WIMM PI
Curriculum Vitae

Personal Data

Name	Terence Howard Rabbitts
Nationality	UK
Date of birth	17.6.46
Email	terence.rabbitts@imm.ox.ac.uk

Present Position

2012-present	Professor of Molecular Biology (WIMM)

Previous Positions

1971	Research Fellow, Department of Genetics, University of Edinburgh
1973	MRC Laboratory of Molecular Biology (LMB), Cambridge
1973	Member of Scientific Staff, LMB
1988	Joint Head, LMB Division of Protein and Nucleic Acid Chemistry
1997	Head, LMB Subdivision of Biology
2007	Visiting Worker, LMB
2007	Director, Leeds Institute for Molecular Medicine (LIMM)
2008	Co-Director, YCR Centre for Pre-Cancer Genomics
2007	Professor & Head of Section of Experimental Therapeutics, LIMM

Research Achievements

Scientific achievements are in three main areas.

Antibodies and antibody genes: I carried out the elucidation of the organization, diversity and rearrangement of human antibody genes. I showed (using a unique genomic S_1 nuclease mapping method) that the variable and constant region parts of antibody genes are separated in germ-line DNA but rearranged in lymphocyte DNA and joined in RNA. I also demonstrated that the heavy chain class switch occurs by deletion of genomic DNA between switch region signals. I defined the human kappa light chain genes and the entire human heavy chain locus (variable and constant regions) demonstrating the duplication of the constant region loci. These studies allowed recombinant antibodies to be developed for treating a wide variety of condition in patients. I also developed (with Michael Neuberger) methodologies for chimaeric antibody production which has allowed development of many antibodies in current use world-wide for patient treatment. I have more recently developed selection methods for isolating antibody single domain fragments for use inside cells based on a designer V-region scaffold and methods to target protein-protein interactions inside cells for disease target validation and as surrogates for the effects of drugs. Current work is aimed as emulating the antibody single domain binding sites in the form of small molecular weight compounds as drug precursors.

Cancer biology and chromosomal translocations: I defined the linkage of antibody and T cell receptor genes with several cancer-specific chromosomal translocations and, by identifying somatic mutations in *CMYC* (in Burkitt's lymphoma), provided the first experimental evidence that hypermutation can alter DNA linked to constant regions genes which is the process that diversifies antibody V genes. My work identified families of new oncogenes including the *LMO2* and *HOX11* families. I discovered the LMO2 multi-protein complex and its distinctive composition in normal and cancer cells and, using a combination of biochemical and mouse functional data, defined the role of LMO2 in haematopoiesis and neoplasias, validating the master gene model of chromosomal translocation genes. I demonstrated the commonality of translocations across all human cancer types by discovering a first fusion gene in a solid tumour (*FUS-CHOP* in liposarcoma). Using a combination of mouse models and biochemical studies, I derived a comprehensive model for LMO2-dependent T cell acute leukemia in man that highlights the importance of protein-protein interactions in cancer. My work in mouse models resulted in the first knock in mouse by making an Mll-Af9 fusion gene and later, using site-specific recombination methods, I developed models for creating *de novo* chromosomal translocations in mouse cancer models. These are currently being used to define the cancer initiating cells in leukemia's and solid tumours and the process of transcriptome evolution in cancer development.

Methods Development: I have pioneered method development during my career. Several of my pioneering methods have been, as are still, used worldwide in research labs and biotechnology.

I pioneered the method of cDNA cloning of mRNA copies, used for production of recombinant proteins for research (e.g. proteins for structural studies), cloned DNA for molecular biology studies (e.g. DNA sequencing and probes) and recombinant proteins products for medicines (e.g. interferon, erythropoietin). By exploiting this seminal technology, and by solving the human VH gene repertoire, I established the methodology for chimaeric antibody production that are antibody molecules used for treatment of patients in many different clinical indications. I developed selection protocols that can be used to isolate human antibody single variable domain fragments (based on a designer scaffold) against resident proteins inside cells and methods to select single variable domain that specifically

block protein-protein interactions. This provides a disease target validation platform and templates for drug development.

