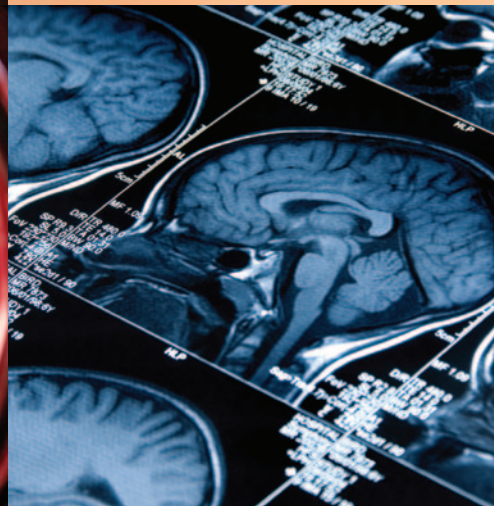


Chemistry for Better Health

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



About the Chemical Sciences and Society Summit (CS3)

The annual Chemical Sciences and Society Summit (CS3) brings together the best minds in chemical science research from around the world and challenges them to propose innovative solutions for society's most pressing needs in the areas of health, food, energy, and the environment. This unique event boasts an innovative format, aiming to set the course of international science, and rotates each year among the participating nations.

Chemistry for Better Health summarises the outcomes of the third annual CS3, which focused on advances in chemistry for modern medicine. Thirty top chemical scientists from the five participating countries assembled in Beijing to identify the scientific research required to address key global challenges, and to provide recommendations to policymakers. The full white paper presents an international view on how chemistry can contribute positively to human health.

The CS3 initiative is a collaboration between the Chinese Chemical Society (CCS), the German Chemical Society (GDCh), the Chemical Society of Japan (CSJ), the Royal Society of Chemistry (RSC) and the American Chemical Society (ACS). The symposia are supported by the National Science Foundation of China (NSFC), the German Research Foundation (DFG), the Japan Society for the Promotion of Science (JSPS), the UK Engineering and Physical Sciences Research Council (EPSRC), and the USA National Science Foundation (NSF).

This white paper was compiled and written by Jon Evans and James Hutchinson.



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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 our society faces, investment in the underlying chemical science research is absolutely vital.

The 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 all nations drug resistance is growing. The exponentially 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 the chemical sciences shouldn't 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 to developing better healthcare lie in a lack of basic molecular-level understanding of biological processes and 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 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 tighter legislation, the pharmaceutical industry now faces threats to its current business model, which it is struggling to overcome.

The discovery and development of new medicines requires a number of technologies, to identify the molecular structure of the biological target:

- searching for lead compounds that bind to the target,
- developing a candidate by optimisation of the lead compound,
- identifying appropriate patient groups and biomarkers and to access efficacy at an early stage of development.

A suite of next generation drug therapies will be complemented by a 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. Cutting-edge materials science deliver drugs more safely, painlessly and efficiently. In the future, automated machinery will streamline screening and manufacturing.

This crisis brings opportunity for evolution and change in the healthcare industry. 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. 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 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 disease diagnosis, including revolutionary 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 adopting a more rational approach to drug design.
- Bringing medicines research and development into the modern age through cutting-edge synthetic chemistry.
- Developing innovative modes of drug delivery and new approaches to treating disease, including personalised medicines, regenerative medicine and improved biological therapeutics
- Embedding innovative and sustainable new chemistry throughout the entire medicines research and development process, to reduce environmental impacts, lower the overall price of healthcare and increase global access to medicines.

Chemists and the chemical sciences have played a critical role in the development of modern medicine, and they will need to play a similarly central role in ushering in the next generation of medical treatments and diagnostic technologies (Figure 1).

