MRC Laboratory of Molecular Biology
The MRC Laboratory of Molecular Biology (LMB) is a world-class research laboratory, dedicated to understanding important biological processes at the molecular level. We seek to understand not just the structures of molecules and molecular machines, but also their fates and functions within cells, and how these contribute to the workings of complex systems such as the immune system and the brain, and to problems of human health and disease.

Founded by the Medical Research Council over 50 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 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 are one of the most powerful therapeutic tools.

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

The aim of the Laboratory today remains that of understanding biological processes at the molecular level. New approaches in chemical and synthetic biology and biotechnology provide the tools for future discoveries and applications. We continue to promote the application of our research findings, both by collaboration with existing companies and by the founding of new ones.

The LMB provides an 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 LMB have made a difference to the world, and will continue to do so.

Hugh Pelham, LMB Director
Research

Science in the LMB is organised in four research Divisions with their own strengths and goals. While the science covers a broad range, the common theme is the emphasis on understanding biological processes at the molecular level. Fundamental studies that offer opportunities for medical applications or technical innovation are supported and encouraged.

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 or electron microscopy are accompanied by the study of major biological questions such as protein degradation, splicing and mRNA control, translation, cellular transport and signalling. Many of these areas are also important for understanding and developing cures for various diseases.

The 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.

The information in our genes is used to make the thousands of proteins that carry out diverse functions in each cell. This essential process of translating the genetic code into protein, which is carried out by the ribosome (a large macromolecular complex present in all cells), has been studied at the LMB since its inception.

Virtually every molecule in the cell is either made by the ribosome or by protein enzymes that are themselves made by the ribosome. However, because of its size and complexity, understanding how the ribosome works is a difficult and long-term problem.

A major breakthrough was achieved in 2000-01 when Venki Ramakrishnan’s group described the atomic structure of the small subunit. Over the next decade, they obtained snapshots of the whole ribosome in many different stages of the process – increasing our understanding of how the ribosome helps to read the genetic code, how it moves along the mRNA and how it terminates the process. Venki shared the 2009 Nobel Prize in Chemistry for his work on the ribosome.

The group’s work also provided insights into how antibiotics bind to specific pockets in the ribosome structure. This could help in the design of antibiotics to treat people who are infected with a bacterium that has developed antibiotic resistance, for example some of the strains of bacteria that cause tuberculosis. Better targeting of the bacterial ribosome should also help to avoid negative effects on human cells, helping to reduce the side effects of taking antibiotics.

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Research

Medical Applications

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Venki comments: ‘I came to the LMB because it offers an ideal and stable environment that allows long-term research on fundamental problems. Our work is an example of how such research can lead to medically important applications. Currently, we are trying to understand how the much larger (one and a half times) ribosomes in animals and plants start the process of making proteins and how viruses hijack this process.’

‘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

Above: The ribosome from bacteria, showing the large subunit that makes the protein chain in blue and the small subunit that reads the code in yellow

Difficult problems - Long-term view
Research

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 also 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 afflict 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. These antibodies have been ‘humanised’ using a method pioneered at the LMB and are undergoing further development to evaluate their therapeutic potential.

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

Research - Better health

Far left: Crystal structure of Parkin, with Parkinson’s disease mutations in red | Left: 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 in the lung

Research

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

Research

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6

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7
Cell Biology

The bodies of complex animals such as humans are made up of billions of individual cells. Whilst our cells share many features, they also have specialist roles to allow the different parts of our bodies to perform different functions. The Cell Biology Division aims to understand the fundamental principles of cellular organisation and how these are modified in cell types that perform important specialised tasks.

The Division’s work has a strong focus on the investigation of membrane-bound compartments and of the cytoskeleton. These are studied in a diverse range of model organisms, including yeast, flies, nematodes, and mice, as well as using cell culture and in vitro techniques, but there is a shared interest in understanding underlying principles that apply both to model systems and to humans.

Within the Division, the research groups also share an interest in methods – including advanced microscopy, genetic methods and protein biochemistry – that can link biology and pathology to the underlying molecular mechanisms.

In addition to examining the mechanisms that underlie processes shared by most if not all cells, the Division also investigates how these mechanisms are varied to allow specialised cells of particular biological and clinical importance to perform their unique roles. These include investigating how neurons are assembled into functional networks or how they sense our environment, how epithelial cells form our organs, and how motile cells migrate to heal wounds and fight infection.

Young scientists - Innovative research

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.

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 begin examining 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.’

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

In Madeline’s words: ‘Innovation is driven by the curiosity to answer fundamental questions.’ Michael Neuberger
Human disease - Novel molecular pathology

Neurodegenerative diseases of the brain affect an increased number of people in our ageing population. Alzheimer’s and Parkinson’s are the most common neurodegenerative diseases, affecting approximately 30 million people worldwide.

