— DELIVERING ON THE PROMISE OF IMMUNOTHERAPY FOR CANCER

Current mechanisms, strategies, and tools for drug developers.

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Chief Scientific Officer
Thomson Reuters
There is no question that immuno-oncology is hot.

While immuno-oncology drugs had combined sales of $2.5 billion in 2015, led by Keytruda (pembrolizumab, Merck & Co. Inc.), Opdivo (nivolumab, Bristol-Myers Squibb Co.), and Yervoy (ipilimumab, BMS), sales could reach as high as $40 billion by 2020, according to a recent report from the Tufts Center for the Study of Drug Development, as reported in *BioWorld*.¹

With players involved across the globe, Tufts found that the number of alliances between large drug companies and smaller biopharmas in the space had jumped from six in 2013 to 58 in 2015. The amount of funds committed increased just as rapidly from $2.8 billion in 2013 to $22.5 billion in 2015, although the report notes that the actual figure is larger since financial considerations aren’t disclosed for some of the partnerships.

And it’s not just for-profit companies involved. Universities and cancer centers have also gotten in on the action. According to the Tufts report, in the U.S. alone, 13 universities and cancer centers have announced research alliances with pharma and biotech companies.

For anyone involved in this rapidly evolving sector, understanding the competitive landscape – who is working on what and how far along they have gotten – is essential.
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THE PROMISE OF IMMUNOTHERAPY

In 2015, former U.S. president Jimmy Carter announced his cancer was in remission. Several months earlier, the former president had been diagnosed with metastatic melanoma, a deadly form of skin cancer that can quickly spread throughout the body. After surgery, President Carter was given a newly approved cancer drug that acts as an immune checkpoint inhibitor by blocking the PD-1 protein. The drug works differently than other cancer treatments in that it directs the body’s own immune system to attack and kill the cancer cells.

This new wave of cancer treatment could not come at a better time. Cancer is currently the second leading cause of death in the U.S., accounting for almost a quarter of U.S. deaths. The approximate lifetime likelihood of developing cancer is 50% in U.S. men and about 35% for women. The National Institutes of Health has estimated that in 2010, the cost of cancer in the U.S. was $160 billion, with more than $88 billion in direct costs, while the American Cancer Society estimates put the total worldwide economic impact of cancer in 2008 at just short of $900 billion.

Cancer immunotherapy, defined as treatments that restore or enhance the ability of the body’s own immune system to fight cancer, has been hailed as the most promising advancement for the treatment of cancer. The journal Science designated “immunotherapy of cancer” as its Breakthrough of the Year in 2013 to recognize the progress made in this area. These new therapies are more precise than the relatively non-specific cytotoxic agents traditionally used. They continue to generate antitumor responses after the completion of treatment, suggesting that the antitumor immune responses generated by these therapies could be more durable than those induced by chemotherapy.

Although currently a hot topic of research, the discovery leading to using the immune system to regulate cancer progression traces its roots back to the 1890s, when William B. Coley observed that bacterial infection often coincided with cancer regression. Coley developed the theory that post-surgical infections had helped patients to recover better from their cancer by provoking an immune response. He later reported the successful creation of a filtered mixture of bacteria and bacterial lysates to treat tumors, although others found it difficult to correctly prepare the toxins and reproduce the results. The field progressed little over the following century until recent advances in our understanding of the mechanisms by which
cancer cells evade detection by the immune system. Armed with this knowledge, researchers have identified several protein targets, most notably Programmed Cell Death-1 (PD-1) and Cytotoxic T-Lymphocyte-Associated protein 4 (CTLA-4), and more importantly, followed up by developing antibodies that act on these targets resulting in the activation of the immune system towards targeting of cancer cells. Clinicians are currently combining these with various other agents and showing synergistic effects with treatment results never previously heard of for cancers.

And the discussion about immunotherapies is not limited to just cancer. Immunotherapies are advancing outside of cancer as well. Studies are ongoing in infectious diseases, cardiovascular diseases, and diabetes, among others. As researchers learn from each of these diseases, they are better equipped to understand how to fine-tune the immune system to fight a host of diseases.

THE IMMUNE SYSTEM

The immune system has evolved to protect the body from foreign invaders such as viruses or bacteria. This protective system also plays an important role in tumor surveillance. The immune system often succeeds in suppressing early tumor growth and development; however, over time, some tumor cells manage to escape immune control and progress to clinical disease. What follows here is a brief explanation of the immune system; readers are directed to several excellent reviews for more in-depth information.

