termsheet

October 2019
Issue 27

Heads of Terms

The power of connections

We are more knowledgeable of how things are connected than ever before. But how they are connected and how those connections are created are of enormous importance to understanding both the natural world and even business. It's our intervention in the connection of things through our creative processes that can drive innovation forward. For example, in healthcare the relationship and connection between diagnosis and therapy can greatly influence the success, or not, of a health outcome. We explore this connectivity in the article entitled *"Are Diagnostics Poised to Lead Healthcare Or Is This Another False Positive?"*.

But connectivity is integral to what we do at PharmaVentures, the connecting of buyer and seller, investor and investee or licensor and licensee that can be transformative for both parties. It is the ability to create that connection through communication of the opportunity, its relevance and the setting of the right terms and that determines the successful outcome.

Another level of connectivity is through networks which enables a rapid assimilation of information and can lead to faster and more robust outcomes. By creating networks we can help our clients achieve their goals faster and at a higher level quality.

One step in that direction is our formation of an International Advisory Board (See article *"PharmaVentures Strengthens Its Global Reach with the Establishment of an International Advisory Board"* on page 4). This will create a new network that will help our clients in their pursuit of their deals.

Dr Fintan Walton
Chief Executive,
PharmaVentures Ltd.

Industry Insight

Are Diagnostics Poised to Lead Healthcare, Or Is This Another False Positive?

Summer Park
Senior
Business Development Director

Eric Liu
Associate

Even though medical diagnosis can be traced back to ancient Egypt in the 26th century BC (Edwin Smith Papyrus by Imhotep), in vitro diagnostics (IVD) as a field really started to take shape from late 20th century. Significant investments and research have been funnelled into early diagnosis of cancer with new products including next-generation sequencing, liquid biopsy and companion diagnostics, whilst payers are increasingly demanding biomarker stratification to justify the use of expensive drugs. Time and time again, the healthcare industry is buzzing with new ideas on how to use next generation diagnostics to achieve "smart healthcare," but to date, this has not been realised. Yet, the unmet needs remain with ballooning healthcare cost, aging society and changes in disease trends.

Brief History of Diagnostic Deals

PharmaVentures' evaluation of the diagnostic M&A, licensing and distribution deal landscape since 2009 shows a wide range of transaction types and values, with the partnership space having been quite active.

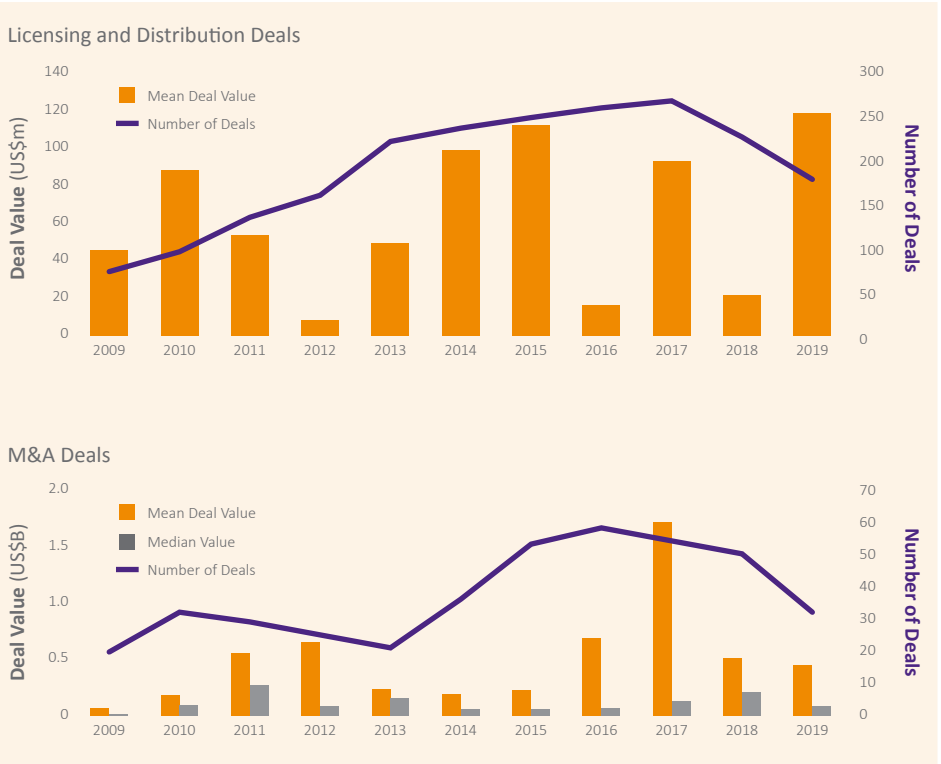

Figure 1
Deals involving diagnositcs from 2009 to present.
Source: Cortellis deals. PharmaVentures analysis.

continued on page 2 . . .

