'The LMB pushes the limits of knowledge and feasibility, illuminating biology with the exactness of chemistry and physics.'

The MRC Laboratory of Molecular Biology (LMB) is an internationally leading research institute dedicated to the understanding of important biological processes at the levels of atoms, molecules, cells and organisms. In doing so, we provide knowledge needed to solve key problems in human health. We seek to understand the structures of molecules and molecular machines, their fates and functions within cells, and how these make up complex systems such as cells, tissues, the immune system and the brain, often with a view on health and disease.

Founded by the Medical Research Council over 60 years ago, in the far-sighted belief that molecular biology would one day be of medical benefit, the Laboratory has indeed made revolutionary contributions to medicine – often through the development of new techniques. Advances in X-ray crystallography and electron cryo-microscopy (cryo-EM) to determine protein structures are now used for structure-based drug design, DNA sequencing is a cornerstone of molecular medicine and diagnosis, and monoclonal antibodies have become one of the most powerful therapeutic tools.

The combination of ambitious goals, a shared budget and stable long-term support has generated a unique collaborative LMB culture that values boldness and originality. It has resulted in twelve Nobel Prizes awarded for work carried out by LMB scientists, and has contributed, in part, to eleven Nobel Prizes awarded to alumni for work done elsewhere.

The LMB pushes the limits of knowledge and feasibility, illuminating biology with the exactness of chemistry and physics: computational approaches are becoming ever more powerful, biophysical methods have revolutionised molecular imaging and new approaches in chemical and synthetic biology and biotechnology provide the tools for future discoveries and applications. We also continue to promote the application of our research findings, both by collaboration with existing companies small and large and by the founding of new ones.

The LMB provides a diverse and unsurpassed environment for both young and established researchers with state-of-the-art facilities and a unique scientific culture. Our scientists are drawn from all over the world, creating a lively international community for the exchange of ideas and technical innovation. Many are inspired by the knowledge that discoveries made at the LMB have made a difference to the world, and will continue to do so.

Jan Löwe, Director
Structural Studies

The Structural Studies Division is working to understand the structure, function and interactions of biologically important molecules, using techniques such as X-ray crystallography, electron microscopy and NMR. The Division’s focus is on long-term challenging problems that go hand-in-hand with advancing the methods used to study them. Thus, efforts to improve data analysis in crystallography and electron microscopy are accompanied by the study of major biological questions such as protein degradation, splicing and mRNA control, translation, cellular transport and signalling, and amyloid formation. Many of these areas are also important for understanding and developing cures for various diseases.

Research groups within the Division are also dedicated to developing computational methods for the analysis, interpretation and use of the wealth of data rapidly accruing from the structures of molecules as well as from sequencing of whole genomes. This work is likely to lead to a better understanding of the large-scale networks that are involved in the regulation of genes and the interactions of proteins in the cell.

Left to right: Structure of the HIV-1 capsid core determined inside the virus by electron cryo-tomography. | The microtubule motor dynein (grey) bound to dynactin (multicolour) via the cargo adaptor BICD2 (orange). Image by J Iwasa. | Cryo-EM structure of the polymerase module of the cellular machinery (CPF) that processes mRNA 3’-ends in eukaryotes

Difficult problems - Long-term view

Protein coding genes in higher organisms are split and are first transcribed into precursor messenger RNA (pre-mRNA) consisting of coding sequences (exons) and non-coding sequences (introns). The spliceosome is the molecular machine which cuts out the introns and stitches the exons together, so that the resulting mature mRNA can be translated to produce proteins. Importantly, many human genes can undergo alternative splicing: some exons can be skipped to produce variant forms of the resulting protein. This helps regulate gene expression and increases the repertoire of proteins that can be made in different tissues and developmental stages.

The spliceosome comprises five short RNAs and approximately one hundred proteins. When Kiyoshi Nagai’s group determined the crystal structure of one of the proteins in 1990 it seemed an impossible task to obtain the atomic structure of the whole spliceosome because of its sheer size and complexity.

The group made slow but steady progress with long-term funding from the MRC and finally made a major breakthrough in 2015 when they determined the first structure of a large spliceosomal assembly by electron cryo-microscopy (cryo-EM).

Subsequently they captured cryo-EM snapshots of the yeast spliceosomes in key states during assembly and catalysis which have provided crucial insights into the molecular mechanism of pre-mRNA splicing.

Kiyoshi comments: ‘Long-term support from the MRC has been crucial in tackling fundamental problems, that seemed impossible to solve when we started working on them. Our work has benefited enormously from equally long-term efforts to develop cryo-EM techniques by Richard Henderson, Sjors Scheres and their colleagues. The collegial atmosphere of the LMB allows us to interact and help each other at all levels’.

