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EDITORIAL

The future is now: cutting edge science and understanding toxicology

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Introduction

In 2016, the scope of Cell Biology and Toxicology was expanded to provide greater emphasis on clinical and translational research, for example, by focusing on gene-/protein-based regulation, single-cell genomics, and systems biology in drug discovery (Gu and Wang 2016). In this editorial, we discuss how this increased outlook is reflected in recent articles covering cutting edge research in the life sciences. We provide an overview of these articles, along with our own personal opinions regarding the future scope of Cell Biology and Toxicology.

Current research in cell biology and toxicology and cutting edge science

The year 2017 has been an exciting and productive year for Cell Biology and Toxicology (CBT), with a large number of research articles published that encompass many diverse fields within the life sciences, alongside numerous informative reviews and editorials by leading scientists. Sixty-two papers were published in the journal, of which 43 were original articles, 12 were reviews, and 7 were editorials. Surveying the titles and keywords for original articles, we observed a greater spread of subjects between 2016 and 2017, such as the inclusion of induced pluripotent stem cells (iPSCs), indicating that the major research fields covered in CBT are increasing in scope. To illustrate this increasing scope, we discuss examples of how cutting edge research fields have been covered in the journal. These include clustered regularly interspaced short palindromic repeats (CRISPR)/Cas genome editing, latest advances in single cell sequencing, clinical influences of the microbiome, and implementation of induced pluripotent stem cell/cell reprogramming technologies. These fields of research have been the subject of numerous publications in CBT. In the next section, we discuss how these fields have been covered in the journal.

Clustered regularly interspaced short palindromic repeats/Cas genome editing

The CRISPR/Cas genome editing technique has been hailed as a major scientific advance and was awarded the American Association for the Advancement of Science breakthrough of the year in 2015 (Ledford 2016). The CRISPR/Cas9 system has many potential applications for gene editing, such as targeting mutated genes in cancer or genes encoding antibiotic resistance (Khan et al. 2016; Muller et al. 2016). In CBT, the potential of CRISPR for gene knock-in applications was elegantly discussed by Sakuma and Yamamoto (2017). The authors described the alternative mechanisms to repair double strand DNA breaks (DSB) that could be utilized

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for efficient gene editing. As different options for achieving less error-prone non-homologous end joining, the authors summarized other end-joining strategies, such as homology-independent targeted integration, alternative end-joining, and single-strand annealing (SSA) (Rodgers and McVey 2016). The authors demonstrated that genome editing-assisted gene knock-in technology has become more diversified and increasingly efficient. It was concluded that in-depth knowledge of these DSB techniques are required to optimize gene knock-in approaches depending on cell or organism type, application, and delivery system. Our own opinion is that this publication provides a very useful and timely overview of the CRISPR/Cas9 technology and provides important context by comparing CRISPR/Cas9 to other mechanisms for repairing DSB. For non-experts in this field, this paper is a source of "level headed" education for toxicology researchers wishing to apply the CRISPR/Cas9 to edit genes in their own experimental systems.

An important application for CRISPR/Cas9 is cancer drug screening and discovery mechanisms producing therapeutic resistance. In CBT, this was discussed by Wang and Wang (2017). For personalized cancer therapy, gene mutations are mapped in tumor biopsies from patients to optimize the chemotherapy regime and highlight any chances of potential drug resistance (Jiang and Wang 2010). Due to tumor cell genetic heterogeneity, single cell analysis can provide information about the large-scale genetic perturbations and phenotypes of individual cells. The CRISPR/Cas9 system can then be used to modify the expression and function of candidate target genes to evaluate potential cancer treatments. Wang and Wang provide a very useful overview of pooled CRISPR screening applications as powerful tools for the systematic genetic analysis of cancer cells: providing in-depth characterization of drug sensitivity, resistance, and possible therapeutic strategies. Pooled CRISPR screening can be used to map cancer cell responses to drug candidates by linking the expression of gRNA (the sequence for Cas9-binding and the targeting sequence) to the transcriptome readout in single cells (Datlinger et al. 2017). Pooled CRISPR screening can also be employed to promote genome editing in response to therapeutics and elucidate the roles of non-coding genome sequences (Andersson et al. 2014). Thus, pooled CRISPR screening can investigate the regulatory mechanisms dictating cancer cell responses to therapeutics, by mapping genome editing and the roles of non-coding elements. These approaches provide a more detailed understanding of the molecular mechanisms underlying cancer cell responses to candidate therapeutics. We believe that subject, which describes the potential applications of a cutting edge technique (CRISPR/Cas9) to a leading research field (single cell sequencing of circulating cancer cells), is ideal for discussion in CBT, as it encourages scientists to apply the latest experimental technologies to their own research area. This is reflected in the high number of citations for this paper (already nine times in Scopus). In addition, a very useful overview of the potential caveats associated with CRISPR/Cas9 was provided by Fang and Wang in CBT (Fang and Wang 2016). These authors mentioned the possible need to implement a "reversal drive" to overwrite initial gene modifications and reverse unwanted effects. The authors also discussed the myriad ethical dilemmas associated with CRISPR/Cas9 and the clinical development of gene therapy products. We feel that this paper, which describes potential pitfalls associated with cutting edge techniques, should also be an important focus of CBT, because it provides readily accessible guidance for toxicology researchers considering the application of these technologies. Accordingly, this paper has already been cited seven times in Scopus.

