

## Establishing the Bladder Cancer Research Centre at the University of Birmingham

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# 1 **Establishing the Bladder Cancer Research Centre at the University of Birmingham**

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12

13 The new Bladder Cancer Research Centre at the University of Birmingham unifies the University's  
14 multidisciplinary bladder cancer research activity within a single research centre, working within five  
15 core research themes, to translate biomedical science into healthcare benefits for patients with  
16 bladder cancer.

17

18 Bladder cancer is the seventh most common cancer in Western society and has a global annual  
19 incidence of >430,000<sup>1</sup>. Most patients (75–80%) present with non-muscle-invasive bladder cancer  
20 (NMIBC), which, although not immediately life-threatening, recurs in up to 80% of patients<sup>2</sup> and  
21 progresses to muscle-invasive bladder cancer (MIBC) in up to 44% of patients<sup>3</sup>. Muscle-invasion is a  
22 crucial step in the disease course, with 5-year survival for MIBC only 27-50% despite radical therapies,  
23 including surgery, chemotherapy and radiotherapy<sup>4</sup>. Of the 20–25% of patients who are initially  
24 diagnosed with MIBC, around half will have incurable locally advanced or metastatic disease, many of  
25 whom will have been diagnosed after symptomatic emergency presentation.

26 Despite international guidelines propagating evidence-based practice<sup>2,4</sup>, outcomes for patients with  
27 bladder cancer have remained stubbornly unchanged for 30 years, and so improvement and  
28 innovation beyond these existing standard-of-care frameworks is needed across all aspects of bladder  
29 cancer practice, from diagnosis (and screening opportunities) to novel therapeutics (and personalized  
30 medicine), and with more focus on patient needs and quality of life. Unfortunately, such innovation  
31 has been stifled internationally by a chronic lack of research funding compared with other cancers<sup>6</sup>  
32 and is particularly true for patients with NMIBC, who could still be affected by the stigma of the  
33 historical term ‘superficial bladder cancer’ that intrinsically suggests unimportant disease and that by  
34 now should have been eradicated from medical terminology<sup>2</sup>. Bladder cancer is also one of the most  
35 expensive malignancies to manage on a per-patient basis from diagnosis to death, the majority of cost  
36 being attributable to the long-term treatment and surveillance of NMIBC<sup>5</sup>. Although the past 10-years  
37 has seen much investment and innovation in MIBC (from chemoradiotherapy to immuno-oncology  
38 agents, and robotic cystectomy to molecular subtyping), the treatment of NMIBC has remained largely  
39 unchanged.

40

#### 41 **Challenges in bladder cancer**

42 Besides the low public awareness of bladder cancer and its symptoms and the potential referral delays  
43 from primary care (especially for women), numerous immediate shortcomings exist in current  
44 urological practice, including use of historical surgical techniques (such as transurethral resection of  
45 bladder tumour, TURBT)<sup>6</sup>; lack of new therapeutic agents<sup>5</sup>; shortage and/or affordability of existing  
46 therapeutic agents<sup>7</sup>; prolonged patient pathways<sup>8</sup>; absence of accurate risk stratification or prediction  
47 tools; high cost of patient management; and poor awareness of the support needs for patients. The  
48 solutions to these interlinked challenges require multidisciplinary collaborations across the traditional  
49 boundaries of academic research groups.

50 The University of Birmingham has a long track-record of tackling the challenges and research priorities  
51 of bladder cancer<sup>9</sup>, with an accompanying history of practice-changing clinical studies (for example

