
# Translational Immunotherapy Research

## Characterization of the immunogenomic landscape of Follicular Lymphoma


### SUMMARY

Mounting evidence suggests that immunotherapies can effectively turn patients' own immune systems against the very molecules that distinguish the tumor from normal cells, allowing the body's T cells to serve as guided missiles that seek and destroy only the intended target. This approach is based on the progressive mutational process that drives cancer evolution and generates antigens that are expressed exclusively in and on tumor cells



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**Report May 2017**

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## Background and Significance

### Overview

Lymphoma is the most common blood cancer. The two main forms of lymphoma are Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL). Lymphoma occurs when cells of the immune system called lymphocytes, a type of white blood cell, grow and multiply uncontrollably. Cancerous lymphocytes can travel to many parts of the body, including the lymph nodes, spleen, bone marrow, blood, or other organs, and form a mass called a tumor.

The body has two main types of lymphocytes that can develop into lymphomas: **B lymphocytes (B cells)** and **T lymphocytes (T cells).**

Follicular lymphoma (FL) is the most common indolent (slow-growing) form of NHL. Common symptoms of FL include enlargement of the lymph nodes in the neck, underarms, abdomen, or groin, as well as fatigue, shortness of breath, night sweats, and weight loss. Often, patients with FL have no obvious symptoms of the disease at diagnosis. 30%-40% of cases undergo histological transformation to an aggressive malignancy, typically represented by diffuse large B cell Lymphoma (DLBCL).[1]

### Treatment Options

There are various treatment options for FL based on the severity of associated symptoms and the rate of cancer growth.

1. If patients show no or very few symptoms, physicians may recommend not to treat the disease right away, an approach referred to as "watchful waiting" or "observation." Studies have shown that patients who are managed with a watchful waiting approach have survival outcomes similar to those who are treated early in the course of their disease. With this strategy, patients' overall health and disease are monitored through regular checkup visits and various evaluations, such as laboratory and imaging tests. Active treatment is started if the patient begins to develop lymphoma-related symptoms or there are signs that the disease is progressing based on testing during follow-up visits.
2. FL is generally very responsive to **radiation** and **chemotherapy**. Radiation alone can provide a long-lasting remission in some patients with limited disease. In more advanced stages, physicians may use one or more chemotherapy drugs or the monoclonal antibody **RITUXIMAB** (Rituxan), alone or in combination with other agents.
3. **Monoclonal antibodies** can act more directly than chemotherapy agents by targeting particular markers found on tumor cells and recruiting immune cells to promote tumor destruction, which can increase response to treatment.

   **Common combination regimens include:**

   - **R-Bendamustine** (rituximab and bendamustine)
   - **R-CHOP** (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone)
   - **R-CVP** (rituximab, cyclophosphamide, vincristine, and prednisone)

4. Some monoclonal antibodies can also be used as **maintenance therapy** for up to two years to prolong remission for patients with no signs of lymphoma.
5. Another treatment sometimes used for FL is **radioimmunotherapy (RIT)** using an agent such as yttrium-90 ibritumomab tiuxetan (**ZEVALIN**), which is a radioactive particle connected to an antibody that targets cancer cells.

After treatment, many patients can go into a remission that lasts for years; however, this disease should be considered a lifelong condition. Thus **relapse** (returns after treatment) and in some cases **refractory** (does not respond to treatment) disease can occur. For patients with relapsed FL, the same management choices as listed above may be utilized, or additional therapies may be successful in providing another

remission. For some patients with relapsed FL, high-dose chemotherapy followed by **stem cell transplantation** may be an option.

### Treatments Under Investigation

Many treatments are currently being tested in clinical trials for patients who are newly diagnosed or have relapsed/refractory FL.

1. For patients who have not previously received treatment for FL, therapies under investigation include various combinations of several agents: rituximab, lenalidomide (**REVLIMID**), bendamustine (**TREANDA**), ofatumumab (**ARZERRA**), bortezomib (**VELCADE**), ibrutinib (**IMBRUVICA**), duvelisib, TGR1202, obinutuzumab (**GAZYVA**), atezolizumab (**TECENTRIQ**), and pembrolizumab (**KEYTRUDA**).
2. Other combinations of treatment modalities, including immunochemotherapy, radioimmunotherapy, and stem cell transplantation are also under investigation and may help patients achieve prolonged remission.

