Nos. 19-2255, -2285

# United States Court of Appeals for the Federal Circuit

**BIO-RAD LABORATORIES, INC., THE UNIVERSITY OF CHICAGO,**
*Plaintiffs-Appellees,*
***v.***
**10X GENOMICS, INC.,**
*Defendant-Appellant*

Appeals from the United States District Court
for the District of Delaware
No. 1:15-cv-00152-RGA, Hon. Richard G. Andrews

## BRIEF FOR THE BROAD INSTITUTE, INC. AS *AMICUS CURIAE* IN SUPPORT OF NEITHER PARTY

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# Certificate of Interest

**FORM 9. Certificate of Interest** **Form 9**
**Rev. 10/17**

**UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT**

Bio-Rad Laboratories, Inc. et al. v. 10X Genomics, Inc.

Case No. 19-2255, -2285

**CERTIFICATE OF INTEREST**

Counsel for the:
☐ (petitioner) ☐ (appellant) ☐ (respondent) ☐ (appellee) ■ (amicus) ☐ (name of party)

The Broad Institute, Inc.

certifies the following (use "None" if applicable; use extra sheets if necessary):

| 1. Full Name of Party Represented by me | 2. Name of Real Party in interest (Please only include any real party in interest NOT identified in Question 3) represented by me is: | 3. Parent corporations and publicly held companies that own 10% or more of stock in the party |
|---|---|---|
| The Broad Institute, Inc. | None | None |
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4. The names of all law firms and the partners or associates that appeared for the party or amicus now represented by me in the trial court or agency or are expected to appear in this court **(and who have not or will not enter an appearance in this case)** are:

Duane Morris LLP: Thomas J Kowalski, Richard L Renck

**FORM 9. Certificate of Interest** **Form 9 Rev. 10/17**

5. The title and number of any case known to counsel to be pending in this or any other court or agency that will directly affect or be directly affected by this court's decision in the pending appeal. *See* Fed. Cir. R. 47. 4(a)(5) and 47.5(b). (The parties should attach continuation pages as necessary).

None

10/25/2019
Date

/s/ Steven R Trybus
Signature of counsel

Steven R. Trybus
Printed name of counsel

Please Note: All questions must be answered

cc: Counsel of Record (via ECF)

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## I. INTRODUCTION

The Broad Institute, Inc. ("Broad"), also known as the Broad Institute of MIT and Harvard, submits this brief as *Amicus Curiae* pursuant to Fed.R.App.P. 29 and Fed.Cir.R. 29.

Broad submits this brief in support of the significant public interest implicated when considering whether a permanent injunction is an appropriate remedy in a patent case and the scope of that injunction. Here, the patents at issue are a subset of numerous patents, made with Government support, that cover advances related to single-cell technologies collected in Essential Technologies necessary to significant ongoing biomedical research, much of which is also Government supported.

Broad takes no position on infringement nor the damages award.

## II. INTEREST OF *AMICUS CURIAE*

Broad is a unique non-profit research organization with laboratories and offices in Cambridge, Massachusetts. Broad is a separate entity from MIT and Harvard, but affiliated with each of these institutions. Broad uses genomics to advance understanding of the biology and treatment of human disease, and to help lay the groundwork for next generation therapies. Broad participates in many Government funded initiatives to leverage this work.

Broad is a mission-driven community that brings together researchers in medicine, biology, chemistry, computation, engineering, and mathematics from across MIT and Harvard, along with collaborators around the world. Broad is committed to addressing medical challenges across the world, including by collaborating with scientists and public health experts to address important needs in developing countries. Broad works to build and sustain international consortia to speed discovery in areas including psychiatric, infectious, and cardiovascular diseases and cancer. Further, Broad is committed to making the data, methods, and technologies it generates rapidly and readily accessible to the scientific community to drive biomedical progress.

Broad makes knowledge and IP related to reagents, platforms, and methods freely available to the academic and non-profit communities and does so non-exclusively for others, except in unusual circumstances in which it is determined that the public interest is better served by exclusive or semi-exclusive licensing. It is Broad's general position that inventions and IP resulting from research based in whole or in part on Government funding should be similarly available and openly licensed whenever feasible so as to maximize public benefit.

Broad also extensively uses, and needs to fully use, single-cell genomics technology as is at issue here. Thus, Broad has a keen interest in the issues before the Court, including that the important research performed by Broad can, and will,

be directly impacted by the Court's decisions on remedies, especially the existence and scope of any permanent injunction and/or the level of ongoing royalties.

Broad buys and uses 10X Genomics, Inc. ("10X") technologies including as at issue here. Broad also buys and uses Bio-Rad Laboratories, Inc. ("Bio-Rad") technologies. In addition, members of Broad serve as consultants and advisors for both Bio-Rad and 10X. And, members of Broad collaborate with members of the University of Chicago. Thus, Broad is not directly concerned with who prevails in this litigation so long as any remedies address the public interest.

No party's counsel authored this brief in whole or in part; no party or party's counsel contributed money that was intended to fund preparing or submitting this brief; and no person—other than the amicus curiae, its members, or its counsel—contributed money that was intended to fund preparing the brief.

## III. SUMMARY OF THE ARGUMENT

The District Court recognized a strong public interest in access to the technology at issue, and crafted an injunction that allowed 10X to continue to sell consumables for use in ongoing research. In doing so, the Court appeared to recognize the unique aspects of the instruments sold by the parties.

Yet, by failing to appreciate the lack of interchangeability among the instruments at issue, the Court improperly imposed an injunction that limits the use

of technology essential to ambitious biomedical research efforts currently being undertaken. Public interest is especially impacted if, as here, the issue is access to Essential Technology being used by researchers at academic and non-profit institutions for important ongoing biomedical research and to advance healthcare.

