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CLL RESEARCH Momentum

MOVING CLL RESEARCH FORWARD – A PROGRESS UPDATE

ISSUE 2-2012

CLL GLOBAL RECIPIENTS ON
trajectory to the moon

"CLL research is about to get a big financial boost. My colleagues at MD Anderson Cancer Center and I spent the summer working on a CLL Moon Shot proposal and successfully competed for funding. All members of MD Anderson's CLL Moon Shot team have been actively involved in the CLL Global Alliance for several years. There is no doubt that camaraderie enhanced by CLL Global played a key role in our Moon Shot achievement. Read below to learn about the momentous launch."

~ Dr. Michael Keating

In late September, the CLL group at MD Anderson was named one of six winners of the Moon Shots Program. Drawing inspiration from President John F. Kennedy's 1961 challenge to put a man on the moon, Dr. Ronald DePinho, MD Anderson's new president, issued a challenge to the faculty. The challenge was to develop a comprehensive action plan to significantly increase survival rates of cancer patients in the near term and accelerate cures in the long term.

Proposals for specific cancers were submitted and focused on the entire cancer continuum from prevention, early detection, treatment and survival. Successful Moon Shot proposals had feasible goals for prolonging and improving patients' lives within the next year while planning for a cure of the specific cancer within a few years. Also important was the inclusion of collaborative efforts, both within MD Anderson and externally.

Dr. Michael Keating led a group of fifteen MD Anderson faculty members, all CLL Global grant recipients, to develop an award-winning Moon Shot proposal. One of the reasons for the group's success was that it had already established a strong collaborative environment as a result of the CLL Global Alliance. Thanks to the Alliance, members had already been working together on integrated projects based on specific themes. These same themes became the basis for the Moon Shot proposal.

inside this issue:

The main focus of the CLL Moon Shot is to apply breakthrough treatments without damaging DNA or the immune system. In other words, the plan is to replace toxic chemotherapy with targeted treatments and immune system modulators. The goal is to replace standard chemotherapy regimens for all patients treated at MD Anderson within one year. Targeted approaches are already being tested. Newer treatments will slowly be integrated into combination therapies and will most likely reduce or eliminate the use of chemotherapy and increase the survival rate of CLL.

The longer-term metrics of the Moon Shot proposal are to double the survival rate and halve the rate of secondary cancers. The current ten-year remission rate for CLL is approximately 35%; the aim is to bring this up to 75%. Dr. Keating also noted that 45% of deaths of CLL patients are associated with secondary malignancies. Removing gene damaging chemotherapy should reduce this number.

The CLL Moon Shot proposal emphasized how close CLL research is to the goal line. Eventually CLL will be a disease which can be easily managed, leaving patients with a high quality of life and a normal life span. The work from the CLL Moon Shot stands to benefit CLL patients worldwide and will likely be applicable to other cancers.

The Moon Shot is just preparing for launch. The accomplishment of the CLL Moon Shot award can be partially attributed to support from CLL Global for funding initiatives before they are ready for "prime time" and for developing collaborations through the Alliance. There continue to be avenues of CLL research, especially at other institutions in the US and internationally, that will not be covered by the Moon Shot. CLL Global is eager to further add to the surge of CLL research with the help of people who believe in the cause and are willing to take part in the mission of a cure. : :

"CLL Global supporters have built the rocket. Now help us take off and land. You are our fellow travelers."

~ Dr. Michael Keating

Dr. Michael Keating, Professor of Medicine at MD Anderson Cancer Center, serves as president and CEO of the CLL Global Research Foundation. He is an internationally renowned CLL clinical scientist dedicated to patient care and to development of potentially curative CLL therapies.

Guest speaker Dr. Freda Stevenson (United Kingdom) and Alliance member Dr. Stephan Stilgenbauer (Germany) having a discussion at the Alliance meeting.

TULIPS, CHOCOLATE AND CLL Science

The Netherlands may be associated with images of Dutch chocolate, tulips and windmills. However, this past summer, the Netherlands were synonymous with CLL research as CLL Global hosted its semi-annual Alliance meeting outside of Amsterdam. The mid-year Alliance meetings usually take place in Europe immediately following the annual European Hematology Association (EHA) meeting. This facilitates getting 30 busy researchers from the U.S. and Europe together and minimizes the cost to CLL Global.

