer

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**Abstract:** Bladder cancer is a complex disease and could be classified into non-muscleinvasive or muscle-invasive subtypes according to the distinct genetic background and clinical prognosis. It is necessary to find a non-invasive, economical, and efficient method for the diagnosis and treatment of bladder cancer. Translational medicine provides such an opportunity. Genomics, proteomics, molecular biology, and bioinformatics that aid in studying and exploring the mechanism of bladder cancer development, bladder cancer-related genes, signaling pathways, key molecules, or targets can be clearly used for the diagnosis and treatment of bladder cancer. Biomarkers have been developed as part of a new detection kit for the early screening, diagnosis, and recurrence monitoring of bladder cancer through translational medicine. In addition, targeted drugs and immunological preparations can be used for the treatment of bladder cancer and further improve its existing diagnosis, treatment, and prognosis.

*Keywords:* bladder cancer; diagnosis; treatment; translational medicine

## 1. Overview of Bladder Cancer

Bladder cancer refers to malignant tumors that originate in the bladder mucosa. The most common clinical manifestation is intermittent and painless gross hematuria. This symptom may be accompanied by bladder irritation such as urinary frequency and urgency, dysuria, and lymph node metastasis, the last of which occurs in the late stage. After distant metastasis, pelvic mass, lower extremity edema, pain, urinary retention, renal failure, anemia, weight loss, and other symptoms may occur and may eventually lead to death.

Globally, bladder cancer ranks 9<sup>th</sup> in malignant tumors and 2<sup>nd</sup> in urinary tumors. The age-standardized incidence rate of bladder cancer for males is about 4.1 times that of females<sup>[1,2]</sup>. The mortality rate of bladder cancer in developed countries has a downward trend, ranking 13<sup>th</sup> among malignant tumors<sup>[2]</sup>. In China, due to increases in both the aging and smoking populations, the intensification of industrialization, and the increase in environmental pollution, bladder cancer has been increasing annually. Its overall incidence rate ranks 6<sup>th</sup> in malignant tumors and 1<sup>st</sup> in urinary system tumors in males. Its incidence rate is 3.3 times higher in males than in females and this increases with age, seriously jeopardizing the health of the Chinese people<sup>[3,4]</sup>.

The histological types of bladder cancer include urothelial carcinoma (or transitional cell carcinoma), squamous cell carcinoma, adenocarcinoma, small-cell carcinoma, mixed carcinoma, metastatic carcinoma, and carcinosarcoma. Among them, urothelial carcinoma

is the most common, accounting for >90% of all types of bladder cancer, squamous cell carcinoma accounts for about 5%, glandular carcinoma accounts for about 5% and is more common in patients with bladder valvulus, while other types of bladder cancer are extremely rare<sup>[5,6]</sup>. Pathologically, bladder cancer is classified into non-muscle invasive bladder cancer (NMIBC) and muscle invasive bladder cancer (MIBC). NMIBC is more common, accounting for about 75% of bladder cancer diagnosis (including Tis, Ta, T1, and carcinoma *in situ* [CIS]). About 50% of NMIBC is low-grade bladder cancer, and even though the prognosis is relatively good, the recurrence rate is high. Although CIS belongs to NMIBC, the degree of malignancy is high, the differentiation is poor, and the rate of progression is high. Another 25% of bladder cancers are MIBC (including T2, T3, and T4) or metastatic bladder cancer. The vast majority of MIBC is high-grade bladder cancer. The tumor is easy to infiltrate and metastasize, and the prognosis is poor<sup>[7]</sup>.

## 2. Current Status of Research on the Diagnosis and Treatment of Bladder Cancer

### 2.1. Research status of bladder cancer diagnosis

Transurethral resection of bladder tumor (TURBT) biopsy and exfoliative cytology of the urine are the most important methods for the clinical diagnosis and followup of bladder cancer. Clinical symptoms and imaging examinations (B-scan ultrasonography, kidneys, ureters and bladder, and intravenous urography), computed tomography (CT), and magnetic resonance imaging (MRI), among others, have certain diagnostic value. Cystoscopy combined with biopsy is still the most accurate diagnosis method. However, its drawback is the invasiveness of the examination and the chances of missing the diagnosis for CIS, microcarcinoma, and inflammatory cancer. Exfoliative cytology of the urine has a high specificity for bladder cancer, but it is not sensitive enough and is susceptible to trauma, inflammation, or other urinary benign lesions with false-positive results. The search for high-sensitivity, specificity, non-invasive, convenient, quick, and economical bladder cancer diagnosis and follow-up methods has been a research challenge in the fields of basic medicine, oncology, and urology. In recent years, a large number of bladder cancer markers have been reported, all of which have certain auxiliary or potential clinical application value. Bladder cancer markers approved by the US Food and Drug Administration (FDA) for clinical use include nuclear matrix protein 22 (NMP22), BTAstat, BTAtrak, FDP, FISH, and ImmunoCyt. To explore bladder cancer markers with high sensitivity and specificity, it is highly crucial to develop early diagnosis methods based on bladder cancer markers.

