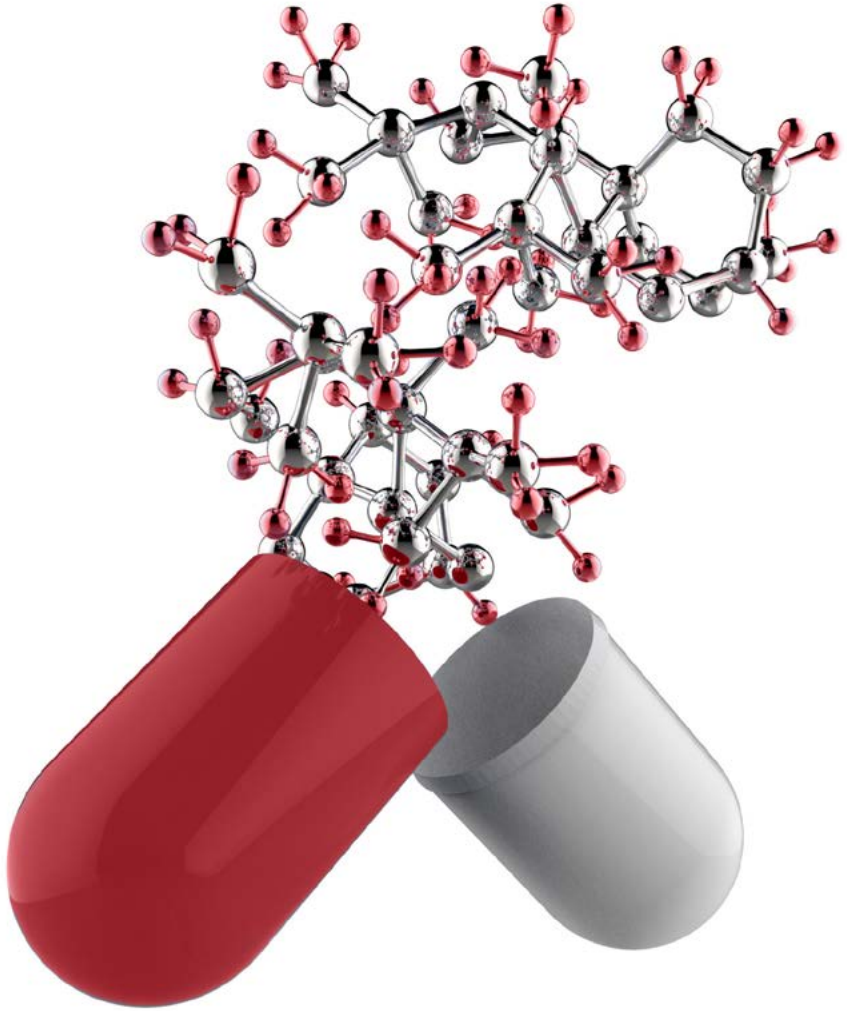
UNIVERSITY OF LIVERPOOL



Molecular and Clinical Pharmacology

From bench to bedside, and back again

LIFE CHANGING
World Shaping

The Department of Molecular and Clinical Pharmacology is part of the University of Liverpool's Faculty of Health and Life Sciences.

The Faculty ranks in the top 100 World Universities for Clinical, Pre-Clinical and Health subjects and the top 150 for Life Sciences. With a research programme that spans the breadth of basic, applied and translational research, the Faculty's five Research Institutes provide the quality and critical mass required to tackle major global challenges.

The Faculty hosts centres of excellence across a range of fields, including Medical Research Council (MRC) Centres for Drug Safety Science and Musculoskeletal Ageing, a Wolfson Centre in Personalised Medicine, and two National Institute for Health Research (NIHR) Health Protection Research Units in Gastrointestinal and Emerging and Zoonotic Infections. The Faculty of Health and Life Sciences offers a first-rate research environment with unrivalled access to technology platforms and associated academic expertise to turn good ideas into ground-breaking research.

We are strongly committed to applying our research and, with a rich patient population and national co-ordinating role, have a proud record of designing and supporting successful clinical trials. Through our complementary partnerships with the NHS, industry and academia, we are building scale and expertise to drive future growth, bringing economic benefits and delivering significant improvements in human and animal health.

