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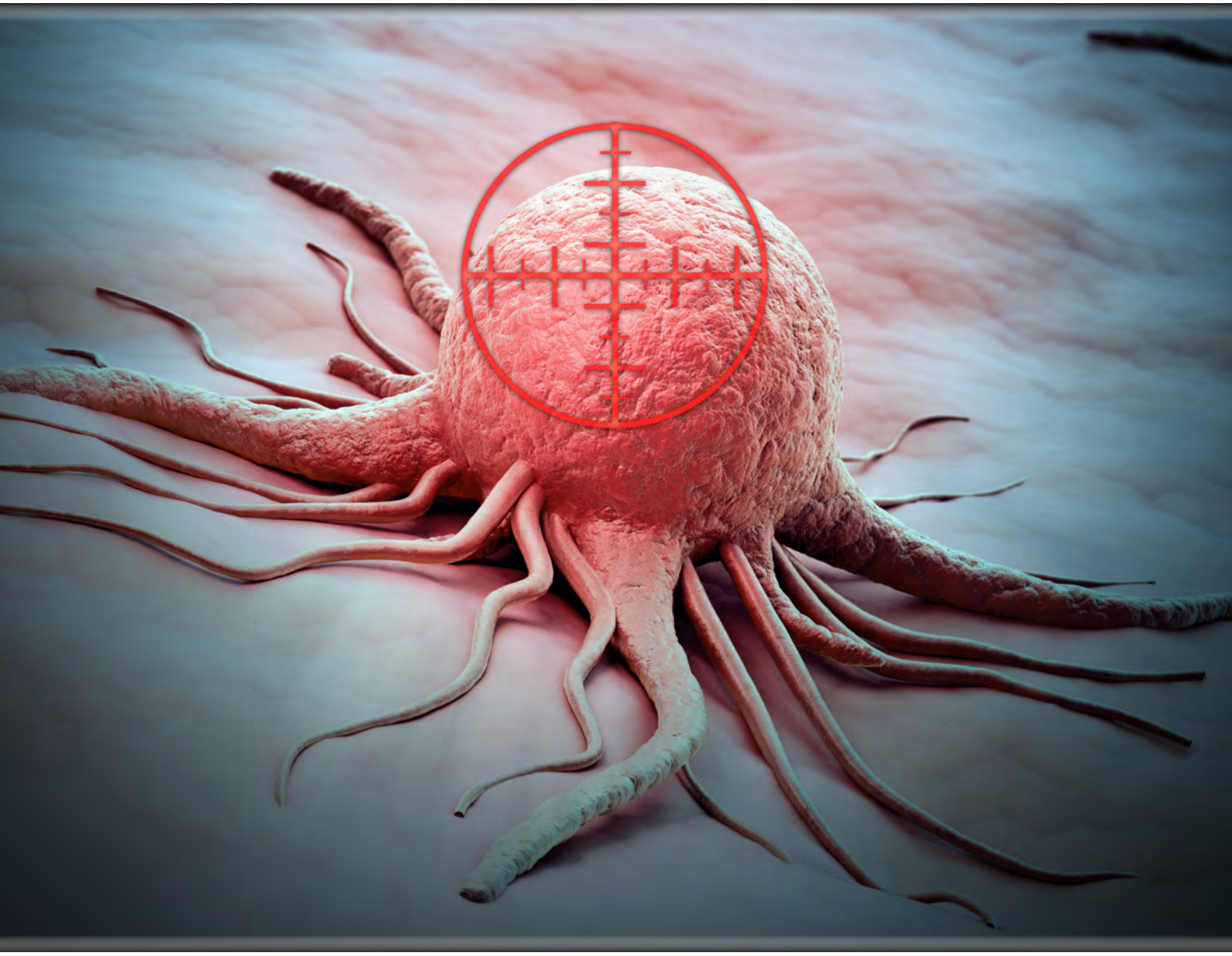

ON TARGET
LABORATORIES

Improve lives of cancer patients with tumor-targeted drugs: Highlights of a future legend

Sumith A. Kularatne, Ph.D., is the Vice President of Research & Development at, On Target Laboratories, LLC (OTL), West Lafayette, IN (March 2012 – present). Dr. Kularatne is a world-class researcher and problem solver within the field of drug design and development for cancer and inflammatory disease. In fact, his distinctive and unparalleled approach to solve the problems associated with the diagnosis and treatment of cancer has been nothing short of unique and groundbreaking.

