SWBio DTP Project Call for intake 2020: standard studentships

Response ID	Start date	Completion date
405379-405370-49903913	9 Sep 2019, 11:14 (BST)	9 Sep 2019, 11:31 (BST)

1	Submitting institution:	University of Bath

2	Please list the main and second supervisor:	
2.1	Main supervisor	
2.1.a	Title	Dr
2.1.b	Name	Mirella Di Lorenzo
2.1.c	Affiliation	University of Bath
2.1.d	E-mail address	m.di.lorenzo@bath.ac.uk
2.1.e	Eligible to act as the listed supervisor	Yes
2.1.f	Any comments	
2.2	Second supervisor	
2.2.a	Title	Dr
2.2.b	Name	Lucia Marucci
2.2.c	Affiliation	University of Bristol
2.2.d	E-mail address	lucia.marucci@bristol.ac.uk
2.2.e	Eligible to act as the listed supervisor	Yes
2.2.f	Any comments	

3	Project title:	Automated T-cell expansion in an integrated bioelectronics microfluidic chip: paving the way for personalised T-cell therapies for blood cancer

4	Research area: Please indicate the BBSRC research area that is most appropriate to your project. Further information about these research areas can be found by clicking on the below link.	Frontier bioscience

5	Research theme: As part of the DTP, all projects are also assigned to 3 research themes (listed below). Please indicate the one research theme that is most appropriate to the project:	Biophysical and Biomolecular Studies
5.a	Please list any secondary themes	Biophysical and Biomolecular Studies

6	Keywords (maximum of 5 - please include the relevant disciplines for the project):	Biosciences –personalised therapeutics– mathematical biology – microfluidics – control algorithms

7	Technical description of project for selection panel (400 words maximum):	Personalised and advanced therapeutics have the potential to transform the precision of healthcare interventions. For this potential to be realised, however, novel approaches to personalised therapeutic manufacture are required to overcome significant economic and technological challenges. Current manufacturing systems are designed with the 'one-size-fits-all' approach, which is not suitable for patient-specific healthcare applications. Our long-term vision is to redefine the manufacture of cell-based therapeutics through the development of a self-regulated on-body micro-manufacturing and processing facility. With this focus in mind, we propose a highly interdisciplinary PhD project, which, by combining engineering with life science, material chemistry mathematics and physics, will develop an innovative bioelectronic device for cell culturing with integrated sensing capability. We will employ the T lymphocyte cell (T-cell) immunotherapy application as an exemplar. This choice was made given the promising curative potential of T-cells for some of the most aggressive forms of cancer, including Acute Lymphoblastic Leukaemia. The following objectives have been designed: Objective 1: Electrochemical monitoring and control of T-cell growth and proliferation. The T-cells will grow onto gold electrodes functionalised with 3D macroporous scaffolds of a conducting polymer, such as poly(3,4-ethylenedioxythiophene (PEDOT), functionalized with collagen to promote cell attachment and proliferation. The presence of cells within the porous architecture affects the impedance of the electrically conducting polymer network. Therefore, impedimetric measurements will be performed to monitor in situ cell growth and viability. This methodology will be also used to investigate the effect of electrical stimulation (i.e. application of a fixed potential to the system) on cell proliferation and will be validated by cell counting and using cell tracker dyes (flow cytometry and microscopy). The 3D polymeric scaffold will be embedded in a microfluidic channel to allow media perfusion, homogenous cell spreading and hence long-term cell viability. Objective 2: Automatization of T-cells culturing. Closed-

		loop, control algorithm approaches will be used to optimise, automatically, T-cell growth (control output) while varying the cell culture conditions (control input); the information gained will be used to refine current protocols for T-Cell expansion. The existing personalised T-cell immunotherapies are time consuming (requiring up to 21 days), with poor levels of process control and limited yields. With this project we aim to develop an innovative engineering system to ensure robust, reproducible and consistent manufacture of T-cells, reduce the culture time, minimise the risk of failure and ultimately facilitate personalised therapeutics.

