

Research Report

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MINIMAL RESIDUAL DISEASE

Minimal residual disease (MRD) is the name given to the small number of cancer cells that remain in the body during or after treatment. This residual disease often results in the recurrence of lymphoma in patients.

Detection of MRD is advantageous because it allows physicians and scientists to: assess a patient's response to treatment, monitor cancer recurrence, detect impending relapse, compare the efficiency of different treatment options and select the best treatment for each individual.

For many years, tests used to detect MRD were not sensitive enough. However, thanks to recent technological advances, this has changed. Tests are now capable of detecting even the smallest number of cancer cells in a sample.

While there are some researchers discovering ways to improve MRD measurement techniques, there are others developing novel strategies to eradicate MRD. By successfully eliminating the cancer cells that remain in the body following treatment, researchers believe they can prevent the recurrence of cancer, ultimately leading to improvements in patient outcomes and survival.

Over the years, the Lymphoma Research Foundation has been funding projects ranging from laboratory studies to clinical trials. Some of these projects have focused on MRD. The following section contains in-depth interviews with Joshua Brody, MD, Christiane Pott, MD, and Wendy Stock, MD, three talented physician-scientists whose contributions are actively advancing MRD detection and elimination in the field of lymphoma research.

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The Lymphoma Research Foundation (LRF) is the nation's largest lymphoma-focused voluntary health organization devoted exclusively to funding lymphoma research and providing patients and health care professionals with critical information on the disease. LRF's mission is to eradicate lymphoma and serve those touched by this disease.

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Joshua Brody, MD
Stanford University, Stanford, CA



Dr. Joshua Brody

Mantle cell lymphoma (MCL) is a relatively rare, aggressive form of non-Hodgkin lymphoma. To date, there is no broadly recognized standard of care for the treatment of MCL. Conventional therapies, such as high-dose

chemotherapy, monoclonal antibodies, stem cell transplants and various combinations of these treatments, can successfully destroy lymphoma. However, some residual cancer cells remain, generally resulting in the recurrence of MCL. For this reason, it is imperative to develop novel ways to rid the body of this residual lymphoma.

In 2007, Joshua Brody, MD, (Instructor, Division of Oncology, Department of Medicine, Stanford University) received a three year Clinical Investigator Career Development Award from the Lymphoma Research Foundation (LRF) to study cancer vaccines as a way to eliminate residual lymphoma and significantly improve cancer-free survival among patients with MCL.

A patient-specific or custom-made cancer vaccine is an immunological treatment based on the genetic makeup of an individual patient's tumor. They are non-toxic and routinely given to a patient during a period of minimal disease, for example, after the patient receives chemotherapy. The vaccine works by enlisting a patient's own immune system to attack their cancer. Many researchers have been studying cancer vaccines, but have had mixed results.

Under the guidance of Ronald Levy, MD, (Professor and Chief, Division of Oncology, Stanford University School of Medicine) Dr. Brody and his colleagues are testing a new method for administering vaccines by giving the vaccine after a patient receives

chemotherapy and an autologous stem cell transplant (ASCT).

Within the treatment protocol, patients first undergo a biopsy to obtain tumor cells that will be used to develop the vaccine. After the biopsy, patients then receive chemotherapy (RB-hCVAD) followed by a "preliminary" vaccine. The body's immune system reacts by producing anti-lymphoma immune cells (primed T-cells), which are harvested from the patient's body two weeks later, using a medical technique called leukapheresis, and then frozen. Patients then receive high-dose chemotherapy and ASCT.

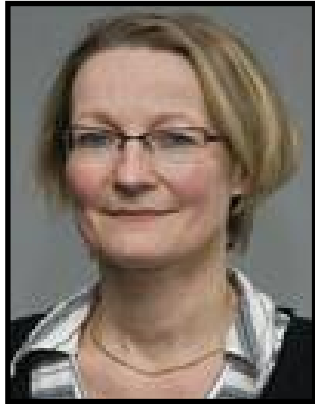
According to Dr. Brody, this is an ideal time to administer a vaccine because the chemotherapy has destroyed the majority of lymphoma cells and wiped out the body's immune cells. "This is a huge opportunity. At this point, the patient's immune system is a clean slate and, if vaccinated against cancer now, the immune system has the opportunity to re-grow as an anti-cancer immune system," says Dr. Brody.

After ASCT, patients receive an infusion of the vaccine and some of their previously harvested anti-lymphoma immune cells to destroy any remaining residual lymphoma. Booster doses of vaccine are also given three and six months post-ASCT.

To date, this treatment method has had tremendous success in eliminating even large lymphoma tumors in animal models. Dr. Brody's next step will be to test the method in a clinical trial. "This 'immunotransplant' approach has increased the power of lymphoma vaccines perhaps 10 to 40 fold. Since our recent clinical trials of lymphoma vaccines in the usual (non-transplant) setting have demonstrated clinical responses in a minority of patients, we hope that clinical trials of immunotransplant will similarly show a great increase in anti-cancer efficacy," says Dr. Brody.

When asked what advice he would give to younger physician-scientists getting started in the field, Dr. Brody replied quickly, "Get yourself a great mentor who believes in your ideas and believes in you. Preferably one who has an excellent grasp of the big picture and all the little details that make it up. I've been fortunate to have some good ideas about how to improve on immunotherapy for lymphoma, but without a great mentor, I'd never have had the chance to bring these ideas to life."

