OMB No. 0925-0001 and 0925-0002 (Rev. 12/20 Approved Through 02/28/2023)

BIOGRAPHICAL SKETCH

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NAME: Samantha A. Morris

eRA COMMONS USER NAME: SAMMORRIS

POSITION TITLE: Associate Professor of Developmental Biology, and Genetics

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
Imperial College, University of London, UK	B.Sc.	10/2002	Biochemistry
University of Cambridge, UK	Ph.D.	01/2007	Developmental Biology
University of Cambridge, UK		09/2011	Developmental Biology
Boston Children's Hospital/Harvard Medical School		06/2015	Stem Cell Biology

A. Personal Statement

I am an Associate Professor of Developmental Biology and Genetics. My expertise in stem cell engineering is rooted in my long-standing interest in developmental mechanisms. Training with Magdalena Zernicka-Goetz at the University of Cambridge, I created live-imaging tools to track cell fate specification in early mammalian development. I took these foundational perspectives on cell identity into my postdoctoral research in George Daley's lab at Harvard Medical School. Here, my work established new computational methods for quantifying and comparing cell identity, demonstrating that a careful, rational investigation into cell fate transitions is necessary to understand these processes beyond rudimentary, phenomenological description. My independent research program at Washington University continues to break new ground by coupling the molecular genetics and cell biology of cell fate transitions, including new experimental and computational technologies to track lineage histories of reprogramming populations *in vitro* and to "record" the molecular events that direct cells toward defined identities. I have applied these concepts across various development, differentiation, and reprogramming paradigms to unpack the complex dynamics of cell fate choice at single-cell resolution, offering new opportunities to quantify the molecular events that control cell identity and behavior. My proposed research project aims to dissect mechanisms of reprogramming, laying the foundation for creating cells and tissue types for disease modeling, treatment, and prevention. In this respect, the project goals align with the mission of the NIGMS. Beyond duties expected at my institution, I have made significant service contributions to the scientific community. I hold and have held several leadership positions, including serving on the Board of Directors for the Society of Developmental Biology; Founding the Stem Cell Computational Biology Working Group with the International Society of Stem Cell Research; Founding the Next-Generation Genomics Conference Series. I am also an Associate Editor at *Development* and serve on the editorial boards of *Developmental Cell, Cell Stem Cell,* and *Cell Systems*.

Ongoing and recently completed projects that I would like to highlight:

New York Stem Cell Foundation Robertson Investigator Award Morris (PI) 01/01/21 – 12/31/25
New York Stem Cell Foundation
New single-cell genomic technologies to dissect and enhance cell fate reprogramming. This project aims to use single-cell genomic technologies to dissect cell reprogramming, focusing on regional reprogramming in the small intestine.

Allen Distinguished Investigator Award Morris (PI) 12/01/19 – 11/30/22
Paul G. Allen Frontiers Group
Reading and writing cell histories: New genomic technologies to unlock cell programming. This project aims to combine single-cell lineage tracing with spatial genomic technologies to dissect mechanisms of stem cell differentiation focusing on kidney and human gastruloids.

R01 GM126112 Morris (PI) 09/15/17 – 08/31/22
National Institutes of Health, NIGMS
Dissecting mechanisms of pioneer transcription factor-mediated lineage reprogramming
The long-term goal of this project is to understand how FoxA pioneer factors direct lineage reprogramming.
Role: PI

Vallee Scholar Award Morris (PI) 09/01/17 – 08/31/21
The Vallee Foundation
Dissecting Mechanisms of reprogramming and Differentiation: a blueprint for engineering cell identity This project aims to employ single-cell sequencing technologies to monitor the reprogramming and differentiation of mouse endoderm progenitor cells in an *in vitro* model of mouse gut regeneration.

R21HG009750 Mitra and Morris (MPI) 06/01/17 – 06/30/19
National Institutes of Health, NHGRI
Single-cell analysis of pioneer binding and function during lineage reprogramming. The central aim of this technology development proposal is to adapt Calling Cards to single-cell-level analyses.