Other factors that must be given adequate weight in assessing the propriety of injunctive relief include that Essential Technology, such as the technology at issue and of both parties here, often incorporates numerous patented elements, such that a series of injunctions or stacked royalties based on multiple infringement actions could effectively negate progress.

An additional factor affecting public interest that must be given appropriate weight, but was not addressed by the District Court, relates to patents that are the result of research funded, at least in part, by the Government. Where present, those facts must be balanced to determine if the equities support a permanent injunction.

In this case, an injunction protects private appropriation of publicly funded research to the clear detriment of the public good. Patents based on publicly funded research should be used to maintain access to innovation—allowing researchers at academic and non-profit research institutions to develop products that enable further research and to build new technologies—not to prevent the distribution of the fruits of research, as is being done here. This can be achieved without

sacrificing the "reward" (and incentive) for undertaking expensive private development.

## IV. STATEMENT OF FACTS

In addition to materials before the District Court, Broad cites herein certain publicly available documents to support the public interest points raised below.

### A. Single-cell Technologies are Key to Biomedical Research

The single-cell technologies involved here are important to research that will result in advances in the care of humans, and aid in understanding of the complexity of biological networks and organisms, both human and non-human. For example, Broad co-founded an international initiative, known as the Human Cell Atlas (HCA), to build comprehensive reference maps of all human cells. Appx28532-34. The HCA initiative requires access to multiple techniques in the single-cell RNA sequencing space.

> The revolution in single-cell genomics has enabled genome-wide quantification of mRNA in thousands of individual cells at once. Additionally, multiple techniques have been developed to study the genetic and epigenomic characteristics of single cells, including DNA mutations (and associated lineage information), cytosine modifications, higher-order chromosome conformation, histone modifications, and regions of accessible chromatin (**Figure 1**). **Each of these methods will need to be further optimized and deployed to generate the HCA — some as the main workhorses and others as auxiliary methods**, with agile reassessment of chosen techniques in a fast-evolving landscape.

"The Human Cell Atlas White Paper," (available at https://arxiv.org/ftp/arxiv/papers/1810/1810.05192.pdf)(emphasis added, internal references omitted); see also, Figure 1:

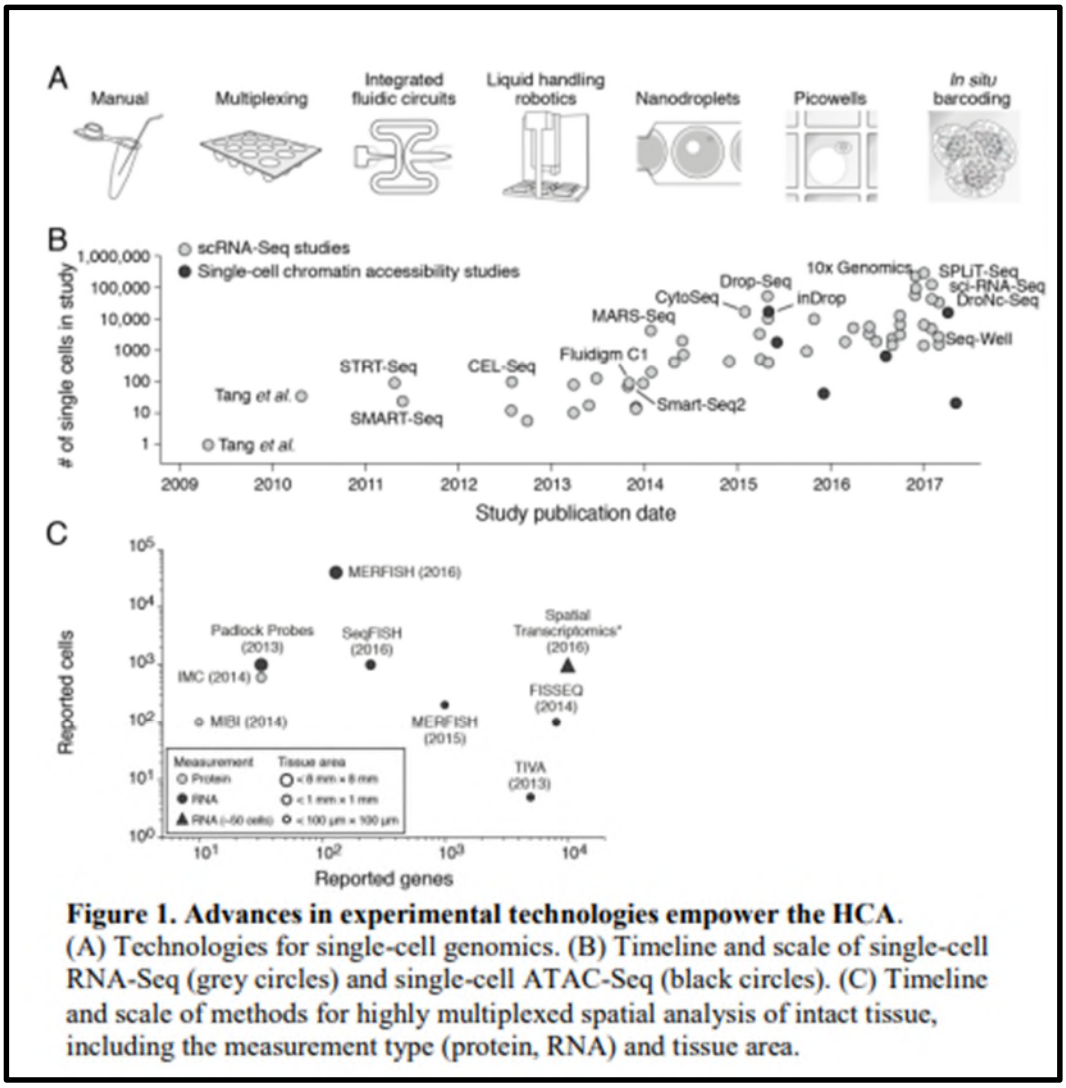



**Figure 1. Advances in experimental technologies empower the HCA.** (A) Technologies for single-cell genomics. (B) Timeline and scale of single-cell RNA-Seq (grey circles) and single-cell ATAC-Seq (black circles). (C) Timeline and scale of methods for highly multiplexed spatial analysis of intact tissue, including the measurement type (protein, RNA) and tissue area.

