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FROST & SULLIVAN BEST PRACTICES AWARD

SINGLE-CELL ANALYSIS - GLOBAL

New Product Innovation 2019

LumaCyte™
Lighting the way to cell discovery

FROST & SULLIVAN
2019 BEST PRACTICES AWARD

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Background and Company Performance

Industry Challenges

Single-cell analysis is transforming disease understanding due to the growing recognition that cell populations harbor far more heterogeneity than expected. Applications such as rapidly measuring viral infectivity and determining infectious virus concentration are critical for both vaccine and cell/gene therapy development and production, as well as for monitoring the safety and efficacy of initiating effective containment efforts for emerging infectious diseases or a pandemic. The predicted utility of single-cell analysis for a host of disease types fuels hundreds of experimental clinical trials evaluating this approach for cancer and infectious diseases. As a result, demand for single-cell analysis tools is soaring. Analysts estimate the value of the global market for single-cell analysis will reach $1.3 billion by 2022.[1]

The use of biological materials, like mammalian cell lines, risks infection from adventitious agents such as viruses. Current cytometry approaches for measuring viral infectivity (e.g., cell-based assays and polymerase chain reaction) are labor-intensive, difficult to standardize, and can create bottlenecks in the development process, with in-process assay times ranging from one to three days. Furthermore, conventional viral quantification systems that leverage fluorescently labeled antibodies can require up to a year to develop and test new viruses. Consequently, it is challenging to respond to emerging and rapidly-changing threats.

Additionally, current cell analysis and sorting methodologies rely almost exclusively on antibody labeling of surface markers. These are inadequate antigens because they can change over time, between patients, and after treatment. Harsh isolation processes and mechanical issues may hamper cell viability and structural integrity, which means conducting downstream analysis on cells that no longer look or function the way they did in vivo.[2] For instance, antibody markers can cause membrane changes and inflammatory responses, resulting in cell damage, death, or significant experimental bias.

Another drawback to these methods is the large sample input required—at least tens of thousands of cells per sample. While current methodologies can process large quantities of single cells, they can only interrogate a few biomarkers from each cell.[3] Widespread capture inefficiencies limit a comprehensive view of the original cellular population. Also, labeling antibodies is only possible for known cell types and the cells in interest possibly do not have a known or available antibody label for many applications. For example, technologies such as mass cytometry help analyze only about 35 markers despite being expensive and requiring significant expertise. Finally, scientists often identify an issue after completing costly genomic, transcriptomic, or proteomic analysis processes.

[1] *Global Single Cell Genomics and Proteomics Market, Forecast to 2023* (Frost & Sullivan, September 2019)
[2] Nguyen QH, Pervolarakis N, Nee K, and Kessenbrock K. "Experimental Considerations for Single-Cell RNA Sequencing Approaches. Front Cell Dev Biol. 2018 Sep 4;6:108.
[3] Heath JR, Ribas A, and Mischel PS. "Single-cell analytic tools for drug discovery and development." Nat Rev Drug Discov. 2016 Mar; 15(3): 204–216.

The impact of sub-optimal cytometry techniques is particularly severe on:

- *Biomanufacturing*. Biomanufacturing firms require rapid detection solutions that provide quantitation of viral vector-based production of proteins and antibodies during research and development (R&D) and manufacturing.

- *Cancer.* Cancer applications include identifying and characterizing T-cell activation, tumor cells, tissues, and circulating tumor cells. Tumor cell analysis is critical for understanding cancer biology and potential response to drug candidates.

- *Cell and gene therapy.* The biomanufacturing process for chimeric antigen receptor (CAR) T-cells (and related cell therapies such as induced pluripotent stem cells [iPSCs]) is challenged by difficult, labor-intensive steps that require highly skilled scientists and bioengineers. Existing techniques used to develop and manufacture these lifesaving treatments currently give rise to time delays, failures, and significant errors across the process, preventing the efficient and cost-effective production of these therapies. Complete tracking of key quality biomarkers will enable process optimization and improvements correlating to the success or failure of the patient therapy.

- *Phenotypic drug discovery.* The use of labels in pre-clinical screening may cause drug failure in human clinical trials. Conversely, many drug candidates might be improperly discarded based upon incomplete or flawed data. Phenotypic drug discovery applications include pre-clinical drug candidate screening, toxicology, and cell biology.

