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Converging global crises are forcing the rapid adoption of disruptive changes in drug discovery

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Spiralling research costs combined with urgent pressures from the Coronavirus 2019 (COVID-19) pandemic and the consequences of climate disruption are forcing changes in drug discovery. Increasing the predictive power of *in vitro* human assays and using them earlier in discovery would refocus resources on more successful research strategies and reduce animal studies. Increasing laboratory automation enables effective social distancing for researchers, while allowing integrated data capture from remote laboratory networks. Such disruptive changes would not only enable more cost-effective drug discovery, but could also reduce the overall carbon footprint of discovering new drugs.

Keywords: COVID-19; Climate disruption; Drug pipeline attrition; Advanced human cell and tissue models; AOPs; Machine learning; Artificial intelligence; Laboratory automation; Decision theory

Introduction

A series of unrelated challenges for drug discovery converged in 2020, creating the 'perfect storm' that could precipitate rapid and disruptive changes in the established drug discovery process. The urgent requirement for new medicines to treat unmet medical needs and the chronic problem of increasing discovery costs continue to apply pressure to improve long-term success rates. COVID-19 and climate disruption are forcing rapid industrial changes: the pandemic is changing safety practices in research-intensive laboratories and personal interactions. Climate change requires a reduction in the carbon footprint of drug discovery. However, emerging synergistic solutions could provide improved outcomes for these seemingly competing requirements.

Preclinical studies need both internal validity (such as good study design with control of bias) and external validity (the reliable application of experimental results to the clinical setting). The external validity of animal studies is compromised by well-documented species differences in anatomy, physiology, metabolism, immunology, biochemistry, and genetic background [1,2]. Advanced *in vitro* human assays avoid interspecies extrapolations and show substantial promise for modelling human physiology and pathology in a relevant and dynamic way [3,4]. If this promise is fulfilled, combined with emerging *in silico* techniques, these assays would provide more relevant preclinical data earlier in drug discovery and reduce costly clinical trial failures. Remotely controlled laboratory automation allows practical social distancing and remote working during pandemics, while improving data

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quality and reproducibility. Integrated machine learning could improve decision-making based on the integration of automated data capture in remote laboratories, 'democratising' global research networks. The key question is: can these ideas be practically implemented in laboratories? Here, we argue that they can.

The multiple challenges for drug discovery

Despite unprecedented investment, therapeutic pipelines are not meeting expected clinical outcomes for drug registrations. A recent analysis of compounds progressing from Phase I to approval found an overall success probability of 13.8% (range 3.4–33.4%). The data set included clinical data from 2000–2015 and more than 21 000 compounds from nine therapeutic groups [5]. More than 90% of drugs in clinical trials do not demonstrate significant patient benefit. Safety issues are a leading cause of clinical failure, accounting for 25% of Phase II and 14% of Phase III failures between 2013 and 2015 [6]. A similar proportion fail because of inappropriate pharmacological properties in humans, with absorption or target organ penetration not being predicted accurately by animal studies [7]. The number of new drugs approved per billion US dollars invested in research and development halved about every nine years from 1950 to 2010: ~80-fold in inflation-adjusted terms and with no sign of an improving trend [8]. Too many failures are weeded out too late during development. Further analysis illustrates how assay validity and reproducibility correlate across a population of simulated screening and disease models [9]. Scannell and Bosley conclude that 'perhaps there has also been too much enthusiasm for reductionist molecular models, which have insufficient predictive validity'. More pathophysiologically and species-relevant cell-based screens need to be incorporated earlier in drug discovery. Screening against human target proteins in cell-free assays, followed by studies in advanced cell and tissue models, would contribute to pathway-based understanding at an earlier stage. Evidence that 'most published research findings are false' exemplifies how the so-called 'reproducibility crisis' is prevalent across research activities beyond drug discovery [10].

The COVID-19 pandemic emerged as an issue for global health, macroeconomics, and society. Treatment options are being used in severe cases with a high risk of mortality [11], several vaccines have been approved [12], and vaccination programmes are ongoing. With emerging new variants, public health measures are likely to continue to enforce disruptive change in how research is conducted in laboratories [13]. Nevertheless, drug discovery has continued during the pandemic, with lower laboratory occupancy, remote working, and implementation of automated assay systems.