*Id.* The HCA has systematically compared these technologies with experimental needs and, to ensure comparability of data, reported on the important differences:

> The latest methods are scalable to thousands of cells, enabling in depth characterization of sample composition without prior knowledge. However, there are important differences between

> scRNA-seq techniques, and it remains unclear which are the most suitable protocols for drawing cell atlases of tissues, organs and organisms. We have generated benchmark datasets to systematically evaluate techniques in terms of their power to comprehensively describe cell types and states. We performed a multi-center study comparing 13 commonly used single-cell and single-nucleus RNA-seq protocols using a highly heterogeneous reference sample resource. Comparative and integrative analysis at cell type and state level revealed marked differences in protocol performance, highlighting a series of key features for cell atlas projects. These should be considered when defining guidelines and standards for international consortia, such as the Human Cell Atlas project.

Mereu et al, "Benchmarking Single-Cell RNA Sequencing Protocols for Cell Atlas Projects," (available at https://www.biorxiv.org/content/biorxiv/early/2019/05/13/630087.full.pdf); *see also*, Ding et al. "Systematic comparative analysis of single-cell RNA-sequencing methods," (available at https://www.biorxiv.org/content/biorxiv/early/2019/05/09/632216.full.pdf)("Single-cell RNA sequencing (scRNA-seq) has emerged as a central tool for identifying and characterizing cell types, states, lineages, interactions between cells and circuitry." (*Id.* at 3.))

Each technology includes a unique combination of elements and techniques that have converged for those methods and equipment to the single-cell revolution. And, these various embodiments of the technology have origins with Government funded research, especially in academic and non-profit research institutions. This includes Broad; Broad had early and frequent advances for devices, tools and methods. These technology packages allow researchers to label, perturb, measure

and analyze cells individually and in tissues. The result was the ability to better analyze cellular types and functions and to better understand diseases and disorders.

As noted by Dr. Francis Collins in the January 2, 2019 NIH Director's Blog highlighting biomedical advances in 2018:

> The 2018 Breakthrough of the Year went to biomedical science and its ability to track the development of life—one cell at a time—in a variety of model organisms. This newfound ability opens opportunities to understand the biological basis of life more systematically than ever before. Among *Science's* "runner-up" breakthroughs, more than half had strong ties to the biomedical sciences and NIH-supported research.
>
> Sound intriguing? Let's take a closer look at some of the amazing science conducted in 2018, starting with *Science's* Breakthrough of the Year.
>
> **Development Cell by Cell:** For millennia, biologists have wondered how a single cell develops into a complete multicellular organism, such as a frog or a mouse. But solving that mystery was almost impossible without the needed tools to study development systematically, one cell at a time. That's finally started to change within the last decade. I've highlighted the emergence of some of these powerful tools on my blog and the interesting ways that they were being applied to study development.
>
> Over the past few years, all of this technological progress has come to a head. Researchers, many of them NIH-supported, used sophisticated cell labeling techniques, nucleic acid sequencing, and computational strategies to isolate thousands of cells from developing organisms, sequence their genetic material, and determine their location within that developing organism.

Appx28536-44 (hyperlinks removed, underlining original at hyperlinks). Important planned and ongoing research will be directly impacted by the existence and scope

of any permanent injunction and/or the level of ongoing royalties in this matter and as may result from other ongoing litigation related to this technology.

Large data projects are currently focused on developing the cell-based data necessary for important advances in human health. For example, the NCI Human Tumor Atlas Pilot Project and the Human Tumor Atlas Network, a part of the Cancer Moonshot$^{SM}$, are US government projects that use single-cell genomic technologies. These major NIH projects involve fresh (must be processed immediately) and frozen tumor samples from human patients that require analysis in a timely fashion and in a cost-effective manner. These initiatives require much data to be collected from many human samples. Use of single-cell genomics, by Broad, NIH and others was envisioned by the Program seeking to improve the ability to understand and treat disease. (See, e.g., Appx28546-49; Appx28551-54).

HuBMAP (https://commonfund.nih.gov/hubmap) is an NIH-sponsored program aimed at generating molecular maps the single-cell level. To achieve this goal, HuBMAP has been designed as a cohesive and collaborative organization, with a culture of openness and sharing using team science based approaches. Technologies, such as those at issue here, are essential for this work.

> Transformative technologies are enabling the construction of three-dimensional maps of tissues with unprecedented spatial and molecular resolution. Over the next seven years, the NIH Common Fund Human Biomolecular Atlas Program (HuBMAP) intends to develop a widely accessible framework for comprehensively mapping the human body

> at single-cell resolution by supporting technology development, data acquisition, and detailed spatial mapping. HuBMAP will integrate its efforts with other funding agencies, programs, consortia, and the biomedical research community at large towards the shared vision of a comprehensive, accessible three-dimensional molecular and cellular atlas of the human body, in health and under various disease conditions.

HuBMAP Working Group, "The human body at cellular resolution: the NIH Human Biomolecular Atlas Program," Nature 2019, (available at https://www.ncbi.nlm.nih.gov/pubmed/31597973). The HuBMAP Consortium (https://hubmapconsortium.org/) actively works with other ongoing initiatives including the Human Cell Atlas, Human Protein Atlas, LifeTime (https://lifetime-fetflagship.eu/), and related NIH-funded consortia that are mapping specific organs (including the brain, lungs, kidney, and genitourinary regions) and tissues (especially pre-cancer and tumors), as well as other emerging programs.