OUR STORY

The Department of Molecular and Clinical Pharmacology is dedicated to defining disease processes, understanding both drug actions and adverse reactions, developing novel therapeutic strategies for intervention and optimising the benefit–risk ratio of current and new drugs. We are based within the Institute of Translational Medicine, whose overall aim is to take basic scientific understanding and translate it into innovations for the benefit of patients, the public and health systems across the world.

Established in the 1960s, we are the UK's largest pharmacology department, bringing together more than 40 leading academics and 110 postgraduate students. "Our research goes from bench to bedside, and then back again," explains Professor Munir Pirmohamed, Head of the Department.

"Clinical and basic scientists work side by side in the laboratory not only to develop new drugs and treatments, but also to look at existing treatments to identify where the problems are and find strategies to improve drugs so they can be used more effectively."

From Manchester to Brazil, Germany to Japan, the Department has links locally, nationally and internationally. We work in partnership with charities, the pharmaceutical industry, NHS Trusts and scientific facilities. Local links include the Centre for Genomics Research, the North West Cancer Research Centre and Liverpool Health Partners (LHP).

The Department leads a very successful undergraduate programme and accepts around 20 graduates each year for postgraduate training.

Students join a rich and vibrant environment, with the opportunity to undertake multidisciplinary studentships involving basic science, and pre-clinical and clinical research.

We have a strong record in securing research funding from major UK, EU and US agencies, including the MRC, Biotechnology and Biological Sciences (BBSRC), and Wellcome Trust. Our research comprises four main themes: Personalised Medicine, Drug Safety Science, Infection and Inflammation, and Neuropharmacology.

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Theme 1: Personalised Medicine

We are researching the genetic basis for the way individuals respond differently to drugs.

Personalised medicine has the power to revolutionise the way serious diseases are treated in the UK and beyond.

When doctors currently prescribe drugs, a patient may experience a sub-optimal response or even severe side effects that can lead to further complications. Genomic, proteomic and metabolomics technologies allow treatments to be personalised, which maximises a drug's potential and minimises its risks to patients.

Operating from the world-renowned Wolfson Centre for Personalised Medicine, the Department's research focuses on identifying predictive genetic markers for drug responses associated with clinical areas, including cardiovascular disease, asthma and epilepsy. Professor Munir Pirmohamed leads a multidisciplinary

team of more than 70 clinical, basic science and administrative personnel, who are dedicated to detecting genes and pathways that can determine a patient's response to a drug.

The ultimate aim of our research is to translate our laboratory findings into clinical care for the benefit of patients and healthcare systems. We are using cutting-edge cell culture and bio-analytical facilities to gain a deeper understanding of how genetic variation may impact a patient's reaction to different drugs.

Our work has resulted in a number of clinical trials aiming to validate the repositioning of commonly prescribed drugs in order to find alternative treatments. We also collaborate with international partners, and have been at the forefront of recruitment efforts to find patients with particularly severe and rare drug reactions.

The Department's 1,000 m² research facility, housed within the former Victorian Liverpool Royal Infirmary, boasts innovative clinical sample handling and archiving, including a fully automated, robotic DNA sample management system that can store up to 300,000 samples.

> "The patient receives the right drug at the right dose at the right time, rather than the current paradigm of trial and error where we don't know how a patient is going to react to a drug."
>
> Professor Munir Pirmohamed

OUR IMPACT

WARFARIN

Warfarin, a widely used drug in the UK, is difficult to prescribe because of the problems in predicting the dose required to maintain adequate anticoagulation, while at the same time preventing bleeding. We have shown in a randomised controlled trial (published in the *New England Journal of Medicine*) that genotyping for two genes before prescribing warfarin can improve anticoagulation control. We are currently evaluating how this genetic test can be implemented in NHS clinics.

Theme 2: Drug Safety Science

We are undertaking ground-breaking research into adverse drug reactions to improve the benefit-risk ratio of current and new medicines.

Adverse drug reactions are a significant problem for patients, healthcare systems and the pharmaceutical industry.

In the UK, 6.5% of all admissions to hospitals are due to adverse drug reactions (ADRs) and 16% of all in-patients experience an ADR, costing the NHS an estimated £2 billion a year. ADRs also contribute to drug attrition and drug withdrawals from the market.