PharmaVentures
Experts in deals and alliances

Industry Insight

. . . continued from page 1

Are Diagnostics Poised to Lead Healthcare?

In recent years, there have been multiple eye-catching acquisitions, such as: Illumina picking up PacBio for $1.2 billion (2018); Roche's acquisition of Foundation Medicine ($1 billion in 2015; then $ 2.4 billion in 2018); Becton Dickinson buying C R Bard for $24 billion (2017), Abbott's Alere purchase for $5.3 billion (2017) and the $4 billion Danaher-Cepheid acquisition (2016). However, the vast majority of the datapoints skew towards deals with low values. This maybe is reflective of the market situation, where most of the technologies licensed and acquired in the past 10 years involve those assets with only incremental improvements on old technologies.

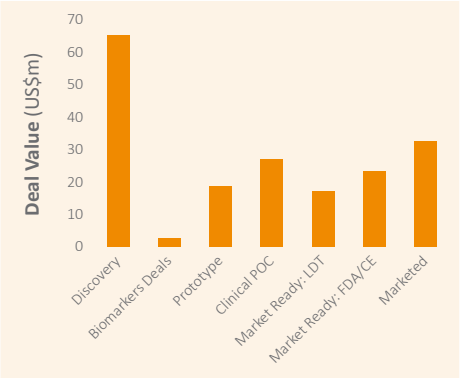

Figure 2
Mean total value of deals involving diagnostics, depending on the stage of development at deal signing.

Source: Cortellis deals.
Deals excluded include instruments, imaging technologies and large company acquisition.

Venture fundraising deals in the last 5 years were also evaluated and have followed a similar pattern to the licensing/M&A transactions for low valuations on traditional technologies. However, the market does reward disruptive approaches, an example of this is Guardant Health. Guardant Health's Guardant360 is a ctDNA-based molecular diagnostic test that measures 73 cancer-related genes from a simple blood sample. Guardant360 was launched as a Laboratory Developed Test (LDT) in 2014 and received breakthrough designation in January 2018, with FDA approval expected in 2020. Guardant Health has a market cap of $7.68 billion despite its negative cashflow and an EV/revenue multiple of close to 50x.

The Industry Rewards Gamechangers

What are the requirements for generating a premium value deal for a diagnostic technology or company? How do outliers in diagnostic deals command such a big premium? One important element seems to be how the new technology will transform the current treatment paradigm. The clinical positioning of innovation is possibly the most determining factor and will be a critical part of the messaging to partners, physicians and patients. It is no longer enough to just save money for the healthcare system with an incremental improvement in diagnostic sensitivity or specificity. The latest diagnostic developments need to change how patients are treated to guarantee better outcomes. We have heard this from diagnostics in the past and it has proven to be a false dawn but now we may be witnessing the perfect storm of technology leaps coupled with commercial and regulatory pressures that will force through change. However, we are dealing with huge, unwieldly and entrenched healthcare systems so this will not be an overnight revolution.

There are some indicators of the direction of travel in the deal space, where gamechanger technologies are generating high-value deals. Examples include start-up Sherlock Biosciences which has come out of stealth mode with $49 million committed to date, Thrive Earlier Detection, having closed a healthy Series A totalling $110 million and California-based Grail, which has raised $1 billion in private equity financing. Although based on individual, unique cutting-edge technologies, upon analysis we start to see some commonalities among these firms.