KEY PUBLICATIONS

a. Kamimoto K, Stringa B, Hoffmann CM, Jindal K, Solnica-Krezel L, **Morris SA.** Dissecting cell identity via network inference and in silico gene perturbation. ***Nature*** 2023 Feb; 614(7949):742-751.
b. Kong W, Fu YC, Holloway EM, Garipler G, Yang X, Mazzoni E, **Morris SA.** Capybara: A computational tool to measure cell identity and fate transitions. ***Cell Stem Cell.*** 2022; Apr 7;29(4)
c. Biddy BA, Kong W, Kamimoto K, Guo G, Waye SE, Sun T, **Morris SA.** Single-cell mapping of lineage and identity in direct reprogramming. ***Nature.*** 2018. Dec 5; 219–224
d. **Morris SA***, Cahan PC*, Li H*, Zhao A, San Roman AK, Shivdasani RA, Collins JJ, Daley GQ. Dissecting Engineered Cell Types and Enhancing Cell Fate Conversion via CellNet. ***Cell****.* 2014 Aug 14;158(4):889-902

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2007-2011	Postdoctoral Research Fellow, Gurdon Institute, University of Cambridge, UK
2011-2015	Postdoctoral Research Fellow, Stem Cell Program, Boston Children's Hospital and Harvard Medical School
2015-2021	Assistant Professor of Developmental Biology and Genetics, Washington University School of Medicine
2018-present	*Cell Systems* editorial board member
2018-present	*Development* editorial board member
2019-present	*Developmental Cell* editorial board member
2019-present	Board of Directors, Junior Faculty Representative, Society for Developmental Biology
2020-present	Consultant, Longitude Capital
2020-2022	Consultant, Third Rock Ventures
2020-present	NIH Center for Excellence in Genomic Science Advisory Board Member
2020-present	*Development* Associate Editor
2020-present	*Cell Stem Cell* editorial board member
2021-present	Associate Professor of Developmental Biology and Genetics, Washington University School of Medicine

Honors

2021	New York Stem Cell Foundation Robertson Investigator
2020	Sloan Research Fellowship in Computational and Evolutionary Molecular Biology

2020	Washington University Distinguished Faculty Award
2019	Allen Distinguished Investigator Award
2019	Cell Stem Cell, 'Best of 2018' for Wu et al., "Comparative Analysis and Refinement of Human PSC-Derived Kidney Organoid Differentiation with Single-Cell Transcriptomics."
2019	St. Louis Academy of Science Innovation Award
2017	Vallee Foundation Young Investigator Award
2014	Sanofi-Cell Research' Outstanding Review Article Award 2013', for Morris and Daley, "A blueprint for engineering cell fate: current technologies to reprogram cell identity."
2013	Cell Reports, 'Best of 2012' for Morris et al., "Developmental plasticity is bound by Fgf and Wnt signaling pathways."
2009	Runnström Medal for Wenner Gren Institute Lecture, Stockholm University.
2009	Gurdon Institute, University of Cambridge, Research Prize
2005	Department of Oncology, University of Cambridge, Research Prize
2000	Eric Potter Clarkson Prize for best use of intellectual property

C. Contributions to Science. [#]marks publications within the scientific mission of NIGMS and resulting from NIGMS support.

1) The central focus of my research program is to understand how cell identity is regulated and to use this knowledge to develop precision reprogramming strategies. Fully differentiated cells can be directly reprogrammed to an array of different cell types using transcription factor (TF) overexpression. However, the cells produced using these protocols often appear developmentally immature or incompletely specified, limiting their therapeutic utility. This infidelity was confounded by the lack of any systematic means by which to assess the fidelity of engineered cells. As a postdoc trainee, I was instrumental in the development of 'CellNet,' a computational platform that accurately evaluates cell identity through gene regulatory network (GRN) reconstruction and generates hypotheses for improving cell derivation protocols[a]. Using this platform, we revealed that most published cell engineering protocols fail to recapitulate cell identity faithfully and that directly reprogrammed cells have much broader potential than anticipated[b].

