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OPPORTUNITIES IN BIOTECHNOLOGY

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Abstract

Strategies for biotechnology must take account of opportunities for research, innovation and business growth. At a regional level, public-private collaborations provide potential for such growth and the creation of centres of excellence. By considering recent progress in areas such as genomics, healthcare diagnostics, synthetic biology, gene editing and bio-digital technologies, opportunities for smart, strategic and specialised investment are discussed. These opportunities often involve convergent or disruptive technologies, combining for example elements of pharma-science, molecular biology, bioinformatics and novel device development to enhance biotechnology and the life sciences. Analytical applications use novel devices in mobile health, predictive diagnostics and stratified medicine. Synthetic biology provides opportunities for new product development and increased efficiency for existing processes. Successful centres of excellence should promote public-private business partnerships, clustering and global collaborations based on excellence, smart strategies and innovation if they are to remain sustainable in the longer term.

Keywords: biomedicine, genomics, m-health, digital science, synthetic biology, gene editing, agriculture, collaborations

1.Introduction

The biotechnology sector operates on an increasingly global basis, with the 25 biggest drug and biotech companies coming from eight different countries (Morrison & Lhäteenmäki 2017; NASDAQ Biotech Index, 2017). The sector has however, undergone considerable consolidation, including the $130 Bn merger of Dow Chemical with Du Pont and Chem China's bid of $43 Bn for Syngenta, leading to a smaller number of truly global players. Major revenue earners include Abvie's Humira monoclonal antibody for arthritis, psoriasis, and Crohn's disease therapy ($15.9 Bn), Gilead's Harvoni small molecule for hepatitis C antiviral therapy ($13.8 Bn) and Celgene's Revlimid for multiple myeloma and mantle cell lymphoma ($6.9 Bn; 1, illustrated in Fig. 1). Approximately 26% of revenue sales are currently spent on research and development, in what is increasingly an expensive escalating biotechnological arms race, with upwards of 40% of venture capital centred on just two areas: Boston Bay and San Francisco (Morrison & Lhäteenmäki, 2017).

Amongst European companies, one of the biggest recent changes has seen Bayer bid $66 Bn for Monsanto, to create a global entity dedicated to innovation in healthcare, including pharmaceuticals, consumer & animal health and agriculture. Digital farming combining big data with the internet of things, is one example of how Bayer will meet the challenges posed by world population increasing to 10 Bn by 2050. Farmland per capita will decline by 17% and climate change

is forecast to reduce yields by a further 17%. This means an effective 60% productivity increase will be necessary to meet the needs of 10 Bn global citizens (Gartland & Gartland 2016; Food & Agriculture Organisation, 2016). Sustainably producing more food with fewer inputs will require precision data on needs and opportunities for growers. Bayer hope to provide an improved quality of life by combining aspects of their current crop protection portfolio with seed, trait and climate change platforms from Monsanto (Bayer, 2017). At a national level, EU28's largest biotechnology products pipeline comes from the UK, where €34.66 Bn was generated from pharma, medtech and biotechnology products in 2015 (PWC, 2017). This activity provides 482,000 UK jobs, €9.81 Bn tax take and equates to a Gross Value Added of €118,500 per employee, being the highest in Europe. What then are the areas of biotechnology where opportunities exist for smart, specialized strategies to emerge and be successful in research and innovation, including economic and future employment prospects?

2.Synthetic Biology

Producing new gene components, epigenetic factors and novel genomes from chemically synthesized nucleic acids is an area which has been growing steadily in recent years. The 'bio-parts' economy is forecast to reach $14 Bn by 2019 and $39 Bn by 2030 through activities which currently have little or no regulation or restrictions on use (Manheim, 2016). This extends from relatively simple genetic switches, to potentially synthesising an artificial human genome in 'Ultrasafe' cell lines, genetically crippled to prevent escape or unforeseen adverse consequences through projects such as 'Human Genome Project Write' (Boeke et al., 2016). Areas where this approach could prove beneficial include virus resistance, improving cancer treatments, testing of novel therapeutics and genome stability studies. A distant goal is to produce sets of pan-human reference alleles for the dissection of disease susceptibility and complex phenotypes through gigabase scale genome engineering. Much progress has been made using yeast as model systems, including the construction of five new yeast chromosomes in Sc 2.0 (Richardson et al., 2017). Combining this type of approach with the search for a minimal genome, the JC Venter Institutes and Synthetic Genomics Inc. have developed JCVI Syn 3.0 through four cycles of design, synthesis and testing to identify life-essential functions using the *Mycoplasma mycoides* Syn 1.0 genome as a starting point (Hutchison et al., 2016). Potential applications include new protein products, increasing the efficiency of existing processes and enhancing biofuel production. The JCVI Syn 3.0 genome consists of a mere 473 genes, with 33 genes associated with preservation of information, although 149 genes have unassigned functions (see Table 1). Much further work is needed to design and build a fully synthetic organism (Service, 2016).