Like projects carried out prior to the ability to generate single-cell data, these initiatives are expected to have a substantial impact on healthcare. As noted in the January 3, 2019 Science News, "Huge trove of British biodata is unlocking secrets of depression, sexual orientation, and more":

> Today, about 7000 researchers have registered to use UKB data on 1400 projects, and nearly 600 papers have been published….The result, every few days, is a new paper using UKB data to link particular gene variants to a disease or trait—arthritis, type 2 diabetes, depression, neuroticism, heart disease. "It's so easy for people who don't collect their own data," says statistical geneticist Danielle Posthuma of Vrije University in Amsterdam, who studies brain

> diseases. By combining data from the UKB and other collections, investigators can amass samples of a million people or more, amplifying the signal of gene variants with subtle effects. For some diseases, dozens or hundreds of genes appear to play a role. The genetic links are suggestive correlations; establishing cause and effect will take more genetics work and lab studies, which could reveal new disease pathways that might be drug targets.

Appx28556-67. Success is largely because of the data that has been amassed and made public.

As showcased on January 5, 2019 on National Public Radio, "Biological Cartographers Seek To Map The Trillions Of Cells In The Human Body," these technologies are presently being used to map the approximately 37 trillion cells in the human body. Appx28569-73. Therefore, scientists are now relying on powerful single-cell technology with high throughput at a reasonable cost to discover the kinds of cells that were not previously recognized.

The ability to access technologies and the price of such access are key drivers of research success. Prohibitive pricing or restricted access requires creative partnering of academic and non-profit research institutions with commercial parties, often delaying release of data, or reduction in data—as well as delay in the delivery of treatments and therapies to patients. Given the complex diseases and disorders (and concomitant treatments and therapies) this data may be able to unlock, the public interest strongly favors remedies that allow ongoing projects to continue efficiently, especially at academic and non-profit research

institutions while providing incentive to technology producers to work together, and with academic and non-profit partners, to ensure that suitable technology is available for both ongoing and new projects.

### B. Single-cell Technologies Are Not Fungible

The present case presents a particular challenge because the equipment embodying the technology at issue is not at all fungible. Given that fact, researchers are particularly affected by injunctive relief that limits their ability to continue using existing instruments in ongoing research as well as in new research that relates back to existing projects.

Broad has taken great care to evaluate and compare technologies, matching capabilities of each with the analysis needed, especially when precious samples (human, disease samples) are being evaluated. For single-cell RNA-seq platforms, the equipment is not comparable, and certainly not interchangeable, on key metrics including transcriptomic data obtained, number of cells that passed quality controls, throughput and barcoding. This is clear, for example, from a systematic comparison of the throughput, sensitivity, cost and other performance statistics for the three current major commercial platforms.

Table 1. Properties of single-cell RNA-seq platforms.

| | C1 96 | C1 HT | iCell8 | Chromium |
|---|---|---|---|---|
| Imaging capability | Yes | Yes | Yes, built-in with 4x magnification | No |
| Transcriptomic data | Full length | 3' | 3' | 3' or 5' |
| # of cells passed QC | 1,248/1,305 (96%) (read depth filtering, median -2SD) | 5,058/5,353 (94%) (read depth filtering, median-2SD) | 411/952 (43%) | 17,531/18,213 (96%) |
| Throughput | Up to 96 cells | Up to 800 cells | ~ 1000 cells | ~ 5000 cells |
| Selection of individual cell | Yes | Per row | Yes | No |
| UMI | No (optional) | No (optional) | No (optional) | Yes |
| ERCC spike-in | Yes | Yes | Yes | No |

Wang et al. "Comparative analysis of commercially available single-cell RNA sequencing platforms for their performance in complex human tissues," (available at https://www.biorxiv.org/content/biorxiv/early/2019/02/05/541433.full.pdf). As Table 1 shows, the unique designs of the various commercial platforms causes different results in throughput, individual cell trackability and final single-cell libraries when the single-cell platforms are tested.

10X users have reported similarly:

- Dr. Dana Pe'er of Memorial Sloan Kettering reports:

  > SCRI constantly evaluates new technologies as these emerge on the market, and we gave BioRad's ddSEQ careful consideration by rigorously testing it on our samples. We identified very serious issues with the ddSEQ and deemed it unsuitable for our needs….Simply put, I would not be able to execute a large part of my research agenda, nor that of many SCRI collaborating labs, without access to 10X Genomics products. The BioRad ddSEQ system, based on the current technical specifications, is not a viable alternative.

- Dr. Greg Gibson of Georgia Institute of Technology reports:

  The Center for Integrated Genomics in the School of Biology at Georgia Tech acquired the ddseq system from BioRad in the Summer of 2017. Despite several visits from the BioRad support team while getting the instrument up and running, we were unable to achieve acceptable results for the primary application that we are interested in. ….[O]ur colleagues in the Center for Cell Manufacturing at Georgia Tech have switched to the 10X system because it provides much greater throughout, greater consistency and repeatability, and for large projects is far more cost-effective. We retain the BioRad ddseq system for small studies of cell lines, and for pilot research by colleagues with less experience in single cell genomics, but to say it is equivalent is unambiguously false.

- Dr. Paolo Guerrero at MD Anderson Cancer Center reports:

  While there are other companies such as Bio-Rad provide [sic] substitute products for single cell sequencing, none of these other products is a true substitute. The Bio-Rad ddSeq doesn't offer the assortment of assays that 10X offers. But the big difference is the lack of performance of the Bio-Rad ddSeq. For example, the 10X's system has much higher cell capture rates, higher data quality and higher sensitivity. This is a difference that makes all the difference for my research. The ddSeq is completely inadequate.

