Part of the conference series
Breakthrough science and technologies
Transforming our future

Delivering novel therapies in the 21st century

Conference report
Held on 24 – 25 October 2018

Supported by AstraZeneca

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Introduction

On 24 – 25 October 2018, the Royal Society and the Academy of Medical Sciences hosted a conference on novel medical therapies. The scientific programme for this meeting was developed by Steve Rees (Vice-President Discovery Biology, AstraZeneca), Professor Molly Stevens FREng (Professor of Biomedical Materials and Regenerative Medicine and Research Director for Biomedical Material Science, Imperial College London), and Sir John Skehel FMedSci FRS (Vice-President and Biological Secretary, the Royal Society).

Image: Conference attendees networking.

Presentations and discussions outlined recent scientific advances in therapeutic modalities and delivery, the infrastructure required to develop novel treatments, and the implications of these advances for policy and healthcare delivery. The conference brought together scientists, technologists and experts from across academia, industry, the NHS and public health, to discuss current challenges in human medicine, what future medicines will look like and how we can prepare for them.

This conference, supported by AstraZeneca, forms part of a series organised by the Royal Society entitled *Breakthrough science and technologies: Transforming our future*, and the Academy of Medical Sciences' FORUM programme.

Transforming our future addresses the major scientific and technical challenges of the next decade. Each conference covers key issues including the current state of the UK industry sector, the future direction of research and the wider social and economic implications. The conference series is organised through the Royal Society's Science and Industry programme which demonstrates our commitment to integrate science and industry at the Society, promote science and its value, build relationships and foster translation.

The Academy's FORUM programme brings together industry, academia and the NHS, and the charity, regulatory and wider healthcare sectors. It provides an independent platform for leaders from across the life sciences sector to discuss scientific opportunities, technology trends, translational challenges and strategic choices in healthcare.

This report is not a verbatim record, but a summary of the discussions that took place during the day and the key points raised. Comments and recommendations reflect the views and opinions of the speakers and not necessarily those of the Royal Society or the Academy of Medical Sciences. Full versions of the presentations can be found on our website at **royalsociety.org/tof-novel-therapies**.

Executive summary

The first day of the conference considered emerging and state-of-the-art therapeutic modalities and drug delivery systems and the impact that these are likely to have on a range of diseases with high unmet need. On the second day of the conference, these therapies were put in the context of the accompanying social and technological environment, including aspects such as data and digital technologies, new ways to value medicines, the vast potential of genomics and how the NHS might be prepared to adopt these new therapies.

- New modalities, drug delivery systems and targeted approaches will lead to therapies that treat high unmet need in a safer and more effective way. However, some novel therapies may require new models of manufacture, supply chain and delivery due to unique challenges, such as being manufactured on a small scale, in a bespoke manner or requiring specialised facilities.

- New tools such as genomics, big data and encoded library technologies will help uncover the biological mechanisms of disease, enabling new targets for treatment to be unearthed.

- Digital technologies will improve healthcare by supporting healthcare professionals and empowering patients to take control of their health.

- The regulation and adoption of new therapies will be made faster and fairer through powerful new methods of conducting clinical trials and value assessments.

- Taking advantage of new medicines and technologies should be a priority for the NHS but challenges such as funding, staffing and strategic priorities may have to change to make this a reality.

Image: Sir John Skehel FMedSci FRS, the Royal Society.

"An enormously optimistic conference, particularly within discovery and genetics."

Sir John Skehel FMedSci FRS, the Royal Society

"We have the great good fortune to be participants in a biomedical and health revolution. The pace of discovery and change is breath-taking."

Welcome address by Professor Sir Robert Lechler PMedSci, Academy of Medical Sciences

Turning science into medicine: the power of precision medicine

In the opening keynote talk, Dr Menelas Pangalos FMedSci of AstraZeneca discussed work AstraZeneca is doing to make every promising drug target 'druggable'.

Finding the right target – a cellular or biological mechanism that influences disease and can be modulated with a drug – is a key challenge in drug discovery. Currently, around 80% of drug candidates taken into clinical trials fail. Other challenges in developing effective therapies include:

- Ensuring they reach the right cells or tissues.

- Ensuring that they are safe.

- Identifying the patient populations most likely to respond to treatment.

- Building the right environment for widespread access and adoption.

A better understanding of disease biology is needed to validate new targets. Most medicines today are based on small molecule, protein or monoclonal antibody mechanisms. However, novel drug modalities have the potential to open up new therapeutic options, bringing new medicines to patients in areas of high unmet need. Progress has been made across multiple different drug modalities including modified messenger RNA (mRNA) therapies, antisense oligonucleotides (ASOs), oligonucleotide conjugates, bicyclic peptides, proteolysis-targeting chimeras (PROTACs), Anticalin® protein and CRISPR genome editing. AstraZeneca is looking to develop future therapies utilising artificial intelligence, digital healthcare, genome editing, and targeted drug delivery.

Image: Dr Menelas Pangalos FMedSci, AstraZeneca.

"The progress we are making in oncology therapy is astonishing, and by harnessing the immune system we are starting to turn a lethal disease into a chronic illness."

Dr Menelas Pangalos FMedSci, AstraZeneca

Antisense oligonucleotides in oncology

PD-L1 checkpoint inhibitor therapy for cancer treatment is highly effective for patients who have the relevant genetic mutations. A key challenge in immuno-oncology is to find the best combination of molecules that effectively harnesses the immune system to attack the tumour. Transcription factor STAT3 enhances the activity of PD-L1 checkpoint inhibitor therapies, but is difficult to target with traditional small molecules. A dual therapy of a novel ASO that targets STAT3 combined with durvalumab (a checkpoint inhibitor) doubles the T cell immune response of patients compared to using durvalumab alone by increasing anti-tumour activity and the efficacy of PD-L1 therapies.

Novel treatments for chronic heart failure

Modified mRNA therapies can help tissue to regenerate after injury. mRNA expressing the VEGF protein is injected directly into damaged cardiac muscle tissue where it is taken up by cells to make new proteins. A single administration improves cardiac function, repairs heart damage, and regenerates blood vessels including arteries two months after myocardial infarction in animal models. Meanwhile, transplanting embryonic-stem cell derived human ventricular progenitor cells has been shown to preserve cardiac function in mouse studies following myocardial infarction. This could be combined with CRISPR genome editing to engineer progenitor cells with wider applications.

Anticalin protein for respiratory disease

Anticalin® proteins are smaller than antibodies, and so can be delivered into the body by inhalation. AstraZeneca is using Pieris' Anticalin® protein platform to create an inhaled version of dupilumab that targets biological pathways involved in asthma. The inhaled drug offers broader patient use than injectables.

Future opportunities for small molecule therapeutics

Dr Tony Wood, GlaxoSmithKline, introduced emerging technologies that use small molecules to influence phenotype by mediating protein degradation.

Historically, most small molecule drug discovery has targeted protein function by blocking activity. However, technologies are emerging that could fundamentally change this, including DNA encoded library technology (ELT), proteolysis targeting chimeras (PROTACs), and proteomic-based screening and target profiling.

ELT greatly increases the number of compounds that can be evaluated against a target and enables rapid hit identification and target validation in the early stages of drug discovery. By labelling each molecule with a unique DNA tag, the best binding molecules can be identified amongst many hundred million compounds. ELT screens augment our understanding of the binding potential of small molecules by mapping the chemical space at the binding site. The platform:

- Gives an unbiased, rapid automated assessment of the druggability of protein targets.

- Identifies and prioritises targets based on their druggability with low reagent costs.

- Provides tools and hits for targets of interest to be used for target validation.

A new mode of action for small molecules targets cellular proteins for degradation. PROTACs enable the selective removal of a specific protein by binding to it and recruiting other proteins to degrade it. They work catalytically, causing the destruction of the target protein, have a long-lasting effect and can degrade "difficult to drug" targets as PROTACS only need to bind to the protein, not inhibit it.

ELTs allow unbiased identification of compounds that bind to the target protein, which, when combined with the PROTAC, enable a targeted protein to be removed from the cell. This is functionally the same as a gene knockout and so can be used to mimic phenotypes for *in vivo* and *in vitro* studies.

Image: Dr Tony Wood, GlaxoSmithKline.

New chemical biology tools including proteomics and other 'omics technologies allow us to understand the impact of protein removal on the cell, and understand how hits from cell-based screens work. This improved understanding increases the likelihood of successful translation of a therapy into clinical trials.

"We stand at the point of a revolution in technologies. We have never been better placed for manipulation of cell phenotype at genotypic level."

Dr Tony Wood, GlaxoSmithKline

The landscape for new biologics formats

Dr Jane Osbourn of MedImmune discussed engineering antibodies to treat diabetes, optimising antibodies using machine learning, and functional screening of antibodies to identify new biologics targets.

Image: Dr Jane Osbourn, MedImmune.

When first developed, biologics almost failed due to inadequate understanding of human biology, lack of patient stratification, and the challenge of manufacturing a stable antibody. Today, seven of the ten best-selling medicines are biologics and by 2022, biologics will contribute 52% of the top 100 product sales.