The immune response begins when the normal cell processes are disrupted. This disruption can occur from outside the cell as with an infection or, as in many cancers, from within the cell. Disrupted cells begin to divide more rapidly than they are destroyed, causing an abnormal growth or tumor. This, in turn, causes the overexpression of proteins that need to be degraded and removed from the cell or destroyed. These smaller antigenic fragments are presented on the surface of the cell by the Major Histocompatibility Complex (MHC). Antigens that can elicit an immune response do so by binding to specific receptors on certain cytotoxic T lymphocytes. This causes the CD4+ or CD8+ cells to multiply, thus beginning a process that eventually kills the altered or infected cancerous cell. Regulatory processes keep the immune system in check by shutting down the immune response before damage to healthy cells can occur. It is important to note that cytotoxic T-cells have receptors that are specific for very specific antigens. This ensures that the immune system does not get over activated. After the infection has diminished, a group of cells called Memory T-cells remain in circulation, constantly on guard in case the same infection or cancerous mutation occurs.
The immune system does try to fight cancer. However, cancer has evolved a remarkable array of strategies to avoid detection and destruction by the immune system. The breakthrough of the rapidly developing field of cancer immunotherapy aims to fight back at cancer with a plethora of novel mechanisms to engage the immune system. These mechanisms include blocking the way cancer avoids detection by immune cells, activating the immune system directly, or enhancing the immune response. The major immunotherapy strategies, which are often used in conjunction with each other, are shown in Table 1 and will be discussed in greater detail below.

<table>
<thead>
<tr>
<th>Strategy</th>
<th>MoA</th>
<th>Drugs</th>
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<tr>
<td>Disrupting the way cancer cells avoid detection</td>
<td>Checkpoint inhibitors</td>
<td>Ipilimumab</td>
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<tr>
<td></td>
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<td>Pembrolizumab</td>
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<td>Nivolumab</td>
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<td>Providing more cancer-targeting T-cells</td>
<td>Adoptive T-cell therapies</td>
<td>Tisagenlecleucel (P II)</td>
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<tr>
<td>Enhancing T-cell function</td>
<td>Increasing cytokine levels</td>
<td>Aldesleukin</td>
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<tr>
<td>Tagging the cancer cells for destruction by the immune system</td>
<td>Control of protein glycosylation</td>
<td>Gazyva (anti-CD20)</td>
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<tr>
<td>Triggering cancer-fighting immune cells</td>
<td>Activated dendritic cells</td>
<td>DCVax-L</td>
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<tr>
<td>Engineering a virus that preferentially infects and kills cancer cells</td>
<td>Preferentially lyses cancer cells</td>
<td>T-Vec</td>
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<td>Reolysin</td>
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TARGETS TO RELEASE IMMUNE SUPPRESSION

CHECKPOINT INHIBITORS

Cancer cells have evolved an ingenious strategy to trick the immune system into thinking the cells are healthy when in fact they are compromised. This strategy involves the control of proteins known as checkpoint inhibitors.\textsuperscript{10, 11}

There are two interactions necessary to elicit an immune response to fight infection or cancer (Figure 3). Receptors on the Antigen Presenting Cell (APC) known as B7 or CD80 must bind to CD28 receptors on the T-cell (green \(+\) at top of Figure 3). Additionally, antigen-loaded MHCs must also bind to the T-Cell Receptor (TCR)/CD3 complex on the T-cell (green \(+\) in middle of Figure 3). These interactions activate the T-cell to proliferate and destroy the cancer cells.

Additional receptors on the surface of T-cells act as “off switches” that, if engaged, can keep the immune system from activating. These receptors are known as checkpoint inhibitors (red \(-\) in Figure 3). Some cancer cells can take advantage of these off switches to keep the immune system from attacking. Antibodies that can block these off switches, and thus block the cancer from stopping immune activation, have been shown clinically to have a profound effect on certain cancers. The first, ipilimumab (Yervoy) from Bristol-Myers Squibb, is an antibody that blocks the interaction between CTLA-4 and B7. First approved in 2011 for stage IV melanoma after surgery, ipilimumab is being studied in a number of other cancer types and in combination with various other agents. While ipilimumab is relatively safe and effective, autoimmune or inflammatory immune-mediated adverse effects have been reported, presumably due to the immune activation it allows. See Table 2 for others in the pipeline.

