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Flagship BIOSCIENCES

2018 Global AI-based Pathology Solutions in Immuno-oncology Technology Innovation Award

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2018 BEST PRACTICES AWARD

GLOBAL AI-BASED PATHOLOGY SOLUTIONS IN IMMUNO-ONCOLOGY TECHNOLOGY INNOVATION AWARD

2018 BEST PRACTICES AWARDS

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Immuno-oncology: New Frontier in Personalized Cancer Care

Cancer is a major cause of mortality and morbidity worldwide. The International Agency for Research on Cancer estimates over 16 million new cancer cases by 2020, with about 10 million people per year dying from the disease—beyond 27,000 people per day.[1]

Over the last decade, the oncology field entered a care paradigm shift from the 'one-size-fits-all' treatment approach toward personalized cancer therapies. Immuno-oncology (I-O), in particular, is fast emerging as a promising treatment path for various cancers. Cancer immunotherapies—e.g., checkpoint inhibitors, monoclonal antibodies, vaccines, and chimeric antigen receptor T-cell therapies—harness the immune system to fight cancer.

Checkpoint inhibitors are taking center stage after the Food and Drug Administration's (FDA) approval for Merck's KEYTRUDA® and Bristol-Myers Squibb's OPDIVO®, both PD-1 inhibitor therapies, late in 2014. With this recent success, I-O revolutionized the cancer treatment landscape, heralded as game-changing approaches to an area with grave need.

Multi-billion dollar early stage I-O deals for innovative targeted therapies via joint ventures, collaborations, acquisitions, and licenses, are driving the current development explosion—over 800 clinical trials. Frost & Sullivan estimates the total immuno-oncology market peak sales at $20 to $50 billion by 2025, with more product approvals and indication expansions for existing products.[2]

A Glaring Caveat in an Otherwise Successful Story

Despite their clinical success, first-wave cancer immunotherapies benefit small patient subsets. For instance, PD-1 inhibitors are effective in 20% to 30% of patients with advanced non-small cell lung cancer, leaving most patients refractory to treatment. The next logical step is incorporating approved I-O drugs in more powerful combination therapies, both with conventional cancer treatments, e.g., chemotherapy, as well as other immunotherapies, to both enhance therapeutic benefits and convert non-responders to responders. I-O drugs, however, are extremely costly, e.g., $150,000 per patient per course treatment, and place a significant burden on patients, payers, and healthcare systems.

With the decision to treat patients bearing both substantial clinical and economic significance, drug-biomarker co-development is critical to advancing I-O therapies, administering treatments only to those patients that benefit to reduce the overall cancer

[1] http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4462533/#b3-conc-22-e134
[2] *The Global Immuno-Oncology Therapeutics Market—Checkpoint Inhibitors* (Frost & Sullivan, July 2016)

burden. In a landmark decision, the FDA granted accelerated approval to Merck's KEYTRUDA® in adult and pediatric microsatellite instability-high (MSI-H) solid cancers. It represents the first instance where the FDA approved a cancer treatment based on a biomarker, MSI-H, as opposed to approvals based on tumor origin, setting the stage for biomarker-driven drug development.

Tissue-based Diagnostics: The Linchpin

Tissue-based diagnostics serves as the gold standard in cancer diagnosis and plays an increasing role in companion diagnostics (CDx) and theranostics.

Traditionally, pathologists look at hematoxylin and eosin-stained biopsy specimens microscopically for abnormalities in cell structure. Advanced staining techniques, such as immunohistochemistry (IHC) and in situ hybridization (ISH), provide additional biological information. Nonetheless, complex tumor tissue structure and inter- and intra-tumor heterogeneity along with intricate tumor-host immune interactions complicate histopathological examinations. Furthermore, both ICH/ISH techniques are inherently subjective with limited reproducibility and accuracy resulting from semi-quantitative scoring methods, i.e., pathologist visual scoring.

