

UNIVERSITY OF BIRMINGHAM

Research at Birmingham

Words of wisdom. Bladder cancers arise from distinct urothelial sub-populations

Bryan, Richard; Ward, Douglas

DOI:

[10.1016/j.eururo.2014.11.058](https://doi.org/10.1016/j.eururo.2014.11.058)

License:

Creative Commons: Attribution-NonCommercial-NoDerivs (CC BY-NC-ND)

Document Version

Peer reviewed version

Citation for published version (Harvard):

Bryan, RT & Ward, DG 2015, 'Words of wisdom. Bladder cancers arise from distinct urothelial sub-populations', *European urology*, vol. 67, no. 3, pp. 590-1. <https://doi.org/10.1016/j.eururo.2014.11.058>

[Link to publication on Research at Birmingham portal](#)

Publisher Rights Statement:

After an embargo period this document is subject to the conditions of a CC-BY-NC-ND license

General rights

Unless a licence is specified above, all rights (including copyright and moral rights) in this document are retained by the authors and/or the copyright holders. The express permission of the copyright holder must be obtained for any use of this material other than for purposes permitted by law.

- Users may freely distribute the URL that is used to identify this publication.
- Users may download and/or print one copy of the publication from the University of Birmingham research portal for the purpose of private study or non-commercial research.
- User may use extracts from the document in line with the concept of 'fair dealing' under the Copyright, Designs and Patents Act 1988 (?)
- Users may not further distribute the material nor use it for the purposes of commercial gain.

Where a licence is displayed above, please note the terms and conditions of the licence govern your use of this document.

When citing, please reference the published version.

Take down policy

While the University of Birmingham exercises care and attention in making items available there are rare occasions when an item has been uploaded in error or has been deemed to be commercially or otherwise sensitive.

If you believe that this is the case for this document, please contact UBIRA@lists.bham.ac.uk providing details and we will remove access to the work immediately and investigate.

Bladder cancers arise from distinct urothelial sub-populations

Jason Van Batavia, Tammer Yamany, Andrei Molotkov, Hanbin Dan, Mahesh Mansukhani, Ekaterina Batourina, Kerry Schneider, Daniel Oyon, Mark Dunlop, Xue-Ru Wu, Carlos Cordon-Cardo and Cathy Mendelsohn.

Nature Cell Biology 2014; **16**: 982–991.

1 Expert's Summary

2 Using lineage-tracing techniques to indelibly label urothelial sub-populations in BBN carcinogenesis
3 mouse models, the authors found that papillary-like and CIS-like lesions developed from different
4 urothelial cell populations: non-invasive papillary lesions from intermediate cells of the urothelium
5 and CIS lesions from keratin-5 expressing basal cells. These findings support a model in which the
6 heterogeneity observed in bladder cancers is determined both by genetic changes and the cell
7 lineage from which the tumour originates. These findings also provide a plausible explanation for
8 clinical observations in humans regarding differences in natural history and prognosis of patients
9 with different types of non-muscle-invasive lesion, and suggest that the difference in clinical
10 outcomes may stem, at least in part, from a fundamental difference in the cell of origin.

11

12 Experts' Commentary

13 "Bladder cancer or bladder cancers?" is a question that urological scientists have been asking for
14 many years [1]: what are the molecular-genetic pathways that give rise to low-grade NMIBC, high-
15 grade NMIBC, CIS and MIBC? Some genetic abnormalities are common to all urothelial bladder
16 cancer (UBC) subgroups such as *TERT* promoter mutations, and others are associated with LG-NMIBC
17 (*FGFR3* mutations) or HG-NMIBC/CIS/MIBC (*TP53* mutations). Previous studies have suggested that
18 invasive or aggressive UBCs can develop from basal cells [2;3], and that some UBCs exhibit protein

19 and gene expression profiles indicative of an intermediate cell or luminal origin [4;5]. Van Batavia et
20 al have now directly demonstrated that papillary and CIS/invasive lesions arise from distinct
21 urothelial sub-populations, albeit in a model system which may not fully recapitulate tumourigenesis
22 in the human bladder. It now seems increasingly likely that the context provided by the 'cell of
23 origin' is key to both the oncogenic effects of the different genetic aberrations observed in LG-
24 NMIBC and HG-NMIBC/CIS/MIBC and to the very different behaviours of these two types of UBC.

25 Many questions still remain. How do papillary tumours progress to MIBCs? Do papillary tumours
26 always originate in the intermediate cell layer in humans? Why do patients seemingly successfully
27 treated for organ-confined disease relapse and succumb? Where do G3T1 tumours with mixed
28 mutation profiles originate? It is these fundamental questions that approaches based upon baseline
29 tumour characteristics, rather than outcomes, are yet to answer. The authors do not discuss
30 important processes such as epithelial-mesenchymal transition or the development of cancer stem
31 cells, but their elegant utilisation of morphologic approaches is refreshing in the era of next
32 generation sequencing and has contributed significantly to our understanding of this challenging
33 disease.

**Richard T Bryan & Douglas G Ward. School of Cancer Sciences, University of Birmingham,
Birmingham, B15 2TT, UK.**

Correspondence to: r.t.bryan@bham.ac.uk

Acknowledgements

RT Bryan's research has been funded by the Medical Research Council (UK), Cancer Research UK, University Hospitals Birmingham Charities, and the University of Birmingham. DG Ward's research has been funded by Birmingham Science City, Cancer Research UK, University Hospitals Birmingham Charities, and the University of Birmingham.

Reference List

- (1) Goebell PJ, Knowles MA. Bladder cancer or bladder cancers? Genetically distinct malignant conditions of the urothelium. *Urol Oncol* 2010; 28:409-428.
- (2) Shin K, Lim A, Odegaard JI, Honeycutt JD, Kawano S, Hsieh MH, Beachy PA. Cellular origin of bladder neoplasia and tissue dynamics of its progression to invasive carcinoma. *Nat Cell Biol* 2014; 16:469-478.
- (3) Bryan RT, Tselepis C. Cadherin switching and bladder cancer. *J Urol* 2010; 184:423-431.
- (4) Dancik GM, Owens CR, Iczkowski KA, Theodorescu D. A cell of origin gene signature indicates human bladder cancer has distinct cellular progenitors. *Stem Cells* 2014; 32:974-982.
- (5) Volkmer JP, Sahoo D, Chin RK, Ho PL, Tang C, Kurtova AV, Willingham SB, Pazhanisamy SK, Contreras-Trujillo H, Storm TA, Lotan Y, Beck AH, Chung BI, Alizadeh AA, Godoy G, Lerner SP, van de Rijn M, Shortliffe LD, Weissman IL, Chan KS. Three differentiation states risk-stratify bladder cancer into distinct subtypes. *Proc Natl Acad Sci U S A* 2012; 109:2078-2083.