Existing therapies focus, at best, on the symptoms of these diseases rather than on finding a cure. The symptoms of Alzheimer’s disease (a dementing disorder) and Parkinson’s disease (primarily a movement disorder) result from the loss or malfunction of nerve cells in particular brain regions. A common characteristic is the presence of abnormal filamentous inclusions within cells. Similar inclusions are found in related disorders, including Pick’s disease, progressive supranuclear palsy, dementia with Lewy bodies and multiple system atrophy.

Work carried out by Michel Goedert’s group helped identify the microtubule-associated protein tau and the protein alpha-synuclein as components of the pathologic filaments, and to show that their deposition causes cell death and neurodegeneration. In the human brain tau and alpha-synuclein inclusions are thought to form in a few cells from where they spread in a ‘prion-like’ manner over time leading to disease.

Michel comments: ‘Our current work is aimed at understanding the mechanisms by which the normally soluble tau and alpha-synuclein proteins assemble into abnormal filaments. To this effect, we are developing experimental models of tau and alpha-synuclein deposition.

In due course, this work may lead to the development of mechanism-based therapies for the tauopathies and the alpha-synucleinopathies.’

‘We’re not asked to find cures for diseases, but to provide the background that allows disease processes to be better understood.’

John Walker
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 Cancer Institute, Cambridge Institute of Medical Research, and the Sanger Institute as well as with industrial partners such as AstraZeneca and MedImmune thrive, aided by the geographical proximity.

*http://www.med.cam.ac.uk/divisions-and-research-groups/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 near-atomic resolution from cryo-EM images can be obtained.’

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

Facilities

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 – and 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.

Environment

Mass Spectrometry and Proteomics The facility, headed by Mark Skehel, employs electrospray ionisation mass spectrometry for both qualitative and quantitative characterisation of proteins. Access to several mass spectrometric technologies, including MALDI, allows investigators to adopt multiple analytical strategies.

Electron Microscopy Primarily intended for hands-on research by students, postdocs and group leaders, who prepare specimens, operate the microscopes and analyse the resulting images or diffraction patterns themselves, the facility is managed by Shaoxia Chen with help from Christos Savva. Three state-of-the-art 300 keV FEG cryo-transmission electron microscopes, two Titan Krios and a Polara as well as six other electron microscopes, including a Scios DualBeam scanning electron microscope, provide flexible options for 2D and 3D structural analysis of biological material.

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

Crystalisation and X-ray infrastructure for crystallography includes robotic stations for formulating and setting up crystallisation trials, in house X-ray generators and a crystal-handling robot for automated screening and data collection, all under the expert assistance of Fabrice Gorrec and Minmin Yu. LMB scientists use the Diamond synchrotron in Harwell and the European Synchrotron Radiation Facility in Grenoble as well as other specialised synchrotrons.

Mass Spectrometry and Proteomics

Electron Microscopy

Light Microscopy

Crystalisation and X-ray
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 60 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 to support the scientific programmes of the LMB and other MRC Units in Cambridge.

Nuclear Magnetic Resonance A state-of-the-art facility – located in a separate, purpose-built building – houses 500, 600, 700 and 800 MHz spectrometers, all equipped with cryoprobes and multichannel configuration. It also provides robotics for screening small molecule compound libraries against potential drug targets 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 1.8PB. An expert team, headed by Jake Grimmett supported by Toby Darling, provides advice on computational problems.

Workshops The LMB’s scientists also benefit from access to what are probably the finest workshops in any UK laboratory, headed by Howard Andrews and Steve Scotcher. In practical terms, having Electronics and Mechanical 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.

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

Sydney Brenner

Christopher says: ‘The LMB houses state-of-the-art mechanical 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.’
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 650 scientists and support staff work in the LMB, with around 450 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 50 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 idiosyncratic antipathy towards rigid hierarchy, by a wealth of freely-shared services and resources and by 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.

Attracting scientists - UK and worldwide

David Barford joined the LMB in 2013, from the Institute of Cancer Research in London, where he was co-head of the Division of Structural Biology. His group studied proteins that contribute to tumour development, and were also starting to determine the structure of the anaphase promoting complex (APC/C), which regulates cell cycle transition. David is a winner of the Colworth medal of the Biochemical Society (1998), a Fellow of the Royal Society and the Academy of Medical Sciences, and a member of EMBO.

David’s group are using single particle electron cryo-microscopy, pioneered at the LMB, to determine atomic resolution structures of APC/C in different functional states. This will help understand how this complex machine regulates the cell cycle, in particular how duplicated sister chromatids are separated at mitosis, and illuminate the design of novel anticancer therapies.

As David explains: ‘The world class facilities at LMB have had a huge impact on my work. Within the first 6 months of work here, using the LMB’s wonderful cryo-EM facilities, the structure of APC/C has improved from 7Å to 3.8Å. I came to the LMB because of these core facilities, the focus on basic science and the great scientists here.’

