Title: Sensitivity and Resistance to Targeting FGFR in Cancer

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Speaker

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Chairman

Nicholas Turner, M.D., Ph.D.

EDUCATION

The Institute of Cancer Research, University of London - PhD	2007
Membership of the Royal College of Physicians (Lond)	2000
University of Oxford Medical School - BM BChir	1997
University of Cambridge Tripos - MA (Hons) Class I	1994

CURRENT APPOINTMENT

Senior Lecturer and Honorary Consultant in Medical Oncology	9/2008-
The Institute of Cancer Research and Royal Marsden Hospital	

PREVIOUS APPOINTMENTS

Specialist Registrar Medical Oncology	3/2007-9/2008
Royal Free Hospital and University College Hospitals	
Clinical Research Fellow	9/2003-3/2007
Breakthrough Breast Cancer Research Centre, The Institute of Cancer Research	
Specialist Registrar Medical Oncology	9/2001-9/2003

Middlesex Hospital and Royal Free Hospitals

Senior House Officer Royal Marsden Hospital, London	4/2001-9/2001
Senior House Officer St Thomas' Hospital, London	8/2000-2/2001
Senior House Officer Whittington Hospital, London	2/1999-8/2000
Senior House Officer Hammersmith Hospital, London	2/1999-8/1999
Senior House Officer Royal Brompton Hospital, London	8/1998-2/1999
House Physician, John Radcliffe Hospital, Oxford	2/1998-8/1998
House Surgeon, Northampton General Hospital	8/1997-2/1998

PROFESSIONAL ACTIVITY

Deputy Editor *Breast Cancer Research*
Programme Committee *IMPAKT breast cancer conference 2012*
San Antonio Breast Cancer Symposium 2012
ESMO 2012
ESMO 2013
Invited speaker *ESMO 2012*
Invited discussant *ASCO 2012*

SELECTED PUBLICATIONS

1. Jain VK, Turner NC. Challenges and opportunities in the targeting of fibroblast growth factor receptors in breast cancer. *Breast Cancer Res.* 2012 Jun 19;14(3):208. [Epub ahead of print] PMID: 22731805 [PubMed - as supplied by publisher]
2. Aarts M, Sharpe R, Garcia-Murillas I, Gevensleben H, Hurd MS, Shumway SD, Toniatti C, Ashworth A, Turner NC. Forced mitotic entry of S-phase cells as a therapeutic strategy induced by inhibition of WEE1. *Cancer Discovery* 2012 Jun;2(6):524-39. Epub 2012 Apr 23.
3. Barton S, Zabaglo L, A'hern R, *Turner N*, Ferguson T, O'Neill S, Hills M, Smith I, Dowsett M. Assessment of the contribution of the IHC4+C score to decision making in clinical practice in early breast cancer. *Br J Cancer.* 2012 Apr 24. doi: 10.1038/bjc.2012.166. [Epub ahead of print]
4. Turner NC, Reis-Filho JS. Genetic heterogeneity and cancer drug resistance. *Lancet Oncol*. 2012 Apr;13(4):e178-85. Epub 2012 Mar 30.
5. Brough R, Frankum JR, Sims D, Mackay A, Mendes-Pereira AM, Bajrami I, Costa-Cabral A, Rafiq R, Ahmad A, Cerone M, Natrajan R, Sharpe R, Shiu K, Wetterskog D, Dedes K, Lambros M, Rawjee T, Linardopoulos S, Reis-Filho JS, Turner NC, Lord CJ, Ashworth A. Functional Viability Profiles of Breast Cancer. *Cancer Discovery.*2011 August 1:260-273
6. Sharpe R, Pearson A, Herrera-Abreu MT, Johnson DA, Mackay A, Welti JC, Natrajan R, Reynolds AR, Reis-Filho JS, Ashworth A, Turner NC. FGFR signalling promotes the growth of triple negative and basal-like breast cancer cell lines both in vitro and in vivo. *Clin Cancer Res.* 2011 Aug 15;17(16):5275-86. Epub 2011 Jun 28.
7. Turner NC, Ashworth A. Biomarkers of PARP inhibitor sensitivity. *Breast Cancer Res Treat*. 2011 May;127(1):283-6. Epub 2011 Feb 8.
8. Turner NC, Seckl MJ. A therapeutic target for smoking-associated lung cancer. *Sci Transl Med*. 2010 Dec 15;2(62):62ps56.
9. Graeser MK, McCarthy A, Lord CJ, Savage K, Hills M, Salter J, Orr N, Parton M, Smith IE, Reis-Filho J, Dowsett M, Ashworth A, Turner N. A marker of homologous recombination predicts pathological complete response to neoadjuvant chemotherapy in primary breast cancer. *Clin Cancer Res.* 2010 Dec 15;16(24):6159-68. Epub 2010 Aug 27.]
10. Turner N, Lambros MB, Horlings HM, Pearson A, Sharpe R, Natrajan R, Geyer FC, van Kouwenhove M, Kreike B, Mackay A, Ashworth A, van de Vijver MJ, Reis-Filho JS. Integrative molecular profiling of triple negative breast cancers identifies amplicon drivers and potential therapeutic targets. *Oncogene*. 2010 Apr 8;29(14):2013-23. Epub 2010 Jan 18.
11. Turner NC, Strauss SJ, Sarker D, Gillmore R, Kirkwood A, Hackshaw A, Papadopoulou A, Bell J, Kayani I, Toumpanakis C, Grillo F, Mayer A, Hochhauser D, Begent RH, Caplin ME, Meyer T. Chemotherapy with 5-fluorouracil, cisplatin and streptozocin for neuroendocrine tumours. *Br J Cancer.* 2010 Mar 30;102(7):1106-12.
12. Turner N, Pearson A, Sharpe R, Lambros M, Geyer F, Lopez-Garcia MA, Natrajan R, Marchio C, Iorns E, Mackay A, Gillett C, Grigoriadis A, Tutt A, Reis-Filho JS, Ashworth A. FGFR1 amplification drives endocrine therapy resistance and is a therapeutic target in breast cancer. *Cancer Res*. 2010 Mar 1;70(5):2085-94. Epub 2010 Feb 23.
13. Turner N, Grose R. Fibroblast growth factor signalling: from development to cancer. *Nat Rev Cancer*. 2010 Feb;10(2):116-29.
14. Turner NC, Jones AL. Management of breast cancer - Part II. BMJ. 2008 Jul 11;337:a540.

