Chemistry a Cambridge



Department of Chemistry University of Cambridge biennial report 2012

Edited and designed by Sarah Houlton Photographs: Nathan Pitt and Caroline Hancox

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Academic staff

Christopher Abell Ali Alavi Stuart Althorpe Shankar Balasubramanian Nick Bampos Paul Barker Ian Baxendale **Daniel Beauregard** Andreas Bender **Robert Best** Peter Bond Sally Boss Jason Chin Alessio Ciulli Jane Clarke Stuart Clarke Aron Cohen Graeme Day **Christopher Dobson** Melinda Duer Stephen Elliott Daan Frenkel Matthew Gaunt **Robert Glen** Jonathan Goodman Clare Grev **Neil Harris** Laura Itzhaki Sophie Jackson **David Jefferson Stephen Jenkins Bill Jones Rod Jones** Markus Kalberer James Keeler David Klenerman **Tuomas Knowles Finian Leeper** Steven Ley **Deborah Longbottom** Mark Miller Jonathan Nitschke William Nolan Ian Paterson John Pyle **Erwin Reisner** Jeremy Sanders **Oren Scherman** Michiel Sprik **David Spring** Sergei Taraskin Michele Vendruscolo **David Wales** Andrew Wheatley Paul Wood Peter Wothers **Dominic Wright**

An introduction to Cambridge Chemistry



This Biennial Report is designed to give a brief introduction to the Chemistry Department of the University of Cambridge. Our department has a long history, yet our national and international position is not determined by our past but by our current performance. Just over 50 research groups form the core of the department. They deliver the research and the teaching that have given the department its position among the very best in the world.

There are many ways to quantify our strength, such as our top ranking in the 2008 UK Research Assessment Exercise, or the fact that nine out of 20 professors are Fellows of the Royal Society.

However, in the end, our success is measured by the recognition that we receive from former students, from our industrial partners, and from the worldwide scientific community. A good measure of this recognition is the fact that 10 of our faculty have currently been awarded personal grants by the European Research Council (ERC).

Scientific excellence and independence are at the basis of our research effort. But with excellence comes societal responsibility. Our faculty members are keenly aware of the great challenges facing the world, and have therefore chosen to collaborate on three strategic themes: chemistry of health, chemistry for sustainability, and chemistry for novel materials.

On these topics, we engage in open collaboration with national and international partners in academia, industry and government.

We are fortunate to attract some of the brightest and the best students – both nationally and internationally. We aim to provide them with the very best undergraduate teaching that will challenge them to excel in whatever they do.

In this biennial report, we highlight a small fraction of the exciting research that is going on in the department. These examples share one important feature with the much larger number of research projects that are not included here: they would not have been possible without the skills and dedication of our PhD students and postdoctoral researchers.

Much more information on our department, its research, its teaching and the people who make it happen, can be found by visiting our website at www.ch.cam.ac.uk.

Daan Frenkel Head of Department June 2012

Chemical science at Cambridge: towards a healthy and sustainable future

Over the past 150 years, chemistry has contributed to the transformation of the world in which we live. Modern industry, healthcare, nutrition and energy needs build on a sustained effort in chemical research and development. Chemical research has been important for the creation of the modern society, and it will become even more important as we address the big issues that confront the world's population today and in the future.

The scope and depth of chemical research will need to be expanded substantially, and in a way that transcends traditional boundaries between disciplines. Here at Cambridge, the chemistry department has embraced this challenge, and will make pioneering contributions to science in the 21st century. We will engage with scientists in other academic fields, and partners outside academia, to ensure we maximise the societal impact of our research.

OUR DELIVERY PLAN

Our vision and delivery plan outlines how we will develop, manage, communicate and apply our targeted research themes, while embracing scholarly investigation and furthering education. The delivery of our vision will focus on the following fundamental principles:

- Identification of key strategic research themes;
- Supporting research leaders;
- Educating the next generation of scientists;
- Industrial partnership and entrepreneurship;
- Communication of research;Management and feedback of
- Management and feedback of success.

The department envisages that chemical science will provide the solutions for a healthy, sustainable future. At the heart of this vision lies a blend of inventive basic chemical research and innovative collaborative strategic themes that form an outline for the next 10 years of research at Cambridge.

BASIC CHEMICAL RESEARCH

The department of chemistry hosts more than 50 research groups that cover a wide spectrum of chemical sciences. In 2010, the department took the strategic decision to organise its research into five areas that would encourage scientific interaction across the department. Academics are encouraged to participate in multiple research interest groups to foster collaboration. At present, research interest groups have been formed with a focus on the following five themes: biology, materials chemistry, physical chemistry, synthetic chemistry, and theory, modelling and informatics.

STRATEGIC COLLABORATIVE RESEARCH

The research interest groups collaborate on a number of strategic themes.

Chemistry of health. Chemical science has a key role to play in improving the health of the world's population. We aim to advance the understanding of health and disease in a number of areas that are of global importance. These include ageing, cancer and infection.

Sustainable energy, environment and climate. We will use our expertise to tackle grand technical and intellectual challenges associated with developing sustainable future energy systems.

Innovative molecular and materials design. We will transform the development and assembly of important functional chemicals to produce new highvalue products that will lead to novel

Our vision is to enhance our reputation as a world-class research institution that is recognised for its innovation, excellence and discovery, and which attracts the best students and staff worldwide.

We aspire to values that are based on the highest professional and academic standards in terms of personal growth and satisfaction offered to our staff and students; growth and excellence in what we do; teamwork that is based on respect; trust and integrity; and innovation to deliver value to our research partners, and to society. applications in healthcare, agriculture, energy and consumer products.

We aim to maintain key chemical expertise, both experimental and theoretical, at the heart of our multi-disciplinary research activities. In parallel, we will expand our translational research to promote collaborative initiatives, both in academia and with industry. We will:

- Strengthen or create interdisciplinary research institutes that provide stateof-the-art infrastructure, equipment and high-level technical support;
- Develop our partnership with industry, with our global partners and with major sponsors of research;
- Prioritise our resources and identify opportunities for the development of key shared research facilities;
- Develop cross-disciplinary doctoral training centres.

SUPPORTING RESEARCH LEADERS

The best way to deliver our vision is to have the best people, and support them to do the best research. We will maintain an environment for innovative research and excellence by:

- Providing a world-leading research training environment that develops and nurtures the skills of the next generation of academic and industrial scientists;
- Appointing the best early- and midcareer scientists in exciting established and emerging areas of science;
- Promoting a culture of equality and diversity;
- Supporting academics to take the lead on collaborative projects;
- Providing mechanisms to facilitate the management of large projects;
- Engendering participation in departmental structures, forums and decision-making bodies.

EDUCATING THE NEXT GENERATION OF SCIENTISTS

The department is committed to providing a stimulating environment for its students and postdoctoral researchers that will enable them to work on today's scientific challenges and equip them to address societal challenges of the future. We aim to achieve this by:

- Training the next generation of chemical scientists for both academia and industry;
- Developing new doctoral training programmes in collaboration with our industrial partners and major stakeholders;
- Providing postdoctoral researchers with an opportunity to develop into research leaders.

Vision & strategy

INDUSTRIAL PARTNERSHIP AND ENTREPRENEURSHIP

The department has a strong track record of commercialising and licensing technologies that arise from basic research in the chemical sciences. It has also had great success in training graduates and postgraduates for careers in industry. Many of our students become leaders in business and commerce.

COMMUNICATION OF RESEARCH

Our research ambitions can only be successful if there is broad societal support for chemical research, and if we can attract the best students. Both objectives imply that we must articulate the importance of our research by raising awareness of the benefits that accrue from our research, and the direct impact on important societal, environmental and economic needs.

We will publicise our important research developments through all aspects of the media, thereby ensuring that there is public dissemination of our science. Specifically, we will:

- Play a leading role in advocating and influencing research policy;
- Ensuring that our staff support and participate in forums that support

the UK and global chemical sciences research base;

- Embrace web-based communication to provide a platform for broader dissemination of our research;
- Increase our outreach activities with industry and not-for-profit sponsors of research through showcase events and virtual institutes.

MANAGEMENT AND FEEDBACK OF SUCCESS

The department's Research Strategy Committee is responsible for monitoring the outcomes and impacts of our research and the success of our research strategy.

