CURRICULUM VITAE

NAME:

Margaret Catherine Frame
BSc PhD FRSE FMedSci

POSITION / TITLE:

Science Director / Professor of Cancer Biology
Edinburgh Cancer Research Centre
Institute of Genetics and Molecular Medicine
College of Medicine and Veterinary Medicine
University of Edinburgh.

Director of Research, College of Medicine and Veterinary Medicine

EDUCATION/TRAINING:

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Glasgow University (Faculty of Science)	BSc (Hons 1st)	1979	Biochemistry
Glasgow University (Faculty of Medicine)	PhD	1983	Molecular Pathology

PREVIOUS POSITIONS:

2002-2007	Deputy Director, Group Leader – Beatson Institute for Cancer Research, Glasgow
1999-2002	Professor of Molecular Cell Biology – Faculty Biological Sciences, University of Glasgow
1995-1999	Group Leader, Senior Scientist – Beatson Institute for Cancer Research
1991-1995	Post-doctoral Scientist, Beatson Institute for Cancer Research
1987-1991	Time taken out for family
1983–1987	Post-doctoral Scientist – MRC Virology Unit, Glasgow

PREVIOUS ROLE AS DEPUTY DIRECTOR, BEATSON INSTITUTE:

I was Deputy Director of the CR-UK Beatson Institute for Cancer Research, Glasgow for five years (2002-2007), where I led the Post Graduate Training Program, played a major role in the recruitment and mentoring of Early Career Researchers, and was closely involved in the design of a £l7M new research facility.

HONOURS AND AWARDS:

Professor JN Davison Prize for Biochemistry -1980
Tenovus Medal – 1999
Fellow of the Royal Society of Edinburgh – 2002
Member of European Molecular Biology Organization (EMBO) – 2008
Fellow of the Academy of Medical Sciences – 2009

MEMBERSHIP - EXTERNAL COMMITTEES (current or recent, within last few years):

AACR/CRUK – "Stand Up For Cancer" : post-doctoral fellowship panel

European Research Council (ERC) Starter grants panel : sub-panel LS3

Chair: Academy of Medical Sciences, Genetics, Cellular and Developmental Biology, Microbiology and Immunology Panel

Royal Society of Edinburgh, Cell and Molecular Biology Panel

Chair: Cancer Research UK (CR-UK), New Investigator Panel

Cancer Research UK, Training and Career Development Board

Cancer Research UK, Science Strategy Advisory Group

Cross UK-North America Cancer Imaging Alliance – joint initiative between CR-UK, NCI-USA and Canadian Institutes of Health Research's Institute of Cancer Research (CIHR-ICR)

Wellcome Trust, Genes, Molecules and Cells Panel

Wellcome Trust Investigator Interview Panel (co-opted member on several occasions)

Previously (of note):

Chair of several review panels for CR-UK (LRI, ICR) and for Wellcome Trust (for example, Cell Matrix Research Centre, Manchester, and University of Dundee)

Melville Trust, Scientific Advisory Committee

Chair: Association for International Cancer Research (AICR) Science Funding Panel

CR-UK Science Funding Committee

Cancer Research Campaign Projects Grants Committee

Advisory/Review Boards for several European Institutions:

- Oslo Centre for Biotechnology
- University of Basel, Department of Biomedizine
- Karolinska Institute Cancer Appointments Advisory Board
- FP7 'Molecular Oncology Pathways' Turin Advisory Board
- Marseilles Institute of Biology, France
- Bristol Myers Squibb, Europe and USA.

Member of 2008 RAE Cancer Panel, Chair of Association for International Cancer Research science funding panel.