8	General description of project for advertising (400 words maximum):	The future of healthcare and advanced therapies will shift toward the delivery of more precise, personalised medicines, where patients are treated as individuals rather than receiving single 'one-size-fits all' treatment. The patient will be at the centre of the healthcare system with tailored solutions that adapt to individual patient needs. Nevertheless, unless novel manufacturing systems are developed, this scientific potential will not be realised. Current manufacturing systems are not suitable for patient-specific healthcare applications, as they are incapable of delivering therapies of sufficient precision and quality. Supervised by an interdisciplinary team of academics, with expertise at the interface of Engineering, Material Science, Life Sciences with Stem Cell Biology, the PhD student carrying out the proposed research will develop an innovative platform for monitoring and controlling, in real time, mammalian cell (specifically T lymphocyte) proliferation and growth. This platform will allow the automation and refining of T cells culture conditions; thanks to an enhanced precision, robustness and control of the process, outcomes of this project could markedly advance the manufacture of cell-based therapies. The project outputs can impact additional fields of research including, but not limited to, biosensing, drug delivery and other stem cell/immunotherapy bioprocesses. At its core, the innovation of this project lies at the interface between multiple disciplines that allows to combine, for the first time, novel biomanufacturing with electronic engineering and mathematics, to develop a T-cell manufacturing platform for robust treatment of chronic, life-threatening and debilitating conditions, such as cancer.

9	BBSRC regard impact as an important and automatic consideration of any research they fund. As such, please very briefly highlight the anticipated impact of the research you propose, including noting any consultations you may have undertaken with stakeholders (2 bullet points maximum).	By working intimately at the interface between engineering, mathematics, biology, chemistry and electrochemistry, this project will pioneer the development of new skills necessary for the 21st century, integrating core concepts of biological and life sciences with mathematics and engineering for advanced therapy production. The PhD student will therefore have a unique skill set of expertise and the ability to integrate all these different disciplines together to face the challenges of developing the next generation of personalised T-cells based therapies. Ultimately, the key beneficiaries of this project will be patients, as this project can pave the way to significant advancement in the field of targeted and personalised medicines, providing a step change over existing 'one-size-fits-all' therapeutics that are currently administered. Developing a transformative manufacturing system for personalised medicines will also have a significant impact on the UK high-value healthcare manufacturing industry. This project complements with activities undertaken by the Precision Medicines and Cell and Gene Therapy Catapults. These organisations also offer a potential vehicle to translate the research beyond the proof-of-concept stage reached by the end of the project. Other key beneficiaries in the long terms will be industry and the commercial sector, interested in the development of personalised, advanced cell therapies. This includes blue-chip companies like GSK, Pfizer and Novartis in addition to SMEs, such as Autolus, Orchard Therapeutics and ReNeuron.

10	Others in supervisory team	
10.1	Second local supervisor (if the listed second supervisor in Q2 is based in a different institution)	
10.1.a	Title	Dr
10.1.b	If you selected Other, please specify:	
10.1.c	Name	Sandhya Moise
10.1.d	Affiliation	University of Bath
10.1.e	If you selected Other, please specify:	
10.1.f	E-mail address	sm2874@bath.ac.uk
10.2	Supervisor 1	
10.2.a	Title	Dr
10.2.b	If you selected Other, please specify:	
10.2.c	Name	Despina Moschou

10.2.d	Affiliation	University of Bath
10.2.e	If you selected Other, please specify:	
10.2.f	E-mail address	dm855@bath.ac.uk
10.3	Supervisor 2	
10.3.a	Title	
10.3.b	If you selected Other, please specify:	
10.3.c	Name	
10.3.d	Affiliation	
10.3.e	If you selected Other, please specify:	
10.3.f	E-mail address	
10.4	Supervisor 3	
10.4.a	Title	
10.4.b	If you selected Other, please specify:	
10.4.c	Name	
10.4.d	Affiliation	
10.4.e	If you selected Other, please specify:	
10.4.f	E-mail address	
10.5	Supervisor 4	
10.5.a	Title	
10.5.b	If you selected Other, please specify:	
10.5.c	Name	
10.5.d	Affiliation	
10.5.e	If you selected Other, please specify:	
10.5.f	E-mail address	

11	Collaborators	
11.1	Collaborator 1	
11.1.a	Title	
11.1.b	If you selected Other, please specify:	
11.1.c	Name	
11.1.d	Affiliation	
11.1.e	If you selected Other, please specify:	
11.2	Collaborator 2	

