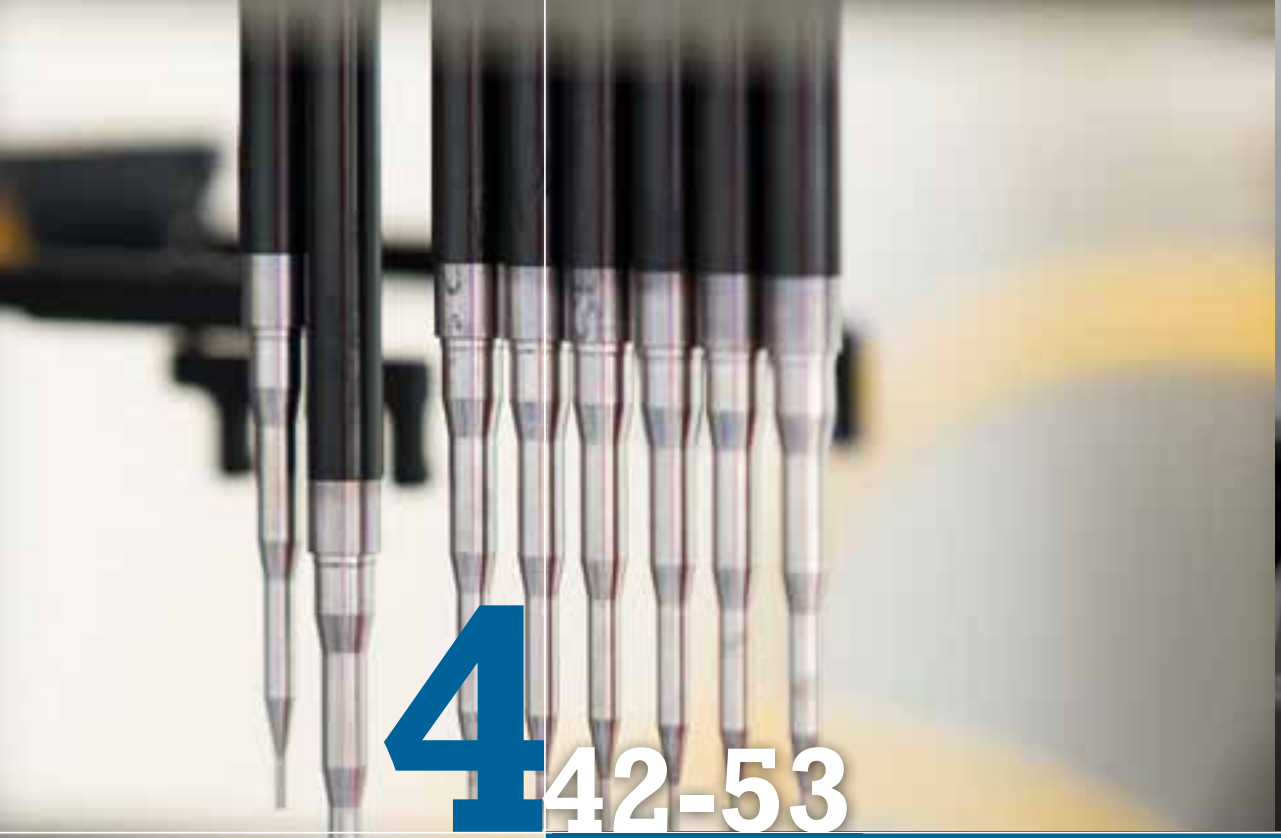
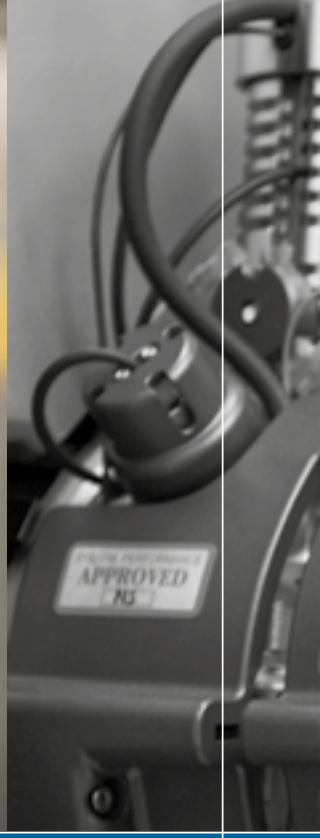
Babraham Institute

