In a recent book on Xenotransplantation edited by Pr. D Cooper (Recollections of Pioneers in Xenotransplantation Research), I was invited to write a chapter on our (modest) contribution in this field. This invitation gives me the opportunity to take some distance to the daily "battle field" of research in xenotransplantation, decades after my first apparition -using "Xenotransplantation" as a key word- on PubMed, to portrait what could be the actual place of xenotransplantation in clinic in the future. In my contribution entitled "A journey in xenotransplantation science, from Mélies illumination to medical wisdom", despite the recent preclinical achievement in preclinical primate models and all amazing possible progresses offered by new technologies (Perv free donors, reduction of pig tissue immunogenicity, chimeric animals hosting human tissues, etc.), I confessed I still had difficulties to envision xenotransplantation of vascularized organs to enter the clinic for replacing allograft long term purposes, mostly due to the tremendous immunological barrier that xenotransplantation is facing. Rather, I suggested that more attention could be paid to the less mediatic approach of using animal engineered tissues (as "biological" heart valves) or animal molecules (as it has been the case for decades for insulin and more recently for monoclonal or polyclonal antibodies) now widely used in clinic. Moreover, the success of such approach initially based on a pragmatic behavior, now benefits of the developments of the xenotransplantation science mentioned above.

The COVID-19 pandemic of course questions researchers engaged in the field of xenotransplantation. The major concern, actually inherent to the topic itself, is the safety issue regarding animal derived viral (Perv) or molecular ("Mad cow") risks, a concern that has actually triggered a schism in our community, particularly following Fritz Bach ethical warning on the risk of introduction of xenotransplantation in the clinic. A major benefit of this crisis has been the extremely active policy of regulatory offices of states and academic institutions (and particularly of IXA) facing this potential risks. In this respect, decades long discipline of all the research community working on xenotransplantation has been remarkable. Interestingly, in the same time, the research efforts spurred by xenotransplantation challenge itself – such as for the progress in the genetic engineering of large animals, have been able in few years to solve the major identified alarm that triggered the debate of "ethic in xenotransplantation": the risk related to Perv.

However, the COVID-19 pandemic, as past pandemics of severe outbreaks from animal viruses, occurred in uncontrolled arena which differ from the arena of laboratories working on "xenotransplantation science". Moreover, the perspective of "soft xenotransplantation" I defended in the book edited by D. Cooper is highlighted by observations directly issued from research in the field of "xenotransplantation science" and which may provide powerful tools to combat COVID-19 disease. As an example IgGs anti- CoV-2 Spike able to neutralize interaction of CoV-2 with their cellular ACE2 receptor present in COVID-19 convalescent plasma are a promising therapeutic tool to prevent severe COVID-19 disease. Interestingly, whereas a large scale production of such neutralizing anti CoV-2 human antibodies may be challenging, animals engineered for producing low immunogenicity polyclonal IgGs (as done by alteration of genes coding for the synthesis of aGal or Neu5Gc xeno antigens in pigs, or by introduction of genes encoding human IgG in the bovine genome) can be utilized to prepare large amounts of neutralizing polyclonal antibodies for passive therapy of the disease. Moreover, we have recently shown that disparate evolution constraints have resulted in a lack of physical and functional interaction between pig IgGs and human cellular Fc-Receptors (1). This absence of pig IgG binding to human Fc-R should prevent the risk of CD-16 stimulation of patient lung macrophages by pig anti-CoV IgGs at a critical stage of the disease which, in the context of a passive humoral therapy, would represent a serious safety hazard. Another

example of “xenotransplantation science” derived research is a monoclonal inhibiting the C5a component resulting from the human complement activation cascade which may also decrease the uncontrolled inflammation of the innate immune response in COVID-19 disease. Thus, facing the devastating consequences of the COVID-19 pandemic on human health, economy, social disparities, research institutions and in fact almost all components of our societies, “xenotransplantation science” may modestly offer opportunities to prevent or combat the severe forms of the disease using targeted strategies. Furthermore the pandemic may also contribute to curve the future of xenotransplantation toward more “soft” clinical applications.

(1): https://www.biorxiv.org/content/10.1101/2020.07.25.217158v1