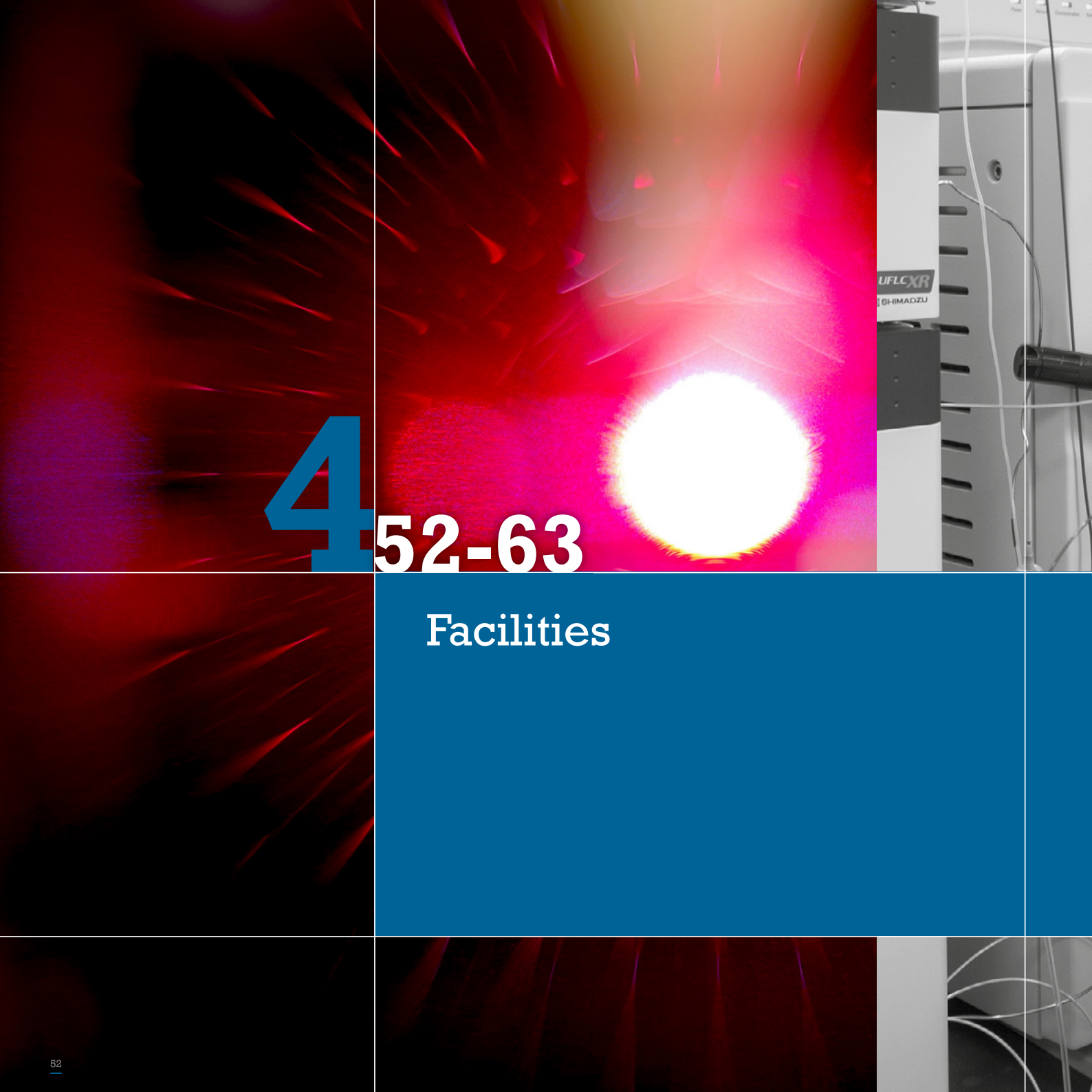


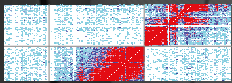
2019/20

Babraham Institute
Annual Research Report
Facilities



452-63

Facilities



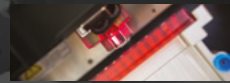
Bioinformatics



Biological Chemistry



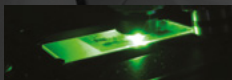
Biological Support Unit



Flow Cytometry



Gene Targeting



Imaging



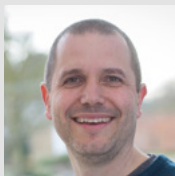
Lipidomics



Mass Spectrometry



Sequencing



Simon Andrews
Facility head

Facility members

Biological statistician:
Anne Segonds-Pichon

Bioinformaticians:

Laura Biggins
Christel Krueger
Felix Krueger
Louise Matheson
Steven Wingett
(Left in 2020)

Lipid Maps web developer:

Caroline Gaud

Training developer:

Jo Montgomery

Bioinformatics

The Bioinformatics facility exists to support the Institute's research groups in the analysis, processing and organisation of their research data. We do this in a number of ways including providing a large compute cluster and an associated suite of software tools. We train scientists in the latest computational techniques and tools and we provide a consultancy service where we can either advise researchers or perform analysis on their behalf.