“In a factory you know what you’re going to make. Here, we plant things that grow and mature. It takes a long time.” Aaron Klug
PNAC

Research groups within the Protein and Nucleic Acid Chemistry (PNAC) Division are working to gain insights into human biology and disease to help develop strategies for diagnosis and treatment. The Division’s research focuses on the biological processes leading to immunity and cancer, employing diverse approaches that range from molecular, cellular and transgenesis to genomics, proteomics and molecular evolution.

Fundamental questions such as how the molecules of life evolved on Earth are approached using organic chemistry and in vitro engineering of synthetic biological polymers. The aim is to discover the chemical origins of RNA and DNA and of the primitive genetic code, but also to evolve novel types of nucleic acids in the test tube and to create a parallel synthetic protein translation system in prokaryotic cells. These new tools will be applied to fundamental biological research and ultimately could lead to novel molecular scaffolds for therapeutic applications.

Research groups in the Division are also studying the inter- and intra-cellular pathways that protect organisms from infection as well as those that maintain tissue homeostasis and which are often aberrantly activated in cancer. Efforts are directed to uncover the mutational processes that underpin genomic changes in cancer and the molecular mechanisms preserving the genomes of stem and proliferating cells from such damage. A common goal is to identify and understand the key molecules which guard against infection and cancer to help develop new strategies for rational, molecule-led therapeutic approaches.

The Centre for Chemical and Synthetic Biology (CCSB) combines molecular and cellular biologists working closely with innovative organic chemists to apply chemical biology and molecular engineering of biological systems to solve fundamental questions in biology.

Andrew McKenzie’s research looks at how immune cells coordinate the body defence against pathogens, in particular the role of soluble molecules, known as interleukins, such as IL-25. This work is providing crucial insights into many diseases where the normal regulation of the immune system goes awry, such as autoimmunity and asthma.

Asthma is a common chronic disorder characterised by inflammation and hyperreactivity of the airways, which affects around 300 million people worldwide. The disease symptoms are complex and variable in severity and the causes are still poorly understood. Although the majority of asthma sufferers respond to medication with steroids, such treatment can be associated with a number of side-effects and a proportion of sufferers (5 – 20%) develop a form of severe asthma that is not controlled by standard treatments.

The discovery of a new immune cell, that is induced by IL-25, has dramatically changed the understanding of allergic diseases and more fundamentally of how immune responses get started, but has also led the McKenzie group to develop inhibitory monoclonal antibodies to human IL-25, which have been shown to prevent many of the symptoms of asthma in models of human disease.

As Andrew explains: ‘By studying the cytokine, IL-13, which induces mucus secretion and contraction in the airways, we discovered a previously unappreciated immune cell type called innate lymphocytes (ILC2). ILC2 cells respond to the cytokines IL-25 and IL-33 by proliferating and producing high levels of IL-13, orchestrating the initiation of allergic asthma.’

‘Discoveries in basic science lead often, in unpredictable ways, to medical advancements.’

César Milstein

Left to right:Activation of human VPS34 complex II by Rab5- associated lipid membranes | Super-resolution image of Salmonella bacteria in the cytosol of a human cell detected by Galectin-8 (green) and NDP52 (blue)

Above: Influx of T cells (red) and IL-13-producing ILC2 cells (green) in the lung

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The cell is the fundamental unit of life. Some organisms, such as a bacterium or yeast, are composed of a single cell whereas many trillions of cells make up a human. The cells in our body are organised into various tissues where they perform specialised functions important for normal health. The Cell Biology Division aims to understand the inner workings of individual cells, how cells become specialised and organised into tissues, and how defects in cellular function or organisation contribute to human disease.

Research groups within the Division employ a range of methods. Tissues, cells, and even individual molecules are directly visualised and tracked using cutting-edge light and electron microscopy. Genetic methods, genome editing, and protein biochemistry are used to dissect and manipulate cellular processes at a molecular level. Collectively, these methods provide understanding of the precise mechanisms underlying complex physiology and pathology.

Studies of how the inside of a cell is organised and built typically use cells in culture, yeast, and protein biochemistry. This research is revealing how new proteins are made and trafficked to the correct location inside cells, how molecular motors move cargo around the cell, and how organelles inside the cell are positioned and communicate with each other. Studies of tissue formation, organisation, and function make use of nematodes, flies, mice, and organ cultures. This work shows how collections of cells migrate and interact to form organs, how neurons assemble into functional networks, and how cell and tissue function is regulated by the time of day.

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The human brain is a big and powerful information-processing machine. The architecture of the cells within is critical to its function, but is inaccessible to researchers. In particular it is difficult to understand how it becomes organised as it grows in the embryo.

Madeline Lancaster is looking at how human brains are built under the microscope. She has developed a model system, called cerebral organoids, or mini-brains for short, that allow her to follow human brain development in a petri dish. Through a process of directed differentiation in a supportive 3D microenvironment, tissues generated from human pluripotent stem cells can spontaneously self-organise to form the stereotypic organisation of the embryonic brain, allowing her to explore how neural precursor tissues develop into the complex structures of the human brain.