Beyond tissue analysis, the patient-to-pathologist histology workflows require consistency for diagnostic accuracy. Instead, tissue-based diagnostics is one of the most labor- and time-intensive processes in clinical molecular diagnostic testing, relying mostly on manual procedures—approximately 70% of the workflow in histology laboratories.[3] Highly dependent on personnel skill level, these functions are prone to errors, introducing operational inefficiencies and analytical inaccuracies to the process with a potentially significant impact on biomarker-driven drug development. Moreover, pathologist's demand is evolving faster than supply capability and exacerbated by global workforce shortage driven by an aging population, increase in disease incidence, and widening applications, e.g., diagnostics, drug development, biomarker discovery, and CDx.

Despite emerging competition from novel diagnostic techniques, such as liquid biopsy and next-generation sequencing, tissue-based testing is the keystone of cancer diagnosis and immunotherapy, as no other technology can capture the complex biological context of the immune response, i.e., solid tumors immune activation and immune competency (content) with immune infiltration (context) factoring into patient outcomes.

Workflow automation coupled with developments in staining methodologies and digital enablers, like advanced imaging technologies, artificial intelligence (AI), and machine learning (ML), for real-world data assessment, digital immunohistochemistry, and pharmacogenomics will open new inroads for better analysis—addressing specificity, sensitivity, efficiency, and robustness—and drive future market growth.

[3] *Global Tissue Diagnostics Market, Forecast to 2022* (Frost & Sullivan, May 2018)

Frost & Sullivan identifies drug development as a prime growth opportunity for pathology vendors leveraging AI-based digital pathology systems to improve diagnostics, achieve greater therapeutic efficacy, and accelerate life-saving immuno-oncology drug-CDx commercialization.[4]

Technology Attributes and Future Business Value

Founded in 2009, Colorado-based Flagship Biosciences, Inc. (Flagship) offers quantitative tissue image analysis and diagnostics services to the pharmaceutical industry. Flagship works alongside pharmaceutical companies worldwide creating biomarker strategies for drug-CDx co-development and commercialization in areas with unmet needs, including I-O (their primary focus), fibrosis, and rare neuromuscular diseases like Duchenne Muscular Dystrophy (DMD).

With more than 500 projects under its belt, the company established a strong reputation and high prestige, providing integrated, end-to-end solutions to over 100 pharmaceutical partners around the globe, including 6 of the largest pharmaceutical multinational companies.

Flagship Biosciences: Pioneering Leadership

Digital image analysis in drug discovery offers quantifiable results with reduced bias and reader variability, enabling improved diagnostic accuracy and, by facilitating better decisions, accelerating time-to-market for novel therapeutics. In this cut-throat field, speed-to-market is crucial to I-O drug success.

An industry pioneer, Flagship jumped early on the digital pathology bandwagon, leveraging AI-based images analysis methods since inception. Backed by world-class subject matter experts—technology developers, biologists, pathologists, and application scientists, the company developed clinically validated computational methodologies over the last 8 years, resulting in reproducible, quantifiable, precise data, helping decision-making through the entire drug development process.

Additionally, in-house wet assay and image analysis laboratories meet internationally recognized quality standards, EU ISO 15189, and are College of American Pathologists (CAP) accredited, and Clinical Laboratory Improvement Amendments-certified—to support development through the regulatory process and commercial strategy.

Flagship's strong intellectual property portfolio, with 12 granted patents and more applications pending, upholds its Computational Tissue Analysis (cTA®) platform, placing a high entry barrier for emerging competitors.

[4] *Growth Opportunities in the Global Digital Pathology Market, Forecast to 2021* (Frost & Sullivan, Nov 2017)

Frost & Sullivan research identifies Flagship as a leading drug development partner, leveraging computational approaches to advance biomarker-based strategies for I-O therapeutic—CDx co-development.[5]

Unique and Customized End-to-End Quality Services

With best practices across all sub-processes, from tissue collection, processing, and IHC/ISH staining to digital whole-slide imaging, computational tissue image analysis, and quantitative tissue biomarker interpretations, Flagship's end-to-end services help its pharmaceutical partners on the quest to successful drug development and commercialization.

