BIOGRAPHICAL SKETCH

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NAME: Frank McCormick, Ph.D., F.R.S.

eRA COMMONS USER NAME (credential, e.g., agency login): MCCORMICKF

POSITION TITLE: Professor, Helen Diller Family Comprehensive Cancer Center and Dept. of Cellular and Molecular Pharmacology, UCSF

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Birmingham, England	B.Sc.	07/72	Biochemistry
University of Cambridge, England	Ph.D.	07/75	Biochemistry

A. Personal Statement

My lab has taken biochemical and genetic approaches to developing therapies for cancer. My group made a number of other contributions to Ras biology and biochemistry, including the discovery of GTPase Activating Proteins, and we launched an effort to discover drugs that block mutant Ras. The central part of this effort was an NCI National Cooperative Drug Development Grant, of which I was PI. Co-PIs were Drs. Wittinghofer (Max Planck), Redfield (Brandeis), and Wood (Hoffmann-La Roche). In 1992, I co-founded ONYX Pharmaceuticals, to increase our efforts to find therapies for Ras cancers. We also started programs in p53, Rb, APC amongst other areas, but the Ras project was the primary focus. I chose Raf kinase as our first target as it was known to be downstream from Ras, though its direct interaction with Ras was not discovered until 1993. We developed Sorafenib, the first Raf kinase inhibitor to enter the clinic. This drug has been extremely successful and has been approved for treating renal cell cancer, hepatocellular cancer and thyroid cancer. However, Sorafenib was not active against cancers with mutant Ras for reasons that we did not understand, as the paradoxical effects of Raf kinase inhibitors on Ras cancers only became recognized as an on-target effect as additional Raf kinases were tested in the clinic. Nevertheless, this was a disappointing outcome, and forced us to re-think ways of attacking these cancers.

At ONYX, under my leadership and with help from an extremely effective advisory group (Drs. Varmus, Harlow, Howley, Wiite, Fearon, White, Levine, Hanahan and Bourne), we also developed a new approach to treating cancer using oncolytic viruses, a CDK4 inhibitor (now known as palbociclib) which will likely be the first in class to receive FDA approval, carfilzomib for multiple myeloma, as well as many scientific contributions. However, as each project matured towards clinical candidates, the ONYX group became less involved in discovery research, and when I was offered the opportunity to move to UCSF and develop a Comprehensive Cancer Center and restart a research lab there, I was happy to do so.

While I was Director of the Cancer Center, from 1999-2014, my lab published 128 peer-reviewed papers including 16 in Cell, Science or Nature journals. Many of these discoveries relate to Ras in one way or another, including discovery that Spred proteins interact with neurofibromin. This was particularly important to me, as I have been working on NF1 and neurofibromin since we discovered that neurofibromin is a GAP in 1990. The discovery that this terrible disease is simply caused by hyperactive Ras led to the false expectation that treatments were within sight. As I became more involved in the NF1 patient community, I became more determined to find new approaches to treatment. This has been a theme of my lab for many years and we are finally making progress in this direction.

In 2014, Dr. Varmus asked me to take a leadership role in the new National Ras Program, and I was delighted

to accept. This is an applied science project focused directly on one of my long-term passions. I committed to spend half my time running this project, including a week a month in Frederick, Md. The remaining time I devote to my lab at UCSF, which is now entirely focused on basic Ras biology. The interaction between my lab at UCSF and the Frederick National Lab has been synergistic: for example, we developed Dr Barbacid's system of expressing single Ras isoforms in a Rasless MEF background as a discovery tool to identify specific biochemical properties of individual Ras proteins in a clean background. We have exported this system to Frederick to use as a primary screen for compounds that hit K-Ras but not H-Ras, amongst other screens. However, my lab at UCSF is devoted to basic discovery science, more than applied drug discovery. Recently we discovered that K-Ras initiates a stem-like program that makes cancer cells drug resistant and metastatic, and we expect to exploit these discoveries to develop new therapies.

