ASPYRIAN’S PHOTOIMMUNOTHERAPY BASED ON THE IRDYE® 700 DX PLATFORM SHOWS EFFICACY IN A NUMBER OF STUDIES

Published on 01st October

A novel, highly specific, anticancer therapy called near infrared (NIR) photoimmunotherapy (PIT) that uses IRDye® 700DX, a phthalocyanine dye also known as IR700, has shown efficacy in a number of studies and several preclinical models in mice. Experimental data confirms that the combinational effect of the mAb conjugated with IR700 (mAb-700DX) offers specific, targeted, delivery of the near-infrared photosensitizer and, as a result, provides rapid in vitro necrotic cell death as well as in vivo tumor shrinkage. Based on the experimental data suggesting clear survival benefit, investigators believe that this novel trial drug offers a potential promise as a new therapeutic agent. [1]

One of the unique characteristics of this novel mAb-700DX conjugate is that it only gains anticancer activity as a therapeutic agent when it is bound to the target cell membrane and is activated with a laser emitting 690 nm near infrared light (NIR) at the tumor site. When this occurs, the mAb-IR700 conjugate causes a rapid disruption of membrane integrity leading to rapid cell death that appears to follow necrotic processes rather than mechanisms of apoptosis. However, if the agent is not bound to the target cell, even upon NIR illumination, there are no discernible effects. As a result, this novel approach has minimal side effects.

In this article, the author discuss the development of the trial drug and how this cutting-edge technology may advance cancer treatment and improves the lives of patients.

1.0 Current treatment options are limited

When it comes to treating cancer, current cancer treatments are often limited by the harm they may cause to healthy, normal, non-cancerous cells. Although traditional chemotherapy has greatly improved survival in many patients with cancer, their limited specificity may lead to significant adverse events. To avoid damage caused by these adverse events, dose reductions, are required. In turn, this limits the effectiveness of these agents.

Hence, there is a significant unmet need for highly targeted and tumor specific treatments that maximize target-cell killing while minimizing damage to normal cells. For this reason there is a great interest in monoclonal antibodies (mAbs) conjugated with a payload such as a cytotoxic drug or radioisotope. These antibody-drug conjugates or ADCs have shown a great ability to target – and reach – specific cancer cells. Advances in engineering tumor specific monoclonal antibodies (IgG, IgM, chimeric, humanized antibodies to fully human antibodies) have, over the last two decades, greatly improved the potential of these unique drugs.

References


Although very promising, traditional antibody-drug conjugates have their limits as well. For example, first generation antibody-drug conjugates with suboptimal toxic load may have reduced efficacy while, on the other hand, highly cytotoxic ADCs are generally associated with increased toxicity. Premature cleavage of the payload from the antibody-linker complex, the inability of the conjugate to breach the cell wall and binding (albeit limited) to non-target sites or getting eliminated from the body early, may further reduce efficacy of the antibody-drug conjugate. Other complications may be caused by the instability of the linker between antibody and cytotoxic drug. To counter these issues, higher drug doses may be required, which, in turn, increases the cost of therapy and the potential adverse events. Factors such as these show that there is still ample room to advance antibody-drug conjugates through novel technologies.

2.0 A revolutionary approach
Aspyrian Pharmaceuticals, a privately funded, clinical stage biotechnology company based in San Diego, California, is developing, what they believe, a revolutionary way to use an antibody-drug conjugate in combination with near infrared light illumination (NIR). [2] Investigators working with Aspyrian Pharmaceuticals have developed a photoimmunotherapy (PIT) based on the IRDye 700DX platform which was originally invented by researchers at the U.S. National Institute of Health (NIH) and the National Cancer Institute (NCI). This novel technology consists of an antibody-drug conjugate that is regionally activated by a red-light emitting diode (690 nm) after it has recognized and is attached to cancer cells. The PIT drug consists of a monoclonal antibody conjugated to the photosensitizer phthalocyanine dye IRDye® 700DX (NHS Ester). [3]

In anticipation of evaluating this technology in clinical trials, Aspyrian Therapeutics Inc. enlisted the support of Goodwin Biotechnology, Inc., a biological Contract Development and Manufacturing Organization (CDMO) that specializes in bioprocess development and cGMP manufacturing of biopharmaceuticals utilizing Mammalian Cell Culture expression systems and Bioconjugation technologies, to optimize and scale up the process, and then perform cGMP manufacturing of their unique antibody-drug conjugate.

