Synthesising a Human Genome: What could go right?

On the 17th September 2018, a one-day meeting was held at the Wellcome Trust in London to discuss the UK's position for the emerging research area of synthetic genomics, and how it would scale to projects in mammalian and human models. Natural scientists, policy makers, social scientists and funders met to understand the UK strengths for synthetic genomics, discuss ways forward and how to align with international projects, such as the US-led GP-Write initiative.

What is Synthetic Genomics?

Synthetic genomics uses large-scale DNA synthesis, editing and assembly to make wholescale changes to natural genomes, chromosomes and chromosomal loci. In doing this it provides ways to ask and answer new and fundamental questions about biology and also offers new opportunities in biotechnology. Three projects to engineer whole microbial genomes are complete or nearing completion but no larger genomes or chromosomes (e.g. plant, fly, human) have yet been synthesised. However, international teams in the US and China are currently finalising roadmaps for such work.

Presentation 1:

'Why now, why UK?': the status of synthetic biology investments, genomic tech and expertise

The UK is in a great position to be a major player in synthetic genomics. Over the last ten years, there has been nearly £300 million of public investment into synthetic biology, which has resulted in high-quality infrastructure for large-scale DNA assembly. This began around ten years ago when the UK invested in networks for bringing the synthetic biology community together. Since 2012, the UK government recognised synthetic biology as one of the 'Eight Great Technologies' and made a major capital investment to found 7 synthetic biology research centres, 5 DNA synthesis and assembly foundries, 2 doctoral training centres and a venture 'seed fund' to invest in synthetic biology start-ups. The MRC has made major investments in this area at the LMB.

A leadership council was established which guided allocation of the funds over the past five years, and helped shape a further strategic plan, 'Biodesign for the Bioeconomy', which was released in 2016. Also, during this time, UK researchers at Imperial College, Edinburgh University, University of Cambridge and Manchester University began work on synthetic genomics projects in microbes. In particular, several of these UK labs have become major contributors to the international Sc2.0 project which is synthesising a yeast genome.

In addition, the UK is a world leader in the areas of functional genomics, chromosome biology and developmental biology that are required in order the assay the function of synthetic vertebrate loci and chromosomes.

The UK's significant expertise in synthetic biology - developing protocols, automation hardware and workforce training - is well-positioned to be applied to large synthetic genomics projects.

Presentation 2:

A synthetic genome case study: Sc2.0 synthetic yeast and the 'lessons learned'

Sc2.0 is an international project that began in the USA and is building a synthetic version of the 12.1 Mbp genome of the Baker's yeast *S. cerevisiae*. The project became a global endeavour in 2012 at the 1st Sc2.0 annual meeting in Beijing which was attended by a small group of people from around the world. Researchers met with funding agencies and key stakeholders to discuss how to take the project to an international level, setting up an International Consortium where each team works on 1 to 2 chromosomes and that will then be collaboratively merge them into a full genome.

The project involves a dozen institutes on four continents, as well as associate member groups who carry out analysis, such as transcriptome profiling. Most of the chromosomes have now been

completed and the project should be finished in the next few years. The lessons learned during Sc2.0 offer useful guidance for future large-scale and international projects in synthetic genomics.

- Synthetic genome projects must be well-defined: specific, measurable, attainable, relevant and time bound
- Members should sign an agreement covering IP, co-publication, quality assurance/standards, adequate lab space, personnel and material transfer *(Note recent developments in establishing an OpenMTA which may be helpful to facilitate IP agreements among future international consortia)*
- Every participant should raise their own funding, and does so with support from the consortium
- Design should be de-coupled from synthesis – design was centralised at John Hopkins University
- International collaboration is crucial, helping provide many of the rewards

The benefits of a large consortium genome project such as Sc2.0 are multiple. It brings a new understanding of the yeast genome, and greater confidence to make more radical changes in further experiments. It provides training, collaboration and outreach opportunities and as a high-profile international project it attracts and helps develop new expertise, new technologies and new methods. In particular, the project has interfaced well with social scientists and with student training.