<p>| Table 2: Checkpoint inhibitors with most advanced stage of development, as of May 2016. |
|----------------------------------------|----------------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Target</th>
<th>Preclinical</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
<th>Filed</th>
<th>Market entry</th>
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<tr>
<td>CTLA-4</td>
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<td></td>
<td></td>
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<td>2011</td>
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<tr>
<td>PD-1</td>
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<td>2014</td>
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<td>PD-L1</td>
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<td>IDO</td>
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<td>B7-H3 (CD276)</td>
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<td>PD-L2</td>
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<td>KIR</td>
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<td>LAG3 (CD223)</td>
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<td>TIM3 (HAVCR2)</td>
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TARGETS TO ENHANCE IMMUNE RESPONSE AND T-CELL FUNCTION

Two approaches to elicit an immune response to cancer cells involve increasing the number of dendritic cells in the tumor environment and turning on or activating immune cells already surrounding the tumor.

ADOPTIVE T-CELL THERAPIES

Chimeric Antigen Receptors-T-Cells (CAR-T) is a technique whereby T-cells are removed from a patient and modified so that they express receptors specific to the particular form of cancer. The T-cells, which can now recognize and specifically kill the cancer cells, are reintroduced into the patient.

CAR-T therapy has repeatedly provided dramatic results in patients with hematologic malignancies. A recent report showed an impressive 70% complete response rate reported in patients with acute lymphoblastic leukemia or non-Hodgkin’s lymphoma.12

One example, tisagenlecleucel-T from Novartis, under license from the Abramson Cancer Center of the University of Pennsylvania, has been developed for the potential IV treatment of B-cell leukemias and lymphomas. Novartis anticipates approval in 2017.

In December 2015, positive data in pediatric patients with relapsed/refractory acute lymphoblastic leukemia (ALL) were reported.13 Development in other indications is ongoing. While demonstrating significant positive outcomes, a number of on-target and off-target adverse events from CAR-T therapy have been reported.14

ENHANCING T-CELL FUNCTION

Cytokines are cell signaling molecules that aid cell-to-cell communication in immune responses and stimulate the movement of cells towards sites of inflammation, infection, and trauma. One reason cited for immune checkpoint efficacy is that the resultant decreased cytokine production in turn decreases the immune response. It is believed that increasing cytokine production will aid in an immune response to cancer. IL-6 and INF are two examples of cytokines necessary for T-cell proliferation; both are potential candidates for immunotherapy strategies.

Two cytokines are currently approved for the treatment of melanoma: interferon alfa-2b (Intron A, Merck & Co.) and interleukin-2 (Proleukin, Novartis). Used alone, both cytokines have been shown to shrink advanced (stage III and IV) melanomas in about 10-20% of patients treated.15 They may also be used in a combination regimen in patients with stage IV disease. Their efficacy, however, may be accompanied by serious side effects and toxicity.16

CONTROLLING GLYCOSYLATION

Alterations in glycosylation regulate the development and progression of cancer, serving as important biomarkers and providing a set of specific targets for therapeutic intervention.17 Several strategies are aimed at taking advantage of glycosylation states in cancer cells.

One example is GAZYVA (obinutuzumab), developed by Glycart and other Roche subsidiaries Genentech and Chugai, and licensees Biogen (previously Biogen Idec) and Nippon Shinyaku. GAZYVA is a humanized type II monoclonal antibody that binds to the CD20 antigen, a proven target for CD20+ CLL. It is engineered for reduced fucose content. Reduced fucose content has been reported to enhance binding and activation of immune effector cells in preclinical studies.

In February 2016, the FDA approved obinutuzumab plus bendamustine followed by obinutuzumab alone for rituximab-refractory follicular lymphoma. Development in other cancer indications is ongoing.

ACTIVATED DENDRITIC CELLS

Dendritic cells (DC) are important in the immune response. They present antigens in the lymph node to activate T-cell proliferation. One strategy in cancer immunotherapy is to increase and expand the number of dendritic cells to boost the immune system to fight cancer.
To do this, companies are using autologous DC to elicit specific T-cell and antibody responses to cancer-associated antigens. Examples include DCVax, products consisting of pure and active DC loaded with specific cancer-associated antigen that is able to migrate to the lymph nodes and stimulate the response pathway cascade.

