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Leveraging a translational research approach to drive diagnostic and treatment advances for autism

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Abstract

Autism spectrum disorder (ASD) is a prevalent and poorly understood neurodevelopmental disorder. There are currently no laboratory-based diagnostic tests to detect ASD, nor are there any disease-modifying medications that effectively treat ASD's core behavioral symptoms. Scientific progress has been impeded, in part, by overreliance on model organisms that fundamentally lack the sophisticated social and cognitive abilities essential for modeling ASD. We therefore saw significant value in studying naturally low-social rhesus monkeys to model human social impairment, taking advantage of a large outdoor-housed colony for behavioral screening and biomarker identification. Careful development and validation of our animal model, combined with a strong commitment to evaluating the translational utility of our preclinical findings directly in patients with ASD, yielded a robust neurochemical marker (cerebrospinal fluid vasopressin concentration) of trans-primate social impairment and a first-in-class medication (intranasal vasopressin) shown in a small phase 2a pilot trial to improve social abilities in children with ASD. This translational research approach stands to advance our understanding of ASD in a manner not readily achievable with existing animal models, and can be adapted to investigate a variety of other human brain disorders which currently lack valid preclinical options, thereby streamlining translation and amplifying clinical impact more broadly.

Introduction

Autism spectrum disorder (ASD) is a complex brain disorder of early childhood onset. ASD is characterized by two core symptoms: persistent social communication and interaction difficulties and restricted, repetitive patterns of behavior, interests, or activities[1]. ASD affects

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Author's Contributions

KJP conceptualized, investigated, wrote, reviewed, and edited this manuscript.

Conflict of Interest Statement

The Board of Trustees of the Leland Stanford Junior University has filed patent applications related to data reviewed herein: PCT/US2019/019029 ("Methods for diagnosing and determining severity of an autism spectrum disorder") and PCT/US2019/041250 ("Intranasal Vasopressin Treatment for Social Deficits in Children with Autism"). These patents have not been granted, nor licensed, and the author is not receiving any financial compensation at this time.

1 in 44 U.S. children and exerts profound functional impacts across the lifespan[2]. ASD also constitutes a significant and rising public health concern: The U.S. expended an estimated $268 billion dollars on ASD in 2015, and without major scientific breakthroughs, this cost is projected to increase to upwards of $1 trillion annually by 2025[3].

Understanding ASD's pathogenesis is central to developing approaches to its detection and treatment. Although it is well established that ASD is a principally polygenic inherited disorder[4–6], the biological basis of ASD's behavioral symptoms remains poorly understood. Consequently, there are no laboratory-based diagnostic tests to detect ASD and no disease-modifying medications to treat ASD's core features. Although behavioral therapy can improve function in some individuals[7, 8], these interventions fall radically short of enabling each person with ASD to reach their full potential.

Progress in the biological detection and pharmacological treatment of ASD has been impeded for three key reasons. First, it is extraordinarily difficult to obtain brain-related biological samples (e.g., cerebrospinal fluid [CSF]; brain tissue) from patients with ASD and healthy controls to study disease biology more directly. Although large-scale genetic and behavioral phenotyping research has been undertaken in people with ASD[9], this approach will not enable experimental unraveling of biochemical, developmental, and electrophysiological mechanisms underlying ASD's behavioral dysfunction. Second, there has been an overreliance on model organisms that fundamentally lack the sophisticated social and cognitive abilities essential for modeling ASD's core features. For example, mouse models of ASD genetic syndromes (e.g., deletion of 16p11.2; duplication of 15q11–13)[10, 11] often fail to show the equivalent symptoms present in patients. These complexities highlight why rodents are unlikely to be the best choice for therapeutic development and testing, particularly since more than 90% of new central nervous system drugs fail in human clinical trials[12–15], and over 50% of those failures are attributable to false positives from poorly selected animal models[16]. There is thus an urgent need for models with greater behavioral and biological homology to human ASD. (See Table 1 for model development criteria and also[17, 18].) Finally, while many primate species do exhibit forms of social cognition relevant to ASD, the paradigms historically used in monkeys to model human social deficits have significant shortcomings. These include: the "lesion model" (which involves irreversible ablation of medial temporal lobe and/or orbital frontal cortical structures)[19, 20], and the pathogenic nursery/peer rearing model (which involves depriving young monkeys of parental contact, like as occurs for severely deprived human orphans)[21–23]. Although these primate models have yielded important insights, their construct validity for ASD is poor: Large brain lesions have not been implicated in ASD's pathophysiology, and ASD's etiology is no longer attributed to parental pathology or absence[24], but rather, to complex polygenetic mechanisms[25, 26]. Thus, for disorders such as ASD, 'spontaneous' models – in which differences in species-typical or pathological behavior occur naturally – are critical for examining early life risk factors and testing putative mechanisms.