**It is critical to remember that today's scientific research is continuously evolving. Treatment options may change as new treatments are discovered and current treatments are improved. Therefore, it is important that patients check with their physician or with LRF for any treatment updates that may have recently emerged. [http://www.lymphoma.org]**

## Immunotherapy

A cancer diagnosis often results in any number of relatively nonspecific treatments, such as surgery, radiation, or chemotherapy, all of which can destroy healthy tissue along with the tumor. Seeking approaches that could successfully eradicate tumors while avoiding such **collateral damage** from aggressive therapy, researchers have developed a number of treatments targeted to specific types of tumors and, more recently, a handful of therapies aimed at modulating the body's immune cells to more effectively fight its cancer. [Stephen P. Schoenberger and Ezra Cohen | April 1, 2017-TheScientist]

Immunotherapy is treatment that uses certain parts of a person's immune system to fight diseases such as cancer. This can be done in a couple of ways:

- Stimulating your own immune system to work harder or smarter to attack cancer cells
- Giving you immune system components, such as man-made immune system proteins

Some types of immunotherapy are also sometimes called **biologic therapy** or **biotherapy.** In the last few decades immunotherapy has become an important part of treating some types of cancer. Newer types of immune treatments are now being studied, and they'll impact how we treat cancer in the future.

Immunotherapy includes treatments that work in different ways. Some boost the body's immune system in a very general way. **Others help train the immune system to attack cancer cells specifically**. Immunotherapy works better for some types of cancer than for others. It's used by itself for some of these cancers, but for others it seems to work better when used with other types of treatment.

### What the immune system does

The immune system is a collection of organs, special cells, and substances that help protect from infections and some other diseases. Immune cells and the substances they make travel through the body to protect it from germs that cause infections. They also help protect from cancer in some ways.

The immune system keeps track of all of the substances normally found in the body. Any new substance that the immune system doesn't recognize raises an alarm, causing the immune system to attack it.

For example, germs contain substances such as certain proteins that are not normally found in the human body. The immune system sees these as “foreign” and attacks them. The immune response can destroy anything containing the foreign substance, such as germs or cancer cells.

### In tumor

Research efforts in last decades have provided clear evidence that **human tumor cells express antigenic determinants (epitopes)** that can be recognized by the patient’s autologous T cells. The short peptides that lead to such specific recognition and elimination of cancer cells are presented on the **human leucocyte antigen (HLA) molecules** and are named the immunopeptidome. CD4+ and CD8+ T lymphocytes have been shown to target epitopes arising from epigenetic, transcriptional, translational and post-translational alterations of tumor cells and up to date, shared **tumor-associated Ags (TAAs**) have been extensively exploited for therapeutic purposes.

More recently, technological breakthroughs have shown that numerous endogenous mutated cancer proteins, **a hallmark of tumor cells**, can be processed into peptides and presented on the surface of tumor cells, leading to their immune recognition in vivo as “non-self” or foreign. Targeting such highly specific neoantigens (**neoAgs**) would enable immune cells to distinguish cancerous from normal cells, avoiding the risk of autoimmunity. [2]

However, neoAgs are in large part patient-specific, since the individual mutations found in any pair of tumors are largely distinct.[3] Thus, based on current knowledge, it is unlikely that a vaccine can be designed to target shared neoAgs in a large group of patients.

**The immune system has a tougher time targeting cancer cells, though. This is because cancer starts when cells become altered and start to grow out of control. The immune system doesn’t always recognize cancer cells as foreign.**

Clearly there are limits on the immune system’s ability to fight cancer on its own, because many people with healthy immune systems still develop cancer.

- Sometimes the immune system doesn’t see the cancer cells as foreign because the cells aren’t different enough from normal cells.
- Sometimes the immune system recognizes the cancer cells, but the response might not be strong enough to destroy the cancer.
- Cancer cells themselves can also give off substances that keep the immune system in check.

[https://www.cancer.org]

## Identify and validate neo-antigens in FL samples through HLA-binding prediction algorithms and in vitro T cell stimulation assays.

### Overall theme

Mounting evidence suggests that immunotherapies can effectively turn patients' own immune systems against the very molecules that distinguish the tumor from normal cells, allowing the body's T cells to serve as guided missiles that seek and destroy only the intended target.

This approach is based on the progressive mutational process that drives cancer evolution and generates antigens that are expressed exclusively in and on tumor cells.

**By training the immune system to target those tumor-specific antigens, called neoantigens, researchers hope to selectively eradicate the cancer cells while leaving healthy tissue unharmed.**

Advances in genomic sequencing and bioinformatics over the past decade have synergized to produce a clearer picture of the immune response to cancer and to move this concept from the laboratory to clinical practice. Hailed as nothing short of a revolution in oncology, immunotherapies have the potential to upend the field's standard of nonspecific, often damaging treatment regimens.