My independent research group continues to develop computational methods to quantify cell identity and improve reprogramming methods. Here, I highlight one of our most recent publications, 'Capybara,' to measure cell identity and state transitions using single-cell RNA sequencing data[c]. Capybara overcomes the previous limitations of assaying cell identity using bulk sequencing methods and thus can pinpoint rare cell types. Moreover, Capybara is unique in treating cell identity as a continuous measure; thus, we can quantify cell state transitions and hybrid states comprising mixed terminal identities, which we frequently detect in non-physiological reprogramming processes. Using Capybara, we diagnosed patterning deficiencies in motor neuron and cardiomyocyte reprogramming, designing **experimental** interventions to increase target cell yield. We also revealed an in vivo correlate for 'induced endoderm progenitors' – a previously poorly characterized reprogrammed cell type. Further, we have applied Capybara to quantify fetal to adult transitions in hematopoiesis[d]. In summary – these studies represent **significant advances** in quantifying and correcting cell identity – a crucial first step in our central goal to improve cell engineering strategies and to diagnose cell type deficiencies in disease, supporting the development of new therapies.

a. **Morris SA***, Cahan PC*, Li H*, Zhao A, San Roman AK, Shivdasani RA, Collins JJ, Daley GQ. Dissecting Engineered Cell Types and Enhancing Cell Fate Conversion via CellNet. ***Cell***. 2014 Aug 14 **Equal contribution.*
b. Cahan PC*, Li H*, **Morris SA***, Lummertz da Rocha E, Daley GQ, Collins JJ. CellNet: Network Biology Applied to Stem Cell Engineering. ***Cell***. 2014 Aug 14 **Equal contribution.* [#]
c. Kong W, Fu YC, Holloway EM, Garipler G, Yang X, Mazzoni E, **Morris SA.** Capybara: A computational tool to measure cell identity and fate transitions. ***Cell Stem Cell*** 2022 Mar 29. [#]
d. Li Y, Kong W, Yang W, Okeyo-Owuor T, Patel RM, Casey EB, **Morris SA***, Magee JA*. Single cell analysis of neonatal HSC ontogeny reveals gradual and uncoordinated transcriptional reprogramming that begins prior to birth. ***Cell Stem Cell.*** 2020. Aug 20. *co-corresponding authors. [#]

2) Once reprogramming deficiencies have been diagnosed (above), the next step is to correct these deficits by identifying regulators of cell identity that will push engineered cells closer to the target cell type. We systematically delineate Gene Regulatory Network (GRN) structures for this goal to produce a logic map of regulatory factor cause-effect relationships. This knowledge of how cell identity is determined and maintained informs new

strategies for cellular reprogramming. However, our previous CellNet method to infer GRNs lacked resolution and any systematic means to identify critical regulators of cell identity from complex network 'hairballs.' Here, I highlight our recent work on CellOracle, an algorithm that combines single-cell transcriptome and epigenome data to infer GRNs[a]. CellOracle is unique in using these network models to simulate the effects of transcription factor (TF) perturbation *in silico*, aiding network interpretation and prioritization of candidate regulators. We validated this machine learning-based tool using well-established paradigms of differentiation and development: mouse and human hematopoiesis, and zebrafish embryogenesis, correctly simulating reported phenotypic changes due to TF perturbation. Via systematic *in silico* TF perturbation in the developing zebrafish, we simulated and experimentally validated a previously unreported phenotype upon loss of *noto*, an established notochord regulator. Further, we identified a novel axial mesoderm regulator, *lhx1a*. Because CellOracle builds network models using prior biological knowledge, extensive training data is not required. Thus, this is a scalable approach we offer for over a dozen species so far (https://github.com/morris-lab/CellOracle), enabling broad adoption of the method. For example, we recently applied CellOracle to identify drivers of medium spiny neuron maturation in the human fetal striatum[b], and cardiac functional recovery[c].

