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New strategies to combat HIV-AIDS

Since the beginning of the pandemic, nearly 60 million people have been infected by HIV, 25 million of whom died as a result of the virus. The various drug cocktails used to stem the ravages of HIV-AIDS have enabled patients to live longer and with a better quality of life. However, these therapies quickly come against a serious obstacle: they fail to eradicate the virus. As well, several aspects of HIV infection remain poorly understood, thereby limiting our ability to improve antiretroviral drugs. A study by a CRCHUM team led by Petronela Ancuta has succeeded in making important inroads in this regard.

By Marie-Josée Richard

HIV-AIDS

HIV attacks our immune system, CD4+ T lymphocyte cells (T cells for short) in particular. Called helper cells, these cells help other cells in our immune system to fight off infections.

During the first phase of the disease, the immune system recognizes the presence of an intruder (HIV), and the body's defense system goes to work. At this point, anti-HIV antibodies can be detected in the blood. However, there is a rapid decrease in the number of T cells mainly at mucosal levels, signifying that these "soldiers" have been killed in action. This phase can last between six and eight weeks.

The second stage, or chronic phase, can last varying lengths of time, as much as 10 years or longer in certain cases when there is a positive response to antiretroviral therapy. The level of T cells remains above 300 cells per microliter of blood, which is an acceptable level. However, the virus persists in discrete cellular reservoirs. This period is known as a latency period.

In the final phase, i.e., the AIDS phase, the immune system is extremely weakened: there are fewer than 200 T cells per microliter of blood. At this point, HIV has more and more free range in our system, not to mention other viruses, bacteria and fungi as well. It is for this reason that AIDS patients often die from other complications as a consequence of the HIV-induced inability of the immune system to fight off infections.

THE CELLULAR MECHANISMS IN PLAY

Petronela Ancuta

HIV only attacks and destroys certain of our T cells, which are the immune system's quarterbacks. It is an extremely selective virus. "Only a small fraction, between 0.1% and 10% of our T cells are infected in treated individuals," notes Ancuta. But which ones?

To be effective, antiretroviral therapies have to be as selective as HIV and act on T cells infected with HIV only. While a certain number of so-called "HIV-permissive" T cells have been identified, how they operate has remained a mystery. "Experimental approaches such as functional genomics and the access to well characterized cohorts of HIV-infected individuals will help us uncover the mystery of HIV selectivity," notes Ancuta. A study by a team led by Ancuta has succeeded in identifying and in characterizing two T cell groups that play an important role in mucosal immunity and that are largely responsible for opening the door to HIV and enabling its spread throughout our body. This discovery has important implications: we now have a better understanding of the "permissiveness" of these cells and can thereby refine our thinking about targeted therapeutic strategies.

The researcher has in mind another intervention strategy. "We discovered that T cells imprinted with the potential to home into the intestine are more vulnerable to the AIDS virus," explains Ancuta, who works with a team of technician Annie Gosselin, postdoctoral fellow Patricia Monteiro and MSc students Vanessa Wec Leche and Hanane Touil. Their research targets chemo-

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Another step towards a cancer vaccine

A cancer vaccine? Using our immune system against tumours? The idea is very appealing and has attracted the interest of many researchers worldwide. However, even though they have succeeded in developing vaccines that can stimulate an appropriate immune response, they have made little headway in tumour regression. Perhaps it is the biology of tumours that prevents our immune system from doing its work once activated? That, at least, is the avenue explored in an recently published study by a team led by the CRCHUM's Réjean Lapointe.

By Dalila Benhaberou-Brun

WHAT DOES THE IMMUNE SYSTEM DO?

Our immune system defends us against viral or bacterial infectious diseases with the help of "killer" lymphocyte T cells (killer T cells). Vaccination uses an analogous defensive process with substances that are able to combat and even eliminate undesirable cells. In this way, the use of vaccines has made it made it possible to completely eradicate several diseases such as smallpox.

When a person has cancer (I out of 3 people will be diagnosed with some form of cancer in their lifetime), "it's as if our natural protection don't work, as if the cancer cells slipped through our defenses and that our killer T cells failed to do their job," notes Réjean Lapointe. So the question is whether a vaccine can be developed to help the immune system.