Many biologics are now engineered with properties beyond standard antibodies such as increased potency, longer half-lives and improved stability. Diverse novel modalities for biologics are coming to market, including antibody-drug conjugates, protein scaffolds and peptide fusions that combine functionality. These enable specificity to the drug target and bring benefits to particular disease settings.

"This isn't about academic science and research, this is about making a difference to patients. Biologics will provide a real opportunity for patient benefit throughout the 21st Century."

Dr Jane Osbourn, MedImmune

CASE STUDY 1

Antibody-peptide bispecific fusion

A new antibody-peptide bispecific fusion combines different functionalities in one molecule. The monoclonal antibody α-PCSK9 lowers low density lipoprotein (so-called 'bad' cholesterol) in patients with cardiovascular disease. When bound to the peptide GLP-1R, which controls glucose levels, this acts as an effective combined therapy to potentially deliver cardiovascular benefits to diabetic patients.

CASE STUDY 2

Cutting-edge technology for structural modelling and affinity optimisation

The P2X4 ligand-gated ion channel has a role in pain, when binding to ATP the channel opens and allows calcium ions to flow through. Use of an antibody library identified a full inhibitor of ion channel opening, mAb151, and structural modelling of the ion channel bound to the antibody identified the potential epitope. Combining machine learning algorithms, *in silico* modelling, and phage display allowed mAb151 to be affinity matured *in silico* to identify a variant that was 1,000-fold more potent.

CASE STUDY 3

Identifying new targets for biologics

Antibodies for novel targets can be selected by screening antibody libraries to confirm function and target. This technique was used to find an antibody that bound to breast cancer cells and was rapidly internalised, while reducing the production of immunosupressive adenosine. Using this in combination with existing checkpoint inhibitors recruits more T cells, which may increase efficacy of the two treatment types.

Antigen-targeted TCRs in cancer immunotherapy

Dr Bent Jakobsen FMedSci of Immunocore discussed two novel platforms that overcome the limitations of the innate T cell response to deliver high-affinity engineered T cell receptors (TCRs) to a validated target antigen.

The immune system can exert long-term control over cancer and cancer immunotherapies can harness the immune system to eradicate cancer cells. The T cell is critical to this process as it directs antigen-specific immune responses. Checkpoint inhibitor immunotherapy initiates a polyclonal T cell response, however, it is toxic and lacks tumour specificity. Furthermore, tumours generally require a high mutational burden, evolving and mutating rapidly, to be sensitive to checkpoint inhibitors. These are known as 'hot' tumours and are targeted by the immune system.

As such, emphasis has switched to targeted therapies localised to the tumour. Targets can be cell surface membrane proteins (approximately 10% of all proteins), targeted mainly with antibodies, or cell surface peptide-HLA complexes (approximately 90% of all proteins), targeted mainly with TCRs or T cells. As most cancer cells produce these proteins, TCR and T cell therapies can access a wide range of cancer-specific targets that limit their side effects.

TCRs are naturally very low affinity, but the large antigen contact surface makes them a good substrate to engineer to have high affinity and specificity to cancer cells, requiring only slight structural changes. ImmTAC (Immune mobilising monoclonal TCR against cancer) molecules are TCR-based bispecific biologics comprising an effector function (an anti-CD3 antibody fragment) and a targeting system (a soluble TCR with the affinity enhanced more than a million-fold). This decorates the cancer cell with ImmTAC molecules and the anti-CD3 can then recruit any T cell, regardless of normal T cell specificity, killing the target cancer cell.

Image: Dr Bent Jakobsen FMedSci, Immunocore.

A soluble ImmTAC molecule, IMCgp100, has entered monotherapy trials for the treatment of patients with metastatic uveal melanoma. This type of melanoma has the lowest mutational burden of any tumour, making it resistant to checkpoint inhibitors. However, TCR targeted immunotherapy using IMCgp100 can restore its sensitivity to checkpoint inhibitors, making 'cold' low mutational burden tumours (ignored by the immune system) 'hot'. This opens opportunities for combination therapy with targeted immunotherapy including radiation, vaccines, and chemotherapy.

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"Immune therapy offers a phenomenal prospect for real breakthrough in cancer treatment."

Dr Bent Jakobsen FMedSci, Immunocore

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Bicyclic peptides as novel therapeutics

Dr Kevin Lee, Bicycle Therapeutics, discussed bicyclic peptides or Bicycles®: a new therapeutic modality that combines the attributes of antibodies, small molecules and peptides in one molecule.

Bicycles® are synthetic, small peptides (9-15 amino acids). Unlike other peptides, a molecular scaffold at the centre creates a two loop bicyclic structure. This structural constraint means that peptides can be designed with very high affinity and selectivity for target proteins. Their large molecular footprint means they are good at interfering with protein-protein interactions, and small size enables the molecules to instantaneously distribute into extravascular space.

Bicycles® can be used as standalone therapeutics or coupled to deliver therapeutic payloads, including cytotoxins, immune modulators, radionuclides or nucleic acids in a tissue selective manner. They are simple to synthesise and can be altered by using different amino acid sequences, peptide sizes, and scaffolds that dictate the 3D shape.

Image: Dr Kevin Lee, Bicycle Therapeutics.

FIGURE 1

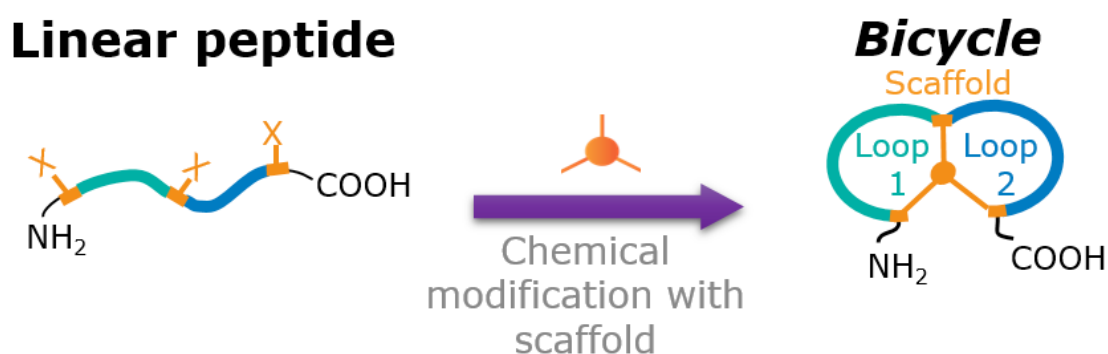Creation of a two loop bicyclic structure.

Image courtesy of Bicycle Therapeutics.

Bicycles® as novel therapeutics for oncology

Currently the main application focus is in oncology, where Bicycles® bind to a specific molecular target to deliver a drug. Bicycle Toxin Conjugates® (BTCs) are used to selectively deliver cytotoxins to tumours, killing them with a high degree of precision and minimal effects on healthy cells. BTCs utilise Bicycles' inherent properties, namely:

- High target affinity and specificity.

- Fast penetration into the tumour due to their small size, over five times smaller than antibodies.

- Low systemic exposure compared to antibodies, due to short half-life outside the tumour.

- Rapid elimination from the body by the kidneys, due to their hydrophilic nature.

The 'fast in-fast out' phenomenon allows use of novel systems for linking to toxins, where the toxin is released indiscriminately inside the tumour regardless of whether it is bound, but is quickly removed from the rest of the body. Bicycles® also have significant potential for immuno-oncology by activating T cells, as well as therapeutic areas outside oncology.

"Bicycles® have potential to be disruptive in oncology and immuno-oncology."

Dr Kevin Lee, Bicycle Therapeutics

Bioelectronics: is the next novel therapy class an electronic implant?

Dr Kristoffer Famm, Galvani Bioelectronics, described the potential for new bioelectronic devices to treat chronic disease by modulating signals in peripheral nerves.
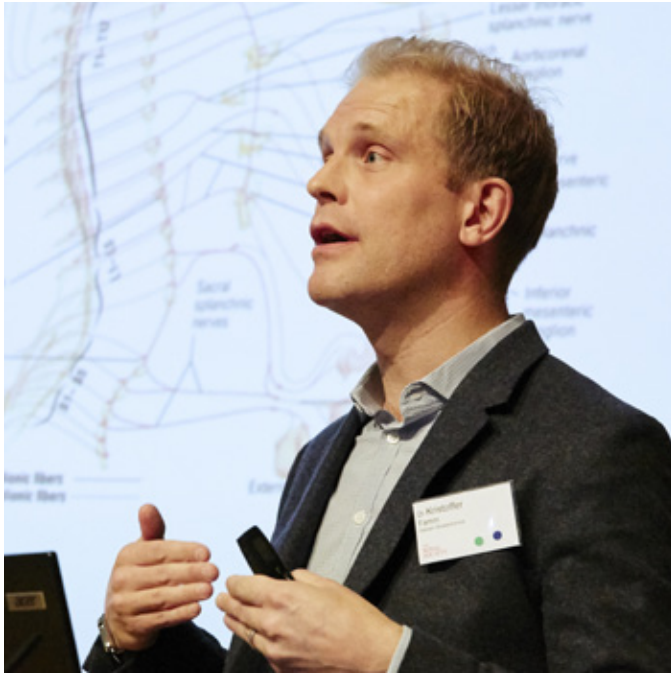

Image: Dr Kristoffer Famm, Galvani Bioelectronics.

