Grand Challenge: New Synthetic Landscapes from CO_2

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Vision

A sustainable chemicals industry to replace the petrochemicals route:
Reinventing the chemicals industry with the UK leading the world.

Globally agreed requirements for major reductions in carbon dioxide emissions (by up to 80% by 2050) and the falling reserves of fossil fuels (world wide production of oil and gas is expected to peak before 2020), coupled with ever increasing global energy requirements necessitates the search for ways to couple emissions reduction to a reliable and sustainable feedstock for carbon based commodity chemicals and fuels. This grand challenge identifies carbon dioxide as a carbonaceous resource for the construction of value-added molecules using new chemical and process approaches.

"***This is the key Grand Challenge: Solve this first!***" (Workshop Delegate)

State of the Art

We constrain ourselves here to free CO_2 rather than CO_2 fixed within biomass which is covered by other themes within the Grand Challenges. Such technologies could however be readily included to give a holistic approach to the production of new chemicals. The UK is reasonably well placed in Carbon Capture and Storage (CCS) technologies but this simply shifts the CO_2 problem from the atmosphere to underground facilities rather than re-using the carbon as a feedstock.

Nationally, the C-Cycle consortium (Sheffield, Newcastle, Birmingham, Warwick, Oxford, UEA, Southampton) is pioneering the integration of carbon dioxide capture and *in situ* activation and chemical conversion to new chemicals. The consortium plans to consolidate its efforts over the next 5 years to identify commercially viable routes linked to new chemical technologies. Nottingham and UCL are also looking at new conversion routes and Leeds have a CO_2 chemistry laboratory. Newcastle, Cambridge and Imperial have a leading position in the application of high temperature ceramic membranes for CO_2 capture from combustion processes.

Internationally, Sandia Laboratories in New Mexico USA have reported a photocatalytic conversion of CO_2 to diesel using solar energy. This is still a laboratory scale procedure and is unlikely to be scalable to meet the requirements of emissions abatement. Furthermore, multinational companies such as Shell, BP, Sasol are active in this area and it is envisaged that the combined use of Water-Gas-Shift (WGS), Steam Reforming (SR), and Fischer-Tropsch chemistries that exploit CO_2 reduction in synthesis will become increasingly important. The importance of selective catalysts to achieve such goals will become of paramount importance.

Research Challenges and Barriers to Progress

The first challenge to consider is one of scale. We could adopt the approach of using the CO_2 in the production of commodity chemicals or intermediate. Here the volume of CO_2 captured and re-used is small and will have a minor impact on remediation targets. A second approach is to use the CO_2 as an energy carrier, converting it back to a combustible fuel. In this scenario the amount of CO_2 captured is potentially large but will produce CO_2 as a waste product. The key will be to strike a balance between the two extremes and both aspects will need to be addressed. One of the major challenges is that CO_2 has a high activation energy in many potentially useful reactions, especially those which involve its reduction through the formation of C-H bonds. Catalysis, both chemical and biological, will play an important role in achieving this Grand Challenge. Many of these processes are however exothermic, for example the reactions of CO_2 with methane to form acetic acid and with ethene to form acrylic acid both have negative enthalpies of reaction. Further evidence for the feasibility of using CO_2 as a chemicals feedstock comes from the industrial synthesis of asprin which starts with the reaction between CO_2 and phenol. However, these chemistries are on a small scale compared to the emissions arising from combustion processes. New routes to synthetic fuels from CO_2 will therefore be an important target as they will help maintain the transportation infrastructure, while at the same time require large volumes of CO_2 to meet demand. Therefore, the main challenges are the development of new catalysts to allow CO_2 chemistry to be carried out at or near room temperature and a re-invention of industrial chemistry pathways to accommodate the chemicals produced from CO_2 which may be different to those obtained from fossil fuel sources.

The CO_2 needs to be readily captured from relatively high concentration sources (3-15%), such as power stations and manufacturing plants, and isolated from diluent gases (nitrogen, water vapour, NO_x, SO_x) so that effective chemistries can be carried out. We need to develop a whole new field of CO_2 (C_1) chemistry. The reactions need to be targeted to value-added products with high impact examples (e.g. kerosene, acetic acid, methanol, organic carbonates) being achievable in the early stages of research. Methods need to be developed to convert CO_2 into reasonable and recognisable chemicals and the chemistries need to be scalable to meet commercial needs. In the longer-term, conversion of CO_2 to less-recognisable chemical intermediates would be advantageous but would need a remapping of the chemicals industry. Reactions need to be not only efficient but chemo-selective so that narrow product distributions are achieved, thus minimising waste. Technologies need to be developed that are cross-disciplinary so that feedstocks are not limited to CO_2 but can draw on oxygenated feedstocks available through, for example, concurrent biomass technologies. Indeed, catalysts could provide products from CO_2 with a range of oxidation levels of carbon. To accommodate reactions with unfavourable thermodynamics, integrated sustainable energy technologies need to be included within this Grand Challenge. The harnessing of solar energy has been identified as a potential solution in a separate Grand Challenge theme and this should be linked to this Grand Challenge, but we should also consider other energy sources including nuclear. A challenging area that is often neglected is that of product separation and recovery. It is important that the whole system is taken into account when designing and developing new processes.

One barrier and challenge will be the scalability of any process developed in the laboratory and its applicability to the real environment. The volumes and flows of CO_2 that need to be converted are huge and will require highly efficient reactors, continuous processing and most likely parallel technologies. The scale will depend on the commercial uses of any products. Commodity chemicals will require smaller scale plant but if the challenge of achieving a route to transportation fuels can be achieved then this will require large plant. It is important recognise that the process will need to be modelled and optimised using computational methods. A further barrier will be resistance to change resulting from conservatism in both industry and academia. There are misconceptions as to what could be achieved in CO_2 activation, primarily arising from consideration only of the reaction thermodynamics. These have been shown in some cases to be unfounded through the design of selective catalysts (e.g. methane reacting exothermically with CO_2 to produce acetic acid). Therefore, we must be prepared to roll out educational material that is multidisciplinary as well as addressing industrial concerns and needs.

Involvement

There is the obvious need to involve scientists, engineers and industry in this Grand Challenge as these are essentially the front-line. It will be important to have an industrial steer as a consequence of the vast quantities and flux of CO_2 that need to be handled. However, the full impact of such ground-breaking research has potential national and global importance such that we need to look beyond the conventional list of collaborators. The financial possibilities of a non-oil based economy necessitate collaboration with economists and market analysts. For example, if a process required a rare and / or expensive metal based catalyst (e.g. rhodium or iridium) would there be a sufficient supply of the metal available and what would this do to the cost of other processes which use the same metal? We need to be looking at commercially viable technologies and this will require external input. There is also a need to involve social scientists to look at the societal and ethical issues arising from the research. The implications are far-reaching and we should certainly consider involving Regional Development Agencies and politicians, especially DIUS Ministers. Outside of the UK, collaborations within Europe should be facilitated by the European Commission, and the United Nations could play a role in establishing global collaborations.

CrossOver

There is a degree of cross-over between this theme and others, particularly “Coupling Clean Energy to CO_2 and H_2O Activation”, “Efficient Synthesis-100% Efficient and No Waste”, “New Chemical Paradigm for Harnessing Light Energy” and “Exploring and Exploiting Chemical Roots Biological Emergence”. However, this theme covers remediation of a climate damaging chemical while at the same time harnessing it in the production of value added chemicals and fuels and so represents an over-arching Grand Challenges that may encompass aspects of the others in order to produce tangible deliverables.

Consultation

In addition to the four ‘Champions’ listed at the start of this document, the paper also went out to wider consultation amongst those academic and industrial participants at the Grand Challenges Workshop, and their colleagues, who had indicated an interest in this theme.

Benchmarking Against the Grand Challenge Criteria

Criteria	Score	Evidence for Score
The Grand Challenge will enable UK scientists and engineers to engage in internationally leading research.	5	• The UK has a strong track record in the science and technology required to achieve success both academically and industrially and has the political will to back up advances. The UK possibly has an international lead in these areas and will consolidate that through the research envisaged under the Grand Challenge. • There is a strong mission in the UK, and internationally, to address these issues. There is global interest and a political will to reduce emissions and address the issue of sustainable energy. • The UK has a strong track record in collaborative (academic-academic and academic-industrial) and inter-disciplinary research and this will be enhanced.
The Grand Challenge has ambitious objectives, which if achieved, would result in a step change in our current knowledge.	5	• This represents a paradigm shift in how industrial processes handle waste and source chemical building blocks. • It heralds a ‘reinvention’ of the chemical process industries. • A New Synthetic Landscape is proposed that reduces reliance on petrochemical feedstocks and takes a holistic approach to chemicals manufacture and sustainability.
The Grand Challenge will encourage researchers to be ambitious; lifting their horizons to the truly novel and innovative.	5	• *“To boldly go……where no chemist has gone before!”* • The search for new synthetic methodology for the sustainable creation of commodity chemicals will have a knock-on effect in that new materials solutions will also need to be addressed, which may well change with the identification of new synthetic goals. • Novel approaches to energy integration will need to be addressed. • Initially, old synthetic approaches will need to be modified to improve selectivity and activity, but totally new methodologies must be established.
The Grand Challenge has the potential to make a positive societal and/or economic impact.	5	• The future of the UK Chemical Process Industries may well rely on the ability of such ground-breaking research. • There is a tangible possibility that this will open up new markets through the generation of new chemicals and materials. The final output may well not be exactly the same as the currently manufactured chemicals: there may be significant improvements. • The research will lead to the development of new skills both in the synthesis of molecules and in process engineering. • New landscapes and improved processing methods should lead to the creation of new jobs in the CPIs. • The technology will be SUSTAINABLE.

Criteria	Score	Evidence for Score
The Grand Challenge has a single vision giving the research community common goals to work towards.	5	• There is agreement that a chemicals industry based on fossil fuel/petrochemical sources is not sustainable. • This fact is reinforced by industry. • Synthetic methodologies starting from carbon dioxide are agreed to be an appropriate goal for the creation of new chemicals while at the same time reducing air-borne carbon dioxide produced through emissions. While biomass is an exciting and viable route to using fixed CO_2 there is not the agrochemical capacity to address the quantities of CO_2 emitted to the atmosphere at current levels. • Renewable and sustainable energy sources are required to integrate all the required processes in to a holistic and sustainable industrially viable proposition. • As one participant on the Grand Challenges Workshop wrote on the Pluses area of the grid, “This is the key Grand Challenge: Solve this first!” Without a renewable and sustainable source of chemicals we have no industry and we lose our quality of life.
The Grand Challenge is forward looking, focusing on what can be achieved in 20-40 years time.	5	• Evidence comes from Biology and laboratory experiments that show that conversions are achievable but that the Chemistry must be improved. • The chemistry must then be developed to create processes that are both sustainable and scalable in order to handle the quantities of CO_2 emitted in industrialised areas. • A 20-40 year timescale is realistic in that current technologies developed on the research scale need to be incorporated into vast industrial processes. By starting the process now we will have a head start. • Current projections are that worldwide production of oil and gas will peak before 2020 so the 20-40 year timescale fits perfectly with industrial needs.
There is sufficient capacity in the UK to respond to the challenge and the potential to build on this capacity in the future.	5	• There is a strong base in catalysis and in the chemicals industry. • The contraction of the pharmaceuticals industry means there is scope to redeploy the expertise in catalysis. • There is a strong chemistry core and strong process engineering capabilities. • There is a growing willingness for Chemists and Chemical Engineers to work together as has been shown by the establishment of joint Chairs and other academic appointments. • The engineering of biological systems and processes will provide an additional route to manufacture. The UK is strong in this area.
The Grand Challenge provides opportunities for collaborations between researchers in different disciplines.	5	• Collaborations are already well established between chemists, chemical engineers and biologists. • More collaborations are being established between the above and physicists and mathematicians. • There is the opportunity here to foster additional collaborations outside the usual norms: with microbiologists, geneticists, social scientists, economists, earth scientists and geographers.

EPSRC Grand Challenge in Chemical Sciences and Engineering

Closing the Carbon Cycle

Conversion of CO_2 into fuels and feedstocks utilising clean energy

John Irvine, Geoff Maitland, Jim Darwent, Christopher Hardacre

Vision

We seek to address the most urgent challenge facing mankind in the 21st century. We propose to remove carbon dioxide from the atmosphere and convert it into chemical feedstocks and fuels utilising clean energy in a sustainable process. This will reduce CO_2 content in the atmosphere, solve energy security issues, remove dependency on fossil fuels and create a new basis for the Chemical Industry.

State of the art

The biosphere currently converts carbon dioxide to useful products through photosynthesis. This is a low efficiency process (typically only 1-2%) yet for many millennia it has successfully achieved equilibrium in the biosphere. Unfortunately the advent of our current fossil fuelled civilisation is driving the atmosphere away from this equilibrium with an ever increasing concentration of CO_2. This imbalance is widely accepted to be a major cause of global warming and civilisation ignores this threat at its peril. Furthermore the increasing use of fossil fuels cannot be sustained and we face catastrophic energy and raw materials (*i.e.* chemical feedstocks) shortages in future decades. It is imperative to reinforce biological conversion of CO_2 with technological solutions offering higher efficiency and use of other energy sources in addition to direct solar, with emphasis on high product selectivity.

Some of the elements required are already available, or will be in the next 5 years, although these are far from optimised for the envisaged Challenge. These include removal of CO_2 from gas streams via amines, although this is very energy costly and more efficient, cleaner and safer methods are required and conversion to hydrocarbon feedstocks via the coupled Water-Gas-Shift (WGS) and Fischer-Tropsch processes.

Research Challenges and Barriers to Progress

This Grand Challenge requires the solution of several interconnected problems. If we are to have the largest impact, multiple technologies are required for different geographic locations, availabilities of energy, local skills etc.

- The critical step is the reduction of carbon dioxide into useful precursors using clean energy, possibly utilising hydrogen as a vector. On a large scale this is possible using the current state of the art through electrolysis and on a small scale in biological systems. New catalytic and photocatalytic solutions are being considered to find means of outperforming nature. There are still very significant advances required for this to be an effective process, although sources of clean energy through dynamic renewables or nuclear will be available and there are clear advantages to increasing baseload or overcoming intermittency by conversion of CO_2 to fuel or feedstock. Utilisation of direct solar energy is still very far from being effective. Subservient to the reduction of CO_2 is the required oxidation counter process. One obvious route is oxidation of water to oxygen and this is probably an even more difficult problem than CO_2 reduction. Some advances have recently been made, but this is still a very challenging process. Alternative oxidants could be waste products or harmful chemicals that require to be degraded. In the long-term an integrated photocatalytic system which could perform both reactions simultaneously is required.

- Once CO_2 has been reduced into reactants such as carbon monoxide it is then essential to reduce it into useful products. On a large scale Fischer-Tropsch processes are well established for the generation of hydrocarbons from CO although they remain energy-intensive, with modifications of these processes being envisaged to better control product outputs (in terms of selectivity) and improve efficiency. For more distributed and smaller scale, systems, including direct solar there is still significant need for developing new catalytic and conversion processes. This will require new classes of catalysts capable of new processes such as multi electron/proton transfer processes and mimic those that are achieved in natural systems

- The third main element is transport of carbon dioxide where considerable advances are required. It is obviously essential that carbon dioxide must be collected either in decentralised mode from the atmosphere, a process which is very far from being currently achievable, or from centralised conversion systems such as coal fired power stations. However, there is little point in utilising electricity produced from coal to convert the CO_2 produced back to fuels such as diesel, due to inherent thermodynamic losses in any cyclic process. Thus, if this CO_2 conversion concept is to be applied to carbon dioxide from coal fired generation – as a future, more sustainable, alternative to geological Capture and Storage CCS – this CO_2 must be reduced and converted locally by co-location of clean fossil and nuclear/renewable generation or transported over long distances to centralised CO_2 conversion plants powered by renewable sources . A major step forward would be to carry out reduction of CO_2 in its captured state (dissolved in solvent or physically/chemically adsorbed on solids), so eliminating the need for the energy-intensive post-capture CO_2 stage and enabling the option of transporting CO_2 in alternative forms.

- The fourth element is the development of a new chemicals industry to succeed the present one based upon petrochemical feedstocks (hydrocarbons). This may be through conversion of CO_2 to short chain hydrocarbons based feedstocks *e.g.* via combined WGS/Fischer-Tropsch processes or a much more radical approach based upon oxygenated feedstocks obtained either from cellulosic biomass (directly from CO_2 via plants) or directly through reactions of CO_2 itself. This will require quite intensive R & D and early successes can be expected in five years but a refocused chemicals industry will require much longer to be implemented, consistent with plant renewal cycles. In particular, establishing new processes for reactions of CO_2 and development of processes for functionalisation and homologation of methanol prepared from CO_2, other than the established Monsanto process must be achieved.

- Underpinning all these elements is process integration and intensification. Due to the complexity of these cycles and essential driver of maximising energy efficiency over the complete life cycle, it is essential to integrate the various components, coupling elements where possible to productively use energy that might otherwise be wasted. This can be integrated into an overall systems analysis of the various process options to incorporate cradle-to-grave carbon footprint analysis alongside energy and economic optimisation. A detailed analysis of the thermodynamic landscape underpinning potential processes must also be undertaken.

Involvement –

This Grand Challenge will require a major collaborative effort involving chemists, chemical engineers, biologists, materials scientists and industrial engineers. Key disciplines include catalysis, solid state science, chemical engineering, thermodynamics, kinetics, process and systems engineering, photochemistry, spectroscopy, electrochemistry, materials chemistry, biochemical engineering and socio-technical economics.

Research Challenges and Barriers to Progress

Consultation

Ioannis Alexandrou, Ray Allen, John Andresen, Panagiota Angeli, Heike Arnolds, Stefano Brandani, Karl Coleman, Phil Dyer, Klaus Hellgardt, Steve Howdle, David Klug, Peter Licence, Jason Love, Ian Metcalfe, Mario Moustras, Matt Rosseinsky, Sven Schroeder, Stef Simons, Hugh Stitt, Peter Styring, Edman Tsang, John Turner, Michael Watkinson, Julia Weinstein, Andrew Weller, Joe Wood

Benchmarking Against the Grand Challenge Criteria

Criteria	Score	Evidence for Score
The Grand Challenge will enable UK scientists and engineers to engage in internationally leading research.	5	Biggest problem facing mankind UK has critical mass to address this Potential for truly revolutionary breakthroughs UK has good/strong relevant expertise and links to industries– oil & gas, petrochemicals, power generation, range of renewables It is natural evolution for conventional oil + gas to green energies
The Grand Challenge has ambitious objectives, which if achieved, would result in a step change in our current knowledge.	5	The science and technology that will enable closing the carbon cycle efficiently CO_2 as the chemical feedstock – complete re-focussing of all the chemicals industry and other manufacturing-based industry Solution to diminishing oil + gas supplies Using solar/renewable sources for chemical processes
The Grand Challenge will encourage researchers to be ambitious; lifting *keeping* their horizons to the truly novel and innovative.	5	Truly multi-disciplinary problem Inspire next generation of scientists/engineers because it is truly challenging, but essential to mankind. Seeks high level solutions Non-incremental = exciting → need to do quickly Great PR for scientists and engineers
The Grand Challenge has the potential to make a positive societal and/or economic impact.	5	Can create a new industry on the scale of the current oil industry, but clean. Take energy off the political agenda Save the planet Potentially everyone has access to energy (developed + non-developed countries) Transforming chemical + energy industry Gives positive value to a currently negative value material (CO_2) Potential 'carbon capture' solution to CO_2 emissions from transport – reduction of CO_2 in atmosphere

Criteria	Score	Evidence for Score
The Grand Challenge has a single vision giving the research community common goals to work towards.	5	New title encapsulates vision Will enable renewable energy to be the source of carbon mitigation as well as carbon avoidance.
The Grand Challenge is forward looking, focusing on what can be achieved in 20-40 years time.	5 3	Forward looking – high score, 5 Achievable in 20-40 years – 3 (a new industry might take longer, but the initial steps are achievable in this time period)
There is sufficient capacity in the UK to respond to the challenge and the potential to build on this capacity in the future.	1 5	Need a significant resource commitment, much more than today, (1) Need a concerted programme, international benchmarking Large 'Hadron Collider' type programme We have the capability, but need a serious managed programme with sufficient resource to do the work (5)
The Grand Challenge provides opportunities for collaborations between researchers in different disciplines.	5	Collaborations between biologists, chemists, chemical engineers., industry, academia, government., social scientists

New Chemical Paradigm for Harnessing Light Energy: BJ Whitaker (Leeds), HH Fielding (UCL), M W George (Nottingham) and M Watkinson (QMUL)

Vision: To design efficient light-driven (supra)molecular "machines" by controlling light-matter interactions. This is a key for many desired technologies, including solar driven systems capable of direct, efficient and cheap conversion of solar energy to high value chemicals and energy rich molecules. It will require *inter alia* a radically new and integrated approach to (i) the synthesis of novel chromophores and catalysts (ii) the measurement and (iii) theory of correlated particle dynamics. Such a programme would profoundly change our ability to control the interaction of light with matter and have significant impact in areas ranging from molecular electronics and quantum computing, through new molecular analytical tools and techniques applicable to a wide range of problems, to the mass production of molecules and fuels by photocatalysis and electrical power generation.

