

Review Article

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F-652 (Recombinant Human Interleukin-22) For Schizophrenia

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Introduction

Emil Kraepelin believed that dementia praecox, the disorder we now call schizophrenia, was the result of brain poisoning with toxins generated in other parts of the body, especially the mouth, intestine, or genitals [1]. In this regard, Kraepelin hinted at the mi

crobiome and believed that microbial molecules could drive the pathogenesis of severe psychiatric illness. However, the infectious model of schizophrenia drew limited attention until the launching of Human Microbiome Project and the discovery of innate lymphoid cells (ILCs).

The gut and schizophrenia

Several recent studies have connected schizophrenia with microbial translocation (MT) from the gastrointestinal (GI) tract into the host systemic circulation, eventually reaching the brain [2-5]. MT refers to the migration of intestinal microorganisms or toxins into host tissues by passing through the intestinal barrier and lamina propria to reach mesenteric lymph nodes and the systemic circulation. In the central nervous system (CNS), bacteria or their components can trigger psychosis by several mechanisms, including inflammation, impaired autophagy, premature cellular senescence, and aberrant microglial activation [6-9].

The evidence of MT in schizophrenia

1. Patients with schizophrenia have a high prevalence of inflam

matory bowel diseases (IBD), such as ulcerative colitis and Chron's disease, conditions associated with increased gut barrier permeability and MT [10-12].

2. Patients with schizophrenia present with elevated bacterial translocation markers, including soluble CD14 (sCD14) and lipopolysaccharide binding protein (LBP), emphasizing microbial migration from the immune tolerant GI tract into the bacteria-intolerant systemic circulation [13-15].
3. Patients with schizophrenia exhibit increased blood brain barrier (BBB) permeability, enabling bacteria and/or toxins to ingress the CNS [16-19].
4. The 2011 outbreak of *Escherichia coli* (*E. coli*) in Germany has been associated with the new onset psychosis, connecting this pathogen to neuropsychiatric illnesses [20-21]. In addition, *E. coli* has been implicated in urinary tract infection (UTI), conditions often associated with new onset psychosis or schizophrenia exacerbation, linking this bacterium to psychopathology [22-23].

Hypothesis

We hypothesize that F-652, a recombinant human interleukin-22 (IL-22) can alleviate psychotic symptoms by blocking MT. In addition, IL-22/ F-652 share several properties with antipsychotic drugs as summarized in Table [1].

Table 1: IL-22/ F-652 comparison with antipsychotic drugs.

Antipsychotic drugs	IL-22/ F-652	References
JAK-STAT activation	JAK-STAT activation	33; 91
Neuroprotective	Neuroprotective	37; 92
IFN-γ inhibitor	IFN-γ inhibitor	60; 64; 93
Activate autophagy	Activate autophagy	86; 88; 94
Antibacterial/antiviral	Antibacterial/antiviral	83; 84; 95; 96

Interleukin-22, the “guardian” of gut barrier.

During the human immunodeficiency virus (HIV) epidemic in 1980s, MT drew the attention of researchers and clinicians as this virus depleted interleukin-22 (IL-22), enabling lipopolysaccharide (LPS) migration into host tissues [22-23] [Figure 1]. Indeed, patients with HIV are more likely to develop new onset psychosis compared to the general population, suggesting that dysfunction-

al gut barrier may play a role in pathology [24-29]. Discovered in 2000, IL-22 is a member of IL-10 family generated by several lymphocyte types, including T helper (Th) 17 cells, γδ T cells, NKCs, and innate lymphoid cells (ILCs) [30]. IL-22 controls several intestinal epithelial cells (IEC) functions, including mucus formation, permeability, synthesis of both complement and antimicrobial peptides (AMPs), indicating that this cytokine functions as the master regulator of gut barrier permeability [31].