I was the first to develop mouse models of cancer based on fusion oncogenes using an homologous recombination method now called “knock in”, that is currently widely used. I used homologous recombination to make *de novo* chromosomal translocations in mice and developed a fully conditional invertor gene fusion method built from the knock in method. My cancer models demonstrated the use of chimaeric mice for fast throughput mouse pre-clinical modeling of human cancer and have been perfected in a new generation of vectors for facile and rapid generation of chromosomal translocation models recapitulating counterpart human cancers by incorporating translocation, supporting oncogenes or reporter genes for cell purification purposes.

What are the Future Aims of Your Current Group?

We are continuing work in two areas related to cancer biology in cancer therapeutics with specific interest in chromosomal translocations found in leukemia’s and lymphomas and in epithelial tumours that are associated with disseminated disease. We will continue to develop strategies for emulating chromosome translocations as initiating events and tagging the cells which acquire these changes in mouse models to enable them to be isolated and studied during progression from the initiating event through to overt disease. Our main technical focus of the work that will occur within the next year or two will be RNA-Seq transcriptomics, with specific focus on cell surface protein encoding genes and genes encoding transcription factors.

In parallel with these objectives will be our work trying to develop novel methodologies for drug development to specifically target protein-protein interactions. Over the last few years we have developed a technology that has been applied to the mutant RAS and to the Lmo2 protein which involves a strategic approach, first identifying single domain antibody fragments that work inside the reducing environment of the cell to target specific parts of the protein-protein interactions. This target validation part of the protocol also identifies regions of protein where interactions are valuable in the therapeutic process. We will continue therefore to develop this line of approach using small molecule emulators of the antibody binding site. We have already identified two chemical series which bind to the mutant RAS protein in the region where the antibody binds and prevents protein-protein interaction of the effector molecules. Our proposal is to continue to work these hits through to drug leads and use mouse models as pre-clinical judgment of the efficacy. This general strategy will be applied also to the Lmo2 protein and, if time and resources allow, we will also be testing our strategy with the interaction of CMYC-MAX and MLL-MENIN-LEDGF.

The approach is specifically applied to RAS for the time being and subsequently to Lmo2 are designed to be generic technology development strategies which will allow the same protocols to be applied to any protein-protein interaction. The toolbox of molecules and protocols which will allow the development of drugs to target specific protein-protein interactions should be valuable for a range of molecular interfaces in cancer.

Lay Summary of Research

The origin of human cancer lies partly in somatic changes that occur during the lifetime of the individual. Our work has two allied objectives; the first is to understand the molecular process by which transcription - which is the way in which the chromosomal material is transferred to information in the cell - controls the development of cancer. Our methods will allow the very first cells which undergo changes towards cancer to be identified and followed, and subsequent things that go wrong with these cells to be identified.

The second strand of our work is to make use of the information identified in the tracking of cancer from initiation to the patient presentation. It will be used for therapeutic drug development. We will try to develop technologies that can be applied to specific cancer changes occurring in the majority of human cancers but also to make our methods general so that a whole range of different tumour types can ultimately be targeted by our methods. The aim of this work is to develop drugs to help treatment of patients with cancers which bi and large have a very lethal affect such as pancreatic cancer, where patients will expect to survive for very short periods after initial diagnosis.

All Publications Over the Past 5 Years

Tanaka, T., Williams, R., & Rabbitts T.H. (2007) Tumour prevention by a single antibody domain targeting the interaction of signal transduction proteins with RAS. *EMBO J.* **26,** 3250-3259. (9.2)

Tanaka, T., Rabbitts, T.H. (2008) Functional intracellular antibody fragments do not require invariant intra-domain disulfide bonds. *J Mol Biol* **376,** 749-757 (4.0)

Rodriguez-Perales, S., Cano, F., Lobato M.N., Rabbitts, T.H. (2008) MLL gene fusions in human leukaemias: *in vivo* modelling to recapitulate these primary tumourigenic events. *Int J Hematol* **87,** 3-9 (1.3)

Andrews, W., Barber, M., Hernadez-Miranda, L.R., Xian, J., Rakic, S., Sundaresan, V., Rabbitts, T.H., Pannell, R., Rabbitts, P.H., Thompson, H., Erskine, L., Murakami, F., Parnavelas, J.G. (2008) The role of Slit-Robo signalling in the generation, migration and morphological differentiation of cortical interneurons. *Dev Biol* **313**, 648-658 (4.1)