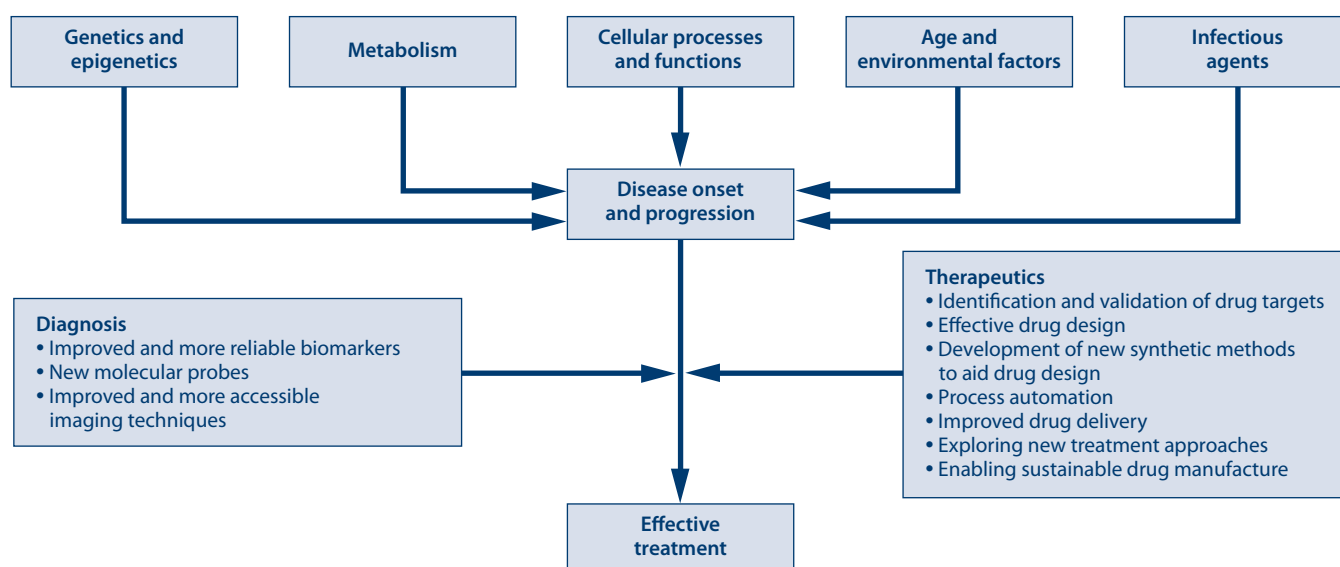


Figure 1: The chemical sciences can help to improve global healthcare from basic research that helps to understand the mechanisms underlying disease, through the development of improved means of diagnosis and through optimising the development of effective drugs.

Recommendations for policymakers

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

The implementation of the recommendations below for policymakers 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.

Summary of recommendations

Data sharing

- Infrastructure and initiatives should be put in place at the early stages of drug discovery 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 sharing data a condition of receiving any research-related tax breaks.

Collaboration

- Improved collaboration between the pharmaceutical industry and publicly-funded academia should be encouraged at the pre-competitive level.
- Further joint appointments across university departments and non-academic governmental research facilities should be promoted, including providing access to industry facilities.
- Greater multidisciplinary collaboration between scientists across disciplines, particularly chemists, physicists, biologists, clinicians, and engineers should be enabled by bespoke funding sources.

Core facilities

- Establish 10 linked international public-private centres of excellence for drug discovery, to focus on clinical needs currently being neglected by the pharmaceutical industry.
- Establish complementary networks of national screening centers to combine biological targets, with international access.
- Establish centralised, freely-accessible compound libraries to deposit compounds and screens and to provide informatics and compound logistics to enable wider access to existing compound collections and screening capabilities.
- Establish global centres to train national drug regulatory agencies to regulatory authority status.

Education

- Ensure chemists, biologists and pharmacologists have sufficient training in both biology and chemical synthesis.
- Offer more interdisciplinary training within fundamental degree courses to empower chemical scientists to collaborate with other scientists and engineers.
- Provide a more comprehensive graduate experience that continues to provide in-depth chemistry training while developing skills in multidisciplinary research, business, communicating with the public and teaching to better equip students to address societal health problems.
- Better international co-ordination on chemistry education.
- Encourage coordinated syllabus discussions between secondary and tertiary level courses.

A new global model for drug discovery

Policymakers, 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 policymakers urgently need to work with chemists and other scientists across academia and industry to prioritise therapeutic areas of significant medical need and to generate innovative new medicines that will improve quality of life and provide global economic benefits.

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

New drug discovery centres could increase the productivity of academic research worldwide by providing 'Centres of Excellence' where screening tools and expertise could be combined to explore new means of drug discovery. Academic drug discovery centres have already been established by some universities, particularly in the areas of cancer and tropical diseases where an innovative drug discovery environment has been fostered, with participation from academia and industry. An example of this is the Dundee Drug Discovery Unit (DDU).¹

Sharing of data, knowledge and resources

Our ability to globally deliver new treatments could be drastically improved by fostering 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 a drug's 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 that are dormant in compound libraries and databases around the world and could greatly enhance drug discovery programmes if disseminated.² Establishing screening centres and compound banks could potentially achieve this without impacting on commercial sensitivities. The Innovative Medicine Initiative (IMI) has made a step towards achieving this through the creation of a European Lead Factory consisting of two topics: the European Screening Centre and the Joint European Compound Collection.³

The pharmaceutical industry generates significant amounts of data during the drug development process, much of which is not released into the public domain due to concerns over confidentiality and intellectual property.⁴ This includes data in compound libraries as well as 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 resources in an effort to fully elucidate and understand why a drug candidate fails. Usually failed candidates are 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 researchers focus on biological targets although chemical tools are 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 an earlier stage. Scientists engaged in drug discovery could take advantage of earlier efforts (such as target validation) instead of duplicating work.