The company's streamlined services, tailored to its partner's needs, optimize costs and increase the chance for early regulatory submission and product launch. Furthermore, Flagship engaged the FDA to establish a regulatory pathway for its technology platform—the company expects FDA clearance as a class II medical device in the third quarter of 2018 for CDx applications. Through a continuous I-O-CDx co-development regulatory path, the company establishes its commitment to its partners' success and pledges to change patient's lives.

Prediction with Confidence: Setting a High Bar

"Our [Flagship] AI-based computational solution makes very discrete and quantitative content and context measurements, which are used to determine drug-response correlation, and reduce the information to a pathology summary score—a yes or no answer regarding the patient's response to the drug. Because the approach is objective, quantitative, reproducible, and assay agnostic, we consistently deliver the right kind of information, with sufficient detail and reproducibility, to provide a path forward for I-O therapies."

-Joseph Krueger, Chief Scientific Officer, Flagship

With its unique cTA® and data-driven-decision support platform, Flagship offers its pharmaceutical partners robust, actionable data for informed decision-making at critical junctures in clinical development.

Meaningful

Flagship's cTA® platform, using fit-for-purpose tissue-based diagnostics and Big Data analytics, e.g., AI and ML techniques, generates vast amounts of cell-specific biological measurements—e.g., spatial tissue organization, cellular interactions and architectures, and biomarker density and distribution—to deliver data-rich tissue content characterizing immune cell infiltration within the tumor microenvironment (TME), i.e., Biofeatures profile.

[5] *Growth Opportunities in the Global Digital Pathology Market, Forecast to 2021* (Frost & Sullivan, Nov 2017)

Flagship's multidisciplinary expert team interprets these profiles, characterizes patient-specific immunomodulation, and predicts patient's response to cancer immunotherapies.

By understanding the TME profiles, drug developers can formulate clinical response-based hypotheses for focused clinical trial design alongside CDx strategies and, ultimately, deliver more valuable therapeutics to patients.

Scalable

Flagship supports its partners throughout clinical trials. In an evolutionary process, the company engages early in clinical development, applying its disruptive, integrated approach to identify patients most likely to respond, boosting efficacy data while avoiding unnecessary toxicity and costs.

Phase Ib—Typically a small trial involving fewer than 30 patients: measures pharmacodynamics and efficacy surrogates to generate immune system profiles; analyzes the pre- and post-treatment biopsies to evaluate the patient's response and facilitates efficient clinical trial strategies, e.g., patient selection; creates predictive tests to enroll patients likely to respond to immune-modulating drugs

Phase II—Typically less than 100 patients: matches patients to drug-CDx co-development strategies to achieve strong efficacy data, paving the way for simultaneous FDA submissions and accelerated approval.

Phase III—Pivotal trials: Large trials where the drug approval is conditional on diagnostic approval, supporting IDE activities as investigator and medical device sponsor activities for the software interpretation component of the integrated device.

Flagship analyzes individual slides within minutes— and can develop useful pathology scores in days compared to months with manual pathology methods. No pathologist scoring development and concordance studies are needed as the software creates the data from the slide only once, with the ability to explore multiple scoring interpretations without developing a new image analysis algorithm. Whether analyzing 1 biomarker and 30 patients, or 100 patients with 10 biomarkers, the company offers its pharmaceutical partners a continuous I-O-CDx co-development path, generating relevant data in weeks, not months; thus, setting the standard of excellence in the industry.

The Power of Foresight: Sustained Leadership

"Right now, we are at an inflection point. Backed by scientific evidence and operational expertise, we have the technology, infrastructure, and support system that allow a global franchise."

-Joseph Krueger

Flagship's cutting-edge, end-to-end quantitative pathology solutions bolster its foothold in drug development applications. While digital pathology and tissue image analysis co-evolutionary development continues, the company is setting its sights to its potential impact on pathology, prioritizing growth opportunities and diversifying accordingly.

