4-Yr (1+3) PhD Programme in Stem Cell Biology and Medicine

Course Manual
2019/20
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# CSCI Induction Day

**Monday 7 October 2019**

**Wellcome - MRC Cambridge Stem Cell Institute**  
Jeffrey Cheah Biomedical Centre (JCBC), Cambridge Biomedical Campus, CB2 0AW

<table>
<thead>
<tr>
<th>TIME</th>
<th>SESSION</th>
<th>VENUE</th>
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</table>
| 09:45  | Report to reception  
meet Jo Jack, CSCI Graduate Administrator                                                            | Reception, JCBC                    |
| 10:00  | Welcome from the Director  
Professor Tony Green                                                                                   |                                    |
| 10:15  | Welcome from the CSCI Training Director  
Dr Brian Hendrich                                                                                  |                                    |
| 10:30  | Introduction to Public Engagement  
Dr Rebecca Jones                                                                                      | Ground Floor Lecture Room          |
| 11:00  | Introduction to the University Counselling Service  
Matt Harding                                                                                         |                                    |
| 11:20  | JCBC Building Induction  
Ross Coates                                                                                           |                                    |
| 12:00  | Internal Seminar                                                                                      |                                    |
| 13:00  | Buffet lunch with current 2nd year students                                                           | Room 2.1, Level 2                  |
| 13:40  | Introduction to the 4-Yr Stem Cell PhD Programme  
Professor Austin Smith & Dr Brian Hendrich                                                             | Room 2.3, Level 2                  |
| 14:10  | JCBC Building Tour  
With Ganesh/Steve                                                                                            | Meet in reception                   |
| 14:30  | Laptop / Printer set-up                                                                                 | Room 3.2, Level 3                  |
| 15:30  | General meet and greet with refreshments                                                              | Room 2.1, Level 2                  |
| 16:30  | Drinks with current 2nd / 3rd year students on the 1+3 programme  
*The current students will meet you in reception to cycle into town together* | Panton Arms                         |
1+3 PhD Programme in Stem Cell Biology and Medicine

Programme Management

PhD Programme Director:  
Prof. Austin Smith, ags39@cam.ac.uk

PhD Programme Co-Director:  
Dr. Brian Hendrich, bdh24@cam.ac.uk

Graduate Administrator:  
Jo Jack - sci-phd@stemcells.cam.ac.uk

Course Overview

Part One: Course Introduction and Orientation (Term 1)

The main aim of these sessions is to introduce you to contributing programme supervisors and their research topics, and to familiarise you with the various buildings and facilities.

Part Two: Lab Rotations & Skills Courses (Terms 1, 2 and 3)

The aims are to:

- enable you to participate in a cross-section of research through three laboratory rotations throughout the first year
- provide a framework for learning fundamental aspects of stem cell and developmental biology through a series of teaching modules
- develop your critical evaluation of science via the literature reviews and seminar programme
- receive training in a variety of technical approaches such as flow cytometry, cell culture and imaging
- develop skills in project management, data presentation and scientific writing

You will rotate in the labs of three different contributing supervisors of your choice. You are expected to select your rotations so that you gain experience of at least two different stem cell types and at least two different working environments (i.e. different buildings/departments). You must complete at least one rotation project at the Addenbrookes Hospital site.

Each rotation lasts for 9 weeks, at the end of which you will have at least 3 weeks to hand in a report. The 9+3 week rotation is to emphasise the need to consolidate, analyse data and write-up during the designated ‘+3’ period, to ensure that you don’t overrun. Your reports will each be evaluated by two assessors whose comments will be discussed with you. Each of your rotation project supervisors will provide an evaluation of your performance in their laboratory.

You should not regard the rotations as trials for a PhD project.
Your key course deadlines in 2019-20 are as follows:

<table>
<thead>
<tr>
<th></th>
<th>Decision deadline</th>
<th>Rotation starts</th>
<th>Rotation ends</th>
<th>Report due</th>
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<tbody>
<tr>
<td>Rotation 1</td>
<td>Thurs 17 October 2019, midday</td>
<td>Mon 21 October</td>
<td>Fri 20 December</td>
<td>Fri 10 January 2020</td>
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<tr>
<td>Rotation 2</td>
<td>Thurs 12 December 2019, midday</td>
<td>Mon 13 January</td>
<td>Fri 13 March</td>
<td>Fri 3 April 2020</td>
</tr>
<tr>
<td>Rotation 3</td>
<td>Thurs 12 March 2020, midday</td>
<td>Mon 20 April</td>
<td>Fri 19 June</td>
<td>Fri 10 July 2020</td>
</tr>
<tr>
<td>PhD Lab Choice /</td>
<td>Mon 22 June 2020, midday</td>
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<tr>
<td>Project Title</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>PhD Proposal</td>
<td></td>
<td></td>
<td></td>
<td>Fri 7 Aug 2020</td>
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</table>

**Note:** Each lab can only support one student per rotation. We suggest that you discuss your preferred rotation option with the other students on the course and try to agree amongst yourselves who should do which projects each term. If more than one student wishes to do a particular project and you cannot agree, please notify Brian Hendrich of your 1st and 2nd choices, and he will make the final decision. In some cases it may be possible for the same/similar project to be offered in subsequent terms.

**Part Three: Choosing your PhD Lab (Term 3)**

Your choice about the lab and the project you wish to pursue for your PhD should be made by Monday 22nd June 2020. You will need to discuss possibilities in detail with your prospective supervisor(s) before coming to any decisions. Once the decision is finalised, you will need to write a research proposal (Critical Appraisal) for your PhD. The submission deadline for this is Friday 7 August 2020. This proposal will be assessed by the internal and external examiners as part of your MRes Viva examination at the end of your first year.

**Note:** each lab may only take on one Wellcome 4-year PhD student per year. PhD projects can only be undertaken with one of the accredited programme supervisors. Supervisors are not able to accept Wellcome 4-year PhD students in consecutive years.

**Department Affiliation**

All students must be formally affiliated to a Department of the University of Cambridge. In Year One, all students on this Programme will be affiliated to the Stem Cell Institute, with Brian Hendrich listed as your official MRes Supervisor. Thereafter, Departmental affiliation is determined by the affiliation of your Principal PhD Supervisor.
# Course Timetable for 2019/20

Please note: any changes to this course schedule will be emailed to you, throughout the year.

<table>
<thead>
<tr>
<th>Date, Time</th>
<th>Event</th>
<th>Location</th>
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<tbody>
<tr>
<td><strong>Mon 7 October</strong></td>
<td>Stem Cell Institute Induction afternoon</td>
<td>Jeffrey Cheah Biomedical Centre</td>
</tr>
<tr>
<td>09:45am onwards</td>
<td>See schedule on page 5</td>
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<tr>
<td><strong>Tues 8 October</strong></td>
<td>Graduate Safety Course, Day 1: General Safety</td>
<td>Babbage Lecture Theatre, New Museums Site, Pembroke Street.</td>
</tr>
<tr>
<td>AM</td>
<td><a href="https://www.safety.admin.cam.ac.uk/training/graduate-safety-course#anchor1">https://www.safety.admin.cam.ac.uk/training/graduate-safety-course#anchor1</a></td>
<td></td>
</tr>
<tr>
<td>12:30pm onwards</td>
<td>School of Clinical Medicine Induction Event</td>
<td>Clifford Allbutt Lecture Theatre</td>
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<td></td>
<td>Recommended for all new students based on the Biomedical Campus.</td>
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<td>Please book a place using the link on the left.</td>
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<tr>
<td><strong>Wed 9 October</strong></td>
<td>Introduction to Stem Cell Biology</td>
<td>JCBC, Room 2.2</td>
</tr>
<tr>
<td>09:00 – 11:00</td>
<td>- Austin Smith &amp; Ben Simons</td>
<td></td>
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<tr>
<td>12:30pm onwards</td>
<td>Graduate Safety Course, Day 2: All Stem Cell students to attend</td>
<td>Mill Lane Lecture Rooms, Mill Lane</td>
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<td></td>
<td>- Safe use of pipettes &amp; computers (VDUs)</td>
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<td></td>
<td>- Biological Safety</td>
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<td></td>
<td>- Glass &amp; sharps hazards</td>
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<td></td>
<td>See page 57 for more details</td>
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<tr>
<td><strong>Thurs 10 October</strong></td>
<td>Facility Introduction: Flow Cytometry</td>
<td>JCBC, Level 0, Room 19 (sorting lab 2)</td>
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<tr>
<td>12:30 – 13:00</td>
<td>- Simon McCallum</td>
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<tr>
<td>14:00 – 14:15</td>
<td>Facility Visit: Gene Services</td>
<td>JCBC, Level 2, break-out area</td>
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<tr>
<td></td>
<td>- Maike Paramor</td>
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<tr>
<td>14:15 – 14:30</td>
<td>Facility Visit: Bioinformatics</td>
<td>JCBC, Level 3, break-out area</td>
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<tr>
<td></td>
<td>- Irina Mohorianu</td>
<td></td>
</tr>
<tr>
<td>14:30 – 14:45</td>
<td>Facility Introduction: Flow Cytometry</td>
<td>JCBC, Level 0, Room 19 (sorting lab 2)</td>
</tr>
<tr>
<td></td>
<td>- Simon McCallum</td>
<td></td>
</tr>
<tr>
<td>14:45 – 15:00</td>
<td>Facility Introduction: Flow Cytometry</td>
<td>JCBC Level 0, Room 20</td>
</tr>
<tr>
<td></td>
<td>- Irina Pshenichnaya</td>
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<tr>
<td>15:00 – 15:15</td>
<td>Facility Introduction: Flow Cytometry</td>
<td>JCBC Basement level, Room 25</td>
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<tr>
<td></td>
<td>- Peter Humphreys</td>
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<tr>
<td>16:30 – 17:00</td>
<td>Lab Visit: George Vassiliou</td>
<td>JCBC, Level 3</td>
</tr>
<tr>
<td><strong>Fri 11 October</strong></td>
<td>Lab Visit: George Vassiliou</td>
<td>JCBC, Level 3</td>
</tr>
<tr>
<td>Time</td>
<td>Event</td>
<td>Location</td>
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<tr>
<td>13:00 – 13:30</td>
<td>Lab Visit: Simon Buczacki</td>
<td>JCBC, Level 1</td>
</tr>
<tr>
<td>13:30 – 14:00</td>
<td>Lab Visit: Ana Cvejic</td>
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<tr>
<td>14:00 – 14:30</td>
<td>Lab Visit: Simon Mendez-Ferrer</td>
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<tr>
<td>15:00 – 15:30</td>
<td>Lab Visit: Ludovic Vallier</td>
<td>JCBC, Level 3</td>
</tr>
<tr>
<td>15:30 – 16:00</td>
<td>Lab Visit: Roger Barker</td>
<td></td>
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<tr>
<td>16:00 – 16:30</td>
<td>Lab Visit: Thora Karadottir</td>
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<tr>
<td><strong>Mon 14th October</strong></td>
<td>JCBC Freezer and Cell Bank Induction</td>
<td>Meet in JCBC reception</td>
</tr>
<tr>
<td>10:00 – 10:30</td>
<td>Ross Coates</td>
<td>JCBC, Level 1</td>
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<tr>
<td></td>
<td>You have all been signed up and should have an email confirmation in your @cam email account.</td>
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<tr>
<td>11:00 – 12:00</td>
<td>Flow Cytometry Workshop - Simon McCallum</td>
<td>JCBC, Room 2.2</td>
</tr>
<tr>
<td>13:30 – 14:00</td>
<td>Lab Visit: Daniel Hodson</td>
<td>JCBC, Level 3</td>
</tr>
<tr>
<td>14:15 – 14:45</td>
<td>Lab Visit: Bertie Gottgens</td>
<td>JCBC, Level 2</td>
</tr>
<tr>
<td>14:45 – 15:15</td>
<td>Lab Visit: Brian Hendrich</td>
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<tr>
<td><strong>Tues 15th October</strong></td>
<td>Tissue Culture Induction</td>
<td>JCBC, Room 3.1</td>
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<tr>
<td>10:00 – 12:00</td>
<td>- Sally Lees</td>
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<tr>
<td>13:30 – 14:00</td>
<td>Lab Visit: Elisa Laurenti</td>
<td>JCBC, Level 2</td>
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<tr>
<td>14:00 – 14:30</td>
<td>Lab Visit: Kevin Chalut</td>
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<tr>
<td><strong>Wed 16th October</strong></td>
<td>CSCI PhD Symposium</td>
<td>JCBC, Ground Floor Lecture Room</td>
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<tr>
<td>All Day</td>
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<tr>
<td><strong>Thurs 17th October</strong></td>
<td>Rotation 1 lab choice due</td>
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<tr>
<td><strong>Thurs 17th October</strong></td>
<td>Epithelial Stem Cells and Cancer</td>
<td>JCBC, Room 2.3</td>
</tr>
<tr>
<td>09:00 – 10:30</td>
<td>- Maria Alcolea, Simon Buczacki, Joo-Hyeon Lee</td>
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<tr>
<td>10:30 – 11:00</td>
<td>Lab Visit: Tony Green</td>
<td>JCBC, Level 2</td>
</tr>
<tr>
<td><strong>Fri 18th October</strong></td>
<td>Chemical Safety Course</td>
<td>Clifford Allbutt Lecture Theatre</td>
</tr>
<tr>
<td>09:30 – 17:30</td>
<td>- Mandatory for anyone working with/handling chemicals defined as hazardous to health under the COSHH regulations and/or dangerous / flammable under DSEAR i.e. almost all laboratory chemicals. Please book a place using the link on the right.</td>
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</tr>
<tr>
<td>14:00 – 14:30</td>
<td>Lab Visit: Jose Silva</td>
<td>JCBC, Level 2</td>
</tr>
<tr>
<td><strong>Mon 21st October</strong></td>
<td>Rotation 1 starts</td>
<td></td>
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<tr>
<td><strong>Wed 23rd October</strong></td>
<td>Normal and Malignant Blood Stem Cells (session I)</td>
<td>JCBC, Room 2.2</td>
</tr>
<tr>
<td>09:00 – 11:00</td>
<td>- Ingo Ringshausen, Dan Hodson</td>
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<tr>
<td><strong>Wed 30th October</strong></td>
<td>Regenerative Medicine and Cell Therapy</td>
<td>JCBC, Room 2.2</td>
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<tr>
<td>09:00 – 10:30</td>
<td>- Sanjay Sinha</td>
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<tr>
<td><strong>Wed 30th October</strong></td>
<td>Gaining, Regaining and Losing Pluripotency</td>
<td>JCBC, Room 2.2</td>
</tr>
<tr>
<td>09:30 – 17:30</td>
<td>Jose Silva, Brian Hendrich, Srinjan Basu</td>
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<tr>
<td><strong>Tues 5th November</strong></td>
<td>Course: Introduction to R for Biologists</td>
<td>Bioinformatics Training Room, Craik-Marshall Blding, Downing Site</td>
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<tr>
<td>09:30 – 17:30</td>
<td>Your booking confirmation, with further course information, has been emailed to your @cam address.</td>
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</table>