Given these considerations, we saw substantial value in developing the first monkey model of naturally occurring social impairment. We also adopted the unusual approach of combining validation of our model with a strong commitment to testing the translational

utility of our preclinical findings directly in patients with ASD (See Table 2). Below I review findings from this research program, spanning studies of low-social rhesus monkeys to people with ASD. This trans-primate research strategy has enabled identification of a robust neurochemical marker of low sociality in monkeys and ASD in people, and paved the way for testing a first-in-class medication shown in a small phase 2a pilot trial to improve social abilities in people with ASD (Figure 1).

Developing a monkey model of low sociality

The "point of entry" for our monkey model was informed by the observation that autistic traits are disproportionally present in relatives of ASD probands (i.e., the "Broad Autism Phenotype")[27–30], and that such traits are common and continuously distributed across the general human population[31–33]. Indeed, ASD is thought to represent the quantitative extreme of an autistic trait continuum which arises from shared additive genetic susceptibility[34, 35]. Given the close phylogenetic relationship between humans and other primates, we reasoned that a similar behavioral trait continuum might likewise be present (and exploitable for study) in other primate species.

Because social interaction impairments are a defining[1], and frequently the most disabling[36], feature of ASD, we focused our initial primate model development efforts on the social behavior domain. We selected rhesus monkeys (*Macaca mulatta*) as our model organism with the intent of studying naturally occurring low sociality. Like humans, rhesus monkeys are a highly social species capable of complex social cognition, which reflects their interest and competence in interacting with others. Rhesus monkeys also display stable and pronounced individual differences in social behavior[37], but rhesus monkeys mature in 1/4th of the time as humans[38], making them an attractive model for developmental studies.

Our monkey research has been conducted at the California National Primate Research Center (CNPRC), where thousands of rhesus monkeys are housed outdoors in half-acre field corrals. Our research has placed a strong emphasis on developing a valid model of human social functioning. Thus, our study animals live in complex, rich social as well as physical environments, thereby ensuring that any social deficits we observe are unlikely to be a consequence of impoverished captive conditions.

We focused our initial efforts on male monkeys due to ASD's male-biased prevalence[2], and given that significantly more scientific information was available from male research participants with ASD for the purposes of modeling in monkeys behavioral symptoms[39]. We used focal animal sampling methods to identify naturally low-social monkeys in the CNPRC colony. Specifically, we determined the frequency that animals were observed alone in a non-social state to create an index for identification of naturally low-social vs. socially competent, high-social animals. We found that low-social monkeys initiate fewer affiliative interactions, spend less time in physical contact and grooming with conspecifics, and display more inappropriate social behavior (e.g., species-atypical gaze aversion in response to conspecific aggression), suggesting lower social motivation and impaired social skills[40–42]. Low-social monkeys also experience a greater number of traumatic injuries[43], a phenomenon in keeping with clinical reports that people with ASD likewise incur a greater

number of traumatic injuries relative to the general population[44–47]. For both low-social monkeys and people with ASD, those with greater social deficits sustain more frequent and more severe injuries than those who are less socially impaired[43, 45].

We recently revised the macaque Social Responsiveness Scale (mSRS)[48], or mSRS-R, which enabled reliable measurement of autistic-like traits in our animals, and allowed us to assess low-social monkeys for autistic-like traits in greater detail[49]. This scale was originally derived from the human SRS, an instrument that quantitatively assesses the presence and severity of autistic traits in the general human population[50, 51]. SRS scores are also strongly correlated with research diagnostic assessment scores on instruments used to confirm a clinical diagnosis of ASD[52, 53].

