Vice President Joe Biden
The White House
1600 Pennsylvania Avenue
Washington, DC 20500

National Cancer Advisory Board
National Cancer Institute at Shady Grove
Division of Extramural Activities
Committee Management Office
9609 Medical Center Drive
7th Floor, West Tower, Room 7W-412, MSC 9750
Bethesda, MD 20892-9750

Dear Mr Vice President,

Congratulations on your Cancer Moonshot initiative, which provides a welcome opportunity to fast-track development of cancer cures by using top quality research and data to accelerate the discovery process. On behalf of the International Cell Line Authentication Committee (ICLAC), a worldwide committee of scientists with expertise in cell culture and authentication testing, I am writing to urge the Cancer Moonshot Task Force to set common principles and requirements for training and quality assurance testing when using biological materials.

Training and quality assurance establish a solid foundation for research into new cancer cures, making such research reliable and reproducible. Recent estimates indicate that $28 billion per year, in the US alone, is spent on preclinical research that is not reproducible[1]. Of that total, roughly $10 billion is misused on poor quality biological reagents and reference materials, including the misidentification of cell lines that are used as essential *in vitro* models to study cancer and other diseases. These problems are long standing and well recognized in life sciences research, resulting in the development of simple guidelines that are not yet universally adopted. A Reproducibility Toolkit is needed to support the Cancer Moonshot, to be used by all projects funded as part of the initiative and applied to all cell-based models.

You, and the Cancer Moonshot Task Force, are in a unique position to establish guidelines for the allocation of new funds, eradicating these problems and accomplishing the goal "to end cancer as we know it". Without specific guidelines for training and quality assurance, money and time allocated to research projects will undoubtedly be wasted and the success of the Cancer Moonshot could be compromised.

Cell-based models can enable – or disable – cancer research

Cell-based models are essential resources for basic cancer research, helping us to understand the disease process and develop new treatments. Cell-based models include cell lines, used by the National Cancer Institute (NCI) and research organisations worldwide to test thousands of anticancer agents and other potential therapies. Novel cell-based models include patient-derived xenografts (PDX), which allow us to optimize treatment choices and study the interactions between cancer cells and their environment. Both have the potential to accelerate cancer research, but only if models are fit for their intended purpose.

Cell lines and PDX models consist of living cells cultured outside the body. Over time, these cells can change to become less representative of the cancer they are used to study. Changes in cell-based models, a long-standing problem in cancer research, can occur if scientists use suboptimal procedures, handling cultures for a long period of time or using inappropriate growth conditions. Cell lines and PDX models can easily become contaminated by micro-organisms or cells from another culture, leading to unexplained or irreproducible results. For example, if a cell line is accidentally cross-contaminated by cells from another culture, the contaminant can overgrow and replace the original, authentic culture.

Changes, including cross-contamination, are often subtle and difficult to detect without testing. As a result, problems with cell-based models may take many years to uncover, resulting in a waste of precious time and research funding. Hundreds of such incidences have been documented as requiring action[2].

Example of Setback in Cell-based Esophageal Cancer Research

Esophageal adenocarcinoma (EAC) research shows the importance of cell-based models and the need for training and quality assurance. Esophageal cancer is one of the commonest cancers worldwide, estimated to result in more than 15,000 cancer deaths in the US during 2016[3]. EAC, a subtype of esophageal cancer, is difficult to study in mouse or rat models; cell lines grown *in vitro* from patients with the disease are key resources to develop new cures. Only seventeen EAC cell lines have been established[4].

In 2010, an international study performed quality assurance testing on fourteen widely used EAC cell lines[5]. Authentication testing showed that three out of fourteen EAC cell lines were not actually from EAC. Instead, they were derived from patients with lung, colon and gastric cancer. The study concluded that these three cell lines were misidentified, with the problem believed to arise early in the process of cell line establishment and thus affecting all subsequent research. The authors found two clinical trials that were recruiting patients partly based on preclinical data using two of these misidentified cell lines. The three misidentified cell lines from this study had been used in more than 100 publications, three NIH grants and eleven US patents[5].

We at ICLAC are aware of almost 500 cell lines that are known to be misidentified[6], many of which continue to be used by the research community under the false guise of cells that they do not represent. Although we curate a database of false cell lines, there is no institutional system to weed out misleading cell models. Some journals and funding bodies now require scientists to test their cell lines for common problems and request a statement on authentication status. However, studies continue to be published on a regular basis using cell-based models where no quality assurance has been performed.