First, they all start with oncology. This is possibly due to the plethora of targeted therapies available in this indication, reflecting our increasingly sophisticated understanding of the genetic and immunologic mechanisms of action involved in this chronic condition. Such depth of knowledge and corresponding richness of available therapies necessitates elegant diagnostic solutions for personalised medicine to truly work for the benefit of the patients, especially as these new treatments tend to be extremely expensive and still, in general, only extend life by a matter of months. Increasing buyer's confidence that a targeted therapy will deliver significant benefit over existing, cheaper alternatives will help alleviate buyer's reluctance to pay for these expensive cancer drugs. Beyond oncology, for which there is clear immediate benefit, these companies' long-term strategies, fuelled by the wide potential of their technologies, reach far beyond and into other areas such as infectious and inflammatory diseases. In fact, according to a recent large-scale inflammatory disease KOL study that PharmaVentures conducted among clinicians, there was a huge demand for diagnostics that could accurately guide a physician to the best treatment options for patients with rheumatoid arthritis and inflammatory bowel disease.

Secondly, whilst earlier versions of diagnostics provided mere confirmation of how the patient would move through the pre-determined treatment pathway for any single indication, new-world diagnostics have ambitions to become the ultimate driver of healthcare by commanding the best treatment option for a patient by profiling their overall (epi)genetic and phenotypic makeup.

Thirdly, these gamechanger companies are fuelling an important question which has the potential to shift the paradigm of the entire healthcare industry, starting with how we detect, classify and treat diseases and ultimately leading to the debate between evidence- vs patient-centric medicine and preventative medicine.

Back to the Diagnostic Future

Since its beginning, the world of diagnostics has seen companion diagnostics, complementary diagnostics and has now come far enough to begin addressing these complex questions (Figure 3, Table 1). The companies mentioned above are a small selection of many trying to solve this fundamental problem. Should they succeed in achieving their ambition, they present the potential to turn medicine on its head, whereby it will no

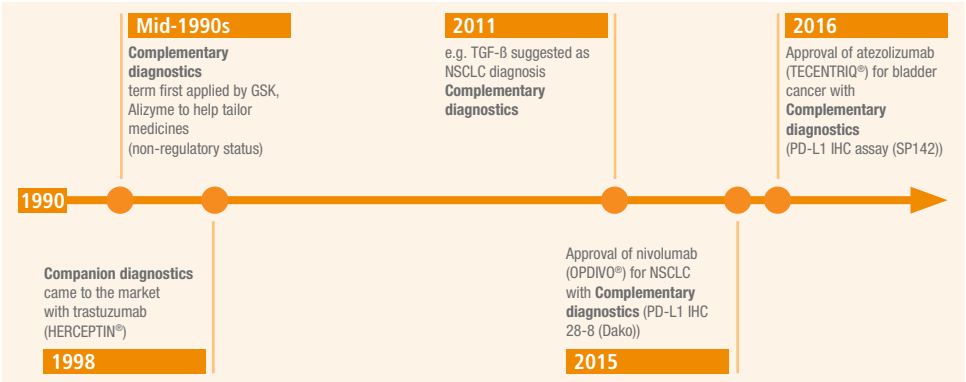

Figure 3
A timeline showing key developments along the history of diagnostics.

Source: Adapted from (Scheerens et al., 2017).

First recorded clinical utility and/or FDA approval	Diagnostic Type	Characteristics	Examples
1950's and 60's	Protein and cellular biomarkers	Typically antibody based, qualitative and quantitative. Assist in disease diagnosis	RIA, ELISA, IHC, Clinical Chemistry
Late 20th century	Traditional molecular tests	Binary; identifies existence vs non-existence or below vs above threshold.	PCR-, fluorescence in situ hybridisation.
1998 (HER2 assay for trastuzumab)	Companion diagnostics	Provides information for the safe and effective use of a corresponding drug or biological product. Only applicable for diseases which are included in the drug label (US FDA, 2019).	NSCLC; EGFR T790M (cobas EGFR Mutation Test v2 /Tagrisso). Melanoma; BRAF V600E (COBAS 4800 BRAF V600 Mutation Test / Vemurafenib). Breast cancer; HER2 overexpression (Trastuzumab).
2015 (PD-L1 IHC assay for nivolumab)	Complementary diagnostics	Aids in the benefit-risk decision-making about the use of a therapeutic product, where the difference in benefit-risk is clinically meaningful, without restricting drug access.	PD-L1 IHC assay (atezolizumab, nivolumab).
?	Precision Medicine	Patient-centred approach based on the following sequence: (i) Comprehensive diagnostic profiling leading to (ii) targeted intervention followed by (iii) outcome tracking, learnings from which are embedded into (iv) treatment pathways to ensure continuous improvement.	Roche's Foundation Medicine and Flatiron. Guardant Health Grail