52 narrow-band imaging cystoscopy<sup>2</sup> (2008), chemoradiotherapy<sup>4</sup> (2012)) and other research  
53 achievements (such as recognition of aggressive bladder cancers derived from the basal layer of the  
54 urothelium (2010), the utility of urinary cell-free DNA for biomarker discovery (2016)). Thus, in autumn  
55 2020, we established the Bladder Cancer Research Centre (BCRC) to unify the University of  
56 Birmingham's multidisciplinary bladder cancer research activities within a single research centre with  
57 an overarching ethos and management structure — the first centre of its kind in the UK and one of  
58 few worldwide (<https://www.birmingham.ac.uk/research/bladder-cancer/index.aspx>). Through the  
59 establishment of the BCRC, we intend to achieve a seamless bench-to-bedside pipeline for innovation  
60 and practice-changing studies, expand collaborative research and research training, and raise bladder  
61 cancer awareness and research funding. Building upon our existing expertise, we have strategically  
62 arranged the BCRC into five core research themes: proteomics and biomarkers; genomics and  
63 bioinformatics; novel therapeutics; biomedical engineering; and clinical research and clinical trials  
64 (Box 1).

65

#### 66 **Proteomics & biomarkers**

67 Transforming the care of patients with bladder cancer is possible through accurate diagnostic,  
68 prognostic and predictive biomarkers observed in urine, blood or tumour tissue — for example,  
69 replacing some cystoscopies with urinary diagnostics. Our approaches include mass spectrometry-  
70 based proteomics and exome and transcriptome sequencing to identify protein, DNA and RNA  
71 biomarkers, respectively, with specific interests in non-invasive diagnosis, and prediction of outcomes  
72 and therapeutic responses in high-risk NMIBC.

#### 73 **Genomics & bioinformatics**

74 Deep sequencing of bladder cancer tumour DNA and RNA has enabled understanding of the crucial  
75 alterations driving bladder cancer development, recurrence and progression. For true patient benefit,  
76 much work is still needed to understand the many genomic, epigenomic and transcriptomic events  
77 that occur in bladder cancer and integrate that understanding with our knowledge of the cell biology,

78 immunology and germline genetics of this disease. To derive meaningful outputs from this plethora  
79 of data, we explore non-standard modelling and machine learning (artificial intelligence); we also  
80 apply computational methods to the 'dark matter' of genomics and transcriptomics (such as non-  
81 coding mutations or unusual transcriptional events) to obtain a more complete picture of bladder  
82 cancer biology.

### 83 **Novel therapeutics**

84 Cancer immunology and immunotherapy is a core theme across oncology, with an almost 50-year  
85 history in the treatment of NMIBC<sup>2</sup>, and we work closely with the University of Birmingham's Cancer  
86 Immunology and Immunotherapy Centre as well as those farther afield<sup>10</sup>. However, despite the  
87 potential of immunotherapy in oncology and its long history in the treatment of NMIBC as intravesical  
88 BCG<sup>2</sup>, this therapy has not proven to be a panacea for all patients with bladder cancer. Our aim is to  
89 combine our growing knowledge of the biology of bladder cancer with innovative screening  
90 approaches to identify novel and adjunctive therapies with low toxic effect profiles that eradicate  
91 disease effectively, including drugs that can be administered intravesically, especially for patients with  
92 high-risk NMIBC. Drug development is co-ordinated with the development of novel assay systems and  
93 integrated with genomic studies to enable the identification of risk-stratifying and predictive  
94 biomarkers for improved patient selection and monitoring.

### 95 **Biomedical engineering**

96 Effective adjuvant therapies should offer the potential to durably control or, preferably, eradicate  
97 local disease, and not just be a substitute for flawed surgery (TURBT). TURBT has its shortcomings<sup>6,8</sup>,  
98 yet the resectoscope has remained fundamentally unchanged for almost 60 years<sup>6</sup>. In the meantime,  
99 robot-assisted radical cystectomy for MIBC has become commonplace<sup>4</sup>. Hence, TURBT truly is the  
100 neglected procedure in the bladder cancer technology race<sup>6</sup>, and the innovation of transurethral  
101 bladder cancer surgery through the use of engineering techniques (including design, mechanical  
102 testing, computational modelling) is long overdue. We will continue to develop new instruments that  
103 facilitate TURBT by working with industry partners. Furthermore, we will continue development of

104 endoscopes and instruments that are currently used in bladder cancer management and develop  
105 novel devices for drug delivery mechanisms.