Cano, F., Pannell, R., Follows, G.A., Rabbitts, T.H. (2008) Preclinical modelling of cytosine arabinoside response in *Mll-Enl* translocator mouse leukemias. *Mol Cancer Ther* **7**, 730-735 (4)

Cano, F., Drynan, L.F., Pannell, R., Rabbitts, T.H. (2008) Leukaemia lineage specification caused by cell-specific *Mll-Enl* translocations. *Oncogene* **27**, 1945-1950 (6.4)

Nam, C-H., Lobato, M.N., Appert, A., Drynan, L.F., Rabbitts, T.H. (2008) An antibody inhibitor of the LMO2-protein complex blocks its normal and tumorigenic functions. *Oncogene*, **27**, 4962-4968 (6.4)

Tanaka, T., Rabbitts T.H. (2008) Interfering with protein-protein interactions: potential for cancer therapy. *Cell Cycle* **7**, 1569-1574 (5.4)

Lobato, M.N., Metzler, M., Drynan, L., Forster, A., Pannell, R. & Rabbitts T.H. (2008) Modelingchromosomal translocations using conditional alleles to recapitulate initiating events in human leukaemias. *J. Natl. Canc. Institute* **38**, 58-63 (13.8)

McCaughan, F., Darai-Ramqvist, E., Bankier, A.T., Konfortov, B.A., Foster, N., George, P.J., Rabbitts, T.H., Kost-Alimova, M., Rabbitts, P.H., Dear, P.H. (2008) Microdissection molecular copy-number counting (□MCC) – unlocking cancer archives with digital PCR. *J Path* **216**, 307-316 (6.3)

Tanaka, T., Rabbitts, T.H. (2009) Selection of complementary single-variable domains for buildingmonoclonal antibodies to native proteins. *Nucleic Acids Research*, e1–8 (8.1)

Rabbitts, T.H. (2009) Commonality but diversity in cancer gene fusions. *Cell* **137**, 391-394 (32.4)

Appert, A., Nam, C-H., Lobato, N., Priego, E., Miguel, R.N., Blundell, T., Drynan, L., Sewell, H., Tanaka, T., Rabbitts, T.H. (2009) Targeting LMO2 with a peptide aptamer establishes a necessary function in overt T-cell neoplasia. *Cancer Res*, **69**, 4784-4790 (7.9)

Assi, S.A., Tanaka, T., Rabbitts, T.H. & Fernandez-Fuentes, N. (2009) PCRPI: Presaging critical residues in protein interfaces, a new computational tool to chart hot spots in protein interfaces. *Nucleic Acids Res.* e1-11 (8.1)

Tanaka, T., Rabbitts, T.H. (2010) Protocol for the selection of single-domain fragments by third generation intracellular antibody capture. *Nature Protocols* **5**, 67-92

McCormack, M. P., Young, L. F., Vasudevan, S, de Graff, C. A., Codrington, R, Rabbitts T. H., Jane, S. M., Curtis, D. J. (2010) The Lmo2 oncogene initiates leukemia in mice by inducing thymocyte self-renewal. *Science* **327**, 879-883 (31.2)

McCaughan, F., Pole, J., Bankier, A.T., Konfortov, B.A., Carroll, B., Falzon, M., Rabbitts, T.H., George, J., Dear, P.H., Rabbitts, P.H. (2010) Progressive 3q amplification consistently targets *SOX2* in preinvasive squamous lung cancer. *Am. J. Respir. Crit. Care Med*. **182**, 83-91 (11)

Pérez-Martinez, D., Tanaka, T., and Rabbitts, T.H. (2010) Intracellular antibodies and cancer: Newtechnologies offer therapeutic opportunities. *Bioessays* **32**, 589-598 (5)

Tanaka, T. & Rabbitts T.H. (2010) Interfering with RAS-effector protein interactions prevent RAS-dependent tumour initiation and causes stop-start control of cancer growth. *Oncogene* **29**, 6064-6070 (6.4)

Tanaka, T., Sewell, H., Waters, S., Phillips, S.E.V. & Rabbitts, T.H. (2011) Single domainintracellular antibodies from diverse libraries: emphasizing dual functions of LMO2 protein interactions using a single VH domain. *J. Biol Chem* **286**, 3707-3716 (4.8)