CANCER AND VACCINATION

Several attempts at vaccination against cancer have been tested in recent years. But as Lapointe notes, "While experiments have demonstrated a clear immune response, despite the use of powerful substances and adjuvants, anticancer vaccination does not always work the way we would like it to." The fact remains, that they have not produced any regression in the cancers in question. Perhaps it is the biology of tumours that prevents our immune system from doing its work once activated?

UNDERSTANDING THE BIOLOGY OF TUMOURS

In tumour samples from human kidneys and breasts, "we looked at how cancer cells behaved in the presences of T lymphocyte and how they neutralized them," explains Lapointe. The expectation was that there would be little if any immune reaction in these tissue, which would signal a deficient protection process. Indeed, the goal of the experiment conducted by Jessica Godin, a PhD student, was to observe the natural immune response in cancer cells. The idea was to see how these cells inhibited the immune system (i.e., killer T cells) from doing its job. "It sounds simple,' says Lapointe, "but it's an extremely long and complex process." The expectation was that there would be little if any immune reaction in these tissue, which would signal a deficient protection process. Oddly enough, it was the opposite that was observed—T cells are indeed activated.

Réjean Lapointe

This work enabled the research team to make an interesting discovery concerning the role of the protein IDO. This protein works a bit like an off switch that neutralizes T cells, thereby rendering them inactive and giving free range to cancer cells. IDO can be found in foetuses and is produced to counter rejection by the mother's body. "Basically, what we discovered is that there is a natural phenomenon at work in the proliferation of cancer cells," notes Lapointe. But what makes this study remarkable is that for the first time a link has been established between IDO induced in cancer cells and activated T cells.

FROM BENCH TO CLINICAL APPLICATIONS

Although he is encouraged by these results, Lapointe remains cautious: "I won't pretend that we have found THE solution and that a vaccine is just around the corner." As well, cancer is complex and it is likely that this particular process is not the only one or even the main one. However, now that this phenomenon is understood, we can now turn our attention to discovering ways of blocking IDO. It could eventually be used as a treatment of last resort, when conventional treatments such as surgery, chemotherapy and radiation therapy have failed, as is the case with 15% of breast cancer patients.

When a person has cancer (I out of 3 people will be diagnosed with some form of cancer in their lifetime), "it's as if our natural protection don't work, as if the cancer cells slipped through our defenses and that our killer T cells failed to do their job"

Lapointe plans to continue his research into IDO and T cells in collaboration with clinical researchers specialized in immuno-oncology and with a focus on kidney and breast cancer, two particularly recalcitrant cancers. ■

HIV programs in Africa: the downside of a success story

Over the past 20 years, developed countries have provided significant aid to Africa in the fight against the AIDS epidemic. While this support has been very successful in saving lives, a number of side effects have weakened an already fragile health system. The CRCHUM's Vinh-Kim Nguyen, a specialist in HIV-AIDS research, looks into these unforeseen consequences.

By Dalila Benhaberou-Brun

SAVING LIVES

In the early 1990s, Western agencies (e.g., UNAIDS, WHO) adopted an approach based on prevention alone. The argument was that drugs were too costly, that Africans did not comply with treatment programs and that caring for patients was too complicated. To the extent that the epidemic was not stemmed, this approach did not work. In light of a worldwide hue and cry denouncing the situation in Africa and a significant drop (95%) in the cost of antiretroviral drugs, these same agencies did an about face. The result was that Africans could finally have access to the same medications as people in the developed world.

"We have saved many lives, but have not dealt with the problem"

The cause is a noble one and the stakes are extremely high. Fewer people now die, and some countries, such as India, have even taken advantage of the situation to develop a thriving drug industry. All the same, Vinh-Kim Nguyen cannot refrain from pointing out the perverse side effects engendered by this apparent success.

THE EMERGENCE OF NEW NEEDS

Notwithstanding the encouraging results, it is not clear that this approach to providing care is the best solution. As Nguyen notes, "Yes, we have indeed saved many lives; however, we have not dealt with the problem. While it is true that the people who have survived the AIDS epidemic are doing much better, new needs have arisen that no one anticipated. Healthy people need to eat, they look for work and they want to educate their children. They want to live!"