State of the Art: More energy from sunlight strikes the earth in 1 hr (4.3×10^{20} J) than is currently consumed on the planet in 1 yr (4.1×10^{20} J) yet currently less than 1.6% of this is provided by a solar source. The enormous technological challenge is that solar energy is diffuse and consequently large surface areas are needed for its effective collection. Hence material costs must be very cheap to make solar-based processes economical. In the area of solar energy conversion systems, there are three categories relating to the primary energy product, namely: solar electricity, solar fuels, and solar thermal systems. Each of these areas requires step-changes in order to exploit the solar resource. For example, photovoltaic (PV) cells developed to date are inadequate for a continuous and reliable energy supply. The state-of-the-art energy conversion efficiency in PV devices currently stands at around 20% in commercial devices, although an efficiency of 42.9% in a system using six different semiconductors to capture different parts of the spectrum has been reported. Whilst such systems are expensive, they may become commercially viable with power concentrator technology. Nonetheless, the DARPA goal for 2030 appears to be to reach 50% efficiency. *The key knowledge for this Grand Challenge is that with current thinking such incremental improvements are only likely to be achieved over a 20 year timescale*. If we are to achieve significantly enhanced efficiencies we need to break away from current thinking.

Critically, because of the intrinsic variability of solar light levels, solar electricity can never be a primary energy source for society without a cost effective solution to storage *viz*. the conversion of solar energy into solar fuels. Advances in this approach will require new materials for the focusing and thermal capture of the energy in sunlight as well as new thermochemical cycles for producing useful fuels and chemicals from the captured solar energy. Currently the cheapest method for energy capture, conversion and storage is solar thermal technology, which can cost as little as \$0.10-0.15 $[\text{kW hr}]^{-1}$ (compared to current fossil-derived electricity production costs of *ca.* \$0.02-0.05 $[\text{kW hr}]^{-1}$).

Nature has perfected the capture of incoherent solar-energy in the photosynthetic apparatus in which chlorophyll molecules in the light harvesting antenna complex (LHC) capture solar energy. The key design features of the LHC are its large optical cross-section with more than 300 connected chlorophylls and carotenoids and the near to 100% quantum efficiency of the energy transfer and charge separation steps. Nature's success lies in coupling this primary step to a complex, but directed, process of coupled multi-electron and proton transfers. However, overall conversion of solar energy into chemical energy is only *ca*. 6%. Thus the basic blueprint for success has been decoded; however, the organisational complexity of the natural system, the low overall power conversion and the necessary operational repair mechanisms due to photochemical damage and oxidation presents a formidable barrier to the preparation of a synthetic analogue. In the medium term, systematic spectroscopic and theoretical studies of biomimetic arrays fabricated for light capture will, nonetheless, provide valuable guidelines for designing artificial photosynthetic systems. *The long-term Grand Challenge is therefore to develop an artificial photosynthetic process capable of capturing solar energy with the quantum efficiency of natural systems but having the critical capability of efficiently transferring this energy to reaction centres capable of high power conversion.* In short the realisation of productive photoelectron-chemical power cells.

Photochemistry is not yet widely used in industry but there are a few examples. Pilot plants using solar irradiation have been developed, but many chemical processes can be driven by light and the long-term goal of chemical plants driven solely by solar energy will require many advances in reaction and process chemistry, and chemical engineering. Solar driven chemistry offers a valuable route for the UK science base to engage with economically developing countries, e.g. in Africa.

Research Challenges and Barriers to Progress: The research challenges related to solar energy conversion have been extensively reviewed in the 2007 DOE Office of Science (USA) report "Directing Matter and Energy: Five Challenges for Science and the Imagination".[1] Broadly the major issues in the context of this grand challenge theme lie in (i) the efficient capture of solar energy and (ii) its transfer and conversion into useful chemical energy and (iii) the long-term stability of such systems under prolonged irradiation. Within all of these areas however, lie a myriad of complex multi-disciplinary problems.

The first challenge facing the efficient collection of light and its conversion to excitation energy requires the development of photostable multi-chromophore absorber assemblies capable of transferring this energy to a reaction centre or molecular wire. Key issues in this context are how to separate charge efficiently over macroscopic distances free of unproductive back reactions without using expensive high purity semiconductor materials, the acceleration and directional control of such electron transfer processes and the efficiency of electron transfer in rigid media. At the root of this challenging series of problems is

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[1] (see http://www.er.doe.gov/bes/reports/abstracts.html).

the quantum mechanical behaviour of electrons – the importance of which is underpinned by the recent discovery that the transfer of light energy to chemical potential energy during natural photosynthesis is also crucially dependent on quantum mechanical coherence. That is the electron excited by the absorption of a photon does not move through the chromophore like a classical particle under the influence of local fields within the molecule but rather transfers its energy through the molecule by quantum mechanical interference. Learning how to predict and manipulate such phenomenon is the subject matter of coherent control, and there is a corresponding theoretical challenge. Critical here is the creation of new theoretical methods, perhaps based on Bohmian mechanics, capable of describing dynamic systems, e.g. photoexcited molecules, of high size and complexity, e.g. LHCs. This cannot be achieved with already developed methods, e.g. DFT, and a completely new approach in which the electron correlations are explicit is needed. Understanding the quantum mechanical details of energy flow in molecular materials and mapping these to experimental studies of spatially and temporarily resolved electron and energy flow, will help develop new chemicals to make poly- or partially-crystalline (e.g. liquid crystal) or other self-organized (and self-repairing) molecular structures perform as if they were expensive single crystal semiconductors. Materials consisting of a network of interpenetrating regions (e.g. as in supercapacitors) can facilitate effective charge separation and collection but we must simultaneously understand how to control the recombination of the photo-generated charge carriers through a description of the many particle quantum mechanics.

Tailoring light-matter interactions creates new opportunities for exciting applications in both fundamental and applied science. Customised laser fields are already being used to probe and control photomolecular dynamics (in isolated molecules and the condensed phase). Coupling theoretical quantum molecular dynamics methods with emerging ultrafast laser technology will allow us to gain further insight into molecular processes with unprecedented temporal resolution (timescales as short as 10^{-18} s are foreseeable). Tailored light pulses also have analytical applications, particularly in multidimensional coherent spectroscopies analogous to those developed in magnetic resonance over the last twenty years or so. *A long term goal would be to exploit the information gained from an improved understanding of molecular dynamics and quantum phase behaviour to design and optimize efficient, light-driven, molecular devices for applications such as data storage and processing*.

Whilst more efficient energy capture is essential to the realisation of this Grand Challenge its conversion into useful chemical energy (low entropy, high information) represents a significant shift from current efforts into the development of improved electrical/energy storage devices. Obvious fuel candidates are hydrogen from water; ammonia from nitrogen as well as high value organic materials from carbon dioxide. Again we have a blueprint from natural systems in which multiple electron/proton transfers are exquisitely controlled to allow electron/charge accumulation in reaction centres to drive these synthetic processes. However, the use of solar energy to drive catalytic processes that convert these reactants to solar fuels and other desirable molecules will require the development of an entirely new class of catalysts, which may be new nanomaterials capable of undergoing multi-electron processes. Since these materials are likely to be complex macroscopic structures a major challenge will be *controlling* the organisation of molecular structures at this macroscopic level. Chemists are extremely good at generating small molecular structures, but designing and then making highly organised multi-component entities akin to the systems seen in biology remains a significant challenge. Whilst supramolecular chemistry is an active field it is still in its infancy in terms of allowing the top-down (function to structure) design and control of functional supramolecular materials and nano-assemblies. Regardless of the nature of the catalysts a profound understanding of the catalytic transformations at the molecular level is required. *A significant challenge on the medium term is to utilise new analytic tools to make real-time, spatially resolved measurements of operating catalysts allowing a fundamental understanding of catalytic processes occurring in multiscale, multiphase environments.* In all of these putative photoactive systems, the development of molecular assemblies resilient to photodamage, and with the facility for efficient and viable self-repair following photodamage and oxidation, represent additional major challenges. *Another significant challenge is the development reactors to exploit the above innovations together with existing photochemical understanding i.e. the development of viable solar plants for the production of fine and speciality chemicals using existing knowledge of photochemistry would be a significant step forward*.

In short, the attainment of a new paradigm in solar energy harnessing represents an enormous challenge for the scientific community, and will require not only a change in current thinking but will also necessitate the building of a new multi-disciplinary community.

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Benchmarking Against the Grand Challenge Criteria

Criteria	Score	Evidence for Score
The Grand Challenge will enable UK scientists and engineers to engage in internationally leading research.		There is a real opportunity here to focus UK research activity on a challenge that will engage and excite current and future generations of scientists. We can benchmark the challenge against other related Grand Challenge proposals suggested by the US DOE and the European Science Foundation. The interconnecting underlying research themes of a new quantum mechanical model of electron transfer and electronic coherence, a new generation of photovoltaic devices and the synthesis of fuels and fine chemical by photo (electro) chemical means, each address a major scientific problem and together provide a highly ambitious project which will indubitably be internationally recognised as leading edge research.
The Grand Challenge has ambitious objectives, which if achieved, would result in a step change in our current knowledge.		Current technologies exist to convert light to electricity such as solid-state PV and Grätzel devices. These cells can capture diffuse light and significant advances in higher conversion efficiency and lower device costs can be expected in the short to medium term, but huge challenges remain. For electricity generation the intermittent character of solar light is a major disadvantage so the chemical storage of the captured energy is a key long term challenge. To succeed, this endeavour will require a more profound understanding of how Nature exploits electronic coherence which in turn requires a step change in our description of many particle quantum mechanics. Out of this, new light-driven, molecular devices for applications such as data storage and processing will also emerge.
The Grand Challenge will encourage researchers to be ambitious; lifting their horizons to the truly novel and innovative.		Solar energy conversion is not a new idea. What is new is the realization that what is required is a new approach that recognizes the quantum nature of molecular matter and energy transfer at its centre. We can only make this happen if we involve diverse scientific disciplines. Building this community would give the UK a competitive edge in the post-oil low CO_2 world economy. The scientific outcome is that we will develop an understanding of the basic principles of electron flow in complex systems and metamaterials that promise a step change to molecular device design.
The Grand Challenge has the potential to make a positive societal and/or economic impact.		This is obvious. But importantly, in addition to the technological and socio-economic developments likely to ensue, e.g. UK energy security, the fundamental challenge of advancing our understanding of essential photo-physics and chemistry at the quantum level will engender an intellectual climate which will excite new generations of young scientists and open up new problem areas which we haven't yet begun to think of.

Criteria	Score	Evidence for Score
The Grand Challenge has a single vision giving the research community common goals to work towards.		From our consultation with the community there is a general feeling that although there is significant activity in the UK in areas such as solar energy conversion a new approach is needed, and moreover that the focus needs to be on the fundamental science out of which the technological advances will flow. The interested community is diverse and already includes synthetic, physical and theoretical chemists, materials scientists and chemical engineers. In the short time available since the Manchester meeting a consensus has not yet fully emerged, however, the process has been strongly convergent and we are confident that a Grand Challenge in the general area we propose will receive significant support.
The Grand Challenge is forward looking, focusing on what can be achieved in 20-40 years time.		We can just about see the first step, but need a lot of fundamental research to get much further. Conventional PVs are aiming for 50% conversion efficiency in the next 20 years as a realistic goal. The thermodynamic limit for a single absorber is 35%. Multilayer cells are already near 60% efficient, but are very expensive. To go further we require a radically new and integrated approach to the design, synthesis and, crucially, assembly of novel chromophores and catalysts. The long term Grand Challenge is to develop a cheap, easily manufactured, artificial photosynthetic process capable of capturing solar energy with the efficiency of natural systems but having the critical capacity of efficiently transferring this energy to reaction centres capable of high power conversion (better than Nature). Whether or not this is achievable within 40 years is moot because out of this endeavour will flow a deep understanding of energy flow in supramolecular assemblies that will engender numerous spin-off technologies ranging from molecular electronics to the mass production of fine chemicals by photocatalysis.
There is sufficient capacity in the UK to respond to the challenge and the potential to build on this capacity in the future.		There are already internationally competitive UK research programmes in inorganic and organic photovoltaic technology as well as molecular electronics, electro- and supramolecular chemistry. Much of the early work in understanding the mechanism of solar energy capture and storage in Nature occurred in the UK. Coherent control and quantum information processing are emerging activities in the UK. There is an equally strong theoretical underpinning to molecular excited state dynamics in the UK. There is therefore existing capacity. EPSRC has already funded the UK semiconductor photochemistry network (ukspc.org.uk), the hydrogen network (www.h2net.org.uk), the coherent control in chemistry network (www.cocochem.bham.ac.uk*)* among others but a more a more focussed approach is needed.
The Grand Challenge provides opportunities for collaborations between researchers in different disciplines.		To make this work participation from Chemists, Chemical engineers, Physicists, Biochemists, Material and Computer scientists and other disciplines (many not represented in Manchester) will be required. This offers great opportunities for collaboration across disciplines but equally significant challenges in organization and structure. We need to bring together a breath of disciplines; physical chemists, synthetic chemists, device physicists, theoreticians, spectroscopists etc., but these are not natural cousins and are unlikely to spontaneously self-organize unless the fundamental intellectual challenge is clearly articulated. A Grand Challenge in the area we propose can do this.

21st Century Science for Nuclear Energy Production and Nuclear Waste Management

Simon M. Pimblott (University of Manchester), Neil Hyatt (University of Sheffield)

Vision: Cheap, clean and plentiful supply of energy from nuclear fission having met the weighty chemical and material science challenges associated with developing next generation reactors, closing the nuclear fuel cycle and the safe management and disposition of new and legacy nuclear wastes. Achieving this goal will require concerned and cooperative inter-disciplinary effort across the various branches of chemistry and fields of material science and chemical engineering.

State of the Art: The generation of electrical power by nuclear fission is technologically well established; but, it suffers from number of perceptual challenges due to a small number of accidents at home and abroad. The operational chemistry and material science of the current "Generation 3" gas- and water- cooled reactors is well understood. Fundamental knowledge is focused in three areas, the physical and chemical performance of (i) construction metals and alloys, of (ii) moderators and fuel, and of (iii) coolant fluids (CO_2 or water) under extremes of pressure and temperature and under exposure to ionizing radiation fields. All three topic areas have been examined in depth within the UK, and before the demise of the nuclear industry in the 1980s, the UK held a position of world leadership in the science of nuclear power generation. The intellectual expertise base is now close to retirement, and very few experimental facilities remain.

The decommissioning and clean-up of legacy nuclear facilities and the management and disposition of nuclear waste are an immediate problem for which engineering solutions are being sort by the Nuclear Decommissioning Agency and the Nuclear Site License Companies. Long term disposal of ILW and HLW in a deep geological disposal facility has been recommended and accepted by government. The scientific basis for the decommissioning, clean-up and disposal solutions proposed is being currently examined by public consultation and the Committee on Radioactive Waste Management. A number of scientific concerns have been raised concerning the nature and the performance of waste packages and their longevity.

Current reactor technology in the UK and world-wide employs a "once through" use of enriched uranium nuclear fuel. This approach makes use of only a small fraction (~3%) of the potential energy available. Estimates suggest that there is a 30 to 100 year supply of U available is the "once-through" use of fuel is continued. After use, spent fuel is then stored or reprocessed. Currently, plutonia obtained by reprocessing is regarded neither as an asset available for use in mixed-oxide fuel nor as a liability waste for disposal. If it is ultimately decided to dispose of reprocessed PuO2, then it and unprocessed spent fuel will be treated as HLW. The chemistry of the current reprocessing technology for the separation of U and Pu from other "waste-products" is well-established, but unsatisfactory.

Research Challenges and Barriers to Progress: Perhaps the most significant societal need for the 21st century is a cheap, clean and plentiful supply of energy. Nuclear fission offers an energy option that has both potential security of supply and does not contribute to global warming. The volume of fuel used (and of waste generated) is small compared to hydrocarbon sources of power and the raw fuel is not sourced from politically "sensitive" regions. The greenhouse gas CO_2 is not a by-product of nuclear power generation of electricity. To accomplish the desired goal of nuclear fission as an acceptable long term source of power, the science and research community need to answer a number of grand challenges. These challenges are associated with (i) safety and security of generation, (ii) long-term supply of fissile material, and (iii) safe disposition and management of new and legacy waste.

Generation 3 power plant are approaching the end of their useful generation lifetimes. Replacement with more efficient water-cooled reactors has been proposed as a short term solution, and new Generation 4(+) reactors are being investigated worldwide. While the replacement water-cooled reactors rely on simple extensions of current technology (employing passive safety features and better thermodynamics), the designs proposed for the next generations of plant are radically different, and in fact the most popular suggested approach employs gas-cooling, a technology originally developed, but an expertise lost, in the UK.

Several of the major research challenges associated with the long-term use of nuclear fission as a universal power supply include:

Adaptive Materials and Coatings for Next Generation Nuclear Power Plant and Reprocessing Facilities. Public acceptance of nuclear fission as a viable power supply will necessitate a science-backed safety case for the new facilities. The generation infrastructures will operate under much more extreme conditions of pressure and temperature than current plant, and will, of necessity, be exposed to significant mixed neutron and β-γ radiation fields over their lifetime. Construction of these plant to meet the stringent requirements will necessitate a new understanding of materials synthesis, performance and chemistry, and particularly the development of new and novel adaptive materials and coatings with high-performance capabilities in extreme environments. Similar but different technological progress in materials chemistry is necessary for nuclear reprocessing facilities and fast “breeder” reactors.

Nuclear Waste Packaging, Management, Disposition and Disposal. Serious questions have been raised about the long term performance and behaviour of proposed nuclear waste packages within a planned deep geological disposal facility. To develop a publically acceptable solution, the chemical behaviour of radionuclides under appropriate conditions must be provided. This safety case has to be built on fundamental science. Currently, there are only very limited facilities available that are capable of addressing this science in the UK.

Closing the Nuclear Fuel Cycle. Current nuclear power technology only uses a small fraction of the available energy. To ensure long-term security of supply, it is desirable to “close the nuclear fuel cycle” and to allow more complete use of the available energy. This approach to nuclear power employs a multiple pass use of nuclear materials and relies upon the use of “breeder” reactor technology to provide additional burnable fuel. The UK has an established, but negative, experience in breeder reactors. Future progress in this direction will have to be underpinned by an extensive chemical and materials research program on the development and performance of systems under extremely harsh conditions. This program will depend significantly on advances in surface and interfacial science.

Involvement: To address the intellectual grand challenges associated with developing next generation nuclear reactors, with closing the nuclear fuel cycle and with the safe management and disposition of nuclear waste will demand new expertise in the fields of: radiochemistry: material synthesis, properties, performance & chemistry; radiation chemistry and radiation effects; interfacial and surface chemistry; and corrosion science. In addition, it will require drawing down on the capabilities already existing in fields such as reaction dynamics; ab-initio computation; solution thermodynamics; Monte Carlo simulation & modelling; and computational fluid dynamics.

Consultation: Discussions concerning future nuclear energy research needs have been held with UK and international academics, members of the National Nuclear Laboratory research community and representatives of the Nuclear Decommissioning Authority and the Sellafield Site licensee.

Those involved included:

Academia - Dr. P.J. Howarth, Dalton Nuclear Institute, University of Manchester; Prof. F. Livens, School of Chemistry, University of Manchester; Dr. J. Weinstein, University of Sheffield; Prof. R. Bisby, Salford University; Prof. M. Mostafavi, CNRS-Université Paris-Sud, France; Prof. Y. Katsumura, University of Tokyo, Japan; Prof. J.A. LaVerne, University of Notre Dame & Notre Dame Radiation Laboratory, USA; Prof. D.M. Bartels, University of Notre Dame & Notre Dame Radiation Laboratory, USA.

NNL & International Equivalents – Dr. G. Fairhall, NNL, Sellafield; Dr. R. Taylor, NNL, Sellafield; Dr. H.E. Sims, NNL Harwell; Prof. C. English, NNL, Harwell; Dr. R. Crowell, Brookhaven National Laboratory, USA; Dr. B. Mincher, Idaho National Laboratory, USA; Dr. S. Pommeret, CEA, France.

NDA & Nuclear Industry – Dr. I. Hudson, Sellafield Site, NDA; Dr. Neil Smart, RWMD, NDA; P. Maher, British Nuclear Group, Sellafield.