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 this 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 favouring journals that adhere to the standard format.

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

Intellectual property and regulation

Current intellectual property laws and practices inhibit the drug discovery process and produce barriers to collaboration between academia and industry.^{5,6} We need a more innovative global intellectual property 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 that reduces the financial burden of drug discovery and development. Regulators must ensure that those investing in the development of intellectual property are appropriately incentivised.

Encouraging patents to be filed later, and extending the lifetime of patents associated with key medicines, 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 some of these changes. However, the rewards of creating an intellectual property landscape with greater freedom are potentially great, if pre-competitive freedoms are encouraged.⁷

1. 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 century. However, an ageing population and the lack of access to modern healthcare worldwide still pose significant challenges.

1.1 Disease

Numerous challenges to human 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.⁸ Even in richer nations infectious disease remains a constant threat, as the swine flu pandemic in 2009 and the dramatic increase of antibiotic resistance has made clear.⁶

Infectious diseases are still the main cause of death in many developing countries, because of a lack of readily available and inexpensive drugs and vaccines treatments. Poverty and a lack of access to modern drugs mean that infectious diseases that are rare or under control in high-income countries (such as diarrheal illness, TB and human immunology virus/acquired immunodeficiency syndrome (HIV/AIDS) are still major causes of death.⁸

In high-income countries, some infectious diseases remain a challenge due to the rise of antibiotic resistance in many bacterial pathogens and the emergence of new strains of viruses.⁹ 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.⁸ This means 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, which represents 63% of all deaths that year (Figure 2).¹⁰

Non-infectious diseases are caused by combined genetic and environmental factors, and cannot be cured, only controlled, by current drugs. Many are more common with increasing age and are becoming increasingly prevalent in countries with ageing populations. It has been predicted that, by 2030, non-infectious diseases will account for 69% of all deaths worldwide and this represents a significant challenge for modern science.¹¹ 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 in many countries and this stress is only going to get worse (see case study 1).

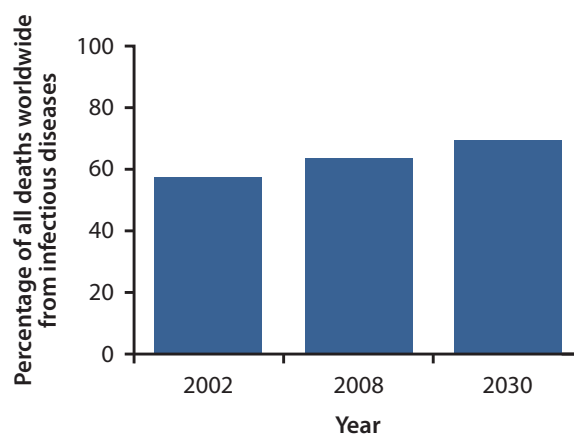
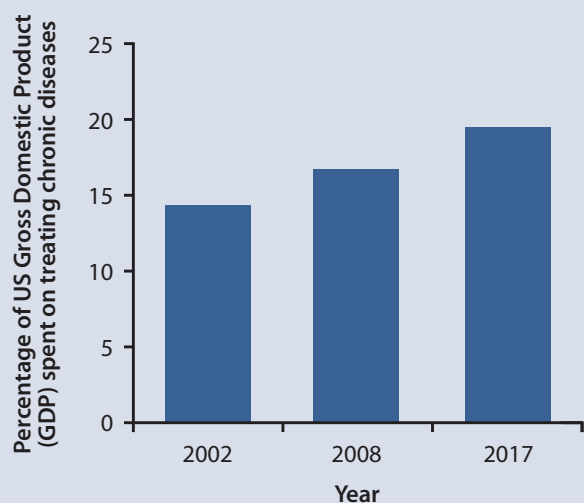


Figure 2: The proportion of deaths due to noncommunicable disease is projected to rise from 59% in 2002 to 69% in 2030. In 2008 the the proportion was 63%.

Case study 1: Chronic Disease US healthcare expenditure



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.

1.2 Diagnosis

Recognising disease early in its natural development is vital for effective treatment. We need to advance to earlier diagnosis and improved methods of monitoring disease.