B. Positions and Honors

Frank McCormick, Ph.D., F.R.S., D.Sc. (Hon) is a Professor of the University of California, San Francisco (UCSF) Helen Diller Family Comprehensive Cancer Center. A native of Cambridge, England, Dr. McCormick received his B.Sc. in biochemistry from the University of Birmingham (1972) and his Ph.D. in biochemistry from the University of Cambridge (1975). Postdoctoral fellowships were held at the State University of New York at Stony Brook and in London at the Imperial Cancer Research Fund. He has been a Fellow of the Royal Society since 1996 and a Member of the National Academy of Sciences since 2014. Prior to joining the UCSF faculty, Dr. McCormick pursued cancer-related work at Cetus Corporation (Director of Molecular Biology, 1981-90; Vice President of Research, 1990-91) and Chiron Corporation, (Vice President of Research from 1991-92) and in 1992 he founded Onyx Pharmaceuticals and served as its Chief Scientific Officer until 1996. His group discovered and developed sorafenib and palbociclib, and pioneered cancer therapy using oncolytic viruses. His laboratory at UCSF focuses on functions of Ras proteins. More recently, he has taken a leadership role at the Frederick National Laboratory for Cancer Research, overseeing an NCI supported national effort to develop therapies against Ras-driven cancers.

Positions and Employment

1975-1978 Professor Seymour S. Cohen, SUNY at Stony Brook (Post Doctoral Fellow)
1978-1981 Dr. Alan Smith, Imperial Cancer Research Fund, London (Post Doctoral Fellow)
1981-1990 Cetus Corporation (Director of Molecular Biology)
1990-1991 Cetus Corporation (Vice President, Research)
1991-1992 Chiron Corporation (Vice President, Research)
1992-1996 Onyx Pharmaceuticals (Founder, Chief Scientific Officer)
1997-2013 University of California, San Francisco, Microbiology & Immunology (Professor)
1997-2014 University of California, San Francisco, Cancer Center (Director, Associate Dean)
2013-2016 University of California, San Francisco, Microbiology & Immunology (Professor Emeritus)
2013-2016 University of California, San Francisco, Cancer Center (Professor Emeritus)
2016-present University of California, San Francisco, Cellular & Molecular Pharmacology (Professor)
2016-present University of California, San Francisco, Cancer Center (Professor)

Other Experience and Professional Memberships

1998-1999 National Cancer Institute Developmental Therapeutics Program Advisory Board
1998-2003 National Cancer Institute Board of Scientific Counselors Advisory Committee
2004-2009 Lawrence Livermore National Lab, Biology/Biotechnology Research Program Advisory Board
2012-2013 President, American Association for Cancer Research
2013- present National Cancer Institute, Frederick National Laboratory for Cancer Research, Scientific Director

Honors

1996 Fellow of the Royal Society
2002 Bristol Myers Squibb Unrestricted Cancer Research Grant
2002 AACR – G.H.A. Clowes Memorial Award
2002 Novartis Drew Award in Biomedical Research
2003 University of Chicago, Cancer Research Center, Shubitz Award
2005 Institute of Medicine
2010 ASCO Science of Oncology Award
2014 National Academy of Science

2015 Memorial Sloan Kettering, Sloan Award
2018 Biochemical Society Centenary Award

C. Contributions to Science

Oncolytic viruses
In 1992, I had the idea that adenoviruses with mutations in E1a or E1b should replicate in cancer cells that lack Rb or p53, respectively, but should fail to replicate in normal cells. This led to the development of ONYX-015 (Bischoff et al 1994) and Delta-24 adenoviruses (Jiang et al 2007). The former is approved for treating nasopharyngeal carcinoma in China, the latter is undergoing Phase II clinical trials for treating glioblastoma. Tumor selectivity for ONYX-015 was based on the assumption that the major function of E1B was to block p53 activity (Ries et al 2000), so that virus could replicate efficiently without p53-medieated apoptosis. However, E1B has additional p53-independent functions relating to translation of viral late mRNAs, leading to a re-examination of the selectivity of this virus and new insights into E1B activity (O'Shea et al 2005).