We measure success through the: Academic, environmental and

- societal impact; Economic impact, for example
- through spin-out companies; Long-term and sustainable funding;
- The destinations and careers of the people we train;
- Quality and impact of the papers we publish;
- Indicators of esteem, such as prizes, awards and invited lectures. We will continue to monitor our success

through external assessment that will include direct involvement of the Scientific Advisory Panel.



EC 199 Biological 23% Synthesis 28% Government Overseas 6% Materials & (including Royal Society) 15%

physical 20%

Grant income has remained stable over the past five years, reflecting to a large extent that the department is working at maximum capacity in the current space available. The department continues to enjoy a sustainable spread of funders.

A fund-raising campaign is being launched to raise money for a new building focused on the chemistry of health. The building will create about 3300m² of vital additional space, and enable us to build on and develop our chemistry in this important field, right across the department.

Teaching

Educating the next generation of chemists

The aim of our undergraduate course is to enthuse and educate the next generation of top-flight chemists. We aim to do this by offering outstanding teaching in an excellent physical and intellectual environment. The research excellence of the department underpins and informs both the way we teach, and what we teach.

ndustry 16%

Undergraduate numbers have remained buoyant in recent years, with just over 100 students taking the third-year course, and around 70 of these carrying on to the fourth year. We have more than 500 students taking first-year chemistry, but because of the structure of the Natural Sciences course, this includes students who are heading off to specialise in physics, materials science or biology.

About half of our graduates go on to take research degrees either here in Cambridge or at other top universities. The other half head off into general graduate employment in areas such as accountancy, patent work, the law, financial services - in fact in just about any role one might think of. One recent graduate is even pursuing a career as a fashion designer!

Our graduates remain in demand even in the current climate, and we take this as a tribute to the special qualities imparted by a Cambridge education.

We continue to receive a significant number of exchange students from around the world, many coming through the Erasmus scheme. These students typically take parts of the third- or fourth-year course and often also undertake a research project. Their presence and the valuable different perspectives they bring help to remind us not that we are part of a worldwide chemistry community.

FUTURE CAREERS

In the past, few of our students have gone into secondary school teaching, but this has changed over the past few years. The increasing status and higher profile of a career in teaching, plus a wider range of options for entering the profession such as the graduate teacher scheme, has made this a more attractive option. It is surely a good thing that Cambridge chemistry graduates are out there teaching and enthusing the next generation of chemists.

For some years now, we have had teaching fellows in the department. These are members of the staff whose focus is on undergraduate teaching, rather than research. Over this period we have added two further teaching fellows, Sally Boss and Deborah Longbottom. Both are joint appointments with colleges, which very much reinforces the vital link between college and university teaching.

These appointments are a particularly clear expression of the department's ongoing commitment to providing a very high standard of undergraduate education.

Many of our students seek placements and some kind of research experience over the summer vacations. There is no doubt about the value of such experience, particularly in the latter parts of the course and as a run-up to starting their final year research project. Funding for such placements is always a problem, but a new initiative from the department's Corporate Associates scheme has provided a significant amount of support, allowing many more students to reap the benefits of summer placements.

Prizes & awards

Perhaps the best confirmation of the great science that goes on in the department is the range of prizes our chemists are awarded from many different societies and organisations.

In the past two years, many of our chemists, from the established, senior member of the department to those just starting out on their independent careers, have been recognised. These include:

Andreas Bender, European Federation for Medicinal Chemistry Young Medicinal Chemist in Academia prize, 2010; Innovation Prize of the German Pharmaceutical and Chemical Societies, 2011; Molecular Graphics and Modelling Society's Silver Jubilee award, 2011;

Robert Best, RSC Marlow Award, 2012;

Chris Dobson, RSC Khorana Prize, 2010;

Daan Frenkel, RSC Soft Matter and Biophysical Chemistry Award, 2010; Joseph O. Hirschfelder Prize, 2011; RSC Spiers Memorial Award, 2012;

Clare Grey, RSC John Jeyes Award, 2010; Ampere Prize, 2010; Kavli Medal, 2011;

Tuomas Knowles, RSC Harrison-Meldola Memorial Prize, 2012; Richard Lambert, ACS Langmuir Lectureship, 2010;

Steve Ley, Tetrahedron Prize, 2010; Swiss Chemical Society Paracelsus Prize, 2010; Royal Society Royal Medal, 2011;

Peter Murray-Rust, ACS Herman Skolnik award, 2012;

Jonathan Nitschke, RSC Corday Morgan Medal, 2011; Dalton Transactions European/African Lectureship, 2011; RSC Cram Lehn Pedersen Prize, 2012;

David Spring, RSC Norman Heatley Award, 2011;

Dominic Wright, RSC Main Group Chemistry award, 2012. Several department members have won best poster and presentation prizes at prestigious conferences, including:

Mark Eddleston, a PhD student with Bill Jones, won the best talk in the Young Crystallographers' session at the British Crystallographic Association's 2010 meeting

Frederic Blanc, a research fellow with Clare Grey, won the best poster prize at the 18th International Conference on Solid-State Ionics in 2011

Sean Hudson, a PhD student with Chris Abell, won best poster prize at the 2010 RSC symposium on the medicinal chemistry of tropical diseases

Gareth Lloyd, a postdoc with Bill Jones, won the CCDC Chemical Crystallography Prize for Younger Scientists in 2011. Best poster prizes at the Lorne conference in Australia were won by **Tim Guilliams** from Chris Dobson's group in 2010, and **Nicole Lim** from Sophie Jackson's group in 2012.

Finally, several awards for teaching and outreach activities have also been received by members of the department: Corporate Associates Junior Faculty teaching awards to **Ian**

Baxendale, Sally Boss and Felipe Garcia;

Deborah Longbottom, Pilkington Teaching Prize;

Peter Wothers, RSC President's Award, 2011.

Fellowships

One of the greatest honours a British scientist can receive is to be made a Fellow of the Royal Society. In 2011, **Clare Grey** was made a fellow; in 2012, the honour was bestowed on both **Shankar Balasubramanian** and **David Klenerman**.

Other organisations have also given Cambridge chemists fellowships. **Shankar Balasubramanian** was made a Fellow of the Academy of Medical Sciences in 2011, and **Chris Abell** also became a Fellow in 2012. And **Chris Dobson** was made a Fellow of the Academia Europaea in 2011.

John Pyle became a Fellow of the American Geophysical Union in 2011, while **Bill Jones** was elected as an inaugural Fellow of the Learned Society of Wales.

And both **Shankar Balasubramanian** and **Jane Clarke** were made Members of the European Molecular Biology Organisation in 2012.



Christian Doppler Lab

The department's Christian Doppler laboratory for Sustainable SynGas Chemistry had its official opening in April 2012.

Headed up by Erwin Reisner, the state-of-the-art lab is focused on research into using sunlight to power the sustainable conversion of carbon dioxide and water into syngas.

This high-energy gas mixture contains hydrogen and carbon monoxide, and can be used to create liquid hydrocarbon fuels. It is also an important feedstock in the petrochemical industry.

The lab is being funded jointly by the Austrian Christian Doppler Research Association, Federal Ministry of Economy, Family and Youth, the

Personal research grants

A department cannot function without funding, and several individual grant awards have been particularly notable.

In the past couple of years, these personal grants have included:

ERC Advanced Investigator Grants to John Pyle, David Wales and Dominic Wright, joining existing awardees Daan Frenkel and Clare Grey;

ERC Starting Investigator Grants to

Sphere Fluidics spin-out

Over the years, a number of spin-out companies have been formed by Cambridge chemists with the aim of commercialising their science.

Several have been real successes, such as DNA sequencing company Solexa, set up by Shankar Balasubramanian and David Klenerman, and Cambridge Display Technology, which built on the work of the Melville Laboratory under its former director, Andrew Holmes.

The latest Cambridge chemistry spinout company, Sphere Fluidics, has gained funding from the Royal Society Enterprise Fund. This is in addition to the seed funding it received from the university's Discovery Fund. It has also signed a research collaboration with a major pharmaceutical company. The company was set up in 2010 and focuses on the picodroplet technology developed by Chris Abell and Wilhelm Huck that allows researchers to carry out large numbers of simultaneous reactions contained within small aqueous droplets just a fraction of a millimetre in size.