Globally more than 33 million people live with HIV, but only 10% are aware that they are infected.¹² There are also 8.8 million new cases of tuberculosis (TB) annually (Figure 3), many of which remain undiagnosed. These diseases, along with 665,000 deaths from malaria per year,¹⁴ 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.⁶

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.¹⁵

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

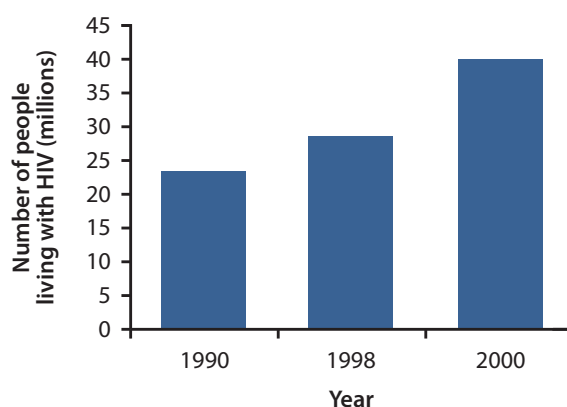


Figure 3: Globally more than 33 million people live with HIV and by 2020 HIV/AIDS will cause more deaths than any other single infectious disease worldwide.

1.3 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 the market is \$1.3 billion, up from \$1.1 billion just five years earlier.¹⁶ Most novel drug compounds do not even reach the market, with over 90% of candidate compounds failing at some point during clinical trials.¹⁷

Only three out of ten new drugs that do reach the market will be major successes that generate enough return on investment.^{18,19}

Historically, most pharmaceutical companies have relied 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. Until 2008, pharmaceutical companies were spending more and more on R&D, but drug success rates have continued to decline. R&D expenditure dropped between 2008 and 2010, reaching a three year low of \$68 billion.²⁰

Financial pressures mean that increasing emphasis is placed on cost/benefit analyses to justify reimbursement. In the past, this has driven the industry to search for so-called 'blockbuster' drugs with annual sales of more than \$1 billion and as a result a handful of drugs now generate the majority of a pharmaceutical company's sales.²¹ For instance just eight products accounted for 58% of Pfizer's annual worldwide sales of \$44 billion in 2007.²² This has seen a shift towards therapies for chronic diseases that require treatment over extended periods of time to provide a longer period for recouping investment.

Companies have seen their sales figures fall by up to 80% when the patent protection on one of their blockbusters expires.^a With fewer blockbusters in the pipeline, pharmaceutical companies have found themselves in trouble.

Even finding candidate drug compounds is getting more difficult. Pharmaceutical companies have to sift through more than 300,000 molecules to come up with a single candidate, which then has a good chance of failing in clinical trials.²³

Despite the latest incorporation of new technologies²⁴ arising out of fundamental sciences (which include the Human Genome Project, advances in compound synthesis and screening technologies), the number of new drugs gaining regulatory approval has stayed constant over the last five to ten years, while the percentage of drug candidates failing during the development process has increased.²⁵ 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 high-throughput screening (HTS) techniques made popular in the 1990s have been successful in delivering lead drug compounds for drug discovery and candidate compounds for clinical development. However, many drugs fail in clinical development as a result of poor biological target validation, suboptimal animal and human safety and heterogeneous clinical trials (rather than those utilising targeted patient sub-groups). The end result is not only a dearth of new drugs, but also that those few drugs that do reach the market are expensive and often less well-understood, further increasing health costs and preventing their use in low-income countries.

By maximising the chances of technical success, the pharmaceutical sector has focused on therapeutic areas likely to generate the most revenue, instead of areas where there is greatest medical need. Therapeutic areas such as neuroscience, obesity, malaria, HIV/AIDS and tuberculosis have been downsized because research is technically challenging and drugs to treat these diseases are costly to develop. This is despite the urgent need for new treatments, limited effectiveness of current therapies and significant healthcare costs in this area.

Many companies are now shifting towards a more targeted approach to drug discovery, coupled with a more balanced portfolio of programmes, each targeting a smaller patient population. However, continued investment in key areas of medical need will be required to address the current and future needs of patients. 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 because of rapid and unchecked increases in microbial resistance.²⁶ The devastating effects of 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.

^a 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's and Bristol-Myers Squibb's annual revenues, respectively.

2. 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 ageing population in high-income countries. Only when chemical scientists 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 gain a more complete understanding of existing biological principles, while harnessing chemical science to answer new biological questions in the world around us.