Manu’s group are interested in the cross talk between the biosynthesis of proteins and the rest of the cellular machinery. The aim is to unravel the mechanisms that cells use to control the quality of their building blocks and of the molecules that carry out their functions.

Manu comments: ‘The LMB brings together a diverse range of scientists exploring nearly every cellular process in considerable depth. Scientists here have the luxury of allowing their curiosity to drive their research. The combination of scientific breadth, mechanistic depth, and complete freedom is rare; that it can be accomplished in a cozy environment with daily interactions with all your colleagues is unique. I spent a day visiting the LMB and the infectious enthusiasm hooked me immediately.’
Building an international science community

‘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

Educating the next generation

‘The LMB provides a wonderful environment for students...although attached to a research group, the whole lab is, in essence, their playground meaning they can - and often do, approach anyone in the building who can help with their project.’

Cristina Rada, LMB Director of Graduate Studies

Training scientific talent

Destination of postdoctoral fellows trained at the LMB from 2009-2014. (258 total)

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MITCHELL R. LAMBERT, M.D.

MRC LMB
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, 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 facilitate their successful projects undertaken by the students and enlarge the scope and ambition of the staff who run lab facilities all conspire 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.

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.

Peter Sarkies (2008-2011) Peter recently started his own group at the MRC Clinical Sciences Centre in London. He did his PhD at the LMB where he uncovered links between impaired DNA replication and the maintenance of epigenetic information. He was awarded the Max Perutz student prize in 2010 and after a short postdoc in the Department of Genetics in Cambridge, he received a Junior Research Fellowship (JRF) from Imperial College London in 2014 as an outstanding early career researcher.


Susan (Sichen) Shao (2012-2016) Susan is about to start her lab at the Cell Biology department at Harvard Medical School as an Assistant Professor. 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 recently has been appointed Director at the Max Planck Institute in Göttingen. After completing her PhD 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.

The LMB has an enviable track record in promoting the application of its research findings. Researchers at the LMB benefit from the Laboratory’s long experience in this field, and from being able to access expert advice on how best to exploit their discoveries – whether by the licensing of patents, collaborations with existing companies or by founding new spin-off companies.

The LMB has also benefited by generating significant sums to invest in future scientific research. For example, in the five years from 2010-15 the MRC received over £350 million from royalties, share sales and licensing intellectual property.

Inevitably, the Laboratory’s focus on curiosity-driven and long-term basic research means that there is often a long ‘development gap’ between discovery and bringing a drug to market. Progress may take time but there have been spectacular successes, including the development of humanised monoclonal and synthetic antibodies – which now make up a third of all new drug treatments for a variety of diseases, including cancer, arthritis and asthma.

When intelligently exploited, this type of research pays handsome dividends for both human health and UK industry. For example, the licensing of the LMB’s work on human antibodies to local start-up company Cambridge Antibody Technology led to the development of Humira® a key drug in the treatment of rheumatoid arthritis.

Other notable contributions include the development of laser-scanning confocal microscopes and the more recent spin-off, Heptares Therapeutics, exploiting structural analysis of G-protein-coupled receptors for drug design.

Scientists at the LMB are engaging with industry to bring promising new methods and discoveries towards practical application. The location of AstraZeneca adjacent to the Laboratory has led to a joint collaboration fund to foster interactions, and other biomedical companies including Pfizer, GlaxoSmithKline, Heptares and Eli Lilly also fund work at the LMB. Methods to determine atomic structures of macromolecules by electron microscopy, developed at the LMB, are being transferred to industry to further their own research and development.

Impact

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). 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.
ubiquitinates proteins during the cell cycle, promoting complex (APC/C) recognises and checkpoint.

Molecular mechanisms of the anaphase-promoting complex and the mitotic centrioles.

Structure and assembly mechanisms of centrioles.

Mechanisms of mRNA localisation and cytoskeletal transport.

Systematic genetic code reprogramming / Centre for Chemical and Synthetic Biology.

Regulatory genomics and systems biology. We are interested in understanding how the regulation of biological systems is organized at distinct levels of organisation (molecules, pathways, genomes) and how these processes shape the evolution of the genome.

Molecular mechanisms of Wnt signal transduction. We study the molecular components and their mutual interactions. Ultimately, we aim at identifying and developing their potential as therapeutic targets in cancer.

Enveloped viruses and coated vesicles - retrovirus assembly processes of enveloped viruses such as HIV-1 and influenza, as well as of membrane trafficking vesicles.

We aim to understand the assembly processes and the potential as therapeutic targets in cancer.

Mechanisms of asymmetric trafficking.

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.

Therapeutic applications of oligonucleotide conjugates.