Our work on CellOracle represents a **significant** advance in emerging computational methods to model and predict the regulation of cell identity. We have recently demonstrated this approach's value in characterizing and improving cell engineering. Applying CellOracle to the direct reprogramming of fibroblasts to induced endoderm progenitors, we identified new TFs to increase the target cell yield. In addition, network analysis revealed a role for the AP-1 subunit Fos with the Hippo signaling effector, Yap1, in successful reprogramming[d]. Together, these results showcase CellOracle's ability to dissect TF-regulation of cell identity, enabling new mechanistic insights across various biological paradigms.

a. Kamimoto K, Stringa B, Hoffmann CM, Jindal K, Solnica-Krezel L, **Morris SA.** Dissecting cell identity via network inference and in silico gene perturbation. ***Nature*** 2023 Feb;614(7949):742-751. #
b. Bocchi VD, Conforti P, Vezzoli E, Besusso D, Cappadona C, Lischetti T, Galimberti M, Ranzani V, Bonnal RJP, De Simone M, Rossetti G, He X, Kamimoto K, Espuny-Camacho I, Faedo A, Gervasoni F, Vuono R, **Morris SA**, Chen J, Felsenfeld D, Pavesi G, Barker RA, Pagani M, Cattaneo E. The coding and long noncoding single-cell atlas of the developing human fetal striatum. ***Science***. 2021 May 7. #
c. Amrute JM, Lai L, Ma P, Koenig AL, Kamimoto K, Bredemeyer A, Shankarn TS, Kuppe C, Kadyrov FF, Schulte LJ, Stoutenburg D, Kopecky BJ, Navankasattusas S, Visker J, **Morris SA**, Kramann R, Leuschner F, Mann DL, Drakos SG, Lavine KJ. Defining Cardiac Recovery at Single Cell Resolution. ***Nat Cardiovasc Res.*** 2023 Apr 6.
d. Kamimoto K, Adil MT, Jindal K, Hoffmann CM, Kong W, Yang X, **Morris SA.** Gene Regulatory Network Reconfiguration in Direct Lineage Reprogramming. ***Stem Cell Reports*** 2023. Jan 10. #

3) From our aforementioned computational analyses measuring reprogrammed cell identity across a range of cell engineering protocols, we uncovered an array of off-target cell identities generated by these protocols. To characterize the molecular mechanisms determining reprogramming fidelity, it is essential to identify the origins and emergence of different cell types over time. Mapping how cells relate to each other via their lineage is vital to these efforts. Although single-cell RNA-seq can deconstruct the heterogeneity that arises during cell reprogramming, lineage relationships are lost during cell processing; thus, lineage is often computationally inferred, producing inaccurate results. To overcome this limitation, my lab developed 'CellTagging,' one of the first experimental techniques that simultaneously captures lineage and cell identity information at single-cell resolution[a]. CellTagging labels cells with combinations of heritable random barcodes delivered using lentivirus, allowing cells to be uniquely labeled and tracked over time. We applied CellTagging to the direct reprogramming of mouse fibroblasts to induced endoderm progenitors (iEPs - driven by the overexpression of two transcription factors: Foxa1 and Hnf4a), revealing two distinct trajectories: a route toward successfully reprogrammed cells and an alternate path into a 'dead-end' mesenchymal-like state. These lineages revealed that successfully reprogramming cells transiently express a putative RNA methyltransferase, *Mettl7a1*, where adding this factor to the conversion cocktail increases iEP yield. We built on the CellTagging technology to support the tracing of cells *in vivo* to demonstrate that iEPs functionally engraft acutely damaged mouse intestine via a stem-cell-like state[b].

Recently, we enhanced CellTagging to capture chromatin accessibility[c] and to record transcription factor binding[d] in the earliest stages of reprogramming. Integration of chromatin accessibility with gene expression and lineage revealed a role for the TF Zfp281 in directing cells toward the off-target mesenchymal-like 'dead-end,' which we could block, redirecting cells to reprogram successfully. This work is **significant** as it represents the

first technology to capture lineage with the multiome, which we are now expanding to histone modification capture. These methods will enable mechanistic insight into gene regulation in the earliest stages of reprogramming, allowing cell identity to be precisely manipulated.