- *Viral infectivity.* Viral quantification plays an essential role in recombinant protein production, viral vaccine production, and infectious disease studies. Viral quantification methods include the viral plaque assay, fluorescent focus assay, and endpoint dilution assay—each of which relies on many viral dilutions added to cells to measure infectivity. However, the methods are often subjective, difficult to standardize and reproduce, and require significant time and skilled labor. This decreases the efficiency of research and development efforts and drives up costs. Other methods, such as quantitative polymerase chain reaction (qPCR) and enzyme-linked immunosorbent assay (ELISA), have good reproducibility and are less time-consuming but rely on viral-specific molecules that are expensive and time-consuming to produce.

Innovative tools are necessary to realize the potential of single-cell analysis. Vendors who can provide a cost-effective cytometry approach maintaining cell structure and viability while capturing all the cells contained in the sample will enjoy rapid market adoption. Other best practices include working with scientists in academic and translational laboratories for a third-party review and validation of new products.

New Product Attributes and Customer Impact of LumaCyte

LumaCyte Radiance™ +Autosampler

Source: LumaCyte

Founded in 2012 and headquartered in Charlottesville, Virginia, LumaCyte, LLC (LumaCyte) is an innovative advanced research and bioanalytics instrumentation company. LumaCyte manufactures label-free single-cell analysis and sorting instrumentation that does not require antibody or genetic labeling for cellular analysis to characterize, select, and sort cell samples.

The company's flagship product, Radiance®, is an automated, high-content, label-free single-cell analysis and sorting platform that measures single-cell characteristics such as optical force via cell velocity changes, refractive index, shape, and deformability. It does this by collecting and automatically analyzing images. Dozens of unique parameters based on biochemical and biophysical cellular properties are collected simultaneously and can be used with multivariate models to better understand cellular systems and develop powerful predictive models.

The platform leverages LumaCyte's revolutionary technology, Laser Force Cytology™ (LFC™), to measure optical and fluidic forces and subsequently identify and measure intrinsic cellular properties. LFC's novel label-free approach empowers the discovery, characterization, and sorting of cells from biological samples based upon their inherent physical, biochemical, and biological characteristics. As a result, LumaCyte can offer direct-from-cell samples to analysis/sorting with no antibody staining, processing, antibody-induced phenotype changes, or fixation. Consequently, LFC technology provides customers with a rapid, automated cell-based assay that delivers significant improvements in speed, accuracy, and sensitivity.

Radiance offers a unique, label-free approach to single-cell analysis that gives researchers significant improvements in the quality and speed of their cell-based assays. By measuring intrinsic biophysical and biochemical properties of individual cells, cellular changes due to viral infection or transfection for example, are rapidly, repeatably, and objectively quantitated. Radiance's label-free technology combines optical pressure, microfluidics, and imaging to discover and sort new cells and phenotype changes. Radiance reduces sample preparation time and lowers the cost per test by enabling the measurement of subtle changes in cells.

LumaCyte's label-free approach enables users to avoid costly, labor-intensive, and difficult validation processes associated with antibody use while providing an unbiased assessment of cell populations. Furthermore, Radiance's small footprint allows it to fit on nearly every laboratory bench.

Capabilities include the analysis of untreated cells with minimal reagent costs, discovery and real-time sorting of new cells and phenotypes, unbiased biophysical measurements of

novel physical properties, detection of new cell states (such as infection, cancer, and differentiation), and reduction of sample preparation time—all of which minimize total analysis time and cost.

Applications for LumaCyte's technology include viral infectivity for cell and gene therapy, vaccine development and manufacturing, cancer biology R&D, iPSCs, infectious disease, and pre-clinical drug discovery. Other label-free applications include gene expression, cell clearance, and epigenetics, as well as quality control and process optimization for biomanufacturing.

Frost & Sullivan's research reveals LumaCyte's new technology is particularly adept at transforming vaccine development through faster viral detection and has the potential to speed vaccine response to emerging infectious diseases. In 2019, the company won the Best Production/Process Development Vaccine Industry Excellence Award over multi-billion dollar companies. Since launching Radiance in 2017, LumaCyte's customer demand currently focuses on rapid viral infectivity measurements for vaccine R&D and production and label-free biomarker phenotyping for cell therapy biomanufacturing. However, the company's breakthrough technology is equally useful for applications in cancer and cell therapy, drug discovery, and iPSC research. Frost & Sullivan firmly believes that the expansion into new applications will further escalate uptake of this innovative technology.

How It Works

LFC is sensitive to agents that perturb cellular structures or change the biochemical composition. Hence, the technology supports high-quality, near real-time viral infectivity as well as a host of other cellular measurements in a small fraction of the time, labor, and cost compared to traditional assays. LumaCyte's cell analysis and sorting philosophy rest on measuring the native response of a cell to its environment and the ability to detect subtle changes in cell morphology, biochemistry, and biophysical properties.

