BIOGRAPHICAL SKETCH—*Pilot Format (To Be Used for Specific FOAs only)*

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME	POSITION TITLE
Ian G. Macara	Louise B. McGavock Professor and Chair
eRA COMMONS USER NAME (credential, e.g., agency login) IGM9CNIH	

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

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YY	FIELD OF STUDY
University of Sheffield, England	B.S. (Hons.)	1970	Biochemistry
University of Sheffield, England	Ph.D.	1974	Biochemistry

A. Personal Statement

Dr. Macara has studied various aspects of cancer biology for several decades, and has focused on cell polarity mechanisms for over 10 years. He has been continually funded by the NIH for over 30 years, and currently holds 3 RO1 grants including one from the NCI, plus a Susan Komen breast cancer foundation grant. A major goal of the laboratory is to tackle fundamental questions concerning the function of cell polarity in mammary morphogenesis and breast cancer, employing biologically-relevant mouse and human models. He has published over 185 research papers, has an h-index of 79 (Google Scholar), and is placed in the top 5% of cited authors for journals in Biology and Biochemistry (per analysis by Thomson Reuters). He is currently the co-chair of the Signal Transduction Program in the Vanderbilt Ingram Cancer Center, has served on the NCI Basic Research Board of Scientific Counselors, and is a member of ASCB Council.
He has collaborated broadly with colleagues both in his own institution and elsewhere, and has an ongoing collaboration (and Komen grant) with Dr. Deborah Lannigan to develop 3D organotypic cultures of human breast ductal tissue and cancer tissues under conditions that closely recapitulate the in situ organization and phenotype of these tissues (1), and to exploit the ability to transduce the cultures with lentivirus to identify driver mutations in triple negative breast cancer. With a former postdoctoral fellow, Dr. Luke McCaffrey, he developed methods for the efficient lentiviral transduction of mammary stem cells and their transplantation into cleared fat pads where they can regenerate new mammary glands, thereby enabling the rapid analysis of gene function in mammary gland morphogenesis (2) and breast cancer (3). Using this system, his laboratory demonstrated that polarity proteins can function as potent tumor growth and metastasis suppressors (3, 4).

1. Pasic, L., Isinger-Matheson, K.T.S., Velayudhan, B.T., Moskaluk, C.A. Brenin, D.R., **Macara, I.G**. and Lannigan, D. A. (2011) Sustained Activation of the HER1-ERK-RSK Signaling Pathway Controls Myoepithelial Progenitor Fate in Human Mammary Tissue. ***Genes & Development***, 25: 1641-1653. PMC3182019
2. Martin-McCaffrey, L. and **Macara, I.G.** (2009) The Par6/aPKC interaction is essential for endbud remodeling and progenitor differentiation during mammary gland morphogenesis***. Genes & Development*** **23**: 1450 – 1460. (*Cover picture*) PMC2701573
3. McCaffrey, L., Montalbano, J., Mihai, C., and **Macara, IG.** (2012) Loss of the Par3 Polarity Protein Promotes Breast Tumorigenesis and Metastasis. ***Cancer Cell*** **12**:601-614. PMC3500525.
4. Archibald, A., Mihai C., **Macara, I.G**. and McCaffrey, L. (2014) Oncogenic suppression of apoptosis uncovers a Rac1/JNK proliferation pathway activated by loss of Par3. ***Oncogene*** (in press).

B. Positions and Honors

1975-1977 Assistant Professor, Dept. of Biochemistry, University of Nairobi, Kenya, East Africa
1977-1979 Postdoctoral Research Fellow, Dept. of Chemistry, Brandeis University, Waltham, MA
1979- 1983 Research Associate, Dept. of Biochem. & Molec. Biol., Harvard University, Cambridge, MA