Consistent with human SRS findings[54], mSRS-R scores were continuously distributed across the general rhesus monkey population. Total scores on the mSRS-R could range between 17 and 119. Observed mSRS-R total scores ranged from 23 to 101 in our sample of N=233 male monkeys[49], indicating that our study evaluated nearly the full range of behavioral functioning in this species. Similar to humans[32, 55], we also found that autistic-like traits were highly heritable in macaques[56]. Further, as would be expected if the mSRS-R is measuring intrinsic traits, we found that neither age nor dominance rank correlated with monkeys' mSRS-R scores. The mSRS-R score likewise robustly and negatively predicted monkeys' behavior as quantified in home corrals, demonstrating the scale's internal construct validity. Finally, monkeys that scored 1.5 standard deviations or greater above the mean on non-social behavior exhibited significantly more autistic-like traits than those which did not, and mSRS-R scores predicted individuals' social classification (low-social vs. high-social) with high accuracy[49]. These findings demonstrated that male rhesus monkeys from a large general population exhibit pronounced individual differences in autistic-like traits, and that naturally low-social male monkeys exhibit an increased burden of them.

With an eye towards identifying behavioral features of young monkeys "at risk" for poor social developmental outcomes, we tested in a quasi-prospective study whether low-social and high-social adult male monkeys differed as infants in their ability to process social information, and whether infant social abilities predicted later social classification[41]. As part of a colony-wide assessment (i.e., the BioBehavioral Assessment [BBA] Program) at CNPRC[57], these monkeys had previously undergone, as 3–4 month old infants, tests of face recognition memory and the ability to respond appropriately to conspecific social signals. Monkeys later identified as low-social showed impairments in recognizing familiar vs. novel faces, such that monkeys later classified as low-social did not differ from a 50–50 preference, whereas high-social monkeys did. Monkeys later classified as low-social likewise showed impairment in the species-typical adaptive ability to gaze avert to conspecific aggression displays. Finally, infant test performance perfectly predicted later social classification of all N=50 monkeys. Studies of human infants at familial risk for ASD have implicated early deficiency in eye gaze to social cues and abnormal processing/recognizing of human faces as robust predictors of a later ASD diagnosis[58, 59]. Thus, our primate model findings are in line with those of clinical research; that is, we likewise can identify rhesus monkey infants 'at risk' for poor social developmental outcomes on the basis of subtle social information processing impairments early in life.

Biomarker discovery for low-sociality

Studies of low-social monkeys stand to advance our understanding of the biology of social deficits and enable us to hone hypothesis-driven questions that can be tested subsequently in valuable and volume-limited patient samples. Since there were no robust neurochemical markers of ASD, we interrogated in our model several biological systems that had strong rationales as candidates[42]. Our measures included the "social" neuropeptides oxytocin (OXT) and arginine vasopressin (AVP), and their receptors (including OXTR and $AVPR_{V1a}$)[60, 61], as well as two kinase signaling pathways, RAS-MAPK and PI3K-AKT (including the kinases ERK and AKT, and the phosphatase PTEN)[62, 63]. We first unobtrusively quantified social functioning in a discovery cohort and collected CSF and blood samples from individuals whose behavioral scores placed them at the top or bottom of our non-social behavioral index. We then repeated this procedure in a replication cohort. Using a statistical winnowing strategy, we found that CSF AVP concentration (but no other biological measure, including blood AVP concentration) was a key driver of group differences in adult monkey social functioning.

As would be expected of a putative biomarker, we found that CSF AVP concentration is stable within individual monkeys over time[42], including across the breeding and non-breeding seasons[64]. These findings led us to test a critical hypothesis: If CSF AVP concentration is a neurochemical marker of quantitative variation in social functioning, including the social features of ASD, individual differences in CSF AVP concentration should predict individual differences in both prosocial behavior and social impairment. This was indeed the case, as CSF AVP concentration positively predicted time spent in social grooming[42]. (This socially motivated behavior maintains social bonds in primates and requires significant competence to perform successfully.) The same was true of social impairment: In a separate adult male monkey cohort, we found that CSF AVP concentration, but no other neuropeptide or kinase-related measure, robustly predicted individual differences in autistic-like traits as measured across a continuous distribution of monkey mSRS-R scores[64].

