

WIMM PI
Curriculum Vitae

Personal Data

Name Sir Walter Bodmer
Nationality UK
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Present Position

1996- Head, Laboratory for Cancer and Immunogenetics, Weatherall Institute for Molecular Medicine, University of Oxford and Emeritus Professor

Previous Positions

1958-1960 Research Fellow, Clare College, Cambridge
1961 Official Fellow, Clare College, Cambridge and
1960-1961 Demonstrator, Dept of Genetics, University of Cambridge
1961-1962 Fellow & Visiting Assistant Professor, Dept of Genetics, Stanford University School of Medicine, Palo Alto, California
1962-1966 Assistant Professor, Dept of Genetics, Stanford University
1966-1968 Associate Professor, Dept of Genetics, Stanford University
1968-1970 Professor, Dept of Genetics, Stanford University
1970-1979 Professor of Genetics, University of Oxford
1979-1991 Director of Research, Imperial Cancer Research Fund, London
1991-1996 Director General, Imperial Cancer Research Fund, London
1996- 2005 Principal, Hertford College, Oxford

Some other Appointments

1984-1985 President, The Royal Statistical Society
1987-1988 President, The British Association for the Advancement of Science;
1989-2001 Vice-President; 1996-2001 Chairman of Council
1989-1990 President, The Association for Science Education
1990-1993 President, The Organisation of European Cancer Institutes
1994-1996 President, EACR (European Association for Cancer Research)
1995- 2005 Chancellor, University of Salford
1998-2002 President, British Association for Cancer Research
2003- 2009 Chairman, Leukaemia Research Fund Medical & Scientific Advisory Panel
2007- 2013 Consulting Professor, Department of Medicine (Oncology), Stanford University School of Medicine

Narrative CV and scientific accomplishments:

Sir Walter Bodmer got his BA in mathematics (1956) and then his Ph.D. in population genetics (1959) under Sir Ronald Fisher at Cambridge University. He did his post- doctoral work in molecular biology under Dr Joshua Lederberg at Stanford and then was on the faculty of the Genetics Department in the Stanford University Medical School until 1970, ending up as a Full Professor. He returned to England in 1970 to become Professor of Genetics and head of a new department at Oxford University, and then in 1979 became Director of Research, and later Director General, of the Imperial Cancer Research Fund. Since 1996 he has been head of the cancer and immunogenetics laboratory at the Weatherall Institute of Molecular Medicine at Oxford University, and from 1996 to 2005 was also the Principal of Hertford College, Oxford. Walter Bodmer became a Fellow of the Royal Society in 1974, a Foreign Member of the US National Academy of Sciences in 1981 and was Knighted in 1986 for his contributions to science. In 2013 he was awarded a Royal Society Royal Medal for seminal contributions to population genetics, gene mapping and understanding of familial genetic disease. He is the recipient of more than 20 honorary degrees and is an Honorary Fellow or member of more than 15 medical and scientific societies and professional bodies. Walter Bodmer was amongst the earliest to suggest the human genome project and was the second President of HUGO, the Human Genome Organisation.

Sir Walter's early research was in population genetics, especially the relationship between selection and linkage. He was one of the first to use computers for the simulation of population genetics models starting in 1957. On coming to Stanford he initiated work on the HLA system with Julia Bodmer and Rose Payne, leading to their discovery of what became the HLA -A locus, and also on somatic cell genetics using human-mouse hybrids. His laboratory described some of the first genetic linkages and chromosomal assignments using this technique, and, in collaboration with others, mapped the *abl* oncogene to chromosome 9, laying the foundations for the discovery of *bcr/abl* at the 9/22 translocation break point in CML. Walter Bodmer, with Hugh McDevitt, provided the first explanation for the association of HLA determinants with disease in terms of linkage disequilibrium with functional variation in the HLA region, and then made the suggestion that, quite generally, association studies with genetic markers could be used to search for the genetic basis of multifactorial disease susceptibility. This has been the whole basis for the more recent development of whole genome association studies to discover the basis for genetic susceptibility to common diseases. His laboratory obtained the first monoclonal antibodies to HLA determinants, which have been widely used in immunological research. They were the first to clone the HLA ClassII genes and the first to map the *FAP/APC* gene to chromosome 5q, following which they have done many studies on mutations in the *APC* and other genes in colorectal cancer.