- Dr. Leslie Kean at Dana-Farber/Boston Children's reports:

  If I had to switch to a new single cell system, it would do great harm to my research, which I would not be able to effectively carry out on Bio-Rad's or anyone else's products. 10X's platform is enabling our research program due to its inherent scale, speed and performance.

- Dr. John Carpten at Keck School of Medicine at USC reports:

  While there are other companies such as Bio-Rad provide [sic] similar products for single cell sequencing, none of these other products represent a true substitute for the types of assays that are

needed for our work, particularly the DNA sequencing and epigenetic (ATAC-seq) assays. The Bio-Rad ddSeq does not offer either single cell DNA or single cell ATAC. The lack of these products would eliminate some of the experiments that I have worked so hard to acquire funding and precious samples for. With regard to single cell RNA Seq, the 10X Genomics system has much higher cell capture rates, higher data quality, and higher sensitivity, providing more robust experimental designs. In essence, the ddSeq single cell RNA seq assay is inferior to the point that it is unusable for my purposes.

- Dr. Jonathan Weissman at UCSF reports:

  The 10x genomic single cell RNA-seq has proven to be an essential and irreplaceable component of the Perturb-seq and molecular recorder approaches. While there are other companies such as Bio-Rad that provide approaches for single cell sequencing, none of these other products would be even close to being an acceptable substitute for our studies. In particular, the Bio-Rad ddSeq simply doesn't offer the scale of assay required for my experimentation.

- Dr. Jason Bielas at Fred Hutchinson Cancer Research Center reports:

  It has come to my attention that Bio-Rad is seeking to prevent 10X from selling their single cell products. If this were to occur, my research, and that of my many collaborators, would be severely impacted as there is no other alternative, with an equivalent technical performance that can be substituted in its place.

- Dr. Calvin Kuo at Stanford School of Medicine reports:

  The Bio-Rad solution appears to be tied to particular sequencing machines which would be a constraint on our studies.

- Dr. Xiaole Shirley Liu at Dana-Farber Cancer Institute reports:

  The 10X's [sic] single cell system allows me to analyze cells in [a] manner not available from Bio-Rad or any other company.

- Dr. Hanlee Ji at Stanford University School of Medicine reports:

  > Importantly, many of the 10X Genomic reagents unique, seeing that there are no practical alternatives, commercial or otherwise, that would enable us to continue our research in discovering and improving new cancer therapies. Furthermore, a halt in sales of these unique reagents would have a major impact on biomedical research - it would practically stop many promising avenues of research leading to improving the treatment of a wide variety of diseases. Many research groups at Stanford and elsewhere rely on these unique reagents to investigate the cause and treatment of various diseases. Without them, much of this work will stop and it will be difficult to move forward.

- Michael Snyder at Stanford University School of Medicine reports:

  > I use 10X's single cell system to perform experiments on large numbers of single cells. ...This platform is essential for our $13M NIH-sponsored PreCancer Atlas grant as well as other projects. Indeed, we are now in a revolution in which genomes and other "omes" can be readily characterized, and I believe that 10X is leading this revolution for single cell analysis.
  >
  > While there are other companies such as Bio-Rad that provide commercial products for single cell sequencing, none of these other products can replace 10X. In developing my research plan and experimental protocols, I considered the pros and cons of a number of different single cell products, including 10X's Chromium system and BioRad's ddSEQ system. Each system gives different data and has different capabilities. I ultimately chose to use 10X's system because of its high cell capture rates, high data quality, high sensitivity, and low cost per cell.

Appx28886-911. Clearly, these 10X users do not consider the technology interchangeable. But the key point—not limited to 10X products—applies to any Essential Technology that is not fungible or interchangeable.

As can be seen in the literature, and echoed in the users' statements excerpted above, the single-cell genomics technology, generally and at issue here, and particularly 10X's products that are the subject here, have unique characteristics and capabilities, and are not fungible with the products of other manufacturers of single-cell genomics technology. Moreover, they cannot be readily replaced by Broad, its members, or its collaborators (including the NIH). Rather, the machines and methods are different, and 10X provides a benchmarked solution that optimizes parameters for high throughput uses.

In order to retain the value of the existing data generated in ongoing projects, there needs to be the ability of researchers at academic and non-profits to continue use of the same instruments and reagents as part of optimized protocols specific thereto. Quite simply, results obtained through the use of other instruments and other reagents will likely not be readily comparable.

Allowing an injunction that requires the relevant public, including researchers at Broad and other academic and non-profit research institutions currently engaged in this critical and high profile research, to switch instruments in the middle of projects will likely result in previous research work being discarded and the work having to be redone on new instruments and with new reagents. Even more to the public detriment, redoing the work can occur only after much time to learn and optimize protocols specific for the new instruments and new reagents—

in order to have the needed consistency. Further, during this period of changeover and re-optimization, precious biological samples (especially from humans) may be lost as they will not be timely used.