Testing the translational utility of our neurochemical marker of social impairment in ASD

A reasonable critique of our primate model is that low-sociality is non-pathological, and thus provides only limited insight into the biology of ASD. To test the translational value of our model, we quantified AVP concentrations in CSF samples from a small "proof of concept" ASD cohort (N=7 ASD case-control dyads; total N=14)[42]. As predicted, we found that CSF AVP concentration was lower in ASD cases vs. controls, and that CSF AVP concentration differentiated individual ASD cases and controls accurately. We next sought to replicate this finding in a larger pediatric cohort (N=36 case-control dyads; total N=72)[65]. Although ASD cases in our first cohort were a sample of convenience (i.e., they were recruited during medical procedures requiring CSF collection), the ASD cases in our second cohort were well-characterized, medically healthy children who had undergone lumbar puncture as part of a research study[66]. In the replication cohort, we again found that CSF AVP concentration

was lower in ASD cases vs. controls, and differentiated individual ASD cases from controls accurately. Moreover, boys with ASD who had the lowest CSF AVP concentrations had the greatest symptom severity[65]. These effects were specific to AVP; no evidence implicating the structurally related neuropeptide, OXT, was found. These clinical findings demonstrate that face valid animal models can illuminate fundamental aspects of human disease biology (Table 2), and possibly even its pathogenesis (as considered below).

Taking stock: The significance of CSF AVP concentration in low-social monkeys and people with ASD

Brain AVP is an important regulator of mammalian social functioning[67–69], and experimental dysregulation of the AVP pathway induces social recognition impairments in mice[70]. Congenital silencing of AVP gene activity is associated with significant social and developmental deficits in Brattleboro rats[71], raising the possibility that early impairment in brain AVP signaling may likewise contribute to social functioning deficits in children. However, AVP is not a high-confidence ASD susceptibility gene. Therefore, it seems more likely that brain AVP signaling is impacted by the convergence of multiple ASD susceptibility variants[64, 72]. This would explain why CSF AVP concentration is closely linked to quantitative variation in autistic-like traits in monkeys[64] and symptom severity in children with ASD[65]. Because early ASD detection stands to maximally improve a child's developmental potential, we next investigated when this putative AVP signaling deficit may be evident, and if it is present before behavioral symptoms emerge.

Neonatal CSF AVP concentration predicts a medical record diagnosis of ASD later in childhood

Although ASD can be reliably diagnosed by 24 months of age[73], sadly, due to many factors (e.g., long clinic wait times to undergo behavioral evaluation), the median age of an ASD diagnosis in the U.S. occurs between 36 and 63 months (as reported recently from 11 state-level monitoring sites)[2]. By the time a child receives a formal ASD diagnosis, cumulative delays in the early processing of basic social stimuli have contributed to an atypical trajectory of poor social learning and abnormal social skill acquisition that is immensely difficult to overcome. The capability of rapidly detecting ASD based on a patient's biology, when a child's symptoms first emerge, or even before the disorder manifests behaviorally, would revolutionize ASD evaluation and enable more timely intervention.

As detailed above, we previously found that CSF AVP concentration differentiates pediatric ASD cases from controls. As an initial step in establishing the causal direction for this association, we used infant CSF samples to conduct a quasi-prospective test of whether this association held true before the developmental period when ASD first manifests[74]. This study exploited a rare archival collection of frozen "leftover" CSF that had been obtained during medical care of 0–3 month old febrile infants (N=913). Medical records were reviewed through 12 years of age to assemble a cohort with and without childhood ASD. Individuals subsequently diagnosed with ASD had significantly lower neonatal CSF AVP concentrations compared to those who did not later receive an ASD diagnosis. The

associations were specific to AVP, as neonatal CSF OXT concentration did not differ between infants later diagnosed with ASD and those who developed typically. These findings suggest that a previously identified neurochemical marker of ASD may be present very early in life, before behavioral symptoms emerge, and that it may be useful for identifying and monitoring infants at risk for poor social developmental outcomes.