Each scientific publication that utilizes misidentified or unauthenticated cell models could slow and corrupt the discovery process. We need a better approach to training and quality assurance so that scientists are more aware of the problems with cell-based models and have the resources to address them.

Training and Quality Assurance are essential for a successful Cancer Moonshot

The scientists and engineers who participated in the original race to the Moon understood the importance of training, standards and quality assurance. NASA's history records show that in the process of rapidly mobilizing the Apollo mission, outsourcing of development and manufacture led to quality concerns. NASA responded by developing the "10 percent rule": ten percent of all funding for NASA was to be spent to ensure in-house expertise and, in the process, check contractor reliability[7].

The race to cure cancer should take a similar approach. In-house expertise and reliability testing are important constants for all aspects of research and development. While ethics and safety are mandatory requirements in preclinical research, scientific training and quality assurance are often overlooked or taken for granted, and can vary from one laboratory to another.

We fear that the push to accelerate science for cancer cures will carry an even greater risk to the quality of cancer research. Without measures to ensure training and quality assurance, the successful development of new life-saving therapies will be slowed. To ensure that the Cancer Moonshot fulfils its stated mission to accelerate the discovery process, we propose that this risk should be managed using thoughtfully implemented initiatives that are designed to help, not hinder the progress of science.

A Reproducibility Toolkit to ensure success of the Cancer Moonshot

The race to the Moon relied on a toolkit of resources that, to our modern eyes, seems incredibly small. Slide rules were still in use for calculations, and NASA's computers had tiny data storage and processing

capacities compared to the powerful devices in use today. However, all items in the NASA toolkit relied on common principles that were understood by all scientists and engineers involved in the project. Industry standards were used for component testing, ensuring that quality requirements were consistently applied.

The Cancer Moonshot initiative needs a Reproducibility Toolkit to establish the common principles needed for research findings to be reliable and reproducible. This is particularly important for cell-based models, although it is applicable to other key resources such as antibodies and chemicals. We urge the Cancer Moonshot Task Force to adopt the following as part of its requirements and recommendations:

1. Commit a proportion of all funding to support training and quality assurance

Funding for training and quality assurance will increase awareness of the problems that can affect cell-based models. Resources for training and testing will benefit science now and in the future.

2. Set out common principles for reproducibility where compliance is required

The National Institutes of Health (NIH) has established principles and guidelines for reporting of preclinical research[8]. Adoption and application of these principles by the Cancer Moonshot initiative would set a consistent benchmark for reproducibility.

3. For cell-based models, mandate authentication as a condition of funding

NIH currently requires authentication of key resources as part of its funding application process[9]. We applaud this step and call on the Cancer Moonshot initiative to adopt mandatory reporting of authentication testing for cell-based models as an important responsibility for funding recipients.

In considering these recommendations, we acknowledge the experts sitting as members of the National Cancer Advisory Board, who will have expertise and knowledge that are relevant to these issues.

Thank you for your commitment to facilitating and enabling new cancer cures.

Yours sincerely,

Amanda Capes-Davis MB BS BSc(Med) PhD
Chair, International Cell Line Authentication Committee (ICLAC)
Children's Medical Research Institute (CMRI), Locked Bag 23, Wentworthville NSW 2145, Australia
Email: acapes-davis@cmri.org.au

Signed on behalf of all ICLAC members by Amanda Capes-Davis
ICLAC member list can be found at: http://iclac.org/members/
A copy of this letter can be found at: http://iclac.org/cancer-moonshot/

References

[1] http://journals.plos.org/plosbiology/article?id=10.1371/journal.pbio.1002165
[2] http://science.sciencemag.org/content/346/6216/1452.long
[3] http://www.cancer.org/cancer/esophaguscancer/detailedguide/esophagus-cancer-key-statistics
[4] http://onlinelibrary.wiley.com/doi/10.1111/dote.12095/full
[5] http://jnci.oxfordjournals.org/content/early/2010/01/14/jnci.djp499
[6] http://iclac.org/databases/cross-contaminations/
[7] http://history.nasa.gov/Apollomon/Apollo.html
[8] http://www.nih.gov/research-training/rigor-reproducibility/principles-guidelines-reporting-preclinical-research
[9] http://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-103.html