The most advanced of these is DCVax for glioblastoma. Northwest Biotherapeutics is developing DCVax-Brain (DCVax-L), an autologous dendritic cell-based immunotherapy, for the potential treatment of glioblastoma multiforme (GBM). In March 2015, promising survival data from the Information Arm in GBM patients were reported.¹⁸

CANCER VACCINES

Autologous cancer vaccination strategies use material derived from a patient’s tumor to create personalized treatments. One type of vaccine encompasses autologous tumor cells irradiated *ex vivo* and then administered back to the patient with an immunostimulatory adjuvant to stimulate an anti-tumor immune response. Other methods of enhancing the immunogenicity of such autologous tumor cells include virally infecting them or engineering them to express immunostimulatory cytokines, such as IL-2, GM-CSF, or costimulatory molecules.

There are currently four cancer vaccines launched worldwide (Table 3).

<table>
<thead>
<tr>
<th>Launched agent (sipuleucel-T)</th>
<th>Developer</th>
<th>Mechanism</th>
<th>Status and indication</th>
<th>Data snapshot</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitespen (Oncophage)</td>
<td>Agenus</td>
<td>Peptide vaccine comprising a patient tumor antigen mixed with endoplasmin (Hsp 90 beta-¹)</td>
<td>Launched (2010) Russia – RCC Phase III – EU – RCC</td>
<td>In July 2014, a meeting was concluded with the FDA to initiate a Phase III trial with newly diagnosed glioblastoma multiforme.</td>
</tr>
<tr>
<td>MVax</td>
<td>AVAX Technologies</td>
<td>Cellular vaccine comprising autologous cells hapten-modified</td>
<td>Launched (2005) Switzerland – melanoma</td>
<td>This is a frozen formulation of a non-frozen launched VMVax vaccine launched in Australia.</td>
</tr>
</tbody>
</table>

Table 3: Launched cancer vaccines.
CURRENT CANCER IMMUNOTHERAPY DEVELOPMENT EFFORTS

There are currently more than 750 clinical trials ongoing for cancer immunotherapy representing 90 targets. Nearly half of the compounds are in Phase II testing. The majority of the trials will be completed over the next two years.

Figure 4: Current clinical trials for cancer immunotherapy (excluding vaccines, cytokines, antibody-conjugates and follow-on biologics). Source: Thomson Reuters Cortellis Competitive Intelligence
CANCER IMMUNOTHERAPY DEALS

The promise of cancer immunotherapy clearly has attracted many players to the space. More than 130 biotechs and 20 pharmaceutical companies are working on immuno-oncology therapies, according to the Tufts report, which also notes that there were 55 deals in 2015 for cancer immunotherapies.\(^1\)

The breadth of coverage is impressive, spanning at least 10 blood cancers and 18 different types of solid tumors. The nature of the deals is shifting as well. The ratio of products to technology deals has shifted to where half of all deals in 2015 were for technologies.

AstraZeneca plc, Roche AG, and Merck lead the pharma industry in immuno-oncology alliances with small biotechs and other enterprises, with 17, 17 and 15 deals, respectively.

It is interesting to note that there are many early-stage technology deals in this area.

REGULATORY PERSPECTIVE

Most clinical studies begin with a Phase I study, where a small group of patients, usually around 20 to 100, are used to demonstrate a drug is safe. They move on to Phase II studies, in which several hundred patients are tested in groups comparing the new medicine to existing standard of care or placebo. If the drug appears to work and there are few side effects, the studies move on to Phase III, where thousands of patients are studied over several years to demonstrate the drug is safe and effective.

According to the Centers for Medical Research, the average time for completion of the three phases of clinical trials is between 8 to 10 years, depending on the indication and size of the organization.

In an effort to reduce the time to getting drugs to market, the Food and Drug Administration Safety and Innovation Act (FDASIA) was signed in 2012. FDASIA Section 902 provides for a new designation, Breakthrough Therapy Designation. A breakthrough therapy is a drug:

• Intended alone or in combination with one or more other drugs to treat a serious or life-threatening disease or condition; and

• Preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development

If a drug is designated as breakthrough therapy,
If a drug is designated by the FDA as breakthrough therapy, the FDA will expedite its development and review in an effort to reduce the time required to get it to market.

the FDA will expedite its development and review. All requests for breakthrough therapy designation are reviewed within 60 days of receipt, and the FDA will either grant or deny the request.