CSF vs. blood surveillance of AVP concentrations in ASD

Early in our ASD biomarker research, we found that blood AVP concentration did not differ between children diagnosed with ASD and typically developing control children, nor did it differ between adult low-social and high-social monkeys[42, 75]. In our adult monkey model, we saw no relationship between concomitantly collected blood and CSF AVP concentrations, but in the same animals, CSF AVP concentration strongly predicted multiple social behavior measures. Although there is evidence that blood and CSF AVP concentrations may be somewhat correlated in childhood[75], blood and CSF AVP concentrations no longer appear to be linked in adulthood[76, 77]. This may be because the relationship between CSF and blood AVP concentrations changes fundamentally during development. In human adults, CSF circulates within the ventricular system of the brain and is thought to be reabsorbed into the vascular system by entering the dural venous sinus via the arachnoid granulations. In neonates, in whom arachnoidal granulations are sparse, CSF largely flows along cranial nerves and spinal nerve roots where it enters into lymphatic channels and subsequently into circulating venous blood[78]. Further, differences in the anatomy of the blood-brain barrier in neonates and adults, whereby the endothelial junctions of the brain's venous system are not as tightly formed during the early stages of life compared with adulthood, potentially allows for larger molecules (including neuropeptides) to flow more freely between the brain and body[79]. Thus, although large molecules such as proteins and neuropeptides are known to be sequestered by the blood-brain barrier, the mechanisms of potential shared central and peripheral circulation of large molecules in neonates are thought to differ meaningfully from adults[80]. Indeed, we previously analyzed AVP concentrations in concomitantly collected CSF and blood samples in a small cohort of human newborns (N=15) undergoing clinical sepsis evaluation (all were sepsis negative) during the first month of life[81]. We found that blood AVP concentration significantly and positively predicted CSF AVP concentration (r=0.73). Our findings from relatively healthy human newborns are in agreement with similar evidence obtained from a study of human infants with hypoxic-ischemic encephalopathy[82]. These collective findings support the hypothesis that blood AVP concentration may be a useful surrogate of CSF AVP concentration during the neonatal period (but increasingly less so later in life). If so, and with evidence showing neonatal CSF and neonatal blood AVP concentrations are equally predictive of social developmental outcomes, a less invasive and more tractable path to routine neurochemical surveillance of ASD risk and detection in human newborns may be feasible.

Intranasal AVP administration as a potential treatment for ASD

AVP-producing neurons send projections throughout the primate brain, including to the basal forebrain, amygdala, and cortex[83, 84 85]. AVP's prosocial effects are largely mediated

via $AVPR_{V1a}$[69, 86, 87], which in primates are likewise distributed throughout these "social brain" regions[88, 89]. This combined evidence suggested the possibility that AVP treatment in humans could directly target neural pathways that regulate social functioning. This idea was supported by several reports that single-doses of intranasal AVP enhance a variety of social abilities including memory for emotional faces[90], identification of social words[91], and cooperative behavior[92] in healthy adult humans. Single-doses of intranasal AVP have also been shown to enhance speech and word formation in patients with post-stroke aphasia[93] and to improve short and long-term memory in patients with central diabetes insipidus[94], suggesting cognitive enhancing properties of this drug. Although the precise mechanisms by which intranasally administered AVP and other peptides achieve behavioral effects in humans remains to be determined[95], intranasal AVP administration results in elevated CSF concentrations of measured AVP in humans, suggesting that intranasally administered AVP achieves access to the central nervous system[96].

Based on this collective evidence, we recently conducted a first-in-class phase 2a clinical trial in children with ASD[97]. This small pilot trial used a double-blind, randomized, placebo-controlled parallel design to test the efficacy and tolerability of 4-week intranasal AVP treatment in children with ASD (N=30), aged 6–12 years. We found that AVP vs. placebo treatment significantly enhanced social abilities as assessed by parent report (i.e., change from baseline in SRS score), clinician evaluation (i.e., change from baseline in social communication and social cognition abilities), and child performance on laboratory-based social cognition tests (i.e., change from baseline in Reading the Mind in the Eyes Test score and Facial Emotion Recognition Test score). These findings were more pronounced when we accounted for pretreatment blood AVP concentration. Finally, AVP was well tolerated with minimal side-effects and had an excellent safety profile. We are currently conducting a phase 2b AVP treatment trial in children with ASD, using a dose found to be effective in our pilot trial. If our findings are replicated in the larger trial, AVP may hold promise as a novel therapeutic intervention for a patient population that currently lacks a pharmacological strategy for its debilitating social behavior symptoms.

