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 optioned 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.

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Although very promising, traditional antibody-drug conjugates have their limits as well. For example, first generation antibody-drug conjugates with suboptimal toxin 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 GMP 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.

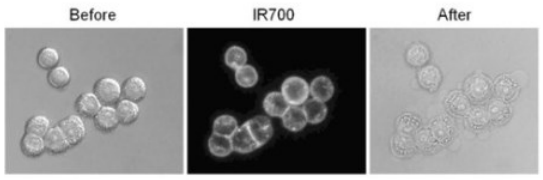

Figure 1.0 *Effects on Photoimmunotherapy on cancer cell membrane integrity. The left panel shows the phase contrast image of cancer cells prior to treatment. The middle panel shows the fluorescence detection of the antibody conjugate with IRDye 700DX bound to the cell membrane, and the right panel shows the phase contrast image of the cells after light illumination. Note that the cell integrity has been severely damaged after treatment (adapted from Mitsunaga M et al., BMC Cancer. 2012 Aug 8;12:345 – Source: Aspyrian Therapeutics, Inc.)*

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 prodrug, 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*

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vitro [6] while progressive tumor shrinkage *in vivo*, was observed 3 – 4 days after a NIR-PIT – even after a single administration of *mAb-IR700* and a single exposure with near infrared light illumination.[5][6]

Photoimmunotherapy (PIT), based on the novel trial drug mAb- IR700, is tumor-specific and has demonstrated specific binding to target receptors on the cell membrane, which is then followed by gradual internalization into endolysosomal compartments. Initial pre-clinical studies seem to suggest that this trial drug may potentially deliver very rapid and potent cancer killing effects while sparing healthy tissue adjacent to the tumor. [6] [7]

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]

Photo 1.0 *Miguel Garcia-Guzman, PhD, President and Chief Scientific Officer, Aspyrian Therapeutics Inc.*

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 Biotechnology, 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.

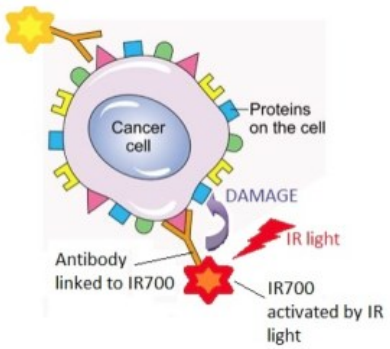

Figure 2.0 *Cancer Killing is mediated by the activation of the antibody conjugate bound to cancer cells with Laser Illumination of the tumor. Photoimmunotherapy with IRDye 700Dx induces cancer killing following a two-step process: (I) systemic administration of the antibody conjugate with IRDye 700Dx that targets antigens at the surface of the cancer cells leading to tumor binding*

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

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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 dug 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]

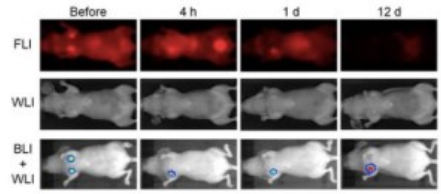

Figure 3.0 *Anticancer effects mediated by Photoimmunotherapy with IRDye 700Dx in vivo are rapid and highly effective. Treatment of both subcutaneous and orthotopic xenografts shows that within hours post light illumination the tumor is effectively destroyed. Experimental data has shown that the effects 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 Photoimmunotherapy 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 Mitsunaga M et al., BMC Cancer. 2012 Aug 8;12:345. Source: Aspyrian Therapeutics, Inc.*

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.

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TAGS

ADC | Anti-CEA-IR700 | antibody-drug conjugate | IRDye® 700DX | mAb | mAb-700DX conjugate | Monoclonal Antibody | near infrared | NIR IR700 | photoimmunotherapy | phthalocyanine dye | PIT | reactive oxygen species | ROS

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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 prodrug 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 *photoimmunotherapy (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, *photoimmunotherapy* 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.

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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].

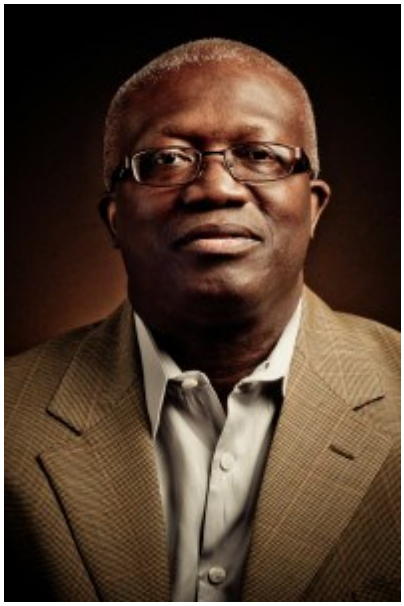

Photo 2.0 *Muctarr Sesay, PhD, Chief Scientific Officer and Vice President of Bioconjugation at Goodwin Biotechnology, Inc.*

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) *photoimmunotherapy* (PIT) with mAb-IR700 may lead to a novel, and widely applicable therapeutic platform.

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Last editorial review September 29, 2015

This article is researched and Written by Sonia Portillo based on interviews with

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- *Muctarr Sesay, PhD,* Chief Scientific Officer and Vice President of Bioconjugation at Goodwin Biotechnology, Inc.

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