Electrical and molecular signalling are the main axes of control in biology. Electrical impulses to and from organs via peripheral nerves regulate diverse physiological processes, from smooth muscle tone to molecular secretion. Bioelectronic medicine is a new therapeutic modality that modulates these signals to treat chronic diseases ranging from immune-mediated to metabolic and respiratory. Miniaturised, implantable devices are used to deliver precise impulses to the nerves close to the organs involved in chronic disease. Advantages include the ability to:

- Control a single organ or organ function via the relevant peripheral nerve.

- Personalise treatment by modifying the electrical signals introduced.

- Use the well-evidenced therapeutic approach of neuromodulation in new therapeutic areas (eg spinal cord stimulation has been used to treat pain, and deep brain stimulation for tremor for decades).

- Treat without risk of side effects from systemic drug exposure.

> "Smart device-based therapies may significantly change medical practice in coming decades, with opportunities for collaborative research."
>
> Dr Kristoffer Famm, Galvani Bioelectronics

Therapeutic potential

Bioelectronic medicine has broad applications, from rapidly reversing bronchoconstriction during an asthma episode, to restoring insulin sensitivity in individuals with Type 2 diabetes and increasing healthy follicles in polycystic ovary syndrome.

Progressing from animal models to humans for device development is challenging in terms of comparative anatomy and surgical feasibility. There is a need for early anatomical mapping to identify a suitable large animal model, working backwards from surgery in human cadavers. Another challenge is that technology must often be tested *in vivo* through multiple chronic iterations during the product development.

Future clinical development steps

1. Move into large animal models and identify the right structure for keyhole implantation of devices.

2. Develop functional, safe neural interfaces to connect electronic hardware to soft biology. This is a longstanding bioengineering challenge that, once solved, will allow application of technology to different nerves impacting a range of diseases.

3. Develop the full device implant system including hardware, a charger, and patient and physician apps.

The pathway to licencing medical devices is shorter than that required for molecular medicines, traditionally requiring only a single pivotal clinical study. The first generation of implants are currently being developed in the clinic, and the next generation medicines researched by Dr Famm's team are expected to be in wider use within ten years.

Introduction to delivery

Professor Molly Stevens FREng, Imperial College London, discussed current research by her group in the field of regenerative medicine.

Novel drug delivery mechanisms are needed to maximise the success of new therapeutic modalities in regenerative medicine. The Stevens Group is developing biomaterial scaffolds to grow cells for use in regenerative medicine, including fibre-based scaffolds, hydrogels and porous structures.

Nanoparticles for the delivery of new therapeutic modalities are also being developed. Nanoparticles are used for delivery of genes, RNA and proteins and are readily translatable into therapies. Helping blood vessels regrow is important in regenerative medicine, and growth factor delivery via nano- and micro-particles has been achieved. Her interdisciplinary team is optimising the delivery profiles and increasing the ability to target the nanoparticle to specific tissues and cells.

Extracellular vesicles (exosomes) are generated by most cells and are potentially harder to translate than some synthetic nanoparticles, but have been successfully engineered by Stevens' group. Both natural and synthetic vesicles can be combined with 3D scaffolds to enable different modes of delivery for regenerative medicines. Exosomes have gained interest over the past years, with advantages including:

- Small size distribution.

- Natural composition.

- Stability in physiological fluids.

- Reduced immunogenicity.

- Ability to modify the vesicles to impart extra functions.

- Ability to modify surface chemistry to introduce new functionality, like changing targeting or distribution, or adding biosensing capabilities.

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"Everything we do in this field is ultimately about helping patients, and there is a massive unmet need across almost every disease."

Professor Molly Stevens FREng, Imperial College London

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Image: Professor Molly Stevens FREng, Imperial College London.

Measuring cell chemistry

Physical triggers to get nanotechnology to interface with cells are being investigated for drug delivery. One mechanism uses small nanoneedles (upwards of 40 per cell) to probe inside the cell and deliver biomolecules *in vivo*, for example to muscles to regenerate blood vessels.

Stevens' group has also pioneered a variety of methods to elucidate the cell-material interface and study what happens when drug delivery vehicles enter cells. Raman microscopy and quantitative volumetric Raman imaging, a novel technique, are used to examine cell chemistry changes and response to small molecules without labelling the cells.

Single Particle Automated Raman Trapping Analysis (SPARTA) is a new technique developed in the Stevens group that is likely to become an enabling technology for the field. SPARTA can be used to analyse mixed particle populations, discriminate compositions with no exogenous labels, and can simultaneously tell a single particle's size and measure chemical processes in real time on particle surfaces at the single particle level.

Early days of gene therapy: are we there yet?

Professor Richard Jude Samulski, University of North Carolina School of Medicine introduced the use of adeno-associated virus (AAV) to optimise gene therapy delivery to treat rare genetic disorders.

Image: Professor Richard Jude Samulski, University of North Carolina School of Medicine.

Rare diseases affect 25 million Europeans (1 in 10): many are genetic disorders and many affect children. There are strong incentives to develop treatments, including substantial economic benefits. Gene therapy using recombinant viral and non-viral vectors is emerging as a new medical modality to treat genetic disorders including heart disease, musculoskeletal diseases, haemophilia, and rheumatoid arthritis.

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"Most kids have a hero, be that Rocky running up the stairs or a favourite baseball player. The children that we treated were able to run like their role model."

Professor Richard Jude Samulski, University of North Carolina School of Medicine

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Adeno-associated Virus (AAV) is a viral vector that has been developed for efficient gene delivery, as the only known human virus that does not cause disease. Therapeutic payloads can be delivered to target cells by swapping viral genes for human genes within the viral capsid.

As a new area of drug development, new issues arise after entering the clinic, including:

- Unexpected immune responses to the capsid.

- Poor transduction efficiency.

- High manufacturing costs.

Applications

Successful examples of gene therapy are beginning to be demonstrated in the clinic for genetic disorders such as haemophilia, blindness, and muscular dystrophy, with further promising therapies in early development. A recent clinical trial using AAV2-AADC to deliver gene therapy to the brain for Amino Acid Decarboxylase (AADC) disease demonstrated transformative results and the treatment is now on its way to be fast-tracked for regulatory approval. Meanwhile, engineered vectors are being devised *in vitro* that locate and target the focal region of epilepsy in the brain, crossing the blood-brain barrier to deliver the therapeutic payload.

The different crystal structures of the AAV serotypes can be exploited to engineer new capsids by a rational design approach that can target particular tissues or organs. Vector targeting has been achieved by Professor Samulski's research group by engineering capsids with properties of both AAV8 (which targets whole body transduction) and AAV2 (which targets the liver) to devise AAV2i8 (which targets heart and muscle). Targeted vector delivery has been successfully demonstrated in treating animals and is moving towards the clinic to treat muscular dystrophy. A single administration of the therapy persists for life, and early data supports recovery of patient mobility.

Nucleic acid delivery systems for RNA therapy and gene editing

Professor Daniel Anderson, MIT, discussed development of lipid and polymer materials to encapsulate and deliver RNA for gene therapy to treat genetic disease, viral infection and cancer.

> "I think that nanoparticles will be key to deliver genome editing tools, making drugs that repair your DNA while you are still using it."
>
> Professor Daniel Anderson, MIT

RNA has broad therapeutic potential in the treatment of these areas. However, it is large, hydrophilic, and can induce an immune response, making it difficult to develop into a therapy. There are three key components to developing small RNA drugs:

- Selection of the disease-causing sequence for target specificity and potency.

- Chemical modification to facilitate delivery, including increasing stabilisation and cell-specific uptake.

- Encapsulation to allow it to enter cells.

Combinatorial chemistry is used to develop combined RNA-lipid nanoparticles that are evaluated *in vivo* for gene knockdown in specific tissues. Small interfering RNA (siRNA) in lipid nanoparticles can be targeted to all liver cells, the endothelium of many organs, leukocyte populations, and tumours (in mouse models). It is particularly effective at silencing genes in the lung endothelium in nonhuman primates. Additionally, multiple siRNAs targeting different genes can be loaded onto one nanoparticle, allowing the silencing of multiple genes. This may have applications for the treatment of many complex genetic diseases.

Image: Professor Daniel Anderson, MIT.

CRISPR-Cas9 mediated genome editing

Functional delivery of nanoparticles inside cells is complex, and once within the cytoplasm of the cell, complexes must enter the nucleus to affect genes. In CRISPR-Cas9 mediated genome editing, guide RNA is used for targeted gene silencing and can be customised to target the enzyme to cut in any desired place in the DNA sequence.

CRISPR genome editing can be used to treat FAH-Trysinemia, targeting the single base pair mutation to restore function using 'scissors' that swiftly leave the body. The repaired cells can be given a growth advantage to repopulate the liver to restore function: while AAV alone repairs only 0.4% of cells, using AAV and CRISPR-Cas9 together repairs 6% of the liver.

