Looking for the Unexpected

Basic scientific research is done to advance our knowledge and understanding of a particular topic or problem, but it does not necessarily produce results that have any immediate practical application in health care. However, the knowledge acquired often lays the groundwork for advances that help us to move in the right direction, opening the door to new discoveries that are directly applicable to patient care or disease prevention.

Basic science is essential because it is an integral part of a continuum that cannot be broken down without rendering it useless. Despite this, in medicine it is customary to divide research into separate phases, each with its own name: thus we have basic, translational, preclinical and clinical science. In practice, however, all these phases form an inseparable whole that can only work on the basis of constant feedback.

So why do so many people find it hard to recognise the great social value of basic scientific research? There are many reasons, but two stand out. Firstly, the force that drives basic research is a delicate balance between pure curiosity and a desire to be useful. While curiosity has provided humanity with amazing discoveries, most agencies now place a low priority on research that does not promise any immediate practical result.

The Impact of Malaria

Malaria is caused by protozoan parasites of the genus *Plasmodium*. Five species of *Plasmodium* cause malaria in humans: *P. falciparum*, *P. vivax*, *P. malariae*, *P. ovale* and *P. knowlesi*, but *P. falciparum* and *P. vivax* are responsible for most of the burden of disease in the world (Figure 1). *P. falciparum* is the cause of more than 200 million clinical cases of malaria and one million deaths a year, especially in children under five in sub-Saharan Africa, and it can cause serious complications in foetal development in pregnant women and even maternal deaths. *P. vivax*, the most common malaria parasite, is widely distributed throughout the world and is responsible for about 100 to 300 million clinical cases every year, including cases of severe illness and death.

The fight against malaria has grown increasingly difficult as the parasites develop resistance to antimalarial drugs such as chloroquine (Figure 1) and because of complex interactions with other infections prevalent in areas where malaria is endemic, including human immunodeficiency virus (HIV).

Figure 1: Malaria and chloroquine-resistant disease: worldwide distribution

Source: Carolina Bustamente (CRESIB)
Second, basic science is the discipline in which the connection between the results and their practical application is the least obvious or foreseeable: the issue is not that there is no link, but that an explanation is required to make the connection apparent.

The malaria parasite resists...

Despite advances in recent years, malaria continues to resist control and elimination. We are still searching for a highly effective vaccine that is easy to administer, inexpensive and widely accessible to those most in need: vulnerable people living in situations where they are at risk of infection. While we do have effective drugs to treat people with the disease, the pathogen that causes malaria is capable of developing resistance to these treatments.

In the same way that antibiotics, such as penicillin, have gradually become ineffective against many bacteria, the protozoan parasites that cause malaria develop resistance to all the drugs currently used to eliminate them. The race to update the arsenal of antimalarial drugs is complicated by the perverse physiology of the parasite and geo-economics conditions. Besides spending most of its life safely hidden inside red blood cells, Plasmodium parasites spend part of their life cycle inside mosquitoes of the genus Anopheles; to add insult to injury, the great apes are infected by Plasmodium species that, in certain circumstances, can also infect humans. Finally, even if all the effort invested in developing a new weapon came to fruition, it might still not be enough to solve the problem because any new drug would have to be not only effective but also inexpensive. As virtually all cases of malaria occur in impoverished regions of the world, the production of antimalarials is not an attractive proposition for large pharmaceutical companies.

The malaria microbe has developed sophisticated mechanisms to avoid being eliminated by the immune system. The human body develops natural immunity to many diseases after only a single infection, a mechanism that provides the basis for effective vaccines. In the case of malaria, however, a single infection does not make us resistant.

Repeated infection is required to generate immunity to malaria: children who live in areas where the disease is common and endemic gradually develop resistance to different forms of the disease, although protection is never complete. Therefore, to develop an effective vaccine it is not enough to induce the immune responses that occur after a single infection, which would be sufficient in the case of certain other diseases.

The First Malaria Vaccine

RTS,S is the most clinically advanced malaria vaccine candidate. Developed by GlaxoSmithKline in collaboration with PATH-MVI and several international research institutions (including CRESIB), the RTS,S vaccine candidate has been shown to be safe and effective, with an efficacy against clinical malaria of around 50% in numerous phase I and II clinical trials. The vaccine is currently being tested in Africa in a large multicentre phase III trial, the last stage in clinical development before submission to the regulatory authorities. In spite of promising results, the effectiveness of the vaccine is still partial, the duration of protection is limited, and the mechanism of action is still poorly understood.

Figure 2: The reproductive cycle of the malaria parasite

Source: Armand Gran (CRESIB)
The genome of the malaria pathogen contains over 5000 genes, each encoding a different protein. Other pathogens, for instance viruses, have very few genes, and some even encode a single toxin that is responsible for the clinical symptoms of the disease. The Plasmodium species are therefore very complex microorganisms. Without a thorough understanding of how the parasite functions, it is almost impossible to identify the proteins that might be its Achilles heel and to develop vaccines targeting them. It is impossible to test all of the proteins systematically, and useless to test them randomly!

Clearly, we need a better understanding of the biology of this parasite and the immune responses it provokes if we are to develop a highly effective vaccine against malaria or develop new treatments. This deeper knowledge and understanding can only be achieved through basic research.

