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Commentary

How close are we to a cAMP- and cGMP-theory-based pharmacological therapy for fragile X syndrome?

Barbara Bardoni,[1,*] Carole Gwizdek,[1] and Thomas Maurin[2,3]
[1]Inserm U1323CNRS UMR7275, Institut de Pharmacologie Moléculaire et Cellulaire, 06560 Valbonne, France
[2]Syneos Health Sophia, 06410 Biot, France
[3]Present address: Domain Therapeutics, 67400 Illkirch-Graffenstaden, France
*Correspondence: bardoni@ipmc.cnrs.fr
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Recent advances in targeting cAMP and cGMP pathways offer hope for treating fragile X syndrome, a leading cause of inherited intellectual disability. PDE4 and PDE2 inhibitors have shown promise in animal models, improving memory, social behavior, and cognitive function. Clinical trials are underway, raising optimism for future therapies.

Fragile X syndrome (FXS) is the most common inherited cause of intellectual disability and autism spectrum disorder (ASD). It arises from silencing the *FMR1* gene due to a hypermethylated CGG expansion in its 5′ untranslated region. The *FMR1* gene encodes the fragile X ribonuclear messenger protein (FMRP), an RNA-binding protein essential for regulating translation in neurons, at both the soma and synapses. FMRP regulates the expression of a substantial number of synaptic proteins, modulating synaptic plasticity and neuronal signaling. It binds to thousands of mRNAs in the brain and is involved in processes, including mRNA transport between the nucleus and cytoplasm, mRNA transport in dendrites and axons, mRNA stability, splicing, editing, and transcription.[1,2]

The *Fmr1* knockout (*Fmr1*-KO) mouse model, which lacks functional FMRP, is widely used in research and is recognized as a robust tool for assessing ASD.[2] Over the past 30 years, FXS has gained significant research attention in genetics, molecular and cellular biology, RNA metabolism, and neuroscience, making it a paradigmatic model for investigating neurodevelopmental disorders (NDDs). Over the past 15 years, the neuropharmacology community has shown increasing interest in FXS due to the absence of specific and effective therapies for this disorder.[1,3] Patients with FXS typically receive symptomatic treatments, including medications to alleviate symptoms, along with educational, behavioral, occupational, physical, and speech therapies.[2] In the past years, considering the preclinical treatments for FXS, the scientific community raised questions about the feasibility of developing effective therapies given the significant challenges in translating preclinical findings into clinical success (e.g., illustrated by the discontinuation of 2 different phase 3 trials). Since then, significant progress has been made, particularly in exploring therapeutic strategies aimed at restoring the homeostasis of second messengers, such as cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP), as potential therapeutic approaches for FXS.[3]

Both cAMP and cGMP are critical for neurodevelopment, synaptic plasticity, and cognitive functions such as learning and memory. These molecules regulate key processes, including axon growth, guidance, and dendritic spine formation, with opposing effects. cGMP promotes glutamate synthesis through phosphoglycerate kinase, whereas cAMP regulates neurotransmitter vesicle dynamics and synaptic plasticity via protein kinase A (PKA) signaling.[2,3] The balance between cAMP and cGMP is crucial for shaping neuronal circuits and regulating neuronal migration.[3] cAMP and cGMP are synthesized by adenylate and guanylate cyclases, which convert adenosine triphosphate (ATP) and guanosine triphosphate (GTP) into their respective cyclic forms. Meanwhile, their degradation is mediated by phosphodiesterases (PDEs), a superfamily of enzymes expressed in various tissues including the brain. The precise spatiotemporal expression of PDEs is essential for maintaining appropriate cAMP and cGMP levels in different brain regions, thus ensuring proper neuronal function. Studies investigating the role of PDEs in brain development and function have highlighted their potential as therapeutic targets for neurological disorders. PDE inhibition was initially explored as a therapeutic approach for neurodegenerative diseases (e.g., Alzheimer's disease [AD] and dementia, depression, and schizophrenia [SCZ][3]). Recent studies have identified PDE4 and PDE2A as promising targets for FXS therapy, with their modulation showing potential for improving synaptic function and behavioral outcomes in preclinical models.[3]

The PDE4 family of enzymes specifically hydrolyzes cAMP and is encoded by 4 genes—*PDE4A*, *PDE4B*, *PDE4C*, and *PDE4D*. These genes produce over 20 isoforms through alternative splicing and the use of different transcriptional start sites. The role of PDE4 in learning and memory has been extensively investigated in both *Drosophila* and mouse models.[3,4] In humans, mutations in *PDE4D* have been linked to the development of acrodysostosis, a disorder often accompanied by intellectual disability. PDE4 inhibitors have been developed and evaluated for their potential to treat conditions such as SCZ and dementia.[3]