Fully synthetic systems are now being developed that do not require viruses for *in vivo* genome editing, by chemically modifying guide mRNA. This is being applied to create a single-administration treatment to lower cholesterol by deactivating the gene PCSK9.

Antisense oligonucleotide therapy for Huntington's disease: results from the first HTT lowering clinical trial

Huntington's disease is a neurodegenerative disease, caused by the mutant huntingtin protein (mHTT), for which there is currently no cure. Professor Sarah J Tabrizi FMedSci, UCL Institute of Neurology, described results from the first HTT lowering clinical trial, which could offer hope for using an antisense oligonucleotide (ASO) to treat the disease.

Suppressing HTT production in rodent models delays disease progression and reverses disease phenotype. A drug discovery effort to design a well-tolerated ASO therapy with high specificity to human HTT mRNA resulted in a molecule that is diffusible, dose-dependent, stable, reversible, and suppresses HTT production.

In preclinical development, ASOs were found to penetrate the central nervous system (CNS) tissue and reach the target mRNA. ASOs were injected directly into the spine (intrathecal injection) because the large molecules do not cross the blood-brain barrier. In preclinical trials, drug distribution across the brain was successful in mice and intrathecally injected ASOs successfully reached the brain in nonhuman primates, which have similar CNS structures to humans. After four monthly injections into the primates, a reduction of the HTT protein and mRNA of at least 50% was observed throughout the brain with ASO penetration into deep structures such as the caudate tissue at high concentrations.

In the first-in-human clinical trial, patients received four monthly intrathecal injections of the ASO IONIS-HTTRx (now called RG6042) or a placebo. The ASO treatment produced significant dose-dependent reductions in the target cerebrospinal fluid mHTT protein of up to 45 – 65% at the maximum 120mg dose with a predicted steady state maximum reduction after six months of dosing. Modelling indicates that a 60% reduction in mHTT in the cerebrospinal fluid represents a 70 – 85% reduction in brain mHTT in the cerebral cortex, and a 35 – 50% reduction in the caudate tissue. This mHTT reduction in cerebrospinal fluid is greater than that required to reverse symptoms in animal models, making RG6042 a promising therapeutic for treatment of Huntington's disease.

This is the first demonstration of ASO-mediated protein suppression in the CNS of patients with neurodegenerative

Image: Professor Sarah J Tabrizi FMedSci, UCL Institute of Neurology.

"Huntington's disease is genetic and I look after families. Eventually I want to do a clinical trial in 18 year olds, decades away from the disease onset, and one day prevent the disease from ever occurring."

Professor Sarah J Tabrizi FMedSci, UCL Institute of Neurology

disease. Intrathecal treatment has introduced a new avenue for drug delivery to the brain. ASO technology has the potential to benefit patients with other neurodegenerative diseases including amyotrophic lateral sclerosis, Alzheimer's disease, spinal muscular atrophy, and Parkinson's disease.

Shaken and stirred: ultrasound-enhanced drug delivery

Professor Constantin Coussios, University of Oxford and OxSonics Ltd, discussed use of ultrasound as a means of increasing the dose, distribution and penetration of drugs into tumours.

Image: Professor Constantin Coussios, University of Oxford.

Across all cancer drug classes, it is challenging to get a significant percentage of the administered drug dose into the tumour due to the elevated interstitial pressure within the tumour, coupled with an irregular vasculature that impedes drug distribution. Administering low-intensity ultrasound from a portable device induces thermal and mechanical effects that enable therapeutics to cross these biological barriers, without necessarily requiring drug modification or encapsulation.

Thermal effect

Focused ultrasound can be used to non-invasively deliver highly localised mild hyperthermia to liver tumours. By using heat sensitive liposomes, drug release can be triggered specifically to the area where ultrasound is applied. Based on the results of the Phase I TarDox clinical study[1], liver tumours receiving combined ultrasound and liposome treatment showed a differential response to tumours treated with liposomes alone. This includes a 3- to 10-fold enhancement of the intratumoural dose for the same systemic dose, improved distribution, and significantly improved therapeutic efficacy. Of particular note was the radiological response of tumour types, such as colorectal, which are not known to respond to doxorubicin treatment when delivered by conventional means.

1. Lyon P.C., Gray M.D., Mannaris C., Folkes L.K., Stratford M., Campo L., Chung D.Y.F., Scott S., Anderson M., Goldin R., Carlisle R., Wu F., M.R. Middleton, F.V. Gleeson, C.C. Coussios (2018) Safety and feasibility of ultrasound-triggered targeted drug delivery of doxorubicin from thermosensitive liposomes in liver tumours (TARDOX): a single-centre, open-label, phase 1 trial. The Lancet Oncology, 19:8, 1027-1039

Mechanical effect

Acoustic cavitation is a mechanical effect of ultrasound that can be exploited to induce convective transport of therapeutics. In this process, ultrasound causes alternating suction and compression in the target area, leading pre-existing bubbles to expand and collapse in regions of low and high pressure on microsecond timescales. Sustaining this generates a pumping effect, turning diffusion-driven delivery into convection-enhanced delivery.

In oncology, co-administering cavitation-inducing sonosensitive particles with biologics increases the penetration and total dose delivered to tumours. For example, using ultrasound and sonosensitive particles to deliver oncolytic vaccinia viruses (Transgene) to tumours saw a 50-fold enhancement of the intratumoural dose, and a 10,000-fold increase in viral activity within 5 days. This enhanced delivery was associated with increased therapeutic efficacy and more consistent therapeutic response.

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"The challenge of delivering drugs to tumours is like pushing water uphill, through a sieve, to more than twice the distance that you would normally carry it."

Professor Constantin Coussios, University of Oxford

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Other applications

- Real-time imaging of the tumour and nanoparticle activation allows assessment of whether particles have reached the required locations.

- Ultrasound use is not drug-specific, and so its use to enhance delivery of cardiovascular drugs and mRNA is being investigated.

- Research is currently ongoing, primarily in France and Canada, exploiting ultrasound and cavitation as a means to reversibly open and deliver therapeutics across the blood-brain barrier.

Generation and testing of clinical-grade engineered exosomes to facilitate therapeutic targeting of oncogenic KRAS in pancreatic cancer

Dr Raghu Kalluri, University of Texas MD Anderson Cancer Center, discussed use of extracellular vesicles, exosomes, to deliver genetic material to cancer cells for treatment.
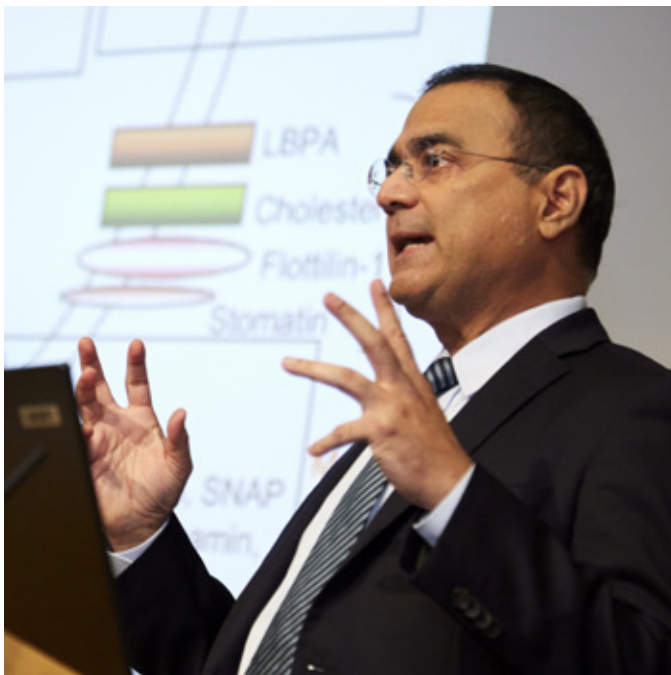

Image: Dr Raghu Kalluri, University of Texas MD Anderson Cancer Center.

Exosomes are 40 – 180 nm nanoparticles naturally generated by cells in the body. They are constantly released by (and provide insight into) all cells and contain many cell constituents, including DNA. However, their physiological role is unknown and their mode of generation is not fully understood. A key feature is that exosomes are very efficient at entering different cells, including organs that liposomes cannot usually enter – the pancreas, kidney, and crossing the blood-brain barrier – making them a promising vehicle for drug delivery.

Application to pancreatic cancer

Exosomes are produced by tumours and often contain tumour DNA. In the coming years, multicomponent analysis of cancer-specific exosomes will yield a multicomponent cancer biomarker for early detection, monitoring and therapy.

Exosomes can be used to transfer therapeutic agents to cancer cells. Mutant KRAS protein is a well-established driver of pancreatic cancer but, despite many decades of effort, has proven to be intractable to small molecule drug discovery, making it a clear opportunity for delivery of new drug modalities by exosomes. Inhibitor exosomes (iExosomes) can be engineered to carry siRNA specific to a common mutation in pancreatic cancer, oncogenic KRAS[G12D], to silence the gene resulting in a decrease in tumour size in mouse models of pancreatic cancer.

iExosomes were found to deliver siRNA to cells more effectively than the control using iLiposomes due to:

- Increased circulation half-life after systemic delivery.

