BIOGRAPHICAL SKETCH

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NAME: Samantha A. Morris

eRA COMMONS USER NAME: SAMMORRIS

POSITION TITLE: Assistant 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

My expertise in stem cell engineering is rooted in my long-standing interest in developmental mechanisms. At the University of Cambridge, I addressed several unanswered questions on the plasticity of mammalian cell fate in the lab of Magdalena Zernicka-Goetz. Here, I developed a novel method of pluripotent stem cell deviation, and applied this in embryologic and genetic experiments to demonstrate that modulation of FGF and Wnt signaling pathways enhance plasticity to promote monozygotic twinning. My continued interest in the plasticity of early cell fate decisions led me to the lab of Dr. George Daley at Harvard Medical School in Boston, where I focused my postdoctoral work on cell fate engineering. Here I addressed an important outstanding challenge in tissue engineering, which was the lack of quantitative and universal methods to assess and compare the identity of various *in vitro* differentiated or reprogrammed cell populations. This led to my instrumental role in the development of CellNet, a computational platform that delineates gene regulatory networks in analyzed cells, enabling the assessment of engineered cell identity, relative to target populations. I demonstrated that CellNet can diagnose aberrant gene regulatory networks and consequently can inform and expedite experiments to enhance engineered conversions. As a result, I discovered an endodermal progenitor cell type with intestinal potential in a model of colitis. I established my lab three years ago at Washington University in St. Louis. Here, I continue to focus on fundamental and translational aspects of reprogramming, regeneration, and disease, leveraging my broad and deep expertise in developmental biology, stem cell engineering, and network biology. I have integrated single-cell technology development to address longstanding questions in reprogramming. To this end, my lab recently developed a methodology to enable simultaneous profiling of lineage and identity at single-cell resolution, revealing mechanisms we exploited to enhance reprogramming efficiency.

KEY PUBLICATIONS

1. 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
2. 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;158(4):903-15.**Equal contribution.*
3. **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.**Equal contribution*
4. **Morris SA.** Direct lineage reprogramming via pioneer factors; a detour through developmental gene regulatory networks. ***Development.*** 2016 143: 2696-2705.

B. Positions and Honors

Positions and Employment

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-Present Assistant Professor of Developmental Biology and Genetics, Washington University School of Medicine

Honors

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

1) Cell differentiation had long been thought a unidirectional process toward restricted potential and increasing specialization. In the past half-century this has been challenged: Mature somatic cells can be returned to a pluripotent state, and subsequently differentiated to desired cell types. Alternatively, adult cells can be 'directly converted' from one mature state to another, bypassing pluripotency. Many reports claim to capture defined fates, however the resultant cells often appear developmentally immature or incompletely specified, limiting their therapeutic utility[d]. This is confounded by the lack of any systematic means by which to assess the fidelity of engineered cells. I was instrumental in the development of 'CellNet', a network biology-based computational platform that accurately evaluates cell fate through gene regulatory network (GRN) reconstruction and generates hypotheses for improving cell derivation protocols[b,c]. Using this platform we surveyed a range of engineered cells from 56 published studies. We found that cells derived via directed differentiation more faithfully recapitulated target cell identity than cells generated by direct conversion. These directly converted cells commonly failed to silence expression programs of the original cell type, and illicit gene expression programs were frequently induced. My developmental and stem cell biology skills were critical in guiding the evolution and utility of CellNet. In the process of experimentally scrutinizing hypotheses generated by the platform, I focused on endoderm engineering strategies, given my experience in the natural genesis of this lineage. Specifically, CellNet analysis of fibroblast to hepatocyte-like cell (iHep) conversion revealed that these cells harbored an unanticipated intestinal identity, predicted to be regulated by the master intestinal transcriptional regulator Cdx2. My experimental work with iHeps revealed that Cdx2 is essential for their generation – a finding that prompted me to investigate the intestinal potential of these cells. I went on to observe long-term functional colon engraftment by iHeps, where the engineered cells were able to mature *in vivo* to cells that were highly similar to colonic epithelium, repairing acute tissue damage[b]. Considering the known hepatic repopulation potential of iHeps, we proposed that they would be better described as 'induced endoderm progenitors' (iEPs). Together, our papers published back-to-back in Cell[b,c] make a critical contribution to efforts in regenerative biology by providing a framework to assess and unlock the full potential of engineered cells.