Presentation 3:

The US GP-write Initiative and current mammalian synthetic genomics pilot projects

Following discussions at the 2015 annual Sc2.0 meeting, US and international synthetic genomics researchers met at Harvard in May 2016 to announce a major new initiative called 'Genome Project – Write'. GP-Write aims to reduce the cost of design, synthesis, assembly and testing of synthetic genomes by 1,000-fold over the next ten years and support technological development of the design-build-test-learn cycle in genome synthesis. This will help make mammalian and plant-scale synthetic genomics projects a reality, while accelerating widespread use of synthetic genomics as a tool for research and biotechnology.

GP-Write is US-led and currently road-mapping project requirements, coordinating pilot projects and seeking to raise larger funds from donors, foundations and agencies. Inspired by the successful international collaboration on the Human Genome Project (HGP) in the 1990s, the initiative is keen to involve the UK due to its expertise and facilities for large-scale DNA assembly.

Over the last three years, GP-write has attracted more than 250 active participants from 15 countries including many from the UK. Eight working groups and a Scientific Executive Committee have been established. White papers are about to be published from these groups, but the main roadmap for synthesising full mammalian genomes remains skeletal.

GP-write has decided on an initial large-scale 'community project' that will act to pull investment, expertise and technologies. Members are also underway with their own pilot projects designed to help push the technology from what is currently achievable.

COMMUNITY PROJECT: Engineering viral resistance into mammalian cells. Viruses use all codons in the genome so by replacing the use of a small number of codons in all human genome exon regions, it should be possible to block infection from natural viruses. This project would require around 30 Mbp of synthetic DNA and GP-write is in the planning phase on how this could be done as a large community project. The consortium has decided that the project would be done only in a human cell line for biotechnology use meaning that there will be no germ line engineering.

PILOT PROJECT: Delivering very large DNAs into mammalian cells. GP-write will use yeast as a platform to assemble DNAs longer than 100 kb. The Boeke group and collaborators in New York have developed a landing pad strategy to deliver 100 kb and above molecules into defined chromosomal loci in mice embryonic stem cells.

PILOT PROJECT: The 'Dark Matter' project. GP-write is using their delivery technology to investigate the function of non-coding areas of DNA implicated by Genome-Wide Association Studies (GWAS) for various human disease. An approach called 'synthetic haplotypes' was presented based on research at NYU. In synthetic haplotypes, DNA synthesis, assembly and editing in yeast is used to create large DNA regions that encode multiple variants of haplotypes not normally seen in nature (haplotypes are sets of DNA base variants that are inherited together as a group). They will look at how these synthetic haplotype variants effect disease phenotypes by placing the synthetic DNA into human stem cells and engineered mice. Part of this work is in collaboration with scientists at Oxford University.

Presentation 4:

PAX6 hypervariation: A UK-USA pilot project for GP-write

A second strand of the Dark Matter pilot project is known as synthetic hypervariation and is being done via collaboration between US GP-write researchers and UK researchers at Edinburgh University. Using synthesis, assembly and editing in yeast, GP-write researchers at NYU are making multiple simultaneous changes to the non-coding areas of DNA that are involved in regulating gene activity. The specific example case that involves the UK is a 450 kb section of DNA surrounding the PAX6 gene that is known to contain the regulatory elements – enhancers – that drive PAX6 expression during development. Synthetic hypervariation is being applied to the regulatory region of this gene to test the fundamental principles of long-range gene regulation and the phenotypes from this work will be assessed in zebrafish and in mammalian eye organoid systems. Variation in sequence in the regulatory regions is involved in congenital eye diseases, such as aniridia. The US and UK team are applying for NSF-Bio/BBSRC co-funding to work on this project together.

Presentation 5:

The Chinese synthetic genomics Initiative and aims of the Chinese genome foundries

The Shenzhen Institutes of Advanced Technology (SIAT) set up a GP-write China centre in December 2017 and held the first GP-write China workshop in January 2018. They have now expanded their centre's remit to all of Synthetic Genomics and rebranded as the China Synthetic Genomics Centre. They have significant funding and plan to work alongside the US GP-write initiative, whilst also undertaking other synthetic genomes projects.

