View metadata, citation and similar papers at core.ac.uk

brought to you by CORE

provided by Explore Bristol Research

Adams, J. (2019). A New Initiative for *AJP-Cell Physiology*: "Making Cell Culture More Physiological". *AJP - Cell Physiology*, *316*(6), C828-C829. https://doi.org/10.1152/ajpcell.00157.2019

Peer reviewed version

Link to published version (if available):
10.1152/ajpcell.00157.2019

Link to publication record in Explore Bristol Research
PDF-document

This is the author accepted manuscript (AAM). The final published version (version of record) is available online via APS at https://www.physiology.org/doi/abs/10.1152/ajpcell.00157.2019 . Please refer to any applicable terms of use of the publisher.

University of Bristol - Explore Bristol Research

General rights

This document is made available in accordance with publisher policies. Please cite only the published version using the reference above. Full terms of use are available: http://www.bristol.ac.uk/pure/user-guides/explore-bristol-research/ebr-terms/

EDITORIAL

A New Initiative for AJP-Cell Physiology: "Making Cell Culture More Physiological"

Josephine C. Adams
School of Biochemistry, Faculty of Life Sciences, University of Bristol,
Bristol BS8 1TD, UK

Correspondence email: jo.adams@bristol.ac.uk

Keywords: Cell culture, microenvironment, homeostasis, organoids, media

The ability to maintain populations of cells *ex vivo* is a practical necessity for basic research into molecules, cells and multi-cellular tissue organisation and for cell-based high-throughput screening for drug discovery. The origins of cell culture go back over 100 years to, for example, pioneering experiments of Roux who showed that cells from chick embryos could be kept alive *ex vivo* in physiological saline over several days [6]. Subsequently, Harrison used clotted plasma, or spiderweb produced by spiders from his garden, to investigate the influence of different surfaces on the shapes and movement of cells dissociated from amphibian spinal cord or chick embryos [2]. These experiments encapsulate the fundamentals of cell culture: cell type, culture surface and nutrient medium, all of which continue to underpin the field today. In the 1950s, other great advances were made in developing cell lines that could be propagated endlessly in culture (e.g., HeLa cervical cancer cells, the world's first immortal cell line, derived by Gey and colleagues, or Chinese hamster ovary (CHO) cells, developed by Puck and colleagues as a clonal cell line) and to devise artificial culture media such as Minimal Eagle's Medium (developed by Harry Eagle) and Dulbecco's Modified Eagle's Medium (developed by Renato Dulbecco). With the inclusion of calf serum, a variety of mammalian cells can be reliably maintained in these media. These tools and reagents remain in widespread use today.

Although cell culture is the methodology of choice for detailed investigative experiments to pin down molecular pathways, instances of unexpected phenotypes in gene-knockout mice, (as one example, cell culture-based experiments led to a view that D- and E-type cyclins are essential for cell cycle progression yet gene-knockout mice were found to develop normally), or limited translation of preclinical research, have led the robustness and value of data obtained from cultured cells, especially cell lines, to be questioned [1]. Nevertheless, experiments with mammalian model animals are expensive and time-consuming and carry many ethical issues. There is also a growing view that data from human cells/tissue are more relevant to human disease than are mouse models [4, 9]. Furthermore, an explosion of new technologies are re-invigorating and expanding the possibilities of cell culture. Ranging from applications of transcriptomics and proteomics to gain global views of cell status in cell populations or single cells (e.g., the Human Cell Atlas, www.humancellatlas.org), to the precision and versatility afforded by new gene-editing methods, and to advancements in super-resolution light microscopy and the combined use of light and electron microscopy [7], these methodologies are

propelling life science researchers into a new era in which cells and their functions can be investigated in unprecedented depth and detail.

In parallel, there are now many alternatives to traditional cell lines and cell culture methods. A major driver for a shift to use of primary cells and cell strains is the availability of human stem cells and induced pluripotent stem cells. Advances in culture media have led to complete defined media that remove the variability inherent in working with foetal calf serum. The rigid culture dish, in use for so many years, can now be switched for culture environments that better reflect the mechanical or topographical properties of specific tissues. These advances in basic tools are also facilitating greater adoption of ‘3-dimensional’ culture systems in which cells form spheroids or organoid structures, can be placed under fluid flow or in microfluidic environments, or different cell types co-cultured at larger scale to form ‘mini-organs”. Together, these cells and culture environments provide a closer reflection of tissue *in vivo* [3].