Dr. Kularatne says that “health holds a very important role in one’s life, as President Thomas Jefferson said. Liberty is to the collective body, what health is to every individual body… Without health no pleasure can be tasted by man… without liberty, no happiness can be enjoyed by society”.

Therefore, Dr. Kularatne uses his diverse set of skills, ranging from medicinal chemistry, organic chemistry, cancer biology, biochemistry, molecular biology, protein and antibody engineering, and animal model development for drug testing that enables him to solve problems from a multidisciplinary approach and to discover better therapies with higher efficacy.

He pursued his postdoctoral studies in molecular biology and biomedicines with Peter G. Schultz, CEO and Professor of Chemistry at The Scripps Research Institute (TSRI), San Diego, CA (Dec 2009-Feb 2012). Dr. Schultz was the founder and former director of GNF, and is the founding director of the California Institute for Biomedical Research (Calibr) La Jolla, CA. Dr. Kularatne’s projects at TSRI focused on selective diminishing of primary tumor masses,

"Men are haunted by the vastness of eternity. And so we ask ourselves: will our actions echo across the centuries? Will strangers hear our names long after we are gone and wonder who we were, how bravely we fought, how fiercely we loved?" – Odysseus (Troy).

metastatic cancers, and cancer stem cells using antibody drug conjugates (ADCs) or using bispecific antibodies (antibody-dependent cell-mediated cytotoxicity or ADCC).

Dr. Kularatne earned his Ph.D. in organic/medicinal chemistry from Purdue University, West Lafayette, IN (Dec 2005-Dec 2009), conducting research under the guidance of Philip S. Low, the Ralph C. Corley Distinguished Professor of Chemistry and Director of the Purdue Center for Drug Discovery at Purdue University. Dr. Low is also the co-founder and CSO of both Endocyte and On Target Laboratories. Dr. Kularatne’s research at Purdue University concentrated on small molecule-targeted drugs for cancers and inflammatory diseases.

His scientific efforts have resulted in 6 drug candidate in human clinical trials with multiple companies, over 50 US and foreign issued/pending patents and over 30 peer-reviewed publications. He has given multiple invited seminars/lectures in

prestigious conferences such as "Gordon Research Conference" on "Drug Carriers in Medicine & Biology", as well as in national and international conferences, universities, and industries. Dr. Kularatne's scientific involvements have also led to several international and national awards including, Distinguished Partners in Hope Award for OTL for fueling innovation, and providing hope to lung cancer patients, Innovation Corps at NIH program for SBIR Award for Drug Development for Non-Small Cell Lung Cancer (2016)", "SBIR Grant Award for Non-Small Cell Lung Cancer Research (2014)", "AAPS Postdoctoral Fellow Award sponsored by Merck (2012) for CXCR4-targeted antibody drug conjugates for metastatic cancers", "the Skaggs Postdoctoral Fellow Award (2010)", "AAPS Graduate Student Award in Biotechnology, sponsored by Pfizer (2009) for PSMA-targeted drugs for prostate cancer, AAPS Graduate Student Symposium sponsored by Eli Lilly (2009) for PSMA-targeted drugs for prostate cancer, Delano Maggard, Jr. graduate research award (2005)", ACS recognition Chemist of the year (2004), E. A. Talaty fellowship (2003) and the B. L. Paker Endowed fellowship (2002).

Throughout his research career, Dr. Kularatne has been dedicated to developing targeted-imaging agents, diagnostic methods, and -therapeutic agents for cancers such as prostate, ovarian, lung, breast, and leukemia and their metastatic disease and inflammatory diseases, such as rheumatoid arthritis and heart disease.