1983-1985 Assistant Professor, Depts of Biophys. & Biochem., Univ. of Rochester Schl of Medicine, Rochester, NY
1983-1985 Mellon Foundation Fellowship for Outstanding Young Faculty
1985-1991 Associate Professor (tenured), Depts. of Toxicol., Biophys & Biochem., Univ. of Rochester School of Medicine, NY
1991-1993 Associate Professor (tenured), Depts. of Pathology and Microbiol/Molec Genetics, Univ. of Vermont Medical School, Burlington, VT. Member, Comprehensive Cancer Center
1993-1996 Professor (tenured), Departments of Pathology and Microbiol./Molec. Genetics Univ. of Vermont Medical School, Burlington, VT. Member, Comprehensive Cancer Center
1996-2012 Professor (tenured), Dept of Microbiology, Univ. of Virginia, Member, Ctr for Cell Signaling
1997 (8/18-12/19) Sabbatical as Visiting Miller Professor, Department of Molec. & Cell Biol., Univ. of California, Berkeley (laboratory of Dr. Jeremy Thorner)
2004-2012 Faculty Director, Advanced Microscopy Facility, Univ. of Virginia School of Medicine.
2005 - 2009 Craig Scholar, Univ. of Virginia Cancer Center
2007-2012 Harrison Distinguished Professor of Microbiology, Univ. of Virginia
2008 Distinguished Scientist Award, Univ. of Virginia
2008 Elected to Univ. Virginia Senate; co-chair of Science & Engineering subcommittee
2012- present Chair of Cell & Dev. Biology, and Louise B. McGavock Professor, Vanderbilt University
2014 – 2017 ASCB Council Member
2009 -2014 Board of Scientific Counselors, NCI, NIH

C. Contributions to Science

1. Discovery of tyrosine kinase associated PI kinase.

Early in my career, I discovered that an oncogenic tyrosine kinase, *v-ros*, is associated with phosphatidylinositol kinase activity (1 - 3). This work, along with that of Lew Cantley and Ray Erikson, was the first to link these 2 signaling pathways, and led to the eventual discovery by Lew Cantley of PI-3-kinase. Later, in the search for factors that might regulate PI turnover, we discovered the first Ras guanine nucleotide exchange activity (4).

1. **Macara, I.G**., Marinetti, G.V., and Balduzzi, P.C. Transforming protein of avian sarcoma virus UR2 is associated with phosphatidylinositol kinase activity: Possible role in tumorigenesis**.** ***Proc. Natl. Acad. Sci. USA*** **81**, 2728-2732 (1984).
2. Faletto, D., Arrow, JA. And **Macara,** I.G. A very early decrease in phosphatidylinositol turnover occurs upon induction of Friend cell differentiation. ***Cell*** **43**, 315-325, (1985).
3. Wolfman, A. and **Macara,** I.G. Ras-transformed 3T3 cells possess increased diacylglycerol levels and decreased responsiveness to phorbol esters. ***Nature*** **325**, 359-361, (1987).
4. Wolfman, A. and **Macara,** I.G. A cytosolic protein catalyzes the release of GDP from $p21^{ras}$. ***Science*** **248***:* 47-69 (1990).

2. Analysis of nucleo-cytoplasmic transport systems driven by the Ran GTPase.

Our interest in Ras led to the investigation of multiple other members of this family of small GTPases. Particularly productive was the work on Ran, which turned out to be essential for the transport of many proteins through the nuclear pore complex. We were the first to show that Ran is required for nuclear protein export (1), and that the factor NTF2 is responsible for uptake of Ran into the nucleus (2). In addition, we were the first group to develop testable, quantitative computational models of nuclear transport (3). We also cloned several nuclear transport receptors, including exportin-5, which in collaboration with Brian Cullen we discovered is the export receptor for micro-RNAs (4).

1. Richards, S.A., Carey, K. and **Macara, I.G**. Requirement of guanosine triphosphate-bound Ran for signal-mediated nuclear protein export. ***Science*** 276, 1842-1844 (1997)
2. Smith, A., Brownawell, A., and **Macara**, **I.G.** (1998) Nuclear import of Ran is mediated by the transport factor NTF2. ***Current Biol*** 8: 1403-1406.
3. Smith, A.E., Slepchenko, B., Schaff, J., Loew, L. and **Macara, I.G.** (2002) Systems analysis of Ran transport into the nucleus. ***Science*** **295**: 488-491.
4. Yi R, Qin Y, **Macara I.G.**, Cullen B.R. (2003) Exportin-5 mediates the nuclear export of pre-microRNAs and short hairpin RNAs. ***Genes Dev.*** **17**:3011-3016.