Dixon, A.S., Constance, J.E., Tanaka, T., Rabbitts, T.H. & Lim C.S. (2011) Changing thesubcellular location of the oncoprotein Bcr-Abl using rationally designed capture mofits. *Pharm. Res.* **29**, 1098-1109 (4.1)

Tanaka T & Rabbitts TH (2012) Intracellular antibody capture (IAC) methods for single domainantibodies. *in Single Domain Antibodies Methods & Protocols (Eds. D. Saerens & S. Muyldermans)* 151-174

Tanaka T & Rabbitts TH (2012) Selection of functional single domain antibody fragments for interfering with protein-protein interactions inside cells: a “one plasmid” mammalian two-hybrid system. *in Single Domain Antibodies Methods & Protocols (Eds. D. Saerens & S. Muyldermans)* 175-182

Tanaka, T., Williams, R., & Rabbitts T.H. (2007) Tumour prevention by a single antibody domain targeting the interaction of signal transduction proteins with RAS. *EMBO J.* **26,** 3250-3259. (9.2)

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Andrews, W., Barber, M., Hernadez-Miranda, L.R., Xian, J., Rakic, S., Sundaresan, V., Rabbitts,T.H., Pannell, R., Rabbitts, P.H., Thompson, H., Erskine, L., Murakami, F., Parnavelas, J.G. (2008) The role of Slit-Robo signalling in the generation, migration and morphological differentiation of cortical interneurons. *Dev Biol* **313**, 648-658 (4.1)

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McCaughan, F., Pole, J., Bankier, A.T., Konfortov, B.A., Carroll, B., Falzon, M., Rabbitts, T.H., George, J., Dear, P.H., Rabbitts, P.H. (2010) Progressive 3q amplification consistently targets *SOX2* in preinvasive squamous lung cancer. *Am. J. Respir. Crit. Care Med*. **182**, 83-91 (11)

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El-Jawhari, J.J., El-Sherbiny, Y.M., Scott, G.B., Morgan, R.S., Prestwich, R., Bowles, P.A., Blair, G.E., Tanaka, T., Rabbitts, T.H., Meade, J.L., & Cook, G.P. (2014) Blocking oncogenic RAS enhances tumour cell surface MHC class 1 expression but does not alter susceptibility to cytotoxic lymphocytes
Mol. Immunol. 58, 160-168 (3.003)

Sewell, H., Tanaka, T., El Omari, K., Mancini, E.J., Cruz, A., Fuentes-Fernandez, N., Chambers, J. & Rabbitts T.H. (2014) Conformational flexibility of the oncogenic protein LMO2 primes the formation of the multi-protein transcriptional complex
Scientific Reports 4, 1-9 (5.078)

Chambers, J.S., Tanaka, T., Brend, T., Ali, H., Geisler, N.J., Khazin. L., Cigudosa, J.C.,Dear, T.N., MacLennan, K. & Rabbitts, T.H. (2014) Sequential gene targeting to make chimeric tumor models with *de novo* chromosomal abnormalities
Cancer Res 74, 1588-1597 (9.284)

Zhang, J. & Rabbitts, T.H. (2014) Intracellular Antibody Capture: a molecular biology approach to inhibitors of protein-protein interactions.
BBA – Proteins and Proteomics epub (3.73)

Key Publications Throughout my Career (including short synopsis of each)

T.H. Rabbitts (1976) Bacterial cloning of plasmids carrying copies of globin messenger RNA. ***Nature* 260**, 221-225
First demonstration of cDNA cloning methodology: Max Perutz quoted this paper as the" the birth of cDNA cloning". cDNA cloning is still widely used for recombinant protein production, DNA probes etc. 96 citations

T.H. Rabbitts and A. Forster (1978) Evidence for non-contiguous variable and constant region genes in both germline and myeloma DNA. ***Cell* 13**, 319-327.
First molecular demonstration that immunoglobulin V & C genes are separate in genome & rearranged in lymphocytes. 61 citations

T.H. Rabbitts, A. Forster, W. Dunnick and D.L. Bentley (1980) The role of gene deletion in the immunoglobulin heavy chain switch. ***Nature* 283**, 351-356.
Demonstration that the heavy chain class switch occurred by deletion of CH gene segments and a prelude to our discovery of repetitive DNA elements responsible (switch region sequences). 164 citations