When the droplets are merged with others containing, say, a specific chemical reagent, they act as miniature reaction chambers.

The technology has potential uses in many different fields. These include analysing and isolating cell types, biomarker discovery in small volumes, and even carrying out molecular labelling and separation using proprietary catalysts and conditions.

Erwin Reisner, his group and guests at the lab's official opening

National Foundation for Research, Technology and Development, and OMV Group, the Austrian-headquartered international oil and gas company, for the next seven years.

'The new laboratory aims to develop the basic principles to allow for a renewable production of syngas,' Reisner says. 'Our long-term vision is a transition from a fossil-based to a sustainable carbon-based economy.'

The main focus of the lab will be the development of molecular catalysts, which will then be integrated into nano-structured materials for syngas generation. Ultimately, the aim is that this will enable small-scale devices that make solar syngas to be assembled.

Matthew Gaunt, Markus Kalberer,

Jonathan Nitschke and David

Oren Scherman;

Ionathan Nitschke:

EPSRC Established Career

Fellowship to David Spring;

Jane Clarke's Welcome Trust Senior

Research Fellowship was renewed.

Spring, joining existing awardee

EPSRC Leadership Fellowships to

Ali Alavi, Matthew Gaunt and

Highlights

Todd-Hamied Laboratory

The new Todd-Hamied Laboratory was officially opened in August 2011. The lab is home to the group of Geoffrey Moorhouse Gibson professor Clare Grey. It was refurbished with the generous assistance of Yusuf Hamied, and named in honour of his supervisor and mentor Lord Todd, Nobel laureate and former head of department at Cambridge.

The new space represents a significant transformation – and a lot of time, work and effort. This area of the basement used to be home to Alfie Maddock whose work on radiochemistry left it heavily contaminated with radioactive protactinium.

Before any refurbishment could take place, the whole area had to be decontaminated. This problem was compounded by the presence of asbestos. Once the complex decontamination was complete, the transformation from an abandoned and dangerous space could begin. The Todd-Hamied Laboratory is now a modern space where the group is carrying out important work on energy storage and conversion materials for use in the next generation of batteries and fuel cells.

At the opening, Grey spoke on her work using NMR spectroscopy to aid the design of next generation of batteries and fuel cells, Melinda Duer gave a presentation on the use of solid state NMR to study tissues, postdoc Elodie Salager gave a talk about NMR crystallography, and visiting speaker Christopher Pickard from UCL spoke about his work on structure prediction and NMR shift calculations from first principles.



Clare Grey shows Yusuf Hamied around the new laboratory



Volker Heine, the centre's first honorary member, at the opening

Lennard-Jones Centre opens

The Lennard Jones Centre for Computational Materials Science was officially opened in December 2011. It is named after Sir John Lennard-Jones, who was the first professor of theoretical chemistry in Cambridge, and also the first director of the mathematical laboratory where the basis was laid for all subsequent 'machine computing' in Cambridge. Its aim is to develop initiatives that will foster teaching and research on all aspects of computational materials science.

At the opening, held in the Unilever

lecture theatre, Haroon Ahmed, former Master of Corpus Christi and emeritus professor of microelectronics in the Cavendish, gave a brief biographical sketch of Lennard-Jones, and described the early history of computing in Cambridge.

Volker Heine was also made the centre's first honorary member for his seminal contributions to the field of electronic structure calculations. He also gave an autobiographical account of the development of computational materials science at the Cavendish.

Cambridge–Elan Centre for Research Innovation and Drug Discovery

A new centre dedicated to research into innovative therapies for Alzheimer's and Parkinson's diseases is being established in the department.

The Irish-headquartered pharmaceutical company Elan will invest \$10 million over the first five years of the initial 10-year collaboration.

The new Cambridge–Elan Centre for Research Innovation and Drug Discovery will provide an interdisciplinary environment to enable translational research. The aim is to discover novel compounds that can alter the behaviour of proteins associated with neurodegenerative disorders, and which could be developed into new treatments.

Work on understanding the fundamental molecular origins of these neurogenerative disorders has been ongoing in Cambridge for more than a decade, and Elan has a long-standing interest in research in the field of neurodegenerative diseases. As well as looking for novel compounds, the aim is for the centre to characterise the fundamental physico-chemical mechanisms by which they alter the behaviour of proteins associated with neurodegenerative disorders.

Chris Dobson, Michele Vendruscolo and Tuomas Knowles are all involved in the centre. 'The department, and indeed the university, is very keen on the venture, and on the opportunities that exist to build on it for the future,' Dobson says.

'The process of bringing together researchers at Cambridge and at Elan has already created novel insights and opportunities in drug discovery,' he adds. 'The new centre builds on the successes of this initial interaction to establish a long-term relationship to lead to novel and effective therapies for the most debilitating, costly and rapidly proliferating diseases in the modern world.'

A visit from President Barroso



The department had a distinguished political visitor in February 2011 – José Manuel Barroso, president of the European Commission.

He was in Cambridge to give the annual Alcuin lecture, speaking about the relationship between the British nation and the European Institutions. Chemistry was asked to host him in the Bristol-Myers Squibb lecture theatre, as it is the university's largest. President Barroso (second left) poses in the department foyer with university vicechancellor Leszek Borysiewicz, Bill Jones and Jeremy Sanders

Biology: the next big challenge for chemists

In the department, we have a particularly vibrant community of research groups with interests in biological molecules and systems. Research within the Biological RIG spans all areas of chemistry: from using state-of-the-art magnetic resonance techniques to study bone, combining the power of chemical synthesis and computational approaches to the development of new drugs and imaging agents, to understanding the molecular mechanisms by which proteins fold or misfold. Much of this is chemical biology, an emerging field in which scientific ideas and approaches developed by chemists are used to understand and manipulate biological systems in a highly controlled and specific manner. In addition to this, a number of research groups are taking inspiration from nature to develop new materials and devices.

CHEMISTRY MEETS BIOLOGY

Chemists have been interested in biological systems for many decades. However, traditionally they have studied isolated biological molecules in vitro, sometimes in an environment very different from that found in vivo. As advances are made in many areas of chemistry, we have begun to bridge this divide and now even have methods for studying chemical processes in live cells and organisms.

Melinda Duer and her group are developing solid-state NMR spectroscopy techniques to investigate the structure of the organic-inorganic interface in biominerals such as bone. This allows them to determine the structures of biomolecules in their native tissues, thus providing much better information on the structure and function of these species in a living organism.

As well as advances in spectroscopic techniques, other groups are using novel chemistries and reagents to investigate biological processes in vivo. **Finian Leeper's** group is using unusual bio-orthogonal reactions, some of which are the fastest yet reported, to develop reagents for the imaging of cancers in live animals. One such reagent, tetra-acetyl N-azidoacetyl-galactosamine, is able to link to tumour cells via their cell-surface glycan and is a powerful imaging agent.

Jason Chin's group is also harnessing the power of chemistry to develop innovative methods for studying biological molecules and processes in vivo. Recently, they have been able to light up proteins both in cells and whole animals for imaging applications. Ultimately, these techniques have the potential to provide a real-time molecular description of complex biological processes such as animal development and neural processing.

MOLECULAR MEDICINE

The power of chemical synthesis to construct reagents to both probe and control biological molecules and systems is also illustrated by research in many other groups whose focus is molecular medicine.

Chris Abell and **Alessio Ciulli**'s groups, for example, are using fragment-based screening methods that were developed in the department to identify small, drug-like molecules that can target proteins associated with diseases such as TB and cancer. They also



Above right: fragment molecules binding to a cytochrome P450 enzyme from Mycobacterium tuberculosis, the bacterium responsible for TB

Below: structure of

such as bone

the organic-inorganic

interface in biominerals



act as lead compounds in further drug development programmes.

Shankar Balasubramanian's group is using similar chemical approaches to elucidate and manipulate the mechanisms that control gene expression, either transcription or translation. This work has demonstrated that noncanonical nucleic acid structures, such as G-quadruplexes, may be associated with various cancers and are potential targets for small drug-like molecules.

The group is also applying and developing chemical strategies to study epigenetic marks in the genome, some of which have been shown to control gene expression during development and in cancer. As part of this programme of work, the group has recently invented chemistry for sequencing 5-hydroxymethyl cytosine in DNA at single base resolution, something that was previously not possible.