- Bischoff, J. R., Kirn, D. H., Williams, A., Heise, C., Horn, S., Muna, M., Ng, L., Nye, J. A., Sampson-Johannes, A., Fattaey, A., and **McCormick, F.,** 1996. An adenovirus mutant that replicates selectively in p53-deficient human tumor cells. Science 274:373-6.
- Jiang, H., Gomez-Manzano, C., Aoki, H., Alonso, M. M., Kondo, S., **McCormick, F**., Xu, J., Kondo, Y., Bekele, B. N., Colman, H., Lang, F. F., & Fueyo, J. 2007. Examination of the therapeutic potential of Delta-24-RGD in brain tumor stem cells: role of autophagic cell death. J Natl Cancer Inst 99:1410-1414.
- Ries S., Brandts C., Chung A., Biederer C., Hann B., Lipner E., **McCormick F.,** Korn M., 2000. Loss of $p14^{ARF}$ in tumor cells facilitates replication of the adenovirus mutant dl1520 (ONYX-015) Nature Medicine 6:1128-33
- O'Shea,C., Choi S., Bagus B., **McCormick, F**. 2005. Heat shock phenocopies E1B-55K late functions and selectively sensitizes refractory tumor cells to ONYX-015 oncolytic viral therapy. Cancer Cell 8: 61-74

Ras GAP and NF1
I began working on Ras in 1984. My group developed antibodies against codon-12 mutants, and showed that blocking these mutant cells reversed transformation. This was one of the first demonstrations that targeting a mutant Ras protein could be an effective therapeutic strategy. I also published the first model for the tertiary structure of Ras p21 (McCormick et al 1985). I discovered GAP activity (Trahey et al 1987) and cloned the first human GAP, p120GAP and the first Rap1GAP. My group showed that neurofibromin is a GAP that works on Ras p21, thus providing a molecular mechanism for NF1, a disease that afflicts 1 in 3500 people worldwide (Martin et al 1990). In collaboration with Dr. Kevin Shannon, I showed that the NF1 gene is a tumor suppressor in malignant myeloid disorders. My group also showed, for the first time, that neurofibromin is mutated in sporadic cancers. More recently, we showed that neurofibromin functions in a complex with SPRED1, the gene responsible for Legius Syndrome (Stowe et al 2012). In collaboration with Dr. Kate Rauen, we showed that another hereditary syndrome, Cardio-Facio-Cutaneous disease, is caused by germline mutations in B-Raf or MEK.

- **McCormick, F.,** Clark, B. F., la Cour, T. F., Kjeldgaard, M., Norskov-Lauritsen, L., and Nyborg, J. 1985. A model for the tertiary structure of p21, the product of the ras oncogene. Science 230:78-82.
- Trahey, M., and **McCormick, F.,** 1987. A cytoplasmic protein stimulates normal N-ras p21 GTPase, but does not affect oncogenic mutants. Science 238:542-5.
- Martin, G. A., Viskochil, D., Bollag, G., McCabe, P. C., Crosier, W. J., Haubruck, H., Conroy, L., Clark, R., O'Connell, P., Cawthon, R. M., and **McCormick, F.,** 1990. The GAP-related domain of the neurofibromatosis type 1 gene product interacts with ras p21. Cell 63:843-9.
- Stowe IB, Mercado EL, Stowe TR, Bell EL, Oses-Prieto JA, Hernández H, Burlingame AL, **McCormick F**. 2012. A shared molecular mechanism underlies the human rasopathies Legius syndrome and Neurofibromatosis-1. Genes Dev 26, 1421-6.