a. Biddy BA, Kong W, Kamimoto K, Guo C, Waye SE, Sun T, **Morris SA**. Single-cell mapping of lineage and identity in direct reprogramming. ***Nature.*** 2018 Dec;564(7735):219-224. #
b. Guo B, Kong W, Kamimoto K, Rivera-Gonzalez GC, Yang X, Kirita Y, **Morris SA**. CellTag Indexing: a genetic barcode-based multiplexing tool for single-cell technologies. ***Genome Biology.*** 2019 May 9;20(1):90.#
c. Jindal K, Adil MT, Yamaguchi N, Wang HC, Yang X, Kamimoto K, Rivera-Gonzalez G, **Morris SA**. Multiomic single-cell lineage tracing to dissect fate-specific gene regulatory programs. ***bioRxiv*** 2022. Oct 23. #
d. Moudgil A, Wilkinson MN, Chen X, He J, Cammack AJ, Vasek MJ, Lagunas T, Qi Z, **Morris SA**, Dougherty, JD, and Mitra RM. Self-reporting transposons enable simultaneous readout of gene expression and transcription factor binding in single cells. ***Cell****.* 2020 Jul 18. #

4) My long-term goal is to apply our knowledge of the regulation of cell identity to develop precision engineering methods to reprogram human cell identity. In this context, it is crucial to understand not only the non-physiological manipulation of cell identity by transcription factor overexpression but also how cell fate is normally specified during human development. Considering that the developing human embryo is inaccessible, *in vitro* models of human development and methods to extend the culture of human embryos have recently emerged. My earliest work made an essential contribution to this field. The core of my training focused on early mouse development[a], where a ‘black box’ to my studies of mouse embryogenesis was the window of implantation into the uterus. To address this, I developed a technology to support embryo implantation *in vitro* that was amenable to live imaging, permitting tracing of endoderm development to previously inaccessible stages. This work represented the platform for future studies to culture human embryos through implantation stages[b].

Here I highlight my long-term interest in *in vitro* models of human development. In collaboration with Lila Solnica-Krezel at Washington University, we cultured human embryonic stem cells extracellular matrix micro-discs, generating gastruloids expressing markers of germ layers and extraembryonic cells[c]. However, the precise assessment of cell identity in this model was highly challenging, considering that these human cell types are inaccessible in normal development. Thus, we do not have complete reference atlases to benchmark against. To overcome this challenge, we performed a series of cross-species comparisons with mouse, cynomolgus monkey gastrulae, and post-implantation human embryos, revealing that gastruloids contain cells transcriptionally similar to epiblast, ectoderm, mesoderm, endoderm, primordial germ cells, trophectoderm, and amnion. This study represents a significant benchmark for using non-human primates to characterize cell identity in *in vitro* models of human development. We followed up on this initial work with a detailed time-course analysis of cell fate specification in the gastruloid model, demonstrating the presence of cell types transcriptionally similar to their *in vivo* counterparts in Carnegie stage 7 human gastrula[d]. Together, these studies represent a valuable reference for understanding how cell identity is regulated in human development.

a. **Morris SA*,** Grewal S*, Barrios F*, Patankar SN, Strauss B, Buttery L, Alexander M, Shakesheff K and Zernicka Goetz M. Dynamics of anterior-posterior axis formation in the developing mouse embryo. ***Nature Commun.*** 2012 Feb 14;3:673. **Equal contribution*
b. **Morris SA**, Teo RT, Li H, Robson P, Glover DM, Zernicka-Goetz M. Origin and formation of the first two distinct cell types of the inner cell mass in the mouse embryo. ***Proceedings of the National Academy of Sciences of the United States of America***. 2010; 107(14):6364-9.
c. Minn KT, Fu YC, He S, Dietmann S, George SC, Anastasio MA, **Morris SA***, Solnica-Krezel L*. High-resolution transcriptional and morphogenetic profiling of cells from micropatterned human embryonic stem cell gastruloid cultures. ***Elife.*** 2020 Nov 18;9:e59445. *co-corresponding authors. #
d. Minn KT, Dietmann S, Waye SE, **Morris SA**, Solnica-Krezel L. Gene expression dynamics underlying cell fate emergence in 2D micropatterned human embryonic stem cell gastruloids. ***Stem Cell Reports***. 2021 May 11;16(5):1210-1227. #

Complete List of Published Work in MyBibliography:
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