J.G. Flanagan and T.H. Rabbitts (1982) Arrangement of human immunoglobulin heavy chain constant region genes implies evolutionary duplication of a segment containing □, □ and □ genes. ***Nature* 300**, 709-713.
Discovery that the human CH gene locus is duplicated and providing an explanation of class switch deletion process. 407 citations

T.H. Rabbitts, P.H. Hamlyn and R. Baer (1983) Altered nucleotide sequences of a translocated c-*myc* gene in Burkitt lymphoma. ***Nature* 306**, 760-765
First demonstration that the chromosomal translocation of CMYC in Burkitt's lymphoma has somative mutations & proposal that the antibody gene hypermutation process was involved, thus providing primary evidence for a hypermutation machinery in germinal centres. 253 citations

M.S. Neuberger, G.T. Williams, E.B. Mitchell, S.S. Jouhal, J.G. Flanagan and T.H. Rabbitts (1985) A hapten-specific chimaeric IgE antibody with human physiological effector function. ***Nature* 314**, 268-270.
The methodology and proof of principle for chimaeric antibody production. 208 citations

R. Baer, A. Forster and T.H. Rabbitts (1987) The mechanism of chromosome 14 inversion in a human T cell lymphoma. ***Cell* 50**, 97-105.
This work describes how the whole chromosome 14 long arm is inverted can be T-ALL by subverting the RAG1/2 VDJ recombinase system. 75 citations

Rabbitts, T.H., Forster, A., Larson, R. and Nathan, P. (1993) Fusion of the dominant negative transcription regulator *CHOP* with a novel gene *FUS* by translocation t(12;16) in malignant liposarcoma. ***Nature Genetics* 4**, 175-180.
The first cloning of a solid tumour (sarcoma) chromosomal translocation and demonstration of gene fusion in solid tumours. 306 citations

Cook, G.P., Tomlinson, I.M., Walter, G., Carter, N.P., Riethman, H., Buluwela, L., Winter, G. & Rabbitts, T.H. (1994) A map of the human immunoglobulin V_H locus completed by analysis of the telomeric region of chromosome 14q. ***Nature Genetics* 7**, 162-168.
The complete map of the human antibody heavy chain variable regions and sequence of the VH genes. The joined our map of the VH with the CH regions on chromosome 14. 247 citations

Warren, A.J., Colledge, W.H., Carlton, M.B.L., Evans, M.J., Smith, A.J.H. & Rabbitts, T.H. (1994) The oncogenic cysteine-rich LIM domain protein rbtn2 (lmo2) is essential for erythroid development. ***Cell* 78**, 45-58.
The first gene knock-out of Lmo2 showing that this gene (translocated in human T-ALL with t(11;4)) is a transcriptional regulator and controls primitive haematopoiesis. This lead to my proposal of the translocation master gene hypothesis (published in my 1991 Cell review, see below). 432 citations

Corral, J., Lavenir, I., Impey, H., Warren, A.J., Forster, A., Bell, S., McKenzie, A.N.J., King, G. & Rabbitts, T.H. (1996) An *Mll-AF9* fusion gene generated by homologous recombination causes acute leukaemia in chimeric mice: A general method to create fusion oncogenes. ***Cell*** **85**, 853-861

The first gene fusion using gene targeting to create a mouse model of human cancer. This method has become known as knock-in and is widely used internationally ot make gene fusions for a variety of applications. 330 citations

Wadman, I.A., Osada, H., Grutz, G.G., Agulnick, A.D., Westphal, H., Forster, A. & Rabbitts, T.H. (1997) The LIM-only protein Lmo2 is a bridging molecule assembling an erythroid, DNA-binding complex which includes the TAL1, E47, GATA-1 and Ldb1/NLI proteins ***EMBO J.*** **16**, 3145-3157

Discovery of the LMO2 DNA-binding protein complex involving LMO2; LDB1; TAL1/SCL; GATA1. This set the scene for studies of transcription in leukaemogenesis and of protein-protein interactions. 489 citations