Signal Transduction
In addition to analysis of proteins that regulate Ras, we have made several contributions to understanding pathways downstream and to other signaling pathways that are important in cancer cells. For example, we showed that cAMP signaling interferes with Ras signaling through direct effects on Raf kinase activity (Cook et al 1993). We were the first group to show that Raf kinase can be activated by Ras in vitro, as long as the Ras protein is fully processed and inserted in a membrane-like environment (Stokoe et al 1997). We showed that Rac and Rho proteins are essential for Ras transformation (Qiu et al 1995).
We also analyzed relationships between Ras signaling and other pathways, and showed that cyclin D1, a

known target of MAPK signaling, is also a target of the β-catenin pathway: this was one of the first targets identified for this critical signaling pathway.

- Cook, S. J., and **McCormick, F.,** 1993. Inhibition by cAMP of Ras-dependent activation of Raf. Science 262:1069-72.
- Stokoe, D., and **McCormick, F.,** 1997. Activation of c-Raf-1 by Ras and Src through different mechanisms: activation in vivo and in vitro. Embo J 16:2384-96
- Qiu, R. G., Chen, J., Kirn, D., **McCormick, F.,** and Symons, M. 1995. An essential role for Rac in Ras transformation. Nature 374:457-9.
- Tetsu O., **McCormick F.** 1999 β-catenin regulates cyclin D1 expression in colon carcinoma cells. Nature 398:422-6.

Targeted therapies

At Onyx, a company that I co-founded in 1992 to develop therapies based on genetic alterations that cause cancer, I initiated a screening campaign to find inhibitors of Raf kinase. This took advantage of our ability to produce significant quantities of active recombinant proteins in insect cells, and the first use of novel epitope tags to purify these proteins (Macdonald et al 1994). This led to development of the first Raf kinase inhibitor to enter the clinic. Sorafenib and fluoro-sorafenib, are FDA approved for treating renal cancer, hepatocellular cancer, thyroid and colorectal cancers. Sorafenib is still the only drug approved for treating hepatocellular cancer. My group at Onyx developed the first Cdk4 inhibitor, in collaboration with Parke-Davis. This compound, now known as palbociclib, recently received FDA Breakthrough Therapy designation for treatment of breast cancer. At UCSF, we showed that CDK2 is not a suitable target for therapeutic inhibition by demonstrating that cancer cells can proliferate despite CDK2 inhibition. This result contradicted the dogma at that time, but was later confirmed by Dr. Barbacid who showed that mice survive after CDK2 deletion.

- Macdonald, S. G., Crews, C. M., Wu, L., Driller, J., Clark, R., Erikson, R. L., and **McCormick, F.,** 1993. Reconstitution of the Raf-1-MEK-ERK signal transduction pathway in vitro. *Mol Cell Biol* 13:6615-20.
- Tetsu, O., **McCormick, F.** 2003. Proliferation of cancer cells despite CDK2 inhibition. Cancer Cell 3:233-246.

Technical innovations

My group at Cetus collaborated with Dr. Gordon Ringold at Stanford, to use dhfr-amplification to produce high levels of beta-interferon in CHO cells. This was the first demonstration that a human protein could be stably over-expressed using this technique and was the basis of extensive use of dhfr-co-amplification technique to produce human recombinant proteins in mammalian cells in the biotech industry (U.S. Patent No. **4,966,843**). We were among the first to use PCR to detect Ras mutations in human tumor DNA. In collaboration with Dr. Chris Marshall, we amplified Ras genes from AML samples and detected mutations by probing amplified DNA (Farr et al, 1988). My group also published the first use of PCR to detect mRNA (U.S. Patent No. **5,057,410)**: in collaboration with Dr. Owen Witte at UCLA, we used reverse transcriptase to produce cDNA from mRNA derived from CML samples, and used PCR to detect breakpoints (Kawasaki et al 1988).

