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From my perspective

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A B S T R A C T

The recent devastating pandemic has drastically reminded humanity of the importance of constant scientific and technological progress. A strong interdisciplinary dialogue between academic and industrial scientists of various specialties, entrepreneurs, managers and the public is paramount in triggering new breakthrough ideas which often emerge at the interface of disciplines. The following sections, compiled by a highly diverse group of authors, are summarizing recently achieved game-

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changing leaps in science and technology. The game-changers range from paradigm shifts in scientific theories to make impact over several decades to game-changers that have the potential to change our everyday lives tomorrow. The paper is an interdisciplinary dialogue of relevance for academic interdisciplinary thinkers, large corporations' strategic planners, and top executives alike; it provides a glimpse into what further breakthroughs the future may hold and thereby intends to spark new ideas with its readers.

1. Introduction

1.1. General outline

Each of us is born into a world we do not fully understand. With time we learn from the results and endeavours of preceding generations creating knowledge on the laws that govern our universe and finally can contribute ourselves to the eternal struggle of science to do its part in discovering the truth (Strevens, n.d.; Rörsch, 2014; Anon, 2005; Betz, 2018a). Over the centuries incredible progress was achieved, although not all areas of science and technology were advancing at the same speed (Anon, n.d.-a) and further progress is inherently difficult to predict (Harwood and Eaves, 2020). The following sections are summarizing recently achieved game-changing leaps in science and technology, sorted on their expected potential to change our everyday lives – tomorrow, the next 10 years, 30 years and beyond - and provide a glimpse into what further breakthroughs the future might hold. While of course there are more specific reviews available deep-diving into each of the respective topics, the importance of maintaining an interdisciplinary overview (Betz, 2018b; Betz et al., 2019; Phillips et al., 2019; Anon, n.d.-b; Anon, n.d.-c), the mind of a generalist or polymath, is often a character trait carried by some of the most impactful individuals in history, such as Marie Curie, Leonardo da Vinci, Charles Darwin, Isaac Newton, Louis Pasteur, Thomas Edison, Benjamin Franklin, Richard Feynman, Bill Gates, or Elon Musk (Murray, 2004; Johnson, 2011). Recent analysis has been published in 2023 that "Papers and patents are becoming less disruptive over time.", (Park et al., 2023), showing that scientific work is increasingly less likely to produce true game changers. While the underlying reasons are not entirely clear the authors propose that a main factor is the decline of diversity in work cited, reflecting a tendency of researchers to expose themselves to narrower and narrower slices of existing knowledge. This is a strong argument to further foster the interdisciplinary dialogue, connecting researchers between fields and develop a polymath mindset of benefit not only to academic researchers but also to entrepreneurs and corporate strategists that need to make decisions in highly uncertain environments (Gilbert-Saad et al., 2023).

1.2. General thoughts on sustainability

Along with technology advancement, sustainability must be considered as a key factor in assessing the tech competitiveness and positive impacts over time and beyond for human's well-being. Within the sustainability space, the environment, economic criteria, and social criteria as independent elements impact smart design. These elements are then linked together and enabled by disruptive technology, which is a fundamental driver to produce innovative business solutions. The topic of "Game Changers for The Future" can be addressed from a "Design Thinking" methodology- where the innovator empathizes with current technologies to define strategies and ideate breakthrough innovations for the future. Some technology and innovative solution prototypes may require further iterations to perfect the model design blueprint. If we approach this exercise using desirability, flexibility and viability as dimensions to propose cutting edge out-of-box innovations, the need to incorporate a 4th independent and moving dimension namely, Sustainability e.g., by building sustainable efficient technologies for a sustainable future. The sweet spot and the dimension driver in the center is innovation, the common denominator for all new discoveries and future game changers. As innovators, we are poised and positioned to accept the need for sustainability in everything we do and there is no better and perfect time than NOW. Sustainability is becoming a strong driver of change- biotechnology can be leveraged by engineering better solutions for optimized processes, e.g., space exploration for microorganism surviving space travel (Anon, 2020a), alternative foods and energy independence from the grid (Anon, 2020b). The concept of sustainable development was described by the 1987 Bruntland Commission Report as "development that meets the needs of the present without compromising the ability of future generations to meet their own needs". Hence, the topics addressed by the authors in the article certainly have the potential to provide a shift towards a more holistic and sustainable value for future technologies and could provide a manifold to think about responsible manufacturing and consumption, strongly supported by industry 4.0 (Moraes Silva Lemstra and de Mewquita, 2023).

The game changer topics are clustered into buckets- Smart Living, Health Enablers, Advanced Biotechnology and Ubiquitous Engineering, dynamic life science and alternate resources for the future.

The topics covered under 'Smart Living' are- Machine Learning and AI, Electronics Future, Robotics, Wearables and Digital Health and 3D printing.

Smart Living: Like smart pills as edible electronics first approved by FDA and released in 2017, healthcare technology continues to accelerate and improve globally across different markets. As innovators, we are constantly learning of new threats from using smart devices related to data gathering and storage - for which security will improve and dealt with prevention priority rather than response. As an example of smart 3D-Printers, the creation of quality and efficiency of care for the future will continue to improve due to groundbreaking bioprinters (Agarwal et al., n.d.) as evolving sustainable technologies.

The topics covered under 'Health Enablers'- mRNA vaccines, Cell Therapies, Gene Editing, and Healthcare vs. Sick Care, condensate as drug targets and Pandemic preparedness.

Health Enablers: Now more than ever poor lifestyle choices can be managed- sickness is encountered as part of damage control rather than proactively creating true health and preventing disease. Cell therapy successes as programmable platforms and next-generation sustainable gene-editing technologies are dramatically expanding and harnessing the genetic material's power to teach the body to make essential proteins as treatments to impact human disease. Highly sophisticated bubbles (Endo-Takahashi and Negishi, 2020) that form well-studied nanoparticles encapsulating gene encoded tools as sustainable technologies will have a significant impact across biomedicine for the future. Our current knowledge will help develop better interventions, more efficient and personalised therapeutic strategies for humans.

The topics covered under 'Dynamic Life-Science' are- Microbiome, Anti-ageing, Fighting Disease- Longevity and The Human Brain.

Dynamic Life-Science: Current state-of-the-art technologies have dramatically improved patient outcomes and life in general. The future trends in health and nutrition to address longevity is at the forefront of the innovation wave that comes as part of bio-revolution in understanding the human brain coupled with microbiome (Allen et al., 2017). Research projects are beginning to assess toxicokinetics and toxicodynamics of environmental chemicals; such assessments could help consider interactions between the microbiota and chemical toxicity. Such connections made from gathered datasets from microbiome and the human brain is prone to set a mark for a new era; the enablement of sustainable technologies poses potential to change the face of bio-innovation as an approach for targeted life-science for prolonged sustainable health.

The topics covered under 'Advanced Biotechnology and Ubiquitous Engineering' are- Resolution Revolution, Nanorobots, Synthetic Biology and Artificial Meat.

Advanced Biotechnology and Ubiquitous Engineering: The future of nanobot production will be to establish a "global superbrain" called the brain-cloud interface (Anon, 2019) where human thought could be transferred onto an artificial interface tested for applications in medicine. A sustainable technology for the future facilitated by the creation of programmable living robots made from living, organic tissue may raise ethical concerns, but biological machines 1–100 nm and their small-scaled properties could be leveraged for new applications making diagnostic technologies for biotech processes, in water remediation, environmental monitoring (Taylor-Smith, 2020) more feasible with global net worth estimations of over $8billion by 2025 (Moore, 2021). A sustainable economy depends on alternate foods like Quorn, a meat substitute from fermented mold fungus with added vitamins and egg protein. Its climate footprint is smaller than that of steak only because production of eggs does not consume as many resources as that of meat (Finnigan et al., 2019).

Engineering design for sustainable development includes new hardware improvements, monochromators, and spherical aberration corrections and energy filters are being pushed to resolve structures at single atoms. Most functional structures of mRNA and ribosome complexes (Bheemireddy et al., 2021) remain to be discovered and with individual mRNA structures having exceptionally diverse architecture, its folds that can regulate gene expression for de novo structure resolution has been challenging. Multi-domain ribosomes- massive protein-RNA complexes as targets are brought into the realm of structure-based drug discovery and hence the technological advancements in imaging analysis by the development of direct electron detectors (Kisonaite et al., 2022).

The topics covered under 'Alternative Resources' are- DNA data storage, Cheap Energy, Fusion, Carbon Capture and Space Exploration.

Alternative Resources: Energy in all its forms is an enabler for growth and prosperity. Space exploration requires careful handling of resources and where possible, harvestable resources. Hence, space flight has been a driver for technology development and can be applied on Earth to improve initiatives by exploiting synergetic effects in sustainability (Volker et al., 2021). The recent report from Intergovernmental Panel on Climate Change (IPCC) on the latest science showed that the world must nearly halve its greenhouse gas emissions this decade and reach net zero emissions by 2050 to keep global warming in check by transitioning away from fossil fuels. Is there a silver bullet to the climate crisis? Nuclear fusion, a near-limitless, zero-carbon source of reliable power where the elements- deuterium and tritium as isotopes of hydrogen found in seawater could be the closest thing to it. As part of sustainable power generation and renewable energy technologies, in Oxfordshire, UK EUROfusion scientists have generated fusion energy by the giant donut-shaped machine, JET tokomak and shares production results of high power 12 MW, which is very impressive but currently capped at 5 s then struggles to sustain it for longer time due to overheating magnets. For an everyday energy source, much longer fusion burn is required at future fusion power plants with higher temperatures as high as 150million degrees Celsius- 10 times hotter than the core of the sun (Gainor and Dewan, 2022).

For companies and organizations to increase their sustainability embracing new technologies are essential. For example, research results indicate that an organization's "digital orientation" has a significant positive effect on its environmental performance, an effect even more pronounced in technologically turbulent business environments (Bendig et al., 2023). The use of digital twins can have profound effects on sustainability and innovation capabilities (Holopainen et al., 2021).

2. Tomorrow

In this first section we are elucidating fields that are already advanced and hold promise for deep impacts within the next few years affecting everyday lives. The following topics are covered: pandemic preparedness, mRNA-based vaccines, single-cell omics, organoids, microbiome, gene editing, cellular therapies, machine learning and artificial intelligence for drug discovery, wearables and digital health tools, the empowered healthcare consumer, cultured meat, synthetic biology, 3D Printing, sustainability, and carbon capture. Looking into the future, these game changers have the potential to short-term improve our lives in many ways.

2.1. Pandemic preparedness

100 years after one of the most devastating health crises in modern history ('1918 H1N1 Influenza pandemic'), and despite significant advancements in medicine, we are once again facing a crippling pandemic (COVID-19) that has shutdown global travel, brought both developing and developed economies to a halt, and forever altered our way of life. The increasing globalization, overpopulation, and encroachment of humans on animal habitats has increased the risk of pathogen spill-over and therefore more pandemic-scale events in the future are unfortunately unavoidable (Jones et al., 2008). Despite this inevitability, game-changing technologies and platforms centred around surveillance and infrastructure will help in controlling and reducing the severity and impact of the next pandemic.

A major factor preventing another widespread pandemic event is active surveillance. After COVID-19 most are at least familiar with a nasal swab and polymerase chain reaction (PCR) used to detect viruses. PCR amplifies the genetic material from a specific organism and is one of the most accurate tools for detecting both viral and bacterial infections. However, its sensitivity is also its Achilles heel. A pandemic pathogen is a novel strain and therefore it will not be detected by established PCR assays. In addition, the pathogen will continue to evolve into new variants throughout the duration of a pandemic, altering its template and undermining the efficacy of detection assays. Next-generation high-throughput sequencing using pan primers can overcome obstacles of intra-virus variation and can also be used to screen a broad spectrum of other pathogen classes at the same time (Cheval et al., 2011). In addition, a pan-viral microarray assay, known as "Virochip", which contains ~36,000 probes bearing the most conserved sequences of all known viruses of humans, animals, and microbes, has been used to successfully detect both known and novel viruses including, but not limited to, new strains of coronavirus, rhinovirus, and retrovirus in patients (Chen et al., 2011).

Pandemic detection and discovery are all about recognizing patterns within population groups, to determine whether a cluster of patients with common symptoms is benign, or if a pathogen has pandemic potential. Big Data is helping to connect the dots. For example, in the US the Center for Disease Control (CDC) has implemented the Illness-Like Influenza Surveillance Network (ILINet) program in which healthcare providers act as sentinels within the community collecting data on patients presenting flu-like symptoms to enable the identification of trends on a national level. A new experimental approach to detect potential pandemics that is under investigation is the use of social media and search engine metadata. We utilize social media to document all aspects of our life, including when we feel unwell, which however can also lead to undesired consequences (Tandon et al., 2021). In addition, in a post-internet era in which information is at our fingertips, it is more convenient to google our symptoms or consult WebMD rather than a real-life doctor. A record of these status updates and search results exists out there on the World Wide Web and it is only a matter of mining through the large data sets. This metadata in combination with geo-positioning data can help identify potential areas of interest/concern. A systematic review of social networking data to track pandemics has shown a high correlation with traditional pandemic surveillance systems (Al-garadi et al., 2016). Limitations include privacy protection and lack of coverage in countries and communities from low social-economic indices.

Although online data may not replace traditional detection methods, it still may prove to be a powerful complementary tool. On top of that, social media data can even be used to identify potential breakthrough research (Li et al., 2022).

Most human diseases originate from zoonotic sources when a pathogen jumps from one species to another. Therefore, pandemic preparedness programs should not only include active surveillance of humans but of animals as well. Based on viral host relationships and patterns of emergence, it is estimated that there are between 600,000 to 800,000 unknown viruses with spill-over potential (Carroll et al., 2018). Initiatives like the Global Virome Project (GVP) take a proactive approach to discover and map these unknown viruses in animals. The GVP database would be an invaluable resource to the research community and could have a profound effect on the field of virology (like the impact that the successful completion of the Human Genome project in 2003 had on medical research) and accelerate the development of vaccines and treatments even before pandemic threats emerge. The limitation of the initiatives is the high infrastructure/manpower requirements to complete the project with the current costs to characterize all remaining unknown viruses estimated at US$7 billion using current technology (Cutler and Summers, 2020). However, given the economic cost of the current COVID-19 pandemic, from one single virus is estimated at over US$16 trillion (Cutler and Summers, 2020), so the return on investment ratio is significantly high. The World Health Organization also has several programs to help address the human-animal interface for health (Anon, n.d.-d).

Once a pandemic has established itself, testing in combination with contact tracing and quarantining remain critical tools in containing and curbing infection rates. The key to public health surveillance programs is testing capacity and infrastructure. Loop-mediated isothermal amplification (LAMP) - Sequencing is a new technique that allows sensitive multiplexed COVID-19 diagnostics (Ludwig et al., 2021). Un-purified biosamples are barcoded and amplified in a single heat step, and pooled products are analysed *en-masse* by sequencing. In samples from 676 patients the technique had a sensitivity of a 100 % compared to conventional RT-PCR. The ability to pool samples into a single reaction tube significantly reduces infrastructure requirements and improves result turnover.

Other emerging technologies include the detection and surveillance of pathogens in wastewater. Wastewater detection, also known as Wastewater-Based Epidemiology (WBE), involves the use of techniques, such as PCR and sequencing, to detect excreted pathogens in samples collected from wastewater treatment facilities. The problem with traditional testing programs is that individuals only come forward if they are symptomatic, and don't capture potentially asymptomatic individuals. Most households in developing countries are connected to a wastewater network and therefore pooled samples can be collected from the whole community. The WBE has been successfully implemented by several countries, including India, Japan, and Australia, to track COVID-19 outbreaks (Kumar et al., 2020; Hata et al., 2021; Ahmed et al., 2020). RNA copy numbers observed in the wastewater have also been used to model the number of infected individuals in the community. A limitation of WBE is that not all infectious pathogens are excreted or detectable in wastewater and that in developing countries wastewater networks are underdeveloped or non-existent thus limiting its broader application. However, WBE still remains a potent ancillary surveillance tool to highlight regions of interest/concern to decision-makers to concentrate traditional testing efforts, and investment in building WBE capacity at wastewater facilities is warranted.

COVID-19 is not the first and not the last pandemic. However, how we prepare for the next one will determine its impact and duration. Building surveillance and infrastructure is crucial in developing pandemic preparedness plans. Key considerations moving forward are balancing surveillance and privacy of individuals, building up surveillance infrastructure at locations at high risk of pathogen spill-over, and adopting new technology platforms so they can be readily implemented and adopted by developing countries also.

2.2. mRNA based vaccines

In December 2020, the first messenger RNA (mRNA) vaccine, targeting the spike protein of the SARS-CoV2 coronavirus, was approved by the FDA and EMA for public use, to fight the COVID-19 pandemic (USFDA, 2021; EMA, 2021). This was the first demonstration of the clinical effectiveness of mRNA vaccines and provided proof that this previously experimental technology could be translated into human use.

The idea to harness mRNA as a vaccine platform emerged in 1989 after researchers showed the ability of mRNA-loaded nanoparticles to transfect cells (Malone et al., 1989). In the following year, researchers were able to transfect mRNA to animal cells without the help of a carrier, showing that in vitro transcribed (IVT) mRNA could be used to express proteins of interest in tissue (Wolff et al., 1990). Later, first in vivo vaccination approaches showed the induction of cellular (Martinon et al., 1993) and humoral immune responses in an animal model (Zhou et al., 1994).

Since these early discoveries, many researchers developed and optimized strategies to enhance mRNA stability and delivery processes for enhanced efficacy. The desired mRNA molecule, including the open reading frame and 5′ and 3′ untranslated region (UTR), is IVT by a phage RNA polymerase (Pardi et al., 2013) from a template DNA molecule. Further processing with a capping enzyme and poly(A) polymerase, forms a mature mRNA molecule including a 5′ cap and a poly(A) tail (Pardi et al., 2018) for increased stability and optimal translation efficacy. The sequence enabling the poly(A) tail can also be included in the DNA template before transcription. In order to prevent rapid degradation by RNases (Tsui et al., 2002), and to ensure in vivo delivery and transfection of target cells, the mRNA is packaged into vesicles made of cationic proteins, lipids or polymers. The best results were achieved with lipid nanoparticles made of self-assembling ionizable cationic lipids, stabilized with cholesterol and phospholipids to enable the formation of a lipid bilayer.

The immunogenicity of mRNA vaccines can be mediated by several key mechanisms that initiate a potent immune response (Pardi et al., 2018; Xu et al., 2020; Wadhwa et al., 2020): i) after intramuscular injection, extracellular mRNA molecules can be sensed by pattern recognition receptors (e.g. toll-like receptors) of antigen presenting cells and induce a type-I interferon response and release of pro-inflammatory cytokines (Chen et al., 2017); ii) mRNAs are taken up by dendritic cells through phagocytosis and are translated into protein by host cell ribosomes. The antigens are processed by the proteasome and can be loaded to major histocompatibility complex (MHC) I molecules that are presented on the cell surface to prime CD8 T cells. iii) The produced antigens can be secreted by host cells and absorbed by phagocytes through endocytosis, where they are degraded and loaded on MHC class II. This can trigger a CD4+ T cell response, including the priming of B cells to induce the production of neutralizing antibodies.

Thus, mRNA vaccines represent a novel mechanism for inducing a long-term immune response. Some of the strengths of this approach include flexible design of the mRNA molecule, no requirement for delivery of mRNA into the nucleus and only transient expression of the protein without risk of genomic alteration of the target cell.

As of July 2021, two mRNA vaccines, BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna) have been approved for use against COVID-19 in 94 and 61 countries, respectively (Basta and EEM, 2021a; Basta and EEM, 2021b). The remarkable effectiveness of both vaccines against COVID-19, at least comparable but often exceeding that of more conventional vaccines, along with limited toxicity has led to widespread acceptance of mRNA vaccines by the general population.

Noteworthy, mRNA vaccines have been investigated for indications far wider than COVID-19. According to ClinicalTrials.gov, the number of active or completed clinical trials in mRNA vaccines jumped steeply from 2020, with 20 % of studies entered into phase III or IV (NIH, 2021).

Out of 96 active or completed clinical trials, nearly 20 % were related to cancer, including melanoma, breast cancer and lung cancer. Meanwhile, 9 % of active/completed clinical trials were performed in other infectious diseases, such as Zika virus, rabies, and cytomegalovirus. The industrial landscape has similarly expanded with multiple companies undertaking research on mRNA vaccines in their product pipeline for various applications (Table 1).

It is evident that interest in mRNA vaccines as a therapeutic tool is rapidly gathering pace. With confirmation of its clinical utility in COVID-19, favourable safety profile, ease of manufacturing customisable vaccines, and patient acceptability, the near future holds great promise for realising the full potential of mRNA vaccine technology for other indications, such as cancer or autoimmune disease (Krienke et al., 2021) advancing on an amazing history of past discoveries of pioneer scientists starting this field (Dolgin, 2021a).