I continue to expand on these studies in my own laboratory. I have recently proposed that pioneer transcription factors, commonly employed to drive lineage conversion, engage developmental gene regulatory networks to drive converting cells through embryonic intermediates. We are examining mechanisms of cell fate conversion in further detail, where we have recently developed a novel single-cell lineage tracing technology, 'CellTagging'[a]. CellTagging and tracking over 100,000 cells converting to iEPs reveals two distinct trajectories: one, a route toward successfully reprogrammed cells, and an alternate path into a putative 'dead-end' state, marked by re-expression of fibroblast genes. We find that very few cells successfully reprogram, although clonally-related cells tend to follow the same trajectories, suggesting that their reprogramming outcome may be determined from the earliest stages of conversion[a].

5. Biddy BA, Kong W, Kamimoto K, Guo G, Waye SE, Sun T, **Morris SA.** Single-cell mapping of lineage and identity in direct reprogramming. 2018. ***Nature.*** 2018. Dec 5; 219–224
   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;158(4):889-902.**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;158(4):903-15.**Equal contribution.*
   c. **Morris SA***, Daley GQ.* A blueprint for engineering cell fate: current technologies to reprogram cell identity. ***Cell Res.*** 2013 Jan;23(1):33-48.

2) Toward the end of my PhD, I became increasingly captivated by the plasticity of early mammalian development, a stark contrast to the rigidity of deterministic embryogenesis. In pursuit of this, I joined the laboratory of Magdalena Zernicka-Goetz (Gurdon Institute, Cambridge) to investigate early mammalian fate specification in mouse. At that time, it was unknown whether preimplantation fate was designated stochastically or related to developmental history[a]. To study this, I developed a novel live-imaging approach[b,c] and showed that these patterning events are influenced by prior cell position and mediated by the transcription factor Sox17[c,d], in concert with FGF receptor expression, permitting cells to respond to endoderm differentiation signals[c,d].

   a. *Zernicka-Goetz M,* **Morris SA***, Bruce AW.* Making a firm decision: multifaceted regulation of cell fate in the early mouse embryo**. *Nat Rev Genet.*** 2009 Jul;10(7):467-77.
   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. ***Proc Natl Acad Sci USA.*** 2010 Apr 6;107(14):6364-9
   c. Meilhac SM, Adams RJ*, **Morris SA*,** Danckaert A, Le Garrec JF, Zernicka-Goetz M. Active cell movements coupled to positional induction are involved in lineage segregation in the mouse blastocyst. ***Dev Biol.*** 2009 Jul 15;331(2):210-21. * *Equal contribution*
   d. **Morris SA,** Graham SJ, Jedrusik A, Zernicka-Goetz M. The differential response to Fgf signalling in cells internalized at different times influences lineage segregation in preimplantation mouse embryos. ***Open Biol.*** 2013 Nov20;3(11):130104

3) One limitation to our embryological development studies was the window of implantation into the uterus that remained a 'black box'. 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[a]. This work represented the platform for future studies to culture human embryos through implantation stages. I was consistently intrigued how early mammalian cell fate remained plastic and able to adapt to changing circumstances. In following this interest, I investigated the mechanisms underlying fate plasticity using half-embryo development as a model system. I demonstrated that modulation of FGF and Wnt signaling pathways enhances plasticity to promote monozygotic twinning, in the process developing a novel method of ESC deviation - work featured in Cell Reports' 'Best of 2012'[c].

   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.** Human embryos cultured in vitro to 14 days. ***Open Biology.*** 2017 Jan;7(1)
   c. **Morris SA,** Gu Y, and Zernicka-Goetz M. Developmental plasticity is bound by pluripotency and the Fgf and Wnt signaling pathways. ***Cell Reports.*** 2012. Oct 25;2(4):756-65

4) I trained with Shin-ichi Ohnuma at the University of Cambridge, UK, where my graduate research on endoderm fate specification in Xenopus laevis provided a solid foundation in developmental biology. Here I demonstrated the role of TGF−β signaling in cell fate specification[a] and helped unlock the mechanism of inhibition of activin signaling by follistatin[b].

   a. **Morris SA,** Almeida AD, Tanaka H, Ohta K, Ohnuma S. Tsukushi modulates Xnr2, FGF and BMP signaling: regulation of Xenopus germ layer formation. ***PLoS One.*** 2007 Oct 10;2(10):e1004
   b. Harrington AE, **Morris SA,** Ruotolo BT, Robinson CV, Ohnuma S, Hyvonen M. Structural basis for the inhibition of activin signalling by follistatin. ***EMBO J.*** 2006 Mar 8;25(5):1035-45.