### 2.2. Research status of NMIBC treatment

TURBT is the most important diagnosis and treatment method of NMIBC. The TURBT biopsy procedure can

confirm the diagnosis of NMIBC. The whole tumor tissue visible to the naked eye under cystoscopy can achieve the purpose of treating NMIBC. Due to the high recurrence rate after NMIBC, a single TURBT is difficult to improve the prognosis of patients. Therefore, post-operative adjuvant intravesical chemotherapy (or immunotherapy) after TURBT has become the first-line program for the clinical treatment of NMIBC. The latest guidelines from the European Association of Urology suggest that, for patients with incomplete tumor resection of TURBT, no myometrial tissue in the tissue specimens and high-grade or T1 phase of the pathological report are recommended for the first time after the first electroresection. Secondary resection within 2-6 weeks and immediate chemotherapy after TURBT are recommended for patients with low-risk NMIBC as well as intermediate-risk NMIBC with a low risk of recurrence. Patients with intermediate-risk NMIBC are recommended for a full dose of bacillus Calmette-Guerin (BCG) perfusion immunotherapy or post-operative intravesical chemotherapy after TURBT not exceeding 1 year. Patients with high-risk NMIBC are recommended for BCG perfusion after TURBT for 1-3 years, while patients with a higher risk of progression may be considered for radical cystectomy<sup>[8]</sup>. Reducing the recurrence rate of patients with NMIBC and improving their sensitivity to chemotherapy drugs are the issues and challenges in current bladder cancer research.

### 2.3. Research status of MIBC treatment

Radical cystectomy with pelvic lymphadenectomy is currently the first-line clinical treatment of MIBC. Radical cystectomy includes open surgery and laparoscopic surgery. However, with the rapid development of minimally invasive urological surgery, open surgery has gradually been replaced by laparoscopic surgery. Laparoscopic surgery can be further divided into traditional two-dimensional laparoscopy, new three-dimensional (3D) laparoscopy, and robot-assisted laparoscopy. 3D laparoscopy in radical cystectomy is beneficial in terms of refined operation and the 3D sense of space, making it the current preferred procedure. Robot-assisted laparoscopy is in development toward future minimally invasive urological surgery. It is widely promoted and applied in European developed countries but has not been popularized in China<sup>[9,10]</sup>.

The need for an extended lymph node dissection for MIBC remains controversial. Most scholars believe that patients with suspected lymph node metastasis should undergo extended lymph node dissection. A meta-analysis indicated that extended lymph node dissection not only significantly prolonged the probability of recurrence-free survival for lymph node-positive patients with pT3~4 but also for lymph node-negative patients<sup>[11]</sup>. Chemotherapy is an important adjunct to MIBC, including neoadjuvant chemotherapy (preoperative) and adjuvant chemotherapy (postoperative). Neoadjuvant chemotherapy has been a subject of debate in recent years though its efficacy is better than adjuvant chemotherapy. The

most commonly used chemotherapy regimen is gemcitabine and cisplatin (GC) regimen and methotrexate, vinblastine, azithromycin, and cisplatin (MVAC) regimen<sup>[12]</sup>. Studies have shown that there is no significant difference in the pathologic complete response rates between GC and MVAC regimens in MIBC patients (31% vs. 29%,  $P=0.77$ )<sup>[13]</sup>. The current mainstream view is that neoadjuvant chemotherapy before radical cystectomy can improve the meticulousness of the surgical resection of the tumor, significantly prolonging the overall survival rate and helping to improve the prognosis of patients<sup>[14]</sup>. The reduction in the MIBC patients' recurrence rate and progression rate, improvement in their sensitivity to chemotherapy drugs as well as improvement in their overall survival rate are the main issues and challenges in current bladder cancer research.

