We have arrived at the end point of our explanation, this one touches specifically on our project, in its form, as well as in its legitimacy.

The backbone on which our IGEM project is based is the one that we have constantly developed in our writings and our explanations: a threatening and globalized context of antimicrobial resistance, to which is added the possibility and the hope that represent bacteriophages and phagotherapy. In this fight against antimicrobial resistance, bacteriophages embody an alternative, or at least a complementary tool of antibiotics that can make a difference; a difference that expresses itself in the most important and symbolic unity, that of the lives saved. Their effectiveness, their safety and their specificity are all useful and interesting for their use. Of course, we are aware that they have limitations, like any therapy. However, their use may be part of the solution to the problem of antimicrobial resistance.

The legitimacy of the fight against antimicrobial resistance, as well as the interest of phages are no longer demonstrated or legitimize again, because these elements were developed in our two previous writings.

Therefore, what can say about the machine that constitutes our project, its mission and the intention of its conception? How do these parameters articulate and integrate with the reality of antimicrobial resistance and bacteriophages? In a nutshell, our project is the development and design of a fully automated system that provides three pieces of information: identifying a specific bacterium, detecting the presence of an antibiotic resistance marker, and finally, select the most effective phage for its elimination.

1) Identify the bacterium

When we talk about the identification of a specific bacterium, we need to understand and explain which we are talking about and justify the relevance of that choice. The "specific" bacterium we are talking about is called *Pseudomonas aeruginosa*, it is also called *pyo* or *pyocyanic bacillus*. First of all, in order to appreciate the threat it poses and the problem it represents, it is necessary to understand its biological mechanisms.

The first element to take into account is that of its great robustness, and for good reason, “it can survive in distilled or salt water, or even develop in some antiseptic or antibiotic solutions.” However, when it becomes pathogenic for a vulnerable or immunocompromised organism, it can cause a mortality rate in its host that can go up to 50%. That's why it is considered, along with other bacteria, as one of the most difficult to treat clinically. In the world

of care, it is recognizable by the very special smell that emanates from a infected wound by this bacterium, just like the color it gives to the wounds it colonizes. *In vivo*, it secretes a "biofilm" (a multicellular community more or less complex, often symbiotic, microorganisms (bacteria, fungi, algae or protozoa), adhering to each other and to a surface, and marked by the secretion of an adhesive and protective matrix.) The latter makes its elimination more difficult, like a bulwark that should be overcome before reaching the heart of the therapeutic target. Thus, this bacterium causes various nosocomial infections when it colonizes devices and medical equipment (fibrescopes, probes ...). In addition, and this is an essential point of its effectiveness in the fight against antibiotics, it has an "efflux pump" which is a real device for evacuation of antibiotic molecules. Finally, it can quite easily, like other bacteria, transmit and receive antibiotic resistance genes from other closely related bacteria or from more distant species.[1]

As a result of all these factors, when WHO published its first-ever list of "priority pathogens" resistant to antibiotics (2017 February)[2] ; a list listing the 12 families of bacteria most threatening to human health, it puts *Pseudomonas aeruginosa* in "Priority 1"[3], a critical threat for which it is essential and urgent to find new antibiotic treatments. The development and the criteria used to establish this list allow us to understand the threat posed by this bacterium. Indeed, the criteria were,

> [...] the criteria for selecting pathogens on the list were: how deadly the infections they cause are; whether their treatment requires long hospital stays; how frequently they are resistant to existing antibiotics when people in communities catch them; how easily they spread between animals, from animals to humans, and from person to person; whether they can be prevented (e.g. through good hygiene and vaccination); how many treatment options remain; and whether new antibiotics to treat them are already in the R&D pipeline.[4]

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[1] Article « *Pseudomonas aeruginosa* », Wikipédia, URL : https://en.wikipedia.org/wiki/Pseudomonas_aeruginosa, Accessed on 09/20/2018.

[2] « WHO publishes list of bacteria for which new antibiotics are urgently needed », New Release, WHO, 02/02/2017, URL : http://www.who.int/news-room/detail/27-02-2017-who-publishes-list-of-bacteria-for-which-new-antibiotics-are-urgently-needed, Accessed on 09/20/2018.

