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TITLE: Therapeutic targeting of 3',5'-cyclic nucleotide phosphodiesterases: Moving beyond inhibition

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Abstract

Phosphodiesterases (PDEs), the only known enzymes to degrade 3′,5′-cyclic nucleotides, are being pursued as therapeutic targets for a number of diseases, including those affecting the nervous system, cardiovascular system, fertility, immunity, cancer, and metabolism. Although clinical development programmes have so far focused exclusively on catalytic inhibition, emerging evidence supports therapeutically targeting PDE function in additional ways, such as enhancement of catalytic activity and/or normalization of altered compartmentalization, as well as the potential use of PDEs as disease biomarkers. Importantly, a more refined appreciation of the intramolecular mechanisms regulating PDE function and trafficking is emerging, making these pioneering drug discovery efforts tractable.

Introduction

Conventional 3′,5′-cyclic nucleotide phosphodiesterases (PDEs) are members of a highly conserved

superfamily of enzymes that degrade the canonical cyclic nucleotides 3′,5′-cyclic adenosine monophosphate

(cAMP) and 3′,5′-cyclic guanosine monophosphate (cGMP) (1-6), as well as the non-canonical cyclic

nucleotides 3′,5′-cCMP, 3′,5′-cUMP, 3′,5′-cIMP and c-di-GMP (7-9) (Figure 1). As extensively reviewed

elsewhere (1), there are 11 families of PDEs that are grouped based on the homology of their C-terminal

catalytic domain, and each PDE family has multiple isoforms that differ in terms of the length and complexity

of their N-terminal regulatory domains (Figure 2). PDEs do not simply control the total cellular content of

cyclic nucleotides, but rather create individual pockets or nanodomains of cyclic nucleotide signaling. It is this

subcellular compartmentalization of cyclic nucleotide signaling that enables a single cell to respond discretely

to multiple extracellular and intracellular signals. Thus, PDEs regulate a myriad of physiological processes,

and their dysfunction has been associated with a number of pathophysiological states including those affecting

the nervous system, cardiovascular system, fertility, immunity, cancer, and metabolism (Box 1). Because the

location of a PDE is just as important to its overall function as is its catalytic activity, how the location of a

given PDE isoform can change based on tissue type, age, or disease status—possibly due to factors such as

activation of receptors, alterations in calcium signaling, or elevations in cyclic nucleotides—is of paramount

importance when considering the therapeutic potential of a given PDE isoform (10-19) (Table S1).

Importantly, no two PDE isoforms share the exact same combination of substrate specificity, tissue

expression profile and subcellular localization (Table S1). This is quite important because there are a number of

diseases where compartment-specific defects in cyclic nucleotide signaling have been identified. For example,

the function of soluble guanylyl cyclase, but not particulate guanylyl cyclase, is significantly impaired in

brains of Alzheimer's patients and *in vitro* models of Alzheimer's disease pathology (20-22), which would be

expected to decrease cytosolic pools of cGMP. In contrast, in colon cancer, membrane-bound guanylyl cyclase

3

appears to be dysregulated/suppressed (23) and membrane-enriched PDE10A appears to be overexpressed (24), both of which would decrease membrane-proximal pools of cGMP. That said, cytosolic pools of cGMP may also be decreased in colorectal cancer cells, as PDE5A is also overexpressed in these cells (24), and—at least in heart and brain—PDE5 regulates pools of cGMP that are downstream of soluble guanylyl cyclases (25, 26).

With regard to compartment-specific changes in cAMP signaling, studies examining brain tissue from patients with bipolar disorder show no change in membrane but increased signaling in the cytosol, which is normalized by the classic mood stabilizer lithium (27-32). Other disease states where compartment-specific defects in cyclic nucleotide signaling have been noted include—but are not limited to—erectile dysfunction (33), hypertension (34), cardiac hypertrophy (25, 35), acrodysostosis (36-39), and Huntington's disease (40, 41). The unique substrate/localization profile offered by each PDE isoform offers multiple degrees of freedom in the context of therapeutic targeting. As such, isoform-specific targeting could enable selective restoration of cyclic nucleotide signaling in affected compartments (i.e., provide efficacy) without affecting cyclic nucleotide signaling elsewhere (i.e., avoid side effects).

As reviewed in detail below, there has been and continues to be strong interest in developing PDE-targeted therapeutics for a number of diseases. Unfortunately, the majority of PDE-targeted therapeutics on the market are simply competitive blockers of substrate binding at the catalytic site that lack the ability to selectively target a specific isozyme within a single PDE family or sub-family. That said, novel therapeutic strategies are currently being explored to increase the selectivity and specificity with which PDEs are targeted (e.g., by targeting protein-protein interactions). Further, PDE activators are now being considered as agents for treating select diseases, as are the exploitation of PDEs as biomarkers for diagnosis and/or patient selection (Box 2). Here, we review the clinical successes and failures of PDE inhibitors to date and describe a number of ways in which the field is moving beyond pharmacological inhibition of PDEs for therapeutic gain.

Successes and failures in the clinic.

Several PDE family-selective inhibitors have successfully reached the market, targeting diseases such as psoriasis, COPD and erectile dysfunction. On the other hand, many potent and selective PDE inhibitors have also failed when tested in clinical trials. We will summarize the main achievements and pitfalls in the development of marketed PDE inhibitors to consider factors that currently limit the effectiveness of such therapeutic agents.

Marketed PDE inhibitors (PDEi's)

The non-selective PDE1 inhibitor (PDE1i) vinpocetine is not FDA approved but is available in over-the-counter supplements (e.g., Cavinton or Intelectol, Richter Gedeon; Cognitex, Life Extension) claiming to improve memory and recovery from stroke, likely due to increasing vasodilation (42). As extensively reviewed elsewhere (42), a number of clinical trials have examined the cognition-enhancing effects of vinpocetine—either alone or in combination with another compound (e.g., caffeine or Ginko Biloba)—and have generally found improvement in healthy volunteers, individuals with cerebral hypofusion, and possibly aged individuals, but no improvement in AD patients. Reports of side effects associated with vinpocetine have generally been minimal (Table 1, (43)).

Several PDE3i's are currently marketed, with Cilostazol and Milrinone perhaps the most widely known. Cilostazol was officially approved by the FDA in 1999 for intermittent claudication; however, its off-label uses include secondary prevention of cerebrovascular accident, percutaneous coronary intervention and coronary stent stenosis (c.f., (44)). Although cilostazol improves function across a number of domains, it is also associated with serious side effects (Table 1). As such, cilostazol is contraindicated for patients with severe heart failure, hepatic impairment, or renal impairment (45). Milrinone increases contractility of the heart and is

FDA approved for short-term management of severe congestive heart failure. It is particularly used in the context of end-stage heart failure for patients who prove resistant to optimal therapy and for those awaiting cardiac transplant (46). That said, the clinical utility of milrinone has been limited by significant side effects (Table 1) and the fact that it is cleared through the kidneys (i.e., generally not used in patients with renal failure) (46).

Three so-called "second-generation" PDE4i's are currently FDA approved, with a 4th compound marketed as an over-the-counter supplement. Roflumilast is a PDE4i that is FDA approved as an add-on therapy for chronic obstructive pulmonary disorder (COPD; Table 1). It is considered a third line treatment due to its gastrointestinal and weight loss side effects; however, it is reported to improve sugar metabolism in obese patients and may decrease cardiovascular events in patients with COPD (47). Apremilast is FDA approved for the treatment of moderate to severe plaque psoriasis and psoriatic arthritis (48-50) and is also being tested in a Phase IV trial for active ankylosing spondylitis (see below). The most common side effects for both of these orally-administered second-generation PDE4i's are the same that plagued first-generation PDE4i's (i.e, gastrointestinal disturbances; Table 1), albeit with much improved therapeutic windows (48). Crisaborole is a topically-applied ointment that is FDA approved for treatment of moderate atopic dermatitis in patients >2 years old. Given the topical nature of the drug, gastrointestinal side effects are avoided and, instead, hypersensitivity reactions are the major possible side effect. Clearly, there is an anti-inflammatory theme shared amongst these FDA-approved PDE4i's. Zembrin in a non-selective PDE4 inhibitor (also acts as a 5-HT uptake inhibitor) that is not FDA-approved but is a component of a number of herbal supplements claiming calming or mood-stabilizing properties (e.g., Calm, Doctor's Best; Mood, Procera; Nutri-calm, Nature's Sunshine) (51). fMRI imaging of the amygdala in humans supports an anxiolytic-like effect of Zembrin (51). Further, a Phase I trial found Zembrin was well tolerated and improved cognitive flexibility,

executive function, mood and sleep (52). As noted below, a number of PDE4i's are currently being pursued to improve cognitive functioning (see below).

There are 4 PDE5i's currently FDA approved and marketed in the U.S., with a 2 additional PDE5i's marketed outside the U.S.. All 6 PDE5i's were originally marketed for erectile dysfunction (Table 1), with the most recent approval for avanafil based on its much more rapid onset of action. Sildenafil later received a secondary approval for pulmonary hypertension (contraindicated for pediatric patients, veno-occlusive disease, or sickle cell disease), as did tadalafil. These FDA-approved PDE5i's are generally considered safe and well tolerated, with no increase in cardiac mortality or myocardial infarction (53). Given their shared mechanism of action, it is perhaps not surprising that they share largely similar side effect profiles (Table 1) with headache, flushing, dyspepsia, and vision disturbances being the most common adverse events (53). Interestingly, udenafil (Zydena, Mezzion Pharma)—one of the PDE5i's used to treat erectile dysfunction in Korea, Russia and Philippines (54, 55)--has also been reported to improve cognitive function in patients with erectile dysfunction (56, 57).

The success of a number of marketed PDEi's validates PDEs as appropriate therapeutic targets in many pathological conditions. However, the presence of unwanted side effects resulting from the inability to target individual isoforms is the major limiting factor to success. It is notable that of the 11 PDE families, only agents that attenuate the activity of PDEs 1, 3, 4 and 5 have made it to market, despite significant efforts targeting the inhibition of other PDE families (see next).

Failed PDEi clinical trials

Despite the successes noted above, a number of PDEi's that entered the clinic failed to make it to market. Pfizer's selective PDE2i PF-05180999 was originally considered a candidate for cognitive impairments associated with schizophrenia based on its preclinical profile (58); however, it was brought into the clinic for

migraine. Despite the completion of earlier Phase 1 safety and tolerability studies, additional trials were terminated early due to safety concerns (Table 2). Exisulind inhibits both PDE2A and PDE5A (which are overexpressed in a number of precancerous and cancerous cell types) and triggers apoptosis in precancerous/cancerous cells with minimal effects on healthy cells (c.f., (59, 60)). Despite promising findings in multiple clinical trials, exisulind failed to secure FDA approval in 2000 due to deficiencies in safety and efficacy (Table 2, c.f., (59, 60)).

As noted above, Cilastozol has gained FDA approval for intermittent claudication; however, clinical trials for other indications, such as type 2 diabetes mellitus peripheral neuropathy, have failed (61). That said, cilostazol significantly improved walking speed in these patients, suggesting improved peripheral blood flow as would be expected based on its current approved indication (61).

The PDE4i cilomilast (Ariflo, GlaxoSmithKline) gained FDA approval in 2003 as a second-line treatment for COPD in patients who are poorly responsive to salbutamol (62). However, cilomilast never made it to market due to the severely dose-limiting nature of gastrointestinal side effects (e.g., nausea and vomiting, diarrhea, and abdominal pain (48)). The fact that cilomilast elicited more pronounced side effects relative to the other systemically-delivered PDE4i's described above may be related to preferential inhibition of the PDE4D family relative to the other PDE4 subtypes (62). A novel PDE4i ASP9831 was tested in Phase I and II trials for non-alcoholic steatohepatitis based on preclinical findings, but failed to improve biochemical biomarkers of the disease (63). As target engagement in the organ of interest was not confirmed (63), the reasons underlying the lack of efficacy remain unclear.

A number of clinical trials have attempted to extend therapeutic indications for PDE5i's, but have failed. As reviewed extensively elsewhere (42), a number of trials have tested the effects of sildenafil or vardenafil on various measures of cognition in healthy volunteers or patients with schizophrenia and have largely found no effects (64-68). That said, one report from an Iranian clinical trial did report an improvement

in negative symptoms in patients with chronic schizophrenia when sildenafil was administered in addition to risperidone (69). Several studies were initiated to study sildenafil and/or tadalafil in patients with Duchenne or Becker Muscular dystrophy, with the hopes that the vasodilatory properties of the drugs would improve muscular ischemia; however, clinical trial outcomes have been mixed (Table 2; (70, 71)).

Two PDE9i's have been tested in the clinic for cognition-enhancing effects. Although PF-04447943 was found to be safe and well-tolerated, it failed to improve either cognition or dementia-related behavioral disturbances in a Phase II clinical trial (72). Similarly, BI 409306 was reported as safe and well tolerated in healthy subjects as well as patients with AD or schizophrenia; however, no positive effects on cognition were observed in either patient population (https://www.boehringer-ingelheim.com/PDE9-Inhibition-in-AD, accessed 04/30/19; (73-76)). Despite a failure to improve cognition in patients with schizophrenia, BI 409306 is still being tested in the clinic for prevention of schizophrenia relapse and prevention of first psychotic episode (Table 3). The failure of PDE9i's to improve functioning in AD may be related to the fact that brain PDE9A is enriched in the nucleus and membrane (10) and, thus, is not in a position to directly regulate the cytosolic pools of cGMP that appear to be dysregulated in Alzheimer's disease (20-22).