Limitations and other considerations

First, although our monkey model enabled identification of a robust trans-primate neurochemical marker of social impairment, it is imperative to acknowledge that this model nevertheless is an approximation for human ASD. Second, the phenomenon of naturally occurring low sociality was the "point of entry" for developing our model. Although the mSRS-R contains repetitive behaviors items[49], and subsequent factor analysis has identified "Inappropriate Behavior" as a factor in the mSRS-R[98], the repetitive features of ASD remain largely unexplored in our model. Third, other than determining that mSRS-R scores are continuously distributed in the general female rhesus monkey population as part of our instrument validation[49], we know little about low sociality in female monkeys. Growing evidence indicates that girls with ASD need to display higher levels of autistic traits to garner medical attention and that they tend to be diagnosed at later ages than boys on the spectrum[99], suggesting that ASD may be under-detected and may manifest differently in girls. For example, we observed that girls with ASD have significantly lower CSF AVP concentrations compared to controls (just like boys with ASD), but we did not observe

a correlation between girls' CSF AVP concentrations and their symptom severity (unlike boys with ASD)[65]. As our scientific understanding of ASD in girls grows, it will be important to model these findings in female monkeys. Fourth, although our human ASD biomarker findings are compelling, this research has often been carried out in samples of convenience in which research participants (including "controls") are sick enough to require CSF collection. Fifth, in our human infant study, we could not rule out the possibility that there were human newborns with low CSF AVP concentrations who nevertheless developed typically (which might be the case if, for example, a second "hit" like a social information processing deficit is also required to produce ASD). Sixth, the case-control study design that we have typically employed does not accommodate a disease differential, and thus, we could have unintentionally overestimated the CSF AVP effect in our work. Future research, inclusive of other brain disorders with and without social impairment, will be required to test whether low CSF AVP concentration is indeed specific to ASD, as opposed to a more general "signature" of altered brain development (and, thus, potentially equally predictive of other disorders). Seventh, ASD is clinically heterogenous and has a high medical comorbidity rate. Although we found that CSF AVP concentration is robustly associated with ASD's social impairments, it is not related to repetitive behavior symptoms[65]. This suggests that other CSF biomarkers may contribute additional explanatory power and, thus, could be incorporated into a multiplex biomarker panel by which to detect ASD, and potentially biologically-defined subtypes. Such a multidimensional biomarker approach would also guard against misclassification of healthy individuals (given ASD's low base rate), and could better distinguish ASD from other disorders (such as attention-deficit/hyperactivity disorder [ADHD]). (In our infant study, CSF AVP concentration individually predicted an ASD diagnosis, but did so with highest precision when cases with comorbid ADHD were removed from the analysis.) Finally, in the vast majority of human CSF studies, and in all of ours involving ASD, blood was either unavailable, previously collected by other teams using protocols suited for their needs but not ours, or too limited in volume or sample number to permit analysis. Thus, research is needed to determine in concomitantly collected CSF and blood samples whether CSF biomarkers of ASD are also reliably detectable in blood, and if so, during which stage(s) of lifespan development.

Future directions

This translational research program is well positioned to generate other discoveries. For example, CSF requires invasive collection procedures that will be difficult to integrate into routine clinical care; the monkey model may therefore be useful in identifying a transcriptional or proteomic "fingerprint" in a more accessible peripheral fluid (e.g., blood, saliva, or urine) that predicts both CSF AVP concentration and social impairment in the same animals. Additionally, the causal mechanism(s) leading to the observed variation in brain AVP signaling and its impact on social behavior variation requires elucidation, as do the molecular and cellular pathways that might govern sensitivity to AVP treatment. To address these gaps, high quality brain tissue can be harvested from phenotypically well characterized monkeys and transcriptomic analyses performed both to identify AVP's functional determinants and to better understand the influence of AVP on brain function following long-term AVP treatment. Complementary brain-relevant studies can likewise be

conducted in people. For example, induced pluripotent stem cell (iPSC)-derived neurons can be used to investigate AVP's effect on *in vitro* brain cells, to identify the receptor that most selectively mediates AVP's response, and ultimately, to ascertain the effects of AVP treatment in iPSC-derived neurons from ASD patients who respond and do not respond to AVP treatment (similar to the approach used to evaluate lithium response in bipolar disorder patients[100]). Transcriptional profiles of AVP treatment non-responders can then be "reverse-translated" to the monkey model, to facilitate development and testing of medications that target new biological pathways in appropriately selected low-social animals.