[Table 1]

Questions also remain about ownership and restrictions on use of synthetic organisms and products developed using synthetic biology tools (Manheim, 2016). Opportunities exist for a limited number of large scale synthetic biology factories, or innovation foundries, such as the SynbiCITE foundry based at Imperial College, providing advanced facilities and expertise at a commercial scale and cost that would be uneconomic for individual universities and institutions. SynbiCITE, established in 2013 with €31 Mn support from a consortium of EU, government, research councils and industrial partners has now grown to more than 146 synthetic biology companies (SynbiCITE, 2017). In total more than €340 Mn was invested to set up six research centres for synthetic biology across the UK.

The breadth of potential applications of synthetic biology, is illustrated in Table 2. This area is accessible to all, requiring only significant design experience and imagination.

[Table 2]

3.Innovative biomedical devices

Identifying, designing and constructing novel devices for biomedical purposes have been areas of massive growth in the last decade. The ever expanding capabilities of smartphones, allied to new LED technologies, wireless internet protocols and cloud data warehousing now allow remote acquisition of real time patient data, interpretation and analysis without the previous necessity of attending a doctor's surgery. This has been recognized by several charitable foundations and companies, such as Qualcom, who offer the Qualcom Tricorder X-Prize. Innovative devices using smartphones have benefitted greatly from 'Health Kit' and 'Research Kit' software from Apple, particularly for diabetes management using iPhone or Apple Watch, and a growing number of android powered platforms, allowing anyone to create health applications. Qualcom, an innovation engine, stimulated development of the first consumer-focussed, mobile diagnostic devices, inspired by the medical tricorder of Star Trek fame through a $10 Mn prize fund. More than 300 entrants had to demonstrate a palm sized device that could capture five key health metrics, provide patient tests on ten core health conditions including chronic obstructive pulmonary disease, urinary tract infection and atrial fibrillation, together with at least three further elective health conditions, such as whooping cough, HIV and shingles (Qualcom, 2017). 2017 Tricorder X-Prize winners were 'DxtER' from the American company Final Frontier Medical Devices, receiving the $2.5Mn first prize and the Taiwan-based Dynamical Biomarkers Group's 'Deep Q' tricorder prototypes, in partnership with HTC, receiving $1 Mn (Basil Leaf Technology, 2017; Dynamical Biomarkers Group, 2017; Fig 2). DxtER integrates emergency medical room data with real time patient data, using non-invasive sensors. Acquired data is used by DxtER's diagnostic engine to make a rapid assessment (18). Other smartphone based devices can be used for multitudinous applications, including fluorescence microscopy, DNA sequencing, mutation analysis, eye scanning and the diagnosis of infectious diseases (Michaud, 2017; Kuhnemund et al., 2017, Feng et al., 2017) with up to 98% accuracy. These devices benefit from low cost (<$500 at scale) and ultimate portability, to allow for remote use in the field (Fig 3). Data can also be uploaded to the Cloud using the smartphone.

[Figure 2]

[Figure 3]

Not all health applications of remote sensing have met with regulatory approval, as the Proteus Digital Health/Otsuka ingestible smart pill, combining a wireless sensor and the antipsychotic Abilify, to treat schizophrenia and bipolar disorder was initially refused USFDA approval (Thadani, 2017). Other similar Proteus sensors use a stomach skin patch and have achieved approval.