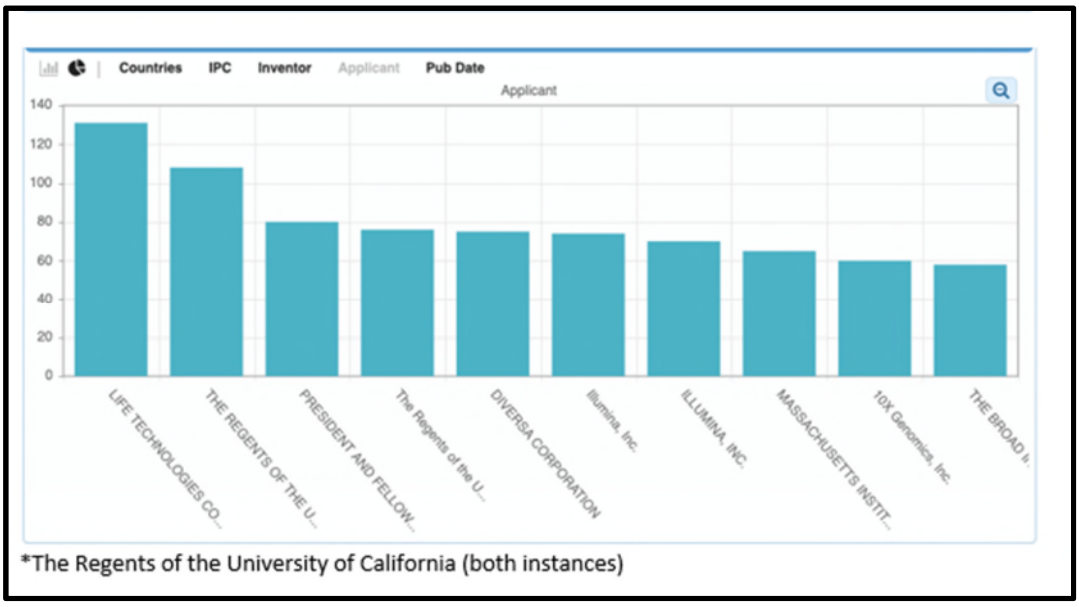
Moreover, if such a switch is required as a result of injunctive relief being awarded, and even if the project is such that the work can be re-done, Broad and other research institutions have no means to recover the monetary costs of re-doing research work nor to make up for the lost time. Entry of an injunction that prevents such ongoing research or makes it too expensive will cause irreparable harm to ongoing research at Broad and elsewhere, and therefore the public interest will be disserved (*e.g.*, because laboratory time and space would be devoted to re-doing past work rather than advancing ongoing research and causing harm that is not compensable by any amount of money).

Many publicly supported advances are reflected in any working system, and those elements need to be combined to enable the progress necessary to address today's complex challenges. An exchange for industry and academic developers and users would enable such cross licensing and co-development opportunities to emerge. This Court will pave the way for these parties and those in single-cell genomics space to join together by allowing all sales of the infringing products to continue, at least for academic and non-profit research use and as part of ongoing

Government funded projects, thus enabling the public to fully benefit from work it is funding.

### C. Single-cell Technologies Reflect Numerous Patented Elements

Single-cell technology is the culmination of many decades of effort, and the products sold by Bio-Rad and by 10X, as well as others in the field, incorporate numerous inventions and patented elements, which accounts in part for the plethora of disputes pending in this area. As shown immediately below, there are thousands of issued patents and pending patent applications with claims that are to "sequencing" and "barcode," "bead" or "oligonucleotide tag," from a search of published applications from the USPTO; and these are only a portion of the many aspects included in a successful instrument, along with advances in sample preparation and handling.



*The Regents of the University of California (both instances)

Key academic developers of such technologies include The Regents of the University of California, President and Fellows of Harvard College, and the Massachusetts Institute of Technology. Companies leverage this academic work heavily in building their commercial products; some even in-license such work, including Illumina (with at least 35 patent publications reporting government funding); Bio-Rad (at least seven patent publications reporting government funding); and Fluidigm (at least 23 patent publications reporting government funding).

Companies taking a license to patent rights held by academic institutions should be able to pursue a remedy from companies that infringe those rights; however, the remedy must be appropriate and take into account how the remedy affects the public interest, and here the relief should be monetary rather than injunctive.

The technology that is the subject of this litigation, e.g., the subject matter of US Patent No. 8,889,083 was developed through the use of US public monies. That mandates that the technology, including as may be embodied in 10X's products, be kept openly and fairly available to academic and/or not-for-profit organizations, such as Broad and Broad's collaborators around the world.

Often, patents themselves recite the use of Government funding. Here that is not the case; but, when this point was raised in the District Court (Appx28517-23),

plaintiffs-appellants did not deny that Government funding was instrumental to work that developed the technology of patents-in-suit, (see Appx29320-21) in view of various articles on the technology that, for example, state, "This work was supported by… Chicago MRSEC funded by the NSF." Chicago MRSEC is the Materials Research Science and Engineering Center (MRSEC) at the University of Chicago (see https://mrsec.uchicago.edu/about). The "NSF" is the National Science Foundation. (See https://www.nsf.gov/funding/pgm_summ.jsp?pims_id=5295, explaining NSF funding of MRSECs).

Beyond the University of Chicago and those noted above, Stanford also has researchers who are "developing new approaches to biological measurement and applying these approaches to problems of both fundamental and medical interest", including single-cell genomics." (See, e.g., https://quakelab.stanford.edu/) And, Fluidigm touts the efforts of co-founder Stephen Quake, not the inventors of the patents at issue here from University of Chicago, as "among the first to pioneer the use of microfluidic tools to study single-cell genomics." (See, e.g., https://www.fluidigm.com/articles/dr-stephen-quake). In addition, Fluidigm recently initiated litigation against Ionpath, another genomics technology provider. Stanford has filed multiple dozens, if not hundreds, of patent applications in this general area, including as licensed to Fluidigm.

In advance of specific initiatives, and to make possible current initiatives such as the Cancer Moonshot discussed above, the US Government has supported the Human Genome Project and countless efforts that have combined to develop Essential Technologies used today to advance biomedical research. Academic institutions such as discussed herein have some degree of public support, and many of these programs are supported directly by Government grants to advance and use single-cell technology.

The suite of technologies that are commercially available today, including the technologies of both parties, would not have been possible without US Government support of development and application on key projects.

## V. ARGUMENT

To enter a permanent injunction under the facts and circumstances here would do a great disservice to the public.

It is well understood that courts "may grant injunctions in accordance with the principles of equity to prevent the violation of any right secured by patent, on such terms as the court deems reasonable." 35 U.S.C. § 283. Key in that statutory grant of authority is that the principles of equity govern and the terms of any injunction must be reasonable.