3.0 Unique Characteristics
In contrast to other ADCs, antibody-photosensitizer conjugates such as the mAb-IR700 are largely independent of the need for internalization.

Furthermore, the conjugate technology can be applied to many antibodies without affecting the binding or the functionality of the antibody. Examples of mAb-IR700 conjugates include trastuzumab (anti-HER2), panitumumab and cetuximab (targeting EGFR) as well as an anti-CD44 monoclonal antibody designed to treat primary and secondary triple-negative breast cancer, and others. [4] As a result, it is possible to develop a host of mAb-IR700 complexes designed target a variety of cancers.

Finally, another unique characteristics observed in preclinical animal (mouse) models is that this photosensitizing compound, when distributed throughout the body, does not do harm unless the dye binds to a cell and an intense infrared light is applied to the prodruk, which is then activated.

In pre-clinical research, single NIR light irradiation was effective without significant side effects [5] Following exposure with NIR, target-selective necrotic cell death was observed in
Another advantage of the mAb drug conjugate is that cellular degradation of the linker is not necessary. As a result, the drug can be activated just by binding to the target cell. Garcia-Guzman clarified that the goal of PIT is not to try to replace any current cancer therapies with activating physical energy, like light or heat – such as in the case of NIR-PIT’s like mAb-IR700 – may be a potential method of improving therapeutic selectivity. [6][8][9]

While other novel therapies may be more effective in tumor targeting with reduced adverse events, the majority offer, so far, only limited success. Combining conventional, targeted, cancer therapies with activating physical energy, like light or heat – such as in the case of NIR-PIT’s like mAb-IR700 – may be a potential method of improving therapeutic selectivity. [6][8][9]

4.0 From mAb-700DX to RM-1929
In an interview with Miguel Garcia-Guzman, PhD, President and Chief Scientific Officer of Aspyrian Therapeutics (Photo 1.0) and Muctarr Sesay, PhD, Chief Scientific Officer and Vice President of Bioconjugation at Goodwin Biotechnologies, we discussed the development of RM-1929 and the reasons why NIR-PIT may be an important breakthrough in ADC-based cancer treatment. Garcia-Guzman and Sesay addressed some of the questions that physicians and researchers may have about this new technology and they shared with us how NIR-PIT is different from current ADC technology, and how these key differences may lead to a new, more effective and better tolerated cancer treatment option.

5.0 Platform technology
Aspyrian Therapeutics, which holds the patent to the exclusive use of the IRDye 700DX platform from Li-COR (Lincoln, Nebraska), is currently investigating RM-1929 in a Phase I clinical trial for the treatment of recurrent head and neck cancer.

This trial drug is based on the IRDye 700DX platform invented by Histaka Kobayashi, MD, PhD., and Peter Choyke MD, at the Center of Cancer Research (CCR) Molecular Imaging Program of the National Cancer Institute. Since the early days of this development, this technology has shown promising results in a number of in vitro and in vivo laboratory settings.

In their initial studies these researchers showed that when the mAb-IR700-cancer-cell-complex was irradiated with near-infrared (NIR) light cancer cells died rapidly but that infrared light alone or mAb-IR700-conjugate alone did not damage normal cells. Furthermore, in treating
and selective accumulation of the drug in the tumor; (II) following binding of the antibody conjugate to the cancer cells, laser-mediated illumination with light in the near-infrared range (690 nm) leads to activation of the drug conjugate and rapid selective destruction of the cancer cells that are bound to the antibody. Unbound drug is inert, even upon light illumination, and consequently the treatment is highly cancer specific sparing damage to healthy tissue around the tumor. (Source: Aspyrian Therapeutics, Inc.)

breast cancer tumors implanted in mice with mAb–IR700-conjugate and near-IR light they observed that PIT could result in massive and immediate cancer cell death and prolonged survival.