**https://www.vle.cam.ac.uk/course/view.php?id=130642**

**https://training.csx.cam.ac.uk/bioinformatics/event/3079285**
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<thead>
<tr>
<th>Date</th>
<th>Event</th>
<th>Time</th>
<th>Location</th>
<th>Details</th>
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<tbody>
<tr>
<td>Wed 6th November</td>
<td>Course: <strong>Introduction to R for Biologists</strong></td>
<td>09:30 – 17:30</td>
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<tr>
<td>Thurs 7th November</td>
<td><strong>Normal and Malignant Blood Stem Cells (session I)</strong></td>
<td>09:00 – 10:30</td>
<td>JCBC, Room 2.3</td>
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<tr>
<td></td>
<td>- Tony Green, Ana Cvejic, Bertie Gottgens</td>
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<tr>
<td>Wed 13th November</td>
<td><strong>Physical &amp; Computational Aspects of Stem Cell Biology</strong></td>
<td>09:30 – 10:30</td>
<td>JCBC, Room 2.2</td>
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<td><strong>Gaining, Regaining and Losing Pluripotency</strong></td>
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<td></td>
<td>- Jennifer Nichols</td>
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<tr>
<td>Wed 20th November</td>
<td><strong>Neural Stem Cells</strong></td>
<td>09:00 – 11:00</td>
<td>JCBC, Room 2.2</td>
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<td></td>
<td>- Anna Philpott, Robin Franklin, David Rowitch, Thora Karadottir</td>
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<tr>
<td>Wed 27th November</td>
<td><strong>Normal and Malignant Blood Stem Cells (session II)</strong></td>
<td>09:00 – 11:00</td>
<td>JCBC, Room 2.2</td>
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<td></td>
<td>- Brian Huntly, Elisa Laurenti, Simon Mendez-Ferrer, George Vassiliou</td>
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<tr>
<td>Wed 4th December</td>
<td><strong>Human Pluripotent Cells to Model Early Development &amp; Disease</strong></td>
<td>09:00 – 09:30</td>
<td>JCBC, Room 2.2</td>
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<td></td>
<td>- Ludovic Vallier</td>
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<tr>
<td>Wed 11th December</td>
<td><strong>Regenerative Medicine and Cell Therapy</strong></td>
<td>09:00 – 11:00</td>
<td>JCBC, Room 2.2</td>
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<tr>
<td>Thurs 12th December</td>
<td><strong>Rotation 2 lab choice due</strong></td>
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<tr>
<td>Fri 19th December</td>
<td><strong>Rotation 1 ends</strong></td>
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<tr>
<td>Wed 18th December</td>
<td><strong>MRes 'Rotation 1' Presentations</strong></td>
<td>09:00 – 11:30</td>
<td>JCBC, Room 2.2</td>
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<td></td>
<td>- with Brian Hendrich</td>
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<td></td>
<td>- See page 42 for details</td>
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<tr>
<td>Wed 8th January</td>
<td><strong>Stem Cell Discussion course</strong></td>
<td>09:00 – 11:00</td>
<td>JCBC, Room 2.2</td>
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<tr>
<td>Fri 10th January</td>
<td><strong>Rotation 1 report deadline</strong></td>
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<tr>
<td>Mon 13th January</td>
<td><strong>Rotation 2 starts</strong></td>
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<tr>
<td>Wed 15th January</td>
<td><strong>Stem Cell Discussion course</strong></td>
<td>09:00 – 11:00</td>
<td>JCBC, Room 2.2</td>
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</tr>
<tr>
<td>Wed 22nd January</td>
<td><strong>Stem Cell Discussion course</strong></td>
<td>09:00 – 11:00</td>
<td>JCBC, Room 2.2</td>
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<tr>
<td>Wed 29th January</td>
<td><strong>Stem Cell Discussion course</strong></td>
<td>09:00 – 11:00</td>
<td>JCBC, Room 2.2</td>
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<tr>
<td>Wed 5th February</td>
<td><strong>Stem Cell Discussion course</strong></td>
<td>09:00 – 11:00</td>
<td>JCBC, Room 2.2</td>
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<tr>
<td>Wed 12th February</td>
<td><strong>Stem Cell Discussion course</strong></td>
<td>09:00 – 11:00</td>
<td>JCBC, Room 2.2</td>
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<tr>
<td>Wed 19th February</td>
<td><strong>Stem Cell Discussion course</strong></td>
<td>09:00 – 11:00</td>
<td>JCBC, Room 2.2</td>
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<tr>
<td>Wed 26th February</td>
<td><strong>Stem Cell Discussion course</strong></td>
<td>09:00 – 11:00</td>
<td>JCBC, Room 2.2</td>
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<tr>
<td>Wed 4th March</td>
<td><strong>Stem Cell Discussion course</strong></td>
<td>09:00 – 11:00</td>
<td>JCBC, Room 2.2</td>
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<tr>
<td>Thurs 12th March</td>
<td><strong>Rotation 3 lab choice deadline</strong></td>
<td>09:00 – 11:00</td>
<td>JCBC, Room 2.2</td>
<td></td>
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<tr>
<td>Fri 13th March</td>
<td><strong>Rotation 2 ends</strong></td>
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<tr>
<td>Wed 18th March</td>
<td><strong>MRes 'Rotation 2' Presentations</strong></td>
<td>09:00 – 11:30</td>
<td>JCBC, Room 2.2</td>
<td></td>
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<tr>
<td></td>
<td>- with Brian Hendrich</td>
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<td></td>
<td>- See page 42 for details</td>
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<tr>
<td>Date</td>
<td>Event Description</td>
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<td>Fri 3rd April</td>
<td>Rotation 2 report deadline</td>
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<tr>
<td><strong>EASTER BREAK</strong></td>
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<tr>
<td>Mon 20th April</td>
<td>Rotation 3 starts</td>
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<tr>
<td>Wed 22nd April</td>
<td>Stem Cell Discussion course</td>
<td>JCBC, Room 2.2</td>
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<tr>
<td>09:00 - 11:00</td>
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<tr>
<td>Wed 29th April</td>
<td>Stem Cell Discussion course</td>
<td>JCBC, Room 2.2</td>
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<td>09:00 - 11:00</td>
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<tr>
<td>Wed 6th May</td>
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<td>Early June (date TBC)</td>
<td>4-YEAR STUDENT PRESENTATION DAY</td>
<td>JCBC, Room TBC</td>
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<td>All day + college dinner</td>
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<td>Fri 19th June</td>
<td>PhD lab choice &amp; project title deadline</td>
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<tr>
<td>Fri 19th June</td>
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<tr>
<td>Wed 24th June</td>
<td>MRes ‘Rotation 3’ Presentations</td>
<td>JCBC, Room 2.2</td>
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<td>09:00 - 11:30</td>
<td>- with Brian Hendrich</td>
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<tr>
<td>July 2020 (date TBC)</td>
<td>OUTLINE PHD PROPOSAL PRESENTATIONS</td>
<td>JCBC, Room TBC</td>
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<td>Fri 10th July</td>
<td>Rotation 3 report deadline</td>
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<tr>
<td>Fri 7th August</td>
<td>PhD proposal (critical appraisal) deadline</td>
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<td>Early-Sept (date TBC)</td>
<td>MRES VIVAS</td>
<td>JCBC, Room TBC</td>
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<td>- See page 42 for more information</td>
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<tr>
<td>October (date TBC)</td>
<td>PHD DAY SYMPOSIUM</td>
<td>Venue TBC</td>
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<td>- See page 46 for more information</td>
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</table>
Rotation Projects – Overview

The following pages list rotation projects on offer for this year (note that available terms are identified on the far right). Please also note that any additional projects for terms 2 and 3 will be distributed later in the year.

### Rotation Projects on offer for 2019-20*  

<table>
<thead>
<tr>
<th>Project No.</th>
<th>Supervisor</th>
<th>Project Location</th>
<th>Rotation Title</th>
<th>Availability</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Note:</strong></td>
<td></td>
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</tr>
<tr>
<td>1</td>
<td>Srinjan Basu †</td>
<td>JCBC</td>
<td>Role of Mll complexes and Fgf signalling in regulating the dynamics of mouse pluripotent stem cell differentiation</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Andrea Brand</td>
<td>Gurdon</td>
<td>Time to wake up: regulation of stem cell quiescence and proliferation</td>
<td></td>
</tr>
</tbody>
</table>
| 3           | Kevin Chalut | JCBC             | **Project 1**: Physical modelling of cell fate choice  
**Project 2**: Mechanical control of stem cell function |              |
| 4           | Cédric Ghevaert | JCBC           | Studying the mechanisms of pluripotent stem cell programming towards blood cells for clinical use |              |
| 5           | Bertie Göttingen | JCBC          | **Project 1**: Using single cell genomics to study early cardiovascular lineage diversification.  
**Project 2**: Define heterogeneity and key regulators of haematopoietic stem cells with single cell genomics |              |
| 6           | Brian Hendrich | JCBC             | **Project 1**: Dissecting the interplay between signalling and chromatin remodelling during cell fate decisions  
**Project 2**: Using single molecule imaging to dissect the function of chromatin remodellers in cell fate decisions |              |
| 7           | Thora Karadottir | JCBC           | Neuronal activity regulation of CNS stem cells fate (various sub-projects listed in descriptions) |              |
| 8           | Andreas Lakatos | Brain Repair   | Investigations of local and systemic influences on astrocyte-neuron signaling in 2D/3D human stem cell models of neurodegeneration |              |
| 9           | Elisa Laurenti | JCBC             | **Project 1**: Molecular regulation of cell fate decisions during human haematopoietic stem cell exit from quiescence |              |
| 10          | Joo-Hyeon Lee † | JCBC             | **Project 2**: Understanding the heterogeneity of human haematopoietic stem cell response to gene therapy |              |
| 11          | Alfonso Martinez-Arias | Genetics | Body plan specification in human gastruloids |              |
| 12          | Manav Pathania | JCBC             | Modelling discrete subtypes of mutant histone-driven gliomas |              |
> Additional projects for terms 2 and 3 may be offered later in the year.

** Lab locations are listed on the individual project descriptions on the following pages, and on the maps at the back.

† PI is offering a rotation project, but unable to take on a Wellcome student for a full PhD (due to taking on a Wellcome student the previous year). Could take on an MRC-funded student.

**Location abbreviations listed above:**

  - Babraham = Babraham Institute, Babraham
  - Genetics = Department of Genetics, Downing Street
  - Gurdon = The Gurdon Institute, Tennis Court Road
  - IMS = Institute of Metabolic Science, Cambridge Biomedical Campus
  - JCBC = Jeffrey Cheah Biomedical Centre, Cambridge Biomedical Campus
  - PDN = Department of Physiology, Development and Neuroscience, Downing Street
  - Sanger = Wellcome Sanger Institute, Wellcome Genome Campus, Hinxton
Rotation Project Descriptions

Project 1

<table>
<thead>
<tr>
<th>Rotation project title</th>
<th>Role of Mll complexes and Fgf signalling in regulating the dynamics of mouse pluripotent stem cell differentiation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lab location</td>
<td>Jeffrey Cheah Biomedical Centre, Level 1 (microscope in Dept of Chemistry)</td>
</tr>
<tr>
<td>Head of laboratory (PI)</td>
<td>Dr Srinjan Basu, <a href="mailto:sb451@cam.ac.uk">sb451@cam.ac.uk</a></td>
</tr>
<tr>
<td>Day-to-day supervisor</td>
<td>Dr Stanley Strawbridge/ Dr Srinjan Basu</td>
</tr>
<tr>
<td>Term(s) available</td>
<td>Terms 2 and 3</td>
</tr>
</tbody>
</table>

**Project Outline**

DISCLAIMER: I cannot accept students from the Wellcome Stem Cell Programme this year but if you are a Physical Biology student or if you wish to experience the approaches in our lab for interest or for possible collaborative projects, please come speak to me about rotations.

Project outline

Alterations in three-dimensional genome architecture occur as pluripotent stem cells differentiate into specific cell lineages but it is unclear how these rearrangements, which occur alongside changes in transcription, influence differentiation.

These changes are regulated by cell-cell signalling and large protein complexes such as the Mll (mixed lineage leukemia) complexes. How these complexes work is still poorly understood, but mutations in Mll complexes lead to early developmental disorders such as childhood cancer.

We are currently studying how specific Mll complexes influence genome architecture and transcription in mouse embryonic stem (ES) cells as they differentiate into neuronal lineages. The aim of this project will be to dissect the role of Mll complexes in controlling genome structure and transcription during this process or to elucidate how signalling molecules influence binding of Mll complexes.

**Rotation Topic**

- **Rotation topic 1:** Tracking genome architecture in the presence and absence of Mll1/2 complexes during ES cell differentiation (partly in collaboration with Dr Kevin Chalut)
  
  We have observed changes in transcription as ES cells differentiate in the absence of Mll1/2. To determine if these changes relate to Mll1/2 regulation of enhancers or promoters, we have established fixed-cell super-resolution imaging of chromatin and a new live-cell protocol for 3D tracking of genomic loci. We now wish to use these protocols to track changes in genome architecture or in enhancer-promoter dynamics in the presence and absence of Mll complexes. Project will involve single-molecule imaging and/or development of algorithms to extract biological information from this data.

- **Rotation topic 2:** Single-molecule imaging of Mll4 chromatin binding kinetics (in collaboration with Prof Francis Stewart)
  
  Mll4 regulate the function of super-enhancers in ES cells and it has been proposed to be involved in liquid-liquid phase separation of these regions. Project will involve single-molecule imaging of tagged ES cell lines we have generated to explore how Mll4 interacts with the genome and/or development of algorithms to extract information as to whether/how it affects genome segregation.

- **Rotation topic 3:** Single-molecule imaging of Fgf2/4 (in collaboration with Prof Jenny Nichols)
To relate the binding of Mll with specific signalling pathways, we have recently developed an approach for imaging the ligand Fgf as it interacts with the plasma membrane and undergoes endocytosis during ES cell differentiation. Little is known about how Fgf is delivered between cells. Project will involve cell line generation, single-molecule imaging and/or development of algorithms to extract biological information from this data.

**Main Techniques**

Based on the interests of the student, the project can involve:

1) ES cell line generation (CRISPR/Cas9)

2) Hi-C, ChIP-seq, RNA-seq protocols and/or computational analysis at the bulk or single-cell level during stem cell differentiation

3) 2D/3D super-resolution imaging approaches capable of localising single proteins or single genomic loci at <15 nm resolution:
   - Determine the chromatin binding kinetics of proteins.
   - Distinguish between proposed models of genome segregation such as liquid-liquid phase separation.
   - Develop approaches to probe enhancer-promoter dynamics.