3D-printing (additive manufacturing) has also been used to develop devices for a range of health applications, including a system for using a $500 consumer 3D printer, with a custom printed magnetic particle processing attachment replacing the usual extruder head. This AI Biosciences/Johns Hopkins device allows extraction and processing of 12 DNA/RNA samples in 13

minutes proving effective for detection of infectious agents, including chlamydia, dengue fever and for general PCR amplification (Chan et al., 2016). Bespoke surgical implants, often made out of unique plastic polymers, or metal alloys, are increasingly being used to repair and protect against head trauma, for example following road accidents (University Utrecht Medical Centre, 2014). The range of 3D printing applications seems almost endless, from bacterially imprinted clothing, with pores able to change size and shape in response to heat and moisture (Wang et al., 2017), to regenerative medicine applications using bioprinted tissues, such as reconstructed ears and heart valves (Ameri et al., 2017). The search for novel antimicrobials is also benefitting from 3D printing, with standardised bacterial or viral impregnated materials being used for standardised testing of candidate molecules. This is an increasingly important area for future research, as the World Health Organisation has recently published a list of 12 bacterial families posing the greatest risk to public health, through multidrug resistance, carbapenem and G3 cephalosporin resistance (WHO, 2017).

4.Sequencing costs continue to decline

The continuing dramatic reduction in the cost of genomic sequencing and increases in speed allow a human genome to be sequenced for considerably less than $1000 in a single day (Hoeksma, 2017). Oxford Nanopore, through their innovative portable MinION device offer a low cost (sub-$1000) entry into the world of genomics, able to sequence 1-20 Gbp per cell, and usable in almost any field setting, being powered from a laptop. This extends the applicability of the technology, based, on voltage changes as a DNA strand passes across a nanopore, greatly. It can be scaled up through devices such as PromethION, combining up to 48 flow cells, each with up to 3,000 nanopore channels, giving up to 50 Gb capacity per run and an ability to sequence a human genome in 2-4 hours (Loose, 2017; Magi et al., 2017). Other massive scale sequencing systems, such as Illumina's multi-channel flow cells (Fig 4), for example, are combining their HiSeqX technology with Philips artificial intelligence platform in the identification of key mutations and the provision of data for clinicians. Illumina, who are also working with IBM Watson Health, now believe that the $100 genome is close to fruition. There is however, a clear and as yet unmet need for genomics to be mainstreamed at the point of care, alongside radiology and pathology services data (Hoeksma, 2017). Perhaps the largest current genomics project is Genomics England – Illumina '100,000 Genomes Project' partnership, aiming to meet this ambitious target by 2018, having reached 36,083 genomes by Oct 1, 2017 (Genomics England, 2017). Genomics England Clinical Interpretation Partnerships (GECIPS), open to international scientists and clinicians, will play an important role in analysing individual rare diseases or conditions from the findings.

[Figure 4]

Together with several bioinformatics and computing companies, big data and artificial intelligence techniques are being utilised to educate a new type of professional, able to translate and interpret such data for incorporation in clinical workflows. Universities and bodies such as the Wellcome Trust/Sanger Institute in Cambridge have recognized this and are now offering big data interpretation apprenticeships to meet burgeoning demand (Sanger Inst/Wellcome Trust, 2017) with the creation of up to 56,000 new jobs forecast by 2030. Amongst other large scale genomics projects, Astra Zeneca aim to analyse 2 million genomes in the coming decade; GSK are working closely with the US sequencers Regeneron, and the UK BioBank to sequence 500,000 exomes from de-identified UK citizens over the age of 40 years, over the next 3-5 years (Withers, 2017; Hirschler,

