THE CHEMO CHRONICLE

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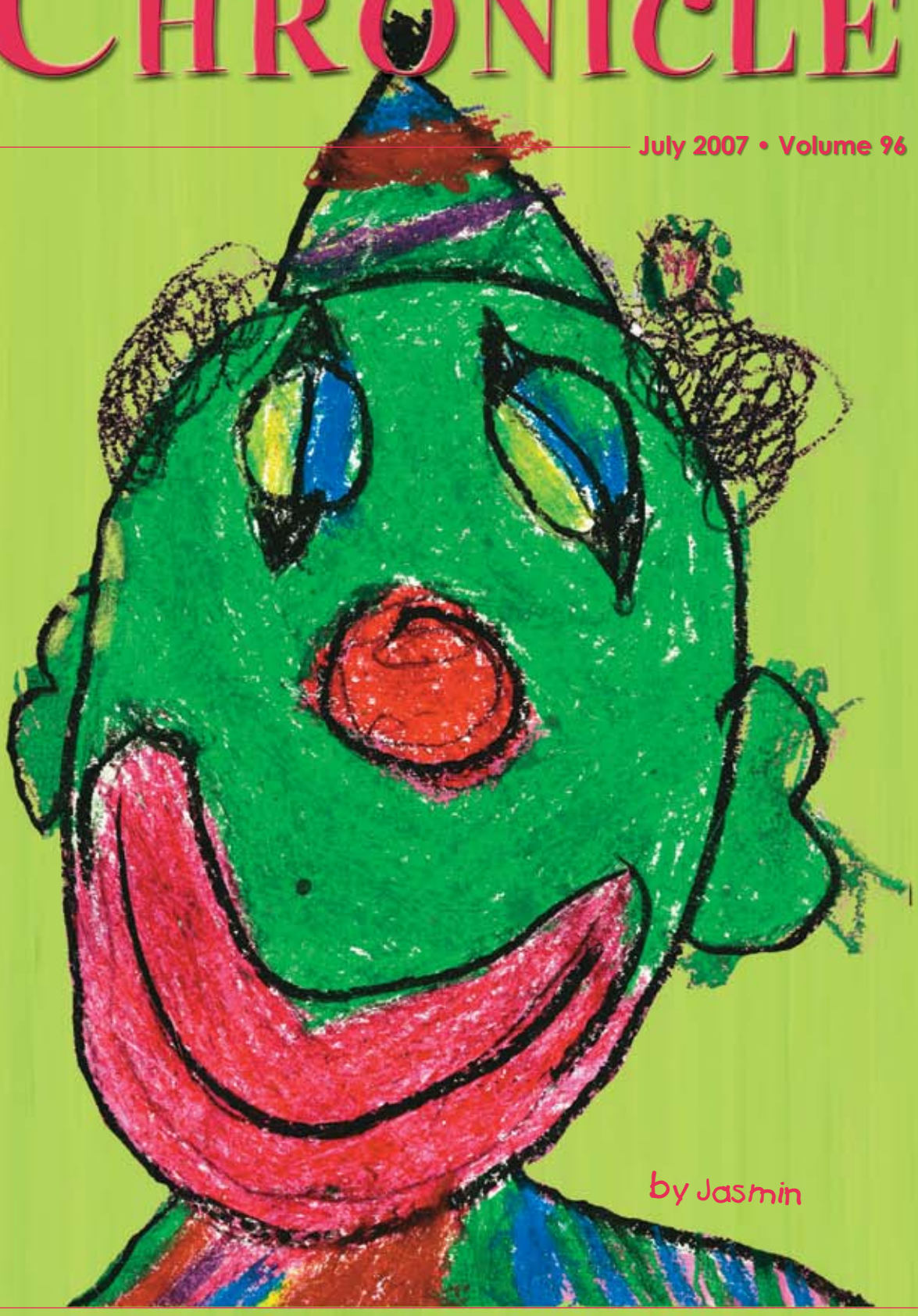

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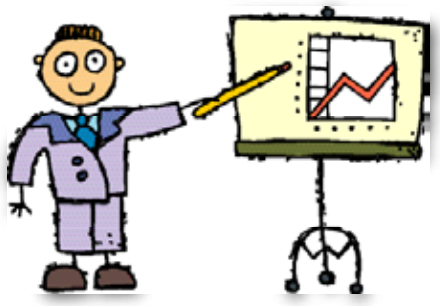


Research ●○○ New faces for the MGMT Gene Therapy Project

Adrienne

Radhika

Jessica

In the past year the Oncology Research Unit has taken some big steps forward in their quest to use gene therapy to alleviate the side effects of chemotherapy. New team members Adrienne, Radhika and Jessica have joined Belinda to get everything in place to get a clinical gene therapy trial up and running – with Dr Geoff McCowage providing the clinical insight into how the science might be translated into practice.