African governments have benefited from this situation. No one can blame them for having accepted this providential aid. However, managing the populations concerned – who now hope for a better life – remains a global challenge which must be dealt with by local authorities. But, according to Nguyen, Africa does not have the necessary resource to adequately take care of the "survivors," who are now overloading an already fragile health system. "What is the point of saving women, for example, if they merely go on to die during childbirth because of lamentable sanitary conditions?" asks Nguyen.

Dr. Vinh-Kim Nguyen

COMING TO GRIPS WITH A PARADOX

Nguyen is aware that claiming that HIV-AIDS programs have also engendered undesirables side effects is not politically correct. However, he stands behind this conviction, inasmuch as his and other fieldworkers' observations support this argument. In public health, the objective is to improve the health of populations. In anthropology, the perspective changes completely. We become aware of the fact that biological survival can be a problem. Nguyen notes that "the people treated feel like cattle given doses of drugs." Armed with their "life-giving power," it is unclear that international agencies had anticipated the effects of their interventions. The significant amounts of money invested meet certain health needs but, as Nguyen stresses, "giving money is not the same thing as getting involved on the ground," which gives rise to the issue of the real impact of aid programs. "People often tell me that seropositives are often treated better than healthy people," Nguyen adds; "Western logic has yet to understand this fact and it is not admitted by Africans." When he presents his findings at conferences, he gets two kinds of reaction: "Africans are happy that someone is saying what he thinks whereas others (from the developed world) are horrified and discouraged."

"What's the point of saving women if they die later during childbirth"

ACTING LOCALLY

Without wishing to pass judgement on international agencies, Dr. Nguyen is worried about the rigidity of the structures established and managed by outside actors. In his view, the responsibility that should be assumed by local actors is taken out of their hands. Africans should take charge of health care within the framework of long-lasting structures and with a logic that is purely African. "Imagine," says Nguyen, "what would happen if the Obama administration stepped in to deal with our problems with emergency rooms or waiting lists for hip surgery? What would the local population here have to say?" Why should this kind of approach be more acceptable in Africa?"

Towards high-performance frontline services

For Dr. Jean-Frédéric Lévesque, a physician specializing in community health and research at the CRCHUM, diagnosing problems and encouraging good practices are a matter of routine. Yet he never receives patients wearing hospital gowns in his office or elsewhere. **His only patient is the health system itself. His work consists in improving the performance of frontline services.**

By Marie-Josée Richard

THE FRONTLINE

Frontline services in Quebec serve as the first contact between patients and a specialist from the health network, which includes health and social service centres throughout the province. With the ageing of the population, however, over the coming years the demand for these services will rise dramatically. Solutions to the problems entailed by this situation need to be found; the health and quality of life of millions of people will hang in the balance.

DOING MORE WITH LESS

"In developed countries, we live longer, but suffer from an increasing number of chronic illnesses such as diabetes, cardiovascular diseases, respiratory diseases and joint diseases," notes Lévesque. The prevalence of these diseases will exert additional pressures on an already burdened health system which has few means for action at its disposal. Worse still, chronic diseases are complex in terms of treatment and require an integrated approach by several specialists.

"Five years later, a similar effort is being made, notes Lévesque, "with a view to studying a variety of aspects, including accessibility, continuity, exhaustiveness, population coverage, care offered to vulnerable groups, and identification of unmet needs."

But to do more with less, it is important to know which practices or models need to be developed. Also, it is necessary to identify both barriers and facilitating elements in order to make frontline services more efficient. These are the issues addressed by Dr. Lévesque, whose principle idea is: think globally, act locally.

MAPPING THE NEEDS

Lévesque and his team surveyed 9,000 patients in 2005 about their experiences with clinics providing frontline services. As well, 450 clinics replied to a questionnaire seeking to provide a portrait of services offered. "Five years later, a similar effort is being made, notes Lévesque, "with a view to studying a variety of aspects, including accessibility, continuity, exhaustiveness, population coverage, care offered to vulnerable groups, and identification of unmet needs."