A number of clinical trials have tested the PDE10i PF-02545920 in schizophrenia and Huntington's disease (Table 2-3). Despite widely replicated efficacy in a number of preclinical assays intended to measure schizophrenia-relevant behaviors (e.g., (77, 78)), PF-02545920 failed to improve symptoms in patients with either exacerbated, stable, or sub-optimally treated schizophrenia (Table 2; (79)). Further, in at least 1 trial, there were reports of motoric side effects such as dystonia (79). Pfizer attempted to reposition PF-02545920 for Huntington's disease based on decreased striatal expression of PDE10A being found in patients (Box 2) and promising efficacy of PDE10i's in preclinical models of the disease (41, 80, 81). Unfortunately, PF-02545920 failed to improve symptoms in patients with Huntington's

(https://clinicaltrials.gov/ct2/show/results/NCT02197130?sect=X70156#outcome1, accessed 04/30/19), and so

efforts for this disease indication were terminated (https://clinicaltrials.gov/ct2/show/NCT02342548, accessed 04/30/19). Several other PDE10i's have also been pursued in the clinic for schizophrenia and/or HD, with some efforts subsequently suspended or terminated (Table 2) and others ongoing (Table 3—see more below).

The unsuccessful translation of these PDEi's from promising preclinical data to human testing suggest that therapeutic approaches targeting PDEs need to extend beyond occlusion of the enzyme's catalytic site. Of particular note are the numerous failures seen in nervous system disorders, even when target engagement was verified. Expression of PDEs in the brain is particularly complex, with PDE isoforms differentially expressed across circuits, cell-types, and subcellular domains (10, 43, 82, 83). Thus, the challenge in evaluating the clinical potential for the next generation of PDE-modulating drugs is to gain novel insights about disease-related changes in PDE structure, function and regulation to understand how PDEs should be targeted in a compartment-specific manner for therapeutic gain.

PDE inhibitors in development.

Given the clinical successes of PDEi's noted above, it is not surprising that traditional PDEi's are still very much being pursued as potential therapeutics, particularly in the context of the central nervous system (CNS), cardiovascular system, reproductive system, cancer and metabolic disorders (Table 3). These efforts include the development of new chemical entities as well as repurposing of existing entities. Thanks to advances in our understanding of structural differences that exist between PDEs, coupled with extensive years-long medicinal chemistry efforts to optimize structure-activity relationships, more recently developed PDEi's have been vastly improved in terms of selectivity and potency and have even demonstrated novel modes of action in some cases (i.e., acting as a negative allosteric modulator instead of direct catalytic inhibitor; (84-87)). Despite these advances in new chemical entities, there is still significant efforts to repurpose older PDEi's. Drug repurposing efforts can be driven by computational or experimental approaches; however, most drug repurposing efforts

have been driven either by a better understanding of pharmacology or by a retrospective analysis of clinical effects that were observed during trials or marketed use of a drug for its original indication (c.f., (88)). Indeed, the PDE5i sildenafil was originally brought into clinical trials for angina but—following observations made by clinicians in that trial—was later repurposed for erectile dysfunction. Drug repurposing has several advantages including reduced risk and substantially reduced timelines and cost (e.g., $300 million for repurposed drug versus $2-3 billion for new chemical entity) due to the fact that the drug would already have passed preclinical and Phase I safety testing and possibly even formulation development (88). That said, there are a number of barriers to recouping expenses incurred by drug repurposing trials, particularly when they are carried forward by an entity other than the patent holder or following the expiration of the original patent (see (88) for further discussion).

Non-selective inhibitor

The non-selective PDE3-4-10-11 inhibitor Ibudilast, which also inhibits glial cell activation, is approved for use in Japan as a bronchodialator and has long been of interest as a therapeutic approach for neuropathic pain and substance abuse/withdrawal (89, 90). Recent clinical trials have tested Ibudilast in the context of amyotrophic lateral sclerosis, pain, as well as opiate, methamphetamine, and alcohol abuse (Table 3) and positive effects have been reported for all trials completed to date (91-94).

PDE1 inhibitors

The broad PDE1 inhibitor ITI-214, which shows picomolar IC50s for PDE1A, PDE1B and PDE1C in enzymatic assays and >1000-fold selectivity versus its nearest neighbor PDE4 (95, 96), is being explored for CNS and non-CNS indications. ITI-214 demonstrates cognition-enhancing effects in rodent models of long-term memory and working memory deficits (95-97), mimicking effects of a dopamine receptor 1 (D1) agonist (97) and occurring

at doses that leave efficacy of the antipsychotic risperidone intact (95). Although the target mediating the cognition-enhancing effects of ITI-214 remains undetermined, PDE1B may be the most likely candidate given its expression in D1-expressing neurons (97) along with the fact that the a PDE1B-selective inhibitor showed similar cognition-enhancing effects (98). ITI-214 was moved into the clinic, with potential applications for cognitive deficits associated with schizophrenia, AD, and Parkinson's Disease (96), with safety and tolerability established in healthy volunteers and patients with schizophrenia (Table 3). ITI-214 is also being explored in the clinic for heart failure (NCT03387215) given its ability to improve cardiac function in dog and rabbit models of heart failure (99) as a consequence of its inhibition of PDE1C (99).

PDE2 inhibitors

Like the PDE1i described above, a number of highly selective PDE2i's have demonstrated cognition-enhancing, anxiolytic and anti-depressant like-effects in animal models (c.f., (100)). TAK-915 entered Phase I trials to correlate plasma exposures with central target engagement with the purpose of informing dose selection for future trials targeting cognitive impairment in schizophrenia (101-103) (Table 3). Looking beyond the brain, PDE2i's may hold relevance for cardiovascular function since elevated PDE2A expression has been found in failing human hearts as well as a large number of animal models of heart disease (c.f., (104)). Further, PDE2i's may hold promise as an antifungal treatment for moderate to severe candidiasis infections, given that genetic deletion of *pde2a* reduces virulence and biofilm integrity of the fungal pathogen (c.f., (105)).

PDE3 inhibitors

Despite its existing FDA approval, the efficacy and safety of cilostazol is still very much a topic of investigation, with 27 active clinical trials registered on clinicaltrials.gov (accessed 04/30/2019) and 54 more drawn to a close within just the past 10 years. Numerous recent Phase IV studies appear focused on

broadening the therapeutic indications of cilostazol to include vasculature-related insults and nephropathies associated with Type 2 diabetes (Table 3), and recent reports suggest largely positive effects (44, 61, 106, 107). One study explored the efficacy of cilostazol in chronic tinnitus, and reported some improvement (108). Several prospective and retrospective studies have examined cilostazol as a primary or adjunctive treatment for cognitive deficits associated with AD and schizophrenia; the majority of which demonstrated positive effects of cilostazol on cognition (see (42) for review). The mechanism by which cilostazol elicits improved cognition has yet to be determined empirically. Given there is very little expression of PDE3A or PDE3B in the brain (83, 109), it may be likely that cognition-enhancing effects of cilostazol are driven by increased cerebral blood flow that comes with chronic—but not acute—dosing as opposed to inhibition of PDE3 isoforms directly in the brain (e.g., (110)).

Novel therapeutic applications of cilostazol are also being explored in preclinical studies. For example, oral cilostazol (30 mg/kg) improved retinal stress, ischemia, and ganglion cell death in a rat model of diabetic retinopathy (111). In addition, PDE3A knockout (KO) mice are infertile (112) and chronic administration of cilostazol blocks pregnancy in naturally-cycling swine (113), suggesting potential utility of PDE3i's for birth control or regulating *in vivo* oocyte maturation in the context of assisted reproduction. Indeed, administration of cilostazol to superovulated mice was able to improve *in vitro* fertilization rates of subsequently harvested oocytes, possibly by virtue of synchronizing the oocyte maturation (114). Because of the promise of PDE3 as a therapeutic target, coupled with concerns over side effect associated with cilostazol, alternative PDE3 inhibitors are currently being sought in hopes of retaining efficacy associated with this target while avoiding side effects (115-117).

PDE4 inhibitors

The PDE4 family is arguably the most studied of all the PDE families. A number of clinical trials have tested

the effect of apremilast for indications beyond psoriasis and arthritis. Two Phase II studies are testing the

efficacy of apremilast in combination with phototherapy to produce repigmentation in patients with Vitiligo

(Table 3). Interestingly, a recent case report showed apremilast dramatically improved repigmentation in a

woman with treatment-resistant Vitiligo (118). Multiple case reports have also described an ability of

apremilast to improve symptoms in patients with treatment-resistant erosive oral lichen planus (119-121),

perhaps motivating the recently registered Phase II study that will test the ability of apremilast to improve

genital erosive lichen planus (Table 3).

Additional indications are also being explored for roflumilast. Phase IV studies showed roflumilast

reduced fat mass and, thus, body weight in obese women with polycystic ovary syndrome (PCOS); however,

these reductions were smaller than those elicited by liraglutide (Table 3; (122, 123)). The PDE4 inhibitor TAK-

648 is being tested in the clinic in patients with Type 2 diabetes, based on preclinical data supporting such an

indication (124). Roflumilast has also been tested for its ability to improve cognition and information

processing in healthy humans, with promising results observed at a dose previously indicated as being devoid

of side effects (125). Patients with stabilized schizophrenia receiving adjuvant roflumilast in a small Phase II

trial showed no improvement in working memory but did show some improvement in verbal learning and

memory (126). Given these positive findings, roflumilast was tested in elderly subjects who demonstrated no

change in spatial memory but improved verbal word memory with roflumilast treatment (127). Numerous

preclinical studies have long pointed to the therapeutic potential of PDE4i's in the context of schizophrenia

and cognition (128-131).

Cognition-enhancing effects have also been reported for the PDE4i HT-0712, which improved long-

term memory for word-lists without serious adverse events in elderly subjects experiencing cognitive decline

(http://www.dartneuroscience.com/press_release/july_22_2008.pdf). The cognition-enhancing effect of HT-

0712 in humans is consistent with previous reports in mice (132, 133). The PDE4D negative allosteric modulator BPN14770 is also being pursued for improving cognitive impairment and has been tested for safety and/or efficacy in healthy elderly subjects, healthy volunteers with scopolamine-induced cognitive impairment, and adult males with Fragile X Syndrome (Table 3). In a press release, BPN14770 was described as having good safety and oral bioavailability and an ability to improve working memory in healthy elderly adults (http://tetradiscovery.com/wp-content/uploads/2016/11/FINAL-Tetra-Phase-1-121616-FINAL.pdf; accessed 04/30/19). These effects in humans are consistent with preclinical studies showing BPN14770 improved a number of behaviors in a mouse model of Fragile-X Syndrome and antagonized the amnestic effects of scopolamine in mice (134, 135). Based on preclinical studies showing anxiolytic and cognition-enhancing effects (136), the PDE4i GSK356278 entered Phase I safety trials for Huntington's disease but adverse events limited the highest dose to that achieving only ~50% occupancy in brain (Table 3; (136)). Other nervous system disorders for which preclinical evidence suggests a therapeutic potential of PDE4i's include ischemic stroke (132, 137-140), traumatic brain injury (141), axon regeneration (142), and substance abuse disorders (both causes and consequences, (143-146)).

McCune-Albright Syndrome is a disease affecting endocrine tissues, skin and bones and is caused by a mutation that results in constitutive activation of the G-protein alpha subunit Gαs (Gαs*). Preclinical studies show that while Gαs* triggers increased cAMP levels in some tissues, it actually results in decreased cAMP levels in other tissues due to a PKA-dependent upregulation of PDE activity, particularly that of PDE1 and PDE4 (129, 147, 148). Consistent with this upregulation of PDE4 activity, the PDE4i rolipram was able to reverse deficits in a Gαs mouse models (129, 130). A clinical trial is currently underway that is using PET imaging to measure PDE4 expression in the brain and peripheral organs of patients with McCune-Albright Syndrome (Table 3).

More recent work is examining PDE4 in the context of cancer. Both preclinical and clinical data suggest roflumilast may exhibit anti-tumor activity for B-cell lymphomas (149). The PDE4i rolipram, in combination with cAMP-elevating agents, has been shown to suppress triple negative breast cancer both *in vitro* and *in vivo* in mice (150). Apremilast similarly induced tumor regression in mouse models of colorectal cancer (151). Perhaps even more interesting, inhibition of PDE4D specifically, either with genetic tools or the PDE4Di Gebr-7b, resensitized chemotherapy-resistant ER-positive breast cancer cells (152). Although PDE4i's have yet to be extensively explored in cancer patients, these early studies provide promise for the chemotherapeutic potential of PDE4is.

PDE5 inhibitors

A number of recent clinical trials have explored additional disease indications that might benefit from the vasodilatory properties of PDE5i's. A cream version of sildenafil has recently been tested in a Phase II study examining female sexual arousal disorder (Table 3) as well as a study in which improved blood flow in patients with secondary Raynaud phenomenon was observed (153). International consortiums are testing sildenafil in intrauterine growth restriction in hopes that the vasodilatory properties of the drug will improve uteroplacental perfusion and, thus, fetal growth (154, 155). Initial results suggest sildenafil improves fetal growth and maternal blood pressure across species, including human, sheep, rabbit, and rodents (156, 157). Several studies have also explored the effects of sildenafil, tadalafil, or vardenafil in the context of metabolic disorders such as Type 2 diabetes and obesity, with the hopes that the vasodilatory properties of these drugs would improve glucose tolerance and insulin signaling and, thus, improve other endpoints such as elevated body weight, nephropathy, and cardiomyopathy (Table 3). Tadalafil improved insulin secretion, endothelial function, and abdominal lean mass content in non-obese men (158), and chronic sildenafil improved glycometabolic control, ameliorated visceral adiposity, and prevented remodeling in diabetic cardiomyopathy

(159-162). That said, vardenafil failed to reduce cardiovascular risk in men with type 2 diabetes (163).