4) Development of novel algorithms to extract information from above datasets, e.g.:
   - Machine learning approaches for classifying single-molecule trajectories and extracting biological information.
   - Modelling of single-molecule trajectories to distinguish between proposed models of genome segregation such as liquid-liquid phase separation.
   - Integration of imaging and high-throughput sequencing datasets e.g. through polymer modelling of genomic loci in collaboration with Dr Collepardo-Guevara

**Key References**


## Project Outline

We use *Drosophila* and mouse models to study how the local and systemic environments influence neural stem cell behaviour. Stem cells spend much of their time in a mitotically dormant, quiescent, state. However, neural stem cells can generate new neurons in the brain in response to a range of stimuli, including exercise, nutrition and injury. Uncovering the molecular mechanisms that control neural stem quiescence and reactivation is crucial for understanding tissue regeneration under normal and pathological conditions and in response to ageing.

Our lab uses cutting edge genetic and molecular approaches and advanced imaging techniques to study stem cells *in vivo*. We developed Targeted DamID (or TaDa) to profile genome-wide binding of transcription factors and chromatin factors in specific cell- and tissue-types. By combining TaDa and single cell sequencing we can profile transcription and epigenetic states throughout development and in response to changing physiological conditions.

## Rotation Topic

**Project 1:** It is widely accepted that quiescent stem cells are arrested in G0, however, we discovered that quiescent neural stem cells in *Drosophila* are arrested in either G0 or G2. Furthermore, we showed that G2/G0 heterogeneity directs stem cell function: G2 arrested cells reactivate much more rapidly than G0 cells ([Otsuki, L. and Brand, A.H. (2018). Cell cycle heterogeneity directs the timing of neural stem cell activation from quiescence. Science 360, 99-102](https://science.sciencemag.org/content/360/6387/99)). The student will use single cell RNA sequencing to identify the transcriptional differences between G2 and G0 stem cells. They will manipulate expression of candidate genes by targeted RNAi or CRISPR to assess their role in regulating quiescence.

**Project 2:** It is critical to learn not only how stem cells can be activated but also how they return to a quiescent state, as uncontrolled stem cell division can lead to cancer. We have developed a model of glioblastoma in *Drosophila* that closely parallels disease progression in the human brain. The student will assess the response of these glioblastoma-like brain tumours to drug treatment, testing both known and previously untested anti-cancer compounds.

There are several other projects in the lab, please drop by for a chat if you are interested in discussing these.

## Main Techniques

- Single cell RNA sequencing; Targeted DamID; CRISPR; RNAi; Confocal microscopy; Live imaging; Transgenesis

## Key References

**Project 3**

<table>
<thead>
<tr>
<th>Rotation project title</th>
<th>Physical modelling of cell fate choice</th>
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<tbody>
<tr>
<td>Lab location</td>
<td>Jeffrey Cheah Biomedical Centre</td>
</tr>
<tr>
<td>Head of laboratory (PI)</td>
<td>Kevin Chalut, <a href="mailto:kc370@cam.ac.uk">kc370@cam.ac.uk</a></td>
</tr>
<tr>
<td>Day-to-day supervisor</td>
<td>James Baye</td>
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<tr>
<td>Term(s) available</td>
<td>Terms 1, 2 and 3</td>
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**Project Outline**
The overarching goal of this project is to apply tools of statistical physics and information theory to understand the process of cell fate choice. Cell fate choice is accompanied by dramatic molecular rearrangements inside the cell. Currently, little is known about the kinetics of such changes, whether these are gradual, or abrupt transitions occur. Dissecting which kinetic profiles occur will provide significant insight into the underlying dynamics taking place in the cell, and allow appropriate physical models to be selected. We propose to approach the question in the first instance by studying cell molecular state changes with single-cell RNA sequencing. The ultimate goal of the project is to study the dynamics of cell fate choice in live cells using a combination of transcriptional reporters and models based in statistical physics.

**Rotation Topic**
Through the analysis of single-cell RNA sequencing (scRNAseq) data, you will explore how kinetic information may be estimated on cells undergoing differentiation. Theoretical models based on the flux-balance law have been proposed in previous work [1]. You will learn how to process scRNAseq data and to perform exploratory data analysis on this high-dimensional data (i.e. each cell measurement is a point in an N-dimensional phase space, N~20,000). By examining changes in cell-cell distance in phase space with different distance metrics (KNN, Hamming, geodesic, ...) and estimating high-dimensional density changes, you will highlight possible changes in molecular kinetics. Such analyses may also be tied together with recent work which allows instantaneous velocities to be estimated from scRNAseq data [2]. Work will be multidisciplinary, using principles of physical sciences to analyse high-dimensional data and extract biological insight.

**Main Techniques**
Single-cell RNA sequencing, high-dimensional analysis, dimensionality reduction, density estimation, flux balance law, pseudotime inference, RNA velocity inference.

**Key References**
## Rotation 4

<table>
<thead>
<tr>
<th><strong>Rotation project title</strong></th>
<th>Mechanical control of stem cell function</th>
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<tbody>
<tr>
<td><strong>Lab location</strong></td>
<td>Jeffrey Cheah Biomedical Centre</td>
</tr>
<tr>
<td><strong>Head of laboratory (PI)</strong></td>
<td>Kevin Chalut, <a href="mailto:Kc370@cam.ac.uk">Kc370@cam.ac.uk</a></td>
</tr>
<tr>
<td><strong>Day-to-day supervisor</strong></td>
<td>TBC</td>
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<tr>
<td><strong>Term(s) available</strong></td>
<td>Terms 1, 2 and 3</td>
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### Project Outline

We have shown, using a novel hydrogel substrate with tuneable mechanical and adhesive properties, that various types of stem cells possess much more robust self-renewal and differentiation capacity on substrates physiologically matched to their native tissue. This is largely because the mechanical microenvironment provides an important context specificity for stem cells, and coordinates regulatory signals to control their function. We have now recently developed these hydrogels in 3D, which will be of particular importance for culturing stem cells in a multicellular context such as organoids. We have a number of highly multidisciplinary projects that will be based on this technology. On the basic science side, we will be using our substrates and their control over the mechanical microenvironment to investigate how mechanical signalling regulates cell fate choice. On the applied side, we will be using our suite of 2D and 3D hydrogels to improve stem cell therapy outcomes in liver, embryonic, cartilage and neural stem cells.

### Rotation Topic

The StemBond hydrogel substrates we have invented not only allow control over mechanics but also extracellular matrix (ECM) composition. The project student will culture human ES cells on both 2D and 3D substrates with different mechanical and ECM properties and compare to standard culture. With this, we will be able to optimise human ES cell maintenance and better understand the importance not only of mechanics but dimensionality in their culture. This study will lead to better and more stable derivation and maintenance of human ES cells while also advancing our understanding of how to deploy the novel hydrogels for culture of other stem cell systems. If time allows we will begin to investigate differentiation of human ES cells on the substrates and start looking at these cells in a multicellular context to develop a means to study early human development events. Also, though culture of other types of stem cells is possible for the rotation project, depending on student interest. This is a highly multidisciplinary project using principles of physics and engineering to shed light on an important biological problem.

### Main Techniques

Hydrogel synthesis, stem cell culture, qPCR

### Key References

## Project 5

<table>
<thead>
<tr>
<th>Rotation project title</th>
<th>Studying the mechanisms of pluripotent stem cell programming towards blood cells for clinical use</th>
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<tbody>
<tr>
<td>Lab location</td>
<td>Jeffrey Cheah Biomedical Centre</td>
</tr>
<tr>
<td>Head of laboratory (PI)</td>
<td>Cedric Ghevaert, <a href="mailto:cg348@cam.ac.uk">cg348@cam.ac.uk</a></td>
</tr>
<tr>
<td>Day-to-day supervisor</td>
<td>Moyra Lawrence</td>
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<td>Term(s) available</td>
<td>Terms 1, 2 and 3</td>
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### Project Outline

The Ghevaert group’s main focus is to produce blood cells (red cells and platelets) from human pluripotent stem cells to generate clinical grade blood products for transfusion to patients. We have developed a forward programming technology based on the overexpression of key transcription factors which generates a highly pure population of terminally differentiated blood cells with huge gain in cell numbers (>10^5 amplification). This protocol is now being applied for translational projects that aim ultimately to carry out a first-in-man study with the iPSC-derived platelets.

To refine the culture protocol there is a need to understand the molecular mechanism by which these transcription factors promote the differentiation of pluripotent stem cells into blood cells. We are using a single cell-based approach to generate single-cell RNA sequencing data of forward programmed cells at key stages of the differentiation process. First, single cells will be sorted on a daily basis for the first 10 days of the forward programming and data will be analysed to follow the pathway taken by the cells from pluripotency to committed megakaryocyte progenitor. Analysis will be done in collaboration with the CSCI bioinformatics teams and the MRC Biostatistics Unit (pseudotime algorithms). In addition, mature cells will be indexed using surface markers and “rainbow” vectors to assess level of transgene expression in individual cells. Using this index individual cells will be sequenced and analysed functionally to understand how the bulk culture can be separated into proliferative progenitors and mature cells capable of forming platelets.

In a second phase of work, the data developed above will be used to assess how we can optimise culture conditions to promote the early formation of proliferative progenitors using a Bayesian optimisation approach allowing variations of multiple parameters all at once. This will ultimately lead to the development of a culture protocol for large scale production using clinical grade cell lines.

### Rotation Topic

Pluripotent stem cells and generation of blood cells for clinical use

### Main Techniques

Culture of pluripotent stem cells, reprogramming using lentiviral vectors, flow cytometry and flow sorting, use of the 10X platform, sequencing library preparation, single cell technology, bioinformatics analysis of sequencing tracks and statistical analysis of large data.

### Key References

1) Moreau et al., Nat Communication, 2016
2) Wilson et al., Cell Stem Cell, 2015
### Rotation project title
Using single cell genomics to study early cardiovascular lineage diversification

### Lab location
Jeffrey Cheah Biomedical Centre

### Head of laboratory (PI)
Bertie Gottgens, bg200@cam.ac.uk

### Day-to-day supervisor
As above

### Term(s) available
Terms 1, 2 and 3

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## Project Outline
Understanding the developmental origins of cardiovascular tissues will be critical to advance translational efforts designed to (i) generate cells for tissue repair in vitro, (ii) stimulate endogenous regeneration processes, and (iii) design cellular programming strategies that can reprogram diseased cells. Cardiovascular tissues develop early during mammalian development, when gastrulation gives rise to a diverse range of mesodermal cells. Recent technological breakthroughs in single cell molecular profiling have made it feasible to study these processes for the first time in the embryo, where cell numbers are limiting. The Gottgens group studies how transcriptional regulatory networks control cell fate decision making, with a particular emphasis on cardiovascular cells including blood, endothelium and cardiac cells. The group has also established an internationally leading track record in applying single cell genomics approaches to reconstruct developmental hierarchies and regulatory networks (Moignard et al Nature Cell Biology 2013; Moignard et al Nature Biotechnology 2015). More recently, they have applied these technologies to study early mesodermal diversification, focussing on the developmental timepoints where the first cardiac, blood and endothelial cells arise (Scialdone et al Nature 2016, Ibarra-Soria et al Nature Cell Biology 2018, Lescroart et al Science 2018).

## Rotation Topic
For a potential rotation project, the student will work alongside a PhD student and a postdoc. Specific experiments are likely to include tissue dissection and single cell RNA-Seq, and potentially ES cell culture coupled with gene targeting to generate new loss of function alleles for single cell analysis. The rotation student would also be able to get some exposure to the bioinformatics approaches that the group uses for single cell RNA-Seq analysis.

## Main Techniques
- Single cell genomics (data generation and data interpretation/analysis)
- Embryo dissection
- ES cell culture and CrispR/Cas9 gene targeting
*There is also scope to have a computational project based on the embryo development datasets available in this group*.

## Key References
## Project 7

<table>
<thead>
<tr>
<th>Rotation project title</th>
<th>Define heterogeneity and key regulators of haematopoietic stem cells with single cell genomics</th>
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<tbody>
<tr>
<td><strong>Lab location</strong></td>
<td>Jeffrey Cheah Biomedical Centre</td>
</tr>
<tr>
<td><strong>Head of laboratory (PI)</strong></td>
<td>Bertie Gottgens, <a href="mailto:bg200@cam.ac.uk">bg200@cam.ac.uk</a></td>
</tr>
<tr>
<td><strong>Day-to-day supervisor</strong></td>
<td>As above</td>
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<tr>
<td><strong>Term(s) available</strong></td>
<td>Terms 1, 2 and 3</td>
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</table>

### Project Outline

Despite recent progress in resolving haematopoiesis at the population level, the molecular mechanisms shaping blood production remain poorly understood. While other lines of investigation in the Gottgens group focus on early embryonic blood development and the perturbation of transcriptional programs in haematopoietic malignancies, the key questions related to this rotation project are:

1) What molecular properties define haematopoietic stem cell (HSC) subtypes associated with specific lineage outputs following transplantation?

2) How do key HSC regulators interact to control self-renewal and differentiation?

### Rotation Topic

It has long been recognised that HSCs are functionally heterogeneous, exhibiting distinct lineage-biases and repopulation dynamics following transplantation. By employing single cell barcoding, we aim to detect the molecular signatures of specific HSC subtypes. Their comparison will reveal new candidate players involved in establishing HSC subtypes and their connections with ageing and diseases.

Using a combination of CRISPR mutagenesis and transcriptomics, we will study new candidate regulators with a specific focus on transcriptional regulators, in order to build a regulatory interaction network based on systematic perturbation of its components. This model will shed new light on the regulatory logic behind HSC self-renewal, differentiation and specification of HSC subtypes.

### Main Techniques

- Single cell genomics (data generation and data interpretation/analysis)
- Flow cytometry
- CrispR/Cas9 gene targeting

*There is also scope to have a computational project based on the adult blood development datasets available in this group.*

### Key References


# Project 8

<table>
<thead>
<tr>
<th><strong>Rotation project title</strong></th>
<th>Dissecting the interplay between signalling and chromatin remodelling during cell fate decisions</th>
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<tbody>
<tr>
<td><strong>Lab location</strong></td>
<td>Jeffrey Cheah Biomedical Centre, Level 2</td>
</tr>
<tr>
<td><strong>Head of laboratory (PI)</strong></td>
<td>Brian Hendrich, <a href="mailto:bdh24@cam.ac.uk">bdh24@cam.ac.uk</a></td>
</tr>
<tr>
<td><strong>Day-to-day supervisor</strong></td>
<td>Nicola Reynolds / Andria Koulle</td>
</tr>
<tr>
<td><strong>Term(s) available</strong></td>
<td>Terms 1, 2 and 3</td>
</tr>
</tbody>
</table>

## Project Outline

Cell identity is defined by gene expression patterns. Changes in cell state require coordinated changes in gene expression. We are investigating how chromatin remodelling complexes facilitate these gene expression changes during cell fate commitment.

How signalling events translate to transcriptional changes at the molecular level is relatively poorly defined and we aim to study this using a variety of ES cell lines and techniques. Rather than examining cells in steady state conditions, we will use the auxin-inducible degron system to determine how two major nucleosome remodelling activities modulate these responses over time. Specifically, we will monitor how induction of specific signalling pathways results in changes to transcription factor binding at key enhancers. We will measure nucleosome positioning, transcription factor binding and subsequently the transcriptional response to changes in signalling. Together this will allow us to build up a comprehensive, molecular picture of how cells respond to inductive cues.