Alliance meetings bring together members of the CLL Global Alliance program which provides an open forum for them to present the latest in CLL research and brainstorm new approaches. The Alliance was developed in 2008 to promote integrated research in CLL. It is comprised of CLL experts divided into working groups focused on specific areas of CLL research. The collegiality and trust among the group becomes stronger with each year.

The agenda and format of each Alliance meeting varies in response to participants' feedback. For this particular meeting, there was an overwhelming request for a discussion on the biology of the B-cell receptor. The B-cell receptor is located on the surface of B-cells (CLL cells are malignant B-cells) and receives signals from the body which promote cell growth and survival. These signals are communicated to the cell via pathways which are targets of several new drugs under study, including ibrutinib (formerly PCI-32765) and GS-1101 (formerly CAL-101).

Research has exploded with regard to the B-cell receptor as a result of the development of these new drugs. However, some researchers such as the pioneering Dr. Freda Stevenson (University of Southampton, UK) have been working in this area for many years. Dr. Stevenson was invited as a guest speaker to educate Alliance members on the mechanisms of the B-cell receptor and other potential therapeutic options.

She provided an overview of the B-cell receptor in both normal and CLL cells. Dr. Stevenson also discussed her research on B-cell receptor inhibitors and the mutation status of CLL cells. Mutation status is a standard prognostic test for CLL.

A major component of Alliance meetings is to share knowledge. Scientists are very involved in their own area of expertise. Listening to presentations from overlapping areas of CLL research stimulates novel ideas. The Alliance is broken up into thematic working groups. Many collaborations have been established within and throughout the working groups.

Each area of CLL research influences another. For example, there is great connection between the Genetics and CLL-Stromal Interactions groups. The CLL-Stromal Interactions group studies the communication between CLL cells and other cells and molecules that provide support to the CLL cells. Research from various projects suggests that certain genes may promote this relationship.

Members of both working groups are collaborating to fully understand this situation. Information gleaned will be beneficial in understanding and further defining subgroups of CLL. The expertise of the New Drugs group of the Alliance will help determine if this relationship can be exploited.

New drugs which target the DNA of CLL are already in the works. Dr. Deepa Sampath (MD Anderson) studies and develops new drugs. She is part of the New Drugs group of the Alliance. Dr. George Calin (MD Anderson) from the Genetics group previously discovered tiny regulatory genes called microRNAs. Together they have been researching microRNA targets for a type of drug called histone deacetylase inhibitors. The goal is to cause CLL cell death by turning on microRNAs that have been silenced in CLL cells. Lab studies are being conducted to test optimal microRNA targets.

Several Alliance investigators have been collaborating to create effective chimeric antigen receptors (CARs). Researchers can now modify a patient's immune cells using gene therapy techniques instead of giving a patient immune cells from someone else (called an allogeneic stem cell transplant). These modified cells are able to target molecules found on cancer cells. The collaboration among Alliance members is contributing to the success of CARs. For more on CARs see article on page 4.

The Alliance was started as an experimental, open-ended initiative. Developments from Alliance projects are starting to come to clinical fruition, and members agree that the Alliance plays an important role in CLL research. One of the great things about CLL Global is the capability to create and fund promising endeavors in a nimble manner. The Alliance format may change as needed to maintain successful collaborations and continue to have a positive impact on CLL research. : :

EXPANDING THE CIRCLE OF collaboration

Collaboration has become a common word in cancer research circles. Some may argue it is a buzzword, but CLL Global believes strongly that collaboration is one of the keys to making advancements in CLL and other diseases. As mentioned earlier in this issue, collaboration is a vital element of the CLL Global Alliance and MD Anderson's new Moon Shots Program.

Partnerships are being developed not only with other researchers but also with pharmaceutical companies. These companies provide access to new drugs and influence clinical trials. At certain Alliance meetings, CLL Global invites a pharmaceutical company with a promising drug for CLL to an interactive discussion. At the Alliance meeting this summer, dialogue was held with Pharmacyclics, the company developing the kinase inhibitor ibrutinib (formerly PCI-32765). Pharmacyclics has partnered with Janssen, a Johnson & Johnson company, to further develop the drug. The discussion centered on the clinical trial experience to date and potential opportunities for the future.