### 3. The Important Value and Significance of Translational Medical Research

#### 3.1. Translational medicine as the only way to achieve precision medicine

In 2003 and 2015, the National Institute of Health (NIH) introduced the concepts of translational medicine and precision medicine, establishing an open and mutual "clinical-basic/clinical" system in the translational medical system. With it being the core of translational medicine, it aims to build a bridge between basic research and clinical application to improve the conversion rates of scientific research results and, in turn, promote the development of modern biomedicine and precision medicine<sup>[15,16]</sup>. The original concept of translational medicine refers to the transformation of basic research results into products that can be applied in the clinic<sup>[17]</sup>. With the development of medical science and technology and precision medicine, the scope of translational medicine has been further expanded. We believe that the more precise concept of translational medicine should be the comprehensive use of cutting-edge biomedical technology and scientific research methods through multifaceted research, multi-angle verification, and multidisciplinary and multiagency collaborations with the aim to explore the mechanisms of disease occurrence and development to transform the research results in the basic field into products or technologies that can be applied in the clinic and ultimately achieve accurate prevention, diagnosis, and treatment of diseases.

#### 3.2. Translational medicine as the basis for research-based medical model

With the rapid development of China's medical and health undertakings, a research-based medical model has gradually become the goal and direction for the construction of major medical colleges and affiliated hospitals<sup>[18]</sup>. Clinical and scientific research is the basis for the research-based medical model, and translational medicine is the most

reliable foundation for its construction. The ultimate goal of translational medicine is to improve the prevention, diagnosis, and treatment of diseases. This includes the need to find problems in clinical practice and establish them as research objectives, to use basic research methods and techniques to explore the root causes of these problems, and, in turn, to apply appropriate clinical solutions in translational medicine so as to ultimately achieve proper clinical treatment and services that benefit the majority of patients.

#### 3.3. Translational medicine as a means to improve the diagnosis and treatment of bladder cancer

Bladder cancer has spatial heterogeneity, recurrence episodes, local invasion, and metastasis as well as high postoperative recurrence rate<sup>[19]</sup>. Currently, there are many methods for the clinical diagnosis and treatment of bladder cancer (such as cystoscopy, imaging technology, surgery, and radiotherapy and chemotherapy), but they all have respective limitations. Therefore, it is urgent and necessary to find a non-invasive, economical, and efficient method for the diagnosis and treatment of bladder cancer, and translational medicine provides such an opportunity. Genomics, proteomics, molecular biology, and bioinformatics that aid in studying and exploring the mechanism of bladder cancer development, bladder cancer-related genes, signaling pathways, key molecules, or targets can be clearly used for the diagnosis and treatment of bladder cancer. Biomarkers have been developed as part of a new detection kit for the early screening, diagnosis, and recurrence monitoring of bladder cancer through translational medicine. In addition, targeted drugs and immunological preparations can be used for the treatment of bladder cancer and further improve its existing diagnosis, treatment, and prognosis.

### 4. Bladder Cancer as the Foundation for the Practice of Translational Medical Research

Currently, China has made positive achievements in the construction and implementation of research institutions for translational medicine and precision medicine. However, from an objective perspective, it is still in the initial stages of exploration and there is a considerable amount of further research required, especially from basic to clinical research, before obtaining international recognition. Nonetheless, there have been a few major original achievements and low conversion rates of scientific research results. In recent years, the research team of the Institute of Biophysics, Chinese Academy of Sciences, has made outstanding achievements in the fields of bladder cancer research and translational medical research, which has effectively promoted the development of translational medicine in bladder cancer in China.

#### 4.1. *In vitro* diagnostic for the new bladder cancer tumor marker AG31

After more than 10 years of intensive research, we have discovered a bladder cancer-specific marker, AG31, and developed a highly specific and sensitive anti-bladder cancer monoclonal antibody known as BCMab1<sup>[20,21]</sup>. On this basis, the peripheral blood circulating tumor cell (CTC) kit and urine exfoliated cell (UTC) kit for the detection of bladder cancer were successfully developed. The BCMab1 monoclonal antibody was used as a probe to modify the magnetic nanoparticles (MNPs), and the BCMab1-MNPs complex was constructed. The target cells were sorted and enriched by magnetic separation, which can be used for both the qualitative and quantitative detections in clinical samples. At present, both the CTC and UTC kits have detected >3700 specimens in seven hospitals across five cities, namely Beijing, Shanghai, Kunming, Hangzhou, and Changchun, with an accuracy rate exceeding 90%. The CTC and UTC kits with BCMab1 as the core can quickly and accurately detect tumor cells in blood and urine. Moreover, it not only can perform dynamic monitoring of tumor metastasis and real-time evaluation of therapeutic effects but also capture tumor cells that can be cultured *in vitro* and detected by genomics. The kits have high scientific value and innovation as they have realized the leap from being original innovations to the clinical application of the first urinary tumor markers with independent intellectual property rights in China.