2.1 Understanding disease onset and progression: chemical medicine

Diseases are fundamentally caused by malfunction 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. 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 understanding of the chemistry of the immune system could allow us to use the body's natural defences 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 initiates 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 0.5% of the world's population.²⁷

Chemists are helping to improve our understanding of the molecular basis for antibiotic resistance mechanisms. This will enable scientists to develop more efficient antibiotics for tackling antibiotic resistant bacteria.

A more detailed appreciation of the chemistry, signalling 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 studying specifically how it binds, for how long and what biological pathways are affected. Chemists are helping to understand how protein folding in biological systems influences the development of diseases such as Alzheimer's and Huntington's disease.^{15,28}

2.2 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 diseases, 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 and how they interact with each other.^{15,28}

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 sequencing of the human genome has made a big impact in understanding 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 are 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 biological dogma states that information flows in one direction, from our genes to the cellular structure. This model is now becoming outdated as we are 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 affects gene expression and 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 even by the oxygen we breathe. It is 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 will enable us to move beyond simply treating the symptoms of many non-infectious diseases towards providing real cures.

2.3 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 highly reactive molecules containing oxygen that are generated by normal cellular metabolism that are responsible for much of the wear and tear our bodies experience during our lifetime. ROS 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 ROS 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.

2.4 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. 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 chemical processes that underpin the progression of diseases 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.^{15,28,29}

The precise role of amyloids 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 to date have been unsuccessful and the Amyloid Hypothesis, like many other hypotheses of disease, remains unproven.

Chemical scientists play an important part 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.

2.5 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 single biological cells.

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 that 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 like these molecules will be able to interact with individual biological molecules, including specific metabolites, proteins and strands of DNA and will therefore improve disease detection.

New analytical technologies will enable us to accurately measure the concentration of proteins in cells, measure the structural changes of proteins in real-time in live cells and determine the structures of membrane-bound proteins (which is 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.

3. 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.

3.1 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 that are 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 specific 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 results in 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 often 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.³⁰ 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.^{31,32}

3.2 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 and thereby providing information on the 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.

Many diagnostic techniques are antibody-based and are often susceptible to false positive or false negative results. New, antibody-free methods of diagnosing disease are needed, particularly if we are to take advantage of point-of-care diagnostic technologies. The probes need to be safe and need to be able to access the target site. Chemical scientists are investigating next 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.

Significant challenges remain, particularly relating to probe delivery 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 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.

3.3 Molecular imaging and diagnostics

To make use of newly discovered biological 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 certain 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 that occur 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 will play 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.

Disease biomarkers tend to be present at very low concentrations in biological fluids, such as blood, 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 small biochemical changes in the body.

In order to reap the benefits of personalised medicine, improvements in 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.^{15,28}

Chemists are helping to develop affordable genome sequencing devices that will enable healthcare professionals to warn individuals that have a genetic predisposition towards a particular disease, which may allow them to take preventative measures. However, the ability to provide individual genome sequences alone will not pave the way for personalised medicine, we need an accompanying molecular understanding of how an individual's genome sequence leads to disease onset and progression. (see chapter 2: Chemistry and disease).

Chemists are investigating a range of cheaper and simpler imaging technologies for clinical use 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 healthcare systems and improve people's lives worldwide.

As new technologies emerge, they will be able to support existing and reliable large scale facilities. A new mass spectrometry technology that can work with solid samples by directly capturing compounds on cell surfaces to produce an image of the diseased tissue is emerging (see case study 2). 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 2: Mass spectrometry at the bedside

Chemists have significant expertise in mass spectrometry (MS), 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.³³

4. Chemistry and drugs

Chemists can help to bring research and development into the modern age by uncovering better-validated biological targets for urgent clinical needs, modernising drug discovery and manufacturing, and developing 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. Chemistry plays an integral part in enhancing our understanding of 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.

4.1 Target validation

Chemists will find new and improved biological targets for drugs to underpin drug discovery programmes that have 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, within both human cells, whether infected or cancerous, and pathogens.³² 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 encoded by just four gene families.³² This suggests that we have yet to investigate a vast proportion of disease targets, any of which could offer entirely novel ways of treating both infectious and non-infectious diseases.³⁵

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 2: 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 disease biomarkers for diagnosis and monitoring will be identified.³⁶

There are vast areas of biomolecular science yet to be fully explored for drug discovery, including protein-nucleic acid interactions.³⁷ Genome mining also has the 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-infective agents. 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.

4.2 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 that make cost effective oral therapies. These are mainstays of advanced healthcare systems. While drugs that are based on specific biological properties are making a significant impact, this therapeutic class will not remove the need for affordable small molecule drugs that can be administered orally to treat chronic diseases.