Capabilities

- An 800 node compute cluster with an extensive collection of bioinformatics software and pipelines.
- An extensive modular portfolio of bioinformatics training courses targeted at biologists.
- A range of custom software, including software focused on next generation sequencing, data visualisation and quality control.
- Experience in the processing, management and analysis of large biological data sets.

Progress in 2019 and 2020

We have continued to work on a wide range of projects covering all of the major research areas at the Institute. We have developed new capabilities in the analysis of single cell data and in data from the Institute's nanopore sequencer. These techniques allow for a more complete analysis of gene activity in biological systems. We have developed our existing suite of software to support new epigenetics techniques such as slamSeq and singleShot and have worked on integrating results from more complex

experimental designs covering a variety of different experimental techniques. Our training courses expanded to encompass

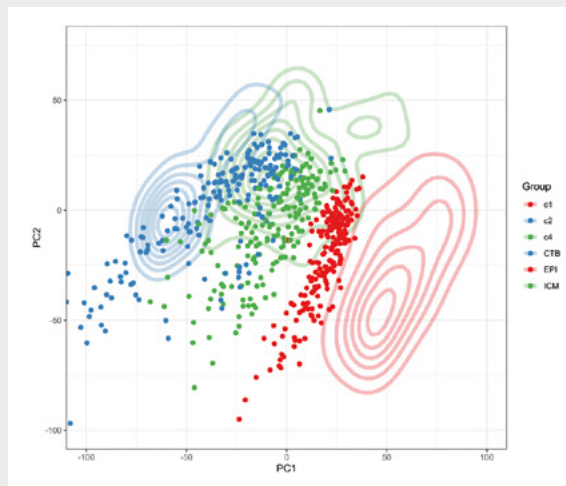
python, R package development, source code management and machine learning.

Selected Impact Activities

- We undertook a major programme of training for AstraZeneca to add to our existing programme for other commercial and academic groups around the world. Our courses can all now be taught remotely using cloud based computational infrastructure.
- We created a series of short online talks 'Bitesize Bioinformatics' to present new and interesting

bioinformatics developments to both the Institute and external organisations.

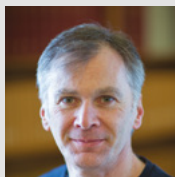
- After a successful in-person event in 2019 we ran the first virtual Cambridge Bioinformatics Hackathon in 2020 attracting over 60 bioinformaticians (from Cambridge and the UK but also internationally) to develop new software and skills.



A comparison of a published single cell dataset with data from Peter Rugg-Gunn's research group, showing that both datasets contain similar cell subtypes.

- Argelaguet, R. *et al.* (2019) Multi-omics profiling of mouse gastrulation at single-cell resolution. **Genome Biol.** 20(1):225
- Wojdyla, K. *et al.* (2020) Cell-surface proteomics identifies differences in signaling and adhesion protein expression between naive and primed human pluripotent stem cells. **Stem Cell Reports.** 14(5):972-988
- Nasrallah, R. *et al.* (2020) A distal enhancer at risk locus 11q13.5 promotes suppression of colitis by Treg cells. **Nature.** 583(7816):447-452





Jonathan Clark
Facility head

Facility members

Postdoctoral research
scientist:
Izabella Niewczas

Biological Chemistry

The Biological Chemistry group provides support for scientists working at the interface between chemistry and biology. We bring an understanding of chemistry and its application to solving biological problems along with the capability to implement our suggestions using chemical and analytical tools.

In addition to our collaborations with the research groups we are investigating

the chemical changes which occur in connective tissues as we age.

Capabilities

- Chemical synthesis of standards and reagents which are not commercially available.
- Analysis of biological molecules by mass spectroscopy.

- Development of new reagents and analytical methods.
- Help and advice on any aspect of the application of chemistry/biochemistry to the exploration of biological problems.

