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The Role of the Gut-Brain Axis on Neurodegenerative Diseases

Hannah Gustafson

Abstract

Parkinson's disease is the second most common neurodegenerative disease, following Alzheimer's disease. It is characterized by a series of motor symptoms, however, there are multiple non-motor symptoms that also occur. At the microscopic level, there is a degeneration of dopaminergic receptors in the neurons, and also an accumulation of the misfolded protein alpha-synuclein, throughout the body. The majority of the depletion of these dopaminergic neurons occurs in the substantia nigra. Recently, research has pointed to a change in the environment of the gut microbiota as being responsible for the development of Parkinson's disease. There is bidirectional communication between the gut and the brain; this is termed the gut—brain axis. When the gut microbiota environment is altered, the patient is susceptible to several issues, including inflammation. When the microbiome is altered, it has also been found that alpha-synuclein will aggregate. Parkinson's is typically instigated by an external trigger, however, it has recently been found that a change in the gut microbiome may be enough of a trigger. Even if the cause of Parkinson's disease is not found to reside within the discovery of the gut-brain axis, there is much potential for future treatments and therapies within it.

Introduction

Neurodegenerative diseases indicate that there is a part of the brain that is losing its ability to function. The two most common neurodegenerative diseases include Alzheimer's and Parkinson's disease. Parkinson's disease, for example, involves losing motor functions and developing symptoms such as tremors, bradykinesia and rigidity. According to Ganjavi and MacDonald, around 3% of the population over 65 currently suffers from Parkinson's disease. These large numbers make Parkinson's disease (PD) an important area to study (2015). Caputi and Giron go on to state that the number of those suffering from PD is expected to double in the next 15 years and that this will be due to the lengthening of the average lifespan. They call it a "paradoxical effect". PD is believed to be due to the accumulation of alpha-synuclein and deterioration of dopaminergic neurons, specifically in the substantia nigra in the brain, however, the

exact epidemiology is currently uncertain (2018).

This protein (alpha synuclein) will misfold and aggregate, which is then called a Lewy Body, and is what leads to the typical symptoms that one experiences when suffering from Parkinson's disease. Also, the degeneration of dopaminergic neurons, especially in the substantia nigra, leads to the development of these motor deficit symptoms (Ganjavi and MacDonald, 2015).

Due to the degeneration of dopaminergic neurons in the CNS, a common and effective treatment has been to provide excess dopamine, in the form of L-DOPA, to the patient. L-DOPA is administered to these patients because it is the precursor to dopamine and it can cross the blood brain barrier. The blood brain barrier is designed to protect the brain from substances that are not intended to affect the CNS, so getting drugs to cross it can be a challenge. When L-DOPA crosses the blood brain barrier, it is able to be converted to dopamine and thus will be able to have an effect on the dopaminergic neurons in the synapses.

During the first stages of Parkinson's development, this treatment works well. As the disease progresses, however, the efficacy has been seen to decrease. This is because the number of receptors present is diminished, so it does not really matter how much one floods the system with L-DOPA, there are not enough receptors to have a noticeable response (Varanese, et al., 2010).

While many people immediately think of the visible motor symptoms associated with Parkinson's, there are many non-motor symptoms that are just as prevalent. Because these aren't seen immediately when observing a patient, they are slower to be treated. Olfactory, Gastrointestinal, cardiovascular, and urogenital systems are some of the regions that are known to be affected by Parkinson's disease. Recently, it has been made evident that other nervous systems in one's body are affected by PD – specifically the autonomic and enteric nervous systems (Mulak & Bonaz, 2015). Some non-motor symptoms can include anxiety, depression, GI issues, sleep disturbances, and an overall decrease in one's quality of life. According to Ganjavi and MacDonald, these non-motor disturbances have been more prevalent with regard to hospitalization compared with motor issues.

Anxiety and depression are two of the most prevalent non-motor disturbances that patients experience. It has been found that 20-50% of patients with PD suffer from anxiety in some form, and 50% experience depression. Anxiety is actually seen before the major motor deficits in most patients (2015).