#### 4.2. Targeted therapeutic drugs based on BCMab1 monoclonal antibody

In May 18, 2015, the US FDA approved Tecentriq (Atezolizumab) for the treatment of urothelial cancer; this is the first new PD-1/PD-L1 inhibitor approved for bladder cancer. We are proud to have also successfully developed BCMab1 monoclonal antibody-targeting drug with very high-specificity and significant antitumor effect. The BCMab1-targeted drug for the infusion treatment of bladder cancer not only specifically kills tumor cells without damaging the bladder mucosa but it is also not absorbed by the bladder mucosa, preventing a series of difficulties encountered by intravenous use. In terms of safety and effectiveness, it is incomparable with other drugs. This is also the first project in China that has been completely developed independently and has successfully transformed the field of clinical precision medicine. This project will further progress the precision medical treatment of bladder cancer in China and across the globe.

#### 4.3. Localization of NMP22 Kit

NMP22 acts as a scaffold for the nuclear structure and is involved in DNA replication and transcription. NMP22 level in the urine of healthy people is usually extremely low. When the cells are malignant, NMP22 is abnormally increased at the end of the division. After a long-term

follow-up study on NMP22, we have successfully developed a domestic NMP22 test kit to fill the gap in bladder tumor detection in China. The sensitivity of the kit is significantly better than that of the Alere NMP22 BladderChek test kit in the US. It has broad application prospects in the screening, early diagnosis, and recurrence monitoring of patients with high risk of bladder cancer, making it another important achievement in bladder cancer translational medicine in China. The successful development of the domestic NMP22 kit has broken the technological monopoly of foreign biomedical industry. The application of the obtained results across China will benefit the majority of patients with bladder cancer.

#### 4.4. Important advances in genetics research on the origin of bladder cancer stem cells (BCSCs)

Cancer stem cells play an important role in tumor cell self-renewal, tumorigenesis, drug resistance, and metastasis. The origin and genetic basis of BCSCs are still unclear. We have published two consecutive articles in the journal *European Urology*, revealing the genetic basis of the origin of human BCSCs while also elucidating on how the driver mutations in cancerous cells regulate the self-renewal mechanism of BCSCs<sup>[22,23]</sup>. Through research, we have found that BCSCs originate from the epithelial stem cells in bladder or bladder cancer non-stem cells. Of the 21 key genes that have been mutated in BCSCs, six have not been reported in bladder cancer (*ETS1*, *GPRC5A*, *MKLI*, *PAWR*, *PITX2*, and *RGS9BP*). The combination of *ARID1A*, *GPRC5A*, and *MLL2* mutations significantly enhances the ability of bladder cancer non-stem cells to convert into BCSCs. This is the first time that the genomics of BCSCs using single-cell all-exome sequencing technology have been described<sup>[24]</sup>. It has experimentally confirmed that BCSCs originate from the scientific problem of the epithelial stem cells in bladder or bladder cancer non-stem cells. This is also the first attempt in the world to use single-cell sequencing technology to explore the genomics of cancer stem cells, which has been verified by functional experiments<sup>[24]</sup>.

#### 4.5. Multi-party collaboration in the launching of China's bladder cancer precision medical plan

In 2016, the media reported<sup>[25]</sup> that the Institute of Biophysics, Chinese Academy of Sciences, the Bladder Cancer Diagnosis and Treatment Centre of Renji Hospital, which is affiliated to the Shanghai Jiao Tong University School of Medicine, the Urological Comprehensive Treatment Centre of the Affiliated Hospital of Qingdao University, the Department of Urology at The Second Affiliated Hospital of Kunming Medical University and the Beijing Taipu-Shunkang Medical Laboratory have jointly formed a research and innovation team and launched the "China Bladder Cancer Precision Medical Plan" to provide early screening and diagnosis, pre-operative risk assessment, prognosis, recurrence judgment, targeted therapy monitoring and

other aspects for bladder cancer patients in order to provide them with comprehensive treatment and care.