Benchmarking Against the Grand Challenge Criteria

Criteria	Score	Evidence for Score
The Grand Challenge will enable UK scientists and engineers to engage in internationally leading research.	5	Research programs centred on advanced nuclear energy systems are at the heart of the energy policies of the US, France and Japan. The UK has demonstrated expertise in nuclear fission research, and has world leading abilities in materials chemistry. These resourses offer the foundations upon which the UK can become an international powerhouse on nuclear power research that is not tied to a specific nuclear fabrication industry – the world's impartial arbiter.
The Grand Challenge has ambitious objectives, which if achieved, would result in a step change in our current knowledge.	4	Energy will be the most important commodity in the 21st Century, and the UK cannot afford to be left in the cold. The scientific basis of nuclear power production technology is about to undergo a paradigm shift, and if appropriate resources are dedicated, UK academia and the recently created NNL can be at the forefront.
The Grand Challenge will encourage researchers to be ambitious; lifting their horizons to the truly novel and innovative.	5	Development of next generation nuclear facilities and closing the nuclear fuel cycle cannot be achieved using current science capabilities. To achieve the desired outcome will require researchers to be ambitious; lifting their horizons to the truly novel and innovative!
The Grand Challenge has the potential to make a positive societal and/or economic impact.	5	A clean, cheap and secure energy supply is a necessary foundation for the UK in the 21st Century.

Scoring: 1 – Strongly Disagree; 2 – Disagree; 3 – Neutral; 4 – Agree; 5 – Strongly Agree

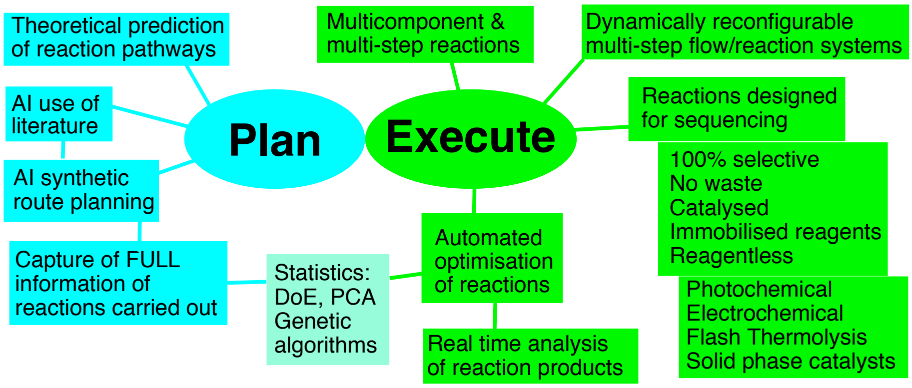
Criteria	Score	Evidence for Score
The Grand Challenge has a single vision giving the research community common goals to work towards.	5	This challenge is focused on the development of nuclear energy for a sustainable future. This is a single vision, which will require contributions from a wide, diverse scientific and engineering community.
The Grand Challenge is forward looking, focusing on what can be achieved in 20-40 years time.	5	Nuclear power has the potential to be the clean, cheap energy source of the 21st Century. Current technology is viable in the short-term of 20-30 years, but fundamental innovation is required to develop new advanced reactors and to close the nuclear fuel cycle. The necessary scientific capabilities are available in the UK and worldwide to make the desire a reality.
There is sufficient capacity in the UK to respond to the challenge and the potential to build on this capacity in the future.	4	The UK has considerable experience in the underlying fundamental sciences need to respond to this grand challenge; however, a number of critical areas, particularly radiochemistry, radiation chemistry and radiation effects, this knowledge base is aging and is desperately in need of young blood. EPSRC's development of a nuclear energy grand challenge would provide the impetus for the reinvigoration of these fields of chemistry and material science.
The Grand Challenge provides opportunities for collaborations between researchers in different disciplines.	5	In its very nature a nuclear energy grand challenge is interdisciplinary, reaching across the fields of chemistry, materials, interfaces, and chemical and mechanical engineering.

‘Dial-a-Molecule’ - 100% Efficient Synthesis

Richard Whitby, David Harrowven (Southampton) and Stephen Marsden (Leeds)

Definition and Impact of the Grand Challenge

Vision – That in 20-40 years, scientists will be able to deliver any desired molecule within a timeframe useful to the end-user, using safe, economically viable and sustainable processes. It will provide an essential enabling technology to many fields which rely on molecules with useful and exploitable properties by removing constraints of time, molecular structure, economics *etc*. Close collaboration with users of synthesis (particularly industry) will ensure maximum benefit, even in the early stages, for example by providing access to difficult to obtain constructs.



Synthesis of molecules is both a central driver for, and a serious constraint in a myriad of research disciplines, associated industries and other grand challenges. For example, a recent pan-industry report on synthetic chemistry in the healthcare environment[†] stated that “when synthetic enablement is lacking, we see projects stall, even those with the best biological or clinical rationale”. Emerging challenges in fields such as (nano)materials, chemical biology and next-generation healthcare pose synthetic problems that are beyond the scope of existing technologies. Representative examples that show the breadth of the challenge and the range of collaborative partners include: expansion of accessible chemical space to facilitate highly specific small molecule interactions with any genomic protein (chemical genomics/pharmaceuticals); next-generation biological drugs (integrated synthetic chemistry and synthetic biology); molecular electronics (*e.g.* for spintronics applications); non-invasive monitoring tools (markers, imaging agents); security-related products (smart-dyes *etc*).

The landscape of synthetic challenges is changing rapidly and this rate of change will only accelerate. The development of methods flexible enough to meet the emerging challenges and drive new research directions is a prerequisite for progress. Finally, training the next generation of researchers to respond flexibly to new challenges outside traditional research silos will also be crucial to the continued technological success of UK plc.

State of the Art – *Synthesis*: Gilbert Stork, one of the pioneering chemists of the 20th century, posed the question over 25 years ago “why can’t a 20-step synthesis be completed in 20 days?” to which we can add “and does it need 20 steps!”. The synthesis of many complex molecules has been achieved in the last 30 years, but even modest target molecules still require many man-years to deliver despite dramatic advances in the number, power and scope of available reactions (asymmetric synthesis and transition metal induced transformations being most notable). Making even simple molecules with an efficiency and robustness to allow commercialisation is a considerable challenge. Synthesis is still largely constrained (by thinking, training and equipment) to step-wise manipulations using reactions and work-up procedures with ‘*accepted*’ inefficiencies (be these in respect of yield, by-products, poor catalyst turnover, high cost *etc.*). An illustration of the limitations is that pharmaceutical development is aimed at the simplest molecule to achieve the required activity, with cross-activity a frequent result.

Synthetic route design: with the exception of the availability of reaction databases, little has changed in the last 30 years. Neither the use of AI techniques nor theoretical prediction of reaction pathways has made a significant impact.

Reaction optimisation: is still mostly a stepwise, hit-and-miss affair. Automated reactors and statistical methods (*e.g.* Design of Experiments (DoE), principle component analysis (PCA)) are gaining ground, but are not widely used. Capture of data on reaction conditions and outcomes (*i.e.* journal papers) is arguably inferior to 30 years ago, though volume is much greater! Analytical methods, particularly MS techniques (*e.g.* ionisation of compounds from solution without fragmentation), have advanced dramatically in the last 10 years to the point where dynamic reaction monitoring and analysis is viable. Integration with other analytical techniques such as IR and NMR and their use for real time reaction optimisation are little used. Extraction of component signals from complex mixtures is a highly refined subject in the area of signal analysis but has seen very limited application in reaction monitoring.

Catalysis: new modes of reactivity are constantly being realised (*e.g.* C-H activation) that approach the paradigm for atom efficiency *etc.* but the cost, selectivity and efficiency of these processes is often far removed from the necessary position (*e.g.* the levels of efficiency possible in some enzymatic systems or petrochemical transformations). Additionally, cross-compatibilities between processes are not at a stage where modular telescoped processes are routinely applicable. Correlation between catalyst structure and catalytic activity, selectivity, and lifetime are important.

Technology: synthetic chemistry is still largely driven to fit available kit and new chemical processes are largely designed without integration of thinking regarding the optimal reactor configuration. Flow reactors are little used, and have severe limitations, for example ability to process mixed phases (eg solid/liquid mixtures). Field effects (photochemical, extreme thermal, electrochemical) are also poorly understood and hence poorly utilised.

Research Challenges and Barriers to Progress

The challenges are immense as are the rewards. Consider the transformative impact synthesis has made in molecular biology by facilitating automated oligonucleotide synthesis. Now consider the potential impact of a similar level of efficiency and predictability applied to *any desired* class of synthetic molecule. It would revolutionise problem solving across diverse disciplines such as biology, pharmaceuticals/agrochemicals, effect chemicals, molecular materials, nanomaterials *etc.* The scale of the grand challenge becomes clear, however, when one considers that oligonucleotide synthesis (a) involves only three basic types of chemistry, (b) is carried out on a very narrow and functionally similar set of building blocks, (c) though extremely high yielding, is massively inefficient in terms of waste and atom economy and (d) it required 20 years of effort to reach this level of sophistication. Therefore to be able to make *any* complex molecular system, with the *additional* focus on economics / efficiency / sustainability, is going to require a step-change in approach.

Synthesis. The challenge is to devise new and powerful strategies for molecular assembly and the sequencing of high yielding chemical reactions (*c.f.* the programmed sequential catalysis of biosynthesis). We need to add robustness as a key consideration in the invention and development of new synthetic methods and aim for 100% efficient reactions with no work-up or by-products to interfere with subsequent steps. ‘Reagentless’ techniques – thermal, photochemical, electrochemical *etc.* will be important as will modular, mutually compatible reactions that allow the ‘one-pot’, multi-step telescoping of reactions. Catalysis and biocatalysis will have a major role to play (new reactivities, selectivities, mutual compatibilities and immobilised). Close collaboration with users (*e.g.* industry) will ensure that effort is focused in areas which will have the greatest immediate impact, without loosing sight of the grand challenge.

Reaction execution and optimisation. One challenge is to combine *real time* reaction monitoring (MS, IR, GC, HPLC *etc*) with efficient methods for extracting compositions from the data, and DoE and/or genetic algorithm methods for smart “self-optimisation” of reactions by intelligent feedback, all at a price that allows routine use. New sensors may be needed. Integration of reaction and reactor design at the conceptualisation/discovery stage; a greater understanding of, and ability to predict properties desirable for a given new process (flow, mixing, heat transfer); and the ability to devise flexible modular reactors capable of adapting to the problems posed are significant engineering challenges (and require chemical- and systems- engineers to work closely with chemists). The project should bring techniques currently used in industrial process design to the ‘every day’ lab. It will be a challenge to change the way in which the vast majority of synthetic chemists carry out (and are trained to carry out) reactions, for example to use flow systems and automated linked batch reactors.

Synthetic route design. It is central to ‘dial a molecule’ that a reliable efficient route to the desired molecule can be determined. A current barrier to progress is the lack of good AI systems for mining data and evaluating synthetic routes – essential if full use is to be made of the literature. The challenge is to develop new approaches using the power of modern computers and algorithms (*e.g.* neural networks). More effective capture of tried reaction conditions and outcomes is a necessary part of the feedback cycle which will result in the ability to predict reliable reactions and conditions to achieve particular transformations. New developments in multi-scaled modelling (e.g. DFT/MD/mesoscale...) are needed to predict reaction pathways and reaction outcomes under actual conditions (solvents; variety of interacting species *etc*), and can be envisioned within the next 10-20 years. The prediction of which new transformations would have particular impact in synthesis will be one output.

Technology. A significant potential barrier is that currently industry, which should be well served by the academic community, is usually ahead of us in the uptake of new technologies (*e.g.* parallel synthesis/purification in the 90s, flow technologies in the 00s, integrated electronic data storage/mining). Progress will require investment to ensure that University-based researchers have convenient access to cutting edge technology and tools which will, as a matter of course, have lasting training and translational benefits.

Involvement

- Synthesis community – to devise new strategies, tactics and reaction manifolds. To assist in the design and uptake of ‘user-friendly’ reactors, technologies and computational tools for synthetic route design and execution.
- Catalysis community – new catalysts and biocatalysts that are efficient and selective, with high-turnovers and economic viability. They need to be mutually compatible and/or multifunctional for reaction telescoping.
- Chemical engineering and systems engineering community – Design of smart, flexible multi-stage reactors with integrated analysis and automated optimisation; prediction of reaction properties; integration of components.
- Analytical community – analysis of, for example, time-varying spectroscopic data; integration with statistical tools such as DoE, genetic algorithms and PCA to complete feedback loops.
- Computational/E-science community – *ab-initio* prediction of reaction outcomes under real conditions; AI systems for data-mining, synthesis planning *etc.* Capture of full information on reactions carried out.
- End-user community - an integrated approach to working across disciplines with end-users of the technology (in industry and academia) is vital to ensure that advances in ‘Dial-a-molecule’ have the maximum immediate benefit. Our ultimate aim is to deliver generic synthesis as the nature of future synthetic targets is unpredictable, however throughout the project the methodology is best developed using targets of current relevance. A strong partnership with industry is vital as they are not only end users, but leading academia in many of the fields which need development.

Consultation: (a) Participants in the GC workshop who expressed an interest (25), (b) Pharmaceutical industry working group under Dr David Fox (see Chemistry World article[†]) who responded: “As a group of senior chemistry research leaders in industry representing UK pharmaceutical drug discovery, we strongly support the grand challenges proposal ‘Dial-a-molecule – 100% efficient synthesis’. It presents a long-term plan for organic chemistry synthesis which is an essential component for growth of our industrial R&D”. (c) OrgNet community (450 academic and industrial members).

Benchmarking Against the Grand Challenge Criteria

Criteria	Score	Evidence for Score
The Grand Challenge will enable UK scientists and engineers to engage in internationally leading research.	5	The UK has a strong, internationally leading Chemical Industry, spanning the global pharmaceutical and agrochemical sectors through to emerging high-tech SME's, each generating huge revenue for the UK exchequer. The UK has recognised strengths in synthetic chemistry and engineering, both within academe and industry. PhD students and PDRAs have excellent career prospects with the majority making a life-long commitment to UK science and a research-led career. UK industry and academia have an excellent track record of innovation, enterprise and the delivery of high value science. UK trained synthetic chemists are named inventors on at least 10 of the best selling drugs world-wide, with over $1 billion annual sales at peak.[†] Fostering better interactions between synthetic chemists, their theoretical colleagues, engineers, statisticians, mathematicians and IT professionals, as well as user groups in biomedical sciences, physics and emerging disciplines, will create new opportunities for internationally leading research at the cutting edge.
The Grand Challenge has ambitious objectives, which if achieved, would result in a step change in our current knowledge.	5	Currently it takes many man-years to synthesise even relatively simple compounds. To be able to deliver any molecule in days rather than years requires a step change in this crucial enabling technology for scientists and engineers in many areas. To achieve that end requires step changes in • catalysis – with a focus on cheap and accessible catalysts to reliably achieve specific transformations (100% selectivity) with excellent turnover numbers and stability. • synthesis – with new methods, strategies and paradigms to achieve useful and entirely predictable outcomes in a safe and efficient manner with minimal waste to avoid downstream processing/cleanup. • the way we conduct experiments – moving from a culture of the round-bottomed flask and towards the best available technology for achieving a given reaction (linked automated batch reactors, flow, array *etc.*). • equipment – user friendly photo-, electro- and flash thermo-chemical equipment and dynamic spectroscopic methods for rapid optimisation. • information technology – to better capture and exploit existing knowledge.
The Grand Challenge will encourage researchers to be ambitious; lifting their horizons to the truly novel and innovative.	5	The requirement for reactions with 100% selectivity for the desired outcome with minimal waste is truly ambitious. Few reactions satisfy this target and new and innovative thinking will be needed to meet these aspirations. Similarly, synthetic chemists will need to develop innovative strategies to tackle complex molecule synthesis, moving them away from lengthy linear sequences with a reliance on protecting groups, towards more holistic paradigms to rapidly build up complexity as and where it is needed.
The Grand Challenge has the potential to make a positive societal and/or economic impact.	5	The fine chemicals industry would be revolutionised by such a step-change, which in turn will open up as yet unforeseen opportunities for science with economic and societal impact (health, food, climate, security). A specific example is to enable more selective pharmaceuticals to be developed and commercialised. Importantly, by positioning UK Chemistry at the forefront of innovation and creativity in synthesis, rather than as a user community, the trend for outsourcing R&D to Asia could be reversed. IP would be retained in the UK, with spin-out and entrepreneurial enterprises having access to highly-skilled scientists and engineers locally with the appropriate expertise. The environmental benefit of 100% efficient reactions with no waste are obvious. Advances in new enabling technologies should lead to safer working practices with a low risk of catastrophic failure.

Criteria	Score	Evidence for Score
The Grand Challenge has a single vision giving the research community common goals to work towards.	5	The focal point is clear – the synthesis of any molecule, safely and in a timely fashion with 100% efficiency and no waste. It embraces all synthetic chemists yet demands their collaboration with a multitude of other disciplines (including theoretical chemists, spectroscopists, engineers, statisticians, IT professionals, biological chemists *etc.*) and industry (health and agrochemical, fine chemical, instrumentation, IT.)
The Grand Challenge is forward looking, focusing on what can be achieved in 20-40 years time.	5	It is clear from the automation of peptide and oligonucleotide synthesis that it is possible to synthesise specific classes of molecule to order on a reasonable timeframe. Those developments took some 20 years to achieve, involved just three reactions and a narrow subset of chemically similar entities. However, it also involved a narrow subset of scientists and engineers! Thus, it is not unreasonable to see how the grander challenge of achieving the synthesis of any molecule could be realised in a 20-40 year timeframe if the whole community bought into the new agenda. It requires people to embrace and have access to new and emerging technologies. They also need to be involved in the design of new equipment and enabling technologies to ensure wide uptake and practicability. As a consortium of leading industrial chemists recently noted, synthetic chemistry must be the central focus as, when synthetic enablement is lacking, progress in other fields is impacted severely.[†] This grand challenge is forward looking given the current state of play, where relatively simple molecules can prove undeliverable in a short timeframe and inefficiencies lead to considerable chemical waste.
There is sufficient capacity in the UK to respond to the challenge and the potential to build on this capacity in the future.	5	The UK has a wealth of expertise in synthetic chemistry, catalysis, engineering, IT and mathematics. It has a long tradition of interdisciplinary research and development, best evidenced by the pharmaceutical and agrochemical industries. This culture is less developed within our Universities. Though there is a willingness to embrace collaboration in the majority of University staff, bridging the knowledge-gap between specialist disciplines is a major obstacle, as is the lack of flexible resource available to prime the pump of interdisciplinary research. The UK is at the forefront of global pharmaceutical and agrochemical research and discovery. It also has a culture of capturing new ideas through spin-out companies and SMEs pioneering new exploitable biotechnology, materials chemistry, and enabling instrumentation. By encouraging work practices that mirror a successful industrial model, the project will facilitate a transfer of university research to wealth creating industry.
The Grand Challenge provides opportunities for collaborations between researchers in different disciplines.	5	Collaboration is at the heart of this Grand Challenge and underpins its very purpose as an enabling technology for scientists spanning medicine, physics, biology, materials, nanotechnology, biochemistry, oceanography, earth science *etc.* Moreover, it can only be solved by closer interactions between synthetic chemists and specialists in other core-disciplines of science and engineering, leading to new opportunities for pioneering research in hitherto unforeseen areas that are truly at the cutting edge. Small molecules had a profound societal and economic impact in the last century, primarily through medicine, hygiene, food production and new-materials. There is every reason to believe that they will have a far greater beneficial impact this century, provided we can overcome the current barriers to their efficient and timely synthesis.

[†] D. Fox, T. Wood, P. Leeson, D. Lathbury, D. Hollinshead, S. Macdonald, P. Jones, L. Castro, D. Rees, K. Jones *Chemistry World*, December **2008**, p 39.

Definition and Impact of the Grand Challenge

Directed assembly of extended structures with targeted properties

The aim of this 'grand challenge' is *to be able to control the assembly of matter with sufficient certainty and precision to allow preparation of materials and molecular assemblies with far more sophisticated* ***and tuneable*** *properties and functions than are accessible in materials synthesised using current methods*.

Submitted by Professors Paul Raithby (University of Bath), Kevin Roberts (University of Leeds), Michael Ward (University of Sheffield) and George Jackson (Imperial College).

Vision: Our control over the assembly of atoms into molecules and materials, and the controlled assembly of molecules into both solid-state and solution aggregates, remains very limited in scope, setting limits on the ability of chemists and materials scientists to design materials with desired properties even in cases where the underlying material requirements for a particular property are understood. Control of covalent bond formation in conventional synthesis of molecules with strong bonds is good and remarkably complex molecules can be prepared with confidence in multi-step (and increasingly in single-pot) syntheses. In contrast, much more limited control is possible in the preparation of solid-state materials, by techniques such as MBE or ALD for infinite structures, crystal engineering (employing non-covalent intermolecular interactions and utilising molecules as the basic building blocks) for molecular solids, or solution-phase assembly of molecular components using non-covalent interactions. Covalent bond formation in small molecules can be seen as the first step in an exploration of chemical assembly that now needs to be extended, by the incorporation of the use of molecular synthons and non-covalent interactions, to drive the assembly of more complex systems with the same degree of certainty and control that is already achievable for molecular synthesis. By achieving this goal, biological levels of complexity and function could be imposed on artificial materials.