The meeting was held right after the European Hematology Association (EHA) meeting where new ibrutinib clinical trial data was presented. Data showed that 81% of patients (≥65 years, treatment-naïve) receiving single-agent ibrutinib responded to the drug. Of those patients, 96% had no sign of disease progression at the time the data was presented. Results from a combination study of ibrutinib and bendamustine/rituximab showed that 93% of patients achieved a response and 13% of patients were found to be in complete remission. There was no added toxicity observed when adding ibrutinib to bendamustine /rituximab. For more on ibrutinib and other kinase inhibitors see article on page 4.

Preliminary results for ibrutinib are significant, and Alliance participants provided Pharmacyclics input on incorporating the drug as a front-line treatment strategy. The benefits of ibrutinib for patients with chromosome 17p/p53 abnormalities and those with minimal residual disease were also discussed. It was established that a clinical trial designed specifically for patients with the 17p/p53 abnormality is needed. A protocol using single agent ibrutinib will hopefully be in place in the beginning of 2013. This should bring great benefit to this particular subset of patients.

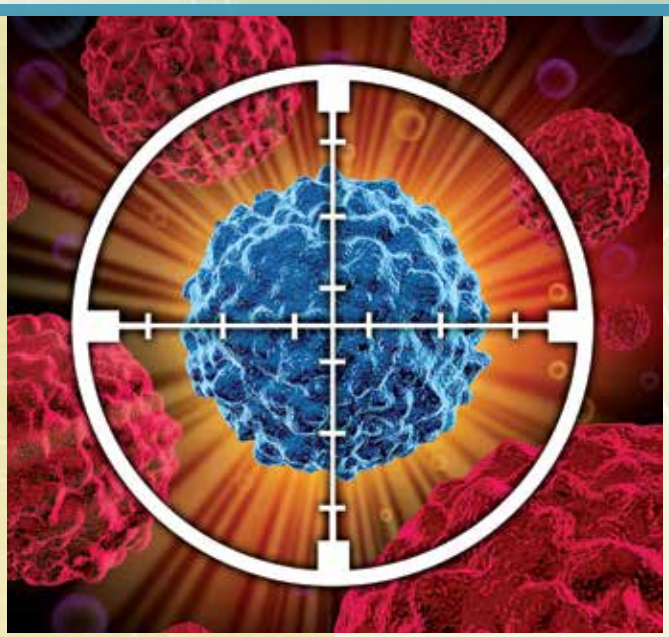
Another collaboration recently revealed is that of ten major drug companies. These companies have formed a nonprofit organization, TransCelerate, to expedite the drug approval process and reduce the cost of developing new drugs. TransCelerate will combine resources from the drug companies to make it quicker and easier to conduct clinical trials which will in turn accelerate new drugs to the market.

Collaborations are the new trend, and with good reason. They allow for a wealth of knowledge to be shared which can spark new ideas. Productivity increases. Resources are greater. Goals are larger and so are the achievements. Continuation of the CLL Global Alliance, initiation of the MD Anderson Moon Shots Program, industry collaborations and everything in between will have an influence on research. Most importantly, it will have an impact on patients. : :

A NEW DAWN, A NEW DAY FOR targeted treatments

There has been a substantial transition in CLL treatments over the past 20 years. Options have gone from non-specific, DNA-damaging chemotherapy to a new era of targeted treatment with minimal side effects, comparatively speaking. This new era has dramatically evolved over the last few years. Doctors are closer than ever to being able to identify the right treatment for each patient.

Below is an update on the most talked about newcomers to the treatment scene which are kinase inhibitors and chimeric antigen receptor (CAR) cells. Versions of both are already being tested in clinical trials; others are still being refined in the laboratory. Options will continue to grow as knowledge is gained, and CLL Global is always ready to fund promising new endeavors as the need arises.



KINASE INHIBITORS

Kinase inhibitors are the "it" drug for CLL treatment at the moment. The most advanced kinase inhibitors in development are ibrutinib (formerly PCI-32765) and GS-1101 (formerly CAL-101). Both drugs have been touted by many CLL researchers and patients for the dramatic results in decreasing the CLL cell burden.

Ibrutinib and GS-1101 target the B-cell receptor by blocking different pathways. The B-cell receptor is located on B-cells (CLL cells are malignant B-cells) and receives signals to keep CLL cells alive. These drugs are becoming available to more patients through phase II and phase III trials.

