

# Chemistry for Better Health

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## A White Paper from the Chemical Sciences and Society Summit (CS3) 2011

*FINAL TEXT*

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## Executive Summary

All of modern medicine is dependent on advances in chemistry. To ensure the development of healthcare keeps pace with the increasing health challenges faced by society, investment in the underlying chemical science research is absolutely vital.

Healthcare goalposts have moved as the century has turned. We all face problems with the spreading of infectious disease on an unprecedented scale. Poor nations are unable to afford or distribute expensive modern drugs, while in richer nations drug resistance is exponentially growing. The increasing prevalence of non-infectious disease in an ageing population brings unforeseen and expensive challenges to healthcare. Chemistry will offer solutions.

When governments allocate funding to healthcare and life science research, however, the chemical sciences can be overlooked. It is vitally important that we support the basic science that enables healthcare research to bloom. If we do, vital opportunities will be created in understanding the molecular processes underlying cell-biology and genetics; the identification of chemical probes for biomedical research; advanced chemistry for the preparation of efficient chemical reagents and pharmaceuticals, and the innovation of new screening and diagnostic methods.

Often the challenges lie in a lack of basic molecular-level understanding of biological processes, of the chemistry of disease progression, or a lack of sufficiently advanced tools and methods to detect and treat disease and to validate drug-targets. These are all challenges that only well-funded chemical science research can overcome.

By developing new chemistry tools to detect disease earlier, and more sensitive detection methods to monitor disease more closely, chemical scientists will enable quicker diagnosis and more effective, less invasive monitoring of disease.

The deep well of innovative new drugs that society has become accustomed to is on the verge of running dry. With a lack of understanding of the biological processes and potential drug targets that underpin disease, rising manufacturing costs and tightening legislation, the pharmaceutical industry now faces threats to its current business model from which it is struggling to recover.

The discovery and development of new medicines includes a number of required technologies – identification of the molecular structure of the biological target, search for lead compounds to bind to the target and the development of a candidate by optimisation of the lead compounds. A suite of next generation drug therapies will be complimented by range of new therapeutic approaches, including medical devices, synthetic biologics and personalised medicine. All of these advances will be crucially underpinned by cutting-edge chemistry and a thorough understanding of the underpinning molecular processes.

To avert the worst of this crisis, and to secure a sustainable source of more effective drugs, we must encourage and support innovation throughout the process: from the molecular medicine that will elucidate and intervene with disease pathways and systems, to the advanced synthetic chemistry that adds to the drug designers' molecular toolkit, through the cutting-edge materials science delivering drugs more

safely, painlessly and efficiently, to the automated machinery of the future that will streamline screening and manufacturing.

This crisis brings opportunity for evolution and change in the healthcare industry. Involving a more open approach to trial and research data would lead to global collaborations for the benefit of society. More efficient use of high-tech equipment and skills could be introduced through centralised facilities and networks. And national and international strategies for supplying a healthcare skills pipeline would lead to linked, coherent and driven workforces working towards common goals.

*Chemistry for Better Health* explores these themes, and sets out not only the immense value the chemical sciences have enabled in healthcare, but the critical importance of supporting future healthcare with a well-funded bedrock of talented chemical scientists developing tools, techniques and treatments to defeat new challenges to global health.

Opportunities for the chemical sciences to improve global health include:

- Delivering a better molecular understanding of biological pathways, and how malfunctions in the molecular machinery of biological systems leads to disease onset and progression
- Developing a better understanding how our genes and environmental factors contribute towards non-infectious and age-related diseases
- Developing improved methods for diagnosing disease, including revolutionary new point-of-care diagnostic and molecular imaging technologies
- Improving the efficiency and probability of success for the drug discovery process by improving the choice and selection of biological targets and pathways for new drug discovery
- Developing technologies for the next generation of specific drugs needed for the treatment of individual patients (personalised medicine)
- Increasing global access to medicines; including those needed for low-income countries by embedding innovative new chemistry throughout the entire medicines research and development process
- Producing health-care products using sustainable chemistry, so as to reduce the contribution of medicines cost to the overall price of health care

Chemical scientists and the chemical sciences played a critical role in the development of modern medicine, and they will need to play a similarly central role in ushering the next generation of medical treatments and diagnostic technologies.

## **Recommendations for policy makers**

Chemically trained scientists have the skills and insight to overcome the challenges outlined in this report. Many of the opportunities will need sustained, collaborative research. The solutions presented herein will not be overcome in our lifetime without the commitment from governments worldwide to a realistic strategy for improving global healthcare. Financial support for the underpinning chemical science research will be of paramount importance.

The recommendations below for policy makers and other stakeholders would significantly advance our abilities to diagnose and treat disease, and would give excellent return on investment for society. The implementation of many of these recommendations could be achieved with modest amounts of financial support.

### **Data sharing**

- Infrastructure and initiatives should be put in place to enable the pharmaceutical industry and academia to share more scientific data in a manner that is free of intellectual property constraints
- The way that data exclusivity and intellectual property influence drug discovery and development should be examined
- Universally-accepted standards for reporting chemical data should be established and integrated into regulation
- Governments should make it a condition of receiving any research-related tax breaks that data should be shared

### **Collaboration**

- Improved collaboration between the pharmaceutical industry and public-funded academia should be encouraged at the pre-competitive level
- Further joint appointments across university departments and non-academic governmental research facilities should be prompted
- Greater multidisciplinary collaboration between scientists across disciplines, particularly chemists, physicians, biologists, and engineers should be enabled by bespoke funding sources

### **Core facilities**

- Establish 10 linked international public-private centers for drug discovery, to focus on clinical needs currently being neglected by the pharmaceutical industry
- Establish complimentary networks of national screening centers with international access
- Establish centralised, freely-accessible compound libraries and screens
- Establish global centres to train national drug regulatory agencies up to regulatory authority status.

### **Education**

- Ensure chemists and cell biologists have sufficient training in both biology and chemical synthesis.
- More interdisciplinary training within fundamental degree courses to empower chemical scientists to collaborate with other scientists and engineers

- A more comprehensive graduate experience that continues to provide in-depth chemistry training while developing skills in multidisciplinary research, business, communicating to the public, and teaching to better equip students to address societal health problems.
- Better international co-ordination on chemistry education
- Coordinated syllabus discussions between secondary and tertiary level courses

## **A new global model for drug discovery**

***Policy makers, scientists and other stakeholders must work together to deliver a new global system of healthcare innovation that can tackle the health challenges of the 21st century. It can no longer be left only to the free market.***

We need a global strategy for drug discovery that capitalises on world class talent with pump priming investment from governments, research funders, charities and the private sector. The fundamental challenges are to balance drug prices, R&D expenditure and risk, with a fair return on investment to fund continued innovation. A more open intellectual property landscape will be required to meet these challenges.

Key stakeholders should work together to develop a sustainable funding model with enhanced public sector participation that will support world class scientists in the discovery and development of innovative new medicines to meet the medical needs of the 21st century and to contribute to economic growth.

Clinicians and policy makers urgently need to work with chemists and other scientists across academia and industry to prioritise therapeutic areas of significant medical need, where innovative new medicines will improve quality of life and provide global economic benefits.