15. Turner NC, Jones AL. Management of breast cancer - Part I. BMJ. 2008 Jul 4;337:a421.
16. Turner NC, Lord CJ, Iorns E, Brough R, Swift S, Elliott R, Rayter S, Smith A, Tutt AN, Ashworth A. A Synthetic Lethal siRNA Screen Identifying Genes Mediating Sensitivity to a PARP Inhibitor. *EMBO J.* 2008 May 7;27(9):1368-77. Epub 2008 Apr 3.
17. Iorns E, Turner NC, Elliott R, Syed N, Garrone O, Gasco M, Tutt AN, Crook T, Lord CJ, Ashworth A. Identification of CDK10 as an Important Determinant of Resistance to Endocrine Therapy for Breast Cancer. *Cancer Cell.* 2008 Feb;13(2):91-104.
18. Iorns E, Lord CJ, Turner N, Ashworth A. Utilizing RNA interference to enhance cancer drug discovery. *Nat Rev Drug Discov.* 2007 Jul;6(7):556-68.
19. Elsheikh SE, Green AR, Lambros MB, Turner NC, Grainge MJ, Powe D, Ellis IO, Reis-Filho JS. FGFR1 amplification in breast carcinomas: a chromogenic in situ hybridisation analysis. *Breast Cancer Res*. *2007* Mar 30;9(2):R23 [Epub ahead of print]
20. Turner NC, Reis-Filho JA, Russell AM, Springall RJ, Ryder K, Steele D, Savage K, Gillett CE, Schmitt FC, Tutt AN, Ashworth A. BRCA1 Dysfunction in Sporadic Basallike Breast Cancer. *Oncogene 2007* Mar 29;26(14):2126-32. Epub 2006 Oct 2.
21. Reis-Filho JS, Simpson PT, Turner NC, Lambros MB, Jones C, Mackay A, Grigoriadis A, Sarrio D, Savage K, Dexter T, Iravani M, Fenwick K, Weber B,Hardisson D, Schmitt FC, Palacios J, Lakhani SR, Ashworth A. FGFR1 emerges as a potential therapeutic target for lobular breast carcinomas*. Clin Cancer Res. 2006* Nov 15;12(22):6652-62.
22. McCabe N, Turner NC, Lord CJ, Kluzek K, Białkowska A, Swift S, Giavara S, O' Connor MJ, Tutt AN, Zdzienicka MZ, Smith GCM, Ashworth A. Deficiency in the Repair of DNA Damage by Homologous Recombination and Sensitivity to PARP Inhibition. *Cancer Res. 2006 Aug 15;66(16):8109-15*
23. Turner N, Tutt A, Ashworth A. Hallmarks of 'BRCAness' in sporadic cancers. *Nat Rev Cancer. 2004 Oct; 4(10):814-9.*

IAAO2012 Title of the Talk:

Sensitivity and Resistance to Targeting FGFR in Cancer

ABSTRACT:

Activation of fibroblast growth factors through mutation or amplification is a common oncogenic event, and multiple FGFR inhibitors have entered clinical trials, yet the mechanisms of activation of signaling are diverse. In breast cancer *FGFR1* amplification is present in 8% unselected cancers, *FGFR2* amplification in 1-2% unselected cancers, and autocrine FGF2 expression in <5% cancers. Clinical development requires robust screening strategies targeted to the breast cancer subtypes that are associated with each aberration, and an understanding of how FGFR signaling affects response to standard therapies.

To identify mechanisms of resistance to FGFR inhibitors we have performed functional siRNA screens on a panel of 11 *FGFR* mutant and amplified cancer cell lines, including cell lines with amplification of *FGFR1* and *FGFR2*, and activating mutation of *FGFR2* and *FGFR3*. Screens were analysed to identify siRNA that that modulated sensitivity to the FGFR inhibitor, identifying both shared pathways that mediate resistance, and mutation specific resistance mechanisms.