More recently, Sir Walter's laboratory has focused its research on (i) the fundamental genetics and biology of colorectal cancer and their potential applications, and ii) the characterisation and population distribution of genetic diversity in the populations of the British Isles. The latter work has been supported by two successive Wellcome Trust grants and the samples collected are now being used in the WTCC2 studies. The current focus of this work is on establishing the genetic basis of a variety of normal traits, including especially facial features. Walter Bodmer has also pioneered the hypothesis that rare variants underlie much of the inherited susceptibility to chronic diseases, using colorectal cancer as a model. His laboratory is now working with a panel of more than 100 well characterised colorectal cancer derived cell lines with a major interest in the identification and functional analysis of cancer stem cells using the colorectal cancer derived cell lines as a model, and in using enriched cancer stem cells for preclinical investigation of novel drug responses. Their research also includes studies on antibody dependent killing of colorectal cancer cells *in vitro* as a prelude to their clinical development for treatment of colorectal cancer and, in collaboration with the Danish Technical University, a microfluidics approach to the analysis of fresh tumour biopsies and rare circulating cancer cells in the blood.

Summaries of three recent grant applications:

Control of differentiation in colorectal cancer cell lines

Project application to CRUK – deferred indefinitely along with all other project grant applications.

“Derangement of cellular differentiation is a key step in carcinogenesis which facilitates progression to uncontrolled growth. Understanding the control of Cancer Stem cell (CSC) differentiation, and concomitantly what drives their growth, is therefore fundamental to understanding the biology of cancer.

Our goal is to use a panel of colorectal cancer (CRC) derived cell lines to improve the definition of pathways of differentiation control, and so enable a much finer classification of CRCs through identification of the relevant differentiation controlling gene functions that are altered in any given cancer.

There is now abundant evidence that, for many cancers, cell lines are good representatives of the cancers from which they are derived. We have developed a system, based primarily on identification of lumen forming colonies, for detection and quantification of the degree of differentiation within our cell line panel. This enables the development of simple in vitro cellular assays for differentiation that can be used to test the effects on cellular differentiation and CSC growth of knocking in and knocking out any chosen gene function.

Novel candidate genes for testing functional effects using such assays have been identified by whole-genome mRNA expression comparisons between CRC lines that retain the capacity to differentiate versus those that mostly do not. Further validation of such candidate genes can be done using qRT-PCR, western blots and analysis of within cell line expression differences between enriched CSCs and differentiated cells.

Recently, we have shown striking early identification of lumen formation using F-actin staining which should enable much earlier lumen detection and be the basis for the development of a relatively high throughput screening assay.

Evidence for the involvement of Notch, CTNNB1, CDX1, BMI1 and ATOH1 in the control of differentiation suggests the use of promoter driven reporters for this set of key transcription factors to augment the analysis of differentiation pathways using gene knocking in and out.

This would enable the definition of the spatiotemporal distribution of these transcription factors in differentiating colonies.

Our novel classification of CRCs with respect to patterns of differentiation can readily be tested on primary tumour material enabling investigation of the associations of different patterns of differentiation with prognosis and treatment outcomes. The genes involved in determining this classification may also suggest novel targets for drug development. Using our cell line panel, with this extra classification, will provide the basis for a finer pre-clinical analysis of drug responses.”

New approaches to cancer therapy based on intracellular delivery of antibody fragments targeting WNT pathway protein-protein interactions in colorectal cancer cell lines

Walter Bodmer and Terry Rabbitts

Project grant application to AICR now World Cancer Research under review

The use of monoclonal antibodies as anticancer therapies has, to date, been limited to accessible targets expressed on the cell surface. Intracellular proteins can be targeted with antibody fragments that fold correctly in the reducing environment of the cell and can block their functions. The Rabbitts laboratory has used this approach to target mutant RAS (constitutively activated) and demonstrated inhibition of cancer growth in a mouse pre-clinical model. Approximately 90% of CRC have mutations in either APC, or CTNNB1,

resulting in stabilisation of CTNNB1 and constitutive activation of the WNT pathway. Targeting CTNNB1 protein-protein interactions (PPI) has therefore been the focus of much research. The Bodmer laboratory has accumulated a panel of about 120 CRC cell lines that reproduce the properties of the tumours from which they are derived and reflect the wide spectrum of types of CRC with respect to mRNA expression profiles and common mutations. We believe that the use of a substantial panel of tissue specific cancer cell lines is key to being able to identify and predict treatment response profiles for any therapy. We will generate a library of CTNNB1 antibody fragments and screen those capable of inhibiting WNT signalling across molecularly defined CRC cell lines. We will explore the nature of the inhibition of PPIs ascribed to candidate antibody fragments and study the effects of the different types and positions of mutations in WNT pathway genes in the cell lines, on the efficacy of the antibody fragments to inhibit specific PPIs and modulate WNT signalling. The clinical application of such an approach would enormously expand the range of disease targets and therapies.