Cerebral organoids can model neurodevelopmental disorders, such as microcephaly, a disorder characterised by a significantly reduced brain size, and potentially can be used to understand the molecular basis of other neurodevelopmental disorders like autism and intellectual disability.

In Madeline’s words: ‘My lab is interested in one of the greatest puzzles in human history: how the human brain is unique. To begin addressing this, we use 3D developing human brain tissue in a dish and examine its many unique characteristics. Our hope is that a greater understanding of human brain development will lead to better treatments for a variety of neurological conditions.’

‘Innovation is driven by the curiosity to answer fundamental questions.’

Michael Neuberger
Human disease - New molecular insight

Alzheimer’s and Parkinson’s are the most common neurodegenerative diseases, affecting over 40 million people worldwide. A shared characteristic is the presence of filamentous amyloid assemblies within brain cells. Similar inclusions are also found in related disorders, including Pick’s disease, chronic traumatic encephalopathy, progressive supranuclear palsy, dementia with Lewy bodies and multiple system atrophy. Existing therapies deal, at best, with the symptoms of these diseases.

Work carried out by Michel Goedert and collaborators has helped to identify tau protein and alpha-synuclein as the major components of the pathological filaments and to show that their formation causes cell death and neurodegeneration. Recent work done in collaboration with the group of Sjors Scheres has used electron cryo-microscopy (cryo-EM) and immunogold negative-stain electron microscopy to determine the first high-resolution structures of disease filaments from human brain, thus identifying different conformers of assembled tau in Alzheimer’s and Pick’s diseases.

Michel comments: ‘Our work is aimed at understanding the mechanisms by which the normally soluble tau and alpha-synuclein proteins assemble into abnormal filaments. In due course, this work may lead to the development of mechanism-based therapies for tauopathies and synucleinopathies.’

Research

Neurobiology

One of the biggest challenges facing the biological sciences is to understand how brains can give rise to minds. The nervous system is a complex machine, but at its simplest it consists of nerve cells (neurons), their connections (synapses) and the circuits they thereby create. The Neurobiology Division aims to understand the fundamental properties of neurons, synapses, and circuits and how they behave both in health and disease. This will increase understanding of how networks of cells give rise to thoughts and control behaviour. What is the molecular basis of synaptic function, how is information processed through circuits and what molecular mechanisms underlie common neurodegenerative diseases?

A broad combination of biochemistry, structural biology, imaging and electrophysiology is used to build up a detailed picture of how synaptic vesicles release neurotransmitters, how ion channels are trafficked to the cell surface and, once there, how neurotransmitters released by synaptic vesicles trigger opening of the channels.

Analysis of sensory transduction and the processing of olfactory information in the brain, as well as the organisation and function of neuronal networks controlling movement and circadian rhythms, such as sleep is revealing how the properties of nerve cells determine the flow of information within circuits and how this translates into behaviour.

Researchers in the Division are also unravelling the molecular and cellular mechanisms by which cells adapt protein synthesis in response to stress, and how the abnormal assembly of a small number of proteins causes common human neurodegenerative diseases. By defining general mechanisms of protein quality control and aggregation, the aim is to identify novel therapeutic approaches to manage conditions such as Alzheimer’s and Parkinson’s diseases.

Top to bottom: The molecule that mediates inhibition in the brain. Cryo-EM high resolution structure of the GABA-A receptor informs our understanding of its function in epilepsy, anxiety, and addiction | Observing living neurons in the transparent worm, C. elegans. Genetically encoded red and green fluorescent markers show where particular neurons are located and when they are active | Top to bottom: Image from the brain of an experimental mouse with neurons and their processes containing filamentous aggregates of human tau (in brown) | Schematic of the Alzheimer and Pick folds, based on cryo-EM analysis. These structural insights will inform understanding of how diseases start and how they may be treated

‘We’re not asked to find cures for the background that allows disease processes to be better understood.’ John Walker

Top to bottom:

Image from the brain of an experimental mouse with neurons and their processes containing filamentous aggregates of human tau (in brown) | Schematic of the Alzheimer and Pick folds, based on cryo-EM analysis. These structural insights will inform understanding of how diseases start and how they may be treated.

Research
The LMB is at the heart of the expanding Cambridge Biomedical Campus, one of the largest and most internationally competitive concentrations of healthcare-related talent and enterprise in Europe. The campus is on the south side of the city, with easy connections by rail and road, and in walking or cycling distance to the University, the countryside and residential areas.

The distinctive LMB building – in the shape of a chromosome, with two laboratory blocks joined by a central atrium, was designed to provide maximum flexibility for the future, including space for specialist new equipment and new facilities as they are developed.

The laboratory is easy to navigate; its open airy walkways, spacious rooftop restaurant, fully equipped lecture theatre and library, and comfortable coffee and breakout rooms on each floor all facilitate the LMB’s distinctive culture – encouraging close interaction within groups, and an open, collaborative and dynamic way of working.