Latest advances in single cell sequencing

Single cell sequencing employs optimized next generation sequencing (NGS) technologies to map DNA or RNA sequences in individual cells (Eberwine et al. 2014). This can provide high-resolution information about the differences between individual cells within a population and allow greater understanding of how cells function within the milieu of different cell types, extracellular matrix, cytokines, and mechanical stresses that constitute their microenvironment. An impressive application is the single cell sequencing of circulating tumor cells (CTCs), which was discussed by Zhu et al. in CBT (Zhu et al. 2017). CTCs are detached from tumor tissues and enter the circulatory system. These cells can form metastases or remain viable in the circulation. Using single cell sequencing, the genome of CTCs can be compared with both the primary tumor and distal metastases. Monitoring these genetic variations provides information about the mechanisms of metastasis and the optimal drug treatment regime. Although CTCs were observed over 100 years ago, their purification from

other blood cells is still challenging (Alix-Panabieres and Pantel 2014). Zhu et al. described examples of the monitoring of clinically relevant genetic mutations in patients CTCs during cancer progression. Novel mutations in the CTCs can also be assessed after chemotherapy. One such commonly detected mutation is p.V777L in the *ERBB2* gene, which may contribute to drug resistance (De Luca et al. 2016). Another example is the androgen receptor gene that shows a high level of mutation and alternative splicing in CTCs and is linked to treatment failure in prostate cancer (Miyamoto et al. 2015). Intra-tumor heterogeneity and evolution can also be traced by sequencing CTCs. This has provided insights into the metastatic progression of breast cancer (McGranahan and Swanton 2017), leukemia (Hou et al. 2012), and kidney cancer (Xu et al. 2012). Zhu et al. also described the application of CTCs single cell sequencing to delineate signaling pathway alterations during tumor evolution, which led to the discovery of the extracellular matrix protein SPARC as a key mediator of dysregulated signaling in pancreatic cancer progression (Ting et al. 2014) and drug metabolism pathway enrichment in refractory colorectal cancer (Grillet et al. 2017; Zhu et al. 2017). We believe that this paper is highly suitable for CBT, because cancer research-related toxicology is a major topic of the journal. By showing examples of the successful application of a cutting edge technique, such as single cell sequencing, Zhu et al. can also inspire readers to implement these techniques in their own laboratories.

The applications and potential of single cell sequencing was also described by Wang et al. in CBT (Wang et al. 2017a). The authors focused on RNA sequencing in single cells (scRNA-seq), which can be used to garner detailed insights into processes such as embryonic development, transcriptome evolution, and drug resistance. Multiple strategies to undertake scRNA-seq have been developed, includingCEL-seq2, Drop-seq, MARS-seq, SCRB-seq, Smart-seq, and Smart-seq2. Significantly, cryopreserved cells are also amenable to single cell RNA sequencing (Guillaumet-Adkins et al. 2017). scRNA-seq has been used to characterize gene expression responses in the minority population of cancer cells that become therapy resistant, via changes in the RNA expression pattern for genes related to common targets for anti-cancer drugs, such as cytoskeleton organization (Lee et al. 2014). Moreover, scRNA-seq was applied to drug target identification for insulin producing β-cell regeneration to treat diabetes. Using xenograft models, it was demonstrated that Arx, a transcription factor associated with glucagon regulation, was rapidly translocated to the cytoplasm in malaria drug-treated tumor cells (Li et al. 2017). This was further integrated with global transcriptomics to identify the gamma-aminobutyric acid receptor subunits, GABRB3 and GABRG2, as factors repressing α-cell identify in pancreatic cells that could facilitate the their conversion to therapeutically relevant β-cells. Interestingly, Wang et al. also describe the application of scRNA-seq to post-transcriptional genome regulation, for example, by assessing the influence of RNA N6-methyladenosine on methylation, translation, and metabolism (Wang et al. 2017a). This illustrates the key roles scRNA-seq can play in characterizing disease networks, biomarkers, and novel drug targets. Our own opinion is that this paper is very desirable for publication in CBT, because it provides insight concerning the latest variations of the single cell sequencing technology, which may be difficult for non-experts to follow. This would allow readers to carefully adopt the methodology that would yield the best quality of data from their experiments. The importance of this paper is indicated by the eight citations that it has already received in Scopus.