Specifically, a plaintiff seeking a permanent injunction must satisfy a four-factor test and demonstrate: (1) an irreparable injury; (2) inadequacy of remedies at

law; (3) the balance of hardships between the parties; and (4) "that the public interest would not be disserved by a permanent injunction." *eBay Inc. v. MercExchange, LLC*, 547 U.S. 388, 391 (2006).

Here, Broad focuses on the public interest factor. The public interest is, indeed, "disserved by a permanent injunction" that restricts access to the technology by researchers at academic and non-profit research institutions when, as here, the technology is Essential Technology, the available alternatives are not fungible, and the patents at issue are the result of Government funded research.

### A. The District Court Got It Half Right

In granting an injunction, the District Court acknowledged the general legal principles including that public interest generally favors upholding patent rights ("It is generally in the public interest to uphold patent rights. *Broadcom [Corp. v. Qualcomm Inc.],* 543 F.3d [683] 704 [(Fed.Cir.2008)](citing *Rite-Hite Corp. v. Kelley Co.*, 56 F.3d 1538, 1547 (Fed. Cir. 1995)).") Appx66. The Court noted that injunctions can be denied in order to protect the public interest ("However, '[i]f a patentee's failure to practice a patented invention frustrates an important public need for the invention, a court need not enjoin infringement of the patent. Accordingly, courts have in rare instances exercised their discretion to deny injunctive relief in order to protect the public interest.' *Rite-Hite,* 56 F.3d at 1547 (internal citations omitted)."). Appx66-67.

The District Court agreed that interrupting long term studies was a compelling reason for considering denying an injunction, and attempted to address this harm by allowing continued sales of reagents:

> 10X's main argument is that its customers, many of whom are in the middle of long-term studies, would lose valuable data and funding if forced to stop using their 10X systems and switch to new systems mid-study. That argument would be compelling if it were true.

(Appx67 (citations omitted)).

Broad agrees with the District Court's conclusion that the argument is compelling. However, Broad submits that the "compelling" argument is broader than that noted by the District Court.

The District Court focused on the perceived improved performance of new products to the exclusion of weighing the lack of fungibility so much so that the Court concluded that the public interest weighed in favor of injunctive relief:

> To extent that the public may be harmed because there are no current alternatives to 10X's products, both 10X and Bio-Rad have indicated that they will be releasing new products soon. As discussed, 10X's design-around is largely complete and expected to work as well as its existing products. Bio-Rad has also asserted that it expects to release a new system this year "to leap-frog 10X in performance." Therefore, I find the public interest weighs in favor of granting injunctive relief

(Appx67 (internal citations omitted)).

The equipment at issue here is not interchangeable, and the equipment and product of 10X, Bio-Rad and the others in this field are tailored differently. If

indeed Bio-Rad introduces a more robust system that leapfrogs 10X systems in performance in the areas key to the 10X instrument (as indicated by Bio-Rad), that new platform will be able to compete in the marketplace for new projects and further uses as the metrics are established and protocols optimized for droplet applications and single-cell processing. This future adoption of supposedly superior instruments will not be advanced by derailing ongoing projects or unnecessary re-commitment of funds to buy other systems available today. This future adoption will succeed on its own merits. However, and without regard to the particular instruments at issue here, because the instruments at issue are not fungible, an injunction that affects ongoing research at academic and non-profit institutions disserves the public interest no matter if improved equipment may be available now or shortly.

In addition, the District Court did not adequately consider the public equities implicated by an injunction on Essential Technology made with public support, Government funding, that is no longer available for the uses intended, particularly for research that is also supported by Government funding.

### B. Essential Single-cell Technologies Should Not Be Enjoined

Single-cell Technologies were developed and are being used to understand human health and to enable diagnosing, monitoring, and treating disease. Broad and others extensively use, and need to continue to use, single-cell genomics

technology such as at issue here. For the research community, the technology at issue here is Essential Technology.

While the right to exclude others is an integral concept in property law, courts have broad discretionary powers under the patent statute to determine whether the facts warrant the entry of an injunction and to determine the scope of such an injunction. *Joy Technologies, Inc. v. Flakt, Inc.*, 6 F.3d 770, 772 (Fed.Cir.1993). An injunction is proper only to the extent that it prevents violation of patent rights and may not be punitive. *Id*. Moreover, courts exercise their discretion and deny injunctive relief when the harm to the public from granting the injunction outweighs the patentee's individual right to exclude. *Wesley Jessen Corp. v. Bausch & Lomb, Inc.*, 209 F.Supp.2d 348 (D.Del. 2002); see also, e.g., *City of Milwaukee v. Activated Sludge*, 69 F.2d 577 (7th Cir. 1934)(denying injunction that would leave community without means to dispose raw sewage other than by polluting its waters and endangering health); *Hybritech, Inc. v Abbott Labs.*, 1987 WL 123997 (C.D.Cal. 1987), aff'd 849 F.2d 1446 (Fed.Cir. 1988)(tailoring injunction so that it would not stop the supply of medical test kits to current users).

Given the numerous patents in this area, each incrementally advancing these Essential Technologies, to allow each an injunction would remove all of the products. Bio-Rad and 10X are each asserting in various actions in various forums

that the other's technology should be enjoined; others in the field are likewise asserting patents and seeking injunctions. This is not in the public interest. Nor is it in the public interest for ongoing royalties to be unreasonably stacked.

The possibility of such extreme remedies encourages the parties to invest in legal shenanigans rather than further advancement of the technology, which is contrary to the purpose of the patent system. This wasted effort is clearly not in the public benefit.