Climate disruption is also forcing changes. Despite the urgent need to curb carbon emissions, pharmaceutical companies have received relatively little attention in terms of their carbon footprint [14]. Surprisingly, the pharmaceutical industry is more emission-intensive than the automotive industry and, although most emissions probably relate to manufacture, drug discovery also significantly contributes [15]. Millions of animals are used in research and toxicity testing globally, including in drug discovery and development. The energy consumed by research animal facilities is up to tenfold more than offices on a square-metre basis [16]. Ventilation of animal research facilities requires large volumes of air, resulting in a high consumption of energy and carbon emissions [17]. Standard laboratories need up to 12 air exchanges per hour, compared with animal research facilities that require up to 20. Additional energy demands result from the environmental and space needs of the animals, barrier protection from outside pathogens, indoor air quality, lighting, and power-intensive equipment in research: 40–50% of energy consumed in animal research facilities is attributed to ventilation and an additional 10–30% of energy is used to chill air or water for cooling spaces and equipment [17].

This article does not provide fully formed solutions to these crises but highlights emerging technologies that could have synergistic effects and repay a significant investment in further development.

Proposed synergistic solutions

Earlier adoption of in vitro assays in drug discovery

In vitro human cellular assays are well established in drug discovery. Since the 1950s [18], cell lines have been developed but are typically grown on (coated) plastic as monolayer or suspension cultures. However, spheroids are typically derived from pluripotent or clonal cells that have been grown in monolayers or suspensions and reassembled into 3D cultures. Spheroids enable cells to communicate with each other and their surroundings, similar to an *in vivo* 3D environment [19], although the lack of vascular flow and tissue–tissue interfaces can be a limitation. Organoids are typically derived from stem cells, which self-organise in culture owing to their self-renewal and differentiation capacities [14]. Organoids are seeded and maintained in 3D for the entirety of their culture [20]. Such clonal organoid-based assay systems can be taken out of cold storage and used to generate pharmacological data within 7 days, allowing flexible use in drug discovery. Fig. 1 shows images demonstrating the heterogeneity of colorectal cancer organoids.

There are many longstanding and unmet medical needs that would benefit from advanced *in vitro* approaches, such as Alzheimer's disease (AD). Here, drug discovery has been overly dependent on animal models that poorly predict human pathology, including transgenic mice [21]. Costly late-stage drug failures are common [22]. Increasingly, advanced human-specific cellular models are filling this void, such as those that recapitulate both amyloid and tau pathologies [23]. *In vitro* translational models are enabling pivotal decisions on compound progression to be made earlier in discovery and are established in conventional tissue culture laboratories. Fig. 2 illustrates human induced pluripotent stem cell (hiPSC)-derived microglia co-cultured with hiPSC-derived neurons. Such approaches are helping identify candidate pathways and targets for clinical intervention in AD and Autism Spectrum Disorders [24].

Considerable research effort is aimed at recapitulating disease models and early-stage efficacy and toxicity screening at the organ level, using *in vitro* microphysiological systems or organs-on-chips [25,26]. These platforms offer controlled, reproducible, and sensitive systems with dynamic flow and tissue–tissue interfaces that support 3D cellular constructs with extended viability. They are amenable to high-throughput and high-content