Implications for modeling other brain disorders

The research strategy employed here exemplifies the power of developing refined primate models in a naturalistic setting for the purpose of identifying robust biomarkers, elucidating disease mechanisms, and testing novel medications. Given the close biological and behavioral homology between non-human primates and humans, there is a tremendous, untapped potential to study naturally occurring disease-relevant phenotypes (e.g., as they relate to neurodevelopmental, emotional, cognitive, sleep, impulse control, and neurodegenerative disorders) in large captive primate colonies. Additionally, state-of-the-art gene editing technologies have recently become more efficient (and, hence, more "affordable" for primate research); these innovations are paving the way for a complementary "genes first" approach by which to engineer high-confidence disease susceptibility genes in primate models, thereby further expanding the range of potential brain diseases that can be modeled and studied. Indeed, there has been an exponential growth in biomedical knowledge over the past several decades, with astonishing brain-relevant advances in genomics, imaging, bioinformatics, and stem cell medicine. Compelling new primate models of human brain disease are now urgently needed, to harness these promising technologies, not only to heal brain disease, but to predict and prevent it.

Conclusion

We created an innovative translational ASD research platform, spanning a monkey model with proven translation potential to clinical biomarker discovery/therapeutic testing capabilities in patients with ASD. This unique structure has enabled us to move fluidly and bidirectionally across each research component, to deliver advances in ASD detection and treatment, in a manner not readily achievable with existing animal models. Findings from this translational research program may ultimately prove useful for developing "standard of care" ASD surveillance protocols in human newborns, particularly if we are able to establish that blood and CSF concentrations of AVP and other disease-relevant proteins are tightly linked in the neonatal period. Moreover, maximally effective medications for ASD will likewise manipulate specific pathways at an early age while the brain still retains much of its plasticity. If we find that neurochemical abnormalities are evident in behaviorally asymptomatic newborn monkeys which later show a high burden of autistic-like traits, we will be poised to intervene precisely when symptoms first emerge in infants, or prophylactically in newborn monkeys "at risk" for poor social developmental outcomes. Any medications found to be safe and effective in our monkey model can be rapidly translated for testing in human clinical trials, thereby accelerating the development of new

and next-generation treatments to improve behavioral functioning, and hence quality of life, for people with ASD. Finally, this translational research approach can be adapted to investigate a variety of other human brain disorders which currently lack valid preclinical options, thereby streamlining translation and amplifying clinical impact more broadly.

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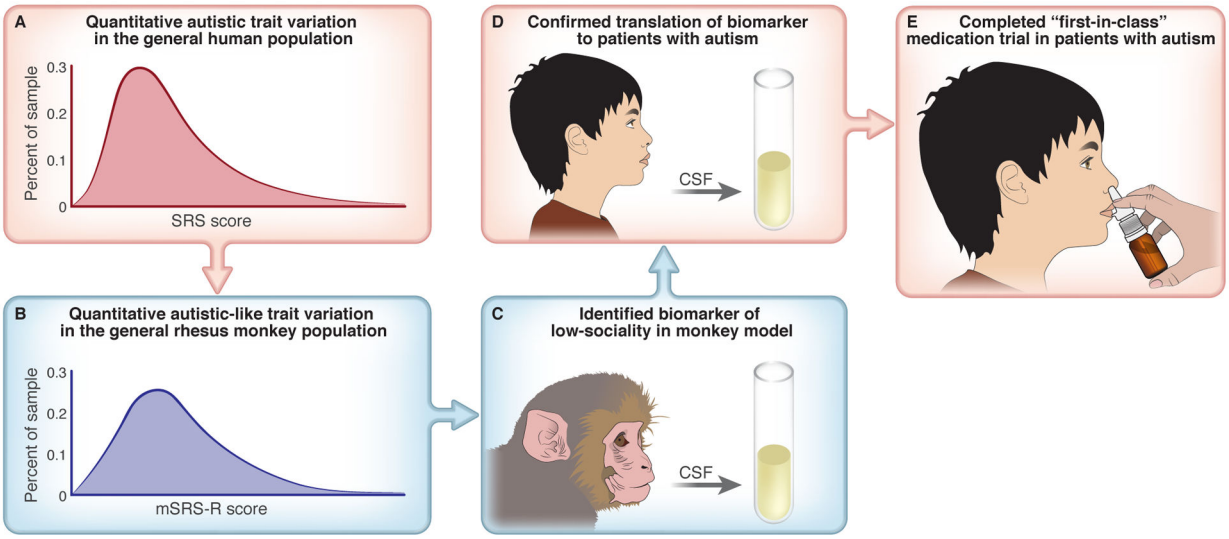

Figure 1. ASD research strategy for streamlined translation and clinical impact.