The teams hope to understand and harness living systems by designing, synthesising and editing their genomes. They are looking at model organisms, such as the chicken and model plant systems. They are also collaborating on projects that aim to remove large regions of non-coding 'junk' sequences of DNA to see if they have any important functions and potentially make genome design and synthesis easier in the future. They are keen to work with the UK and can set up UK-China specific projects, meetings and workshops

Following the morning scientific presentations, the afternoon session of the meeting was focused on discussion among attendees as to the UK position for synthetic genomics and involvement in GP-write. This consisted of four breakout groups on specific topics, ending with full-group discussion.

Breakout Group 1: Infrastructure and coordination

How should we coordinate an international project? How should the UK engage with the GP-write confederation?

The group discussed a wide-range of issues around establishing a coordinated UK GP-write type project including the opportunity, challenges and requirements for such a project. The discussion was initiated by reflection on the Human Genome Project (HGP), leading to the suggestion that an international project similar to the Human Genome Project (HGP) was premature. The purpose for HGP was clear but the purpose for a similar GP-write project is currently less clear and would need to be clearly articulated. For example, there will likely be trade-offs between technology development, fundamental biological understanding and biotechnology/biomedical applications so an appropriate balance will need to be struck.

The group felt that several technological barriers needed to be overcome and that, rather than expedite innovation, a large HGP-style project could potentially stagnate innovation if it meant that people had to agree on common experimental/technological approaches. However, Sc2.0 consortium members currently use a variety of DNA assembly tools which countered this viewpoint. There was however enthusiasm for some grassroots coordination around synthetic genomics in the UK, especially in developing generic technology platforms in synthesis, assembly and delivery that could be used by a variety of researchers. The view was that synthetic genomics offered a perfect project for coordinated action if the overall goals and aims can be clearly defined and articulated. The group also favoured engaging with diverse communities, such as specialists in high-throughput assays or in model organisms such as Drosophila that have a smaller genome than mammalian model organisms.

It was agreed that a UK regional coordinated action in synthetic genomics could fit well into any future potential funding opportunities by UKRI.

The group also agreed that one clear requirement and possible outcome from a future synthetic genomics initiative was a reduction in the cost of DNA synthesis. It was noted that the UK already has global impact and a track record in DNA sequencing technology development, some of which is now focusing on novel DNA synthesis approaches. It was agreed that a future initiative should include these groupings and companies. This led to two open questions-

(1) Is the UK playing in the premier league in synthetic genomics?

(2) Given the unique combinations of innovation in the UK (e.g. DNA sequencing and synthesis), can this be capture for synthetic genomics and if so how?

The discussion then led to the identification of existing technologies within the UK research base that could be applied in a synthetic genomics initiative –

(1) Scaled HTP assays to assess cell phenotype (imaging / omics) including single cell analyses

(2) Computation tools, large scale databases and data standards

It was noted that the European Bioinformatics Institute and the Wellcome Trust Sanger Centre provided the UK with a leading edge in several of these technologies.

The group concluded with discussion around framing a UK synthetic genomics project and linking this to fundamental biological understanding. Several model organisms were identified including Drosophila and also mice where the ground-breaking work of Alan Bradley was highlighted in humanising the mouse for antibody production. Also noted was the need to define the problem including the benefits to society and also why an international grouping is needed. As stated earlier, the project should also avoid lock-ins to technology platforms to ensure diverse innovation and technology development

The group strongly favoured engaging with the GP-write project, but suggested that the GP-write branding was not very suitable for a UK project as it is currently a top-down US-centric effort, focused on securing US funding that is not is accessible in the UK. In conclusion the group were very enthusiastic about the opportunities for a coordinated UK synthetic genomics project if it can be framed and articulated in a compelling way.

Breakout Group 2: Technologies and technical barriers

How would the UK complete a genome-scale project and help reduce costs 1,000-fold?

To reduce the cost of a synthetic genome by 1,000-fold, the group recognised the need for cheaper DNA synthesis, more efficient and specific DNA editing and improvements in DNA assembly and delivery. In addition, it would be vital to transfect very large pieces of DNA with high efficiency, which is currently a major bottleneck.