Essentially, this Grand Challenge can be split into two parts: (1) The ability to "design" a material, which may be a solid, a liquid, a gel or a non-Newtonian fluid, with a desired function, this implies a thorough understanding of structure/property relationships in molecules, materials and multi-component assemblies. (2) The ability to "engineer" that material, which implies control over the assembly of matter on scales ranging from molecular, through meso, micro, macro to manufacturing and market-scale and mastery of all of the strong and weak forces that are involved in chemical processes across all the length scales. This, it can be argued, is really the ultimate 'Chemical Grand Challenge' which eclipses all others: the goal is to establish complete control over the preparation, properties and functions of condensed matter over the complete range of length scales. Achieving all of this within the timescale of a few decades is very unlikely, but substantial progress is realistic and will underpin developments across all of chemistry as well as related sciences. This Grand Challenge is essential to permit other Grand Challenge activities requiring specific functions from currently unidentified or inaccessible materials to succeed. Such progress does, however, require a paradigm shift in our approach to materials design and synthesis. In realising this Grand Challenge we must move beyond synthetic approaches to single molecule design (traditional synthesis), and beyond recently attempted Combinatorial methods, which have shown much success but have also emphasised the complexity of the molecular phase space that is accessible in synthetic chemistry, to a fully rational and sophisticated "one-pot" methodology in which the complex sets of reactions being carried out in that pot are understood, designed and controlled. This way lies the next generation of chemical synthesis.

State of the Art: Many useful functions of matter are associated with molecular properties (*e.g.* pharmaceuticals; many homogeneous catalysts; single-molecule magnets; fluorescent markers, labels and sensors; liquid crystalline and polymeric materials, electron donors or acceptors… etc.), and such functions are accessible using incremental advances based on the current state of the art. However, more sophisticated functions are often based on assemblies containing many types of molecular component. These assemblies, and the associated rich variety of controllable properties are common in biological systems, but in general are currently synthetically inaccessible.

In contrast, many useful functions arise from *bulk* electronic, magnetic, ferroelectric, mechanical and thermophysical properties of solid assemblies, but capability is limited by the extent to which assembly of the solid materials can be controlled, particularly in the creation of anisotropic structures. Currently it is not even possible to control reliably polymorphism in simple molecular crystals.

Looking at naturally occurring systems, a good illustration is the photosynthetic reaction centre, in which a large number of molecular components are combined in a spatially precise array that permits correct interfacing of their individual properties, so that light can be converted into an electrical potential. Synthesis of this complexity is completely beyond our current abilities. In like vein, complex bulk properties based on multi-component (>2) systems, such as photoactivated ferromagnetic ferroelectrics for information storage and room-temperature superconductivity, are currently inaccessible.

Research Challenges and Barriers to Progress: Addressing this Chemical Grand Challenge will require the following capabilities:

1. 'Reverse engineer' a target from its desired function, so that the function can be used as a starting point for defining the components that need to be included and how they should be combined. This could be a high-temperature superconductor (what atoms should the lattice contain, in what order, and how can they be incorporated into the structure?). Alternatively, one could envisage a catalyst assembled from a mixture of molecular components which between them will recognise a substrate, absorb light, and trigger the photoinduced decomposition or conversion of the substrate.

2. The prediction of the outcome of a combination of weak, non-covalent interactions acting together. Currently genuine control of self-assembly in solution and the solid state is limited to simple one-or two-component systems that assemble through relatively strong, directional and predictable interactions. Extension of this to controlling the outcome of a large number of weak interactions will require a much more detailed understanding of, and computational models for, a wide range of weak interactions (dispersion, hydrophobic, $\pi \ldots \pi$ interactions, etc).

3. Many functional assemblies of the forms described above are not in a thermodynamic minimum or at equilibrium. It will be necessary to control the course of an assembly process such that it can be pushed into a desired local minimum, so that we can select one end state from a multiplicity of accessible structures. It may also be necessary to maintain a non-equilibrium state by introducing an external potential, thereby introducing a "metabolic" component to a process. One example is to control crystallisation of a polar molecule such that it forms a polar crystal with 2nd order NLO properties, rather than the more thermodynamically stable non-polar crystal in which neighbouring molecules alternate in orientation, leading to the cancellation of the NLO effect.

In solution the equivalent would be to directly assemble the components in a virtual combinatorial library along one kinetically desired pathway. This is currently challenging for an assembly based on one or two molecular components: it is beyond our reach in more elaborate assemblies. It could be achieved by

(i) Pre-programming the reagents with sufficient information to self-assemble reliably (these processes should be reversible to allow error – correction, which means extending reversible bond formation to as many bond types as possible). This amounts to control of assembly via final structural stability and can be enabled by informatics approaches to build on existing knowledge.

(ii) Intercepting the assembly process at the critical stage ("nucleation" of the complex structure) with directing action, *e.g.* light, temperature, chemical potential changes, or the delivery of reactive species.

The ability to achieve goal (3) successfully and reliably will necessitate the development of new fast, time-resolved spectroscopic and analytical techniques that allow real-time monitoring of all stages of an assembly process, from the first combination of two components to the finished product, at all stages of a process from laboratory to plant. This will allow intervention in an assembly process at a particular point to push it in the desired direction. New modelling techniques and the development of new theories to control and analyse the equilibrium and dynamical properties of the systems is also essential.

4. We will need to be able to control the combination of *functions* of components as well as their assembly. For example, combination of molecules displaying the properties of a 'molecular wire', a 'molecular switch' and a 'molecular motor' (all known individually) will be of no use unless their functions are also correctly combined and interfaced: the switch must switch on/off electron flow through the wire, which in turn will activate or deactivate the motor. Again inspiration comes from biological systems.

Furthermore, it will be necessary to not only control and monitor the chemical state but also the temporal and spatial state of the material at all stages of a process from laboratory to plant.

Involvement: This is a wide ranging multidisciplinary challenge that will involve chemists, chemical engineers, material scientists, systems engineers, computer scientists, physicists and, potentially, life scientists. Because of the breadth of the project and its many potential applications to modern industry, we would anticipate that industrialists will become involved at an early stage and play a significant role in the development, progress and implementation of this Grand Challenge for the next 20-40 years as the socio-economic impact is realised.

Consultation: H. Bock (Heriot-Watt); K. S. Coleman (Durham); R. J. Errington (Newcastle,); D. Frenkel (Cambridge); M. Gutowski (Heriot Watt); C, Hardacre (Queen's Belfast); S. Higgins (Liverpool,); J. T. S. Irvine (St Andrews); G. C. Maitland (Imperial); H. Makatsoris (Brunel) ; I. Metcalfe (Newcastle); R. Ocone (Heriot-Watt); R. K. O'Reilly (Cambridge); M. J. Rosseinsky (Liverpool); J. Seddon (Imperial); R. Sheikholeslami (Edinburgh,); K. Theodoropoulos (Manchester, k.theodoropoulos@manchester.ac.uk) , E. Tsang (Oxford); R. J. Whitby (Southampton); B. J. Whitaker (Leeds); J. Zhang (Newcastle).

Benchmarking Against the Grand Challenge Criteria

Criteria	Score	Evidence for Score
The Grand Challenge will enable UK scientists and engineers to engage in internationally leading research.	5	This is arguably the ultimate Chemical Grand Challenge, to control the assembly of materials across the molecular to macroscopic length scales in a sufficiently precise way so as to “design” in properties and function. It underpins other grand challenges that require specific functions from currently unidentified or inaccessible materials to succeed. While controlled covalent bond formation at the molecular level is now routine, the controlled formation of larger assemblies is in its infancy, and the ability to assemble a material with a pre-designed function remains a key ambition for the future. Thus, UK scientists who become engaged in this project will undoubtedly be undertaking internationally leading research. This Grand Challenge can usefully be benchmarked against other related Grand Challenge proposals emanating from the USA, mainland Europe and Japan.
The Grand Challenge has ambitious objectives, which if achieved, would result in a step change in our current knowledge.	5	The Grand Challenge objectives are extremely ambitious. If the development of chemistry and materials science is viewed as a book, we are currently still on chapter 1, “the use of the covalent bond to develop targeted molecular chemistry”. This Grand Challenge will allow us, over the decades, to write the rest of the book by developing methods for controlling self assembly using non-covalent interactions, and pre-designing function and property into the materials that is simply not possible at present. The new science will represent a paradigm shift in our understanding of the relationship between structure and function by focussing on design with molecules as the enabling building blocks.
The Grand Challenge will encourage researchers to be ambitious; lifting their horizons to the truly novel and innovative.	5	Nature is notably successful at self assembly to produce systems with specific properties and function: by definition, therefore, the challenge is feasible. Researchers need to develop systems that mimic “life”. This requires a paradigm shift in the way that we think about carrying out science and in developing new ideas that are truly multidisciplinary incorporating chemistry, physics, materials science, computer science and biology. Adopting this multidisciplinary approach will widen the horizons of the researchers and allow them to think “outside the box”.
The Grand Challenge has the potential to make a positive societal and/or economic impact.	5	Because of the fundamental and wide ranging nature of this Grand Challenge there are a range of new technologies that could develop from the project that would lead to positive economic and societal impacts. Applications include: Self-assembling molecular computers/molecular electronics; Self-replicating systems; Templatedorganic/inorganic composites; Designed green fuels with optimum combustion properties and low emissions; Solid form selection processes incorporate the ability to predict and control processability; Catalysts for CO_2/N_2 fixation; Sustainable materials production with controlled life-cycles; Designed NLO and metamaterials; Room temperature superconductors; Photonic band gap materials; New classes of microphase separated liquid crystalline and polymeric systems with controlled functionality.

Criteria	Score	Evidence for Score
The Grand Challenge has a single vision giving the research community common goals to work towards.	5	This Grand Challenge unifies many high level goals that are of key importance to modern science and society. These include: 1. Developing the relationship between structure and property and structure and function from the molecular to the meso and macroscopic scales. 2. The invention of self assembly processes with controlled outcomes. 3. The real-time monitoring of assembly processes 4. The development of better calculations/modelling/understanding of weak interactions over a range of length scales. 5. The better understanding of reaction paths and non-equilibrium states across multiple electronic states.
The Grand Challenge is forward looking, focusing on what can be achieved in 20-40 years time.	5	Of the goals 1-5 outlined in the previous section there are a range of mixed timescales 1. 40 years 2. 40 years 3. 20 years 4. 20 years 5. 20 years Clearly progress towards these goals will be iterative and the feedback process using knowledge gained over the next 10-20 years will be essential if the ultimate targets are to be reached.
There is sufficient capacity in the UK to respond to the challenge and the potential to build on this capacity in the future.	4	There is expertise in all the areas described already available in the UK, however, at present, many of the groups that are capable of making the major breakthroughs that will result in the desired paradigm shift of understanding are working in isolation. Further investment is required to match the Grand Challenges vision that will encourage national and international collaboration right across the sciences and engineering disciplines that will provide the core centres to drive this research forward.
The Grand Challenge provides opportunities for collaborations between researchers in different disciplines.	5	By its very nature this Grand Challenge is multidisciplinary in nature and in order to achieve the targets it is vital to involve chemists, physicists, chemical engineers, material scientists, system engineers, computer scientists and life scientists. Their expertise can be combined to develop the project from molecular science to supramolecular assemblies, to involve a range of measurement techniques and modelling studies over a range of length scales in equilibrium and non-equilibrium situations, and to develop the new materials from the laboratory to industrial production by developing reactor design and process control. Inspiration will be taken from key biological systems and processes, and also from unexpected non-biological systems with initially unexpected functions, such as high temperature superconductors.

Exploiting Molecular Understanding for Personalised Intervention in Health & Disease

Submitted by Paul Taylor (Warwick) & Pankaj Vadgama (Queen Mary, London)

Vision

To apply a molecular understanding of disease and 'wellness' to early stage therapeutic interventions that are fully individualized, and thereby to achieve disease reversal, reduced drug side effects and lower health care costs.

State of the Art

Current therapies utilise a traditional broad-spectrum approach to disease management, rationalised on the basis of population rather than individual needs. As a result, therapeutic outcome is unpredictable, potency and efficacy an educated guess, with significant percentages of "non-responders" to most therapies, and side effects inherent to treatment, particularly with high potency drugs. In a post-genomic era, emphasis is shifting to functional proteomic and metabolomic analysis; a drosophila protein interaction map (BMC Genomics 9, 461 (2008)) for example provides data on thousands of protein-protein/protein-gene interactions coupled with computational predictions. By contrast, only limited proteomic/metabolomic data exists for human studies. There is, moreover, reliance on sampling that is both temporally and spatially out of context and functionally limited to the few classes of proteins whose activity is understood. Current analytical and imaging methods are underpinned by limited databases, annotation is variable and is not molecular. For therapeutic drug monitoring, blood chemistry monitoring of drug levels provides a limited basis on which to adjust therapy. Functional imaging is beginning to provide us with 3-D localised measures of simple metabolic processes, e.g. PET scanning for glucose metabolism and NMR/BOLD for oxygen. Supporting datasets, libraries and registries are disparate, limited and temporally out of context, and methods may require days or weeks to screen one drug and cannot uncover all interactions. Whilst in silico modelling and prediction of health and wellbeing is an ongoing area of research that attracts significant funding, it is focused on physiology, whole organs and circumscribed diseases. Current computer architectures handle large volumes of data in research (CERN) and commercial settings (Google) but are not capable of addressing the complexities inherent in this Grand Challenge (GC). The European Bioinformatics Institute provides some relevant data support. Notwithstanding this, we see a need for: (i) Better approaches to information management supported by new database systems; (ii) Systems models spanning multiple length (molecular to whole organism) and time scales; (iii) Bespoke computing infrastructures and ontologies; all of these require to be focused on the dynamics of change, particularly at the margins of 'wellness' and disease.

Good computation infrastructure for the GC will be critical to its success. We will align with the EU's Virtual Physiological Human (VPH) framework, while recognizing that VPH makes relatively little reference either to small molecule therapeutics or to societal context. According to the VPH (2008) "the difficulties of implementing an effective infrastructure should not be underestimated". Appropriate infrastructure "promotes synergies, rewards integrative effort and inspires confidence in those that engage with it". The major gap this GC would fill is not just support for such data exchange and interoperability, but the lack of appropriate ontologies, languages that allow communication of data well beyond the current standards for biomedical science.

According to Peterson (Nat. Chem Biol, 4, 635, 2008) protein inhibitors with a ubiquitous biological action are largely unavailable; at a domain between the molecular level and systems biology lie the tools for predicting the mix of molecular properties that would be required, and through this 'mesodomain' can be charted a pathway to optimal drug activity. What is needed is both to make much better use of existing drugs, through combination therapies and tailoring of dosing and timing and to approach the selection of new drugs in a much more holistic manner. Additionally, the GC will not be limited to the predictable, nor map simply onto accepted clinical models and theories of causation, but will account for heterogeneous etiology and perceptions of disease causation in society that in any case are not constant, or predictable, and may not accept contemporary clinical norms. This has implications for the social success of the GC, and we consider research in this field to be fundamentally important, a viewpoint supported by the recent establishment by the Nuffield Foundation working party on personalised medicine:
http://www.nuffieldbioethics.org/go/ourwork/personalisedhealthcare/introduction.

This GC foretells a fascinating and significant paradigm shift in the conceptualisation of disease, in the way diagnoses are formulated, and the treatment models applied (organ/whole body to molecular scale; population based to smaller units of analysis and intervention); all this will be felt not just by patients, but importantly by practitioners and clinicians. Shifts on such a scale are seldom seen and will have wide ranging social and cultural implications for the ways in which medicine is practised. For example: 1.Personalised biological data capture creates new forms of knowledge, but bioethicists and social scientists have raised concerns about the ethical issues that this provokes and the ways in which this knowledge impacts on the choices people make. 2. Medicine (as currently taught, learned and practised) and health and illness (as currently experienced, described and lived) are anything but solely individual/personal pursuits, but rather highly social and collaborative. 3. Society often voices great scepticism when health is linked to revenue saving.

By our incorporating Medical Anthropology as an essential part of this GC, we aspire to locate the scientific achievements accurately in society and, through engagement of science with the notional "public", change the relationship between all healthcare stakeholders.

Challenges and Barriers to Progress

The GC tackles the following themes, which will deliver healthcare benefits in their own right during the span of the GC:

1) Temporally and spatially resolved, personalised proteomic and metabolomic data collection tools.

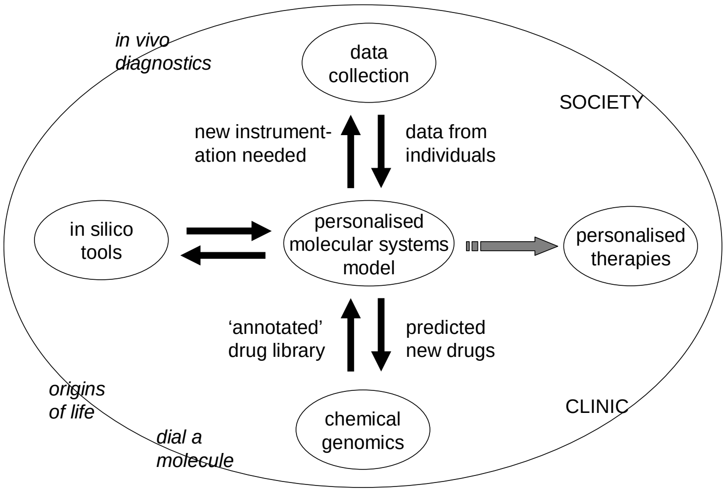
2) Analysis and modelling tools for “omic” data that incorporate both small molecule interactions and personal variations.

3) Chemical biological and synthetic methodology yielding rich libraries of small molecule therapeutics.

4) Medical anthropological studies of the social and cultural implications for the way in which medicine will be practised.

Better analytical tools are required for temporal, high density data for 3-5000 major metabolites, all proteins and their posttranslational modifications. Imaging techniques that improve voxel resolution and provide us with in vivo data on metabolic, physiological and blood flow outcomes of therapy will be needed for target tissue outcomes. The expansion of meaningful protein and metabolite libraries will be needed, based on specific disease models through their entire evolutionary period, assimilating ultradian and longer term proteome and metabolome cycles. Underpinning this would be high throughput techniques, establishment of target populations and exploitation, as appropriate, of available datasets and registries. This will enable us to map therapy to the individual, as well as to establish therapeutic regimens that can be extrapolated to specific genotypes. A particular, positive outcome will be the pre-selection of drug combinations that are effective for a given genotype. Point of care diagnosis with combined, portable, user-friendly instruments would potentiate clinical rollout (eg Imperial Chemical Biology Centre have developed optical spectroscopy, alongside NMR and mass spec, as a potential proteomics tool).

New types of data management frameworks will be required that are capable of handling very large quantities of data across extended computing grids. Semi-structured data would need to be handled without imposing strict data structures (c.f. relational database management systems). Flexibility will be needed for responsive dynamic evolution of data schemas, much of it recorded as it evolves. We believe a core clinically focused capability will be possible within the next 10 years; the challenge is to develop these systems so they enable fully patient individualized, temporal modeling. Realistic disease models at the molecular scale are needed; currently, how a virus attacks a healthy cell remains difficult, but a model for drug-membrane interaction is equally complex. An even bigger challenge is to extrapolate such results to organ and whole body level and from these to personalise the model to an individual. The critical phase will be the rationalisation of drug-protein binding and binding resolution on the basis of structural motifs coupled with cell based study to correlate cell physiological and metabolic outcome. Network biology and chemistry are both needed to identify putative secondary targets (Nat. Chem Bio. 4,666, 2008). The chemical genomics and genetics part of the GC will address these needs as follows: (i) engagement with the NIH PubChem programme to access their planned network of major centers holding small molecule collections (~500,000, of both known and unknown activity), aimed for expansion to target larger domains of biomolecular surfaces (http://www.genome.gov/11508738); (ii). chemical genomics tools to uncover the links from small molecules to the "interactome", i.e. the biological molecules they interact with; the chemical genomics tools required will need to be orders of magnitude more effective than currently; (iii). chemical genetics tools to test the model in whole cells; the model will predict the phenotypic effect of one or a combination of small molecules. There will be methodological issues to assaying combination therapies; (iv) model development to predict entirely new drugs. Advances in synthetic chemistry will be needed to deliver these rapidly, and on demand.



Involvement

Relevant research expertise will be from: synthetic organic chemistry, analytical science, bio-/medical informatics, systems engineering, protein chemistry, intermediary metabolism, pharmacogenetics, toxicology, bioethics and social anthropology. Participation from industry and healthcare providers will be necessary to engage in downstream activities and scale-up.

Consultation

This document was authored collaboratively by Peter Coveney (Director, Centre for Computational Science, UCL), Cathrine Degnen (Sociology, Newcastle), David Klug (Chemistry, Imperial), Harris Makatsoris (Engineering, Brunel), Paul Taylor (Chemistry, Warwick), Jane Thomas-Oates (Chemistry, York), Pankaj Vadgama (Director, IRC in Biomedical Materials, Queen Mary London), Raman Vaidyanathan (Chem. Eng. Sheffield), Andrew Wilson (Chemistry, Leeds), Jie Zhang (Chem. Eng, Newcastle), with wide consultation around these institutions.