In CBT, the applications of single cell sequencing to benefit both basic and applied medical research was described by Ruderman, with an emphasis on the need to apply cross-disciplinary techniques to understand the dynamic phenotypes revealed by single cell sequencing (Ruderman 2017). Using p53 nuclear accumulation in response to DNA damage as an example, Ruderman discussed how dynamic phenotyping revealed novel modulators of p53 activity and the cancer cell types that are most sensitive to DNA damage (Stewart-Ornstein and Lahav 2017). The limitations of dynamic phenotyping were also outlined, such as the need to account for circadian rhythms within cells, the accuracy of computer models to predict dynamic phenotypes at the cellular level, the need to develop new theories for identifying response variables, and building multidisciplinary research teams to thoroughly investigate these phenotypes (Ruderman 2017). Our own opinion is that this paper is very applicable for the journal. It is a timely reminder that building cross-disciplinary collaborations and combining expertise produces a higher chance of gaining valuable insights these cutting edge technologies, such as the study of p53 dynamic phenotyping described by Ruderman.

Clinical influences of the microbiome

Research into the microbiome, and how this influences many aspects of human disease, is a major area of cutting edge research. Recently, high-profile studies have demonstrated the role of the microbiome in regulating diverse processes, such as the efficacy of PD-1 treatments for carcinoma/melanoma, the promotion of metastasis in colon cancer, and whole body composition via the circadian clock (Wang et al. 2017b; Gopalakrishnan et al. 2017; Routy et al. 2017; Bullman et al. 2017). The exciting potential of understanding the microbiome for translational research was outlined by Miko et al., in CBT (Miko et al. 2016). The influence of the microbiome on human physiology is so great that some researchers have classified it as an additional organ and proposed the term "metagenome" to describe the combined human and microbiome genomes (Han et al. 2016). Miko et al. discussed the relationship between changes in the microbiome and disease, such as the severity of autoimmune disorders, susceptibility to obesity/diabetes, aging, and developmental disorders. Emerging fields with high translational potential are also outlined, including the bacterial metabolites as possible therapeutics, the influence of the microbiome on the efficiency of digestion and drug metabolism, and the application to personalized medicine. Our own viewpoint is that discussions of the potential of microbiome-related research is an important subject for CBT, due to its effect on drug metabolism and disease pathogenesis. In addition, the human microbiome is likely to significantly affect potential toxicological responses to bioactive compounds. Therefore, further submissions covering the latest progress in microbiome research should be encouraged.

Implementation of induced pluripotent stem cell/cell reprogramming technologies

Cell reprogramming and the therapeutic applications of induced pluripotent stem cells (iPSCs) remain a cutting edge research area (Normile 2017; Choi et al. 2017; Kikuchi et al. 2017). The promise and challenges of implementing this technology has also been covered in CBT (Devine and Patani 2017; Kim et al. 2016; Driessen et al. 2017). Devine and Patani provided a very useful, focused overview of the application of iPSC technology for neurological applications. Neurodegenerative diseases are predicted to become an increasing burden on society, and iPSCs can be used to generate disease models for compound screening to identify new drug candidates, such as Parkinson's disease and, notably, Zika virus infection (Kikuchi et al. 2017; Xu et al. 2016). Devine and Patani also describe the latest progress in scaling up the production of therapeutically relevant cell types derived from iPSCs for cell therapy applications, for example, developing 3D cultures that allow the harvesting of billions of uniform, mature neurons from a single flask (Rigamonti et al. 2016). The most recent approaches for iPSC-based cell therapy were also described, such as the intracerebral injection of human iPSC-derived oligodendrocytes to treat primate models of multiple sclerosis (Thiruvalluvan et al. 2016). Our opinion is that discussions of the applications of iPSCs and cell reprogramming strategies are especially relevant for CBT, because of their potential to be utilized for disease modeling and predictive toxicity for candidate therapeutics. For example, hepatocytes derived from human iPSCs have the potential to be an important resource for toxicology research. Therefore, iPSC-based research can become a significant focus for CBT.