Governments should prioritise the establishment of non-profit public-private centres for drug discovery, jointly funded by the pharmaceutical industry and academia. Lacking the commercial pressures of a pure private company, such centres would have more scope to discover new anti-infectives and drugs for treating rare diseases.

New drug discovery centers could increase the productivity of academic research worldwide by providing 'Centres of Excellence' where screening tools and expertise could be combined to move explore new means of drug discovery. Academic drug discovery centres have already been established by some universities. Most of these centres focus on medicinal chemistry and early drug discovery for cancer, neurological diseases and infectious diseases, and appear to be fostering an innovative drug discovery environment with participation from academia and industry.

## **Sharing of data, knowledge and resources**

***Our ability to globally deliver new treatments could be drastically improved by improved domestic and international sharing of data, knowledge and resources. Early stage sharing will facilitate public and private drug discovery.***

***Pre-competitive sharing and collaboration***

Pre-competitive drug discovery data (including bioinformatics and information on drug mechanism-of-action) should be made public with an ethos of reduce, reuse and recycle. Even opening access to data already in existence would dramatically increase our collective understanding of disease processes, drug mechanism-of-action and drug failure. This understanding would be highly beneficial for the discovery and development of new medicines across the entire drug discovery sector. Governments should encourage sharing of pharmaceutical industry data by making data-sharing a condition of receiving any research-related tax breaks.

Initiatives to improve sharing of dormant and redundant compound libraries are needed. Large quantities of chemical compounds and data are dormant in compound libraries and databases around the world which could greatly enhance drug discovery programmes if disseminated. The establishment of screening centres and compound banks could potentially achieve this without impacting on commercial sensitivities.

The pharmaceutical industry generates significant amounts of data during the drug development process, much of which is not released into the public arena due to concerns over confidentiality and intellectual property. This includes data in compound libraries, and data on screening, drug candidates and clinical trials, much of which becomes redundant in private databases when drug discovery programmes come to a close. There is little perceived value in a company expending human and financial resource in an effort to fully elucidate and understand why a drug candidate fails: usually it is simply abandoned. There is, however, a long-term benefit to the industry in determining the common factors involved in the failure of drug candidates, in order to try to reduce failure rates.

Duplication of drug discovery efforts often occurs when pharmaceutical researcher focus on biological targets where there are chemical tools already available to support target validation and drug discovery. As a result, many researchers are often unknowingly duplicating efforts already made elsewhere.

Academic institutions, many of which often build up their own unique chemical compound libraries, can also greatly benefit from data sharing. Sharing of academic data and compounds would enable those engaged in academic drug discovery to 'bring something to the table', which in turn would encourage data sharing from industry.

Shared knowledge of pre-competitive activity would help to reduce redundancy and duplication of data across the pharmaceutical sector, and enable companies to abandon flawed drug discovery programmes at earlier stage. Scientists engaged in drug discovery could take advantage of earlier work (such as target validation) being duplicated elsewhere.

### ***Global data and publishing***

Publishers of chemical science need to work together to develop a global strategy towards a universal data format for compound characterisation. At present, most scientific publishers have their own house format which makes it difficult to create shared global databases. Data sources are in effect each in a different language.

A standard format should be expanded to patent literature and should include structural annotation, spectroscopic data, formatting and standardised software for data sharing. This would facilitate easier data searching and mining of large repositories. It should no longer be acceptable for publicly-funded data to be re-sold by database companies. As a first step towards this goal, society publishers should agree on a common chemical data format. Academic scientists could consider boycotting journals that do not adhere to the standard format.

A transition to open access model across scientific publishing would assist data dissemination and sharing. Governments and publishers need to work together to ensure that moves towards a new publishing model is concerted and sustainable for the publishing sector.

### ***Intellectual property and regulation***

Current intellectual property laws and regulations inhibit the drug discovery process and produce barriers to collaboration between academia and industry. We need a more innovative global regulatory IP framework that better facilitates scientific collaboration, provides financial incentives for those that develop the drugs needed to combat the diseases of the 21st century, and which reduces the financial burden of drug discovery and development. Enabling patents to be filed later would have a positive impact by allowing companies that deliver drugs to the market to gain longer market exclusivity. Political support will be needed to make the regulatory changes that are required. However, the rewards of creating an IP landscape with greater freedom are potentially great, if pre-competitive freedoms are encouraged.



## Chapter One: Challenges to Human Health

*Chemists and the chemical sciences have been integral to the development of modern medicine, from diagnostics to drugs and the creation of the pharmaceutical industry. The result has been a steady improvement in our health and life expectancy over the past 100 years.*

### **Disease**

Numerous challenges to health still remain. Deadly infectious diseases including malaria, cholera and tuberculosis may have been largely conquered in high-income regions of the world, but remain a major threat in poorer regions such as Africa. Even in richer nations infectious disease remains a constant threat, as the swine flu pandemic of 2009 and the dramatic increase of antibiotic resistance make clear.

Infectious diseases are still the main cause of death in many developing countries, due to a lack of readily-available and inexpensive drug and vaccine treatments. Poverty and lack of access to modern drugs mean that infectious diseases that are rare or under control in high-income countries (such as malaria and HIV/AIDS) are still major causes of death.

In high-income countries, infectious disease remains a challenge due to the rise of antibiotic resistance in many bacterial pathogens and the emergence of new strains of viruses. Modern health systems are struggling to cope with the demand for novel and more effective antibiotics, as pathogens develop resistance to existing treatments. There is an urgent need for new drugs to fight multi-resistant infectious agents as our present antibiotics become ineffective due to global misuse in medicine and the food industry.

Our ability to better treat infectious disease has resulted in longer life expectancies in high-income countries. This has meant that non-infectious diseases such as cardiovascular disease, cancer, diabetes and Alzheimer's disease are becoming more prevalent. The United Nations (UN) has stated that 36 million people worldwide died from non-infectious diseases in 2008, representing 63% of all deaths that year.

Non-infectious diseases are caused by combined genetic and environmental factors, and can't be cured by current modern drugs, only controlled. Many become more common with age and are becoming increasingly prevalent in countries with ageing populations. By 2030, it is predicted that non-infectious diseases will account for over 80% of all deaths worldwide and this represents a significant challenge for modern science. These diseases require treatment over extended periods of time and necessitate alternative treatment models. Treating the growing number of elderly people with chronic diseases is already placing stress on the healthcare systems of many countries and this stress is only going to get worse.<sup>1</sup>

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<sup>1</sup> To give one example, by 2030 around 20% of the US population will be over 65 years old and 42% of the population will suffer from at least one chronic disease. Chronic diseases account for 75% of all US healthcare expenditure, which has grown from 13.7% of US Gross Domestic Product (GDP) in 1993 to 16.6% in 2008. By 2017, US expenditure is predicted to rise to 19.5% of GDP.

## ***Diagnosis***

Recognising disease symptoms and progress of how a disease develops is vital for effective treatment. We need to advance to earlier diagnosis and improved methods of monitoring disease.

Globally there are over 33 million people living with HIV, but only 10 per cent are aware that they are infected. There are also 8.8 million new cases of TB annually, many of which are undiagnosed. These diseases, along with one million deaths from malaria per year, place a huge burden on developing countries. To overcome this, better systems are required that can be used in resource-limited settings to detect diseases as early as possible to monitor the effectiveness of treatments, and to direct treatments to where they are needed.