6.0 Bioluminescence imaging

Bioluminescence imaging or BLI, is a non-invasive imaging modality used in pre-clinical oncology research. This imaging modality involves the generation of light by luciferase-expressing cells in vivo following administration of a substrate. This relatively new technique allows a variety of tumor-associated properties to be visualized dynamically in living models. Using BLI, investigators were able to analyze disease processes at the molecular level. BLI is also an efficient way to measure tumor progression and metastasis. [6][10]

Although tumor sizes did not change after the PIT treatment given in initial studies with EGFR target-specific mAb-IR700 conducted by investigators at Aspyrian Therapeutics, the BLI signals decreased by >95% immediately after PIT. Additionally, BLI revealed that when the tumors were treated with the prodrug, no pharmacological activity occurred without or before irradiation. The fact that the drug was inactive without irradiation reveals its potential for creating a very regionally specific treatment, since the near infrared laser is focused only on the tumor area. [11][12]

In a separate study on mice implanted with pancreatic cancer tumors, PIT resulted in a significant reduction in tumor size and, once again, cell death was seen immediately after irradiation.

“In this case, immediate means that you can actually monitor instantaneously that you are affecting the cancer in vivo and in vitro,” noted Garcia-Guzman. Again, no significant effect was seen without both tumor attachment of the ADC and irradiation with light thereafter. [11]

7.0 Clinical Trials

The results of these initial studies sparked the interest of researchers at Aspyrian Therapeutics working in conjunction with their colleagues at Goodwin Biotechnology to manufacture the product candidate. Based on the investigational data, these researchers have developed the RM-1929, an antibody-drug conjugate, which, they expect, will show promising results in a current, ongoing, Phase I clinical trial (NCT02422979). The trial drug is being investigated for the treatment of patients with head and neck cancer (HNC) that – according to the patient’s physicians – cannot be satisfactorily treated with surgery, radiation or platinum chemotherapy.

Figure 3.0 Anticancer effects mediated by Photoinmunotherapy with IRDye 700Dx in vivo are rapid and highly effective. Treatment of both subcutaneous and orthotopic xenografts shows that within hours post light illumination the tumor is effectively destroyed. Experimental data has shown that the effects are highly cancer specific so that damage to healthy surrounding tissues are spared. This figure shows the anticancer response upon one round of treatment in an xenograft model implanted with two orthotopic breast cancer tumors, one serving as control and a second one treated using Photoinmunotherapy with IRDye 700Dx. The upper panels of full body fluorescence imaging (FLI) detecting the accumulation of the antibody-IRDye 700Dx conjugate at the two tumors. The upper tumor (right tumor in the mice) is then treated with 690 nm light illumination while the lower tumor (left in the mice) is not illuminated and serves as control. Treatment triggers rapid effects on tumor integrity as visualized with bioluminescence imaging (BLI). The treated tumor (upper tumor in the image) is completely destroyed while the untreated tumor (lower tumor in the image) is unaffected (adapted from Mitsuanga M et al., BMC Cancer. 2012 Aug 8;12:345. Source: Aspyrian Therapeutics, Inc.)
In April 2015 the US Food and Drug Administration (FDA) accepted Aspyrian’s first Investigational New Drug (IND) application allowing the company to initiate clinical studies.

In this first of its kind trial, investigators are trying to establish the Maximum Tolerated Dose (MTD) or Maximum Feasible Dose (MFD) of RM-1929, whichever is lowest, determine the adverse event profile for each dose, and assess the safety of the combination of the drug with low energy localized light irradiation (NIR) which includes skin photosafety (sunburn) testing designated to determine skin Minimal Erythema Dose (MED).