## Rotation Topic

- Pluripotency
- Lineage commitment
- Chromatin remodelling
- Transcription
- Enhancers
- Signalling

## Main Techniques

- ES cell culture, manipulation, and differentiation
- Protein manipulation via auxin-inducible degron
- RT-qPCR, ChIP, ATAC-seq, western blots, Immunoprecipitation

## Key References


Rotation project title | Using single molecule imaging to dissect the function of chromatin remodellers in cell fate decisions
---|---
Lab location | JCBC Level 2
Head of laboratory (PI) | Brian Hendrich, bdh24@cam.ac.uk / Ernest Laue
Day-to-day supervisor | Nicola Reynolds/David Lando
Term(s) available | Terms 1, 2 and 3

**Project Outline**
The aim of this project will be to understand how NuRD-mediated modification of chromatin at enhancer sequences impacts transcriptional kinetics both in self-renewing cells and as cells exit the self-renewing state. Using a cell line in which a key NuRD component protein can be manipulated, we will visualise transcription factor binding kinetics at specific target genes and measure how the presence or absence of NuRD function impacts transcription factor and transcriptional kinetics in live cells. This forms part of our ongoing investigation of chromatin remodeller function at the single cell level during lineage commitment.

**Rotation Topic**
Embryonic stem (ES) cells either self-renew or differentiate into all the different cells in a body. The multi-subunit nucleosome remodelling and deacetylase (NuRD) protein complex plays an essential role in facilitating ES cell lineage commitment by controlling transcription. Although NuRD is found at all sites of active transcription in ES cells, only a subset of genes are sensitive to its activity. We have recently shown that NuRD reorganises transcription factor binding to fine-tune enhancer activity during ES cell differentiation (Bornelöv et al. 2018). We have also used single-molecule imaging to visualise NuRD component activity in ES cells (Zhang et al., 2016), and to show that NuRD components form clusters on chromatin within the nucleus (Stevens et al., 2017). We have now created ES cell lines that will allow single molecule imaging in live cells of Halo- or SNAP-tagged transcription factors, and how they affect the expression kinetics (bursting rates/duration) of particular NuRD regulated genes tagged with fluorescent RNA aptamers. The project will take advantage of a custom-built microscope for 3D single molecule super resolution imaging.

**Main Techniques**
ES cell culture, manipulation, and differentiation
Protein manipulation via auxin-inducible degron
Live cell single molecule imaging
ChIP, western blots, Immunoprecipitation, qRT-PCR

**Key References**
## Project 10

<table>
<thead>
<tr>
<th><strong>Rotation project title</strong></th>
<th>Neuronal activity regulation of CNS stem cells fate</th>
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<tbody>
<tr>
<td><strong>Lab location</strong></td>
<td>Jeffrey Cheah Biomedical Centre, Level 3</td>
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<td><strong>Day-to-day supervisor</strong></td>
<td>As above</td>
</tr>
<tr>
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### Project Outline

The brain’s white matter provides an information superhighway that links ~100 billion neurons situated in the grey matter. Its function depends on oligodendrocytes wrapping myelin around axons to provide fast neurotransmission, synchronization and maintenance of neuronal function. Despite its importance, the regulation of myelination is poorly understood. White matter plasticity is increasingly invoked as a mechanism for learning, and in disease destruction of myelin disrupts cognitive and motor function. The underlying process likely for white matter plasticity and regeneration are brain stem cells called oligodendrocyte progenitor cells (OPCs). Important recent findings have revealed the presence of functional synaptic connections between unmyelinated axons (neurons) and OPCs. Recently we, among others, have now identified that OPCs differentiate throughout life into myelinating oligodendrocytes, perhaps for maintaining myelin and in response to learning.

Thus we offer different rotation projects to address the key questions of whether, and by what mechanisms, neural activity regulates OPCs differentiation, myelination and learning evoked myelination and myelin regeneration.

### Rotation Topic

**A. Promoting myelin regeneration**

Multiple sclerosis (MS) affects around 2.5 million people worldwide. In recent years, great advances have been made in modifying the immunological aspects; however, this approach is only partially effective, as of yet no myelin regenerative treatments exist.

Myelin regeneration can occur spontaneously in demyelinating diseases, such as MS, and is essential for functional recovery. However, it often fails, due to oligodendrocyte precursor cells (OPCs) failing to differentiate into new myelinating oligodendrocytes, leading sustained clinical disability.

We recently identified that OPCs receive glutamatergic synaptic input from demyelinated axons and this signalling is essential for effective myelin regeneration. Our preliminary data demonstrate that remyelination can be increased by augmenting glutamate signalling in demyelinating lesions, using glutamate signalling modulators (GSMs). The aim of this project is to determine the mechanisms and effectiveness of GSMs as a treatment to enhance myelin regeneration.

**Main Techniques**

- Histology, deep learning analytical approaches and calcium imaging

### B. Learning evoked OPC differentiation

Complex motor learning evokes new myelination (McKenzie et al., Science 2014), and now we have recently showed that cognitive learning does too. However, both of these behavioural paradigms are long term learning, thus the question arise is myelination only needed for persistent learning or is it a general mechanism for learning. To address this we will employ our recent mouse model where we can fate-map OPC differentiation in time dependent manner and subject adult mice to a number of behavioural tasks and evaluate whether myelination occurs.

**Main Techniques:**
The project will involve transgenic animals, behavioural paradigms, immunohistochemistry and imaging.
If interested in this project a home office animal handling course attendance is essential thus please discuss with the lab with a good advance so that this can be set up. (in collaboration with Dr David Belin at Department of Psychology)

C Is myelination important for neuronal circuit development?
A critical period in brain development is the point at which a sensory experience regulates the proper development of a particular brain circuit. If the circuit is tampered with during this period, that circuit will be permanently compromised. The developing visual circuit pathway is one of the most extensively studied circuits. However, the role myelination has during circuit development, which potentially regulates the timing of retinal ganglion cell inputs, is unknown. To assess this we will use a set of transgenic mice and block myelin formation at critical times during development.
Main Techniques:
The project will involve transgenic animals, single cell patch clamping, immunohistochemistry and imaging.

D Does neuronal firing frequency regulate OPC fate
At the start of myelination, there are ~3.5 fold more axons present than in adulthood, and more than half of the axons in the corpus callosum, for example, remain unmyelinated in the adult. How an OPC decides on which axon to myelinate and when, remains unknown. Intriguingly, in the CNS apparently identical neighbouring axons are differentially myelinated, indicating an axon-specific induction signal for myelination, rather than control by long-range environmentally released factors alone. This signal could be firing frequency since myelination varies with firing rate and OPCs receive synaptic inputs from unmyelinated axons in the adult, each of which might fire at different rate, and synaptic strength could potentially be differentially regulated along an axon by altered axonal surface protein expression, resulting in differential myelination along a single axon and between identically sized neurons.
Main Techniques:
The project will involve tissue culture, microfluidics, optogenetics and super resolution imaging
If interested in this project please discuss with the lab with a good advance so that this can be set up. (in collaboration with Dr Steven Lee at Department of Chemistry)

E. Mechanical regulation of OPC differentiation
Oligodendrocyte progenitor cells (OPC) are equally distributed throughout the brain. They are the main proliferative cell present in the brain. Their function is to produce myelinating oligodendrocyte throughout life. Currently, the regulation of myelination is unclear, it seems that it depends either on axonal diameter, especially true for large diameter axons, or axonal firing rate, which seems to be more important for small diameter axons and dependent on NMDAR activation. One common explanation is that large diameter axons stretch OPC cell membrane raising intracellular calcium levels that lead to differentiation, whereas, small diameter axons cannot generate sufficient stretch on OPC cell membrane and thus OPCs depend on glutamate receptor activation to raise intracellular calcium levels to initiate differentiation. In this project, we will first detect which mechanosensitive ion channels OPCs express and how they are activated, before testing their role on myelination in myelinating co-culture
Main Techniques:
The project will involve Cell culture, transfections, immunohistochemistry, calcium imaging, Atomic force microscope, cell stretcher
If interested in this project please discuss with the lab with a good advance so that this can be set up. (in collaboration with Dr Kevin Chalut, Stem Cell Institute, and Dr Kristan Franze, PDN)
F Generating iPSC model of the CNS grey and white matter

In this project we will derive glia cells and neurons from iPSC in microfluidics to generate model of human CNS grey and white matter.

**Main Techniques:**
The project will involve Cell culture, transfections, immunohistochemistry, electrophysiology

<table>
<thead>
<tr>
<th>Key References</th>
<th>Background reading:</th>
</tr>
</thead>
<tbody>
<tr>
<td>3) Lundgaard I et al. (2013). Neuregulin and BDNF induce a switch to NMDA receptor dependent myelination by oligodendrocytes. PLoS Biol 11(12):e1001743</td>
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# Project 11

<table>
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<tr>
<th>Rotation project title</th>
<th>Investigations of local and systemic influences on astrocyte-neuron signaling in 2D/3D human stem cell models of neurodegeneration</th>
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<tbody>
<tr>
<td>Lab location</td>
<td>Cambridge Centre for Brain Repair, Cambridge Biomedical Campus</td>
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<tr>
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## Project Outline

Glial cells, such as astrocytes emerge as central players in the regulation of normal neuronal network development, function and also in its disruption in neurodegenerative diseases. Astrocyte responses to neuronal signals can be beneficial or detrimental to neuronal recovery, but the mechanisms that regulate these responses remain elusive. A detailed understanding of these fundamental processes may also provide alternative neuroprotective therapeutic targets for a range of neurodegenerative disorders. We use 2D/3D human stem cell based disease model systems combined with cell-type specific transcriptomics and computational approaches to mechanistically explore astrocyte-neuron interactions in health and in models of Amyotrophic Lateral Sclerosis (ALS).

## Rotation Topic

A particular aspect of this project is to explore how astrocyte-neuron interactions are influenced by either inflammation, induced immune responses or genetic risks.

## Main Techniques

- Human 2D and 3D iPSC and EC models with various ALS causing mutations
- Single cell transcriptomics
- Live imaging
- Manipulation of gene expression (e.g. Cre-lox, cas9)
- Standard cell and molecular biology techniques

## Key References


Human haematopoietic stem cells (hHSC) divide extremely infrequently and are essentially maintained quiescent (in the G0 phase outside of cell cycle). Quiescence is understood as a poised and reversible state in which cell cycle entry and proliferation are prevented, actively maintained by a complex regulatory network. Upon ex vivo culture, hHSCs sense changes in their microenvironment (including in cytokines, oxygen and nutrients), exit quiescence (from G0 to the end of early G1) and progress through the cell cycle (from late G1 to M) in a process collectively termed “activation”. Activation leads to a strong reduction in hHSC repopulation capacity, thus constituting a barrier to functional HSC expansion in vitro and optimal gene therapy protocols. It is commonly assumed that loss of self-renewal and induction of differentiation is occurring because of cell cycle progression, but no studies to date have formally examined when cell fate decisions occur during the activation process.

Recent work in our laboratory has distinguished the transcriptional and functional changes associated with quiescence exit from those occurring during cell cycle progression. We found that quiescence exit is accompanied by more drastic changes in hHSC gene expression and cellular properties than cell cycle progression. In addition, and in contrast to what previously thought, the reduction in HSC repopulation capacity driven by ex vivo culture occurs independently of cell cycle progression (Belluschi et al., in preparation). The relevance of the extensive transcriptional changes occurring during quiescence exit remains unclear. We hypothesize that some of these lead to irreversible lineage decision events. Hence transient manipulation of gene expression during quiescence exit could be sufficient to permanently alter HSC fate ex vivo, which may be clinically relevant.

Are lineage fate decisions determined during quiescence exit?
Bioinformatic analysis has identified a number of genes which expression is strongly downregulated already within the first 6 hours of quiescence exit. These include the transcription factor MAFF, whose function in HSC remains unknown. In preliminary experiments, constitutive overexpression of MAFF promoted hHSC differentiation towards NK cells. In this rotation, the student will overexpress the transcription factor MAFF both constitutively (cOE by lentiviral vector transduction) and transiently (tOE by mRNA electroporation) and compare the effects on lineage differentiation and time to first division of hHSCs. These experiments will determine if MAFF influences hHSC function, and more generally if transiently retaining expression of quiescence associated transcription factors during quiescence exit can lead to permanent changes in lineage acquisition.

mRNA synthesis, HSC electroporation, lentiviral vector production and HSC transduction, cloning, HSC isolation from cord blood, single cell in vitro HSC differentiation assays, time to first division assays.

# Project 13

<table>
<thead>
<tr>
<th>Rotation project title</th>
<th>Understanding the heterogeneity of human haematopoietic stem cell response to gene therapy</th>
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<tbody>
<tr>
<td>Lab location</td>
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<td>Term(s) available</td>
<td>Terms 2 and 3</td>
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## Project Outline
Correction of disease propagating haematopoietic stem cells (HSC) by gene therapy generates functional progeny, providing curative potential for many inherited monogenic disorders. The clinically approved HSC gene therapy procedure targets heterogenous stem and progenitor enriched CD34+ cells using viral vectors during a ~60hr culture protocol. The success of gene therapy is underpinned by the expectation that corrected HSCs are long lived and will continue to provide therapeutic benefit over the patient’s lifetime. HSCs capable of long-term repopulation after transplant (LT-HSCs) are extremely rare within the CD34+ compartment (<1%) and exhibit striking molecular and functional heterogeneity. However current clinical efforts to improve the gene therapy protocol don’t focus on the biology of these cells.

Our lab recently performed single cell RNA-sequencing of LT-HSC before and after the gene therapy protocol. Bone marrow (BM) and Mobilized Peripheral Blood (MPB) HSCs become more molecularly heterogenous following 60 hours ex vivo culture and lentiviral transduction. A subset of protocol modified LT-HSCs, exclusively residing in the G1 phase of the cell cycle, retain a transcriptional profile most similar to uncultured LT-HSCs. We hypothesize that these cells may have the highest repopulation potential of ex vivo modified LT-HSCs.

## Rotation Topic
Identify biomarkers of functional LT-HSCs after the gene therapy protocol

Bioinformatic analysis has identified a number of candidate genes marking these most primitive protocol modified LT-HSCs, including several cell surface markers. In this rotation, the student will have the opportunity to:

1. Develop bioinformatic methods to identify additional candidate markers and define a signature of “stemness” retained through the gene therapy protocol.

   AND/OR

2. Test if these cell surface candidates may help enrich for quiescent, multipotent, long-term repopulating HSCs. The expression of candidate markers will first be examined by flow cytometry. Then protocol modified LT-HSC that express high and low levels of these markers will be sorted by flow cytometry and tested in in vitro stem cell assays to assess their multilineage potential, clonogenic efficiency, cell cycle status and position in hematopoietic hierarchy.