2018

Babraham Institute
Annual Research Report
Facilities





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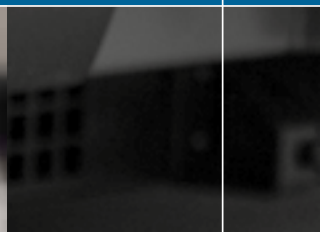
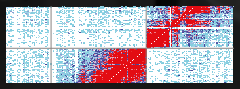
Facilities

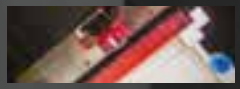




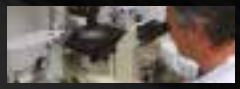
Bioinformatics

Biological Chemistry

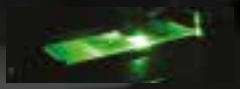
Biological Support Unit



Flow Cytometry

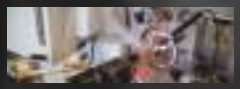


Gene Targeting



Imaging

Lipidomics



Mass Spectrometry

Sequencing

Simon Andrews
Facility head

Facility members

Biological statistician:
Anne Segonds-Pichon

Bioinformaticians:
Laura Biggins
Christel Krueger
Felix Krueger
Steven Wingett

Training developer:
Jo Montgomery

Bioinformatics

Research increasingly includes the creation of large amounts of data and the use of computers to manage and process that information. The Bioinformatics facility provides infrastructure to support the analysis of biological data. We provide guidance and training in data analysis, statistics and data management to both internal and external groups. We also develop novel tools, and administer the Institute's computing cluster.

Capabilities

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

Progress in 2018

In 2018 the Bioinformatics group has greatly expanded its training programme. We have established a set of larger training bootcamps running over several days that provide an in-depth introduction to a number of relevant topics covering sequence analysis, programming and technical skills. As well as running these on site at the Babraham Research Campus, we have also run training courses for academic and commercial groups in the UK, Germany, Spain and Australia.

This year, we expanded our toolsets to support technologies such as NMT-Seq and single-cell RNA-Seq, BS-Seq, and RNA–interaction data.

Selected Impact Activities

- We established a new set of bioinformatics training bootcamps, covering next generation sequencing, R programming and Linux systems administration.
- We organised the Second Cambridge Bioinformatics Hackathon at the Centre for Computing History, bringing together over 50 bioinformaticians from around Cambridge and the surrounding areas.
- Two members of the group undertook an extended trip to the Hunter Medical Research Institute, Australia, to run a series of bioinformatics and statistics training courses and establish a longer term relationship between our institutes.

Publications

www.bioinformatics.babraham.ac.uk

@babraham_bioinf

- Clark, S.J. *et al.* (2018) scNMT-seq enables joint profiling of chromatin accessibility DNA methylation and transcription in single cells. ***Nat. Commun.*** 9(1):781
- Chovanec, P. *et al.* (2018). Unbiased quantification of immunoglobulin diversity at the DNA level with VDJ-seq. ***Nat. Protoc.*** 13(6):1232-1252
- Wingett, S.W. *et al.* (2018) FastQ Screen: A tool for multi-genome mapping and quality control. ***F1000Res.*** 7:1338