It is still a challenge to synthesise compounds that are specifically designed to bind to a biological target and at the same time mimic toxicity and maintain sufficient exposure at the site of action. It is important to design drugs with previous drug failures and problems in mind (see Executive summary). 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.³⁶ New molecular approaches may help us to take advantage of the medicinal properties of complex natural products (derived from organisms such plants or microbes) more efficiently. 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.

4.3 New synthetic methods

Cutting-edge organic chemistry gives modern drugs and designers of therapies 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.³⁷

Synthetic chemistry continues to develop breakthrough methods to expand our access to new and exciting molecular architectures. Emerging methodology is using 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. They will deliver new synthetic biology methods, based on a detailed understanding of molecular mechanisms, which will support traditional synthetic approaches but apply these to biomolecules or inside organisms.

4.4 Process automation

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

Chemists are increasingly taking advantage of robotics and automated processes for performing simple reactions, leaving them free to concentrate on the more complex and innovative methodology. The development of microwave and flow chemistry and other technologies has enabled chemists to access new chemical scaffolds while providing new options for safe and reproducible large-scale procedures.

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 bespoke, designed and made for a specific user and application. 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.

Implementing 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.

4.5 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.

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. We need a far better understanding of the chemistry of these processes in order to develop more effective drug delivery systems.

New, innovative drug delivery systems need to be developed in parallel with new therapies. Traditionally, drugs are formulated to make them stable and to maximise 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 (nanomedicine), 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 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 drugs to treat heart disease 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.

4.6 New approaches to treating disease

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

Small molecule therapy will be important for the short to medium term and for treating 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, signalling 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.

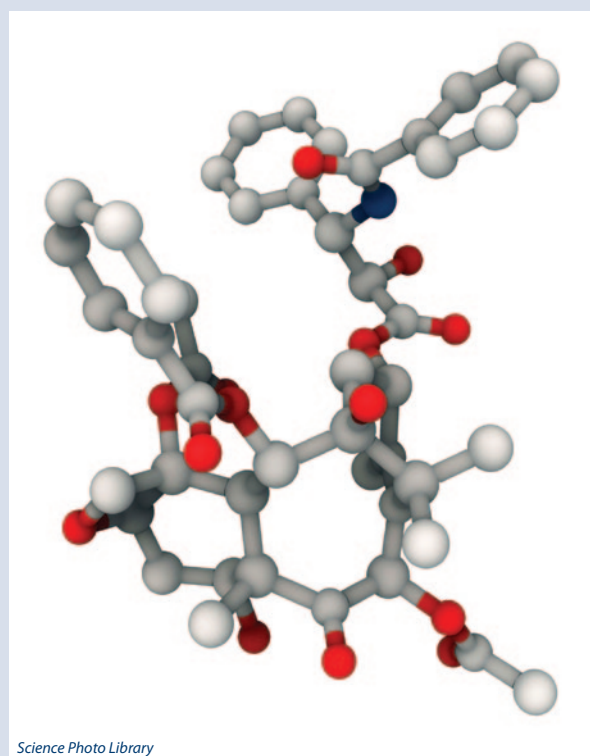
Chemistry is now being used to build very large biomolecules and convert promising biologically-active molecules into effective therapeutic agents. It has already been shown that small parts of DNA can be built using chemical synthesis. It may eventually be possible to create larger systems such as synthetic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

Case study 3: Nanotechnology increases efficacy in cancer drugs

Pacitaxel (sold as Taxol®) is a potent anti-tumor agent that was originally isolated from a natural product, the bark of the Pacific Yew tree (*Taxus brevifolia*). It is a cancer chemotherapy drug that inhibits cell division by interfering with the internal protein scaffold in cancer cells.

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 in the treatment of certain types of cancer. Abraxane is Taxol® that is bound to albumin nano-particles, which act as an alternative delivery agent. The bound protein assists in targeting the drug towards tumour cells.^{40,41}



Science Photo Library

The cancer chemotherapeutic Taxol

4.7 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.

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.⁴⁵

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 (Figure 4). 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.

Case study 4: Chemical analysis ensures drug purity and quality

Counterfeit medicines continue to be a problem, particularly in developing countries.⁴² 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 imported heparin with oversulfated chondroitin sulfate (OSCS) led to several deaths in the US 2008.^{43,44} 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 healthcare system.

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 is not 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 are 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 polluting waterways with high levels of endocrine disrupters, such as estrogen from oral contraceptives and hormone replacement therapies.