Dopamine therapy has also been used to treat anxiety, in addition to the motor symptoms, however, some researchers

question its efficacy. Some explain that dopamine aides in the treatment of anxiety, but most argue that dopamine actually increases the anxiety that most people experience (Ganjavi and MacDonald, 2015). Studies many years ago indicated that the L-DOPA treatment for PD also had an effect on patient's mood. They used this observation to explain that depression could be treated along with the motor issues. However, there have not been studies performed since then to directly indicate that the current treatment method can be applied to one's mental health. The data obtained have not been statistically significant.

Some patients have indicated that L-DOPA has improved their anxiety, however, researchers have come to the conclusion that this is an indirect treatment. Many patients are anxious due to their motor symptoms, and the L-DOPA therapy reduces the deficits that they observe. This, therefore, will lead to a decrease in anxiety. This happens in a cyclic pattern, however. When the patient takes their prescribed drug, their symptoms lessen. Then, as the drug wears off toward the end of its cycle, the symptoms begin to reappear, and in turn, the anxious symptoms accompany them. If the L-DOPA therapy could become more constant, then perhaps the associated anxiety could become more constant as well (Jaunaris and Eskow, 2011).

Other common non-motor symptoms that are experienced by those with PD include psychosis and dementia. They are often seen in these patients because they have a similar pathological development. Non-motor symptoms are often overlooked during consultations because it is not immediately understood if they are symptoms of the disease directly, or if they are a side effect of the medication the patients are taking (Varanese, et al., 2010).

One of the most recent theories pertaining to Parkinson's Disease involves the gut-brain axis's role on the development of it. Mulak and Bonaz explain that PD consists of the involvement of the central, autonomic, and enteric nervous systems. They state that the microbiome in the gut has been found to have an impact on neuronal activity. Communication happens between the gut and the brain, and this communication is not limited solely to diseased patients. It happens continuously in all people, and it happens bidirectionally (2015).

Caputi and Giron explain that the bidirectionality indicates that there is crosstalk leading to issues with the central nervous system (CNS) as well as the gut. These symptoms include gastrointestinal disorders, decreases in hormone concentrations, inflammatory diseases, and "stress induced GI dysfunction" (2018). A diagnosis of Parkinson's may be preceded or followed by a variety of GI symptoms. The severity of PD may be directly related to the severity of the GI symptoms. Around 80% of people living with PD display GI

disorders, such as constipation, dysphagia, irritable bowel syndrome, nausea, and hypersalivation. The prevalence of GI disorders in people with PD either indicate that having PD predisposes one to GI disorders, or that GI disorders are part of the cause of PD (Mulak and Bonaz, 2015).

Constipation has been observed as the most prevalent GI issue in PD patients before they are actually diagnosed with Parkinson's. It is developed many years before any of the initial motor symptoms appear. Obviously, constipation does not always indicate that one will develop Parkinson's disease, but this is an interesting fact that could be useful in the future for earlier diagnosis of PD (Caputi and Giron, 2018). Constipation also needs to be managed in patients because as PD develops, it can decrease the absorption of L-DOPA from the bowels. This is especially prevalent as the patient progresses to late stage PD (Varanese, et al., 2010).

It has been hypothesized that neurodegenerative diseases begin in the gut and travel to one's brain. This is where research is currently moving. The Enteric Nervous System (ENS) is broken down into four main levels. The first consisting of the neurons – myenteric, submucosal plexi, enteric glial cells, and reflexes such as peristalsis(Mulak and Bonaz, 2015). The neurons in this level communicate directly with the microbiome in the gut, which is why changes in the GI tract are detected by the ENS. The intertwining of microbiota and neurons is what has driven researchers to pursue the effects of gut environment changes on the brain, specifically in neurodegenerative diseases. The connectedness of these two factors could be where PD actually develops, but it could also signify a new course of action to treat this disease – as well as many other diseases. There is much to be learned from this rather new information; in fact, the gut microbiome is actually beginning to be referred to as its own organ or system (Caputi and Giron, 2018).

The next level of the ENS consists of prevertebral ganglia that regulate visceral reflexes, and the third level consists of the autonomic nervous system from the spinal cord and the brain stem. The fourth level consists of higher functions coming from the cortical regions. These regions include areas such as the basal ganglia, and the information travels down the brainstem. This is important because mechanisms that control the local enteric reflexes, as well as neuronal control, exist here. The GI tract is not able to function normally or optimally when these mechanisms are altered (Mulak and Bonaz, 2015).