In September 2014, Merck received approval to market pembrolizumab for the treatment of patients with advanced or unresectable melanoma who are no longer responding to other drugs. What was unique and interesting about this is that Merck did not follow the normal course of clinical studies to approval.

Merck began the first clinical trial for melanoma in February 2012 with an expected completion date of January 2018. Phase I trials generally last several months. Merck continued to add patients to the Phase I trial, and used this data to support the approval. In April 2013, the FDA designated the drug as a breakthrough therapy for advanced melanoma. In January 2014, a rolling submission of a BLA was initiated in the U.S. for patients with advanced melanoma who have been previously treated with ipilimumab. In May 2014, the FDA accepted the BLA for Priority Review. The drug was approved in September 2014. The length of time between the initiation of Phase 1 and approval was under three years.

The approval of Keytruda was based on data from a multi-center, open-label, randomized, dose-comparative study cohort of the ongoing KEYNOTE-001 Phase 1b trial in patients with unresectable or metastatic melanoma and progression of disease. Keytruda’s efficacy was established in 173 clinical trial participants with advanced melanoma whose disease progressed after prior treatment. All participants were treated with Keytruda, either at the recommended dose of 2 milligrams per kilogram (mg/kg) or at a higher dose of 10 mg/kg. In the half of the participants who received Keytruda at the recommended dose of 2 mg/kg, approximately 24 percent had their tumors shrink. This effect lasted at least 1.4 to 8.5 months and continued beyond this period in most patients. A similar percentage of patients had their tumor shrink at the 10 mg/kg dose.

Keytruda’s safety was established in the trial population of 411 participants with advanced melanoma. The most common side effects of Keytruda were fatigue, cough, nausea, itchy skin (pruritus), rash, decreased appetite, constipation, joint pain (arthralgia), and diarrhea. Keytruda also has the potential for severe immune-mediated side effects. In the 411 participants with advanced melanoma, severe immune-mediated side effects involving healthy organs, including the lung, colon, hormone-producing glands, and liver, occurred uncommonly.

Merck is now conducting more than 200 clinical trials with pembrolizumab alone and in combination with other drugs. Other checkpoint inhibitors are seeing similar levels of clinical development.

Due to the rapid advances in the field of immune therapy and the need to get medicine to patients as quickly as possible, guidance was published summarizing ideas that would be helpful to those who plan to develop cancer immunotherapies.19
COMBINATION THERAPIES

One of the major trends in immuno-oncology drugs is the testing of their use in combination with other chemotherapeutics or other immuno-oncology agents. It is hypothesized that targeting two or more pathways, including two or more immune checkpoints, will be a more effective approach to fighting the disease. For example, checkpoint inhibitors targeting CTLA-4 and PD checkpoints could be combined, as the costimulatory pathways do not completely overlap in their functions, and this dual blockade could bring additive or even synergistic benefits.

Chemotherapy/radiotherapy could be combined with vaccines. For example, docetaxel may increase tumor-associated antigen expression, thus sensitizing the cancer to vaccine-induced killing, while radiotherapy promotes an inflammatory response that promotes the presentation of tumor-associated antigens from dying cancer cells to immune-triggering APCs. Stimulation of antitumor immunity by anticancer vaccines or other immunostimulants could be combined with inhibition of tumor immune suppression by checkpoint inhibitors to provide complementary and synergistic anti-tumor effects. However, combination trials may also present additional complexities and risks, such as tolerability profiles, timing of the therapies, and regulatory hurdles.

As reported by the Cancer Research Institute in 2014, scientists have identified between 20 and 35 ligands and receptors that are involved in the immune response, yet only two of them – CTLA-4 and PD-1/PD-L1 – are in use. Scientists expect there will be more successes with additional antibodies targeting other molecules in the future. This is in agreement with data in Thomson Reuters Cortellis Competitive Intelligence that suggests that studies involving immunotherapy as both a cancer treatment and prevention method is a thriving field in biomedical cancer research, which lists more than 500 antibody-based therapies and more than 600 cancer vaccines in clinical development today.

