

Biomarkers

A new test for routine assessment of immune defenses

Its name: Divpenia. Its role: to estimate a patient's "immune shield" or defense capacity. Doctors are starting to take an interest, and it has already attracted the pharmaceutical industry. It also contributes to our understanding of the links between immunity and disease. In short, this is almost certainly not the last time you'll be hearing about it.

There's no need to hold a medical degree to know that in terms of immunity, not everyone is equal. Some people seem to resist infections and illness, while others have to fight, and yet others succumb. This uncertainty has come to be accepted by both patients and doctors. Modern medicine adds another unknown to the equation: that of how each patient will react to aggressive treatments such as chemotherapy or immunosuppression. Once again, some people seem to resist against all the odds, while others falter despite the highest hopes. Although we lack tools to predict the outcomes in these cases, when things go wrong the doctor may feel responsible, or be blamed.

Since 2010 four clinical research studies on over 600 patients have examined the potential of a new biomarker of immune status, Divpenia, to help predict patient responses to treatment. "The results are novel. They add to our understanding of immunosuppression in cancer patients" comments Jean-Yves Blay, coordinator of the medical oncology department at the Centre Léon-Bérard (CLB) Lyon, one of the sites where the tests were run. This is history in the making.

Measuring the quality of our immune defenses

Today, assessing immune status starts out with counting lymphocytes. For several neoplastic diseases, total lymphopenia, as well as CD4, CD8 and CD56, counts are prognostic and predictive factors which have been known for fifteen years. But, in clinical applications, nothing is ever completely reliable. In 2004, young doctors Nicolas Pasqual and Sébastien Weisbuch launched a novel idea: the immune shield is a wide range of defenses, each of which must be present in adequate quantities. Because they really believed in this concept, they created ImmunID Technologies, a start-up dedicated to this new biomarker (see box).

The technique they developed is based on measuring the potential of T and B lymphocytes to produce their specific receptors. This measurement relies on semi-quantitative PCR to analyze V-D-J gene rearrangements, which code for the specific parts of the receptors responsible for antigen recognition. This *actual* diversity can then be compared to the maximum number of *possible* genetic combinations. Today, 1 ml of blood is enough (for the first tests in 2004 they needed over 100 ml).

So what does this biomarker indicate? In the conditions developed in 2010 by ImmunID, immunocompetent, healthy subjects are expected to have a diversity between 50 and 85% for the T cell receptor Beta chain (TCR beta), and between 60 and 90% for the immunoglobulin heavy chain (IgH). Divpenia is what you have if your diversity falls below these figures. This measurement is linked to a clinical score, NDL® (Numération Diversité Lymphocytaire/Lymphocyte Count and Diversity), which allows patients to be ranked based on both their lymphocyte count and diversity. This allows mixed T and B divpenia to be identified, as well as mainly T (AIDS, anti-CD3 immunosuppression) or B (anti-CD20 or CD19 immunosuppression) divpenia.

The promising clinical elements

In 2006 the inventors of the concept met up with two decisive partners: Professor Jean-Yves Blay and Dr. Christophe Caux from the CLB. From the outset there was a great "buzz". And for good reason, the oncologist and immunologist were actively seeking a predictive factor to allow them to target a group of breast cancer patients who would most benefit from a "strong" chemotherapy treatment. The correlation between poor prognosis and lymphopenia is imperfect, and they were interested in a tool to refine the identification of patients at risk of a poor outcome.

The first tests using this new biomarker went well, and a trial on two cohorts of about one hundred women has now been conducted. The results are promising, and will be presented at the AACR (American Association for Cancer Research) conference in April. In patients with metastatic breast cancer, divpenia is effectively associated with a higher risk of death. Thus, where divpenia is present, doctors can adapt the treatment to make it less immunosuppressive, or offer and assess corrective measures.

"The technique is easy to use and the results can be interpreted rapidly, which is important for routine applications." says Jean-Yves Blay. But, it is probably Divpenia's capacity to help understand the cancer which completes the picture. This reaction is to be expected of the president of EORTC (1).