The following organizations were also consulted during the preparation of this document: the bioethics community, social anthropologists, AstraZeneca (medchem and bio), Biocopea, Glaxo SmithKline, LGC, Merck Serono, NPL, the Association of Clinical Biochemists (ACB), UK Sports and the Royal Colleges of Pathologists and of Physicians.

Individuals consulted: Perdita Barran (Edinburgh), Helen Cooper (Birmingham), Mario Moustras and Rodney Townsend (RSC), Rachel O’Reilly (Cambridge/Warwick), Constantinos Theodoropoulos (Manchester), Professor Donald Singer (Warwick Medical School and Convenor, Personalised Medicines International Symposia).

Benchmarking Against the Grand Challenge Criteria

Criteria	Score	Evidence for Score
The Grand Challenge will enable UK scientists and engineers to engage in internationally leading research.	5	One of the most important global scientific challenges this century. At the moment we have such a rudimentary grasp of the proteomic and metabolomic make-up of the individual, and almost zero spatial localisational information, that we have an enormous data gathering and data management/modelling task on our way just to secure this huge, unmet, objective, which will be a GC in itself. The topic is of huge international interest (NIH, EU) and will enable ‘buy in’ to international activities. The drug design will be a second GC, and is already a target of academic and industrial screening initiatives (viz patient experience with the human genome). The integration of both synergistic topics in this GC will give exceptional opportunities to the UK to engage internationally.
The Grand Challenge has ambitious objectives, which if achieved, would result in a step change in our current knowledge.	5	“An important challenge facing the life sciences is to quantitatively describe the bewildering complexity of living organisms, both to appreciate the elegance of nature and to make medically relevant predictions. The scope of this complexity is vast. Even the function of a single mammalian cell typically involves coordinated activities among over 20,000 genes, 100,000 proteins, and thousands of small molecule lipids, carbohydrates and metabolites, each of which may be expressed at differing levels over time.” [Lehár, (2008), Nature Chemical Biology 4, 674] Mapping this on to the individual level is indeed a Grand Challenge. For the end user, the engineered exquisite selectivity and affinity binding of synthetic small molecules will eliminate current dependence on bio-derived therapeutic agents (e.g.antibodies), which are unpredictable in their dose/effect ratio and difficult to administer orally. “Small molecules also lend themselves more readily to combination interventions, making them especially useful for integrating systems and chemical biology” [Lehár , 2008]. The essential step change is drug combinations with engineered potential to fully arrest disease progression.
The Grand Challenge will encourage researchers to be ambitious; lifting their horizons to the truly novel and innovative.	5	The interplay of our four themes, that is –omics data collection, analysis and modeling, chemical genomics/genetics and societal context will “lift the horizons” of researchers in all the four themes, engaging them in systems wide activities rather than compartmentalized projects and encouraging active dialogue between science, medicine and society. For example, development of new analytical instrumentation and computational tools that can both handle complex proteomic and metabolomic data and be used by a healthcare practitioner with their client in a local healthcare setting presents a tremendous challenge.
The Grand Challenge has the potential to make a positive societal and/or economic impact.	5	According to a former director of NIH: Systems and network thinking is where the future of healthcare lies, and interpreting and intervening in networks will need technological, medical and business structures that reflect this. Future therapies will also involve cocktails of compounds tuned to the individual and their particular disease state at given time and in a particular context. The GC outcome thus has both economic and societal benefits. However, recent history cautions against making simple assumptions, since societal uptake also has a cultural dimension. What is clear is that potent, personalised therapies will have wide ranging social and cultural implications for the entire way in which medicine is practised. Parallel understanding of this will increase the likelihood of a positive societal and economic impact.

Criteria	Score	Evidence for Score
The Grand Challenge has a single vision giving the research community common goals to work towards.	5	The *molecular* viewpoint embodies the Grand Challenge, with other facets enabling a practical realization. The research community will be inspired to develop molecular level descriptions of temporal, spatial and personal variations in biomedical phenomena, while locating them clearly in contemporary society. “The overall concept of personalized therapeutic intervention is very attractive” [Association for Clinical Biochemists]
The Grand Challenge is forward looking, focusing on what can be achieved in 20-40 years time.	4	While it is visionary, the GC does touch on existing concepts developing elsewhere. But importantly, the GC adds molecular level thinking linked to a holistic whole body approach. Leverage of other activity (VPH, systems biology and other EU/US work) will potentiate the UK effort, and concept to reality is partially feasible at 20 years, with fully realized therapies at 40 years: analytical science and miniaturization are accelerating due to new forming techniques, computational handling is becoming more sophisticated (CERN, Google), and the pace of application is rapid, viz the translation of the cardiome to therapeutic relevance.
There is sufficient capacity in the UK to respond to the challenge and the potential to build on this capacity in the future.	3	According to the Technology Strategy Board, “UK medicines and healthcare industries are in a strong international position both industrially and scientifically to generate significant revenues. Given this strength, there is significant potential for government support through the Technology Strategy Board to leverage our world-class science and technology base and our major global presence in the (Bio)- pharmaceutical and healthcare sectors by stimulating the development of new technologies and consequent products and services.” This said, the GC team recognise the need for global engagement and data sharing to fully realise this potential, but believe that the core capability in the UK is such that (i) matched participation in other international efforts is possible (ii) a specially promoted programme can refocuss UK skills to considerable advantage (cf energy research)
The Grand Challenge provides opportunities for collaborations between researchers in different disciplines.	5	There will be extensive scope for cross-council research activity involving not just EPSRC, but also BBSRC, ESRC and MRC. Clinical and laboratory medicine, biochemistry, imaging research, synthetic and analytical chemistry, physics, computational science, informatics, systems engineering and social sciences would all be engaged. The collaborative, visionary nature of the programme will have the benefit of appealing to wide sections of society, and may encourage under-represented groups to aspire to and continue research careers [Lober-Newsome, ‘The chemistry PhD: the impact on women’s retention’, Royal Society of Chemistry, 2008 and ‘The Molecular Bioscience PhD and Women’s Retention: A Survey and Comparison with Chemistry’, The Biochemical Society, 2008]

EPSRC Grand Challenge: In Vivo Molecular Monitoring and Surveillance

Submitted by – Dr. Andy Mount, University of Edinburgh, Prof Pankaj Vadgama, Queen Mary University of London, Dr. Seetharaman Vaidyanathan, Sheffield University.

Vision: The vision is to enable a paradigm shift in clinical diagnosis by developing integrated molecular monitoring and surveillance systems to access intra-body processes dynamically, either non-invasively (a practical realisation of Dr. McCoy's tricorder from Star Trek) or minimally invasively. The development and use of these diagnostic systems to define and monitor wellness and loss of wellness will transform diagnosis from the detection of established clinical disease to the detection and treatment of the earliest pre-clinical stages of disease onset, or health deficiency. Implementation in a cost-effective manner will enable large-scale monitoring and surveillance of public health; it will inform and lead health policy development, facilitate new treatments and reduce healthcare costs through more local and earlier diagnosis and intervention.

State of the Art: The last few decades has seen the production of highly developed analytical platforms for biomolecular sensing. These are mainly based on specific, single biomarker measurement, and are often of low sensitivity and semi-quantitative when deployed as extra-laboratory systems. Moreover they provide discrete, rather than continuous measurement and if in vivo suffer from poor biocompatibility and short lifetime. Thus, although often technologically well advanced, these systems lack transferability, cannot operate in a complex biological environment and are often only specifically designed for the marker in question. The basic principles of in vitro array-based detection for e.g. antibodies and cytokines (Adelsteinsson V et al Anal Chem 80, 6594, 2008) are well established and increasingly, new arrays for multiparameter detection are being developed (Salas VM et al Adv Clin Chem 45, 47, 2008) Whilst body sensor techniques do exist for non-invasive imaging, including PET, SPECT, CT, MRI, ultrasound and optical (fluorescence based) methods, these operate within a limited parameter space that make each well suited to some applications but poorly suited to others; the current technologies are also not cost-effective for population level wellness monitoring and they do not have molecular imaging functionality. Although the introduction of contrasting or activatable reporter agents (for instance in fluorescence (Weissleder and Pittet, Nature, 452, 580, 2008)) could provide in vivo molecular imaging, this is not well established and only provides macroscopic spatial resolution. The necessary miniature transduction techniques, e.g. optical, electrochemical, mass spectrometric, have been or are being developed to enable small volume monitoring and detection. Effective in-situ micro- and nano-sampling has also been developed (Kajiyama S et al J Biosci Bioeng 102, 575 2006). Real advances in proteomics and protein sensing are expected within the next few years, though the equivalent metabolomic progress is lagging somewhat behind at present. Throughput in both sampling and analysis is also set to improve dramatically. There are strong synergies with the EU FP7 Virtual Physiological Human Network of Excellence (www.vph-noe.eu) which is a project which seeks to support and progress European research in biomedical computer modelling and simulation of the human body, aimed at improving the ability to predict, diagnose and treat disease. In vivo sensors for glucose monitoring are the classic system developed for a huge, worldwide disease problem (type I diabetes), but provide an inadequately miniature system and only a partial solution to single parameter tracking, given their poor performance and lack of longterm reliability (Siontorou CG et al IEEE Trans Instrum and Meas 57, 2856, 2008). The molecular information produced by this Grand Challenge would be invaluable in leveraging enhanced computer modelling and simulation. Techniques for the latter are already highly developed, and embody many of the expert systems and self-learning methodologies that are used in contemporary process engineering and biotechnology (Glassey J et al Trends Biotech 18, 136, 2000; Rodiguez et al J Chem Tech Biotech 83, 1694, 2008) .

Research Challenges and Barriers to Progress: The first step in the Grand Challenge is in defining the nature and combination of molecular targets that are necessary to monitor for wellness. Characterising the healthy state in terms of first establishing the crucial multiple molecular parameters and then the acceptable range of these parameters which in combination define wellness for the general populace poses a huge challenge, not least because the so-called normal is a highly dynamic state, variable across populations and even within individuals. This requires sensor and transducer development followed by multimodal systems engineering and device production to meet this measurement need at an economic cost. The problem of adequate statistically significant data collection, analysis, parameter definition and modelling presents an unprecedented measurement and interpretation challenge which also requires a major effort. Developments in personalised medicine on the Grand Challenge timescale may enable the mapping of apparently random variation in some parameters to genomic and proteomic-population subset-specific variation, which as well as informing clinical understanding could decrease multiparameter space and make the problem more tractable. There are the real technological challenges of developing parallel methods for dynamic measurement of diverse molecular species in vivo and in complex samples and then implementing them in a system. Wellness monitoring in the human body is likely to require analysis in and of several different body compartments, potentially including interstitial tissue, cells, organelles, blood, sweat and tears. Distributed sensing and analysis will also be required to give spatially resolved information. It is likely that both biomolecular and symptomatic physiological/physical indicators will need to be tracked. Sensitivity will need to increase dramatically to produce the technology able to probe low level fluctuations, hitherto undetectable with conventional techniques, e.g. microdegree temperature fluctuations exist in tissues and represent the net balance of a host of energetic fluxes. High resolution measurement, both of physical and biochemical parameters, will also enable better monitoring, analogous to high resolution imaging, to determine new parameters such as the localised dynamic health and energy economy of the body. Thus, early tracking of energy use may well give a better alert to disease onset, than say awaiting a patient alert on weight loss, a current early predictor of cancer or other chronic disease. In particular, new methods and systems for tracking and understanding in vivo cell membrane solute exchange (ionic, neutral, energy demanding) and their correlation with gross electrophysiological processes (currently very poorly understood) should provide early indicators of a departure from health which may presage motor diseases and epilepsy. Systems for characterisation of membrane exchanges over cell populations, also embodying cell-cell signalling, should also be invaluable as will the development of chemical monitoring to gauge and understand tissue electrical conduction, its mechanical coupling and the interplay of mechanical and electrical processes, e.g. as seen with biological piezo structures. These are simply given as exemplars of the need to achieve combination measurements that follow an individual biological process by using different physicochemical modalities. Our understanding is developing, with contemporary biophysics, for example, already able to link biological properties to quite distinct and separate phenomenological characteristics, but any translation to the in vivo context is highly constrained in the absence of the required platform technologies for measurement. There are then the further real system related challenges of integrating these into viable, clinically acceptable devices, eventually for direct societal use outwith the clinical environment. These include the continual validation of sensor response without calibration; materials development for biocompatibility for long-term dynamic measurement; the metastability of transduction elements; the miniaturisation and development of appropriate analytical methods; the development and integration of technologies (including sampling, measurement and appropriate robust analysis through processing of signals, perhaps from a variety of transduction types) to produce robust, reproducible and affordable systems; the avoidance or minimisation of immune response. One also needs to develop the smallest possible sampling technique for tissue, so that measurement does not perturb the system. The production and integration of such systems with appropriate feedback, control and delivery technology should enable automated treatment, e.g. the creation of artificial organs. There are real ethical issues to be addressed concerning the public perception of such applications of this technology and the management and dissemination of the information which is thereby obtained (Gorman U, Health and Nut 1,13, 2006).

Involvement: Multidisciplinarity is key to addressing this challenge, with the required scientific and technological goals being developed in partnership with clinical research, and clinical and pre-clinical targets and measurement specifications informing what is required to be measured. There is also the need to engineer robust, cost-effective systems to enable these measurements and for informatics expertise to analyse the data. The need for systems will drive partnership, particularly with the UK biotechnology, electronics and informatics industries. This will require chemists and biochemists (e.g. synthetic for molecular sensor synthesis, physical/analytical for transduction/sensor development), biological scientists, clinicians (human and animal), chemical, mechanical and electronic engineers for integrated systems development, informaticians for multiparameter data analysis and processing, biophysicists for modelling of biomolecular interactions, biomaterials scientists for biocompatible materials development, modellers to integrate all the data and allow the monitored samples to be compared to the healthy norm, legislators and regulators to ensure applicability and acceptability of developed systems, social scientists for resolution of ethical issues with users. Stakeholder involvement (e.g. patient groups, the European Diagnostic Manufacturers Association, http://www.edma-ivd.be/) would be invaluable.

Consultation: National Microelectronics Institute; Association for Clinical Biochem; RSC Electrochem Gp, Scottish Microelectronic Centre; Dr, A. Mount, Chem, Edinburgh; Prof. P. Coveney, Chem, UCL, Dr. S. Vaidyanathan, Chem & Process Eng, Sheffield; Prof. J. Thomas-Oates, Chem, York; Dr. J. Zhang, Chem Eng & Materials, Newcastle; Dr. R. O'Reilly, Chem, Cambridge; Prof. P. Vadgama, Clin. Biochem & BiomedBiomed Materials, QML; Prof. D. Klug, Chem, Imperial; Prof. E. Hall, Institute of Biotechnology, Cambridge; Dr. H. Makatsoris, Engineering & Design, Brunel; Dr. S. Schroeder, Chem, Manchester; Prof. K. Roberts, Process, Environmental & Materials Eng, Leeds; Dr. M. Moloney, Chem, Oxford; Prof N. Turner, Manchester Interdisciplinary Biocentre; Dr. T. Bachmann, Pathway Medicine, Edinburgh.

Benchmarking Against the Grand Challenge Criteria

Criteria	Score	Evidence for Score
The Grand Challenge will enable UK scientists and engineers to engage in internationally leading research.	5	Multidisciplinarity is key to achieving the goals of this grand challenge and will require internationally leading expertise in the identified areas. There are a few multidisciplinary US and European groups working in this integrated healthcare sensor systems production space. The necessary physical sciences/engineering/analytical/clinical and industrial expertise and infrastructure (healthcare and biosensor companies) exist in the UK to facilitate development and exploitation. This challenge will unite these UK activities. The NHS is a key UK advantage as research provider, partner and end-user.
The Grand Challenge has ambitious objectives, which if achieved, would result in a step change in our current knowledge.	5	Providing the systems and the underpinning research knowledge to enable in vivo molecular clinical diagnosis and the dynamic monitoring of wellness (the earliest possible stage of disease or health deficiency) is highly ambitious. It would transform healthcare, for the first time enabling multiple benchmark parameters and biomarkers for wellness to be established. It would also allow wellness to inform public health policy.
The Grand Challenge will encourage researchers to be ambitious; lifting their horizons to the truly novel and innovative.	5	There is much multidisciplinary UK activity in the area of molecular sensing and diagnosis. This grand challenge requires the marshalling, focussing and a huge enhancement of this activity to deliver the required information to inform pre-clinical care. It requires the development of novel and innovative solutions to such problems as truly non-invasive multiparameter sampling and monitoring in the complex matrix which is the body, long term uncalibrated detection in vivo, long term materials biocompatibility, multitransduction systems integration and control, low (near zero) sample detection and complex data analysis.
The Grand Challenge has the potential to make a positive societal and/or economic impact.	5	The achievement of this grand challenge would result in several major societal impacts. The prevention and early intervention enabled by this technology would allow doctors to diagnose departure from health in terms of the earliest signs of disease, which would significantly reduce the length, complexity, and cost of treatment, optimising efficacy. This would reduce the cost of healthcare, reduce the cost to the UK exchequer of e.g. sick leave and enhance the length and quality of life and productivity. The information obtained would (if it were ethically advantageous to the patient to divulge it) empower the individual, giving them more information about their own health and enabling proactive involvement in diagnosis and treatment. This has the potential to increase the feeling of involvement and well-being.

Scoring: 1 – Strongly Disagree; 2 – Disagree; 3 – Neutral; 4 – Agree; 5 – Strongly Agree

Criteria	Score	Evidence for Score
The Grand Challenge has a single vision giving the research community common goals to work towards.	5	The Grand Challenge articulates a single goal of achieving dynamic in vivo monitoring. This requires a systems approach which necessitates a multidisciplinary community to work towards producing individual system elements with a view to their integration into a monitoring, informed by the clinical pull of the monitoring requirements. This provides common research goals.
The Grand Challenge is forward looking, focusing on what can be achieved in 20-40 years time.	5	The basic understanding of individual analytical systems exist, along with the infrastructure and associated skills to develop them; this has been developed over the past 25 years. However, there remains real scalability, materials compatibility and detection compatibility and integration issues which need to be addressed to produce the required multiparameter monitoring systems. Furthermore, a real partnership between scientists, engineers and clinicians is required to develop the appropriate systems for clinical application. In many cases, the appropriate biomarkers for wellness have not yet been identified, let alone their appropriate detection range, their location in the body and suitable method(s) for dynamic in vivo measurement. This is a challenge on this timescale.
There is sufficient capacity in the UK to respond to the challenge and the potential to build on this capacity in the future.	5	The core skills and expertise all exist in the UK, but targeted growth is required to build capacity on the timescale required to deliver this grand challenge. In particular, the need for research and integrated systems development will require multidisciplinary teamwork at the physical science/lifesciences interface. .
The Grand Challenge provides opportunities for collaborations between researchers in different disciplines.	5	This partnership will require chemists and biochemists (e.g. synthetic for molecular sensor synthesis, physical/analytical for transduction/sensor development), biological scientists, clinicians (human and animal), chemical, mechanical and electronic engineers for integrated systems development, informaticians for multiparameter data analysis, biophysicists for modelling of biomolecular interactions, biomaterials scientists for biocompatible materials development, legislators and regulators to ensure applicability and acceptability of developed systems, social scientists for discussion and resolution of ethical issues.

Provision of regenerative medicine therapies through molecules and materials

A submission to EPSRC following the Chemical Sciences and Engineering Grand Challenges workshop.

Submitted by – Dr Stephen Rimmer (University of Sheffield) and Prof. Neil Cameron (Durham University).

Vision – This grand challenge aims to develop the molecules and materials that will enable human stem cell isolation, controlled differentiation and delivery to the patient, without the requirement for ill-defined feeder cells or human or animal derived macromolecules. In the long term (20-40 years), this will allow the production of robust and reliable cell-based regenerative medicine therapies that are entirely free of any animal or human derived products, other than the cells of immediate use.

State of the Art Current research in regenerative medicine is heavily dependent on our knowledge of tissue engineering, where mature adult cells are taken from a patient and expanded in culture then returned to the body, often with biomaterials that act as carriers or scaffolds. Here the tendency has been to work with materials that have been approved for medical use but which are not necessarily ideal as cell scaffolds. However, regenerative medicine potentially offers much more. The central idea encapsulated in this grand challenge is that **stem cells that have not yet committed to a terminal line of differentiation can be induced to form the cell or tissue type required**. Currently, work in this area uses the concept that placing stem cells in an appropriate environment (e.g. within a wound) will persuade them to take on the phenotype required through a combination of genetic and environmental signals. However, it should be possible to **induce** stem cells to take on a particular phenotype using combinations of both molecular and physical signals. Thus, for example, it is feasible that biomaterials containing particular peptides, glycosequences, small molecules and/or genes would be capable of both trapping and differentiating endogenous stem cells into the phenotype required. This is a highly ambitious challenge but one which will greatly enhance tissue engineering and regenerative medicine.