(A) Development of our monkey model was based on evidence that autistic traits are common and continuously distributed across the general human population, with ASD representing the quantitative extreme of this continuum. (B) We documented a similar continuum of quantitative autistic-like traits in rhesus monkeys by reverse-translating and revising a clinically relevant instrument, the Social Responsiveness Scale (SRS), for use in rhesus monkeys (i.e., the macaque SRS-Revised, or mSRS-R). Higher scores indicate greater impairment on both instruments. (C) We performed biomarker discovery in rhesus monkey cerebrospinal fluid (CSF) and blood samples and identified low CSF arginine vasopressin (AVP) concentration as a robust neurochemical marker of social impairment in rhesus monkeys. (D) We then forwarded-translated this biomarker finding to several cohorts of patients with ASD, showing that CSF AVP concentration distinguishes ASD cases and controls accurately. (E) Finally, we conducted a double-blind, randomized, placebo-controlled phase 2a pilot trial and found that AVP treatment was well tolerated and increased social abilities in children with ASD.

Table 1.

Key validity criteria for developing and evaluating animal models of autism

Validity criterion	Ideal model feature(s)
Face validity: Degree of outward similarity in appearance between the animal model's phenotypic attributes and patients' symptoms.	Presence of complex social interaction impairments and repetitive behaviors in an altricial, highly social, diurnal species with vision as its primary sensory modality.
Construct validity: Degree of similarity in the underlying causes and biological underpinnings of the animal model's phenotypic attributes and patients' symptoms.	Phenotype emerges spontaneously (i.e., due to additive polygenic risk, not due to an impoverished captive environment) or is induced through natural presence or gene-editing of highly penetrant autism susceptibility gene(s). In either case, phenotype emerges early in development and persists into adulthood. Better results will be achieved with decreasing phylogenetic distance between the model organism and humans, thereby ensuring greater homology in relevant genes, pathways, and circuits.
Predictive validity: Animal model's ability to identify and evaluate medications for therapeutic safety and efficacy in patients; medications that are efficacious for treating patient symptoms should likewise ameliorate similar phenotypic attributes in the animal model.	Medications should safely target core autism features. Thus, they should ameliorate social impairments and/or diminish repetitive behaviors with minimal side effects in both the animal model and in patients with autism.

Table 2.

Autism-relevant findings in rhesus monkeys and humans

Characteristic	Rhesus monkeys	Humans
Quantitative autistic/autistic-like traits are common and continuously distributed across the general population	Talbot et al., 2020	Constantino & Todd, 2003; 2005
Quantitative autistic traits are heritable	Garner et al., under review	Constantino & Todd, 2005; Lyall et al., 2014
Quantitative autistic trait continuum arises from additive genetic susceptibility	Currently unknown	Robinson et al., 2011 Lundstrom et al., 2012
Abnormalities in species-typical perception and reaction to social stimuli present at phenotypic extreme of general population	Capitanio, 2002 Sclafani et al., 2016	APA, 2013
Subtle social information processing deficits in infancy predict later social impairment	Sclafani et al., 2016	Jones & Klin, 2013; Keehn et al., 2015
Comorbid occurrence of social impairment with repetitive behavior	Currently unknown	APA, 2013
Lower CSF AVP concentration in individuals with social impairment vs. controls	Parker et al., 2018	Parker et al., 2018; Oztan et al., 2018; Oztan et al., 2020
CSF AVP concentration correlated with degree of social impairment	Parker et al., 2018; Oztan et al., 2021	Oztan et al., 2018
Trait-like consistency in CSF AVP concentration across measurements	Parker et al., 2018; Oztan et al., 2021	Currently unknown
CSF AVP concentration in infancy predicts later social impairment	Currently unknown	Oztan et al., 2020
CSF OXT concentration does not differ between individuals with social impairment vs. controls	Parker et al., 2018	Oztan et al., 2018; Oztan et al., 2020
AVP treatment improves social cognition in socially impaired individuals	Currently unknown	Parker et al., 2019
Early AVP treatment improves social developmental outcomes in “at risk” individuals	Currently unknown	Currently unknown

Abbreviations: AVP, arginine vasopressin; CSF, cerebrospinal fluid; OXT, oxytocin