Radiance's multi-variant capabilities allow cell health to be monitored at the beginning of an infection process and it can measure dozens of multivariate parameters—providing users uniquely comprehensive and rapid results that can help eliminate failed batches across bioproduction efforts. The technology also uses a laser wavelength to analyze and sort cells of interest without using labels. As optical forces correlate with changes in the intrinsic properties of the cells passing through the system, there is no need for antibody or genetic labels. As a result, LFC eliminates research bias when investigating changes in cell populations, a major advantage over other technologies on the market.

Furthermore, LumaCyte's microfluidic technology gently handles cells, resulting in reduced cell damage when compared to other technologies. This leads to higher recovery rates of viable cells, which is a crucial consideration for sensitive cells or small samples. Radiance also evaluates single, suspended cells directly, capturing robust multivariate data parameters to analyze physical properties, including eccentricity, shape, surface morphology, refractive index, and internal structure. The system can automatically collect and analyze data and identify changes across cell populations. Combined laser force

measurements and imaging facilitate robust analysis that is not possible using conventional label-based flow cytometry.

In a peer-reviewed study, researchers from Thermo Fisher Scientific and LumaCyte demonstrated two scenarios for improved detection of viral infection of vesicular stomatitis virus (VSV)—commonly used for vaccine production—using Radiance. The first scenario examined cells already infected with VSV, with Radiance determining viral infectivity between five and ten minutes. In the second scenario, researchers used Radiance to determine rapid viral infectivity in crude or purified virus solutions.

Stakeholders experienced a turnaround time of 16 hours using Radiance compared to 72 hours using conventional endpoint dilution methods. The capability is game-changing as Radiance offers researchers real-time process control and monitoring of viral infectivity—something of great value to the vaccine industry and not currently possible using standard techniques. In addition to the shorter incubation period, the results do not rely on operator interpretation and require less labor, further reducing costs.[4]

Applications include:

- *Adventitious virus detection.* Radiance can monitor mammalian cell production by measuring multiple parameters simultaneously to find adventitious agents. It also rapidly detects biological or chemical contamination in the cell population. As Radiance does not rely on antibodies or other prior knowledge, the technology can expose previously unknown threat agents.

- *Biomanufacturing.* Radiance can quickly and cost-effectively detect viral infection during manufacturing processes, making it invaluable for real-time process monitoring, optimization, and scale-up. For example, it can monitor biological production systems in periodic sampling or continuous monitoring configurations, as well as mammalian, insect, yeast, or other cells for production parameters.

- *Cancer and Cell Therapy.* In cancer applications, Radiance can identify changes in cell phenotype in response to drug candidates in pre-clinical research and testing. Additionally, it can provide label-free T-cell activation detection and analysis and quantification of the tumor cells' response to drug candidates. Radiance also identifies and characterizes cancerous cell phenotypes and quantitatively measures the changes in the cell's cytoskeleton—known to correlate with metastatic potential. Using LFC and Radiance for cell therapy can also speed the biomanufacturing process, drive costs down, and ensure therapy effectiveness while maintaining patient safety. Radiance has application in all stages of the biomanufacturing process, including qualification/testing of patient samples and expansion/growth of the modified T-cells.

[4]"Rapid Quantification of Vesicular Stomatitis Virus in Vero cells using Laser Force Cytology", Colin G. Heberta, Nicole DiNardob, Zachary L. Evansa, Sean J. Harta, and Anna-Barbara Hachmannb* https://www.sciencedirect.com/science/article/pii/S0264410X(18)312374 It appears in Vaccine, Volume 36, Issue 41 (2018), Published by Elsevier.

- *Determining drug candidacy and phenotypic drug discovery*. Due to its ability to detect subtle cell changes, LumaCyte's Radiance instrument enables better drug candidate assessment through enhanced evaluation of phenotypic effects on cells without using labels.

- *iPSC research.* Radiance detects and sorts cells based on subtle intrinsic differences, such as deformability, aiding in the analysis of cell population composition and differentiation state.

- *Infectious disease.* Radiance can rapidly measure changes in sepsis and disease-related red blood cell deformability, discover and isolate phenotypically altered cells due to infection, and measure host response to viral infection and bacterial exposure. Through the identification and collection of previously unknown cell populations undergoing subtle phenotypic changes, it is possible to develop new biomarkers to improve research as well as diagnostic speed and accuracy.

- *Virus infectivity*. Radiance can quickly assess recombinant adenovirus infectivity in less than 24 hours of incubation with the target cells. The technology can monitor production via sequential aliquots or through continuous monitoring of the infection and production process. Radiance can also monitor the infectivity of live and attenuated viruses both during and after production to verify killed or inactivated viruses. Radiance has been studied across more than 30 viruses and cell lines, including AAV, lentivirus, and retrovirus.