CLL Global grant recipient Dr. Spencer Gibson (University of Manitoba, Canada) is analyzing another kinase inhibitor called gefitinib (Iressa). This drug blocks a different pathway involved in the B-cell receptor signaling and is currently used in the treatment of non-small cell lung cancer. Dr. Gibson established in laboratory studies that gefitinib is effective in killing CLL cells that are positive for the ZAP-70 protein. ZAP-70 seems to be correlated with more aggressive disease, although tests have not been standardized.

Kinase inhibitors that target proteins other than those involved in the B-cell receptor pathways are becoming available. The drug companies Abbott and Genentech are collaboratively developing a kinase inhibitor called ABT-199. This drug blocks proteins known as the Bcl-2 family.

These proteins help keep CLL cells alive by preventing the cells from going through apoptosis, or programmed cell death. In CLL cells (and other types of cancer cells), there is an abundance of Bcl-2. Targeting this family of proteins should kill CLL cells without causing much harm to normal cells. ABT-199 is currently in phase I testing.

Dr. Varsha Gandhi (MD Anderson) receives funding from CLL Global to study Bcl-2 and other proteins that prevent CLL cells from dying normally. The aim of her project is to develop compounds that most effectively remove or weaken the survival advantage of CLL cells by blocking these proteins. Part of her project is to define an optimal sequence/combination of experimental drugs.

Alliance member Dr. Håkan Mellstedt (Karolinska Institute, Sweden) has produced kinase inhibitors targeting ROR1, a protein found almost exclusively on CLL cells. Laboratory tests have been successful, and Dr. Mellstedt has established collaborations with biotech companies in Sweden to further develop the drugs. Additional targets for kinase inhibitors and other small molecules will appear in the upcoming months and years as more is discovered about CLL. : :

CHIMERIC ANTIGEN RECEPTORS (CARs)

August 2011 marked a milestone for CLL research with news that three high-risk CLL patients were successfully treated with CARs at the University of Pennsylvania (UPenn). The trial results reduced skepticism of cellular therapy and have broken the field wide open.

CARS are part of a class of treatments known as cellular therapy, or immuno-therapy, which is the process of manipulating cells to generate an immune response to fight a disease. For decades the concept has been full of ups and downs. Significant advances and failed experiences have reduced the risk and expanded the knowledge.

CARs are delivered to and attach to the surface of T-cells which are immune cells responsible for eliminating foreign invaders. The CAR T-cells are programmed to look for a specific antigen and attack the cell associated with the antigen. There are several trials around the country open to CLL patients and patients with other types of B-cell malignancies.

UPenn and other sites are using CARs that target the CD19 protein. CLL Global is currently funding a CD19 CAR study at Memorial-Sloan Kettering under Dr. Renier Brentjens. The CD19 protein is expressed on CLL cells, but is also present on normal B-cells. This means that healthy B-cells are killed in the process which is an obstacle that researchers are trying to overcome.

CARs are also being produced that target the ROR1 protein which is found on CLL cells and other types of cancer cells. ROR1-specific CARs will be a major new initiative at MD Anderson Cancer Center. Regulatory approval is still needed before clinical trials can open.

Clinically speaking, CARs are still in their infancy. The architecture of a CAR varies from one laboratory to another. It will take several years to establish the most optimal means of use. The technology is constantly evolving, and there are an increasing number of targets to be studied. Additionally, CAR technology will likely expand to immune cells other than T-cells.

It is anticipated that CARs will play an important role in curing CLL. The potential is such that earlier this year Novartis, a prominent drug company, teamed up with UPenn to establish a new research center dedicated to cellular therapy. This is a result of the success of the three CLL patients mentioned above. : :

Brad and Rita Baker in front of their home with their 1948 Indian Chief Roadmaster

SUPPORT CLL GLOBAL -

it's the "write" thing to do!

Brad Baker has been living with CLL for five years. For the last four years, his wife Rita has been fundraising for CLL Global. Rita spearheads an annual letter-writing campaign which was initially designated to family and friends and has since expanded to the broader community. The Bakers discussed their lives since Brad's diagnosis and how they have involved others in the fight against CLL.

MR. BAKER, HOW WERE YOU DIAGNOSED WITH CLL?

BRAD: I was diagnosed with CLL in April 2007. Before my official diagnosis, I had a lump on the left side of my neck. My doctor originally determined it was lymphoma and was ready to rush into treatment. It just did not feel right. I was 45 years old. We were not going to fool around. We knew of a lot of people who had been to MD Anderson, and we went there on May 15th, 2007.

