Establishing the Bladder Cancer Research Centre at the University of Birmingham

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

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

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

Challenges in bladder cancer

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

The University of Birmingham has a long track record of tackling the challenges and research priorities of bladder cancer[9], with an accompanying history of practice-changing clinical studies (for example, narrow-band imaging cystoscopy[2] (2008) and chemoradiotherapy[4] (2012)) and other research achievements (such as recognition of aggressive bladder cancers derived from the basal layer of the urothelium (2010) and the utility of urinary cell-free DNA for biomarker discovery (2016)). Thus, in autumn 2020, we established the Bladder Cancer Research Centre (BCRC) to unify the University of Birmingham's multidisciplinary bladder cancer research activities within a single research centre with an overarching ethos and management structure — the first centre of its kind in the UK and one of few worldwide. Through the establishment of the BCRC, we intend to achieve a seamless bench-to-bedside pipeline for innovation and practice-changing studies, expand collaborative research and research training, and

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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. Coordinating 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 twenty-first century technologies and practices, such as non-invasive diagnosis and multiparametric MRI staging.

raise bladder cancer awareness and research funding. Building upon our existing expertise, we have strategically arranged the BCRC into five core research themes: proteomics and biomarkers; genomics and bioinformatics; novel therapeutics; biomedical engineering; and clinical research and clinical trials (BOX 1).

Proteomics and biomarkers

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

Genomics and bioinformatics

Deep sequencing of bladder cancer tumour DNA and RNA has enabled understanding of the crucial alterations driving bladder cancer development, recurrence and progression. For true patient benefit, much work is still needed to understand the many genomic, epigenomic and transcriptomic events that occur in bladder cancer and integrate that understanding with our knowledge of the cell biology, immunology and germline genetics of this disease. To derive meaningful outputs from this plethora of data, we explore non-standard modelling and machine learning (artificial intelligence); we also apply 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

Cancer immunology and immunotherapy is a core theme across oncology, with an almost 50-year history in the treatment of NMIBC[2], and we work closely with the University of Birmingham's Cancer Immunology and Immunotherapy Centre as well as those farther afield[10]. However, despite the potential of immunotherapy in oncology and its long history in the treatment of NMIBC as intravesical BCG[2], this therapy has not proven to be a panacea for all patients with bladder cancer. Our aim is to combine 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. Drug development is co-ordinated with the development of novel assay systems and integrated with genomic studies to enable the identification of risk-stratifying and predictive biomarkers for improved patient selection and monitoring.

Biomedical engineering

Effective adjuvant therapies should offer the potential to durably control or, preferably, eradicate local disease, and not just be a substitute for flawed surgery (TURBT). TURBT has its shortcomings[5,8], yet the resectoscope has remained fundamentally unchanged for almost 60 years[5]. In the meantime, robot-assisted radical cystectomy for MIBC has become commonplace[4]. Hence, TURBT truly is the neglected procedure in the bladder cancer technology race[5], and the innovation of transurethral bladder cancer surgery through the use of engineering techniques (including design, mechanical testing and computational modelling) is long overdue. We will continue to develop new instruments that facilitate TURBT by working with industry partners. Furthermore, we will continue development of endoscopes and instruments that are currently used in bladder cancer management and develop novel devices for drug delivery mechanisms.

Clinical research and clinical trials

Clinical research and clinical trials are a fundamental component of the BCRC, ultimately delivering the translation of laboratory-based discoveries. We also consider that changes to the patient pathway are where considerable gains can be made with the implementation of twenty-first century technologies and practices, such as non-invasive diagnosis and multiparametric MRI staging[8]. Clinical trial activity is supported by the University's Cancer Research UK Clinical Trials Unit (CRCTU) and the University of Birmingham Clinical Trials Unit (BCTU).

Clearly, no single organization can achieve the huge change that is required for patients with bladder cancer and, therefore, collaboration is key, accompanied

by the standardization and sharing of clinical and research datasets. The BCRC will continue to expand its outward-looking, internationally collaborative approach, driven by a desire to maximize the value of our extensive biospecimen collection and datasets and to undertake clinical trials as soon as evidence permits. We have strong existing partnerships with the Structural Genomics Consortium (University of Oxford, UK), the Translational Oncology and Urology Research team (King's College London, UK) and the Institute of Cancer Research (London, UK), and we are actively engaged with UK bladder cancer charities and the UK's National Cancer Research Institute research groups.

The future

In many instances, cutting-edge science and technologies are both more effective and more cost-effective than existing clinical approaches and 'just' require the research funding to generate a regulatory level of supportive evidence — for patients with NMIBC especially, the dedicated funding is lacking, and not the efforts, inspiration and innovation of the research community. Moreover, many of these innovations could facilitate the post-COVID recovery of bladder cancer diagnostic and surveillance services[8], in parallel with providing the fundamental long-term change that is urgently required. The BCRC at the University of Birmingham intends to catalyse and drive such improvements in practice — to translate biomedical science into health-care benefits for patients with bladder cancer.

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Competing interests

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RELATED LINKS

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