Improved diagnosis is required in the developed and developing world. Quick and accurate diagnosis benefits individual patients by improving their treatment, in addition to ensuring the efficient use of resources and limiting the spread of infectious diseases. New, less-invasive, technologies are needed for the early detection of non-infectious diseases such as cancer, cardiovascular disease and Alzheimer's disease, to enable healthcare professionals to intervene at an earlier stage of disease progression. This will require an improved molecular understanding of disease onset and progression as well as a new suite of diagnostic technologies.

In addition to detection, there is a need to better monitor the effectiveness and safety of therapies and medication.

## ***Pharmaceuticals***

We need new and more effective treatments for both infectious and non-infectious disease, but the pharmaceutical industry – historically the main source of new medical treatments – is finding it increasingly difficult to develop them.

A new estimate for the average cost of bringing a new drug to market is \$3.0 billion, up from \$1.1 billion just five years earlier. Most novel drug compounds don't even reach the market, with over 90% of candidate compounds failing at some point during clinical trials.

Only three out of ten new drugs that do reach the market will be major successes that generate enough return on investment. Most pharmaceutical companies rely on very few successful drugs to generate the revenue required not only to pay for their development, but also to pay for the development of other less-successful drugs and the thousands of failed drug candidates that never reach the market.

Even finding candidate drug compounds is getting more difficult. Pharmaceutical companies have to sift through upwards of 300,000 molecules to come up with a single candidate, which then has a good chance of failing in clinical trials. Despite the latest incorporation of new technologies arising out of fundamental sciences (that include the Human Genome Project, advances in compound synthesis, and screening technologies), the number of new drugs gaining regulatory approval has

fallen, while the percentage of drug candidates failing during the development process has increased. The entire process of drug discovery and drug development has become so diverse and complex that only a limited number of countries possess the full range of R&D experience to fully contribute to this undertaking.

The outcome is that pharmaceutical companies are paying more and more to discover less and less: the number of drug approvals in the US fell to an all-time low in 2007 despite annual R&D spend by the pharmaceutical industry more than tripling over the past 20 years, to around \$50 billion in 2008. Seemingly-promising drug candidates are too often failing at the late stage of development, following years of research and billions of dollars invested.

Reasons for the recent lack of success include an over-reliance on high-throughput mass compound screening at the expense of fundamental knowledge about the molecular basis of disease and how existing drugs work. The end result is not only a dearth of new drugs, but also that those few that do reach the market are expensive and less understood, further increasing health costs and preventing their use in low-income countries.

Many drugs are failing in clinical trial due to poor biological target validation, suboptimal animal and human safety, heterogeneous clinical trials (rather than targeted patient sub-groups) and insensitive methodologies. The high-throughput screening (HTS) techniques made popular in the 1990's have been successful in delivering lead drug compounds for drug discovery, however they have too often been directed at the wrong biological targets that are not the primary cause of disease. These approaches have meant that pharmaceutical researchers still don't understand in detail how many successful drug candidates actually work.

Financial pressures mean that increasing emphasis placed on cost/benefit analyses to justify reimbursement. This has driven the industry to search for so-called 'blockbuster' drugs with annual sales of more than \$1 billion and a handful of drugs now generate the majority of a pharmaceutical company's sales. There has been a shift towards therapies for chronic diseases that require treatment over extended periods of time. This provides a longer period for recouping investment. Just eight products accounted for 58% of Pfizer's annual worldwide sales of \$44 billion in 2007. Companies are seeing their sales figures fall by up to 80% when the patent protection on one of their blockbusters expires.<sup>2</sup> With fewer blockbusters in the pipeline, pharmaceutical companies are finding themselves in trouble.

Continued investment in key areas of medical need will be required to address the existing and future needs of patients. The search for blockbusters has led to a focus on therapeutic areas likely to generate the most revenue, and with high chance of technical success, rather than necessarily areas where there is greatest medical

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<sup>2</sup> The patent on Pfizer's cholesterol-lowering drug Lipitor, which had sales of \$12.5 billion in 2009, expired in 2011. Bristol-Myers Squibb's blood clotting inhibitor Plavix, which had sales of \$9.8 billion in 2009, is due to expire in 2012. It has been estimated that the expiry of the patents for these and other drugs between 2010 and 2013 will knock almost \$30 billion and \$11 billion off Pfizer and Bristol-Myers Squibb's annual revenues, respectively.

need. This strategic narrowness has created a weakness in global healthcare that is now a looming primary political issue. Therapeutic areas such as neuroscience, obesity, malaria, HIV/AIDS and tuberculosis have been downsized because they are technically challenging and costly to develop. This is despite the urgent need for new treatments, limited effectiveness of current therapies and significant healthcare costs.

Meagre returns on investment have largely forced the pharmaceutical industry to exit antibiotic R&D even though the World Health Organisation has forecast a disaster due to rapid and unchecked increases in microbial resistance. The devastating effects of Human Immunodeficiency Virus (HIV) and Methicillin-resistant Staphylococcus aureus (MRSA) underline the need for a strong pharmaceutical R&D sector to invent new drugs to control known and unexpected medical challenges in the 21st century.

## Chapter Two: Chemistry and disease

***Infectious disease is a continuing risk to the developing world, and non-infectious diseases like Alzheimer's disease pose a growing risk to the developed world's ageing population. Only when chemists further understand the molecular processes of disease, and the biochemical action of drugs, will we be able to better diagnose and treat these diseases.***

Chemistry needs to be fully integrated at the early stages of life science research. Chemical scientists can provide the necessary fundamental understanding of the molecular processes that underpin all biological systems, both in healthy and diseased states. Chemical scientists are already helping us to gain a more complete understanding of existing biology principles, while harnessing chemical science to answer new biological questions in the world around us.

**Understanding disease onset and progression: chemical medicine**  
***Diseases are fundamentally caused by malfunctions of the molecular machinery in biological systems. A better understanding of the chemistry of disease is needed to tackle global health challenges of the 21st century.***

Many existing biological explanations of disease remain unproven because we do not have the detailed understanding of the molecular processes and mechanisms that are involved. Our current simple models have been useful, but are now outdated. We need to move beyond simply identifying the structure of biological molecules towards gaining a full understanding of their mechanism-of-action. A detailed understanding of how the molecular pathways of disease vary between, and even within, individuals will enable healthcare systems to take advantage of the emerging field of personalised medicine.

By way of example, a better comprehension of the chemistry of the immune system could allow us to use the body's natural defenses in more sophisticated ways to tackle disease. In addition to priming the immune system against specific diseases (using vaccines), we can find ways to increase its ability to fight infectious disease and even non-infectious diseases such as cancer. An increased understanding of the immune system would also allow us to intervene when it goes awry. Autoimmune diseases such as rheumatoid arthritis, multiple sclerosis and type I diabetes result from the body mistakenly recognising its own constituent parts as *non self* (which allows an immune response against its own cells and tissues) and are becoming increasingly prevalent in the developed world. Rheumatoid arthritis is thought to affect approximately 1% of the world population.

Chemists are helping to develop an improved understanding of the molecular basis for antibiotic resistance mechanisms. This will enable scientists to develop smarter antibiotics for tackling antibiotic resistant bacteria as they emerge.