Table 1
Types of diagnostic technologies in chronological order of invention.

longer be driven by expensive drugs, rather by diagnostics. They will help physicians personalise treatment without having to go through the pre-set treatment algorithm and present an opportunity to unleash the potential of many permutations of already approved drugs, which in concert, may be able to address the complex pathophysiology of a patient. Current clinical trial and regulatory practices will have to change dramatically to accommodate such a brave new world.

Time and time again in cancer, across clinical trials and in practice, having a biomarker for a targeted therapy has been associated with significantly better prognosis (Figure 4). According to Wheler et al. (2014), in 57 consecutive patients with metastatic breast cancer, no two patients had the same mutation profile. A study by Kato concurs with this finding, wherein among 42 patients with advanced mesothelioma, no two patients had the same mutation profile (Kato, 2016). If all cancer patients were stratified according to the entirety of their mutations, each patient would represent an orphan indication and perhaps they also need specially tailored combination treatments. Under the assumption that there are 300 approved drugs in oncology today, mathematically this would lead to around 45,000 two-drug combinations and 4.5 million three-drug combinations; which with conventional evidence-based clinical trial system, would take over 1,000 years to figure out for a single patient (Kurzrock, 2016). Not to mention that there were 17 million new cases of cancer in 2018 alone (Cancer Research UK, 2019). The scale of the challenge is immediately obvious.

continued on page 4 . . .

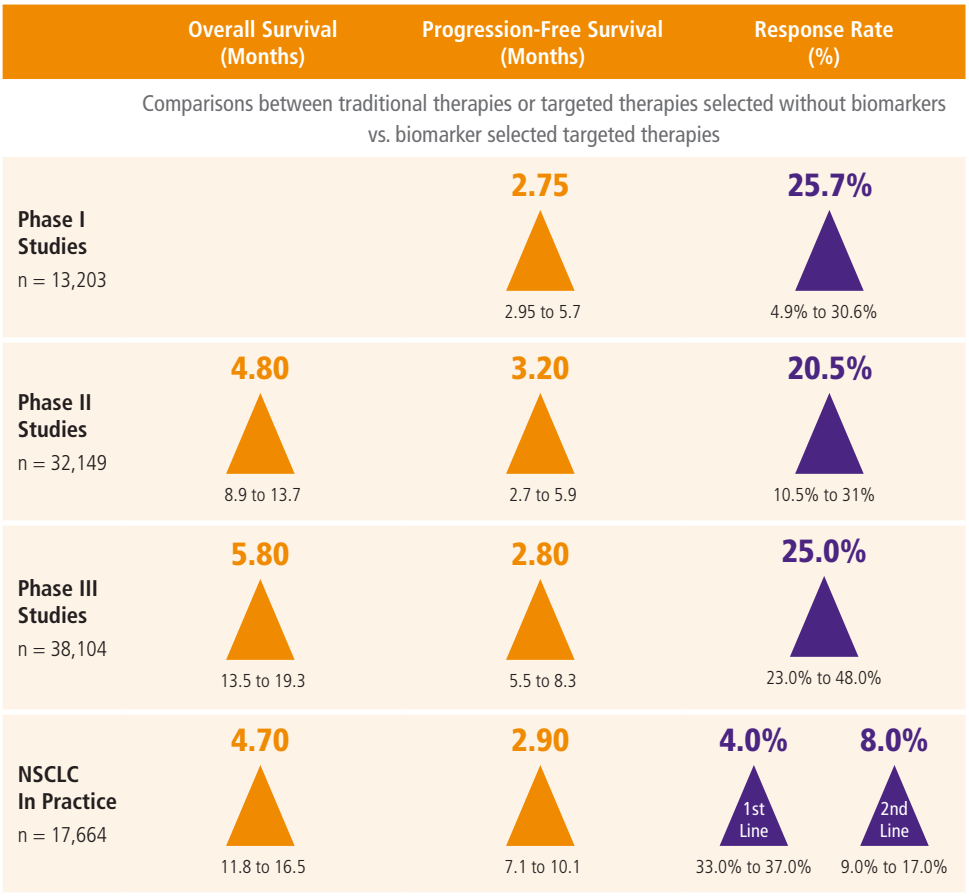

Figure 4
Having a biomarker for a targeted therapy yields significantly better outcomes in clinical trials and in practice