Questionnaires were distributed throughout the Montreal and Montérégie regions of Quebec in March 2010 to family physicians in more than 700 clinics and to family medicine units. The latter group together family physicians who work with other health professionals to provide ongoing general care to their patients. As well, 9,000 patients were also contacted, as was the case in 2005.

A SHAKE UP IN THE WAY THINGS ARE DONE?

"This new study provides us with a unique point of comparison, notes Lévesque, "We will be able to see the extent to which the 2005 recommendations were implemented." Among other things, the 2005 study recommended a more global approach to health care and great accessibility of services. That is, policies that would bring Quebec closer to international standards. To what extent have these groups succeeded in incorporating these recommendations? Have they improved health care et service provision? The current study will provide answers to these questions. ■

Jean-Frédéric Lévesque

Tell me what you eat...

...and I'll tell you whether you are at risk of developing a cancer. For the past ten years, cancer has ranked as the number one cause of death in Quebec. Nearly 42.5% of the population will be diagnosed with cancer during their lifetime. Just what are the causes? It turns out that our eating habits head up the list: they are the main risk factor, accounting for 35% of cancer causes and mortality. Parviz Ghadirian, who heads up the CRCHUM's Epidemiology Research Unit, devotes his research to developing precise evaluations of food-related risks for cancer.

By Marie-Josée Richard

FOOD HABITS THAT CAN LEAD TO CANCER

Dr Ghadirian has been studying the links between nutrition and cancer for the past 30 years. The major focus of his research is the identification of the risk factors for cancer associated with different food habits, nutrients and food groups. He has developed a unique classification as function of specific cancers, which serves as an extremely useful weapon in the struggle against this complicated disease. Two examples:

In short, studying the effects of nutrition on health is a long-term effort, requiring both patience and a wide range of studies.

DAIRY PRODUCTS

Ghadirian's most recent study, which appeared in 2010, reported a startling discovery: men who consume more than 470 grams of dairy products or around 400 ml milk a day run a twofold higher risk of prostate cancer, compared with a daily consumption of 125 grams. In other words, one or two glasses of milk per day is alright, but more than two can cause a problem. On the other hand, a diet rich in nuts can diminish this risk by 47%. Perhaps squirrels know something we don't !

These findings were the result of a case-control study of 197 patients diagnosed with prostate cancer and the same number in a control group, carried out by Ghadirian's group in Quebec and his Italian colleague Sara Raimondi. But to do so, they had to measure the correlation between this cancer and more than 200 food products. A tall order!

Over and above his concern for this phenomenon, Ghadirian is also worried about the fact that prostate cancer receives little attention: "Although this cancer affects nearly one in eight men and has attained the same proportions as breast cancer in women, we hardly ever hear anything about prostate cancer. Yet it is the most diagnosed cancer in men and third in cancer-related deaths behind lung cancer and colorectal cancer."

MEAT EATERS BEWARE

In another study, Ghadirian discovered a link between pancreatic cancer and the intake of red meat. People with diets rich in red meat run a twofold higher risk for this cancer. "I have to admit that I enjoy eating meat; however, I try to do so only occasionally," says Ghadirian. In contrast, a diet rich in vegetables has an opposite effect.

He also warns that barbecues using high heat (charcoal or gas) produce carcinogens. "At least we live in Quebec, with its short summer, and not in California where the temptation to use the barbecue is always present," notes Ghadirian.

SO WHAT SHOULD WE EAT?

Should we only eat biological food products to ensure good health? "There is no easy answer to this question at the present time," explains Ghadirian, "because we will only be able to see their effects on health over a long period of time, 15 or 20 years." In addition, it is necessary to determine the extent to which the person interviewed actually ate biological food products, while bearing in mind a variety of other factors. In short, studying the effects of nutrition on health is a long-term effort, requiring both patience and a wide range of studies.