### C. The Public Should Receive Benefit From Its Investments

In Broad's view, industry plays an essential role in making commercial products available to speed research (such as reagents and technologies) and to benefit patients directly (such as diagnostics and therapeutics). Industry is often able to undertake efforts that cannot be readily undertaken in academia—because, for example, they require funding at a scale that can typically be obtained only from private investment; specialized scientific expertise about drug development that may not be readily available in academia; or the ability and infrastructure to run large clinical trials.

Clearly, academic non-profit research institutions and industry are at different positions in the biomedical ecosystem. However, for this ecosystem to function properly, academic and non-profit research institutions and industry should not be at loggerheads, but should function symbiotically. While industry is

an important part of this ecosystem, industry should not be a bottleneck through patent-based permanent injunctions or onerous royalty rates. Such a bottleneck is to the detriment of research and the academic and non-profit research institutions, such as Broad, that explore fundamental questions and work on risky, early-stage projects that often lack clear immediate or direct economic return. This is especially so if the industry-controlled patents being enforced were generated through Government funding, as in this case. Research that is supported by Government funding (public monies) should not be the basis of patents for research tools where the patents are then used to restrict the ability for the public and research institutions to use those very tools—especially as to further Government projects. Government funding dictates that the tools developed be made available for use by the public. (Broad expresses no view on whether commercial, for-profit entities should be treated differently, especially where the technology is used directly to support their profitability.)

It is therefore respectfully asserted that a key fact, namely, that Government funding was used to develop the subject matter at issue here, must be taken into account. It is further respectfully asserted that because Government funding (public monies) was used to develop patents-in-suit, and these patents are for research tools that are necessary for public interest research (including such research as discussed herein), the patents-in-suit should not be used by Bio-Rad to restrict the

ability of the public, as represented by academic and/or not-for-profit research organizations, such as Broad and Broad's members and collaborators (including the NIH) to use and to continue to use those research tools. Quite simply, as an equitable matter, the Government funding dictates that the tools developed by that funding, i.e., the subject matter of the patents-in-suit, be made available for use by the public; and, that to do so means that the Court should not grant any permanent injunction as to 10X's products that restricts that availability to the relevant public.

By allowing the single-cell genomics technology at issue in the subject litigation, including as embodied in 10X's products, to continue to be available, the Court will prevent serious setbacks in biomedical research and thereby advance the public interest. And, of course, the public interest is one of the reasons that injunctions are available in certain circumstances and not available in others as well as public interest informing any appropriate ongoing royalty.

Here, for the ongoing projects of academic and research institutions and other non-profit activities, injunctions that limit or destroy the ability to conduct research (especially when the patented technology has, at least in part, been the fruits of public funds/Government grants), are contrary to the public interest.

By rejecting an injunction, Broad submits that this Court can pave the way for all parties (not just the litigants here) in the single-cell genomics space to join together, thereby enabling robust development of technology in this space. Broad

is available to work with 10X and Bio-Rad and other academic and commercial parties and patent holders to come together and collectively work together to create an exchange through which patent barriers to using single-cell genomics technology may be addressed, while still recognizing the need for patents as an important reward for the risks of research. As an additional benefit to the parties, the public, and the courts, not entering an injunction and so allowing research to continue could also result in a reduction of patent litigation around single-cell genomics technologies, and advance the interests of justice.

To encourage academic non-profit research institutions and industry to function symbiotically, Broad ensures that its work ultimately benefits patients, by (i) engaging in scientific collaborations with industrial partners who share Broad's vision, and (ii) responsible licensing of innovations to industry.

### D. Remedies Should Not Be Harmful To Progress

Certainly no less important, the proliferation of patents is itself often a problem, for reasons as discussed in the standard-setting area, which are applicable here as well:

> Many thousands of patents can thus read on various aspects of a standard. Each patent that claims any one of the myriad technologies imbedded in the adopted protocol is thus "standard essential." To adopt a standard without infringing proprietary technologies, then, a manufacturer must obtain the necessary licenses.

Hon. Maureen K. Ohlhausen, *The Elusive Role of Competition in the Standard-Setting Antitrust Debate*; 20 Stan.Tech.L.Rev. 93, 124 (2017). Here also, end users should not have to to work their way through a patent thicket. Indeed, injunctions based on patents for essential technologies can be inefficient and introduce a complicating factor:

> a property rule is not always the most efficient way to protect an entitlement. For example, when transaction costs rise to the point that ex ante bargain is infeasible, then imposing a punitive sanction on an infringer ex post will not spur licenses ex ante. It would bestow a windfall on the property owner.

*Id*. at 126.

Even without a contractual relationship as is present with standard setting organizations, there are valuable public interest reasons at issue here that the Court should consider in evaluating what remedy is appropriate.

## VI. CONCLUSION

For the foregoing reasons, because of the public interest, the Court should reject an injunction. In a case, such as here, an injunction protects private appropriation of a wealth of publicly funded development and research that was necessary to the patents at issue, to the clear detriment of public good. Patents should be used to maintain innovation—allowing multiple parties to develop

products enabling further research and to build new technologies—not to prevent the distribution of the fruits of research, as is being done here.

A fair remedy can be achieved without sacrificing the "reward" (and incentive) for expensive private development efforts. The Court should advance the public interest and the interests of justice, by requiring a remedy that provides reasonable incentive without an injunction that denies access to technology essential to ongoing and critical biomedical research.

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Respectfully submitted,

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## CERTIFICATE OF SERVICE

I certify that I served a copy of the foregoing **Brief for The Broad Institute, Inc. As Amicus Curiae In Support Of Neither Party** on counsel of record by electronic means by filing it via CM/ECF.

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## CERTIFICATE OF COMPLIANCE

This brief complies with the type-volume limitation of Fed.Cir.R. 29 and 32(a) because it contains 6970 words, excluding the parts of the brief exempted by Fed.R.App.P. 32(f). The undersigned used Microsoft Word 2016 to compute the count.

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