Genetic analysis of human facial variation

Application for Wellcome Trust Senior Investigator award (continuation of two successive programme grants- under review)

Nearly all of us have distinctive faces, with the obvious exception of identical twins, indicating that facial features are almost entirely genetically determined. The existence of specific regions of the brain for facial recognition emphasises that it has clearly played an important role in human and primate evolution. Even closely related populations have different frequencies of facial types, suggesting that the frequency of genetic variants for facial features differs between populations, possibly because of assortative mating. The extent to which our face influences how we are judged by others is emphasised by the difficulties faced by those who have had serious facial disfigurements. The aim of this project is to define the specific genetic factors that are involved in facial variation.

Our research questions are:

- What are the specific genetic variants that have major detectable effects on normal variation in facial features?
- How do the frequencies of these variants differ among populations, for example, the subgroups we have observed in the UK population, or the major ethnic groups?
- Which genes are responsible for the particular facial features of multi-genic syndromes, such as Down syndrome (DS)? How can discovering these genes help our search for genetic variants determining normal facial variation?
- What are the functional mechanisms by which the genetic variants mediate their effects on normal and abnormal facial features? Do the genes involved share common properties, for example, in affecting neurological functions?

PUBLICATIONS

The Genetics of Human Populations. Cavalli-Sforza, L. L. and Bodmer, W. F., W.H. Freeman & Co.: San Francisco, 1971. (Reprinted, Dover Publications 1999)

Our Future Inheritance: Choice or Chance? A study by a British Association Working Party. Bodmer, W. F. and Jones, A., Oxford University Press: Oxford, 1974.

Genetics, Evolution and Man. Bodmer, W. F. and Cavalli-Sforza, L. L., W. H. Freeman & Co: San Francisco, 1976.

The Book of Man. Bodmer, W. F. and McKie, R., Little Brown: 1994.

And more than 700 publications mainly in scientific and medical journals

Recent Publications

Neil Ashley, Matthew Jones, Djamila Ouaret, Jenny Wilding and Walter F Bodmer(2014) Rapidly derived colorectal cancer cultures recapitulate parental cancer characteristics and enable personalized therapeutic assays. *J Pathol* 2014 published on line 7th July

Dmitri Mouradov, Clare Sloggett, Robert N. Jorissen, Christopher G. Love, Shan Li, Antony W. Burgess, Diego Arango, Robert L. Strausberg, Daniel Buchanan, Samuel Wormald, Liam O'Connor, Jennifer L. Wilding, David Bicknell, Ian P.M. Tomlinson, Walter F. Bodmer, John M. Mariadason, and Oliver M. Sieber(2014) Colorectal Cancer Cell Lines Are Representative Models of the Main Molecular Subtypes of Primary Cancer *Cancer Res* June 15, 2014 74:3238-3247

Neil Ashley, Trevor Yeung and Walter F Bodmer (2013) Stem cell differentiation and lumen formation in colorectal, cancer cell lines and primary tumours. *Cancer Research*. 73(18): 5798-5809.

Yeung T.M, C Buskens, L M Wang, N J Mortensen and W F Bodmer (2013) Myofibroblast activation in colorectal cancer lymph node metastases. *Brit.J.Can.* 108, 2106-2115

Shazad Q. Ashraf, Angela M. Nicholls, Jennifer L. Wilding, Triantafyllia G. Ntouroupia, Neil J. Mortensen and Walter F. Bodmer (2012). Direct and immune mediated antibody targeting of ERBB receptors in a colorectal cancer cell-line panel. *Proc Natl Acad Sci USA* 109, 21046–21051

Yeung, TM, Gandhi, SC, Bodmer, WF. (2011) Hypoxia and lineage specification of cell line-derived colorectal cancer stem cells. *Proc Natl Acad Sci U S A*. 108(11):4382-7.

Wilding JL, McGowan S, Liu Y, Bodmer WF. (2010) Replication error deficient and proficient colorectal cancer gene expression differences caused by 3 UTR polyT sequence deletions. *Proc Natl Acad Sci U S A*. Dec 7;107(49):21058-63.

Bonilla C, Lefevre JH, Winney B, Johnstone E, Tonks S, Colas C, Day T, Hutnik K,

Boumertit A, Midgley R, Kerr D, Parc Y, Bodmer WF. (2010) *J Hum Genet*. Cyclin D1 rare variants in UK multiple adenoma and early-onset colorectal cancer patients. Epub date 2010/11/26.

Yeung TM, Gandhi SC, Wilding JL, Muschel R, & Bodmer WF. (2010) Cancer stem cells from colorectal cancer-derived cell lines *Proc Natl Acad Sci U S A* 107(8):3722-3727.