A more detailed appreciation of the chemistry, signaling and function of all cells (including stem cells), and their networks, would give us a more thorough

understanding of developmental biology and would enable health systems to more quickly reap the benefits of regenerative medicine.

Our understanding of enzymes and other large biomolecules is improving through the study of kinetics and applying chemical understanding to the fields of systems biology and synthetic biology. Chemists are moving beyond looking at whether a molecule simply binds to a biological target, towards specifically *how* it binds, for how long and what biological pathways are affected. Chemists are helping to understand how folding of proteins in biological systems influences the development of diseases such as Alzheimer's disease and Huntington's Disease.

### **Genes and non-infectious disease**

***Genes play an important part in the development of many non-infectious diseases, but a detailed molecular understanding of this is lacking.***

A detailed understanding of exactly how our genetic information influences the onset and progression of many non-infectious diseases is urgently needed. Some, such as Huntington's disease, are caused by a single genetic defect whereas other more widespread conditions, such as cardiovascular disease, cancer and Alzheimer's disease, can result from the complex interaction between our genes and a number of environmental factors. Scientists have yet to piece together the full suite of factors involved in most non-infectious diseases, nor to establish how they interact with each other.

Chemical scientists are now developing a better understanding of the genetic causes of non-infectious disease by increasing our understanding at the molecular level. The determination of the human genome has made a big impact in human diseases such as cancer. However, sequencing the genome is only the starting point towards determining which molecular processes are responsible for disease, and how therapeutic intervention can be achieved.

Environment and diet is likely to have a greater impact on diseased tissue than healthy tissue and chemists can help to develop a better appreciation of the impact of environmental factors in these systems. The central dogma of biology states that information flows in one direction from our genes. This model is now outdated as we are now learning that environment can influence our genes. Despite the fact that the human genome was sequenced over 10 years ago, the interaction between our genes and environmental factors is so complex that scientists are still far from working out the details.

Epigenetics is the study of changes in gene expression caused by mechanisms other than changes in the underlying DNA sequence. Chemists are helping to elucidate how our genes are modified by environmental influences, how this effects their expression, and how this affects the development of many non-infectious diseases. One of the ways our cells switch genes on and off is through chemical modification, and this pattern of chemical modification is influenced by environmental factors such as diet, ageing, smoking, lifestyle and the even the oxygen we breathe. It now known that these patterns of genetic modification can be inherited, providing a way for traits acquired during our lifetime to be passed on.

Epigenetics is beginning to offer an innovative way to explore non-infectious diseases, and chemical scientists are beginning to make significant breakthroughs. Better understanding of epigenetic processes (and others) will enable us to move beyond simply treating the symptoms of many non-infectious diseases towards providing real cures.

## **Oxygen and disease**

***Chemists will provide a greater understanding of the role of oxygen in disease progression.***

Oxygen is involved in regulating multiple biochemical pathways in all aerobic organisms, including humans. Reactive oxygen species (ROS) are generated by normal cellular metabolism, are responsible for much of the wear and tear our bodies experience during our lifetime and have been implicated in the development of many age-related diseases. Lack of oxygen in cells is linked with diseases including cancer, cardiovascular disease and diabetes.

Chemists are helping to elucidate a better understanding of the role of reactive oxygen species in regulating gene expression at a number of different levels. Understanding, harnessing and sensing oxygen in biological systems offers new routes towards developing a better understanding of disease progression.

## **The brain and disease**

***Understanding the little-known chemistry of the brain will be essential to treating neurodegenerative disorders such as Alzheimer's disease.***

An improved understanding of the molecular basis of memory and the chemistry of the brain could enable us to better tackle many neurological disorders.

Chemists are working to develop a better understanding of the chemistry of the brain, and the molecular basis of memory, as a first step towards providing more effective treatments for many debilitating neurological disorders. Diseases such as depression and schizophrenia can strike at any time during our lives, but often first appear in young adults. It is known that there is a strong genetic influence on the development of these diseases, but scientists are yet to pinpoint the molecular processes involved. Indeed, we are very far from a working model for understanding the underlying chemical processes in the brain.

An improved understanding of the effects of ageing on the brain would enable us to better appreciate the role of the fibrous protein aggregates implicated in many age-related diseases. Amyloid aggregates are famously thought to play a major role in the development of Alzheimer's disease. They may also play an important role in other diseases, including Parkinson's disease, Type II diabetes and amyloid A (AA) amyloidosis.

The precise role of amyloid in these diseases remains theoretical, yet the Amyloid Hypothesis has led to the development of Alzheimer's therapeutics that target the amyloid protein and the enzymes responsible for its production. Many of these treatments have to date been unsuccessful and the Amyloid Hypothesis, like many others, remains unproven.

Chemical scientists have an important part to play in gaining a better molecular understanding of brain and age-related diseases, by helping to test existing biological hypotheses and developing new molecular theories. This will lead to the development of innovative and better-targeted drugs and therapies.

## **Analysing biological processes**

***A new generation of measurement techniques and analysis is needed to better understand disease.***

Chemists are helping to integrate many analytical “omics” techniques in biology (such as genomics, glycomics and proteomics) by uniting them through a fundamental understanding of the underlying chemical principles. Chemists are combining traditional detection techniques with new technology to deliver cutting-edge devices that can analyse tiny samples, including the contents of a single biological cell.

Chemists are developing improved methods for quantitatively measuring molecules in biological systems and for detecting biological events both inside and outside of the cell with remarkable resolution and accuracy. Shedding light on the interactions between individual molecules in a cell will allow us to study biological processes in greater detail and to understand how we can fix malfunctions that occur during disease development.

Many existing methods for detecting chemical events and identifying biomolecules in biological systems rely on antibodies which bind to specific biological targets. Unfortunately antibodies are often inadequate for studying processes inside cells, due to their large size. Chemists are developing streamlined antibody-like molecules that retain the unique specificity of an antibody while being small enough to gain access to biological processes inside cells. New molecular probes will be able to interact with individual biological molecules, including specific metabolites, proteins and strands of DNA.

New analytical technologies will enable us to accurately measure the concentration of proteins in cells, measure the protein structural changes in real-time as they occur in live cells and determine the structures of membrane-bound proteins (a challenge using existing standard techniques).

Chemists are now building complex biomolecules from simple starting materials and the burgeoning field of ‘in vivo’ chemistry is enabling specific chemical transformations to be carried out inside live cells and, one day, inside whole organisms.



## **Chapter Three: Novel chemistry for diagnosis**

***Recognising the molecular origins, symptoms and progress of a disease is vital for effective treatment. By developing new chemistry tools to detect disease earlier, and more sensitive detection methods to monitor progress more closely, chemical scientists will enable quicker diagnosis and more effective, less invasive monitoring of disease.***

### **Biomarkers**

***We need to identify more reliable, specific biomarkers to detect disease at early stages, and chemists will be central to discovering and harnessing them.***

Biomarkers are specific proteins or metabolites produced by infected or defective cells, or generated by damage to tissues or organs. For instance, they can be proteins produced by cancer cells or metabolites generated as a result of damage to heart cells. Detecting biomarkers at an early stage of disease would allow cancer to be treated before it has a chance to spread and cardiovascular disease to be treated before it causes a heart attack.