HOW DID YOU FIRST BECOME AWARE OF CLL GLOBAL?

BRAD: There is a patient, Andrew Schorr. Before I went to MD Anderson, I was lucky enough to stumble across his internet broadcasts which were really useful and encouraging. That is how I came to know that Dr. Keating was involved in CLL Global. Dr. Keating told us more after we met him. We realized that this was kind of ground zero for CLL research. It was reassuring and exciting.

HAD YOU EVER HEARD OF CLL BEFORE YOU WERE DIAGNOSED?

BRAD: Not CLL specifically, but I remember learning about different cancers in high school and distinctly thinking that leukemia would be the worst because it will contact every centimeter of your body. Thirty years later, here I am.

HAS LIFE CHANGED SIGNIFICANTLY FROM BEFORE CLL TO NOW?

BRAD: I think so. I do not approach things at the same breakneck speed that I used to, and I have a different appreciation for what is important in life.

RITA: You always have that [CLL] in the back of your mind. Until it touches you directly, it seems like something that always happens to somebody else.

MRS. BAKER, WHAT COMPELLED YOU TO GET INVOLVED WITH CLL GLOBAL?

RITA: It was something I could do to help Brad and everybody who has CLL. I started with family and friends. Then I branched out to some companies and local doctors and attorneys. When sending to companies you almost have to do it a year before because they only allocate so much to donations. Many companies that cannot donate write back and let me know.

BRAD: She also reminds family and friends that a lot of employers match donations up to fairly substantial amounts. I think sometimes people forget that.

ARE THE LETTERS THE SAME FROM YEAR TO YEAR?

RITA: Generally, yes. If I am resending to the same people I will say something like, "The time has come again…" It has gotten to the point where some people look for it. If I am sending it to someone I know, I usually write a little note at the bottom which I think is better than a straight form letter.

BRAD: Rita is my complete caregiver and case manager. Much the same, she is the solicitor general for CLL. This was her idea and something that she took on as a personal challenge. You feel kind of helpless, but it is one way to take control and feel like you have joined the war. The only investment, besides the emotional investment, is your time and a stamp.

RITA: Because CLL Global provides all of the brochures and things for me to include with my letter, it is not hard and is very rewarding. It is a joy knowing that you can help even if it is just a little bit.

WHAT WOULD YOU TELL POTENTIAL SUPPORTERS OF CLL GLOBAL?

RITA: Go for it! CLL Global needs as much money and as much help getting that money as possible. If there is a way to find a cure then let's find it fast.

BRAD: Cancer is going to touch everybody. It is just a function of how and when. CLL Global happens to be a research organization that is focused on CLL. But the work that CLL researchers are doing will ultimately touch all forms of cancer, so it is bigger than just CLL. The Foundation cuts through a lot of bureaucracy and pulls the best minds in the world together for a common cause. In that sense CLL Global deserves all of the help they can get.

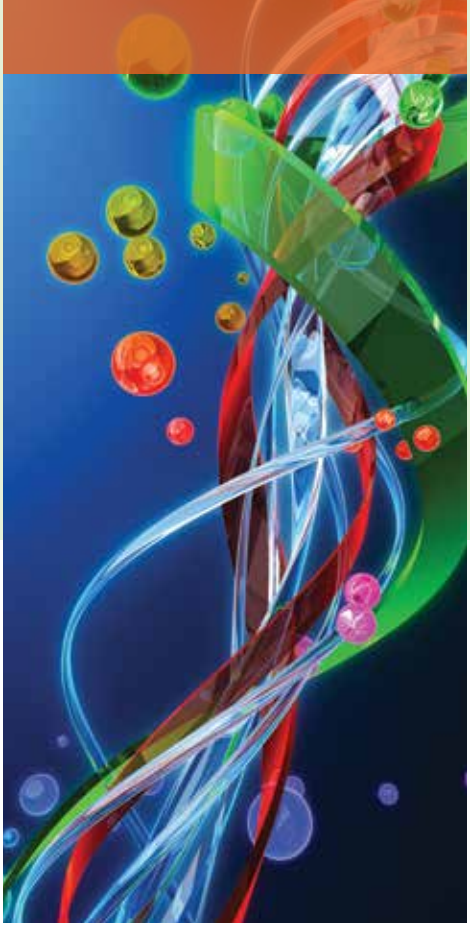
WHAT ADVICE DO YOU HAVE FOR NEWLY DIAGNOSED PATIENTS?