- Rapid phagocytosis by circulating monocytes, by engineering CD47 deficient iExosomes.

- Efficient intracellular entry facilitated by micropinocytosis.

- Higher frequency localisation with cancer cells than normal pancreatic cells.

- No localisation with lysosomes, so iExosomes do not degrade after entering a cell.

In preclinical studies, treatment of mouse models using GMP-grade iExosomes successfully suppressed oncogenic $KRAS^{G12D}$ in pancreatic cancer tumours to significantly increase survival. The exosomes produced complete control of the pancreatic tumour, in the first example of a single agent working in a pancreatic cancer mouse model.

Recent studies show promise for using CRISPR genome editing to eliminate oncogenic $KRAS^{G12D}$ for the cancer genome. Future applications of engineered exosomes include stimulation of tumour immunity and potential to treat Alzheimer's disease and other brain conditions by crossing the blood-brain barrier to deliver siRNA and potentially other large new drug modalities.

"iExosomes can be used for the delivery of many new drug modalities, and I believe they provide a plug-and-play platform for us to explore."

Dr Raghu Kalluri, University of Texas MD Anderson Cancer Center

Cancer evolution and immune escape: TRACERx

Professor Charles Swanton FMedSci FRS, the Francis Crick Institute, discussed the role of nonlinear tumour evolution and immune-editing in solid tumour progression, presenting data from the longitudinal lung cancer evolution study, TRACERx: Tracking Cancer Evolution through Therapy (Rx).

Historically, cancers have been thought to evolve linearly by clonal mutations that produce homogeneous tumours. However, patients rapidly become resistant to therapy. Solid tumour exome sequencing revealed that most mutations are heterogeneous, indicating that nonlinear evolution by subclonal mutations is the norm.

TRACERx aims to understand this nonlinear evolution, sampling the tumour to understand which mechanisms drive metastasis and which tumour subclones have metastatic potential. This may enable prediction of tumour evolution, to improve patient treatment.

Tumour diversification and immune-editing in lung cancer
Diversification of tumours occurs through mutation and chromosomal instability (CIN). There are three main mutational signals in lung cancer tumour DNA, associated with spontaneous deamination, tobacco carcinogen, and APOBEC (a cytidine deaminase). APOBEC subclonal mutations dominate tumour evolution.

Loss of HLA on the surface of cancer cells provides evidence of immune-editing in 40% of early stage lung cancers. HLA loss is mostly a nonlinear/branched evolutionary event. This increases the number of coding mutations, allowing high mutational burden cancers like lung cancer to evade immune system detection. Meanwhile, rapid evolution of tumours means that one drug is unlikely to provide a transformational cure and so they often need to be used in combination.

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"There is a lot of hope for harnessing the immune system to target heterogeneous tumours."

Professor Charles Swanton FRS FMedSci,
the Francis Crick Institute

....

Image: Professor Charles Swanton FMedSci, the Francis Crick Institute.

CIN is where the chemical constituents of the chromosome rearrange, significantly changing the cancer phenotype. High CIN in tumours drives evolution and immune evasion, and so is associated with poor treatment outcome.

Therapeutic progress
Currently, epidermal growth factor inhibitors are used to target clonal mutation events and slow the progress of disease. However, most patients develop resistance within three years. Targeting subclonal events would help avoid resistance, but this presents a challenge as each patient would need a unique therapy.

Homogenous tumours with lots of clonal neo-antigens benefit most from immunotherapy, while heterogeneous tumours with subclonal neo-antigens will progress during therapy. There is hope that recently discovered cytotoxic T cells which recognise clonal neo-antigens could be harnessed to treat prevalent, heterogeneous tumours.

Panel discussion: manufacturing challenges

This discussion considered the ways in which manufacturing is changing to address the challenges posed by new therapeutic modalities such as customisation, batch size and supply chain. Chaired by Dr Nicholas Medcalf, UKRI, the panel comprised Keith Thompson, Cell and Gene Therapy Catapult; Dr Annette Bak, AstraZeneca; Dr Derek Adams, Bluebird Bio; and Professor Richard Jude Samulski, University of North Carolina School of Medicine.

Image: The panel members, from left to right: Keith Thompson, Dr Annette Bak, Dr Derek Adams and Professor Richard Jude Samulski.

Manufacture of personalised medicine and novel therapies

- Manufacturing must evolve to allow for the development of innovative technologies. Emerging advanced therapeutics mean that industry needs to consider new challenges in areas such as cost, reproducibility and reliability which have been optimised for the discovery and commercialisation of long-standing therapies such as small molecules and antibodies.

- 'Ultra-personalised' medicines that require one unique batch per patient pose new challenges for manufacture and control, especially scaling of therapies.

- Challenges in drug stability and the supply chain can make the supply of biologic medicines (RNA and protein) and personalised medicines complex and costly. The fast turnaround of days or weeks required by some therapeutics due to their limited stability will

> "Advanced therapeutics are forcing industry to consider manufacture in a way they haven't in an awfully long time."
>
> Keith Thompson, Cell and Gene Therapy Catapult

limit the checks that can be performed for quality, potency, and effect in this time and may require just-in-time manufacture and supply.

- There is a need to improve non-invasive delivery technologies and digitalisation of manufacturing. Learnings can be taken from commercialisation of current advanced products to inform future development programmes.

- Manufacturing 'to order' for these advanced, personalised medicines may become more of the norm over manufacturing to stock.

- Manufacturing is currently expensive, but automation (including use of decentralised 3D printers) will enable a reduction of cost and complexity in production of personalised medicines, and increased consistency in the manufacturing process. This will make room for greater profit margins and lower drug prices.

- Platform technologies may be important to bring back to research but must have generic applications to justify their development.

Learning from other industries

- Use of multiple small facilities worldwide rather than centralised manufacturing, as in the food industry, will aid product manufacture and distribution speed.

- The medical sector should use existing manufacturing solutions from other industries, including custom manufacture, real-time analysis and rapid production of different product types.

- High costs of scaling up can halt the manufacture process, but scaling solutions can be found in the chemical industry.

"Start-ups, biotechnology companies, and even pharmaceutical companies in this space are infants when it comes to real manufacturing and can learn from other sectors, such as looking to the chemical industry to solve scale-up challenges."

Dr Derek Adams, Bluebird Bio

"Manufacturing to order is likely to become the norm for novel therapies, rather than manufacturing to stock."

Dr Nicholas Medcalf, UKRI

"A challenge of these therapies is the short turnaround time of weeks, or sometimes days. This will really limit the tests for quality control, potency, and effect that can be done."

Dr Annette Bak, AstraZeneca

"Autologous therapies are the ultimate challenge, and their fantastic clinical results represent a paradigm shift."

Keith Thompson, Cell and Gene Therapy Catapult

Regulation

- We are applying regulations that have evolved from those designed to assure the quality of medicines based on small-molecule active ingredients. Some categories of novel therapies are unlikely to fit this paradigm, notably bioprinted cell-scaffold constructs that have customised features. A process of open dialogue between researchers, regulators, and manufacturers will aid successful product development.

- There is not yet a clear definition of personalised medicine from regulatory bodies (ie whether it depends on starting material, manufacturing process, patient population, product or effect) providing an opportunity for drug developers to help define and influence this.

- A more adaptive and flexible approach for regulation of novel therapies, in alignment with the spirit and purpose of the Competent Authorities, would help the UK to adopt a leading position post-Brexit.

- Regulatory expectations of batch reproducibility are not proportionate or achievable in terms of manufacture of rare disease treatments, where only one batch would be made at a time. It was suggested that pilot manufacturing runs are used as part of the reproducibility analysis.

- Regulators will continue to ensure that the product is efficacious and safe. This will require controls of comparability of process performance in spite of changes in manufacturing site, some aspects of the manufacturing process, and natural variation in starting material.

- Intellectual property (IP) is important to attract investment into risky areas for development of novel therapies. Biosimilars in particular are faster to develop than disease treatments, and can therefore be competitive in securing new IP.

"Regulators will be challenged by advanced personalised medicine, and will need to be reassured that the product is made consistently and safely and will carry out the intended function."

Keith Thompson, Cell and Gene Therapy Catapult

"We need to change the paradigm that if a process doesn't integrate with existing regulations it cannot go forward: both researchers and regulators need to be educated."

Professor Richard Jude Samulski, University of North Carolina School of Medicine

The potential for genomics to transform drug discovery

Professor Peter Donnelly FMedSci FRS, Genomics plc and the University of Oxford, discussed using machine learning on genetic information to support more successful drug target identification.

Image: Professor Peter Donnelly FMedSci FRS, Genomics plc and University of Oxford.

Identifying the right target for treatment is a key challenge in drug discovery and currently 90% of drug candidates taken into clinical trials will fail. Potential drug targets are often found through studies in model systems. However, modulating these targets often fails to be effective in humans, underlining our relative lack of understanding of human biology. Selecting targets by using human genetics where possible will improve the probability of success in clinical development[2].