This culture is mirrored by the Cambridge Biomedical Campus – by mixing together basic academic science, hospital practitioners and clinical research together with international industrial enterprises, the Campus offers a unique environment to enable the exchange of ideas and technical innovation.

Scientists from the University of Cambridge Clinical School* are already working alongside LMB scientists, and collaborative links with academics at the CRUK Cambridge Institute, Cambridge Institute of Medical Research, and the Wellcome Sanger Institute as well as with industrial partners such as AstraZeneca and MedImmune thrive, aided by the geographical proximity and shared interests.

*http://www.med.cam.ac.uk/university-research-unit/

‘There have been very good research institutions that have tried to capture the flavour and spirit but they haven’t got it.’

Joan Steitz, discoverer of snRNPs, on the LMB
New challenges - Technological advances

The LMB is noted for its development of new techniques and technologies to help advance research. LMB’s researchers have easy access to some of the world’s highest quality scientific technologies on site and the right environment to foster innovation.

Since the mid 1980s, the LMB along with other institutions has helped to pioneer electron cryo-microscopy (cryo-EM) techniques to help study the three-dimensional structure of macromolecules both as two-dimensional crystalline arrays as well as single particles without the need to crystallise the samples first. Following a procedure invented by Jacques Dubochet’s group at EMBL in the 1980’s, a solution of the chosen biomolecule is frozen in a thin layer of ice, and this layer is imaged in an electron microscope. Many thousands of images, from different orientations, are needed to determine the structure of each biomolecule. These are then computationally assembled into a three-dimensional image to give the structure of the macromolecule.

Richard Henderson’s identification of key bottlenecks in the process led to the development of a new type of direct-electron detector – with impetus from him and Wasi Faruqi. Work by Sjors Scheres’ group at the LMB has combined data from such detectors with new methods of image processing, resulting in structures of greatly increased resolution.

Sjors comments: ‘The recording of movies by these new cameras allows tracking of the movement of individual complexes while the sample is exposed to the electron beam. As a result, structures to near-atomic resolution from cryo-EM images can be obtained.’

Above: Average cryo-EM images of 80S ribosome particles

A cornerstone of LMB science is the provision of excellent facilities and support services – freely available to all members of the Laboratory, from PhD students to group leaders. These are led and staffed by experienced scientists with the expertise to carry out large-scale projects and to aid collaborative research across the LMB’s Divisions.

Biological Mass Spectrometry & Proteomics
Mass spectrometry has changed the way systems-level analysis of biological samples is undertaken. Headed by Mark Skehel, the facility aims to cover all aspects of protein mass spectrometry, with a particular focus on structural proteomics. The facility is equipped with a comprehensive range of instrumentation including a Thermo Scientific Q Exactive HF-X and a Waters SYNAPT G2 Si HDMS.

Electron Microscopy
The facility, managed by Shaoxia Chen, has ten electron microscopes, which provide flexible options for 2D and 3D structural analysis of biological material by cryo-EM. These consist of five state-of-the-art 300 keV FEG cryo-transmission electron microscopes (three Titan Krios and two Polaras), as well as five other electron microscopes, including a Scios DualBeam scanning electron microscope.

Light Microscopy
Headed by Nick Barry, an optical physicist and specialist in light microscopy, it houses four new super-resolution microscopes and supports specialist advanced microscopy throughout the building.

Crystallisation and X-ray Infrastructure for crystallography includes automated systems for formulating and setting up crystallisation trials, under the expert assistance of Fabrice Gorrec. The usefulness of the crystals obtained is determined with in-house X-ray diffractometers. To solve structures, LMB scientists can proceed with remote data collection after shipping crystals to the Diamond synchrotron in Harwell or the European Synchrotron Radiation Facility in Grenoble.

Environment

Facilities
Facilities

Biophysics
The facility, overseen by Chris Johnson and Stephen McLaughlin, has a wide range of instruments to investigate the affinity and dynamics of molecular processes at a multi-scale level, from ensembles in solution down to single molecules. State-of-the-art instruments, such as the SwitchSENSE, support cutting-edge research.

Flow Cytometry
The facility operates jointly with the University of Cambridge School of Clinical Medicine and is run by Maria Daly. It enables researchers to characterise, quantify and separate cell populations on the basis of surface and intracellular markers. It includes high-speed cell sorters, several multifluorescent analysers and a spectral analyser.

Biological Services
A group of more than 70 animal technicians maintain the facilities to house breeding and experimental colonies of rodents. They provide the highest standard of modern transgenic production services and experimental resources, with a strong emphasis on animal welfare and the 3Rs, to support the scientific programmes of the LMB and some MRC University Units in Cambridge.

Nuclear Magnetic Resonance
The solution-state NMR facility houses 500, 600, 700 and 800 MHz Bruker systems in a dedicated building. LMB groups have instant access to wide-ranging expertise in all aspects of biomolecular NMR methods. This includes help with protein expression, data acquisition and often the complete data analysis in a collaborative effort, under the direction of Stefan Freund.