Our work focuses on chemical synthesis of modified oligonucleotides and their peptide conjugates for treatment of neuromuscular diseases by targeting intracellular RNA.

Understanding and preventing the deposition of misfolded proteins. Our goal is to understand the mechanisms that govern the degradation of misfolded proteins, why they persist in aged cells and to identify strategies that could reduce their burden in disease.

We are reprogramming the genetic code of living organisms via biological engineering. We are using reprogrammed codes and innovative chemistry, to provide new insight into biological processes.

We use structural biology approaches and single molecule microscopy to understand 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.

We study the molecular components and their mutual interactions. Ultimately, we aim at identifying and developing their potential as therapeutic targets in cancer.

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We are unravelling the detailed mechanisms and regulation.

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We study the architecture of synaptic connections and how this process results in nerve cell degeneration and human diseases.
Our aim is to understand the molecular mechanisms of secretory pathways for therapeutic intervention.

Richard Henderson
High-resolution 3D structures by electron cryo-microscopy. We aim to determine the atomic structure of interesting or important membrane proteins and membrane protein complexes using cryoEM.

Leo James
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 Jeffers
Olfactory 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.

David Komander
Specificity in the ubiquitin system. Our work focuses on atypical ubiquitin chains, and we aim to understand their roles in the cell, and reveal how proteins distinguish between the different chain types.

Rob Kay
Chemotaxis and macropinocytosis. We are interested in two major overlapping cell biological processes: chemotaxis and macropinocytosis, both ancient processes that use the actin cytoskeleton and cortex to produce projections of the plasma membrane.

David Kukulski
Membrane curvature as an organising principle for eukaryotic cell biology. The bacterial cytoskeleton.

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

Michael Hastings
Molecular neurobiology of circadian timing. We aim to provide a molecular genetic explanation for the ancient conserved process of circadian timing, to understand how the central and peripheral clocks together co-ordinate our metabolic and physiological rhythms.

Ramanujan Hegde
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.

Philipp Holliger
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.

Richard Neuhaus
Protein transport and quality control in the endoplasmic reticulum. We study the structure and the interactions of biological macromolecules and their complexes in solution employing modern NMR and isotope labelling techniques.

Andrew McKenzie
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.

Garib Murshudov
Computational crystallography. We develop computational, statistical and structural bioinformatic tools for the analysis of macromolecular crystal structures, in particular dealing with limited and noisy data.

Zachary Gage
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.

Madeline Lancaster
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.

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Cell biology of the plasma membrane. We are interested in how regions of the plasma membrane specialised for different functions, and how proteins and lipids are internalised from the cell surface.

**Ben Nichols** ben@mrc-lmb.cam.ac.uk

We are interested in how certain viral sequences disrupt the process in both bacteria and eukaryotes, as well as how interventions in this process might be used to elucidate the mechanisms of resistance.

**Roger Williams** rlw@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.

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

Vesicle trafficking and internalisation of proteins into the cell interior against them. We study how invading pathogens and protect their interior against them.

**Joe Yeeles** jyeeles@mrc-lmb.cam.ac.uk

Atomic resolution imaging of biological specimen by electron cryomicroscopy. We aim to improve cryo-preparation and imaging methods to the point where we can use the electron microscope to image the atomic resolution structure of purified macromolecular complexes.

**Christopher Russo** crusso@mrc-lmb.cam.ac.uk

Molecular machines that regulate mRNA polyA tails. Our aim is to establish fundamental principles underlying the assembly of multi-protein complexes, like the Cleavage and Polyadenylation Factor (CPF) in order to understand their cellular function.

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

We study the origins and identity of genotoxic metabolites, the nature of the DNA damage they cause and how cells, in particular stem cells, remove and repair it.

**KJ Patel** kjpatel@mrc-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.

**John O’Neill** oneill@mrc-lmb.cam.ac.uk

Membrane protein sorting. We study how proteins are sorted within cells for subsequent destruction.

**Ben Nichols** ben@mrc-lmb.cam.ac.uk

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.

**Marco Tripodi** mtripodi@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.

**Chris Tate** cgt@mrc-lmb.cam.ac.uk

Mechanisms of chromosome replication. We aim to understand how the chromosome replication machinery keeps vast amounts of DNA while minimising mistakes that cause mutations.

**John Sutherland** johns@mrc-lmb.cam.ac.uk

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**Christopher Russo** crusso@mrc-lmb.cam.ac.uk

Structure of the translational apparatus. We are currently interested in translation in both bacteria and eukaryotes, as well as how certain viral sequences disrupt the process in eukaryotes.

**Venki Ramakrishnan** ramak@mrc-lmb.cam.ac.uk

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**William Schafer** wschafer@mrc-lmb.cam.ac.uk

We are interested in uncovering prebiotically plausible syntheses of the informational, catalytic and compartment-forming molecules necessary for the emergence of life.

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