The composition of the gut microbiota remains relatively constant throughout life. There are a few instances that will lead to the environment of the gut being altered. These include taking antibiotics, changing one's diet or lifestyle, and fighting an illness or disease. Depending on the issue that one is facing, the microbiome may return to

normal rather quickly, or the recovery may be prolonged. In some instances, the environment of the gut may never fully return to normal, leaving its host susceptible to a wide variety of issues. While steps may be taken to avoid this in young, strong adults, it is more difficult to prevent the weakening of the gastrointestinal environment as one ages. People with Parkinson's Disease have been found to have an altered composition of their gut microbiota, as well as a noticeably higher rate of developing *Helicobacter pylori* infections. This bacterium is the most prevalent factor in typical gastrointestinal disturbances, such as peptic ulcer disease, active chronic gastritis, and gastric adenocarcinoma (Caputi and Giron, 2018).

While the GI symptoms that are experienced with PD may not always be as cut and dry as researchers would like, one thing that is constant among those suffering with PD is the accumulation of misfolded alpha synuclein. This protein has been found to accumulate in olfactory bulbs, as well as the submucosal and mucosal plexi mentioned above. The accumulation of this protein occurs from the esophagus throughout the entire GI tract, ending at the rectum. It is believed that alpha synuclein is able to accumulate due to leaky gut syndrome (increased permeability of the gastrointestinal tract). The beginning of this accumulation may begin in the olfactory bulbs or in the ENS. It is currently unknown whether it travels in a retrograde fashion from ENS to CNS, or if it travels from CNS to ENS, but it has been found to be instigated by exposure to some toxin (Samson, et al., 2016). One environmental toxin that has been shown to cause PD – like symptoms in mice is the pesticide rotenone. When mice are exposed to this pesticide, they begin to develop Parkinson's symptoms, as well as a GI environment changes resembling those with PD (Caputi and Giron, 2018).

Studies have been performed where the vagus nerve is removed in patients, and the development of Parkinson's is actually delayed. This could be an indication of the involvement of the vagus nerve in Lewy Body transport from ENS to CNS. When the vagus nerve is removed from the mice in the experiment mentioned above, exposing them to rotenone had little effect on the development of PD. The symptoms and the pathology were drastically delayed. These findings may indicate that toxins or other environmental factors may play a larger role in the development of PD than even genetic predisposition. The dysfunction of microbiota in the gut may actually be enough of a trigger to cause PD development – the trigger does not necessarily need to be an external factor (Caputi and Giron, 2018).

The gut-brain axis is currently being pursued as a possible cause for Parkinson's disease. Even if it is found that the cause doesn't lie here, the gut-brain axis still holds potential for future treatments and therapies for neurodegenerative diseases. A

couple of recent studies that have been performed are explained below.

Previous Studies

Due to the degradation of dopaminergic neurons in the substantia nigra, an effective treatment has been to reintroduce L-DOPA, or other dopamine receptor agonists, to the patient. The first goal with regards to treatment has been to reduce these first motor symptoms (Ganjavi and MacDonald, 2015). One of the problems with this method is crossing the blood brain barrier. This barrier is designed to protect the brain and CNS by limiting what it gets exposed to. In order for the L-DOPA to be effective, it has needed to be able to access the CNS because that is its target area. Also, Dr. Lange from the University of the Netherlands explains that the only drug that has an effect on its target is the free drug – it cannot be bound to something.

She also explains that in order to fully know a drug's efficacy, we need to know what it does in its unbound form both in the plasma as well as at its target in the brain. The drug can either be toxic and not beneficial, toxic and beneficial, non-toxic and not beneficial, or non-toxic and beneficial. She and her lab performed a study on mice using rotenone, like the one mentioned previously. They observed the substantia nigra in a control mouse brain, as well as mice exposed to the pesticide. They wanted to know if the blood brain barrier could be weakened and penetrated after exposure. They also wanted to observe the development of Lewy Bodies.

They wanted to determine what the concentration of the drug in human cerebral spinal fluid (CSF) would be similar to the target concentration, so they determined the areas from where they would draw CSF from humans as well as the mice. They compared brain extracellular fluid to CSF by obtaining samples from the striatum, lateral ventricles, and cisterna magna. They began to predict the ideal physiological markers for concentration of the CSF in humans and compared that with the rodents. Using their animal experiments and pharmacokinetic models, they were able to predict values in humans, and then they finally were able to confirm those values in humans (De lange and Hammarlund – Udenaes, 2018).