Tissue engineering scaffolds, usually porous polymeric materials or gels, are used as substrates for the culture of differentiated cells in 3D prior to introduction into the body. Developments such as the production of injectable scaffolds are a valuable addition to this thinking. These scaffolds may contain cell attachment motifs or specific peptides such as growth factors that can be released over time to enhance cell function. Our knowledge of stem cell biochemistry, however, is still at a low level. Consequently, the molecules that are used to affect stem cell fate are all derived from our knowledge of adult cell responses to various biomolecules. The long term challenges for the progress of regenerative medicine are therefore highly dependent on understanding all types of stem cells (embryonic, adult and induced pluripotent) at both the molecular and longer length scales. The grand challenge for chemists is to provide this understanding and then to prepare materials and molecules that can be used to produce translational regenerative therapies. There is a small but developing body of evidence that indicates how discrete molecules can steer stem cell differentiation. For example, retinoic acid is known to induce human embryonic stem cells to differentiate into neurones. A synthetic retinoic acid analogue has been shown to cause neural differentiation but a very closely related isomer causes differentiation into epithelial cells. It is not known why such a subtle change in molecular structure has a profound effect on stem cell differentiation but this gives us a tantalising glimpse of how discrete molecules may provide exquisite control of stem cell fate.

The advancement of stem cell research and its translation is dependent on the parallel development of technologies to improve and enhance stem cell growth and controlled differentiation, to enable cells to form complex tissues and function in a realistic manner. Broadly stated, there are four areas in which chemists can contribute. The first three are the initial isolation of stem cells, their expansion and differentiation within the laboratory and their delivery to the patient. The fourth area is the logical but ambitious extension of these: introducing biomaterials that interact with endogenous stem cells to achieve the desired repair in the body. There is a clear flight path that starts with our knowledge of tissue engineering and biomaterials that can be harnessed and progressed to tackle the problems of stem cell isolation, proliferation and differentiation. We envisage that this eventually progresses to the long term goal of developing injectable biomaterials that are capable of attracting and enhancing the differentiation of endogenous stem cells within the body to perform the repairs necessary. There are also opportunities for chemists in the emerging new field of induced pluripotent stem cells, in which primary cells are de-differentiated into a pluripotent state upon treatment with specific genes.

Research Challenges and Barriers to Progress Without doubt the biggest challenge to developing molecular regenerative therapies is complexity. However, considerable progress in computational biology, which is another area in which the UK has a growing and considerable degree of expertise, using systems and integrated biology approaches, can be used to address these aspects. Clearly, very significant advances in the field can be achieved by the formation of integrated teams of chemists, materials scientists and life scientists working along side computational biologists. Stem cell differentiation and function and the adhesion and proliferation of differentiated cells are influenced by a number of factors, which can broadly be classified as either genetic (the selection of a particular array of genes within the cells which dictate the proteins expressed by the cell, both intracellularly and on the cell surface) or environmental (signalling molecules and the immediate physical environment in which the cell exists, such as substrate modulus, roughness, porosity, swelling and form) in nature. These factors are interconnected. All attempts to identify single dominant parameters that can be used solely to determine cell behaviour have met with only limited success. An important aspect of this grand challenge therefore will be a drive to investigate simultaneously the effects of physical and molecular parameters on (stem) cell function. Recent work indicates that scaffold physical factors, such as stiffness, surface area and roughness play an important role in determining how cells adhere to and behave on biomaterials surfaces. There is also an increasing realisation that 2D cell culture does not provide information that is necessarily relevant to cell behaviour *in vivo* where cells experience a complex 3D environment. Another barrier to progress is the widespread belief that regulatory frameworks do not allow the introduction of new biomaterials, despite the fact that recent developments such as siloxane conetworks (contact lenses), phosphorylcholine functional polymers (non-fouling coatings on blood contacting devices, eg stents) and phosphate functional polymers (dentistry) clearly illustrate the potential for new materials to enter clinical application. These barriers to innovation, whilst understandable from a commercial perspective, are preventing truly ground-breaking developments in regenerative medicine.

We envisage that the only way to tackle this complex challenge will be to coordinate multi-disciplinary teams in several grand challenge projects. There is a considerable amount of work ahead for these teams. For example, identification of chemical factors will require high throughput techniques both for synthesis, cell culture and data accumulation. One of the biggest challenges may lie in the coordination of a potentially huge amount of data and it will be vital to ensure that the separate projects are synchronised, managed and coordinated effectively, and have extensive inter-project dialogue. The UK is world-leading in stem cell research so the community is well-placed to tackle this ambitious programme. There are several well-established academic centres that involve close collaboration of physical and life scientists, providing the knowledge base to produce high quality applications for a grand challenge project call in this area. EPSRC funding would attract additional investment from other sources including BBSRC, MRC (in particular, for translation research) and the Wellcome Trust. The topic is of relevance to current cross-RC priority areas such as healthy ageing (BBSRC). Furthermore, industry is investing heavily in stem cell science in the UK, for example, the £40M Pfizer Regenerative Medicine Unit in Cambridge, providing a mechanism for effective translation of scientific developments into new therapies. Investment at this level would not occur without a world-leading academic base in stem-cell science in the UK.

Involvement Clearly, whilst chemists will make major contributions to this field, highly interdisciplinary teams will be vital to success and we envisage strong contributions from several disciplines in which the UK already has a strong position. Consequently, we aim to build teams composed of scientists from several of the following areas: synthetic organic chemists, polymer chemists, analytical chemists, (stem) cell biologists, tissue engineers, clinicians, process engineers, biomaterials scientists, chemical biologists, pharmacists, computer scientists and social scientists. The Grand Challenge will also increase UK capacity in the field and will build on and use trained staff emerging from the DTCs in tissue engineering (Sheffield/Leeds/York and Nottingham/Keele/Loughborough) as well as producing newly trained researchers.

Consultation

Professor Sheila MacNeil, Professor of Tissue Engineering, University of Sheffield; Dr Stefan Przyborski, Reader in Stem Cell Biology, Northeast England Stem Cell Institute & Durham University; Professor Karim Nayernia, Professor of Stem Cell Biology, Northeast England Stem Cell Institute & University of Newcastle; Professor Kevin Shakesheff, Professor of Advanced Drug Delivery and Tissue Engineering, Nottingham University; Professor Ben Davis, Professor of Chemical Biology, University of Oxford; Professor Jenny Southgate, Chair of Molecular Carcinogenesis, University of York; Professor Cameron Alexander, Professor of Polymer Therapeutics, Nottingham University; Professor Richard Oreffo, Professor of Musculoskeletal Science, University of Southampton; Professor Molly Stevens, Professor of Biomedical Materials and Regenerative Medicine, Imperial College; Professor David Williams, Professor of Healthcare Engineering, University of Loughborough; Dr Paul Genever, Head of Biomedical Tissue Research Group, University of York; Dr Dafydd Owen, Senior Principle Scientist, Pfizer Global R & D; Professor Robert Field, Professor of Biological Chemistry, John Innes Centre; Dr. Catherine Merry, School of Materials, University of Manchester

Benchmarking Against the Grand Challenge Criteria

Criteria	Score	Evidence for Score
The Grand Challenge will enable UK scientists and engineers to engage in internationally leading research.	5	The UK has developed major strengths in stem cell biology and this excellent scientific and regulatory environment is encouraging the establishment of several major industrial initiatives (e.g. the Pfizer Regenerative Medicine Unit: Financial Times, 14th Nov 2008). However, the improving environment for stem cell research in the USA (eg see USA Today 23rd Nov 2008) will increase competition and it is vital that the UK invests to enhance its position. Until now, most stem cell research has been carried out within the context of medical engineering and fundamental biological studies. However, internationally the concept of designing molecules to control stem cells is beginning to move forward (eg see Chen et al "Self-renewal of embryonic stem cells by a small molecule" PNAS **46**, 17266, (2006); Diamandis et al "Chemical genetics reveals a complex functional ground state of neural stem cells" Nat. Chem. Bio. **3**, 268, (2007)) and it will be vital for UK scientists to compete in this new field in the medium and long term. The Grand Challenge will bring a much needed molecular input that will make a major contribution to the UK's lead in stem cell science and technology.
The Grand Challenge has ambitious objectives, which if achieved, would result in a step change in our current knowledge.	5	We aim to elucidate the molecules and materials required to control stem cells and thus realise the concept of stem cell regenerative therapies. The area is at a very early stage and so the potential for rapid developments is great. Since there is currently so little knowledge, the discovery of molecules that affect stem cell differentiation will quickly produce step changes in both our understanding of stem cells and their application. Advances made in the biomaterials community will enable the creation of scaffolds for stem cell based therapies, which will in turn create further step changes. Thus, once the relevant molecules have been discovered, several scaffold platforms, including injectable formulations, porous materials and hydrogels, are available within UK laboratories for their delivery and exploitation.
The Grand Challenge will encourage researchers to be ambitious; lifting their horizons to the truly novel and innovative.	5	The grand challenge will require close collaboration between chemists and other scientists, engineers and clinicians and we expect many new collaborative partnerships to be born out of this programme. The necessity for close partnership will naturally lift the horizons of all grand challenge team members, producing new challenges that would not be apparent in single discipline research. The focus of the programme is highly ambitious and success will require innovative approaches from all aspects of the projects. For example, even when molecules are identified it will be necessary to control how these molecules are presented and delivered to the cells. This will produce new challenges and new solutions. Success will also require engagement with emerging disciplines including synthetic biology, systems biology and integrated biology.
The Grand Challenge has the potential to make a positive societal and/or economic impact.	5	Stem cell based therapies have the potential to revolutionise medicine. The area has captured the imagination of many commentators in all areas of the popular press. Several new companies have been formed based on the idea that stem cell therapies will provide both the new medicine of the 3rd millennium and generate some of the new pharma and healthcare businesses. The area is now attracting considerable attention from the large pharmaceutical corporations (eg GSK initiative in the USA and Pfizer in the UK). These activities will clearly make major contributions alongside the smaller focused activities of the newer SMEs in the area. Thus the scene appears to be set for the beginning of a major activity in the chemical aspects of stem cells, which this Grand Challenge programme will accelerate.

Scoring: 1 – Strongly Disagree; 2 – Disagree; 3 – Neutral; 4 – Agree; 5 – Strongly Agree

Criteria	Score	Evidence for Score
The Grand Challenge has a single vision giving the research community common goals to work towards.	5	The Grand Challenge has a very clear vision: the ability to control stem cell fate through the intervention of molecules and materials. This will then enable the development of robust technologies that will produce pure populations of stem cells without the requirement for ill-defined animal-based products. In turn, effective, reliable and clinically applicable therapies can be developed from such advances in basic stem cell science and technology. Scientists and engineers will be able to see easily how their expertise maps onto this vision, allowing rapid progress to be made towards the common goals.
The Grand Challenge is forward looking, focusing on what can be achieved in 20-40 years time.	5	Given the paucity of current knowledge regarding the control of stem cell differentiation, there are major advances required before we can even begin to develop effective tools for reliable stem cell culture. These are necessary to ensure reliable sources of pure stem cells with which to develop translatable therapies. Certainly, therefore, the vision of this Grand Challenge topic is towards what is achieveable over a 20-40 year timescale, rather than what is achievable in five years. Undoubtedly the topic is forward looking: stem cell science is at the forefront of modern research and is a topic that is currently of great scientific, technological and societal importance.
There is sufficient capacity in the UK to respond to the challenge and the potential to build on this capacity in the future.	5	The UK has seen significant investment in several areas required to respond to this challenge. There are already excellent examples of relatively well-established interdisciplinary centres that bring together life scientists with physical scientists and engineers, including several Doctoral Training Centres. A number of interdisciplinary stem cell institutes (e.g. Edinburgh, Newcastle/Durham, Nottingham, Cambridge, London, Southampton) are already in existence and there is a government-endorsed UK National Stem Cell Network (UKNSCN) that links these centres. The parallel investment by major industry, as well as the creation of a plethora of SMEs in the area, provides the framework required for the translation of basic research emerging from universities into effective stem cell based therapies.
The Grand Challenge provides opportunities for collaborations between researchers in different disciplines.	5	There is clearly a thriving interdisciplinary community of scientists and engineers who will undoubtedly jump at the chance to contribute their expertise to tackle this Grand Challenge. At the heart of this community are chemists: biomaterials chemists to create new scaffolds; organic chemists to prepare small molecules to intervene in stem cell fate; analytical chemists to develop high throughput assays of cell function; chemical biologists to elucidate molecular pathways that control stem cell differentiation. However, the chemists alone cannot tackle this challenge. Other disciplines are required, including cell biologists, biomedical engineers, computer scientists, bioethicists, geneticists and clinicians. Working together, the interdisciplinary teams created through this Grand Challenge call will produce truly innovative and transformative research.

EPSRC GRAND CHALLENGES SUBMISSION

Systems Chemistry: Exploring the Chemical Roots of Biological Organisation

Submitted by:
Donna G Blackmond (Depts. of Chemistry and Chemical Engineering, Imperial College), John Murphy, Dept. Pure and Applied Chemistry, University of Strathclyde, Terrence Kee (Dept. Chemistry, Leeds), John Sutherland (Dept. Chemistry, Manchester) Christopher Hunter (Dept. Chemistry, Sheffield), Alan Armstrong (Dept. Chemistry, Imperial College), Perdita Barran (School of Chemistry, University of Edinburgh).

Grand Challenge Vision

Probing how life originates from simple chemical precursor systems is one of the most basic unanswered questions for scientific endeavour. It encompasses critical challenges of increasing complexity involving simple isolated molecules, supramolecular chemistry and self-replicating systems on a trajectory from chemistry through physics to biology. Research based on the classical knowledge of chemistry – the language of molecules, their structures, reactions, and interactions – must be combined with aspects derived from the fields of theoretical biology and complex systems research with the goal of ***probing the collective emergent properties of complex systems to uncover the chemical roots of biological organization***.

An integrated approach to understanding molecular interactions, via simulation, model systems, and design optimisation – over a wide range of scales – must be combined with new synthetic methods and processing technology. Studies will probe small molecule reactions and the physical processes that allow complex systems behaviour in small (~2-1000) to large (10^3 upwards) collections of molecules. The use of chemical engineering tools coupled with studies of isolated molecules, computational techniques and organic synthesis in conjunction with analytical methodologies represent a compelling integrated approach to bring this interface together. Collaboration between chemists, biologists, mathematicians, and chemical engineers will be needed to create an exciting opportunity not only to understand the origin of life but also to exploit this understanding to ***create new functions and systems.*** This will establish a new research paradigm termed ***"systems chemistry".***

Building systems that can self-assemble, process information, transport and react chemicals, produce and consume energy, fabricate materials, and ultimately self-replicate will undoubtedly have a major impact on evolving technology. For example, biopharmaceuticals account for over a third of all drugs now under development, and the number of licensed biopharmaceuticals is forecast to grow at a rate of around 20% per annum. Major benefits will accrue to nations who can capture knowledge on the processes by which life may have originated, and who endeavour to apply this knowledge to the development of new goods and services.

State of the art

In the 2003 report "Chemistry at the Centre"[1] assessing university research in the United Kingdom, the question of the Origin of Life was highlighted as one of the most important research problems of our day. The Whitesides report noted "the origin of life is prototypically a molecular problem" and presaged our terminology ***"systems chemistry***" with the statement that "chemistry has historically worked comfortably with complex systems of molecules and reactions, and will be one field leading in this new area of science." One of the most significant questions in science today, the report stated, is the question of "learning how this most remarkable of systems began." This is echoed in other prestigious academic statements, including Harvard University's announcement of the "Origins of Life in the Universe Initiative."[2] Significant efforts in chemistry research concerning the origin of life are ongoing in countries around the world, including a European Community COST Action and Protocell Project. Within the UK, only the fledgling EPSRC-funded "CHELLnet" programme[3] presents a joined-up chemistry effort in this area, with the goal of "unifying investigation in artificial cellularity and complexity." This programme represents a modest entry into this area, with ca. £1 million spread over ca. 15 research groups.

Biology is arguably the leading science for the 21st century; biologists today make use of a wealth of information about the various parts making up a living system. However, despite the formidable success of the Human Genome project, the science of biology has not yet been able to answer the most fundamental questions concerning the origin of life; this detailed molecular understanding belongs to the realm of chemistry. At a recent European workshop on the origin of life,[4] the group proposed to define a new area called ***"systems chemistry"*** encompassing research seeking to understand the chemical roots of biological organization.

As synthetic and analytical techniques continue to advance, chemistry is now entering a phase where complex systems can be prepared, or initiated, and their behaviour studied at the molecular level. The emergent properties of such systems may include properties not possessed by the individual components of the system, and it is this emergent behaviour that gives rise to the term “systems chemistry”. This general area has developed gradually alongside its underpinning synthetic and analytical methodologies, and includes, *inter alia*, dynamic combinatorial chemistry, experimental and theoretical studies of molecular interactions and chemical kinetics, and molecular self-replication. There are clear parallels to the development of systems biology, and the emergence of life from inanimate materials represents the transition between these two subjects.

Research challenges and barriers

The rapid expansion of knowledge and capabilities in life sciences has not yet been paralleled by an expansion in chemistry and chemical engineering research at the Life Science interface. The major scientific challenge in this area of research is to establish an internationally leading research initiative based on the application of chemical engineering tools and methodologies to the intersection of chemistry and biology. The unique features of such an initiative are its focus on understanding, at the chemical level, how components behave to create complex biological systems, and the exploitation of this fundamental understanding to develop new devices, medicines, materials and processes.

An important barrier to accomplishments in this area is overcoming the societal implications that could ensue from the misleading impression that scientists are attempting to create artificial life; visions of “Frankenstein” might deflect attention from the important goals of this work in the same way that the cloning of Dolly sparked debates about the ethical impact that technology such as genetic manipulation may have. Therefore we wish to emphasise that our goal is not to create life but to understand and learn from the chemical and processes that combine to bring about life.

Involvement

The critical mass of researchers needed to build a self-sustaining interdisciplinary research group at the forefront of the newly emerging field of systems chemistry will be comprised of scientists in in chemical engineering, chemistry and the life sciences. Given that this is very much an embryonic field at present, the primary need is for underpinning new knowledge building a fundamental understanding of the molecular detail of supramolecular systems in the life sciences. However, the strategic nature of this field of research and the entrepreneurial environment mean that exploitable knowledge and technology is highly likely to result. Once established, it is envisaged that research in this area will generate a flow of high quality, multi-skilled researchers for employment in industry and academia, and a flow of new ideas, leading to patents and knowledge transfer in new growth areas of the economy, including healthcare and pharmaceuticals.

Consultation

All UK academic participants of the Grand Challenges Workshop were consulted in the preparation of this document, along with all others who expressed an interest in this Grand Challenge. In addition, this Grand Challenge was discussed with European and American leaders in Origin of Life research, including Guenter von Kiedrowski (Bochum University, DE), Ben Feringa (Groningen University, NL), Jerry Joyce (Scripps Institute, US), Jack Szostak (Harvard University, US).

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[1] “Chemistry At The Centre: An International Assessment Of University Research In Chemistry In The UK”; commissioned by the EPSRC and the RSC; 2003.

[2] “Harvard Out To Uncover Life's Origin: Interdisciplinary project will attempt to demystify the origins of life”, The Harvard Crimson online edition, Dec. 9, 2005.

[3] http:// www.chellnet.org

[4] “Systems Chemistry”, European Center for Living Technology, Venice International University, Venice, Oct 3-4, 2005, organized by Günther von Kiedrowski, Ruhr-Universität Bochum.

EPSRC GRAND CHALLENGES SUBMISSION

Benchmarking Against the Grand Challenge Criteria

Criteria	Score	Evidence for Score
The Grand Challenge will enable UK scientists and engineers to engage in internationally leading research.	5	Prof John Sutherland (Manchester) and Prof Donna Blackmond (Imperial) are internationally recognized in origin of life research, and in the last two years have been invited as Plenary or Keynote speakers at over a dozen international venues, including The Royal Swedish Academy of Sciences Nobel Workshop, Harvard University's Institute of Advanced Research and the Gordon Research Conference on the origin of life. Along with Sutherland and Blackmond, Prof. Douglas Philp (St Andrews) is a member of the European COST Action entitled "Systems Chemistry." This Grand Challenge holds the potential to unify excellent individual ongoing research and to bring in young researchers by providing the umbrella area of "systems chemistry".
The Grand Challenge has ambitious objectives, which if achieved, would result in a step change in our current knowledge.	5	Understanding the origin of life on earth is one of the premier scientific challenges of our time, and revealing aspects of this phenomenon is sure to have major impact on the scientific community. The potential for major and lasting impacts of this initiative derive from the importance of the fundamental science it will lead, the engineering applications it will enable, and the unprecedented degree of integration it will create. This proposed collaboration between chemists, biologists, mathematicians, and chemical engineers creates an exciting opportunity not only to understand the origin of life but also to exploit this understanding to create new functions and systems.
The Grand Challenge will encourage researchers to be ambitious; lifting their horizons to the truly novel and innovative.	5	The concept of an interdisciplinary approach to the discovery and development of evolvable chemical systems is one of the most ambitious ideas in modern science and will only be achieved by truly synergistic collaborations across a broad range of scientific disciplines. The goals and the promise that success holds brings together an apt mix of fundamental science, application, and entrepreneurial motivation that will allow the truly innovative to emerge. The approach combines fundamental organic synthetic chemistry with chemical engineering modelling tools and physical/analytical chemistry methodologies applied to a research problem that has traditionally been outside the mandate of chemical engineering.
The Grand Challenge has the potential to make a positive societal and/or economic impact.	5	Making sense of science's basic questions is one of the boldest and most lofty goals for societal impact. Understanding how life on earth began, and exploiting that understanding to produce new devices, materials, medicines and systems that help society, is an inclusive way of bringing the benefits of fundamental science to the community.