2017). Typically, such large scale projects involve commercial partners having closed access to public data for nine months, followed by freely available public access through for example, UK BioBank . A focus of such operations has emerged in the UK 'Golden Triangle', between London, Oxford and Cambridge, where a critical mass of facilities and specialist expertise is being constructed. Synergies provided by companies such as Oxford Nanopore, Horizon Discovery, Eagle Genomics and Congenica are well placed to take advantage of these developments, although as yet, there is not a large scale sequencing facility quality assured to international clinical standards (Hirschler, 2017). This means that Astra Zeneca, for example, continue to have to send diagnostic samples for processing to the United States. This is an opportunity for a European 'Mega-Hub' to evolve, able to compete with American and Chinese facilities, creating thousands of jobs, as well as technological, economic and societal advantages. This has been recognized by the UK Chief Medical Officer (Dame Sally Davies) who has described a new genomics era 'Gold Rush' in her 2016 annual report 'Generation Genome' (Davies et al., 2017). As the largest organised health system in the world, the role of the National Health Service (NHS) in finding new and innovative ways to bring genomics data and interpretations to point of treatment facilities across the UK, to realise these benefits cannot be underestimated (Davies et al., 2017). Other countries, both within Europe and further afield, are developing similarly ambitious genomics and clinical bioinformatics targets, such as American plans to link up more than 1 million genotypic, phenotypic and lifestyle data sets to speed up biomedical discovery, with a €441 Mn budget (Obama, 2016). Precision medicine initiatives extend to ROADMAP, combining US National Institutes of Health EpiGenomics Consortium and ENCODE data to boost understanding of the role of individual genetic variants in disease susceptibility and prognoses (Herceg et al., 2017; Kuiper et al., 2015), as well as the EU Innovative Medicines Initiative, with a 10-year budget of €5.3 Bn to identify and address bottlenecks in the development of novel drugs, therapies and biomedical devices, including rapid approvals. So far, 90 projects have involved 863 participants, delivering 6995 project outputs and 2686 publications (Innovative Medicines Initiative, 2017). Bottlenecks in drug discovery have been addressed by making trials more reliable, improving translatability, and helping companies to predict patient safety earlier on in the development process, by encouraging collaboration in a pre-competitive space, sharing knowledge and skills, and data pooling. Recent examples include establishing a European biobank for quality assured human induced pluripotent stems cells (De Sousa et al., 2017), developing a portable rapid diagnostics device for filovirus nucleic acids testing (e.g. Ebola virus), in 75 minutes (MOFINA Project, 2017), and discovering new ways to target drug-resistant bacteria (Chan et al., 2017). By combining different cutting edge expertise and stakeholders, this EU-led public private partnership is successfully identifying new ways to tackle global health challenges.

The combination of mobile (m-) health and big data tools is providing new insights into disease prevention, diagnostics and therapies, especially when allied to artificial intelligence, novel sensors, smartphones and decision making tools in a market estimated to exceed €26 Bn by 2020 (Albrecht, 2016). The e-Estonia Portal is an early example of a European model for such systems, based on an efficient 'once only' principle of data acquisition, allowing multiple interrogation of cloud data using standardised formats and a capture-analyse-improve approach. Other European states are adopting similar, common format systems, including several German lände (Liiv, 2017; Becker et al., 2014). Direct to consumer tests for DNA ancestry (23andMe, 2017), pharmacogenomic predictions of the suitability of particular drugs for individual patients to identify poor metabolisers (Somogyi and Phillips, 2017) and predictive genotypic analyses for as little as €100, can all contribute to the m-

health revolution, but not without careful interpretation of results (Genes-for-Good, 2017). For example, two *CYP2C19* alleles found in up to 14% of patients, are associated with poor clopidogrel (Plavix) metabolism, linked to a high risk of treatment failure for this globally significant medicine used to reduce heart attack and stroke risk (Topol & Schork, 2011). This also represents a substantial waste of resources, perhaps as much as $1.5 Bn annually. A further area of blossoming personalised activity is consumer demand for gut microbiome profiling. 'SmartGut' (µBiome) testing assesses gut bacterial diversity from faecal samples, using 16s ribosomal RNA sequencing and comparison with a 100,000 microbial gut sample database, at a cost of $89 for US health workers. Interpretable data includes information on 26 microbial species with risk factors for disease or long term conditions (Costandi, 2013; Shankar, 2017). 'Map My Gut' is a $381 assessment of faecal microbes, allowing comparison with 16s rRNA and metagenomics sequence databases and can be commissioned by NHS health professionals (Beaumont & Goodrich, 2016). As public understanding of personalised genomics rises, the links between microbial diversity and disease are enhanced, assessments such as these will become increasingly popular and less expensive.