Forster, A., Pannell, R., Drynan, L. F., McCormack, M.M., Collins, E.C., Daser, A. & Rabbitts, T.H. (2003) Engineering *de novo* reciprocal chromosomal translocations associated with *Mll* to replicate primary events of human cancer. ***Cancer Cell*** **3**, 449-458

The first application of gene targeting & Cre-loxP recombination to create chromosomal translocations de novo during mouse development to recapitulate the primary events in human cancer. 62 citations

Tanaka, T, Lobato, M.N. & Rabbitts, T.H. (2003) Single domain intracellular antibodies: a minimal fragment for direct *in vivo* selection of antigen-specific intrabodies. ***J. Mol. Biol.*** **331,** 1109-1120

Discovery of single antibody domains as an effective intracellular protein that can fold in the reducing environment of the cell and bind with high affinity to target proteins. 47 citations

Forster, A., Pannell, R., Drynan, L.F., Codrington, R., Daser, A., Metzler, M., Lobato, M.N. & Rabbitts T.H. (2005) The invertor knock-in conditional translocation mimic ***Nature Methods*** **2**, 27-30

Development of a conditional knock-in method, using gene targeting, to activate gene fusions as primary events that cause cancer. 22 citations

Tanaka, T., Williams, R., & Rabbitts T.H. (2007) Tumour prevention by a single antibody domain targeting the interaction of signal transduction proteins with RAS ***EMBO J.*** **26,** 3250-3259

The first molecule that is able to discriminate the active, mutant form of KRAS form the inactive, GDP-bound form. The paper also demonstrates for the first time that blocking RAS-effector protein-protein interaction is a valid tumour therapeutic target. 37 citations

Tanaka, T., Rabbitts, T.H. (2010) Protocol for the selection of single-domain fragments by third generation intracellular antibody capture ***Nature Protocols*** 5, 67-92

Development of protocols for isolation of single domains to block protein-protein interactions. 5 citations

Two reviews

Rabbitts, T.H. (1991) Translocations, master genes and differences between the origin of acute and chronic leukaemias. ***Cell*** **67**, 641-644.

This mini-review compare the types of effect of chromosomal translocations in human cancer and articulates the master gene model of transcription factor interaction that is a consequence of chromosomal translocations in some forms of cancer. This led us to focusd on protein-protein interactions as potential therapeutic targets in cancer. 277 citations

Rabbitts, T.H. (1994) Chromosomal translocations in human cancer. ***Nature*** **372**, 143-149.

This review established the framework for understanding the role of human chromosomal translocations in leukaemia/lymph; sarcoma and epithelial tumours. 1213 citations

Markers of Esteem

1981	Member of European Molecular Biology Organization (EMBO)
1981	Colworth Medal of the Biochemical Society
1987	Fellow of the Royal Society (FRS)
1993	CIBA Medal and Prize of the Biochemical Society
1998	Fellow of Academy of Medical Sciences (London) (FMedSci)

Scientific Advisory Board Membership

1990–1997 Cambridge Antibody Technology Ltd (SAB Chairman)
1992–2000 Quadrant HealthCare Ltd. (SAB Chairman)
1997-2000 Iclectus Ltd.
2001-2008 Domantis Ltd.
2002-2007 Oakes Lyman & Co. Ltd. (SAB Chairman)
2007-2010 Oakes Lyman Kampinga & Co. Ltd

Current

2009-present Oryzon Genomics
2009-present DiThera
2010-present Kymab (SAB Chairman)
2011-present Biosceptre
2012-present Avacta

Non-Executive Company Directorships

Iclectus Ltd.	1997-2000
Aptuscan	2009-2012
Abeterno	2013-present

Current Grant Support

Bloodwise (Formerly known as Leukaemia and Lymphoma Research) Programme Grant 2008- 2013 £1,025,276

Prostate Cancer Charity 2010-2013 Project Grant £245,761

Medical Research Council 2010-2013 Project Grant £479,629

Medical Research Council 2012- 2017 Programme Grant £2,223,000

Wellcome Trust 2012- 2017 WT Senior Investigator Award £2,200,000

Bloodwise (Formerly known as Leukaemia and Lymphoma Research) 2013- 2018 Programme Grant £1,400,000

EPSRC Co-Investigator (PI: Prof. Constantin Coussios) - OxCD3: Oxford Centre for Drug Delivery Devices - 2014- 2019