[3] « The WHO list is divided into three categories according to the urgency of need for new antibiotics: critical, high and medium priority. The most critical group of all includes multidrug resistant bacteria that pose a particular threat in hospitals, nursing homes, and among patients whose care requires devices such as ventilators and blood catheters. They include *Acinetobacter*, *Pseudomonas* and various Enterobacteriaceae (including *Klebsiella*, *E. coli*, *Serratia*, and *Proteus*). They can cause severe and often deadly infections such as bloodstream infections and pneumonia. » *Ibid*.

[4] *Ibid*.

The main objective of this list is « [...]intended to spur governments to put in place policies that incentivize basic science and advanced R&D by both publicly funded agencies and the private sector investing in new antibiotic discovery. It will provide guidance to new R&D initiatives such as the WHO/Drugs for Neglected Diseases initiative (DNDi) Global Antibiotic R&D Partnership that is engaging in not-for-profit development of new antibiotics. »[5] Note that we are talking here about the research for new antibiotics, only it would not be inaccurate to talk about new "therapies", a term that could include phagotherapy. And for good reason, the treatment of *Pseudomonas aeruginosa* infection is one of the main indications of phagotherapy. We want for example the European study "Phagoburn" which we have already mentioned the existence.[6] In essence, it focuses on the use of bacteriophages to treat *Pseudomonas aeruginosa* and *E. coli* skin infections in severely burned patients. Moreover, *Pseudomonas aeruginosa* is generally one of the targets of broad-spectrum bacterial "phage cocktails" available in countries that use phage therapy (Georgia, Poland, Russia ...). Regarding France, there is currently a "phage cocktail" on the sites of referencing of French drugs, that is to say a grouping of different species of phage to obtain a broad therapeutic spectrum, this taking into account the specificity of action proper phages. This cocktail is *P. aeruginosa PHAGE PP113* from the company Pherecydes Pharm. It should be noted that the latter is available only in the case of a "temporary authorization for nominative use" (ATUn), that is to say for people who have a conventional treatment failure situation.

To the question that could legitimately arise: why do we choose this bacterium? We can answer that it is a priority issue in microbial control. In addition, our resources and the time allocated to the project did not allow multiple identification. This does not detract from the interest and relevance of our project because it targets a bacterium against which it is necessary to fight in priority. This step of identifying the bacterium *Pseudomonas aeruginosa* is necessary for any use of the machine since the latter was designed to inform its user of the best possible phage elimination. The information of the absence of this bacterium in the sampling submitted to the machine is not in itself a failure, since it informs that *Pseudomonas aeruginosa* is not there: thus the user has then information useful to the therapeutic caring for the patient. However, and this is the case that is of most interest to us, if the machine detects the presence

[5] *Ibid*.

[6] « Final Report Summary - PHAGOBURN (Evaluation of phage therapy for the treatment of Escherichia coli and Pseudomonas aeruginosa burn wound infections (Phase I-II clinical trial)) », Community and Research and Development Information Service, European Commission, 16/11/2017, URL : https://cordis.europa.eu/result/rcn/208478_en.html, Accessed on 09/20/2018.

of *Pseudomonas aeruginosa*, then it will be absolutely necessary to know the other pieces of information for which the machine was also designed.

2) Detect the presence of an antimicrobial resistance marker

This detection of a marker of antimicrobial resistance of the bacterium is the second piece of information necessary for the most efficient therapeutic caring for the patient. As we have already pointed out, this bacterium is a master in the art of antimicrobial resistance (efflux pump, biofilm and exchange of genetic material). However, as we noted in our analysis of antimicrobial resistance and its challenges, appropriate and proportionate management by antibiotics is one of the keys to the fight against acquired antimicrobial resistance. Thus, the systematic treatment as "antibiotic-resistant" of a *Pseudomonas aeruginosa* is an error when the latter can be eliminated by means of conventional antibiotics, not reserved for antibiotic-resistant bacteria. Regarding our project, we chose a marker of antimicrobial resistance to the "fluoroquinolone" family. This family of antibiotics is still "[...] effective against this superbug, [...] but only on a variety of restricted bacterial strains. "[7]

Nevertheless, it must be recognized that in an initial situation, even without selection or reinforcement by prior antibiotherapy, [*Pseudomonas aeruginosa*] will often be sensitive to only a few antibiotics [...] ".[8] However, this "therapeutic advance" that we have on bacteria must be carefully preserved, which is why the identification of antibiotic resistance markers is an essential element of infectious therapeutic care, for the patient himself (for the greatest possible efficiency), but also for the general preservation of effective therapeutic tools.

