A Novel Perspective on the Use of Anti-Retroviral & Anti-Inflammatory Treatments for Schizophrenia

Schizophrenia Society of Canada National Conference
September 10, 2013
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I had always had a keen interest in science and aspired to become a physician.

In high school at the age of 16 my struggles with the early manifestations of my illness began.

This was a difficult and confusing time for me and my family.

Despite this, I graduated a year early and earned a full scholarship to University of Ottawa to study Biomedical Sciences.
Upon arriving in Ottawa my symptoms took a turn for the worse.

Although my symptoms had been growing over that summer, I woke up one October morning to a foreign and frightening world.

After fighting with the unknown alone for three months I returned home to Winnipeg and the support of my family.

At the age of 18, a name was put to these things I was experiencing: schizophrenia.

That marked the beginning of my recovery journey.
I slowly returned to University, reaching towards an Honours BSc in Biochemistry and finding once again that love of science and research.

Seven years later, I am now working on my Honours thesis and entering my final year of full time undergraduate studies at the University of Winnipeg.

During this time I have known the challenges of finding the right balance of medications and quality of life, going through medication change after medication change in the last 7 years.
These experiences have left me inspired to search for answers through research and answer the question that has been on my mind throughout my journey...

**What contributes to people getting schizophrenia?**
Ideas about the causes of schizophrenia

- Genetics
- Complications at birth
- Stress
- Infections
- Drug Abuse
- Head Injury
- Exposure to toxic factors
Infections as a factor in the onset of schizophrenia

Infections and the inflammation they lead to could be key in the development of schizophrenia
Viral infections have been associated with schizophrenia:

Herpes simplex virus
Borna disease virus
Influenza
Rubella
Retroviruses, like HIV
There is a link between these infections and a virus that is in everyone!

HERVs
HERVs: The viruses within us

**HERV stands for Human Endogenous Retrovirus**

There are HERVs in everyone’s DNA; 8% of our DNA is retrovirus!

DNA is what codes for our development and functioning

Reactivation of HERVs in disease

**Neurological**

**Infectious**

**Cancer**

HERV reactivation is associated with certain diseases

**Neurological disease**
- Multiple Sclerosis (MS)
- Amyotrophic Lateral Sclerosis (ALS)
- Schizophrenia

**Autoimmune disease**
- Rheumatoid Arthritis and SLE

**Virus-triggered expression**
- HIV & Herpesviruses

**Cancer**
- Melanoma
- Breast cancer & lymphoma
- Leukemia
- Prostate cancer
- Ovarian cancer
Higher rates of HERV expression in schizophrenia

There is a link between schizophrenia and HERV expression

DNA → RNA → Protein

HERV viral RNA and protein has even been found in the blood and brain tissue of people with schizophrenia
Polymorphisms: gene differences

Polymorphisms are in human genes and HERVs

Some change the way our immune system fights disease

These differences may affect how HERVs are expressed and controlled

Dickerson et al. (2008) shows that certain types of these polymorphisms in HERV DNA may be a risk factor for type 2 diabetes in people with schizophrenia
How could HERVs promote psychosis?

50% of HERVs co-regulate human genes

HERV proteins can promote inflammation in the brain

Some HERV proteins bind glutamate receptors, known to play an important role in schizophrenia
Why do clozapine and other drugs work?

Is it because they have anti-retroviral properties?

Metabolites of clozapine have properties against HIV...

Could they also inhibit HERVs?
Studies have looked at using anti-inflammatory medications for the treatment of schizophrenia, along with antipsychotics (Müller et al., 2005, 2010).

These anti-inflammatory medications were helpful, especially in recent onset of schizophrenia.
Why more successful in early onset?

Inflammation can lead to damage in the brain.

Catching the inflammation early may stop this damage.
There is great potential for the use of anti-retrovirals and anti-inflammatory medications for the treatment of schizophrenia.

My research focuses on this hope for the future:

- Exploring the interaction of HERVs and the immune system
- Effects of antipsychotic medication on HERV expression
Inflammation can be caused by the immune system detecting viral RNA.

One of the questions my research asks is if the innate immune system can detect viral RNA from HERVs.

If it can, would that lead to inflammation in the brain?
The immune system is complex
How could the innate immune system recognize HERV?

RIG-I binds RNA; this can lead to inflammation

RIG-I can recognize HIV

This probably has to do with how the RNA folds, called secondary structure

Both HIV and HERV RNA have complex folding
My research:

I am making synthetic versions of folded HERV-K RNA

I chose three folded structures that stay the same throughout different strains of HERV-K

The next step is to present these pieces of RNA to cells to see if they trigger an immune response
I will stimulate three types of brain cells with synthetic HERV-K RNA:

**Neurons** are cells that send messages in the brain through electrical and chemical signals

**Astrocytes** are cells that support proper neuronal function

**Microglia** are the brain’s resident immune cells

One component of my project, is to culture microglial cells from individual human blood samples
If the brains of people with schizophrenia have higher expression of HERV, and this expression leads to immune response, the result could be chronic inflammation that damages the brain.

If there was a way to prevent both:

- HERV expression using specific anti-retrovirals
- Neuroinflammation using anti-inflammatory medications

This could potentially help in the treatment of schizophrenia, especially in the earlier part of its onset.
I feel that I have found my place in society in the scientific community

I have found an enormous amount of support from Accessibility Services at the University of Winnipeg and my “lab family” at the Douville Lab, who accept me as a person and scientist, illness and all
Not only does science have a lot to offer me, but I feel that I have a lot to offer it!

As a person living with schizophrenia, I have a great knowledge and insight into this disease, as well as an immense passion for the research and discovery surrounding it.

There is nothing I would rather do more than contribute to the understanding and treatment of schizophrenia, not only for myself, but for the rest of that 1 in 100 who battle this illness.
Thank you!

**Douville Lab Team**
Dr. Renée Douville
Sheena Manghera
Matthew Turnbull
Sam Fineblit
Samah AlSaadi
Jennifer Fergusson
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**Collaborators**
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Research funding  Bursary provided for conference attendance

Interested in collaboration?  carr-h@webmail.uwinnipeg.ca
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The Douville Lab is CrowdFunding!
It’s a great way to support student research on Schizophrenia

Be sure to check out our email campaign starting on Sept 16th 2013!

Did you know that your DNA contains thousands of human endogenous retroviruses? These viruses are active in the brains of people with neurological diseases like ALS and Schizophrenia. Our lab has recently discovered a novel human endogenous retrovirus protein, and using confocal microscopy we will attempt to determine if this neurotoxic protein is associated with neuronal damage and inflammation in brain tissue.