2.3. A resolution revolution: how single-cell omics are changing the future of medicine

> "The brain is an assemblage of cells; a painting is an assemblage of pigments. But what is important and interesting is the pattern and structure - the emergent complexity."
> Martin Rees, "On the Future"

Humanity has seen exceptional health improvements in the past century. Its foundations are deeply rooted in our increased understanding of human biology and disease, a process largely driven by progress in the research tools underlying the biomedical sciences. We now appreciate that the human body is a highly organized complex system where single cells within tissues collaborate and interact to deliver specific functions. However, until recently, the understanding of normal biology and disease mechanisms was based on bulk population studies - crude analyses that lacked the resolution necessary to detect the cell-to-cell variability and functional heterogeneity present in all tissues.

How can the inherent complexity of human biology be captured?

Single-cell omics, a new set of specific technologies which allow the application of high-throughput 'omics' technologies to the study of single-cells, can help in providing an answer. Single-cell omics are now an integral part of biomedical research and have allowed researchers around the world to capture and dissect the complexity of biological systems at an unprecedented resolution.

In this section, we will first provide the reader with an overview of the technical aspects of the many single-cell omics technologies available on the market. We will then focus on the current applications of single-cell omics in the biomedical field, highlighting how these technologies have already generated a profound impact on our understanding of human basic biology together with human diseases.

Table 1
Examples of mRNA vaccine projects pursued.

Company	mRNA vaccine product
BioNTech	Infectious diseases: HIV, TB, COVID-19, influenza Cancer: multiple solid tumours
Moderna	Infectious diseases Cancer Rare diseases VEGF - cardiac disease
CureVac	Infectious disease prophylaxis: COVID-19, rabies (CV7202), Lassa/yellow fever, RSV, rotavirus, malaria, influenza Cancer: CV8102 (melanoma, SCC, head & neck, adenoidcystic carcinoma), CV9202 (NSCLC), tumour associated antigens, shared neoantigens
Translate Bio Inc	Cystic Fibrosis (from Shire Pharmaceuticals and RaNA Therapeutics)
Gritstone/Gilead	HIV
Kernel Biologics	Leukaemia
Arcturus Therapeutics Inc	Influenza, COVID-19, CF, heart disease
Ethris	Asthma, respiratory diseases

RSV = Respiratory Syncytial Virus, CF = cystic fibrosis, SCC = squamous cell carcinoma, NSCLC = non-small cell lung cancer, HIV = human immunodeficiency virus, TB = tuberculosis, COVID = coronavirus disease, VEGF = vascular endothelial growth factor.

Single-cell analyses and their underlying technologies have progressed rapidly to cover almost every single "ome" possible. Many of these have already seen commercial implementation and thus have been made widely available to the research community. These include single-cell methods for DNA methylation (scBS-seq) (Smallwood et al., 2014), genome sequence (SCI-seq) (Vitak et al., 2017), chromatin accessibility (scATAC-seq (Lareau et al., 2019), 10× Genomics), histone modifications (scChIP-seq) (Grosselin et al., 2019), mRNA (Drop-seq (Anon, n.d.-e), 10× Genomics), spatial position (smFISH (Anon, n.d.-f), MERFISH), cell surface proteins (CITE-seq) (Stoeckius et al., 2017), and intracellular proteins (proximity extension assay). Furthermore, technologies have been made available to trace single-cell lineages and differentiation trajectory through pseudotime evaluation. Even more recently, single-cell in situ technologies have shown promise to reveal novel spatial patterns of gene and protein expression.

Many of these technologies have been combined to form multimodal, multi-omic methods for single-cell measurements. For example, CITE-seq can be used to measure the whole transcriptome and cell surface proteins, whereas scNOMe-seq can be used to measure DNA methylation and chromatin accessibility across the whole genome. These technologies rely on combining existing instrumentation and technologies in novel ways. For example, combining FACS and scRNA-seq can enable the RNA and cell surface protein levels to be correlated and analysed jointly in the same cells.

In line with these novel methods of data generation, equally innovative analytical tools have been introduced to make sense of the abundance of data being generated in these experiments. While separate analyses of different "omes" may lead to conflicting identification of cell clusters, joint analysis of multiple modalities, such as through joint dimension reduction or multi-view kernel, can enable more accurate cell clustering that can identify unique or rare cell states. Once cell clusters have been accurately identified across data sets, cell-type specific expression patterns can be used to interrogate the data to extract novel insights into human biology and disease.

The development of these novel technologies, enabling omics analyses to be applied at the single-cell level, has given researchers a new powerful tool to dissect the complexity of human development and disease. Notably, this single-cell resolution is already driving a revolution in the field of biomedicine.

Single-cell omics are used increasingly to study healthy human tissues and organs at single-cell resolution with the main aim to drive forward our understanding of human development and function. A main initiative in this field is The Human Cell Atlas project (www.humancellatlas.org/), a global consortium focused on generating a map of all cell types in the human body and their interaction (akin to a "Google maps" of the human body). The Human Cell Atlas project has already generated seminal discoveries across several tissue types highlighting the value of single-cell omics data in generating fundamental knowledge of healthy tissues.

Branching out from the study of normal human development, single-cell approaches have also been applied to a broad range of diseases such as cancer, brain disorders, autoimmune and infection diseases. Harnessing the power of single-cell omics, researchers and clinicians can now investigate in high resolution the transition from "healthy" to "disease" states, dissect the cellular and molecular mechanism of disease, finely characterize responses to drugs and identify potential novel biomarkers of response. In the past year, single-cell technologies have been also used in the fight against COVID-19, providing key insights into the biological mechanisms underlying viral infection and transmission. Single-cell omics are thus emerging as a game-changer for our understanding of health and disease, leading to a new wave of innovation and

knowledge generation that is sweeping across the biomedical field.

In the coming years, the continued, rapid development of single-cell technologies will enable more complex profiling of cells in human health and disease. This will result in the generation of vast amounts of data in the form of omics datasets covering genomic, transcriptomic, metabolomic, and proteomic states together with epigenetic modifications at the single-cell level across multiple organs and disease states.

The unprecedented resolution powered by single-cell omics technologies will drive our next decade of discoveries in the biomedical field, paving the way to novel precision medicine approaches that will result in improved treatment options for patients around the world.

2.4. Organoids

The application of combining cell culture modules and animal systems have been successful in improving our understanding of cellular signal pathways, identifying potential drug targets, and informing the design of drug candidates (Kim et al., 2020). Nonetheless, the critical step in developing new drugs for patients is still the extrapolation of data from in vitro and animal model systems to humans. Certain biological processes e.g., metabolism, brain development or drug efficacy studies, are specific to humans and cannot easily be modelled in animals. The development of human organoid models using stem cells from different organs are offering new opportunities to overcome these limitations. Although, there is still considerable debate on their predictivity and comparison to organs-on-chips and body-on-chip approaches. Organoids which are generated from pluripotent or adult stem cells, are self-organising 3D culture systems which are uniquely similar-to-histologically-indistinguishable to actual human organs (Sato et al., 2009; Takasato et al., 2015; Fujii et al., 2018; Hu et al., 2018a; Dekkers et al., 2013; Lancaster et al., 2013; Turco et al., 2017).

The need for human-cell-based models: Numerous biological phenomena like the brain are specific to humans and are not adaptable to being extrapolated from animal models. Due to human-specific developmental milestones and mechanisms, the human brain is extremely complex compared to the rodent counterpart (Lui et al., 2011). For example, neurons in the human cortex develop from outer radial glia which are not present in rodents (Lui et al., 2011). Furthermore, substantial difference in liver metabolism can be found between humans and rodents (Kuzawa et al., 2014). The non-steroidal anti-inflammatory drug ibuprofen commonly used to treat fevers and pain in humans is toxic for rodents (Kim et al., 2020).

In general, when creating an organoid, the entirety of all biological processes that drive differentiation need to be mimicked, whereas in vitro is sheerly impossible. In brief, the process of organoid formation involves 3 essential steps: First, key signalling pathways regulating developmental patterns need to be activated or inhibited to facilitate correct differentiation. Secondly, media formulations that allow ideal terminal differentiation must be optimized. Thirdly, cultures are grown in a way that allows for the formation of 3D structures.

For brain organoids, human pluripotent stem cells are differentiated into embryoid bodies that distinguish neuroectodermal cells which result in formation of brain tissue patterns (Lancaster et al., 2013). For intestinal organoids used in cystic fibrosis, organoids are formed after crypt isolation from intestinal human biopsies (Dekkers et al., 2013).

Biomedical applications: A myriad of human diseases such as genetic diseases e.g., cystic fibrosis, infectious diseases or cancers have been studied after the successful establishment of human stem-cell based organoids. For example, human brain organoids have revealed the relationship between Zika virus and microcephaly; furthermore, several chemical compounds have been identified to alleviate the hypomorphic effect of Zika virus on brain development (Yoon et al., 2017). Studies like these emphasise the importance of human brain organoids in understanding the pathology and mechanistic foundation of genetic and infectious factors together with discovering potential drug targets. Human organoids further offer the potential for individualised therapy and personalised medicine approaches. Cystic fibrosis is a life-limiting disease caused by defective or deficient cystic fibrosis trans-membrane conductance regulator (CFTR) activity leading to multi-system organ failure, including the lungs (Schneider et al., 2017). Forskolin-induced swelling of in vitro–expanded CF organoids corresponds quantitatively with forskolin-induced anion currents in freshly excised ex vivo rectal biopsies resulting in a functional assay that facilitates diagnosis, personalised medicine approaches, and potential drug development (Dekkers et al., 2013). Likewise, in the understanding of human cancer, human organoids play an instrumental role in increasing our knowledge in mechanistic pathways as well as providing a screening platform for individualised therapy. In fact, a recent analysis of drug response in patients and their matched cancer organoids demonstrated efficacy in 90 % of all cases (Kim et al., 2020).

Opportunities and challenges: Different to animal models, organoid models can directly be generated from the individual patient without the knowledge of the specific gene that is responsible for their condition. Particularly for diseases where organoids can be derived directly from the patient e.g., cystic fibrosis, cancer, or where multiple genes are responsible for the disease genotype, this is of high importance. Furthermore, human organoids are often faster, more consistent, and easily accessible compared to animal models. However, one clear drawback is the missing link between inter-organ communication when using organoid models. Hence, organoid systems are limited to tissue/organ-specific physiology which limit their clinical application.

In conclusion, despite some remaining challenges, human organoid models hold great potential for clinical translation and personalised medicine approaches. Given the fast innovations and improvements in the field human organoid technologies offer unparalleled possibilities in diagnosing, treating, and improving human health.

2.5. Microbiome

The human microbiome, comprising all living microbes residing within a human organism, has become a major area of interest, not only in academic research, but also in private enterprise. One time described as our “last organ” (Baquero and Nombela, 2012), the microbiome represents one of the final frontiers in our quest to fully understand the human body. With newly discovered implications on immune regulation, drug modification, human cell development, and host metabolism, harnessing or targeting the microbiome will have a profound impact on human health and disease. As such it is not surprising that the commercial market in human microbiome therapy is projected to reach more than 1.5 billion US dollars by 2028, with a compound annual growth rate of more than 20 % between 2025 and 2028 (Marketsandmarkets, 2021).

The burst in microbiome research has arisen in part from technological advancements in probing the genomic content of the microbiota, through methods such as whole metagenome shotgun sequencing, alongside developments in bioinformatics (Arnold et al., 2016). Coupled with complementary information through other -omics disciplines, including meta-proteomics, metatranscriptomics and meta-metabolomics, we can now more strongly infer specific microbial activity within a community. Improvements in microbiome modelling, from in vitro models, such as organ-on-chips that more faithfully recapitulate the microbial habitat, to in vivo models using gnotobiotic (germ-free) or humanised animals, has allowed more detailed experimental investigation of the microbiome. Moreover, the wealth of experimental data in this field means that computational modelling is being used to deeply delve and discover novel insights into microbe-host and microbe-microbe interactions.

Interest in the human microbiome is exemplified by the National Institute of Health (NIH)-funded Human Microbiome Project (HMP), viewed as a natural extension to the Human Genome Project. Launched in 2007, and funded to a total bill of 215 million USD by the end of the project’s 10-year lifespan (Green, 2019), the HMP set out to fully map

the diversity of human microbial flora relevant to health and disease at a population level. Major accomplishments of the HMP include sequencing of approximately 3000 reference bacterial genomes isolated from the human body and generation of the world's largest metagenome sequence dataset from one human cohort (Fund NNIoHOoSC-TC, 2020). Although the HMP has ended, it played a defining role, alongside other major international efforts such as the European MetaHIT (META-genomics in the Human Intestinal Tract) project (CORDIS EC, n.d.), in sparking an exponential growth in human microbiome research.

Among the numerous advances in microbiome research, one of the most fascinating has been the microbiota-gut-brain axis. Within the past decade, several studies in mice have revealed that changes in gut microbiota affect behaviour, neurodevelopment, and gene expression in the brain. The mechanisms of interaction between the central nervous system and microbiota remain under research but may be modulated both indirectly through disruption of the host immune function, as well as directly through absorption and systemic circulation of microbial-sourced metabolites (De Vadder et al., 2014; Sampson et al., 2016). These findings suggest that therapies targeting the microbiota-gut-brain axis may be on the horizon to treat a wide range of neuropsychiatric disorders.

In cancer, some gut microbes are already known to be mutagens capable of directly causing cancer, for example, *Helicobacter pylori* in gastric cancer and mucosa-associated lymphoid tissue (MALT) lymphoma (Schistosomes, liver flukes and Helicobacter pylori. IARC working group on the evaluation of carcinogenic risks to humans. Lyon, 7-14 June, 1994). However, more recently there is increasing evidence linking perturbations in gut microbiota with tumorigenesis and cancer growth. Besides the toxic effects of direct inflammation in the gastrointestinal tract, gut microbiota has also been implicated in more distant cancers including hepatocellular carcinoma and breast cancer. The impact on systemic anti-cancer therapy, through directly altered drug metabolism or indirect disruption of the immune response in the case of immune checkpoint inhibitors, is particularly intriguing due to the potential for new treatment strategies that can be rapidly translated for clinical benefit.

In summary, the microbiome carries a vast potential to alter the way we understand and treat human diseases in the future. The opportunity for rapid growth is led by several key innovative startups that are beginning to disrupt the market. However, advancements in this area will be constrained by inadequate expertise and knowledge, thus highlighting the need for continued investment and partnerships between academia and private enterprise.

2.6. Gene editing

Gene editing refers to the process of inserting, deleting, modifying, or replacing genetic elements in a living organism. Gene editing technologies have been used in the scientific community for several decades. However, the field has recently revolutionized by a new genome-editing tool, called Clustered Regularly Interspaced Short Palindromic Repeats/Cas9 (CRISPR/Cas9). CRISPR/Cas9 was originally discovered in bacteria, which use the system to fight off viruses (Barrangou et al., 2007). In 2012, it was adapted to modify mammalian DNA sequences (Jinek et al., 2012). CRISPR/Cas9 is faster, cheaper, simpler, and more accurate than previously existing methods. In the past year, the method has been constantly advanced and expanded, for example by improving efficiency and specificity (Slaymaker et al., 2016), building controllable systems (Polstein and Gersbach, 2015), addressing different stretches of the genome (Kleinstiver et al., 2015), introducing precise mutations without the need for cutting the DNA (Komor et al., 2016) or editing RNA (Abudayyeh et al., 2019). The technology has become a mainstay of discovery with both basic and translational scientists, illuminating new insights into biological processes and human disease.

Hopes are high that CRISPR/Cas9 will also transform the pharmaceutical industry by enabling ultimate precision medicine. While current medicines are often geared towards treating symptoms, gene-editing will be able to act on the underlying drivers of disease by correcting mutated genes. The focus of first-generation CRISPR/Cas9 therapeutics will be on monogenic diseases that are caused by just one defective gene, like sickle cell anaemia (Frangoul et al., 2020) and cystic fibrosis (Schwank et al., 2013). While the genetic cause of these diseases is well understood, hurdles like off-target effects, potential human immune response to the old generation bacterial gene editing system, and its efficient delivery to tissues of interest still must be overcome. A more imminent therapeutic setting is the application of CRISPR/Cas9 in cancer immunotherapy with the use of gene-modified chimeric antigen receptor T-cell (CAR-T) cells, a type of immune cell that is reprogrammed to efficiently kill cancer cells (Roth et al., 2018).

In addition to enabling the holy grail of therapeutic editing of human DNA, CRISPR/Cas9 already offers improvements to many other steps of the drug development process, including genetic screens for target identification, high-throughput analysis of gene functions, and fast and flexible pre-clinical models for drug testing. Moreover, CRISPR/Cas9 can detect viruses in point-of-care diagnostic tools, which have for example been applied during the recent COVID-19 pandemic (Broughton et al., 2020). Cost-efficient, fast, and reliable genome editing has an impact on other areas of society as well, like agriculture. CRISPR/Cas9 can increase crop yields, make plants climate- or pest-resistant, or add nutritional value to food products (Zhu et al., 2014).

The applications of gene editing are almost unlimited. New discoveries in this field will enable technologies we can't even envision right now. In fact, CRISPR/Cas9 has enabled science to move faster than its regulators. This disconnect became apparent when a researcher at the International Summit on Human Genome Editing in 2018 claimed to have created the world's first gene-edited babies (Cyranoski, 2019). The scientific community despised the work and called for tighter regulations. Further research is needed for responsible risk-benefit calculations of germline editing, which affects every cell of the body and is inherited to the next generations, and other future applications of genome editing. Needless to say, there are severe ethical questions involved ranging beyond healthcare applications e.g., on gene modified food, etcetera.

In the future, genome editing could treat polygenic disorders, including obesity, psychiatric or heart disease. Applications of the technology to such complex conditions might influence personal traits, as genes often serve multiple functions in different networks. The healthcare field might move from sick care to prevention. Individuals predisposed to genetic disorders might get their genes rewritten or risky DNA pieces removed. The next logical step is moving from reading and editing DNA to writing it through DNA synthesis (Hughes and Ellington, 2017), which might provide further unforeseen opportunities and challenges for humanity. Progress in these fields will be driven by collaboration and open discussion between professionals of different disciplines, including research, healthcare, ethics, law, social science, and advocacy groups.

Cell therapies have enormous potential to vastly improve the treatment of many diseases. Especially, with the introduction of genetic engineering techniques, such as CRISPR, cell therapies have led to major improvements in cancer immunotherapy and may revolutionize regenerative medicine.

Many intractable diseases are characterized by ongoing tissue destruction and an associated progressive deterioration of organ function. Classical pharmacological therapy aims to identify protein targets whose modulation by small molecules or biologics would halt further deterioration of tissue destruction and organ function loss. However, following this approach, a replacement of already destroyed tissue and associated restoration of organ function is hardly possible. In contrast, regenerative medicine, which is the application of stem cells as cellular therapeutics, has the possibility to not only halt progressive diseases, but also to replace or repair already destroyed tissue and restore organ function.

Cell therapies, based on multipotent somatic stem cells, such as

hematopoietic stem cells (HSCs) or mesenchymal stem/stromal cells (MSCs) have been applied for several decades with bone marrow transplants containing HSCs as an established therapeutic approach in many hematological cancers (Kimbrel and Lanza, 2020). However, thus far wider application and successes of multipotent somatic stem cell therapies have failed to materialize with few exceptions despite ongoing clinical trials for over two decades (Squillaro et al., 2016).

With the advent of new technologies of induced pluripotent stem cell (iPSC) generation and gene engineering, such as CRISPR, new hope has risen for the field of regenerative medicine. A plethora of preclinical animal models in species ranging from rodents to monkeys demonstrated that cell therapies based on pluripotent stem cells have the potential to substantially improve treatment for spinal cord injury and intractable diseases, such as Parkinson's disease (Harding and Mirochnitchenko, 2014). However, while PS-based cell therapies are already in or are about to reach clinical trials in over 14 diseases, efficacy in patients has yet to be shown (Yamanaka, 2020). Moreover, even if efficacy can be shown, challenges remain.

As pluripotent stem cells have the intrinsic ability to self-renew and give progeny to several different cell types, they pose the threat of teratoma and tumour formation (Yamanaka, 2020). Another challenge is immunogenicity (Yamanaka, 2020). As is the case with organ transplantation, transplanted cells can be rejected by the recipient organism. Next to the abovementioned challenges of tumorigenicity and immunogenicity, manufacturing challenges remain (Sabinina and Hildebrand, 2021). For instance, there are substantial differences in terms of growth curve and differentiation properties when comparing different iPSC lines, making large scale therapeutics production challenging. Other challenges include the need for cGMP compliance with its associated need for in-process and final release assays that track critical quality attributes. Moreover, commercial production of allogeneic cellular therapeutics needs the inclusion of 3D computer-operated bioreactors and associated monitoring of critical process parameters. Cost challenges include the need for a highly skilled workforce, single vendor supplied specialty reagents and scalable, automated, closed cell culture systems among other factors (Anon, n.d.-g).