Aside from Radiance, LumaCyte also offers powerful ancillary products, including Illuminate™, LumaCyte's software suite for instrument control, data analysis, and data conversion. Illuminate consists of three applications—Instrument, Analyzer, and Sampler—to seamlessly integrate with modern laboratory procedures and practices.

- Instrument offers an intuitive control and monitoring interface for Radiance instrumentation, the ability to develop custom interfaces for specific users, samples, and tasks, and advanced hardware logging and instrument health reports.

- Analyzer includes a highly customizable graphical user interface, sample population selection tools and masks for extensive data mining and correlation examination, and simple data export from an entire 96 well-plate.

- ReportR, LumaCyte's end-to-end cloud-based platform provides research teams the ability to analyze multiple experiments at once and rapidly visualize data all within minutes of experimental completion.

- +Autosampler can significantly increase sample analysis throughput, allowing unattended and automated analysis of up to 96 samples at a time. Autosampler is precision-tuned for microfluidic flow rates and is fully programmable via Illuminate Sampler and seamlessly integrates with Radiance's Illuminate software suite.

Leveraging Partnership to Spur Innovation

In 2017, LumaCyte joined the National Institute for Innovation in Manufacturing Biopharmaceuticals (NIIMBL) to translate existing technologies into biomanufacturing contexts. In 2019, researchers at Carnegie Mellon University collaborated with LumaCyte and Genentech to develop an advanced biomanufacturing technology for adventitious agent testing. The research received $1.5 million in funding through NIIMBL to further advance and test technologies to improve the safety testing of biologic medicines during production and before batch release.

The project aims to rapidly and accurately detect viral infectivity in biopharmaceuticals. Currently, LumaCyte is also working toward broadening its cell and gene therapy applications and is in the process of launching a new product, ReportR, a cloud-based analytics platform. ReportR allows users to easily upload and process data from the cloud, automatically formatting results into a PDF format for subsequent transmission.

Frost & Sullivan notes that top five global life sciences, contract development, and manufacturing organizations are applying the company's innovative technology in their R&D and biomanufacturing processes. The European biopharma market is also indicating a high demand for Radiance. To that end, LumaCyte recently received CE marking and looks to support future European sales requests.

The company's growing customer base finds it via NIIMBL, industry publications, and conferences. LumaCyte recently announced the third doubling of its manufacturing and laboratory space to supply customer demand. The company expects to grow another 60% by early 2020 and remains focused on providing researchers with a transformational diagnostic tool that can accelerate medical and pharmaceutical discoveries through novel cell analysis and sorting.

Conclusion

Current single-cell analysis methodologies are limited, significantly hindering clinical research and diagnosis, prognosis, and treatment. LumaCyte's groundbreaking Laser Force Cytology™ (LFC) innovation accelerates therapies and analytical insights through enabling the discovery and characterization of new cells and phenotypes across applications. With the recent launch of Radiance®, its flagship, label-free single-cell analysis platform, the company can cost-effectively optimize viral quantification methods—leading to easier sample preparation, shortened detection time, and high-quality and objective data. For its thought leadership, exceptional value proposition, and potential to revolutionize cytometry in applications ranging from biomanufacturing to cancer biology research and drug discovery and development, LumaCyte is recognized with Frost & Sullivan's 2019 Global New Product Innovation Award in the single-cell analysis market.

Significance of New Product Innovation

Ultimately, growth in any organization depends upon continually introducing new products to the market and successfully commercializing those products. For these dual goals to occur, a company must be best-in-class in three key areas: understanding demand, nurturing the brand, and differentiating from the competition.

Understanding New Product Innovation

Innovation is about finding a productive outlet for creativity—for consistently translating ideas into high-quality products that have a profound impact on the customer.

Key Benchmarking Criteria

For the New Product Innovation Award, Frost & Sullivan analysts independently evaluated two key factors—New Product Attributes and Customer Impact—according to the criteria identified below.

New Product Attributes

Criterion 1: Match to Needs
Requirement: Customer needs directly influence and inspire the product's design and positioning.

Criterion 2: Reliability
Requirement: The product consistently meets or exceeds customer expectations for consistent performance during its entire life cycle.

Criterion 3: Quality
Requirement: Product offers best-in-class quality, with a full complement of features and functionalities.

Criterion 4: Positioning
Requirement: The product serves a unique, unmet need that competitors cannot easily replicate.