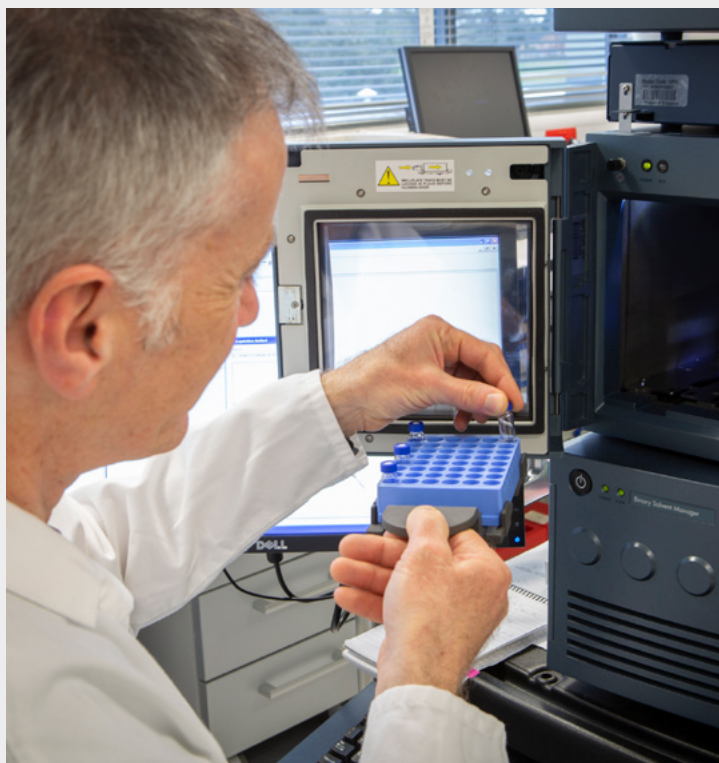
Progress in 2019 and 2020

During 2020 we have continued to supported groups throughout the Institute on a wide range of varied projects. These have ranged from synthetic chemical projects to make compounds which are not commercially available through to developing new analytical methods to analyse lipids in cell extracts. In addition to these activities we have also continued to run routine lipid analysis for a number of groups, both within the Institute and externally.

2020 saw the publication of key results from our research describing how the chemistry of collagen changes dynamically during tendon stretching and the implications for this when considering changes in tendon with age.

Selected Impact Activities

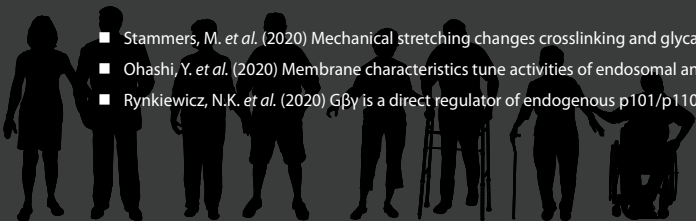
- Through 2020 we have provided phosphatidyl inositide analysis on samples for commercial and external academic groups.
- We collaborate with external academic groups studying the ageing of connective tissue.



Publications

www.babraham.ac.uk/science-services/biological-chemistry

- Stammers, M. *et al.* (2020) Mechanical stretching changes crosslinking and glycation levels in the collagen of mouse tail tendon. *J. Biol. Chem.* 295(31):10572-10580
- Ohashi, Y. *et al.* (2020) Membrane characteristics tune activities of endosomal and autophagic human VPS34 complexes. *eLife*. Jun 30;9:e58281
- Rynkiewicz, N.K. *et al.* (2020) Gβγ is a direct regulator of endogenous p101/p110γ and p84/p110γ PI3Kγ complexes in mouse neutrophils. *Sci. Signal.* 13(656):eaaz4003



Paul Symonds
Co-Facility Head

Marc Wiltshire
Co-Facility Head

Facility members:

- 6 Managers
- 8 Supervisors
- 4 Deputy Supervisors
- 30 Experienced Animal Technicians
- 4 Trainee/Apprentice Animal Technicians
- 4 Support Services Technicians
- 1 Technical Services Technician
- 1 Veterinary Services Manager

Biological Support Unit

The use of animals in research continues to be key in helping to understand biology and disease. The Biological Support Unit provides state-of-the-art housing and care for pathogen-free rodents used in both academic and private company research programmes. Our professionally qualified animal technicians provide expert technical support to researchers by undertaking regulated procedures, maintaining the animal health barrier and undertaking animal husbandry.