INDICATIONS OUTSIDE OF CANCER

The power of the immune system can be applied to other indications outside of oncology. Literature is emerging for indications such as HIV infection, cardiovascular disease, and diabetes. It is expected that the list of indications will expand as the knowledge of the working of the immune system advances.

In type 1 or juvenile diabetes, the immune system abnormally attacks beta cells – the cells that secrete insulin – thus disrupting the body’s insulin levels. Therapies aimed at treating type 1 diabetes normally work to suppress the immune response in order to stop the attack against beta cells. However, these treatments also make the body more susceptible to infection and diseases like cancer.

In a paper published in *Science Translational Medicine*, Bluestone and colleagues developed an immunotherapy treatment for patients with type 1 diabetes by harnessing regulatory T-cells (Tregs), from the patients’ own bodies. Regulatory T-cells have been shown to be defective in autoimmune diseases. The cells were then grown outside the body to as much as 1,500 times more than the extracted amount and were reintroduced to the patients’ systems. Initial human studies demonstrated the technique was safe, and efficacy testing is ongoing.

Meanwhile, in patients with atherosclerosis, a chronic inflammation of the arterial wall, the immune system is believed to be involved in the pathogenesis of atherosclerosis. Immune suppression mediated by Tregs is a potential method to regulate pathogenic chronic inflammation in atherogenesis. Down regulation of effector T-cell response and/or Treg predominant condition was shown to induce atherosclerosis regression and inhibit the progression of aneurysm. While of limited utility in human studies to date, several randomized placebo-controlled clinical trials evaluating anti-inflammatory agents are being conducted to clarify whether targeting the inflammation itself will reduce cardiovascular events and risks.

FUTURE OF CANCER IMMUNOTHERAPY

As reported by the Cancer Research Institute in 2014, scientists have identified between 20 and 35 ligands and receptors that are involved in the immune response, yet only two of them – CTLA-4 and PD-1/PD-L1 – are in use. Scientists expect there will be more successes with additional antibodies targeting other molecules in the future. This is in agreement with data in Thomson Reuters Cortellis Competitive Intelligence that suggests that studies involving immunotherapy as both a cancer treatment and prevention method is a thriving field in biomedical cancer research, which lists more than 500 antibody-based therapies and more than 600 cancer vaccines in clinical development today.
CONCLUSIONS: REALIZING THE PROMISE OF CANCER IMMUNOTHERAPY

It is an exhilarating time as scientists press forward at a rapid pace in immuno-oncology, developing a deeper understanding of how nature does its work against tumors by unfettering and bolstering the immune system. While the progress to date has been uplifting, so much remains unknown about which of these complex approaches will work best. And new strategies are being discovered every day.

Immuno-oncology holds huge promise, not just for drug developers but especially for cancer patients and the physicians who treat them – a truly and incredibly significant breakthrough.

For the companies developing technology or products in the space, or looking for an alliance to help with either or both, Thomson Reuters has a deep portfolio of solutions that can help all throughout the drug development process:

• Discovery: Which targets are best for which cancers? Which combinations may yield the best opportunities? Thomson Reuters MetaCore disease pathways allow a customer to analyze experimental data and explore/rank diseases in the context of pathways, networks, and maps, while Thomson Reuters Integrity provides rapid insight on the current treatment landscape to allow identification of the current target development activities.

• Market sizing: With coverage of thousands of diseases, the Thomson Reuters Incidence & Prevalence Database is a powerful tool to investigate unmet needs and gauge market size across the spectrum in oncology.

• Competition and portfolio management: Thomson Reuters Cortellis Competitive Intelligence and Cortellis Clinical Trials Intelligence can help customers quickly and easily develop an in-depth and comprehensive picture of the competitive landscape around them. They can see what other drugs are being developed, for what likely indications, the likelihood of success of trials based on industry metrics, and likely timelines.

• Deal structures and terms – As the land grab in immuno-oncology continues, would-be partners or companies that are buying or selling need a deep understanding of the commercial value of the assets involved. Thomson Reuters Recap provides rapid insights that help determine how much an asset is worth, identify ideal partners for the best alliance, determine which type of transaction is best for you, and compare market-based deal terms for different types of transactions.
REFERENCES

15. Chiron Corporation, Chiron’s Proleukin granted a marketing license by the FDA for new metastatic melanoma indication. (1998).
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