



## How far will the Voyager<sup>®</sup> take us?

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### Need for better treatments for glioblastoma

Overall survival of people afflicted with glioblastoma (GBM) has improved modestly over the past 30 years and ranges between a median overall survival of 10 and 16 months depending on factors such as age, gender, extent of surgery, molecular-genetic features of resected tumors, radiation therapy and chemotherapy. Treatment options for people afflicted with GBM have changed somewhat based on molecular-genetic profiles that define worst-case scenarios [1–3] and improvements in radiation therapy that have also reduced CNS toxicity somewhat [4]. Based on patient convenience and outcomes, temozolomide has become the major anticancer drug therapy for these tumors [5]. Most recently, chronic treatment with alternating electric tumor treating fields to the head has gained US FDA approval for the treatment of GBM [6,7].

New therapies, especially new chemotherapy drugs, have been limited to brain penetrant alkylating agents (i.e., carmustine, lomustine, and temozolomide) since the 1970s. There are several reasons for this, which relate to drug delivery to infiltrative tumor cells behind the blood–brain barrier (BBB), drug residence time on tumor cell target, appropriateness of cellular target and the need to inhibit more than one cellular target, drug pharmacokinetics and drug safety [8,9].

### The Voyager potential for new GBM therapies

In this issue, the first clinical reports are published for the Nativis Voyager<sup>®</sup>, an investigational therapeutic medical device under development for the treatment of brain cancer in adults and children that exerts its action by mimicking drug effects on tumor targets [10,11]. How this is accomplished and what targets might be amenable to the Voyager approach may have tremendous implications for the future treatment of high-grade gliomas.

The Voyager utilizes proprietary ultra-low radio frequency energy (ulRFE<sup>®</sup>) technology to produce a cognate reflecting the binding of a molecule (e.g., chemotherapy drug or siRNA) to a cellular target by measuring and recording the subtle oscillating magnetic field produced by molecules in solution using a superconducting quantum interference device (SQUID). Binding molecules generate a unique electrostatic surface potential that is critically important to the chemical properties of that molecule and how that molecule interacts with and in a biological system. The Nativis company developed a sensitive magnetometer to measure the minute magnetic field fluctuations generated by the molecules in solution. They took these magnetic field changes and converted them to a ulRFE cognate that can be delivered locally to cells in culture and animals with tumors using specially designed coils. For people with cancer, Nativis developed the Voyager to deliver the recorded ulRFE cognate locally to the brain to induce a magnetic field that readily penetrates tissues. Preclinical studies suggest that some ulRFE cognates can regulate biological pathways and slow tumor development in xenograft models [12]. In that publication, it was shown the EGFR expression was reduced by a cognate to siRNA and that this led to decreased cell viability and survival of cultured cells and increased survival of mice with U87 tumors.

The two studies published in this issue – one conducted in the USA and the other conducted in Australia – are the early feasibility studies of the Voyager in adults with recurrent GBM. Early feasibility studies, like first-in-human

Phase I studies of drugs or biologics, are small studies with the primary goal of determining safety of a new medical device. It is important to understand that the stages of development for medical devices differ from that of drugs and biologics. Instead of following the familiar path of Phase I, II and III, clinical studies for devices are categorized as either feasibility studies or pivotal studies.

In the two feasibility studies, the patient populations were similar in both studies and consisted of patients with GBM who progressed/recurred following surgery, external beam irradiation with temozolomide and one or more forms of adjuvant chemotherapy. Most patients were enrolled after a first or second recurrence of their GBM. The first Voyager study, NAT-101, was a multisite study conducted in the USA [10]. Investigators could choose to treat patients with recurrent GBM with Voyager alone or with Voyager plus concurrent chemotherapy or immunotherapy of their choice. Treatment was permitted to continue postprogression, and patients were followed until death. In this study, the Voyager was programmed with the A1A cognate, which was derived by measuring and recording the electrostatic surface potential of paclitaxel in solution. Paclitaxel is restricted in the BBB passage primarily because of an efflux transporter [13]. Even with these caveats, it has been evaluated in GBM patients in combination with radiation therapy [14–16] and in combination with other drugs [17,18]. In all cases, therapy with paclitaxel has been intravenous and restricted to infrequent dosing on a weekly or multiweek basis. While some clinical efficacy was observed, the schedule of paclitaxel used was insufficient to produce a valuable patient-survival benefit. The Voyager approach eliminates those therapeutic restraints since no drug is distributed, and the mimic of paclitaxel binding will last if the Voyager is on to produce the uRFE cognate.

The second Voyager study, NAT-105, was a single-site study conducted in Australia [11]. Again, investigators could choose to treat patients with recurrent GBM with Voyager alone or with Voyager plus concurrent chemotherapy or immunotherapy of their choice. In addition, investigators could choose to treat all patients with Voyager as monotherapy. Treatment was permitted to continue postprogression (in addition to other therapies), and patients were followed until death. Also, in this study, the Voyager was programmed with one of two different cognates. For the first cohort, the Voyager was programmed with the same A1A cognate used in NAT-101. For the second cohort, the Voyager was programmed with A2HU, which consisted of two cognates: one derived by measuring and recording the electrostatic surface potential of a CTLA-4-directed siRNA, and the other derived by measuring and recording the electrostatic surface potential of a PD-1-directed siRNA. This is again a whole new concept where no drug is given systemically, but in the tumor microenvironment PD-1 protein will not be produced or, at the least, reduced if the Voyager signal is on.

## Conclusion

The results of both studies demonstrate a benign safety profile of the Voyager in a total of 28 patients treated by with one of two unique cognates (17 with A1A and 11 with A2HU). There were no serious adverse events and few adverse events attributed to the device; no adverse event led to discontinuation of Voyager.

Given the small size of the studies and the uncontrolled study design, conclusions cannot be drawn from the clinical utility data. However, the fact that 30–50% of patients were alive 12 months after starting Voyager therapy is encouraging. Clearly, larger controlled clinical trials of monotherapy and combination approaches with multiple cognates and systemically administered drugs will be needed to determine the full impact of Voyager therapy on overall survival for people afflicted with GBM.

## Financial & competing interests disclosure

The author is the Founder and Senior Medical Adviser for Orbus Therapeutics, DMC Chair for Bristol-Myers Squibb clinical trials and a member of SAB for Nativis, Inc.

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