Capabilities

- The BSU is made up of four bio-science units, each performing a unique role in the provision of flexible services to meet the dynamic requirements of biological research. Our highly trained animal technicians and service technicians perform daily animal husbandry duties and provide essential services to the facility.
- Our animal technicians hold Home Office Personal Licences enabling us to provide technical support for researchers. We have a commitment to uphold the highest standards of animal welfare in all aspects of our work.
- Our Central Services unit utilises robotic cage-washing technology and automated sterilisation processes to provide equipment and consumables to the bio-science units.

Progress in 2019 and 2020

- The BSU has formed a successful partnership with Avidity Science and become a recognised 'Centre of Research Excellence'. This partnership allows the BSU input and access to the latest technology and R&D discussions. The facility is currently trialling a new drinking valve prior to global launch.
- Working in collaboration with Agenda Life Sciences, the first three apprentice animal technicians all completed the programme and passed their Institute of Animal Technology (IAT) Level 2 qualifications. All three are now continuing their careers in animal care within the commercial sector. Two further apprentice candidates are now undertaking their training within the facility. The facility continues to provide advice to industry on best practice with regards to foundation training, evidence gathering and record keeping.

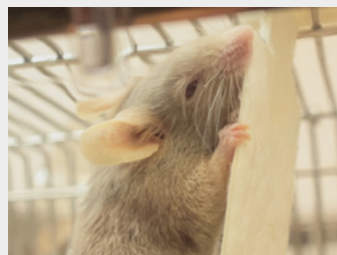


Image courtesy of Datesand.

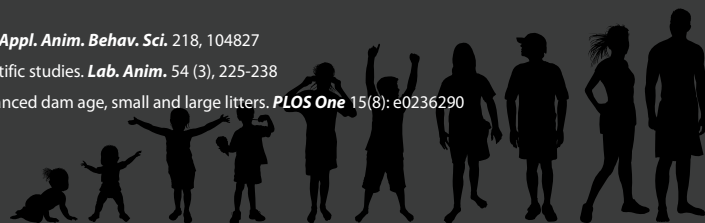
Selected Impact Activities

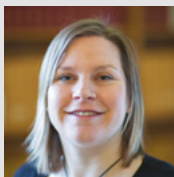
- The CellPad, a new cellulose hanging environmental enrichment for mouse cages, designed by Luke Mercer (BSU employee), was made commercially available in 2020 by Datesand, a developer and supplier of animal welfare and environmental enrichment products. The device is designed to provide environmental enrichment for mice kept in research facilities, while offering several additional benefits such as being low cost, compostable and easily sterilised and stored.
- Having contributed to the IAT syllabus review in 2020, the IAT have now advertised the release of the updated syllabus which will be rolled out in full.
- The BSU co-heads were keynote speakers at the Avidity Science Biomedical Symposium Virtual Event in October 2020. The BSU presented a virtual tour of the facility to a global industry audience, highlighting the unique design features and approaches to animal technology used on the Babraham Research Campus.

Publications

www.babraham.ac.uk/science-services/biological-support-unit

- Brajon, S. *et al.* (2019). Social environment as a cause of litter loss in laboratory mouse: a behavioural study. *Appl. Anim. Behav. Sci.* 218, 104827
- Wilkinson, M.J. *et al.* (2019) Progressing the care, husbandry and management of ageing mice used in scientific studies. *Lab. Anim.* 54 (3), 225-238
- Morello, G.M. *et al.* (2020) High laboratory mouse pre-weaning mortality associated with litter overlap, advanced dam age, small and large litters. *PLOS One* 15(8): e0236290





Rachael Walker
Facility head

Facility members

Deputy manager:
Rebecca Roberts

Flow cytometry specialists:
Attila Bebes (Left in 2020)
Christopher Hall

Flow cytometry technicians:
Isobel Darling
Aleksandra Lazowska-Addy

Flow Cytometry

Flow cytometry is a single cell technology that allows cells to be identified, counted, analysed, and sorted on the basis of specific features including the expression of proteins labelled with fluorescent antibodies. The Flow Cytometry facility provides a number of services to support the work of scientists from both the Institute and external companies. These include an expert cell sorting service, analyser training, help with experimental design, troubleshooting and data analysis.

Capabilities

- Cell sorting service: The facility provides an expert cell sorting service for Institute and external users. A range of sorters in biosafety cabinets allows for a wide range of cell types and experimental designs

to be accommodated. Europe's first Thermo Fisher Bigfoot Spectral Sorter was installed in the facility in August 2020 for beta development.