Many biomarkers in current clinical use are unreliable and not specific to the disease they are being used to diagnose. Biomarker levels are often found to vary dramatically between patients. The levels of Prostate Specific Antigen (PSA) in blood, for instance, are not necessarily specific to prostate cancer at the levels they are commonly measured. Diseases such as cancer are highly variable and differ in their physiology and biochemistry between patients. As such, two patients suffering from the same form of cancer may express an entirely different set of biomarkers associated with their disease.

Chemists are helping to identify better biomarkers by gaining a greater understanding of disease progression in each case (see Chapter Two: Chemistry and Disease). Long-term studies are needed to record how proteins and metabolites associated with disease change over time. This will help to identify truly useful biomarkers that can be detected at very early stages of disease development.

Chemists will help to provide better tools for validating biomarkers, to ensure they are accurate and specific, and for determining their normal function in biological systems. This in turn will help to reveal whether a biomarker plays an important role in a disease process or is more likely produced in response to general physiological stress.

### **Probes**

***Chemical scientists will design and use new molecular probes for diagnosis and imaging.***

Chemical probes enable scientists to explore biological systems by interacting specifically with a biomolecule to provide information on their biological role, or to measure the levels of a biomarker in a patient. It is difficult to deliver existing probes into the patient and to localise them to the specific site at which they are needed.

New, antibody-free methods of diagnosing disease are needed, particularly if we are to take advantage of point-of-care diagnostic technologies. Many diagnostic techniques are antibody-based and are often susceptible to false positive and false negative results. Chemical scientists are investigating new-generation probes that can specifically bind to target biomarkers to enable their concentration to be measured and for potential use in new point-of-care technologies.

There remain significant challenges, particularly relating to delivery of probes to their biological site-of-action. Many nucleic acid probes are now available as a research tool for the discovery of gene function, however the chemistry underlying many technologies needs enhancing to improve efficiency and cost. These probes enable scientists to target specific genes in a cell (usually by turning off their function) in order to understand their role in biological systems. Chemistry will help us to better target nucleic acid probes to cells improve cell entry, and better understand gene function, with the eventual aim of developing therapeutic nucleic acids.

### **Molecular imaging and diagnostics**

***To make use of newly discovered targets, chemists will develop new methods for molecular imaging and measuring biomarker levels.***

Molecular imaging differs from traditional imaging in that specific biomarkers are used to detect specific molecular patterns and characteristics in a targeted biological system. The biomarkers interact chemically with their surroundings and in turn alter the image according to molecular changes occurring within the area of interest. This ability to image fine molecular changes opens up an incredible number of exciting possibilities for medical application, including early detection and treatment of disease and basic pharmaceutical development.

Chemists are playing an important role in delivering new, sensitive (and ideally non-invasive) techniques to measure novel biomarker properties inside individual cells, for probing the molecular basis of disease.

Novel approaches to diagnosis include the measurement of alternative biomarker properties in addition to classical measures of concentration in blood. Molecular changes associated with disease are often so subtle that they remain undetected in a blood sample. Many of the sensitive tools needed to learn more about the molecular basis of the disease will be directly useful for diagnosis (see Chapter Two: Chemistry and Disease).

Disease biomarkers tend to be present at very low concentrations in biological fluids and can be difficult to detect using traditional methods. In the future we should be able to diagnose disease, and start appropriate treatment before the appearance of physical symptoms, by detecting tiny biochemical changes in the body.

In order to reap the benefits of personalised medicine, improvements to our ability to identify genes associated with certain diseases is urgently needed. This will require cheap, accurate and efficient technologies for screening individual genomes for genes known to be associated with certain diseases. Chemists are working with other scientists and clinicians to deliver a new set of personalised diagnostics and imaging technologies to detect unique abnormalities associated with cancer and

amyloid diseases, such as Alzheimer's disease, at an early stage of disease development. New approaches will move beyond simply detecting protein expression in a biological sample towards understanding relative patterns of protein expression and real-time monitoring of changes in these patterns. This in turn will lead to a new suite of personalised treatments that selectively tackle the disease while avoiding unwanted side effects.

Chemists are helping to develop affordable genome sequencing devices that will enable healthcare professionals to warn individuals with a genetic predisposition towards a particular disease, which may allow them to take preventative measures. However, individual genome sequences alone will not allow personalized medicine, and will prove inefficient and ineffective, without an accompanying molecular understanding.

Chemists are investigating a range of cheaper and simpler imaging technologies, for use in the clinic, that are able to cover a wide range of scales. Imaging for diagnosing disease in the clinic is currently carried out on large scales using expensive equipment. Point-of-care technologies that can swiftly and accurately make a diagnosis at the bedside have the potential to change health systems and improve people's lives worldwide.

As new technologies emerge, they will be able to support existing and reliable large scale facilities. New mass spectrometry technology is emerging that can work with solid samples, by directly capturing compounds on cell surfaces to produce an image of the diseased tissue. New imaging methods to make biological cells as 'transparent' as possible will be important for rapid and accurate diagnosis at the bedside. Emerging techniques will help to distinguish cancerous from healthy tissues for guided cancer surgery.

#### *Case Study: Mass spectrometry at the bedside*

Chemists have significant expertise in mass spectrometry, and it may be possible to couple MS with new point-of-care technologies for rapid and accurate diagnosis at the bedside. MS could be coupled with Polymerase Chain Reaction (PCR) techniques to rapidly identify genetic biomarkers for personalised medicine and diagnosis of many non-infectious diseases. New MS technology will enable us to undertake quantitative analysis of the protein expression patterns associated with many cancers for more rapid diagnosis.

## Chapter Four: Chemistry and drugs

***Chemists can help to bring medicines research and development into the modern age by uncovering better validated biological targets for urgent clinical needs, modernising drug discovery and manufacturing, developing new modes of drug delivery and new therapeutic approaches***

Chemistry can assist in expanding the available sources of new drugs, and improving success rates and costs for bringing new drugs to the market. New, low-cost and readily-available drugs for infectious diseases will improve the lives of billions of people around the world.

A new, more rational approach to drug discovery is emerging that embeds chemistry at all stages of the development process. This often begins with the identification of a biological target that represents a critical point in a disease pathway or in a pathogen's metabolism, followed by the design and synthesis of a compound that efficiently binds to that target. Novel probe compounds and phenotypic assays will help identify new targets. Chemistry will be integral to better measuring and understanding how drugs interact with disease pathways inside cells, and for creating new inventions and products that can better control the biological systems involved with disease.

### Target validation

***Chemists will find new and improved biological targets for drugs to underpin drug discovery programmes with a higher success rate and that can deliver more effective and targeted medicines.***

Target validation aims to link specific genes and their biological products with disease.

Drug discovery programmes that have pursued non-validated biological targets have been heavily responsible for the high attrition rate (or failure) of many drug candidates over the last 20 years. Many drug candidates have failed not simply because of toxicity or safety concerns, but often because the biological target was not the main cause of disease. Pharmaceutical researchers have often found that a drug candidate simply does not work as well in humans as in the laboratory animals used earlier in the development process. Current preclinical models cannot predict human pharmacology, pharmacokinetics and drug metabolism with a high degree of certainty.