11.2.a	Title	
11.2.b	If you selected Other, please specify:	
11.2.c	Name	
11.2.d	Affiliation	
11.2.e	If you selected Other, please specify:	
11.3	Collaborator 3	
11.3.a	Title	
11.3.b	If you selected Other, please specify:	
11.3.c	Name	
11.3.d	Affiliation	
11.3.e	If you selected Other, please specify:	
11.4	Collaborator 4	
11.4.a	Title	
11.4.b	If you selected Other, please specify:	
11.4.c	Name	
11.4.d	Affiliation	
11.4.e	If you selected Other, please specify:	

12	Details of potential rotation projects:	
12.1	Rotation project 1 (Sept-Mar, part-time)	
12.1.a	Rotation project supervisor (only one supervisor to be listed)	Mirella Di Lorenzo
12.1.b	Role in supervisory team	Main supervisor
12.1.c	Location of rotation project	University of Bath

12.1.d	Brief details (200 words maximum)	Design of microfluidic platforms for T-cells growth The student will receive 2-weeks training on the fundamentals of T-cells culturing by working together with other team members in Dr Moise's group. Following this, they will receive training on the fabrication and handling of microfluidic devices, along with fluid dynamics studies supervised by team members in Dr Di Lorenzo's and Dr Moschou's teams. These training will be followed by pilot experiments to familiarise with the learn concepts over a period of 4 weeks.
12.1.e	Have you identified additional support to cover accommodation/travel costs if the £1k budget is exceeded.	Yes
12.2	Rotation project 2 (Apr-Jul, full-time)	
12.2.a	Rotation project supervisor (only one supervisor to be listed)	Lucia Marucci
12.2.b	Role in supervisory team	Second supervisor
12.2.c	Location of rotation project	University of Bristol

12.2.d	Brief details (200 words maximum)	Design of segmentation and closed-loop control algorithms The student will firstly receive 4 weeks training on the design of segmentation algorithms. S/he will both implement Otsu based segmentation algorithms, and then move to deep-learning based algorithms. The student will test the segmentation performance on images of T-cells cultured in the microfluidics device developed in the first rotation project, and imaged within the Wolfson Bioimaging Facility (University of Bristol). This will be followed by training in feedback control algorithms (e.g. Relay, PD, Model Predictive Control –MPC- and adaptive MPC algorithms). Pilot experiments to test the effectiveness of simple control strategies for cell proliferation control while varying cell culture conditions (i.e. media composition), combined with online segmentation during time-lapse, will be performed. Finally, the student will work towards the design of a platform for directly controlling changes in the impedance, instead of proliferation; this will involve refinements of the control output quantification, actuation strategy and control inputs specification.
12.2.e	Have you identified additional support to cover accommodation/travel costs if the £1k budget is exceeded.	Yes

13	Project fit (/10): Briefly describe how your project meets these criteria:
13.1	Fits within current BBSRC remit (Frontier bioscience; Bioscience for sustainable agriculture and food; Bioscience for an integrated understanding of health)

13.1.a	-	This project will develop novel platform for the control of T-cell growing that can overcome the limitation of current manufacturing strategies. The platform will also provide an understanding on T-cell growth and viability on chip, which is paramount for pharmacology, synthetic biology and systems biology related research including the enhancement of T-cell therapies that can be targeted to the patient. Therefore, the project fits very well with the “Frontier Bioscience” and “Bioscience for an integrated understanding of health” remits involving the development of novel tools and modelling to underpin biological research. The student involved will get broad-based training in T-cell culturing, bio-electrochemistry, microfluidics and control engineering
13.2	Interdisciplinarity	
13.2.a	-	The intrinsic interdisciplinary nature of this project will expose the student to different research fields, including life science, bio-electrochemistry, microfluidics, cells imaging and feedback control algorithms. Not only the methodologies proposed are innovative, but also their combination has never been attempted, and can lead to unprecedented improvements on cell manipulation, due to the continuous and real-time monitoring of T cells that will be achieved. This demonstrates that the proposed team of supervisors can work well together despite coming from different departments and backgrounds. As a consequence, the student will learn and use a wide range of techniques and acquire a unique skill set that will be very valuable for their future career either in or outside academia.
13.3	Research is underpinned by a mathematical approach	