- State-of-the-art analysers: BD LSRFortessa, Propel Labs YETI, and the Cytek Aurora spectral analyser allow high parameter analysis.
- Image cytometry: The Merck Millipore Imagestream MkII allows quantitative flow cytometry data to be produced with images of each cell.
- Training: The facility delivers modular training courses alongside practical training to enable scientists to use the analysers independently.

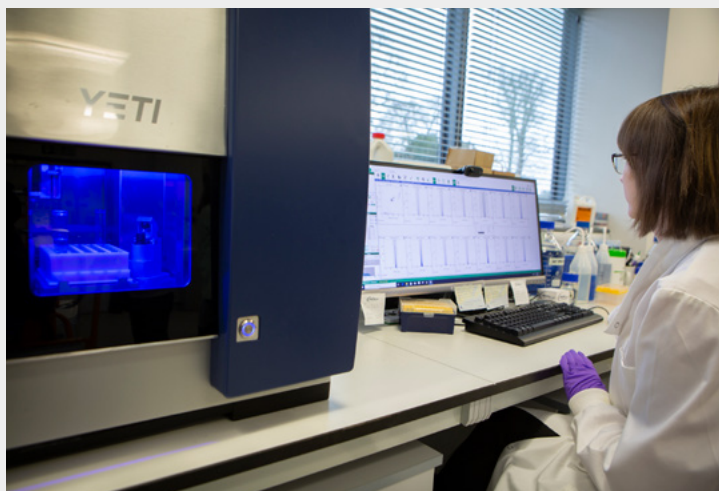
Progress in 2019 and 2020

In 2019, the facility expanded with the acquisition of two BD Jazz sorters. These high-speed sorters have increased capacity

and capability for cell sorts such as large CRISPR screens. A Cytek Aurora Spectral analyser was purchased through a BBSRC Alert-18 grant in 2019, expanding the core's multicolour capabilities. In August 2020, through a collaboration with Propel Labs (now part of Thermo Fisher) a Bigfoot 60 parameter high-speed Spectral Sorter was installed in the facility. The interactive flow cytometry training programme is in its sixth year and has supported nearly 1000 scientists. During 2020, the face-to-face training was adapted into an online virtual format.

Selected Impact Activities

- The Flow Cytometry facility hosted the 2019 flowcytometryUK one day meeting in November 2019, bringing together over 125 delegates from all over the UK and Europe.
- In September 2019, Attila Bebes visited several flow cytometry core facilities in Belgium and the Netherlands, including two in EU-LIFE institutes, to share best practice.
- Rachael Walker organised and co-hosted three virtual flowcytometryUK facility meetings in May, June and July 2020 to establish safe working practices in the COVID-19 era. Each meeting was attended by over 150 delegates from over a dozen countries.

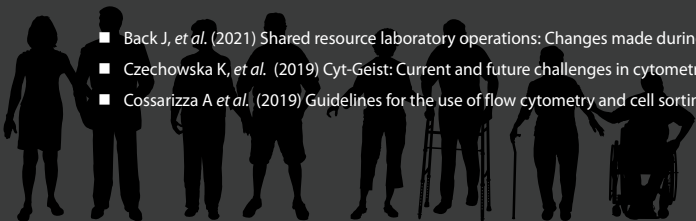


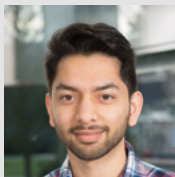
Publications

www.babraham.ac.uk/science-services/flow-cytometry

@babraham_flow

- Back J, *et al.* (2021) Shared resource laboratory operations: Changes made during initial global COVID-19 lockdown of 2020. *Cytometry A*. 99(1):22-32 (E-published Nov 2020)
- Czechowska K, *et al.* (2019) Cyt-Geist: Current and future challenges in cytometry: Reports of the CYTO 2019 conference workshops *Cytometry A*. 95(12):1236-127
- Cossarizza A *et al.* (2019) Guidelines for the use of flow cytometry and cell sorting in immunological studies (2nd edition). *Eur. J. Immunol.* 49(10):1457-1973





Asif Nakhuda
Facility head

Gene Targeting Facility

The main purpose of the facility is to produce new mouse strains for use in the Institute's research, aiding in the design, generation, screening and evaluation of genetic modifications. The facility also provides expertise and guidance on the use of CRISPR/Cas9, including on the design and production of CRISPR reagents such as sgRNA, Cas9 protein and long single-stranded DNA (LssDNA).