Jonathan Clark
Facility head

Facility members

Postdoctoral research scientists:
Izabella Niewczas
Mel Stammers

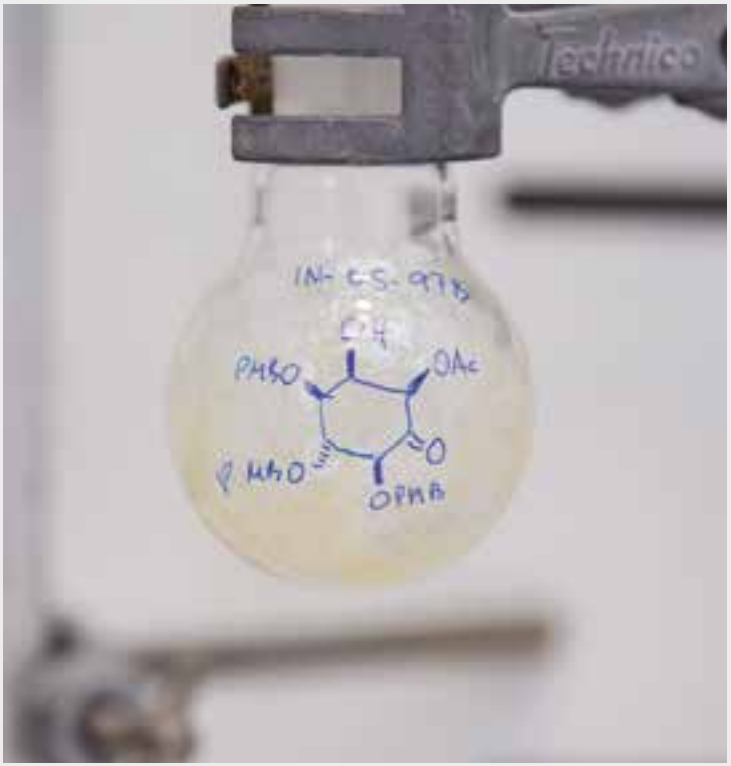
Biological Chemistry

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 Institute's 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 2018

During 2018 we have supported groups throughout the Institute on a wide range of varied projects. These have ranged from synthetic chemistry 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.

Separately in the connective tissue project, we have shown for the first time that the chemistry of collagen dynamically changes in response to stretching. In this work we have been able to describe the changes that occur to this chemistry with age and provide an explanation for the changes in the physical properties of tendons observed in ageing and in diabetes.

Selected Impact Activities

- Through 2018 we have run many commercial PIP3 analysis samples for a number of pharmaceutical companies studying the action of PI 3-kinase inhibitors in a clinical setting.
- We have provided lipid analysis for a number of external academic groups throughout 2018.

Publications

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

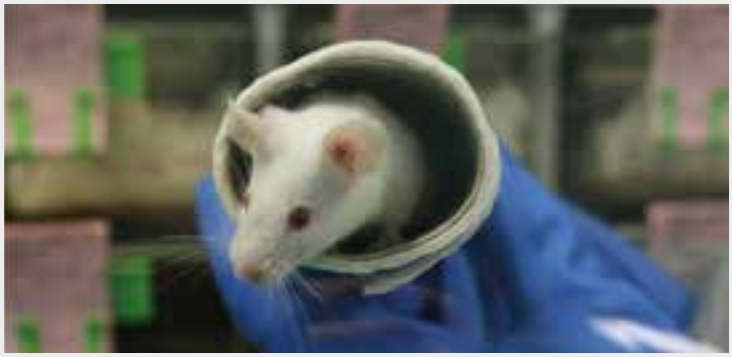
- Stark, A. K. *et al.* (2018) PI3Kδ hyper-activation promotes development of B cells that exacerbate Streptococcus pneumoniae infection in an antibody-independent manner. ***Nat. Commun.*** 9: 1-16
- Riento, K. *et al.* (2018) Flotillin proteins recruit sphingosine to membranes and maintain cellular sphingosine-1-phosphate levels. ***PLoS One*** 13: 1-18
- Chow, W. Y. *et al.* (2018) Essential but sparse collagen hydroxylysyl post-translational modifications detected by DNP NMR. ***Chem. Commun.*** 54: 12570-12573

Tim Pearce
Facility head

Facility members:

2 Deputy Facility heads
7 Managers
7 Supervisors
3 Deputy Supervisors
30 Experienced Animal Technicians
4 Trainee/Apprentice Animal Technicians
3 Support Service Technicians
1 Administrator

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 team of 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 team of 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 2018

- In 2018, the BSU successfully formed a collaboration and partnership with Agenda Resource Management creating an ongoing recruitment initiative for apprentice animal technicians, with the BSU fast becoming acknowledged as a centre-of-excellence for foundation training and beyond.
- The BSU continues to provide rentable space and technical support to commercial companies, with a 12% increase in income from this venture compared to 2017. Throughout the year the facility has continued to draw a high level of interest from new companies wanting to utilise the facility's services.