Scientific Computing
Computational resources at the LMB include GPU and large memory servers, together with a 3912 CPU High Performance Computing (HPC) cluster, and additional data storage of up to 4.6PB. An expert team, headed by Jake Grimmett, provides advice on computational problems.

Workshops
The LMB’s scientists also benefit from access to state-of-the-art workshops, headed by Andy Howe and Steve Scotcher. In practical terms, having Electronics and Technical Instrumentation Workshops on site means that design, prototyping and development happen far faster at the LMB than in most other laboratories, which rely on outside contractors.

Facilities

Engineering - At the edge of biology

Many of the outstanding questions in biology and medicine are difficult to address because there is no way to directly look at the complex molecular machines responsible for life.

Christopher Russo works on developing new instruments and methods for imaging biological molecules (DNA, RNA and proteins) at atomic resolution using electron microscopes. This requires improved cryo-preparation and imaging methods that can be applicable to any biological specimen. Christopher is studying the physical principles underlying the current resolution limits and reengineering the critical components in the imaging system to improve resolving power using recent advances in nanoscience, solid-state physics, surface chemistry, electrical engineering and materials science.

Christopher says: ‘The LMB houses state-of-the-art technical instrumentation and electronics workshops that allow us to design and build our own scientific instruments and push forward what is possible. This is essential to our work on improving electron microscopy and to the advancement of biology generally.’

‘Progress in science depends on new techniques, new discoveries and new ideas, probably in that order.’

Sydney Brenner

Right: 3D representation of an ultrastable, all gold specimen support developed and made at the LMB. Scale bar is 10 micrometers

Facilities
Supporting scientists and sustaining a robust and flourishing environment for world-class research will be a key element in the LMB’s continuing success.

More than 800 scientists and support staff work in the LMB, with around 550 directly carrying out research in more than 50 groups. The LMB attracts some of the best people from around the world – at all stages of their careers. Over 50 nationalities are represented, with more than half of the group leaders originating from outside the UK – a truly international community of PhD students, postdoctoral scientists and researchers.

The LMB’s intellectual base and unique culture – developed over the last 70 years – remains important in attracting and retaining key scientists. Many groups in the Laboratory are small, consisting of eight or fewer people under the leadership of a senior researcher. These small groups help to maintain the dynamism and flexibility of research at the LMB, and encourage close interactions both within groups and throughout the Laboratory. This interaction is further fostered by an open intellectual environment, a wealth of freely-shared services and resources, and generous central funding.

Although it can claim to be the birthplace of modern molecular biology, the LMB is now one of many laboratories carrying out outstanding research and competing to recruit the world’s best scientists. The LMB’s state-of-the-art laboratory space, equipment and facilities help the Laboratory to compete for new talent.

In addition to dedicated administrative help, all staff at the LMB have access to a wide range of support services including high quality IT support, an expert Library and Information Service, experienced creative help from the Visual Aids team and practical support from stores and purchasing. The aim is to free scientists from distractions and enhance their ability to disseminate their science.

<table>
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<th>STAFF (approximate numbers)</th>
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<tr>
<td>Group leaders</td>
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As John explains: “Our research has really benefited from collaborations in the past and there is enormous potential for developing new collaborations within the LMB. We are already learning a lot from our new LMB colleagues and they are excited to use the methods we are developing in their own research.”

As Radu explains: “Our research is tackling big questions about synaptic function, and the LMB is the ideal place where one can pursue such long-term goals. The electron cryo-microscopy facilities and expertise at the LMB are world-class, and will be of huge value to my group in our quest to ultimately determine the molecular mechanisms of neurotransmission in a physiological context.”
Building an international science community

Scientific alumni: known locations [December 2015]

Educating the next generation

Origin and destination of research students working at the LMB 2009 – 2015.

Scientific research is one of the most exciting and rewarding of occupations. It is like a voyage of discovery into unknown lands, seeking not for new territory but for new knowledge.” Fred Sanger

Training scientific talent
Training

The LMB International PhD programme attracts students of outstanding potential for research from the UK and all over the world, and then provides them the freedom, guidance and resources to pursue cutting-edge projects from the day they arrive.

Students are at the heart of, and in many cases lead, some of the most important science emerging from the LMB. Although attached to individual groups, they are encouraged to seek any relevant expertise or resource in the building that helps their research. The small group sizes, the communal nature of the resources within the Lab and the dedicated staff who run lab facilities all conspire to enlarge the scope and ambition of the projects undertaken by the students and more importantly facilitate their successful completion.

Encouragement to promptly complete their PhD thesis, coupled with support for short post-doctoral extensions to finalise and publish work, enables LMB students to make their mark and fully develop their potential. LMB students produce on average 3.4 publications over their time in the Lab, with more than half of those as first authors. After completing their PhD, 74% of LMB students move to postdoctoral positions in academia, and many start their own research groups within 5-10 years – our most recent survey shows 29% of female and 26% of male students have done so.