3. Discovery of the N-methyl transferase NRMT and its role in chromosome segregation.

During our work on the mechanisms of nucleo-cytoplasmic transport, we discovered that the Ran exchange factor, RCC1, is tethered to chromatin by histones H2A and B (1), which is essential for normal mitosis. Further investigation revealed that a very unusual type of post-translational modification of RCC1 is involved in its chromatin association. The N-terminal methionine of RCC1 is removed and the new free N-terminal Ser residue is methylated on its alpha amino group (2). This unusual methylation is necessary for stable association of RCC1 with chromatin and mutants that cannot be methylated cause mitotic defects, related to perturbation of the RanGTP gradient around the chromosomes (2). Although α-amino methylation of proteins had first been reported over 25 years ago, nothing was known about its enzymology. A postdoctoral fellow in my group, Christine Tooley, purified the activity and cloned the gene, which we called N-terminal RCC1 methyl transferase (NRMT) (3). We subsequently identified dozens of targets for methylation by NRMT, including the important tumor suppressor gene, Rb1 (3) and CENP-A (4).

1. Nemergut, M.E., Mizzen, C.A., Stukenberg, T., Allis, D. and **Macara, I.G**. (2001) Histones H2A and H2B dock the Ran exchange factor, RCC1, on chromatin and regulate its activity. ***Science* 292**: 1540-1543.

2. Chen, T., Muratore, T.L., Schaner-Tooley, C.E., Shabanowitz, J., Hunt, D.F., and **Macara, I.G**. (2007). N-terminal alpha-methylation of RCC1 is necessary for stable chromatin association and normal mitosis. ***Nature Cell Biol***. **9**: 596 – 603. (*Commentary in Nat. Cell Biol*)

3. Tooley, CES, Petkowski, JJ, Muratore-Schroeder, TL, Balbaugh, JL, Shabanowitz, J, Satab M, Minor, W, Hunt DF and Macara IG (2010) NRMT is an α-N-methyltransferase that methylates RCC1 and retinoblastoma protein. ***Nature*** 466: 1125-1128. (*Commentaries in Nature Reviews and Cell*).

4. Bailey, AO, Panchenko T, Sahtyan KM, Petkowski JJ, Pai P-J, Bai DL, Russell DH, **Macara IG**, Shabanowitz J, Hunt DF, Black BE, Foltz DR. Posttranslational modification of CENP-A influences the conformation of centromeric chromatin (2013) ***Proc Natl Acad Sci (USA)*** 110: 11827-11832.

4. Discovery of the mitotic spindle orientation mechanism in mammalian cells.

Asymmetric divisions of stem cells and the organization of epithelial tissues both rely on mitotic cells to orient their spindle poles in the correct plane. Work on *Drosophila* had identified the proteins Inscuteable and Partner of Inscuteable (Pins) to be essential for this process. We discovered that the mammalian homologue of Pins, called LGN, associates with NuMA, a nuclear matrix protein (1). NuMA is released from the nucleus when the envelope breaks down in mitosis. We found that the binding of NuMA to the N-terminus of LGN triggers a conformational change that opens up the protein enabling it to bind to the G-protein αi subunit a the plasma membrane and that these interactions are essential for correct orientation of the mitotic spindle apparatus (2). Moreover, NuMA binds directly to microtubules, and this interaction is blocked by LGN association with NuMA (3). Only some years later was a *Drosophila* homologue of NuMA discovered (Mud). We have since demonstrated that in epithelial cells phosphorylation of LGN by aPKC blocks the migration of LGN onto the apical surface, thereby ensuring that cell divisions remain horizontal, rather than occurring perpendicular to the plane of the epithelial sheet (4).

1. Du, Q., Stukenberg, T. and **Macara, I.G**. (2001) A mammalian Partner of Inscuteable (Pins) binds NuMA and regulates mitotic spindle assembly and organization. ***Nature Cell Biol***. **3:***1069-1075*

2. Du, Q. and **Macara, I.G.** (2004) Mammalian Pins functions as a conformational switch that links NuMA to heterotrimeric G-proteins. ***Cell* 119**: 503-516. (*Commentary in Cell*)

3. Du, Q-S, Taylor, L. Compton, D, **and Macara IG** (2002) LGN blocks the ability of NuMA to bind and stabilized microtubules - a mechanism for mitotic spindle assembly regulation. ***Curr. Biol.*** (2002) **12:** 1928-1933

4. Hao Y, Du Q, Chen X, Zheng Z, Balsbaugh JL, Maitra S, Shabanowitz J, Hunt DF, Macara IG. (2010) Par3 controls epithelial spindle orientation by aPKC-mediated phosphorylation of apical Pins. ***Current Biol*** 20: 1809-18.