Here, are some of his major highlights on contributions to improve cancer patience's lives and to the scientific community

Under his guidance, the OTL team has developed a strong pipeline for a wide range of cancers and inflammatory diseases. OTL is delivering drugs to receptors that overexpressed on cancer cells by attaching to a receptor-specific ligand via a suitable spacer. This ligand-targeted drug delivery technology is based on the pioneering work of Dr. Low, PhD, at Purdue University. OTL technology provides surgeons a precise "lighted road map" to more effectively and efficiently diagnose and surgically treat diseased tissue ranging from cancer to autoimmune diseases.

OTL38, OTLs lead candidate for ovarian and lung cancer, is a folate receptor (FR)-targeted near infrared (NIR) dye that conjugated to a ligand with similar properties to folic acid (vitamin B9) via a linker. Dr. Kularatne said that the linker plays a pivotal role. It is a part of the ligand and improves the binding affinity and specificity to FR. It also a portion of NIR dyes and enhances the brightness at an unique wavelength. FR is overexpressed in many cancers, including the lung, ovarian, kidney, and breast, etc. but not in healthy tissues. Based on the successful preclinical data, OTL38 entered into a Phase I clinical trial in Leiden, the Netherlands in January 2014. OTL38 has proven safe in the Phase I trial and effective in a completed Phase II clinical trial for the treatment of ovarian cancer. A Phase III clinical trial in ovarian cancer and a phase II clinical trial in lung cancer patients will be starting in Fall, 2017. Commercialisation of OTL38 for ovarian and lung cancer patients is scheduled for early 2019 and 2021 respectively.

The same NIR dye has been conjugated to a prostate-specific membrane antigen (PSMA)-targeting ligand (DUPA) via a spacer to improve the binding affinity and pharmacokinetic properties of the clinical candidate named OTL78. PSMA is a protein that overexpressed on the cell surface of most of the prostate cancer (PCa) cells, yet absent in normal cells. After finishing IND-enabling safety studies, a Phase I clinical trial for OTL78 in PCa patients will began in 2017. PSMA is also expressed in tumor-associated blood vessels of most of the solid tumors, including lung cancer, colon cancer, and brain tumors but not expressed in healthy blood vessels. Therefore, OTL78 can be used to detect and surgically treat solid tumors other than PCa.

Additionally, OTL team has developed carbonic anhydrase nine (CA IX)-targeted NIR conjugates (OTL338) has been developed by conjugating to CA IX-targeting ligand named C-SPA to the NIR dye via a hydrophobic linker to match the chemistry of the CA IX protein. CA IX is a receptor that is expressed in the hypoxic regions of all solid tumors including microscopic lesions (< 1 mm lesions) whereas, since normal tissues are not hypoxic, CA IX is not expressed

in normal healthy tissues. Expression of CA IX has been observed in malignancies of the kidney, colon, breast, lung, head & neck, liver, pancreas, and gastric epithelium. OTL will be expecting to start a Phase I clinical trial for OTL338 in 2018. OTL has also been exploited in overexpression of the cholecystokinin 2 receptor (gastrin receptor, CCK2R, or CCKBR) on certain human cancers of the thyroid, colon, lung, pancreas, and gastrointestinal stroma to target the same NIR dye (OTL81). There are a few more tumor-targeted ligands which are under pre-clinical development. The aforementioned ligands can also be conjugated to a photodynamic therapeutic (PDT) agent, giving surgeons the option to visualise and "burn" targeted-tumor using the same light source and camera at different energy levels. Currently, FR-targeted PDT agents (OTL228) have been developed and preclinical evaluations have been successfully completed.