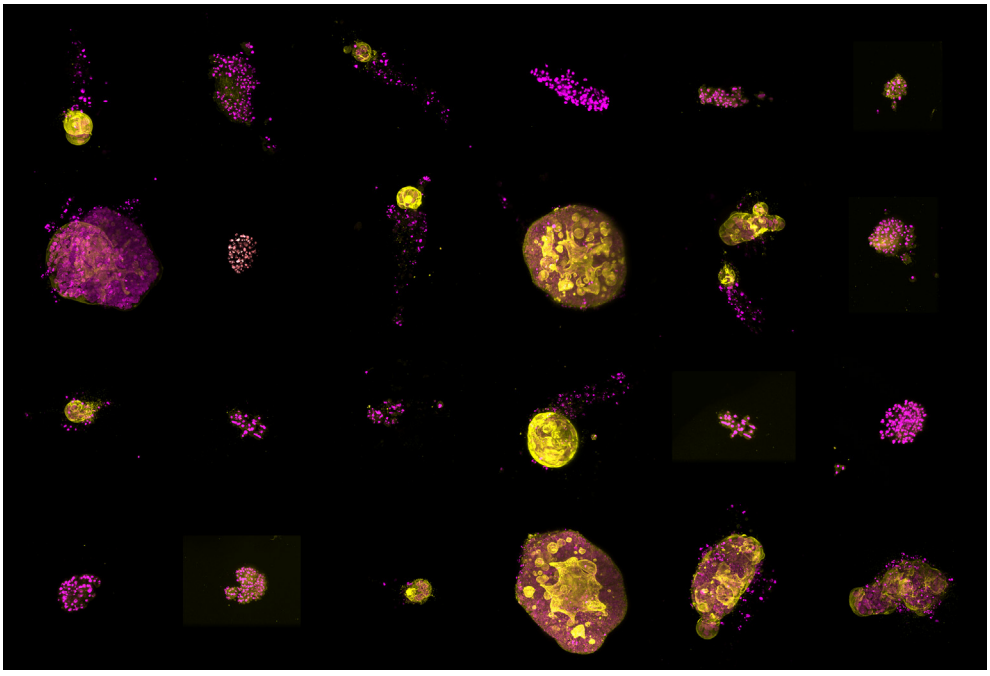

FIG. 1

Projections of 3D image stacks of colorectal cancer organoids illustrating their heterogeneity captured using light sheet fluorescence microscopy. The organoid lines were provided by Cellesce Ltd. The yellow channel is F-actin (phalloidin) and the magenta channel is DNA/cell nuclei (Hoechst). Images captured and processed by Paula Gomez, Craig Russell, and Michael Shaw at the National Physical Laboratory.

analysis, accommodating electrical, chemical, mechanical, and optical sensors (separately and in combination) [4], and recreating complex human physiology and pathology [3]. Disease modelling in these systems uses human primary cells, conventional cell lines, or hiPSCs. Cells can also be gene edited or subjected to environmental triggers to generate disease pathologies. Unlike simpler cultures, organs-on-chips and fluidically coupled human body-on-chip platforms give more detailed mechanistic insights into disease processes and the effects of compounds [4,22] and permit analysis of drug effects on specific cell types. Awareness is needed of their limitations; [3,4] for example, neuronal cells derived from hiPSCs can be relatively immature and do not always express spontaneous disease phenotypes. No single platform will solve the productivity problem in drug development, but it is plausible that carefully selected and validated panels of new methodologies could do so.

Research breakthroughs are being made. In Huntington's disease (HD) research, neither mouse models nor post-mortem tissue analysis reveals the underlying mechanisms of blood–brain barrier (BBB) dysfunction. An *in vitro* model of HD showed that hiPSC-derived brain microvascular endothelial cells (from a patient) had intrinsically dysfunctional BBB and angiogenic properties [27]. Similar cells derived from a healthy subject were then incorporated with neurons and astrocytes into a human-specific BBB-on-a-chip, with vessel-like structures allowing perfusion of human blood [28]. The platform demonstrated normal functional activities and predicted known BBB permeability characteristics of drugs, including antiepileptics (retigabine and levetiracetam). It also showed increased BBB permeability when cells derived from a patient with HD were used. Thus, the combination of organ-on-chip technology and hiPSC-derived cells has relevance for disease modelling, target validation, and drug discovery.

Recently, quantitative drug pharmacokinetics (PK) has been measured using human body-on-a-chip platforms that couple fluid flows between endothelium-lined vascular channels of organ chips, achieved by robotic sequential transfers of perfusing fluid. Physiologically based PK modelling applied to *in vitro* data predicted PK parameters for oral nicotine (using gut, liver, and kidney chips) and for intravenously injected cisplatin (using bone marrow, liver, and kidney chips). The predictions matched existing patient data [29]. Linked organs-on-chips, including liver cells, provide a means of measuring drug metabolism and the effects of metabolites on target tissues, not easily conducted in animal studies.

Developments in organ-on-chip and related human molecule- and cell-based assays continue to support the possibility of *in vitro* disease modelling and predictions of drug efficacy and toxicity early in drug discovery, as well as the replacement of animal experiments [4]. A meta-analysis, comparing *in vivo* animal toxicity studies with *in vitro* human-cell high-throughput screening assays, revealed that animal studies did not perform significantly better in predicting adverse drug effects in humans [30]. Both kinds of test performed only moderately well. However, adding a small set of drug targets to the