**Understanding the nature of cancer neoantigens is critical to continued development of these precision therapies.**

### Cancer as a disease of mutations

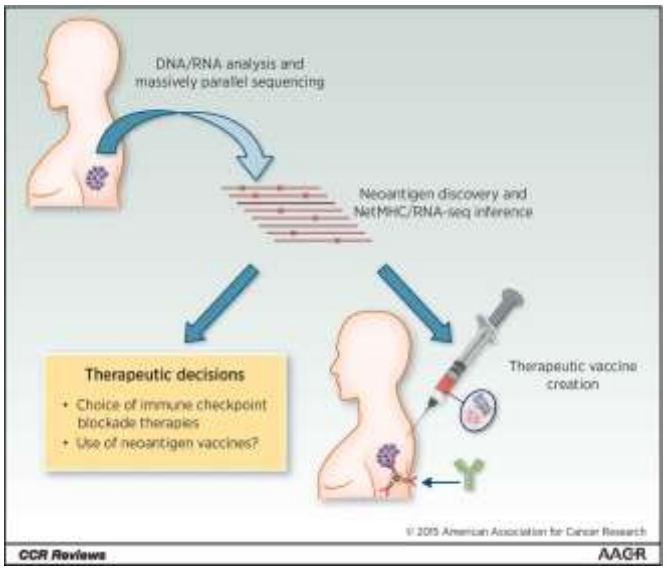



**Figure 1- A paradigm of neoantigen utility.**

Proposed strategy to use neoantigen repertoire in a predictive and therapeutic manner. Sequencing of tumor DNA leads to the discovery and assessment of the "neoantigenome." In parallel, creation of a personalized therapeutic vaccination could also be possible.

Cancer typically develops from a single cell that, as it divides into a clonal population, accumulates function-altering mutations in the genes that control cell growth, survival, and differentiation. This conceptual framework has become a central tenet of how the disease is both understood and treated.

[By Stephen P. Schoenberger and Ezra Cohen | April 1, 2017-TheScientist]

The accumulation of mutations that control critical cellular functions is believed to occur throughout a normal cell's progression towards neoplasia—the stage at which a cell can be considered cancerous. In support of this notion, researchers have observed that early events in cancer development frequently involve loss-of-function mutations in DNA-repair proteins, thereby accelerating the rate of mutation accumulation in the tumor. [4]

Recent advances in both the cost and capacity of genomic sequencing and the development of powerful new computational methods for its analysis have enabled the mutational landscape of a number of histologically distinct tumors to be evaluated and cataloged. (fig.1)[5] These efforts have revealed that a surprising range in the mutational burden exists among different tumor types, with those arising in mutagen-exposed tissues such as skin, lung, and bladder containing the greatest numbers,

second only to those tumors lacking DNA mismatch repair (MMR) or proofreading functions, as occurs most commonly in certain subsets of colorectal and endometrial cancer. [6]

There are a number of lines of evidence which indicate that the host immune response plays a role in the surveillance of B cell lymphomas, particularly classical Hodgkin lymphoma (cHL) and follicular non-Hodgkin lymphoma (FL).

**The central hypothesis of this project is that somatic mutations generate neo-antigens which are the targets of T cells in patients with FL, and that numbers of such mutations directly correlate with the ability of the host to generate a spontaneous anti-lymphoma immune response**.

While some of these mutations are in known "driver" oncogenes, the majority occur in genes whose functions play no obvious role in either establishing or maintaining the transformed state, and are collectively referred to as "passenger" mutations. Both driver and passenger mutations can lead to the cell's production of tumor-specific neoantigens, which can be recognized by the T lymphocytes that are tasked with detecting foreign invaders in the body. T cells typically recognize short, linear peptides derived from proteins of intracellular and extracellular pathogens and presented on the major histocompatibility complex (MHC) molecules found at the surface of nearly all the cells in the body. While MHC-bound peptides that are derived from normal self proteins are largely ignored—a process known as tolerance—those that differ in sequence, even by a single amino acid, can be efficiently targeted for destruction by T cells. (fig.2)

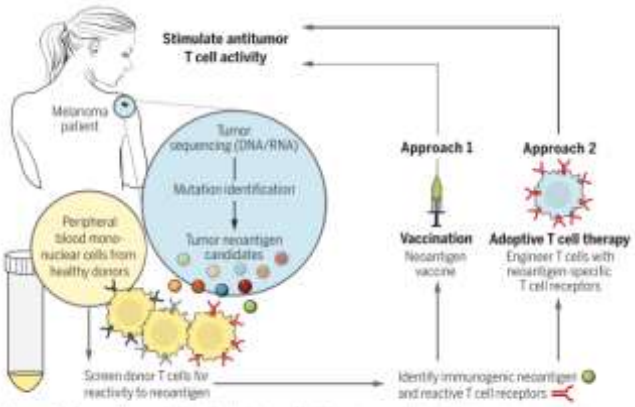



**Figure 2-Improving immunotherapy**

Use of healthy donors' T cells can improve the identification of immunogenic neoantigens for the development of neoantigen-based vaccines or T cell–based adoptive cell therapy.