Fortunately, the development of new technologies raise hope that most of the challenges can be addressed. For instance, techniques such as Human Leukocyte Antigen (HLA)-cloaking where HLA molecules are completely or partly removed from transplanted cells, further decreases the threat of immune rejection of transplanted cells (Yamanaka, 2020). Likewise, the generation of banks of iPSC lines further decrease the challenge to reoptimize differentiation protocols for different iPSC lines (Yamanaka, 2020). To better predict tumorigenicity, novel in vitro systems are under development (Sato et al., 2019) and new techniques of reprogramming that omit gene integration of the Yamanaka factors are actively employed (Silva et al., 2015).

Next to advances in regenerative medicine, cell therapies have led to major breakthroughs in the field of cancer immunotherapy. In fact, therapies, such as Kymriah and Yescarta, have led to a substantial increase in patient survival and a complete tumour remission in a significant number of patients (Subklewe et al., 2019).

Adoptive cell therapy is a type of cell therapy in which cancer patients' immune cells are manipulated ex vivo and injected back into the patient. Based on the type of therapy, immune cells can be either expanded or genetically modified before infusion. There are mainly 2 types of immune cell therapies: Tumour Infiltrating Lymphocyte (TIL) Therapy and CAR-T cell therapy.

Tumour Infiltrating Lymphocyte (TIL) Therapy: Tumour-specific lymphocytes with the ability to infiltrate tumours naturally occur in cancer patients. Among these TILs, cytotoxic CD8 T cells are one category of lymphocytes which are tumour reactive with the ability to target tumour-specific antigens. However, these lymphocytes usually do not exist in the tumour microenvironment (TME) in sufficient numbers and due to the immunosuppressive nature of the TME, they remain inactive in the TME. In TIL therapy, these CD8 T cells are isolated from tumour biopsies and are expanded through CD3 stimulation and IL-2 cytokine treatment ex vivo (van den Berg et al., 2020). After expansion, these CD8 T cells are infused back into the patient. In clinical trials, lymphodepleting chemotherapy is given to patients prior to TIL infusion to open the niche for TILs in the TME (Dudley et al., 2005).

CAR-T cell therapy: TIL therapy requires the presentation of tumour antigens on MHC I molecules of cancer cells. Cancer cells most often downregulate the expression of their MHC I molecules and therefore they can escape from the anti-tumour immune response. In CAR-T cell therapy, blood circulating T cells of cancer patients are isolated and genetically modified to express a chimeric antigen receptor (CAR). The CAR has intracellular signalling domains which activate T cells upon ligand engagement and subsequently leads to T cell mediated tumour killing. A single chain antibody (ScFv) exists on a CAR extracellular region, specific for a tumour surface antigen. This enables the CAR expressing T cells (CAR-T cells) to bind to tumour surface markers and perform tumour killing regardless of MHC I expression (Larson and Maus, 2021a). CAR-T cell therapy has revived significant hope in cell therapy aimed at eradicating tumours. In 2017, the FDA approved the first CAR-T cell therapy for large B-cell lymphoma with upregulated CD19 surface protein and so far, four other CAR-T cell therapies have been approved by the FDA.

It is an exciting time for cell therapies. The upcoming years will show whether current challenges can be overcome, and cell therapies can celebrate more successes in oncology and become treatment options for yet intractable diseases.

2.7. *Machine learning and artificial intelligence for drug discovery*

Machine learning is a rapidly advancing field focused on the development and application of methods for the discovery of patterns in data. Its origins trace back to computational neuroscience in 1943 as a result of the experimentation on artificial neurons used to study how the brain works (McCulloch and Pitts, 1990). These decades of machine learning history have been turbulent due to the dynamically changing popularity of the field that survived several periods of waxing and waning scientific interest (Umbrello, 2021). At present, a type of machine learning known as deep learning has grown in popularity since the 2010s due to its ability to learn from extensive and noisy datasets, often without the dependence on a time-consuming engineering process (Cao et al., 2018).

There are three main machine learning paradigms to date: supervised, unsupervised, and reinforcement learning. These methods differ in their requirement for additional information about the underlying structure of data (supervised versus unsupervised methods) or the task definition (reinforcement learning) where the algorithms learn through trial and error in a manner that is suggested to be similar to how humans learn (Joshi et al., 2020).

Supervised learning algorithms are the dominating machine learning methods used at present. They rely on labelled data and can be applied to a diverse set of applications such as computer vision, natural language processing, and forecasting. However, there is a vast corpus of information where no labels and truth sets are available. In theory development and applications of unsupervised, self-supervised, and reinforcement learning could help us learn and build better models of our environment, and help us predict protein and gene interactions, uncover complex orchestration of metabolic processes, navigate through drug development and personalised medicine and many more (Liu et al., 2021; Sidey-Gibbons and Sidey-Gibbons, 2019).

Machine learning has the potential to improve individual steps in drug development and was also proposed to transform the current, linear process into a more interconnected form (Boniolo et al., 2021). While a comprehensive review of machine learning's intersection with drug development is beyond the scope of this paper, it shows great promise in diverse areas such as disease subtyping, biomarker discovery, drug repurposing, or the design of new drugs, including cancer vaccines for precision oncology (for a review, see reference (Boniolo et al.,

2021)).The application of machine learning in key technologies of protein science is impacting drug discovery as seen in substantial breakthroughs recently made in protein structure prediction, as well as de novo protein design (Pearce and Zhang, 2021).

The vast amount of available sequence and structural data in combination with deep learning allows for the prediction of structural features of proteins (Pearce and Zhang, 2021; Baek et al., 2021; Jumper et al., 2021). A breakthrough in machine-learning-based protein structure prediction is provided by AlphaFold. AlphaFold is an AI system developed by DeepMind at Alphabet Inc., that predicts a protein's 3D structure from its amino acid sequence. AlphaFold has enabled the prediction of three-dimensional structures of proteins with unprecedented accuracy (Jumper et al., 2021). It regularly achieves accuracy competitive with experiment. Using this technique, structures have been predicted for the whole human proteome, which represents a highly valuable resource for scientists in diverse fields (Tunyasuvunakool et al., 2021). Notably, a similar approach, termed "RoseTTAFold" also shows great promise (Baek et al., 2021). The accurate prediction of protein (complex) structures is expected to impact both basic and applied research, including early drug discovery. Using a language model enabled an order of magnitude speed-up in high resolution structure prediction (LIn, n.d.).

While structure prediction seeks an unknown structure for a protein with a known sequence, computational protein design aims to determine sequences that can fold into the desired structure. Protein design, especially in the framework of the Rosetta software suite (Leman et al., 2020), has enabled non-natural proteins with novel folds (Kuhlman et al., 2003) as well as new, often highly customized functions. Among the latter, important breakthroughs of biomedical relevance include the design of therapeutic protein-based binders for disease-relevant target proteins (Chevalier et al., 2017), as well as the design of immunogens (Sesterhenn et al., 2020), and cytokine mimics (Silva et al., 2019). Despite not being based on natural proteins, de novo designed proteins have so far not been found to exhibit immunogenicity-related concerns, which has been suggested to be due to their high stability (Chevalier et al., 2017; Silva et al., 2019), and which may facilitate their translation into the clinic. In other studies, protein-based binders for small molecules have been designed (Tinberg et al., 2013), as well as small-molecule-controlled sensors (Feng et al., 2015), and sense-response systems (Glasgow et al., 2019). Moreover, small-molecule-controlled protein switches of potential use for cell therapeutic applications have been computationally designed (Foight et al., 2019; Giordano-Attianese et al., 2020a). Recently, machine learning has increasingly been applied in protein design (Anishchenko et al., 2021; Tischer et al., 2020). For example, a method based on deep learning has been described to automatically build a protein backbone to accommodate functional sites for target protein binding (Cao et al., 2022) and protein-binding proteins could be designed from the target structure alone (Cao et al., 2022).

In conclusion, computational protein structure prediction and protein design open exciting opportunities in biomedicine and progress in these areas is enhanced by the application of machine learning methodologies. The ultimate dream of having an algorithm capable of designing a drug *de-novo* for a given disease could become a reality.

2.8. Wearables and digital health tools

Health informatics began sometime in the 1950s and has developed extensively over time. The development of the microprocessor, the internet of things (Belfiora et al., 2022), and wearable or implantable bio sensors provides health data at the level of the individual. Data collected from these sensors can provide current information to physicians for improved diagnosis of a patient and customizing medical care. The consumer is now informed with information from such devices and can adjust behaviours that can improve their condition.

Wearables and digital health tools as visualized in the fictional example below hold great promise for the future:

> "Waking up on the 3rd July 2030, Katarina winces at the dull ache radiating out from her lower back; it has not ameliorated overnight as she'd hoped. Looking at her phone; seven hours sleep isn't so bad and she has to rush anyhow for a hectic day ahead. Sitting down for breakfast, she books a teleconsultation with her doctor via her tablet computer. She reaches for the honey to drizzle over her cereal - but decides against it. The lower third of her watch face is softly glowing orange - her glucose is still high from last night's dinner out. There was no real need to purchase the glucose monitor as part of her MeUSB wearable patch; but both her aunts suffer from diabetes and she wants to avoid it if possible. Over lunch she takes the appointment. At the other end of the call, Dr. Xian requests access to her DigitalPhenotype dashboard. With a quick biometric fingerprint scan on her smartphone, it all pops up. Although a plethora of digital biomarkers can be viewed; from salt levels to sentiment analysis, the medical record API directly compares these signals to historical records, drug regimens and personal as well as familial genetic databases. The most likely results are flagged: a lower back injury from three years prior, a slight genetic propensity for kidney stones, and rare renal side effects of a medication she started two months ago. The doctor rules out injury exacerbation as her activity and gait biomarkers show no variation or degradation in recent weeks. Kidney function is the key concern, and speed is important. A specialist consultation is booked for two weeks ahead, but in addition a home albumin test is ordered for next day delivery - alongside the Healthy.io smartphone app that enables consumer urinalysis to be conducted. A provisional note of potential side effects is forwarded to the drug supplier and central government database as part of their ongoing Phase IV study."

The ubiquitous digital transformation is seeing a revolution in the healthcare market; and wearable devices are sitting at the forefront. Combined with machine learning, data science, and homogenised patient, stakeholder, and data systems – the aforementioned fictional healthcare experience of Katarina is only a few years into the future. The potential of augmented reality and metaverses add additional and almost limitless possibilities for an informed, healthy, and safe, live interaction with others and training/consulting options.

Provisionally brought to the consumer through the sports tech and chronic disease markets, personalised perpetual health monitoring is turning mainstream. Cultural and commercial shifts are demonstrating the desire of individuals to take control of their wellbeing, self-educate on health matters, and monitor their physiological state. This is heavily evidenced by the 43 % of US adults who in 2020 utilized smart wearables to monitor their health (Anon, n.d.-h), with new-adoption rates exceeding expectation due to the pandemic. These customers represent part of the burgeoning $10.28B wearable healthcare technology market in 2021 (23.1 % CAGR) (Anon, n.d.-i).

Wearable devices are no longer merely nice-to-have gadgets and are making their way into patient and disease management, insurance appraisal, geriatric monitoring, biohacking, and health optimisation. This is achieved by both the development of new sensors and the intelligent use of traditional sensors (e.g., speech and movement analysis for monitoring neurodegeneration). This more robust and scientific value can be seen by the sudden and rapid adoption of wearables in clinical trials, with 70 % of all studies being estimated to use at least one wearable by 2025 (Anon, n.d.-j).

As a growing and desirable market, corporations with core operations outside of the healthcare market are moving to expand within healthcare. This can be seen by recent movements made by companies like Polar, Omron, Fitbit, Apple, Uber, Amazon, and Alphabet. However, at the other end of the spectrum, digital health start-ups are flourishing with 2020 doubling in total venture funding compared to 2019 despite COVID-19, and 2020s total already being surpassed by mid-2021 (Anon, n.d.-k). A large driving force behind these changes is the value realisation of the vast amount of data being produced. Bellwethers of this

realisation include Google's acquisition of Fitbit at a market capitalisation of $2.1B (Anon, n.d.-l), and $3.5B IPO of 23andMe (Anon, n.d.-m).

Wearables certainly seem to be vital to realising the promises of personalised healthcare, which as outlined above can lead to a vast improvement in health, prognosis, and quality of life. The flexing of big tech and large amounts of capital will no doubt help achieve this. However, the industry's track record brings to the forefront the considerations of data collection, use, and ethics. In particular, questions have arisen about the role of big tech companies that harvest and store the information recorded by wearable devices. Optimization for specific groups e.g. the elderly is particularly required (Frishammar et al., 2023).

Therefore, when considering the exciting opportunities the future holds, one must also consider a range of important questions. What is the exchange rate of personal data to money, and should it be monetized by private institutions? How much privacy can a consumer like Katarina expect with regards to control of her data? Should her insurance premium be affected because she failed to acutely control her glucose level, or because of her genetic propensity to certain chronic conditions? Is it ethically correct when her data will be sold to health analytics companies, or used to target ads for weight loss supplements and other personal wellness products? Is monetization of data the way to finance skyrocketing healthcare costs of an ageing population in the future?

Inter- and intranational policies on data sharing, ethical frameworks, and cybersecurity will need to accompany the data collection and analytics trend. However, the vast potential humanitarian and economic benefits and thus driving forces will no doubt lead inexorably to the adoption of these technologies - and for the sake of consumers and patients like Katarina, they certainly should. The positives will be remarkable, the pitfalls simply need to be managed sensibly - an exciting revolution awaits.

2.9. The empowered healthcare consumer: the fundamental game changing game-changer

The vision of the healthcare systems in many countries is currently shifted towards engaging consumers to actively participate in their own healthcare [1149]. Since information is fundamental to achieve empowerment, this framework allows citizens to have sufficient health knowledge and information which enable them to have more control over their health-related decisions. This can be achieved through implementing innovative strategies which allow the healthcare consumers to access information in a comprehensive and timely manner. Some of these strategies employ communication technologies such as smart phones to access health-related information (Gil-Quevedo et al., 2017).

Healthcare technology is the incorporation of dynamic changes in the technological sector into the healthcare practice, thus giving rise to a novel health informatics model. Consequently, health informatics is progressing from being individually-centred towards having more community-based interaction and engagement (Mancuso and Myneni, 2016). A recent study carried out on diabetic patients assessed their perspectives on using the consumer health information technology application. The study revealed the empowerment felt by the patients through gaining access to health information, and interaction with other patients and with guides who helped them enhance their technological skills. The application was also efficient in changing the behaviour towards better self-management in terms of health coping, monitoring behaviours, and healthy eating habits (Pemu et al., 2019). Another study reported that innovative technologies and merging health informatics with human psychology impact sustainable health management behaviours and enable the healthy physical and mental lifestyle management for the ageing individuals who are at risk of developing chronic conditions as heart diseases, diabetes, high cholesterol, and arthritis (Faiola et al., 2019). In addition, an Australian study suggested that higher consumer engagement for populations at risk of digital exclusion can be accomplished through improved assistance and promotion of their national electronic health record system (Van Kasteren et al., 2017).

Consumer activism is also evident through working towards a common goal by the provider and the patient to reduce the incidence of diseases that can be prevented through vaccination. Consumer engagement empowers people by leveraging the health data assets' value in online healthcare systems with the aim of proactively managing their own healthcare and making informed decisions (Popovich et al., 2018; Thapa et al., 2021). Useful analytical tools and value-based models need to be aligned with the consumers' sociotechnical system to successfully implement health technology (Faiola and Holden, 2017).

Finally, healthcare can be improved through educational approaches on different levels, namely the clinical practice, service delivery, and policy. Moreover, capacity building, digital health solutions, and delivery of integrated care can drive innovation that promotes improved healthcare access (Chehade et al., 2020).

2.10. Synthetic biology

Synthetic biology is a relatively young field that has existed roughly since the beginning of the 21st century and is broad in scope (Auslander et al., 2017). Engineering principles are an important foundation of the field. In this spirit, the design of synthetic, genetic (Elowitz and Leibler, 2000), and protein circuits (Gao et al., 2018) are based on interchangeable functional modules that can likewise be built from libraries of (ideally) standardized parts. In this framework, synthetic biologists can harness the vast diversity of existing biological parts (e.g., well-characterized genes, proteins, and regulatory elements) and slightly reengineered versions of existing parts. In a complementary fashion, synthetic parts such as de novo designed proteins or nucleic acids can be used. By combining such parts into large-scale networks, biological or biomimetic systems with emergent properties can be designed. Notable examples include the toggle switch (Gardner et al., 2000), programmable oscillations (Elowitz and Leibler, 2000; Tigges et al., 2009), pattern formation (Basu et al., 2005) and logic gates (Andrews et al., 2018). Besides testing hypotheses and achieving fundamental insights into biological design principles via bottom-up reconstitution and engineering (Jia and Schwille, 2019), synthetic biology promises to address key problems in medicine and sustainability via biological engineering, which we focus on in the sections below. While we highlight important case studies, we note that this is by no means a comprehensive review but rather a starting point for further reading.

In the framework of metabolic engineering, high-value chemicals including small-molecule drugs can be synthesized by microorganisms, whose metabolism has been deliberately manipulated. Considering the limited resources of fossil fuels and the urgent need to mitigate climate change, such approaches have the potential to facilitate more sustainable manufacturing of relevant compounds. Important examples that have been successfully produced via metabolic engineering of microbes include the synthesis of an anti-malarial drug precursor (Ro et al., 2006) as well as opioids (Galanie et al., 2015) in engineered yeast cells.

In the biomedical context, synthetic biology has also enabled many innovative applications based on engineered input-output circuits (Kitada et al., 2018). Such engineered circuits form the basis of diagnostic and "theranostic" (a combination of diagnostic and therapeutic) applications (McNerney et al., 2021). With regards to diagnostics, low-cost (paper-based) sensors for viruses have been developed using cell-free systems, which show responses triggered by viral RNA molecules (Pardee et al., 2014). Moreover, engineered bacteria have been used for diagnostic purposes, e.g., for sensing gut inflammation (Riglar et al., 2017). On the therapeutic side, notable examples include bacteria that have been engineered to release an anti-cancer payload in a synchronized fashion once they reach a certain cell density (Din et al., 2016). Moreover, several approaches utilizing bacteria have focused on the gut microbiome with the intention to treat metabolic disorders (Kurtz et al.,

2019) or infection (Hwang et al., 2017). Of note, biocontainment and safety strategies have been devised to manage potential risks of bacterial cell therapies, which have been covered in a recent review article (McNerney et al., 2021).

Mammalian cells are also used extensively in synthetic biology for therapeutic purposes. Expression of Chimeric Antigen Receptors (CARs) in T cells to direct their killing function towards cancer cells is the most typical example of using mammalian cells in synthetic biology. Here we focus on CAR-T cell technology and different engineering approaches used to address different issues.

CARs are engineered receptors with the ability to bind to a special surface cancer-specific antigen and signal upon binding to that ligand. Binding occurs through the ScFv on the extracellular region of the CAR and signalling occurs through the signalling domain in the intracellular region. Currently, four generations of CARs have been created. First generation CARs contain three CD3 immunoreceptor tyrosine-based activation motifs (ITAM) and second generation CARs have one additional activation domain derived from CD28 or 4-1BB or OX40 (Larson and Maus, 2021b). The goal of the second generation was to synergize ITAM signalling with another activation signal which confers better proliferation, survival, or persistence to T cells. Third generation CARs contain one ITAM motif and two activation domains and fourth generation CARs couple CAR signalling with the inducible expression of a cytokine (mainly IL-12) to enhance T cell function (Larson and Maus, 2021b). Five CAR-T cell therapies, mostly second generation, are approved by the FDA for hematological malignancies and many other CAR-T cell therapies are in clinical trials (Han et al., 2021).

Also, strategies to increase safety need to be defined. CAR-T cells may attack normal cells which have a low expression of the cancer antigen. New designs are used to address this issue. Inhibitory chimeric receptors with intracellular domain of CTLA-4 or PD1, which can bind to markers of healthy cells, can create a NOT logic gate where CAR-T cells will be inhibited when they bind to normal cells (Fedorov et al., 2013). "AND logic gate" has been created such that a chimeric Notch-based receptor would release a transcription factor upon binding to the first cancer antigen. The transcription factor induces the expression of a CAR which binds to the second cancer antigen and performs killing (Choe et al., 2021; Hernandez-Lopez et al., 2021). With the AND logic, cancer cells should express both antigens to be recognized by the CAR-T cell.

Excessive CAR-T cell activity can also lead to toxicity. Engineered suicide proteins (iCASP9 or HSV-TK) are designed with the addition of dimerization domains (Diaconu et al., 2017; Casucci et al., 2018). T cell apoptosis is induced with the addition of a small molecule which induces dimerization. Similarly, dimerization-based regulatory systems have been developed for small-molecule-based regulation of the CAR itself. In this system, the activation domain is separate from CAR and the addition of a small molecule either induces their dimerization (Wu et al., 2015) or disrupts their constitutive assembly (Giordano-Attianese et al., 2020b). Moreover, ZipCARs which contain an extracellular leucine zipper domain instead of a ScFv are designed for this purpose. An adaptor protein which contains a ScFv against a cancer antigen and a complementary leucine zipper (ZipFv) can induce the binding of the ZipCAR to cancer cells (Wu et al., 2015). Withdrawal of the ZipFv is seen as a means to mitigate the T cell toxicity, as its withdrawal will shut down the function of ZipCARs.