There are however many questions relating to personal genomics, ethics and privacy which have not yet been fully addressed. For example, do direct-to-consumer kits sold as part of a €9.6 Bn market sector provide adequate privacy protection (Aitken et al., 2016)? A recent survey found that 28% of UK consumer genetic tests did not comply with UK Human Genetics Commission guidelines (Geoghegan, 2016; Hall et al., 2017). Questions regarding informed consent, preservation of anonymity, data confidentiality, de-/re-identification, ownership of intellectual property arising from personal data and the ability to withdraw at any time are not yet fully answered (Krieger et al., 2016). Whether informed consent also relates to future rather than merely present research is also frequently unclear. Without adequate consideration, these questions could adversely impact on risk perception, medical decision making, current and future participation in personal genomic testing. American survey data suggests that direct to consumer test users learn from their individual results and modify their beliefs, particularly when seeking further medical actions relating to large or unexpected risks (Aitken et al., 2016; Hall et al., 2017). Whether this applies equally in other marketplaces remains unclear. There is however, a clear need for greater public education around the issues related to personal genomic testing, so that medical decision making, can be better informed, especially by and for the benefit of patients (Krieger et al., 2016). One area where big data, artificial intelligence and transcriptomics, the study of the complete set of RNA sequences produced by the genome under particular conditions, are likely to bring substantial benefits is in modelling the cancer transcriptome. Using the Swedish national supercomputer, University of Stockholm scientists mapped the transcriptomics of 315 genes to 17 major cancer types using RNA, protein and outcome data from 8,000 individual patients and clinical metadata, to produce 900,000 patient survival profiles for personalised patient models (Uhlen et al., 2017). Findings from this, the biggest study of its kind to date, suggest that within tumour variation can be as large as that between tumour types, reflecting the heterogeneity of cancers. An overall tendency for shorter survival to be associated with up-regulation (increased transcription) of genes associated with mitosis and cell growth was observed, together with down–regulation of cell differentiation associated genes. That there is a need for actions and not just words on issues of patient data and public health has been highlighted (Parry, 2017), alongside recognition of the need to consider implications for other family members, both current and future, in making decisions on what to do with personal genomics data. Inter-generational differences in how insurance companies and

pension funds might choose to interpret such data must also be taken into account (Economist, 2017).

5.CRISPR Genome editing systems take command

Clustered regularly interspersed short palindromic repeats (CRISPR) have in recent years become a ubiquitous system for altering the genome of almost any organism (Zetsche et al., 2015). In the first nine months of 2017, 2,568 publications citing CRISPR were found in PUBMED and the cumulative total of publications or patent applications citing CRISPR exceeded 64,500 since 2002 (Makarova, 2011). The diversity of CRISPR systems and the associated CRISPR effector proteins, such as Cas9, provide bacterial adaptive immunity, having a defensive role not unlike restriction endonucleases. Crucial to their effectiveness is an ability to recognise double stranded DNA, or sometimes RNA, and produce precise cuts in a predictable, structured fashion (Makarova, 2011; Makarova et al., 2015, Fig 5). A guide RNA can be programmed to match any specific sequence, to which Cas9 is attached. The guide RNA binds to target DNA, following the rules of base pairing, allowing Cas9 to align precisely and cut both DNA strands. The cut DNA can be altered with extra DNA sequences inserted, or the target DNA sequence eliminated by deletion (Barrangou & Doudna, 2016; Charpentier, 2015, Fig 5). The range of CRISPR-Cas systems are classified by the nature and configuration of their Cas proteins. Although other gene editing systems exist, such as Zinc finger nucleases and TALENS (Ruiz de Galaretta & Lujambio, 2017), these do not appear to have as much programmable flexibility as CRISPR systems. Class 1 CRISPR systems use several Cas proteins and the CRISPR RNA (crRNA) in cleaving DNA, whilst Class 2 systems use a larger single Cas Protein together with crRNA (Makarova et al., 2015). Cpf1 for example, is a Class 2 CRISPR system based on a 1,300 amino acid protein from *Prevotella* and *Francisella* (Zetsche et al., 2017), with a single RNA guided endonuclease, which may have wider and simpler applicability in manipulating genomes (Zaidi et al., 2017). Other Cpf1 enzymes have been isolated from, amongst others, *Acidaminococcus* and *Lachnospiraceae* bacteria and shown to be effective in editing human genomes (Zetsche et al., 2015).

[Figure 5]

CRISPR systems have been used to reduce HIV-1 retroviral load and virus production 20-fold in cultured cells (Zhu et al., 2015), and to excise HIV-1 progenomes in human T-cells (Kaminski et al., 2016), whilst also being useful in screening for protein domains in disease target genes (Shi et al., 2015) and in the epigenetic mapping of p53 'Guardian Angel' binding sites (Korkmaz et al., 2016). CRISPR-Cas is also being used as a DNA-based search tool for smart antimicrobials, for selective eradication of microbial pathogens without risking the development of antibiotic resistance (Barrangou & Ousterout, 2017) and has even been used to store static images and a digital movie of a galloping mare in the *E. coli* genome (Shipman et al., 2017). Food based applications of CRISPR technology to improve crop plants such as non-browning white mushroom (*Agaricus bisporus,* Fig 6) have been declared as not requiring regulation in the United States (Waltz, 2016), in a similar fashion to browning resistant Arctic Apples produced using RNAi and non-browning potatoes silencing up to four polyphenol oxidase genes (Waltz, 2015). The EU continues to avoid making a decision on whether products of CRISPR use would be categorised as genetically modified or not, even though they may reach the commercial marketplace before CRISPR-derived medical drugs (Bomgardner, 2017). Public acceptance may however, be uncertain.

