Blue Wave Therapeutics

Executive Summary

Blue Wave Therapeutics GmbH is an early-stage radiopharmaceutical company founded in late 2021 to develop novel treatments aimed at significantly improving the survival of cancer patients. Blue Wave Therapeutics is based in Switzerland, and has an affiliate and an R&D laboratory in Norway.

Blue Wave's foundational work and first patent are based on the groundbreaking science from Michael Dornish, PhD and Jostein Dahle, PhD, both of whom spent many years developing radiopharmaceuticals in academia as well as in biotech companies. Michael Dornish, Blue Wave Therapeutics' co-founder and Chief Scientific Officer (CSO), is the former CSO of Algeta (now part of Bayer), where he led the scientific development of Xofigo®; he has over 15 years of experience in cancer drug development and 15 more years in biopolymers for drug delivery. Jostein Dahle, Blue Wave Therapeutics' co-founder and Chief Technology Officer, formerly co-founder and CSO at Nordic Nanovector, has 25 years of experience in cancer research and biotechnology.

Blue Wave Therapeutics' proprietary radioactive biopolymer platform can selectively kill tumor cells using alginate nanoparticles coated with a binding peptide to deliver a radionuclide payload to targeted tumor cells. The IP covers the use of alginate nanoparticles with various peptide sequences and different radionuclides, making the platform highly scalable for targeting a wide range of solid tumors.

Blue Wave Therapeutics is advancing its first product candidate, ^{225}Ac-RGD-Alginate nanospheres (ARAspheres), through preclinical development to demonstrate proof of concept in glioblastoma (GBM), the most common and deadliest type of brain cancer.

The company has raised approximately CHF 500k from founders and angel investors and recently received a NOK 16m (around CHF 1.3m) non-dilutive grant from the Norwegian Research Council, requiring matching external funding. These funds have initiated a robust R&D program at both the company's Norwegian R&D lab and in collaboration with partners Minerva Imaging in Denmark and Sintef in Norway. The program aims to optimize ARAspheres, improve their manufacturing process, and evaluate toxicity, biodistribution, and therapeutic efficacy in rats with GBM, 3D models, and GBM patient-derived xenografts.

Current GBM treatments include surgical resection followed by radiotherapy, possibly combined with chemotherapy. Despite these treatments, most patients relapse, and survival rates are low, with a median overall survival under 15 months. Systemic therapies often fail due to the blood-brain barrier, leaving few options for recurrent GBM patients.

Blue Wave Therapeutics' first product candidate consists of radioactive nanoparticles targeted at integrin receptors overexpressed on GBM cells. The nanoparticles can be injected directly into the resection cavity following surgical resection or via a catheter for other tumors. A parenteral formulation is also possible.

ARA-spheres can be used alone or integrated into the standard of care treatment (adjuvant radiotherapy and/or chemotherapy).

The company is currently seeking CHF 1.5m in three tranches, with the first installment of approximately CHF 300k expected in Q3-4 2024. A series of milestones have been agreed upon with the Norwegian Research Council, including a preclinical Proof of Principle in Q2 2025.

Project Description

1a. The management team

Marco G. Renoldi, MD, Chief Executive Officer

2017-present Board member, RESPINOR AB, Norway
2022-2024 Chairman, Phi Pharma, Switzerland
2021-2024 Managing Director, Bonafide Associates GmbH
2014-2021 COO, Nordic Nanovector, Norway
2012-2014 CCO, Shionogi, UK
2003-2012 Executive Director, International Franchise Head, Oncology Amgen, Switzerland

Michael Dornish, PhD, co-founder and Chief Scientific Officer

2015-present Managing Director, Dornish Consulting
2009-2015 Scientific Director & QC Manager, Nova Matrix/FMC Bio Polymer, Norway
2006-2009 Chief Scientific Officer, Algeta, Norway
1996-2006 VP, Research & Development, Pronova Biomedical/FMC Bio Polymer, Norway
1990-1995 Head of Dept. Department of Pharmacology, Pronova, Norway

Jostein Dahle, PhD, co-founder and Chief Technology Officer

2024-present Head of Research and Innovation, Dep of Oncology, Ahus University Hospital, Norway
2011-2023 Co-founder and Chief Scientific Officer, Nordic Nanovector, Norway
2023-present Managing Director, Jostein Dahle Consulting
2004-2010 Group Leader, Dep of Radiation Biology, Norwegian Radium Hospital, Norway