Dr. Kularatne has a proven track record in drug design and development of PSMA-targeted imaging and therapeutic agents for PCa and won him many awards for academic excellence and research during his Ph.D. studies. Guided by in silico docking studies using a high resolution crystal structure of PSMA, Dr. Kularatne developed a high affinity PSMA-targeting ligand (DUPA), which selectively binds and enters to PSMA-expressing cells by PSMA mediated endocytosis. Then he developed a PSMA-targeting radioimaging agent (DUPA-SPECT) to detect and stage of PCa. DUPA-SPECT has been evaluated in clinical trials at Indiana University Medical School and has shown promising results over ProstaScint, a FDA approved radio-imaging agent for PCa. The PSMA-targeted fluorescence imaging agent (DUPA-FITC) that he developed was successfully employed to detect and quantitate PCa cells (circulating tumor cells or CTC) in blood samples from PCa patients and is a method that is now being practiced in IV Diagnostic Inc, West Lafayette, IN for human clinical trials. The PSMA-targeted NIR dyes that Dr. Kularatne has developed are used in detecting prostate tumor margins during surgery by OTL, West Lafayette, IN. Encouraged by specificity of DUPA for PCa in humans, Dr. Kularatne has developed therapeutic conjugates of DUPA for treatment of PCa. Endocyte, West Lafayette, IN, has been conducting multi-center clinical trials on the PSMA-targeted chemotherapeutic agent in USA including MD Anderson Cancer Center, Houston, TX and Memorial Sloan Kettering Cancer Center, NY. Dr. Kularatne was able to resolve the problems associated with the delivery of siRNA therapeutics using DUPA as a targeting ligand. Despite their enormous potential as biopharmaceutical therapeutics, systemic delivery of naked siRNA to malignant sites remains a major hurdle owing to rapid enzymatic digestion in plasma, renal elimination, limited penetration across the capillary endothelium, and inefficient uptake by tissue cells. Dr. Kularatne concludes that the PSMA-specific targeting ligand, DUPA, could potentially prove useful in targeting imaging to PCa, as well as many solid tumors for the purposes of locating primary and metastatic disease, detecting and quantitating CTCs, monitoring response to therapy, locating positive margins during surgery, and selecting patients for subsequent DUPA-targeted chemotherapy. DUPA should also prove beneficial in treating PCa and other solid tumors with minimal side effects.

During his doctoral studies, Dr. Kularatne has also developed FR-targeted PET imaging agents ([18F] and [68Ga]) and compared their uptake with [18F]-fluorodeoxyglucose (FDG) in arthritis models by collaborating with Nuclear Medicine & PET Research, VU MEDICAL CENTER, Amsterdam, Netherlands and with Merck Research laboratories, Merck & Co., Inc., West Point, Pennsylvania. Rheumatoid arthritis (RA) is an autoimmune disease characterised by chronic inflammation of the synovial membrane of the joints, which can lead to the destruction of cartilage, bone, and ligaments. Trace macrophage (a type of immune cells) infiltration of the synovial tissue is characteristic of the earliest stages of RA. FR-β is expressed on activated macrophages associated with inflammatory disease states, but not on quiescent or resting macrophages. As a result, the folate-targeted PET imaging agents are ideal for the detection of early stage inflammatory diseases. Based on the preclinical data, folate-PET traces are currently in further pre-clinical development for RA at VU medical center. Encouraged by the specificity

of folate-PET agents for RA, Dr. Kularatne has developed a folate-targeted immunotherapeutic agent (folate-trinitrophenyl or folate-TNP or folate-hepten) and proven potency of FR-targeted immunotherapy for RA. He was also a major contributor of developing self-immolative disulfide-bridged folate chemotherapeutic conjugates such as folate-didemnin B and folate-camptothecin. He was also a player in the team that demonstrate the disulfide-mediated drug release mechanism inside the cancer cells using animal models with folate-targeted fluorescence resonance energy transfer (FRET) imaging agent.