The scientific thinking behind our quest to set up a clinical gene therapy trial is this:

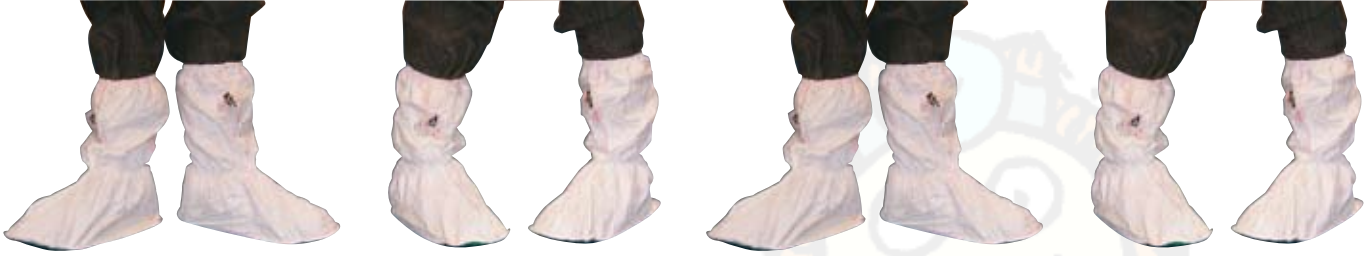
One reason that cancer sometimes comes back after treatment is that not all of the cancer cells are killed off by the chemotherapy. Most chemotherapy drugs kill cancer cells by damaging their DNA – but sometimes cancer cells are able to repair the damage and survive until after the chemotherapy has finished. One way that cancer cells can repair their DNA is with an enzyme called **MGMT.**

All cells in the body have MGMT to repair their DNA if they need to – but some cells have more than others. Cancer cells have more MGMT than bone marrow stem cells – so the dose of chemotherapy that's needed to kill them will also badly affect the bone marrow. This is one reason why chemotherapy has such a big impact on a patient's blood counts, since all red cells, platelets and white cells are produced in the bone marrow.

There are a few ways that chemotherapy can be made to work better in cells that have lots of MGMT – and one of these is to use a new drug, called **O6BG** to stop the MGMT from working. If the MGMT isn't working then the chemotherapy can do its job and kill the cancer cell.

A big problem with this strategy is that the O6-BG also stops MGMT in bone marrow stem cells from working – and that means the bone marrow is even more badly affected than before.

One way of getting over this problem is to take out the bone marrow stem cells and keep them safe from the O6BG and chemotherapy (frozen down in liquid nitrogen, which is as cold as –196 degrees, almost 10 times colder than the freezer in your kitchen). After the chemotherapy, the stem



cells can be given back, and help all the blood counts recover.

Another way to protect the bone marrow would be to give them an extra dose of MGMT – so they could repair the damage to their DNA that is caused by the chemotherapy. Even better would be to give them a dose of a new type of MGMT called **MGMT(P140K)** – which can work even after cells have been treated with O6BG. Protecting bone marrow stem cells from O6BG and chemotherapy using MGMT(P140K) might mean that the side effects of treatment would be less, and that the chemotherapy might work better, with fewer delays between treatments.

This kind of strategy is called **Gene Therapy** – since we'd be putting in a gene as a part of treatment. In the past few years, we have made an agent (or vector) that can carry the MGMT(P140K) gene into stem cells. We have tested the vector to check that the MGMT(P140K) gene can protect cells that are treated with O6BG and chemotherapy. We've also made some transgenic mice that have MGMT(P140K) in their bone marrow stem cells, and when we give these mice O6BG and chemotherapy, their bone marrow is protected from the side effects of the drugs. Other gene therapy researchers in the USA have transferred the MGMT(P140K) gene into bigger animals – dogs and baboons – and the strategy has worked to protect the bone marrow stem cells from the side effects of increased doses of chemotherapy drugs. The results of all of these studies make us believe that this strategy might be able to alleviate the side effects of chemotherapy in patient's here at CHW, and that's why we're working towards setting up a clinical trial.

In the Lab, our next step is to make a large amount of vector to use in a clinical trial. To do this, we are going to use the new clean room facility called HAL (Human Applications Laboratory) that has been built as part of the new Research Building. This set of labs is specially designed to allow us to grow our vector producing cell line in especially clean conditions, like those that would be used to make up TPN (Total Parenteral Nutrition for intravenous feeding). When we work inside these labs we wear suits with hoods, and boots and masks and gloves and glasses to make sure that we keep all of our own germs to ourselves and the lab stays clean.

We can also use HAL to do the gene transfer step, which involves incubating the bone marrow stem cells for 5 days in the vector, and keeping them happy with growth factors (including G-CSF) before we give the cells back to the patient.

Adrienne's and Belinda's job in the lab is to make the vector, with Radhika making sure that everything in HAL is working as it should (keeping her eagle eye on us all). Jessica's job is to look at the cells after we've put the MGMT(P140K) gene into them – and to check whether they're doing their job in alleviating the side effects of chemotherapy. As well as the Oncology Research team and Dr Geoff McCowage, there are other people at CHW that are involved in getting everything done, including Ian, Margot, Samantha and Maolin, from the hospital's Gene Therapy Research Unit. Projects like this one – where we're trying to translate research findings into a complicated clinical protocol, take a long time (Belinda's been working in the lab for 8 years now…). At times the course of this project has seemed a bit like a game of snakes and ladders – where we build a few rungs and get going, only to slide backwards when faced with a new problem. But we have a sound plan, a terrific team of skilled scientists and clinicians, specialised facilities, and ongoing financial support to help us reach our goal. All together, we are hoping that this work will lead to improved treatments and outcomes for children with cancer at CHW.

Last, but definitely not least, we need to acknowledge the generous support of our key donors (please excuse this "Logie moment") -

The initial support of the first researcher on the project, Belinda, was critical in the early years of the project, and we are truly grateful to the Sporting Chance Foundation for their support. A new and very substantial rung in the ladder has recently been provided by the Oncology Children's Foundation with their staggering 5-year commitment to fund the entire MGMT Cancer Gene Therapy program. We wholeheartedly thank them for their generous and inspirational support.