Luca Sereni, co-founder and Chief Operating Officer

2015-present CEO, Cell Dynamics (med-tech company), Italy
2018-present Co-founder, Special Carbon Products, Italy
2015- 2018 Co-founder and CEO at Freedom Waves (med-tech company), Italy

Luigi Costa†, co-founder and formerly a member of the management board (2021-2024)

2020-2023 CEO, Noema Pharma, Switzerland
2020-2024 Chairman, Pin Cell Srl, Italy
2021-2023 Board member, Phi Pharma, Switzerland
2019-2024 Entrepreneur in Residence, Sofinnova, France
2018-2024 Entrepreneur in Residence, Pureos Bioventures, Switzerland
2014-2018 CEO, Nordic Nanovector, Norway
2012-2014 International Region Head, Onyx Pharma, US

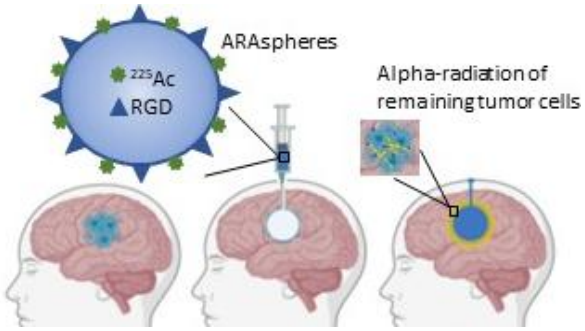
1b. Company structure

Blue Wave Therapeutics GmbH, a Swiss company, is owned 86% by the founders (and Luigi's community of heirs) and 14% by one CRO (5%) and angel investors (9%). Blue Wave Therapeutics GmbH wholly owns Blue Wave Therapeutics AS, a Norwegian subsidiary that is responsible for the research program outlined in this application.

2a. Scientific rationale

Glioblastoma multiforme (GBM) is the deadliest and most common type of brain cancer, with a median survival of only 14-16 months. Current GBM treatments are ineffective at significantly improving patient survival. These treatments are too toxic, administered too late after surgery, and lack targeted delivery.

One major issue with the current standard of care is that radiotherapy (RT) or RT combined with chemotherapy fails to significantly prolong overall survival, especially in relapsed patients. These treatments typically begin 4-8 weeks after surgical resection and are not targeted approaches. Our goal is to address the primary cause of treatment failure: the recurrence of tumor growth around the resected area.



Blue Wave's ^{225}Ac-RGD-Alginate nanospheres (ARAspheres), is the first product candidate originating from our radioactive biopolymer platform. It consists of a suspension of integrin-targeting alginate nanoparticles that can be delivered locally, immediately after surgery (Fig. 1). These nanoparticles specifically irradiate integrin-expressing glioblastoma tumor cells with highly effective, short-range alpha-particle radiation. Our aim is to potentially double the life expectancy of these severely ill patients.

2b. Results achieved so far

ARAspheres with nanometer diameters have been produced using a scalable pharmaceutical milling process. This represents our prototype of ARAspheres for use in *in vivo* studies.

A critical milestone was determining whether the alginate particles could bind the radionuclide ^{225}Ac and its daughter nuclides. More than 95% of the available radioactivity from ^{225}Ac and its daughters were associated with the particles at all time points over a 35-day period after labeling. Importantly, decay daughters were not detected in the wash solution from the particles prior to measurement, indicating that they will remain with the alginate particles and irradiate the tumor cells with alpha particles.

2c. Project description

Blue Wave's first product candidate is differentiated in several ways:

- Alginate nanospheres are exceptionally effective chelators for radionuclides, thanks to the flexible properties of alginate and the abundance of helating molecules. Blue Wave employs alpha-particle radiation, which is more efficient at cell killing and has a shorter range than beta particles because alpha particles are 8000 times heavier and have a 2+ charge, compared to the -1 charge of beta particles. Recently, actinium-225 has become more readily available for preclinical and clinical development due to increased manufacturing capacity by several companies. Alginate nanospheres can stably chelate both the alpha-emitting radionuclide and its daughter radionuclides for more than 30 days.