## Main Techniques

1. Single cell RNA-seq bioinformatic analysis (dimensionality reduction, differential gene expression, pseudotime analysis, projection onto other datasets, pathway enrichment analysis...)

2. HSC purification and in vitro culture differentiation assays (single cell and bulk), cell cycle assays, flow cytometry, lentiviral transduction

## Key References

   doi:10.15252/emmm.201809958

**Project 14**

<table>
<thead>
<tr>
<th>Rotation project title</th>
<th>Elucidating the dynamics of niche cells during lung regeneration and early tumorigenesis</th>
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<tbody>
<tr>
<td>Lab location</td>
<td>Jeffrey Cheah Biomedical Centre</td>
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<tr>
<td>Head of laboratory (PI)</td>
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**Project Outline**

Stem cell behaviour is strongly influenced by the surrounding cells called ‘niche cells’ in tissue regeneration and oncogenic stress (1-3). We have recently developed the novel strategy to label niche cells by utilising a secreted fluorescent protein (sLP-mCherry) (1). In this project, we will generate *in vivo* inducible mouse model system to further characterize the labelling niche cells that communicate with lung stem cells during damage repair process, senescence, and tumour initiation.

**Rotation Topic**

1) Examine the local niche changes induced by region specific lung damages  
2) Characterize the cellular and molecular behaviours of labelling niche cells in various different context at a single cell level  
3) Define the impact of labelling niche cells on stem cell behaviour and vice versa  
4) Map the dynamic changes of stem-niche interactions  
5) Identify the relevant stem-niche interactions in human lung

**Main Techniques**

- Dissection and isolation of mouse lung cells  
- Lung organoid cultures of human and mouse  
- CRISPR/Cas9 construct design  
- Deep tissue clearing and imaging using Confocal microscopy  
- Live cell imaging  
- Single Cell Sequencing Analysis  
- Mathematical modelling of clonal dynamics  
- Single Cell Sequencing Analysis

**Key References**

**Body plan specification in human gastruloids**

<table>
<thead>
<tr>
<th>Lab location</th>
<th>Department of Genetics, University of Cambridge</th>
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<tbody>
<tr>
<td>Head of laboratory (PI)</td>
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**Project Outline**
Over the last few years we have develop an experimental system that allows us to generate structures that mimic early mammalian embryos from Embryonic Stem Cells (ESCs). We call these structures gastruloids. Our work to date has focused on mouse ESCs but recently we have extrapolated the technique to human ESCs. This is allowing us to explore the process of mammalian gastrulation ex vivo. In this project we shall explore the role that different signals have on the specification of the different kinds of mesoderm in human gastruloids.

**Rotation Topic**
It is clear that differentiation is different in 2D and 3D. Gastruloids are 3D structures that approximate the organization of the embryo. The project will explore how signals (BMP, Nodal and Wnt) interact with geometry and mechanics to generate lateral and paraxial mesoderm in the correct proportions and relative spatial organization in human gastruloids.

**Main Techniques**
- Culture and differentiation of human ESCs
- Generation of human gastruloids
- Live microscopy
- Antibody stain
- Multicolour in situ hybridization.

**Key References**
### Project 16

<table>
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<th>Rotation project title</th>
<th>Modelling discrete subtypes of mutant histone-driven gliomas</th>
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<tr>
<td>Lab location</td>
<td>The Milner Institute, JCBC</td>
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<tr>
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<td>Day-to-day supervisor</td>
<td>Manav Pathania, Antonella De Cola, Michael McNicholas</td>
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<td>Term(s) available</td>
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#### Project Outline

Paediatric high-grade gliomas (pHGGs) and diffuse midline gliomas (DMGs) are incurable malignant brain tumours and a leading cause of cancer-related death in children. We recently developed 3 different mouse models of pHGG/DMG tumour subtypes by surgically delivering different combinations of co-segregating mutations into neural stem cells during foetal development. This new approach to generating brain tumour models is quick, reliable and efficient, and allows evaluation of the numerous additional co-segregating mutations found in pHGGs/DMGs as either drivers or passengers. Because these brain tumours are heterogeneous and rare, the development of more effective therapies is limited by the dearth of well-controlled patient-derived cells representing the different tumour subtypes. To overcome this bottleneck, we propose developing more representative mouse models of this disease. These can be used to identify experimental therapies that are specific for one combination of mutations vs another (in a whole body, immune-competent context).

#### Rotation Topic

This project aims to develop mouse models of discrete tumour subtypes harbouring different combinations of co-segregating mutations. For the rotation project, the candidate will clone transposable and lentiviral vectors encoding the different mutations found in pHGGs/DMGs and will validate their efficacy in a mouse neuroblastoma cell line (Neuro2a). This will involve learning techniques such as lentiviral cloning, transduction, qPCR, immunofluorescence and biochemistry. Following validation, the candidate will deliver these vectors into embryonic neural stem cells and K27M tumour cells in vitro and assess their effects on proliferation and differentiation using FACS and immunofluorescence. The candidate will also compare the effects of mutations on histone posttranslational modifications at key genes involved in neurodevelopment, the cell cycle and tumour suppression via chromatin immunoprecipitation and qPCR. If the candidate continues on for a PhD project, they will validate their in vitro data in vivo, using transposon and CRISPR in utero electroporation-based models of mutant histone-driven pHGG/DMG. They will liaise with myself, a postdoctoral associate and a research assistant to gain all the technical and intellectual competencies required to complete this project.

#### Main Techniques

- Molecular biology
- Lentivirus production
- Cell culture
- Immunofluorescence
- Confocal and epifluorescence microscopy
- Chromatin immunoprecipitation
- FACS
- In utero electroporation
- Animal handling
- Perfusion fixation
- Brain sectioning
- qPCR

#### Key References

### Project 17

<table>
<thead>
<tr>
<th>Rotation project title</th>
<th>Epigenetic regulation of cell fate decisions in mammalian development</th>
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<tbody>
<tr>
<td>Lab location</td>
<td>Babraham Institute</td>
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<tr>
<td>Day-to-day supervisor</td>
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<td>Term(s) available</td>
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#### Project Outline
The mammalian embryo makes fundamentally important cell fate decisions during gastrulation which set up the primary germ layers (endoderm, mesoderm, ectoderm) with subsequent development of all major organ systems. While signaling systems, mechanical forces, transcription factors, and epigenetic regulation are all implicated in cell fate decisions, how these systems integrate information to switch cell fate is not known. You will use state of the art single cell multi-omics methods to interrogate individual cells as they make decisions to become particular cell types during gastrulation. You will use CRISPR/Cas genome and epigenome editing to manipulate epigenetic regulators and marks to understand their impact on cell fate.

#### Rotation Topic
We have already gained some preliminary insights into germ layer commitment from our preliminary studies. We find that neuroectoderm enhancers are already epigenetically primed (hypomethylated, chromatin accessible) in the early epiblast, but mesoderm and endoderm enhancers are not. They instead become acutely demethylated and accessible as cells ingress into the primitive streak and become committed to mesoderm and endoderm, respectively. We have also identified DNA binding proteins that are involved in priming of regulatory elements for future expression during lineage-commitment and organogenesis.

#### Main Techniques
In order to understand the integration of epigenetic regulation and transcription during differentiation we have developed single cell sequencing methods which interrogate the transcriptome, methylome, and chromatin accessibility all in the same single cell. Novel computational and statistical algorithms connect transcriptional with epigenome variability, for example at the level of enhancer or promoter methylation and nucleosome accessibility. We have also established dCas9 based editing techniques which can epigenetically edit hundreds of regulatory elements the effects of which on gene expression and phenotype can be read out in single cells.

#### Key References
5. Berrens et al 2017 *Cell Stem Cell*
6. Rulands et al 2018 *Cell Systems*
7. Eckersley-Maslin et al 2019 *Genes Dev*
8. Pijuan-Sala et al 2019 *Nature*

[http://www.babraham.ac.uk/our-research/epigenetics/wolf-reik](http://www.babraham.ac.uk/our-research/epigenetics/wolf-reik); [http://www.sanger.ac.uk/people/directory/reik-wolf](http://www.sanger.ac.uk/people/directory/reik-wolf)
# Project 18

## Rotation project title
Oct4 and the Transcription Factor network paradigm

## Lab location
Jeffrey Cheah Biomedical Centre

## Head of laboratory (PI)
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## Day-to-day supervisor
TBC

## Term(s) available
Terms 2 and 3

## Project Outline
Cell identities are postulated to be governed by gene regulatory networks made of Transcription factors (TFs). This is particularly well exemplified in naïve pluripotent stem cells (PSCs). Although defined relationships between pluripotent TFs have been established, their relationship to Oct4 remains obscure. Unlike other pluripotent network TFs, modulation of Oct4 levels results in counterintuitive phenotypes such as differentiation upon elevation of its expression. However, Oct4 remains the only factor to be strictly required for the self-renewal of PSCs. Recently Stuart et al defined that distinct reprogramming pathways converge on the fine-tuning of Oct4 expression to pluripotent levels and that this is sufficient, within a conducive signalling environment, to reprogram all tested cell types. As a result we hypothesize that the key role of the pluripotent network is to both fine-tune Oct4 expression and/or to ensure Oct4 accessibility to regulatory genomic regions. We aim to test this by performing CRISPR/Cas9 knockouts, of otherwise essential TF combinations for PSC self-renewal, in our Oct4−/− PSCs expressing constitutive PSC levels of Oct4. With this work we expect to test the sufficiency of Oct4 for the self-renewal of PSCs and thus address the strict requirement of a TF network.

## Rotation Topic
TF networks, Pluripotent stem cell self-renewal

## Main Techniques
Cell culture (ESCs), including maintenance, expansion, genetic manipulation (Using CRISPR/CAS9) and flow cytometry. RNA extraction for RNAseq and RT-qPCR. Genotyping. Chromatin Immunoprecipitation (ChiP).

## Key References


Project 19

<table>
<thead>
<tr>
<th>Rotation project title</th>
<th>How do developmentally regulated processes unfold upon Transcription Factor induced cell fate?</th>
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<tbody>
<tr>
<td>Lab location</td>
<td>Jeffrey Cheah Biomedical Centre</td>
</tr>
<tr>
<td>Head of laboratory (PI)</td>
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<td>TBC</td>
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**Project Outline**

We want to address if bypassing a normal developmental path, i.e. in cell fate induction by Transcription Factor (TF) modulation of Embryonic stem cells (ESCs), affects the execution of developmentally regulated processes such as X-chromosome Inactivation (XCI) and chromatin bivalence. We use the process of XCI not as a marker of developmental progression but instead as a first-line reporter of misregulation of an essential developmental process, which may be indicative of more widespread issues. If misregulation is found this will have implications in terms of using Embryonic stem cells for the creation of a true cell fate identity by TF modulation. Importantly, we also expect that found anomalies will bring new knowledge on how these processes, are regulated and that way also provide clues for new strategies aiming at overcoming these during TF induced cell fate.

**Rotation Topic**

Forward programming and X-chromosome inactivation

**Main Techniques**

Cell culture (ESCs), including maintenance, expansion, genetic manipulation, Forward programming, timecourses, flow cytometry. RNA extraction for RNAseq and RT-qPCR. Genotyping. Chromatin Immunoprecipitation (ChiP).

**Key References**


In cancer, tumours develop through a multi-stage Darwinian-like process, transferring from a phase of neoplasia to invasive carcinoma and metastatic transformation. Entry into this programme is often preceded by phase of “field cancerization” in which the acquisition of oncogenic DNA mutations enables cells to outcompete their neighbours, expanding the “canvas” of cells on which further mutations can impact. To resolve pathways leading to cancer, emphasis has been placed on resolving the mutational signature of tumour types – the “cancer genome”. However, while the repertoire of cancer genes is becoming increasingly well-characterized, the impact of mutations on the fate behaviour of individual cells remains underexplored. To probe the earliest stages of malignancy, in vivo genetic lineage tracing studies by our group and others have begun to probe the fate of mutant cells and their progeny – known as “clones” – following the activation of oncogenic mutations (Sánchez-Danés et al., 2016). However, current cell labelling strategies struggle to resolve how the fate of neighbouring wild type cells are subverted by the oncogenic activation of neighbours, and how these changes can drive field cancerization and cancer progression, with consequences for our understanding of early cancer-detection and risk management strategies.

To understand the mechanisms that drive tumour development, there is a pressing need to understand the pathways that regulate cell fate in normal tissues, and how these programmes become subverted during tumour initiation and progression. To advance this programme, we developed novel variants of the Rosa-Confetti 4-colour reporter allele (Red2cDNA series).

Building on insights into the dynamics of normal adult epithelial populations, lineage tracing strategies have been developed to address cell fate following the activation of oncogenic mutations. By coupling a single reporter gene to an oncogenic mutation, these studies have allowed tumour cell dynamics to be quantified over time in multiple epithelial tissue types. These studies have shown that oncogenes can confer a fitness advantage, allowing mutant cells to outcompete their neighbours, driving field cancerization. In the mouse small intestine and colon, work by our lab and others show that clones mutant for expression of Kras or APC rapidly colonize individual crypts and accelerate crypt fission, driving the expansion of mutant clones (Kozar et al., 2013). Intriguingly, molecular profiling of epithelial tumours frequently report elevated expression of genes upregulated in development, suggesting that tumour progression may involve the activation of aberrant tissue repair programmes.

Yet, although these studies reveal evidence for, and the cellular basis of, selective survival advantage of mutant clones, the mechanisms that drive cell competition remain in question. Is non-neutral cell competition associated with the direct exchange of signalling factors between neighbouring wild type and mutant cells, or is it indirect, mediated by mutation-driven changes to the local microenvironment?

Based on current findings, we hypothesize that the balance between stem cell duplication and differentiation in columnar epithelial tissues is mediated by competition...
for autocrine and paracrine signals from the stromal niche. By perturbing the niche, mutant cells are able to change the local environment, providing a pathway to drive cell competition and field cancerization. Using a novel genetic labelling mouse system, the aim of the current project is to challenge this hypothesis, defining the niche-based mechanisms that regulate stem and progenitor cell fate in epithelial tissues, and how these programmes become subverted following the activation of oncogenic mutations.

With a focus on columnar epithelia, where a foundational understanding of associated signalling pathways and transcriptional programmes is in place, our goal is to **define at clonal resolution the changes that take place in cell fate following the acquisition of oncogenic mutations, targeting tumour cells and the reaction of surrounding tissue – the tumour microenvironment.**

We will make use of new variants of the multicolour Rosa-confetti reporter allele (Snippert et al., 2010) – the “red2cDNA series” – in which a different oncogene, such as KrasG12D, PI3KH1047R, Notch1 and B-catenin.

### Main Techniques
The rotation student will be trained with confocal imaging, organoid culture and quantitative imaging analysis etc. This student will be responsible for performing lineage tracing experiments using our modified Confetti alleles in the small intestine and colon. Depending on the obtained data, we will try to deliver theoretical elements of the mutant and normal clonal behavior.