## Study Design

To address the hypothesis that somatic mutations generate neo-antigens which are the targets of T cells in patients with FL, genomic DNA (gDNA) libraries has been generated from FACS-purified malignant B cells (CD10+CD19+ cells) and pool of T cells population used as matched control from 7 diagnostic FL tissue samples (6 cases), whose one of these was DLBCL (fig 4). To examine the mutational burden and neo-antigen landscape of these diseases, whole exome sequencing (WES) has been performed. (fig.3-**A**)

Following exome sequencing of FL samples, the HLA haplotype of each patient has been determined using hla-genotyper or HLAreporter software. Neo-antigens has been predicted from mutated proteins.

To identify expressed genomic NSV, to limit candidate NSV to those actually expressed at the mRNA level, transcriptome analysis (RNAseq) should be performed on mRNA libraries from lymphoma cells and on autologous T cells. Numbers and location of expressed NSVs in each lymphoma genome will be enumerated and catalogued. (fig.3-**B-Integration of exome and Transcriptome analyses**)

Four peptides with the highest affinity to a patient's HLA-A molecules will be synthesized. Matched peripheral blood T cells will be isolated and stimulated in the presence of autologous monocyte-derived dendritic cells and candidate peptides in vitro for 10 days according to a validated protocol. Specific T

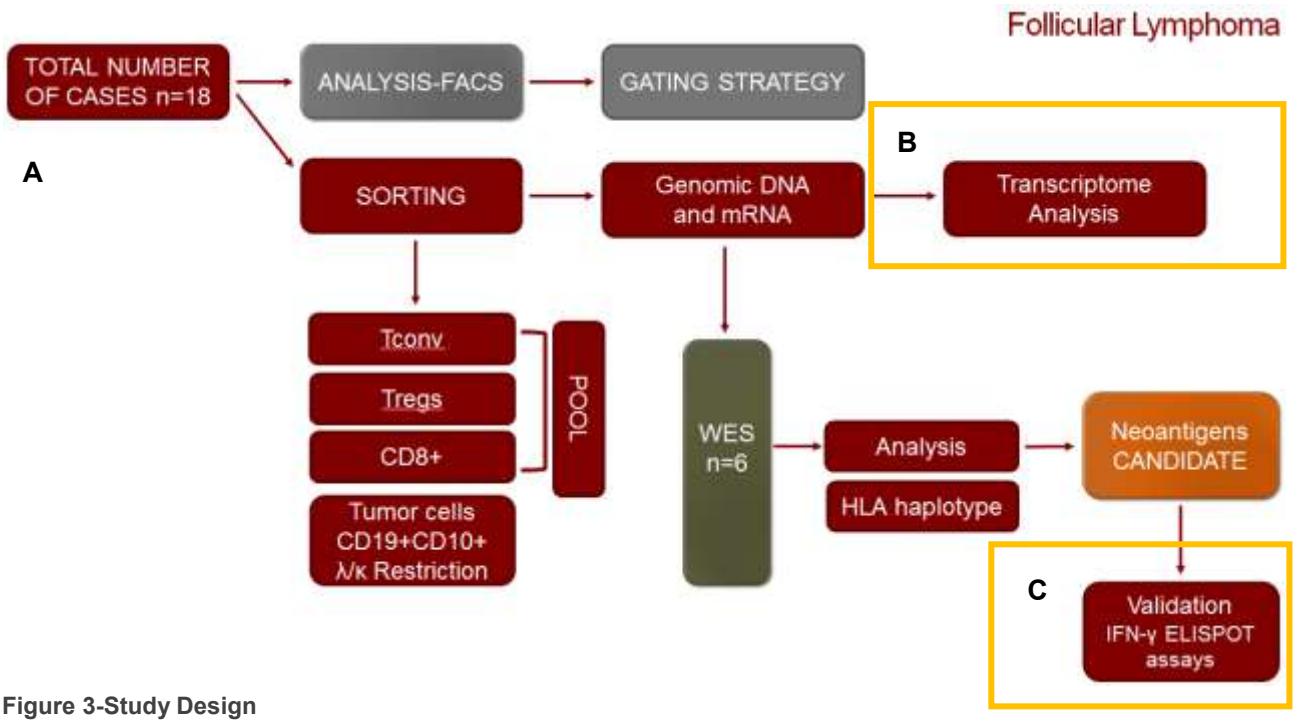



**Figure 3-Study Design**

In this figure the study design is represented. From six cases of FL we collected tumor cells matched with healthy cells as control, for the detection of somatic mutation and then the prediction of the neoantigens candidate.