Analysing human genetic variation and its impact on phenotype offers the potential to study perturbations of human biology directly. Combining large-scale genomic datasets with statistical and machine learning methods allows simultaneous analysis of thousands of phenotypes to understand how genetic variability relates to the presence or absence of disease. Using machine learning techniques on data from genome-wide association studies can reveal which genes are involved in a disease, which cells or tissues are affected, and the biomarkers or mechanisms that could help treat it, creating a 'human wiring' diagram.

Therapeutic drugs typically aim to perturb some aspect of our biology. Genetic studies allow a direct assessment in humans of the consequences of such perturbations. The key idea is to identify genetic variants which perturb the same aspect of biology as a proposed drug. Rare loss of function mutations in a particular gene can mimic an inhibitor of the protein produced by the gene, while more common variants that decrease expression of the gene are like a weak version of the inhibitor. 'Nature's Clinical Trial' can be analysed by studying the consequences of genetic perturbations in humans that are similar to the effect of the proposed drug. This allows an assessment of efficacy and potential on-target safety consequences of the intervention before embarking on expensive pre-clinical and clinical studies.

2.   Nelson M.R., Tipney H., Painter J.L. Shen J., Nicoletti P., Shen Y., Floratos A., Sham P.C., Li M.J., Wang J., Cardon L.R., Whittaker J.C., Sanseau P. (2015) The support of human genetic evidence for approved drug indications. Nature Genetics, 47, 856–860

Over the last decade of genome-wide association studies, almost 60,000 unique trait associations have been revealed, yet there are only a few dozen examples where the underlying biology is fully understood. Genomics plc has combined hundreds of studies from more than 3 million people to link genetic variation at 14 million genetic variants across the human genome to 7,000 phenotypes, including molecular, cellular, and physiological measurements and disease outcomes. Machine learning is used to analyse these data simultaneously to identify traits driven by the same genetic change. For example, changes in expression of the TWIST1 gene in specific tissues drives hypertension, coronary disease, and stroke. These diseases could therefore be treated using the same therapeutic target.

In the near future, genomics will facilitate analysis of 'wiring paths' which link genes, proteins and phenotypes, enabling both the identification and targeting of intermediate cellular 'pressure points' and patient stratification for personalised medicine.

"The Genetic Revolution is incredibly exciting as it gives us a whole new foothold into disease physiology and pathophysiology."

Professor Peter Donnelly FMedSci FRS, Genomics plc and University of Oxford

Is Digital Health the snake oil of the 21st century?

Keith Errey, Isansys Lifecare Ltd, explored the potential for digital health in research and patient care.

Digital health includes digitisation of processes and information such as through electronic health records, and direct-to-consumer digital health products to improve the efficiency of healthcare systems and patient care. One application of AI in digital health is patient monitoring to detect and flag key moments for intervention. While manual measurement of patients can miss true patterns and extremes, constant patient monitoring by wireless connected devices would recognise when metrics such as heart-rate and blood pressure fall below a safe threshold, generating an early warning. Three applications of digital technologies and AI in patient monitoring were outlined: wearable sensors, connectivity of hospital systems, and clinical apps to support decision-making. High-resolution patient data from constant monitoring would allow patients' statuses to be better observed for more effective care.

Automated measurement of vital signs and biomarkers allows patient trajectories to be mapped, using real-time AI to predict changes and prompt early action. In a study with Birmingham Children's hospital, 1,400 children were monitored using real-time AI to create a personalised, self-learning early warning system that identified patterns suggesting deterioration towards cardiac arrest. Flagging high-risk patients allowed doctors more time to intervene before serious adverse events. Constant monitoring also opens up new digital biomarkers, such as use of reduced heart rate variability as a predictive biomarker in hepatology.

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"Digitisation of the Physionome – creating data rich, dynamic, digital images of our physiology – will be the truly disruptive step in digital health."

Keith Errey, Isansys Lifecare Ltd

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Image: Keith Errey, Isansys Lifecare Ltd.

Big data and machine-assisted learning will potentially enable more efficient ways of delivering care both in and out of hospital. Following trends in other industries, Errey predicted that in ten years all patients will be monitored wirelessly, with associated economic and efficiency benefits compared to traditional monitoring. The volume of data generated will necessitate analysis by machine learning, requiring many more medical data scientists to provide informed diagnostic and therapeutic decisions. This will enable personalised medicine to become a reality, combining quantitative physiology, data science and genomics.

Companion AI: seeking dynamic precision and better drug-AI-outcomes

Professor Iain Buchan, University of Liverpool, explored the governance and e-infrastructure required for AI to become a companion to drug therapy. He called for new multi-sector partnerships across industry, academia, and health systems to avert a combinatorial explosion of drug-specific apps and develop better integrated, continuously-learning support of prescribing and medication behaviours.

Health systems face growing pressures as more people live longer with multiple long-term conditions. The number of people aged 65 and over living in the UK with two or more long-term conditions is predicted to increase from 54% to 68% (2015 – 2035), and from 10% to 17% with four or more conditions[3]. However, research and innovation tend to focus on single-condition care.

The number of apps to support patients with treatments is growing, and technology companies are adopting common standards for interfacing these apps with clinical records. A global healthcare app network is appealing for coupling clinical and self-care. However, one app per drug, device or clinic may compound the problems of polypharmacy and treatment burden. Professor Buchan proposed a more integrated 'health avatar'[4] or 'digital twin' model of care needs, preferences and resources to help patients and clinicians build their understanding and improve multi-morbid drug outcomes.

Image: Professor Iain Buchan, University of Liverpool.

Harnessing data and AI at scale

As healthcare becomes digital by default and general consumer technologies generate health data from daily living there is an opportunity to develop cross-cutting AI that supports health and care in more precise and continuous ways. For example, the use of smartphone location data to target advertising could also be translated to personalise medication reminders and support allied behaviours such as physical activity. The underpinning machine learning would need access to person-level linked data across a diversity of contexts over many learning-loops. The development of general personal assistant technologies has similar requirements for learning a person's habit engine and integrating different services. AI-linked supply chains could also better integrate discovery science, technology engineering and quality management for healthcare, not only in the pursuit of continuous learning health systems[5] but also in understanding multi-morbidity.

3. Kingston A., Robinson L., Booth H., Knapp M., Jager C.; MODEM project (2018) Projections of multimorbidity in the older population in England to 2035: estimates from the Population Ageing and Care Simulation (PACSim) model. Age and Ageing, 47:3, 374-380

4. Buchan I., Winn J., Bishop C. (2009) A unified modelling approach to data intensive healthcare. In The fourth paradigm: data-intensive scientific discovery. Eds Hey T., Tansley S., Tolle K. Redmond, Washington: Microsoft Research, 91-98

5. Ainsworth J. and Buchan I. (2015) Combining health data uses to ignite health system learning. Methods of Information in Medicine, 54:6, 479-487

Data protection, digital autonomy and empowering communities

A detailed, avatar-like model of personal health goes beyond records of historical care to predictions of habits, likely responses to prompts and other sensitive information and interactions. So, data protection will need to evolve. General Data Protection Regulation (GDPR) has forward-looking provisions in this regard, including the right to personal data portability, which may need to extend to personalised algorithms for ensuring the freedom of the citizen's avatar to combine services across different clouds or companies according to their needs.

....

"A public health approach is needed to weave different threads of machine learning into a tapestry of governable algorithms the public trusts and innovators use."

Professor Iain Buchan, University of Liverpool

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AI that is sufficiently integrated to support multi-morbid care requires consent to very complex purposes for processing personal data. A simple dialog box, even presented in a dynamic consent framework, may be insufficient to inform a patient meaningfully. Community engagement and involvement is necessary for smart governance of health data processing, as shown for example by the Citizens' Juries work of MRC Health eResearch Centre with NHS Digital and Wellcome's Understanding Patient Data.

Novel approaches to assessing the safety and efficacy of new medicines

Randomised clinical trials are traditionally used to investigate the safety and efficacy of new medicines. However, there is increasing interest in the potential for novel trial design and analysis techniques. Sir Michael Rawlins GBE Kt FMedSci, Medicines and Healthcare products Regulatory Agency, outlined emerging trial designs that may be important in the development of new therapies.

Traditional study designs for the assessment of medicines include randomised controlled trials (placebo controlled or with an active comparator), historical controlled trials, case-controlled studies, and case series. The strengths of these are that they minimise selection bias, confounding factors due to randomisation, and random error. Weaknesses include their reliance on p-values and other statistical issues, lack of generalisability particularly regarding safety and patient adherence, and resource implications with some trials costing billions of dollars.

Emerging study designs

Adaptive pathways
Initial regulatory approval is given after an initial experimental phase, with full licensure awarded after an observational phase.

Mendelian randomisation
Patients with a specific phenotype are all treated with a specific product. The responses are observed for patients with, and lacking, a specific genotype.

Basket trials
Patients with different tumours expressing the same specific mutation are all given targeted therapy, and results observed.

Umbrella trials
Patients with a single tumour type expressing different mutations are each given different targeted treatment at the site of the mutation.

Image: Sir Michael Rawlins GBE Kt FMedSci, Medicines and Healthcare products Regulatory Agency.