Selected Impact Activities

- A team of animal technicians and managers attended a LifeLab event held in Peterborough in September to promote careers in animal technology and engage members of the public in line with our commitment to the Concordat on Openness on Animals in Research.
- Facility tours and visits: All campus staff are invited to take a virtual tour of the Institute's animal facility to find out how our facility operates and how animals are used in our research. The facility ran three tours for campus staff in 2018. In addition, we continued to host visits from industry representatives, with respect to animal facility design for new builds and refurbishments, and to share technical expertise and guidance for their projects.
- The 2018 KEC prize (and also the Datesand group's Janet Wood Innovation Award) was awarded to a BSU Manager recognising their invention and development of an innovative animal enrichment device.

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

Rachael Walker
Facility head

Facility members

Flow cytometry specialist:
Attila Bebes
Rebecca Roberts

Flow cytometry technician:
Isobel Darlington
Aleksandra Lazowska

Flow cytometry assistant:
Arthur Davis

Flow Cytometry

Flow cytometry is a powerful technology allowing cells to be identified, counted, analysed and sorted on the basis of specific physical or chemical features, including using fluorescently labelled antibodies. The Flow Cytometry facility provides a world-class service to enable the research goals of the Institute. We help scientists from both the Institute and external companies with experimental design, training, troubleshooting and data analysis.

Capabilities

- State-of-the-art analysers: BD LSRFortessa and Propel Lab YETI analysers allowing up to 30 parameters to be simultaneously analysed.
- Image cytometry: The facility houses a Merck Millipore Imagestream MkII allowing quantitative flow cytometry data to be produced with images of each cell.
- Cell sorting service: The facility provides an expert cell sorting service for Institute and external users.

Progress in 2018

In 2018, the facility expanded with the acquision of a new, high-end BD AriaFusion sorter to strengthen our cell sorting capabilities. The facility also welcomed two new members of staff to support the sorting service.

Selected Impact Activities

- Flow cytometry training: Throughout 2018, the facility's modular courses continued to sell out with 240 delegates being trained in 2018 (178 unique delegates).
- The facility delivered bespoke flow cytometry training at the Pirbright Institute.

Our future services for this facility are currently under review.

Gene Targeting & Genome Editing

Introducing targeted changes to the mouse genome enables researchers to alter individual genes to study their functions. The Gene Targeting service is trialling new gene editing opportunities and technologies to produce genetically altered mouse models. Once up and running, the service will be able to aid in the design, generation, screening and evaluation of genetic modifications.

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

Imaging

Simon Walker
Facility head

Facility members

Deputy manager:
Hanneke Okkenhaug

SEM specialist:
Chieko Itakura
(Started in 2018)

The Imaging facility provides a number of services to support the Institute's research. These include access to advanced light microscopy technologies, an electron microscopy service, and an advanced image analysis service. Training is a key part of our remit, with users encouraged to learn how to operate our equipment independently, with expert advice on hand to help when required.

Capabilities

- Scanning Electron Microscope with Focussed Ion Beam (FIB SEM).
- N-SIM/N-STORM super resolution imaging system.
- Multi-photon microscope for intravital imaging.
- Image acquisition and data analysis for cell-based assays.

Progress in 2018

2018 has been a landmark year in the development of the Institute's Imaging facility as we can now offer an electron microscopy capability to complement our advanced light microscopy resources. The primary driver for this acquisition is a need to study cellular ultrastructure at high resolution in 3D, providing contextual information on organelle formation. Installation of the microscope was completed in April and a new member of staff joined our team in October to run the instrument and provide expertise on sample preparation. We anticipate this resource to be fully operational in early 2019.