She and her lab explain that one of the biggest challenges regarding drug development is ensuring the drug crosses the BBB "at the right place at the right time, and at the right concentration." It needs to be lipophilic enough to be able to travel across the barrier, but it needs to be lipophobic enough to get a wide distribution throughout the brain (De Lange, et al., 2017).

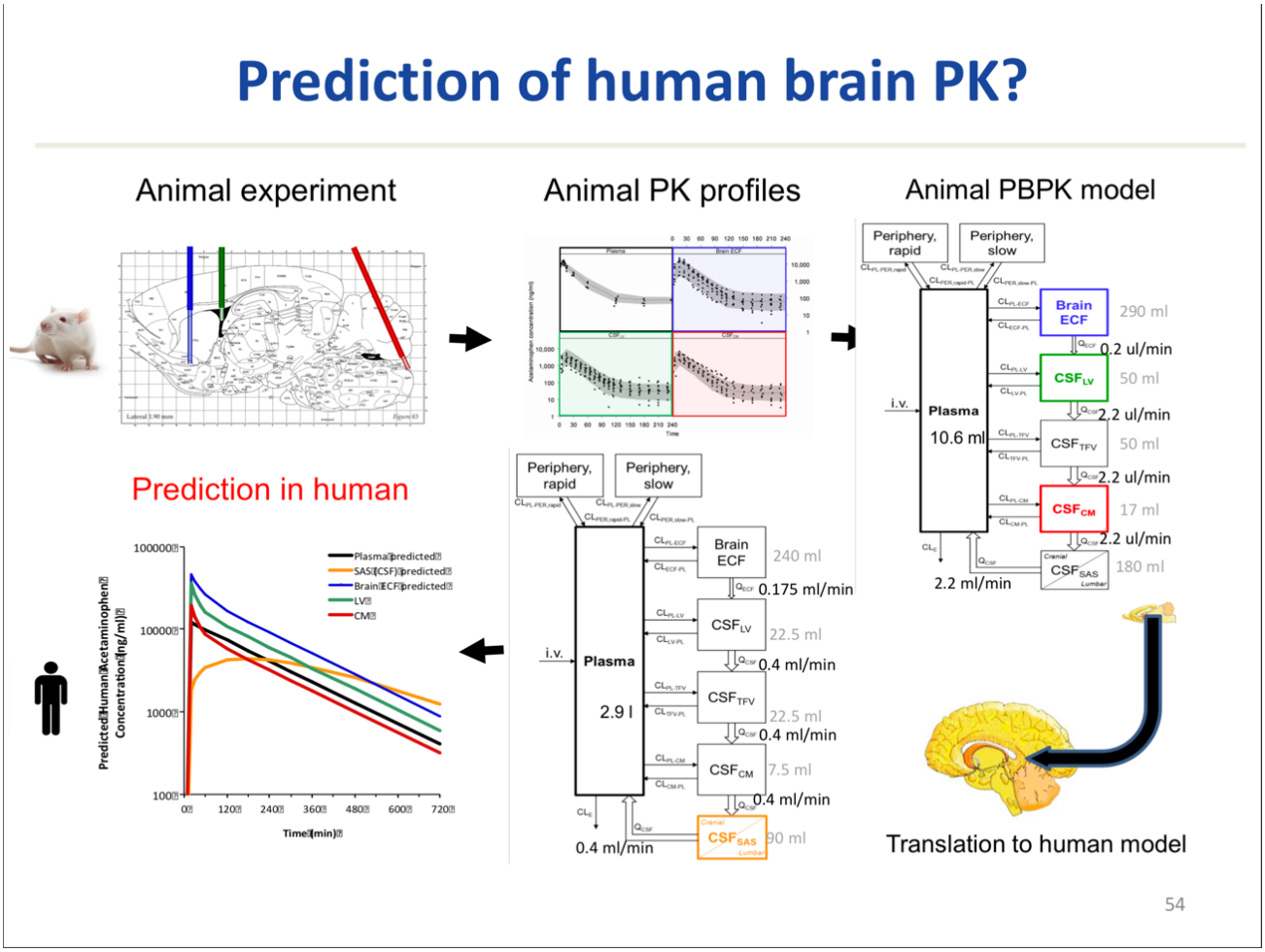

Figure 1: Dr Lange, et al., explains their prediction for BBB penetration and target system utilization of L-DOPA in humans (2018).