As a starting point, the group discussed the white paper drafted by the GP-write 'Technology & Infrastructure Working Group' and based on international discussions on the technological hurdles that need to be overcome. On synthesis, the group were concerned that the bulk price of nucleotides would set a hard limit on costs. Technologies in development, such as enzymatic DNA synthesis methods, liposome-based polymerisation and microfluidics, could reduce the cost of synthesis and the UK should do what it can to be involved in these areas. In terms of delivery, GP-write hoped to use microbes or viruses to deliver large DNA segments to the nucleus of target cells and recommended work in microbiology, virology and parasitology be considered where natural systems may already do this. Mimiviruses in particular are of interest as they have very large viral genomes. Conjugation from bacteria into nuclei may also be possible.

There was also discussion about building chromosomes in mammalian cells and how this will be different to existing HACs. Human Artificial Chromosomes (HACs). HACs and Mouse Artificial Chromosomes (MACs) are an area that the UK has world-leading expertise in, but even the best HACs are very unstable in cells. Methods to bring large pieces of synthetic DNA together from different cells were also touched on, for example by creating some form of synthetic meiosis with CRISPR-guided crossovers. The group also discussed recombination into landing pads engineered into mammalian cell lines and the need for an approach to do this at any point in the genome.

The group discussed the feasibility of the GP-write community project, and then whether full-synthesis of a human genome was feasible or useful, or whether they should synthesise a smaller genome such as Drosophila or a relevant non-human genome, such as a plants pigs, or even the pigeon or chicken genome.

Breakout Group 3: Pilot projects and research applications

Which pilot projects are desirable and achievable? How could existing technology be developed and applied? And why should the UK taxpayer fund this work?

The group discussed the potential advantages of synthesising the genomes of several model organisms as an alternative to the human genome. In particular the group discussed the potential of the mouse genome as an alternative model mammalian system. It was noted that the UK has excellent existing underpinning resources in the Mary Lyon Centre (MLC) - a national facility providing world-class expertise, tools and resources to generate and characterise genetically altered mouse models and includes genome engineering, advanced phenotyping and cryopreservation. The MLC also hosts an internationally recognised mouse archive, facilitating third party access to existing and novel models. Specific suggestions were humanising large regions of the mouse genome and phenotyping at scale. Another potential model organism discussed was the fruit fly with its relatively small genome and existing extensive research community, tools, resources and crucially the ability to do large-scale population genetics. The zebra fish was also put forward as an option due to the potential exciting

imaging opportunities afforded. In addition, there was discussion around the engineering of the chicken genome to make it resistant to viruses such that chickens would not be vectors for human diseases. However, this was recognised as being extremely challenging particularly because the chicken genome sequence is incomplete.

Opportunities for working with cell lines were discussed and there was interest in using DNA synthesis to investigate and recapitulate the DNA segments implicated in leukaemia and other cancers to enhance our understanding of disease state and for use in testing new therapeutics. It was suggested that synthesising a universal stem cell could provide opportunities for creation of initially organoids for drug testing applications. The de novo synthesis of a genome would allow the grouping different functionalities as modules in the same part of the chromosome (genome refactoring) and removal of large segments of non-coding DNA and repetitive sections of DNA. The group discussed the importance of non-coding DNA in gene regulation and the role of redundancy and repetitive elements in evolution and "evolvability". By synthesising genomes and removing or minimising these elements the group discussed the opportunities for learning key features of fundamental biology and evolution and also the potential for engineering more stable or more evolvable genomes.

The group discussed the minimisation of the mitochondrial genome and the location of some mitochondrial relevant genes in mitochondrial DNA and others on the cell genome. Discussions focussed on the variability between species and whether using a synthetic genomics approach we could swap genes between organelle genomes and the cell genome and what impact that might have and what we could learn from such an approach. The group discussed the potential importance of removing certain genes from reactive oxygen species damage and the potential relevance of mitochondrial genetic dosage control.

Finally, the group discussed the ethical and societal issues around synthetic genomics. How could synthetic genomics benefit society as a whole? What are the red lines for synthetic genomics? Should a multi criteria strategy be developed for deciding work programmes and applications? There were concerns raised that the vast majority of human genomes sequenced to date are Western with the number Chinese genomes rapidly expanding but what about others. Should societal needs drive the work and is there a scientific responsibility to benefit large sections of society? Will any therapeutic applications and benefits be available only to a small section of society? Again, the group emphasised the need to be clear about why this research should be undertaken and who would benefit in a world with a vast wealth discrepancy.

Breakout Group 4: Who benefits and how?