Recognising its excellence in the field of drug safety, the Medical Research Centre (MRC) awarded the Department a Centre grant in 2008. The MRC Centre for Drug Safety Science (CDSS) is the only centre of its kind within Europe, and the prestigious grant was renewed in 2014 for another five years.

The CDSS carries out clinical and basic research into the causes, characteristics and consequences of ADRs and focuses on the mechanisms and genetic predisposition of ADRs.

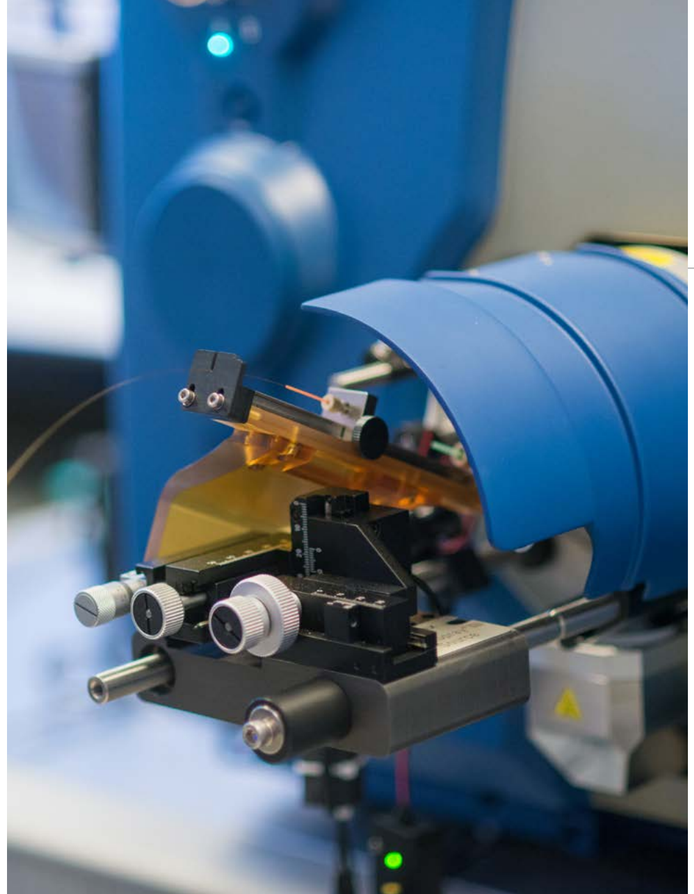
Our mission is to improve the diagnosis and clinical handling of these reactions through the following four-pronged approach:

- Development of novel pre-clinical test systems to identify toxicological potential in new drug candidates
- Development of novel clinical genotyping screens to identify those patients susceptible to ADRs and so inform their treatment
- Development of biomarkers for earlier diagnosis coupled with interventions to both prevent and reduce the severity of ADRs
- Informing the drug design process at an early stage to avoid the incorporation of potentially toxic chemical structures.

Within our research at the Centre, we cover three major themes: drug-induced liver injury (DILI), drug hypersensitivity and gastrointestinal toxicity. Our work is supported by cross-cutting technology, which includes mass spectrometers and proteomic analysis suites, biomarker research, medicinal chemistry expertise, informatics infrastructure, and imaging facilities.

We also coordinate the UK Regenerative Medicine Platform, Safety Hub, which examines the safety hazards of Regenerative Medicine Therapies (RMTs) and develops new methodologies to assess the risks.

> “Our aim is to look at the safety of drugs from both a clinical and chemical perspective in order to determine who may experience an ADR and to develop safer medicines.”
>
> Professor Kevin Park

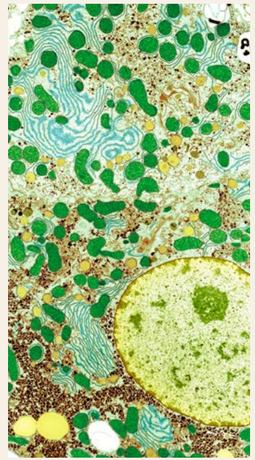


A mass spectrometer

OUR IMPACT

INNOVATIVE MEDICINES INITIATIVE (IMI) MIP-DILI PROJECT

Estimates suggest one in seven cases of liver failure are triggered by an ADR, making drug-induced liver injury (DILI) the leading cause of liver failure and transplantation in western countries. However, predicting which drugs will be toxic to the liver is extremely difficult and many problems are not spotted until the drug is already on the market. The IMI project, MIP-DILI, led by the CDSS, brings together a consortium of pharmaceutical companies, universities and SMEs to develop improved pre-clinical tests that will aid researchers in detecting issues with drugs much earlier in their development.