8.0 Mechanism of Action
RM-1929 consists of the monoclonal antibody cetuximab, designed to target EGFR, conjugated to the payload drug IR700 by a covalently bonded linker.

Because EGFR is highly expressed in squamous cell carcinomas of the head and neck, it is expected that systemic administration of RM-1929 will lead to tumor accumulation of RM-1929 and binding to EGFR expressed at cancer cells.

Following administration of RM-1929, subsequent light irradiation (NIR) should induce rapid tumor destruction of recurrent head and neck carcinoma (HNC) and provide an effective therapy to manage the disease.

Just as in the case of the platform trial drug, preclinical pharmacology demonstrated that light-induced activation of RM-1929 elicits rapid tumor destruction of human cancer xenografts implanted in mice, thus enhancing progression-free survival and overall survival with a better Quality of Life (QoL) than when using existing current Standard of Care (SOC) approaches.

As shown, two factors need to be met before the inert prodruk is able to have any pharmacological activity or what is called a “precision dual-targeting cancer treatment” effect. First, the monoclonal antibody must recognize and bind to tumor cells by targeting epidermal growth factor receptors (EGFR) present on the tumor cell surfaces. Second, laser-mediated illumination with light in the near-infrared range is only ‘activating’ on those mAbs that are bound to the tumor cells.

9.0 Adverse Events
Since both of these factors must be met for the drug to activate, there is a potential for more specific targeting of tumors. This means that activation of IR700 can be kept at the tumor site and systemic toxicity of the payload may be avoided. “If it is not bound, even if you irradiate with NIR light, there is basically no effect,” noted Garcia-Guzman. “What this approach provides is very exquisite cancer specificity.” [12]

In mAb-IR700-conjugates or such as with RM-1929, the fact that the drug remains inert before irradiation means there is a lesser degree of toxicity on healthy cells. In contrast, in traditional ADCs, the cytotoxic molecule or payload is not inert. Even though antibody recognition is able to target tumors, the drug may still be activated in healthy, surrounding tissue. Furthermore, conventional photodynamic therapy (PDT) photosensitizers lack tumor-specificity. In photoinmunotherapy (PIT), “Even if the antigen is bound to another tissue or organ somewhere else in the body,” noted Garcia-Guzman, “You only irradiate the tumor, and therefore, there is no pharmacologic trigger required to activate the dye.” And, since the payload drug will remain inert until activation by irradiation, photoinmunotherapy is very safe from a systemic prospective. [13]

10.0 Linker
Using a light source for activation means there is no need for degradation of a linker. This contrasts with currently available ADCs as well as most ADCs in clinical trials who require linkers to be optimized in order to degrade in tumor cells and release the active cytotoxin or payload. However, with PIT, the mechanical activation – by heat or light – of the drug means that cellular degradation of the linker is not necessary. As a result, the drug can be activated in as little as 24 hours! Emphasizing this crucial difference, Garcia-Guzman made clear that this means that it is not as important whether or not the parts of the ADC remain conjugated.

“From the pharmacological point of view, it doesn’t make a difference whether or not the antibody remains on the surface bound to the antigen,” he said. “There is very little difference in the effect of IR700 when the linker remains intact as opposed to when it is cleaved.
Because the light is only concentrated on the tumor site, the drug becomes active affects the tumor cells. An important additional characteristic of the trial drug is that the infrared light used to activate the payload is completely safe in humans. [14].

11.0 Impact on Drug Resistance

“One major issue with traditional ADCs is a limited potency because of cellular resistance," noted Goodwin Biotechnology’s Muctarr Sesay (Photo 2.0). “Conventional ADCs rely on cellular mechanisms for activation. Therefore, cells can adapt and become resistant to the drug after being exposed to it more than once. [15] [16] Since RM-1929 is activated by a physical process as opposed to reliant on cellular mechanisms, resistance is not a problem.”