Parviz Ghadirian

MODERATION IN ALL THINGS

This said, Ghadirian has come up with a list of recommended eating habits: limit your intake of fatty foods, increase your intake of fibres, make sure your plate contains a generous heaping of fruit and vegetables, maintain a healthy body weight, limit your intake of alcohol, moderate your consumption of salt-cured, smoked and nitrite cured foods. In short, avoid excesses. ■

BIXIs, active transportation and health

In the spring of 2009, Montreal created a fleet of more than 5,000 bicycles or BIXIs (BIcycle and taXI) for use by local inhabitants and tourists. They are available seven days a week, 24 hours a day, and can be rented at more than 400 stations from May to September. This idea is to provide an alternative to buses and automobiles as a means of inner-center transportation. A team of researchers led by the CRCHUM's Lise Gauvin, is looking at their potential impact on our health.

By Dalila Benhaberou-Brun

WHAT IS POPULATION HEALTH?

"Our patient is not the individual but the entire population," explains Gauvin. One of the major research objectives is to understand how various interventions can nfluence behaviour related to health in general. "The prospect of studying the BIXI phenomenon seduced the team members because the conditions of its implementation and use were uncontrolled, says Gauvin. The project was developed within the framework of a Canadian Institutes for Health Research competition, and was completely independent on municipal authorities.

To maintain good health as well as to prevent certain diseases, it is important to exercise on a regular basis. Other than sports, active transportation (walking or bicycling) has an impact on our health. As such, walking or riding a bicycle on a regular basis will improve both physical condition and health. Hence, the interest for studying the BIXI phenomenon.

THE FOCUS OF THE BIXI PROJECT

Lise Gauvin works with a team composed of colleagues from the CRCHUM, a PhD student and public health physicians. The socio-demographic and health characteristics of BIXI users are currently being explored as well as why and how often people use them. Information about the use of bicycle paths and the risk of accidents (collisions with pedestrians or cars) will complete the study.

Lise Gauvin

FIRST RESULTS

Two telephone surveys were conducted with 4,500 randomly-selected Montreal residents in the spring and the fall of 2009. The initial findings provided information about behavioural aspects. People who indicated that they walked for practical purposes or used their bicycle regularly were more likely to notice the existence of the BIXIs, which established a positive association between active transportation behaviour and awareness of the BIXIs. But does the fact of making the existence of the BIXIs known have an impact on the level of physical activity? Gauvin's team is currently looking into this question.

PROJECT ORIGINALITY

The novel aspect of this project is the use of several data bases (census, geographic information system, etc.). Gauvin notes that "we are sharing methodological and conceptual tools with the Department of Public Health." In addition to looking at BIXI statistics, their impact on health-related behaviour will be evaluated in light of the answers to the survey questions. The results will be given to decision makers and other actors in the health sector, who will then be better equipped to make any necessary changes.

Other follow-up questions will be addressed in the summer of 2010. Does the BIXI alter active transportation habits? Does the population view bicycle use as a good way of improving their health? Will they leave their cars at home and use bicycles instead? The answers remain to be seen. ■

Continued from page 1

kine receptors (CCR6 in particular), molecules that act as biomarkers for cells homing into the gut and permissive to infection. This will allow the identification of molecular mechanisms for HIV permissiveness and the design of new strategies to limit HIV replication in these cells".

TOWARDS MORE EFFECTIVE TREATMENTS

These research findings open the door to new therapeutic strategies aimed at either reducing the presence of the virus in the blood or in strengthening the immune system of infected patients. Ancuta's research focuses on the cellular mechanisms in the early and chronic phases of the disease, that is, prior to the complete alteration of immune system functionality and to the onset of AIDS. "Clearly, the ideal would be to be able to completely eradicate the disease," notes Ancuta. For now, however, the objective is to improve the efficacy of drug treatments and thereby increase the quality of life and life expectancy of HIV patients.

In Ancuta's view, appropriate investments in cutting-edge research technologies are essential to furthering research into HIV-AIDS. The tools they afford make it possible to fully understand the complex nature of this disease as well as our body's response to its presence. In this regard, the CRCHUM recently received funding from the Canada Foundation for Innovation. The researcher notes that "we will now be able to improve our investigation potential in cytometry, microscopy and real-time PCR and access to patient samples". More importantly, this boost to investigative capacities will also contribute directly to the development of more effective therapeutic strategies. ■

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