cell reactivity will be tested using IFN-γ ELISPOT assays, along with HLA multimers and flow cytometry. (fig.3-**C**)

Whereas the presentation of foreign peptides on the surface of cells infected with viral and bacterial pathogens is a well-studied phenomenon, only recently have researchers begun to consider the facts that tumor cells also display foreign molecules (in the form of mutated peptides) and that these antigens could be exploited for tumor control.

**Many studies suggest that the mutational landscape of cancer is tightly coupled with host anti-tumor immunity, and that neo-antigens drive immune responses against cancer.**

One type of immunotherapy in which a tumor's neoantigens are suspected to play a role is immune checkpoint inhibitors, which block inhibitory signals that would otherwise repress the body's cancer-fighting T cells. In both preclinical models and human cancer patients, administration of antibodies to block immune checkpoint pathways, including PD-1/PD-L1 and CTLA-4, can elicit strong antitumor T-cell responses. In 2015, several groups discovered that responsiveness to immune checkpoint blockade correlates with neoantigen load;[7] the more tumor-specific antigens the cancer cells have, the greater chance the body's army of T cells will include some lymphocytes with matching receptors. Similarly, a growing number of clinical studies testing the use of T-cell transfusions, also known as adoptive cellular therapy, have demonstrated that

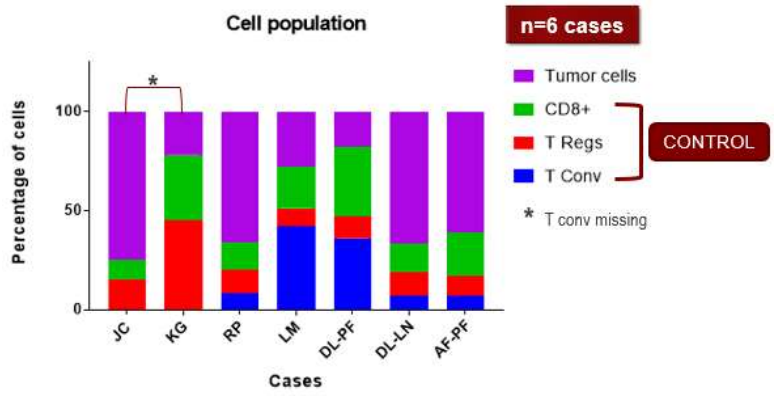



**Figure 4- FACS-purified cell populations**

In this figure is shown the percentage of different cells population purified for each specimen (6 cases).

mutant gene products are the immunological targets of the transferred lymphocytes. These fundamental studies and single-patient results have provided a compelling case for targeting neoantigens as a class across a range of cancers. **The next key developments must be to rapidly identify unique cancer markers and train the immune system to effectively target them.**

[By Stephen P. Schoenberger and Ezra Cohen | April 1, 2017-TheScientist]