Capabilities

- Generation of mouse models: ranging from single nucleotide polymorphisms (SNPs), domain deletions, multiplex gene knockouts and large knock-ins such as Mini-Turbo.
- Guidance in CRISPR/Cas9-based technologies for producing transgenic cell lines and mice.
- High-throughput production of single-guide RNA with efficiency validated in embryos.
- Production of CRISPR/Cas9 reagents such as Cas9 protein and LssDNA.
- Designing strategies for Gibson assembly and recombineering in bacterial artificial chromosomes (BACs) for complex constructs.
- Advice on reagents based on mechanisms of DNA repair, such as single-strand template repair, microhomology mediated end-joining and homologous recombination.
- High-throughput screening of gene-edited cell lines using Next Generation Sequencing.

Progress in 2019 and 2020

Since re-establishing the facility in 2019, the facility has supported the Institute's researchers in achieving desired genome modifications in cell lines and mice. The facility specialises in using Cas9-sgRNA ribonucleoprotein combined with electroporation to target various cell types, and we share our methodologies with groups across the Institute to help optimise their gene editing experiments. Also, for generating mouse models, the facility has optimised electroporation and microinjection protocols for embryos. During 2020, the facility has made three new mouse lines and multiple loss-of-gene-function embryos. These new lines were made without using embryonic stem cells, meaning that mouse models can

be delivered in a shorter time frame and overall using fewer mice in the process. We have also developed protocols to make in-house Cas9 protein and other Cas9 variants.

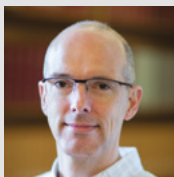
Selected Impact Activities

- Created the first mini-turbo gene-tagged mouse using pronuclear injection.
- Created a mouse with two SNPs on the same gene, where the SNPs are in different exons.
- Generated PCV-Cas9, which is a Cas9 variant that tethers ssDNA to increase the efficiency of homology-directed repair.



www.babraham.ac.uk/science-services/gene-targeting





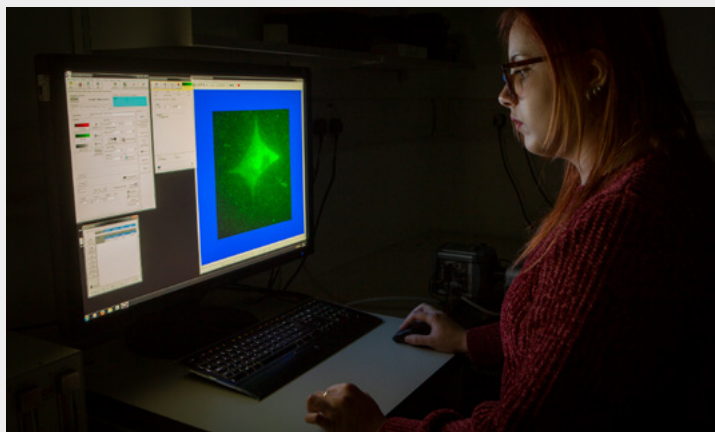
Simon Walker
Facility head

Facility members

Deputy manager:
Hanneke Okkenhaug

SEM specialist:
Chieko Itakura

Imaging



The Imaging facility provides supported access to advanced light microscopy and electron microscopy resources. Our aim is to deliver a comprehensive solution to meet the imaging demands of our user base: whether it's looking at dynamic processes in living cells, imaging cellular ultrastructure in 3D, or providing bespoke image analysis solutions, we aim to cover it all.

Capabilities

- High resolution fluorescence imaging: We have advanced wide-field microscopes, point scanning and spinning disk confocal systems and a super resolution imaging system, all of which can be used with both fixed and live samples.
- High content imaging: We have an InCell 6000 system which can image cells at high resolution in up to 1536-well format. We provide bespoke analysis solutions for high content imaging data.

- Focused ion beam-scanning electron microscope (FIB SEM): Our dual beam Zeiss CrossBeam 550 can acquire nanometer resolution volumetric EM data and is also equipped with a STEM detector to provide TEM-like images.
- Image analysis: We provide access to advanced commercial image analysis software and can provide tailor-made image analysis solutions for demanding applications.

Progress in 2019 and 2020

The biggest challenge of 2019 was the full integration of our Zeiss 550 CrossBeam electron microscope into the facility. The acquisition of this microscope means we can now offer a full electron microscopy service to our users, including sample fixation and labelling, ultrathin sectioning and 3D image acquisition. Combining these capabilities with our fluorescence imaging technologies facilitates correlative imaging workflows,

where samples are imaged on one of our fluorescence microscopes and then re-imaged using the electron microscope.

