Recent research suggests *L. reuteri* can be used to treat social deficits in genetic, environmental, and idiopathic mouse models of AD and that this rescue depends upon the vagus nerve as well as the oxytocinergic and dopaminergic signaling in the brain[10].

Oxytocin is a hypothalamus derived, posterior pituitary stored nonapeptide which has gained recent interest as an important neuropsychiatric and metabolic hormone, beyond its classic role in lactation and parturition. Oxytocin is central to complex social cognition and behaviors, such as attachment, social exploration, and recognition. In healthy humans, oxytocin binds to receptors in social brain regions such as amygdala and anterior cingulate cortex[1]. It is a key component of the network regulating social brain functions such as modulation of social stress, emotion recognition and memory formation[2]. In AD, intranasal administration of oxytocin in several[3,4,5] but not all[6] studies reported improvement in emotion recognition. Oxytocin treatment may be most efficacious in a subset of individuals with AD who have insufficient or low basal oxytocin levels[4,7].

Circulating oxytocin is a useful marker of central oxytocin activity because the peptide is synthesized by the same neurons with axons that terminate in the posterior pituitary and secrete the hormone into the blood and axons that project to social brain regions. Oxytocin is secreted in pulses[8] and the peptide has a very short half-life. Further, oxytocin does not cross the blood-brain barrier when sytemically administered. This could potentially be overcome by intranasal administration. However, intranasal oxytocin is unable to achieve sustained physiological levels for pulsatile oxytocin signaling. This may be accomplished by oral delivery of SB-121, that contains an activated *L. reuteri* and could stimulate the release of oxytocin via the gut-brain axis.

L. reuteri is a bacterium that naturally colonizes the outer mucous layer of the intestines. It stimulates production of mucin by goblet cells, and protects intestinal cells from opportunistic pathogens. *L reuteri* also stimulates oxytocin release into the circulation and onto neurons in the ventral tegmental area of the brain.[9,10,11,12] Studies of AD animal models demonstrate that impairments in social interactions can be overcome through oral administration of *L. reuteri.* Mechanistic studies revealed that this was due to an increase in oxytocin facilitated through vagus nerve signaling.[10] Administration of *L. reuteri* has also been shown to enhance wound healing in both animal models and human subjects by increasing circulating oxytocin levels via afferent vagus nerve signaling.[9,11]

As described below, the increase in oxytocin associated with the administration of SB-121 is transient, with oxytocin levels returning to baseline within 3 days. Hence, administration of SB-121 for AD will require daily dosing.

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Below is a Table of Clinical Trials demonstrating safety of L. reuteri

Identifier	**Subjects**	**Dose of *Lactobacillus reuteri* (CFUs)**	**Adverse Events Related to *Lactob***
NCT01531179	Very-low birth weight infants (<1500 g), <32 weeks gestational age	10^8 daily for for duration of hospitalization	None
NCT01837940	Adults ≥ 65 years	2×10^8 daily for 12 weeks	No serious adverse ever
NCT01737983	Patients 6-29 years old with cystic fibrosis	10^{10} daily for 6 months	None
NCT01855269	Infants less than 3 months old with colic	10^8 daily for 28 days	None
NCT01285830	Mothers and their babies	10^8 daily to mothers from gestational week 36, birth to 1 year for their babies	No adverse effects at ag
NCT00774163	Healthy adults 18-65 years old	10^8 daily for 5 days	No serious adverse ever
NCT01388712	3-7 year old children with constipation	10^8 daily for 8 weeks	Abdominal pain
NCT02734446	6-14 year old patients with asthma	10^8 daily for 90 days	No clinically relevant adverse
NCT01870700	Adults 20-50 years old with functional constipation	10^8 twice daily for 4 weeks	None
NCT02124122	Healthy children, 2-5 years old	10^8 daily for 5 days	No safety signals; no SA
NCT01046617	Infants with colic, <5 months of age	10^8 daily for 21 days	None
NCT01927094	Children 3-60 months of age with acute diarrhea	10^8 daily for 5 days	None
NCT01235884	Term neonates (<1 week)	10^8 daily for 90 days	None
NCT01249911	Children 6-36 months old	10^8 daily for 3 months	None
Not registered	Infants with functional chronic constipation	10^8 daily for 8 weeks	None
NCT01295918	100 children aged 3 to 12 years	10^8 daily for duration of hospital stay + 7 days	None
NCT00727363	750 infants <2000g	10^8 daily until discharge from the NICU	Safety not reported
NCT00767988	Catheterization-dependent girls with spina bifida	2×10^9 each of *L. reuteri* RC-14 and *L. rhamnosus* GR-1 daily for 3 months	None
NCT00985816	Preterm neonates <37 weeks	10^8 daily for 1 month	None
NCT01115296	Adults 18-65 years old with *H. pylori*	1×10^8 each of *L. reuteri* DSM 17938 and *L. reuteri* ATCC PTA 6475 daily for 96 days	None
NCT00922727	Healthy adults 18-60 years old	5×10^8 daily for 2 months	No serious adverse ever

Identifier	Subjects	Dose of *Lactobacillus reuteri* (CFUs)	Adverse Events Related to *Lactob*
Not registered	Healthy pregnant women with pregnancy gingivitis in third trimester	10^8 DSM 17938 plus 10^8 ATCC PTA 5289 twice a day until birth	Safety not reported
Not registered	HIV patients	10^{10} daily for 21 days	None
NCT00893711	Healthy term neonates less than 2 months old	10^8 daily for 30 days	None
NCT01046656	Children 1-48 months	10^8 daily for duration of hospital stay	None
NCT01836796	Adults 50-75 years old with type 2 diabetes	10^8 or 10^{10} once daily for 12 weeks	No differences between placebo a

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Table 10-1: Adverse Events Observed in Clincal Trials Using *Lactobacillus reuteri*

Abbreviations: ATCC = American Type Culture Collection; DSM = Deutsche Sammlung von Mikroorganismen und Zellkulturen; CFUs = colony forming units; HIV+ = human immunodeficiency virus positive; *L. reuteri* = *Lactobacillus reuteri*; *L. rhamnosus* = *Lactobacillus rhamnosus*; NICU = neonatal intensive care unit

a References are listed below.

b Adverse events were reported (feeling constipated [n=3], diarrhea [n=1], abdominal pain [n=1], undefined GI problems [n=1], urinary tract infection [n=1], inguinal hernia [n=1], feeling of "swollen legs" [n=1]) but relatedness to *L. reuteri* was not discussed.

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