Interestingly, the positive effects of sildenafil on adiposity and diabetic cardiomyopathy are suggested to be independent of sildenafil's vasodilatory properties, rather being mediated by epigenetic signaling and/or a reduction of inflammatory chemokines (159-162). It is important to note, however, that one of the studies examining the effect of sildenafil on glucose homeostasis was terminated early due to safety concerns (Table 2). With regard to other indications related to nephropathy and cardiomyopathy, sildenafil has also been tested against media-induced nephropathy, and tadalafil is being explored in the context of kidney stones and endocrine cardiomyopathy (Table 3). A meta-analysis of older clinical studies suggest PDE5i's could be an effective medical expulsive therapy for distal ureteral calculi, albeit not significantly improved relative to tamsulosin (164). With regard to the brain, two early-stage clinical trials are testing the ability of sildenafil to reverse concussion-related reductions in cerebrovascular reactivity (Table 3).

As described for PDE4i's, a number of trials are exploring the therapeutic potential of PDE5i's as chemopreventives for solid tumors, multiple myeloma, and head and neck squamous cell carcinoma. Early reports suggest combining sildenafil with the chemotherapeutic regorafenib is safe in patients with solid tumors (165). Further, a number of *in vitro* and animal models of colorectal cancer suggest that PDE5i's, either alone or as part of a multi-chemotherapeutic regimen, demonstrate an ability to prevent tumor growth (e.g., (24, 165, 166)). Similarly, reports from both retrospective and prospective trials suggest tadalafil promotes tumor immunity in patients with head and neck squamous cell carcinoma (Table 3, (167, 168)). Although PDE5i's show significant anti-tumor effects, particularly with regard to colorectal cancer, they do not produce complete anti-tumorigenic effects (23). This lack of complete efficacy may be related to the fact that membrane GCs are inhibited in colorectal cancer (23), but PDE5 may be primarily regulating cytosolic GCs (25, 26). Alternatively, it may be related to the fact that both PDE5 and PDE10A—the latter a membrane-enriched PDE (82, 169)—are overexpressed in colorectal cancer cells (24). Indeed, PDE10i's also inhibit growth of colorectal

cancer cells (170, 171); however, when both PDE5 and PDE10 are inhibited, anti-tumor efficacy is improved in preclinical models (24). Although enthusiasm for PDE5i's as chemopreventives is growing (172), it should be noted that PDE5i's similarly prevented prostate carcinogenesis in preclinical models but did not appear to reduce risk or recurrence in clinical studies (173). Perhaps even more concerning, PDE5A appears to suppress melanoma cell invasion in mice (174) yet a recent systematic review and meta-analysis showed that PDE5i's actually increase risk for melanoma and basal cell carcinoma in humans (175).

PDE9 inhibitors

Although PDE9i's thus far have failed in the clinic for brain diseases, they may hold therapeutic potential for cardiovascular diseases. In a mouse model of sickle cell disease, the PDE9i BAY73-6691 had immediate benefits on acute vaso-occlusive events (176), and a Phase 1 clinical trial has recently completed looking at safety, tolerability and PK/PD of the PDE9i PF-04447943 in patients with sickle cell anemia (Table 3). PDE9i's may also hold therapeutic potential for cardiovascular indications as PDE9A expression is upregulated by cardiac hypertrophy and cardiac failure. Indeed, the PDE9i PF-04449613 reverses heart disease in animal models by controlling pools of cGMP downstream of pGCs (25).

PDE10i inhibitors

Despite the PDE10i clinical failures described above, TAK-063 was tested in healthy controls and patients with schizophrenia. In healthy controls, TAK-063 was reported to be safe and well tolerated (177), altering the effects of ketamine on brain activity in healthy controls, particularly in the striatum, substantia nigra, and ventrolateral prefrontal cortex (

https://clinicaltrials.gov/ct2/show/results/NCT01892189?sect=X70156#outcome1, accessed 04/30/19). In patients with schizophrenia, although TAK-063 failed to demonstrate a significant effect on the total PANSS score,

there was a trend that mirrored effects sizes normally seen with risperidone (178). Furthermore, TAK-063 did

significantly improve a number of secondary endpoints relative to placebo (178). It is not entirely clear why

TAK-063 was able to succeed where PF-2545920 failed. While one study suggested that TAK-063 activates the

striatal direct and indirect pathways in a balanced manner and PF-254920 activates the direct pathway more so

than TAK-063 (179), other studies have reported that PF-254920 activates these pathways equally (77, 180). It is

notable that TAK-063—but not PF-254920—increased sensorimotor gating in rodents as measured by prepulse

inhibition of acoustic startle (PPI) (179), suggesting PPI may more accurately predict antipsychotic-like effects

of novel compounds. Preclinical studies are also exploring the therapeutic potential of PDE10i's in the context

of L-DOPA-induced dyskinesias (181) and alcohol abuse disorders (144).

Inhibition of PDE7, PDE8 or PDE11

Studies describing the physiological function of the PDE7, PDE8, and PDE11 families are now emerging;

however, inhibitors have not yet reached the clinic. Like many of the PDE families discussed above, early

research suggests that PDE7i's and PDE8i's may have positive effects in diseases where cognition,

neuroprotection, neuroinflammation, and/or motor function are impaired (e.g., multiple sclerosis and/or

Parkinson's disease; (182-186)). Similarly, PDE11i's may hold potential for treating age-related cognitive

decline (83) or as an adjunctive treatment to improve lithium responsiveness in patients with bipolar disorder

(187, 188). PDE7i's may also hold promise in treating leukemia (189, 190), and PDE8i's may have potential for

treating disorders associated with reduced androgen production in males as PDE8i's, particularly when

applied in combination with PDE4i's, stimulate Leydig cell steroidogenesis (191, 192).

Therapeutic strategies beyond inhibition

Activating PDEs

Although efforts to pharmacologically modulate PDE activity to date have largely focused on inhibition, there are several disease states where PDE activation may be warranted. Tissue-, brain region-, and subcellular domain-specific decreases in PDE expression/activity and/or increases in cyclic nucleotide signaling have been implicated in select disease states, including some age-related deficits (193-195), Huntington's disease (196), social isolation (197), migrane (198-202), retinitis pigmentosa (203), infertility (112), prostate cancer (204), melanoma and basal cell carcinoma (175), cardiac hypertrophy (35, 205), acrodysostosis (36), and polycystic kidney disease (206). Indeed, Mironid have developed PDE4 longform specific activators (mechanism as yet unknown; Table 4) for the treatment of polycystic kidney disease where increased adenylate cyclase activity caused by overexpression of vasopressin V2R receptors results in elevated cAMP levels that drive cyst growth and disease progression (207). There are several natural mechanisms by which PDE activity can be activated (Figure 3), and it is our contention that these avenues could be manipulated phamacologically to trigger PDE activation.

One route to PDE activation is by way of tandem GAF (c**G**MP-specific and stimulated PDE, **A**nabaena adenylyl cyclases, and E. Coli **F**hlA) domains (208) (Figure 3B). Although GAF domains have been identified in over 7400 proteins, in mammals they are only are found in the PDE families 2, 5, 6, 10 and 11 (6, 209). For a vast majority of non-PDE GAF domains the activating ligand is unknown, however for PDEs we know that cyclic nucleotides bind to these pockets (Figure 3). PDE2 and PDE5 are activated when cGMP binds the GAF domain (210-212), and PDE10 is activated by cAMP binding the GAF domain (213). In the context of activation, binding of cyclic nucleotides to GAF domains is thought to cause structural changes that relieve autoinhibition of the PDEs (Figure 3). In contrast, cGMP binding the GAF-A domain of PDE6 enhances protein-protein interactions that inhibit PDE6 catalytic activity (214). This suggests that blocking cGMP binding of the PDE6 GAF domain may provide a means of promoting PDE6 activity. It also suggests it may be possible to both activate and inhibit GAF-containing PDEs with small molecules at a site distinct from the catalytic domain.

Indeed, PDE11A is activated when a cGMP analog—but not cGMP itself—binds the GAF domain (213).

Further, even though cGMP binding of the GAF domain activates PDE5 (210), a number of other types of

molecules that bind the GAF domain inhibit PDE5 in its activated—but not basal—state (215). This is

consistent with the fact that GAF domains are known to bind a diverse array of small molecules that are

unrelated to cyclic nucleotides (208). The fact that GAF domains are only found in PDEs in mammals (6)

makes GAF domains of high interest in the context of drug targeting (216). Importantly, mammalian GAF

domains are sufficiently structurally divergent from one another (e.g., low degree of homology between PDE

families and the tandem GAF domians are preceded by variable N-terminal stretches) as to allow selective

pharmacological targeting of individual PDE families (210). Together, this suggests the GAF domains may

provide an inroad for targeting reagents that selectively activate a given PDE isoform while avoiding off-target

activity.

PKA or PKG phosphorylation of PDE3 (217, 218), PDE4 (217, 219), PDE5 (220), and PDE8 (221) is also

known to activate catalytic activity in a negative feedback loop. In the case of PDE4, for example, catalytic

activity is inhibited when the UCR2 regulatory domain "trans-caps" the catalytic site; thus, occluding cAMP

from reaching the enzymatic core of PDE4 (85, 222) (Figure 3C). PKA phosphorylation of the UCR1 regulatory

domain blocks the ability of UCR2 to trans-cap the catalytic site, which locks PDE4 in the active state (85).

Notably, select PDE4Di's allosterically inhibit catalytic activity by promoting "trans-capping" (141); whereas,

phosphatidic acid activates PDE activity by inhibiting trans-capping in a similar but mutually exclusive

manner to PKA (223-225). Furthermore, the dominant negative peptide "UCR1C", which corresponds to UCR1

sequence, also activates PDE4 activity by inhibiting trans-capping (226). These results provide proof of

principle that activation of PDE4 may be achieved by either small molecules or biologics that prevent UCR2

from adopting a trans-capping conformation.

PDEs may also be activated by manipulating protein-protein binding interactions. PDE6 is unique in the fact that the heterodimeric holo-enzyme includes two inhibitory subunits that span the catalytic pockets of the dimer, thus occluding cGMP from the catalytic site (227) (Figure 3D). Binding of the GTP-bound α-subunit of the heterotrimeric G-protein transducin relieves PDE6 inhibition by binding to the C-terminal region of PDE6 and its inhibitory subunits (228). The full crystal structure of PDE6 is not yet available (229); however, recent cryo-EM work (230) has confirmed the predicted structural organisation of the holo-enzyme, albeit without sufficient detail to inform pharmacological targeting. The success in upregulating PDE6 activity via gene transfer to combat retinitis pigmentosa (203) (see following section) suggests that PDE6 activation could be a viable therapeutic strategy for the treatment of vision loss. As discussed in greater detail below, it may also be possible to increase PDE activity by preventing the binding of PDEs to binding partners that sequester or suppress activity.

Gene therapy

Viral transfer of PDE genes, agents that silence PDE gene expression (e.g. antisense, silencing or microRNAs) (174, 231-235), or gene editing (e.g., Crispr/Cas9) (236) might also prove a useful means of therapeutically targeting individual PDE isoforms (Figure 4). The best characterized PDE gene therapy approach to date targets PDE6 activity in the retina. A loss of transducin-mediated activation of PDE6 results in elevated cGMP levels, which causes the loss of primary rods and, ultimately, vision (237). Expression of recombinant PDE6α in the retina via an adeno-associated virus (AAV-PDE6α) preserved retinal structure, photo-transduction, and vision in retinal degeneration (rd) mice, as did AAV-PDE6β (238, 239). AAV-PDE6α similarly rescued retinal deficits in a mouse model that mimics human retinitis pigmentosa mutations (240). Experiments injecting AAV-PDE6γ into the retina have also proven successful in mice (241). In dogs, delivery of recombinant PDE6α using a tyrosine capsid-mutant AAV8 was able to stabilize cGMP levels and improve survival of

photoreceptor rods and cones in PDE6α-mutant dogs; however, several adverse effects related to the AAV injection were identified (203). The recent development of synthetic AAV vectors that target the retina in non-human primates may provide the answer to these problems in the future (242). Notably, two clinical trials are underway testing the safety and efficacy of PDE6 gene therapy in retinitis pigmentosa (PhI NCT02759952, PhII NCT03328130; clinicaltrials.gov accessed 12/04/18).

A rapidly evolving approach within the gene therapy field is optogenetic medicine, which combines viral delivery of recombinant, light-activated proteins with biomedical devices that emit light of the specific intensity and wavelength needed to activate those proteins (243). With the field of personalized bioelectronic implants quickly evolving, optogenetic-based biomedical approaches are being pursued for neurological diseases, cancer, cardiovascular disease and metabolic disorders (243). Given that optogenetic-based approaches have now entered clinical trials (243), it is worth noting here that light-activated PDEs have been identified in lower organisms (244-246) and engineered in the lab (247). Both are being explored as biological tools in higher organisms. Activating or inhibiting a given PDE by a spatially and temporally restricted light emission, as opposed to a systemically administered pharmacological agent, may prove an ideal approach for treating diseases where cyclic nucleotide signaling is down regulated in one tissue yet upregulated in another (e.g., aging; c.f., (248)). It might also provide a means of avoiding side-effects associated with targeting PDE activity in a specific tissue (e.g., nausea/emesis associated with inhibiting PDE4 in the area postrema).