The LMB supports the wider scientific community by supplying highly trained leaders in academic research. They leave the LMB to develop and support molecular science in the UK and around the world. Between 2005-2010, 85% of the postdocs trained at the LMB continued onto research careers, 41% of the females and 60% of the males became group leaders by 2015.

Shaping science across wide horizons

Tanmay started his own group at the Sir William Dunn School of Pathology, University of Oxford in 2017. He was a post-doctoral fellow with Jan Löwe at the LMB and had previously trained as a graduate student with John Briggs at the EMBL in Heidelberg. Whilst at the LMB, Tanmay solved the structure of the bacterial actin homologue ParF to reveal how it drives plasmid DNA segregation in growing bacteria.


Susan (Sichen) Shao (2012-2016)
Susan started her lab at the Cell Biology department at Harvard Medical School as an Assistant Professor in 2016. She was a PhD student with Manu Hegde and moved with him to the LMB. During her subsequent postdoc, she performed the reconstitution and functional analysis of the ribosome-associated ubiquitination pathway and solved its structure. She has since applied her methods to investigate the process of stop codon decoding, and in collaboration with the Ramakrishnan lab she has determined the structure of the ribosome in combination with mammalian release factor.


Melina Schuh (2009-2016)
Melina was appointed Director at the Max Planck Institute in Göttingen in 2016. After completing her PhD in 2008 at the EMBL in Heidelberg, Melina started her own research group at the LMB in 2009 looking at how diploid oocytes mature into haploid eggs. Her work explained some of the causes of aneuploidy – a defect in the assortment of the chromosomes in the egg and a common cause of infertility – and developed methods to systematically analyse defects linked to abnormal chromosome segregation during meiosis.

In 2007 the LMB’s Richard Henderson and Chris Tate co-founded Heptares Therapeutics to exploit pioneering new technology to stabilise G-protein-coupled receptors (GPCRs). Heptares is now wholly owned by Sosei.

Because they play a crucial role in many diseases, GPCRs are the targets of 25-30% of all modern drugs.

As Chris comments: ‘GPCRs are an important family of proteins found in cell membranes, which are responsible for triggering responses inside cells to external factors such as hormones, neurotransmitters and sensory stimuli. Commonly prescribed drugs, such as beta-blockers and anti-migraine drugs, specifically interact with these receptors. Understanding the structure of GPCRs at a molecular level is important in designing new and more effective drugs to combat many human illnesses.

Heptares’ StaR (Stabilised Receptor) technology platform allows us to apply contemporary drug discovery approaches to stabilised GPCRs – improving the chances of finding drugs to previously intractable targets and enabling the development of safer and more selective therapeutic agents.’

Heptares is using this technology to work on its own and with partners to discover new medicines to target key diseases such as Alzheimer’s, schizophrenia, type 2 diabetes, cancers and HIV. In 2015, Heptares was bought for 400 million USD by the Sosei Group, a leading Japanese biopharmaceutical company. Four drug candidates have recently entered clinical trials for cognitive decline, psychosis and cancer.
Research Groups

Radu Aricescuaudu@mrc-lmb.cam.ac.uk
The structural biology of synaptic connectivity. We study the architecture of neurotransmitter receptors and their super-molecular assemblies, using purified components and in situ, aiming to understand the physiology of neuronal synapses.

M. Madan Babu
madam@mrc-lmb.cam.ac.uk
Regulatory genomics and systems biology. We are interested in understanding how the regulation of biological systems is achieved at distinct levels of organisation (molecules, pathways, genomes) and how these processes shape the evolution of the genome.

Gerry Crossan
gcrossan@mrc-lmb.cam.ac.uk
Maintenance of genome stability in stem cells. We use a combination of mouse genetics and state-of-the-art molecular biology tools to investigate the mechanisms that prevent mutagenesis in the germine.

Molecular mechanisms of the anaphase-promoting complex and the mitotic checkpoint. We study how the anaphase-promoting complex (APC/C) recognises and ubiquinates proteins during the cell cycle, and the basis for its regulation by the spindle assembly checkpoint.

David Barford
dbarford@mrc-lmb.cam.ac.uk
Dynein.

Anne Bertolotti
abertol@mrc-lmb.cam.ac.uk
Understanding and preventing the deposition of misfolded proteins. Our goal is to understand the mechanisms that govern the deposition of via biologic-prone proteins, why they persist in aged cells and to identify strategies that could reduce their burden in disease.

Mechanisms of asymmetric trafficking. Our goal is to understand the molecular mechanisms by which the cytoskeleton controls the polarized segregation of cell fate determinants during asymmetric cell division.