PDE2A is a dual-specific PDE that hydrolyzes both cAMP and cGMP. It is activated by cGMP and expressed as 3 alternatively spliced isoforms with high expression levels in the brain—particularly in association with synaptic vesicles. Mutations in PDE2A have been associated with the occurrence of NDDs, including intellectual disability, ASD, and epilepsy. In the past, PDE2A inhibitors have been developed as potential treatments for depression, SCZ, dementia, and pain.[3]

The role of cAMP in FXS pathophysiology was initially explored in 1993. Initial findings showed that cAMP production was reduced in platelets of patients with FXS following exposure to the broad PDE inhibitor 3-isobutyl-1-méthylxanthine (IBMX), cAMP-stimulating prostaglandin PGE1, and forskolin, which directly activates the catalytic subunit of adenylate cyclase.[2] Subsequent studies in various FXS models, including *Fmr1*-KO mice and human neural cells, observed consistently reduced cAMP levels in the absence of FMRP.[4] A similar defect was also observed in *Drosophila* models of FXS, where the reduction in cAMP was reversed by reintroducing dFMR, the fly homolog of *FMR1*. These findings demonstrated that cAMP deficit caused by FMRP loss is conserved across species, highlighting its potential as a biomarker for FXS in clinical trials. This evidence contributed to the development of the cAMP theory for FXS, which complements the previously established mGluR theory of the disorder.[2]

The therapeutic potential of targeting dysregulated cAMP levels gained further attention when PDE inhibition was shown to improve FXS phenotypes in *in vitro*, *ex vivo*, and *in vivo* models. In 2015, PDE4D inhibition with the specific inhibitor rolipram significantly improved learning (courtship behavior) and memory (olfactory test) deficits in a *Drosophila* model of FXS. Additionally, structural brain defects in these flies, such as the aberrant midline crossing of the β lobes of the mushroom bodies, were also ameliorated by rolipram treatment. Consistent with these findings, both acute and chronic rolipram treatments rescued the mGluR-dependent long-term depression (LTD) phenotype in brain slices obtained from treated *Fmr1*-KO mouse, bridging the cAMP and mGluR theories of FXS.[4]

Recently, we discovered that during synaptogenesis in the mouse brain, *Pde2a* mRNA is directly regulated by FMRP, which increases its translation and transport to synapses.[1,5] In *Fmr1*-KO mice, the PDE2A expression is elevated in the cortex and hippocampus.[5] To determine whether the increased expression of PDE2A leads to higher enzyme activity, we measured the cAMP and cGMP levels in cerebral cortical cultures using enzyme-linked immunosorbent assay (ELISA). As expected, both cAMP and cGMP levels were reduced in *Fmr1*-KO mice compared with those of wild-type (WT) mice. Remarkably, treatment with BAY60-7550, a PDE2A inhibitor, for 24 h normalized the levels of both cAMP and cGMP.[5] We also employed a specific bio-probe to measure cAMP levels at a single-cell resolution in the CA1 region of *Fmr1*-KO mice in an *ex vivo* assay. Our results showed that cAMP hydrolysis was accelerated upon PDE2A activation in *Fmr1*-KO mice compared with cAMP hydrolysis in WT mice.[5] Additionally, PDE2A inhibition corrected the exaggerated mGluR-dependent LTD observed in the CA1 region of the hippocampus.[5] In cultured cortical neurons from *Fmr1*-KO mice, BAY60-7550 treatment also restored the immature spine morphology, a hallmark of FXS and other NDDs.[2,5] Notably, acute treatment with BAY60-7550 in *Fmr1*-KO mice led to significant improvements in social behaviors. This improvement included enhanced social communication and discrimination in early life, which were assessed by ultrasonic vocalization assays and homing tests performed in pups at 7 and 13 postnatal days (PNDs), respectively. In the same study, we acutely administered BAY60-7550 during early adolescence (28–30 PNDs) and observed that the treated *Fmr1*-KO mice exhibited social interaction levels comparable to those of both treated and untreated WT mice, whose behavior remained unaffected by the drug.[5] The elevated PDE2A activity was also confirmed in the brains of *Fmr1*-Δexon 8 rats, another rodent model of FXS. In these rats, the inhibition of PDE2A with Bay60-7550 further alleviated socio-cognitive deficits, improving social communication in pups and enhancing memory and social interactions in adolescent and adult animals.[6]