Targeting location

As production of cAMP is utilized by a variety of different Gs-coupled receptors to transduce signals, compartmentalization of signaling intermediates is crucial to define physiological outcomes specific to each receptor (249). This compartmentalization of cyclic nucleotide signaling is achieved by virtue of PDEs being tethered to a precise cellular location via binding partners (Table S1). Thus, promoting or disrupting isoform-

specific protein-protein interactions may prove a viable approach to therapeutically target PDEs in an isoform-specific manner, a level of specificity that has not been achieved with pharmacological inhibitors to date (Figure 4).

Proof of principle for such an approach first emerged with studies using dominant negative (DN) PDEs, catalytically inactive mutants that would displace their endogenous PDE. Using specific DN-PDE4 isoforms, *in vitro* studies have successfully altered perinuclear cAMP signaling (250), β-arrestin-dependent desensitization of the beta2-adrenergic receptor (251, 252), growth control of prostate cancer cells (204), prostanoid receptor-mediated cAMP signaling (253), glucagon-like peptide-1 release (254), and cAMP gradients at the centrosome (255). DN-PDE4 tools have also yielded beneficial effects *in vivo*. For example, viral delivery of a DN-PDE4A5 to the mouse hippocampus was able to rescue localized cAMP signaling deficits and hippocampus-dependent memory impairments that were caused by sleep deprivation (256-258). In contrast, overexpression of a DN-PDE4B1 in the forebrain of mice did not affect hippocampus-dependent memory, although it did enhance hippocampal long-term potentiation in male mice (259). This finding underscores the importance of understanding the role of specific PDE isoforms, because a homozygous mutation in PDE4B (Y358C) that greatly reduces activity of all PDE4B isoforms by virtue of attenuating interactions with the scaffold protein Disrupted In Schizophrenia 1 (DISC1) improves both long-term potentiation and memory as well as other mood-related behaviors (260). It is interesting to note that nature has developed its own dominant-negative approach with PDE4A7, a PDE isoform that is targeted to specific subcellular compartments but is catalytically dead (261).

One point to consider in adopting a DN approach is the fact that a single PDE isoform can contribute to more than one function in a cell via its participation in multiple distinct signaling complexes, which involve mutually exclusive protein-protein interactions (262) (Table S1; Figure 4). For instance, PDE4D5 is involved in a number of processes common in almost all cells, such as cell

growth, cell orientation, desensitization of Gs-coupled receptors, and inactivating the

phosphorylation of ubiquitous chaperone HSP20 (263). The ability for PDE4D5 to have all these

functions in a cell is a result of it being localized in different compartments by different anchors (e.g.,

RACK1 at leading edge of cells, beta-arrestin at transmembrane receptors, and HSP20 in the cytosol;

Figure4; (263)). It is clear that this is also the case for a number of other isoforms based on proven

protein-protein binding interactions (e.g., in heart tissue/cells, PDE4D3 can bind to either the

ryanodine receptor, HSP20, or an AKAP9/Potassium channel complex—see Table S1) or based on

inference from the fact that the exact same isoform can be found localized to multiple subcellular

domains (e.g., ~50% of PDE11A4 in neurons localizes to the cytosol while 25% is localized to the

nuclear fraction and another 25% to the membrane compartment (82)). Thus, a non-selective DN

approach has the potential to influence multiple domains within the cell. To achieve a compartment-specific

manipulation of a given PDE isoform, one could mutate the binding site(s) that mediates a particular protein-

protein interaction. Mutating isoform-specific binding sites has also proven a useful approach, revealing an

integrin α5-PDE4A5 complex regulates endothelial inflammation (264), a PDE3A1-SERCA complex regulates

myocardium contractility (265), and DISC1-mediated sequestering of PDE4B regulates hippocampal function

(260). An alternative approach is to develop a peptide or small molecule that specifically competes for a given

protein-protein binding site (266). This approach would displace only a specific "pool" of a given PDE isoform,

while leaving the vast remainder unfettered in their respective signaling complexes (Figure 4).

Indeed, a recent review suggests cell-permeable, peptide disruptors effectively manipulate specific

PDE isoforms in a compartment-specific manner (266) and evidence continues to build. More recently, a

PDE4D-FAK disrupting peptide prevented direction sensing and invasion of melanoma cells (267, 268) and a

PDE8A-Raf1 disruptor retarded cancer cell growth promoted by a Ras mutation (221). Interestingly, the same

PDE8A-Raf1 peptide has also been used to target T cell adhesion and migration and was more potent than a PDE8-specific inhibitor in reducing inflammatory signaling (267). The effectiveness of PDE displacement has also been demonstrated *in vivo*, where intraperitoneal injections of a PDE4-HSP20 disruptor significantly attenuated hypertrophy-induced cardiac remodeling (269). Disrupting PDE homodimerization (that is, a PDE monomer binding to itself) may also prove an effective way to target PDE function in a domain-specific manner. Disrupting PDE11A4 homodimerization using a peptide recognizing its GAF-B domain was shown to selectively remove PDE11A4 from membrane-bound complexes but not the cytosol, which may hold utility for improving responsivity to the mood stabilizer lithium (187) or age-related cognitive decline (83). Conversely, a peptide or mutation that could stabilize PDE11A4 homodimerization might prove useful in treating the deleterious psychological effects of social isolation (197). Targeting homodimerization of PDE2, PDE4, or PDE5 may also relocate the enzymes by virtue of changing susceptibility to regulatory post-translational modifications (6, 270). Indeed, nature appears to have taken advantage of dimerization as a mechanism to regulate PDE trafficking. For example, when PDE10A2 heterodimerizes with PDE10A19, PDE10A2 is prevented from trafficking to the membrane as it normally does under conditions of homodimerization (271). Such complex-specific targeting of PDE function may be required to achieve efficacy in absence of unwanted side effects, particularly in cases where multiple subfamily isoforms orchestrate a variety of physiologic responses by virtue of different protein-protein interactions (e.g., targeting various PDE3 isoforms for cardiovascular disease (272)).

Targeting post-translational modifications

As post-translational modifications (PTM) directly regulate PDE activity and location, PTMs could be considered a point of therapeutic control (Figure 5). As described above, PKA or PKG phosphorylation of PDE3 (217, 218), PDE4 (217, 219), PDE5 (220), and PDE8 (221) will stimulate catalytic activity. Phosphorylation

can also influence PDE cellular location by virtue of preventing other PTMs that promote membrane association (e.g., Palmitoylation) or changing protein-protein binding interactions. A great example to illustrate these principals is PDE10A2. PDE10A2 is palmitoylated in its N-terminal region, which directs membrane targeting and trafficking to dendrites (169). If, however, PDE10A2 undergoes isoform-specific phosphorylation by PKA on Thr16 (273), palmitoylation of PDE10A2 is attenuated and the specific membrane localization is lost (169). Interestingly, phosphorylation on the same site also interferes with the scaffolding of PDE10A2 by AKAP150 (274). Hence, although PDE10A catalytic activity is not directly affected by this PTM, cyclic nucleotide levels should increase within this compartment due to the absence of PDE10. Preliminary evidence also suggests that PDE11A4 can similarly be shuttled between membrane and cytosolic compartments by virtue of phosphorylation of N-terminal serines, although this is likely by virtue of altering protein-protein interactions as opposed to a direct insertion into the membrane (275). PKA phosphorylation of PDE4D3 drives an association with the mAKAP signaling complex to evoke rapid signal termination in the muscle compartment (276), which may have therapeutic implications given that polymorphisms in the PDE4D3-mAKAP binding site lead to a higher susceptibility to cardiovascular disease (277). PDE4D enzymes also get phosphorylated by both casein kinase 1 (CK1) and glycogen synthase kinase 3β (GSK3β) in the catalytic region on a motif known as a "phosphodegron" (278). This action increases the affinity of the PDE for a ubiquitin ligase complex (Cullin 1 containing SCF E3 ligase) which promotes proteosomal degradation of the enzyme (278). Hence PDE phosphorylation not only affects activity, localization, and protein-protein interactions, it also regulates protein turnover.

It has been known for some time that increases in PKA activity promote the proteosomal degradation of short-lived proteins, an action that can be enhanced by PDE inhibitors (c.f., (279)). However, we are just starting to understand that the stability of PDEs can themselves be influenced by the ubiquitin-proteosome system (Figure 5). Ubiquitin conjugation is known to target proteins for degradation by the proteasome and

specificity is introduced at the level of E3 ligase-substrate interaction. We now know of multiple instances where PDEs interact definitively with one of the over 600 E3 ligase types to dramatically shorten PDE half-life and this could be a new point at which to direct innovative therapeutics. As mentioned above, PDE4Ds can be degraded by virtue of an SCF E3 (278), whereas PDE4B levels can be down-regulated by a different E3, Smurf2, to promote anti-fibrotic signaling in the liver (280). PDE4D5 can also be targeted for ubiquitin modification by the RING type MDM2 E3 ligase; however, this beta-adrenergic driven ubiquitination of PDE4D does not signal a degradation of the enzyme. Instead, it shifts PDE4 from binding RACK1 to binding β-arrestin (281). PDE4s are similarly regulated by the ubiquitin-like protein SUMO (small ubiquitin-like modifier) (5). SUMO-conjugation tends to alter the location, activity or protein-protein interactions of a protein rather than tagging for destruction via the ubiquitin-proteosome system (282). Unlike ubiquitination, sites of SUMOylation can be predicted in the amino acid sequence of putative substrates as conjugation usually occurs on a lysine residue within the consensus h-K-X-D/E (where h is a bulky hydrophobic and X is any residue) (282). PDE4s from subfamilies A and D contain the consensus motif, whereas subfamilies B and C do not. This adds an extra layer of sub-family-specific regulation as SUMOylation serves both to protect against the inhibitory phosphorylation by ERK MAPkinases (283) and further enhances activity of the PKA phosphorylated longform PDE4 by locking it in the "open" non-UCR inhibited conformation (5).

Two additional PTMs that trigger PDEs for destruction include S-nitrosylation and proline hydroxylation (Figure 5). PDE5 can be S-nitrosylated by NO on Cys220 (284), which targets the enzyme to the proteasome and reduces PDE activity. Under conditions of reduced NO bioavailability, as in heart disease, PDE5 is upregulated due to a loss of this S-nitrosylation-induced degradation (284). Proline hydroxylation has also been identified as a modification that can tag substrates for recognition by E3 ligase complexes (285). In the heart, proline hydroxylases domain-containing proteins (PHDs) hydroxylate surface-associated prolines on

PDE4D enzymes, triggering their degradation (286). In this way, direct binding of PHDs to PDE4s increase cAMP without affecting adenylate cyclase activity.

Challenges

Although this is clearly an exciting time in the PDE field, there is much work that remains to be done. For therapeutics to be efficiently developed, we need to have a more thorough understanding of exactly where cyclic nucleotide signaling is disrupted in a given disease—in which tissue, cell types, and subcellular compartments. We then need to target a PDE in a defined locale, with the understanding that subcellular compartmentalization of a given PDE may vary depending on species, age, tissue type, or disease status (10-19). This consideration is equally important in the evaluation of potential efficacy and potential side effects. To maximize potential efficacy while minimizing potential side effects, one would target a PDE that is enriched, if not exclusively expressed, in the tissue of interest and that controls the same pool of cyclic nucleotides that is altered by the disease. At the same time, efforts to unravel the intramolecular signals responsible for trafficking each PDE also need to continue to inform more sophisticated therapeutic approaches that can preferentially target a given PDE in a given subcellular compartment. Along these same lines, we need to grow our understanding of how to stimulate PDE activity and how to target the PDE catalytic activity of dual-specificity PDEs in a functionally-selective manner (i.e., target only its cAMP- or cGMP-hydrolytic activity, see (216) for further discussion). Perhaps by increasing the specificity of our approach, we can retain efficacy while mitigating the numerous side effects described above that have plagued PDE inhibitors to date.

An additional challenge is gain a better understanding of which physiological/disease processes are governed by PDE regulation of canonical versus non-canonical cyclic nucleotides. Research into the role of non-canonical cyclic nucleotides is rapidly evolving as new techniques and reagents facilitate functional studies (9). Cyclic cytidine monophosphate (cCMP) and cyclic uridine monophosphate (cUMP) are

synthesized by soluble guanylate and soluble adenylate cyclases in mammalian systems, although an as-yet-to-be identified generator likely accounts for the majority of production given the dissociation between sGC/sAC and cCMP/cUMP expression patterns (9). ExoY, a bacterial nucleotidyl cyclase, is known to generate cUMP in non-mammalian systems (7). Hydrolysis of cCMP is catalyzed by PDE7A whereas cUMP is broken down by PDE3A, PDE3B and PDE9A (7). Functionally both nucleotides have been shown to activate PKA/PKG (287), cyclic nucleotide gated channels (288), and cCMP is described as a partial agonist of EPAC (289). In a disease context, the non-canonical cyclic nucleotides play roles in promoting virulence of Pseudomonas aeruginosa infections (290) and triggering apoptosis of cancer cells (291); however much more research is needed to accurately characterize the pathophysiology involving these signaling molecules. Difficult issues facing the field will be defining specific non-canonical cyclic nucleotide signaling systems that are aberrantly regulated in disease, determining the mechanisms by which PDEs might preferentially degrade non-canonical vs. canonical cyclic nucleotides, and visualising the compartmentalisation of non-canonical signalosomes in specific locations within cells and tissues.