What are some of the important ethical, social, political and regulatory dimensions to consider? How could they be addressed?

The workshop group considered some of the tensions in exploring and addressing ethical, social and political dimensions of synthetic genomics in a way that can influence the course and conduct of scientific research. They also reflected on the possible opportunities for the synthetic genomics community and any UK-based projects.

The group discussed two prominent approaches to 'Ethics, Policy & Society'. One approach is to attempt to define a set of ethical principles and use such principles to guide scientific practice through, for instance, codes of conduct and moral boundaries (so-called 'red lines'). Another approach tends less to offer clear 'yes' or 'no' *a priori* principles and instead emphasises the emergence of ethical and social issues from scientific practices. This latter approach is encapsulated in the notion of responsible research & innovation.

These two approaches are distinct but do not have to be mutually exclusive because they can play different valuable roles: Principles essentially function to be juridical in the sense that they define

differing extents of freedom, whereas responsible research and innovation is in essence about governance and on-going modulation and negotiation of the ends and means of synthetic genomics. However, it is important for an international project to be aware of the potential tensions in these (and other) approaches for the following reasons. First, there are national and disciplinary differences that colour the approach taken and that can make transnational projects challenging. For example, US biomedical science has a strong emphasis on the former, principle-based approach. Second, responsible research and innovation tends to occur in close collaboration between social and natural scientists over an extended period of time, which often requires explicit support from funders. There are several examples demonstrating the value of real-time exploration of these and similar issues, but this requires a commitment from all involved (e.g. scientists, social scientists, funders) to support and engage with the complexities that may arise. This is an opportunity for a UK-based initiative because there is already extensive experience working in close collaboration with scientists, especially in synthetic biology.

The initial discussion built into an exploration of different policy and regulatory frameworks, the ways in which the life sciences may or may not challenge the status quo and the most appropriate focus for social scientific research. GP-write (and all scientific projects) should be located within a broad landscape of governance practices that includes ethics review, biosafety and containment protocols, standard setting, Human Fertilisation and Embryology Authority (HFEA) and Home Office licensing, environmental risk assessment, product regulation, and certification and labelling. It is tempting to defer to such a regime to guide and govern decision making and rely on an institutional capacity to catch 'qualitatively different' developments during particularly important moments (e.g. ones that set precedents). Examples here include proposals to develop Stratospheric Particle Injection experiments in the mid-2000s and more recently with Gene Drive Technologies; both instances have mobilised communities of policy makers, social scientists, natural scientists and non-governmental organisations to discuss, debate and design new ways of governing such technologies. At the same time, however, there are numerous examples of the life sciences challenging the norms and categories established to regulate previous practices and technologies. (The group discussed gain of function experiments, cell-free synthetic biology, challenges to the 14-day rule in embryo research and the production of synthetic human entities with embryo-like features). In each case, governance is challenged in different ways and in each case social scientific or bioethics research has been important. Maintaining capacity for near-term foresight studies, under an 'anticipatory governance' approach would be valuable.

There was a sense within the group that existing governance frameworks miss many of the issues that are important for citizens outside scientific communities because they focus primarily on questions of risk, harm and benefit rather than on questions of common values visions of a desirable future, and the relative distribution of benefits. It was suggested that there would be relevant and real cultural differences in the way that some of synthetic genomics proposals were perceived and that the issues deemed attention-worthy by people in the workshop would not necessarily be the same as those in other parts of society or in different countries.

Since the GP-write initiative was announced (as Human Genome Project Write), one persistent thread of discussion has questioned its purpose and potential value. The group was conscious that such questions connect with findings from a series of public dialogues around the biosciences and a range of emerging technologies in the UK, which suggest broad support with calls for candid articulations of who would benefit and how. They also connect to broader contemporary discussions, including: the relative consolidation of research in a small number of universities; the ability of governments to 'steer' research trajectories to produce returns on public investments; and the relationship between technology and inequality. Engaging substantively with these debates would require any future project to engage with questions around (for instance) openness, data sharing, intellectual property

agreements and accountability arrangements (e.g. which groups guide decisions about what to synthesise?). These questions are challenging to address (e.g. because they require collective action at an organisational level) but doing so could demonstrate a commitment to engaging with the broad impacts of synthetic genomics. In this regard, the potential funding arrangements and the presence of major research institutes may offer an opportunity. It was noted that providing mechanisms to engage with such questions may also be valuable scientifically — because they would encourage the free exchange of material and help to expose and clarify any tensions in the goals of a future initiative and the way it would be organised.