2020 required adapting to new working conditions brought about by Covid-19. The facility was quick to install remote training and user support systems, which have proven to be very effective at maintaining our day-to-day operations. The Imaging facility was awarded funding from BBSRC to support a major equipment upgrade, ensuring that the facility's light microscopy capabilities remain at the cutting edge.

Selected Impact Activities

- The facility continues to provide imaging solutions for a significant number of commercial organisations, and despite the challenges, researchers from five additional companies were trained during 2020.
- The facility showcased its resources at the Babraham Research Campus as part of the virtual 2020 Campus Science Week event.
- During extended periods of lockdown, our staff have continued to work productively from home, including helping external collaborators with their image analysis requirements.

Publications

www.babraham.ac.uk/science-services/imaging

- Okkenhaug, H. *et al.* (2020) Worm-align and Worm_CP, two open-source pipelines for straightening and quantification of fluorescence image data obtained from *Caenorhabditis elegans*. *J. Vis. Exp.* (159):10.3791/61136
- Dalle Pezze P. *et al.* (2020), ATG13 Dynamics in nonselective autophagy and mitophagy: Insights from live imaging studies and mathematical modeling. *Autophagy* 1, 1
- Odle, R.I. *et al.* (2020) An mTORC1-to-CDK1 switch maintains autophagy suppression during mitosis. *Mol. Cell.* 77(2): 228-240.e7



David Oxley
Facility head

Facility members

Senior research assistant:
Judith Webster

Postdoctoral researcher:
Kranthikumar Yadav G

Mass Spectrometry

The facility's expertise is in analytical biochemistry, and we use (bio)chemical methods in combination with mass spectrometry to study a range of biomolecules, especially proteins. Working in collaboration with scientists from across all three Institute research programmes and beyond, we use these methods to identify, quantify and obtain structural information on proteins that are involved in important biological processes, in order to help us understand how they function.

Capabilities

- The facility has three high-resolution tandem mass spectrometers (Orbitrap Eclipse, Q-Exactive Plus and Q-Exactive), each interfaced to nanoLC systems.
- We can undertake a full range of high-sensitivity mass spectrometric protein analyses including:

- quantitative proteome analysis (label-free, SILAC, isobaric tagging);
- identification/quantitation of proteins in purified complexes;
- identification, localisation and quantitation of post-translational modifications;
- detailed structural characterisation of individual proteins;
- targeted protein quantitation.
- Quantitation of DNA modifications, particularly cytosine modifications 5mC, 5hmC, 5fC and 5caC.

Progress in 2019 and 2020

Following a successful bid for funding to BBSRC, our ageing Orbitrap Velos was replaced with a state-of-the-art Orbitrap Eclipse. This new instrument,

which was installed at the end of 2019, has far superior performance in terms of scan speed, sensitivity and resolution, and has some additional capabilities (including FAIMS interface, high mass-range, and UVPD fragmentation). This enhanced performance will enable us to analyse complex, low abundance samples in much greater detail, which is essential in trying to identify critical regulators of important biological processes, and to understand how they function.

During the Covid-19 pandemic in 2020, access to the mass spectrometry facility was restricted, however many projects were able to be progressed. Significant optimisation of the Eclipse instrument was carried out and the first large experiments have been completed.



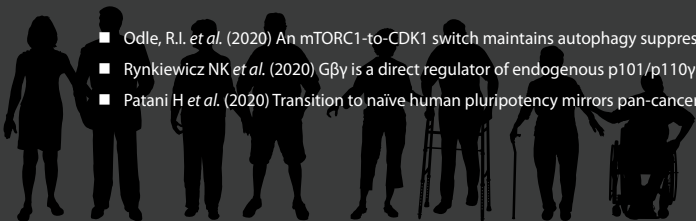
Selected Impact Activities

- Provided mass spectrometry analyses for external companies and academics.
- Facility staff joined the Covid-19 Mass Spectrometry Coalition (<https://covid19-msc.org>), which is an international group whose aim is to use mass spectrometry skills/ best practice to increase knowledge of the Covid-19 virus mechanisms and drive therapeutic/vaccine development.
- Showcased the Mass Spectrometry facility at various campus events such as Campus Science Day and Babraham Campus Science Week (virtual event, 2020).

