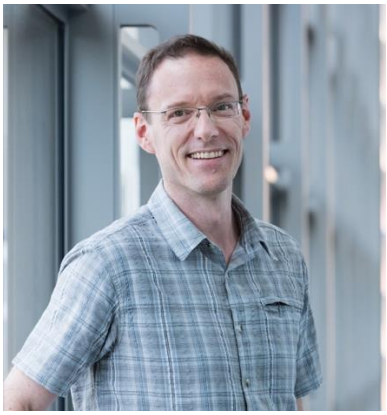
Name	ALEX GOULD
Position	Senior Group Leader
Year joined *(Crick or founder institute)*	1998



Career History

1986-1990: PhD in Developmental Genetics, University of Cambridge
1990-1991: Postdoctoral Research Associate, University of Cambridge
1992-1997: Beit Memorial Fellow & MRC training Fellow, MRC National Institute for Medical Research
1998-2005: Tenure Track Programme Leader, MRC National Institute for Medical Research
2005-2011: Programme Leader, MRC National Institute for Medical Research
2011-2015: Head of Division, Physiology & Metabolism, MRC National Institute for Medical Research

Major Awards, Honours and Prizes

1986: F.P Bedford Prize, King's College, Cambridge
1991: Junior Research Fellow, King's College, Cambridge
1992: Beit Memorial Fellow
2008: Elected, Member of EMBO
2011: Hooke Medal (British Society for Cell Biology)
2013: Elected, Fellow of The Academy of Medical Sciences
2014: Wellcome Trust Senior Investigator
2018: Elected, Member of Medical Research Club

Membership of external committees, editorial boards, review panels, SABs etc

2007-2011: Wellcome Trust Molecules, Genes and Cells Funding Committee
2012-2016: Wellcome Trust Peer Review College
2013-2016: Academy of Medical Sciences Sectional Committee 2
2013-present: Editorial Advisory Board of Development
2013-present: SUSTAIN & Mentorship programme, Academy of Medical Sciences
2014-present: Scientific Advisory Board, Metabolic Research Laboratories, University of Cambridge
2014-present: Tenure and mid-term review panels (e.g Beatson, Dundee)
2015-present: Editorial Board of PLOS Biology
2017-present: Royal Society/Wellcome Sir Henry Dale Fellowship Interview Committee
2017-present: Expert for UCL Food, Metabolism and Society Research Domain
2018-present: UK Nutrition Research Partnership (MRC, BBSRC & NIHR)
2020-present: European Drosophila Board

Lab Name	*Physiology and Metabolism Laboratory*

Research programme and achievements

Our overarching aim is to understand how developing animals cope with, and sometimes benefit from, exposure to environmental stresses. This is a fundamental problem in developmental biology that is also clinically important, yet mechanistic knowledge in this area remains sparse. Our past work pioneered the study of the role of metabolism in stress adaptation to nutrient restriction during *Drosophila* development.

The main achievements of the laboratory since 2015 are:

1. Establishment of several *Drosophila* and mouse models for the long-term effects of transient developmental stresses on adult physiology.

2. Discovery of a molecular mechanism for selective protection of the CNS (brain sparing) during developmental hypoxia. In response to low oxygen tension, the *Drosophila* neural stem cell niche synthesises lipid droplets with antioxidant functions that are essential to protect neighbouring neural stem cells.

3. Discovery of a mechanism whereby expression of the sex determination pathway in a few identified neurons in the brain regulates the sexual size dimorphism of the entire *Drosophila* body. It overturns long-standing dogma in insects that sexual dimorphism is regulated in a strictly cell-autonomous manner. The morphometric methods developed in this study are now being used to investigate how some developing organs but not others are spared during nutrient restriction.

4. Demonstration that early-life nutrient restriction or mild oxidative stress can significantly extend rather than shorten *Drosophila* lifespan and identification of the underlying mechanisms. Early-life nutrient restriction decreases the concentration of toxic hydrocarbons in the protective lipid barrier coating the adult body, improving its function and thus extending lifespan. Transient exposure to low-dose oxidants permanently changes gut microbiota, eliminating the Acetobacter that trigger age-related hyperimmunity, thus preserving the gut barrier and extending lifespan.

