Resisting relapse

Dr Felipe Samaniego, Associate Professor at the Department of Lymphoma/Myeloma at the University of Texas’ Division of Cancer Medicine, discusses his current research efforts to understand and fight causes of relapse of non-Hodgkin’s lymphoma

Why is further research on non-Hodgkin’s lymphomas (NHLs), specifically mantle cell lymphoma (MCL), so important?

NHLs represent a group of over 30 different lymphoma subtypes. By knowing the exact biological properties of each distinct NHL type, we can tailor therapies for each patient and thus significantly improve treatment outcomes.

MCL has a characteristic and exclusive translocation between chromosomes 11 and 14 that drives overexpression of cyclinD1, making it a seemingly simple cancer model. Furthermore, even though initial remissions are readily attained, the majority of patients relapse, often with a chemoresistant form of MCL. Analysis of this simple cancer model will help us to understand more complex lymphomas such as small lymphocytic and follicular lymphoma.

What breakthroughs have been made regarding MCL biology in recent years?

Our first discovery was the isolation of the elusive MCL-initiating cells (MCL-ICs), which represent only a minor population (less than 1 per cent) of MCL cells that carry tumour-inducing and chemoresistant properties.

Previously it was not possible to study MCL cells obtained from patients. However, we have established a culture system that supports growth of primary MCL cells for over four weeks and maintains a subpopulation of MCL-ICs. This system allows us to study MCL directly from patients.

Existing therapies to target MCL have so far had minimal affect. Why is this so? How will your research contribute to improved diagnostic and treatment opportunities?

Current therapies offer incomplete elimination of MCL cells in patients, and so, MCL-ICs remain after chemotherapy and become the source of relapsed MCL. The new culture system allows us to study MCL-ICs’ biology in detail. By identifying their weaknesses, we can design new therapies to target these areas to eliminate MCL-ICs and thus prevent relapse.

What has your team learned about the factors and signalling pathways supporting growth, survival and maintenance of MCL-ICs?

It appears that a combination of signalling cytokines provided by stromal cells, as well as signalling between MCL-ICs themselves, is essential for MCL-IC survival and maintenance. More importantly, we found that by interfering with MCL-ICs’ specific wingless/integrated (Wnt) signalling, we can selectively reduce the number of MCL-ICs in cultures. We are examining whether other signalling pathways cooperate with Wnt targeting agents to kill MCL-ICs.

We will next test these effects in animal models and expand our findings to clinical trials. Models of MCL tumours grown in human bone marrow grafted into severe combined immunodeficient mice will allow us to study human-MCL-human stromal cell interactions in vivo.

Which of your drug testing trials have been most successful in the fight against MCL? Why have you decided to explore the potential of Wnt and fibroblast and vascular endothelial growth factors (FGF/VEGF) signalling inhibitors to eliminate MCL-ICs?

The approaches targeting the B-cell receptor signalling, recently approved by the US Food and Drug Administration (FDA), show success in some lymphomas, but are also prone to the development of resistant disease, indicating these will be short-lived incremental advances and not the answer for long-term cures of MCL. Over the coming years we expect to identify agents that block essential pathways for MCL-ICs’ Wnt and FGF/VEGF signalling, among other pathways. We expect that numerous signals will impinge on Wnt signalling and help determine the MCL-ICs survival and proliferation.

Our work toward improving therapy for lymphoma also involves other approaches; for example, we have an ongoing clinical trial for relapsed lymphoma using a CD74 antibody linked with doxorubicin. This antibody should guide doxorubicin to lymphoma cells which overexpress CD74 on their cell surfaces and minimise damage to non-cancer cells.

Ultimately, what are you hoping to achieve through your research?

Our aims are to understand the biology of MCL-ICs and to confirm their role in the chemoresistance and relapse of MCL. We expect our findings to provide important information guiding our selection of therapies for MCL and related lymphomas. What we learn about MCL will also apply to related cancers such as small lymphocytic lymphoma, chronic lymphocytic leukaemia and other lymphomas that rely on a similar model in which tumour-initiating cells harbour chemoresistance and produce cells that cause relapse.

At this juncture, I would like to offer our gratitude to the organisations and individuals who support our research. Our scientific and clinical trials teams would like to thank the National Cancer Institute, National Institute of Diabetes and Digestive and Kidney Diseases, the Richard Spencer Lewis Memorial Foundation and patients and their families who have placed their confidence in our projects. Often patients with cancer feel powerless over their diagnosis and supporting research is a way they can regain hope and direction during times of uncertainty. The results of these efforts culminate in clinical trials testing new agents and drug combinations at MD Anderson Cancer Center, ultimately keeping more patients cancer free.
NON-HODGKIN’S LYMPHOMA (NHL) is a cancer of the lymphatic system – part of the immune system. In NHL patients, infection-fighting white blood cells (lymphocytes) multiply abnormally, collecting in parts of the lymphatic system. Furthermore, they lose their capacity to fight infection, making the individual highly vulnerable to other risks. Over 65,000 NHL cases are diagnosed annually in the US, making it the eighth most widespread cancer and the sixth most common in males.