CARs have also been designed for other immune subsets. Macrophages have been recently used to express a first generation CAR. CAR-expressing macrophages were able to phagocytose cancer cells and secrete pro-inflammatory cytokines upon CAR signalling (Klichinsky et al., 2020).

Additionally, CARs have been expressed in Tregs to dampen autoimmune diseases (Boardman et al., 2017) and in natural killer cells to kill cancer cells (Liu et al., 2020a) and HIV-infected cells (Lim et al., 2020).

2.11. Cultured meat

The growing number and the increasing wealth of the human population are expected to raise the demand for animal products, especially meat, by up to 70 % in 2050 (Anon, n.d.-n). This comes at a high cost: meat production is known for its enormous usage of resources, such as land, water, and feed, and its contribution to the production of greenhouse gases, like CO_2 or methane. Luckily, current innovations in the production of cultured meat, also called "artificial", lab-grown, cultivated, or clean meat, set the path to substantially improve the ecological and ethical footprint of meat production. Producers of cultured meat and independent research organizations claim a reduction of greenhouse emission by up to 96 %, reduced land use of up to 99 %, and up to a 96 % cut in water usage and up to 50 % energy savings, depending on the species with bovine cultured meat showing the highest level of environmental benefit.

Cultured meat is genuine meat and comparison studies show that it provides equivalent nutritional value (Anon, n.d.-o; Anon, n.d.-p; Anon, n.d.-q; Anon, n.d.-r). It likens in composition, taste, appearance, and nutritional value to the conventional meat from livestock but differs from the way it is produced. Instead of sourcing the tissue directly from an animal, it is made by putting together its basic components in the laboratory and production plants.

The ingredients for cultured meat are mainly three: muscle cells, a supporting matrix, and additional taste-enhancing complements such as fat cells. The cellular component can be obtained from muscle biopsies of living animals to isolate muscle precursor cells or even from a feather from a chicken to isolate stem cells. Cells are grown and expanded in large quantities using bioreactors and the appropriate culture medium containing nutrients (e.g., amino acids, sugars, trace elements), hormones, and growth factors. The sizes of these bioreactors are similar to those known from breweries. Currently, replacements for the animal-derived fetal bovine serum (FBS), which is expensive, rate-limiting, and makes cultured meat not animal-origin free, are successfully evaluated. Many companies, including a dedicated team in the Merck Science and Technology Office and Silicon Valley Innovation Hub (Anon, n.d.-s), are investigating cost-effective and scalable alternatives that are truly animal-free. Advances in the space are already seen in practice, with Future Meat Technologies being able to produce meat using animal-free cell culture media at a scalable rate.

The main challenge in cultured meat, however, is not only to replicate taste, but mouthfeel. While it is easy to generate ground-meat products such as mince, burger patties, and chicken nuggets, it remains a challenge to move from "mush" to a solid steak. Lab-grown cells need to be organized and supported onto edible scaffolds to provide a shape and texture to the final product. Tissue engineers are currently exploring different biomaterials and structures that meet the texture expectations of consumers while being cost-effective, scalable, and reproducible. Some options are decellularized plants, recombinant collagen, carbohydrates, gelatine, silk, textured soy protein, microcarrier beads, and 3D printing.

In 2013, the first lab-grown burger, developed by Mark Post and colleagues, was tasted in London (Anon, n.d.-t; Anon, n.d.-u). Although its record price of $335,000, this product was the first proof-of-concept in the feasibility of lab-grown meat. Since then, the idea of cultured meat has been followed up by numerous researchers and food start-ups around the globe and resulted in the first commercial market entry in Singapore in 2020, that allowed the restaurant sale of cultivated chicken bites by Eat Just Inc. (Anon, n.d.-v; Anon, n.d.-w; Anon, n.d.-x) and the opening of a test restaurant in Tel Aviv (Anon, n.d.-y; Anon, n.d.-z) by SuperMeat to investigate consumer reactions. Meanwhile, technological advances led to the opening of first pilot industrial cultured meat facilities, for example by Upside Foods in California or Future Meat Technologies, in Israel. Future Meat Technologies claims a production capacity of 500 kg a day (Anon, n.d.-aa; Anon, n.d.-ab), and offering a record low price below $4 for an artificial chicken breast. Although

some regulatory aspects remain to be cleared, first products in US restaurants are expected by 2023. The market is expected to grow rapidly, reaching between $2.7 to 90 billion by 2030 (Anon, n.d.-ac; Anon, n.d.-ad; Anon, n.d.-ae).

The market is not just limited to beef and chicken production, given the technology can be adapted to different source cells. For instance, Vow Food aims to produce cultured exotic meats, such as kangaroo and alpaca (Anon, n.d.-af). Moreover, several start-ups are working on making lab-grown seafood aiming to help marine conservation. Some studies demonstrated the possibility of growing cultured fish from well-characterized research model organisms such as zebrafish (Anon, n.d.-ag) or muscle cells from invertebrates like fruit flies (Anon, n.d.-ah).

The production of "clean" meat offers a sustainable and cruelty-free alternative to conventional meat. However, scalability, product texture and regulatory issues are still limiting its ability to fulfil the demand for human consumption today. Once this technology is widely adopted and accepted by the public, not only will it provide a slaughter-free alternative to meat, but also the opportunity to enhance the nutritional value and health benefits or to remove the health risks associated with conventional meat. For instance, Stout and colleagues showed that the introduction of three antioxidant genes into muscle cells could reduce the carcinogenic effects of red meat (Anon, n.d.-ai).

Adopting new technologies, when it relates to health and food consumption, can be scary. While a big percentage of the population are still not convinced about changing their meat consumption habits, few surveys show that there is a big interest in people from different ages and cultural backgrounds to at least try lab-grown meat, especially in younger generations (Anon, n.d.-aj; Anon, n.d.-ak; Anon, n.d.-al). Cultured meat taste and price parity to real meat will be a key milestone for reaching higher levels of adoption as a protein source.

Considering the ongoing global trend to adopt more environmentally friendly habits and the increasing uptake of plant-based meat alternatives, we expect cultured meat to slowly become widely accepted by the public in the next years, especially once the safety for human consumption of these products has been thoroughly evaluated.

2.12. 3D-printing/additive manufacturing

3D printing is a fundamental building block driving the ongoing fourth industrial revolution by introducing mass customization and creating flexibility into all aspects of business processes. Originally, 3D printing was confined to the production of simple plastic objects, however in recent years the number of materials that can be utilized by 3D printers has drastically increased from metals and ceramics to bioinks, leading to an explosion in potential new applications. 3D printing is also extremely versatile operating at multiple levels from printing nanoscale fibres to entire buildings. 3D printing is driving transformative change in several fields including supply chain logistics, medicine, and construction.

In the current manufacturing setting, items are produced in locations that maximize economies of scale and then shipped to consumers. However, the process of transporting items requires a significant amount of energy and fuel, creating a large carbon footprint (Nadagouda et al., 2020). With 3D printing, designs can be sent electronically anywhere in the world and printed locally or even directly by the consumer. In this new 3D printing paradigm 'files are sent, not products', reducing pollution and product lead times. Modelling performed by the Center for Energy and Environmental Sciences in Netherlands showed that 3D printing could maximally reduce the energy and CO2 emission intensities of industrial manufacturing by 5 % by 2025 (Gebler et al., 2014). In addition, 3D printing has been shown to use material more efficiently than traditional subtractive processes such as cutting, milling, and drilling, and newer models can utilize recyclable material inputs, therefore the technology has the potential to reduce tons of material waste per year (Thomas et al., 2011). Places where adoption of 3D printing will have the most transformation impact are locations that are underserved due to their small market size/remoteness. Real world case studies have already shown that 3D printing can be successfully implemented in locations even with the most finite of resources, ranging from indigenous reindeer herding communities (Obydenkova et al., 2018) to outer space (O'Hara et al., 2018; Wong, 2015). 3D printing has also been shown to critical when traditional supply chains are disrupted, such as in the case of COVID-19 pandemic wherein 3D printing was used to source millions of medical instruments and personal protective equipment to address shortages in hospital supplies (McCarthy et al., 2021; Niranjan et al., 2022). A key theme identified throughout the case studies is the need to develop versatile 3D printing platforms, for example instruments that can operate with broad range of input materials that can be sourced locally, or that can operate independent in off-grid environment (i.e. solar powered systems).

3D printing has several medical applications and can be broadly split into two branches, namely (i) 3D printing of prosthetics/implants and (ii) bioprinting of scaffolds and/or cells for the purpose of regenerating tissues and whole organs. One of the core competencies of 3D printing technology is its product design flexibility. In a clinical setting, imaging technologies, such as MRI and CT scans, can be used to map defect sites and create virtual models of tissues of interest (Nam et al., 2015). Custom implants can then be extrapolated and fabricated from these models to match the complex geometries of human body parts. Similar to other medical devices, 3D printed prosthetics and implants need to ensure assembled materials can cope under repeated stress/strain and interface with tissue without generating localized tissue damage or a foreign body reaction. A recent trend in 3D printing prosthetics and implants is the integration of 3D printed sensors to create 'smart' prosthesis/implants. Mannoor and team were able to 3D print a bionic ear with biological tissue and functional electronics which possessed enhanced functionalities over their human organ counterpart, including radio frequency reception (Mannoor et al., 2013).

On the other spectrum of medical applications, 3D printing can also be used to not only replace, but regenerate, whole organs and tissues. 3D printing mediums, such as biomimetic scaffolds, hydrogels, and bioinks (Yan et al., 2018), providing cells with critical structure and transform a cluster of unorganized cells into complex tissue. The 3D printed constructs act like scaffolding on a construction site enabling cells to freely work in the defective site to rebuild native tissue. To put this into perspective, even a small defect of a few millimetres in length, from the viewpoint of a cell (20-50 μm in size) can be equivalent to trying to bridge the Grand Canyon. The 3D printed constructs, like traditional scaffolding, are only temporary structures and therefore once the work is complete, are selectively degraded and safely reabsorbed into the body. For example, Polycaprolactone (PCL), one of the most common biodegradable polymers used in tissue engineered, degrades into acidic intermediates, however its degradation profile is gradual (1–2 years) and the by-products can be metabolized by the body and secreted with little to no negative effects observed on local tissue (Sin et al., 2013; Sun et al., 2006). Surface area, hydrophilicity, mechanical properties, and crystallinity are all important design features that affect the degradation rate and biocompatibility of a biomaterial, and are often interconnected, with alteration of one parameter effecting the properties of other design elements (Mitragotri and Lahann, 2009). Newly developed biomaterials are also opening the door to the possibility of 3D printing directly into patients in the hospitals of the future. A research group from the University of New South Wales developed a cell-based bioink which can be printed via light portable 3D printer and harden within 5–10 min in the presence of water or bodily fluids (Romanazzo et al., 2021; Min, 2021). The properties of the novel bioink and instrument open the door to print directly into the defect site of patients in real time during surgeries after trauma or injury, potentially mitigating the need to reopen a patient for corrective surgery later.

A final sector where 3D printing is driving change is the construction industry (El-Sayegh et al., 2020). Several companies and research groups around the world have developed industrial printers capable of

3D printing homes and offices using cement and other locally-sourced materials, only within a matter of days. Recently a research team at the University of Nantes, France, was able to print a simple cement house design in less than 30 min (Olsson et al., 2021). The ability to rapidly construct buildings is particularly advantageous in emergency responses and recovery. Buildings are not just shelter and they house critical infrastructures necessary to sustain a community. The ability to rapidly 3D print buildings will help displaced people return home sooner and attract businesses and investment back to the affected region. Limitations of 3D printing buildings is the high cost of specialized 3D printing machines, insufficient information on long-term strength/durability of 3D printed constructions (i.e. resistance to earthquakes, high wind speeds and natural weathering) and a lack of building codes/regulations for 3D printed constructions in several countries (Florea et al., 2020).

Overall, the versatility and multidisciplinary aspects of 3D printing means that the technology platform will continue to push boundaries in science and technology. If adoption rates continue to increase, 3D printing could follow a similar trajectory and product evolution to personal computers and smart phones in the turn of the century and integrate into all aspects of our modern lives. Keys to 3D printing's success will increase user friendliness of the technology, consumer education, support ancillary businesses such as 3D printing hardware, material, and software developers, and leverage the existing 3D printing community ('Technology Champions') to continue expanding the 3D maker-verse. As the 3D printing ecosystem grows, so will the innovations from the technology.

2.13. Carbon capture

Capture, utilization, and storage technology carry an essential role in decarbonizing the world's fossil fuel-dominant power systems and in helping to shift to net-zero emissions. Owners of existing power plants and buildings can upgrade carbon capture technologies, particularly in Asia, with a large, relatively young fleet of existing fossil-powered plants to avoid the potential "lock-in" of emissions. System operators can take advantage of Carbon Capture Utilization and Storage (CCUS) power plants, which integrate a growing share of renewable energy into the power system by providing flexibility in the short and long terms. Combining these technologies with bioenergy allows harmful emission plants to compensate for emissions in the most demanding sectors and support "net-zero" climate objectives. Essential cost reductions and improvements for these technologies have already been achieved, and further improvements are anticipated by research, development, and deployment. Target policy measures, like U.S. tax credits 45Q and 48A, are crucial for realising CO_2 capturing technologies' potential in electricity generation.

Phase 1 (~2030): focus on capturing emissions from existing power plants and factories

Researchers are identifying numerous technical approaches to achieving carbon neutrality at CCUS-equipped power plants. With strong climate ambition, a long-term energy system analysis shows that the world's power sector's carbon emission becomes negative around 2050. However, the coal power plant still emits 125 g CO_2/kWh with a CO_2 capturing rate of 85 % (commonly assumed by modelling) and an efficiency of 41 % with post-combustion CO_2 capture. The CO_2 capture of oxygenated fuels produces 83 g CO_2/kWh at a usually assumed rate of 90 % with the same efficiency. Thus, the sector needs to deal with residual emissions for fossil-fuel plants with carbon capture technologies in the fully decarbonized energy system. Increasing the catch rates reduces the remaining emissions and thereby increases the attractiveness of carbon captured fossil-fuel power plants.

Higher capture rates are possible from a technical point of view. By increasing CO_2 absorption capacity, the capture rate at post-combustion plants can be improved. The regenerated solvent that enters the absorber with a lower CO_2 concentration can be done with a lean absorber solvent. That calls for more regenerative energy and a faster recirculation of solvents between absorber and desorber columns.

Theoretically, oxygen-powered power plants could achieve a 100 % capture rate. The capture rate can be increased by removing CO_2 from the ventilation streams, leaving the plant via an additional scrubbing step. Due to balance conditions in the physical absorption process, a 100 % catch rate cannot be achieved for pre-combustion-catching plants, which are integrated combined-cycle carbon gasification plants.

The International Energy Agency Green House Gas (IEAGHG) suggests that CO_2 capture rates of up to 99.7 % in coal- and gas-power plants equipped with carbon capture techniques can be achieved at low additional costs. More specifically, CO_2-neutral (99.7 % capture) can be made from a highly supercritical pulverized coal plant at an increment to 7 % of the cost of electricity generation over the usual 90 % capture rate with an increase of just 3 % of CO_2 avoided costs.

Co-consumption of 10 % biomass with CO_2 capture of 90 % may be the most economical choice to achieve a highly supercritical coal-fuel carbon-neutral plant.

CO_2 capture is benefiting from numerous research initiatives. For post-combustion, pre-combustion, and oxyfuels capture systems, new technology, and improvements will be developing. The most efficient technology for CO_2 capture is unclear, as several types of technology will continue to be developed and demonstrated at an early stage.

2.13.1. Post-combustion capture

This track divides CO_2 from flue gas combustion. The most mature CO_2 separation technique for power plants is chemical adoption using amine-based solvents and is used in today's two large-scale projects (Boundary Dam and Petra Nova). The scope is available for cost reduction, primarily through the use and standardization of innovative solvents and large-scale deployment that results in economies of scale and apprenticeships. Several technological approaches, which include sorbents and membranes, are on the horizon with the potential to improve post-combustion capture. Some of these technologies may, over time, be able to surpass solvents, but each has its challenges and needs to be further developed and demonstrated.

2.13.2. Pre-combustion capture

On this path, steamer and/or oxygen processes the fuel to produce the so-called syngas (a process called reformation/gasification), a gaseous mixture of carbon monoxide and hydrogen. A carbon monoxide reaction with more steam (WGS) produces additional hydrogen and converts carbon monoxide to carbon dioxide. A gas is generated for electricity (in combined cycle gas turbines or fuel cells) when CO_2 is removed from the high-pressure gas mixture. Coal and gas reform are mature technologies. Research focuses on new technologies, including membranes and absorbents, separating CO_2 and hydrogen from the gas mixture during the WGS reaction. Other fields of study include coal gasification technologies such as enhanced turbines and technology for fuel cells.

2.13.3. Oxy-fuel combustion capture

This capture route uses (nearly) pure oxygen instead of air to combust fuel, resulting in a flue gas composed of CO_2 and water vapor. A highly pure CO_2 stream results in dehydration of the flue gas. Combustion oxygen is usually produced by separating it from the air by using an Air Separation Unit (ASU). The main objective of the research is to improve the efficiency and economic efficiency of ASUs and novel technologies for oxygen production, such as oxygen mucosa. Another advanced technology in development for oxyfuel is chemical looping; it shows excellent energy reductions but remains in its infancy. Cycles of supercritical CO_2 (sCO_2) promise high cost and reductions in emissions, and in recent years have gained particular interest. While flue gas or steam in conventional power stations are used to drive one or more turbines, supercritical CO_2 at a critical temperature and a pressure of CO_2 are used in s CO_2 cycles. Cycles of supercritical CO_2, including

higher plant efficiency, lower air pollutants emissions, lower investment cost, and more elevated CO_2, are many possible advantages.

The two large-scale CCUS power projects currently in operation and the 20 in development have a combined potential capacity of over 50 $MTCO_2$ per year. This is compared with the IEA Sustainable Development Scenario's 2030 energy generation of around 310 $MTCO_2$, reflecting that carbon capture, use, and energy storage are currently not in progress.

Phase 2 (~2030–2050): CCUS deployment expands most rapidly in the cement, steel, and chemicals sectors, which together account for around one-third of the total growth in global CO_2 capture during that period.

This phase requires technology that is currently in development to scale up massively. It is not clear at this point which technology will be more suitable to both achieve relevant price points and be deployed on the giga scale.

Phase 3 (~2050–2070): CCUS needs to expand into bioenergy and direct air capture (DAC) to go the last mile to net-zero.

Direct air capture is a technology that removes CO_2 directly from the air via a CO_2 absorbent. This sorbent is regenerated by heat which then releases its stored CO_2, and the cycle can start over. A crucial piece is to figure out how to reduce the impact of the regeneration process onto energy consumption and CO_2 generation. According to the IEA, "the deployment of these carbon removal technologies is constrained by their cost-competitiveness with other mitigation measures and (potentially) access to suitable storage, with [bioenergy carbon capture] also constrained by the availability of sustainable bioenergy and DAC by the availability of low-cost electricity and heat".

Overall, there is no silver bullet in carbon capture, but many silver buck shots, all necessary to eventually reach net-zero. Oil companies are forging alliances to heavily invest in carbon capture and to form powerful public-private partnerships now. However, it must be clear that there is no scenario in which we can broadly continue using fossil fuels and rely on carbon capture alone. Instead, we need to heavily reduce the amount of CO_2 we take out of the ground via fossil fuels and at the same time capture emissions from power plants and factories, rethink industrial processes to produce steel, cement, and chemicals, and lastly, expand our efforts in sequestering carbon biologically and via direct air capture. Reduce and reuse.

3. The next 10 years

The game changers explored in this second section have an estimated impact at around ten years, although first results are already visible today, the greater potential lies many years down the road. The topics covered here are biological condensates as novel drug targets, new microchips beyond Moore's law, robotics, micro/nanorobots, breakthroughs in anti-ageing, a true paradigm shift in medicine on early intervention: healthcare instead of sickcare, DNA data storage, fusion, and space exploration.

3.1. Biological condensates as novel drug targets

In the classic textbook example, cellular structures are organized in membrane-separated organelles, compartmentalizing the cell into the nucleus, mitochondria, endoplasmic reticulum, and cytoplasm. The cytoplasm is thereby viewed as a "hot stew", where ingredients are randomly distributed and only occasionally run into binding partners, substrates, or small-molecule drugs. However, within recent years, evidence has emerged that cells indeed organize their cytoplasm to achieve spatiotemporal control of grouped sub-compartments through membrane-less, micron-scale, biomolecular condensates, challenging the classical textbook dogma (Banani et al., 2017; Shin and Brangwynne, 2017).