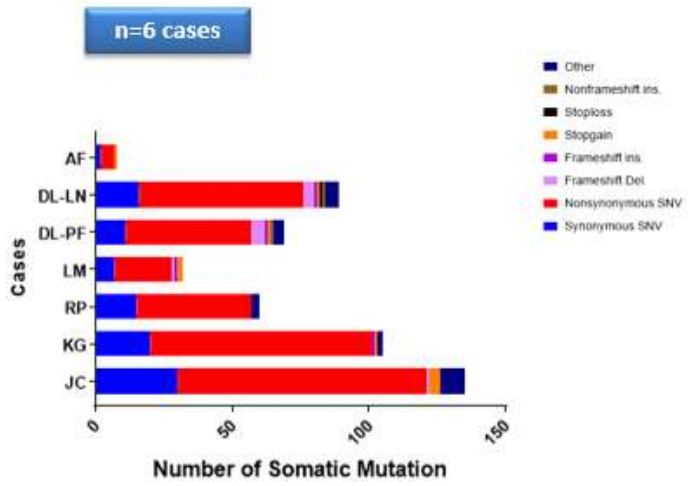


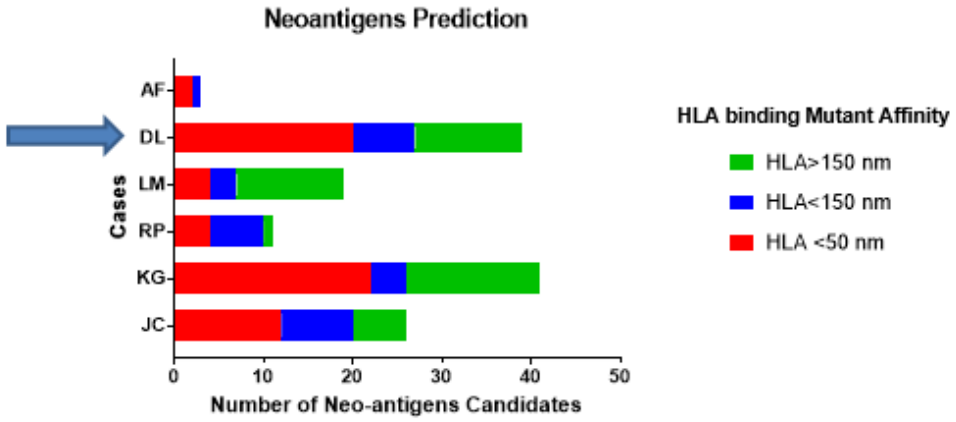

**Figure 5-Number and type of mutations across cases**

Total number of mutations for each human sample. In red, the number of Nonsynonymous variation.

Neoantigens derive from somatic mutations that produce modified or novel peptide sequences within a tumor cell's repertoire of expressed proteins. These include missense mutations, frameshifts, translocations, and mRNA splicing variants, as well as mutations that influence posttranslational processing, such as phosphorylation and glycosylation. All of these mutations can result in molecular changes that can be discriminated by an appropriate T-cell receptor.

In the fig.5, we show the load of genetic mutations for each human sample, in total 6 cases analyzed.

Major histocompatibility complex (MHC)-binding affinity was predicted across all possible 9- and 10-mer peptides generated from each somatic mutation and the corresponding wild-type peptides using NetMHCpan v2.8 (fig.6). These tiled peptides were analyzed for their binding affinities (IC50 nM) to each class I allele in the patients' HLA profile. An IC50 value of <150 nM was considered a predicted strong binder; between 150 and 500 nM, an




| gene | amino_acid | chr | chr_pos | ref | alt | length | peptide_mut | affinity_mut(nM) | peptide_wt | affinity_wt(nM) | Δaffinity(wt-mut) | HLA |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| PNPT1 | Y432F | chr2 | 55883496 | T | A | 11 | NFMLHYEFPPF | 49 | NFMLHYEFPPY | 5111 | 5062 | HLA-A 24:02 |
| SMARCA4 | T910M | chr19 | 11132513 | C | T | 11 | LLMGTPLQNKL | 94 | LLTGTPLQNKL | 1171 | 1077 | HLA-A 02:01 |
| HIST1H4D | V82L | chr6 | 26189061 | C | G | 10 | TLTAMDVVYA | 230 | TVTAMDVVYA | 4475 | 4245 | HLA-A 02:01 |
| CCDC150 | G762A | chr2 | 197586271 | G | C | 8 | SLQKALAV | 289 | SLQKALGV | 344 | 55 | HLA-A 02:01 |

**Figure 6-Neoantigens Prediction**

Number of neoantigen candidates represented with their binding affinities (IC50nm) to each class I allele in the patient's HLA profile. Table shows the four candidates for further experiments.

intermediate to weak binder; and >500 nM, a nonbinder. We'll empirically confirm predicted peptides binding to HLA molecules (IC50 <300 nM) by competitive MHC class I allele-binding experiments.

## Discussion: The rocky path to the clinic

Identification of tumor-expressed somatic mutations by sequencing is a relatively straightforward exercise that is increasingly within the grasp of most clinical research centers. The general strategy is to perform genomic or whole-exome sequencing of both a tumor and a reference genome (usually obtainable from peripheral lymphocytes or buccal swabs), as well as RNA sequencing to confirm that variants identified are indeed expressed in the tumor.

Predicting whether a patient will have an immune response to a particular mutation is challenging, however, as this depends not only on the presence of a suitable T cell within an individual's immune repertoire, but also on myriad factors pertaining to the mutant protein's ability to be processed and shuttled to the lymph nodes for interrogation by antigen-presenting cells.