13.3.a	-	Closing the loop on T-cell culturing will be underpinned by mathematical and data-analysis methodologies. The student will gain training in closed-loop control algorithms; this will involve both the synthesis of control algorithms and, where needed, the derivation of mathematical models. Furthermore, the student will gain expertise in data analysis, including quantification via segmentation algorithms of time-lapse imaging data. The student, while gaining programming skills in Matlab and Python, will acquire skills in state-of-the-art deep learning-based methods and control algorithms (e.g. adaptive MPC) for cell segmentation and control, that could be used for other cell types and systems. The use of feedback control strategies to control mammalian cells using microfluidics, pioneered by the co-supervisor Dr Marucci (who recently awarded an EPSRC Fellowship on this topic) is novel, and promises to aid in the design and improvement of cell culture protocols.
13.a	All of the above criteria are essential, but in addition please identify if your project meets any of the following desirable criteria:	
13.a.1	Within a BBSRC responsive mode priority area (see below)	
13.a.1.a	-	This project falls into multiple BBSRC priority areas, including: “Data-driven biology”; “New strategic approaches to industrial biotechnology biology”; “Synthetic biology”; “Systems approaches to the biosciences”; and “Technology development for the biosciences”.
13.a.2	Involves ‘in vivo’ and/or niche skills (see below)	
13.a.2.a	-	9. bioscience: physics interdisciplinarity; 10. research software engineering

14	Research environment (/10): Please specify how many postdocs/fellows and other graduate students are in the supervisor's research group:	
14.1	Main supervisor	
14.1.a	Post docs/fellows	3
14.1.b	Other graduate students	3 PhDs 2 Master Students
14.2	Second supervisor	
14.2.a	Post docs/fellows	2 (Marucci)
14.2.b	Other graduate students	PhDs: 6 (Marucci), 4 (Moshou), 1 (Moise)
14.a	For the main and second supervisor, please list:	

14.a.1	Current BBSRC grants (title, applicants making clear whether as the PI or Co-PI, amount, start and finish dates):	
14.a.1.a	Main supervisor	none
14.a.1.b	Second supervisor	none
14.a.2	Any previous BBSRC grants active in the past 5 years (title, applicants making clear whether as the PI or Co-PI, amount, start and finish dates):	
14.a.2.a	Main supervisor	none
14.a.2.b	Second supervisor	Marucci: 07/2014-06/2019 BBSRC/EPSRC BrisSynBio (BB/L01386X/1) “Harnessing synthetic oscillators” and “Orthogonal components for controlling gene expression”. Total grant for BrisSynBio £13,794,610, Co-I 07/2018-06/2019 Bristol BioDesign Institute “Big ideas in BioDesign” (BBSRC/EPSRC, BB/L01386X/1) “Next-generation agent-based model featuring diverse and dynamic cell morphologies” £138,633, co-I 05/2018-06/2019 Bristol BioDesign Institute “Big ideas in BioDesign” (BBSRC/EPSRC, BB/L01386X/1) “Combating Stroke with Astrocyte-Mimetic Designer Cells” £129,326, co-I
14.a.3	Other current funding. Only list awards over £40k. (Do not include studentship funding unless it is externally and competitively awarded specifically to the project supervisor(s):	

14.a.3.a	Main supervisor	2019-2020 SmARTER: Sustainable Approaches for Resilience Building in North-East Brazil. Resarch England, £120,000, PI 2018-2021 GREENER: InteGRated systems for Effective ENvironmEntal Remediation, CE-BIOTEC-04-2018 Horizon2020, € 5 M, co-I 2017-2020 OMMS: Optimising Me Manufactoring Systems, EPSRC, £1,800,000, co-I 2015-2019 Vaccinating the Nexus, EPSRC, £1,581,410, co-I
14.a.3.b	Second supervisor	Marucci: LM: 10/2019-09/2024 EPSRC Early Career Fellowship" (EP/S01876X/1) "COMBO: control-based biodesign of mammalian cell dynamics" £1,478,669, PI 02/2018-12/2019 EPSRC "Engineering for a prosperous nation" (EP/R041695/1) "Automatic cell fate engineering using microfluidics devices" £310,368, PI 09/2016-03/2020 MRC New Investigator Award (MR/N021444/1) "Unravelling the role of beta-catenin in ground state pluripotency". £518,777, PI 10/2017-09/2020 Horizon 2020 FET-Open action "Control Engineering of Biological Systems for Reliable Synthetic Biology Applications" €2,996,856 total (€298,195 to UoB). co-I.