[Figure 6]

Gene editing is not, as yet, globally regulated, with at least partially unanswered questions relating to off-target effects and mosaicism, where chimaeric products could be counter-productive (Broad Institute, 2017). Issues surrounding consequential liability and ultimate patent rights are also being contested, although the Broad Institute, together with Harvard University and MIT, who have been granted US patents on CRISPR, have adopted an enlightened approach to licensing for uses excluding human germline editing, tobacco and 'terminator' seed type applications, based on 'inclusive innovation' principles (Luo et al., 2016). Perhaps the best efforts to develop a set of guidelines for the application of genome editing technologies has come from the National Academies and Wellcome Trust, who concluded that significant scientific progress was needed before genome editing could satisfy risk/benefit standards for starting clinical trials for anything beyond treatment or prevention of disease or disability (National Academies Press/Wellcome Trust, 2017). These authors, amongst many others, also distinguish between uses for somatic cells in humans and potential germline applications, which could affect future generations.

Whilst earlier research-led studies in human embryo genomic editing using CRISPR proved successful, using abnormal and therefore waste embryos, low efficiency and mosaicism proved problematic, as expected from animal studies (Chen et al., 2015). By combining CRISPR-Cas9 treatment with intra-cytoplasmic sperm injection (icsi) in metaphase II of meiosis, scientists from Oregon Health & Science University, Salk Institute and University of Korea were able to overcome some of these problems. A team led by Shoukhrat Matalipov, has corrected the dominant pathogenic gene mutation *MyBPC3* in viable human embryos (Ma et al., 2017). This mutation, found in up to 8% of some Indian populations and affecting up to 1 in 500 adults, leads to hypertrophic cardiac myopathy. This is a significant cause of heart failure in young adults (Maron et al., 1995)). The combination of icsi and metaphase II editing (Lin et al., 2014) successfully corrected 72% of embryos to wild type genotypes with mosaicism limited to 25%, with no evidence of off-target effects when these embryos were allowed to reach the blastocyst stage, as assessed by whole exome and genomic sequencing (Fig 7). This approach which has significant efficiency, accuracy and safety advantages over other methods, has great potential as an adjunct to preimplantation genetic diagnosis in the correction of heritable mutations in human embryos. Sun Yat-sen University scientists recently successfully swopped a single adenine-thymine base pair for a guanine-cytosine base pair using base editing (Kim et al., 2017), to correct a beta-thalassemia gene defect in human embryos (Liang et al., 2017). As with the Oregon study none of these edited embryos were allowed to develop beyond the blastocyst stage, meaning that none were implanted. Despite massive global media hype, these studies are as yet a long way from clinical application, but do represent significant staging posts on the journey towards human germline editing in years to come. Faster progress is likely around opportunities in understanding more fully how tools like CRISPR work (Stella et al., 2017) and in agricultural gene editing leading to enhanced crops and animals. For example, CRISPR edited pigs produced using the uncoupling protein *UCP1* gene from mice lowers fat content and increases cold tolerance in modern breeding pig genotypes (Zheng et al., 2017).

[Figure 7]

6. Increasing scope for novel cancer therapies

Two single-shot chimaeric antigen receptor T-cell (CAR-T) therapies have received US Food & Drug Administration approval, as novel cancer therapies move forward. CAR-T therapies combine an antibody derived targeting fragment fused to signalling domains capable of activating T-cells (Gross & Eshhar, 2016). Although not without significant risks, Novartis' CAR-T Kymriah and Kite Pharma's (a recent $10 Bn purchase by Gilead) Yescarta offer hope for certain types of relapsed leukaemia and possibly other blood cancers. Yescarta clinical trials showed a 72% therapy response rate, with 51% of patients showing complete remission (Rodriguez Fernandez, 2017). Caution is needed when considering CAR-T therapies, however, as several deaths due to side effects probably related to cytokine storms have been observed, and a number of other CAR-T trials have been abandoned. Such single-shot infusions come at a very high price, with Gilead listing Yescarta therapy at €316,000 and Novartis' Kymriah priced at €398,000, for blood cancer patients already having had two other failed treatment lines. The development of novel biotech cancer therapies is likely to continue to be an emotive, exciting and profitable vista for the future, especially if costs can be reduced as more alternatives approach regulatory approval (Sadelain, 2017). Such approaches would seem ideal candidates for Innovative Medicines Initiative or Breakthrough Drug support (Innovative Medicines Initiative, 2017).