3) Select the most effective phage:

Once the antimicrobial resistance is proven or not, the choice of appropriate therapy is essential, it must be measured and base on solid and predictive data that provide a justification and legitimacy in the choice made by caregivers. However, antibiotics (some in any case) are still effective against the bacterium *Pseudomonas aeruginosa*. Nevertheless, in the case where we can have another therapeutic, equally effective, and also less inclined to iatrogenic events,

[7] « New EU project AEROPATH takes on 'superbugs' », Community and Research and Development Information Service, European Commission, 11/17/2008, URL : https://cordis.europa.eu/news/rcn/30104_en.html, Accessed on 09/20/2018.

[8] Article « *Pseudomonas aeruginosa* », Wikipédia, URL : https://en.wikipedia.org/wiki/Pseudomonas_aeruginosa, Accessed on 09/20/2018.

it would be a pity to deprive ourselves of it. Bacteriophages represent a necessary and life-saving complementarity in the fight against antimicrobial resistance, a precious time of advance and rest in the overuse of the antibiotic treatments that we still have; an equally useful time frame for pharmaceutical research.

As we have already discussed on several occasions, the specificity of phages can be considered in a double way: as a guarantee of safety and comfort of use, but also as a limit which greatly hinders its use. Indeed, it is necessary to identify the precise bacterium that is at the origin of the infection, then to find the specific and effective phages able to eliminate it.

However, our project aims to provide quickly (approximately 12 hours) information that allows to know specifically and relatively from a starting sample, whether the phages are effective and especially which should be administered to the patient. Like the phage therapy already in use in some countries, the use in our machine of a phage diversity, rather than a single species of phage allows us to bring increased efficiency in the elimination of the bacteria. The information on the successful phage removal of the target bacterium may allow and encourage their use as first line. For example, in the case of an antibiotic contraindication, or else as palliative to the use of antibiotics as in the case of the use of bacteriophages against multidrug-resistant bacteria antibiotics. The more or less recent interest in phages is the marker of a changing therapeutic situation, the need for a diversified approach of effective and complementary therapies, not the end of the hegemony of antibiotics, but a new therapeutic composition, made compulsorily more diversified by the current problematic situation. In this sense, the machine we produce is part of this new approach. Note that the use of phages is not the only interest of our machine, indeed, it also represents an approach more and more accepted and called his wishes: automation and digitization of certain human activities.

4) <u>The interest of an automated system</u>

In recent years, and concomitantly with the explosion of technological innovations and their potential, it is often mentioned in the media the possibility of replacing certain trades through automation or even by digital tools. Henceforth,

> [...] Robots and computers can not only perform a range of routine physical work activities better and more cheaply than humans, but they are also increasingly capable of accomplishing activities that include cognitive capabilities once considered too

> difficult to automate successfully, such as making tacit judgments, sensing emotion, or even driving. Automation will change the daily work activities of everyone, from miners and landscapers to commercial bankers, fashion designers, welders, and CEOs.[9]

Thus, according to some studies « one job out of two would present a high risk of being automated over the next twenty years, in France, Europe or the United States. »[10] However, these studies focus only on the trades as a whole, and not on the tasks that constitute them. If we are interested in the skills that make up these trades, the figure of a possible automation actually falls to 30% of skills for 60% of the total percentage of trades. Indeed,

> [...] The right level of detail at which to analyze the potential impact of automation is that of individual activities rather than entire occupations. Every occupation includes multiple types of activity, each of which has different requirements for automation. Given currently demonstrated technologies, very few occupations—less than 5 percent—are candidates for full automation.[11]