Mark van Breugel
vabreug@mrc-lmb.cam.ac.uk
Structure and assembly mechanisms of centrioles. We aim to understand the assembly mechanisms and molecular architecture of centrioles, essential cell organelles with key roles in cell division, sensing and movement.

Molecular mechanisms of Wnt signal transduction. We are optimising and applying electron cryo-microscopy methods to understand the assembly processes of individual Wnt signalling components and their mutual interactions. Ultimately, we aim at identifying and developing their potential as therapeutic targets in cancer.

Mariani Bienz
m2b2@mrc-lmb.cam.ac.uk
Regulatory genomics and systems biology. We are interested in understanding how the regulation of biological systems is achieved at distinct levels of organisation (molecules, pathways, genomes) and how these processes shape the evolution of the genome.

Enveloped viruses and coated vesicles. We aim to study viral assembly and budding using cryo-tomography methods to understand the physiology of neuronal synapses.

John Briggs
jbriggs@mrc-lmb.cam.ac.uk
We are interested in understanding how neural networks are functionally assembled, how they integrate information, and how they evolve.

Simon Bullock
sbullock@mrc-lmb.cam.ac.uk
Mechanisms of mRNA localisation and cytoskeletal transport. Our goal is to shed light on how cellular components are sorted and dispersed by microtubule-based motor complexes, and how these transport processes contribute to the functions of cells within organisms.

Ingo Greger
ig@mrc-lmb.cam.ac.uk
Mechanisms of asymmetric trafficking.

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Andrew Carter
cartera@mrc-lmb.cam.ac.uk
The structure and mechanism of dynein. We use structural biology approaches and single molecule microscopy to understand how the microtubule motor dynein, the largest and most complicated of the cellular motors, transports its cargo.

Systematic genetic code reprogramming / Centre for Chemical and Synthetic Biology. We are reprogramming the genetic code of living organisms, how cells handle mistakes in these pathways, and the diseases that arise from their failure.

Jason W. Chih
jwchih@mrc-lmb.cam.ac.uk
We are reprogramming the genetic code of living organisms, how cells handle mistakes in these pathways, and the diseases that arise from their failure.

Membrane protein biosynthesis and quality control. We seek to understand how secreted and membrane proteins are assembled, how cells handle mistakes in these pathways, and the diseases that arise from their failure.

Ramanujan Hegde
rhegde@mrc-lmb.cam.ac.uk
We are interested in understanding how neural networks are functionally assembled, how they integrate information, and how they evolve.

Molecular mechanisms of the anaphase-promoting complex and the mitotic checkpoint. We study how the anaphase-promoting complex (APC/C) recognises and ubiquinates proteins during the cell cycle, and the basis for its regulation by the spindle assembly checkpoint.

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Research Groups

**Philipp Holliger**  ph@mrc-lmb.cam.ac.uk

Synthetic biology of nucleic acid replication. We are developing in vitro systems for directed evolution to create novel, DNA-like polymers, for applications in nanotechnology and material science.

**Leo James**  lj@mrc-lmb.cam.ac.uk

Intracellular Immunity. Viral and bacterial pathogens evading the immune system are still able to infect cells. We are investigating how cells defend themselves against infection by intracellular pathogens.

**Gregory Jeffries**  jeffries@mrc-lmb.cam.ac.uk

Off-axis perception in the fruit fly. We use a combination of genetic labelling and manipulation, targeted in vivo whole cell patch clamp recording and high resolution computational neuroanatomy to understand how smell turns into behaviour in the fruit fly.

**Wanda Kukulski**  kukulski@mrc-lmb.cam.ac.uk

Linking membrane architecture to function by correlative microscopy. We study how membrane dynamics control cargo traffic through the network of endosomes, and the role of membrane architecture at contact sites between organelles.

**Madeline Lancaster**  mancaster@mrc-lmb.cam.ac.uk

Human brain development in cerebral organoids. We are studying cellular mechanisms underlying human brain development to understand neurodevelopmental disease progression and to identify potential therapeutic avenues.

**Jan Löwe**  jll@mrc-lmb.cam.ac.uk

The bacterial cytoskeleton. We investigate biological systems involving prokaryotic filamentous proteins that are involved in mechanical processes such as construction and DNA segregation during cell division.

**Andrew McKenzie**  am@mrc-lmb.cam.ac.uk

Transgenic models of immune and haematopoietic disorders. We focus on understanding the molecular regulation of the immune responses underlying allergy and asthma, with the aim of identifying novel pathways for therapeutic intervention.

**Harvey McMahon**  hrm@mrc-lmb.cam.ac.uk

Membrane curvature as an organising principle for eukaryotic cell biology. Our work is elucidating the mechanisms of membrane bending, their role in membrane trafficking and fusion to understand how certain viral sequences disrupt the process in eukaryotes.

**Liz Miller**  emiller@mrc-lmb.cam.ac.uk

Protein transport and quality control in the secretory pathway. Our work is aimed at understanding basic mechanisms of secretory protein biogenesis, focusing on protein quality control within the ER.