It has been estimated that scientists have so far uncovered 4500 possible molecular targets for drugs, encompassing both our own cells, whether infected or cancerous, and pathogens. Yet all the drugs approved by the US Food and Drug Administration focus on just 324 molecular targets, around 60% of which are found on the cell surface and half of which are coded for by just four gene families. This suggests that we have yet to investigate the vast proportion of disease targets, any of which could offer entirely novel ways of treating both infectious and non-infectious diseases.

Chemists will be able to uncover a huge suite of novel drug targets by helping to better understand the molecular basis of disease (see Chapter Two: Chemistry and

Disease). This would empower pharmaceutical researchers to design a modern set of safer drug candidates with a greater chance of successfully making it through the drug development process and onto the market. By working with biologists and other scientists, chemists can investigate the full suite of interactions between drug candidates and biological molecules such as proteins and DNA.

New cell-surface and intracellular receptors will be revealed as drug targets, and will enable us to better understand the causes of drug side-effects to improve drug discovery strategies. More reliable biomarkers of disease for diagnosis and monitoring will be identified (see Chapter Three: Novel Chemistry for Diagnosis).

There are vast areas of biomolecular science yet to be explored for drug discovery, including protein-protein and nucleic acid interactions. Genome mining also has potential to unveil a number of important biological targets and biomarkers of disease, while adding to our mechanistic understanding of disease pathways.

Chemistry will enable us to understand how genetic differences between people cause them to react very differently to drugs, such that a drug that works perfectly well in certain people fails to work in others. This would lead us towards developing better targeted medicines. Rather than trying to develop one drug that can treat a disease in all people, which may not always be possible, we may develop multiple drugs targeted at specific groups or people with specific sets of genes (personalised medicines). This will require scientists to move beyond sequencing the genome, towards a molecular understanding of its biomolecular products.

A targeted approach offers a better way to deploy novel anti-infectives. Instead of developing a broad-spectrum antibiotic that kills all bacteria inside us, even beneficial ones, chemists will help to develop more selective antibiotics that target specific bacterial species.

## **Designing more effective drugs**

***Using chemical insight and advanced computer software, chemists will replace the mass screening approach of drug testing with strategies that use fewer, more targeted drug candidates.***

Chemists are particularly successful in inventing the synthetic molecules, as cost effective oral therapies. These are mainstays of advanced healthcare systems. While biological based drugs are making a significant impact, this therapeutic class will not remove the need for affordable small molecule “drug pills” taken by mouth for chronic diseases.

The synthesis of compounds that are specifically designed to bind a biological target remains a challenge. Chemists are developing new approaches to drug design, based on a better understanding of disease pathways and biological targets. We may eventually be able to better predict and design drug candidates using advance drug discovery software before carrying out a synthetic step in the laboratory.

The drug discovery process has been limited for many years by the use of quantitative measures of drug effectiveness. By incorporating improved knowledge of drug mechanism-of-action (such as speed of drug binding, length of stay and time

of release) into our drug design, chemists will be able to focus on more qualitative measures to assemble more rational chemical compound libraries.

The natural world remains a rich source of biologically active molecules that could form the basis for novel drug compounds. It has been estimated that less than 1% of all microorganism species are easily cultured and less than 15% of higher plant species have been examined for bioactivity. New molecular approaches may help us to take more advantage of the medicinal properties of complex natural products (derived from organisms such as plants or microbes). Genome mining technology offers a means of screening the genomes of plants and microbes for genes that may give rise to natural products of therapeutic interest.

## **New synthetic methods**

***Cutting-edge organic chemistry gives modern drug and therapy designers cheaper, more varied starting materials, and a wider toolbox to craft them.***

For many years, synthetic chemists around the world have provided breakthroughs in the way in which we are able to assemble organic (carbon-based) molecules which form the basis of the living world around us. Indeed, most of the drugs on the market today originate from (or are closely related to) molecules found in nature.

Synthetic chemistry continues to develop breakthrough methods to expand our access to new and exciting molecular architectures. Emerging methodology is utilising cheaper and more readily-available starting materials, reagents and catalysts than ever before. Procedures are becoming more reproducible, making them more reliable for large-scale manufacturing. New catalysts are emerging that are made from readily available and inexpensive materials, to replace those based on rare and expensive materials.

Our understanding of chemistry and chemical reactivity will expand significantly to access the hundreds of novel disease targets that are beyond the reach of current drug templates. Chemists will deliver new suites of reactions that are able to modify specific parts of a molecule while keeping other parts intact, and new ways to synthesise biomolecules.

Chemists are developing a better understanding of the molecular transformations taking place in biosynthesis and are exploiting these processes for use on an industrial scale. Chemists will deliver new synthetic biology methods, based on a detailed understanding of molecular mechanism, which will support traditional synthetic approaches.

## **Process automation**

***Robotic processes will take mundane, routine jobs away from skilled chemists, enabling them to focus on creative new chemistry.***

Chemists are taking more advantage of robotics and automated processes for performing simple reactions, leaving them free to concentrate on the more complex and innovative methodology.

Improved robotic and automated synthetic methods offer the opportunity to make drug discovery and manufacture more efficient. Highly skilled and creative chemists often spend large amounts of their time on simple, routine or repetitive tasks that could be automated. Such tasks include purification, the production of building blocks for chemical synthesis and the synthesis of chemical analogues (of drug candidates) that rely on the same or very similar synthetic methods used to make the original compound. Improved automation offers the opportunity for highly-trained chemists to spend their time exploring new synthetic methods, chasing further breakthroughs and expanding scientific knowledge. Chemists, working with engineers, can develop new automated methods for carrying out routine and repetitive laboratory tasks in both the academic laboratory and the industrial plant.

Many existing technologies are often bespoke, designed and made for a specific user and use. As such, standardisation is the key challenge and costs are high. Optimisation becomes difficult for new users which in turn creates barriers to widespread adoption.

The development of these new robotic technologies may even open the opportunity to explore new synthetic chemistry, especially for catalysis, in a way that was previously the realm of the bench chemist. This will succeed only if methods for generic implementation are explored.

The implementation of robotic technologies also requires well-trained chemists or technicians to operate them. Operators will need a solid fundamental training in chemistry together with sound technical skill to efficiently replicate the automated procedure.

## **Drug delivery**

***Chemists are helping to develop new technologies that give us more control over where a drug is released, while enabling continuous release over time to maintain the right therapeutic concentration.***

We need a far better understanding of the chemistry of these processes in order to develop more effective drugs delivery systems. Drugs have to pass several hurdles to get to their location of action and the first step for many therapies is getting from the gut into the bloodstream. Treatments for diseases of the brain must cross the blood-brain-barrier in order to reach their site of action, and many drugs need to gain access to the inside of cells to have the desired effect.

New, innovative drug delivery systems need to develop in parallel with new therapies. Traditionally, drugs are formulated to make them stable and to maximize their delivery to the bloodstream. The weakness of this approach is that drugs are then distributed quite widely throughout the body, rather than targeting the specific sites where they are needed for therapeutic action. We need ways to transport drugs to specific areas of the body, and then get them inside tissues and cells.