Adapted from Walker, 2018.
Sources: Schwaederle M et al. JAMA Oncol 2016:2(11):1452-1459 Jardim DL et al. J Natl Cancer Inst. 2015:107(11)
Schwaederle M et al. JCO 2015:33(32):3817-3825 Barlesi F et al. The Lancet 2016:387(10026):1415-26

. . . continued from page 3

Are Diagnostics Poised to Lead Healthcare?

A key determinant in all of this is the robustness of diagnostic testing, which will allow genomic profiling of each patient. For this model, companion and complementary diagnostics are no longer useful, as each patient must be tested using multiple assays, one for each mutation. Instead, it has been proposed that clinicians test a large number of genomic alterations in a single assay – a proposal made feasible by next-generation sequencing.

What Next?

So far, we've already had two or three false dawns in diagnostics. Is this the latest in a series or will it prove to be a true positive this time? Other than providing better information about a patient, there are other pressures being brought to bear such as payors and the overarching need to understand the biology of diseases in greater genetic and 'omic' detail, rather than broad categorisations such as 'cancer' or 'diabetes'. Maybe we will reach a time where we will no longer call cancer, cancer? Instead, any single patient's condition will perhaps be known by their genetic mutations and be treated by drugs targeting those specific mutations? This is already beginning with drugs such as Tagrisso® and the T790M mutation in Non-Small Cell Lung Cancer. There will be many questions along the way, such as continuous monitoring to reflect the progressive and evolving nature of disease and treatment, as well as the consequential vs causal nature of any given mutation. How the regulatory model will change to accommodate this brave new world is also yet to be figured out.

PharmaVentures has current and recent experience in working with a number of leading diagnostics companies who are embarking on the journey to this new world. A key question for these and others will be how to attract attention and investment under today's paradigm to develop tomorrow's solutions.

References

André, F. (2018). Developing Anticancer Drugs in Orphan Molecular Entities — A Paradigm under Construction. The New England Journal of Medicine, 368: 763-765.

Cancer Research UK, https://www.cancerresearchuk.org/health-professional/cancer-statistics/worldwide-cancer, Accessed September 2019.

Kato, S. et al. (2016). Genomic Landscape of Malignant Mesotheliomas. Molecular Cancer Therapeutics, 15 (10): 2498-2507.

Kurzrock, R. (2016). 2016 ASCO Annual Meeting Presentation.

Scheerens et al. (2017). Current Status of Companion and Complementary Diagnostics: Strategic Considerations for Development and Launch. Clinical and Translational Science, 10(2): 84-92.

U. S. Food and Drug Administration, https://www.fda.gov/medical-devices/vitro-diagnostics/companion-diagnostics, Accessed September 2019.

Walker, I. (2018). Every Patient Counts: The shift towards Precision Medicine in Oncology. Massachusetts: Foundation Medicine | Roche.

Wheler et al. (2014). Unique Molecular Landscapes in Cancer: Implications for Individualized, Curated Drug Combinations. Cancer Research, 74 (24): 7181-4.

Note

All $ values are in US Dollars.

Team News

PharmaVentures Strengthens Its Global Reach with the Establishment of an International Advisory Board

PharmaVentures is pleased to announce the establishment of a new International Advisory Board, comprised of pharmaceutical, medical, transactional and investment banking experts from around the world. In addition to maximising the benefits for our clients worldwide, this Advisory Board will strengthen its connection with the heart of the global healthcare network.

Dr Fintan Walton, Founder and CEO of PharmaVentures, who will chair the Board said "Our business is global and with that we need to ensure our clients can benefit from our extensive networks at all functional levels within our organisation. The International Advisory Board will be an enormous benefit to our clients".

Additional members covering parts of the Far East, Asia and North America will be announced later.