Criteria	Score	Evidence for Score
The Grand Challenge has a single vision giving the research community common goals to work towards.	5	Our focus on using fundamental knowledge to devise new functions and systems rather than to "create life" will help to demonstrate to the lay community how research into science's basic questions can be applied to important current problems. The inclusion of the fundamentals of chemical engineering, with its emphasis on systems and processing, simulation, optimisation and modelling, on a problem of such fundamental significance will bring scientists from all aspects of the chemical community and reach across both the engineering and the life sciences interfaces.
The Grand Challenge is forward looking, focusing on what can be achieved in 20-40 years time.	5	This grand challenge responds to what has been called one of the most important unanswered scientific questions of our time; as stated in the Whitesides report in the section entitled **The Future**: *"Chemistry is now beginning to work at the foundations of several of the most intellectually important problems of modern science. Two examples are complexity, and the origin of life."* Our approach ensures that both fundamental and tangible advances in understanding and exploiting how biology uses chemistry to create complex systems and organisation.
There is sufficient capacity in the UK to respond to the challenge and the potential to build on this capacity in the future.	5	As mentioned above, the UK has several internationally leading researchers in this area as well as a wealth of young talent that has not yet been directed toward this problem.
The Grand Challenge provides opportunities for collaborations between researchers in different disciplines.	5	The highly interdisciplinary nature of this challenge, weaving organic and analytical chemistry into chemical engineering and biology, ensures that significant opportunities for synergistic collaborations will unfold. This Grand Challenge offers tremendous potential for collaboration with non-chemical disciplines such as condensed matter physics, computer science, artificial intelligence/machine learning, mathematics (complex systems). There is no doubt that we will need all of these disciplines to achieve our goals.

EPSRC GRAND CHALLENGES SUBMISSION: 'ACHIEVING ARTIFICIAL LIFE'

Submitted by: Mark Haw, Strathclyde University; Oscar Ces, Imperial College London; Lee Cronin, Glasgow University; Sven Schroeder and Simon Webb, Manchester University; Peter Coveney, University College London; Sean Bew, University of East Anglia; Harris Makatsoris, Brunel University; Rachel O'Reilly, Warwick University.

GRAND CHALLENGE VISION

Our vision is **to understand how chemistry and physics make life, and use this understanding to assemble, 'bottom-up' from component chemical building blocks, the first artificial living system**.

Understanding how self-sustaining living systems arise from the structure, functions and interactions of fundamental physico-chemical building blocks will require unprecedented advance in basic science, measurement, analysis and synthesis. Characteristic features of life include energy conversion/metabolism, multiscale compartmentalisation from membrane to organelle to cell, self-repair, information origination, storage and retrieval, replication, adaptation and evolution: all of which must arise as the (non-linear) consequences of the fundamental physical/chemical behaviour of matter. Unlike 'top-down' attempts essentially to recombine existing biology into 'artificial' life (*eg* by the Venter group, not to mention Dr Frankenstein…), the core of our more ambitious and *fundamental* vision is to generate the basic knowledge and revolutionary platform technologies necessary to fully ***understand*** how chemical and physical principles combine to make life, and so how to assemble artificial living systems 'from the bottom up'.

Due to the breadth of chemical and physical fundamentals clearly involved in living systems, addressing this Challenge will have profound and wide-reaching scientific consequences, bringing step-change across disciplines and problem areas including functional and systems chemistry, microscopic/non-equilibrium/open-system thermodynamics, non-linear chemical dynamics, mechanisms of macromolecular interaction, molecular motors and other biomolecular functions, catalysis, controlled self-assembly; and, vitally, the 'network engineering' of these features to form complete self-sustaining systems.

The economic, social and cultural impacts will be similarly unprecedented: medical care becomes rational engineering of macromolecules, cellular processes and organisms; the origin and nature of life is transformed from a philosophical conundrum to the natural consequence of the behaviour of matter and energy; materials and bio-engineering are revolutionised by fundamental understanding of the capacity for matter to assemble complex functional systems; chemistry becomes a science of rational design based on understanding the non-linear consequences of basic functional principles, rather than a blind-man's-buff hunt for efficient synthesis routes and useful molecules; and physics steps beyond the currently dominant LHC quest for *what is matter made of?* toward an even bigger, all-encompassing question: *what can matter do?*

Significant advance in *any* of the above areas would transform technologies ranging from materials to pharmaceuticals to medicine to industrial chemistry. Yet put together, and motivated by this Grand Challenge as a whole, the consequences for the way science is done in the UK go much further. The step-change in research *cohesion* across chemistry, physics, engineering and biology that the Grand Challenge demands, promises to transform UK research from a set of undeniably world-leading yet unavoidably piecemeal projects, into a joined-up, globally outstanding effort, driven by a common inspiration. The ambitious, far-reaching and inspiring goal of the Challenge will enable UK research to compete in drawing the best talent from the worldwide research community, making the UK *the* source for global technological transformation and *the* key player in global collaborative science over the next decades. Understanding the chemical and physical basis of life is the ultimate challenge to science, one that *will* be addressed in the next decades, and hence a pioneering frontier that UK science and technology cannot afford to ignore.

State of the art There is significant ongoing research in world-leading groups in the UK and elsewhere on key problems relevant to the Challenge: techniques such as dynamic and structural spectroscopies; protein/macromolecular structure, function and dynamics, and their interrelationship; molecular autocatalysis; metabolic pathways; microscopic/non-equilibrium/open-system thermodynamics and molecular motors; non-linear chemical dynamics; systems chemistry; molecular evolution; emergence and complexity; self-assembly; non-equilibrium phase behaviour; role of chirality; molecular signalling and directed transport; network engineering in living systems (systems biology); astrobiology and extremophiles; and so on. Many of these areas are constantly advancing: *eg* real-time observation of chemical reactions and protein/enzyme dynamics[1]; experiments exploring non-equilibrium, microscopic, open-system consequences of the Laws of Thermodynamics and chemical strategies for benefitting from them, *eg* chemical ratchets, shuttles etc[2]; improvements in controlled self-assembly [3]; microfluidics and soft matter approaches to cells and cellular processes[4]; and growing knowledge and understanding in emergence, complexity and network systems biology[5]. Progress in all these areas is inevitable over the next 5 years.

However, our key point is that ***few of these problems have been approached as integral parts of the overall challenge of turning fundamental chemistry and physics into life***. Progress in individual areas, without a guiding, inspiring Grand Challenge as a 'flag to gather around', is likely to remain isolated, only slowly integrated into a full understanding of how the nature and behaviour of chemical building blocks results in self-sustaining living systems (or indeed even in key aspects of living systems such as metabolic chemical cycles, compartmentalisation, self-assembly, adaptation etc). This is why, rather than simply enhanced focus on particular areas, an encompassing *Grand Challenge* is necessary: much of the expertise and interest are in the right places already, but the science is not being done (or funded) in a coherent way to promote its groundbreaking potential. Our vision is that the Challenge can be a guiding force for global science as a whole over the next decades, and as such a key element to ensure UK competitiveness in growing a sustainable world-leading science/technology base to underpin our economy.

Research challenges and barriers Expertise in the wide range of problem-areas key to the Challenge already exists in world-leading UK research groups: but the major practical barrier is precisely the lack of ***cohesion*** across disciplines that is **required** if we are to understand how chemistry and physics make life and how we may directly assemble living systems or their component functional parts. To achieve this cohesion the Challenge must **inspire a wide range** of researchers to want to be part of it, not simply for strategic (funding) reasons but from a fundamental desire to address the most ambitious science questions of the day. The Challenge poses fundamental questions that concern each of us personally as well as scientifically, philosophically and culturally: what is life and how does it work? How did life arise? Can it have arisen elsewhere in the Universe? This multi-level scientific and cultural inspiration is the key to achieving the necessarily wide-ranging impact of the Challenge: how chemistry and physics make life is the ultimate question of what matter and energy can do, and thus will appeal to scientists from the entire spectrum of research, as well as to non-scientists, showing the power and ability of science to address fundamental personal concerns as well as technological issues.

Consequences of answering the Challenge in fact range far across technology, industry and health, from transforming medicine into rational engineering/repair of physico-chemical systems, to transforming chemistry into rational molecular functional design based on required material features and behaviour. The necessary scientific ingredients thus stretch across disciplines: including controlled self-assembly; measuring and understanding energy-harvesting/conversion in microscopic (non-equilibrium) systems; measuring and understanding interaction mechanisms in complex macromolecules; measuring and predicting the non-linear dynamics of chemical interactions and networks; understanding the origins of physical compartmentalisation, from membrane formation to organelle arrangement; understanding dynamic chemical signalling; molecular evolution and adaptation, including information storage and retrieval to enable replication; basic mechanisms of self-repair on a range of scales of complexity; and formation and functioning of chemical interaction and metabolic (energy processing) networks, again at different scales of complexity.

All these are profound challenges to current science, yet with recent advances we can begin to see how they will fit together to answer how chemistry and physics make life and how a living system may be directly assembled. Significant progress in any *subset* of these problems would itself represent a step-change in science, whether in the non-linear chemistry of complex molecules, controlled self-assembly of materials, operation of non-linear dynamic chemical or energetic networks etc. Thus the Challenge is composed of major elements which have an ‘independent’ value on shorter timescales as well as a key role in the overall bid to understand and exploit how chemical and physical principles lead to living systems.

Involvement and multidisciplinarity It cannot be over-emphasised that the Challenge demands involvement across more or less all disciplines in physical and biological sciences, mathematics, engineering and ICT. Methodologies include chemical synthesis, nano-/micro-/macroscale dynamic time-resolved measurement, large-scale data management/analysis, statistical mechanics, quantum chemistry, chemical and biomolecular engineering, mathematics of non-linear systems, physical chemistry, molecular, genetic, and protein biology, network, complexity and emergence, medicine, and astrobiology. The great **advantage** of the Challenge is just that this very wide range of scientists and industries can place their expertise as fundamentally part of the goal. This is also the practical **challenge**, since current science still suffers from compartmentalisation and the actual operation of the Challenge must overcome this; and the great **opportunity**, as bringing scientists together under the umbrella of the Challenge will enable unprecedented breaking down of discipline-walls. The Challenge will thus mean a step-change in science *and* in the way we *do* science, with consequences beyond the scientific areas directly addressed: UK research will pioneer both new science and a new *approach* to science, one vital if this greatest science challenge, the marrying of physics, chemistry and biology in the phenomenon of life, is to be successfully addressed.

Consultation Stakeholders consulted include a range of individual physicists/chemists/biologists (incl. C. Laughton, Nottingham; R. Templer, ICL; D. Astumian, Maine); journal editors (*eg Nature, Nature Chemistry, Chemistry World*); key organisations (*eg* Royal Society of Chemistry); industry (*eg* R. Elliot, Syngenta).

References **[1]** S.J.L Billinge & I. Levin, *Science* **316** 561 (2007); D.D. Boehr &P.E. Wright, *Science* **320** 1430 (2008); S.J. Benkovic & S. Hammes-Schiffer, *Science* **301** 1196 (2003); E.Z. Eisenmesser *et al*, *Nature* **438** 117 (2005). **[2]** D.A. Leigh *et al*, *Angew. Chem*. **46**, 72 (2007); D.M. Carberry *et al*, *Phys. Rev. Lett.* **92** 140601 (2004). **[3]** J.S. Moore & M.L. Kraft, *Science* **320** 620 (2008). **[4]** *eg* http://www.nanowerk.com/news/newsid=8412.php. **[5]** *Thinking in Complexity*, K. Mainzer, Springer-Verlag 2007.

Benchmarking Against the Grand Challenge Criteria

Criteria	Score	Evidence for Score
The Grand Challenge will enable UK scientists and engineers to engage in internationally leading research.	5	Understanding life is the ultimate challenge for physics/chemistry/biology and is therefore **the** globally outstanding challenge for modern science. The inspiration, ambition and multidisciplinarity of the challenge will enable and motivate a wide range of UK scientists to work under its umbrella. Such an outstanding, inspiring and ultimately socially-transforming challenge will also label the UK as **the** outstanding location to do and apply science: maintaining our current high-quality population of scientists and engineers, enhancing the take-up of science in future generations, maximising public support and interest in science, and bringing the highest-quality researchers and industries from elsewhere to be part of this 'ultimate challenge' for science.
The Grand Challenge has ambitious objectives, which if achieved, would result in a step change in our current knowledge.	5	The challenge promises to take physics, chemistry and biology to the 'next level': beyond current 'static' or 'isolated system' knowledge (isolated chemical interactions, isolated protein function, isolated near-equilibrium physical processes) to the next level of how matter and energy dynamically create and achieve functionality, network engineering, adaptation, evolution—and hence create living systems. The challenge is to fill the gap between physical science and life, an ultimate scientific challenge of enormous ambition. Significant advances in any of the underlying components of the challenge—*eg* macromolecular interactions, self assembly, chemical network formation and dynamics etc—would in themselves generate step-change in science knowledge and more importantly in understanding and applications, from materials engineering to medicine and pharmaceuticals to new chemical processes.
The Grand Challenge will encourage researchers to be ambitious; lifting their horizons to the truly novel and innovative.	5	The longer-term nature and scientifically demanding scale of the Challenge will encourage and demand true ambition and novel innovation, rather than play-it-safe short-term piecemeal work. Novel ideas and innovation in techniques will be required by **all** aspects of the challenge, across the range of the biggest current challenges in science: there is no element which could be described as incremental or simply 'filling in the details'. Finally the required multidisciplinarity of meeting the Challenge will encourage and enable a maximally wide range of scientists to contribute and focus on the goal: a large proportion of the research community will find a place for their interests, expertise and ideas without having to artificially shoehorn themselves into a narrow discipline-area.
The Grand Challenge has the potential to make a positive societal and/or economic impact.	5	This Challenge addresses the science of us: what it means scientifically for a system to be 'alive'. The philosophical, social and cultural impact of the Challenge is thus unprecedented. The challenge engages with the public's basic desire to answer the most fundamental questions about our existence, relating closely to areas of recent intense public interest such as the search for the origins of living systems and for evidence of extra-terrestrial life. However, the emphasis on *understanding* the chemical and physical basis of life rather than simply trying to 'cook up' artificial life is the key element, ensuring we generate a positive and inspired social and cultural response, not a 'Frankenstein' reaction. Scientifically, addressing the Challenge and its components will mean fundamental advances in applications ranging from medicine, molecular design, and innovative chemical engineering to non-equilibrium energy processing, complex chemical system design, tailored cell-engineering and self-assembly for nanostructured functional materials. Hence the economic impact will be similarly significant. And most importantly it will not be a case of waiting half a century for the completion of the challenge before these benefits are felt: advances in the component areas of the challenge will lead to economic, social and scientific impact on a range of timescales from the immediate to the full multi-decade timescale of the Challenge as a whole.

Criteria	Score	Evidence for Score
The Grand Challenge has a single vision giving the research community common goals to work towards.	5	Life is the ultimate combination of all chemistry and physics, the ultimate product of matter and energy: the Challenge's vision of how chemistry and physics make life and how to directly assemble living systems provides a clear, unambiguous, ambitious goal, but because of this encompassing multidisciplinarity allows space for research across all areas to flourish within it, rather than be stifled or straitjacketed by a narrow task. Researchers will be thus be inspired to align their work with the well-defined common vision, yet will be enabled to make fullest use of their expertise and explore their scientific interests to the greatest degree while following the single vision of 'assembling life'.
The Grand Challenge is forward looking, focusing on what can be achieved in 20-40 years time.	5	The history of science and technology demonstrates that over a 40-year timescale essentially *unimaginable* advances can be made (*eg* computer technology, where the algorithm concept was barely grasped in the early 1950s, yet by late 1990s the world was covered by a global web of information technology; or the science of energy, where Carnot's first ideas of the 1830s were transformed into the full science of thermodynamics and the height of industrial power by the time Maxwell died in 1879). Any truly *grand* challenge must aspire to match this sort of unimaginable transformation in how we understand and exploit our universe, for this is clearly what science is capable of: aiming any lower would be a failure of ambition. Current significant and growing work in the component areas of the challenge means that this is the ideal time to focus *now* on the Challenge, as key advances *will* be made in these areas over the next decade: the Challenge is then about ensuring the longer-term focus to add these advances together into a real answer to the question of how living systems assemble from basic chemical building blocks.
There is sufficient capacity in the UK to respond to the challenge and the potential to build on this capacity in the future.	5	The UK has hosted major research and exploitation in areas such as biotechnology, genetics, protein dynamics, self-assembly, biophysics, high performance computing and innovative chemical engineering: all the building blocks underpinning the Grand Challenge are in place. However, the key will be bringing *cohesion* to the UK's high-quality research population and future generations of scientists: to add together and enhance the UK's strengths using the inspiring power of the Challenge. Such cohesion is increasingly **necessary** in addressing complex technological issues: the focus of the Challenge, building on current initiatives *eg* Life-Science Interface DTCs, will thus be key to ensuring the UK's capacity to play a major role in global science over the next half-century. The Challenge provides an encompassing, inspiring goal which will bring the highest-quality scientists to the UK (not just in search of funding but attracted by the most ambitious science), will maintain our already high-quality research/engineering base, and will be vital in encouraging the most talented members of future generations to choose careers in science and technology.
The Grand Challenge provides opportunities for collaborations between researchers in different disciplines.	5	In demanding combination of disciplines, skills and ideas across physics, chemistry, biology, mathematics and engineering, the Challenge automatically makes collaborative work, expertise-sharing and cross-fertilisation the **required** working method. The breadth of expertise required to meet the Challenge removes the risk of its being 'hijacked' by one or other narrow specialism, while in many of its component areas, such as self-assembly, network system dynamics, measurement etc, a cross-disciplinary work habit is already well-established. The challenge of bringing these areas together to understand how life assembles from chemical building blocks promises to go beyond current collaborations, to provide an 'umbrella' under which scientists, while enhancing their own expertise, can focus their work toward a key common objective. The Challenge promises not simply to build isolated tunnels through discipline barriers, but to break the barriers down, and transform long-term the way we do science across disciplines, aligned and inspired by a common ambition.

Format of Grand Challenges Submission to EPSRC

Definition and Impact of the Grand Challenge

Title of Grand Challenge: WATERFALL (Water for All)

Submitted by: David H Bremner (University of Abertay Dundee) and Barbara Kasprzyk-Hordern (University of Huddersfield).

Vision: To develop clean and sustainable solutions for water supply and use for the global population

State of the Art:

Limited understanding of human impact on water quality:

Minimal knowledge exists concerning the fate of many man-made chemicals which have a high capacity to reach the water supply.

Monitoring technologies exist but are still expensive and time consuming:

Many reliable existing analytical techniques used for water characterisation are expensive, time consuming and very often require specialised knowledge. These techniques are often unaffordable for developing countries where the accessibility of clean water is one of the major objectives.

Existing treatment technologies are very often inefficient and expensive:

Existing water technologies based on physical, chemical and biological processes are very often inefficient and ineffective, and often lead to the formation of hazardous by-products and require substantial energy.

Comprehensive management of water infrastructure:

To date there is a vision but no implementation of a global water management structure and this requires a sea change in international outlook and collaboration.

Research Challenges and Barriers to Progress

The focus of the Grand Challenge should be on providing a solution to the increasing pressure on global clean water resources that will come about as a consequence of demographic change and global economic development. The Grand Challenge has to be undertaken using a multidisciplinary approach leading to a step change in the development of knowledge and expertise in the following complementary themes:

- Comprehensive understanding of human impacts on water quality;
- Impact of climate change on water quality, purification and management;
- Introduction of novel monitoring techniques;
- Development of new treatment technologies;
- Comprehensive management of water infrastructure;
- Increased use of sea-water.

To understand human impacts on water quality:

Full understanding of human impacts on water quality is crucial in maintaining water sustainability. This should undoubtedly involve assessment of the risks associated with the presence of man-made chemicals in raw and treated water. In particular, research into the impacts of mixtures of very low levels of pharmaceuticals, nanoparticles and emerging contaminants on human and other bio-systems is required. Assessment of the risks to humans and the environment of mixtures of chemicals at very low levels as well as appropriate modelling is required.