Liver cell electron micrograph

Theme 3: Infection and Inflammation

We are leading research activities on the pharmacology of infectious diseases, including HIV, Hepatitis C, Cryptococcal Meningitis and Tuberculosis.

The Department is committed to understanding the relationship between pharmacokinetics (drug exposure) and pharmacodynamics (drug response) for both licensed medicines and new nanotechnology-enabled medicines.

Our research impacts those people who need it most, extending from the laboratory to the clinic through to application at a population level. We are developing optimal therapies for large populations of patients, as well as individual patients, encompassing premature neonates, children and adults.

The Department is equipped with state-of-the-art facilities, including molecular and cellular biology suites, containment level III pathogen culture laboratories and bioanalytical facilities, which are accredited by the Good Clinical Laboratory Practice (GCLP). These facilities allow us to define the key mechanistic processes of infectious diseases by using evidence synthesis, pre-clinical and clinical evaluations, and therefore truly bridge the gap between the lab and the real world.

The research theme is renowned for its work in HIV and Hepatitis C. This has resulted in more evidence-based prescribing regimens, and identification and prediction of drug–drug interactions. Our work is internationally recognised, and cited in treatment guidelines in a number of countries. In recent years, the Department has received large amounts of grant research funding from the Engineering and Physical Sciences Research Council, the MRC, the European Commission and the United States National Institutes of Health for the development of nanomedicines. The aim here is to improve and rationalise the complex drug regimens used not only in HIV but also in other disease areas.

> “We are looking at the drugs available for serious infectious diseases and developing better dosage strategies for them.”
>
> Professor William Hope

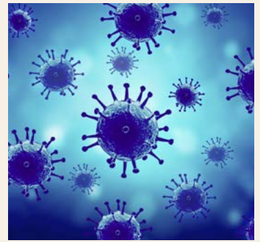
ANTIMICROBIAL THERAPY

The research theme covers the activities of the Antimicrobial Pharmacodynamics and Therapeutics Group, which focuses on achieving a better understanding of antimicrobial pharmacology and finding the best use of antimicrobial agents for humans. Using a range of experimental systems and sophisticated mathematical modelling techniques, the Group is identifying appropriate dosages for patients, and examining how antimicrobial agents are distributed in the body (pharmacokinetics) and their effect on killing microorganisms (pharmacodynamics). Current projects focus on bacterial sepsis, fungal diseases, and the individualisation of antimicrobial therapy.

OUR IMPACT

DRUG INTERACTIONS DATABASE

We want our research to have benefits for society and in particular improve health outcomes. The HIV Pharmacology Group has developed prescribing resources for HIV (www.hiv-druginteractions.org) and hepatitis (www.hep-druginteractions.org) treatments. These are widely accessed, and are recommended by treatment guidelines from the World Health Organization, as well as across Europe, the US, Australia, South America, SE Asia and sub-Saharan Africa. In the UK, every clinic letter to a patient receiving HIV treatment carries a recommendation to check for drug interactions using our website. New apps have also been developed, with more than 50,000 downloads to date.



HIV particles

Our websites have more than

100,000

unique users each year

Theme 4: Neuropharmacology

We are working to discover the underlying causes of common nervous system disorders, examine their consequences and identify new treatments.

Understanding the central nervous system (CNS) is one of the great challenges of medical science. Its complexity and relative inaccessibility mean that the mechanisms behind most brain and spinal cord diseases are still unknown, and consequently, why drugs for neurological conditions have been so difficult to develop.

Covering everything from basic science to clinical work, the Department's multidisciplinary research team works across three key therapeutic areas: epilepsy, pain, and mental health and behaviour.