**Nonetheless, researchers are now working to improve methods for identifying neoantigens in human cancer, in hopes of being able to develop personalized vaccine and cellular therapy approaches.**

To this end, a number of computational tools have been developed to analyze a range of features thought to be relevant to a given peptide's ability to be a T-cell target. These include the amino acid sequence of the mutated peptide, its similarity to the corresponding wild-type sequence, its predicted ability to undergo proteolysis, and its predicted binding affinity to relevant MHC molecules. The success rate of these analyses in forecasting which somatic mutations can be neoantigen targets is, to date, less than impressive, however. As an alternative approach to neoantigen identification, researchers have used sensitive mass spectrometry techniques to define the spectrum of peptides bound to a tumor's surface MHC molecules. While this strategy has successfully identified neoantigen targets in murine tumors, its applicability to human cancers has yet to be established.

We would use the third approach, that is to marry the empiricism and sequence analysis themes inherent in the first two, but instead of working purely in computational space, we test a patient's peripheral or tumor-infiltrating T cells for recognition of predicted neoantigens ex vivo.

**This has the advantage of confirming, rather than presuming, what the relevant targets are likely to be and allowing for the discovery of responses that would not have been evident from the computational models.**

As our tools for the cellular- and molecular-level interrogation of tumors and for the identification of neoantigens continue to improve, other challenges to their development as therapeutics have become increasingly clear—namely, cancer's ability to adapt. Tumor cells' adaptations to maximize growth and therapeutic resistance likely represent the most significant impediment to neoantigen-guided precision immunotherapy. Tumors can counteract immune control via a number of extrinsic pathways of adaptive resistance, including those that exploit normal physiological pathways of immune suppression.[8] By eliminating the presentation of antigens, for example, such pathways can render the tumor invisible to the immune system.

The genetic heterogeneity that results from tumor cells' evolution can also present a significant obstacle to neoantigen-focused immunotherapeutic strategies, as not all cells will carry the targeted antigens. Retrospective studies on patients who underwent checkpoint blockade immunotherapies have found that positive responses were associated with targeting clonally expressed neoantigens, which are present on most or all tumor cells. Treatments targeting subclonal mutations, on the other hand, tended to result in little or no response in the patients.[9]

As sequencing costs continue to decrease, research efforts should be aimed at capturing the clonal diversity of somatic mutations present within an individual patient over the course of his or her disease. In this way, clinicians can have a chance of identifying the mutations present in the majority of tumor sites (the “trunk” mutations) versus those that arise either late in the development of the cancer or in a select subclonal population (the “branch” mutations). Although it is tempting to imagine that driver mutations would, by virtue of their potent effects on enhancing self-renewal, more likely be found in the trunk than the branches of a tumor’s mutational tree, it is just as likely that passenger mutations can provide the type of target coverage desired for an effective neoantigen-focused immunotherapy, in light of their greater number. The wide variety in mutational burden among different cancers, however, may limit the number of instances in which this concept can be meaningfully tested. Cancers at extreme ends of the mutational burden spectrum may be less amenable, since those with a low mutational load will provide few neoantigen targets, while those with a high mutational load will have too many to test.

## Early trials

Although it is still early in terms of clinical development, investigators have launched the first trials of neoantigen-guided immunotherapy, with methods ranging from peptide-loaded dendritic cells to lipoplexed mRNA being evaluated in Phase 1 clinical trials.9,10 A handful of trials are under way, and many more are being planned through numerous industry-academic collaborations. One hurdle for the routine clinical use of such personalized approaches will be to establish platforms to manufacture clinical-grade reagents for use in a single patient that are cost-effective and completed in a timely manner to avoid disease progression. This will clearly require an unprecedented degree of cooperation and alignment among clinicians, biopharmaceutical companies, and regulatory entities.

Given the personalized nature of a neoantigen-based vaccine, this strategy might be best employed when some cancer remains after prior treatment or in successfully treated cancers with a high rate of recurrence. More-aggressive therapies, such as the delivery of cancer-fighting T cells and checkpoint inhibitors to take the brakes off the immune system, will likely remain the better option for those with advanced disease and a high tumor burden. Nonetheless, it is unlikely that any monotherapy will be as effective as a combination. The pairing of two or more of these approaches could prove to be a synergistic intervention—one that provides a durable treatment benefit for the majority of cancer patients.

## Appendix

### Types of cancer immunotherapy

The main types of immunotherapy now being used to treat cancer include:

- Monoclonal antibodies: These are man-made versions of immune system proteins. Antibodies can be very useful in treating cancer because they can be designed to attack a very specific part of a cancer cell.
- Immune checkpoint inhibitors: These drugs basically take the 'brakes' off the immune system, which helps it recognize and attack cancer cells.
- Cancer vaccines: Vaccines are substances put into the body to start an immune response against certain diseases. We usually think of them as being given to healthy people to help prevent infections. But some vaccines can help prevent or treat cancer.
- Other, non-specific immunotherapies: These treatments boost the immune system in a general way, but this can still help the immune system attack cancer cells.