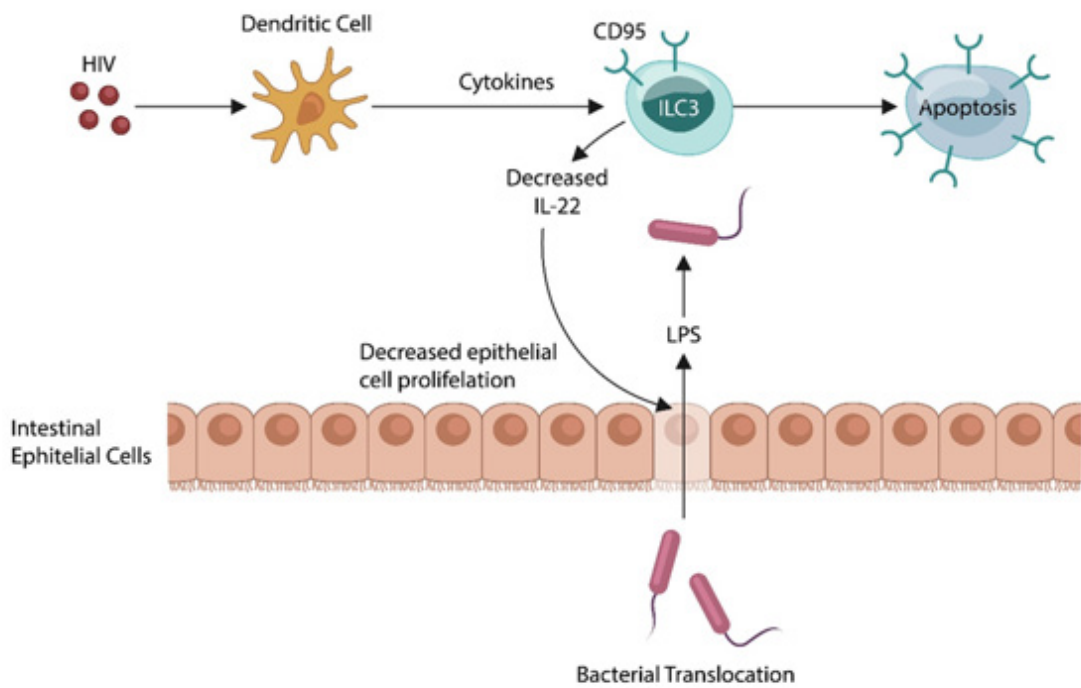


Figure 1: HIV induces apoptotic loss of innate lymphoid cells, type 3 (ILC3), lowering IL22, the guardian of gut barrier. This, in turn promotes MT into the systemic circulation. Activated host immunity maintains a state of low-grade inflammation, a pathology found in schizophrenia.

The crosstalk between IL-22 and its receptor (IL-22R), a dimeric protein comprised of IL-22R1 and IL-10R2, activates the JAK/STAT pathway, a key antibacterial and antiviral system, protecting against pathogens [32-33]. As IL22R contains IL-10R2, it can be cross-activated by IL-10, a cytokine previously connected to schizophrenia [34-36]. In addition, several studies have shown that IL-22

possesses neuroprotective properties, and its disruption has been associated with schizophrenia [37-39]. Moreover, aside from safeguarding neuronal cells, IL-22 protects against COVID-19, influenza, and IBD, indicating that supplementation with this cytokine via F-652 may ameliorate or totally alleviate these pathologies [39-42].

IL-22 and innate lymphoid cells (ILCs)

Novel studies have reported that a subgroup of NKCs produce IL-22, enhancing the gut barrier thus, averting MT [43-45]. Indeed, research over the past two decades has connected defective NKCs with both IBD and schizophrenia [46-49]. Moreover, in the CNS, NKCs participate in adult neurogenesis, cognition, and cellular senescence, suggesting that under pathological circumstances, these processes may be disrupted [50-53].

NKCs belong to innate lymphoid cells (ILCs), mucosa-anchored non-T, non-B lymphocytes, which also include ILC-1, ILC-2, and ILC-3 [52] [Figure 2]. These systems play a pivotal role in gut barrier homeostasis, nutrient transport, and immune tolerance of both food proteins and gut commensals [52-53]. The ILCs in CNS have been implicated in neuropathology, including schizophrenia, major depressive disorder (MDD) and neurodegeneration [55-57].