Flagship recently launched a tumor immunology review portal to share results with its drug development partners, as a distributed model. With digitized slides, the company moves large amounts of data across the web for more efficient information exchange. While Flagship's pathology laboratory can directly support drug development needs in the US, remote laboratories across the world can simply deliver their slide images to Flagship for analysis. Once a pre-determined analysis runs, the remote pathologist can review the performance of the image analysis algorithm by analyzing an annotated markup of the tissue slide, and accept the resultant score. As answers often begot questions, the company can further interrogate the database to deliver additional information to customers promptly without redoing the analysis. The portal is currently a communication tool for clients; however, Flagship anticipates 2 strong future values:

- Cloud-based delivery solutions with growing functionalities, applications, geographies, and customer segments. For example, as specific tests with clinical utility emerge, commercial, academic, and hospital laboratories can stain slides (pre-analytical) and upload digital images for analysis.

- Create a central database and, overtime, profile tissues for patient stratification. These data profiles can serve as tools to aid drug developers in their hypothesis generation.

As its database and experience expands, the company is seeking real-world applications for its cTA® platform beyond its current pharma drug development services model, under a productized model that enables widespread use in clinical laboratories. Flagship is developing a suite of tools with specific purposes that are relatively simple and easily consumed by the end user in the clinical laboratory.

Flagship's brand is growing strong; with laboratories increasingly incorporating its technology into patient profiling activities, the company is steadily becoming part of the patient's routine oncology diagnostic survey. More importantly, Flagship will reveal some of its commercial partnerships within one year, cementing its role as a leader and extending its brand beyond drug development.

Frost & Sullivan believes that Flagship will continue to be a front-runner in this fast-evolving market opportunity.

Conclusion

Immuno-oncology (I-O) is fast emerging as a promising treatment path for various cancers. However, first wave cancer immunotherapies benefit small patient subsets. With

the decision to treat patients bearing both substantial clinical and economic significance, drug-biomarker co-development is critical to advancing I-O therapies, administering treatments only to those patients that benefit to reduce the overall cancer burden.

Flagship Biosciences (Flagship) combines world-class expertise—technology developers, biologists, pathologists, and application scientists—and its unique patented artificial intelligence (AI) enabled cTA® pathology platform to deliver comprehensive tissue profiling for predictive diagnostic applications for science-driven, decision-making across the drug development continuum. Scalable and capable from start to finish, the company's fit-for-purpose image analysis tissue-based diagnostics and companion diagnostics enhance drug safety and efficacy profiles, gain cost-efficiencies and accelerate clinical trial timelines, and improve the odds of regulatory and commercial success.

With its industry-leading cTA® platform and a strong commitment to expediting patients' access to potentially life-saving cancer immunotherapies, Flagship Biosciences earns Frost & Sullivan's 2018 Global Technology Innovation Award for AI-based pathology solutions in the immuno-oncology market.

Significance of Technology Innovation

Ultimately, growth in any organization depends upon finding new ways to excite the market and upon maintaining a long-term commitment to innovation. At its core, technology innovation, or any other type of innovation, can only be sustained with leadership in three key areas: understanding demand, nurturing the brand, and differentiating from the competition.

Understanding Technology Innovation

Technology innovation begins with a spark of creativity that is systematically pursued, developed, and commercialized. That spark can result from a successful partnership, a productive in-house innovation group, or a bright-minded individual. Regardless of the source, the success of any new technology is ultimately determined by its innovativeness and its impact on the business as a whole.

Key Benchmarking Criteria

For the Technology Innovation Award, Frost & Sullivan analysts independently evaluated two key factors—Technology Attributes and Future Business Value—according to the criteria identified below.

Technology Attributes

Criterion 1: Industry Impact
Criterion 2: Product Impact
Criterion 3: Scalability
Criterion 4: Visionary Innovation
Criterion 5: Application Diversity

Future Business Value

Criterion 1: Financial Performance
Criterion 2: Customer Acquisition
Criterion 3: Technology Licensing
Criterion 4: Brand Loyalty
Criterion 5: Human Capital

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

Frost & Sullivan analyst 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.

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