These highly diverse condensates form through a process called liquid-liquid phase separation and are made up of dedicated proteins and nucleic acids to allow the cell to perform functions such as concentrating regulatory proteins spatiotemporally with interaction partners or grouping related enzymes to speed up reaction kinetics. As these dynamic sub-structures are important for cellular physiology, genomic mutations that perturb the assembly or disassembly have direct implications for neurodegenerative diseases, cancer, and infectious diseases (Alberti and Dormann, 2019). Biomolecular condensates also alter the biophysical properties of potential drug targets and therefore can affect efficacy and engagement of small-molecule drugs (Klein et al., 2020). Drug development should therefore take a more holistic approach, when looking at their compounds, considering physical properties, possible interaction partners, and the potential transition of target molecule into biomolecular condensates.

Growing evidence suggests that biomolecular condensates are not only important for cellular homeostasis but implicated in several disease phenotypes, including ALS, Huntington, muscular dystrophy, tau pathology, viral infection, and cancer (Boija et al., 2021; Spannl et al., 2019). In particular, the linkage between condensates and ALS has received considerable attention and a potential causality between the disease phenotype and the proteins TDP-43 as well as FUS is emerging (Hallegger et al., 2021; Rhine et al., 2020). Both proteins are characterized by intrinsically disordered regions that are thought to mediate liquid-liquid phase separation. Intrinsically disordered proteins are challenging to target by small-molecule efforts since they do not form traditionally druggable stable pockets. However, shifting the equilibrium of the phase separation in general or solubilizing the aggregated TDP-43 in the case of ALS, might enable new treatment opportunities for neurodegenerative diseases.

Regarding oncology, many dysregulated cellular processes have been shown to occur in biomolecular condensates (Boija et al., 2021). Cancerous cells acquire mutations in key physiological processes, like transcription, chromatin structure, signalling and others. One example showed that the tumour suppressor Speckle-type POZ protein (SPOP) is part of condensates and that mutations within SPOP lead to a type of prostate tumour that is involved in over 15 % of all prostate cancers (Bouchard et al., 2018). These mutations interfere with the protein's ability to phase separate and colocalize with its substrate, thereby diminishing its activity as a tumour suppressor. Therefore, targeting liquid-liquid phase separation properties could directly influence these condensates in their composition or dynamic equilibrium with the surrounding bulk phase and opens new therapeutic modalities and opportunities. Alternatively, since many cancer targets occur in condensates, these sub-compartments also lead to an increased localized concentration of drugs within biomolecular condensates (Klein et al., 2020). The partitioning of drugs in specialized condensates can increase their pharmacological activity and target specificity.

The emerging picture of condensate dysregulation in disease allows the development of new therapeutic modalities (Mullard, 2019; Strzyz, 2020). Altering or even selectively disrupting condensates offer new ways of modulating specialized compartments that are associated with disease biology. Small molecule screens that selectively affect condensate formation identified compounds that can indeed dissolve dysfunctional condensates within cancers and could therefore lead to new therapeutic approaches. Similarly targeting intrinsically disordered regions (IDRs) have long been considered undruggable, but recent approaches have successfully drugged IDRs, thereby also disrupting their contribution to specific condensates. This has been shown for the oncogenes MYC, where small molecules can target their effect on the transcription or cell cycle machinery, or for the androgen receptor, where researchers have identified drug candidates that bind to its disordered region. Alternatively, researchers can target the regulatory mechanisms that control the upstream formation of condensates, such as developing candidates against helicases and ATPases that are known to play a role in phase transitions. As further insights into condensate biology are derived, different approaches to drugging condensates will likely be discovered.

Condensate biology has started to move out of academia and into the biotech industry (Dolgin, 2021b). Many start-up biopharmaceuticals have started to pursue condensates as targets for various diseases. While their exact target or mechanism of action has not been publicly disclosed, these companies have announced the indications they are pursuing in partnerships with larger, established biopharma. Faze Medicines has started programs for myotonic dystrophy type 1 (DM1) and neurodegenerative diseases such as ALS. Nereid Therapeutics is investigating neurodegenerative diseases and oncological indications. Dewpoint Therapeutics is the most mature of these start-ups, with programs targeting cardiopulmonary, neurodegenerative, oncologic, repeat expansion-based, and viral diseases. Transition Bio, Etern BioPharma, and Vivid Sciences are other recently formed start-ups in this space and are likely not to be the last—as the field of condensate biology matures, interest from entrepreneurs and established biopharma will continue to grow.

The new paradigm that the cell actively organizes its cytoplasm into phase-separated compartments that concentrate host proteins, nucleic acids, and target molecules enables new possibilities for drug development and therapeutic intervention. While many drug targets are organized in biomolecular condensates, an improved understanding of the biophysical properties, the composition, and the formation mechanisms of condensates should lead to more efficient strategies to specifically target these specialized compartments and reveal new opportunities. Since biomolecular condensates are relevant in a wide range of different disease pathologies, a profound understanding of their precise role might have broad implications for the treatment of diseases. Similarly, drug resistance and efficacy of small molecules will certainly be impacted by condensates in these phenotypes and drug development should consider the interaction of therapeutic modalities with these specialized compartments to gain a more thorough and more integrated view on their mode of action within the cell.

3.2. The future of electronics: beyond Moore's law

For several decades, the electronics and computing industries have been governed by Moore's Law, which suggests that electronic devices double in speed and capability every two years (Schaller, 1997). While Samsung and Taiwan Semiconductor Manufacturing Company (TSMC) entered volume production of 5-nm Fin Shaped Field Effect Transistors (FinFETs) in 2020, IBM recently announced a proof-of-concept 2-nm technology. Quantum tunnelling effects through the gate oxide layer, that allow electrons to continuously flow from one gate to the next, have become increasingly difficult to manage (Liu et al., 2020b).

Consequently, present day electronics research is primarily focused on identifying new materials and devices that can augment and/or potentially replace the ageing ~50-year-old Silicon transistor (M. G, 2015). In this section, we briefly review four solutions emerging beyond Complementary Metal-Oxide-Semiconductor (CMOS), which are envisioned to reinvigorate the future of electronics: graphene processors, photonic or optical computing architectures, memristors, neuromorphic processors and quantum computing.

3.2.1. Graphene processors

Carbon-based nanomaterials such as metallic single-walled carbon nanotubes, multiwalled carbon nanotubes (MWCNTs), and graphene have been considered some of the most promising candidates for future high-speed electronics because of their high current-carrying capacity and conductivity in the nanoscale, and immunity to electromigration, which has been a great challenge for scaling down the traditional copper interconnects (Chen et al., 2010).

Recently, Carbon Nanotube Field-Effect Transistor (CNFET)-based digital circuits constructed using carbon sheets with diameters of approximately 10–20 Å have been successfully used to fabricate beyond-silicon microprocessors (Hills et al., 2019) paving the way for next-generation beyond-silicon electronic systems.

3.2.2. Photonic or optical computing architectures

Photonic or optical chips can surpass conventional electronic chips by processing information in parallel and more rapidly. It has widely been envisioned that the integration of electronic and photonic circuits on a single silicon chip could enable unprecedented functions and performance in computing, communications, and sensing at a low cost.

Photonic Tensor Core Units (PCUs) have been demonstrated to be capable of operating at speeds of trillions of Multiply-Accumulate (MAC) operations per second (Feldmann et al., 2021) Photonic processors benefit from the modularity and scalable fabrication methods of integrated circuits while having two key advantages over their conventional electronic counterparts: (1) massively parallel data transfer through Wavelength Division Multiplexing (WDM) in conjunction with multichannel sources; and (2) extremely high data modulation speeds limited only by the bandwidth of on-chip optical modulators and photodetectors (Feldmann et al., 2021; Miscuglio and Sorger, 2020).

3.2.3. Memristors

Memristors, widely referred to as the fourth missing fundamental circuit element (Chua, 1971), are non-linear two-terminal electrical components with inherent memory relating electric charge and magnetic flux linkage. Unlike transistor-based memory elements, such as Static Random-Access Memory (SRAM) and Dynamic Random-Access Memory (DRAM), memristors can be directly integrated with a low thermal budget over the processor through very-high density local interconnects, thus eliminating the slow and energy-hungry off-chip communications between memory banks and processors (Zidan et al., 2018).

Computation-in-memory (CIM) architectures exploit fundamental characteristics of memristive technologies, such as Phase Change Memory (PCM), use the same device (e.g., the memristor) to perform computation and storage in the same physical location (Sebastian et al., 2017), overcoming the memory-wall (Wulf and McKee, 1995), and demonstrating unprecedented performance in myriad computing applications (Mehonic et al., 2020).

3.2.4. Neuromorphic processors

It is widely known that computers are nowhere near as versatile as our own brains. Inspired by the brain's structure, neuromorphic processors and architectures aim to emulate biophysical processors that occur in the brain and are capable of low-power asynchronous real-time adaptable operation (Azghadi et al., 2020). Tremendous efforts have been made to implement artificial neurons and artificial synapses using a variety of emerging devices, such as memristors (Mehonic et al., 2020). Consequently, neuromorphic processors have attracted significant attention in the past decade as a key enabler of new computing and electronic paradigms (Schuman et al., 2017; Sun et al., 2021; Stern, 2014).

3.2.5. Quantum computing

In the last decade, there has been tremendous acceleration in the progress on quantum computing, e.g., the development of computers that use quantum states to perform calculations. While the world's first quantum computer was created in 1998 (by researchers from the Los Alamos National Laboratory, MIT, and UC Berkeley), now for the first time ever, quantum supremacy was achieved. Google published that their "Sycamore processor takes about 200 seconds to sample one instance of a quantum circuit a million times—our benchmarks currently indicate that the equivalent task for a state-of-the-art classical supercomputer would take approximately 10,000 years. This dramatic increase in speed compared to all known classical algorithms is an experimental realization of quantum supremacy" (Arute et al., 2019). At the beginning of 2019, IBM brought to the market the first commercial quantum computer (IBM Quantum System One) and recently unveiled a new breakthrough 127-qubit quantum processor which brings commercial quantum computing into dimensions where it cannot anymore

be reliably simulated on a classical computer (Anon, n.d.-am). Recently quantum engineers from University of South Wales, Sydney managed to generate another important breakthrough allowing control of millions of qubits simultaneously (Vahapoglu et al., 2021). Progress in quantum computing would be truly game-changing as real artificial intelligence could be within reach.

The combination of biological and electronical components opens-up additional dimensions. One of the breakthroughs published 2022 is clearly the demonstration, that neurons cultured in a dish connected to microchips can learn to play the game Pong (Ledford, 2022; Kagan et al., 2022).

3.3. Robotics

The field of robotics has developed quickly in the last decade, solving major challenges in bringing a huge variety of robotic innovations and solutions to reality. Technology developments like high-torque motors (Wensing et al., 2017) enabled stronger advances in the mechanical structures, often through bio-inspired approaches (Schumacher et al., 2020), and led to quicker and more reliable performance. Developments in the control algorithms improved the overall efficiency and safety of movements (perturbation responses or balancing) to create more agile behaviours. In addition, recent developments in AI-based approaches, especially in computer vision and language comprehension, provided a promising future for robots to interact with humans in a natural way. For example, with AI-powered technology, the performance (e.g., object recognition, navigation, or path planning) of self-driving vehicles has greatly improved in the last decade. The tremendous efforts in the development of novel machine learning techniques will overcome current challenges in the control of robots, will enable efficient learning of robotic motor skills as well as generalizable object or environmental representations (Kroemer et al., 2021). Soon, important steps await to be taken to seamlessly integrate the current state of the art of robotic technology into our "real-world" environment with direct human-robot interaction.

A key challenge to be solved is the high power consumption and related energy storage requirements for robots (McNulty et al., 2022).

3.3.1. Service robotics and humanoids

Like the fields of other autonomous systems of self-driving vehicles, AI will enable service, care, and humanoid robots with real-time object recognition and integrated context information about its environment. This will allow robots to safely manoeuvre in more challenging and unstructured environments that are prone to create collisions or obstacles for the robot, such as pedestrian streets, hospitals, or office rooms. Another application of AI-powered object recognition is the correct handling of objects with different properties and geometries like fluids, rigid and compliant objects, e.g., when operating in kitchens.

In addition, recent studies (Hwangbo et al., 2019; Lee et al., 2020) have shown that AI-based controllers can produce versatile, agile, and robust locomotion for quadruped robots in both indoor and outdoor environments. This, combined with environment perception modules, enables the deployment of autonomous or semi-autonomous legged robots in complex environments which are dangerous for humans and inaccessible for other types of mobile robots (e.g., wheeled or tracked), such as disaster rescue scenarios.

3.3.2. Wearable robotics & cobots

Collaboration between humans and robots, (e.g., in cases of exoskeletons, active prosthetics, or collaborative robots) can become a challenging scenario if the intention of the user is unknown or changes throughout the operation. Interesting developments come from the field of soft-robotics - systems with controllable or inherently compliant structures - that allow for flexible and self-adjusting contacts that offer safe and easy human-robot interaction (Kim et al., 2013; Quinlivan et al., 2017). Additionally, neural interfaces might provide more direct information exchange between the user or patient and the robotic counterpart (Hochberg et al., 2012). These interfaces through either embodied or artificial intelligence hold promise to bridge the 'information' gap in human and robot collaboration. Robotic technology has improved the design and structure to create safe, efficient, and high performant behaviours. Until some years ago, mainly simple, and unperturbed movements could be reliably performed, like with industrial arm robots. Robotic systems are now becoming "smarter" in recognizing their environment, integrating context information or novel interfaces, and predicting steps ahead. This leap forward will open a new door for robotics, namely, to step out of the lab and interact in real-world scenarios under high uncertainty and non-ideal conditions. This could likely make the field of robotics one of the game changers of the next decade, not only affecting production plants but being able to conduct work in real-life. In combination with machine learning and artificial intelligence, the possibilities would be almost endless. Imagine a robot learning real-time what all other robots are learning all over the world.

3.4. Micro/nanorobots

Nanotechnology is widely regarded as a field that holds the keys to solving wide ranging challenges by improving battery efficiency, unlocking novel filtration and purification methods, and addressing health care needs. In particular, high hopes are placed on the future of nanomedicine. For instance, the 2010 U.S. Science Policy Report, *Nanotechnology Research Directions for Societal Needs in 2020* envisioned that by the end of the decade nanodiagnostic tools will become a backbone of clinical medicine, and at least 50 % of all drugs will be enabled by nanotechnology (Roco et al., 2011). However, while advances in some areas of nanoscience, such as nanofabrication, have brought significant improvement in our day-to-day life, nanoscience has not yet delivered on its promise of efficient drug delivery, imaging, surgery, and diagnostics. Considering recent advances, it is time for a new era of micro/nanorobotics and molecular machines.

To distinguish between various nanocarriers widely used for drug delivery and micro/nanorobots, we will define the latter as any micro/nanostructure capable of transforming energy into mechanical force. At present most nano-scale drug delivery platforms rely on passive diffusion methods rather than directed guidance. Such an approach raises difficulties in overcoming the drag forces resulting from low Reynolds numbers and Brownian motion. To surmount this obstacle, nanobots exploit an energy source (e.g., magnetic field, ultrasound, chemical gradients, etc.) for their locomotion (Soto et al., 2020).

The ability to guide micro/nanorobots directly into diseased tissue could enable the delivery of various types of cargoes ranging from small molecule drugs and inorganics to biologics. Furthermore, this could be combined with a carrier engineered in a way that provides triggered release of the therapeutic payload. Active directed delivery has obvious advantages over the passive diffusion approach, mainly by limiting the off-site toxicity. This makes it possible to use higher dosages as well as more potent ingredients.

Particularly interesting science is done on biohybrid nanorobots that make use of bacteria's innate properties. Examples include bacteria that are engineered such that they carry gene or protein payloads or contain a magnetic element, making it possible to guide them with an external magnetic field. Using bacteria has multiple advantages, as they constitute a naturally biocompatible form of nanobots and have been widely studied. In addition, one can exploit their characteristics such as propulsion systems and combine them with externally engineered properties. We expect that even more exciting discoveries will come from a merger of synthetic biology, nanotechnology, and molecular engineering.

Therapeutic agents are not the only thing that can be loaded onto a nanorobot. Living cells represent another attractive cargo class. Although many cellular therapies have shown promise in the preclinical setting, clinical results have been largely suboptimal in solid tumours,

while showing efficacy in hematological malignancies. Ineffective delivery of cells is considered one of the main contributors to this failure (Ng and Thakor, 2020). Microbots could address this challenge, enabling direct cell delivery into the target tissue or stem cell niche.

Even more exciting are developments in which nanobots are used to manipulate and improve natural processes in the human body, such as assisted fertilization. Here nanobots can supplement or substitute the normal process such as the delivery of sperm. Furthermore, 3D-printed biodegradable scaffolds were tested in targeted neuronal cell delivery (Dong et al., 2020). Other systems were developed to manipulate sperm cells, oocytes, transport macrophages, erythrocytes, and stem cells (Soto et al., 2020). While the field of biohybrid micro/nanorobots is still in a knowledge accumulation stage, it holds promise to generate transformative outcomes for disease treatment. Cardiovascular and liver diseases, stroke, knee injury, and Alzheimer's are among the most likely disease indications which will directly benefit from advancements in directed cell transplantation. Aside from targeted cargo delivery, nano/micro-scale robots are expected to complement current surgical tools, as they can access places that catheters and blades cannot. At present, most small-scale robotic devices are still in the millimetre range. But miniaturisation efforts have led to some promising technologies such as star-shaped grippers, used to excise tissue samples, and neutralise or grab e.g., blood cells. Nano/micro-robotic surgery is yet to gain widespread adaptation, though the advantages of a minimally invasive protocol are clear. Further improvement of the scale and precision, as well as safety and control of microbots, will be necessary, but when completed may lead to the next revolutionary transformation in clinical surgery.

To realise the whole potential of nanobots, it is likely that a combination of their functions and properties will be used. An example could be Alzheimer's disease, which is thought to be caused by toxins and proteins accumulating in the brain. A treatment using nanobots could be a combination of a precise delivery of drugs that loosens such toxins and proteins via nanobots in combination with other nanobots which flush them out of the brain or transform them into less harmful substances. Finally, successful translation of nano/microrobots to a clinical application will not be possible without significant advances in microbot imaging since any application from cargo delivery to precision surgery requires effective monitoring tools. The main challenge here is to distinguish between signals originating from micro/nanorobot structures in motion and those coming from the surrounding 3D environment (Soto et al., 2020). This challenge will require substantial machine learning and sophisticated algorithms applied to state-of-the-art analytical techniques. Bringing down the cost of such monitoring is equally important. While some data could be easily acquired in academic research labs, expanding the same methods to hospitals may prove an expensive and inefficient solution.

It is worth noting that while scientists find the micro/nanorobotic field hugely exciting, those on the business side often don't hold the same level of optimism. Ultimately, there needs to be a significant potential advantage and cost/risk-benefit in translating microbots to the clinic as compared to expected future advancement of more classical state-of-the-art techniques. Thus, micro/robotics could either find a unique application where there is a strong unmet medical need or they should challenge already existing standards of care, providing more efficient and cheaper alternatives to existing therapies or clinical tools.

As with all new technologies, the transfer from lab to clinic will be a function of cost and benefit, which nanobots stand a very good chance of improving substantially as their precision and utility increases.

3.5. Advances and challenges in science on anti-ageing

Our world is experiencing a sustained age-structural shift from predominantly young to predominantly older societies. This is the result of widespread declining fertility and increasing longevity in industrialized countries. According to the United Nations (UN), the share of the population aged 65 years or older is expected to almost double from 9.3 % in 2020 to approximately 16 % by 2050 (UN, 2020). Given the strong relationship between the ageing process and age-related diseases like cancer, cardiovascular, and neurodegenerative diseases, increasing efforts are directed at developing interventions that preserve health in old age and postpone the onset of age-related diseases. If successful, the economic implications of such interventions would be enormous; increasing interest from the public, corporations, as well as investors, including big names from Biotech and IT in Silicon Valley. A model of future health and spending in the U.S. illustrates the effect of delayed ageing – adding 2.2 years additional healthy life expectancy would yield US$7 trillion in savings over 50 years (de Magalhaes et al., 2017).

The growing interest of many stakeholders in healthcare in anti-ageing research is driven by recent scientific breakthroughs spanning from the partial reprogramming of old cells and regrowing functional ectopic organs in tissue culture to reversing epigenetic ageing. In fact, a recent MIT Technology Review selected anti-ageing drugs as one of Top 10 Breakthrough Technologies in 2020 that are expected to make the biggest impact towards solving humanity's most important problems (Anon, 2020c). What do we already know about human ageing and how far away are we from translating evidence-based bioscience to medical means for supporting healthy ageing? What can ageing models actually tell us and what is holding translational medicine back?