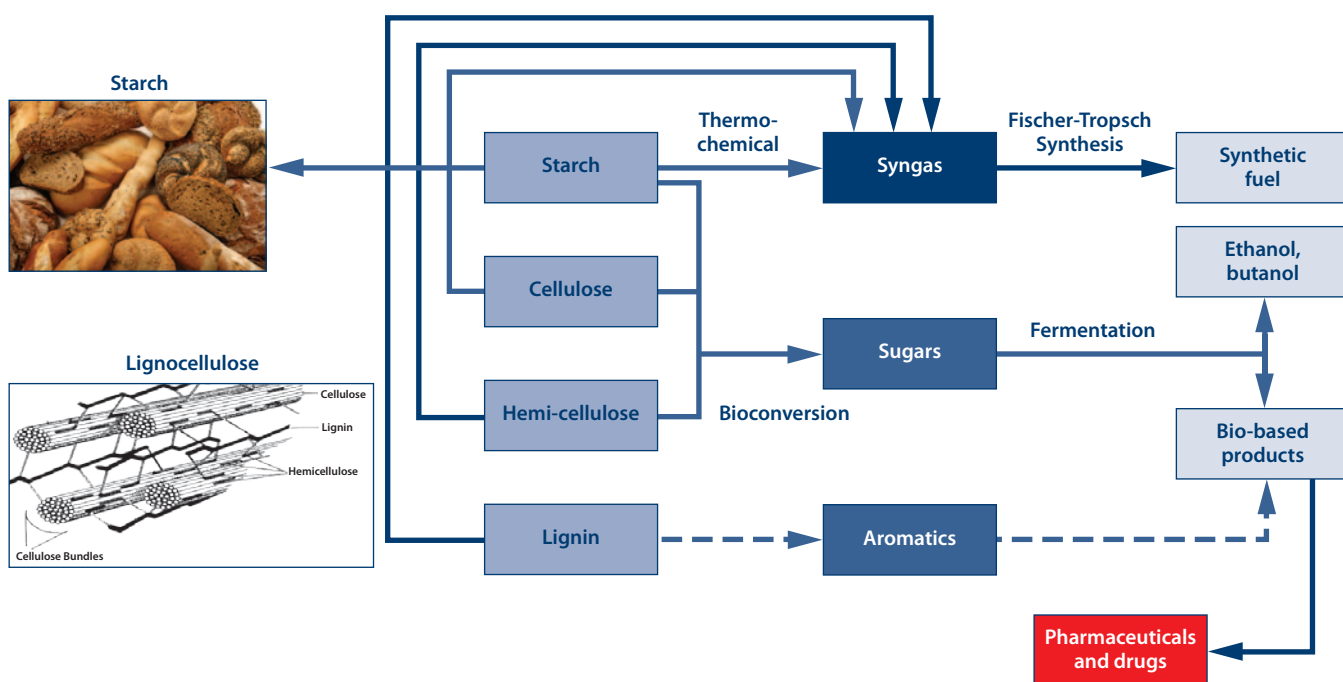


Figure 4: The production of pharmaceuticals and other important materials from renewable biomass

5. Opportunities for the chemical sciences

5.1 Chemistry and disease

5.1.1 Understanding disease onset and progression: chemical medicine

Validating 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 into 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 resistance mechanisms in infectious pathogens

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 signalling in reprogramming biological 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 of 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

5.1.2 Genes and non-infectious disease

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

Developing new methods to analyse post-translational modifications of biological molecules 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 modification of proteins leads to different phenotypes and how we can modify and control epigenetics in vivo 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 age to enable us to better understand and treat diseases of the brain

5.1.3 Analysing biological processes

Helping to integrate the 'omics' disciplines through a fundamental understanding of the underpinning chemistry

Developing more applicable versions of existing analytical techniques like nuclear magnetic resonance (NMR) spectroscopy, liquid chromatography and mass spectrometry

Developing new devices for accurately analysing tiny biological samples, including the contents of a single biological cell

Developing further new non-invasive analytical methods for understanding disease at the molecular level

Creating 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 enter 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 *in vivo* techniques for carrying out chemistry inside cells and organisms

Developing new methods for delivering RNA and DNA into cells

5.2 Novel chemistry for diagnosis

5.2.1 Biomarkers

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 develop new, alternative markers of disease, including patterns of protein expression

Identifying new biomarkers that can better predict the progress of disease as a step towards selecting the most appropriate treatment

5.2.2 Probes

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 individual genome sequencing

Development of delivery systems for nucleic acids (eg RNA interference (RNAi))

5.2.3 Improved imaging and diagnostics

Exploring methods to measure specific molecular changes to biomarkers, including protein stability and misfolding, and changes caused by reactive oxygen species (ROS)