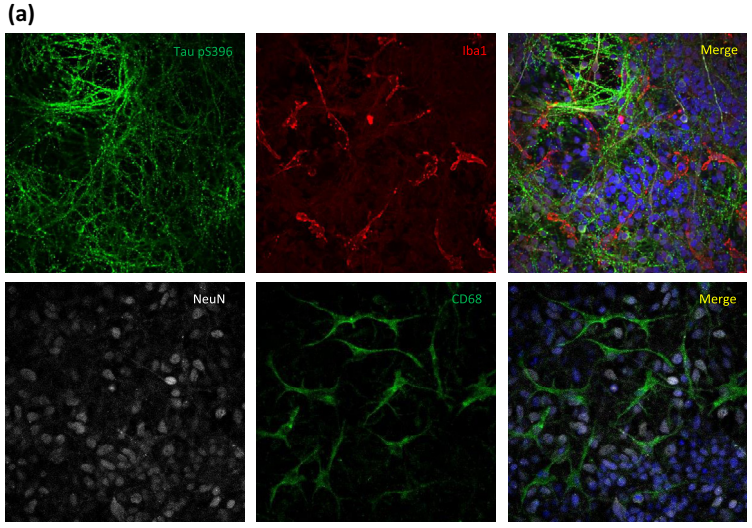

FIG. 2

(a) Human induced pluripotent stem cell (hiPSC)-derived microglia display a more ramified morphology, similar to that observed *in vivo*, when maintained in co-culture with human iPSC-derived neurons. Images show immunofluorescence for microglial proteins, Iba1 and CD68, and neuronal proteins, Tau and NeuN. (b) By contrast, microglial monocultures display a more rounded morphology with a proportion of elongated cells. Images provided by Talisman Therapeutics Ltd.

human-specific *in vitro* data resulted '...in models that greatly outperform those built with the existing animal toxicity data' in predicting drug side effects.

The US Food and Drug Administration (FDA) has been supporting microfluidic research for several years and signed a cooperative research and development agreement with Emulate Inc. in 2020 [31]. Emulate develops organ-on-chip platforms that address the FDA's priority research areas (including AD, drug-induced liver injury, intestinal microbiomes, and COVID-19), with the aim of studying disease mechanisms, drug safety, and drug efficacy. Other agencies, including the US National Institutes of Health and the Environmental Protection Agency, continue long-term support of human cell models and assays [32].

Adverse outcome pathways in drug discovery and biomedical research

Adverse Outcome Pathways (AOPs) are constructs that describe the causal linking of a molecular initiating event (MIE), the first interaction of a compound with a molecular target, with an adverse outcome (AO), via identified sequential critical steps (Key Events or KEs). AOPs are chemically agnostic, and KEs can be common to AOPs with different toxic endpoints; thus, AOP networks are also being developed [33,34]. The AOP concept provides a unified and curated framework for describing pathophysiological and toxic pathways, organising and interpreting mechanistic data across several biological scales, from molecular through to organism (or population) levels [35]. Representation of multiple levels of biological organisation by AOPs distinguishes them from simple mechanism-based or mode-of-action approaches.

AOPs were introduced originally to chemical toxicology and ecotoxicology to facilitate regulatory decision-making. Since 2012, the Organisation for Economic Co-operation and Development, which coordinates international agreement on chemical safety, has run a programme to develop and implement AOPs. It hosts the AOP Wiki as a crowd-sourcing platform to support international regulatory decisions about chemical safety. There is a growing interest in repurposing the AOP approach for disease modelling, drug discovery, and drug toxicology [3,32,36]. Complex mechanistic data from *in vitro*, human-specific models can be exploited to develop 'disease AOPs'. Disease AOPs are a means of capturing and representing disease pathways from their MIE (e.g., chemical interactions or infection) through multiple scales of biological organisation to 'adverse outcomes' of disease at the individual level [22,36].

COVID-19 has stimulated a concerted research effort globally, resulting in unprecedented amounts of data and providing an opportunity to map and understand human biology. The AOP framework facilitates structured and formalised data analyses, enabling collaboration by crowdsourcing, exemplified in the European Commission-funded research to model COVID-19 pathology and turn data into useful knowledge. During the pandemic, interdisciplinary research has continued globally by 'virtual' collaboration [37]. By developing AOPs and AOP networks relevant to COVID-19 outcomes, the data can be organised systematically to create practical understanding of the disease. KEs and KE relationships from existing AOPs, for example for lung fibrosis and acute respiratory distress, are applicable to COVID-19 and could 'jump-start' efforts toward understanding the disease [37].

Disease AOPs are already yielding benefits. The sequence of KEs resulting in an AO defined as parkinsonian motor impairment, triggered by exposure to environmental chemicals, was described using the AOP framework [34]. The authors sta-

ted that a transition toward more mechanistically based disease classifications would complement the paradigm shift in toxicity testing, '...moving away from adverse effects evaluation in whole-animal models to human relevant *in vitro* methods, measuring early biomarkers, predictive of late adverse outcome'.