In the past two decades, a variety of well-designed biological studies on cultured cells, tissue samples, and model organisms like yeast cells, fruit flies, *Caenorhabditis elegans*, and *Nothobranchius furzeri* (a short-lived fish species), have identified various biological mechanisms which are involved in ageing. Research on genetically modified mice strains and genome–wide searches for longevity-associated genetic traits in centenarians add to this toolbox. By 2013, the list of hallmarks driving the ageing of cells and tissues included altered communication between cells, genetic instability, telomere attrition, epigenetic alterations, dysfunction of mitochondria, dysregulated cellular metabolism, loss of proteome homeostasis, inflammation, stem cell exhaustion, and cellular senescence (Lopez-Otin et al., 2013; Campisi et al., 2019a). Recently, a tremendous biomedical interest arose regarding the biology underlying immune-senescence partly due to the life-threatening lack of resistance of the elderly to COVID-19. Worldwide there are now numerous research activities underway aiming to identify biomarkers for immunosenescence. A current focus is seen on age-correlated signatures of blood proteins such as circulating cytokines/chemokines. Soon, such biomarkers will provide an unprecedented clinical utility by virtue of their prognostic value. This includes measuring the level of readiness of both, the innate and the adaptive immune system to enable an individual to fight viral infections as well as managing repair of tissue damage and quantifying an individual's response to vaccination.

Past and ongoing research has provided evidence for a variety of cellular processes, pathways and molecular components which have shown a strong impact on ageing in model organisms. Metabolic alterations resulting from the insulin-like signalling pathway, changed outputs of the target of rapamycin (TOR) pathway, sirtuin action, NAD+ levels, disruption of circadian clocks, dietary restrictions, mitochondrial dysfunction and oxidative stress, cellular shift to become senescent cells, local or systemic chronic inflammation processes, disturbed proteome homeostasis, mitoautophagy, and autophagy (Campisi et al., 2019a). The expression of these age-related cellular mechanisms across multiple tissues and organs is seen now as the underlying cause of multimorbidity in the elderly. Cellular ageing is the system-wide pathophysiological basis for many age-associated diseases, which on a phenotypical level are considered as unrelated (Partridge et al., 2020; Robbins et al., 2021).

In cellular biology research to elucidate why and how we age, the concept on senescent cells (SNCs) is entering the central stage (Dolgin, 2020). SNCs in a tissue are frozen in the resting stage (G0) of the cell cycle. They are characterized by a special set of functional markers, such as expression of beta-galactosidase, high expression of the cell cycle kinase inhibitors p16 INK4a and p21 CIP1, signs of DNA damage, and expression and secretion of proinflammatory cytokines such as IL-1b and

IL-6 and others, known as senescence-associated secretory phenotype (SASP). Various of these senescence markers are also found in post-mitotic terminally differentiated tissue cells (Anon, n.d.-au). SNCs drive chronic inflammatory processes in tissues. Senolytics were shown to hit senescent postmitotic cells, and therefore these compounds do not offer a fully clinically validated promise to become drugs for therapeutic applications in age-related diseases. Anti-ageing drug development is currently in an immature stage but is predicted to become a main drain in pharmacology in the coming years (Anon, 2020c; Partridge et al., 2020; Robbins et al., 2021; Dolgin, 2020; Mahmoudi et al., 2019a). In cancer, a dual role of senescent cells is currently discussed: a cellular shift to SNCs can be seen as a physiological reaction to prevent premalignant cells from proliferating, but the activities of SNCs in the tumour microenvironment may also promote tumour growth. In addition, immuno-senescence weakens the body's ability to fight tumour progression or recurrence (Dolgin, 2020).

Moving forward, ageing research will advance to unravel some of the current challenges. These include the development of new age-associated disease models, the identification of novel ageing biomarkers that will enable a better understanding of age-related diseases, and the integration of big data analytics to advance multidisciplinary in longevity research.

Most research on ageing and longevity is conducted in classical model species, such as mouse, rat, and fruit fly. However, many successes in these animal models failed to translate to humans. However, short-lived species are more sensitive to life extension than humans, and current research strategies focus on solving the end stage of the disease, which is more vulnerable to differences between species than targeting the root causes of ageing (Anon, 2018). Offering sufficient complexity to study age-associated damage at the molecular, cellular and tissue level, organoids hold promise as a powerful emerging tool for longevity research in the translational setting (Hu et al., 2018b).

To better describe the ageing process, define ageing-related pathologies, and manage multimorbidity, there is a growing interest in identifying biomarkers of ageing. Eligible pathways which lead to discovery of such biomarkers are derived from the aforementioned list of hallmarks for ageing (Lopez-Otin et al., 2013; Colloca et al., 2021). Despite current efforts, however, ageing biomarkers are still far from a clinical application, as they do not meet the ideal criteria of a validated biomarker (Ferrucci et al., 2020). More than a single biomarker, a thoroughly validated signature of biomarkers could provide a more comprehensive assessment of ageing in research or in clinical practice. With the advent of novel technologies on data exploration, such as artificial intelligence and deep learning, we can now integrate multidisciplinary findings at different molecular, cellular, and biological levels. These technologies thus hold great potential to facilitate the advancement towards a combination of ageing-related biomarkers in the upcoming years.

Lastly, one of the limitations of longevity research today is the lack of big data. The interdisciplinarity of ageing research will be essential to define the complex interactions of the multiple biological, physiological, and behavioural pathways that contribute to age-related declines in health. Current research will greatly benefit from integrated datasets including studies ranging from R&D to human trials to better understand early pathogenesis and progressive stages of age-related diseases and development of diagnostic tools. To this end, international cooperation and open data platforms should be developed to provide the right framework to facilitate the exchange and enrichment of available information. One example of such initiative is the INSPIRE project, a translational research platform in geroscience to promote healthy ageing which was launched by the Toulouse University Hospital Gerontopole (Anon, n.d.-an). INSPIRE is aimed at constituting a bioresource platform going from animals to humans, from cells to individuals, from basic research to clinical care. The further development of this and similar initiatives will form a stepping-stone for the future of longevity research.

New insights into the biology of ageing and the intersection between biological research and new technologies will continue to deepen our current understanding of ageing. We believe that translational research for healthy ageing has great potential to overcome current challenges and will enable the development of innovative therapies to prevent and even reverse ageing-associated diseases. However, we need to further discuss the very nature of senescence. Reaching consensus on the central question of what constitutes healthy ageing or whether ageing by default should be considered a disease will be necessary to reach the full potential going forward.

3.6. Early intervention: healthcare instead of sickcare

According to the World Health Organization, the aim of primary healthcare should be to maximize the level and distribution of health and well-being (World Health Organization &amp and United Nations Children's Fund (UNICEF), 2018). In sharp contrast to this goal, the global disease burden of diabetes, cardiovascular disease, and certain types of cancer has risen over the last decade and is expected to increase even further (Khan et al., 2020; Liu et al., 2020c; Roth et al., 2020; Sung et al., 2021). Even more troublesome, the costs of healthcare have increased concomitantly during the same period (World Health Organization, 2020).

Clearly, the current healthcare system needs improvement. Its underlying logic is that patients are served and treated once they turn sick. A paradigm that some believe has its roots in the ground-breaking success of antibiotics at the beginning of the 20th century (Fani Marvasti and Stafford, 2012). While there are ways to improve the present system, academic researchers, companies, payers, and regulators are starting to explore a paradigm shift: emphasising prevention rather than treatment (Fani Marvasti and Stafford, 2012; Mallilk, 2016; Solbach et al., 2016).

Depending on author and context, disease prevention can mean everything from stopping the disease-causing injury/stimulus and thereby preventing disease occurrence or enabling earlier detection of an already present or soon-to-surface disease (Fani Marvasti and Stafford, 2012; Mallilk, 2016; Solbach et al., 2016).

In the past, pharma companies focused on preventive medicine approaches that pharmacologically modulate known risk factors of diseases, such as high blood pressure or cholesterol levels. Examples of already approved drugs of that kind are found for asthma, heart diseases and stroke, high blood pressure, diabetes, migraines, and different kinds of cancers in remission, among others.

Arguably, the most effective approach of preventive medicine would be to omit major risk factors of cardiovascular diseases, diabetes, and cancer, such as obesity and smoking, by non-pharmacological means. These approaches challenge companies with complicated clinical trial designs and/or hardly patentable preventive strategies. However, some pharma companies have started to incorporate disease prevention approaches in their corporate strategy. For instance, the Novo Nordisk Network for Healthy Populations, founded by Novo Nordisk and the University of Toronto aims at not only funding innovative research on preventive solutions for type 2 diabetes, but also on strengthening partnerships in the health care and public health systems (Sustainable business, 2021). The Network develops community outreach activities related to raising awareness of this disease and recommendations for its prevention (Anon, 2021).

In undertaking the initiation of the paradigm shift from providing care for the sick towards fostering healthcare for all, many players are currently focusing on changing lifestyle habits and promoting health monitoring. Instead of aiming at traditional drug development, these companies focus on user-friendly healthcare monitoring apps or certified monitoring wearables as medical devices with the aim to omit major disease risk factors and/or enable early diagnosis. Especially with the emergence of artificial intelligence and digital technologies, new preventive health solutions at the convergence of healthcare, data science,

and technology are on the rise. Two preventive care areas experiencing rapid growth are general health monitoring and cardiac health. Fitbit developed widely-used health trackers that empower people to have a healthier life (Anon, n.d.-ao). After 14 years in the market, the efficacy of Fitbit's solution on shaping healthier behavioural changes is supported by quantitative analysis (Ringeval et al., 2020). With regards to cardiac health, digital solutions are being built to track heart parameters for an early diagnosis of potential cardiac malfunctions. Among others, eMurmur and Acorai are two innovative start-ups in this space. eMurmur, is developing an AI-enhanced digital auscultation platform for virtual cardiac and pulmonary health screening and monitoring (eMurmur corporate website, n.d.). Acorai, is enabling non-invasive intracardiac pressure monitoring through novel sensor technologies and AI (Acorai corporate website, n.d.).

Other players in the preventive care field aim at providing data-driven health consulting to end-users based on digital self-measurements, genetics, gut microbiome, and/or blood analytes. Although the increasing number of start-ups that fall into this category indicate a market with growth potential, the bankruptcy of the scientific wellness start-up Arivale illustrates that challenges remain. While testing services for blood have proven feasible, microbiome and genetics are still relatively costly and certain studies cast doubt on the overall clinical effectiveness of wellness programs (Anon, n.d.-ap). Customer acquisition seems to be a key challenge in the field and points to an even bigger issue: how can we make people not only understand that their current behaviour can determine their health 20 years down the line, but get them to change their lifestyle accordingly? Health promotion is a relatively new concept which refers to the practice of educating and encouraging individuals to take greater care of their own health by adopting lifestyle changes and regular medical check-ups to reduce the risk of illness.

Prevention and health promotion is a responsibility to be shared among all health care providers but is now mostly delivered by general practitioners. Despite positively endorsing healthcare prevention, some general practitioners could view it as time consuming and distracting from curative medicine. Lack of patient motivation, concerns regarding intrusion into personal choices, and ambivalence towards the effectiveness further complicates implementation. Educating people, identifying at-risk patients in the community, and enabling them to make better lifestyle choices by triggering long-term critical thinking processes that produce positive health outcomes will be instrumental to help people live longer, have healthier lives, and reduce the demand for treatment and medical care.

Another challenge for healthcare promotion and disease prevention is the reimbursement of these activities by the public healthcare system. To overcome the reimbursement challenge, many start-ups make the patient pay directly for the services provided. While it is currently still a limitation, government institutions are addressing the need to reimburse health promotion programs. The Affordable Care Act, for example, requires insurers to cover certain preventive care services at no cost to the patient, although confusion abounds over which services qualify and for which patients (Anon, 2020d). Medicaid and Medicare, US federal programs that provide health coverage for people aged over 65 and/or people with very low income, also support the reimbursement for evidence-based health promotion programs in the community (Anon, 2020e).

Overall, the number of initiatives and programs focused on healthcare prevention and promotion are currently on the rise. The preventive care field will continue to evolve to face current challenges, such as the general awareness and recognition of the population and the available reimbursement options for preventive care strategies. Once these key challenges can be overcome, disease prevention – especially in its purest form – will be a game changer for public health.

3.7. DNA data storage

In 1975 Intel co-founder Gordon Moore observed that the number of transistors on a silicon chip doubles around every two years while the cost halves. This trend, commonly known as Moore's law, has recently begun to show deceleration. Today's transistors are just several nanometres wide, only tens of silicon atoms apart from their hard physical limit. So, computer scientists must start taking creative approaches to satisfy an ever-growing demand for fast data processing and efficient storage. One such approach they could adopt is DNA computing and cryptography.

Just as engineers spent decades creating the first silicon chip that could enable information processing, nature took eons to perfect a universal storage code for biological systems in the form of DNA. The main advantage of a DNA-based circuit board lies in parallel computing, where a multitude of DNA molecules enables many different functions to be processed at once. DNA can effortlessly produce more copies of itself at the same time, while conventional computers would have to resort to an increasing number of cores and processors to solve a similar array of tasks. This means that in the case of very complex calculations, the slow processing speed of a DNA-based computer could be compensated for by millions of molecular interactions happening simultaneously.

Molecular computers have been on the research playground since the 1990s. Like a conventional computer, they use logic gates which process incoming signals using simple rules. In research labs, DNA-machines were able to solve 'Hamiltonian path' (Lee et al., 1999) and 'NP-compete' problems (Bach et al., 1998), compute a square root (Benenson, 2011), play tic-tac-toe games (Stojanovic and Stefanovic, 2003), and recognise 100-bit hand-written digits (Qian et al., 2011). Unfortunately, slow processing speeds, difficulties in interpreting results, replication and sequencing errors, and its extreme cost held this technology back from widespread commercialisation. Not to mention that molecular machines (similarly to Von Neumann machines) are limited to the same set of computationally solvable problems. So rather than taking jobs from conventional computers, biochemical circuits are better suited to the development of new diagnostic devices. For instance, DNA molecular computation platforms for the analysis of miRNA profiles in clinical serum samples have achieved rapid and accurate cancer diagnoses with 86 % accuracy (Zhang et al., 2020).

While personal molecular computers are not coming into our lives any time soon, DNA-based information storage might be closer than we think. The fast digitalisation of the world's population of 7.9 bn makes the development of such storage technology a dire necessity. Most of the world's data today is stored on magnetic and optical media. Although these technologies have improved tremendously, they are approaching their density limits at a time when the demand for data storage is growing exponentially (Ceze et al., 2019). Under such circumstances using DNA to store data seems particularly attractive (and arguably an inevitable development). DNA storage density is approximately six orders of magnitude denser than the densest media available today: it stores all information required for human development in just one nucleus, and in principle, could store every single datum ever recorded by humans in a container about the size and weight of several pickup trucks (Anon, n.d.-aq).

The rate at which DNA-storage technology is progressing is somewhat like that observed in the early stages of semiconductor development. Today we are seeing a storage capacity improvement of approximately three orders of magnitude in a mere six years. In 2012 Goldman et al. and Church et al. nearly simultaneously presented methods for storing about 1 MB of digital information in DNA (Church et al., 2012). And in August 2020, Twist Bioscience announced that it had used its DNA as a data-storage medium for full episodes of the Netflix series Biohackers (Anon, n.d.-ar). Just a year prior, Microsoft and the University of Washington demonstrated an automated DNA data storage and retrieval system which could store a gigabit of data (Takahashi et al., 2019).

To store any information in a form of DNA it must be encoded first. Actual DNA molecules must then be synthesized, physically conditioned, and organized into a library. Finally, there comes retrieving and selectively accessing encoded information, sequencing it, and decoding it back into digital data. Each step of this process comes with its own hurdles. At this point in time a significant limitation to the scalable application of DNA-storage technologies lies in its high price tag. In 2017 the cost of synthesising 2 MB of data amounted to US$7000 with an extra US$2000 spent on sequencing. Recent progress in parallelised DNA synthesis and DNA sequencing technologies, such as portable sequencing devices (Oxford Nanopore MiniOn and Illumina iSeq 100) is driving down the costs associated with DNA-storage.

While scalable manufacture of millions or billions of sequences has not been achieved yet, one can expect that with the fast-pacing progress of biotechnology and appropriate financial incentives, even this barrier can be taken down. For instance, the US's Intelligence Advanced Research Projects Activity (IARPA) has awarded a multi-phase contract worth up to $23 million to develop DNA-based technologies for achieving exabyte-scale data storage (Anon, n.d.-as). Meanwhile, Microsoft is teaming up with other companies including Twist Bioscience, Illumina, and Western Digital, allying to advance the field of DNA data storage (Anon, n.d.-at). Nonetheless, the DNA-storage technologies will only become possible with parallel advances in related files such as polynucleotide synthesis, fast sequencing, new microfluidic devices, and many more technologies that are yet to emerge. In the end, large-scale investments (Stanley et al., 2020) and collaborations are of paramount importance when the challenge at hand is the appropriation of nature's finest invention – the genetic code.

3.8. Fusion

Fusion technology breakthroughs and a clear path to commercialisation has always been "10 years away". Starting after WW2 and with the development of nuclear power plants, a substantial amount of research, resources, and funding has flown into the field. Yet a fusion power plant is not likely to be realized in the near future. However, this does not mean that the last 70 years have been wasted and nothing has been achieved. Various barriers to the realisation of controlled fusion on earth have been cleared and while realising fusion reactions is an inherently applied science problem, a deeper understanding of fundamental physics phenomena such as high-temperature plasmas has been developed in the process. In addition, since a successful realisation of fusion power generation has a substantial payoff, even with a sometimes-murky path to success, a significant investment is still justified. In this article, we will give an overview of the field of fusion, current developments, as well as an outlook on the future.

Other than nuclear fission, which, as the name suggests, is the process of splitting atoms and which is used in nuclear power plants, fusion is the process of fusing atoms together. To achieve this, one must collide nuclei with high enough energy to overcome the Coulomb repulsion between them such that they are bound together by the strong nuclear force. While there is a high number of fusion reactions possible, the easiest to facilitate on earth is between deuterium (heavy hydrogen) and tritium (superheavy hydrogen), which combine to produce helium. The difficult aspect of fusion research is to produce more energy than is put into facilitating the reaction. To reach conditions in which the Coulomb force is overcome, one needs to use a large amount of energy to achieve high pressures and temperatures. In addition, tritium is not naturally occurring in sufficient quantity and would need to be produced, ideally within the fusion reactor in a so-called breeding layer.

Yet, despite these large obstacles and an abysmal track record of swift commercialisation the case for fusion research remains a strong one. Fusion energy is one of the cleanest and small footprint energy sources we know. It only leads to small transmutations within the fusion reactor material, cannot result in runaway reactions such as in nuclear reactors and the resources on earth needed for fusion power could provide more power than oil by a factor of 10^5 (Cowley, 2016).

Currently, there are three main pathways that are explored towards a successful implementation of fusion power. The most promising and advanced technique is probably the Tokamak reactor, which stands for toroidal chamber with magnetic coils (a Russian acronym). Here, plasma is confined within a large chamber via magnetic confinement, where the magnetic field is a combination of an induced field from a current flowing in the plasma and external magnetic fields (Ongena et al., 2016). This applied current in combination with external heating mechanisms is also used to bring the plasma to sufficient temperatures. While this is the most promising and advanced fusion energy technology available, it has some drawbacks including a high risk of magnetohydrodynamic instabilities and the necessity to be operated in a pulsed fashion, both due to the fundamental principle of running a current through the plasma. A similar technique is the stellarator approach, which also uses a magnetic field to confine the plasma. However, here the magnetic field is fully externally created and not induced by the plasma. A stellarator is much more difficult to realise than a Tokomak reactor since the plasma behaviour and magnetic field need to be very well understood and modelled and as a result the construction is rather complex (to get an idea of how complex, watch the time lapse of the construction of the Wendelstein X-7 Stellerator in Germany (Max Planck Institute for Plasma Physics, n.d.)). The third technique is called Inertial-Confinement fusion, where fusion fuel is compressed into a capsule and ignited with lasers. After ignition, the plasma inertia maintains sufficient pressure long enough to achieve a fusion reaction and create energy (Craxton et al., 2015). This technique has the advantage of not requiring a large magnetic field but cannot be operated in a continuous fashion as each plasma ignition and burn needs to be followed by the loading of a new target. Each of these three techniques aims to achieve a fusion burn to produce surplus energy after accounting for heating and magnetic field energy needs. In a controlled fusion burn, which has not been achieved yet, the energy and heat required to keep the fusion reaction going are coming from the product of previous fusion reactions, energetic Helium nuclei.

While we do not know yet whether we will be successful in creating a fusion reactor that is able to output more energy than is needed to operate it, it seems we are now within reach of getting definite answers. ITER, the largest tokomak project is projected to start up within the next 20 years and is expected to be able to output 10 times more energy than is needed for operation, providing a preliminary estimate of energy budgets. Similarly, Wendelstein 7-X, a demonstrator for the Stellarator principle in Germany, is currently being modified and will be fully operational by 2022, while Inertial-Confinement fusion research is exploring a variety of new techniques to achieve a higher fusion yield. A certain uneasiness with the amount of time needed for breakthroughs and verifications is warranted but it is important to keep in mind that realising a fusion reactor is an incredible feat of engineering and physics. In magnetic confinement fusion, plasma temperatures in the hundreds of millions of degrees need to be achieved, higher than any temperature in the solar system. Yet, this plasma is only about 1 m away from the superconducting coils that must be kept at close to absolute zero to create the magnetic confinement field.