Step wedge trials
The drug is tested on a subgroup of patients, and efficacy observed before extending the trial to increasing patient subgroups until the whole cohort is assessed.

Ring trials
Confirmed cases of infectious disease and close contacts are randomised in clusters or 'rings'. Treatment efficacy is assessed for immediate versus delayed vaccination.

Alternative analytical approaches

Frequentist approach
Probability of specific data conditional on a particular hypothesis.

Bayesian approach
Probability of a particular hypothesis conditional on specific data (pre-existing and new evidence), without requiring a null hypothesis or p-value. Weaknesses of Bayesian statistics include subjective probability, difficulty establishing the prior, computational difficulty, and disfavour by regulators.

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"New clinical trial techniques would benefit from merging experimental and observational techniques, particularly using Bayesian approaches."

Sir Michael Rawlins GBE Kt FMedSci, Medicines and Healthcare products Regulatory Agency

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Biomarkers as surrogate endpoints

Biomarkers are widely used in clinical research to measure efficacy and may be used as surrogate endpoints in clinical research. Sir Michael suggested that in appropriate circumstances, biomarkers may need to be accepted as a basis for marketing authorisation – for example authorisation for the use of ASO treatment for occurrences of Huntington's disease in children, without the requirement to put children through a Phase 3 clinical trial.

Panel discussion: the future for data, technology and regulation

Chaired by Professor Dame Angela McLean FRS, the panel comprised Professor Peter Donnelly FMedSci FRS, Genomics plc, University of Oxford; Keith Errey, Isansys Lifecare Ltd; Professor Iain Buchan, University of Liverpool; Sir Michael Rawlins GBE Kt FMedSci, Medicines and Healthcare products Regulatory Agency; and Professor Jonathan Knowles, University of Oxford.

Image: The panel members, from left to right: Professor Peter Donnelly FMedSci FRS, Keith Errey, Professor Iain Buchan, Sir Michael Rawlins GBE Kt FMedSci, Professor Dame Angela McLean FRS (chair), and Professor Jonathan Knowles.

Current use of digital health in the UK and NHS

- The panel agreed that digital health tracking will soon become available in the UK. Companies are already offering apps for access to a patient's primary care record in return for greater convenience, such as repeat prescriptions.

- Clinical trial data is being made available for longitudinal studies, and publishers are working to make data from the early 2000's more searchable. Access to data from failed trials would also be valuable.

- Connected location data allows us to tap into daily life as patients' locations can be monitored using Wi-Fi tags. In the future, location tracking by digital healthcare apps could be combined with AI-aided

> "Digital health is happening in the UK but it is not yet within a coherent framework. Now is a good time to have this conversation."
>
> Professor Iain Buchan, University of Liverpool

analysis of brain scans and other data, to help diagnose and monitor treatment of diseases such as psychiatric and neurodegenerative disorders.

- There is a need for a coherent data framework, enabling data flow so that the outputs of one organisation could become inputs of another.

- Most NHS hospitals lack electronic health records, and they are often not optimised where they are in place. Improvements in this digitisation is needed before more progressive digital health can be implemented in the UK.

- There is a need to prioritise data management better across NHS trusts nationwide rather than focusing on near-term costs and savings.

- There is optimism regarding progress in information management as the methods of collecting, collating, analysing, and integrating data are becoming cheaper and more standardised. However, management may impede progress as data sits in silos and is not used effectively.

- A disruptive step will be use of patient data as a civic asset rather than an organisational asset.

Cost of digital health

- Novel types of clinical trials will enable new drugs to be brought to market much sooner and more cheaply.

- Much of the value added by digitisation will accrue downstream in the NHS, compared with the upfront cost of addressing this. This value needs to be understood and extracted.

- Transparent inputs and outputs are required to measure and remunerate the value added by digitisation. Current monetisation of digital health involves services, like Cloud data storage. Future monetisation involves innovation by the NHS, tech companies, and pharmaceutical companies. There is a need to develop a consistent business model to help innovating groups work together, developed between partners rather than by government.

- The costs of large clinical trials can be reduced by ensuring there is sufficient data for effective patient stratification. Genetics will help this, and regulators will be able to help by pushing back on organisations with inadequate data.

> "Effective data management needs to be raised in the hierarchy of priorities for trusts across the country."
>
> Professor Jonathan Knowles, University of Oxford

Regulations that protect data while enabling innovation

- Regulating data usage is challenging. One solution may be using consent: if data is freely available it does not have the same commercial value, and requires different commercial models.

- Digital health will require cyber security issues to be assessed by regulatory bodies, which currently provide guidance. Collaboration between computer sciences, mathematics, security, and creators of health apps could address a number of problems including security.

- The panel suggested that, post-Brexit, the UK could change its regulatory procedures to enable more pragmatic regulation of low-risk devices such as smart watches, and benefit from the using the data generated from such devices for research, public health and service planning.

- Approaches to software regulation for medical devices for particular applications are changing, like analysing medical images. Less quantifiable data uses are harder to regulate, as in mental health and multi-morbidity, but can be regulated if the end point is defined.

- GDPR is a start to addressing the data protection issue, but effective regulation will require societal change and transparent legislation.

- There is concern that we have lost public trust and confidence in sharing data, but this could be rebuilt beginning by working with consenting patients. This will help advisors understand how to regulate and what the benefits of data use may be.

- Outlooks on data sharing vary between healthy groups (including ethics advisory boards) and groups of patients who understand the benefit it can bring.

> "The NHS provides our society with a really valuable resource that we can get value from downstream as a consequence of good data use."
>
> Professor Peter Donnelly FMedSci FRS, Genomics plc and University of Oxford

How can we value novel medicines? A health economic perspective

Professor Lou Garrison, University of Washington, gave an overview of the recent report, *A Health Economics Approach to US Value Assessment Frameworks*[6], with implications for assessing the value of novel medicines globally.

Image: Professor Lou Garrison, University of Washington.

Value frameworks measure, evidence and value elements for medical products and technologies then aggregate them for a total value. Increasing use of value frameworks in the US is informing the shift to a value-driven healthcare system, influenced by factors including:

- Flat industry productivity, despite growing investments.
- Prices not strongly correlated to health gains.
- US healthcare prices rising relative to other countries.
- More specialised and orphan drugs.

Value-based approaches encourage companies to bring products optimised by the frameworks to market. These should promote medical products and technologies that efficiently improve population health. Different frameworks use different elements of value, such as clinical benefit and affordability, some of which have unclear relevance (eg novelty, population burden). Value is further complicated as it varies with time and between individuals and indications for the same medicine.

Conventional Cost-Effective Analysis (CEA) compares the cost and outcome of two alternatives to produce the cost per quality-adjusted life year (QALY). To assess the potential value of novel medicines, the Special Task Force recommended that US public and private payers begin by using QALYs gained to compare incremental costs with incremental health benefits, as used by the National Institute for Health and Clinical Excellence in the UK. The concept of value should then be expanded beyond cost-per-QALY to create an Augmented CEA that includes novel elements such as insurance value and peace of mind, the value of hope, real option value, and scientific advancement. In this way value can be measured with multi-criteria decision analysis, weighting the importance of each criterion.

The following steps could help support the efficient development and use of innovations in personalised and precision medicines:

- Broaden the concept of value to identify and reward the contribution of diagnostics better.
- Reform how we value innovation and invention.
- Invest more in real-world evidence generation.
- Implement indication-specific, value-based pricing.
- Apply consistent value metrics founded on the health benefit based on the patient.

"We lack an appropriate system of differential pricing for R&D of novel medicines. Reforming how we define and measure value would help create a level playing field for innovators from a regulatory and reimbursement perspective."

Professor Lou Garrison, University of Washington

6. Neumann P.J., Willke R.J., Garrison L.P. Jr. (2018) A Health Economics Approach to US Value Assessment Frameworks-Introduction: An ISPOR Special Task Force Report. Value Health 21(2):119-123

Health technology assessment of histology independent cancer drugs

Unlike traditional therapeutics, histology independent cancer drugs target tumours with certain biomarkers regardless of where the tumour is located. Dr Jacoline Bouvy, National Institute for Health and Care Excellence, discussed the challenges that health technology assessment (HTA) bodies will face when assessing histology independent drugs.

Challenges for health technology assessment

It will be complicated for HTA bodies to assess whether histology independent drugs provide clinical and cost effectiveness to a healthcare system. This is because a single drug can target a wide range of tumour types, and clinical evidence for the drug's efficacy may differ significantly to what regulatory agencies and HTA bodies are familiar with. Challenges include:

- Technology appraisals. Traditionally, the marketing authorisation specifies a medicine's therapeutic indications based on tumour histology. It will be challenging to make recommendations for a drug with a range of tumour types.

- Cost-effectiveness analysis. Analyses currently use economic models of costs and health effects for the NHS. However, an economic model for an histology independent drug might look very different, because lots of subgroups of patients would need to be included.

- Population heterogeneity. As cost effectiveness can vary between clinically distinct subgroups, it may not be feasible to estimate this for the entire population covered by the marketing authorisation. The feasibility of subgrouping the population should be explored.