### Key References


**Project 21**

<table>
<thead>
<tr>
<th>Rotation project title</th>
<th>Function of Nodal in maintaining the pluripotent state of human epiblast</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lab location</td>
<td>JCBC</td>
</tr>
<tr>
<td>Head of laboratory (PI)</td>
<td>Ludovic Vallier, <a href="mailto:lv225@cam.ac.uk">lv225@cam.ac.uk</a></td>
</tr>
<tr>
<td>Day-to-day supervisor</td>
<td>Anna Osnato, Rodrigo Grandy</td>
</tr>
<tr>
<td>Term(s) available</td>
<td>Terms 1, 2 and 3</td>
</tr>
</tbody>
</table>

**Project Outline**

Generation of all the adult tissues occurs by progressive cell fate decisions, starting with the specification of the three primary germ layers (ectoderm, mesoderm and endoderm). Molecular mechanisms controlling specification of the germ layers have been extensively studied in amphibian and fish. However, the understanding of these mechanisms in mammals (especially in human) is more limited, and this represents a major drawback for regenerative medicine. Indeed, the generation of fully functional cell types from stem cells may only be achievable by recapitulating a normal species specific succession of cell fate decisions starting with germ layer specification.

The studies of these mechanisms at the molecular level in vivo are restricted particularly in humans, by the difficulty of obtaining biological material. The availability of human pluripotent Stem cells (hPSCs) offers possibilities to resolve this major limitation. We developed fully defined 2D culture system to differentiate hESCs into neuroectoderm, mesendoderm, endoderm and extra-embryonic cells. These systems was used the study of a diversity of molecular mechanisms involving transcription factors, epigenetic modifiers and cell cycle regulators. However, our 2D approach lack the complexity of in vivo germ layers formations and thus preclude the study of mechanisms involving interactions between different cell types, morphogenic movements and tissue patterning. The main objective of this rotation is to develop a new 3D culture system allowing specifications of the 3 germ layers in vitro using an organoid platform.

**Rotation Topic**

The main objective of the rotation will be to test different 3D culture conditions to differentiate hPSCs into self-organised “epiblast” organoid by controlling Activin/Nodal signalling. The resulting “epiblast” organoids will be then induced to differentiate by modulating signalling pathways known to direct germ layer specification including WNT and BMP. The differentiated organoid will be then characterised for the expression of specific markers of differentiation, the formation of primitive streak like structure and anteroposterior patterning. If successful, this culture system could provide the first step toward the development of an in vitro model for human gastrulation.

**Main Techniques**

- Cell culture and differentiation of hPSCs
- Organoid culture system
- Cell culture biology techniques including immunostaining, QPCR, etc.
- RNA-Seq if time allows.

**Key References**


7) Chng ZZ et al. (2010) SIP1 mediates cell fate decisions between neuroectoderm and mesendoderm in human embryonic pluripotent stem cells. Cell Stem Cell. 6(1). 59-70


The myeloid cancers are a group of clonal disorders of the haematopoietic stem cell (HSC) that comprise acute myeloid leukaemia (AML), myelodysplastic syndromes (MDS) and myeloproliferative neoplasms (MPN). They are driven by a well-characterised set of somatic mutations, some of which are shared between them and others, which are more specific to one of the subtypes. Perhaps the most intriguing group of these mutations are those affecting splicing factor genes \textit{SF3B1}, \textit{SRSF2}, \textit{U2AF1} and \textit{ZRSR2}, which are very common in MDS (~70% of cases), but also occur in AML and MPN. The mutations lead to splicing aberrations in many gene transcripts throughout the genome and act as disease-initiating events by driving clonal expansion of mutant HSCs. However, their mechanism of action remains poorly understood. In fact, available evidence suggests that these mutations can be detrimental to cellular fitness, making their role as oncogenes as puzzling as it is obscure. An important focus of our lab is to derive insights into the molecular effects of these mutations and the way in which they drive clonal expansion and myeloid leukaemogenesis.

The aim of this project is to generate cellular models of \textit{SF3B1} and \textit{SRSF2} mutations by targeted modification of the endogenous gene loci in MDS-L, one of the few available human MDS cell lines. Once generated, these cellular models will be used to carry out transcriptomic and proteomic studies to correlate the impact of splicing aberrations on protein isoforms and total protein levels.

### Rotation topic
Splicing gene mutations and their mode of action in clonal haematopoiesis and myeloid malignancies.

### Main techniques
- Cell culture (leukaemia cell lines)
- Generation of lentiviral vectors
- Genome editing using CRISPR-Cas9
- Single cell cloning
- Validation using PCR/sequencing

### Key references
# Project 23

<table>
<thead>
<tr>
<th>Rotation project title</th>
<th>Epigenetics in intestinal stem cell biology: Assessing DNA methylation dynamics in the human intestinal epithelium during development, health and Inflammatory Bowel Diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lab location</td>
<td>Cambridge Biomedical Campus (Addenbrookes Hospital)</td>
</tr>
<tr>
<td>Head of laboratory (PI) name</td>
<td>Matthias Zilbauer, <a href="mailto:mz304@cam.ac.uk">mz304@cam.ac.uk</a></td>
</tr>
<tr>
<td>Day-to-day supervisor name</td>
<td>As above</td>
</tr>
<tr>
<td>Term(s) available</td>
<td>Terms 1, 2 and 3</td>
</tr>
</tbody>
</table>

## Project Outline
DNA methylation is a key epigenetic mark known to be implicated in regulating cellular function during physiological development. In this project we will use human intestinal mucosa derived organoids to investigate the role of DNA methylation intestinal stem cell biology during physiological development, healthy homeostasis as well as pathogenesis of Inflammatory Bowel Diseases. This is a highly translational project that aims to implicate findings into clinical practice. The candidate will therefore be joining a highly diverse and welcoming team of scientists, clinicians, research nurses, clinical fellows and data managers.

## Rotation Topic
*Rotation project will be based around the Project Outline.*

## Main Techniques
- Human intestinal epithelial organoid culture (generation, culturing, functional assays such as barrier function, viral infection model etc.).
- Genomic editing of human intestinal organoids (e.g. CRISPR/Cas9).
- Basic molecular biological methods including RT-PCR, immunostaining and organoid co-culture experiments.
- Application of single cell RNA sequencing to human mucosal tissue samples and patient derived organoids.
- Genome wide DNA methylation profiling of organoids including bioinformatic analysis of generated data.
- Correlation of molecular signatures with clinical patient data.

## Key References
1. Howell KJ et al. *DNA Methylation and Transcription Patterns in Intestinal Epithelial Cells From Pediatric Patients With Inflammatory Bowel Diseases Differentiate Disease Subtypes and Associate With Outcome*. Gastroenterology. 2018 Feb;154(3):585-598.

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Assessment Information

Year One Assessment
The 1st year of your 4-year PhD Programme forms the basis for an MRes in stem cell biology. The assessment for the MRes, which is awarded on a pass/fail basis, is based on the following work that you are required to produce/participate in during year one:

Stem Cell Discussion Course (Terms 1, 2 & 3)
As part of the MRes course you are expected to attend the weekly Stem Cell Discussion Course. In term 1, ‘Introduction to the CSCI’ sessions are led by CSCI PI’s as an introduction to their research fields. In terms 2 & 3, the ‘Stem Cell Biology discussion sessions’ are group discussions. Each week the lead PI(s) will provide papers for you to read, and discussion topics for you to think about prior to the session. These will form the basis of the discussion.

Rotation Reports (Terms 1, 2 & 3)
At the end of each lab rotation, you will have a minimum of 3 weeks to write a short report on the research you have performed. The report will be assessed by Dr. Hendrich and one other CSCI PI, who will each provide you with feedback. You may be asked to make corrections based on this feedback, and re-submit. These comments will also be available to the MRes external examiner. It is advisable to do these as soon as possible, but certainly within 3 weeks of receipt of the corrections. See course schedule for submission deadlines, and page 46 for content and formatting guidelines.

Rotation Presentations (Terms 1, 2 & 3)
At the end of each rotation, you will give a 15 minute presentation on your project to Dr. Hendrich and your fellow students, prior to submitting your rotation report. See course schedule for dates.

Outline PhD Proposal Presentation (Term 3)
Prior to submitting your Research Proposal (see below) you will give a 20 minute presentation of your PhD project to the Programme Directors. They will want to know the background, the specific questions or hypothesis you’ll be addressing and an outline of the experimental methods. See course schedule for presentation date.

PhD Research Proposal/Critical Appraisal (Term 3)
Once you have chosen the laboratory in which you will carry out your PhD project, you will be required to write a research proposal (also referred to as the “critical appraisal”). This proposal should describe the background to the field, the aims of the project and the experimental approach that you plan to pursue. This proposal will be sent to the MRes examiners and will be the main focus of your oral examination/presentation (MRes Viva). See course schedule for deadline, and pgs 46-47 for guidance.

MRes Viva (End of Term 3)
Your formal MRes Viva will take place in Sep 2020, with an External Examiner, a Senior Examiner and the Chair of Examiners, with the Programme Directors fulfilling at least one of the latter two roles. You will be required to give a 15 minute presentation of your PhD project, to include some background to the project, questions/hypotheses to be addressed and a good indication of how you intend to go about doing your project. The remainder of your Viva will involve discussion with the examiners of your submitted Research Proposal and rotation reports. The examiners will then write a joint report on your performance based on your written work and oral presentation. This report will be used to determine whether or not you have met the criteria for an MRes Degree. The examiners will also make a recommendation to the Degree Committee about your suitability to pursue a PhD. MRes viva date TBC.
Wellcome Research Project Proposal (Oct 2020)
At the end of year one, students on Wellcome funding will be required to complete a PhD Research Project Proposal. Instructions will be received from Wellcome in July, with a submission deadline in October. Your PhD supervisor should help you to complete this. There will also be an opportunity to apply for an animal costs supplement for your PhD project.

Events
You will discuss your PhD Project plans with the PhD Management Committee at the annual 4-Year Stem Cell Student Presentation Day. You will also present a poster at the annual Stem Cell PhD Symposium (in year 1, your poster should be based around your PhD proposal; an intro, preliminary data generated during your rotation and future plans (you could also include data from your prospective supervisor for background information).

Subsequent Monitoring

Year Two
In Year 2 you will be required to write a Progress Report for assessment. This report and assessors’ comments will provide the basis for progression to PhD registration. You will present your work at the annual Four-Year Stem Cell Student Presentation Day, and will receive feedback from the PhD Management Committee. You will also present a poster at the annual Stem Cell PhD Symposium.

You will meet informally as a group with the Programme Directors / members of the Graduate Committee three times in year 2, to discuss your progress and any concerns / issues you might have.

Year Three
During year 3, and certainly by the end of year 3, you should begin to consider directions for your Post-Doctoral career. It is often advisable to apply a year in advance of an intended start date to allow time for visits/interviews and to apply for funding. You will present your work at the annual Four-Year Stem Cell Student Presentation Day, and will receive feedback from the PhD Management Committee. You will also be expected to verbally present your work at the annual Stem Cell PhD Symposium in your 3rd year (see page 46 for event details).

You will meet informally as a group with the Programme Directors / members of the Graduate Committee twice in year 3, to discuss your progress and any concerns / issues you might have.

Year Four
Students on the Wellcome PhD Programme are required by the funders, to submit their thesis by the end of September of your 4th year (September 2023, for 2019 starters).

You will be required to submit a thesis plan, in outline form, by the end of Jan in your final year. This will be discussed with your PhD Supervisor and the Programme Coordinator, to check how your project is developing and that you are on track to submit on time. They will provide feedback and guidance for the completion of the work. You will present your work at the annual Four-Year Stem Cell Student Presentation Day, and will receive feedback from the PhD Management Committee.

You will meet informally as a group with the Programme Directors / members of the Graduate Committee twice in year 3, to discuss your progress and any concerns / issues you might have.

The procedures for submission of your PhD thesis and appointment of examiners will follow those presently in operation at The University of Cambridge as required by the Degree Committee.

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CSCI Student Opportunities

1st Year Wellcome Students’ Meeting (July 2020)
You will be invited to attend a meeting for all 1st year students on Wellcome studentships. The aim of this meeting is to provide an overview of Wellcome’s activities/history, their expectations of students, and further opportunities available to you. All invited students are expected to attend. Date TBC.

Four-Year Stem Cell Student Presentation Day (Annually, June)
Annual presentation event for all students on the Four-Year (1+3) Stem Cell Biology & Medicine Programme. Each student will give a presentation to their fellow students and the PhD Management Committee. You will receive feedback from the Committee. A College dinner for all participants is held in the evening. All Four-Year (1+3) Stem Cell Students are expected to attend. Date TBC.

PhD Day Symposium (Annually, October)
Annual event for CSCI PhD students in their penultimate year, to present their work orally. All other students are expected to present a poster (your first poster (in year 2) should be based around your PhD proposal; an intro, preliminary data generated during your rotation and future plans (you can also include data from your supervisor for background information). All CSCI members are invited. It is an excellent opportunity to hear about other labs’ work and prepare for when your turn comes to give an oral presentation (in year 4). Date TBC.

Final Year Wellcome Students’ Meeting (Oct/Nov 2022)
In your final year, you will be invited to attend a meeting at Wellcome for all final year students on Wellcome studentship funding. Students are given an opportunity to present a poster of their results to fellow students, meet with members of Wellcome staff, and find out about potential career paths. All invited students are expected to attend.

CSCI Seminars
The CSCI and affiliated departments organise regular seminars for internal and external participation. You are expected to attend all seminars in whichever department you find yourself. All students are expected to attend the CSCI Internal Seminars, which are held every Monday at midday in the JCBC lecture theatre, and the CSCI External Seminars, which are more ad-hoc.

Core Skills Training Programme
The Graduate School of Life Sciences (GSLS) provide an online Core Skills Training Programme for new graduate students. The GSLS views researcher development as an essential part of your research degree course and this programme has been designed as a starting point, aiming to:
- Help you identify existing skills and skill gaps
- Gain training in key areas of personal effectiveness and communication
- Provide a foundation for further skills development in subsequent years
- Gain recognition of training upon completion of the CSTP

The programme has four compulsory components:
- A skills analysis survey to help you identify the skills that you want to develop
- Time management training, a key skill for being a researcher
- Presentation and performance training as it is just as important for scientists to be able to communicate their research to other people as well as being able to obtain results in the lab
- Scientific writing to aide you to be prepared for report writing that you will need in your first year.

We strongly recommend that all students participate in this online programme. You will be sent an invitation by the GSLS, and the course should then be available to you on your Moodle course list.
Public Engagement
At the CSCI we have embedded a culture of engaged research that runs through all levels of the Institute. We encourage and support all students and researchers to take part in, and develop, their own public engagement activities. This will help you gain skills and expertise to support your personal and professional development, and is a great way to meet new people and have fun too!

The Institutes Public Engagement team, led by Public Engagement Manager Dr Rebecca Jones and Coordinator Dr Selen Etingu Breslaw, provide opportunities and advice to help you share your research with the public in engaging ways.