PharmaVentures' International Advisory Board

In addition to **Fintan Walton**, Chairman & CEO, PharmaVentures, the current members of PharmaVentures' International Advisory Board include:

Aki von Roy, based in Auckland, New Zealand, is the former European president of Bristol-Myers Squibb, where he was responsible for US$ 2.2 billion in sales, more than 7,500 employees and some 40 subsidiaries. Aki has over 30 years' experience in big pharma and 16 years in biotech and has been involved in over 18 start-up or merger ventures as chairman, director and investor.

Paul MacLeman, based in Melbourne, Australia, brings over 25 years' board and executive experience across the life science, agricultural and not-for-profit sectors. His experience ranges from strategy formulation to capital raising, business development, technology commercialisation and sales & marketing. During his working life Paul has been responsible for launching a variety of products in Australia, Asia and the US. He has also founded life sciences start-ups and worked in investment banking.

Sue MacLeman, based in Melbourne, Australia, has more than 30 years' experience as a pharmaceutical, biotechnology and medical technology executive having held senior roles in corporate, medical, commercial and business development. Sue has also served as CEO and Board member of several ASX and NASDAQ listed companies and is currently Chair of Australia's Industry Growth Centre for the sector MTPConnect (MTPII-GC Ltd).

Christopher Berry, based in Paris, France, worked on R&D Transactions within Sanofi R&D, where he was responsible for building research collaborations (ranging from material transfer agreements through to multi-scaffold drug discovery deals) in the areas of anti-infectives, biologics, and regenerative medicine. He has had over 14 years' experience in research alliance building and alliance management.

Morten Faester, based in Copenhagen, Denmark, brings over 20 years' experience as a Business Development Director with both large and specialty pharmaceutical companies such as Nycomed-Takeda, AstraZeneca and Grünenthal. Morten has a strong track-record of partnering and deal-making in the pharmaceutical, biotech and medical technology industries.

Team News

PharmaVentures in Action

PharmaVentures attended the Sachs 19th Annual Biotech in Europe Forum in September, a meeting recognised as the leading international stage for those interested in investing and partnering in the biotech and life sciences industries. During this two-day event, we learnt that 2018 was a record year not only for IPOs, but also investment, M&A and licensing deals. So far, 2019 is considered to be equally successful. However, it is important to note that there has been a notable shift in the types of deals taking place; moving from later stage transactions to earlier stage and platform technologies.

Additionally, it is not unexpected that key discussions also focused around gene and cell therapies. The FDA expects to approve around 10-20 new gene and cell therapies annually by 2025. With these innovations beginning to reach the market, new challenges for both pharmaceutical and biotechnology companies have arisen, particularly in terms of reimbursement and key logistical hurdles concerning manufacturing processes. Throughout the event, both digitalisation and integration of the bioprocessing steps were topics widely discussed, not only by large Pharma (Lonza and Novartis) but also by some smaller players such as Anocca and Bone Therapeutics.

Our CEO, Dr Fintan Walton, also chaired the Global Partnering Panel, which provided a very insightful analysis of the current partnering landscape. Furthermore, it was inspiring to see his panel populated by successful women who hold senior roles in the pharmaceutical industry. The industry might not be there yet with gender equality, but we are definitely moving in the right direction!

At the 19th Biotech in Europe Forum hosted by Sachs Associates in Basel, Switzerland, Dr. Fintan Walton, Founder and CEO of PharmaVentures moderates the "Global Partnering" panel. Panellists included:

- **Corinne Venot**, Senior Director Business Development, BeiGene Ltd.
- **Florence Dal Degan**, Director, External Innovation, Novo Nordisk A/S.
- **Nathalie ter Wengel**, European Lead, Worldwide Business Development, Pfizer, Inc.
- **Neil Johnston**, Global Head, BD & Licensing Pharma, Novartis International AG.
- **Patrick Benz**, Sr. Director Alliance Management, The Janssen Pharmaceutical Companies of Johnson & Johnson.
- **Phil L'Huillier**, Head of Business Development, Europe & Middle East, MSD.

Team News

PV Agreement with FTI Consulting on the N-Site collaboration

PharmaVentures enters into a collaboration agreement on **N-Site** with **FTI Consulting**, a global communication, tax, non-life science transactions consultancy firm. N-Site is an online portal which is designed to be a hub of expert guidance for UK based Life Science companies and contains guideline documents for a number of business-related aspects that are of relevance to life science businesses.