Christiane Pott, MD
University of Schleswig-Holstein,
Kiel, Germany



Dr. Christiane Pott

Current techniques for measuring minimal residual disease (MRD), such as quantitative polymerase chain reaction (PCR), are effective, but are often expensive and time consuming. Other methods have been

developed to monitor MRD, such as 2 or 4-color flow cytometry, but they are not as sensitive. Recent technical advances have created a more sensitive flow cytometer that uses 6-color technology.

With funding from the Lymphoma Research Foundation (LRF), Christiane Pott, MD, and her colleagues are testing the sensitivity, specificity and ability of 6-color flow cytometry to measure MRD in mantle cell lymphoma (MCL) in hopes of finding a faster, more reliable and cost-effective MRD assessment method.

Flow cytometry is a laboratory technique used to identify cells and their components by staining them with a light-sensitive fluorescent dye and detecting the fluorescence with a laser beam or other type of light. It allows scientists to measure several different cellular characteristics at the same time. By increasing the number of lasers and detectors, more cellular characteristics can be assessed, allowing for greater sensitivity and precision.

Cancer cells have specific markers (antigens) on their cell surface which differentiate them from normal cells. Scientists can develop molecules (antibodies) that specifically detect and bind to these antigens. By attaching the fluorescent dye to an antibody and allowing it to bind to the antigen on the cancer cell, the flow cytometer can easily identify and measure the presence of cancer cells.

Dr. Pott is currently performing a comparative analysis of the 6-color flow cytometer and quantitative PCR for MRD detection in MCL. She is collecting samples for analysis from clinical trials currently being conducted by the European MCL Network, an international group of clinicians, pathologists and researchers investigating MCL in Europe.

In recent publications, Dr. Pott has shown that, beside the clinical response to lymphoma treatment, the achievement of a “molecular remission” is of high prognostic relevance for patients with MCL. “Patients with residual malignant cells detected by quantitative PCR have a higher risk of relapse and an adverse prognosis. Therefore, MRD detection helps to identify different risk groups of MCL patients allowing early therapeutic intervention according to an individual risk profile,” says Dr. Pott.

Dr. Pott adds, “By applying 6-color flow cytometry, MRD results might be available much faster in the near future facilitating a more individualized patient management in daily clinical routine. The results of this study will contribute to improved risk stratification for MCL.”

Wendy Stock, MD
The University of Chicago,
Chicago, IL



Dr. Wendy Stock

In 2007, Wendy Stock, MD, (Professor and Director of Leukemia Program, The University of Chicago) received a two-year Mantle Cell Lymphoma Correlative grant from the Lymphoma Research Foundation (LRF)

to conduct two research projects focused on the elimination of MRD in MCL patients.

The first project is measuring MRD during treatment on a national clinical trial (conducted through the Cancer and Leukemia Group B – CALGB 50403; Principal Investigator – Lawrence Kaplan, MD) that is testing the combination of an effective new agent (bortezomib) with autologous stem cell transplantation (ASCT) for patients with previously untreated MCL. In previous studies, bortezomib has shown significant clinical activity in MCL making it an ideal agent to study MRD. Dr. Stock and her colleagues will be correlating MRD measurements during and following treatment with each patient’s clinical outcome.

“For this study, bortezomib is administered on two different schedules following ASCT. We are using quantitative techniques to measure MRD during various times of treatment in hopes of identifying whether bortezomib further reduces MRD after ASCT and whether this treatment improves progression-free survival. To date, we have over 50 patients enrolled and have completed the initial screening on 40 of those patients. We are hoping to accrue about 100 patients and are projecting that the trial will be fully accrued by next spring,” says Dr. Stock.

Dr. Stock’s second aim involves early laboratory studies of a novel treatment strategy designed to specifically and selectively inhibit the growth of MCL cells. This new strategy uses small molecules known as peptides that can easily penetrate the cell membrane and disrupt the cell cycle.

“We thought it would be interesting to look at MCL because all cases have an over-expression of cyclin D1 (a cell cycle regulator). This over-expression alters the cell cycle and results in abnormal cell growth. By targeting a master regulatory protein of cell cycle progression, known as CDK2, with a peptide designed by Steve Dowdy, PhD (University of California, San Diego), we are hoping to inhibit the growth of MCL cells and thus eradicate MRD,” says Dr. Stock. “This is an exciting concept. If an optimized peptide can be used to purge MRD from autologous stem cell products, it could improve the efficacy of autologous stem cell transplants for MCL.”

To date, this experimental aim is progressing nicely. Dr. Stock will soon begin testing optimized peptides for their ability to eradicate MRD from autologous stem cell samples that

have been collected and stored (for research purposes) from patients who have undergone autologous stem cell transplantation for MCL. Dr. Stock believes that one day peptide therapeutics may be combined with and compliment traditional chemotherapy and stem cell transplantation. She is hopeful that this strategy could be used for other forms of lymphoma and leukemia in the future.

“This correlative sciences award from the Lymphoma Research Foundation is very special since it really allows investigators to focus on identifying new prognostic markers that will guide future treatments for patients with MCL and result in improvements in survival,” says Dr. Stock.

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