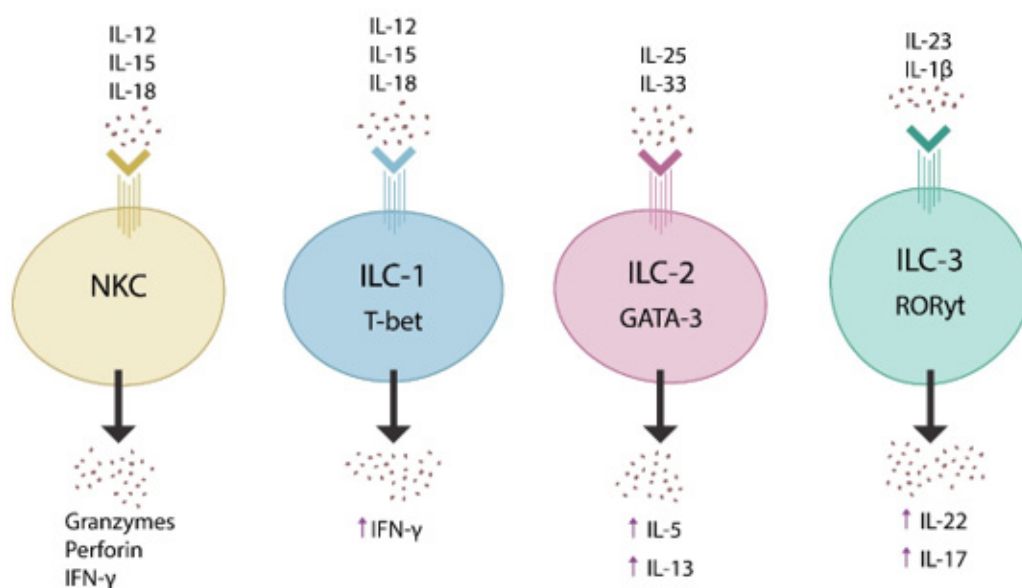


Figure 2: Innate lymphoid cells are comprised of NKCs, and innate lymphoid cells type 1, 2, and 3 (ILC-1, ILC-2, and ILC-3). These cells are activated by various cytokines (top), release other cytokines (bottom), and express transcription factors, including T-bet, GATA-3 and ROR γ t. Under pathological circumstances, these lymphoid systems may lead to IBD and microbial translocation (MT), contributing to schizophrenia. A subgroup of gut NKCs produce IL-22, maintaining the gut barrier homeostasis (not shown).

For example, aberrant activation of NKCs by IL-12, IL-15, and IL-18 was reported in IBD and schizophrenia, linking ILCs to both conditions [58-59]. In addition, NKCs-generated interferon- γ (IFN- γ) has been linked to schizophrenia, emphasizing the key role of ILCs in neuropathology. On the other hand, conventional antipsychotic drugs have been shown to suppress IFN- γ , suggesting that at least in part, IL-22 may contribute to the pathogenesis of schizophrenia [60-62]. Indeed, dysfunctional IFN- γ was associated with the loss of dopaminergic neurons in Parkinson's disease (PD), connecting ILCs to dopamine pathology [63]. Like antipsychotic agents, IL-22 is an IFN- γ inhibitor, suggesting a mechanism through which F-652 may ameliorate the schizophrenia symptoms [64]. Taken together, dysfunctional ILCs, including NKCs, connect IBD with schizophrenia. In contrast, IL-22 (and F-652) likely exhibit antipsychotic properties not only by lowering MT, restoring the integrity of intestinal barrier, but also by suppressing IFN- γ .

Psychosis and gut microbes

The BBB regulates CNS entry of peripheral molecules, including gut microbes and toxins, by being comprised of specialized endothelial cells kept together by tight junctions. Interestingly, experimental colitis has been shown to increase BBB permeability, indicating a close crosstalk between the gut barrier and BBB that under pathological circumstances may enable intestinal microbes to reach the brain [65].

The link between gut bacteria and schizophrenia has been documented for several decades. For example, antibodies against various *E. coli* proteins were detected in patients with schizophrenia but not in healthy controls [66]. In addition, schizophrenia and colibactin, an *E. coli* toxin, were demonstrated to trigger premature cellular senescence and thymic dysfunction [67-70]. On the other hand, IL-22 drives the regeneration of the thymus, restoring the ho-

meostasis of senescent cells and, according to one study induces rejuvenation [71-73].

Several gut and urinary tract microbes, including *E. coli*, were associated with schizophrenia, while IL-22 was shown to neutralize this pathogen [74-78]. Other gut microbes, including *Hafnei alvei*, *Pseudomonas aeruginosa*, *Pseudomonas putida*, and *Klebsiella pneumoniae* have been associated with schizophrenia, further substantiating the infectious paradigm in this disorder [79-80].

Taken together, intestinal inflammation can alter the BBB, enabling microbes, including *E. coli*, to enter the CNS. Antibodies against microbial antigens (which often mimic human proteins) trigger pathology in distant organs, including the brain. IL-22 opposes MT by lowering gut barrier permeability and by enhancing thymic function to strengthen host immune defenses.

IL-22 safety, pharmacokinetic and pharmacodynamic data

F-652 is a recombinant human IL-22 currently in Phase II clinical trials for the treatment of COVID-19, COVID-19 pneumonia, acute pancreatitis, chronic acute liver failure, alcoholic hepatitis, and graft versus host disease (GVHD)(NCT02406651). Several studies have evaluated the safety, pharmacokinetics, pharmacodynamics, and tolerability of F-652, demonstrating that this is a safe compound with favorable pharmacological parameters [81-82].

Aside from functioning as the guardian of intestinal barrier, IL-22 possesses antibacterial and antiviral properties probably by enhancing autophagy [83-85]. Impaired autophagy has been documented in both schizophrenia and IBD, while IL-22 (or F-652) enhances autophagy, a property of many antipsychotic drugs, including clozapine [85-89]. Moreover, like antipsychotics, F-652 lowers INF- γ and protects intestinal barrier against IBD and MT [89-94].

Conclusions

Recombinant Human IL-22 is an antibacterial and antiviral molecule that promotes tissue repair and autophagy. Like antipsychotic drugs, F-652 suppresses INF- γ , promoting neuroprotection. In addition, F-652 drives thymic regeneration, opposing premature cellular and immune senescence. In clinical trials, F-652 decreased serum triglycerides, correcting dyslipidemia (often found in patients with schizophrenia), and presented with anti-inflammatory properties, warranting further evaluation for schizophrenia.

Acknowledgement

None.

Conflict of Interest

None.

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