For more information on N-Site, contact enquires@pharmaventures.com.

Meet the Team

Qize Ding
Associate

Qize joins PharmaVentures as an Associate and brings experience from Pharmaceutical R&D and academic research, as well as equity research experience.

Qize was an Equity Research Associate covering global pharmaceutical and retail industries in the Investment Research department at Citigroup. Qize has also worked at University of Oxford and Adaptimmune Therapeutics, where as a Research Scientist, he focused on inflammatory diseases and cancer therapeutics.

Qize has a BSc in Biochemistry, MSc in Immunology and Ph.D in Cancer Research from Imperial College London.

qize@pharmaventures.com

Join the Team

Business Analyst

To assist in the research and analysis of pharmaceutical biotechnology, medtech and diagnostic companies, products and technologies.

Visit our website at www.pharmaventures.com/content/careers for further details and to apply.

Conference Update

CPhI Worldwide
5-7 November 2019
Frankfurt Germany

BIO-Europe 2019
11-13 November 2019
Hamburg Germany

Genesis 2019
11 December 2019
London UK

J.P. Morgan 38th Annual Healthcare Conference
13-16 January 2020
San Francisco

If you would like to meet with PharmaVentures at any of these events, please contact Summer Park, Business Development Director

summer@pharmaventures.com

PharmaVentures Ltd
Triumph House, Parkway Court, John Smith Drive, Oxford Business Park, Oxford OX4 2JY
www.pharmaventures.com

PharmaVentures
Experts in deals and alliances

Valuation Experts

Top tier pharmaceutical companies, biotechs, medtechs and start-ups all trust PharmaVentures to provide expert valuation and deal structuring services.

Over the last 26 years we have helped hundreds of clients understand the value of their assets and companies during their transactions. Many major pharmaceutical companies rely on our independent valuation expertise in the demanding environments of litigation and arbitration cases. Successfully meeting their needs has equipped us to provide comprehensive valuation and deal structuring services to companies across the healthcare sector.

How do we help?

PharmaVentures combines classic valuation methodologies such as discounted cash flow (DCF), net present value (NPV) and VC method with deal comparables and innovative in house approaches to provide a comprehensive suite of valuation tools. Using these tools and our deep analytical capabilities, epidemiology, primary and secondary research on multiple databases and our own proprietary data sources, we deliver robust, defensible, real world valuations and deal structures to address all scenarios.

Who do we help?

PharmaVentures' clients include major pharmaceutical companies, biotechs, medtech, diagnostics companies, governments, start-ups and spin-outs.

Further information

Summer Park
Business Development Director, PharmaVentures Ltd

Mobile: +44 (0) 7387 101 283
summer@pharmaventures.com

Case Studies

Immuno-Oncology Deal Support

PharmaVentures provided extensive epistemological analysis, full patient pathway segmentation and drug positioning for our client's clinical NSCLC asset with territorial breakdowns. Our client was able to use this valuation to gain a strong position in the licensing deal negotiation.

✓ Deal currently in progress.

Licensing

MedGenesis sought a development and commercialisation partner for its GDNF asset for Parkinson's Disease. PharmaVentures used various valuation techniques to build strong arguments for value and provide effective negotiation support to underpin and optimise the deal structure for MedGenesis.

✓ Deal successfully completed with Pfizer.

Fundraising/IPO

Prior to its IPO, Evgen engaged PharmaVentures to prepare an independent expert report, covering technical assessments and commercial valuations of its assets. This report included a comprehensive market analysis, comparable benchmarks, evaluation of applicable deal terms and a DCF valuation.

✓ Evgen completed a successful IPO.

Strategy

PharmaVentures' client was seeking to set a long-term commercial strategy for its pipeline of assets. We conducted a commercial assessment and full valuation on its R&D portfolio and advised the client on the best steps forward.

✓ Strong R&D and commercial strategy developed and implemented.

M&A

Nanosight had developed and begun to commercialise a range of sophisticated nanoparticle tracking technologies. PharmaVentures conducted a valuation to build a defensible evidence of value to support the negotiations during the transaction process.

✓ Nanosight successfully acquired by Malvern Instruments.