EPILEPSY

Affecting almost 500,000 people in the UK and an estimated 50 million people worldwide, epilepsy is one of the most prevalent neurological disorders. Only 70% of patients achieve long-term remission with their antiepileptic drug therapy and patients commonly experience side effects and chronic adverse reactions to their medication. We are leading some of the largest clinical trials in the world, and our programme addresses some of the most significant issues in epilepsy therapeutics, using basic laboratory investigations through to patient focused projects.

PAIN

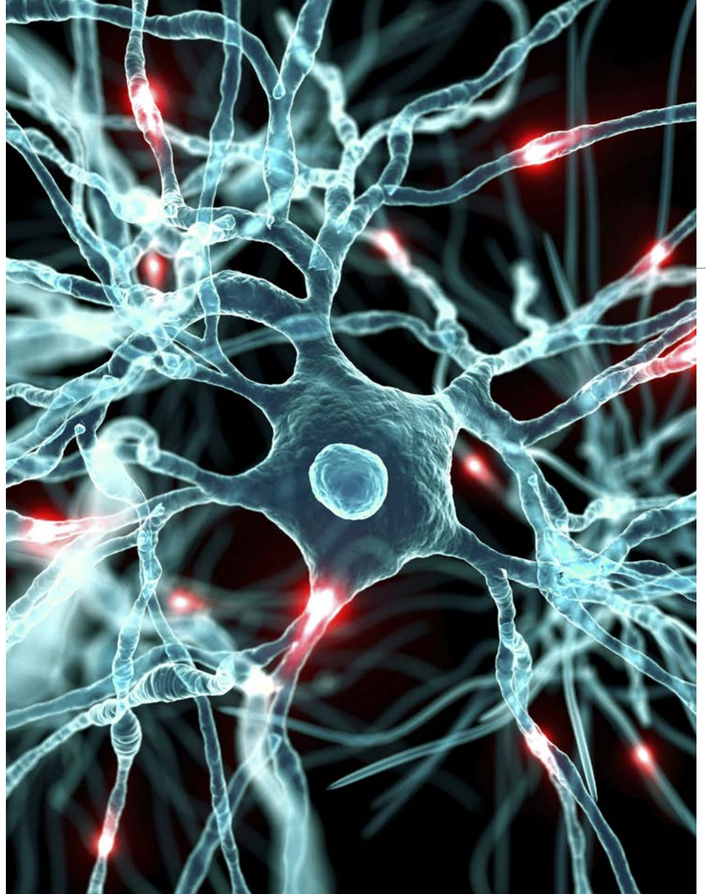
More than eight million adults in the UK are living with persistent or chronic pain, significantly affecting their quality of life. There is a critical need for more effective therapies: current medication is only successful in around 40% of sufferers and many of these patients face adverse reactions to their therapy. Our research has specifically focused on the glycine receptor, one of the main receptors in the CNS that is crucial to the sensation of chronic pain. We are also evaluating the use of immunomodulatory drugs for unexplained chronic conditions.

MENTAL HEALTH AND BEHAVIOUR

The nature versus nurture debate is pivotal to how our behaviour develops, and is believed to be a combination of genetics, environment and life experiences. The research aims to understand how these parameters interact to shape our brain function and how this results in CNS disorders. We use molecular genetics and biochemistry integrated with clinical, psychological and psychiatric data to investigate CNS dysfunction. Ongoing work is concentrated on non-coding DNA that can influence how, when and where individual genes are expressed.

> "We need to develop diagnostic tests, new drugs and improve the use of existing drugs by analysing the mechanisms of these diseases."
>
> Professor Martin Leuwer

20%
of adults are affected by persistent or chronic pain



OUR IMPACT

EFFICACY OF EPILEPSY TREATMENTS

Led from Liverpool, a clinical trial called SANAD-I began in 1999 and compared the effectiveness and cost-effectiveness of standard and new treatments that were available at that time. SANAD-I identified lamotrigine (a new drug) as an effective and cost-effective first-line treatment for patients with a focal epilepsy, and confirmed that valproate (a standard treatment) should remain a first-line drug for patients with a generalised epilepsy or seizures that clinicians find difficult to classify. Since SANAD-I, a number of newer treatments have become available, the most promising of which are levetiracetam and zonisamide, and so a new trial SANAD-II has started. This will compare the effectiveness and cost-effectiveness of these drugs and examine quality of life in patients with newly diagnosed epilepsy.

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