Selected Impact Activities

- Simon Walker presented the facility's work at the first meeting of BBSRC-funded imaging facilities.
- Hanneke Okkenhaug hosted two GCSE school students on a week's work experience.
- Simon Walker attended a LabLife event in Peterborough, sharing STEM-related books that challenge gender stereotypes with children.

Publications

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

- Chrysanthou, S. *et al.* (2018). A critical role of TET1/2 proteins in cell-cycle progression of trophoblast stem cells. ***Stem Cell Rep.*** 10(4): 1355-1368
- White, M. A. *et al.* (2018). TDP-43 gains function due to perturbed autoregulation in a Tardbp knock-in mouse model of ALS-FTD. ***Nat. Neurosci.*** 21(4): 552-563
- Dautova, Y. *et al.* (2018). Calcium phosphate particles stimulate interleukin-1beta release from human vascular smooth muscle cells: A role for spleen tyrosine kinase and exosome release. ***J Mol Cell Cardiol.*** 115: 82-93

Michael Wakelam
Facility head

Facility members

Facility manager:
Andrea Lopez-Clavijo

Postdoctoral research scientist:
Aveline Neo

Research assistant:
Gregory West

Lipidomics

Lipidomics identifies and quantifies the large array of lipid (fat) molecules found in cells, tissues and biological fluids. The lipidome is separated chromatographically and comprehensively characterised by high-accuracy and high-resolution tandem mass spectrometry. 15 novel chromatography methods have been developed, tested and validated to identify and semi-quantify a range of neutral, phospho-and sphingolipids with the aim of providing a detailed view of the lipids in a biological system. This knowledge is then used to contribute to an understanding of cell structures, signalling and regulation in a systems-wide investigation of metabolic changes in health and disease.

Capabilities

- The facility uses liquid chromatography hyphenated to high resolution/high mass accuracy mass spectrometry for untargeted lipidomics (Orbitrap technology).
- Targeted lipidomics is performed by liquid chromatography or gas chromatography hyphenated to triple quadrupole mass spectrometers.
- Shotgun throughput analyses couples an Advion NanoMate to a high resolution /high mass accuracy mass spectrometer.
- Semi-quantitation of the lipids levels when compared to control samples prior to normalisation of the data to the weight/DNA/protein content.
- Hydrophobic extraction of the lipids present in cell lines and tissues from mouse, worm and human samples.

Progress in 2018

We have successfully re-established the Lipidomics facility adopting normal phase chromatography methods for the separation of phospholipids. The methods have been validated using targeted and untargeted approaches. In addition, reverse phase chromatography has been implemented for the separation of neutral lipids.

We are developing ion mobility methods for the separation of ceramides with similar elemental composition coupled with chromatography and targeted approaches. Methods to measure free fatty acids, cholesterol and cholesterol ester are also under development, to offer a comprehensive range of lipids to cover the lipidome. Finally, we have introduced a fast and reliable cold homogenisation of soft and bland tissue, including worms (*C. elegans*) using a Precellys homogenizer.

Selected Impact Activities

- Active collaborations with research groups from the University of Cambridge, King's College London, Birmingham University, Newfoundland University (Canada) and the University of Oxford.
- A service agreement for the analysis of commercial samples by the facility has been initiated with a company based in Oxford.
- Facility members promoted the science carried out in the facility at the British Mass Spectrometry Society annual conference.

Publications

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

- Sadej, R. *et al.* (2018). CD151 regulates expression of FGFR2 in breast cancer cells via PKC-dependent pathways. ***J Cell Sci.*** 131(21)
- Burla, B. *et al.* (2018) MS-based lipidomics of human blood plasma: a community-initiated position paper to develop accepted guidelines. ***J Lipid Res.*** 59(10): 2001-2017
- Nguyen, A. *et al.* (2018) Host lipidome analysis during rhinovirus replication in HBECs identifies potential therapeutic targets. ***J Lipid Res.*** 59(9): 1671-1684

Mass Spectrometry

David Oxley
Facility head

Facility members

Senior research assistant:
Judith Webster

Postdoctoral researcher:
Katarzyna Wojdyla

Mass spectrometry is unrivalled in its potential to identify, characterise and quantify almost any biological molecule, at very high sensitivity and in highly complex samples. The Mass Spectrometry facility uses the latest approaches and develops novel methods to analyse biological molecules, particularly proteins and nucleic acids, working with colleagues from across the institute and campus companies.

