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Ex-Novartis Oncology Leader Riva Takes On Challenge Of Transgene Turnaround

Can Its Oncolytic Virus And Therapeutic Vaccine Platforms Finally Come Good?

by Andrew McConaghie

After AstraZeneca walked away from a oncolytic virus vaccine partnership in May, French biotech Transgene was in sore need of a new direction. Enter new CEO Alessandro Riva, a man determined to deliver a proof of concept for the company.

French biotech company *Transgene* has endured multiple setbacks over the last 15 years as it tries to develop ”cancer vaccines” to stimulate an immune response to tumors, but its new CEO, Alessandro Riva, believes he can finally steer it to its first R&D success.

The Strasbourg-headquartered firm, established back in 1979 as one of France’s first biotech companies, has long had the backing of its majority shareholder, the family-run Institut Merieux.

The company is developing two separate cancer vaccine platforms – a name that stuck long ago because they use viruses, though the products are better understood as immunotherapies. The first platform uses oncolytic viruses (OVs) to enter tumor cells and destroy them from within, while the second consists of therapeutic vaccines, which target surface antigens to nudge the body’s immune system into identifying and killing the cancer cells.

This latter category includes TG4050 a “personalized” vaccine targeting neoantigens – an approach that is generating renewed interest this year thanks to an apparent breakthrough by *Merck & Co.* and *Moderna* with mRNA-4157/V940.

However, confidence in Transgene’s platform is much lower, and the firm was dealt a hit in May to its OV platform when AstraZeneca opted to walk away from an alliance.

The blow convinced Transgene's main shareholders that a fresh approach was needed, and recognizing the need for a leader with experience in biopharma R&D and deal-making called on Riva (already the company's chairman) to become CEO in place of Hedi Ben Brahim.

ALESSANDRO RIVA

Riva is a biopharma veteran, having made his name as oncology R&D leader at *Novartis*, where he was involved in developing more than 20 drugs including targeted and immune-oncology therapies, before moving on to *Gilead* in 2017, where he oversaw the launch of its CAR-T drug, Yescarta (axicabtagene ciloleucel).

He followed that up with subsequent CEO roles at *Glenmark* spin-off *Ichnos Sciences* and cell and gene therapy company *Intima Bioscience*. But turning around Transgene may well be Riva's biggest challenge yet: not only must he bring a first drug development success, but he also urgently needs to address the company's fast-dwindling cash reserves.

Transgene is critically low on funds, having just €17m in cash and cash equivalents as of 31 March, which are expected to last it only until early 2024.

Riva believes he can help turnaround the company's fortunes. "I'm here to bring the company to the next level. For me, it's about the science, and the challenge from an operational perspective, and on a personal level, I'm a European and this is a European company," he said.

"I believe Transgene can continue the journey to becoming a competitive biotech with a dynamic operating model."

New Approaches To Overcome Immunotherapy Limitations

One of the main reasons for the failure of many previous OV-based therapies is that immune system is quick to shut down virus interlopers and so most OVs have recorded very limited clinical impact in clinical studies.

That was the fate of Transgene's earlier lead candidate, Pexa-Vec, partnered with *SillaJen*, which failed in a Phase III study in 2019 as a first-line liver cancer therapy.

The company's first-generation therapeutic vaccines fared no better, its TG4010 candidate failing in a Phase II study combining it with chemotherapy and Bristol Myers Squibb's PD-1 immunotherapy Opdivo (nivolumab) in non-small cell lung cancer in the same year.

Since then, the company has developed next-generation technologies: myvac, a personalized therapeutic vaccine platform targeting patient-specific neoantigens, and Invir.IO, a new OV platform based on the vaccinia virus, which aims to modulate the tumor micro-environment to mount a stronger attack on cancers.

One of Transgene's lead oncolytic virus-based candidates is TG6050, currently in Phase I development in metastatic non-small cell lung cancer. It selectively replicates within tumor cells, and once there genes encoded into its DNA see it produce the cytokine IL-12 and an anti CTLA-4 antibody, with the goal of triggering an immune cascade to fight the tumor and metastases.

This is an intravenously administered therapy, and Riva believes this could show a greater impact than the traditional OV delivery direct into a tumor site, as long as it can avoid the "allo rejection" that scuppered its earlier attempts.

Meanwhile, TG4050 is the first myvac candidate, and is Phase I trials as an adjuvant treatment for ovarian cancer and head and neck cancer.

Preliminary Phase I data were presented at the recent American Society of Clinical Oncology meeting in Chicago, showing encouraging efficacy in head and neck cancer. All 16 patients who received TG4050 remained disease-free, with a median follow-up time of 10.4 months, comparing favorably to the control arm, in which two patients with similar characteristics experienced relapse. Two other patients also showed biochemical signs of relapse.

The study also showed that patients developed a specific immune response after treatment, which Transgene said was in spite of patients having unfavorable systemic immunity and tumor micro-environment at baseline (including non-functional immune cells or with low/negative PD-L/1 expression).

The hope is that TG4050 can help turn so-called 'cold' tumors, which normally show limited responses to PD-L/1 immunotherapies treatments, into 'hot' ones which do respond.

The company expects to have longer follow-up results by summer 2024, which could allow it to move into a potentially confirmatory Phase II trial.

CAR-T Comparisons

The neoantigen based approach requires each immunotherapy to be tailored to target the particular mutations in each individual patient's tumor. In this sense, the approach has parallels with the CAR-T model, which Riva played a lead role in bringing to patients at Novartis and then at Gilead.

He acknowledged that neoantigen candidates currently involved a ”cumbersome” manufacturing process, but was confident it could be refined, as CAR-T continues to be.

“You have to see personalized cancer vaccines in the same kind of dynamic. Transgene and other companies are only just beginning, but we believe that this approach can have a profound impact on solid tumor patients.”

He added that one advantage over CAR-Ts would be lower incidences of adverse events, but at the same time, as neoantigens require repeat dosing and target solid tumor patients, it would be less instructive to make comparisons on issues such as market share and pricing.

Undoubtedly, the biggest catalyst in the field will be the progress of Merck and Moderna’s mRNA-4157/V940, which is set to move into Phase III after showing promise in a Phase IIb study. This saw it combined with Merck & Co’s anti-PD1, Keytruda (pembrolizumab), in Stage III/IV melanoma patients with high risk of recurrence following complete resection. (Also see "*Could Moderna/Merck Cancer Vaccine Succeed Where Others Have Flopped?*" - Scrip, 16 Apr, 2023.)

This echoes Transgene’s study in shifting to an adjuvant setting, where the thinking is that tumors will be more responsive to immune cues than in more advanced disease. mRNA-4157/V940 employs Moderna’s mRNA platform to deliver the immunotherapy, but whether or not the vector is among the key designs factors in neoantigen therapies and their trials is yet to be seen.

Looking At Finance Options

Meanwhile, Riva indicated that new financing was a priority for Transgene in order to fuel its R&D ambitions, and this includes seeking out new US-based groups to broaden its investor syndicate.

However, the company will have to demonstrate further encouraging clinical trial progress to attract new funds – a classic “chicken and egg” problem for many cash-strapped biotechs.

This year has seen a number of financially challenged companies seek out mergers with peers, and Riva said this could be of interest to Transgene, providing it could find a synergy in solid tumor immuno-oncology, but he said there were “many permutations” in deals which would require evaluation.

Riva added that he would also bring experience of what big pharma and investors want to see from biotech, and help his Transgene colleagues identify the optimal way to get to proof of concept and unlock the company’s potential.