All students are expected to take part in at least one public engagement activity per year during their studentship. This can be led by you, with support to develop your own project, or part of a larger activity organised by the PE team (e.g. local festivals, talks, tours, arts collaborations, patient workshops, films etc.). Training can be provided before participation in any event, to give you the confidence and skills to engage effectively. You may also decide to take part in externally-organised public engagement activities. In this instance, please notify the public engagement team (scipe@stemcells.cam.ac.uk) so that they can acknowledge your contribution, and provide advice and resources if required.

Other things to look out for at the CSCI:
Public Engagement Seed Fund: Apply for £500 - £2,000 to fund your own public engagement initiative. The next call opens in October 2019.
Prizes: Win one of our awards for outstanding contribution to engagement, presented by the Institute Director at the Institute Retreat.
Committee: Support our Public Engagement Steering Committee with new ideas and insights from the student community. The current PhD rep to approach is Daniel Bode (Kent/Gottgens Lab).

For more info: www.stemcells.cam.ac.uk/about-us/publicengagement

You can also stay up to date with the latest opportunities via the CSCI weekly bulletin.

If you would like to discuss an idea, please get in touch or pop by and see Becky or Selen in the JCBC (Level 3, Room 39)
Guidelines for Assessed Work

The cover page for all assessed reports should be laid out as follows:

----------------------------------------------------

<Project Title>

<Your Name>
MRes + PhD Programme in Stem Cell Biology and Medicine 2019/20

<Report type & rotation dates>
  e.g. Term One Rotation Project, Oct 2017 – Dec 2018

<Report Submission/Revision Date>

<Supervisors Name(s)>
<Supervisors Laboratory>

----------------------------------------------------

1. Rotation Report Guidelines

For the rotation reports, we ask for a maximum of 6000 words (including figure legends, but excluding words in tables and bibliography).

We suggest you break the report down into the following:
  i. Summary
  ii. Introduction
  iii. Methods
  iv. Results
  v. Discussion
  vi. References

- It is recommended to prepare figures in Photoshop, Illustrator or Freehand.
- If submitting a revised version, please remember to include ‘version 2’, on the cover page.
- A binding machine is available in the JCBC admin office, and binding materials can be obtained from the Graduate Administrator.
- One bound copy (including any figures) plus an electronic copy must be submitted to the Graduate Administrator by the given deadlines. A second bound copy should be given to your rotation supervisor. See your course schedule for submission deadlines.
2. Research Proposal (Critical Appraisal)

- You should inform Dr Hendrich and Jo Jack, of your PhD lab choice and Critical Appraisal title by Midday on Monday 22nd June 2020.
- Maximum 6000 word limit (including figure legends, but excluding tables, footnotes, bibliography and appendices).
- Experimental Design section ideally to be approx. 2 pages in length.
- Two bound copies (including any figures) plus an electronic copy of your Critical Appraisal should be submitted to the Graduate Administrator by Friday 7th August 2020.
- Your Critical Appraisal must include a signed statement (on the inside page) along the following lines:

“I confirm that the material in this Critical Appraisal is not copied from any published material, nor is it a paraphrase or abstract of any published material unless it is identified as such and a full source reference is given. I confirm that, other than where indicated as such, a full source reference is given. I confirm that, other than where indicated as above, this document is my own work.”

(Your signature)

The order of your Critical Appraisal should be as follows:

i. **Aims of the project** - This should be concise, with perhaps a few sentences of overview explaining the general focus and then listing some specific objectives/goals.

ii. **Background and work that has led up to the project** - This should set the scene for the research, so needs to be a summary of the relevant literature, perhaps beginning more broadly and getting more specific. It may include preliminary unpublished data from yours or other work in the lab (if relevant). It may also include diagrams or pictures of data. We suggest about 1/3 of the proposal might be background, but there is no set rule.

iii. **Experimental design and methods to be used in investigating this problem** - This should describe your plan of investigation. It is often helpful to subdivide this into sections. These might represent sequential steps in the investigation (e.g. genetic screen; molecular characterisation of genes; etc.) or parallel approaches (e.g. loss of function studies; gain of function studies; etc.) or different questions to be addressed (e.g. does X regulate Y? Is X essential for mesoderm development?). See what works best for your proposed project.

Remember to think about issues such as:
- If you will be doing a screen and then characterising some of the genes isolated, how will you choose which ones to characterise?
- Will you be able to distinguish control from experimental animals? How?
- What controls will you use to test whether your results are meaningful?
- Do you foresee any pitfalls? If so, how might you handle them if they arise?
- You may also like to include a time-line or flow diagram.
iv. **Budget** - This should be an appendix. Don’t feel the need to go into too much detail here, but think about where the major costs of your project will lie. Subdivide the budget into: animals and animal costs, consumables (e.g. enzymes; molecular biology kits; antibodies; tissue culture reagents; tips; tubes - check out the basic costs of some of these and consider where the bulk of your costs are going to lie), equipment (if you don’t need any specific equipment, there may not be anything in this category). You should try to find out as much of this financial information for yourself as possible, rather than relying on your supervisor (they can of course check it for you, but will not be happy to do it for you!). You will have access to catalogues and the web, so do some research. The aim is to increase your awareness of the costs associated with different kinds of experiments.

Please allow yourself plenty of time for discussion and feedback with your supervisor - they have extremely busy schedules, so remember to take this into consideration when planning your time.

**Report-writing tips from the Programme Directors:**

- **Use first person singular, “I”,** when describing your experiments – this is very important!
- Do not summarise your results in the Introduction - this should end with stating clearly the aim of the project (hypothesis under investigation)
- Do summarise your results at the beginning of the Discussion
- Present all elements of a Figure on a single page
- State numbers of biological and technical replicates for all experiments
- Be critical about your experimental approach and results
- Propose the next key experiment(s)
- **Only** large datasets that cannot be included in normal figures/tables should be added as “Supplementary Data”. Do not use this as a dumping ground for all of the other experiments you did, that don’t fit into the main narrative.
Positive Research Culture

The Cambridge Stem Cell Institute is a vibrant community where an inclusive culture is promoted and diversity is valued. We subscribe to the University’s Equal Opportunities Policy and have an active Equality and Diversity Working Group to ensure best practices are maintained and new strategies are developed to promote an inclusive and thriving environment at the Institute.

Research Culture & Integrity Committee
Ensuring high standards of research culture and integrity are central to the mission and success of the CSCI. The remit of this committee will include setting guidelines, procedures and policies related to research reproducibility, misconduct, and data management. Importantly, the committee will not just set boundaries and establish procedures for when "things have gone wrong", but instead develop proactive guidelines that facilitate a research culture which promotes a positive working environment. The ‘excellence’ of our institute in future will be evaluated not just by what we produce, but how we produce it. The remit of this committee therefore includes to help establishing a positive research environment. This Committee is Chaired by Prof. Bertie Gottgens.

Any members of this Committee or the CSCI Graduate Committee can be contacted should you have any issues or concerns.

The CSCI also supports the following University-led initiatives:

Breaking the Silence
There is no place for any form of harassment or sexual misconduct at the University of Cambridge. The ‘Breaking the Silence’ initiative aims to prevent harassment and sexual misconduct, and provides a range of resources for staff and students.

Childcare Office
The Childcare Office oversees the facilities and assistance offered to University staff with Children. The support offered included Workplace Nurseries, a Holiday Play scheme, salary exchange schemes and an information service.

Counselling Service - Students
Many personal decisions are made and problems solved through discussions with friends or family, a College Tutor or Director of Studies, a Nurse, Chaplain, colleague, line manager or a GP. However, at times it is right to seek help away from one’s familiar daily environment. The University Counselling Service exists to meet such a need.

Dignity at Work
The aim of the Dignity at Work policy is to support and sustain a positive working environment for all staff and students, free from any form of unacceptable behaviour.

Equality & Diversity Section
The E&D section seeks to help the University progress equalities policy in line with legislation, and to develop good practice in supporting under-represented groups.

Mediation Service
The mediation service can help resolve disagreements between members of staff with support from impartial, trained mediators.
Office of Postdoctoral Affairs (OPdA)
The OPdA supports the postdoctoral community. They provide academic, administrative and pastoral focus and aim to enhance the physical and intellectual experience of postdocs.

Personal and Professional Development (PPD)
The PPD team offers a wide range of practical training and development opportunities to help staff explore their potential and get the most from their time at the University.

Reflection & Prayer Facilities
A number of rooms are made available by the University for its students, staff and authorised visitors, with the primary purpose of providing safe, clean and inclusive places for prayer and reflection.

SPACE (Supporting Parents And Carers @ Cambridge)
SPACE provides support and information for members of the University with caring responsibilities for children or other dependents.

WellCAM
The University is committed to providing a healthy and fulfilling working environment and improving the quality of working lives for all staff.

The definition of research integrity used in this document is adopted from Universities UK, The concordat to support research integrity (July, 2012). For guidance provided at the European and global level see: European Science Foundation, The European Code of Conduct for Research Integrity (March, 2011); 2nd World Conference on Research Integrity, Singapore Statement on Research Integrity (July, 2010); National Institutes of Health, NIH Policies and Procedures for Promoting Scientific Integrity (November, 2012).

Wellcome Guidelines on Good Research Practice
Wellcome expects the researchers it funds to adhere to the highest standards of integrity. To facilitate this it has drawn up these guidelines on Good Research Practice. Wellcome funds a wide range of research, including biomedical science, biomedical ethics, social sciences and history of medicine. These guidelines are designed to apply to all of the research that Wellcome funds.

Integrity
- Researchers should be honest in respect of their own actions in research and in their responses to the actions of other researchers. This applies to the whole range of research work, including experimental design, generating and analysing data, applying for funding, publishing results, and acknowledging the direct and indirect contribution of colleagues, collaborators and others.
- Plagiarism, deception or the fabrication or falsification of results should be regarded as a serious disciplinary offence.
- Researchers are encouraged to report cases of suspected misconduct and to do so in a responsible and appropriate manner.
- Researchers should declare and manage any real or potential conflicts of interest.
University of Cambridge Guidelines on Research Integrity

The University is committed to achieving excellence in research and scholarship. The pursuit of excellent research and the fulfilment of our responsibilities to participants in research, research users and the wider community require the maintenance of the highest standards of integrity and ethics.

To maintain the high standards of research practice at Cambridge, the University will uphold the commitments outlined in Universities UK’s Concordat to Support Research Integrity. The information below sets out the principles to which all research and scholarship at the University of Cambridge should adhere and provides guidance on where to seek further advice on specific research integrity issues. The University expects all researchers, be they staff, students or visitors to the University, to abide by national, European and international standards of research integrity. This includes:

Honesty in all aspects of research, including:
- presentation of research goals, intentions and findings
- reporting on research methods and procedures
- gathering data
- using and acknowledging the work of other researchers
- conveying valid interpretations and making justifiable claims based on research findings

Scrupulous care, thoroughness and excellence in research practice:
- in performing research and using appropriate methods
- in adhering to an agreed protocol where appropriate
- in drawing interpretations and conclusions from the research
- in communicating the results

Transparency and open communication:
- in declaring conflicts of interest
- in the reporting of research data collection methods
- in the analysis and interpretation of data
- in making research findings widely available, including sharing negative results as appropriate
- in presenting the work to other researchers and to the general public

Care and respect for:
- all participants in and subjects of research, including humans, animals, the environment and cultural objects
- the stewardship of research and scholarship for future generations.

In addition to these core principles, researchers should ensure that their research is conducted according to appropriate ethical, legal and professional frameworks, obligations and standards. This includes seeking ethical approval for research where appropriate. Researchers are also expected to treat colleagues with integrity, honesty and collegiality, including the fair provision of references and peer review.

As part of its commitment to the principles of the Concordat, the University will support researchers to maintain the highest standards of integrity in research by:
- providing clear policies and procedures, as well as training and guidance to help researchers better understand how to maintain high standards of research integrity
- having suitable mechanisms for reviewing ethical issues raised by research
- using transparent, robust and fair processes to deal with allegations of research misconduct
- defending researchers who live up to high standards in difficult circumstances and any individual who, in good faith, reports research misconduct at the University
continuing to work to strengthen the integrity of its research through regular review and monitoring of its support, policies and procedures.

The University has a number of policies that relate to research integrity issues. These include:

- Guidelines on Good Research Practice
- Policy on the Ethics of Research Involving Human Participants and Personal Data
- Misconduct in Research Policy
- Policy on the use of Animals in Research and Teaching
- University Financial Regulations
- 'Whistleblowing' Policy
- Policy Against Bribery and Corruption

For more guidance on good research practice and research integrity see:

- RCUK Policy and Guidelines on the Governance of Good Research Conduct
- UK Research Integrity Office guidance documents

Open Access

Our funders require that all papers coming from the Cambridge Stem Cell Institute be made Open Access. In order to comply with their policies, please contact our CSCI Records Assistant, Susana Camacho (sci-records@stemcells.cam.ac.uk) as soon as you have an article accepted for publication.

Susana will assist you with the administrative processes relating to publications, including uploading articles to the University’s repository, compliance with funders’ open access policies and payment of open access charges.

Code of Practice

We expect all students in the CSCI to read and be familiar with the University’s Code of Practice for Research Students:

https://www.cambridgestudents.cam.ac.uk/files/cop_research_1920_final.pdf
CSCI Research Culture – Best Practice for PhD Supervisors

- New supervisors are required to attend the Supervising Graduate Students workshop provided by the University prior to, or within 3 months of accepting their first CSCI PhD Student, and experienced supervisors are encouraged to attend update sessions.
- The Supervisor should have regular 1:1 meetings with the student (monthly in Year 1), and the student should be made aware of the planned meeting schedule. During these meetings, in addition to considering research matters, the Supervisor should pay attention to the general wellbeing of the student.
- The supervisor must ensure that the student is trained in the principles of good research practice and research integrity (as summarised in University guidelines [https://www.research-integrity.admin.cam.ac.uk/research-integrity/research-integrity-and-good-research-practice-checklist](https://www.research-integrity.admin.cam.ac.uk/research-integrity/research-integrity-and-good-research-practice-checklist)) and should reinforce these principles in meetings with the student.
- PhD projects may be closely related to or fall within ongoing projects in the lab, but the student must be given their own area of responsibility with scope to pursue new directions. Extent of delegation of supervision over experiments should be discussed and agreed between postdoc, student and supervisor. The supervisor must ensure the post-doc understands their responsibilities to the student and must monitor the relationship between post-doc and student, intervening if any difficulties arise.
- The student should learn that research involves teamwork. However, after any initial training period, students should not work on studies outside on their thesis project without careful consideration by the supervisor for the impact on PhD quality and completion, and without full consent of the student.
- Students should present regularly at group meetings and receive supervisor feedback on both scientific content and presentation skills.
- Students should be expected to attend all CSCI internal and invited speaker seminars, and relevant external seminars. Students should also be encouraged to participate in relevant journal club(s) and the PhD student discussion club.
- Supervisors are encouraged to use preprint servers when appropriate for early dissemination of student results. Note that this forum may be used flexibly to publish sets of results prior to a final manuscript for journal publication. Preprints provide an opportunity for students to experience manuscript preparation, allow them to receive recognition for their work, and make the work visible to potential employers.
- Supervisors should provide advice and mentoring on future career choices, including opportunities outside academic research.
- Supervisors should advise on timing and planning of thesis writing and should be available to provide feedback on drafts up to and including the final submission.