In fact, what is changing with automation is not the need for workers themselves, but the activities of these workers. Indeed, « it is not because an activity is robotized that it can dispense with employees! The German car industry is one of the most robotized in the world. Yet, it employs 100,000 more people than twenty years ago. »[12] It should be noted that this increase in the wage bill of the German car industry (14%) is greater than the overall increase in the German labor force (9%).[13] In a nutshell, « these changes will force workers around the world to deepen existing skills or acquire new ones. Companies will also have to rethink the

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[9] MANYIKA James, CHUI Michael, MIREMADI Mehdi, BUGHIN Jacques, GEORGE Katy, WILLMOTT Paul, DEWHURST Martin, «Harnessing automation for a future that works », McKinsey Global Institute Report, January 2017.

[10] MAREUGE, Celine, *L'effet de l'automatisation sur l'emploi : ce qu'on sait et ce qu'on ignore*, Note d'analyse n°49, *France Stratégie,* 19/07/2016.

[11] MANYIKA James, CHUI Michael, MIREMADI Mehdi, BUGHIN Jacques, GEORGE Katy, WILLMOTT Paul, DEWHURST Martin, «Harnessing automation for a future that works », McKinsey Global Institute Report, January 2017.

[12] MAREUGE, Celine, *L'effet de l'automatisation sur l'emploi : ce qu'on sait et ce qu'on ignore*, Note d'analyse n°49, *France Stratégie,* 19/07/2016.

[13] Fact Checking : PFLIMLIN, Edouard, « What is the automotive industry in Germany in ten figures? », *LeMonde.fr*, 11/09/2017, URL : https://www.lemonde.fr/automobile/article/2017/09/11/ce-que-represente-l-industrie-automobile-en-allemagne-en-dix-chiffres_5184129_1654940.html, Accessed on 09/20/2017.
OECD (2018), Labour force (indicator). doi: 10.1787/ef2e7159-en (Accessed on 10 October 2018).

organization of work within their organizations. »[14] In addition, we can expect an « increased need for social and emotional skills, a need that will accelerate. On the other hand, the need for basic cognitive skills and physical and manual skills will decrease. »[15]

We can question the interest and the report of such data with our IGEM project. In fact, it is all found, we seek to show that a progressive automation of work, activities and human skills is at work. This is why it is necessary to understand, consider and integrate this automation and the digital tools that are added to it, at the heart of the jobs we do. Therefore, the health professions are not excluded. In essence, the machine we have implemented is not intended to replace the doctor and his diagnostic judgment, but rather to provide him, in an automated way, the information necessary for the constitution of his diagnosis and therapeutic judgment.

Laboratory technicians, who until then had returned the task of manipulating, transforming, and interpreting the specimens and their results will be relieved of this task. In addition, the interest of automating a task also lies in reinforcing its character of "repeatability", in other words, the possibility of an exact reproduction of the conditions of an experiment guaranteeing the least variations possible. The collection of diagnostic data carried out by our machine, in other words, the identification of a specific bacteria and its possible antimicrobial resistance, then the manipulation of a diversity of phages that we put in contact with this species of specific bacteria represent the steps of an activity that can be automated. It is also this automation that makes this same collection free of contingent events specific to work and human manipulation (fatigue, manipulation error, health risk for the technician etc.) The goal is then to gain in speed and relieve humans of tedious and repetitive tasks. In addition, with regard to a pecuniary and managerial reasoning, we can consider this automation as a means of saving money and relieving workers of an already substantial workload.

Finally, and this is surely of paramount importance in our project, automation is not only a technological issue, as is phagotherapy in general. These are choices of society, acceptance and societal involvement and investments that must be decided and discuss between members of the same human community. In this sense, the "*human practice*", ie the establishment of a dialogue between society and our project, as conceived in the IGEM project, are useful, even necessary.

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[14] BUGHIN Jacques, HAZAN Eric, LUND Susan, DAHLSTRÖM Peter, WIESINGER Anna, SUBRAMANIAM Amresh, « Skill shift: Automation and the future of the workforce », *McKinsey Global Institute Report*, May 2018.

[15] *Ibid*.

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