Treating this very common liver disease, which currently has no cure.

Non-alcoholic fatty liver disease (NAFLD) is a common condition. The growing incidence of NAFLD is tightly linked to the obesity epidemic. NAFLD can also lead to other health problems including diabetes and heart disease, and affected individuals may require a liver transplant if inflammation and liver damage develop. The number of people who develop severe liver damage is likely to increase further as the rate of childhood obesity becomes more prevalent. Fat metabolism in the liver is being regulated by an enzyme that is switched on by the AMP-activated protein kinase (AMPK).

Ms Emma Torbicki, The Hospital for Sick Children, Toronto, Ontario
Supervisor: Dr Nicola Jones
Project title: Investigating the role of autophagy in ischemia reperfusion injury.

Currently, the short-term outcome after pediatric liver transplantation is excellent. However, the long-term outcomes for children who require liver transplantation need to be improved. During a transplant, when the liver is taken from the donor, the blood flow is cut off, causing lack of oxygen. Once the organ is placed in the patient and the blood vessels reconnected, the organ receives blood once again. This results in tissue damage due to the formation of toxins and invasion by white blood cells. Recent studies indicate that a specific cellular recycling pathway known as autophagy may help to remove the toxins and limit inflammation due to immune response. The results of this study will be the first step in determining whether autophagy is protective in this injury that occurs in transplanted livers.

ANNUCING THE 2012 GRADUATE STUDENTSHIP RECIPIENTS ($20,000/YEAR FOR TWO YEARS)
Ms Elizabeth Kucynski, Sunnybrook Health Sciences Centre, Toronto, Ontario
Supervisor: Dr Robert Kerbel
Worldwide, liver cancer is the third most common cause of cancer-related deaths. Sorafenib is a drug that targets blood vessels that supply tumours with blood. Eventually, however, patients stop responding to drug treatment and develop resistance. Ms Kucynski is studying how, contrary to common perception, resistance may be reversible and not permanent. By giving a prolonged time off a drug, cancer cells can be ‘reset’ and resensitized to once again respond to therapy. This research may have important implications for the clinical management of liver cancer and, potentially, other cancer-drug combinations in which resistance may be reversible.

Mr Daniel Pang, University of Alberta, Edmonton, Alberta
Supervisor: Dr Lorne Tyrell
Project title: Studying hepatitis A virus (HAV) infection, replication and clearance in a chimeric mouse model.
Hepatitis A virus (HAV) and hepatitis C virus (HCV) are two similar viruses that cause liver disease in humans. However, HAV primarily causes short-term disease while HCV usually causes long lasting disease for reasons that are not fully understood. While a better comparison of these two infections is needed, there is currently no small animal model to study HAV. Dr Tyrell’s laboratory has developed a mouse model with mixed human/mouse livers that are susceptible to HCV infections. The purpose of the study will be to test the model’s susceptibility to HAV infection and to analyze its metastatic potential.
Depletion of B cells as a treatment for autoimmune hepatitis

Autoimmune hepatitis (AIH) is a liver disease caused by the body's own immune system, which attacks the liver resulting in inflammation and scarring. If left untreated, AIH is always fatal. AIH may present both as an aggressive form of acute hepatitis or a chronic illness that can progress to cirrhosis. Recently, Dr. Alvarez and his team have discovered that a complete remission of AIH could be achieved in some patients with an antibody (rituximab) that temporarily destroys a type of white blood cells called B lymphocytes. However, AIH is believed to be caused by the attack on the liver by T lymphocytes and not by B lymphocytes. The goal of this research is to explain the mechanisms by which destruction of B cells help in the control of AIH. The research findings may lead to new treatments for AIH, with fewer side effects than what are reported with current available therapy.

Dr. Fernando Alvarez, CHU Sainte-Justine, Montreal, Quebec

Project title: Depletion of B cells as a treatment for autoimmune hepatitis

Dr. Mathieu Laplante, Laval University, Quebec City, Quebec

Project title: Determination of the role of Deptor in the development of liver cancer.

Liver cancer is one of the most common cancers worldwide. Liver cancer is resistant to both conventional chemotherapy and radiation. This leaves liver cancer patients with no effective therapeutic options and a very poor prognosis. Therefore, the development of more effective therapeutic tools to treat this disease is needed. A protein called mTOR is known to be commonly overactivated in cancer. This protein contributes to cancer growth by promoting protein and lipid synthesis. Recently, Dr. Laplante has identified a new protein called Deptor that can inhibit mTOR. Deptor levels are low in liver cancer cells and preliminary experiments indicate that Deptor loss promotes tumour formation. The objectives of this research are to determine the role of this protein in liver cancer and to determine whether it could be targeted for the development of new treatment of liver cancer.

Dr. Andrew Mason, University of Alberta, Edmonton, Alberta

Project title: Mouse models of genetic and environmental factors in primary biliary cirrhosis.

It is believed that primary biliary cirrhosis (PBC) results from an abnormal reaction of the body's immune system, possibly initiated by an infection. Designed to protect the body from infection, the immune system of PBC patients attacks the liver causing slow, progressive damage to the bile ducts. When the bile ducts are damaged, bile and other substances cannot be eliminated and accumulate in the liver. This eventually leads to cirrhosis. It is believed that both genetic and environmental factors may play a role in the development of PBC. Dr. Mason has recently discovered that a virus found in PBC patients resembles a mouse virus known as mouse mammary tumour virus. A mouse model has been developed. This model has the same immune features that have been found in patients with PBC. Dr. Mason has discovered that mouse mammary tumour virus is associated with the development of autoimmune biliary disease (similar to PBC) in these mice. Furthermore, Dr. Mason has discovered that this biliary disease can be blocked by antiviral therapy. This research should lead to the development of treatments for patients with PBC.

Dr. Christopher Richardson

Co-applicant: Dr. Eric Arts, Dalhousie University, Halifax, Nova Scotia

Project title: Development of a novel hepatitis C virus cloning system in yeast to screen for infectious genomes and determine the role of neutralizing antibodies in viral clearance at acute infection.

Hepatitis C virus is responsible for 170 million infections worldwide and is a major cause of cirrhosis and liver cancer. However, 30% of those infected with the hepatitis C virus never develop chronic disease and get rid of the virus during the acute stage of the infection. Dr. Richardson's research team proposes that the virus clearance is related to the rapid development of antibodies that neutralize the specific hepatitis C strains infecting the patients. This research requires the development of a unique yeast-based cloning system to produce infectious virus based on specific proteins derived from recently infected patients that either get rid of the infection or go on to develop chronic disease. Findings of this research will lead to the development of more effective treatments for chronic hepatitis C.

Dr. Naglaa Shoukry, Centre de Recherche du CHUM (Hôpital St-Luc), Montréal, Quebec

Project title: How does the IL-28B polymorphism influence the outcome of acute hepatitis C?

Chronic hepatitis C is a major cause of liver disease and liver cancer. We still do not understand how a small fraction of people exposed to the virus can get rid of it while the rest cannot. Recent studies have established a correlation between the variations in one gene known as IL-28B and the capacity to eliminate hepatitis C infection. However, how this gene variation influences the immune response against the virus is not yet known. Dr. Shoukry believes that this gene controls the type of immune response that develops upon infection, in which patients who have the bad gene variant are not able to respond and, consequently, cannot clear the infection. The research findings will lead to the development of new treatments for hepatitis C.