Finally, development of PDE-targeted therapeutics faces the same challenges as does all drug discovery—namely the high rate of failure in clinical trials. A recent study suggests that from 2000-2015, only 13.8% of all compounds made it from Phase I to approval (292). When considering success rates for individual indications, we may gain insight into the likelihood that a PDE-targeted therapeutic will achieve success within a given disease area. For example, oncology saw only 3.4% of compounds made it from Phase 1 to approval; whereas, metabolic/endocrinology, cardiovascular, CNS, autoimmune/inflammation, genitourinary, and opthamology saw a success rate of 19.6%, 25.5%, 15%, 15.1%, 21.6%, and 32.6%, respectively (292). This certainly paints a grim picture for pursuing any type of therapeutic in the context of cancer; however, this failure rate also underscores the desperate need to develop novel therapeutic options. It is then important to note that success rates were doubled for cancer compounds when patient selection biomarkers were employed

in the trials; the success rate for cardiovascular compounds similarly benefited (292). Importantly, expression

or activity of PDEs themselves may prove viable biomarkers in this context (Box 2).

Outlook

Although the challenge of targeting localized pools of PDEs for purposes of correcting pockets of aberrant

cyclic nucleotide signaling has proven difficult in the past, there are indications that innovative approaches

and technological advances are making headway (see Table 4 for recent patent activity that includes PDE

activators, biomarkers, and viral approaches). For example, agents that show remarkable selectivity for sub-

families of PDE4 are showing promising results in mouse models of learning and memory and translation to

human disease would be a game changing advance (135). Additionally, novel delivery systems are being

developed that can transport PDE inhibitors to precise tissues or cell types, thereby abrogating complications

associated with systemic distribution (e.g., (293, 294)). In the future, novel delivery systems such as these could

be employed to deliver agents that specifically disrupt the anchoring of single isoforms. Another approach

with potential is the intelligent design of a new generation of PDE inhibitors that preferentially accumulate in

or segregate from certain tissues or organs. The mild side-effect profile of Apremilast is largely due to its

inability to penetrate the brain and engineering of similar restricted distribution profiles may unlock the latent

abilities of other PDE inhibitors. Gene therapy that seeks to abrogate or enhance activity of single PDE

isoforms in a cell type-specific manner may provide a way to combat disease or fight complications associated

with ageing. There is also the possibility that an improved therapeutic window might be achieved by

combining sub-optimal doses of PDEi's with ineffective doses of downstream-target activators, which would

result in an effective combined dose only in tissues and subcellular compartments where both molecules were

present (e.g., (295)). Indeed, PKA, PKG, and Epacs have been implicated as therapeutic targets in their own

right for a number of indications for which PDEi's are being pursued, including diseases of the cardiovascular,

immune, and nervous systems as well as cancer (e.g., (129, 130, 296-300)). Further, several studies in a variety

of tissues have attributed the beneficial effects of PDEi's to the activation of PKA, PKG and/or Epac (e.g., (135,

301-303)). As we learn more about the functional role and molecular interactions of each PDE splice variant,

and how the function and/or localization of an individual variant may be altered in a given disease, it will

become clearer how we can successfully target PDEs in a specific fashion to achieve efficacy while avoiding

side effects. Only with this detailed level of knowledge will we be able to realize the full potential of PDEs as

therapeutic targets.

BOXES

Box 1. Physiological roles of PDEs.

Because PDEs are ubiquitously distributed and are the only enzymes to degrade 3′,5′-cyclic nucleotides, this superfamily of enzymes plays a role in numerous biological processes in health and disease. That said, the biological roles played by a given PDE isoform are unique due to its unique expression pattern at the level of tissue/organ, cell-type and subcellular compartment (Table S1).

Most PDEs families are expressed in the **nervous system** where they regulate neurodevelopment and apoptosis, neuronal excitability, synaptic transmission and neuroplasticity (83, 109). Every brain region expresses more than one PDE, but no two PDEs exhibit the exact same regional distribution (83). For instance, PDE11A is the only PDE with brain expression restricted to the hippocampus. While PDE11A regulates how well an individual responds to the mood stabilizer lithium, it does not regulate basal anxiety- and depression-related behaviors (187). In contrast, PDE4D is expressed in most brain regions and does appear to regulate basal depression-related behaviors (e.g., (304)). PDE1B, PDE2A, PDE7B, PDE8B and PDE10A are enriched in the striatum relative to other brain regions (83), and each has been implicated in regulating basic motor function; whereas, PDE5A and PDE9A have not (for review, see (83, 305)). In the **retina**, PDE6 function is central in mediating activation of the light response in rod and cones photoreceptors, and PDE6 mutations cause photoreceptor degeneration in retinitis pigmentosa (237, 306).

In the **cardiovascular system**, PDE2, PDE3 and PDE4 isoforms control different subcellular pools of cyclic nucleotides to regulate important cardiac functions from myocardial contraction/relaxation to chronic cell growth and survival, and disruption of this PDE signaling has been associated with disease (for review, see (1)). For example, heart failure has been associated with reduced levels of PDE3A and PDE4D, which results in myocyte apoptosis and cardiac arrhythmias, respectively (235, 249).

33

Many **cancers** have been associated with reduced levels of cAMP and/or cGMP secondary to an elevation in PDE activity. For example, chronic lymphocytic leukemia cells exhibit increased PDE7B expression; leukemia, colon cancer, and glioma cells overexpress one or more isoforms of PDE4; and colon cancer cells and adenocarcinmoas exhibit elevated PDE5 activity (23, 307, 308).

Inflammation of numerous tissue types can be increased by a drop in cAMP levels that is caused by an increase in cAMP-PDE activity. For example, activity of PDE4—the predominant cAMP-hydrolyzing enzyme in the immune system—is elevated in the context of various inflammatory diseases, including psoriasis, COPD and asthma (309, 310).

PDEs are also implicated in **reproductive health**. Several isoforms are present in granulosa cells as well as oocytes in preovulatory follicles of mammalian ovary regulating the meiotic cell cycle (311). Furthermore, many PDEs are expressed in cells of the spermatogenic pathway where they may regulate sperm motility (312, 313), and PDE5 is expressed in the contractile tissues of the male excurrent tract and accessory where its increased activity contributes to erectile dysfunction (e.g., (34)).

Box 2. PDEs as disease biomarkers.

PDEs are also being explored as both diagnostic and patient-selection biomarkers. This super family of enzymes, like other genes, can be genotyped from blood samples to assess risk for specific diseases (e.g., high suicide risk, (314); PDE8A, NCT02855918). PDE mRNA and protein expression can be measured *ex vivo* in an isoform-specific manner from biopsied samples (e.g, excised tumors). Further, imaging compounds can be engineered with relative ease to selectively target a given PDE family/sub-family *in vivo.* Thus, PDEs can be explored as biomarkers in diseases where tissue is readily biopsied (e.g,. cancers) and diseases where tissue is not (e.g., diseases of the brain).

Ex vivo biomarkers. Measurement of PDE4D7 is seen as a valuable biomarker for both pre-surgical and post-surgical risk stratification to optimize treatment decisions (314, 315) (Table 4). Studies in patient samples showed that PDE4D7 expression is initially upregulated with the development of primary tumours but then is downregulated when the disease progresses to an androgen-independent state (e.g., in castration-resistant tumours) (316, 317), consistent with *in vitro* reports using prostate cancer cells (204). The analysis of PDE4D7 expression in biopsy/surgery samples has been applied to develop InformMDx™ (licensed by MDxHealth from Philips), a tissue-based prognostic prostate cancer biomarker test to stratify patients by risk of disease progression and secondary tumors and, thus, inform post-biopsy/post-surgery treatment decisions (https://mdxhealth.com/press-release/mdxhealth-launch-agreement-philips-prognostic-prostate-cancer-biomarker; accessed 12/03/18).

PDE3A may also represent a useful cancer biomarker as it is greatly expressed in certain cancer cell types such as squamous carcinoma cell lines or gastrointestinal stromal tumour (GIST) cells (318, 319). Furthermore, cancer cell lines with the highest PDE3A expression proved the most susceptible to the chemotherapeutic effects of PDE3i's (320). Thus, PDE3A expression could qualify as a biomarker for patient selection which improves patient care by reducing exposure to ineffective drugs and accelerates clinical development of novel therapeutic agents by testing them in targeted populations.

In vivo biomarkers. Altered cyclic nucleotide signaling has been implicated in a variety of age-related diseases of the brain (c.f., (248)). PDE10A is widely reported as downregulated in both the striatum and cortex of patients with Huntington's disease, with the extent of PDE10A loss corresponding to the genetic burden associated with the disease (41, 80, 321, 322). A loss of PDE10A expression has also been observed in the basal ganglia of patients with Parkinson's disease (323).

Importantly, highly-specific PDE10A positron emission tomography (PET) tracers shows that

PDE10A expression in HD patients continues to decline over years (41). Thus, PET imaging of

PDE10A could be a useful biomarker for assessing the initial diagnosis and subsequent progression

of these neurodegenerative diseases (324). PET ligands also exist for PDEs 2, 4, 5, and 7 (325).

FIGURE LEGENDS
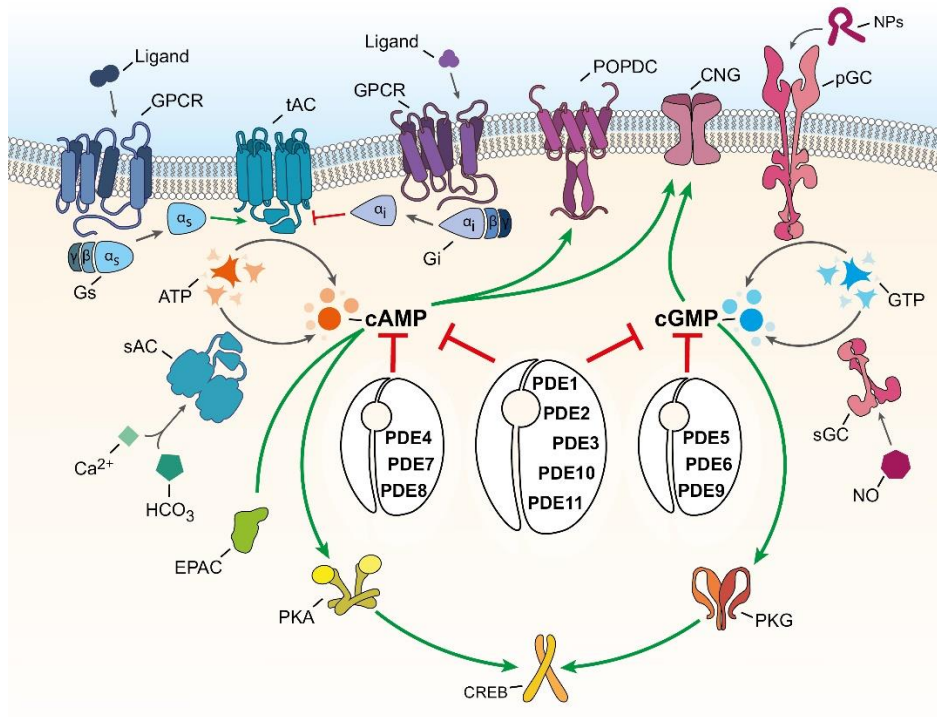
Figure 1. 11 families of PDEs degrade cyclic nucleotides. Both of the canonical cyclic nucleotide signaling

pathways (cAMP and cGMP) are composed of numerous molecules responsible for the synthesis, execution,

and breakdown of their signals. cAMP is synthesized by transmembrane adenylyl cyclases (ACs) that are

activated by Gαs and inhibited by Gαi (326) as well as soluble ACs that are activated by bicarbonate and

calcium (327). cGMP is synthesized by particulate guanylyl cyclases (pGCs) that are activated by natriuretic

peptides and soluble guanylyl cyclases (sGCs) that are activated by nitric oxide (NO) (328). Both cAMP and

cGMP activate cyclic nucleotide gated channels and allosterically modulate activity of select PDEs (6). In