FINAL OPEN DISCUSSION SECTION

Q1: What do we think of GP-write versus alternative efforts?

The group discussed the organisation, branding and executive board style approach of the US GP-write initiative and how this contrasts with academic research community efforts that the UK typically are involved in and help fund. The group felt that the US GP-write top-down style doesn't fit for the UK. Due to the different funding models, the UK's approach to synthetic genomics should be more decentralised and community-based. The group agreed that the UK should engage with GP-write, but shouldn't be constrained in their own projects. The involvement of UK researchers in the GP-write working groups should be encouraged so that the UK can keep a watching brief, and be involved in international decision making. Chinese researchers agreed that this is effectively the same feeling in their country.

There was an appetite for some involvement in the GP-write community project, but more enthusiasm for developing the platforms that enable work such as that outlined in the pilot project presentations.

Q2: What are the opportunities for the UK? Strengths, talents?

The UK's strong bases in both fundamental biosciences and synthetic biology are key assets that need to be brought together on this project. The UK Foundries are among the best in the world for automating large-scale DNA assembly efforts. The UK also has world-leading expertise in areas such as chromosome biology, development and bioinformatics and high-quality facilities for cell line development and genomics research. The UK biobanks and model organism communities should be engaged with, as well as new large-scale projects such as the Human Cell Atlas. It was recognised that emerging machine learning approaches to predict function from sequence is somewhere where UK talent in AI could interface with the design of synthetic genomic regions.

There was discussion about how the UK has invented the three most-used DNA sequencing technologies (Sanger, Solexa, Nanopore) and whether the large role the UK had in the Human Genome Project (HGP) directly catalysed that or not. It was agreed that innovation and invention of technologies is down to individuals but there was a debate whether proximity to large high-profile projects help push and pull new inventions at the local level or not.

The UK is also a world-leader in Responsible Research and Innovation and one of the UK's other great strengths in research is a track record of major contributions to international collaborations. The group all agreed that collaboration with the likes of the US, China and EU is much more preferable than an isolationist approach. The group agreed to explore these points more at a follow-up meeting.

Q3: What could go right? What should the UK position be?

The group briefly discussed what the definition of synthetic genomics is, and how it is different to synthetic biology, which is already actively funded in the UK. The group agreed that synthetic genomics was not just synthetic biology with big DNA but was geared more towards a new way to perform fundamental bioscience research and lacked many of the engineering aspects of synthetic

biology, such as modular design and the engineering cycle. It was termed “systems biology via synthesis” by one participant.

There was a push from some in the group that the UK strategy should be to develop shared platforms that would benefit many pilot-scale projects and encourage an immediate phase of technology development for these platforms from all areas: biology, chemistry, engineering, physics. Common projects using shared technology would bring the UK community together, with the goal being to kick-start a whole field rather than just be part of the US-led GP-write. Participants also discussed the UK having its own grand challenge project that could be used for synthetic genomics pilot-scale projects. There was some debate as to how to assay successful design and integration of synthetic DNA libraries in such a case.

Next Steps and Future Actions

In terms of next steps, it was suggested that the UK hold an international meeting on synthetic genomics and mammalian genomes to keep discussions going at an international level. Those interested in developing synthetic genomics in the UK should be aiming for cross-council coordination from all relevant funding agencies to help establish work in the country and fund common infrastructure.

The group agreed to follow up the workshop with a future Open Meeting hosted by Sanger (tba) at the Hinxton Genome Campus in 2019.

Synthesising a Human Genome: What could go right?

Genome synthesis is an emerging part of synthetic biology where whole genomes are engineered with thousands of changes throughout by full genome reconstruction from many synthesised DNA modules or via massively-parallel genome editing *in vivo*. Three megabase-scale projects on microbial systems are completed or near-completion giving synthetic genomes for *E. coli* (George Church lab), mycoplasma (Craig Venter Institute), and yeast (Sc2.0 international consortium).