... but we are still rummaging around inside

The Centre for International Health Research (CRESIB), ISGlobal’s research centre, currently has several lines of basic scientific research focused on identifying weaknesses in the armour of the malaria parasite.

A Sweet Target

The proteins that are secreted or expressed on the surface of cells are usually bound to sugars. This process, called glycosylation, is essential to the proper functioning of these cell surface proteins.

Until now, the only glycosylated structures reported in P. falciparum have been glycolipids that anchor certain essential proteins to the surface of the parasite and which, according to some studies, have a toxic effect on the host. However, the Plasmodium genome contains metabolic pathways for the synthesis of previously unknown sugar precursors that may be involved in other, as yet undescribed, glycosylations.

In CRESIB, we are working on the reconstruction of the synthesis pathways of these precursors in order to identify new therapeutic targets: reactions that are essential to the parasite and which, if inhibited, would make it possible to eliminate them.1

Catch That Plasmodium!

One of the greatest obstacles to eliminating malaria is the ability of the causative pathogen to evolve and adapt to changes in its environment. Recent work carried out by CRESIB indicates that this ability is largely due to heritable differences in populations of genetically identical organisms, a phenomenon called epigenetic variation.

In effect, research has shown that not all the parasites in a population with identical genes (twins) use the same genes. This epigenetic variation is the basic mechanism through which the parasite adjusts to natural changes in its environment and even to the presence of certain drugs or vaccines. A clear understanding of how the organism evolves and adapts to new situations is essential if we are to stay one step ahead of the parasite and develop tools to which it cannot adapt. These findings may help prioritise research and the selection of drugs and vaccines that are worthwhile taking forward to the clinical development phase, thereby saving time and money. Another line of research in CRESIB is investigating how to interfere with the parasite’s ability to adapt.

Avoid Crowds

Another CRESIB team is investigating how the malaria parasite binds to molecules in the organs of the human host (for example, the placenta or the brain), allowing it to reach high densities in these sites. Accumulation of P. falciparum in these organs gives rise to complications such as cerebral coma, severe anemia, and preterm delivery. Identification of the molecular mechanisms involved in these interactions and those of the immune responses capable of blocking such adhesions could open the door to the development of new strategies for reducing the severity of malarial infection and save millions of lives every year.2

A Change of Jacket

To understand the molecular basis of P. vivax pathology we are studying the variant genes of this species, which play a major role in its pathology. It is difficult to study these genes because of their variability. To understand the problem, just imagine that a hotel employee is sent down to the street to identify a guest. The employee goes down, imagines that a hotel employee is sent down to the street to identify a guest. The employee goes down, identifies the person, who is wearing a red jacket, and brings back the description. Armed with that...

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information, a second person is then sent to find
the same visitor and bring them upstairs; howe-
ver, during the intervening period, the guest has
changed his red jacket for a green one. This is what
happens to our immune system: each time we de-
velop an immune response against one of these ge-
nes, the parasite changes its jacket and the whole
task of identifying the pathogen has to start again
from zero. Our research in CRESIB is aimed at
gaining a better understanding of the mechanisms
involved in these changes so that we can eventually
make a definitive identification of the parasite and
destroy it.

**The Magic Bullet**

When the malaria parasite invades red blood cells
it leaves traces of its presence on the cell surface;
these locks (or receptors) can be recognised by a
key (or ligand). The aim of our research is to de-
sign small capsules of antimalarial drug equipped
with the appropriate key. These nanovehicles can
be created by attaching a suitable key to a small
capsule (or nanoparticle).

**Perpetuating the Memory**

A key issue in the design of the second gener-
ation of malaria vaccines is to characterize the protective
immune responses induced by the RTS,S candidate
vaccine and the factors that determine the duration
of the immunity it confers. To address this question,
we must once again turn to basic science. The aim
of our research in CRESIB is to identify the physiologi-
cal processes that must be stimulated to combat the
parasite. The immune system of an individual who
has received effective vaccination functions as a com-
plex network of cells and a signalling cascade that is
activated whenever the body is reinfected; it recogni-
ses the parasite and attacks it more quickly, thereby
stopping the disease before it develops.

Our research is focussed on identifying the T cells,
B cells and immune mediators (antibodies, cytoki-
nes and chemokines) found in the blood of children
vaccinated with RTS,S that perpetuate the immuno-
logical memory. This knowledge would allow us to
manipulate, if necessary, the induction of immune
responses through improved adjuvants and formu-
lations that would extend the duration of the protec-
tive response.

Basic scientific research is one of the fundamental
pillars of medical research. It paves the way for ad-

tances needed to address the major health challenges
faced by humanity. In CRESIB we are passionate in
our support of basic research because we know it is
an essential weapon in the fight to eradicate malaria
from the face of the earth.

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6 The green capsule on the left contains the drug (pink capsules), which is coated with molecules that recognize the red blood cells infected with Plasmodium. The diagram on
the right shows the result of the magic bullet: drug is delivered only to infected cells and bypasses healthy cells.

7 Martin-Juslar L, Nakayasu IS, Ferrer M, Almeida IC, Del Portillo HA. “Exosomes from Plasmodium yoelii-infected reticulocytes protect mice from lethal infections.” PLoS