### 106 **Clinical research & clinical trials**

107 Clinical research and clinical trials are a fundamental component of the BCRC, ultimately delivering  
108 the translation of laboratory-based discoveries. We also consider that changes to the patient pathway  
109 are where considerable gains can be made with the implementation of 21<sup>st</sup> century technologies and  
110 practices, such as non-invasive diagnosis and multiparametric MRI staging<sup>8</sup>.

111 Clinical trials activity is supported by the University's Cancer Research UK Clinical Trials Unit (CRCTU:  
112 <https://www.birmingham.ac.uk/research/crctu/index.aspx>) and the University of Birmingham Clinical  
113 Trials Unit (BCTU: <https://www.birmingham.ac.uk/research/bctu/index.aspx>).

114

115 Clearly, no single organization can achieve the huge change that is required for patients with bladder  
116 cancer and, therefore, collaboration is key, accompanied by the standardization and sharing of clinical  
117 and research datasets. The BCRC will continue to expand its outward-looking, internationally-  
118 collaborative approach, driven by a desire to maximize the value of our extensive biospecimen  
119 collection and datasets and to undertake clinical trials as soon as evidence permits. We have strong  
120 existing partnerships with the Structural Genomics Consortium (University of Oxford, UK), the  
121 Translational Oncology and Urology Research team (King's College London, UK) and the Institute of  
122 Cancer Research (London, UK), and are actively engaged with UK bladder cancer charities and the UK's  
123 National Cancer Research Institute research groups.

124

### 125 **The future**

126 In many instances, cutting-edge science and technologies are both more effective and more cost-  
127 effective than existing clinical approaches and 'just' require the research funding to generate a  
128 regulatory level of supportive evidence – for patients with NMIBC especially the dedicated funding is

129 lacking, and not the efforts, inspiration and innovation of the research community. Moreover, many  
130 of these innovations could facilitate the post-COVID recovery of bladder cancer diagnostic and  
131 surveillance services<sup>8</sup>, in parallel with providing the fundamental long-term change that is urgently  
132 required. The BCRC at the University of Birmingham intends to catalyse and drive such improvements  
133 in practice — to translate biomedical science into healthcare benefits for bladder cancer patients.

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## Box 1 | The five core research themes of the Bladder Cancer Research Centre

### **Proteomics and biomarkers**

Investigating non-invasive diagnosis, prediction of outcomes and therapeutic responses in high-risk non-muscle invasive bladder cancer (NMIBC) using proteomics and exome and transcriptome sequencing to identify biomarkers.

### **Genomics and bioinformatics**

Exploring non-standard modelling and machine learning (artificial intelligence) and applying computational methods to the 'dark matter' of genomics and transcriptomics (such as non-coding mutations or unusual transcriptional events) to obtain a more complete picture of bladder cancer biology.

### **Novel therapeutics**

Combining our growing knowledge of the biology of bladder cancer with innovative screening approaches to identify novel and adjunctive therapies with low toxic effect profiles that eradicate disease effectively, including drugs that can be administered intravesically, especially for patients with high-risk NMIBC. Co-ordinating drug development with the development of novel assay systems and integrating genomic studies to enable the identification of risk-stratifying and predictive biomarkers for improved patient selection and monitoring.

### **Biomedical engineering**

Innovating transurethral bladder cancer surgery by using engineering techniques including design, mechanical testing and computational modelling. Developing new instruments that facilitate transurethral resection of bladder tumour by working with industry partners. Continuing development of endoscopes and instruments that are currently used in bladder cancer management and developing novel devices for drug delivery mechanisms.

### **Clinical research and clinical trials.**

Delivering the translation of laboratory-based discoveries to the clinic and understanding that changes to the patient pathway are where considerable gains can be made with the implementation of 21<sup>st</sup> century technologies and practices, such as non-invasive diagnosis and multiparametric MRI staging.

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## **COMPETING INTERESTS**

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