To respond to climate change

The influence of climate change and the existence of extreme weather conditions (e.g. long droughts or floods) on the quality of water and performance of existing and new water/wastewater treatment technologies, potential new contaminants and water distribution must be thoroughly evaluated.

To develop new monitoring technologies:

New fast, sensitive, selective and cheap methods giving unequivocal results are absolutely necessary to identify threats associated with the deterioration of water quality and also to maintain water quality. Particularly, real time measurements and remote analysis need extensive development as they will allow for immediate response to any change of water quality.

To develop new treatment technologies:

There is an urgent need to develop new low cost, low energy and low carbon footprint technologies (both selective and non-selective). This is of particular importance in many areas of the developing world where existing water resources are under considerable pressure as a result of demographic change and industrialisation. New technologies should investigate physical, chemical and biological processes and should include new materials working, for example, as catalysts to increase efficiency but decrease hazardous by-product formation as well as cost and energy requirements.

- Superior schemes for water use and re-use in agriculture (vertical farming) and for household products and appliances must be introduced. Development of secondary reservoir systems - flooded rivers diverted into storage facilities to protect downstream assets and provide free hydroelectric power later – i.e. turning flood protection into a valuable asset.
- Invention of new detection methods for water leakages as well as development of corrosion resistant pipe work is necessary.
- New effective technologies (e.g. Advanced Oxidation Processes) utilised for water reuse will be especially important in regions with poor water supply. The handling of domestic water needs to be studied so that micro-treatment strategy is adopted. Standards and technologies for use of rain-water and grey-water need to be introduced. Enhanced bio-systems need to be developed to overcome the drawbacks of current sludge generation – increase anaerobic treatment with new bacteria. Possible to get useful products from bacterial sewage sludge?
- Cost effective desalination might bring clean water solutions for worldwide consumers but require breakthroughs in membrane technologies, ultrafiltration, reverse osmosis and decrease of membrane bio-fouling and precipitation of inorganic species.

To comprehensively manage water infrastructure

As quoted by Rene Coulomb in Water Challenges for the 21st Century (Water Science and Technology 2002, 45, 130) what is needed is

- Holistic systemic approaches based on Integrated Water Resources Management
- Participatory institutional mechanisms
- Full-cost pricing of water services with targeted subsidies for the poor
- Institutional, technological and financial innovation
- Governments as enablers, providing effective and transparent regulatory frameworks for private action

Sea-Water as a Resource

Vastly increase the use of the sea as a resource. Along with the utilisation of sea water for conversion into fresh water as discussed above, it is also possible to employ the sea as:

- Growth medium for algae for renewable biofuels
- Carbon capture
- Mining of rare metals by selective filtration of ions
- Wave power

Involvement

A multidisciplinary approach is required. Professionals, academics and policy makers in the fields of environmental science and engineering, physical sciences and the applied social sciences need to work collaboratively across academia, industry and the governmental sector.

Consultation: The Royal Society of Chemistry, European Environmental Agency, International Water Association, Chartered Institution of Water and Environmental Management, U.S. House of Representatives: Committee on Science And Technology, the Water Industry.

Benchmarking Against the Grand Challenge Criteria

Criteria	Score	Evidence for Score
The Grand Challenge will enable UK scientists and engineers to engage in internationally leading research.	5	Clean water supply is and will be one of the key issues facing humanity over the 21st Century. Scientific and technological advances in this area are of particular importance in many areas of the developing world where existing water resources are under considerable pressure as a result of demographic change and industrialisation. Furthermore, there is a pressing global need to reduce the energy consumption in water treatment processes and significantly improve efficiency.
The Grand Challenge has ambitious objectives, which if achieved, would result in a step change in our current knowledge.	5	This grand challenge has a number of objectives ranging from those easily achievable in 5 years to extremely ambitious over 50 years. However this is an opportunity for a clear plan to be developed and to devote resources to this area. The level of current knowledge in this area is insufficient to meet the pressing requirements for cost effective supply of clean water globally. The rewards of advances in this field include dramatic benefits to the quality of life of many of the World's poorer citizens.
The Grand Challenge will encourage researchers to be ambitious; lifting their horizons to the truly novel and innovative.	5	This grand challenge has a very human objective, to meet the basic needs of the entire population of the world with cost-effective technology supplying clean water (See Red Button Design). This powerful objective will serve to motivate researchers to further knowledge in this area and to seek innovative solutions to the existing obstacles. The adoption of this objective will enable UK researchers to build greater international links and become world leaders in the development of technology 'for life' that will be vital for the world in the 21st Century.
The Grand Challenge has the potential to make a positive societal and/or economic impact.	5	This achievement of this grand challenge will have a transformative impact on society, both in the developed and developing worlds. For those societies where a supply of clean water is problematic and expensive, new technology will revolutionise lifestyles, enabling greater social and economic progress, and helping to stabilise those regions where water shortages will increasingly result in conflict. As industrialisation continues globally, water will become more valuable and resources will be put under pressure. Cost-effective technologies for water treatment and re-use are vital if water resources are to be effectively sustained as the global economy develops. Moreover, the environmental consequences of the development of the global economy will result in a significant increase in the requirement for more advanced technologies focusing on the detection and removal of pollutants. Without these technological advances, there will be a heightened risk of widespread environmental contamination. Demand for the most effective technologies will increase and these technologies will become increasingly economically valuable as this scenario develops.

Criteria	Score	Evidence for Score
The Grand Challenge has a single vision giving the research community common goals to work towards.	5	This Grand Challenge has the advantage of a single clear powerful vision which has enormous motivating potential. The concept of 'Water for All', as expressed in terms of the provision of clean water supply for the global population of the 21st Century, is an objective that is fundamental for the continued well-being of all humanity. It is an objective that focuses scientific energies on a problem of the greatest significance, and, if achieved, will have a huge impact on global social and economic progress.
The Grand Challenge is forward looking, focusing on what can be achieved in 20-40 years time.	5	The enormity of the challenge of meeting the requirements of the global population for a clean water supply implies that objectives can be set for the 21st Century, bearing in mind the increasing pressure on global water resources as a result of demographic change and the increasing risk of pollution of the water supply. This grand challenge has the distinct advantage of requiring multi-disciplinary expertise across science and engineering to achieve long term goals that will have verifiable impacts and colossal direct human benefits.
There is sufficient capacity in the UK to respond to the challenge and the potential to build on this capacity in the future.	5	There is significant capacity and expertise in the water sector in the U.K. Academia, the Water Industry and Government bodies are actively involved in collaborative research to develop new technologies and processes. There is great potential for further joint activity through the piloting of different technologies. Additionally, the relationship the UK has with the developing world would enable UK based partners to engage with local workers in the effective piloting and introduction of new technologies and monitoring systems in a wide variety of local environments. The close links the UK has with a great range of countries (i.e. in Africa, the Middle East and Asia) where clean water supply is a very important local issue could facilitate a swift introduction of effective technologies, with multiple benefits to local economies, societies and human health.
The Grand Challenge provides opportunities for collaborations between researchers in different disciplines.	5	A major advantage of this grand challenge is the opportunity it offers to bring together researchers from a range of disciplines, especially in the fields of pure and applied chemistry, environmental science and engineering, water treatment technology, and social and political science. As the focus of this grand challenge is on solving one of the greatest problems facing humanity in the 21st century there is a real opportunity for making the very best use of the insights and advances of a range of different areas of expertise.

THE NON-PETROCHEMICAL INDUSTRY:
A SUSTAINABLE CHEMICAL ECONOMY BASED ON RENEWABLE RESOURCES

Professor Matthew Davidson, Department of Chemistry, University of Bath
Professor Kevin Booker-Milburn, Department of Chemistry, University of Bristol

VISION

TO REALISE A SUSTAINABLE CHEMICAL ECONOMY BASED ON RENEWABLE RESOURCES TO SUPERSEDE THE PETROCHEMICAL ECONOMY OF THE 20TH CENTURY

Note: A distinction is drawn between utilization of bio-fixed CO_2 (this challenge) and *chemical* fixation of free CO_2 (the focus of the Grand Challenge “New Synthetic Landscapes from CO_2”) since the fundamental issues facing the two approaches are very different. The former is focused on the utilization of broad, highly oxygenated product distributions available from biomass and the latter requires the development of technology to concentrate atmospheric CO_2 and new ‘C1’ chemistry to yield chemically pure feedstocks.

STATE-OF-THE-ART

Sustainable development must meet the needs of the present generation without compromising the ability of future generations to meet their own needs. It is the key global challenge of the 21st century. Unprecedented and rapidly growing demand for fossil-based resources, coupled with diminishing reserves, geopolitical uncertainty, and the threat of climate change are all factors that make the current petrochemical industry unsustainable. Thus, a transition in carbon-based fuels and chemicals from fossil-based to renewable resources is imperative. Although the vast majority of chemical processes still utilize petrochemical feedstocks, this transition has begun. A number of platform chemicals can be generated from renewable resources (if not always efficiently), polymers from renewable resources such as polylactide have niche markets, bioalcohols and biodiesel are produced to meet targets for renewable fuels, and renewable solvents can be used as alternatives to petrochemical solvents. However, these isolated examples tend to utilize highly refined (and therefore inefficient) feedstocks rather than deal directly with the complex mixtures that nature presents (e.g., carbohydrates). Chemical advances, such as the development of new catalysts, are often incremental and relevant only to very specific transformations, and the overall sustainability of processes is often (rightly) questioned. In the next five years, further incremental and isolated advances will be made but the challenge of developing tools for the *general and systematic* utilization of biomass as a sustainable and economically viable alternative to petrochemical feedstocks will not have been realized.

RESEARCH CHALLENGES AND BARRIERS TO PROGRESS

The overall challenge is to accelerate and generalize the trends identified above towards shifting the current portfolio of petrochemical feedstocks towards a more diverse (and challenging) range of bio-based alternatives. Nature provides a wide range of potential feedstocks that differ significantly in their composition from hydrocarbon-based petrochemicals. Their utilization requires the transformation of complex and variable mixtures of highly oxygenated feedstocks into a wide range of valuable products that the chemical industry relies upon. Bio-based feedstocks can either be converted into platform chemicals for the direct replacement of petrochemically-derived feedstocks (essentially by removing oxygen to leave hydrocarbon-rich products) or new and alternative processes can be developed that retain the intrinsic advantages of biomass such as chirality and biodegradability. The former can be considered as the concept of ‘accelerated fozzilisation’. The latter, potentially more challenging approach provides opportunities for developing new oxygen-rich products with enhanced properties for the fine chemical and pharma industries.

Key to both approaches is the development of new families of catalysts that are able to operate under the highly oxygenated and aqueous conditions imposed by the feedstocks. Robust and benign combinations of homogeneous, heterogeneous and bio-catalysts with multifunctional capabilities will be required to perform multiple steps under mild conditions without requiring energy-intensive separations. Current catalyst technologies are not sufficient to realize this goal and a step change in the understanding and design of complex catalytic processes at the molecular level is required to provide general approaches to these new chemical transformations that are required.

A combination of these catalyst systems will need to be integrated into large-scale, efficient processes that are able to extract full economic and chemical value from biomass. The prospect of achieving such economically viable 'biorefinaries' remains a major challenge requiring step changes in analytical, separation and process technologies.

Integration of biological and chemical technologies to produce significant quantities of chemically feasible bio-based building blocks is also a considerable challenge. For example, manipulation of metabolic pathways by genetic modification or directed evolution to provide biomass of specific and targeted compositions will be a necessary tool for the future large-scale sustainable exploitation of renewable resources.

A further important intellectual challenge to be addressed concerns the degree of complexity associated with sustainable utilization of biomass. On various levels, this is orders of magnitude greater than that dealt with by the current chemical industry. On the molecular level, systems analysis techniques will be required to understand the interaction of complex and variable feedstocks with highly integrated chemical processes. On a different scale, but no less important, is the current lack of systems-level understanding of large-scale chemical processes which presents a significant barrier to the assessment of the sustainability of new processes. Development of these systems-level approaches to chemical problems requires a new sub-discipline and a shift in the traditional 'reductionist' approach to problem-solving.

Significant progress must be made in the research challenges outlined above in order to overcome the socio-economic barriers that will be associated with such a major shift in emphasis from petrochemical to renewable resources. Economic viability must be demonstrated in order to overcome the technological inertia of what is largely a commodity manufacturing industry. Societal implications must also be clearly assessed and communicated to ensure social acceptability, and to overcome potential legislative barriers. The recent volatility on the oil markets is a sobering warning that the cost of fine and effect chemicals will soar rapidly. This can only get worse at an accelerating pace and will seriously damage the global economy. Inaction is simply not an option, we must act now.

INVOLVEMENT

Interdisciplinary collaboration is essential for significant progress to be made in all of the research challenges outlined above. Close involvement of industry as well as academia is essential. Core expertise in molecules, materials and processes is essential, such that developments will be driven by a combination of chemists and chemical engineers. Important additional expertise will come from biologists, biotechnologists, mathematicians and material scientists. Key contributions will also be made by social scientists, agronomists and economists. As a truly global issue, this challenge will involve considerable input from international practitioners working with UK researchers in all the disciplines listed above.

CONSULTATION

This document was prepared and submitted by the two 'champions' using input from all of the interested participants provided during the Grand Challenge Workshop.

Benchmarking Against the Grand Challenge Criteria

Criteria	Score	Evidence for Score
The Grand Challenge will enable UK scientists and engineers to engage in internationally leading research.	5	• UK strength in chemical process technology, catalysis and excellent industrial track record of exporting process technology (e.g., BP, Johnson Matthey, Davy Process Technology) • Global challenge – of international importance • Cross-disciplinary, international collaboration required
The Grand Challenge has ambitious objectives, which if achieved, would result in a step change in our current knowledge.	5	• New approaches to chemistry explicit in the challenges outlined above including: • New chemical processes • New feedstocks • New products • New tools • New catalysts • Holistic, integrated approach • Systems analysis to chemical problems
The Grand Challenge will encourage researchers to be ambitious; lifting their horizons to the truly novel and innovative.	5	• New mindset required to achieve an integrated, sustainable approach to the chemical industry • Wide-ranging interdisciplinarity necessary for success: reinventing ways of doing research and training (chemical sciences, engineering, biological sciences, etc) • An ambitious goal of replacing a cornerstone industry of the 20th century with a new sustainable alternative for the 21st century
The Grand Challenge has the potential to make a positive societal and/or economic impact.	5	• Sustainability is the most significant global challenge of this century in terms of its societal, economic and environmental impacts • Improve global quality of life • Petrochemical feedstocks are finite – not switching to renewable resources is not an option • Developments made will have a significant economic impact on the only profitable UK manufacturing industry

Criteria	Score	Evidence for Score
The Grand Challenge has a single vision giving the research community common goals to work towards.	5	• The single vision is clear – to replace peterochemicals with renewable alternatives in a sustainable way • Involves the whole of the chemical sciences community – synthetic, materials, process, computational, physical, inorganic, organic, reaction engineering, analytical, bioorganic, bioinorganic, biophysical, etc.
The Grand Challenge is forward looking, focusing on what can be achieved in 20-40 years time.	5	• Little will be achieved within the next 5-10 years in a general sense • General solutions to the petrochemical vs biomass problem will take 20 years to begin to solve • We will still be reliant on ever-dwindling fossil resources in 20-40 years so the problem will remain as relevant as it is now.
There is sufficient capacity in the UK to respond to the challenge and the potential to build on this capacity in the future.	5	• Strength in synthesis and catalysis • Significant chemical industry base • Capacity building at the interface of chemistry and chemical engineering is ongoing but needs to be accelerated to make sufficient progress • Interface between chemical and biological sciences traditionally strong
The Grand Challenge provides opportunities for collaborations between researchers in different disciplines.	5	• This is necessarily a highly interdisciplinary problem. • Core of Chemistry and Chemical Engineering • Major inputs from biological sciences, mathematics, social sciences, economics, etc

Theory and Modelling in Chemistry:
Underpinning Grand Challenges in the Chemical Sciences

Vision

To develop, extend and apply theory and modelling to further the aims of the Chemical Sciences Grand Challenges.

Theory and modelling are essential if the goals of the Chemical Sciences and Engineering Grand Challenges are to be realised. The grand challenges identified at the recent EPSRC Workshop require scientific input from a huge range of disciplines and subdisciplines, but input from computational molecular sciences stood out as being universally important. Developments in this area promise to transform what is possible across all areas of chemistry.

Research challenges

The main research challenges fall into three main areas:

- High-level calculations on small molecules now rival experiments in accuracy: the central challenge is to achieve comparable accuracy for large, complex systems in chemistry, biochemistry and nanotechnology.
- Developments in computer architecture promise new levels of computational power: harnessing this power requires theoretical and algorithmic developments, and the design of flexible and powerful software.
- Deployment of state-of-the-art theory and modelling, integrated with experimental work, to deliver new science in the Grand Challenge areas.

There is still a gulf between experimentalists' expectations and what theory and modelling can deliver. As a specific example, there is no *ab initio* 'computational wet chemistry', in the sense of being able to specify reactants, solvent and temperature, then being able to zoom in and out along length and time scales to focus on specific events, or to see global changes.

Methodological developments

To realise the aims of the Chemistry Grand Challenges, a wide range of new theoretical tools and modelling methods must be developed. Faster computers are part of the solution, but fundamentally new theory and methods are needed. Examples of areas where breakthroughs are needed are:

- Multi-level/multi-scale modelling: the development of rigorously integrated multi-scale modelling and simulation methods, to span length and timescales. Integrating mesoscale and microscopic molecular simulation, reactivity and dynamics. Coupling methods on more than two scales, e.g. coupling quantum electronic structure with molecular mechanics with coarse-grained modelling with a kinetic Monte Carlo model, to describe biochemical networks; or using molecular quantum mechanics to build force-field models to compute fluid properties that govern hydrodynamics of mixing in an industrial reactor.
- Black-box electronic-structure methods applicable to the whole range of chemical problems (i.e. for breaking bonds and for radicals, ions and excited states) and for prediction of molecular properties. Methods must be easily used by non-specialists.
- Achieving the level of accuracy for solids, liquids, interfaces and biomolecules that has been achieved for molecules in the gas phase (both in terms of electronic structure and quantum dynamics).
- More sophisticated, physically-based force fields to provide more accurate treatments of structure, dynamics and interactions of large molecules, solids, surfaces, solutions and biomolecules.
- More effective phase-space-sampling and time-evolution methods, parallelized over the time dimension as well as the spatial dimensions to capitalise on petascale computing facilities.

High-performance computing

Grand challenges require grand computer resources. HPC will become a completely indispensable enabling tool in the planning, execution and analysis of any large experimental project. In order to remain scientifically competitive, new computational methodologies have to be developed and young researchers must to be trained in HPC. Such an effort should be coherent, rather than fragmented over many separate research projects, to benefit from natural synergies across application areas. Modelling methods have to be developed to harness systems of thousands to hundreds of thousands of processor cores, arranged as multiple cores per CPU, multiple CPUs per node, and multiple nodes per machine. Use of heterogenous accelerators will also be needed, if maximal use is to be made of existing and future architectures. This all implies robust, scalable software designed to harness any available computing resource, irrespective of its configuration.

Role in Grand Challenges

As noted above, over a timescale of decades, computational science, and more particularly computational molecular science, will have an increasingly central role in all of the grand-challenge areas. Some specific examples include:

- The Grand Challenge of exploring the chemical roots of biological complexity will fundamentally depend on new ideas on how to model across multiple length scales, and how to describe the emergence of complex structures (in the broadest sense) from basic interactions of smaller units.
- The grand challenge of designing materials with arbitrary properties again requires modelling that can predict macroscopic properties starting from the atomic scale. Currently there is no way to predict *ab initio* properties of complex materials, and certainly no way that can be applied routinely or in a high-throughput manner.
- Harnessing light energy – to bring about chemical change or for generating electricity – is a grand challenge of urgent importance. Progress requires modelling methods that can describe transport of energy and electrons in electronically excited states of complex systems.
- Exploiting molecular understanding in healthcare: this Grand Challenge area fundamentally requires accurate modelling techniques from the molecular level up. This includes modelling drug-protein and protein-protein interactions; transport, absorption and metabolism of drugs; impact of pharmaceuticals at a systems level.

Involvement

Development of theory and modelling in the molecular sciences is performed by academics from a wide range of backgrounds, but certainly chemists, physicists and biochemists would have to be involved.

Development of new theoretical models and in particular development of models that can exhibit emergence of complex behaviour, and phenomena that transcend single lengthscales will benefit from input from mathematicians and complexity scientists.

Utilization of large, heterogeneous computing facilities will require input from computer scientists and computational scientists from a wide range of backgrounds.

Recommendations

It is recommended that Theory and Modelling in Chemical Sciences be recognised as a priority research theme, owing to its unique role as an underpinning technology for all of the Grand Challenges in Chemical Sciences and Engineering. It should be recognised that to fully realize the Grand Challenges, developments in theory and modelling are essential, and this requires investment in terms of people, training and computational facilities. To maximise the long-term scope of the grand challenges, long-term method-development and software-development projects must be supported.

The authors

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