Consistent with observations in patients carrying *PDE2*A gene mutations,[3] *Pde2a* deletion in C57BL/6J mice led to sex-dependent socio-cognitive deficits during development.[7] Indeed, *Pde2a*$^{+/-}$ mice only exhibited reduced cognitive performance in young adulthood, whereas male mice showed socio-deficits throughout their lifespan[7] and increased hyperactive behavior after 3 months of life.[8] Phenotypes of young mice were associated with microglia activation and increased externalization of glutamate receptors in the CA1 region, leading to reduced mGluR-dependent LTD.[7] This latter phenotype appears linked to elevated cAMP and cGMP levels, as they mirror the opposite patterns observed in FXS where the levels of second messengers are decreased compared to those of WT controls.[7]

Overall, these findings provide new insights into the FXS pathophysiology, demonstrating that FMRP, through PDE2A, regulates the homeostasis of both cAMP and cGMP. This highlights the involvement of both second messengers in the disorder and introduces the cAMP and cGMP theory. Specifically, PDE2A plays a pivotal role in cGMP degradation during early postnatal development, contributing to 50% of the reduction in cGMP levels during synaptogenesis in the rat brain.[6] These results suggest that early intervention targeting PDE2A could significantly alter the disrupted developmental trajectory of FXS. In line with this, a 2-week chronic treatment with Bay60-7550 during infancy in *Fmr1*-KO mice led to improvements in social interactions in adolescent animals within 9 days of the washout period. These animals were sacrificed at 4 months of age, and their brains exhibited restored dendritic spine morphology in the hippocampus and cortex, similar to the changes observed in the *in vitro* cultures of *Fmr1*-KO neurons.[5] This underscores the potential for long-lasting effects of early therapeutic intervention on brain development.

Given these advancements, the question is no longer whether effective therapy for FXS is possible but rather when it will become available. Although gene therapy for FXS is still in the early stages of development, new PDE4 and PDE2 inhibitors are already undergoing clinical trials. Recently, a novel PDE4D inhibitor, BPN14770 (zatolmilast), was synthesized with high selectivity for the dimeric, PKA-activated form of the enzyme.[3,9] In preclinical

Table 1. Clinical trials using the PDE4D inhibitor BPN14770

Trial	Title	Condition	Location	Status
NCT03030105	Study to Evaluate the Effects of BPN14770 on Scopolamine-induced Cognitive Impairment in Healthy Volunteers	Alzheimer's disease	Austin, Texas (USA)	completed
NCT03861000	Evaluation of a Novel PET Radioligand for Phosphodiesterase-4D (PDE4D)	depression	Bethesda, Maryland (USA)	completed with results
NCT03569631	A 2-Period Crossover Study of BPN14770 in Adults Males With Fragile X Syndrome	fragile X syndrome	Chicago, Illinois (USA)	completed
NCT02648672	BPN14770 Single Ascending Dose Study in Healthy Male and Female Subjects	Alzheimer's disease	Kalamazoo, Michigan (USA)	completed
NCT02840279	A Multiple Ascending Dose Study of BPN14770 in Healthy Young and Elderly Male or Female Subjects	Alzheimer's disease	Kalamazoo, Michigan (USA)	completed
NCT04044781	A Phase 1, Open-Label, PET Study of T2310 & BPN14770	to determine brain target occupancy of BPN14770	New York, New York (USA)	withdrawn
NCT05163808	A Randomized Study of BPN14770 in Male Adolescents (Aged 9 to <18 Years) With Fragile X Syndrome	fragile X syndrome	17 locations in USA	recruiting
NCT05358886	A Study of BPN14770 in Male Adults (Aged 18 to 45) With Fragile X Syndrome	fragile X syndrome	17 locations in USA	recruiting
NCT0536796	An Open-Label Extension Study of BPN14770 in Subjects With Fragile X Syndrome	fragile X syndrome	17 locations in USA	enrolling by invitation
NCT03817684	Tetra PICASSO AD Trial: Study to Evaluate Effects of BPN14770 in Early Alzheimer's Subjects	Alzheimer's disease	41 locations in USA	active not recruiting
NCT06717438	Study of Zatolmilast (BPN14770) in Participants With PPP2R5D Neurodevelopmental Disorder (Jordan's Syndrome [JS])	Jordan's syndrome PPP2R5D neurodevelopmental disorder	3 locations in USA: Chicago, Illinois Seattle, Washington Boston, Massachusetts	new—not yet recruiting

studies, a 2-week sub-chronic treatment with BPN14770 in *Fmr1*-KO mice led to improvements in several behavioral phenotypes, including hyperactivity, social interaction, nest building, and marble burying. Moreover, the treatment positively affected the synaptic structural plasticity, promoting dendritic spine maturation.[3]