- Decision uncertainty. Uncertainty making recommendations for the NHS grows, and that might increase the probability of making an incorrect recommendation (such as not recommending a technology that is clinically and cost effective).

With a growing pipeline of histology independent cancer drugs, it is important to explore the challenges posed to HTA methods. There is urgency to resolve these challenges as the first histology independent cancer drug is under regulatory review in the US and Europe and may be on the market within a year.

Image: Dr Jacoline Bouvy, National Institute for Health and Care Excellence.

Conclusions

The European Medicines Agency has not yet approved an histology independent cancer drug. It remains to be seen whether marketing authorisation will be histology independent or restricted to key patient subgroups. Biomarker-driven drug development is not limited to oncology. This could be the beginning of a paradigm shift in how technologies are developed and approved.

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"We could be at the beginning of a paradigm shift in how technologies are developed and approved, impacting how they are approved for use in the NHS."

Dr Jacoline Bouvy, National Institute for Health and Care Excellence

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The boundary between cognitive enhancement and treatment

Professor Barbara Sahakian FBA FMedSci, University of Cambridge, described the increasing use of cognitive enhancing drugs by healthy individuals, and 'gamification' of treatment to improve cognition and functional outcome in people with neuropsychiatric disorders.

Image: Professor Barbara Sahakian FBA FMedSci, University of Cambridge.

Cognitive abilities are important for work performance but are reduced by stress, long hours and lack of sleep. Cognitive enhancing drugs, like methylphenidate (Ritalin) and modafinil, are used increasingly by healthy people.

....

"For good mental capital and wellbeing, mental health should be considered as equally important as physical health."

Professor Barbara Sahakian FBA FMedSci, University of Cambridge

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Cognitive enhancing drugs to treat neuropsychiatric disorders

Working memory (WM) is important for most executive function tasks, like planning and problem solving, and relates to psychosocial function. Many neuropsychiatric disorders affect WM, including ADHD and schizophrenia. Methylphenidate improves WM performance in both adult patients with ADHD and healthy volunteers[7] with no difference in drug action. Modafinil improves WM in patients with first episode psychosis[8], patients recovered from depression, and healthy volunteers[9].

7. Turner D.C., Blackwell A.D., Dowson J.H., McLean A., Sahakian B.J. (2005) Neurocognitive effects of methylphenidate in adult attention-deficit/hyperactivity disorder. Psychopharmacology 178(2-3):286-95

8. Scoriels L., Barnett J.H., Soma P.K., Sahakian B.J. & Jones P.B. (2011) Effects of modafinil on cognitive functions in first episode psychosis. Psychopharmacology 220, 249–258 DOI 10.1007/s00213-011-2472-4

9. Müller U., Rowe J.B., Rittman T., Lewis C., Robbins T.W. & Sahakian B.J., (2013) Effects of modafinil on non-verbal cognition, task enjoyment and creative thinking in healthy volunteers. Neuropharmacology 64, 490-5

Lifestyle use of cognitive enhancing drugs by healthy individuals

n 2017, 10% of healthy people in the UK surveyed had used modafinil as a stimulant in the last 12 months, and 5.1% reported using other stimulants such as methylphenidate[10.] It is now estimated that around 90% of modafinil use is by healthy individuals. The reasons for healthy people using cognitive enhancing drugs include:

- Increased performance and competitive edge. Small increments in performance can significantly improve outcome: a 10% improvement in memory score could lead to an improvement in an A-level grade or degree class[11].

- Increased task-related motivation and ease of getting into 'flow'.

- Reduced effects of jetlag and staying awake.

Potential concerns of cognitive enhancing drug use include long-term side effects, especially in the developing brain; coercion into taking cognitive enhancers in a 24/7 society; dangers of buying prescription drugs online; unfair advantage; and neuroethical concerns.

Games development to improve episodic memory

Cognitive training games based on neuropsychological and neuroimaging evidence have been developed to improve learning, episodic memory and motivation in patients with mild cognitive impairment and schizophrenia. The games are titrated by difficulty, making them personalised. Games are now being developed to improve concentration in healthy young adults.

10. Maier L.J., Ferris J.A., Winstock A.R. (2018) Pharmacological cognitive enhancement among non-ADHD individuals – A cross-sectional study in 15 countries. International Journal of Drug Policy 58, 104-112
11. Academy of Medical Sciences Report on Brain Science, Addiction and Drugs, 2008

How does the healthcare system need to evolve to take advantage of new medicines?

In the closing keynote, Professor Dame Julie Moore, Warwick University, discussed how the NHS needs to evolve to take advantage of new medicines and technologies, and to increase its impact on UK industry and wider society.

Image: Professor Dame Julie Moore, Warwick University.

It takes 15 – 17 years from drug discovery to routine use by the NHS due to the extensive testing and evaluations required. Rapid adoption within the NHS requires appropriate resources and prioritisation, while conditions must also be right across public policy and in the NHS's relationship with industry.

Budgets
Grants are required to undertake research, as well as introduce and monitor new drugs and technologies, but financial constraints limit such innovation. The NHS faces pressures including increasing demand, an expectation to introduce new treatments, targets, and other costs such as increasing pension contributions. To meet these pressures, staff are reallocated away from research to deliver frontline care.

> "If we want a thriving life sciences sector, we have to have an innovative NHS."
>
> Professor Dame Julie Moore, Warwick University

Staffing
10% of NHS positions are vacant. These vacancies should be attractive, appropriately remunerated, and need to be filled to allow staff time to introduce innovative medical techniques. Many NHS staff are international, and there is concern about the impact of Brexit on UK science.

NHS strategic priorities
Taking advantage of new medicines and technologies should be valued by the entire health system. While R&D and innovation are understood to be important, they are often viewed as displacing NHS work and should be incorporated into Care Quality Commission assessments. The Best Practice Tariff attempts to address restrictive 'established pathways', but there is concern that this is not updated regularly enough.

National infrastructure and industry
An effective NHS is essential for the rest of the national infrastructure. Rather than looking at the short-term costs of the NHS in isolation, long-term societal benefits should be considered when assessing the cost of new therapies. Benefits of increased NHS expenditure often accrue elsewhere, such as:

- Healthy workforce – returning to work faster, benefiting taxation, and reducing benefits.

- No health insurance costs and bureaucracy for employers.

NHS support has an impact on the life sciences industry and associated industries such as digital, engineering, and materials science. The life sciences sector is a key part of the Government's Industrial Strategy, but often new medicines discovered and developed in the UK are not adopted here, making it a less appealing destination for life science industries. This means that short-term financial constraints in the NHS may lead to long-term negative impacts on the economy. The establishment of a mature relationship between the NHS and life sciences industry would allow industry to flourish and the NHS to take advantage of new medicines earlier.

Image: Steve Rees, AstraZeneca.

"The nature of medicine is changing as the ability to create DNA, RNA and protein therapeutics, alongside gene and cell therapy, makes every target druggable and leads to the potential to cure rather than treat disease. This offers huge benefits to patients that will only be realised through innovation in drug development, manufacturing, approval and reimbursement."

Steve Rees, AstraZeneca

"We are undertaking transformational scientific research that may revolutionise the way patient care looks in ten years' time."

Welcome address by Professor Sir Robert Lechler PMedSci, Academy of Medical Sciences

How the healthcare system can evolve to take advantage of new medicines

- Demonstrate willingness to use new products, with fair pricing and transparency.

- Provide adequate funding to support frontline care and introduction of new drugs and technologies for long-term efficiency increases and cost reductions.

- Acknowledge that this is an issue wider than the NHS, and consider the cost of the whole system beyond healthcare.

- Ensure certainty of NHS funding for more than one year at a time to enable systematic planning.

- Attract and invest in staff who are implementers and innovators.

- Prioritise innovation and adoption equally with all other NHS activities.

- Establish a new relationship with industry, including timely and appropriate use of UK life sciences products. Industry also needs to establish a new relationship with the NHS, with fair and transparent pricing and sharing of all research results.

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The Royal Society

The Royal Society is a self-governing Fellowship of many of the world's most distinguished scientists drawn from all areas of science, engineering, and medicine. The Society's fundamental purpose, as it has been since its foundation in 1660, is to recognise, promote, and support excellence in science and to encourage the development and use of science for the benefit of humanity.

The Society's strategic priorities emphasise its commitment to the highest quality science, to curiosity-driven research, and to the development and use of science for the benefit of society. These priorities are:

- Promoting excellence in science
- Supporting international collaboration
- Demonstrating the importance of science to everyone

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The Academy of Medical Sciences

We are the independent body in the UK representing the diversity of medical science. Our mission is to promote medical science and its translation into benefits for society. The Academy's elected Fellows are the United Kingdom's leading medical scientists from hospitals, academia, industry and the public service.

The Academy FORUM

The Academy's FORUM was established to catalyse connections across industry, academia and the NHS. The network brings together researchers, research funders and research users from across academia, industry, government, and the charity, healthcare and regulatory sectors. We are grateful for the support provided by the members and are keen to encourage more organisations to take part. If you would like further information on the FORUM or becoming a member, please contact forum@acmedsci.ac.uk.

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