5. Discovery of cell polarity mechanisms in mammalian cells

Although the Cdc42 GTPase had been known to be key to cell polarization in budding yeast and in mammalian cells, nothing was known concerning the downstream effectors of Cdc42 in mammalian cell polarity. We cloned the mammalian homologues of the *C. elegans* Par6 proteins and showed that it bound directly to Cdc42:GTP (1). We also discovered that Par6, Cdc42, aPKC and Par3 could form a tetrameric complex (1). We solved the crystal structure of a Par6/Cdc42 complex, and discovered that Par3 controls the activity of the Rac GTPase through sequestration of the exchange factor Tiam1 (2), and that these proteins are

all required for synapse formation in hippocampal neurons. In a separate project on cell polarity we performed the first genome-wide screen in mammalian cells for localized mRNAs and discovered that the APC tumor suppressor protein anchors a set of mRNAs to the + ends of microtubules in cell protrusions (3). Most recently we have discovered the first biological function for the Par3-like protein, PAR3L (4)

1. Joberty, G., Petersen, C., Gao., L. and **Macara, I.G.** (2000) The cell-polarity protein Par6 links Par3 and atypical protein kinase C to Cdc 42. ***Nature Cell. Biol.*** **2**: 540-547.

2. Chen, X. and **Macara, I.G.** (2005) Par-3 regulates tight junction assembly through the Rac exchange factor, Tiam1. ***Nature Cell Biol.*** **7**: 262 - 269.

3. Mili, V., Moissoglu, K. and Macara, I.G. (2008) Genome-wide screen identifies APC-associated RNAs in cell protrusions. ***Nature*** **453:** 115 -119. (*Cover picture; commentaries in Nature Reviews, Cell Migration Gateway, ACS Chemical Biology*).

4. Huo, Y and Macara IG (2014) The Par3-like polarity protein, Par3L, is essential for mammary stem cell maintenance. ***Nature Cell Biol.*** (2014) **16**: 529-537 (*Cover picture*).

List of Published Work
http://www.ncbi.nlm.nih.gov/pubmed/?term=macara+ig

D. Research Support

Current Support:

1. Mammary Gland Morphogenesis and Breast Cancer (NCI R01CA132898) Macara (PI)
09/01/2010 – 02/28/2015
Project Goals: The major goals of this project are to determine the role of polarity genes in breast cancer growth and metastasis, and to screen for new genes that promote breast cancer growth.

2. Mechanisms of Cell Polarity Establishment (NIGMS R01GM070902-09) Macara (PI)
04/01/2004 – 07/31/2016
Project Goals: The goals of this project are to determine the roles of PAR3 and PAR-6 proteins, and their binding partners, in cell polarization, and to establish the mechanisms that initiate cell polarity in epithelial cells.

3. Identification of Driver Mutations in TNBC Using Primary 3D Organoids. (Susan G. Komen Breast Cancer Foundation) Macara (PI) 08/01/2012 - 07/31/2016
Project Goals: Goals are to develop a robust organotypic human breast culture model for breast cancers that can be used in personalized medicine to select appropriate chemotherapeutic treatments.

4. The Ran GTPase (NIGMS R01GM050526-20) Macara (PI)
08/01/1994 – 06/30/2015
Project Goals: The major goal of this project is to study the regulation and function of Ran, a small nuclear GTP-binding protein, which is a key factor in nuclear protein import and nuclear export processes.

Previous support

Human Mammary Organoid Cultures. (Susan G. Komen for the Cure FAS0703854) Macara (PI)
01/11/2007-31/10/2010
Project Goals: The major goal of this project was to develop a 3D culture model that would recapitulate normal ductal development in vitro.

In Search Of Conserved mRNA Localization And Anchoring Mechanisms. (Human Frontier Science Program RGP0031**)** Macara (PI) 06/01/09 – 05/31/12
The goals were to identify the zipcodes in localized RNAs, both in yeast and in mammalian cells, in collaboration with two other laboratories, one in Switzerland and one in New Zealand.