- **McCormick, F.,** Trahey, M., Innis, M., Dieckmann, B., and Ringold, G. 1984. Inducible expression of amplified human beta interferon genes in CHO cells. Mol Cell Biol 4:166-72.
- Farr, C. J., Saiki, R. K., Erlich, H. A., **McCormick, F.,** and Marshall, C. J. 1988. Analysis of RAS gene mutations in acute myeloid leukemia by polymerase chain reaction and oligonucleotide probes. Proc Natl Acad Sci U S A 85:1629-33.
- Kawasaki, E. S., Clark, S. S., Coyne, M. Y., Smith, S. D., Champlin, R., Witte, O. N., and **McCormick, F.,** 1988. Diagnosis of chronic myeloid and acute lymphocytic leukemias by detection of leukemia-specific mRNA sequences amplified in vitro. Proc Natl Acad Sci U S A 85:5698-702.

Complete list of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/frank.mccormick.1/bibliography/45609917/public/?sort=date&direction=ascending

D. Research Support

Ongoing Research Support

1R35CA197709 McCormick(PI) 04/01/2016-03/31/2023
NIH/NCI
New ways of targeting K-Ras
To identify ways to suppress the function of hyper-active Ras proteins for cancer therapy we need to understand how these proteins and their normal counterparts function at the molecular level. This award focuses on three research areas, analysis of: a) GTPase Activating Proteins (GAPs) that regulate Ras b) the

distinct biochemical functions of different K-Ras mutants and c) a novel, unique function of K-Ras 4B that activates a stem cell phenotype.

(no grant #) McCormick (PI) 04/01/2017–03/31/2019
Daiichi-Sankyo Pharmaceuticals Contract
Target identification of Ras-related drug resistance
The major goals of this project are to investigate drug resistance pathways, and to identify Ras-binding compounds using Second harmonic generation (SHG) screening techniques.

(no grant #) McCormick (PI) 01/01/2015–12/31/2017
Lustgarten Fdn.
New ways of treating pancreatic cancer based on reversing K-Ras-mediated stemness
The goal is to rapidly develop new ways of treating pancreatic cancer, by exploiting a new function of KRas that we have recently discovered.

(no grant#) McCormick (Subcontract PI) 08/01/2015—07/31/2018
Subcontract through Massachusetts General Hospital
Targeting KRAS mutant lung cancers
This site will conduct preclinical evaluation of prostratin and LIF for treating lung adenocarcinoma.

NF140038 McCormick (PI) 09/30/2015 – 09/28/2018
DoD/CDMRP
Identifying neurofibromin-specific regulatory nodes for therapeutic targeting in NF1
The objective in this project is to identify signaling mediators that are most sensitive to loss of Neurofibromin and thus make candidate drug targets, as well as determine signaling pathways that regulate the Spred/Neurofibromin interaction to identify drug targets that may work to boost the function of Neurofibromin in NF1 deficient cells.

Completed Research Support

1U01 CA168370 McCormick, McManus, Weissman (MPI) 05/01/2012-04/30/2017
NIH/NCI
Bay Area cancer target discovery and development network
The identification and cataloguing of large numbers of variations is only the first step in efforts to provide a scientific foundation for therapeutic breakthroughs. To achieve this broader goal, we must now understand how these variations alone and critically in combination contribute to the malignant properties of human tumors. This program aimed to fill this void.

U54CA143836 Liphardt (Co-Investigator) 09/29/2009-07/31/2014
UC Berkeley
Fundamental mechanobiology of tumor progression
The major goals of this project are to evaluate potential therapeutic applications of the projects and addressing questions that of highest clinical impact

2P30 CA82103-14 09/19/2012-05/31/2017
(McCormick (PI); role on grant ended June 1, 2014)
NIH/NCI ***Cancer Center Support Grant***
The Cancer Center Support Grant provides support for administration and infrastructure for the UCSF Comprehensive Cancer Center.

(no grant #) McCormick (PI) 04/01/2011-03/31/2013
Lustgarten Foundation
Developing targeted nanoparticles to interfere with K-Ras expression using siRNA
The major goal of this project is to develop and utilize human antibody-targeted nanoparticles to deliver small interfering RNAs to pancreatic tumor cells to inhibit K-Ras function.