PROTEIN FOLDING, MISFOLDING AND DISEASE

Proteins are not only the target of most therapeutic drugs but, as a result of misfolding or misfunction, are themselves the underlying cause of almost all disease states and conditions.

In order to function, the large majority of our proteins need to fold into a specific three-dimensional structure and failure of proteins to fold correctly, or remain folded, has been found to be the origin of a wide variety of pathological conditions, including cancer and neurodegeneration.

Chris Dobson's group has pioneered the study of protein misfolding and

Biological

established some of the fundamental principles that govern protein aggregation and its associated toxicity.

They have worked with many other groups in the department who have developed innovative experimental and theoretical methodologies to understand the molecular origins of protein misfolding diseases, particularly focusing on neurodegenerative diseases such as Parkinson's and Alzheimer's diseases.

David Klenerman's group has led the development of sensitive single-molecule spectroscopic methods to detect and characterise aggregated species both in solution and in the membrane of living cells.

The group of **Tuomas Knowles** is developing physical tools to study protein aggregation, and **Michele Vendruscolo's** group has successfully applied state-of-the-art computational approaches to study and predict the physico-chemical determinants of protein aggregation.

In collaboration with **Sophie Jackson**'s group, they are investigating how some of the body's natural defence systems – molecular chaperones – deal with misfolded and aggregated proteins in vivo. Together, this extensive programme of research aims to develop new and rational therapeutic strategies against many disease states.

The group of **Jane Clarke** also employs cutting-edge single-molecule techniques to study the complex problem of how multi-domain proteins fold. Their recent work has established that misfolding may be far more common than expected.

Laura Itzhaki's group, meanwhile, studies the misfolding (or in this case unfolding) of a different class of proteins which have a very distinctive architecture, including the ankyrin, HEAT and ARM repeat proteins. These proteins also play an important role in disease, in particular cancer, and insights gained from the research are being used to develop novel therapeutic strategies. Many of these groups also



study the pathways by which proteins with complex structures fold productively in order to understand how nature has solved some of the problems associated with misfolding.

Jane Clarke's group focuses on multi-domain proteins, Laura Itzhaki's group on repeat proteins which have a modular architecture, while Sophie Jackson's group studies an unusual set of proteins which have a knotted topology. In all cases, computational methods are used alongside experimental work in order to gain further detail of the complex processes involved.

The groups of **Michele Vendruscolo**, **Robert Best** and **David Wales** are all developing and applying theoretical and computational methodology to the study protein folding and unfolding.

DEVELOPING NEW METHODOLOGIES

Many groups within the department have been instrumental in pushing the boundaries of what is possible with both computational and experimental methods, and this is no better illustrated than with the protein folding and misfolding studies described above.

Other groups are also making considerable headway in other directions. **Chris Abell** runs a leading microdroplets group, and this technology is now being applied in a wide variety of research programmes within the department. His group is using this



Above: when proteins misfold, diseases such as Alzheimer's are the result technique to study algae for algal biofuel development and, along with **Oren Scherman's** group, they have recently developed a novel way to generate microcapsules. This technology is also being further developed and used by the groups of both **David Klenerman** and **Tuomas Knowles** groups to study protein folding and misfolding.

TAKING INSPIRATION FROM BIOLOGY

Using chemical tools and methods to interrogate and manipulate biological molecules and systems is the approach of many groups in the Biological RIG described above. Other groups, however, take their inspiration from nature, and use it to create novel solutions to some of the pressing issues of the 21st century.

Paul Barker's group, stimulated by the wide variety of roles of haem in biology and by the ability of biological systems to self assemble, is creating new biomaterials which can be used as electron carriers or transistors in molecular electronic devices.

Erwin Reisner's group takes its inspiration from the highly efficient processes by which nature harvests energy from the sun, and is developing novel chemistries and molecules to generate devices which can address some of the major issues associated with energy and sustainability.

light-driven H2 e production with II an enzyme- g nanoparticle s hybrid system V Research into bi

Below left: visible

Research into biological molecules and systems has grown considerably within the department in the past 10 years, providing both great strength and depth and making Cambridge a world leader in this area. Starting from and centred around collaborations within the department, research programmes in chemical biology, molecular medicine and molecular and cellular biophysics now extend across Cambridge, the UK and around the world. Our research is addressing many of the most important issues that are facing society today.

7

New materials: from energy to medicines

Modern materials chemistry is a wide-ranging topic and includes surfaces, interfaces, polymers, nanoparticles and nanoporous materials, self assembly and biomaterials, with applications relevant to oil recovery and separation, catalysis, photovoltaics, fuel cells and batteries, crystallisation and pharmaceutical formulation, gas sorption, energy, functional materials, biocompatible materials, computer memory, and sensors. There are several common themes that run across the RIG. Research is carried out in energy production, storage and conversion; surfaces, crystals and catalysis; biomaterials; sensors and transducers; and self-assembling functional materials.

MATERIALS FOR ENERGY

Clare Grey's group uses a range of analytical techniques to study the local structure of a wide range of technologically important, but disordered, materials and the role this local structure plays in controlling the materials' physical properties. The primary technique is nuclear magnetic resonance (NMR), which probes the local environment around a particular nucleus, and is ideal to study such materials. The key tools in this research are four solid state NMR spectrometers, the most recent of which was installed in late 2011. There is one high field machine and three low, which reflects the breadth of research, with the low field machines particularly suitable for paramagnetic samples.

Specially designed probes that can be used inside the spectrometers enable the materials to be studied. For example, one probe can reach very high temperatures – up to 700° C – which allows invaluable information on phase transformations and dynamics to be obtained. The group is also able to carry

A schematic representation of the void structure of a unit cell. Yellow spheres represent voids inside D cages and orange bars 1D channels running through T cages. The outline of one D cage and two T cages are shown to illustrate the structural relationship to Type I gas hydrates

Clare and her group in the new Todd-Hamied lab





out in situ studies of lithium ion batteries that capture the short-lived metastable phases which appear at various stages of battery cycling. These studies are carried out using a flexible plastic bag battery, which is placed inside the NMR spectrometer. Other equipment includes furnaces for high temperature synthesis, glove box for handling air/moisture sensitive compounds, and battery cyclers for electrochemical studies.

BUILDING POROUS LATTICES BASED ON FULLERENE

Research in **Dominic Wright's** group focuses on metal–organic frameworks, or MOFs. A myriad of these discrete and extended molecular assemblies have been prepared by chemists worldwide by coordinating metal ions to organic ligands, yet few have relied on planar components with a five-fold symmetry. Pentagonal or star-shaped building blocks cannot tile into a planar surface without tilting or curving and, to date, the few metal–organic structures that have been assembled with such ligands have resulted in discrete spherical cages exhibiting fullerene-like morphology.

Recently, however, the group has described a three-dimensional metalorganic framework based on the fullerene units. These arrangements can act as air-stable, responsive hosts for solvent and, potentially, gas molecules. The $\{C_5(CN)_5^-\}$ anion – a five-membered aromatic ring decorated by five cyanide moieties – is the simplest member of the extremely rare family of fivefold-symmetric nodes, and was chosen as the ligand.

On crystallising this ligand with sodium ions by slow vapour diffusion of ether in a nitromethane solution, an assembly of a highly solvated, highly metastable, three-dimensional metal– organic framework was seen, directed by the solvent molecules.

Characterisation by X-ray diffraction revealed that each ligand binds five sodium centres through nearly linear C N–Na bonds. These, in turn, organise into a coordination network comprising sodium–ligand pentagonal and hexagonal faces, making up units that resemble fullerene moieties. The resulting MOF exhibits both discrete cavities and linear non-intersecting channels that run through the empty faces.

Removal of the solvent molecules under mild conditions does not cause the MOF to collapse, but instead leads to a different morphology. The unsolvated framework adopts a more densely packed layered arrangement, favoured by π -stacking between the ligands, in which the C N–Na bonds are no longer linear.

SELF-ASSEMBLED STRUCTURES

Jonathan Nitschke's group is investigating the self-assembly of complex, functional structures from simple molecular precursors and metal ions. One area of research is looking at molecular containers for greenhouse gases. Sulfur hexafluoride (SF₆) is the most potent greenhouse gas known, with a global warming potential more than 22,000 times that of CO₂, and a lifetime in the atmosphere of up to 3000 years.