“PIT will, in most circumstances, only need to be administered in a single dose,” Garcia-Guzman adds. “In fact, another unique characteristic of this application,” he points out, “is that antibodies that may have not yet been activated by the initial light treatment may re-accumulate in the remaining tumor cells. “When that happens, you can actually follow-up with a new light treatment and basically have an even more extensive anticancer killing effect,” Guzman noted. [17]

12.0 Potential for Combination Therapy

“As shown in a number of preclinical trials, the payload molecule IRDye (IR700) has the potential to be attached to several different monoclonal antibodies,” Sesay said. “This makes the targeting of various different cancers a real possibility.”

Depending on the results of the RM-1929 trial, there are hopes for PIT potential as first line therapy. “If we can prove that this translates into the clinic, and the safety and cancer specificity is really as high as predicted,” Garcia-Guzman confirms, “then we can expect that this technology when combined with other monoclonal antibodies may indeed become an alternative to front line therapies for a number of specific cancer types.”

In addition to being used as an individual therapy, there is potential for combining PIT with surgical resection and chemotherapy. The use of PIT in conjunction with other treatments is expected to increase the anticancer response with a significant reduction of tumor burden and lower the chances of tumor recurrence after standard treatments.

13.0 Bright Light Surgery

A study on PIT in combination with bright light surgery (BLS) showed significantly less tumor recurrence in mice treated with this combination, in comparison to those that received only BLS. With BLS, even after a tumor is removed, recurrence is not uncommon. Garcia-Guzman noted that after BLS, the use of PIT can eradicate any remaining micro-tumors that remain in the body after surgery. That’s why the clinical development of PIT will include evaluation of its activity in combination with surgery and other cancer modalities, as well as its effect in preventing recurrence. [18]

Garcia-Guzman clarified that the goal of PIT is not to try to replace any current cancer modalities, but instead provide a novel approach to cancer treatment on its own or when used in combination with existing treatments. “We see this technology being treated in conjunction with other cancer modalities to maximize anticancer activity,” Garcia-Guzman said.

Researchers at Aspyrian Therapeutics are confident that near infrared (NIR) photomunotherapy (PIT) with mAb-IR700 may lead to a novel, and widely applicable therapeutic platform.
Figure 1.0 Effects on Photoimmunotherapy on cancer cell membrane integrity. The left panel shows the phase contrast image of CD44 monoclonal antibody designed to treat primary and secondary triple-negative breast cancer xenografts implanted in mice, thus enhancing progression-free survival and overall survival of the cancer cells, laser-mediated illumination with near-infrared light they observed that PIT with mAb-IR700 may lead to a novel, and widely applicable prodrug, which is then activated.

RM-1929 consists of the monoclonal antibody cetuximab, designed to target EGFR, and a payload IR700-doped phthalocyanine, which, in turn, increases the cost of therapy and the potential adverse events. Factors such as photoimmunotherapy (PIT) with mAb-IR700 may lead to a novel, and widely applicable prodrug, which is then activated.

Following administration of RM-1929, subsequent light irradiation (NIR) should induce rapid light-induced activation of RM-1929 eliciting rapid tumor destruction of human cancer xenografts implanted in mice, thus enhancing progression-free survival and overall survival of the cancer cells, laser-mediated illumination with near-infrared light they observed that PIT with mAb-IR700 may lead to a novel, and widely applicable prodrug, which is then activated.

Antibody-drug conjugates (ADCs) combine antibody and cytotoxic drug. To counter these issues, higher drug doses may be required, example, first generation antibody-drug conjugates with suboptimal toxin load may have to post a comment.

Hence, there is a significant unmet need for highly targeted and tumor specific treatments that maximize target-cell killing while minimizing damage to normal cells. For this reason ADC Review / Journal of Antibody-drug Conjugates is a registered trademarks and trademarks of InPress Media Group around the world.