An illustration of the value of AOPs in drug toxicology is provided by drug-induced liver injury (DILI): the commonest cause of acute liver failure in the USA and Europe. It is a major cause both of high attrition rates in drug development and of drug withdrawals, and its incidence continues to rise [38]. This reflects poor translation between preclinical animal models and human clinical outcomes [39]. DILI has several causal mechanisms that lead to different types of injury, including cholestasis (impaired bile secretion), steatosis, and fibrosis. The AOP Wiki contains AOPs for all these outcomes.

Drug-induced cholestasis is a severe endpoint of DILI and is mechanistically complex. AOP27, Cholestatic Liver Injury induced by Inhibition of the Bile Salt Export Pump (ABCB11) [40], identifies one MIE as the inhibition of the bile salt export pump in the liver. Bile salt accumulation is the KE that activates mechanisms driving a deteriorative cellular response including inflammation, oxidative stress, and cell death, leading to the AO of cholestasis. There are also adaptive cellular and organ-level responses. Several drug companies have been developing *in vitro* human-cell assays for DILI; and 3D human-cell liver platforms are improving overall in terms of DILI prediction accuracy. Their performance is expected to progress further with the incorporation of multiparametric endpoints [39].

There is a clear synergy between human-specific *in vitro* models, *in silico* approaches, and AOPs. For example, to improve predictions of the DILI endpoint of hepatic steatosis, an AOP network was constructed to represent the four KEs: lipid uptake, efflux, synthesis, and oxidative metabolism [41]. Based on this AOP network, assays were developed and evaluated using cryopreserved HepaRG human hepatocytes [42]. Six compounds known to affect the KEs, including three drugs, were used in the study. The results showed the value of human *in vitro* assays developed from AOP network information for predicting adverse health outcomes. Further development of quantitative AOPs, already underway [33], would improve the value of AOPs for risk assessment. An AOP-guided, automated *in silico* model for predicting MIEs across 39 human pharmacological targets has achieved an overall quality of 93% for its quantitative predictions [43].

High-throughput assays create huge but unwieldy data sets, whereas mechanistic data remain essential to select relevant endpoints for each context and purpose. AOPs provide a way to integrate high-throughput data with mechanistic knowledge, collaboratively and in a standardised manner. With DILI, an AOP framework was used experimentally as a source of mechanistic knowledge and to select relevant predictors from high-throughput assays. Existing AOPs were used to narrow the selection of potential predictors from high-throughput *in vitro* data sets, and a predictive logistic regression model was developed using these predictors and knowledge of drug properties from the literature [44]. The model achieved a sensitivity of 0.96 and a specificity of 0.83, with an accuracy of 0.91, in assessing the risk of liver injury from drugs. These examples show that robust, advanced *in vitro* models, interpreted through AOPs, can predict human toxicity and provide mechanistic knowledge.

Improved clinical translation remains key to resolving pipeline attrition and reducing carbon emissions from drug development. Systems biology has a role in bridging the preclinical–clinical gap. New bioinformatics and mathematical tools aid the integration of data from multiple biological levels, help build disease AOPs and generate better clinical disease classifications [22,45]. Additionally, research supports the validity of extrapolation from clinical microdosing and other Phase 0 applications to full clinical trials, together with modelling and simulations that address nonlinear scenarios. These approaches provide data on PK, bioavailability, and mechanistic pharmacodynamics in humans [46]. The question is being discussed: '...as to whether we should spare resources and bypass animal models to evaluate therapy in humans directly' [7].

Remotely controlled and integrated laboratory automation

Automation can improve data quality and reproducibility. Integrating *in vitro* biology with chemistry is essential in drug discovery and automated screening systems were based on large centralised high-throughput screening processes designed to screen 100 000 compounds or more in one location [47]. More recently, remotely controlled laboratory automation, allowing social distancing and remote working, has been introduced into the drug discovery process. Remote automated synthesis [48] using flow chemistry feeding directly into biological assays can be integrated into a smaller platform footprint, requiring scientists to spend less time in the laboratory. Such platforms were used to identify a novel compound against Abl kinase, the protein target for the highly effective cancer drug Gleevec [49], for both wild-type and clinically relevant mutants [50]. Integrated microfluidic synthesis and screening have the potential to reduce the adverse environmental impact of synthetic medicinal chemistry [51] by requiring very little compound for screening. Smaller targeted chemical libraries are compatible with most screens [52] and have successfully enabled kinase inhibitor drug discovery over the past two decades and revealed novel target opportunities for 'drugging the undruggable' [53]. Targeted libraries can be shipped to laboratories worldwide and screened in the assay systems described earlier, without the need to invest in synthetic chemistry capabilities internally. Even conventional medicinal chemistry approaches can be adapted to remote working by using mobile 'robot chemists' in standard chemistry laboratory configurations [54]. To deliver effective solutions, these remote technology platforms need to interact with each other using the 'internet of things', which comprises the collection of data by remote sensors, relevant analytics, and other workflow changes, enabling data-driven decision-making and automation of the tasks required [55].