The group has designed a metalorganic capsule that is able to selectively encapsulate SF_6 from a mixture of atmospheric gases and store it under ambient conditions. The application of

Materials



Right: the doublehelical metalcontaining polymers are good conductors of electricity, allowing them to function molecular wires



mild physical or chemical stimuli allows the gas to be controllably released from the host molecule, opening up the opportunity for it to be recycled. Systems such as this could reduce the amount of SF_6 that is released from industrial processes, and could be highly effective in abating global warming.

Larger molecular containers to encapsulate more complex guest molecules are also being developed. An example is a porphyrin-faced cube, which is able to selectively bind and encapsulate large aromatic molecules such as coronene, C₆₀ and C₇₀-C₈₄.

Other systems being investigated include molecular containers, which might have applications as molecular flasks for new types of reaction or in drug delivery, by delivering a specific payload upon receipt of a specific chemical signal. The dynamic assembly of cages from subcomponents might also be used to trap harmful molecules, preventing hydrophobic toxins or chemical warfare agents from doing damage by isolating them from the environment.

Molecular wires represent another fascinating area of research. Supramolecular polymers use reversible bonds to hold their chains together, resulting in striking dynamic properties compared to traditional polymers joined together by inert covalent bonds. These 'smart' polymers can respond to changes in temperature, solvent, or the presence of chemical signals.

The group has designed and synthesised new double-helical metal-containing polymers that are good conductors of electricity, allowing them to function as molecular wires. The polymers' properties can be reversibly modified by application of stimuli such as heat resulting in a sol-to-gel transition. At the same time, the colour and luminescent intensity of the material changes in an interconnected way, generating the Above: a metalorganic capsule that is able to selectively encapsulate SF₆ from a mixture of atmospheric gases

type of complex behaviour found in natural and man-made systems such as neurons or transistors.

The new polymers are held together by reversible imine and coordinative bonds and are capable of dynamic reconfiguration, allowing them to be built into self-healing materials – a fracture in the polymer could be repaired simply by pressing the two broken edges of the material together. The dynamic properties of these materials opens up the prospect of many new applications.

SUPRAMOLECULAR DESIGN OF NEW DELIVERY SYSTEMS

A collaboration between the groups of **Chris Abell** and **Oren Scherman** has resulted in the development of a new technique for manufacturing 'smart' microcapsules in large quantities in a single step, using tiny droplets of water. The encapsulation of materials for protection and phase separation has evolved into a major research focus in biology, chemistry, nanotechnology and materials science.

For microencapsulation applications it is important to accurately control

both the capsule structure and the core contents. However, it is still challenging to fabricate microcapsules in an efficient and scalable process without compromising functionality and encapsulation efficiency.

The approach uses microdroplets, dispersed in oil as templates for building supramolecular assemblies which form highly uniform microcapsules with porous shells. The microdroplets are loaded with copolymers, gold nanoparticles and small barrel-shaped molecules called cucurbiturils, or CBs. These CBs act as miniature 'handcuffs', bringing the materials together at the oil-water interface.

The major advantage over current methods is that all of the components for the microcapsules are added at once, and they assemble instantaneously at room temperature.

The technique allows for a variety of cargoes to be efficiently loaded during the formation of the microcapsules and the dynamic supramolecular interactions provide control over the porosity of the capsules and the timed release of their contents using stimuli such as light, pH and temperature.



Cucubiturils act as miniature 'handcuffs', bringing materials together at the oil-water interface of atmospheric gases

Physical chemistry: the underpinning science

The primary focus of the Physical Chemistry RIG is the description and understanding of the properties of molecular systems in terms of physical principles. This knowledge impacts other branches of chemistry, and underlies many technological applications in rapidly developing areas such as climate change, nanotechnology and molecular medicine. Much of the research in the interest group is interdisciplinary, and the topics of study range from biomolecular systems to the atmosphere.

ENGINEERING ON A PLANETARY SCALE

Geoengineering is the deliberate modification of the earth's climate system to offset the global warming that results from increasing greenhouse gases. Focusing on solar radiation management, or SRM, there are two futuristic proposals: space mirrors to attenuate the incoming solar radiation, and the deliberate injection of particles into the stratosphere, 15–55km above the earth's surface.

Large volcanic eruptions provide a natural analogue to aerosol injection. The most significant eruption in recent times was the 1991 eruption of Mount Pinatubo in the Philippines, which led to the formation of a sulfuric acid aerosol layer that reflected light and reduced the average global temperature at the Earth's surface by around 0.5°C for about two years. In addition to reflecting radiation this, sulfuric acid aerosol from Mount Pinatubo was involved in ozone-destroying chemical reactions.

The ideal particle type for deliberate stratospheric injections would maximise the reflection of incoming solar radiation, while at the same time minimising the stratospheric chemistry impact and any effect on stratospheric circulation. Moreover, the particle choice would ideally have minimal impact on precipitation, ecosystems and human health.

The economic viability of SRM by stratospheric particle injection will be dependent, among other criteria, on the particle size and composition.

To date, studies investigating this scheme have focused upon the injection of sulfuric acid or precursor gases to mimic the volcanic aerosols. However, the composition and size of volcanic aerosol are far from optimal for reflecting solar radiation. Aerosol compositions other than sulfuric acid could be used to dramatically increase the amount of light scatter achieved on a per mass basis, thereby reducing the amount of aerosol required for injection.

In Cambridge we are investigating the consequences of different aerosol types on atmospheric chemistry and dynamics. Groups in the Physical and Atmospheric RIG are researching properties of proposed candidate particles for deliberate injections.

Laboratory experiments are performed by **Markus Kalberer** and **Francis Pope** to investigate chemical reactions involving particles that could potentially interfere with the chemistry of the stratospheric ozone layer and model calculations are performed by **John Pyle** and **Peter Braesicke** to understand the natural analogue in the context of ozone change attribution (the Mount Pinatubo eruption and its Right: Leftand right-handed alaninate molecules respectively form mirror-image leftand right-slanting patterns on a copper surface. The images were obtained by scanning probe microscopy, and each separate feature is an alaninate molecule

Below: perturbation of the atmospheric radiative budget and the chemistry of the atmosphere by aerosol particles injected into the ctratorphore







impact on the chemistry climate system), and assess consequences of general solar radiation management on the atmospheric circulation. This forms part of the due diligence required before any such scheme could be utilised.

HANDY SURFACE CHEMISTRY

Ongoing research in the surface science group, led by **Stephen Jenkins**, promises to reveal new insights into the ways in which biologically important molecules, such as amino acids, can self-organise into complex patterns when deposited onto a metal at sub-monolayer thickness.

The existence of these patterns has been recognised for some time, and the Cambridge group has long been at the forefront of progress in this field, but little knowledge has hitherto emerged about the fundamental processes of diffusion, nucleation and growth that determine the long-range ordering of molecules on the surface.

Of particular interest is the link between the chirality displayed by certain molecules – the property of coming in either left-handed or right-handed versions – and the handedness that this imprints upon their global arrangement.

Now, with the help of a substantial grant from the US National Science

Physical

Foundation (NSF) and the UK Engineering and Physical Sciences Research Council (EPSRC), the Cambridge team will join forces with the group of Jane Hinch at Rutgers University to pick apart the details of precisely how this imprinting happens. A unique combination of techniques will allow the researchers not only to address key questions about the structures formed by molecules on the surface, but also to gain an understanding of the dynamic properties of these ultra-thin organic films.

WARNING – MISFOLDING PROTEINS AHEAD

Physical chemistry techniques are increasingly applied outside of the area in which they were first developed, and in particular several groups within the Physical Chemistry RIG are pioneering the use of physical approaches in the study of the behaviour of biomolecules.

Aberrant aggregation of proteins and peptides has been linked to a number of diseases. The most well-known of these are a number of neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis and Huntington's disease. Each of these diseases is pathologically characterised by the presence of large aggregates of a particular protein.

In the case of Alzheimer's disease, the characteristic protein is a small peptide cleavage product called amyloid- β (38-42 amino acids, most commonly 40 or 42 amino acids). Proteinaceous plaques in the brains of patients suffering from Alzheimer's disease are comprised of highly ordered fibrillar forms of the amyloid- β peptide.