BRAD: There is always hope. And the biggest thing you can do is take control. Educate yourself. Find out where and how you can help. Do not just accept that first diagnosis.

If you are interested in starting your own letter writing campaign, contact us at info@cllglobal.org or 713-443-3746 for supplies or for more information. : :

GRANT RECIPIENT PROGRESS and future goals

CLL Global grants are initially awarded for one year. Subsequent funding is dependent on sufficient progress in the first year. Several grant recipients recently received additional funding for their research projects based upon accomplishments made to date. Below, find a list of the grant recipients, their initial progress and aims for the next year. More information about specific projects can be found on the website (www.cllglobal.org). ::



ALLIANCE GRANTS

George Calin, M.D., Ph.D.
University of Texas MD Anderson Cancer Center

Initial Progress: Focused on prognostic implications of microRNAs which are part of a new class of genes called non-coding RNAs. Found that some microRNA plasma levels are profoundly altered in most CLL patients. A specific microRNA was associated with longer survival and improved response to treatment.

Current Aim: Establish if the plasma microRNA "signature" of each patient can predict response to therapy. Evaluate the presence of viral microRNAs in the plasma which may contribute to the development of CLL.

Laurence Cooper, M.D., Ph.D.
University of Texas MD Anderson Cancer Center

Initial Progress: Generated and optimized chimeric antigen receptor (CAR) T-cells recognizing and targeting the proteins CD19 and ROR1.

Current Aim: Finalize preclinical studies and initiate clinical trials with the specific CARs in 2012-2013.

Ulf Klein, Ph.D.
Herbert Irving Comprehensive Cancer Center, Columbia University

Initial Progress: Discovered that the protein IRF4 is deficient in CLL cells which changes where the cells localize in the body. Also, IRF4 is critically involved in controlling factors called NOTCH regulators which may be responsible for the changed biology of CLL cells.

Current Aim: Dissect IRF4 and NOTCH interplay; determine if NOTCH can become a new therapeutic target.

INDIVIDUAL GRANTS

Renier Brentjens, M.D., Ph.D.
Memorial Sloan-Kettering Cancer Center

Initial Progress: Approval and initial enrollment of phase I clinical trial for high-risk CLL patients. Trial uses CAR T-cells targeting CD19 following chemoimmunotherapy.

Current Aim: Continue to treat patients, collect data and enroll additional patients.

George Calin, M.D., Ph.D.
University of Texas MD Anderson Cancer Center

Initial Progress: Using a highly technical process called deep sequencing, identified non-coding RNAs in patient samples with trisomy 12 abnormalities, which have an indolent disease course, and chromosome 6q abnormalities, which have a more aggressive disease course.

Current Aim: Characterize and define the non-coding RNA region on trisomy 12 and 6q to determine the biological effects. Do they play a role in cell proliferation, death or differentiation?

Spencer Gibson, M.D.
University of Manitoba (Canada)

Initial Progress: Analyzed gefitinib, a drug currently used in lung cancer, to determine the effect on CLL cells. Lab studies showed that CLL cells positive for the protein ZAP-70 were killed and the cells became more sensitive to traditional CLL treatments.

Current Aim: Compare how gefitinib induces cell death in samples with specific genetic abnormalities. Pilot a clinical trial of gefitinib in relapsed CLL patients.

Marco Herling, M.D.
University of Cologne (Germany)

Initial Progress: Evaluated ways to increase reactive oxygen species (ROS) to a toxic level which specifically targets CLL cells, leaving normal cells undamaged. Studied a variety of compounds in the lab with promising selective activity against ROS, which may represent a vulnerable target for CLL.

Current Aim: Perform additional laboratory studies with next-generation substances especially on samples from hard-to-treat patients like chromosome 11q, 17p deletion and/or fludarabine resistance.

Satoshi Nagata, Ph.D.
Sanford Research/ University of South Dakota

Initial Progress: Production of a monoclonal antibody targeting FCRL5, a highly and specifically expressed protein on CLL cells. Conducted studies to characterize the role of FCLR5 in B-cell differentiation.

Current Aim: Prepare and test anti-FCRL5 antibody in preclinical setting using CLL cells. ::

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