A notable phase 2 randomized, placebo-controlled, crossover study was conducted in 30 adult male patients (aged 18–41 years, predominantly White non-Hispanic/Latino) with a molecular diagnosis of FXS (>200 CGG repeats) treated with BPN14770. Following a 28-day screening period, the treatment regimen involved 2 consecutive 12-week double-blind periods. The study demonstrated that BPN14770 was well tolerated by all participants, with no toxicity observed and plasma levels within the expected range. Daily administration of this treatment significantly improved cognitive function, particularly language, in patients who received the drug. This improvement was assessed using the National Institutes of Health Toolbox Cognition Battery and the Test of Attentional Performance for Children. Additionally, parents/caregivers reported improvements in daily functioning, which were examined based on the following 3 criteria: daily functioning, anxiety/irritability, and language.[9] Efficacy and biomarkers were assessed 6 weeks after the conclusion of the second treatment period. For this purpose, the researchers performed an electroencephalographic evaluation to assess neural activity during treatment. In patients with FXS, consistent with cortical hyperexcitability, an enhanced N1 event-related potential (ERP) response to auditory stimuli has been reported.[9,10] Interestingly, an analysis of the trial data revealed that reductions in N1 amplitude were correlated with the drug's plasma concentration, suggesting that BPN14770 helps reduce neural hyperexcitability. From a clinical perspective, the N1 ERP is associated with language processing and behavioral reactivity. Therefore, the reduction in N1 amplitude observed following treatment may explain the improvements in clinical outcomes observed in the trial[9,10] and may serve as a useful biomarker for future studies.

Table 1 presents the different clinical trials involving the use of BPN14770, both completed and ongoing, and 4 of them concern FXS. Notably, one recent trial (NCT05163808 – Table 1) is evaluating FXS patients aged 9 to <18 years, providing a promising opportunity to assess the impact of zatolmilast on younger patients. Furthermore, 2 clinical trials with BPN14770 (NCT03817684 and NCT06717438) for AD and Jordan's syndrome, respectively, are in the initial phases of implementation (Table 1).

Similarly, the novel PDE2A inhibitor BI 474121 has been evaluated in several phase 1 trials involving healthy volunteers in Japan, the Netherlands, and Germany.

Table 2. Clinical trials involving inhibitors of phosphodiesterase 2A

Trial	Title	Condition	Location	Status
NCT04716894	A Study in Healthy Men to Test How Itraconazole Influences the Amount of BI 474121 in the Blood	healthy	Biberach (Germany)	completed results
NCT04964453	A Study in Healthy Men to Test How BI 474121 is Tolerated	healthy	Tokio Sumida-ku (Japan)	completed results
NCT04672954	A Study in Healthy Men to Test How Different Doses of BI 474121 Are Taken up and How They Influence the Amount of a Molecular Messenger (cGMP) in the Spinal Fluid	healthy	Leiden (the Netherlands)	completed results
NCT04194645	A Study in Healthy Men to Test How the Body Takes up and Tolerates Different Doses of BI 474121, and Whether it Makes a Difference if BI 474121 is Taken as a Tablet or a Drink	healthy	Biberach (Germany)	completed results
NCT04537897	A Study in Healthy Men and Women Who Are Either Between 18–45 Years or Between 65–80 Years to Test How Different Doses of BI 474121 Are Tolerated	healthy	Mannheim (Germany)	completed results
NCT05451095	A Study in Healthy Men to Test Whether BI 474121 Can Reverse the Memory Problems Caused by Ketamine	healthy	–	withdrawn
NCT01981499	A Study of the Safety, Tolerability, Pharmacokinetics, And Effects On Histamine-Induced Wheal Of PF-05180999 In Healthy Adults	migraine	St Paul, Minnesota (USA)	terminated
NCT01981486	A Study Of The Safety, Tolerability, And Pharmacokinetics Of Multiple Doses Of PF-05180999 In Healthy Adults	migraine	–	withdrawn
NCT02584569	Phase 1 TAK-915 Single-Dose Positron Emission Tomography (PET) Occupancy Study	healthy	New Haven, Connecticut (USA)	completed