MCL: A GROWING THREAT

Although the number of NHL cases has remained fairly stable over the past two decades, the incidence of mantle cell lymphoma (MCL) – a currently incurable, particularly aggressive form of NHL – has doubled; in males it has almost tripled. MCL patients are particularly prone to relapse and their often advanced age (the median being 68 years) seriously reduces their tolerance to standard chemotherapy treatments. MCL tumour growth and maintenance is prompted by MCL-initiating cells (MCL-ICs), which are cancer stem cells (CSCs). Because CSCs are resistant to chemotherapy and radiotherapy, and are able to recreate tumours after treatment has eradicated them, new therapies must therefore be able to eliminate these cells.

Such issues are part of what prompted Harvard Medical School graduate, now Associate Professor of Lymphoma/Myeloma at the University of Texas, Dr Felipe Samaniego to conduct further research into MCL. He hopes that, with increased understanding of the mechanisms which initiate and perpetuate MCL, he and his team will be able to develop more effective, targeted treatments that will prove more beneficial to older patients.

NOVEL METHODS, NEW DISCOVERIES

Two important developments in the study of MCL have facilitated the earliest stages of Samaniego’s research. Firstly, it has been shown that the overexpression of cyclin D1, caused by translocation, is present in over 90 per cent of MCL patients, and therefore appears to be the driving force behind the disease. Secondly, scientists have been able to isolate MCL-ICs in mice as well as develop a culture system for primary MCL cells. Both of these developments enable extensive analysis of MCL biology. Samaniego’s initial research focused on revealing the factors that support MCL growth and MCL-IC maintenance, as well as identifying signalling pathways vital to MCL-IC survival.

Samaniego’s latest research proposes to explore the potential of wingless/integrated (Wnt) and other signalling inhibitors to eliminate MCL-ICs. As the source of relapse appears to be MCL-ICs, this research will eventually lead to the development of a new clinical strategy that integrates MCL-IC directed therapy into conventional therapy. The aim is to determine the drug sensitivity of MCL-ICs in order to tailor treatment to each individual case and greatly increase its efficacy.

SPURRED ON BY DISAPPOINTMENT

In late 2013 there was hope that, where standard chemotherapy drugs doxorubicin and vincristine have little effect on MCL-ICs (demonstrated using the new MCL culture system), the BTK inhibitor ibrutinib may have more success. Several reports attested to this, therefore in November 2013 the Food and Drug Administration (FDA) granted accelerated approval for the drug as a secondary therapy for MCL patients. Unfortunately, these hopes were dashed when further research showed that BTK is a negative regulator of Wnt signalling in B-cell leukaemia, thus its elimination can in fact support maintenance of MCL-ICs. This concern may become a reality if researchers start to see high rates of MCL relapse after BTK directed therapy.

Eager to continue the search, Samaniego and his team have prepared an in-depth research strategy with which they hope to achieve their goal of eliminating MCL-ICs and improving MCL cure rates. Research methods utilise both the newly developed culture and isolation of MCL and MCL-ICs in vivo in severe combined immunodeficiency (SCID) mice.
This research will eventually lead to the development of a new clinical strategy to target MCL and work towards preventing relapse.

A CLEAR PATH

After delineating the role of Wnt and fibroblast and vascular endothelial growth factors (FGF/VEGF) signalling pathways in MCL growth and MCL-ICs maintenance, the effect of inhibitors in these pathways on MCL-ICs will be tested. This testing will be carried out firstly from MCL samples isolated from the blood of MCL patients and then on primary MCL cells grown in co-cultures with bone marrow stem cells. Samaniego and his group wish to ascertain the difference in sensitivity of MCL-non-ICs and MCL-ICs to inhibitors. It is expected that FGF/VEGF inhibition will affect both types of cell, thus they will be co-cultured separately in order to examine specific effects of inhibitors on each.

Once small molecule inhibitors potentially capable of eliminating MCL-ICs have been identified, they will be tested in vivo. Human extramedullary bone marrow will be used in severe immunodeficient mice to establish an MCL xenograft model. It is expected that once treated with Wnt and FGF/VEGF inhibitors, there will be a marked reduction in tumour size in the mice. However, this may not be comparable with reduction rates afforded by standard chemotherapy; the crucial factor will be highlighted when tumour tissue is analysed for MCL-non-IC and MCL-IC subpopulations. It is hoped that the inhibitors will demonstrate their potential in this capacity, reducing MCL-ICs in tissue and therefore minimising opportunities for relapse.

Finally, relapse rates of MCL xenografts treated with Wnt and FGF/VEGF signalling inhibitors will be compared with those treated with standard chemotherapy. Mice that achieved clinical response in the previous stage of research will be monitored for six months to a year for signs of relapse. If findings are consistent with preliminary research, delayed or decreased rates of relapse can be hoped for in mice treated with inhibitors, compared with those treated with conventional chemotherapy. The results of this phase are of great importance to the project as a whole, as they will demonstrate whether it is possible to target MCL-ICs in vivo, as well as revealing whether the elimination of MCL-ICs does indeed prevent MCL relapse.

PATHWAYS TOWARDS BETTER CANCER CARE

If this in vivo research model is successful, it will prove to be suitable for future studies in the field. Looking further into the future, Samaniego sees its potential as a model for investigating the role of allogeneic tumour environment on the growth and chemoresistance of MCL.

This research also has the potential to make waves outside of MCL research, for there is much that is applicable to other related cancers. Samaniego’s focus on MCL-ICs marks a commitment to working to understand CSCs and other cancer-causing mechanisms. The more knowledge gathered in this area, the more likely it is that medical science will be able to develop the tools to reduce cancer relapse. Furthermore, an individually targeted approach to treatment has the potential to herald a more effective cancer care.