Margaret Frame : Research contribution statement

Over two decades my lab has studied tyrosine kinases that contribute to oncogeneisis – namely Src and its effector substrate Focal Adhesion Kinase (FAK). While both are catalytically active, it has become clear that their protein adaptor functions – predominantly the SH3 and SH2 domains in Src and the FERM domain in FAK – have a huge impact of the signalling output and biological activities controlled by these proteins. Indeed, FAK essentially functions as a self-regulating scaffold protein, with auto-phosphorylation controlling protein partner binding specificities to its kinase-adjacent FERM domain (reviewed in Frame et al., 2010, Nat Rev Mol Cell Biol). This led us to propose that the FERM domain of FAK controls the assembly of large protein complexes in space and time, and the shuttling of these between sub-cellular locale is critical for multiple cancer phenotypes, including invasion, metastasis, neo-angiogenesis and aberrant tumour cell survival (McLean et al., 2003, Nat Rev Cancer). The long-term work that has led to the current proposal is summarised below (incorporating some of our relevant group publications).

Src was the first oncoprotein, identified, providing many landmarks in cancer research (Frame et al., 2002, Nat Rev Mol Cell Biol), amongst them the discovery of the integrin effector adhesion protein FAK as a key binding partner and substrate. Work in my laboratory identified the mode of trafficking of Src to the plasma membrane, via RhoB- and actin-regulated recycling endosomes (Fincham and Frame, 1998, EMBO J; Fincham et al., 1996, J Cell Biol), showing that this was linked to catalytic activation (Sandilands et al., 2004, Dev Cell). We also determined the mechanisms by which the Src and FAK signalling axis controls dynamic regulation of integrin adhesion complexes (Fincham and Frame, 1998, EMBO J), cadherin-based inter-cellular (Avizienyte et al., 2002, Nat Cell Biol), the actin cytoskeleton (Fincham and Frame, 1998, EMBO J; Serrels et al., 2007, Nat Cell Biol; Tang et al., 2013, Curr Biol), cancer cell polarity (Serrels et al., 2010, Curr Biol) and directional migration (Serrels et al., 2010, Curr Biol; Serrels et al., 2007, Nat Cell Biol). My group was also first to publish that FAK acts as a molecular scaffold for other signalling second messenger complexes, controlling nascent cell-matrix adhesions via effects on new actin polymerisation at the leading edge of motile cells (Serrels et al., 2010, Curr Biol; Serrels et al., 2007, Nat Cell Biol).

We identified a novel interface between FAK and the scaffolding of cellular proteases as a critical mechanism by which this tyrosine kinase pathway controls adhesion dynamics and migration (Carragher et al., 2003, Curr Biol; Tang et al., 2013, Curr Biol). We showed the inter-dependence between integrin signalling and cadherin function at cellular adhesion sites (Avizienyte et al., 2002, Nat Cell Biol), and demonstrated that Src-induced phosphorylation of FAK, together with activation of the MEK/ERK/MLCK actomyosin cascade, is a determinant of the epithelial to mesenchymal transition (EMT) associated with invasive and metastatic cancer (Avizienyte et al., 2004, Mol Biol Cell; Canel et al., 2013, J Cell Sci). Recently we have also shown context-dependency of signalling between FAK and the MAP kinase cascade, as FAK acts as a signalling suppressor during development in the fly (Macagno et al., 2014, PLoS Genetics, in press). As a result of our work, and that of others, we proposed that FAK is, in fact, a self-regulating molecular scaffold, which crucially builds complexes in space in time, and in response to environmental cues, so controlling actin and adhesion assembly and stress and survival signalling, proliferation and cell motility (Frame et al., 2010, Nat Rev Mol Cell Biol; Serrels et a;., 2007, Nat Cell Biol; Serrels et al., 2010, Curr Biol; Tang et al., 2013, Curr Biol). Importantly, the molecular complex-building adaptor functions of FAK are vital for cancer phenotypes associated with over-expressed FAK in epithelial tumours, and lead to enhanced cell cycle progression (Serrels et al., 2012, Int J Cancer), direction sensing, invasion (Serrels et al., 2010, Curr Biol) and metastasis (Lahlou et al., 2007, PNAS), as

well as the ability of tumour cells to permit immune evasion (our unpublished observations).