So, while fusion energy is at this point still at least a few decades away, there is a realistic hope that at the end of 20 years we will have a more concrete time plan. In the meantime, research into fusion will continue to advance our knowledge of fundamental science and plasma processes in our universe as well as improve our engineering capabilities.

3.9. Space exploration by many players

The very first person to ponder our place among the stars probably couldn't have imagined that the quest to find an answer would one day bring us thousands of miles away from the Blue Planet. Today, the space industry is experiencing a transition resembling what happened decades

ago with air travel, sea shipping, and railway journeys. History teaches us that all of those industries started as enormously expensive, technologically challenging, and dangerous ventures sponsored by wealthy governments. But the picture changes once exploration identifies assets worth capitalizing on. From this point on, government takes a step back and merely provides the infrastructure to stimulate the private sector, leading to rapid technological advancement. In the case of space exploration, industry commercialisation is long overdue.

Strictly speaking, commercial companies had their foot in the space game from the early 1960s. But their products were too expensive, so only governments could afford them. Such an environment meant little competition and hence little incentive for cost/benefit optimization. The Commercial Crew Program has turned this page of spaceflight history, with companies like Boeing and SpaceX having joined the initiative. In 2020 the launch of the Crew Dragon spacecraft made headlines as the first crewed mission to launch from the United States in nearly a decade (Anon, n.d.-au). More recently, space tourism has gained a lot of traction, with Blue Origin and Virgin Galactic racing to provide the first private space flight experiences (Anon, n.d.-av). While extra-terrestrial vacations are undoubtedly a once-in-a-lifetime experience it is not the sole commercial path for space development. In fact, it may merely serve as a stepping-stone to other private space industries.

It is expected that developing transportation infrastructure and competition among the rocket builders will continue to drive down the cost of commercial space launches. If the price per pound is reduced to 1000 US$ it is expected to generate significant commercial interest, resulting in near-term economic opportunities (Greason, 2019). For instance, Starlink, a satellite constellation developed by SpaceX, consist of thousands of mass-produced small satellites in low-Earth orbit (LEO). Assembly line production of satellites brings in economies of scale. Placing smaller and cheaper satellites in LEO will significantly reduce the cost of telecommunications, delivering internet and mobile connectivity to developing nations and isolated areas. Remote sensing is another field that can benefit from falling prices. At present, limited NASA's satellites generate expensive data sets with a 0.5 m resolution, which can be replaced by higher resolution sensing at a lower cost. Accurate and timely data will support sustainable agriculture and fishing, wildlife preservation, and security monitoring.

Transporting people and other cargo to space is generally considered a 'low-hanging fruit' of space commercialisation. Unlike other commercial opportunities, this one requires comparatively modest infrastructure expansion and technology development, while generating meaningful returns upon investment. But the potential for further space industry development here goes far beyond satellite communication and data generation. Prospective future avenues include space-based clean energy sources, mining, in-space manufacturing and research, upcycling/elimination of hazardous debris, and space-water exploitation (Greason, 2019). While they may sound ambitious, those directions of future development are technologically feasible.

Some may argue that space activities are still prohibitively expensive, and earthlings have other pressing issues where money and resources are better spent - climate change and biodiversity crises to name a few. This could not be further from the truth, however. Space holds potential for solving some major environmental problems. For instance, solar power satellites (SPSs) in Earth orbit could collect solar power and convert it to electricity, which could then be transmitted by microwave or laser beams to sites on Earth, where it would be fed into the existing power grids. Such technology can overcome the operational limitations of terrestrial solar power: by virtue of its location, SPSs are exposed to solar radiation 24/7, and could achieve a power density twice as high as solar panels on Earth. This technology could provide rapid ways of overcoming grid failures in states of emergency. The Chinese space program has recently announced that the construction of such satellites will be among its long-term goals (Anon, 2016).

Aside from continuously growing energy needs, there is an increasing strain on Earth's natural resources. The manufacture of electronic goods from smartphones to airplanes is impossible without secure sources of precious and rare earth metals. A simple back-of-a-napkin calculation suggests that there won't be enough supply to satisfy growing consumer appetites (Humphries, n.d.). Asteroids, on the other hand, are packed with materials, which can be broadly divided into those that are precious on Earth, and those that are valuable in space. Successful sample return missions like Hayabusa have demonstrated the technical feasibility of bringing minerals from orbit. Unfortunately, with an ongoing price tag of 157 million US$ per gram, any commercial activity in this field is currently restricted to science fiction. Whether space mining will one day become an attractive option largely depends on respective commodity prices, the state of industrial innovation, environmental risk/benefit profiles, as well as the per kg value of space launches.

Water is more abundant on Earth than in space. Asteroid-sourced water could be used for human sustenance and radiation shielding, as well as a precursor of space fuels and oxidizers. Thus, sourcing materials for use in space is the most economically viable choice for technological development. Those resources will be particularly valuable to achieve in-space manufacturing.

If brought to scale, there are many products that could be produced in space with economic benefit. The unique properties of space provide humans with experimental environments otherwise unattainable on Earth. For instance, microgravity allows control of convection in liquids or gases, and the elimination of sedimentation, which would result in the growth of high-quality crystals. LambdaVision for example has used this property for the layering of its high-quality protein-based artificial retina (Anon, n.d.-aw), while the wider pharmaceutical industry has also shown interest in improved protein crystallisation (Anon, n.d.-ax). Furthermore, the ultraclean vacuum of space allows the creation of very pure materials and objects, a feature particularly handy when it comes to semiconductor manufacturing (Anon, n.d.-ay). Finally, in-space 3-D printing can supply space stations with easily customisable and optimized parts avoiding the additional costs of exporting any necessary equipment from Earth (Anon, n.d.-az).

To make in-space manufacture worthwhile it is imperative to bring down operational costs and mitigate the risks. One can do so through the upcycling and removal of space-junk. Our increasing use of satellites and spaceships have led to 170 million pieces of debris flying in near-Earth orbit. A collision with any of these may cause great damage to operational space equipment. To tackle this problem, NanoRacks is building tools for the re-purposing of in-space hardware. Additionally, Made In Space, Inc. and Tethers Unlimited both have plans to upcycle parts from rocket stages as construction material for large, low-density space structures, such as large aperture antennas or as supports for large solar arrays (Greason, 2019). Aside from private initiatives, debris capture, and debris removal/repurposing should be a global effort where every country plays its part in extra-terrestrial housekeeping.

Reaching any of the above-mentioned goals requires establishing a basic space infrastructure, which includes fuel and water depots, shuttle travel to the lunar surface, as well as lunar and orbital facilities. With over a dozen countries capable of launching space missions, and an ever-growing number of privately funded space companies, now is the best time to reimagine the future of the space industry. It is worth keeping in mind that every new frontier has always provided humanity with greater benefits than originally anticipated and resulted in world-changing discoveries.

4. 30 years and beyond

Finally, in this third section we dare to explore the wider horizon and dive into topics that are characterized by largely uncharted territories today but where an enormous game-changing impact, even a shattering of current scientific world view and unprecedented applications with worldwide deep consequences can be expected in the future. The topics covered are the secrets of the human brain, fighting all diseases and

becoming immortal, the creation and exploitation of virtually endless sources of ultra-cheap and clean energy, and the exploration of mind over matter effects. Lastly, we describe the theoretical limits of knowledge where there are things we can and will never know.

4.1. Understanding how the human brain works

The human brain is the most intricate structure in the universe and has been evolving and growing in complexity for 7 million years in a way that we have not yet elucidated. We know that the brain has anatomical symmetry, but how does this correlate with studies showing that handedness, language, cognition, and emotions are processed in a striking pattern of left–right asymmetry (Nielsen et al., 2013 Aug; Bassett and Gazzaniga, 2011). The evolutionary advantage of lateralization is that each hemisphere is specialized for different functions resulting in efficiency, by reducing transmission or processing errors (Corballis, 2014). For example, the left hemisphere is associated with language functions, such as sentence construction, vocabulary, and contains centres processing syntax and semantics. The right hemisphere is associated with visuospatial functions such as image processing, depth perception, and spatial navigation. The most obvious brain lateralization consequence is that 90 % of the population is right-handed. Perhaps the most fascinating belief about brain lateralization is that the right hemisphere is the creative side of the brain that also controls emotions and is involved in imagination, intuition, non-verbal communication, and daydreaming (Mihov et al., 2010a). The left side of the brain is the logical side, involved in analysis, mathematics, and processing facts. The hemispheres are not truly separate, both sides of the brain need to work together to process and respond to complex cognitive tasks. One key example of this are gun-shot wounds - if a bullet penetrates both hemispheres the patient can be left disabled for life, but if a bullet penetrates only one hemisphere, the patient makes a full recovery. Furthermore, the existence of inter-hemispheric plasticity makes it possible for functions that were typically associated with one side of the brain to function from the other side, when the brain area becomes damaged (Mihov et al., 2010b; François et al., n.d.).

An emergent theory postulates a multi-directional relationship existing between neurons from different brain regions and parts of the body. Our brain can significantly modulate cardiovascular physiology, which confers a higher susceptibility to develop acute myocardial infarction or heart failure in patients with depression. Conversely, mind-body interventions, such as meditation and yoga, can affect cortisol secretion, blood pressure and heart rate. In addition, the fact that peripheral stimulation can affect the central nervous system is also of particular interest and has been used as an innovative neuromodulation strategy for treating psychiatric and neurological disorders, such as trigeminal nerve stimulation to mitigate post-traumatic stress disorder and depression or targeting peripheral somatosensory neurons to modulate the basal ganglia dopaminergic system and reduce pathological tremor in Parkinson's disease (Cook et al., 2016). Another topic of recent research is related to the gut-brain axis, given that the gut contains more than 500 million neurons that communicate with the central nervous system. The bidirectional connection between the brain and gut has been shown to affect human emotion, motivation, and cognition (Jang et al., 2020). Even more intricate is the relationship between the brain and the enteric microbiota. An increasing body of evidence suggests that psychiatric disorders are associated with intestinal dysbiosis, but whether there is a causal relationship, or such changes are due to a physiological response to chronic stress is yet to be determined (Rea et al., 2020).

It seems clear that the brain can control the body, but what about the mind? Research shows that our beliefs and expectations can indeed affect our brain chemistry and body. This is seen constantly in clinical trials when the administration of an inert substance – the placebo – triggers an effect in patients. This outcome can be either beneficial (placebo effect) or detrimental (nocebo effect). A big branch of research, called "placebome", aims to combine high-throughput data obtained by different "omics" technologies to elucidate the mechanisms underlying such effects. Although still a new concept, placebome studies have shown that the activation of opioid, endocannabinoid, serotonin, and dopamine pathways could mediate placebo responses. Patient's perspectives and thoughts do indeed matter as studies showed that these effects depend on psychosocial factors such as expectancy (Cai and He, 2019; Linde et al., 2007) dispositional optimism (Geers et al., 2005; Morton et al., 2009; Geers et al., 2010), and anxiety (Lyby et al., 2011; Flaten et al., 2011). This effect can be substantial; for instance, a study using Rizatriptan, a migraine drug, where the placebo and drug exchanged labels, showed that there was no difference between the patients who took Rizatriptan and those who believed they had taken it, but were administered the placebo instead (Láinz, 2006). To which extent can the power of the mind reach? It is believed that, while the placebo effect can treat symptoms, it is usually not sufficient to address the cause of the disease. However, it seems clear that an optimistic and hopeful perspective in life can be beneficial to our bodies.

Today technology is growing faster than we can blink, with the current pandemic expediting the adoption of digital health and virtual office hours and enabling the administration of medications at the patient's own home. This demonstrates that the implementation of bioelectronic medicine is feasible. The brain controls all physiology whether it is conscious or unconscious through stimulating nerves that send electrical activity to transfer information rapidly to different cells in the body either activating or inhibiting a specific action or task. However, we have also seen that yoga, meditation and body language can affect the brain. The principle of bioelectronic medicine is to use electricity to stimulate a nerve and provide an external sensory input, making the body believe it came from the brain and thereby modulating physiology (Pavlov et al., 2020). One of the first bioelectronic devices, the pacemaker, uses low-energy electrical pulses through wires, to stimulate the heart rate and rhythm. Recent technology advances include wireless, Bluetooth-controlled pacemakers that can recharge their battery using the energy from the beating heart. Since we fully understand the electrical pathway from the brain to the peripheral body, why should we not use electricity to secrete specific hormones, like insulin or estrogen, induce sleep, inhibit seizures, limit pain, reduce depression and even modulate the immune system? Not only can we use this technology to treat diseases, but we can also diagnose disease by just measuring the electrical signal produced by nerves. The 2021 Nobel prize in Medicine was awarded for the discovery of piezo channels that can sense tension or touch, showing that bioelectronic medicine has the potential to revolutionize our lives. This technology could not just help us diagnose disease earlier, but it could also enable us to rewire the brain from a diseased state back to health. Research needs to be undertaken to make this a reality, but all the current results are promising. Try to imagine a future where these electrical devices collected data that enable us to use artificial intelligence not only for disease diagnosis and treatment but also for predicting outcome and progression. With these types of technological developments, it will be easier for physicians to interact with patients remotely and deliver personalised treatments. The working of the brain might just make bioelectronics the medicine of the future.

4.2. Victory over ALL diseases – being healthy forever

In the last 100 years human life expectancy has increased exponentially as public health policies, such as infectious disease control measures, availability of therapeutic treatments for many (but not all) frequent cardiovascular or neurological diseases, sanitation, and improved food access, have significantly decreased overall mortality rates. However, the average 'healthy' life expectancy, which also takes into account the quality of life, has not kept pace, with an increase in chronic diseases associated with longevity (Beltrán-Sánchez et al., 2015). Humans were not designed to live forever, and just like machines,

wear down and break over time. In this section of the White Paper on unsolved questions of science, we review emerging technologies to overcome ageing and associated diseases.

The fundamental issue with ageing may lie in the building blocks of our bodies, our cells, in dysfunctions of their organelles, metabolic networks or their regulatory pathways. Several molecular pathways have been associated with senescence including, but not limited to, NF-kB and mTOR (Rando and Chang, 2012). Several groups have targeted these pathways to reverse ageing. Notably, a consortium in the US demonstrated that Rapamycin (an mTOR inhibitor) administered late in life, significantly extended the lifespan of mice (Harrison et al., 2009) and a Swiss research group showed that Rapamycin slowed sarcopenia (loss of skeletal muscle mass and strength) in mice (Ham et al., 2020). In addition, another research group demonstrated that selective inhibition of NF-kB in the skin of aged mice reverted the expression profile and physical appearance of the animals tissue to match that of younger control mice (Adler et al., 2007). Although these studies are at the early stages of development, they still provide proof of concept that enzymes or regulatory proteins as products of age-related gene expression can be effectively therapeutically targeted. Other emerging anti-senescence strategies concentrate on blood factors, special diets or specific metabolic manipulations and cellular reprogramming (Mahmoudi et al., 2019b). Various academic groups and researchers in drug companies are also working now on senolytics (selectively clear senescent cells), which however still need future validation of their efficacy by clinical trials (Campisi et al., 2019b; de Magalhães, 2021).

The extent of our cells' ability to regenerate indefinitely may be fundamentally limited by the constraints of our DNA. In 1961, the American anatomist Dr. Leonard Hayflick performed crucial experiments which demonstrated that normal somatic, differentiated human cells are not immortal and can only divide up to 40–60 times before becoming senescent (cessation of cell division) (Hayflick and Moorhead, 1961), a phenomenon later named the 'Hayflick limit'. Seminal work by Prof. Alexey Olovnikov, Prof. Elizabeth Blackburn, and others recognized that repeating DNA regions at the end of chromosomes, known as telomeres, are lost in every cell division leading to a critical point in which cells are no longer able to divide. Since this landmark discovery, telomeres and associated proteins have long been a target for treating and even reversing the effects of ageing.

For example, scientists at the Spanish National Cancer Research Centre recently generated genetically modified mice with super-long telomeres. The transgenic mice lived on average nearly 13 % longer, had less incidence of cancer, were leaner with less white fat tissue, and had better metabolic health in comparison to mice that had normal length telomeres (Muñoz-Lorente et al., 2019). Moreover, in a phase I/II clinical trial at the US National Institutes of Health, patients with telomere diseases, that show a predisposition to accelerated telomere attrition, were treated with Danazol, a synthetic hormone, to pharmacologically target telomeres (Townsley et al., 2016). Remarkably, not only did the drug reduce telomere attrition, but 92 % of patients had a gain in telomere length after 2 years compared to their original baseline. Together, these studies show great promise. However, one of the key limitation of approaches targeting telomeres and other self-renewal proteins is the potential risk of inducing cancer as these targets for reversing ageing are also known oncoproteins (Harley, 2008). Of note, telomeres are not exhausted at the same rate in all cell types and exhaustion may vary in individuals depending on genetic and environmental factors. Therefore, a holistic approach that targets all tissue types may not be necessary nor generally beneficial. Recent studies on 17 organs and in plasma proteomics in 10 age stages over the lifespan of mice elucidated the ageing dynamics of gene expression and indicated that an asynchronous inter- and intra-organ progression of ageing has to be considered (Schaum et al., 2020). In addition, a reduced response to infections and the ability to develop humoral and cellular immunity after vaccination (immuno-senescence) are observed in ageing persons. At present, in view of prevention and treatment of pandemic infections deeper insights into the causes and markers of immune-senescence in the elderly are a major demand and further support for basic and applied biomedical research activities are needed to improve immune functions and extend healthy ageing (Aw et al., 2007; Yousefzadeh et al., 2021).

Alternative research fields, such as tissue engineering for regenerative medicine, focus on replacing, rather than restoring, existing organs and tissues due to cell dysfunction. Tissue engineering uses a combination of cells, scaffolds, or growth factors to recreate native human tissues. The field has shown great promise in various areas, such as bone, nerve, heart, and skin regeneration, with several applications in the later stages of clinical development. Larger organs, however, still require a significant amount of research and development (Mao and Mooney, 2015; Dzobo et al., 2018; O'Donnell et al., 2019). Typically, the larger the organ, the more structurally and functionally complex the tissue becomes to replicate. In addition, for several organs, such as the brain (which is particularly susceptible to age-related diseases such as Alzheimer's disease or Parkinson's disease), significant knowledge gaps remain surrounding how the organ, its special regions and network's function (see section of the white paper on 'How The Brain Works' for further reading). Finally, another major limitation in regenerating large tissues is restricted by supply because of diffusion. Most cells are located within 50-100 μm of a capillary or a blood vessel which provides the cells with essential oxygen and nutrients (Alberts, 2002). Therefore, a vasculature network that can be readily perfused is a pre-requisite for successful tissues/organs engineering.

An alternative approach to generating de novo tissues is to use a host/biological system to source suitable replacement organs. Large animals, such as pigs, have organs of similar size closely matching the vascular network to humans, and from a structural and functional perspective, could be adapted for applications in humans. However, the high specificity and sensitivity of the human immune system to recognise self and non-self-markers in cells and tissue make it difficult to find matching allograft tissue from other human donors let alone tissue from a xenograft source. A rise in the number of genetic engineering techniques is enabling researchers to knock-out, or even humanize target immunogenic genes/proteins to break through species-specific immune barriers, and increase tolerance for xenografts. However, the complex nature of cells in a tissue or organ means that both tissue-engineered and xenogenic products, are still a long way off before they might become common off-the-shelf medical products.

In contrast to transplanting cells and tissues, medical implants are man-made devices used to replace biological structures. Although medical implants have been around for several decades, there is still significant room for development and improvement in the field. For those aged patients who need medical implants, such as knee or hip prostheses or dental implants, it will be of great benefit to increase the life cycle of the prostheses. New implant materials with drug-eluting properties for antibiosis and/or local bone regeneration could significantly improve patient outcomes. The field of nanobiotechnology on composite biomaterials, such as for controllable delivery mechanisms could help provide a solution to this challenge.

Other strategies circumvent the use of cells altogether by promoting technology-driven solutions to the problem of ageing. A joint research team from Spain, US and the Netherlands partially restored the vision of a completely blind patient enough to discern letters and shapes by using intra-cortical microelectrodes inserted in the human occipital cortex that interfaces with custom visual glasses (Fernández et al., 2021). In addition, other groups have developed exoskeletons that have enabled patients suffering from cerebral palsy or paralysis to regain mobility (Soekadar, 2016; Strausser, 2010; Lerner et al., 2017). In the future, there will be good prospects for improving the quality of life in the elderly by digital combination therapies (smart medicines with digital identifiers) to improve patient adherence to proper drug use. Developing artificial intelligence with smart home devices with sensors (i.e. infrared motion, contact, light, temperature, and humidity) will support nurses for health-care on chronically ill patients, to react and adapt to patients'

needs in real-time (Fritz and Dermody, 2019). These technology platforms highlight that intervention strategies other than a pharmaceutical treatment can work in overcoming some biological challenges of physical and neurophysiological dysfunctions associated with ageing. Key to their success is human-machine interface and end-user education.