GP-Write: Inspired by the international sequencing efforts in the 1990s on the human genome project (HGP), the lead researchers in synthetic genomes met at Harvard in May 2016 to roadmap a major new project called 'Genome Project - Write' (*see attached letter to Science*) which aims to make full synthesis of mammalian genomes possible in the next 20 years. Due to the scale of this, global co-ordination is essential to (a) define the design rules of large synthetic chromosomes, (b) propose pilot projects, (c) develop the tools and workflow for construction and testing, (d) reduce the costs of synthetic DNA, and (e) respond to diverse social and ethical concerns and develop new models of public inclusion.

While synthesising a whole human genome is somewhat provocative, being able to have synthetic designer chromosomes replace natural chromosomes in mammalian cell models is an attractive idea as it will allow us to investigate the human genome and study chromosome biology in ways inaccessible via standard mutation/testing approaches, even those using genome engineering. In parallel, GP-Write would also enable new applications of mammalian cells, such as streamlined ultrasafe cell lines engineered for induced stem-cell production e.g. for producing organoids.

GP-Write is US-led and is currently focused on roadmapping the required technical, infrastructure and social and governance developments and coordinating several pilot projects while trying to raise larger funds from donors, foundations and agencies. The ambition of GP-Write has also attracted significant funding to groups in China beginning large chromosome synthesis projects.

The UK position: The GP-Write project is keen to involve the UK due to the expertise and facilities for large-scale DNA assembly in the UK. The UK has 4 DNA Foundries that are scaling-up for automation of chromosome-scale projects, while groups at Manchester and Imperial are part of the Sc2.0 synthetic yeast genome project, and *E. coli* and chloroplast genome synthesis projects are underway at Cambridge. The BBSRC and the Wellcome Trust have expressed interest in supporting synthetic genome research and The Sanger Institute has recently appointed associate faculty in synthetic genomics. Already the microbial synthetic genomes written with codon reassignment (*E. coli*), reduced content (mycoplasma), and rearranged order (yeast) have yielded fundamental discoveries in our understanding of genome structure and life, while also offering new specialist applications for industrial and pharmaceutical biotechnology.

Meeting Outline: This initial UK meeting will discuss the possible routes towards UK involvement in the GP-Write initiative and other large-scale international synthetic genomics projects. The aim is to inform policy for funding and coordinating UK research in this area, while helping to establish a national position and scope-out next steps and further meetings. An online report will be published within 4 months of the meeting summarising expert opinions on the main issues and giving a a draft roadmap recommendation for synthetic genome research and funding in the UK and how it should tie-in with global efforts.

Synthesising a Human Genome: What could go right?

Location	**Wellcome Trust, 6th floor**
Date	**Monday 17th September 2018**

Time	Agenda	Led By
10.00 am	**Refreshments**	
10.20 am	Welcome – to include aim of meeting and guidelines	
10.30 am	'Why now, why UK?': the status of synbio investments and genomic tech and expertise in the UK	Susan Rosser and Paul Freemont
11.00 am	Sc2.0 'Lessons Learned'	Patrick Cai and Tom Ellis
11.20 am	US GP-write: aims, status, funding, main project, pilot projects, timeline and partners	Jef Boeke
12:00 pm	GP Write Pilot Project: Re-writing and functional testing of a human developmental regulatory landscape	Wendy Bickmore
12.20 pm	Chinese GP-write and China Foundries	Junbiao Dai
12.50 pm	Summary of morning and overview of afternoon	
1.00 pm	**LUNCH BREAK**	
1.40 pm	Intro to breakout sessions	
1.50 pm	4 breakout groups tackling questions 1) Technologies and technical barriers 2) Pilot projects and research applications 3) Who benefits and how? 4) Infrastructure and coordination	 Tom Ellis Susan Rosser Rob Smith Paul Freemont
2.25 pm	Group feedback	
3.00 pm	**Refreshments**	
3.30 pm	Open room discussion session	
3.40 pm	Q: What do we think of GP-Write vs alternative efforts?	
4.00 pm	Q: What are the opportunities for UK? Strengths, talent?	
4.30pm	Q: What could go right? What should be the UK's "statements"?	
5.00pm	**CLOSE**	

Synthesising a Human Genome: What could go right?

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