Criterion 5: Design
Requirement: The product features an innovative design, enhancing both visual appeal and ease of use.

Customer Impact

Criterion 1: Price/Performance Value
Requirement: Products or services offer the best value for the price, compared to similar offerings in the market.

Criterion 2: Customer Purchase Experience
Requirement: Customers feel they are buying the most optimal solution that addresses both their unique needs and their unique constraints.

Criterion 3: Customer Ownership Experience
Requirement: Customers are proud to own the company's product or service and have a positive experience throughout the life of the product or service.

Criterion 4: Customer Service Experience
Requirement: Customer service is accessible, fast, stress-free, and of high quality.

Criterion 5: Brand Equity
Requirement: Customers have a positive view of the brand and exhibit high brand loyalty.

Best Practices Recognition: 10 Steps to Researching, Identifying, and Recognizing Best Practices

Frost & Sullivan analysts follow a 10-step process to evaluate Award candidates and assess their fit with select best practice criteria. The reputation and integrity of the Awards are based on close adherence to this process.

STEP		OBJECTIVE	KEY ACTIVITIES	OUTPUT
1	**Monitor, target, and screen**	Identify Award recipient candidates from around the globe	• Conduct in-depth industry research • Identify emerging sectors • Scan multiple geographies	Pipeline of candidates who potentially meet all best-practice criteria
2	**Perform 360-degree research**	Perform comprehensive, 360-degree research on all candidates in the pipeline	• Interview thought leaders and industry practitioners • Assess candidates' fit with best-practice criteria • Rank all candidates	Matrix positioning of all candidates' performance relative to one another
3	**Invite thought leadership in best practices**	Perform in-depth examination of all candidates	• Confirm best-practice criteria • Examine eligibility of all candidates • Identify any information gaps	Detailed profiles of all ranked candidates
4	**Initiate research director review**	Conduct an unbiased evaluation of all candidate profiles	• Brainstorm ranking options • Invite multiple perspectives on candidates' performance • Update candidate profiles	Final prioritization of all eligible candidates and companion best-practice positioning paper
5	**Assemble panel of industry experts**	Present findings to an expert panel of industry thought leaders	• Share findings • Strengthen cases for candidate eligibility • Prioritize candidates	Refined list of prioritized Award candidates
6	**Conduct global industry review**	Build consensus on Award candidates' eligibility	• Hold global team meeting to review all candidates • Pressure-test fit with criteria • Confirm inclusion of all eligible candidates	Final list of eligible Award candidates, representing success stories worldwide
7	**Perform quality check**	Develop official Award consideration materials	• Perform final performance benchmarking activities • Write nominations • Perform quality review	High-quality, accurate, and creative presentation of nominees' successes
8	**Reconnect with panel of industry experts**	Finalize the selection of the best-practice Award recipient	• Review analysis with panel • Build consensus • Select recipient	Decision on which company performs best against all best-practice criteria
9	**Communicate recognition**	Inform Award recipient of Award recognition	• Present Award to the CEO • Inspire the organization for continued success • Celebrate the recipient's performance	Announcement of Award and plan for how recipient can use the Award to enhance the brand
10	**Take strategic action**	Upon licensing, company is able to share Award news with stakeholders and customers	• Coordinate media outreach • Design a marketing plan • Assess Award's role in future strategic planning	Widespread awareness of recipient's Award status among investors, media personnel, and employees

The Intersection between 360-Degree Research and Best Practices Awards

Research Methodology

Frost & Sullivan's 360-degree research methodology represents the analytical rigor of our research process. It offers a 360-degree-view of industry challenges, trends, and issues by integrating all 7 of Frost & Sullivan's research methodologies. Too often companies make important growth decisions based on a narrow understanding of their environment, leading to errors of both omission and commission. Successful growth strategies are founded on a thorough understanding of market, technical, economic, financial, customer, best practices, and demographic analyses. The integration of these research disciplines into the 360-degree research methodology provides an evaluation platform for benchmarking industry participants and for identifying those performing at best-in-class levels.

360-DEGREE RESEARCH: SEEING ORDER IN THE CHAOS

About Frost & Sullivan

Frost & Sullivan, the Growth Partnership Company, enables clients to accelerate growth and achieve best-in-class positions in growth, innovation and leadership. The company's Growth Partnership Service provides the CEO and the CEO's Growth Team with disciplined research and best practice models to drive the generation, evaluation, and implementation of powerful growth strategies. Frost & Sullivan leverages more than 50 years of experience in partnering with Global 1000 companies, emerging businesses, and the investment community from 45 offices on six continents. To join our Growth Partnership, please visit http://www.frost.com.