contrast, only cGMP stimulates protein kinase G (PKG); whereas, cAMP activates protein kinase A (PKA), exchange protein activated by cAMP (Epac) and popeye domain-containing proteins (POPDC)(329). Signaling through either the cAMP or cGMP pathways ultimately leads to phosphorylation of a myriad of downstream targets, including the transcription factor cAMP response element binding protein (CREB). In addition to cAMP and cGMP, several PDEs also hydrolyze the non-canonical cyclic nucleotides (not included) cUMP (PDE3A, PDE3B, PDE9A), cCMP (PDE7A), and c-di-GMPa (bacterial PDEs), albeit with much lower affinity (7, 8).
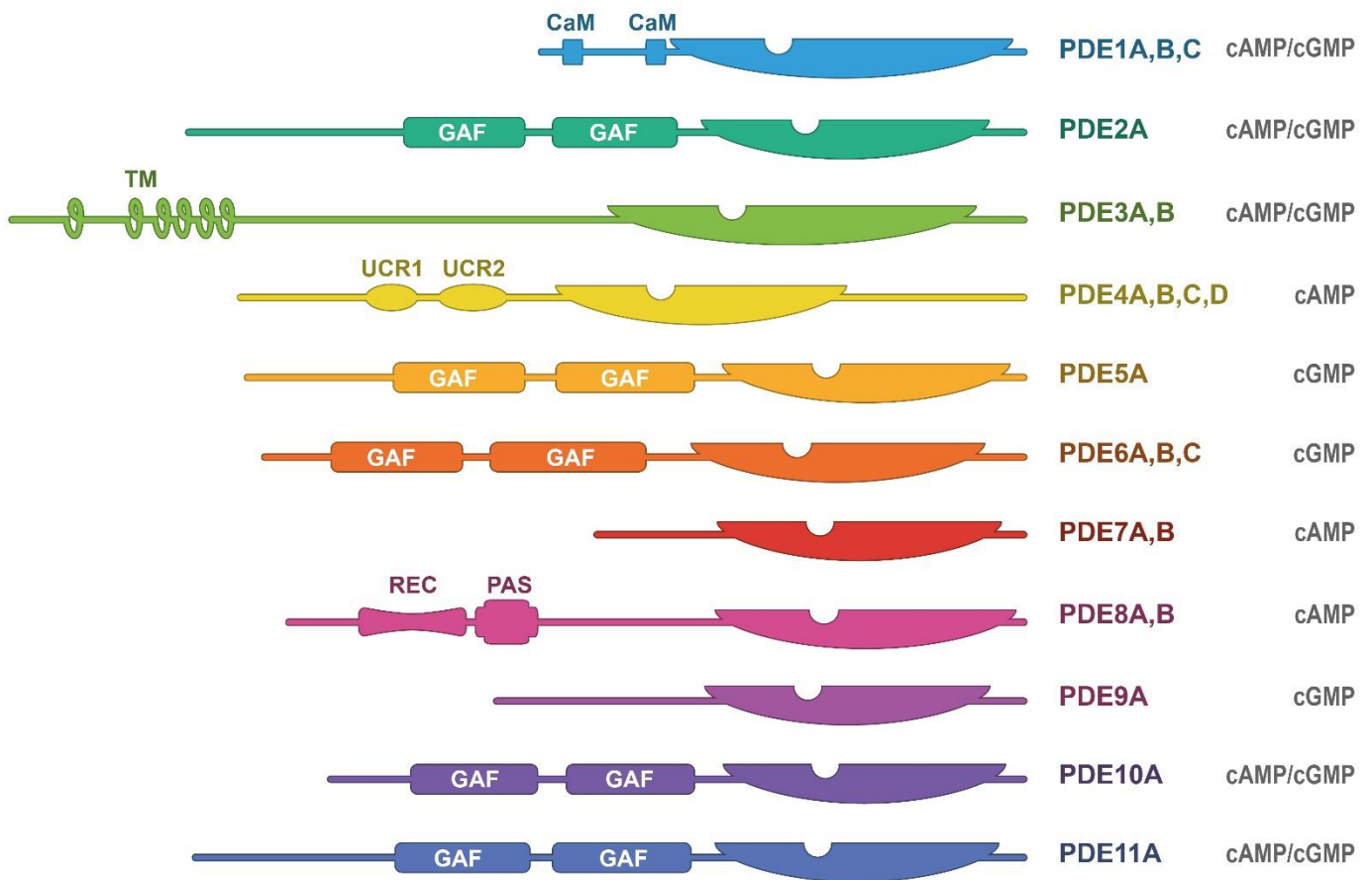
Figure 2. The 21 phosphodiesterase (PDE) genes are grouped into families (name and substrate specificity listed to right of each illustration) based on the homology of their C-terminal catalytic domain (represented as a semi-ellipse). Due to alternate promoters and splicing events, each PDE family has multiple isoforms that differ in terms of the length and complexity of their N-terminal regulatory domains (depicted with different

shapes), which are thought to regulate subcellular trafficking, substrate affinity, and catalytic activity. The relative size and domain distances were drawn based on estimations from the Pfam/uniprot database, with the exception of the REC domain of PDE8 (estimated from (330)) and the second CaM domain of PDE1 (estimated from (313)). Illustrations represent the longest isoform for gene A of each PDE family. CaM, calmodulin-binding domain; GAF, cGMP-binding PDEs Anabaena adenylyl cyclases and E. coli FhlA; TM, transmembrane domain of PDE3; UCR, upstream conserved region; REC, signal receiver domain; PAS, Per-Arnt-Sim domain.

a. Calcium-Calmodulin

b. cNMPs

PDEs Activators

c. Phosphorylation

d. Proteins/peptides
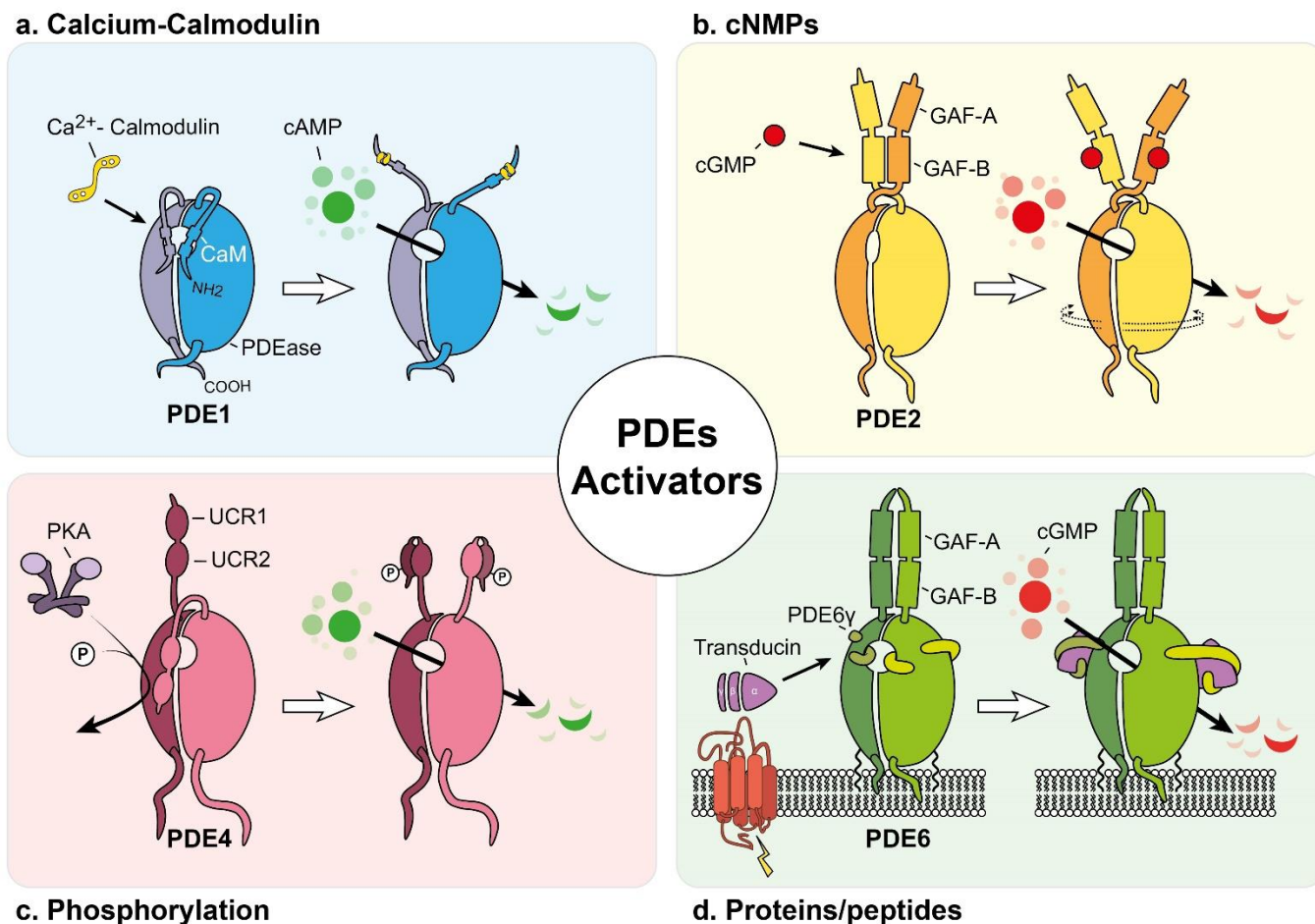
Figure 3. **Mechanisms that activate phosphodiesterase (PDE) catalytic activity. A)** Calcium-calmodulin (CaM) binding to the CaM domains of PDE1 relieves N-terminal auto-inhibition of the catalytic site, thereby promoting enzymatic activity (331). B) Cyclic nucleotides binding to GAF domains of dimeric PDEs (shown here: cGMP binding the GAF-B domain of PDE2) are thought to promote catalytic activity by inducing an outward rotation of the catalytic domains and, thus, enabling access to substrates (332).C) Phosphorylation by PKA or PKG activates several PDEs (6). In the case of PDE4D, phosphorylation of the UCR1 domain by PKA causes UCR1 to bind its own UCR2 domain instead of the catalytic site of the other monomer, thereby locking the enzyme in an active state. **D)** PDE activity can also be modulated by protein-protein binding interactions. One such well-characterized example involves membrane-bound PDE6, where the rhodopsin-activated G-

protein α-subunit transducin displaces the inhibitory PDE6γ C-termini from the catalytic sites on PDE6αβ, thus, promoting cGMP hydrolysis (333).
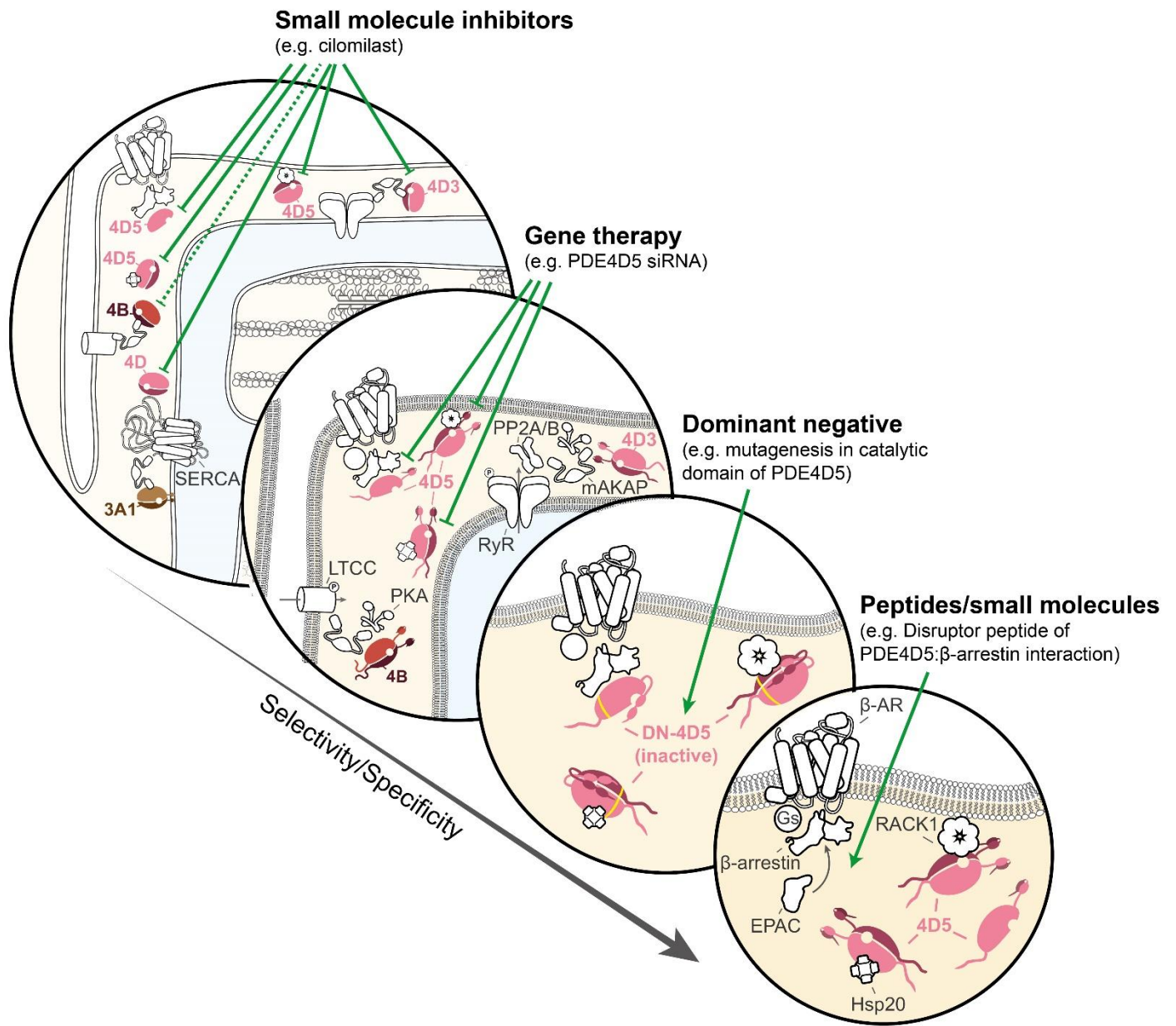
Figure 4. Methods for targeting phosphodiesterase signaling with increasing specificity. Given the vast diversity of PDE isoforms, each with unique tissue expression profiles, subcellular compartmentalization, and protein-protein interactions, it is becoming clear that selective targeting of PDE function will be required to achieve efficacy while diminishing undesirable side effects. **Small molecule inhibitors (e.g.,** cilomilast) are readily developed with family-specific selectivity (e.g., targeting PDE4 over PDE3); however, isoform