Policy dated May 2019
Plagiarism: Information for Students

Plagiarism is defined as submitting as one's own work, irrespective of intent to deceive, that which derives in part or in its entirety from the work of others without due acknowledgement. It is both poor scholarship and a breach of academic integrity ([https://www.plagiarism.admin.cam.ac.uk/what-plagiarism/universitys-definition-plagiarism](https://www.plagiarism.admin.cam.ac.uk/what-plagiarism/universitys-definition-plagiarism)). In the context of a first year report or a PhD thesis, this might involve copying text or a figure from another source without giving due acknowledgement to the original source. Even if you paraphrase you should acknowledge this by referencing the original source. Plagiarism is considered unacceptable by the University and can lead to severe penalties.

Students are responsible for ensuring they have read and understood the University’s Statement on Plagiarism, available at [https://www.plagiarism.admin.cam.ac.uk/](https://www.plagiarism.admin.cam.ac.uk/), as well as your own Department’s guidance on plagiarism ([http://www.admin.cam.ac.uk/univ/plagiarism/students/depts.html](http://www.admin.cam.ac.uk/univ/plagiarism/students/depts.html)).

Further information for students can be found at [https://www.plagiarism.admin.cam.ac.uk/what-plagiarism/students-responsibilities](https://www.plagiarism.admin.cam.ac.uk/what-plagiarism/students-responsibilities).

**Turnitin UK**
The University of Cambridge uses Turnitin UK to screen student work. Screening is only generally carried out if concerns are raised about the originality of work, however please check your department’s individual status on this, at the above department policy link. All work screened will be reviewed by the Academic Integrity Officer to determine whether further action may be necessary.

Use of Turnitin UK complies with UK Copyright and Data Protection Laws. Submission to Turnitin does not affect your ownership of the work; the copyright and intellectual property of all work remains with the original owner (normally the student, with the exception of some sponsored research projects). No personal or sensitive data will be transmitted. Work screened by Turnitin UK will be retained in the Turnitin database for comparison with future submissions; if matches are identified, the full text is not accessible to other institutions, only the matching text. You may request that your work is removed from the Turnitin UK database at the conclusion of the examination process, but this must be done separately for each piece of submitted work. Retaining your work on the database will help to ensure that your work remains protected from future attempts to plagiarise it, will help maintain the integrity of the University’s qualifications, and will maximise the effectiveness of the software.

Full details about Turnitin UK and your rights and responsibilities can be found on the University’s website, [www.cam.ac.uk/plagiarism](http://www.cam.ac.uk/plagiarism). Queries about plagiarism or your Department’s use of Turnitin UK, should be addressed in the first instance to your Director of Studies or College Tutor.
JCBC Building Information

Website and Intranet

1. **CSCI Website**: [http://www.stemcells.cam.ac.uk/](http://www.stemcells.cam.ac.uk/)

2. **CSCI Intranet**: [http://www.stemcells.cam.ac.uk/](http://www.stemcells.cam.ac.uk/) then click Log in. Accessed via your Raven login (accessible to CSCI members only), it contains useful staff-only information including a contacts directory for CSCI staff members, useful forms and templates.

Fire Alarm Tests

JCBC fire alarm testing takes place every Thursday at 10:00am.

Travel / Training expenses

Your student grant includes an allowance for travel and training related to your course. If you would like to attend a meeting/conference in year 1 please email Dr. Hendrich, providing him with all the details of the meeting and a short justification of why you want to attend. For meeting/conference attendance in years 2-4, you should obtain authorization from your PhD supervisor.

You can contact the finance team (sci-grants@stemcells.cam.ac.uk) to check on your current budget and for instructions on claiming the funds back. In most cases you will be required to make the payment yourself, then claim the funds back afterwards via an expense claim form.

Photocopying and Printing

There is a printer/photocopier located on each floor of the JCBC. Please speak to the IT team, support@cscr.cam.ac.uk if you need assistance with the printers.

During your first rotation year, you should have access to the printer/photocopier located nearest to your rotation lab. Your College will also have printing facilities.

Binding your Reports

Binding materials for your student reports (i.e. cover/backing sheets, binding combs) can be obtained from Jo Jack. The binding machine is located in the JCBC admin office on the ground floor.

Reception

The JCBC Building reception is open **Mon - Fri, 08:30-17:00**. If you are expecting a visitor please let the receptionist know, and make sure you are available when they arrive. If you have visitors arriving out of reception hours, it is your responsibility to meet them in reception.

Stationery

Standard stationery items can be obtained from the Goods-in team, on the ground floor at the rear of the JCBC. For more specialist items, please speak to your supervisor/lab manager to place an order.

Canteen

The JCBC canteen is open **Mon-Fri, 07:30 – 16:00**. There is also a shared kitchen located on each floor.

Meeting Rooms

The JCBC has a number of meeting rooms available to use in different layouts and sizes. There are meeting rooms on all floors of the building but only the rooms on the Ground Floor and levels 1, 2 and 3 are bookable by members of the Stem Cell Institute (meeting rooms on Levels 4 / 5 are for CITIID).
All rooms are equipped with AV equipment for presentations. Rooms are booked via the **Booker system** using your Raven login: [https://booker.eventmapsolutions.com/Account/Login](https://booker.eventmapsolutions.com/Account/Login)

**Holiday**
The University holiday year runs from 1st October - 30th September. For Graduate students, holiday should only be taken outside of the academic term dates (you **cannot** take holiday during your rotation periods) and not on any of your report/presentation deadlines, event dates etc. **(be sure to check your course schedule before arranging holiday)**. Holiday must be agreed by your current PhD supervisor or Dr. Hendrich.

**Sickness / Absence**
If you are unable to come in, you must contact your rotation / PhD supervisor as soon as possible.

If you are unable to attend one of the Discussion Course sessions, you must inform Jo Jack by email as soon as possible. Should we receive a number of apologies, it may be necessary to cancel the session, and is important that we inform the session leader(s) urgently so as not to waste their time.

**Safety & Security Information**

This basic information is in addition to the ‘**CSCI Safety Manual**’, which you have also been issued with.

**Building Access**
Your college will issue you with a University ID card. Once you have attended the JCBC building induction, this ID card will be programmed to give you access to the JCBC. Access to other departments (for rotations with affiliate labs for example) must be arranged by yourself via those buildings.

**Emergency Procedures**
Trained first aiders are on hand to provide immediate first aid. Contact telephone numbers are displayed on notice boards throughout the building and on the intranet.

University Security provide 24-hour operation and can be contacted as follows:

- **Routine calls**: 01223 (3)31818
- **Emergencies**: 101 or 01223 (7)67444

**Working Out of Hours**
Out of hours is defined as **before 07:00 and after 19:00 Monday to Friday** and **all day Saturday, Sunday and Bank Holidays**. When this is operationally necessary, research groups and facility managers must provide adequate supervision, communication and contact arrangements. **The worker must sign the out of hour’s sheet located in reception**.

Contact security in the event of an incident:

- **Routine calls**: 01223 (3)31818
- **Emergency calls - internal**: 101
- **Emergency calls - external**: 01223 767444
About the Safety Course

The Safety Office runs an ‘Introduction to Health & Safety in the University’ each October, which is mandatory for all new graduate students in science-based Departments/Institutes.

This is supplemented with the JCBC building talk to ensure you are familiar with local procedures.

Information about the Safety Course is sent directly to graduate students by the Safety Office.

Day One: Graduate Safety Course (General Safety)
Tuesday 8th October 2019
Babbage Lecture Theatre, New Museums Site, Pembroke Street

- Attendance at the General Safety session is mandatory.
- You must arrive at least 15 minutes before the event. Late arrivals will not be admitted.
- See https://www.safety.admin.cam.ac.uk/training/graduate-safety-course for details.

Day Two: Graduate Safety Course (optional sessions)
Wednesday 9th October 2019
Mill Lane Lecture Rooms, Cambridge

- CSCI students MUST attend all 3 sessions highlighted “green” in the list below.
- You can attend as many other sessions as you wish.
- Sessions start promptly at the advertised times. Late-comers will not be allowed in.

Choosing which sessions to attend
- ‘Safe Use of Pipettes & Computers’
- ‘Biological Safety’ (for people working with micro-organisms)
- ‘Glass and Sharps Hazards’ (for anyone working in the laboratory)
- 'Working with Ionising Radiation'
- ‘Laser Safety’
- ‘Cryogenic Safety’ (for anyone working with cryogenic gases (liquid or solid))
- ‘Pressurised Gas Safety’ (for anyone using cylinder gases)
Graduate School of Life Sciences (GSLS)

As a student on this PhD Programme, you are a member of the Graduate School of Life Sciences. For more information about the GSLS, visit: https://www.gradschl.lifesci.cam.ac.uk/

The GSLS provide many resources for students, including:

**Researcher Development**

Take a moment to visit the RD website at https://www.rdp.cam.ac.uk/research-students

**What is Researcher Development?**

Researcher Development (RD) encompasses all of the learning and development that you might wish to experience and acquire during your time in Cambridge. It will provide you with the skills and experiences that you need as a professional researcher, both today for your degree, and for the future, whatever that might be!

The Cambridge Researcher Development Framework (CamRDF) presents these skills as 15 core competencies. You can use the CamRDF to explore why these skills are helpful for a researcher, understand what they look like in the real world and point you towards how you can further develop them. Examples include:

- Personal Skills e.g. Leadership and Resilience
- Core Skills Training Programme
- Professional Skills e.g. Presentation Skills and Time management
- Career-related Skills e.g. Writing CVs and Interview Technique
- Academic Skills e.g. Paper writing and Teaching
- Entrepreneurial Skills e.g. Commercial Awareness and Innovation

**The Core Skills Training Programme (CSTP)**

The Graduate School of Life Sciences (GSLS) has developed a Core Skills Training Programme (CSTP), which you are strongly recommended to complete in your first year. Completing the CSTP will ensure that you are informed of the range of RD opportunities available in Cambridge and provide the foundational skills in personal effectiveness and scientific communication that are essential for progression.

You will be enrolled onto the CSTP Introductory Moodle in early October, which can be accessed from your dashboard at www.vle.cam.ac.uk with your Raven login. This will provide you with all the information you need about the components of the CSTP. The first is the online Skills Analysis Survey, which introduces you to the CamRDF, helps you identify your training needs, and allows you to create a personal development plan. The other components will be available from November and you will receive regular updates by email.

**Completing the CSTP**

Completion of the CSTP is sufficient for the training requirements that are assessed in your First Year Report. We will track your engagement, update your department on your progress and present you with a certificate when you finish the CSTP. You should also maintain a training log of other activities that contribute to your professional development, and be aware of any department-specific requirements.
Useful CSCI Admin Contacts

These staff members can be found in the Jeffrey Cheah Biomedical Centre admin office (Ground Floor).

<table>
<thead>
<tr>
<th>Cambridge Stem Cell Institute: Admin Contacts:</th>
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</table>
| **Graduate Administrator, sci-phd@stemcells.cam.ac.uk** | Jo should be your first point of contact, but especially for:  
○ Your course schedule, rotations, student events, discussion course etc.  
○ PhD mailing list  
○ Updates to your studentship, i.e. extensions, changes to funding etc.  
○ Expense claims |
| **Principal Technician, slh60@cam.ac.uk** | Contact Steph regarding:  
○ Equipment issues  
○ Health & Safety issues (lab or general building) |
| **Research Grants Administrator, sci-grants@stemcells.cam.ac.uk** | Contact Paul regarding:  
○ Your studentship grant, incl. travel, training, consumables etc. |
| **HR Administrator, hr@cscr.cam.ac.uk** | Contact Edita regarding:  
○ stipend payment information  
○ studentship extensions |
| **Public Engagement Manager, scipe@stemcells.cam.ac.uk** | Contact Becky to:  
○ Get involved in CSCI public engagement & outreach activities  
○ Tell her about PE activities you’ve done outside of the CSCI |
| **Records & Data Assistant, sci-records@stemcells.cam.ac.uk** | Contact Susana to:  
○ Notify her of new publications/reviews/other outputs from your lab  
○ Get assistance with administrative processes regarding your publications  
i.e. compliance with funders’ open access policies, uploading articles to the University’s repository, payment of open access fees.  
○ Your Symplectic profile |
### Useful University links for students:

<table>
<thead>
<tr>
<th>Link Name</th>
<th>URL</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Student Registry</strong></td>
<td><a href="http://www.student-registry.admin.cam.ac.uk/">http://www.student-registry.admin.cam.ac.uk/</a></td>
</tr>
<tr>
<td><em>(Information for current students)</em></td>
<td><a href="http://www.cambridgestudents.cam.ac.uk/">http://www.cambridgestudents.cam.ac.uk/</a></td>
</tr>
<tr>
<td><strong>CamSiS</strong></td>
<td><a href="http://www.camsis.cam.ac.uk/cam-only/log_in_students/">http://www.camsis.cam.ac.uk/cam-only/log_in_students/</a></td>
</tr>
<tr>
<td><em>(‘Self-Service’ student area)</em></td>
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<tr>
<td><strong>International students</strong></td>
<td><a href="http://www.internationalstudents.cam.ac.uk/">http://www.internationalstudents.cam.ac.uk/</a></td>
</tr>
<tr>
<td><strong>Student Counselling Service</strong></td>
<td><a href="http://www.counselling.cam.ac.uk/studentcouns/students">http://www.counselling.cam.ac.uk/studentcouns/students</a></td>
</tr>
<tr>
<td><strong>University Map</strong></td>
<td><a href="http://map.cam.ac.uk/">http://map.cam.ac.uk/</a></td>
</tr>
<tr>
<td><strong>Stem Cell Institute Website</strong></td>
<td><a href="http://www.stemcells.cam.ac.uk/">http://www.stemcells.cam.ac.uk/</a></td>
</tr>
<tr>
<td><strong>Graduate School of Life Sciences (GSLS)</strong></td>
<td><a href="http://www.gradschl.lifesci.cam.ac.uk/GSLSRD/RDBIDS/DATES">http://www.gradschl.lifesci.cam.ac.uk/GSLSRD/RDBIDS/DATES</a></td>
</tr>
<tr>
<td><strong>Thesis submission information</strong></td>
<td><a href="http://www.cambridgestudents.cam.ac.uk/your-course/examinations/graduate-exam-information/submit-and-examination/phd-msc-mlitt/submit">http://www.cambridgestudents.cam.ac.uk/your-course/examinations/graduate-exam-information/submit-and-examination/phd-msc-mlitt/submit</a></td>
</tr>
<tr>
<td><strong>Student complaints procedure</strong></td>
<td><a href="www.studentcomplaints.admin.cam.ac.uk/student-complaints">www.studentcomplaints.admin.cam.ac.uk/student-complaints</a></td>
</tr>
</tbody>
</table>