Much recent research has focused on understanding the fibrilisation process of this peptide, and has discovered that a number of disordered smaller, oligomeric forms of the peptide that vary in size and structure are found prior to fibril formation and that these oligomers have been correlated to the detrimental effects observed in Alzheimer's disease.

Therefore, it has become of primary importance to characterise these oligomers, which has been a challenge using bulk techniques because of the transient nature and heterogeneity of the oligomeric population.

David Klenerman's group has turned to single molecule fluorescence techniques to resolve and accurately characterise these oligomeric populations. In order to do this, researchers in the group have used amyloid- β_{1-40} monomers, which are each singly labelled with either a red or blue fluorescent dye molecule. When red-labelled and blue-labelled amyloid-monomers are combined in equal ratios and allowed to aggregate into oligomers, it becomes possible to dis-



tinguish the single-colour monomers from oligomers as they will be dualcolour because they contain both red and blue-labelled monomers.

Furthermore, it is also possible to estimate the size of the oligomers based on their total fluorescence intensity. This work has recently revealed that that clusterin, a naturally occurring extracellular chaperone, not only prevents oligomer formation when added in equimolar ratios to monomeric amyloid- β_{1-40} peptides, but when oligomers are present, clusterin binds them in long-lived complexes and prevents their further growth into fibrils or dissociation into monomers by this sequestration.

These results suggest a mechanism for the observations of abated cytotoxicity and increased peptide degradation in the presence of clusterin, and provide a molecular basis for the genetic link between clusterin and Alzheimer's.

DISCOVERING AND CHARACTERISING POLYMORPHS

Research in the groups of **Bill Jones** and **Graeme Day** is directed at understanding structure-property relationships in molecular organic solids, applying their expertise in experimental and computational methods to develop strategies for characterising and designing materials with interesting and useful properties.

Recent highlights from their research groups this year include new methods for characterising polymorphs, developments in computational methods for guiding the synthesis of new materials Above, from the left: predicted *ab initio* molecular structure, predicted crystal structure and observed crystal structure of a molecular cage, showing the accessible surface area in yellow

Below: Probing protein aggregation at the single molecule level



and co-crystallisation strategies for tuning materials properties.

Both groups have an active interest in characterising the crystal structures of pharmaceutical molecules. A subject of particular interest is polymorphism – the ability of a molecule to crystallise in more than one crystal structure – which is particularly prevalent in pharmaceuticals. The importance of identifying and characterising polymorphs when developing a future drug relates to the dependence of crucial properties such as solubility and hardness on the crystal structure; the occurrence of a new polymorph can influence the processability, bioavailability or shelf-life of a drug.

Combining computer-generated models of possible crystal structures with diffraction data from transmission electron microscopy (TEM), the two groups have developed a novel approach to identify and determine the crystal structure of polymorphic impurities in samples.

This approach has been applied to the determination of the crystal structure of a new crystal phase of the pharmaceutical compound theophylline, whose previously unknown polymorph was identified from analysis of a single crystallite with a mass of about 3 picograms that occurred as a minor component in a mixture with a second crystal phase.

The estimated concentration of the new polymorph (less than 0.1% by weight) is below the limits of detection of analytical methods routinely used for characterisation of organic samples.



Synthesis: molecules under construction

The science of building molecules is at the heart of synthetic chemistry at Cambridge. The foundation upon which synthetic chemistry rests is the fundamental understanding of how and why molecules react with each other. Studies to further this knowledge are critical to inform the design and development of new chemical methods. Each new method is a new tool, empowering chemists to build the molecules they need. As academic discoveries are channelled into practical applications, synthesis meets society's needs in the most disparate of areas.

MODEL BEHAVIOUR

Although chemists cannot directly observe molecules reacting with each other, technology allows us to simulate what we might see if we could. **Jonathan Goodman's** group predicts molecular structure and reactivity using computer modelling, comparing predictions to experimental results to validate the model. The insight gained can then be applied to the design of new reactions.

The group recently rationalised the outcome of the asymmetric Strecker reaction, an important method for forming amino acids. The reaction involves forming a new chemical bond on one side or the other of a flat intermediate structure, leading to the production of the amino acid in either of its opposite mirror images. Catalysts can be used to hold the reacting molecules in a conformation that only allows the new bond to form on one side of the intermediate – making only one mirror image configuration of the product.

A common catalyst for this reaction is chiral BINOL-phosphoric acid. Through computer modelling studies and calculations, the group established that the relative stability of the key reaction intermediate is crucial, a prediction that was confirmed by experiment. This stability can be tuned by synthetic chemists in the design of their intermediate, and this new insight makes rational reaction design easier.

EXPANDING THE SYNTHETIC CHEMIST'S TOOLBOX

The effect of a medicine is often determined by how a drug molecule physically interacts with targets such as protein receptors. Both the reactivity and shape of the molecule are important.

In order to find a match between a drug candidate and a target receptor,

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pharmaceutical companies have built up vast libraries of compounds to screen against various diseases for the discovery of new medicines. New tools for the generation of rationally designed libraries are valuable for improvement of the screening process. Two complementary approaches being investigated within synthetic chemistry are diversity-oriented synthesis (DOS) and fragment-based screening (FBS).

If little is known about the shape or reactivity of a particular receptor, then chemists seeking to target it with a new drug do not know what kind of molecule to start from. DOS is one approach to solving this problem. A number of different reactions are performed on a common initial core, which radically alter its structure. This gives a library of molecules with common medicinal chemistry motifs on a number of structurally varied cores. Once screening of such a library returns a 'hit', the area of chemical space it occupies can be examined using traditional medicinal chemistry techniques.

David Spring's group is working on the generation of structurally varied The equipment in the ITC looks very different from the round bottomed flasks found in a traditional organic synthesis lab



libraries for screening using DOS. This has been used to synthesise a library of macrocyclic peptidomimetics, starting from simple amino acid building blocks. As well as furthering understanding of biological systems, libraries of complex small molecules created by DOS can provide new drug candidates. A previous library developed by the group yielded two compounds with activity against multi-drug resistant MRSA strains.

PICKING THE LOCK

The fragment-based approach to drug design involves the screening of small molecules to see how strongly they bind to proteins implicated in disease. It is heavily influenced by prior knowledge of the chemical constituents and structure of a receptor protein when designing molecules for screening. These small molecules are not always drug-like compounds, but chemical entities that could be incorporated into therapeutics, enabling them to bind to the desired protein.

Research within **Chris Abell**'s group has used fragment-based screening to identify small molecules that could represent starting points for the development of drugs for the treatment of *Mycrobacterium tuberculosis* infection, or TB. Almost two million people die each year as a result of TB, highlighting the importance of research into effective therapeutics for its treatment.

They identified a small, readily synthesised molecule as an effective binder to the targeted protein. By looking at how the small molecule binds to the protein, they identified the important chemical features for binding. Small modifications to this first hit were made, leading to a more potent binder.

Further screening revealed some molecules that also bind strongly to the protein, but in a different location. When the protein was treated with both molecule A and molecule B, they were found to bind at the same time but in different regions of the protein.

This discovery led the researchers to incorporate molecules A and B as parts of a larger molecule, joined by a flexible chemical backbone that allowed both to bind in their original orientation. These individual fragment and fragment-linking strategies enabled direct comparison of these two methods for the first time. Both methods resulted in similar compounds of comparable potency.

Synthesis

GO WITH THE FLOW

Flow chemistry uses mechanisation to allow the components of a chemical reaction to flow continuously in a stream rather than stirring in a single flask. A network of tubes can deliver different chemicals at different times, meaning that either several reactions can take place in a single tube, or that large amounts of material can be produced.

The Innovative Technology Centre (ITC) was established by **Steven Ley** to apply flow chemistry to traditional synthesis. By designing and building the right machines and computer programs, it is possible to add the required chemicals to the system, leave the machine to run and then collect the desired product in high purity ready for use.

Recently, researchers in the ITC have designed systems that can use carbon dioxide to make important molecules for drug discovery. Expensive infrastructure is often required to ensure that gases can be stored and used safely without risk of leakage or explosion.

Gas-permeable tubing has enabled scientists from the ITC to deliver carbon dioxide gas safely, as a cheap and readily available reagent to form carboxylic acids in very high purity and yield. The reaction works on multigram scales, which is highly encouraging for application in industry where kilogram quantities of chemical compounds are required to manufacture medicines.