Chemists will help to develop a whole suite of sophisticated methods for delivering drugs, incorporating novel targeting molecules, novel materials and novel mechanisms of release. Therapeutic agents particularly sensitive to degradation by the body's metabolism (such as emerging nucleic acid therapies) could be housed in

protective nanoparticles, for instance, to enable them to reach their site of action. Controlled release of therapeutic agents at their site-of-action would be especially valuable for drugs that are toxic to healthy cells, such as cancer chemotherapy drugs, to reduce the severity of commonly-experienced side effects.

The development of nanomedicine is not without its problems, however, with one of the main concerns being the fate of medicine-containing nanoparticles in the environment. To lessen these concerns, chemists are helping to develop, for example, nanoparticles that naturally break down into harmless compounds either in the body or in the environment.

New implant technologies, which act as a long-term store of drug in the body, also offer the opportunity for controlled drug release. Next generation implants could monitor physiological conditions within the body and only release the drug when it's needed. Chemical scientists are already developing implants that release heart drugs at the first physiological signs of an oncoming heart attack, which could be abnormal behaviour of the heart or the presence of specific biomarkers in the blood.

### **New approaches to treating disease**

***Chemists are looking beyond the traditional conventions of drug design and investigating the potential of newly-discovered chemistry, including tissue engineering and synthetic biologics***

Small molecule therapy will be important for the short to medium term and for many common diseases long into the future. Chemists are also developing whole new approaches to treating disease.

Chemists are helping to improve stem cell technology, for the regeneration of diseased or damaged tissue, by delivering a more detailed appreciation of the chemistry, signaling and function of stem cells, and their networks. Novel chemistry is being deployed on surfaces to promote cell adhesion, improve cell function and encourage the development of functioning tissue. By incorporating stem cells into three-dimensional scaffolds, scientists are working towards the longer-term goal of growing whole genetically-matched organs in the laboratory before transplanting them into patients.

Chemistry is now being used to build very large biomolecules and convert promising biologically-active molecules into effective therapeutic agents. It has already been shown that small parts of DNA can be built using chemical synthesis. It may eventually be possible to create larger systems such as synthetic genomes.

The synthesis, manipulation and redesign of naturally-occurring biomolecules allows biochemical mechanisms to be probed and potential therapeutic strategies to be developed. Better biological therapeutics can be designed based on a greater understanding of the molecular interactions underlying the intended biological response. Chemical synthesis enabled the invention of the synthetic biologic *Abraxane* – a protein-bound form of the anti-cancer drug *Taxol* that has been successfully used as injectable formulation used in the treatment of certain types of cancer. The bound protein assists in targeting the drug towards tumour cells.



## **Sustainable manufacturing**

***New approaches to drug manufacture will provide opportunities to re-use and recycle waste products to improve cost- and resource-efficiency and to reduce the amount of pharmaceutical waste entering the environment.***

There is a huge opportunity for chemistry to improve the entire pipeline of drug manufacture to increase global access to medicines, but there are many challenges to overcome. We are limited by the current number of synthetic chemical reactions (or transformations) available. The cost of manufacturing drugs is high due to the need to ensure quality and purity. The current technology for manufacturing drugs means that many people around the world have limited supplies of the drugs needed to treat both common and rare diseases. Many of the solutions to these challenges would improve both upstream drug discovery and development and downstream manufacturing.

Counterfeit medicines continue to be a problem, particularly in developing countries. We urgently need improved methods of guaranteeing the purity and quality of registered drug products, while detecting and monitoring products on the market for dangerous counterfeits and impurities. Contamination of an import of heparin with oversulfated chondroitin sulfate (OSCS) led to several deaths in the US 2008. Heparin is used clinically as a blood thinner and is commonly given to patients undergoing heart surgery or dialysis. Even a basic chemical analysis could have been performed on the samples to detect any impurities and would have avoided widespread distribution throughout the US health system.

The reactions we use in drug manufacturing need to be more sustainable, efficient, flexible and scalable. The perfect chemical reaction would be 100% efficient and generate zero waste. It is unlikely that any manufacturing process would ever be entirely efficient or generate no waste at all: however chemists will enable us to get extremely close, in particular by developing new catalysts.

Pharmaceutical and chemical scientists will be able to develop and take advantage of new feedstocks from plants and other biomass, to help reduce global dependency on feedstocks from fossil fuels. Chemists will be central to the development of industrial biotechnology methods for making new platform chemicals available from biomass that will replace petrochemicals as starting materials for making numerous consumer products including fuels, plastics and drugs, and will link these processes with biosynthesis. Chemists will help to adapt existing manufacturing processes to accommodate a new generation of chemical feedstocks, such as those available from carbohydrates.

Any waste generated from manufacturing should be degradable. Chemists can help to deliver a better understanding of the pathways of biological and chemical degradation of manufacturing waste in the environment, together with a better appreciation of the role and effect on soil ecosystems. This understanding will require a better appreciation of how different chemical functional groups are transformed and degraded in the environment. This will in turn lead to the

development of improved manufacturing processes that minimise the impact on the environment.

We need a better understanding of the long-term fate of drugs in the environment after use. Pharmaceutical waste isn't just generated by the manufacture of drugs, but also by their use. Drugs are administered to patients, metabolised in the body and the resultant drug metabolites excreted, eventually finding their way into the environment. We know little about what happens to drug metabolites when they reach the environment, although they have been blamed for certain environmental problems, such as high levels of endocrine disrupters in waterways.

## Chapter Four: Opportunities for the chemical sciences

### Chemistry and disease

<b><i>Understanding disease onset and progression: chemical medicine</i></b>
Validation of existing biological hypotheses and using chemistry to gain a detailed molecular understanding of biological systems and processes
Making new breakthroughs in systems biology by providing the molecular understanding and technologies needed to manipulate biological networks
Developing a better insight of the molecular principles of infection and the chemistry of important infectious diseases such as malaria, HIV/AIDS and tuberculosis (TB)
Developing a better molecular understanding of the mechanisms of resistance in infectious disease
Developing a greater understanding of the immune system to enable infectious, non-infectious, inflammatory and auto-immune diseases to be treated more effectively
Understanding the role of chemical signaling in reprogramming cells
Improving our understanding of large biological molecules (such as DNA and proteins) by deciphering the specific molecular interactions that give rise to biological function
Understanding partially unfolded proteins or protein domains and investigating their interaction with other biomolecules, to give a deeper understanding how to influence biological systems important in disease
Achieve a more rigorous understanding of the kinetics of enzymes and other biomolecules in cells and organisms

<b><i>Genes and non-infectious disease</i></b>
Developing a better understanding of the molecular basis of disease and how molecular malfunction leads to the onset of disease
Delivering new methods for analysing individual genes involved in non-infectious diseases and their relationship with other genes in disease pathways
Developing better tools for investigating the chemical changes that genes undergo during disease progression
Development of new methods to analyse post-translational modifications and their role in diseases
Delivering new methods for analysing the effect of environment and diet on both healthy and diseased tissue
Understanding how epigenetic modification of DNA and proteins leads to different phenotypes and how we can modify and control it <i>in vivo</i> to affect disease progression
Clarifying the role of reactive oxygen species (ROS) in important biochemical and disease progression pathways
Improving our understanding of the chemistry of the brain, the molecular basis of memory and aging to enable us to better understand and treat diseases of the brain