specificity remains a challenge (e.g., cilomilast inhibits PDE4D with only 7-fold selectivity versus PDE4B) (334). Conversely, **gene therapy** (i.e., expressing a recombinant construct to knock down or restore expression of a given PDE isoform) and **dominant negative** approaches (i.e., expressing a catalytically inactive PDE4D5 that displaces the endogenous isoform from its interacting partners) can target isoform subtypes exclusively (e.g., targeting PDE4D5 but not PDE4D3 nor PDE4B). That said, dominant negative approaches would influence signalling within all microdomains regulated by that isoform. The greatest specificity can be achieved with **peptide/small molecule binding disruptors** or mutagenesis approaches (not shown) that are designed to prevent a specific PDE isoform from binding a specific partner, thus, altering signaling only within one specific complex. As shown here, a disruptor peptide that specifically prevents the interaction between PDE4D5 and β-arrestin would lead to the recruitment of EPAC1 to β2 adrenergic receptors (βAR), but would leave PDE4D5 regulation of heat shock protein 20 (HSP20) and RACK1 complexes intact (249, 335, 336).
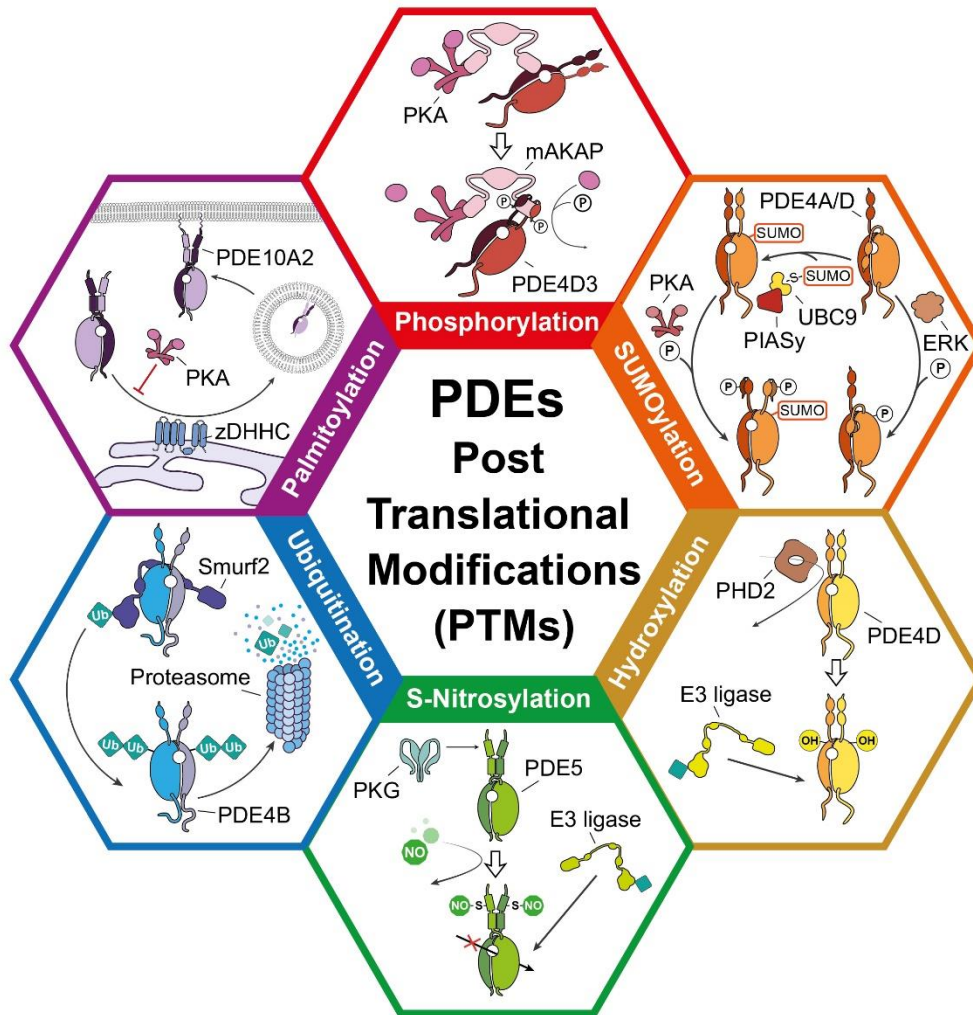
Figure 5. Phosphodiesterase (PDE) regulation by post-translation modification (PTM). Cyclic nucleotide dynamics can be modulated by the addition of different functional groups to PDEs. **Phosphorylation** is a very common mechanism to control PDE activity as depicted by the action of PKA on PDE4D3. Both enzymatic activity and binding affinity of PDE4D3 for mAKAP are increased by PKA phosphorylation, allowing a faster signal termination in myocytes (276). **Palmitoylation** of PDE10A2 in its N-terminal region translocates the enzyme to the plasma membrane, although its phosphorylation by PKA can prevent the action of the palmitoyl acyltransferase (zDHHC) (169). **Ubiquitination** can influence PDEs function through the control of their stability. For example, the E3 ubiquitin ligase Smurf2 targets PDE4B for degradation which leads to the attenuation of liver fibrosis (280). **S-nitrosylation** can also tag PDEs for destruction. Thus, the covalent

incorporation of nitric oxide (NO) to the GAF-A domain of a PKG-phosphorylated and active PDE5, directs

the enzyme to the proteasome (284). **Hydroxylation** of proline residues has emerged as another PTM to

stimulate turnover of PDEs. Prolyl hydroxylase domain protein 2 (PHD2) action on PDE4D increases its

recognition by E3 ligase complexes in cardiomyocytes (286). Finally, **SUMOylation** can intensify the activity of

PDE4A and PDE4D. The SUMO transfer from the E2 conjugase UBC9-E3 enzyme PIASy complex to the PDEs,

enhances their activation by PKA phosphorylation and repress their inhibition induced by ERK activity (5).

Table 1. Marketed PDE inhibitors

Generic name (Trade name)	Indication	Approved (year)	Side effects
Nonselective			
Theophylline	Asthma and Bronchoconstriction	FDA (1979), Canada (1965), approved worldwide	Nausea, vomiting, diarrhea, headache, irritability, flushing and palpitations.
Aminophylline	Asthma and Bronchoconstriction	FDA (1940), Canada (1957), several countries	Stomach pain, diarrhea, headache, irritability, restlessness and insomnia
Oxtriphylline	Asthma and Bronchoconstriction	FDA (1981), Canada (1975), Europe	Stomach pain, nausea, vomiting, diarrhea, headache, irritability, restlessness, insomnia flushing, and increased urination
Dyphylline	Asthma and Bronchoconstriction	FDA (1951), Canada (1962), Europe, Japan	Stomach pain, nausea, vomiting, diarrhea, headache, irritability, restlessness, insomnia flushing, and increased urination
Pentoxifylline	Intermittent Claudication	FDA (1984), Canada (1984), approved worldwide	Belching, bloating, upset stomach, nausea, vomiting, indigestion, dizziness, and flushing, headache
PDE1			
Vinpocetine	Cerebral vascular disorders and memory impairment	Europe, Mexico and Asia. USA as an over-the-counter dietary supplement	Flushing, rashes, and minor gastrointestinal disturbances

PDE3

Cilostazol	Intermittent Claudication	FDA (1998), EMA (2000), Japan (1988), Asia and South America	Headache, palpitations, diarrhea, dizziness, nasal irritation and pharyngitis
Milrinone	Congestive Heart Failure	FDA (1987), EMA (2016), Canada (1995), Japan, China	Ventricular/supraventricular arrhythmias, hypotension and headache
Amrinone	Congestive heart failure	FDA (1984), Canada (1984), China	Thrombocytopenia, nausea, diarrhea, hepatotoxicity, arrhythmias and fever
Enoximone	Congestive heart failure	Some countries in Europe	Headache, diarrhoea, insomnia, hypotension, vomiting, nausea, tachycardia and arrhythmias
Olprinone	Heart failure	Japan (1996)	Cardiac dysrhythmias and thrombocytopenia
Pimobendan	Heart failure	Japan (1994)	Headache, palpitation, nausea and ventricular arrhythmias
Anagrelide	Thrombocythemia	FDA (1997), EMA (2004), Canada (1998), several countries	Headache, diarrhea, unusual weakness/fatigue, hair loss, nausea and dizziness

PDE4

Roflumilast	Chronic Obstructive Pulmonary Disease (COPD)	FDA (2011), EMA (2010), Canada (2010), Russian Federation, South Korea	Diarrhea, weight loss, nausea, headache, insomnia, decreased appetite
Apremilast	Psoriasis and psoriatic disorders	FDA (2014), EMA (2014), Canada (2014)	Diarrhea and vomiting, weight loss, mood changes
Crisaborole	Moderate Atopic dermatitis (patients >2 years old)	FDA (2016), Canada (2018)	Hypersensitivity reactions of the skin
Drotaverine	Functional bowel disorders and alleviating pain caused by smooth muscle spasm	Asia and Eastern European countries	Fainting, nausea, vomiting and dry mouth
Ibudilast (also inhibits PDE3, 10, 11)	Asthma and dizziness related to cerebral infarction	Japan (1989), South Korea (2002)	Nausea, diarrhea and abdominal pain, depression, rash and fatigue
	Allergic conjunctivitis	Japan (2000)	

Tofisopam (also inhibits PDE10, 3, 2A)	Anxiety	Japan (1985), several European countries (Hungary, 1974), Jamaica, Thailand and Argentina (1982)	Nausea, stomach discomfort, dry mouth, skin rash, insomnia, vomiting and drowsiness
PDE5			
Sildenafil	Erectile Dysfunction	FDA (1998), EMA (1998), Canada (1998), approved worldwide	Headache, flushing, dyspepsia, nasal congestion, and impaired vision, including photophobia and blurred vision
	Pulmonary arterial hypertension (PAH)	FDA (2014), EMA (2005) Canada (2006)	
Vardenafil	Erectile Dysfunction	FDA (2003), EMA (2003), Canada (2004), several countries	Headache, flushing, and dyspepsia
Tadalafil	Erectile Dysfunction, benign prostatic hyperplasia	FDA (2003), EMA (2002), Canada (2003), approved worldwide	Headache, dyspepsia, back pain and myalgia
	PAH	FDA (2009), EMA (2008), Canada (2010)	
Avanafil	Erectile Dysfunction	FDA (2012), EMA (2013)	Headache, flushing, and nasopharyngitis
Udenafil	Erectile dysfunction and hypertension	South Korea (2005), Russian federation (2008), Thailand, Colombia, Malaysia and the Philippines	Headache, dizziness, reddening, nasal congestion, dyspepsia and impaired vision
Mirodenafil	Erectile Dysfunction	South Korea (2007)	Flushing, headache, nasal congestion, eye redness, nausea and dizziness
Dipyridamole	Postoperative thromboembolism	FDA (1961), Canada (1962), several European countries, Japan, Taiwan, Russian Federation	Headache, dizziness, nausea, diarrhea, muscle pain and vomiting
PDE10A			
Papaverine	Visceral spasm and vasospasm and erectile Dysfunction	FDA, Canada (1951), approved worldwide	Ventricular tachycardia, diarrhea, somnolence, vertigo, flushing and headache

Table 2. Clinical trials involving PDEs inhibitors that <u>failed to reach the market for the described indication</u>

Compound / Manufacturer	Indication	Phase / Status	Clinical trial ID	Failure cause
PDE2				
PF-05180999 / Pfizer	Healthy volunteers (schizophrenia)	Phase I / Completed 2011	NCT01429740	Safety concerns
	Healthy volunteers	Phase I / Completed 2012	NCT01530529	
	Migraine	Phase I / Terminated early 2014	NCT01981499	
	Migraine	Phase I / Withdrawn prior to enrollment 2014	NCT01981486	
PDE2/5				
Exisulind (Aptosyn) / Cell Pathways	Breast cancer neoplasms and metastases	Phase I/II / Completed 2003	NCT00037609	Safety and efficacy deficiencies
	Breast cancer	Phase II / Completed 2008	NCT00039520	
	Non-small cell lung cancer	Phase I/II/III / Completed 2003-2007	NCT00072618, NCT00085826, NCT00041314	
	Small cell lung cancer	Phase II / Completed 2008	NCT00041054	
	Prostate cancer and prostatic neoplasms	Phase II / Completed 2006-2011	NCT00078910, NCT00166478, NCT00166426, NCT00052845, NCT00283803	
	Melanoma	Phase II / Completed 2011	NCT00841204	
PDE3				
Cilastozol (Pletal) / Otsuka Pharmaceuticals	Type 2 diabetes polyneuropathy	Phase IV / Completed 2009	NCT01076478 (61)	Lack of efficacy
PDE4				
ASP9831 / Astellas	Non-alcoholic	Phase II / Completed	NCT00668070	Lack of

Pharma	steatohepatitis (NASH)	2010	(63)	efficacy

PDE5				
Sildenafil (Viagra or Revatio) or Tadalafil (Cialis or Adcirca) / Pfizer and Eli Lilly, respectively	Duchenne Muscular Dystrophy (DMD)	Early Phase I/Phase I / Completed 2013	NCT01359670, NCT01580501 (70)	==Lack of efficacy==
Sildenafil (Viagra or Revatio) / Pfizer	DMD and Becker Muscular Dystrophy (BMD)	Phase II / Terminated early 2014	NCT01168908	Safety concerns
	Impaired glucose tolerance	Phase IV / Terminated early 2016	NCT01409993	
Tadalafil (Cialis or Adcirca) / Eli Lilly	BMD	Phase IV / Completed 2012	NCT01070511 (71)	Lack of efficacy
	DMD	Phase III / Terminated early 2017	NCT01865084	
Vardenafil (Levitra) / Bayer/GSK	Type 2 diabetes	Phase II / Completed 2014	NCT02219646 (163)	Lack of efficacy