Overall, nonwithstanding expansion of the scope *in vivo* models and methods for fluorescent imaging of proteins and other molecules in native tissue, there remains an enormous need for cell culture, both to expand fundamental knowledge of cellular organisation and function and to facilitate pre-clinical drug discovery. Over the last three years, the American Physiological Society has taken initiatives to increase the rigor and transparency of research reporting and define best practices, with the goal to enhance data reproducibility, as discussed in several editorials, e.g., [10]. At *AJP-Cell Physiology*, we see a parallel need to encourage authors to embrace newer resources for cell culture: fully-defined cell culture media, 3D cultures and organoids, specific conditions for hard-to-study primary cells, use of molecular reporters of the status of living cells, are a few of many possible examples. These resources can both help researchers to maintain and monitor their cultures more accurately, assisting reproducibility, and, by delivering conditions that more closely reproduce the physiological milieu, will enhance the biological relevance of research findings.

This topic aligns closely with the mission of *AJP-Cell Physiology* to publish research on the molecular and cellular basis of physiological processes. The Journal also has the goal to publish research that takes “innovative approaches to the study of cell and molecular physiology”, as reported through Methods in Cell Physiology articles. In addition, several recent ad-hoc articles have raised issues of general importance for experimentation with cells in culture. Examples include an article by Bradbury and

colleagues “Do you know the sex of your cells?” which pointed up the importance of reporting the sex of primary cells or lines [8]. McKee and Komarova posed the question “Is it time to reinvent basic cell culture medium?”, emphasizing that many cell culture media poorly replicate the physiological environment of cells [5].

To address this important issue on a systematic basis, *AJP-Cell Physiology* is launching Review invitations and a new Call for Papers under the general title “Making Cell Culture More Physiological”. Through this initiative, the Editors wish to promote greater uptake of, and improvements to, physiologically relevant forms of cell culture as used in discovery research. Under this Call for Papers, the Editors will welcome submissions of Research Articles or Rapid Reports which include use of non-traditional, more physiological, cell culture: either currently available methods to sustain the cells used in the experiments, or novel approaches that are investigated as part of the experimental goals. Methods papers that demonstrate the setup and benefits of more physiological or cell-type specific culture conditions, or new methods that better report on cell status are also called for. *AJP-Cell Physiology* will also publish associated editorial content in the form of Reviews, Viewpoints or Perspectives on topics relevant to “Making Cell Culture more Physiological”. Prospective authors are welcome to raise suggestions for topics or make pre-submission enquiries by contacting the *AJP-Cell Physiology* office at ajpcell-office@bristol.ac.uk. Our goal is for this initiative to inform and stimulate researchers at all career stages to take steps to make cell-based, *ex vivo* experimentation more physiological.

Acknowledgements. I thank the Editors and APS members with whom I have discussed these ideas. There are no conflicts of interest to declare.

REFERENCES

1. Begley CG, Ellis LM. Drug development: Raise standards for preclinical cancer research. *Nature* 483:531-533, 2012. doi: 10.1038/483531a

2. Harrison, R. G. The reaction of embryonic cells to solid structures. *J. Exp. Zool.* 17: 521-544, 1914.

3. Holloway EM, Capeling MM, Spence JR. Biologically inspired approaches to enhance human organoid complexity. *Development* 146: pii: dev166173, 2018. doi: 10.1242/dev.166173.

4. Jackson SJ, Thomas GJ. Human tissue models in cancer research: looking beyond the mouse. *Dis Model Mech.* 10: 939–942, 2017. doi: 10.1242/dmm.031260

5. McKee TJ, Komarova SV. Is it time to reinvent basic cell culture medium? *Am J Physiol Cell Physiol.* 312:C624-C626, 2017.

6. Roux, W. Cytotropismus. *Arch. f . Entw. Mech.*, Bd. 1, 1894.

7. Schermelleh L, Ferrand A, Huser T, Eggeling C, Sauer M, Biehlmaier O, Drummen GPC. Super-resolution microscopy demystified. *Nat Cell Biol.* 21:72-84, 2019.

8. Shah K, McCormack CE, Bradbury NA. Do you know the sex of your cells? *Am J Physiol Cell Physiol.* 306:C3-18, 2014.

9. Sundstrom L. Thinking inside the box. To cope with an increasing disease burden, drug discovery needs biologically relevant and predictive testing systems. *EMBO Rep.* 8:S40–43, 2007.

10. Yosten GLC, Adams JC, Bennett CN, Bunnett NW, Scheman R, Sigmund CD, Yates BJ, Zucker IH, Samson WK. Revised guidelines to enhance the rigor and reproducibility of research published in American Physiological Society journals. *Am J Physiol Regul Integr Comp Physiol.* 315:R1251-R1253, 2018.