7. The power of partnerships and international collaboration

Few biotechnological opportunities can be effectively exploited by single countries alone, as the complexity and cost of research and development continues to rise and applications increasingly require multidisciplinary inputs. This could be in m-health where health-apps have been recognised as a global opportunity for the insurance industry (Guest, 2017) or web-based data sharing platforms such as MyGene2 which allow families and clinicians seeking molecular diagnoses to share data (Karow, 2017). International and public-private partnerships will become increasingly important in realising potential such as in understanding the basis of so-called 'rare' diseases. These affect less than 1 in 2,000 people in the EU28. Collectively however, such rare diseases are actually quite common (Boycott et al., 2017). International partnerships and shared data can improve the probability of finding other mutations in the same or similar genes. MyGene2 has accumulated 1,225 freely available data sets in its first year from 880 clinicians, families and researchers on 723 genes including many unique disease gene variants (Karow, 2017). The International Rare Diseases Research Consortium is developing strategies for enabling the diagnosis of all rare genetic diseases using common standards, tools and genomic analysis utilities (Parry, 2017; Boycott et al., 2017; Global Alliance for Genomics and Health, 2017; Im et al., 2015; Gabrielczyk, 2017). This should ultimately improve rapid diagnosis and treatment prospects for rare disease sufferers through collaborative partnerships. Regions seeking opportunities in biotechnology should seek to input their unique expertise and where possible facilities and investment to international and public-private partnerships such as these to create the new knowledge, jobs, economic and societal advantage that further progress will bring (Hirschler, 2017; Davies et al., 2017).

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Table 1 JCVI Syn 3.0 Gene Functions

Function	Genes
Gene Expression	41%
Cell Membranes	18%
Cytosolic Metabolism	17%
Genome Preservation	7%
Unknown Function	17%

Source: Hutchison et al., 2016; Service, 2016

Table 2 Application Areas for Synthetic Biology

Application	Example	Refs
Gene Circuits Assembly	Strand displacement switches in serum-free media	Fern & Schuman, 2017; Re, 2017
Synthetic Theranostics	Stem cell manipulations	Rathman et al. 2017
Alginate Bead Delivery Systems	Protection against liver failure in mice	Service, 2016
Novel Flavours, Food and Drinks	'Raspberry' ketones from wine yeasts	Jagtap et al., 2017
Identity Preservation	Reversible data hiding using DNA computing	Wang et al., 2017
Precision Oncology	Tailored tumour diagnosis and gene based therapy	Re, 2017

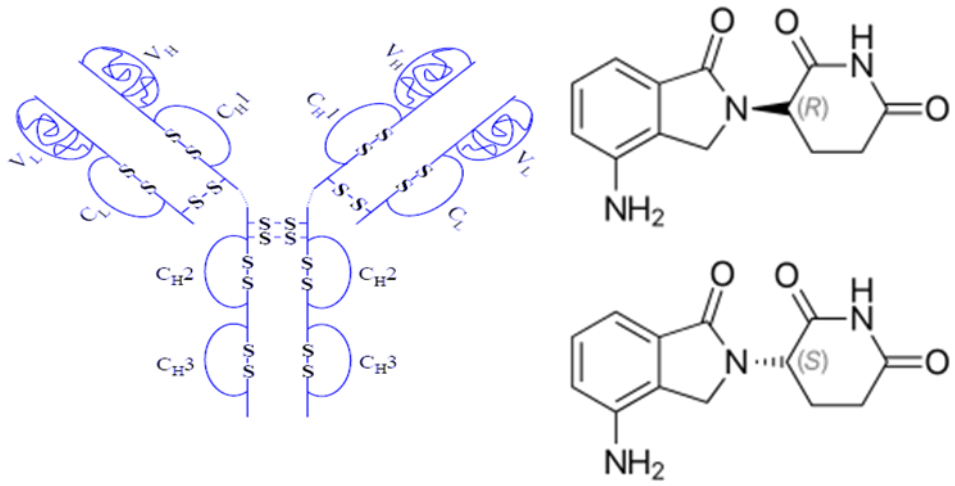

Figure 1 Humira (left) and Revlimid (right) structures. Source: Wikiwand

Figure 2 The Qualcom Tricorder 2017 X-Prize Winning DxtER portable diagnostic device