- Blue Wave leverages an anti-integrin peptide (RGD) conjugated to the nanoparticles, enabling targeting and binding of integrin-expressing tumor cells. Integrins are a clinically validated target, and the RGD peptide has been clinically validated in a phase 3 trial of the product candidate Cilengitide (Merck). Although the trial failed due to the lack of efficacy of the active compound, it confirmed that integrin targeting is safe. RGD has also been shown to bind to and inhibit integrins both preclinically and in phase 1-3 clinical trials (Li ZB et al., 2007. J Nucl Med. 48(7):1162-71; Stupp R et al. 2014. Lancet Oncol. 15(10):1100-8). The integrin αvβ3 is overexpressed in brain tumor cells but has low expression in normal brain cells. Several preclinical and clinical projects for glioblastoma, led by Tel Aviv University, U-Cell Therapeutics, NanoPharmaceuticals, Radiopharm Theranostics, EvaThera, and Novartis, are targeting integrins as a potential brain cancer treatment.

The NOK 16 million non-dilutive grant from the Norwegian Research Council, which must be matched by an equivalent amount of external funding, has enabled the launch of a comprehensive R&D program. This research program is being conducted both in-house and in collaboration with two external partners: Minerva Imaging in Denmark and Sintef in Norway.

The primary objective of the program is to document the preclinical proof of concept for Blue Wave's technology, by demonstrating that ARAspheres can be used to treat GBM in animal models.

The secondary objectives include:

(1) Optimizing the GMP manufacturing process for ARAspheres.

(2) Assessing the binding and cytotoxicity of ARAspheres in GBM cells and other cell types that metastasize to the brain.

(3) Evaluating the toxicity and safety of radioactive and non-radioactive RGD-alginate nanospheres in the brains of rodent GBM models.

(4) Evaluating the effectiveness of ARAspheres for GBM treatment in a GBM model with an infiltrative growth pattern.

(5) Demonstrating the effectiveness of ARAspheres in patient-derived xenograft (PDX) GBM models and in tumor cells metastasizing to the brain.

2d. Investment needed at this stage

Blue Wave is currently seeking a seed investment of CHF 1.5 million to match the non-dilutive grant received from the Norwegian Research Council. This investment can be divided into three tranches: approximately CHF 300,000 by Q3-4 2024, a second tranche in 2025, and a third tranche in 2026. The combination of the non-dilutive grant and the seed funding will enable Blue Wave's team to complete the R&D program within the next 30 months and achieve a series of related milestones.

2e. Specific goals and deliverables with investment requested

The goals of the R&D program are as follows:

- Develop an optimal method to produce alginate nanoparticles with appropriate size, size distribution, stability, and radionuclide binding;
- Develop an optimal method to radiolabel alginate nanoparticles to achieve the highest binding efficiency;
- Confirm that ARAspheres can bind to glioblastoma cells and are cytotoxic;
- Confirm the infiltrative growth of the C6 GBM model;
- Confirm the diffusion of ARAspheres into the rat brain;
- Determine the Maximum Tolerated Dose (MTD) in rats;
- Determine the absorbed radiation doses to critical organs and tumors;
- Achieve preclinical proof of principle for ARAspheres;

The related milestones agreed upon with the Norwegian Research Council, pending funding, are as follows.

- Production of RGD-alginate nanoparticles: Q4 2024
- Optimization of ARAspheres for radionuclide labeling: Q2 2025
- Acceptable toxicity in the rat C6 GBM model: Q2 2025
- Preclinical Proof of Principle in the rat C6 GBM model: Q2 2025
- Establishment of an in vitro 3D model of glioblastoma: Q3 2025
- Manufacturing readiness for tech transfer to CMO: Q1 2026
- Preclinical Proof of Concept confirmed: Q1 2027

2f. Time to next investment

Blue Wave is seeking a CHF 1.5 million seed investment to be disbursed in three tranches: the first (CHF 300k) in Q3-4 2024, the second in Q1-Q2 2025, and the third in Q2 2026. Subsequently, by late 2026 to early 2027, we aim to secure a Series A investment of up to CHF 15 million to fund a Phase 1-2a clinical program.