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Date: 10/02/2011

"We have to continuously build bridges between basic and clinical research. With Divpenia we see the cancer/patient relationship in a different light, which helps to understand the role of immunity in clinical progression. If immunity drops, is it because of a drop in production or due to increased destruction of the immune cells? Is there a link with remission, long-term survival? Finally, we can attempt to restart the system." he explains, with a smile, and adds "Here at the CLB, Divpenia could soon be one of the routine examinations performed at the start of patient management."

The studies for medical applications are ongoing, but the test is already being used by the pharmaceutical industry

While the studies led by Jean-Yves Blay are ongoing as part of a prospective study on breast and lung cancers, the RIPAL (2) prospective study was started at the end of 2010 with the Hospices Civils, Lyon. Directed by professor Gilles Salles, head of the hematology department, this study of lymphomas and chronic lymphoid leukemia will show whether Divpenia can be used as a biomarker to identify a risk of infection and help adapt treatments. As part of clinical trials aiming to restore immune function, this biomarker will demonstrate the importance of the immune response in controlling tumor progression.

The pharmaceutical industry is interested too. By selecting, or ranking, the patients enrolled in clinical trials, costs can be lowered and the study's chances of success will be increased.

The final trump for Divpenia is that it is a tool with potential applications in personalized medicine, which can only be promising. So, although it's still too early to say what will become of this biomarker, maybe we won't be holding our breaths for too long.

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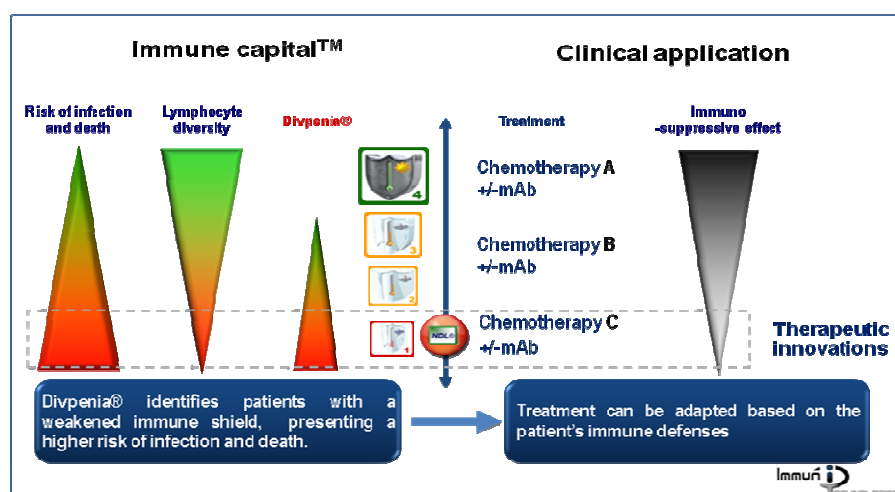
www.divpenie.com

(1) European Organization for Research and Treatment of Cancer

(2) Répertoire Immunologique chez les Patients Atteints de Lymphomes et de leucémies lymphoïdes chroniques (Immune repertoire in patients with Lymphoma and chronic lymphoid leukemia)

ImmunID Technologies

The immunomonitoring-specialized start-up was launched in 2005 in Grenoble, based on the idea that it was possible to assess the immune defenses of an individual from their DNA. The problem was that it was difficult to do. Everything had to be developed: tests, software, and proof of the utility. The creators of the SMB set to with conviction. Several decisive advances were made in 2010: a technical collaboration with Roche Diagnostics to improve their IFS PCR station, clinical trials etc. In particular, the team was nearing their ultimate goal, defining the biomarker known as Divpenia. Between now and 2013, the concept should be confirmed. And now? "We hope to make our small contribution to medicine, to help improve patients' quality of life and survival rates" confides Nicolas Pasqual, one of the founders. www.immunid.com



For a patient with a poor Divpenia score, the risk of infection is high. It is preferable to choose a treatment with lower immunosuppressive effects.

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