15	Supervisory team (/5): For the main and second supervisor, please specify:
15.1	Main supervisor

15.1.a	Number of PhD students completed in past 10 years (please include whether as a main or second supervisor)	6 (of which 3 as a second supervisor)
15.1.b	Number of PhD students withdrawn in past 10 years (please include whether as a main or second supervisor)	0
15.1.c	Of these, number who have submitted theses within 4 years of registration (please include whether as a main or second supervisor)	all
15.1.d	Of these, number who have submitted theses beyond 4 years of registration (please include whether as a main or second supervisor)	none
15.1.e	Number of previous/current SWBio DTP students (please include whether as a main or second supervisor)	none
15.2	Second supervisor	
15.2.a	Number of PhD students completed in past 10 years (please include whether as a main or second supervisor)	Marucci: Completed 5 –2 thesis submitted waiting for Viva, 1 as third supervisor. No students completed for Moise and Moschou as these are two Early Career Academics
15.2.b	Number of PhD students withdrawn in past 10 years (please include whether as a main or second supervisor)	Marucci: 1
15.2.c	Of these, number who have submitted theses within 4 years of registration (please include whether as a main or second supervisor)	Marucci: 3
15.2.d	Of these, number who have submitted theses beyond 4 years of registration (please include whether as a main or second supervisor)	2 –both due to suspension of studies, still submitted by the postponed deadline although beyond 4 years of registration
15.2.e	Number of previous/current SWBio DTP students (please include whether as a main or second supervisor)	none

16	Added value (/5): Please use this space to identify if your project has added value, such as (i) is cross institutional, especially if with our SWBio DTP core partners (Bath, Bristol, Exeter, Cardiff, Rothamsted) and associate partners (MBA, PML, Swansea University, UCB, UWE); (ii) has other external collaborators; (iii) you already have an offer of partial funding (e.g. 50% funding available from another source).	While based in Bath, the student will necessarily need to work in the two institutions (Bath & Bristol) during the whole period of his/her research, which will be carried out in Di Lorenzo's bio-electrochemistry laboratory, Marucci's synthetic biology laboratory, Moschou's microfluidics and electronics laboratory and Moise' mammalian cells'. From the project onset, the student will be immersed in the cross-disciplinary environment the supervisors have already developed both between them and with further collaborators from other disciplines (clinicians, social scientists, pharmacists). Transferable skill development will be further facilitated through both Universities' research training programs. Personalized therapeutics is an inherently cross-disciplinary field, requiring a broad range of expertise from biology and biomaterials to biosensing and microsystems engineering. Hence, future academic and industry researchers need to build on their fundamental knowledge in one of these areas, but also expand their skillset and expertise to the other disciplines. Soft-skill development concerning cross-disciplinary research is also essential, since effective communication and collaboration with experts of diverse backgrounds is required on a day-to-day basis. In this project the student will gain core technical skills in stem cell culturing, bio-electrochemistry, microfluidics and control engineering. Therefore, the output of this project will constitute the basis for several different bids to the BBSRC including both standard and IPA/Link responsive mode grants as well as CASE studentships. Finally, the PhD student working on this project will receive a uniquely interdisciplinary training spanning from biophysics to chemistry, from mathematics to bioelectrochemistry, and T-cell biology.

Supporting the DTP in the past

17	Please indicate how you have supported the DTP through teaching or marking as part of the taught first year? This is in addition to what is normally expected from a main/second supervisor (refer to the Supervisor Handbook >>). Please only indicate when the teaching has been provided specifically for the SWBio DTP students.	
17.1	Main supervisor	
17.1.a	Unit	
17.1.b	Details	so far no support but willing to be involved
17.2	Second supervisor	

17.2.a	Unit	
17.2.b	Details	so far no support but willing to be involved

Supporting the DTP in the future

18	Please indicate how you could support the DTP in the future through teaching or marking. This is in addition to what is normally expected from a main/second supervisor (refer to the Supervisor Handbook >>)	
18.1	Main supervisor	
18.1.a	Unit	
18.1.b	Details	
18.2	Second supervisor	
18.2.a	Unit	
18.2.b	Details	

19	In addition, there are a number of core roles which support the running of the SWBio DTP. If you would be interested in being considered for one of these core roles in the future, please indicate below:	
19.1	Main supervisor	
19.1.a	Role	• Research Theme Champion • Implementation Group representative
19.1.b	Details	
19.2	Second supervisor	
19.2.a	Role	• Research Theme Champion • Unit Director (only University of Bristol staff eligible) • Management Group representative • Implementation Group representative
19.2.b	Details	