Despite the pandemic altering how many people work and interact with each

other, people remain at the centre of decision-making. Location independence has changed considerably with a technology shift to support this new way of working. Resilience is key and research organisations that pivot and adapt are more likely to prosper. Technological and working trends build on and reinforce each other, enabling organisational plasticity. However, carbon footprint analyses are needed, and some energy consumption could be moved into homes from the laboratory during remote working, offsetting the benefits of reduced travel to and from work.

Machine learning and data analysis

Integrated machine learning enables improved decision theory [33] and integration of automated data capture in smaller remote laboratories, democratising research networks. Decision theory implemented into drug discovery [9] could reduce research and development expenses, diminish failure rates, and discover superior therapies. Statistical analysis of large data sets and development of machine-learning algorithms have led to artificial intelligence (AI)-based start-up companies forging alliances with larger pharmaceutical companies. AI was used in the identification of baricitinib as a repurposed potential treatment for COVID-19-associated acute respiratory disease, using BenevolentAI's knowledge graph [56]. In 2020, the drug received FDA approval for emergency use [57]. A network-based, deep-learning methodology was also used to identify dexamethasone as a treatment for COVID-19 [58]. Drug repurposing has a lower carbon footprint than drug discovery and development, as well as fast-tracking drugs to approval in a public health crisis. Analytical methods based on decision theory have demonstrated that small changes in the 'predictive validity' of an assay or test have a remarkably significant impact on success rates in drug discovery [9]. It is argued that this explains much of the fall in productivity observed between 1950 and 2010 [8]. The mathematical basis of decision theory can analyse and validate the effectiveness of the proposals set out in this article.

Discussion

The question posed in the Introduction was: can these ideas be integrated and implemented practically in drug discovery? This article suggests that they can. Changes are accelerating and synergistic solutions can be integrated.

New methods need further validation before industry and regulatory agencies will accept them. However, their full potential cannot be realised if constrained by conventional over-reliance on animal data. The UK National Centre for the Replacement, Refinement and Reduction of Animals in Research [59] suggests novel test methods could instead be validated against performance standards directly relevant to humans. AOPs can provide a bridge to enable this and be a link between disease and toxicological pathways. The Dutch national committee on animal use is phasing out all regulatory animal safety tests for medicines and chemicals by 2025 [60]. The Committee envisages that risk assessment will be improved and safety standards maintained by the transition. Regulatory agencies are clearly gaining confidence in these 21st-century approaches.

Increasing the predictivity of *in vitro* human assays and using them earlier in discovery have synergistic benefits and the AOP framework enables (remote) collaboration and crowdsourcing. Applying it to *in vitro* data builds on early cell-free molecular screening (e.g., receptor binding), while improving predictivity compared with potentially misleading animal models. Effort and funding currently expended on animal studies should be refocused toward developing progressive approaches, which already demonstrate recapitulation of human physiology and disease states, as well as patient responses to drug PK exposures, 'with higher fidelity than other *in vitro* models or animal studies' [4]. Improving drug pipeline efficiency will also reduce wastage and carbon production.

Remotely controlled laboratory automation has changed conventional working practices by altering how researchers work and interact. Location independence reinforces greater organisational plasticity. Analytical methods based on decision theory demonstrate that small changes in the 'predictive validity' of an assay have a remarkably significant impact on success rates. The mathematical basis of decision theory is now poised to be implemented through AI algorithms. Drug repurposing is a fast, low-resource, and low-carbon means of finding new treatments. Implementing novel human-specific models in drug discovery and development, together with new modes of working, require further funding and multidisciplinary collaborations. We believe the benefits would include increased clinical success, lower carbon emissions, and safer working environments during pandemics.

Declaration of Competing Interests

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: J.M.T. is a director of Talisman Therapeutics Limited and Ubiquigent Limited as well as a shareholder of Cellesce Limited. G.R.L. has no interests to declare.

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