Complete List of Published Work in MyBibliography:
https://www.ncbi.nlm.nih.gov/myncbi/browse/collection/48094218/?sort=date&direction=descending

D. Research Support

Ongoing Research Support

Vallee Young Investigator Award Morris (PI) 09/01/17 – 08/31/21
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 endoderm progenitor cells in an *in vitro* model of murine gut regeneration.
Role: PI

R01GM126112-01 Morris (PI) 12/01/17 – 11/30/22
Dissecting mechanisms of pioneer transcription factor mediated direct lineage reprogramming.
The aim of this proposal is to employ single-cell and transcription factor binding assays to dissect the mechanisms of direct lineage reprogramming.
Role: PI

R21HG009750-01 Mitra and Morris (MPI) 06/01/17 – 05/31/19
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. We propose to apply this to monitor the binding of pioneer factors during lineage reprogramming as a proof-of-concept study.
Role: PI

HCA2-A-1708-02799 Morris (PI) 03/01/18 – 02/29/19
Chan-Zuckerberg Initiative
scClassifier, a bioinformatic tool to assess and evaluate identity at single cell resolution.
The aim of this project is to create a new single-cell analytical tool to support quality control for data submitted to the Human Cell Atlas.
Role: PI

R01HL136504 Magee (PI) 04/01/17 – 03/31/22
Temporal changes in mechanisms of HSC self-renewal and Myeloid Leukemogenesis.
The goal of this project is to understand how normal developmental programs shape the genetic and epigenetic landscapes of acute myeloid leukemia (AML).
Role: Co-investigator

Hyundai Quantum Award Druley (PI) 06/01/18 – 05/31/22
Improving pediatric AML survival by implementing RNA-specific error corrected sequencing for residual disease.
The aim of this project is to improve pediatric acute myeloid leukemia survival by implementing RNA-specific error corrected sequencing to increase residual clonal AML detection.
Role: Co-Investigator

ALSF Innovation Award Druley (PI) 10/01/18 – 09/30/20
RNA-ECS to quantify rare clonal RNA species at diagnosis, remission and relapse from the COG AAML1031 study.
The aim of this project is to implement single-cell resolution error corrected RNA-sequencing to detect rare clones arising during AML.
Role: Co-Investigator

Completed Research Support

CZI Human Cell Atlas Pilot Award Morris (PI) 08/01/17 – 07/31/18
Single-cell RNA-sequencing tools to evaluate and enhance experimental replicability of the Human Cell Atlas.

The aim of this project is to create new single-cell technology benchmarking and multiplexing approaches to enable standardization of the Human Cell Atlas, ensuring rigor and reproducibility.
Role: PI

NIDDK RBK U01DK107350 Humphreys (PI) 10/3/16 – 10/2/18
Human Kidney Biopsy Single Cell Protocols and Analysis.
Role: Co-investigator

NIDDK P30 Pilot/Feasibility Award Morris (PI) 05/01/16 – 05/01/18
Single-cell RNA-seq mapping of an in vitro intestinal regeneration model.
This project aimed to develop an *in vitro* model of mouse intestinal regeneration to monitor the differentiation of induced endoderm progenitor cells.
Role: PI

Children's Discovery Institute Award Morris (PI) 02/01/16 – 07/31/17
Reprogramming colon to small bowel as a therapy for short bowel syndrome.
The major goal of this project was to reprogram portions of colon to small bowel in an effort to restore nutrient absorption in SBS.
Role: PI

American Cancer Society IRG Morris (PI) 3/1/2016–2/28/2017
A network biology approach to dissect the etiology and progression of hepatoblastoma.
The major goal of this project was to identify dysregulated nodes in tumor GRNs for novel therapeutic targeting.
Role: PI