Immunotherapy drugs are now used to treat many different types of cancer.

### Clinical Trials

Clinical trials are crucial in identifying effective drugs and determining optimal doses for lymphoma patients. Patients interested in participating in a clinical trial should talk to their physician or contact the LRF Helpline for an individualized clinical trial search by calling (800) 500-9976 or emailing helpline@lymphoma.org.

### Follow Up

Since FL is generally characterized by multiple disease relapses after responses to a variety of treatments, patients in remission should have regular visits with a physician who is familiar with their medical history and the treatments they have received. Medical tests (such as blood tests and computed tomography [CT] or positron emission tomography [PET] scans, and biopsies of suspicious masses or the pelvic bone marrow) may be required at various times during remission to evaluate the need for additional treatment.

Some treatments can cause long-term effects or late effects, which can vary based on duration and frequency of treatments, age, gender, and the overall health of each patient at the time of treatment. A physician will check for these effects during follow-up care. Visits may become less frequent the longer the disease remains in remission.

Patients and their caregivers are encouraged to keep copies of all medical records and test results as well as information on the types, amounts, and duration of all treatments received. This documentation will be important for keeping track of any effects resulting from treatment or potential disease recurrences.

## For more information:

### Support

A lymphoma diagnosis often triggers a range of feelings and concerns. In addition, cancer treatment can cause physical discomfort. One-to-one peer support programs, such as LRF's Lymphoma Support Network, connects patients and caregivers with volunteers that have experience with FL, similar treatments, or challenges, for mutual emotional support and encouragement. You may find this useful whether you or a loved one is newly diagnosed, in treatment, or in remission.

### Resources

LRF offers a wide range of resources that address treatment options, the latest research advances, and ways to cope with all aspects of lymphoma and FL, including our award-winning mobile app, Focus On Lymphoma. LRF also provides many educational activities, from in-person meetings to teleconferences and webcasts for people with follicular lymphoma, as well as FL e-Updates that provide the latest disease-specific news and treatment options. . For more information about any of these resources, visit the website at www.lymphoma.org or www.FocusOnFL.org, or contact the Helpline at (800) 500-9976 or helpline@lymphoma.org.

### Our Team

Physicians at the University of Chicago Medicine Comprehensive Cancer Center are experts in the care and treatment of patients with all types of lymphoma. We treat close to 250 new lymphoma patients each year. Our experts have been awarded grants to conduct research on lymphoma and have been extensively published in respected medical journals. We actively participate in national and international committees and research groups devoted to finding a cure for these diseases. University of Chicago Medicine physicians organize a yearly lymphoma symposium in Chicago and are frequently invited to speak at national and international meetings. (UC Medicine Lymphoma)

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## Glossary

**T cells**
A lymphocyte of a type produced or processed by the thymus gland and actively participating in the immune response.

**B cells**
A lymphocyte not processed by the thymus gland, and responsible for producing antibodies.

**Precision Oncology**
The use of systematic assessment of cancer genomic information for personalized diagnosis and therapy

**Cancer Immunotherapy**
Activation of the immune system to specifically target and kill cancer cells using checkpoint blockers, therapeutic vaccines or engineered T cells

**Antigens**
Short peptides that are produced from digested proteins and presented on the surface on the cell by the major histocompatibility complex or the human leukocyte antigen

**Immune checkpoint**
An inhibitory pathway of the immune system, commonly a ligand-receptor pair, that maintains self-tolerance and modulates immune responses in peripheral tissues in order to minimize collateral tissue damage

**Checkpoint blockers**
Antibodies that target immune checkpoint molecules to activate the immune system

**Therapeutic Vaccines**
Cancer treatment or therapeutic vaccines use specific antigens to boost the immune system's ability to recognize and to destroy cancer cells

**Engineered T cells**
Genetically modified T cells (for example, by expressing a chimeric antigen receptor) that are designed to recognize particular tumor antigens as non-self and lead to tumor destruction

**Neoantigens**
Acquired somatic mutations in the cancer genome that lead to new antigens recognized by the immune system

**Major histocompatibility complex**
MHC. Protein complex that presents antigens on the cell surface. In humans, the MHC is encoded by the human leucocyte antigen HLA gene locus

**Human Leucocyte antigen**
HLAs. Loci of genes that encode for proteins on the surface of cells and present antigens from inside (class I) and outside (class II) of the cell to T lymphocytes. HLA is the human form for the major histocompatibility complex