3a. Project status and next steps

Blue Wave's first product candidate, ARAspheres, is currently in the late discovery to early preclinical stage, with an ongoing IND-enabling R&D program. Simultaneously, Blue Wave is actively engaging with other biopharmaceutical companies interested in radiopharmaceuticals, which may seek to leverage Blue Wave's alginate nanospheres technology to develop new lead assets targeting other indications.

3b. Patent portfolio

Blue Wave has a patent family application titled "Peptide-Coupled Alginate Gels Comprising Radionuclides," with Michael Dornish and Jostein Dahle as inventors. The Norwegian patent (NO 347755) was granted on March 18, 2024, with priority from October 21, 2021. Additionally, Blue Wave entered the national application phase of the PCT application (WO2023066994A1) in April 2024. Blue Wave has strategically managed the application process in key global regions to ensure broad and effective protection of our innovations. This robust IP estate grants Blue Wave's platform unique flexibility, allowing for the inclusion of alternative radioisotope payloads, such as other alpha emitters besides actinium-225, as well as beta emitters. It also accommodates alternative targeting peptides beyond integrins, including those that bind to LDL, MMP-2, IL13R2a, VDAC1, NBD, c-MYC, CXCR4, and MDGI, along with combinations of these peptide sequences.

4a. Targeted market need

Blue Wave was established with a mission to offer improved treatment options to patients suffering from underserved forms of cancer. The first area of focus, serving as a proof of concept for the first product candidate, is on glioblastoma (GBM), a medical condition with significant unmet needs. GBM, the most common primary malignant brain tumor, represents an aggressive form of cancer with few available treatment choices, marked by a grim prognosis and limited overall survival rates. Annually, there are over 80,000 cases of glioblastoma reported by Global Data across the largest 16 countries, with the majority of patients succumbing to the disease. GBM grows quickly and can double in size in 10 days. Due to the aggressive nature of the disease, patients with a diagnosis of GBM suffer severe neurological deficits, and the disease can be rapidly fatal. GBM patients have a median survival of 14-16 months, a 2-year overall survival rate of less than 30% and a 5-year survival rate of less than 10% with the current standard of care. Blue Wave's aspiration is to improve the lives of brain cancer patients substantially.

Glioblastoma also presents a substantial business opportunity. The forecasted market value for treatments targeting this condition is estimated by Global Data to reach USD 3 billion by 2031 in the eight largest markets. This market growth is expected to be propelled by the introduction of new therapeutic options, including enzyme inhibitors, cytotoxic T-cells, peptide inhibitors, and

radiopharmaceuticals. New therapies that can prolong overall survival are expected to command a price premium compared to currently approved drugs.

4b. Major players/competition

There are only three approved drugs for treating GBM, each offering minimal survival benefits. Temozolomide (Temodar/Temodal) by Merck is an imidazotetrazine derivative used as adjuvant chemotherapy for newly diagnosed and advanced GBM. It minimally affects adjacent brain tissues and lacks severe systemic toxicity, but its efficacy is limited, extending median survival by only 2.5 months when used with surgery and radiotherapy (14.6 months vs. 12.1 months without it). Avastin (bevacizumab) by Roche/Genentech is a monoclonal antibody inhibiting VEGF, approved in the USA for recurrent GBM. In two non-randomized studies, Avastin showed response rates of 19.6% and 25.9%. A phase 2 study comparing Avastin with lomustine vs. lomustine alone found no overall survival benefit, with progression-free survival at 4.2 months vs. 1.5 months. Consequently, Avastin is not marketed in Europe for GBM. Gliadel (carmustine wafer) by Arbor Pharmaceuticals is an implant used post-surgery that reduces systemic adverse events and slightly improves survival by about two months in recurrent and newly diagnosed GBM.

Numerous projects are in various stages of development, with enzyme inhibitors, cytotoxic T-cells, and peptide inhibitors among the most advanced in clinical trials. Despite these efforts, the attrition rate is notably high, with many projects failing during development, likely due to the inability of drugs to penetrate the blood-brain barrier. This highlights the ongoing need for innovative therapies. Reflecting the strong interest seen in other areas of oncology, several radiopharmaceuticals are also being developed for glioblastoma. However, these use different technologies than ours. Blue Wave Therapeutics is unique in developing the only integrin-targeting radioactive biopolymer for glioblastoma.