The impressive clinical potential of human iPSCs was also covered by Kumar et al. in CBT (Kumar et al. 2017). Importantly, the crucial safety measures that must be adopted for clinical applications in humans were discussed, with focus on issues such as quality control for potential epigenetic aberrations, long-term integration of transplanted cells, and functional integration into the host tissue. The authors also describe progress in utilizing the domesticated pig model for testing the safety of iPSC-based therapies, which has multiple similar characteristics with humans, including physiology, pathology, body weight, and life span (Kumar et al. 2017; Schook et al. 2016). Alongside iPSC-based technologies for treating degenerative diseases, direct cell reprogramming has emerged as an alternative strategy that does not produce a potentially oncogenic stem cell intermediate (Drouin-Ouellet et al. 2017; Ghiroldi et al. 2017). This can be achieved by the application of master transcription factors for the cell type of interest or with small molecule-based approaches (Cao et al. 2016; Um et al. 2017; Qian et al. 2012; Julian et al. 2017; Jung et al. 2014). In CBT, Driessen et al. explored the clinical potential of reprogramming for cartilage repair (Driessen et al. 2017). Mechanical degradation of joints due to aging or overloading wears down articular cartilage and can produce osteoarthritis, which is the most common form of arthritis affecting over 237 million

people (Glyn-Jones et al. 2015). Driessen et al. compared iPSC-based and direct reprogramming strategies to generate sufficient numbers of functional chondrocytes, which is a major limitation of cell therapy approaches for arthritis. It was shown that the quality of chondrocytes generated by reprogramming is heavily dependent on in the methodology used, although this can be enhanced by cell culture techniques, for example, 3D-based systems. Direct reprogramming strategies were shown to have some advantages over iPSC-based protocols, including a more rapid generation of chondrocytes. However, this was also restricted by the need for constitutive transgene expression, such as exogenous Sox9, which appears to be indispensable for reprogramming (Leung et al. 2011). The use of biomaterials containing cartilage extracellular matrix components could further enhance reprogramming into higher quality chondrocytes (Mao et al. 2017; Driessen et al. 2017). We believe that this type of focused discussion of the application of cell reprogramming for a specific disease, such as arthritis, is desirable for publication in CBT, because direct reprogramming is a major alternative approach to iPSCs for producing clinically useful cell types. In addition, a focused discussion of the application of a cutting edge technology, such as cell reprogramming for arthritis, should encourage future submissions of research articles related to this subject.

Summary and opinion

In this editorial, we have shown that the research fields of articles published in CBT are diversifying, as indicated by an increasing range of keywords for recent publications. We have surveyed published articles in CBT from 2016 to 2017 to provide examples of the widening scope of the journal and its coverage of cutting edge research. Our own opinion is that CBT is addressing pertinent issues associated with these research fields by publishing useful editorials and reviews from experts, which cover the impressive potential and possible caveats associated with these technologies. This can provide guidance for researchers in the diverse areas of toxicology research that are interested in applying these new technologies to their own work. Encouragingly, research-based articles also being published in CBT, for example, the application of iPSC and cell reprogramming strategies for predicting drug toxicity (Kim et al. 2017; Gao and Liu 2017). If CBT can continue to expand its scope to encompass cutting edge technologies, while still providing a high-quality resource for toxicology research, we believe the journal can continue to expand and publish high quality research and reviews. Therefore, it is the responsibility of the editors to stay updated with the latest trends in life science research and suggest contributions to CBT, in the form of editorials, commissioned reviews, or basic research papers. In the long term, this should increase the impact and further widen the readership of CBT. It can be envisaged that CBT will increasingly publish papers that cover recent progress in these cutting edge research areas as well as emerging, high-profile new technologies in both basic and applied life sciences.

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