The realisation that many of FAK's roles in cancer are due to scaffolding functions has huge implications for the clinical use of FAK kinase inhibitors that we are addressing. Our realisation that FERM-mediated protein scaffolding is vital for FAK's biological functions led us to also examine the activities of the FERM-only protein Kindlin-1 (Kin-1; a FAK-binding partner), which is an integrin activating scaffold protein that is genetically altered in the skin-blistering disease Kindler Syndrome, pre-disposing sufferers to Squamous Cell Carcinoma. We recently showed that in addition to functions in cell adhesion and integrin signalling, a distinct pool of Kin-1 is a substrate for Plk-1 at the mitotic spindle and is required for proper spindle assembly during mitosis (Patel et al., 2013, Nat Comm). Hence, the FERM domain-only Kin-1 protein also shuttles between cellular integrin complexes and the mitotic spindle in cancer cells, coordinating adhesion and integrin function with spindle assembly, chromosome segregation and cell division in concert with mitotic kinases (Patel et al., 2013, Nat Comm). This suggests a more general role for FERM domain-containing proteins in spatial signalling.

In recent work, we, and others (mainly the group of David Schlaepfer), showed that the FERM domain of FAK mediates formation of many important molecular complexes (Serrels et al., 2010, Curr Biol; Serrels et al., 2007, Nat Cell Biol), including those in the nucleus that change gene expression and deal with stress responses and protect against apoptosis. As a result, we proposed that FERM domain-containing proteins, like FAK and Kin-1, act as an 'adhesion to nucleus' information shuttle that permits two way sensing between transcriptional apparatus and the state of cell adhesions (Frame et al., 2010, Nat Rev Mol Cell Biol). Moreover, loss of the adaptor functions of FAK in cancer cells also causes 'untethered' over-active oncogenic tyrosine kinase FAK partners, including Src and Ret, to be trafficked into autophagosomes for ultimate lysosomal degradation, and that this a compensatory survival mechanism that cancer cells adopt in the face of severe adhesion stress (Sandilands et al., 2012a, Nat Cell Biol; Sandilands et al., 2012b, EMBO Rep).

In translational work, we have used complex genetically engineered mouse (GEM) models to study the role of FAK in malignancy. We reported the first tissue-specific conditional FAK knockout mouse (McLean et al., 2004, Genes and Dev), in which progression of skin cancer was blocked. Since epithelial cells give rise to most clinically relevant solid cancers, and many show deregulation of Src and FAK activity, our work has resulted in a fuller appreciation of the importance of these kinases as therapeutic targets for inhibition of cancer spread. Our FAK-deficient mice have been used more widely to show requirements for FAK in intestinal and breast cancer progression (Ashton et al., 2010, Dev Cell; Lahlou et al., 2007, PNAS). In addition, we provided the first demonstration that Src inhibitors suppress metastasis in a genetically engineered model of pancreatic cancer (Morton et al., 2010, Gastroenterology).

Finally, a key feature of my lab's work during the recent past has been to embrace inter-disciplinary team science that brings new innovative approaches to cancer biology questions. We have been working with chemists, physicists and engineers to develop new high throughput chemical biology screens and multi-modal label-free imaging techniques that are providing new insights. Pre-clinical and clinical imaging of responses to agents that target invasion rather than tumour cell proliferation is particularly challenging. In exciting on-going work, my laboratory leads a multi-disciplinary imaging consortium that is developing new forms of whole body and dynamic molecular intra-vital cancer imaging, including label-free multi-modal Raman-based imaging. Essentially, we are coupling novel imaging approaches, (for example, two colour photo-switchable probes and biosensors (examples in (Canel et al., 2010, Cancer Res; Timpson et al., 2011, Cancer Res; Welman et al., 2010, J Biol Chem) with mouse modelling of skin, breast and other cancers, using optical window technology to optimise the predictive value of pre-clinical studies. Together with colleagues in the Edinburgh Cancer Research Centre, we aim of mapping cancer phenotypes on to cancer pathways, using mouse- and human patient-derived material as

biological source (new operating model descried in (Carragher et al., 2012, Drug Discov Today)). This is attracting huge attention from pharmaceutical alliance partners, and we aim to improve the predictivity of pre-clinical therapeutic testing.