Publications

www.babraham.ac.uk/science-services/mass-spectrometry

- Odle, R.I. *et al.* (2020) An mTORC1-to-CDK1 switch maintains autophagy suppression during mitosis. *Mol Cell* 77(2):228-240.e7
- Rynkiewicz NK *et al.* (2020) Gβγ is a direct regulator of endogenous p101/p110γ and p84/p110γ PI3Kγ complexes in mouse neutrophils. *Sci. Signal.* 13(656):eaaz4003
- Patani H *et al.* (2020) Transition to naïve human pluripotency mirrors pan-cancer DNA hypermethylation. *Nat. Commun.* 11(1):3671





Paula Kokko-Gonzales
Facility head

Facility members

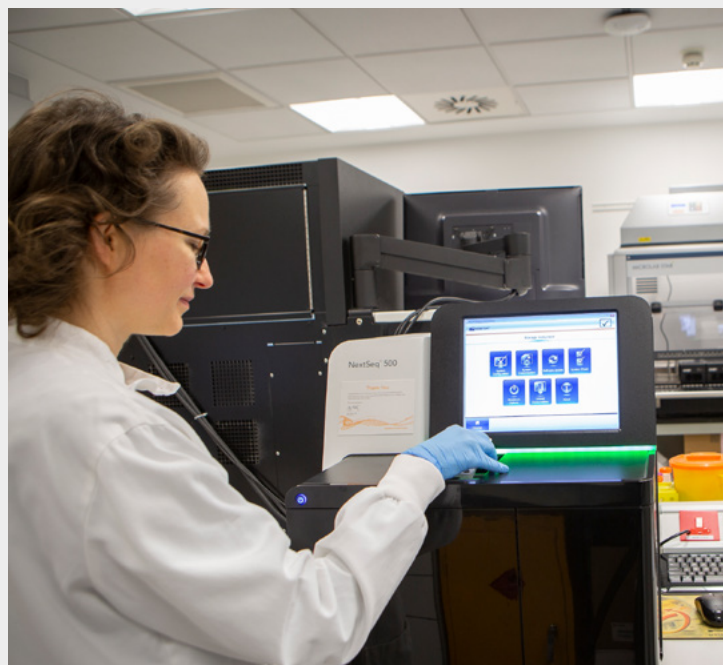
Sequencing specialist:

Amelia Edwards
(left in 2020)

Research assistant:

Nicole Forrester
(left in 2020)

Sequencing



Sequencing large amounts of DNA from many samples, a process called high-throughput sequencing, has the potential to further our understanding of mechanisms for gene regulation. It can also help to enhance our knowledge of DNA organisation and structure. The Sequencing facility provides researchers with access to cutting-edge sequencing technology to advance their research.

Capabilities

- Sequencing service using a range of sequencing instruments (NextSeq500, HiSeq2500 and MiSeq) that enables

researchers to select the sequencing depth and read length needed for their project.

- Quality control services for RNA to improve success in library preparation and for DNA libraries to ensure optimal sequencing quality and yield.
- Library preparation services using the automated liquid handling technology of the Hamilton NGS Star. Currently automated protocols include the SmartSeq v2 and NEB Next Ultra II RNA-seq library preparation protocols.

- Single cell library preparation using the 10x Genomics Chromium Controller.

Progress in 2019 and 2020

During 2019 and 2020 the Sequencing facility continued to improve automated RNA-seq library preparation services to make this powerful investigative tool available to a wider range of researchers. Library preparation using the Hamilton NGS Star liquid handling system with on-deck thermal cycling provides an integrated sample-to-library solution with enhanced reproducibility and throughput.

Introduction of the 10x Genomics Chromium Controller single cell partitioning and barcoding system allowed researchers to study gene expression, copy number variation and chromatin accessibility as well as to profile the immune system repertoire at an unprecedented level of resolution.

Selected Impact Activities

- Nicole Forrester attended the Research Institute Technician Symposium (RITS2019), The Crick Institute, London, November 2019.
- Facility participated in a public engagement event presenting to Chesterton Community College students, June 2019.
- The facility showcased its resources as part of the virtual 2020 Babraham Research Campus Science Week event.

Publications

www.babraham.ac.uk/science-services/sequencing-facility

- Hull, R. M. *et al.* (2019). Transcription-induced formation of extrachromosomal DNA during yeast ageing. *PLoS Biol.* 17 (12):e30000471
- Hill, D. L. *et al.* (2019). The adjuvant GLA-SE promotes human Tfh cell expansion and emergence of public TCRβ clonotypes. *J. Exp Med.* 216 (8):1857-1873
- Argelaguet, R. *et al.* (2019). Multi-omics profiling of mouse gastrulation at single-cell resolution. *Nature* 576:487-491







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