Capabilities

- Three high-resolution tandem mass spectrometers (Q Exactive Plus, Q Exactive and Orbitrap Velos Pro) situated within the facility, and the facility has shared access to a state-of-the-art Orbitrap Fusion Lumos instrument located in the Biochemistry department at the University of Cambridge.
- 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.
- Development of novel mass spectrometric analytical methods.

Progress in 2018

During 2018 we worked with many of the Institute's research groups on a range of projects and also continued method development. For example, in collaboration with Wolf Reik's group, we extended our methodology for the analysis of cytosine modifications in DNA to measure uracil, a very rare base in genomic DNA, which may play a role in DNA demethylation. Working with the Kelsey lab, we used our low-level TMT method for quantitative proteome analysis of small numbers of mouse oocytes. We also initiated a new project using a cell-surface labelling technique to investigate the cell-surface proteomes of naive vs primed human pluripotent stem cells (with Peter Rugg-Gunn).

Selected Impact Activities

- Participated in the Institute's 'Race Against the Ageing Clock' exhibit at the 2018 Royal Society Summer Science Exhibition in London (July).
- Showcased the facility at the Babraham Research Campus science morning.
- Commercial work for several Babraham Research Campus companies.

Publications

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

- Tsolakos, N. *et al.* (2018) Quantitation of class IA PI3Ks in mice reveals p110-free-p85s and isoform-selective subunit associations and recruitment to receptors. ***Proc Natl Acad Sci USA.*** 115(48):12176-12181
- Olova, N. *et al.* (2018) Comparison of whole-genome bisulfite sequencing library preparation strategies identifies sources of biases affecting DNA methylation data. ***Genome Biol.*** 15;19(1):33
- Smyrnias, I. *et al.* (2018) Contractile responses to endothelin-1 are regulated by PKC phosphorylation of cardiac myosin binding protein-C in rat ventricular myocytes. ***J Mol Cell Cardiol.*** 117:1-18

Next Generation Sequencing

Kristina Tabbada
Facility head

Facility members

Research assistant:
Nicole Forrester

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 Next Generation Sequencing (NGS) facility provides researchers with access to cutting-edge sequencing technology to advance their research.

Capabilities

- A range of sequencing instruments (HiSeq 2500, NextSeq 500 and MiSeq) enabling researchers to select the sequencing depth and read length needed for their project.
- Library preparation services using the automated liquid handling technology of the Hamilton NGS Star. Protocols currently automated include the SmartSeq v2 protocol and NEB Next Ultra II RNA-seq library preparation.
- Quality control services to ensure optimal yield and sequence quality.
- Coming in 2019 – automated single cell library preparation using the 10X Genomics Chromium Controller.

Progress in 2018

The Next Generation Sequencing facility has continued to expand its range of services. In 2018, the facility began to offer 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-sequence solution with enhanced reproducibility and throughput.

The 10X Genomics Chromium Controller single cell partitioning and barcoding system will allow 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

- Attended the Core Technologies for Life Sciences (CTLS2018@VIB) Conference, Ghent, Belgium, 1-4 July 2018.

Publications

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

- Cruz, C. *et al.* (2018) Tri-methylation of histone H3 lysine 4 facilitates gene expression in ageing cells. ***eLife*** 7: 34081
- Koohy, H. *et al.* (2018) Genome organization and chromatin analysis identify transcriptional downregulation of insulin-like growth factor signaling as a hallmark of aging in developing B cells. ***Genome Biol.*** 19: 126
- Clark, S.C. *et al.* (2018) scNMT-seq enables joint profiling of chromatin accessibility DNA methylation and transcription in single cells ***Nat. Commun.*** 9: 781

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The Babraham Institute

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The Babraham Institute receives core funding in strategic programme grants from the BBSRC.

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