There are several different emerging technologies, from gene editing to electronic prostheses, to fight ageing. However, given the diversity of the human population and wide range of potential age-associated diseases, in the end no single universal ('panacea') solution exists to the problem of ageing. Instead, we must focus on cultivating multiple technology avenues and provide personalised treatment strategies/plans for patients that are tailored to meet their specific needs so they can enjoy the later years of their life to the fullest.

4.3. Creating endless cheap energy to solve (nearly) all problems (food, water, mobility etc.)

From utopian science fiction literature in the early 20th century to U. S. President Dwight D. Eisenhower's famous "Atoms for Peace" speech in 1953 to the UN, humankind has long envisioned a future in which we can tap into an endless source of cheap energy to solve some of our world's most pressing challenges. For example, an endless cheap source of energy could increase annual global food production through artificial light or heating crops during winter, overcome the major limitation of energy-intensive technologies such as desalination plants, and transform industries, such as the transport sector by facilitating the switch from internal combustion engines to batteries in vehicles. Crucially, such technology plays a key role in limiting global warming and mitigating the catastrophic effects of climate change. Several key technology platforms, including nuclear fission, wind, solar and biomass, are already helping us towards achieving this goal, while others, such as nuclear fusion, are still under active development/research. In this section we cover the potential and challenges of these energy sources and how they could change the world.

4.3.1. Nuclear fusion/fission

Nuclear fusion is often regarded as the holy grail of energy generation. Fusion reactors can be thought of as artificial suns where energy is released when two lighter atomic nuclei combine to form a heavier nucleus (Pacchioni, 2019). Fusion reactors create far less radioactive material than fission reactors, and one of the primary fuel sources, deuterium, exists abundantly in the ocean (Pacchioni, 2019). International collaborations, such as the International Thermonuclear Experimental Reactor (ITER) in France and Wendelstein 7-X in Germany (Prager, 2019), have made significant strides in the field. The latter successfully produced contained helium plasma which provided a key proof of concept for the stellarator concept (Sunn Pedersen et al., 2017). The current challenge is to generate more energy than is used to start the system as well as safely maintain and contain the plasma. The plasma can reach temperatures of up to 40 million degrees Celsius. This cannot be done by contact with any currently known material but rather needs to be achieved through magnetic or inertial confinement (Ongena and Ogawa, 2016). Considerable research and resources are still needed to bring this technology to fruition, otherwise, the reality of nuclear fusion will always remain just a concept that is "10 years away". 2022 has seen a breakthrough in the field with Lawrence Livermore National Laboratory (LLNL) reaching energy breakeven, meaning it produced more energy (3.15 megajoule) from fusion in an experiment than the laser energy used to drive it (2.05 megajoule) (Betti, 2023). Nevertheless, significant issues still remain for real energy production from fusion, as to generate the 2.05 Megajoule energy for the experiment, in total ~ 300 megajoule in electrical energy had to be spent for the 192 lasers (Anon, n.d.-ba).

At the same time, new approaches to nuclear fission are being established. One interesting approach is the MYRRHA initiative, which uses a particle accelerator-driven fusion reactor and can reduce volume (100-fold less) and radioactive lifespan (300 vs. 300,000 years) of nuclear waste through partitioning and transmutation (Abderrahim, 2020). In this way, technology can mitigate the risk of traditional nuclear fission and provide a transitory solution until the promise of nuclear fusion can become reality. An additional trend in nuclear reactor design has been the development of small modular reactors (SMRs). Typical nuclear fission power plants require large amounts of space and capital overhead. SMRs are nuclear reactors that generate 300 MWe equivalent or less and have a modular design that simplifies fabrication processes, reduces production costs and allows flexibility to add additional modules incrementally based on changing energy requirements (Vujić et al., 2012). SMR technology is particularly advantageous for remote communities and locations where space is limited. Examples of projects under development include the Rolls-Royce SMR in the UK or SMART reactor in South Korea, while other countries, such as France, have recently announced major investments in this technology. One of the main disadvantages of both nuclear fusion and fission technologies, that are not regularly considered, are the cost as well as the high infrastructure and technology requirements. This necessitates a high upfront investment to enable these technologies and could further widen the energy divide between high-income and low-income nations.

4.3.2. Wind energy

From the application of windmills in agriculture to propelling ships across the Atlantic we have long used wind as a source of energy. Wind energy currently makes up 6 % of global energy production, however according to a report in 2019 by the International Energy Agency (IEA) if wind energy was fully utilized it could generate 420,000 terawatt-hours of electricity globally per year (11 times more than the world currently uses annually) (International Energy Agency, 2019). In addition, the technology does not produce CO or release harmful products into the air. Limitations of the technology are the variability in wind patterns and finite locations where the turbine structures can be set up. This is, in particular, true for cities (where energy is often needed the most) leading to the need for complex infrastructure and losses in energy due to transmission from supplementary locations. Airborne wind turbines may be able to overcome such constraints by harnessing high altitude winds, which are usually more energetic (have a higher velocity), more constant/persistent and do not require physical space on the ground (Cherubini et al., 2015). Examples of such a system include the Magenn Air Rotor System (M.A.R.S.) lighter-than-air tethered wind turbine.

4.3.3. Solar

Solar energy via sunlight is theoretically an endless source of energy. The portability aspects of the technology and potential to decentralize the power grid, make it well-suited to remote or isolated communities. Limitations include high upfront costs for individual households. Moreover, current solar panel technology can convert only 22–23 % of the incident light energy to electricity (Zhang et al., 2021). There is therefore a need to develop more efficient solar panels, however, there are physical limits. The Shockley-Queisser limit (maximum theoretical efficiency of solar cells) for silicon, currently used for most solar modules, is 30 % (Richter et al., 2013). This highlights a need to research novel materials. Recently, The National Renewable Energy Laboratory in Colorado was able to demonstrate solar conversion efficiency of 47 % by combining six different materials into a multi-junction cell (Geisz, 2020). In addition, new technologies are helping to adapt solar energy to new environments. One of the biggest issues in deploying solar panels in locations, such as the desert, is sand which can cover panels reducing energy efficiency and requiring continued ongoing maintenance. A new approach, known as the Sandstock project, at the Masdar Institute of Science and Technology in the UAE instead uses the sand itself as a heat collector to capture and store solar energy. A prototype using a solar concentrator was able to heat up sand to 800–1000 °C that can then be used for energy generation (Diago et al., 2018).

4.3.4. BioEnergy (Biomass)

Bioenergy is also an energy source that harnesses energy from the sun and stores it as chemical energy in the form of biomass. Biomass can be burned to release stored energy and new plant material can be planted to capture the released CO_2 and form new biomass (Long et al., 2013). In this sense, biomass is a circular energy source. In addition, biomass can be readily converted to biofuels that can easily implement with current combustion-based transportation vehicles. A limitation of the energy source is the high water and arable land requirements, which can put pressure on food supply and the loss of input energy required to harvest/process biomass (Popp et al., 2014).

4.3.5. Other considerations and future directions

To unlock the full potential of an endless cheap energy source requires it to be easily accessible at any time. Particularly, one of the major hurdles in capitalizing on an endless energy source is the ability to effectively capture and store it after it has been created and be on-demand. In addition, the electric grid infrastructure, that transport a majority of generated energy, (in many countries, including the US) is rapidly ageing and is less amendable to integration with new energy suppliers (Lesser, 2014). All these factors limit the widespread application of any potential endless source of energy and its ability to transform our everyday lives. Therefore, in addition to supporting the development of new alternative energy sources, we also require simultaneous investments in the complementary sectors, such as energy conversion, energy transmission/distribution networks and energy storage.

4.4. Understand if parapsychological effects do exist

The term parapsychology originated in the late 1800s by the German philosopher Max Dessoir (Bringmann and Lück, 1997) and describes paranormal effects, triggered by the mysterious power "psi", such as telepathy, precognition, telekinesis, near-death experiences, reincarnation, and others (Bringmann and Lück, 1997; Thouless, 1942). Although it is estimated that around 50 % of the population believe in the existence of such paranormal phenomena, this area is not formally accepted as a serious field of research among the scientific community, thus hindering its empirical study (Brenda and Jahn, 1985). Are parapsychological effects pseudoscience or can we prove their existence? *We* have all been amazed by the telepathic or telekinetic abilities of magicians or illusionists. But are they all just tricking us, or is there scientific proof that people with these abilities truly exist? The necessity and approach if and how to explore such phenomena scientifically and questions around corresponding publications are intensely debated (Philipp, 2009).

To investigate telekinesis or psychokinesis, the ability to manipulate objects by thoughts alone without the use of physical force, a multitude of experimental techniques are used. For example, using random number generators, test subjects were asked to alter the number distribution to create a bias (Bösch et al., 2006). Even though a multitude of studies reported potential positive findings, larger scale meta-analysis indicated the marginal effect was most likely due to publication bias (Frazier, 1991). Motivated by the interest in using such abilities to intervene with enemy weapons, the US Army commissioned a study in 1984 to assess experimental results from laboratories that claimed to be able to scientifically prove the existence of such powers. However, the conducted experiments were deemed to be unfit for good scientific practice (Hyman, 1985). Furthermore, famous illusionists like Uri Geller have been caught using sleight of hand (Randi, 1982).

Telepathy describes the ability to perceive other people's thoughts or feelings. A popular experimental method to investigate telepathy is the so-called "Ganzfeld" test. Here, the subject or "receiver" is placed into a controlled, sensory-deprived environment, while a "sender" in a different room tries to transmit information (e.g., pictures) telepathically. Interestingly, a meta-analysis of 29 published experiments seemed to support the theory of "psi-conductive" people performing superior in Ganzfeld tests (Storm et al., 2010). However, this claim was battled by sceptic Ray Hyman, who criticized a majority of the Ganzfeld experiments being flawed by, for example, lacking proper sensory deprivation (Hyman, 2010) and failing to be replicated. Overall, there is to date no reliable scientific proof for the existence of telekinetic or telepathic abilities (Hines, 2003).

Another popular parapsychological phenomenon is precognition, or future vision. Legends about prophecies and fortune telling have been around for hundreds of years. Modern techniques to investigate the possibility of precognition included the usage of random event generators (Druckman et al., 1988). One popular investigator in the field was the parapsychologist Helmut Schmidt, who claimed to detect an above average success rate of random participants in predicting the event in many trials (Tucker, 2006). However, his research was not replicated by other groups and Schmidt was criticized for performing the experiments alone, without oversight of a second experimenter (Hansel, 1980). Other researchers failed to provide reproducible, significant results for the existence of precognitive abilities. Potential explanations for the observations of so-called "precognitive dreams" or visions are rather explained by the feeling of déjà vu, memory biases or simply by coincidence.

Religious beliefs are one of the biggest reasons why people believe in parapsychology. The existence of a soul and an afterlife implies that there is something in us beyond the physical body and the mind that is independent and able to persist after death. In 1975, the psychiatrist Raymond Moody published a collection of interviews of 150 people that reported to have lived a near-death experience (NDE) and realized that there were commonalities in their descriptions, such as out-of-body experiences or floating through a tunnel (Moody, 1975). Could these experiences be created by the physical changes of a dying or a stressed brain or are they truly evidencing the existence of an afterlife? In his recent book *After*, Dr. Bruce Grayson proposes that NDEs could be a result of the mind, which could work independently to the brain as shown in clinically dead patients (Grayson, 2021). Despite the advances in brain-imaging technology, we still do not have an empirical and scientific approach to study these phenomena. The consistency in experiences suggests that, even if the afterlife might not be real, the NDE sensations are. Interestingly, similar experiences have been reported after consumption of psychedelic substances such as Dimethyltryptamin (DMT) (Timmermann et al., 2018), supporting that NDEs are a result of significant changes in brain's function rather than some other entity beyond the body. Further understanding on the effect of DMT in the brain might shed some light into the mechanisms by which NDEs are lived, although it remains unknown whether the endogenous DMT is responsible for these experiences.

The idea of the existence of a soul or spirit, however, is hard to ignore after looking at research done in reincarnation by Dr. Ian Stevenson and his successor Dr. Jim B. Tucker. Both researchers studied correlations between children's memories from a past life with deceased people's descriptions (Stevenson, 1974; Tucker, 2005; Tucker, 2014). Among their research subjects, two remarkable cases stand out. One subject, James Leininger, a 2-year-old boy seemed to remember both by statements and behaviours a past life as a World War II pilot named James Huston, who was killed 50 years before. The other subject, Ryan Hammons, a 6-year-old, remembered having worked in Hollywood and was able to recognise his past self in a picture as Marty Martyn, who had died 39 years before Ryan was born. Whether these cases are a result of a vivid imagination and coincidence or actual evidence of reincarnation, remains a debate.

Lots of effort has been put in proving and using parapsychology, either financially motivated by the "One Million Dollar Paranormal Challenge" by James Randi (Anon, n.d.-bb) or with military and secret intelligence interests, with the $20 million CIA's secret program, Stargate Project (Marks, 2000), even genetic studies have already been conducted (Wahbeh et al., 2021). Despite these efforts, there is, to date,

no sufficient evidence supporting the existence of paranormal and psychic phenomena. Current studies have been either correlative or giving debatable results due to lack of reproducibility and study design flaws. Technological advances that allow the measure of psi and more reproducible techniques are therefore needed to further investigate these alleged psychic abilities and events that remain unexplainable. Should a scientific proof on the existence of such parapsychological phenomena ever be possible, due to the lack of explain ability with the currently known laws of nature, this would be a major paradigm shift for science.

5. The limits of knowledge, what we will never know

Of course, the topics covered above are just a limited although illustrative subset of recent breakthroughs. There is progress in many areas and fields that one would think are finally understood. As an example, amazing discoveries continue to be made in things as "simple" as water. The properties of water that can form at high pressure and temperature are two crystalline phases known as hot black ices constitute a superionic phase with ionic conductivity almost as high as the electronic conductivity of a typical metal. Such ices occur in giant icy planets such as Neptune, but the mechanism is also relevant for cryopreservation (Anzellini, 2021; Ball, 2022).

However, with the expansion of the sphere of knowledge also grows the surface exposed to the unknown. Despite the tremendous progress visualized in the preceding sections there are a series of fields with numerous open questions.

The existence of dark matter for example, has long been hypothesized, as without it the coherence of galaxies could not be explained. The exact composition of this dark matter and associated dark energy, however, remains completely enigmatic and no corresponding particles have ever been detected in any experiments. The findings from 2021 at the University of Groningen on the existence of dark matter free galaxies, increases the mystery even further (Anon, n.d.-bc).

Amazingly, the debate around the existence or non-existence of parapsychological phenomena got some new traction from the experiments from Daryl J. Bem (Cornell University) (Anon, 2011) and has recently been summarized (Cardeña, 2018).

Likewise, an amazing development was the release of the Unidentified Aerial Phenomena (UAP) Report by the OFFICE OF THE DIRECTOR OF NATIONAL INTELLIGENCE (USA), stating that "Most of the UAP reported probably do represent physical objects given that a majority of UAP were registered across multiple sensors, to include radar, infrared, electro-optical, weapon seekers, and visual observation" (Anon, n.d.-bd).

In general, there are theoretical limits to our ability to know. There are things we will never know (Anon, n.d.-be; Gamez, n.d.) and some we might be able to guess or grasp by intuition (Brockman, n.d.). On the big scale there is the speed of light limit that caps what we can see, it hampers any hope for us to ever observe most of our universe (the famous event horizon). In the small dimension, quantum mechanics teaches us there is a built-in limit to our understanding of the universe too, determined by the wave function that does not allow prediction on the position and fate of these objects beyond the Planck scale. It is clearly evident that our current understanding of reality is entirely incomplete from the fact that for decades it remained impossible to come up with a theory beyond the standard model of physics, unifying quantum mechanics and relativity, describing all fundamental forces including gravity, and being able to explain why there is more matter than anti-matter in the universe. One of the most enigmatic and disturbing findings is quantum entanglement which means that our universe either is non-local, non-causal or super-deterministic (Anon, 2020f). 2021 delivered another breakthrough with the demonstration that such effects translate into the macroscopic world (Anon, n.d.-bf). That reality is more complicated than we think became clear with the proof in 2021 that the square roots of negative numbers are deeply embedded in the structure of the physical world (Wootters, 2021).

And finally, moving into the realms of religion and philosophy, science forever stays silent on the most important questions in life: why does the universe exist? How did it come into existence? How will it end? Why do we live and what should we do? Despite this, there is a lot science can and will do, and all your support for this noble endeavour is required.

6. Conclusion

Although the path and progress of scientific progress is largely unpredictable, exploring the trajectories of advancement and elucidating the currently rapidly progressing fields with potential to change our everyday lives in the future can reveal important insights. Among the game changers covered here there are interesting interdependencies, such as e.g., a convergence currently happening between the fields of life science and electronics, neural dust, or electronic implants not only for round the clock diagnosis but also therapeutic applications. Likewise, the ability to run biological experiments in a "lab-on-a-chip" or "organ-on-a-chip" needs to be mentioned here.

With the game-changer for all game-changers, a breakthrough in AI and cognitive computing would revolutionize all other fields with an expected unprecedented acceleration all over the place. A combination with robotics to conduct experiments quickly and automatically in the real world would further potentiate the impact. Some have called self-improving AI the last invention humanity would ever have to make.

In general, the field of machine learning has made significant advances in 2022 with the release of ChatGPT, a version of GPT-3, in November 30th, 2022 by OpenAI, San Francisco, CA. ChatGPT is a chatbot that essentially passes the Turing test and very quickly after its release garnered considerable attention for its detailed responses and articulate answers across many domains of knowledge. The program can write essays, articles, computer code and can be considered a milestone breakthrough (Anon, n.d.-bg). The chatbot, for example, when asked on the importance of science & technology for the history of humanity, end of 2022 came back with the following answer:

"Science and technology have played a crucial role in the history of humanity. From the earliest tools used by our ancestors to the advanced technology we use today, science and technology have helped us to survive, thrive, and understand the world around us.

One of the most important ways in which science and technology have impacted the course of human history is through advances in medicine. Throughout history, people have struggled with various diseases and health problems, but thanks to the advances made by scientists and medical researchers, we now have a better understanding of how the human body works and how to treat various illnesses. This has led to the development of effective treatments and vaccines for many diseases, improving our quality of life and increasing our lifespan.

Another way in which science and technology have had a major impact on human history is through transportation and communication. In the past, people were limited in how far they could travel and how quickly they could communicate with others. However, with the development of cars, trains, planes, and other forms of transportation, we are now able to travel long distances quickly and easily. Similarly, the invention of the telegraph, the telephone, the radio, and the internet have made it possible for us to communicate with people across the globe almost instantly.

In addition to these practical applications, science and technology have also helped us to understand the world around us and our place in it. Through scientific research and experimentation, we have learned about the laws of nature, the origins of the universe, and the evolution of life on Earth. This knowledge has not only allowed us to make more informed decisions about our own lives, but it has also helped us to develop a deeper appreciation for the world we live in.

In short, the importance of science and technology in the history of humanity cannot be overstated. From improving our health and well-being to helping us to understand the world around us, science and

technology have played a crucial role in shaping our history and will continue to do so in the future."

The further penetration of such large language models (LLM) will have disruptive effects on the job market and also on the future of science, widely discussed shortly after its release (Van Dis et al., 2023).

Nature has for example commented:

> "Some argue that because chatbots merely learn statistical associations between words in their training set, rather than understand their meanings, LLMs will only ever be able to recall and synthesize what people have already done and not exhibit human aspects of the scientific process, such as creative and conceptual thought. We argue that this is a premature assumption, and that future AI-tools might be able to master aspects of the scientific process that seem out of reach today. In the future, AI chatbots might generate hypotheses, develop methodology, create experiments, analyse and interpret data and write manuscripts."

Likewise, the same company, OpenAI, released DALL-e-2, a program that can within seconds draw pictures of whatever content defined by the user, including in the style of past artists (Anon, n.d.-bh).

Google and DeepMind published a preprint in December 2022 about a clinically-focused LLM called Med-PaLM that was able to answer open-ended medical questions comparable to an average human physician (Anon, n.d.-bi).

Overall coming back to the introductory comments of this paper and the role of the polymath. The combination of a world where the knowledge of humanity is available to everybody at our fingertips with a press of a button, combined with empowering AI-tools and robotics, a new golden age for the polymath is dawning.

Having reviewed all these current and future game changers the future is still unpredictable. As it often happened in the past, the decisive game changing breakthrough might come from an area nobody expects today. Stay curious. "Somewhere something incredible is waiting to be known. (Newsweek, 1977)".

Data availability

No data was used for the research described in the article.

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