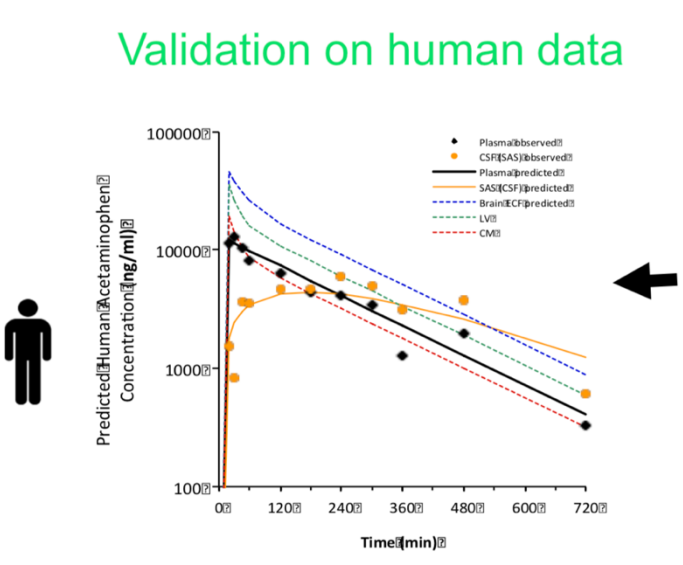

Figure 2: Dr Lange, et al., demonstrate the data they obtained based on their predictions above. They were able to confirm their predictions (2018).

These results have been beneficial to treat patients with Parkinson's, however, one issue that needs to be dealt with involves the cyclic patterns of taking L-DOPA. These cycles are termed "on-off fluctuations" or "wearing off". The wearing off period happens as the drug wears off and loses

some of its effect and is also due to the "pulsatile" pattern of activating the dopaminergic neurons. The on-off fluctuations involve a more random and uncontrolled switch between experiencing the typical PD symptoms (similar to a relapse) and existing in an almost over treated state (similar to a remittance).

The response to these cycles has evolved over the years, and now consists of taking multiple lower doses instead of one large dose. In addition to these lower, more frequent doses, a COMT inhibitor, MAO inhibitor, and dopamine agonists are also utilized. The COMT inhibitor is able to prolong the duration and effect of L-DOPA, because the COMT enzyme is blocked. As with everything, there are some negative side effects to this. The buildup of dopamine in the synaptic cleft could lead to worsening of the psychosis and dementia that patients may experience. It has become almost standard to decrease the amount of dopamine taken by a patient if their psychotic state is too high. Clinicians will decrease the dose even if that means causing the Parkinson's symptoms to worsen (Varanese, et al., 2010).

For a long time, researchers had thought that L-DOPA was converted to dopamine in the nigrostriatal pathway in the brain by "dopaminergic terminals." This dopamine would then travel to the striatum and elicit the relief from the motor symptoms that is seen. However, it has recently been observed that L-DOPA is converted by serotonin neurons and released to the striatum. These neurons take exogenous L-DOPA and decarboxylate it to provide the effect. Even areas that don't have dopaminergic neurons will have an increase in dopamine due to the presence of 5HT neurons.

The increase of dopamine in these areas can lead to unpleasant side effects, such as more motor issues, increased psychosis, and depression. Neurotoxicity can occur due to the increase of dopamine, and 5HT production can decrease. Dopamine can be converted to one of its metabolites, and this will inhibit the enzyme that converts tryptophan in the serotonin pathway. These issues were studied in rats by giving them L-DOPA for 10 consecutive days and observing the concentration of 5HT neurons as well as 5HT neurotransmitters. It was found that L-DOPA decreased the number of 5HT cell bodies as well as the amount of neurotransmitters. It caused 5HT to be displaced from the vesicles as led to a decrease in the concentration of 5HT in tissues. Extracellular levels were also decreased and there was less dopamine released. This led the researchers to believe that 5HT neurons are damaged with excess L-DOPA because they normally release dopamine as well. The Parkinson-like symptoms that were seen during treatment may actually be due to the imbalance of DA and 5HT in the striatum. Also, L-DOPA has been found to lose some of its effects the longer it is taken. This may be due to the fact the dopaminergic receptors continue to

deplete due to PD pathology, but it may also be due to the fact that L-DOPA is harmful to 5HT neurons. More research needs to be done in this area to know for certain (Stansley and Yamamoto, 2015).