During his postdoctoral studies at Schultz's lab, Dr. Kularatne learned to incorporate unnatural amino acids into proteins that Peter G. Schultz has pioneered. This is a method for adding new building blocks to proteins or antibodies), beyond the common 20 amino acids. Using this technology, Dr. Kularatne developed a chemically defined anti-CXCR4 antibidy drug conjugate (ADC) to selectively eliminate tumor cells that express CXCR4. In a more detailed account, the unnatural amino acid p-acetylphenylalanine (pAcPhe) was site-specifically incorporated into an anti-CXCR4 antibody and conjugated to auristatin via a stable oxime linkage. The anti-CXCR4 ADC has promoted Auristatin-mediated killing of CXCR4+ cancer cells in vitro and eliminated metastatic lung tumor masses in mouse models, with no overt toxicity or off-target effects. It is important to emphasise here that most deaths associated with cancer are not due to the primary tumor, but due to the metastatic form of the disease. Therefore, effective cancer therapeutics must not only eliminate primary and metastatic tumor masses but also be able to selectively target tumor cells over normal tissues. The CXCR4 ADC is currently being evaluated at Ambrx Inc, La Jolla, CA, for further preclinical development.

Dr. Kularatne's outstanding research work on redirecting T-cells (a type of immune cells) to kill malignant cells using bispecific antibodies is a novel approach to cancer drugs (named as a Fab-ulous killer). In this avenue, Dr. Kularatne designed a bispecific antibody that simultaneously targets clusters of differentiation 3 (CD3) in T-cells and tumor associated antigens to recruit cytotoxic T cells from the patient's own immune system to eliminate cancer cells. After site-specifically incorporating pAcPhe into anti-CD3 fragment antigen-binding (Fab), folate was site-specifically conjugated to anti-CD3 Fab via an oxime bond. The anti-CD3 Fab-folate has eliminated T cell mediated killing of FR expressing ovarian cancer in cell culture and in animal models. Dr. Kularatne said that "this approach can be generalised to other ligands that bind cancer and the project is under clinical development at Ambrx Inc."

Looking back on his 11 year career, Dr. Kularatne said that "I am fortunate and blessed to develop drugs that can possibly make a tremendous impact on human life, especially those who are suffering from cancer and their loved one". He believes what Michael Jordan said "talent wins games, but teamwork and intelligence wins championships".

Dr. Kularatne stated that "I want to emphasise that all the accomplishments I have been involved with were a team effort. I have always been around a great group of people committed to work in cohesion with one another. I have been guided by great leaders and mentors. I have great parents, family and friends who support me unconditionally." +

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Cancer research and training take centre stage in NCI's work

Open Access Government spoke to the US National Cancer Institute's Dr S Percy Ivy about the importance of clinical trials and the agency's role in cancer research and training.

The National Cancer Institute (NCI) is one of 27 institutes that make up the National Institutes of Health (NIH). The NCI is the US federal government's primary agency for cancer research and training, and coordinates with the National Cancer Program, which supports research, training, health information dissemination, and other programmes with respect to the cause.

Cancer is a term that everyone worldwide is aware of, with new research suggesting that 1 in 2 people will be diagnosed with cancer in their lifetime. The NCI estimated that in 2016 1,685,210 new cases of cancer would be diagnosed in the US and that 595,690 people would die from the disease. However, the number of people living beyond cancer diagnosis reached nearly 14.5 million in 2014 and is expected to rise to almost 19 million by 2024.

Research is an integral (but not the only) part of the work conducted at the NCI. Research helps to learn more about various forms of cancer and how to treat and prevent the disease. Clinical trials are research that involves people, in order to help find to find new ways to improve treatments and the quality of life for people living with the disease.

Open Access Government Editor Laura Evans speaks to Dr S Percy Ivy at the NCI about the role of clinical trials and how cancer research has evolved over the years.

"Cancer clinical trials are essential for advancing the treatment of patients. These trials are a controlled framework in which selected populations of patients with cancer can be treated in a clinical research setting, based on results of earlier studies," explains Dr Ivy. "Essentially, for patients the goal is to prolong their life and, hopefully, be cured of the disease.

"The trial accomplishes several objectives from a medical and scientific point of view; we hope it changes the standard of care and improves the care and management of cancer patients. Patients are looking for response, slowing of their disease and improvement in their overall quality of life, and in some instances even remission and cure.