Bracht K, Nicholls AM, Liu Y, Bodmer WF. (2010) 5-Fluorouracil response in a large panel of colorectal cancer cell lines is associated with mismatch repair deficiency. *Br J Cancer* 103 (3):340-6

Lefevre J H, Colas C, Coulet F, Bonilla C, Mourra N, Flejou JF, Tiret E, Bodmer W, Soubrier F, Parc Y (2010). MYH biallelic mutation can inactivate the two genetic pathways of colorectal cancer by APC or MLH1 transversions. *Fam Cancer* 9(4):589-94

Bodmer W, Tomlinson I. Rare genetic variants and the risk of cancer. (2010) *Curr Opin Genet Dev*. 20(3):262-7

Carvajal-Carmona LG, Churchman M, Bonilla C, Walther A, Lefevre JH, Kerr D, Dunlop M, Houlston R, Bodmer WF, Tomlinson I. (2010) Comprehensive assessment of variation at the transforming growth factor beta type 1 receptor locus and colorectal cancer predisposition. *Proc Natl Acad Sci U S A* 107(17):7858-62.

Matthew D. Johnston , Philip K. Maini , S. Jonathan Chapman , Carina M. Edwards , Walter F. Bodmer.(2010) On the proportion of cancer stem cells in a tumour. *Journal of Theoretical Biology* 266 (2010) 708– 711

Yardy G W, Bicknell D C, Wilding JL, Bartlett S, Liu Y, Winney B, Turner GD, Brewster SF, Bodmer WF. (2009) Mutations in the AXIN1 gene in advanced prostate cancer. *Eur Urol*. 56(3):486-94.

Evseeva I, Nicodemus KK, Bonilla C, Tonks S, Bodmer WF. (2010) Linkage disequilibrium and age of HLA region SNPs in relation to classic HLA gene alleles within Europe. *Eur J Hum Genet.* 18(8):924-32

Chan CW, Wong NA, Liu Y, Bicknell D, Turley H, Hollins L, et al. Gastrointestinal differentiation marker Cytokeratin 20 is regulated by homeobox gene CDX1. (2009) *Proceedings of the National Academy of Sciences of the United States of America.* Feb 10;106(6):1936-41

Ashraf SQ, Umana P, Mossner E, Ntouroupi T, Brunker P, Schmidt C, Wilding JL, Mortensen NJ, Bodmer WF. (2009) Humanised IgG1 antibody variants targeting membrane-bound carcinoembryonic antigen by antibody-dependent cellular cytotoxicity and phagocytosis *Br J Cancer* 101(10):1758-1768.

Ntouroupi, T.G., Ashraf, S.Q., McGregor, S.B., Turney, B.W., Seppo, A., Kim, Y., Wang, X., Kilpatrick, M.W., Tspouras, P., Tafas, T., and Bodmer, W.F. (2008). Detection of circulating tumour cells in peripheral blood with an automated scanning fluorescence microscope. *Br J Cancer* 99, 789-795.

Bodmer, W. (2008). Genetic instability is not a requirement for tumor development. *Cancer Res* 68, 3558-3560; discussion 3560-3551.

Bodmer, W., and Bonilla, C. (2008). Common and rare variants in multifactorial susceptibility to common diseases. *Nat Genet* 40, 695-701

Conaghan, P., Ashraf, S., Tytherleigh, M., Wilding, J., Tchilian, E., Bicknell, D., Mortensen, N.J., and Bodmer, W. (2008). Targeted killing of colorectal cancer cell lines by a humanised IgG1 monoclonal antibody that binds to membrane-bound carcinoembryonic antigen. *Br J Cancer* 98, 1217-1225.

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Bredberg, A., and Bodmer, W. (2007). Cytostatic drug treatment causes seeding of gene promoter methylation. *Eur J Cancer* 43, 947-954.

Johnston, M.D., Edwards, C.M., Bodmer, W.F., Maini, P.K., and Chapman, S.J. (2007). Mathematical modeling of cell population dynamics in the colonic crypt and in colorectal cancer. *Proc Natl Acad Sci U S A* 104, 4008-4013.

Markers of Esteem

1972	Foreign Honorary Member, American Academy of Arts and Sciences
1974	Fellow of The Royal Society
1974	Member of EMBO
1981	Foreign Associate, The National Academy of Sciences, USA
1984	Fellow of The Royal College of Pathologists
1985	Honorary Fellow of The Royal College of Physicians
1986	Knight Bachelor
1986	Honorary Fellow of The Royal College of Surgeons of England
1988	Hon. DSc, University of Oxford
1989	Member of Academia Europaea
1989	Foreign Member of the American Philosophical Society
1989	Honorary Member of the British Society of Gastroenterology
1992	Honorary Fellow of The Royal Society of Edinburgh
1995	Romanes Lecture, Oxford University
1996	Harveian Orator, The Royal College of Physicians
1997	Honorary Fellow of the Royal Statistical Society
1998	Honorary Member Royal Irish Academy
1998	Founding Fellow of Academy of Medical Sciences, UK
2002	Dalton Medal, Manchester Literary & Philosophical Society
2002	D.K. Ludwig award
2013	Royal Society Royal Medal