Table 1. A selection of studies highlighting the 5-HT deficits caused by chronic L-dopa.

Model	L-Dopa concentration (mg/kg/day)	Treatment duration (days)	5-HTerigc deficit(s)	Brain region(s) affected	Reference
Rat (non-lesioned)	250	60	↓ 5-HT tissue content	STR, Cortex	Borah and Mohanakumar [63]
Rat (unilateral 6-OHDA)	12	10	↓ 5-HT tissue content ↓ 5-HT extracellular	STR, Cortex STR, HIPP, SNr, PFC	Navailles *et al.* [65]
Rat (unilateral 6-OHDA)	12	28	↓ 5-HT tissue content	Amygdala	Eskow-Jaunarajs *et al.* [66]
Rat (bilateral 6-OHDA)	12	75	↓ 5-HT tissue content	STR, Amygdala, PFC	Eskow-Jaunarajs *et al.* [58]
Rat (non-lesioned)	12	10	↓ 5-HT cell bodies ↓ 5-HT tissue content	Dorsal DRN Dorsal DRN, PFC	Stansley and Yamamoto [17]
Macaque (MPTP-lesioned)	40	~90 (3 months)	↓ 5-HT tissue content	STR, Motor cortex, HIPP, Amygdala	Engeln *et al.* [67]

Table 1: This table indicates the concentration of L-DOPA given per day to rats in different conditions. It also displays what happened to the serotinergic neurons and concentration as the study went on. Consistently, 5HT was shown to decrease whether that be with the concentration in tissues or in the extracellular fluid (Stansley and Yamamoto, 2015).

Current Studies

As mentioned previously, one of the largest issues with the current L-DOPA treatment is the fluctuating response of taking the drug orally. It is currently broken down into many small doses taken throughout the day in order to avoid the high highs and the low lows. This semester, I was able to assist with part of a study that was designed to make the release of L-DOPA consistent. Drs. Mochel, Allenspach, and Kanthasamy created this study to work with the gut-brain axis and wanted to determine if that could be utilized to make treatment more

constant. If the treatment can become constant, the symptoms that occur during the on-off fluctuations as well as the wearing off phase could be more controlled. The anxiety that is present during the wearing off phase, when the drug concentration is low, is also something that they hoped to control.

L-DOPA induced kinesia (LID) is the name for the motor system side effects that occur when taking L-DOPA. These symptoms are due to the excess of dopamine present in the body as mentioned above. When L-DOPA administration and conversion are not able to be tightly controlled, more of these symptoms may be witnessed.

Knowing that the microbiota in the gut has a noticeable effect on the brain and neurodegenerative diseases, this was an important area to target. They hypothesized that getting L-DOPA to be released from the gut would lead to a steady release. In order to get L-DOPA produced consistently, they designed a probiotic (E. coli Nissle 1917 strain (EcN)) to do it. For approximately one month, the dogs were administered a treatment with the probiotic. Their blood was drawn and their feces were sampled. An endoscopy was also performed on each dog at the beginning and end of the study to sample the endothelium of their GI tract (Mochel, Allenspach, and Kathasamy, 2019).

Conclusions

Parkinson's disease is the second most prevalent neurodegenerative disease. Due to the number of people suffering from it, many people have dedicated their lives to researching it. The exact cause of the disease is unknown at this time, however much progress is being made to determine that. Until recently, the gut brain axis and its role in the development of neurodegenerative diseases was unknown, but now it is a huge point of study among researchers.

Even if the gut-brain axis is not the exact cause of Parkinson's disease, it may lead researchers to identifying what is the cause. For now, the gut-brain axis has provided a potential new way to treat Parkinson's disease that would drastically deplete the number and severity of symptoms associated with the current treatment. The drug is not necessarily a new discovery, but its delivery via probiotic to the gut is what is new and exciting.

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