Source: X-Prize.org

Figure 3 iScope smartphone mobile device

Source: NIH

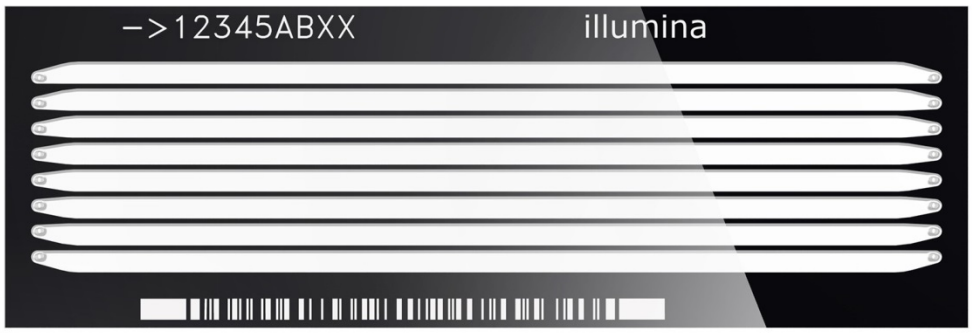

Figure 4 Illumina 8 channel sequencing flow cell

Source: Illumina.org

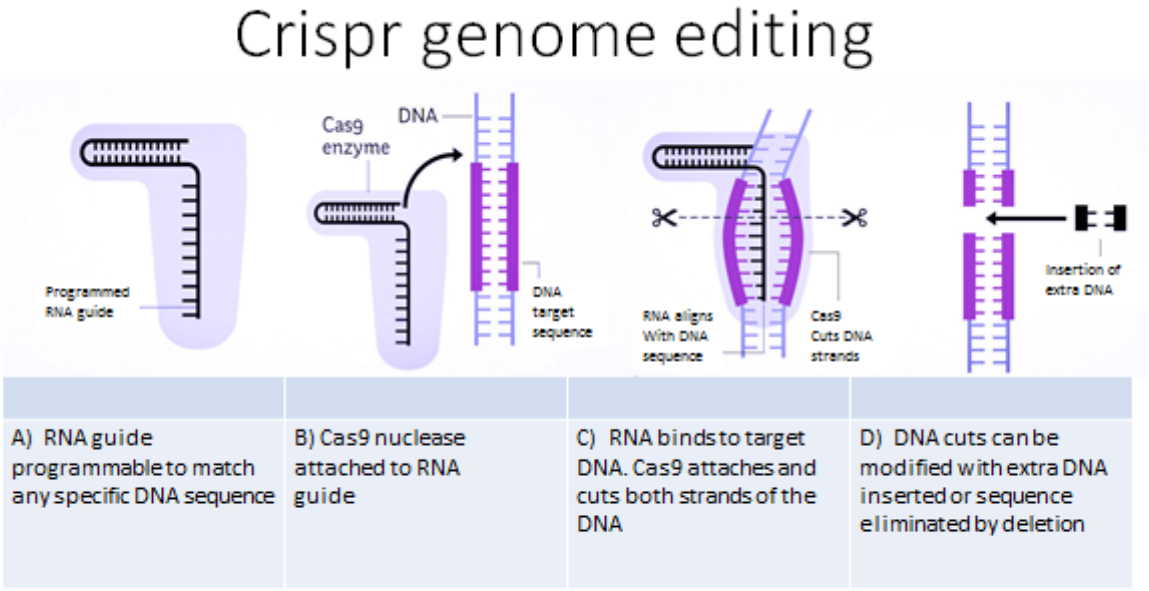

Figure 5 CRISPR structure and function

Figure 6 The common white mushroom (*Agaricus bisporus*) has been gene-edited with CRISPR to reduce browning.

Source: USDA

Figure 7 Human blastocyst

Source: Open i- Open Access Pub Med Central