5. The development of an improved chemically defined diet for *Drosophila*, enabling study of the contributions of individual macro- and micro-nutrients to organ growth during development.

6. Multiple technology developments in metabolomics and in mass spectrometry imaging. These have been essential for the laboratory to be able to quantify and to image metabolism with high precision and single-cell resolution within complex tissues.

Future work of the laboratory will build upon our *Drosophila* findings to provide an in-depth mechanistic understanding of how developing animals cope with environmental stresses. We will embrace new technologies such as mass spectrometry imaging, where we have already invested considerably in method development. We will also embark on a major new research direction - translating key *Drosophila* findings into mice and humans. Recent results indicate exciting and unanticipated parallels between insect and human stress-protective mechanisms. One of these involves a rewiring of lipid metabolism and we will be testing new drugs that target this pathway as a potential therapeutic strategy for glioblastoma.

Research outputs

Bailey AP, Koster G, Guillermier C, Hirst EM, MacRae JI, Lechene CP, Postle AD and Gould AP (2015). *Antioxidant Role for Lipid Droplets in a Stem Cell Niche of Drosophila*. Cell 163:340-353. DOI: 10.1016/j.cell.2015.09.020
This paper is a continuation of our major research theme on how dividing stem cells in the CNS are able to resist environmental stresses that shut down proliferation in most other developing tissues. It reports the first identification, in any species, of lipid droplets as protectors of stem cells. We discovered that hypoxia induces lipid droplets in the neural stem cell niche and that these protect the neural stem cells themselves from damaging polyunsaturated fatty acid (PUFA) peroxidation reactions. This study laid the foundation for our current mechanistic studies into the antioxidant functions of lipid droplets during development and tumorigenesis.

Stefana MI, Driscoll PC, Obata F, Pengelly AR, Newell CL, MacRae JI and Gould AP (2017). *Developmental diet regulates Drosophila lifespan via lipid autotoxins*. Nature Communications 8:1384. DOI: https://www.nature.com/articles/s41467-017-01740-910.1038/s41467-017-01740-9
This reports the first identification, in any species, of barrier lipids as key mediators of diet induced longevity. We discovered that moderate dietary restriction during development decreases toxic barrier lipids and can more than double lifespan - an effect size comparable or greater than was previously observed with dietary restriction during adulthood. This study has widespread relevance because toxic barrier lipids also influence how longevity is regulated by many other factors, including insulin signalling.

Sawala A and Gould AP (2017). *The sex of specific neurons controls female body growth in Drosophila*. PLoS Biol 15:e2002252. DOI: 10.1371/journal.pbio.2002252
This study identifies a surprising neurohormonal mechanism that links sex to growth and proliferation during development. It overturns long-standing dogma in insects that sexual dimorphism is regulated in a strictly cell-autonomous manner. It also suggests that the principles of sexual differentiation in insects and mammals may be more similar than previously thought.

**Obata F, Fons CO, and Gould AP (2018). *Early-life exposure to low-dose oxidants can increase longevity via microbiome remodelling in Drosophila*.
Nature Communications 9:975. DOI: 10.1038/s41467-018-03070-w**
This reports the first identification, in any species, of the microbiome as a key mediator of developmental stress-induced longevity. We found that mild oxidative stress during development robustly increases lifespan via the selective elimination of Acetobacter from the microbiome. This study also highlights that targeted remodelling of the early-life microbiome can provide an efficient strategy for extending healthspan and lifespan.

**Newell CL, Vorng J-L, MacRae JI, Gilmore, IS and Gould AP (2020). *Cryogenic OrbiSIMS Localizes Semi-Volatile Molecules in Biological Tissues.*
Angewandte Chemie. DOI: 10.1002/ange.202006881**
This paper reports a technical advance in mass spectrometry imaging. The new cryogenic method decreases molecular fragmentation of lipids and expands the chemical space that is amenable to mass spectrometry imaging with high spatial and mass resolution. For the first time, semi-volatile and non-volatile molecules can now be imaged simultaneously in biological tissues. This recent advance is crucial for our future studies of lipid metabolism at single-cell resolution in complex tissues such as the developing CNS.