**Patrycja Koziol**  pk@mrc-lmb.cam.ac.uk

Dendritic cells and initiation of the immune responses. Our goal is to build a detailed picture of the molecular events involved in antigen cross-presentation by dendritic cells, and to understand how antigen processing is regulated in viral infection and cancer.

**Wanda Kukulski**  kukulski@mrc-lmb.cam.ac.uk

Membrane protein sorting. We are currently interested in translation initiation in both bacteria and eukaryotes, as well as how certain viral sequences disrupt the process in eukaryotes.

**Sean Munro**  sean@mrc-lmb.cam.ac.uk

The organisation of membrane traffic by G proteins. We investigate how each G protein acquires a unique set of active G proteins, and how these then control the structure of organelles and direct the traffic between them.

**Kiyoshi Nagai**  kn@mrc-lmb.cam.ac.uk

Crystallographic and functional studies of the spliceosome. Our aim is to understand the molecular mechanism of pre-mRNA splicing and provide insights into the evolutionary origin of the spliceosome.

**John O’Neill**  oon@lmb.cam.ac.uk

Cellular rhythms, signalling and metabolic regulation. We explore the biochemical basis of circadian timekeeping and how biological rhythms integrate with other cellular systems to orchestrate temporal control of metabolism.

**Hugh Pelham**  hp@mrc-lmb.cam.ac.uk

Membrane protein sorting. We study how proteins are sorted within cells and in particular how, if they are damaged or unwanted, they are marked by ubiquitination for subsequent destruction.

**David Neuhaus**  dne@mrc-lmb.cam.ac.uk

Solution structure by NMR spectroscopy. We study the structure and the interactions of biological macromolecules and their complexes in solution employing modern NMR and isotope labelling techniques.

**Felix Randow**  fr@mrc-lmb.cam.ac.uk

Cell-autonomous and innate immunity. Guided by the importance of cell-autonomous immunity as the sole defender of unicellular organisms, we investigate how mammalian cells sense invading pathogens and protect their interior against them.
**Research Groups**

**Katja Röper**  kroeper@mrc-lmb.cam.ac.uk
The cytoskeleton in tissue morphogenesis. We investigate how the formation of epithelial tissues is driven by cellular and molecular changes, with a particular focus on the role of the cytoskeleton and its regulators during these processes.

**Christopher Russo**  crusso@mrc-lmb.cam.ac.uk
Atomic resolution imaging of biological specimen by electron cryo-microscopy. We aim to improve cryo-preparation and imaging methods to the point of using the electron microscope to image the atomic resolution structure of purified macromolecular complexes.

**Julian Sale**  jsale@mrc-lmb.cam.ac.uk
Vertebrate mutagenesis and DNA damage tolerance. We aim to understand how impediments to DNA replication lead to mutation and to changes in the epigenetic signals that control gene expression.

**William Schafer**  wschafer@mrc-lmb.cam.ac.uk
Cellular and molecular mechanisms of behaviour. We try to elucidate the mechanisms by which nervous systems process information and generate behaviour, and the cellular and molecular basis of sensory transduction and neuromodulation.

**Sjors Scheres**  scheres@mrc-lmb.cam.ac.uk
Visualising molecular machines in action. We develop new collection and processing methods for cryo-EM structure determination, and use these to understand how macromolecular machines work.

**John Sutherland**  jsuth@mrc-lmb.cam.ac.uk
Chemical origins of molecular biology. We are interested in uncovering prebiotically plausible syntheses of the informational, catalytic and compartment–forming molecules necessary for the emergence of life.

**Joseph Yeeles**  jyeeles@mrc-lmb.cam.ac.uk
Mechanisms of chromosome replication. We aim to understand how the chromosome replication machinery copies vast amounts of DNA while minimising mistakes that cause mutations.

**Roger Williams**  rwilliams@mrc-lmb.cam.ac.uk
Structural studies of phospholipid signalling. We are trying to develop a detailed structural understanding of the network of interacting pathways involved in phospholipid signalling, including the structures of endosomal and autophagosomal protein complexes.

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**Joe Yeeles**  jyeeles@mrc-lmb.cam.ac.uk
Mechanisms of chromosome replication. We aim to understand how the chromosome replication machinery copies vast amounts of DNA while minimizing mistakes that cause mutations.

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‘Discoveries cannot be planned. They pop up, like Puck, in unexpected corners.’

Max Perutz
LMB Nobel Prizes

2018 Greg Winter
2017 Richard Henderson
2013 Michael Levitt
2009 Venki Ramakrishnan
2002 Sydney Brenner, Bob Horvitz, John Sulston
1997 John Walker
1984 César Milstein, Georges Köhler
1982 Aaron Klug
1980 Fred Sanger
1962 John Kendrew, Max Perutz
1962 Francis Crick, James Watson
1958 Fred Sanger