In this comprehensive treatment for bladder cancer, the diagnostic system and targeted drugs based on the BCMab1 monoclonal antibody are the first in China to apply original scientific research results to precision medicine in clinical trials for bladder cancer. The series of research results have been published in international peer-reviewed journals such as *Clinical Cancer Research* and *Cancer Research and European Urology*, among others, and have obtained three Chinese patents and one US patent, which were evaluated by international peers as “a revolutionary breakthrough in the field of bladder cancer in 40 years<sup>[21]</sup>.”

## 5. Current Issues and Challenges in Bladder Cancer and Translational Medical Research

Based on bladder cancer research and translational medical research practices, this review has elaborated on precision medicine, genomics, epigenetics, non-coding RNA, BCSCs, bladder cancer markers, animal models, neoadjuvant chemotherapy, recurrence, and metastasis as the ten critical research areas that have been reviewed in the diagnosis and treatment of bladder cancer and translational medicine.

Currently, the main challenges in bladder cancer research and translational medical research can be summarized as follows: (1) The realization of multidisciplinary and multi-technology integration<sup>[26]</sup>, the rational and effective use of clinically existing bladder cancer diagnosis and treatment procedures and their new research frontiers, the improvement of early diagnosis of bladder cancer, the reduction in post-operative recurrence rate, and the attainment of an accurate diagnosis and treatment of bladder cancer<sup>[27]</sup>; (2) the use of genomics, epigenetics, and cancer stem cell research to further reveal the origin of bladder cancer and its molecular mechanism during its occurrence and development to establish a more accurate molecular classification of bladder cancer and to guide the diagnosis and treatment of bladder cancer<sup>[28]</sup>; (3) the exploration of the regulation of non-coding RNA in the occurrence and development of bladder cancer so as to determine its application value in the diagnosis and treatment of bladder cancer<sup>[29]</sup>; (4) the detection of bladder cancer markers with high sensitivity and specificity to develop early diagnosis kits, targeted therapeutic drugs, and immunological preparations based on bladder cancer markers through translational medicine so as to improve the conversion rate of scientific research results<sup>[26]</sup>; (5) the selection and establishment of the best animal model in bladder cancer, making full use of the similarities between animal and human bodies but additionally improving animal models for basic and clinical research<sup>[30]</sup>; (6) the improvement of patients' sensitivity to neoadjuvant chemotherapy as well as screening for their sensitivity to certain types of chemotherapy drugs<sup>[31]</sup>; (7) the accurate prediction of the effectiveness of chemotherapy and immunotherapy so that

patients' treatment plans can be adjusted<sup>[31]</sup>; (8) new endoscopic techniques, imaging techniques<sup>[32]</sup>, and a combination of multiple bladder cancer markers that are expected to improve the rate of early diagnosis of bladder cancer. However, the challenge lies in achieving the most accurate diagnosis with the lowest detection cost; and (9) the types of drugs combined with chemotherapy, chemotherapy combined with immunotherapy, chemotherapy-assisted surgery, and other comprehensive treatment programs that are expected to improve the prognosis of patients with bladder cancer. However, the increase in efficacy may also be faced with adverse reactions caused by the combination of multiple drugs which, in turn, may further aggravate the problems<sup>[33]</sup>.

## 6. Conclusion and Outlook

Precision medicine is a new direction and objective in the development of translational medicine. At the same time, translational medicine is the only way to achieve precision medicine. With the cross-integration of information technology, biological science, and technology in recent years, as well as the rapid development of omics technology, second-generation sequencing technology, molecular biology technologies, and minimally invasive urological surgery, modern medical models have gradually moved toward a multidisciplinary, multicentered direction of precision medicine. On this basis, there are unprecedented opportunities in the fields of bladder cancer research and translational medical research. Targeted therapy and immunotherapy will certainly serve as a new research direction to promote the development of bladder cancer research and translational medicine. With the diagnosis and treatment of bladder cancer as the pivotal point, the researchers will carry out multidisciplinary integration of basic medicine, clinical medicine, and imaging medicine, among others, to build a multicenter cooperation model involving universities, hospitals, scientific research institutions, and commercial organizations, all of which will certainly produce more social and economic benefits and better serve the majority of bladder cancer patients.

## Competing Interests

No potential conflicts of interest were disclosed.

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