A disruptive platform for monoclonal antibody production

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As a species, we owe our survival to the immune system. As intelligent beings, we have also been taking advantage of the immune system, from the centuries-old vaccination strategies to the immunotherapy approaches that got two of its leading scientists the 2018 Nobel prize in Medicine. During an immune reaction, high-affinity antibodies are generated that bind to molecules from invading viruses and bacteria, triggering a set of reactions that eventually clears the infection. More broadly, antibodies can be defined as a remarkable class of proteins that recognize molecular shapes with unmatched specificity and range. The ability to manipulate biological systems at the molecular level is of enormous importance for both basic and translational Biomedical Research, and ultimately Medicine. Antibodies are currently used in medical diagnostics and to treat diseases such as immune deficiencies, multiple sclerosis, rheumatoid arthritis, psoriasis and cancer.

Particularly relevant and with growing importance are the monoclonal antibodies for cancer treatment. These tools resulted from two major technologies: the invention in the 1970s of a technique that immortalizes the cell secreting the antibody of interest and, since the 1980s, the use of transgenic mice in which the antibody genes have been progressively replaced by the human antibody genes. These breakthroughs were instrumental to build a global monoclonal mouse antibody market of **7,330 million US$** (2017) that is expected to reach **11,200 million US$ by the end of 2025**, with a **CAGR of 5.4%** during 2018-2025 (Reuters).

The traditional transgenic approaches based on the manipulation of the antibody genes have efficiently solved the species incompatibility problem. In fact, this technology has reached its zenith, as there are currently transgenic mice producing antibodies indistinguishable from the human antibodies that are safe to use in therapy (*e.g.*, the Trianni mice). Yet, the generation of monoclonal antibodies with clinical relevance remains a lengthy and expensive process with a considerable abort rate. *Divab*'s (acronym of "diversifying antibodies") aims at developing a new and disruptive line of transgenic mice. Antibody gene editing is essential to produce high-affinity antibodies. Until now, all antibodies have been generated by the natural editor of antibody genes (an enzyme called Activation-Induced Cytidine Deaminase). Our goal is to make transgenic mice expressing enhanced forms of this natural gene editor that will potentially produce antibodies with improved affinities compared to normal mice. *Diyab*'s vision is to become a reference in the way antibodies are produced to feed the needs of the increasingly demanding area of Biologics Healthcare.

Our international team is comprised of two experts on the editor of immunoglobulin genes (Almudena Ramiro and Vasco M. Barreto), a world-renown immunologist (Gabriel D. Victora) and a theoretical biologist (Jorge Carneiro). VM Barreto has filed a European Patent (EP19158047) on the generation of new editors of immunoglobulin genes. The strategy is partially based on the repurposing of gene editing tools that have been emerging in the context of the CRISPR/Cas9 revolution in gene editing. *Divab* will generate disruptive transgenic mice that will be combined with the state of the humanised antibody murine platforms to produce antibodies with enhanced affinity that are fully adapted for clinical use. Furthermore, our approach can be extended to other animal species used in the production of antibodies (goats, rats, rabbits and camelids).

We need **300,000 €** for the *in silico* and *in vitro* validation of our editors (1st year), the generation and characterization of the *divab* mice (2nd-3rd years) and the benchmarking of the *divab* antibodies (4th year). *Divab* could then grow through the licensing of this technology to other antibody companies, the production of our own *divab* antibodies or a combination of both revenue streams. We believe we are facing a narrow window of great opportunities that demands an urgent call to action.