Following the safe and successful use of carbon dioxide, ITC researchers are now developing the system to incorporate other useful reactive gases for the synthesis of important molecules.

EXPEDIENT METHODS FOR ELUSIVE BONDS

Research in **Matthew Gaunt**'s group focuses on C–H activation – the strategy of making new chemical bonds by direct reaction with a comparatively inert carbon–hydrogen bond, rather than a less common but more reactive bond to a non-hydrogen atom (C–X).

Although C–X bonds may be easier to react with, and easier to differentiate from other bonds for a selective reaction, they often serve no other purpose and so must be installed prior to the reaction or removed afterwards. C–H activation is at the cutting edge of synthetic chemistry and seeks to eliminate these inefficient 'pre-functionalisation' steps, as well as providing new tools to complement existing methods and access challenging chemical architectures.

The group's recent development of a meta-selective arylation reaction, which links aromatic building blocks together, fulfils both of these criteria. It operates on aromatic C–H bonds, and of the three possible sites of bond formation, the reaction cleanly selects the meta-position – the most difficult to access by conventional chemistry in this class of



compound. The ability of this operationally simple process to build previously elusive bonds in a single step should grant access to novel drug candidates and functional materials.

Chloptosin, as synthesised by the Ley group

CAGING THE BEAST

In its natural state, white phosphorus (P_4) reacts violently with oxygen in the air, a property that makes it a destructive weapon. This reactivity can be used productively by chemists, but the material is dangerous and difficult to handle.

Pioneering work in **Jonathan Nitschke**'s group has demonstrated that a reusable molecular container can make P_4 stable to air and soluble in water, apparently indefinitely. It is thought that reaction with oxygen is prevented by the restrictive size of the cage, which is constructed in a selfassembly process from four iron atoms and six organic linkers.

 P_4 can be ejected from the cage by the addition of a replacement molecule – in this case, benzene – and then reacted as required. In addition to aiding the lab manipulation of P_4 , this technology could also be applied to the clean-up of phosphorus spills. The group is now investigating larger molecular containers in the hope of encapsulating more complex guest molecules.

MAKING NATURE'S MOLECULES

Some of the most influential drugs of the past century have not been discovered in a laboratory, but in the natural world. While nature provides these potent molecules, isolation from their natural sources can be inefficient, impractical and hugely damaging to the environment, as they often only contain tiny amounts of the molecules.

Steven Ley's group has recently achieved the synthesis of chloptosin, a naturally occurring molecule with potential activity against pancreatic cancer. The development of new chemistry was pivotal to the design of the synthetic route, with a new method to make the piperazic acid components present in the structure of chloptosin, which are important structural features of many other bioactive molecules.

This new methodology was implemented successfully and, overcoming a number of synthetic challenges along the way, they assembled chloptosin in an efficient and elegant fashion. The synthesis offers the opportunity to make significant quantities of the natural product, allowing the promising bioactivity of both chloptosin and its analogues to be assessed.

Natural product synthesis is one of the

great strengths of our department, and also features large in the research carried out in **Ian Paterson**'s group. Targets include dictyostatin, which has the same anticancer mechanism as the drug Taxol, spirastrellolide A, a potent inhibitor of protein phosphatase 2A, and two novel macrolides isolated from natural sources, chivosazole A and reidispongiolide A.

Efficient and flexible synthetic routes for the modular construction of these, and other complex polyketide natural products, are being sought to provide a sustainable supply for detailed biological evaluation, as well as designing simplified analogues and hybrids that retain activity but are simpler to make.

Another important feature of the group's research is the discovery and development of new synthetic methods. More efficient methods of synthesis are needed that give high levels of stereochemical control in the synthesis of biologically important natural products.

DYNAMIC MATERIALS

Oren Scherman's group has developed a 'smart' polymeric material – a hydrogel with controllable viscosity. Traditionally, polymer properties can be altered by cross-linking – the formation of chemical bonds between individual polymer chains. These processes are generally irreversible, and so the materials are very difficult to reuse or recycle. A current area of research is the development of reversibly cross-linked polymers, the properties of which can be controlled by external stimuli such as heat, light, pH or electrical current.

The group designed and synthesised two polymers with complementary linker groups, and combined them with a barrel-shaped molecular container in water, forming an aqueous gel. The container molecules hold the linker groups together and enable a network of crosslinks to form, greatly increasing the viscosity of the gel. No discrete chemical bonds are formed, so the change is reversible and can be controlled by heating, cooling, and addition of more container molecules.

Materials of this type have many potential applications, including the simple but significant concept of slowrelease drug delivery – instead of pills to be taken daily, an entire course of treatment could be administered in a single injection of the medicine dispersed in a viscous hydrogel.

Cambridge has a proud tradition of research in synthetic chemistry. Its strength and depth is illustrated in the understanding, discovery and application of new chemistry – addressing society's needs from the design of new functional materials to the treatment of disease.

Property prediction and modelling reactions

The Theory, Modelling and Informatics RIG focuses on the development and application of theoretical and computational chemistry techniques. The overall aims are to deepen our understanding of the properties of classical, quantum and molecular systems, to model and interpret experimental data, and to design new algorithms and tools for modelling, simulation and data manipulation. Topics are broad in range, from the prediction of properties of small molecules to large biomolecular systems such as protein-ligand complexes, and from modelling chemical reactions to mesoscopic systems and the atmosphere. By its nature, the group is highly interdisciplinary and collaborative, and projects span academic as well as industrial research partners.

MOLECULAR DESIGN

Robert Glen's group uses molecular informatics approaches to predict properties of molecules in chemistry and chemical biology. In the context of drug discovery, significant progress has been made in the design of new active molecules targeted to G-protein-coupled receptors (GPCRs).

One such GPCR is activated by apelin peptide hormones, and is a putative target for treatment of cardiovascular and metabolic diseases. Experimental data have suggested that a conserved, secondary structural feature called a β -turn may exist in apelin and is likely to be critical for recognition. In the absence of high-resolution information for the interaction of apelin with its receptor, the group has used a combined in silico and in vitro approach to unravel the structure-activity relationships of apelin receptor ligands.

Molecular dynamics simulations, in which Newton's equations of motion are used to propagate a molecular system via an empirically derived energy function, were used to study the solvated conformations of a series of cyclic apelin peptides. Subsequent experimental screening showed the apelin receptor recognises only those peptides predicted by simulation to contain β -turns.

Following this work, novel, bivalent ligands were designed, in which two cyclic β -turn moieties are proposed to act as anchors, separated by a linker motif that may act as a receptor switch. One of the ligands was shown experi-

mentally to be a competitive apelin

antagonist, exhibiting the highest affinity of any novel compound for this receptor to date. The group is now synthesising and testing further agonist, partial agonist, and antagonist molecules.

TAKING A TOLL

Not all drug binding events fit the simple one ligand, one target case. As our knowledge of the biochemical interactome expands, it is becoming clear that many biological processes and chemical reactions within a cell are propagated by heterogeneous assemblies of macromolecules, hampering traditional drug design approaches.

The group of **Peter Bond** is utilising molecular modelling and simulation approaches to understand how such assemblies function in signalling cascades, and how they may be targeted therapeutically. Recently, progress has been made in unravelling the mechanisms by which toll-like receptors, Below, molecular switches: transmembrane GPCRs, represented here by a model of the apelin receptor, are important signalling proteins that transduce a wide range of signals into cellular responses, and are hence major therapeutic targets



associated with a wide range of inflammatory diseases in the mammalian immune system, recognise and become activated by pathogenic molecules.

The group is simulating systems of receptor complexes – in some cases approaching a million atoms in size – and probing the thermodynamic contributions by individual components of the complex. This molecular-level information is being combined with in vivo assays to identify the determinants of selectivity, towards the design of drugs or vaccines.

CAUSE AND EFFECT

Even when furnished with structural information on the interactions of molecules with targets, do we really understand how drugs work? When a drug is taken, it will – or will not – be dissolved and absorbed in the stomach and digestive tract, become distributed into target organs (as well as those responsible for causing side-effects) and, finally, be metabolised by enzymes and excreted. Given the complexity of even a single human being – let alone variation between people – it is, in reality, still very difficult to predict how a new drug works, or its potential side-effects.