We recommend

Aspyrian’s Photodynamictherapy based on the IRDye® 700 DX Platform Shows Results
ADC Review, ADC Review, 2015

Goodwin Biotechnology partners with Aspyrian Therapeutics in Near-Infrared Photoimmunotherapy (PIT) Process Development and Manufacturing
Peter Hofland, ADC Review, 2015

Looking Ahead to 2020: Global Antibody-drug Market Prediction
adcreview, ADC Review, 2015

Improving Tumor Targeting Through Nanoparticle Encapsulation of Miniaturized Biologic Drug Conjugates
Peter Hofland, ADC Review, 2015

FDA Grants Priority Review for Brentuximab Vedotin in the Post-Transplant Consolidation Treatment of Hodgkin Lymphoma Patients at High Risk of Relapse (AETHERA Setting)
peterhofland, ADC Review, 2015

Doctors’ role in physical activity adherence: how can we keep patients on the road to better health?
chaggis, BJSM Blog, 2015

PTH-143 Application of gold nanorods for in vivo thermoanostics of human oesophageal adenocarcinoma
DS Elson et al., Gut, 2015

Sun Exposure in Athletes - 10 Tips to Prevent Cancer
ikhlan, BJSM Blog, 2012

Living with Leukaemia - The Expert Patient
gmitchell, EB Nursing blog, 2015

Molecular Profiling Transforming Care of Advanced Lung Cancer
The Oncology Practice
A novel, highly specific, anticancer therapy called Anti-CEA-IR700 has shown efficacy in a number of studies and several preclinical models in mice. This trial drug is based on the IRDye platform, which consists of an antibody-drug conjugate that is regionally activated by a red-light (690 nm) source. The light used to activate the payload is completely safe in humans.\[14\]

In their initial studies, these researchers have developed a payload system based on the hypothesis that antibody-drug conjugates (mAbs) conjugated with a payload such as RM-1929, the fact that the drug remains inert upon irradiation with near-infrared (NIR) light, there is basically no effect, noted Garcia-Guzman. What this approach delivers is expected that systemic administration of RM-1929 will lead to tumor accumulation of RM-1929, an antibody-drug complex. According to the Global Pharmaceutical and Biotechnology Industry, over the last 50 years, changed patient's physicians – cannot be satisfactorily treated with surgery, radiation or platinum chemotherapy.

In April 2015 the US Food and Drug Administration (FDA) accepted Aspyrian's first therapeutic indication for Brentuximab Vedotin in the Post-Extends Progression-Free Survival in Primary-Particle Therapy of Hodgkin Lymphoma with Brentuximab Vedotin Consolidation Analysis of Phase III Refractory Hodgkin Vedotin Consolidation

Choyke MD
Kobayashi, MD, PhD
Sesay, PhD
1.0

Infrared light irradiated with near-infrared (NIR) light leads to a new, more effective and better tolerated cancer treatment option. Physicians and researchers may have about this new technology and they shared with us what this technology consists of an antibody-drug conjugate that is regionally activated by a red-light (690 nm) source.

Great ability to target – and reach – specific cancer cells. Advances in engineering tumor microenvironments have shown that the tumor environment is significantly different from normal tissue. In vivo Anti-CEA-IR700 therapy significantly extends patient's life. Brentuximab Vedotin in the Post-Extends Progression-Free Survival in Primary-Particle Therapy of Hodgkin Lymphoma with Brentuximab Vedotin Consolidation Analysis of Phase III Refractory Hodgkin Vedotin Consolidation


References


Choyke MD, Kobayashi, MD, PhD, Sesay, PhD. Infrared light irradiated with near-infrared (NIR) light leads to a new, more effective and better tolerated cancer treatment option. Physicians and researchers may have about this new technology and they shared with us what this technology consists of an antibody-drug conjugate that is regionally activated by a red-light (690 nm) source. Great ability to target – and reach – specific cancer cells. Advances in engineering tumor microenvironments have shown that the tumor environment is significantly different from normal tissue. In vivo Anti-CEA-IR700 therapy significantly extends patient's life. Brentuximab Vedotin in the Post-Extends Progression-Free Survival in Primary-Particle Therapy of Hodgkin Lymphoma with Brentuximab Vedotin Consolidation Analysis of Phase III Refractory Hodgkin Vedotin Consolidation