"I believe that clinical trials are essential for the advancement of cancer treatment. Networks of clinical investigators allow clinical researchers to evaluate large cohorts of patients, and more efficiently evaluate new treatments together across the country," Dr Ivy adds.

Developing new cancer treatments

The Cancer Therapy Evaluation Programme is one of the many programmes within the NCI and is focused on developing new cancer treatments. The clinical trials are made up of different phases which are used to detect how cancer responds to specific treatments.

As Dr Ivy outlines further: "Within the Cancer Therapy Evaluation Programme there are 2 very large programmes. The first is the Experimental Therapeutics Clinical Trials Network, made up of academic investigators across the US and Canada, who perform early phase clinical trials. The goal of those trials is to determine how to use a drug, what the drug properties are, and how it should be used in humans, as well as developing preliminary information on how the cancer responds to specific therapeutic interventions.

"The other large group in the US is the National Clinical Trials Network," she adds. "This is a group of

more than 3,000 investigators who perform much larger randomised phase 2 and phase 3 trials. They are looking for signs of activity, efficacy and survival or response to a treatment or combination treatment that will lead to a pivotal trial. The goal is to move to phase 3 trials that may result in licensing the treatment for a specific disease indication."

Orphan diseases and rare types of cancer

The NCI is aiming to find treatments for all types of cancer; however, they also focus on rare forms of the disease besides what are known as the big 4 – colon cancer, breast cancer, lung cancer and prostate cancer. The rare forms are ones that are not as actively studied or used in clinical trials by pharmaceutical companies and have less than 200,000 cases per year, although this landscape is changing.

"Orphan diseases, are defined as affecting fewer than 200,000 cases a year, and have not been as actively studied," says Dr Ivy. "In the past these orphan cancers have been much less attractive targets for pharmaceutical companies, so the NCI has filled this niche as an unmet medical need. Pharma is also changing and starting to work more in niche diseases. As we find that cancers, for example breast cancer, are really made up of a group of biologically distinct diseases that require different treatments, the challenge is to provide effective treatments for all different kinds of cancer and the challenge for pharma is to define a sustainable niche market.

"The goal of the NCI is to provide those treatment opportunities to the U.S public. The US Congress recently passed a bill called the '21st Century Cures Act' that will fund $4.8bn in medical research with approximately $1.8bn cancer related research. This means that we are able to develop synergies between programmes and initiatives that can effectively use that money in service of the public. We will do that collaboratively with researchers, organisations and companies and with our academic co- investigators, with the primary goal to make treatment for cancer widely available and accessible no matter how rare your disease is."

A revolution in cancer research and training

As our knowledge of cancer evolves, new ways to treat the disease are also established. Along with new technology and key innovations, research and clinical trials are able to understand the best treatment for a specific type of cancer. Dr Ivy explains that cancer research is in the middle of a revolution, with new therapies such as precision medicine and immunotherapy coming to the forefront.

"With the exception of immunohistochemistry for PDL1, there are no biomarkers to select patients to receive anti PD-1/PDL-1 immunotherapy," she says. "The tumours that have responded to these so-called checkpoint inhibitors have been those that were treated in the past with other immunotherapy agents, especially melanoma and renal cell carcinoma.

"However, there are areas in immunotherapy treatment that clearly stand out for the favourable response rates that have been seen, including lung cancers and Hodgkin's lymphoma, as well as some rare diseases, such as Merkel cell tumours. However, the utility of the PD-1 biomarker to identify patients who are likely to respond is limited, and more work is needed to develop more robust biomarkers. What is becoming very clear with immunotherapy, as is the case for most effective cancer treatments, is that it needs to be combined with other therapies, including chemotherapy, molecular therapies and radiation therapy.

"Cancer treatment globally will be changing. In addition to the scientific challenges, the high cost of treating cancer patients with immunotherapies and other therapies remain an issue. We must ensure that academic clinical research in the public interest is available widely and not simply to those who can afford it." +

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