Developing a new suite of rapid point-of-care diagnostic technologies that will diagnose a range of diseases, including disease-causing microorganisms, in a non-invasive fashion at the bedside

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 patient-specific abnormalities in disease (eg cancer)

Developing advanced imaging techniques to characterise cancer and differentiate benign from cancerous areas during surgical intervention

5.3 Chemistry and drugs

5.3.1 Target validation

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 quantitative 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 to 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

5.3.2 Designing more effective drugs

Establishing 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 synthesising new chemical compounds as drug candidates

Building improved compound libraries containing compounds that are likely to bind to new, validated disease targets, which 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

5.3.3 New synthetic methods

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, which 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

5.3.4 Process Automation

Developing new automated methods for producing the 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

5.3.5 Drug delivery

Improving drugs to overcome biological barriers, such as stability against degradation in the gut, liver and blood

Improving transport from gut to blood, from blood to brain and from blood into the cytosol of target cells

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

Converting biologically active peptides into oral drugs

Developing methods for selectively targeting therapeutic agents to receptors in specific tissues

Developing a better understanding of zwitterion systems drug delivery

5.3.6 New approaches to treating disease

Exploring novel chemistry for tissue engineering, including new scaffolds for optimising the growth and remodelling of specific cells and tissues

Deploying novel chemistry to scaffold surfaces to promote cell adhesion, improve cell function and encourage development of functioning tissue for regenerative medicine

Designing, modifying and synthesising biomolecules as synthetic biologics for understanding and treating disease

Developing synthetic capability to create new 'building blocks' for synthetic biology

5.3.7 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 make them 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 of pharmaceuticals and waste in the environment

Developing a more robust understanding of how different chemical functional groups are modified during waste degradation 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

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Appendix: Chemical Sciences and Society Summit (CS3) 2011 participants

Lihe Zhang (Scientific Chair)

Duanqing Pei

Xiaohong Fang

Zhen Xi

Biao Yu

Weiliang Zhu

Peking University, Beijing

Guangzhou Institute of Biomedicine and Health, CAS

Institute of Chemistry, CAS, Beijing

Nankai University, Tianjin

Shanghai Institute of Organic Chemistry, CAS

Shanghai Institute of Materia Medica, CAS

Horst Kessler (Co-Chair)

Gerhard Klebe

Rolf Müller

Stephan A. Sieber

Günther Wess

Andreas Marx

Technical University Munich

The Philipp University of Marburg

Saarland University, Saarbrücken

Technical University Munich

Helmholtz Center Munich

University of Konstanz

Tohru Fukuyama (Co-Chair)

Kazunari Akiyoshi

Kazuya Kikuchi

Hideaki Oikawa

Hiroaki Suga

Takashi Takahashi

University of Tokyo

Kyoto University

Osaka University

Hokkaido University, Sapporo

University of Tokyo

Tokyo Institute of Technology

Ben Davis (Co-Chair)

Tim Bugg

Neil Cameron

John Overington

Chris Schofield

Tony Ng

University of Oxford

University of Warwick

Durham University

European Bioinformatics Institute, Saffron Walden

University of Oxford

King's College London

Gunda Georg (Co-Chair)

Joseph Fortunak

Cynthia Burrows

Wilfredo Colón

Shaoyi Jiang

Nicola Pohl

University of Minnesota, Minneapolis

Howard University, Washington

University of Utah, Salt Lake City

Rensselaer Polytechnic Institute, New York

University of Washington, Seattle

University of Iowa

Jon Evans

Science Writer

Organising committee

Zhigang Shuai

Yongjun Chen

Hans-Georg Weinig

Markus Behnke

Nobuyuki Kawashima

Hiroyuki Ohno

James Hutchinson

Clare Bumphrey

Steven Meyers

Zeev Rosenzweig

Chinese Chemical Society

National Science Foundation of China

German Chemical Society (GDCh)

German Research Foundation (DFG)

The Chemical Society of Japan

Japan Society for the Promotion of Science

Royal Society of Chemistry

Engineering Physical Sciences Research, UK

American Chemical Society

National Science Foundation, US

Royal Society of Chemistry

Email: sciencepolicy@rsc.org

Registered charity number 207890

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Thomas Graham House

Science Park, Milton Road

Cambridge, CB4 0WF, UK

Tel: +44 (0)1223 420066

Burlington House

Piccadilly, London

W1J 0BA, UK

Tel: +44 (0)20 7437 8656

RSC International Offices

São Paulo, Brazil

Beijing, China

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Bangalore, India

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Philadelphia, USA