However, in recent years large databases such as ChEMBL have been published, so we can now use data mining algorithms from the computer science domain for the analysis of chemical and biological information to explain the bioactivity profile of a potential drug.

Andreas Bender's group is currently devising new ways to integrate chemical and biological data relevant to these types of questions, using principles of chemoinformatics to create statistical models around chemical fingerprints for the design of novel compounds with increased potency or a more favourable side effect profile. In turn, this work can also be used for a more comprehensive safety assessment of drugs – work which is part of currently ongoing studies within the group.

ASSEMBLING THE PIECES

The groups of **Daan Frenkel**, **David Wales** and **Mark Miller** are working together to understand the spontaneous self-assembly of complex structures from simple building blocks. Selfassembling molecular systems are of great interest in nanotechnology,

Theoretical

nanomedicine, colloidal science, and crystal formation processes.

They are also used by nature in biomolecular recognition, protein folding and macromolecular complex formation. When biological self-assembly turns against its host, diseases such as Alzheimer's can result. Unfortunately, such processes take place on scales difficult to access by experimental methods. The groups therefore use simulations and energy landscape exploration algorithms to understand the design principles of self-assembly and aggregation.

A major difficulty in understanding self-assembly processes is the large phase space, or dimensionality, of the system – there are often likely to be many possible arrangements separated by multiple barriers, making it difficult to explore the underlying energy landscape that defines the mechanisms and pathways towards assembly. Therefore, it makes sense to simplify the models used, in order to speed up calculations and unearth fundamental rules.

One approach has been to restrict the problem to two dimensions and, in particular, to uncover the basic design principles of self-assembly on curved surfaces. Computational algorithms are being used to explore the energy landscape of assembling particles and extended objects on curved surfaces, with a particular focus on the emergence of defect patterns that are known to occur experimentally.

The exploration of such processes will help to understand commonly observed assemblies in nature, and will guide template self-assembly of new materials with desirable technological properties.

Another area of interest is crystal nucleation. Nucleation and growth are fundamental to many organic and inorganic processes, and it would be desirable to control and optimise the early stages of crystallisation that ultimately determine the structure and properties of novel synthetic or biocomposite materials.

Typically, crystal nucleation is rare – for the process to occur, a high free energy barrier must be crossed, making direct observation of freezing events difficult in conventional simulations. Algorithms based on geometry optimisation techniques are being used to identify pathways and transition states along the energy landscape, and hence provide structural and mechanistic insights into the crystallisation process.

FROM SEQUENCE TO STRUCTURE

Robert Best's group is interested in simulating the dynamics of biomolecules, particularly in the context of protein folding and assembly. Protein folding is an important field in biomedical research as a range of debilitating diseases result from protein misfolding. Simulation approaches can help to understand the mechanisms of folding of complete proteins, while many biomolecular conformational changes also often involve folding transitions.

However, the results of such simulations are highly dependent upon the accuracy of the underlying force field. With this in mind, the group has undertaken the refinement of existing force fields by matching the properties of simple peptides measured in simulations and experiment. This effort yielded a highly optimised force field with an accurate balance of protein conformations, enabling the group to simulate the complete, *ab* initio folding of a variety of small proteins to their native structures.

THE RIGHT REACTION

When modelling molecular processes, accuracy is key, but at what cost? There is always a trade-off between the precision of the method and the time required to complete a calculation. A very accurate method might require more computer resource than is available within the time required for an answer to be found.

Jonathan Goodman's group carries out computational calculations to understand reaction mechanisms, particularly in organocatalysis, and recently studied the reliability of the many computational methods that are available to study molecular processes.

The group's detailed survey of a wide range of reactions in organic chemistry looked at the reliability of different methods based on density functional theory (DFT), a quantum mechanical approach to electronic structure calculation, for transition state calculations, which are the key requirement for analysing molecular processes.

From this extensive study, recommendations could be made regarding a selection of methods that gave particularly good value in terms of the ratio of its precision to its computational cost, while also giving good absolute precision in its results.

MOVING CALCULATIONS

Ali Alavi's group is interested in the electronic correlation problem: that is, how to account in electronic structure



Right, pathways to crystallisation: the energy landscape for low-energy crystalline clusters is illustrated via a disconnectivity graph. Four truncated lines corresponding to energetic minima reveal a mixture of face centred cubic (FCC) and hexagonal close packed (HCP) structures

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calculations for the fact that electrons 'move' in a correlated fashion with respect to each other. This is a crucial feature of any accurate description of chemical bonds.

An electronic correlation is, in fact, a quantum manifestation of 'entanglement' of combinatorially many different electronic configurations, called Slater determinants. Ali's group has been developing a novel Monte Carlo method in which a vast number of electronic configurations, called Slater determinants, are sampled, using population dynamics of walkers which inhabit Slater determinant space.

The method has allowed accurate quantum mechanical calculations of electronic correlation to be performed on quite sizeable molecules – up to 60 electrons, Slater determinant spaces of more than 10^{100} determinants. Because of the sheer volume of calculations, such systems have previously thought to be tractable only with quantum computers, which have yet to be built! The new algorithm developed in the group, therefore, provides a significant boost for classical computation, in other words, computing with ordinary machines.

Advances in the RIG have significant impact in areas ranging from the identification of safe therapeutic small molecules, the development of new approaches to exploit experimental data, and the design of self-assembling nanostructures, catalysts, sensors, and crystals.

Enthusing future chemists

Outreach is an important part of the department's mission. From the annual open day to hosting visits from students and teachers, the aim is to encourage young people to study chemistry, and promote an interest in science among the wider public.



The department has a rich and varied outreach programme interacting with children as young as five to secondary school teachers. One of the most important areas of outreach is forging links with school pupils to maintain their interest in science. The department acts as a host for a number of summer schools organised by external organisations who can make full use of teaching staff, technicians and lab facilities.

Salters' Festival of Science provides



the opportunity for 80 year 7 and 8 students to spend a day in a university department where they take part in practical chemistry. The Salters' Chemistry Camp is a two-day residential course aimed at year 10 pupils giving them an opportunity to explore the fun of chemistry and develop a longterm interest in the subject and its applications in modern life.

SUMMER SCHOOLS

An important part of departmental outreach is participation in the Sutton Trust summer schools. These free residential courses are specifically designed for year 12 students from state-maintained schools, and priority is given to those who come from schools with a low overall A-level point score, and who would be the first generation in their family to attend university.

The school is an ideal opportunity to discover what it is like to live and study as a first-year undergraduate student of Cambridge and encourage the students to consider taking a degree at the University of Cambridge.

Teaching staff also participate in a similar scheme run by the educational charity Teach First – called Higher Education Access Programme for Schools (HEAPS) for teenagers aged 16 Hundreds of children and their parents visit the department every March for our open day, with Peter Wothers' lecture packing the theatre, and students helping the kids with fun experiments to 18. It aims to raise aspirations and encourage students to focus on their higher education choices.

Teachers have an opportunity to access the facilities of the department with the free residential courses offered as part of The Goldsmiths' Company Science for Society Courses. Science teachers attend lectures aimed at broadening their perspective on subjects allied to the A-level syllabus.

The department is also involved in the International Chemistry Olympiad, and helps set the questions and select the team in association with the Royal Society of Chemistry. Once selected, the team spends a week in the department preparing for the competition.

In 2009, the University of Cambridge acted as joint host of the 41st International Chemistry Olympiad, providing the infrastructure for 260 students from 69 countries to undertake a practical and theory exam. Accompanied by teacher mentors, the occasion showcased the facilities of the department and the university.

CHEMISTRY OPEN DAY

The open day run by the department as part of the University Science Festival offers an ideal opportunity for undergraduates and PhD students to engage with members of the public. Although the emphasis is necessarily on 'fun' chemistry, schools also make full use of the day to allow pupils to get involved in a way which is often not available in class. Peter Wothers' lecture has a strong educational basis, and is given to 1000 local school children, in addition to the public lectures on the day.

The department is enthusiastic when approached by external organisations – engaging the interest of the wider community in science is an essential part of providing for the future.



For more information about the department's people and science, please visit our website at www.ch.cam.ac.uk



Department of Chemistry University of Cambridge Lensfield Road Cambridge CB2 1EW www.ch.cam.ac.uk