<b><i>Analysing biological processes</i></b>
Helping to integrate the '-omics' disciplines through a fundamental understanding of the underlying chemistry of the biology
Developing more applicable versions of existing analytical techniques like NMR spectroscopy or liquid chromatography and mass spectrometry
Development of new devices for accurately analysing tiny biological samples,

including the contents of a single biological cell
Further developing new non-invasive analytical methods for understanding disease at the molecular level
Methods to study the molecules present in living cells and to monitor how they change over time
Exploring combinations of NMR spectroscopy, X-ray diffraction, electron microscopy and new technologies for understanding biological processes, to identify ways to interfere when malfunctions in biological systems lead to disease
Developing a better chemical understanding of how molecules get into cells in order to exploit different types of compounds for discovery biology
Developing alternatives to antibodies as analytical tools
Investigating candidates for molecular probes that are able to interact with specific biomolecules (including metabolites, proteins, RNA and DNA strands) to measure biomolecule concentration
Developing new <i>in vivo</i> techniques for carrying out chemistry inside cells and organisms
Developing new methods for delivery of RNA and DNA inside cells

## Novel chemistry for diagnosis

<b><i>Biomarkers</i></b>
Developing new and better tools for validating disease biomarkers to ensure they are accurate and specific
Discovering new and improved biomarkers for the identification of many infectious and non-infectious diseases
Working with biologists and clinicians to measure new, alternative markers of disease including patterns of protein expression
Identification of new biomarkers that can better predict the progress of disease as a step towards selecting the most appropriate treatment

<b><i>Probes</i></b>
Developing new probes with improved properties for delivery and localisation into cells, in order to access all biological targets
Delivering new probes that are more stable than existing probes, more resistant to metabolism and enable the concentration of disease biomarkers to be determined more accurately
Designing new 'activation-specific' probes for molecular imaging
Developing new small-molecule alternatives to antibodies for rapid and accurate diagnosis of disease
Developing new antibody-free diagnostic technologies for point-of-care diagnostics
Improving the chemistry of nucleic acid diagnostics to dramatically reduce the need for sequencing of individual genomes
Development of delivery systems for nucleic acids (e.g. RNAi)

<b><i>Improved imaging and diagnostics</i></b>
Exploring methods to measure specific molecular changes to biomarkers, including protein stability and misfolding, and changes caused by reactive oxygen species.
Developing a new suite of rapid point-of-care diagnostic technologies that will diagnose a range of diseases in a non-invasive fashion and at the bedside, including

disease-causing microorganisms
Developing methods to measure specific molecular changes and monitor single molecules in biological systems, to monitor disease progression in real time
Delivering new personalised medicine technologies for the rapid identification of genes associated with many non-infectious diseases
Developing new molecular imaging tools, such as by using positron emission tomography (PET) for quick and safe recognition of disease biomarkers
Developing new recognition tools for detecting abnormalities in patients that are specific to their disease, for instance cancer
Developing advanced imaging techniques to characterise cancer and differentiate benign from cancerous areas during surgical intervention

## Chemistry and drugs

<b>Target validation</b>
Developing a better understanding of disease pathways and validating improved targets for drug discovery
Achieving a better mechanistic understanding of the causes of many common drug side effects
Developing <i>quantitative</i> measures of drug effectiveness, based on understanding of molecular mechanism-of-action, including kinetics and lifetime-of-action
Developing a better understanding of drug resistance in both infectious and non-infectious disease
Working with other scientists and clinicians to deliver a better capacity to monitor resistance as it emerges in health systems and develop strategies for mitigation
Using the principles of kinetics to study the mechanism-of-action of drug candidates to garner information on slow effects, such as time taken to bind, time bound to target and release time
Identifying new cell-surface and intracellular receptors as validated drug targets for drug discovery programmes
Using analytical genome mining techniques to identify 'sleeping' gene clusters associated with many disease pathways

<b>Designing more effective drugs</b>
Working to establish focused compound libraries, based on the complete knowledge of the origins of a disease, and of existing biological compounds from synthetic or natural sources
Developing fundamentally new simulation methods for designing therapeutic agents to fit validated disease targets
Identifying new drug-like natural products and synthesis of new chemical compounds as drug candidates
Building improved compound libraries containing compounds with properties likely to bind to new, validated disease targets, that include fragment-based design principles
Gaining a greater understanding of molecular binding kinetics and advances in both computer modeling and chemical synthesis, in order to bring about more rational drug design and development

<b>New synthetic methods</b>
Expanding known and exploring unknown 'chemical space' for new molecular

scaffolds and architectures
Developing more reproducible and modular synthetic methods, especially catalysts, that work under sustainable, mild, standard conditions, on a range of diverse chemical substrates, and that do not rely on rare and expensive metals
Developing new C-C and C-H activation methods for synthesis that avoid the need for reactive and unstable functional groups, while creating the opportunity to explore new molecular scaffolds and architectures
Developing new chemical 'redox' methods for changing the oxidation state of substrate molecules
Developing sustainable reactions that are functional group specific yet avoid the need for wasteful and problematic catalysts and protecting groups
Developing new 'microreaction' methods that will enable us to perform chemical transformations on an extremely small scale
Improving our understanding of the molecular transformations taking place within biosynthesis

#### ***Process Automation***

Developing new automated methods for producing standard building blocks required for exploring chemical synthesis, drug discovery and drug manufacture
Developing standardised and cost-efficient robotics equipment that can be universally adopted for automated laboratory procedures

#### ***Drug delivery***

Improving drugs to overcome barriers such as stability against degradation in gut, liver and blood
Improving transport from gut to blood, from blood to brain and from blood into the cytosol
Improving control of drug release at the site of action by developing systems that respond to biological signals and feedback
Developing new drug delivery systems that include implants and nanomedicines
Conversion of biologically active peptides into orally available drugs
Developing methods for selectively targeting therapeutic agents to receptors in specific tissues
Developing a better understanding of zwitterion systems of drug delivery

#### ***New approaches to treating disease***

Exploring novel chemistry for tissue engineering, including new scaffolds for optimizing the growth of specific cells and tissues that are remodeled as cells grow and form tissues
Deploying novel chemistry to scaffold surfaces to promote cell adhesion, improve cell function and encourage development of functioning tissue for regenerative medicine
Design, modify and synthesise biomolecules as synthetic biologics for understanding and treating disease
Develop synthetic capability to create new 'building blocks' for synthetic biology

#### ***Sustainable manufacturing***

Developing new, cost-effective and reliable analytical methods for detecting impurities in drug products and guaranteeing quality during manufacturing
Improving manufacturing processes to be more efficient, flexible and scalable
Developing new manufacturing processes that maximise atom economy and

minimise waste products as far as possible
Developing a more complete understanding of the biological and chemical degradation pathways in the environment
Developing a more robust understanding of how different chemical functional groups are modified during degradation of waste in the environment
Working with other scientists and engineers to develop new industrial biotechnology methods for drug manufacture
Delivering new and efficient synthetic methods that utilise biomass-derived starting materials for drug manufacture
Developing new 'retrosynthetic' or design strategies for drug discovery and manufacture that utilise biomass-derived platform chemicals as starting materials