_Leish_MANIA: From pathogens to drug delivery systems

TECHNO-MORAL SCENARIOS

Our project proposes the use of a transformed pathogenic parasite to specifically deliver drugs into macrophages, modulating their inflammatory profile. Even if the parasite is non-pathogenic, due to their virulent factor deletion, the safety and bioethics issues involved are noteworthy. There is a small probability of the centrin 1- knockout *Leishmania* suffer a reversion and start causing infection again, due to the existence of a centrin 1 gene on another form of the protozoan's life. Also, *Leishmania* could suffer from misregulation leading to an uncontrolled synthesis of IFN-β. To prevent those undesired situations, a tight quality control must be developed, if the project develops into a product. The team foresees scenarios where the project affects the population in many different ways.

The protozoan *Leishmania* has a high infective potential which could not only be used to deliver beneficial molecules, but harmful as well. That would classify it as a potential biological weapon. Regarding this issue, there is no controlling it, still helping to raise a constant discussion, informing and educating the general public about SynBio's implications, could be a start to prevent the bad use of this technology. Some other less evident questions also emerge from the proposal of a new chassis for synthetic biology. IFN-β-producing-*Leishmania*'s anti-inflammatory potential could be used by athletes to keep their joints more resistant, which could present new challenges for the anti-doping industry.

Patients that have been previously infected with the parasite would not be able to use this proposed chassis because they might carry considerable amounts of inhibitor antibodies that would destroy the modified *Leishmania* before it reaches its target, making the treatments impossible for these patients. On the other hand, the production of an anti-parasite immune response in patients treated with our modified *Leishmania* might have a beneficial vicinal effect, making patients treated with this approach more resistant to pathogenic leshmanial infection and other related parasites, as proposed in the initial work with the Cen1 deleted strain.

The production of *in situ* medications would probably cause impacts on the pharmaceutical industry. Once developed, drug-producing microorganisms can be cheaper than chemical synthesis of the drugs. If this actually happens, pharmaceutical companies may lose market or they can change their way to produce drugs. These changes will make the factories raise their bioreactor production to grow organisms that will be transformed into products of interest, and as a consequence, the current system would be less needed. Either way, unemployment in this area may raise and some companies can go bankrupt.

Unveiling the use of pathogens as tools for the treatment of other diseases could diminish the concern of these parasites by general public, leading to a neglected

prevention, resulting in higher rates of parasitic diseases. Other than that, patients in treatment could suffer discrimination for being faced as potential contagion sources.
As for SynBio as a whole, regulatory policies have to be discussed in order to properly assure the application of such innovative proposals. Using modified pathogenic chassis would foment even more the discussion of the regulations, rights and restraints of the actual application of Synthetic Biology devices. Once this technology proves itself to be safe and efficient, the development of other chassis would be encouraged.

Examples of how the scenarios predicted could work are shown in the “Global Metropolitan Observer” newspaper’s 2015 edition.