BI 474121 was initially developed for the treatment of SCZ and AD.[11] 4 phase 1 clinical trials were conducted to evaluate the drug's safety, tolerability, and pharmacokinetics in male and female participants of varying ages and of Caucasian and Japanese origins (Table 2). Although each trial involved a small sample size, the results confirmed that BI 474121 was well tolerated, with no dose-dependent effects, and only mild treatment-related adverse events were reported.[11] To determine whether BI 474121 could affect the central nervous system by crossing the blood-brain barrier, its presence in rat cerebrospinal fluid (CSF) was measured using high-performance liquid chromatography-tandem mass spectrometry. Starting from these preclinical findings, a phase 1 clinical trial was conducted in 24 healthy male participants (aged 18–65 years) and was organized into 3 parts. Part 1 was a randomized, placebo-controlled, single-blind study; part 2 was non-randomized; and part 3 was a randomized open-label study (Table 2). The drug was administered to participants, and the BI 474121 levels were measured in both plasma and CSF. Results showed a dose-dependent increase in the drug's concentration in both tissues. The maximum concentration of BI 474121 in both CSF and plasma was reached simultaneously, except at the lowest dose, where peak concentrations were achieved earlier in the CSF.[12]

As suggested as early as 1993,[2] measuring cAMP and cGMP levels in the tissues of patients with FXS, as well as in induced pluripotent stem cell (iPSC)-derived neurons or brain organoids, could serve as valuable biomarkers for both preclinical and clinical trials. Moreover, these measurements could serve as an important tool for patient stratification. In this context, the reason why cAMP levels—at least in platelets—are not routinely measured in patients with FXS remains unclear. In line with this need, the cGMP levels were measured in the CSF using ELISA in participants of the clinical trial with BI 474121. Results showed increased cGMP abundance in participants who received the drug.[12] These findings provided a direct biomarker of the drug, further supporting the potential of BI 474121 as a therapeutic agent. In sum, drugs capable of reducing the activity of both PDE2A and PDE4D with no toxic effect for humans have been generated, and in the future, they will potentially be useful to treat psychiatric disorders as well as FXS.[3]

Table 2 lists all clinical trials involving PDE2A inhibitors, highlighting the limited amount of research investigating PDE2A as a therapeutic target to date.

Given the limitations of targeting individual PDEs for treating FXS (such as PDE4's selective degradation of cAMP without affecting cGMP[3] and the very low expression level of PDE2A in the cerebellum,[2,5] a brain region implicated in the FXS phenotype[1,2]), combination therapy has been suggested.[13] This approach would be contingent on confirming that PDE4-specific inhibitors do not indirectly reduce cGMP levels. Furthermore, combining PDE4 and PDE2 inhibitors could enable lower doses of each drug, as these enzymes have been shown to exert synergistic effects, potentially minimizing the risk of side effects.[13]

Overall, data obtained so far[1,5,6] suggest that cAMP- and/or cGMP-based therapies require careful consideration of an age-dependent therapeutic window to reach the maximum positive effect of the drug.[3] For example, in *Fmr1*-KO mice, PDE2A expression is higher in the cerebral cortex of adolescent animals compared to those of adults, highlighting potential age-related differences in drug response.[5]

Lastly, these findings raise the question of whether these treatments could be extended to other NDDs. Our recent studies suggest that PDE2A inhibition can improve behavioral deficits in a valproic acid-induced rat model of ASD, highlighting its potential for treating other forms of ASD beyond FXS.[6] Interestingly, the genetic inhibition of PDE2A in a mixed C57Bl/6-129 mouse strain has been reported to improve long-term memory, with aged mice exhibiting enhanced long-term spatial memory.[14] These mice harbor a deletion in the disrupted in schizophrenia 1 (*DISC1*) gene, which is implicated in SCZ, and consistently exhibit behaviors typical of psychiatric disorders.[15] In this context, DISC1 regulates cAMP homeostasis by binding to PDE4B, modulating its activity in response to elevated cAMP levels. DISC1 mutations in patients disrupt the association between DISC1 and PDE4B, resulting in reduced PDE4B activity in the brain. Altered DISC1-PDE4B interaction has been proposed to underlie the symptoms of some cases of depression and SCZ.[15]

In addition to male *Pde2a*$^{+/-}$ mice exhibiting an early onset of NDD, mice with *DISC1* deletion also show sex-dependent alterations in spontaneous locomotor activity, with hyperactivity in male mice and hypoactivity in female mice.[14] Furthermore, PDE4D has been reported to be differentially regulated in the male brain compared with the female brain.[3] These findings suggest that PDE2A and/or PDE4 inhibition—or, likely, the modulation of cAMP and cGMP homeostasis—may produce sex-dependent effects on behavior. This underscores the importance of including both male and female participants in clinical trials, even though ASD, SCZ, and FXS predominantly affect men. Excluding women could limit the broader applicability of future treatment.

In conclusion, as we await the results of a phase 3 clinical trial in male patients with FXS, the potential of PDE2A inhibition-based therapy appears promising. We are optimistic that effective therapies for FXS and other NDDs are within reach.

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DECLARATION OF INTERESTS

The authors have no conflicts of interest to declare.

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