PDE9				
BI 409306 / Boehringer Ingelheim	AD	Phase II / Completed 2017	NCT02240693, NCT02337907 (76)	Lack of efficacy
PF-04447943 / Pfizer	AD	Phase II / Completed 2010	NCT00930059 (72)	Lack of efficacy

PDE10				
PF-02545920 (a.k.a. MP-10) / Pfizer	Schizophrenia	Phase I / Completed 2007	NCT00463372	Lack of efficacy
	Schizophrenia	Phase II / Terminated early 2008	NCT00570063	
	Healthy volunteers (glucose metabolism)	Phase I / Completed 2011	NCT01103726	
	Schizophrenia	Phase II / Completed 2011	NCT01175135 (79)	
	Schizophrenia	Phase I / Terminated early 2012	NCT01244880	
	Schizophrenia	Phase I / Completed 2013	NCT01829048	

Compound / Manufacturer	Indication	Phase / Status	Clinical trial ID	
	Schizophrenia	Phase II / Terminated early 2014	NCT01939548	
	Healthy male volunteers (PET imaging)	Phase I / Completed 2014	NCT01918202	
	Huntington's Disease	Phase II / Completed 2015-2016	NCT01806896, NCT02197130	
	Huntington's Disease	Phase II / Terminated early 2017	NCT02342548	
OMS643762 / Omeros	Schizophrenia	Phase II / Completed 2014	NCT01952132	Safety concerns / Lack of efficacy MP-10
	Huntington's Disease	Phase II / Terminated early 2016	NCT02074410	
PBF-999 / Palobiofarma	Huntington's Disease	Phase I / Completed 2015	NCT02208934	Change in therapeutic indication (cancer)
	Huntington's Disease	Phase I / Terminated early 2016	NCT02907294	

Reported on Clinicaltrials.gov (accessed 04/30/19). Information is included for all clinical trials involving molecules whose pursuit was terminated after April 2009.

Table 3. Selected clinical trials involving PDEis pursued for new indications

Compound / Manufacturer	Indication	Phase / Status	Clinical trial ID
PDE3, 4, 10, 11			
Ibudilast (AV-411, MN-166) / MediciNova	Opioid withdrawal	Phase II / Completed 2012-2017	NCT00723177, NCT01740414
	Methamphetamine-dependence	Phase I / Completed 2013	NCT01217970 (91, 92)
	Alcohol use disorder	Phase I / Completed 2015	NCT02025998 (94)
	Alcohol use disorder	Phase II / Recruiting	NCT03489850

	Opioid abuse	Phase II / Completed 2017	NCT01740414 (93, 337)
	Amyotrophic lateral sclerosis (ALS) (Biomarker study)	Phase II / Active, not recruiting	NCT02714036

PDE1			
ITI-214 / Intracellular Therapies	Schizophrenia	Phase I / Terminated early 2014	NCT01900522
	Parkinson's Disease	Phase I/II / Completed 2018	NCT03257046
	Healthy volunteers (CNS engagement)	Phase I / Recruiting	NCT03489772
	Systolic heart failure	Phase I/II / Recruiting	NCT03387215
Vinpocetine / Rxmidas Pharmaceuticals/ Nootrobox	Ischemic stroke	Phase II/III / Completed 2013-2015	NCT01400035, NCT02878772 (338)
	Cognition enhancement	Not Applicable / Completed 2017	NCT02857829

PDE2			
TAK-915 / Takeda	Healthy volunteers (PET imaging, schizophrenia)	Phase I / Completed 2016	NCT02584569
	Healthy volunteers	Phase I / Completed 2016	NCT02461160

PDE3			
Cilostazol (Pletal) / Otsuka Pharmaceuticals	Type 2 diabetic atherosclerosis	Phase IV / Completed 2010-2012	NCT01252056, NCT00823849 (339)
	Chronic tinnitus	Not applicable / Completed 2013	NCT01378650 (108)
	Alzheimer's Disease	Phase IV / Completed 2013	NCT01409564 (340)
	Atherosclerotic events in type 2 diabetes	Phase IV / Unknown	NCT00886574
	Mild Cognitive Impairment	Not applicable / Completed 2015	NCT01872858
	Ischemic events in type 2 diabetic artery obstruction	Phase IV / Recruiting	NCT02983214
	Antiplatelet aggregation in type 2 diabetes	Phase IV / Active, not recruiting	NCT03248401
	Antiplatelet aggregation in	Phase IV / Recruiting	NCT02983214

	type 2 diabetes		
	Antiplatelet aggregation in type 2 diabetes	Phase IV / Unknown	NCT02933788
PDE4			
Apremilast (Otezla) / Celgene Corp.	Vitiligo	Phase II / Active, not recruiting	NCT03036995, NCT03123016
	Lichen Planus of Vulva	Phase II / Not yet recruiting	NCT03656666, NCT03836885
BPN14770 / Tetra Discovery	Alzheimer's Disease	Phase I / Completed 2016-2017	NCT02840279, NCT03030105
	Alzheimer's Disease	Phase II / Not yet recruiting	NCT03817684
	Fragile X Syndrome (FXS)	Phase II / Recruiting	NCT03569631
Crisaborole (Eucrisa) / Pfizer	Morphea	Phase II / Recruiting	NCT03351114
GSK356278/ GlaxoSmithKline	Huntington's Disease	Phase I / Completed 2012	NCT01573819, NCT01602900
Roflumilast (Daxas or Daliresp) / Astrazeneca	Polycystic Ovary Syndrome	Phase IV / Completed 2014	NCT02037672, NCT02187250 (122, 123)
	Cognitive deficits in schizophrenia	Phase II / Completed 2015	NCT02079844 (126)
	Cognition (Dementia)	Phase II / Completed 2013-2015	NCT01433666, 2013–001223-39 (EudraCT) (125, 127, 341)
	Insulin and Blood Sugar Levels in Prediabetic Overweight and Obese Individuals	Phase I/II / Completed 2017	NCT01862029 (342)
HT-0712 / Dart Neuroscience	Age-associated memory impairment (AAMI)	Phase II / Completed 2015	NCT02013310
N/A	McCune-Albright Syndrome (PET imaging)	Phase I/II / Recruiting	NCT02743377
TAK-648 / Takeda	Type 2 diabetes	Phase I / Completed 2015	NCT02480439, NCT02684396, NCT02430870
Zembrin / ND	Aged Individuals	Phase I / Completed 2012	NCT01805518 (52)
PDE5			

ND	Contrast Media-induced Nephropathy (CMN)	Not Applicable / Unknown	NCT01564303
ND	Diabetic nephropathy	Not Applicable / Unknown	NCT01566006
Sildenafil (Viagra or Revatio) / Pfizer	Diabetic cardiomyopathy (type 2 diabetes)	Phase IV / Completed 2009	NCT00692237 (159-162)
	Metabolic syndrome (Skeletal muscle insulin signaling)	Phase IV / Completed 2016	NCT02129725
	Urolithiasis/urinary stones	Phase IV / Active, not recruiting	NCT02519153
	Migraine aura	Early Phase I / Recruiting	NCT02795351
	Solid tumors	Phase I / Active, not recruiting	NCT02466802 (165)
	mTBI or concussion	Phase I / Recruiting	NCT03417492, NCT02990078
Sildenafil cream (SST-6007) / Strategic science and technologies/Dare	Sexual arousal disorder	Phase II / Completed 2017	NCT02570282
Tadalafil (Cialis or Adcirca) / Eli Lilly	Type 2 Diabetes (Postprandial Hyperglycemia)	Phase I / Terminated early 2011	NCT01238224
	Head and neck squamous cell carcinoma	Phase II / Completed 2012-2016	NCT00894413 (167)
	Head and neck squamous cell carcinoma	Phase II / Active, not recruiting	NCT01697800
	Obesity	Phase IV / Completed 2015	NCT02554045 (158)
	Insulin secretion/ sensitivity in obesity	Phase IV / Completed 2015	NCT02595684 (343)
	Aortic stenosis (AS) left ventricular remodeling/hypertrophy	Phase IV / Terminated early 2017	NCT01275339
	Multiple myeloma (MM)	Phase II / Terminated early 2017	NCT01374217
	Insulin Resistance in Type 2 Diabetes	Phase II / Recruiting	NCT02601989
	Diabetic cardiomyopathy (DC)	Phase IV / Recruiting	NCT01803828
	Endocrine cardiomyopathy	Phase II / Recruiting	NCT02611258 (344)

	in Cushing Syndrome (CS)		
	Access sheath deployment (Nephrolithiasis/kidney stones)	Phase IV / Enrolling 2019	NCT03229889
	Lower urinary tract symptoms (prostatic hyperplasia)	Phase IV / Recruiting	NCT02252367
	Obesity-related cardiometabolic dysfunction	Phase II / Recruiting	NCT02819440
	Anti-tumor Mucin 1 vaccine efficacy in head and neck squamous cell carcinoma (HNSCC)	Phase I/II / Recruiting	NCT02544880
	Small Vessel Disease	Phase II / Active, not recruiting	NCT02450253 (345)
PDE9			
PF-04447943 / Pfizer	Stable sickle cell disease	Phase I / Completed 2016	NCT02114203 (346)
BI 409306 / Boehringer Ingelheim	Healthy volunteers	Phase I / Completed 2011-2018	NCT01343706, NCT01493570, NCT01505894, NCT01611311, NCT01841112, NCT02597998, NCT03505151, NCT02222168, NCT02438683 (74, 347, 348)
	Alzheimer's disease, schizophrenia	Phase I / Completed 2017	NCT02392468
	Schizophrenia	Phase I / Completed 2013-2016	NCT01892384, NCT02281773 (73, 75)
	Schizophrenia or attenuated psychosis syndrome	Phase II / Recruiting	NCT03351244, NCT03230097
	Drug-drug interactions	Phase I / Completed 2016-2017	NCT03151499, NCT03193307, NCT02853136, NCT02635750, NCT02248259
PDE10			

[18F]MNI-659	Huntington's Disease (PET imaging)	Early Phase I / Completed 2016/2017	NCT02061722, NCT02956148, 2012–003808-13 (EudraCT) (349)
PBF-999 / Palobiofarma	Cancer	Phase I / Recruiting	NCT03786484
EVP-6308 (now FRM-6308) / En Vivo Pharmaceuticals (now Forum Pharmaceuticals)	Schizophrenia	Phase I / Completed 2014	NCT02001389, NCT02037074
RO5545965 / Hoffmann-La Roche	Schizophrenia	Phase I / Completed 2013-2017	NCT01923025, NCT01711801, NCT01864226, NCT02019329, NCT02824055
TAK-063 / Takeda	Schizophrenia	Phase I / Completed 2014	NCT02370602, NCT01892189, NCT01879722 (177)
	Schizophrenia	Phase II / Completed 2016	NCT02477020 (350)

Reported on Clinicaltrials.gov (accessed 04/30/19) with an end date after April 2009
PK/PD, Pharmacokinetics and Pharmacodynamics; ND, not described

Table 4. Selected recent patents involving PDEs

Patent #	Subject	Assignee	Author	Priority Date	Publication Date
CN108904493 A	PDE4 inhibitor and purpose for preparing novel anti-inflammatory drugs	Hu Y	Hu Y	12/08/2018	30/11/2018
WO2018167142	Treatment of idiopathic pulmonary fibrosis [with a PDE4 inhibitor]	Takeda GMBH	Hanauer G, Nikam S, Hazama M	16/03/2017	20/09/2018
CN107163052 A	Immunodetection method for various PDE5 inhibitor drugs	Univ South China Agricult	Shen Y, Hua Y, Xu Z, Yang J, Wang H, Sun Y, Lei H	18/04/2017	15/09/2017
CN107412214 A	Application of PDE4 Inhibitor	Guangzhou Lanssonpharm	Xu L	31/07/2017	01/12/2017

	[FCPR16 for the treatment of PD]	Jianzhi Tech Co Ltd			
US2019046528	Method of preventing hair loss or promoting hair growth by using PDE3 inhibitor	Seoul Nat Univ Hospital	Kwon O, Choi HI, Jo SJ, Kim KH	08/08/2017	14/02/2019
JP2019047763 A	Rhodopsin PDE [as an optogenetic tool for light control of intracellular cyclic nucleotides]	Nagoya Institute Of Technology	Kandori H, Tsunoda SP, Yoshida K	12/09/2017	28/03/2019
US2018369188	Application of PDE4 inhibitor ZL-N-91 in preparation of medications for lung cancer proliferation and metastasis	Guangzhou Sinogen Biomedical Tech Ltd	Zhao AZ, Gong S, Lin Y, Li F, Li X	05/02/2016	27/12/2018
CN107287239	Gene therapy vector and medicine for retinal pigment degeneration [adenovirus encoding PDE6B]	Shenyang Fuming Biological Tech Co Ltd	Pang J	11/04/2016	24/10/2017
CN107312824	Applications of PDE3A in determination of tumor treatment effect of Anagrelide	Shanghai Inst Materia Medica Cas	Yu Q, Liu J	26/04/2016	03/11/2017
CA2975049	PDE inhibitors to repair brain and/or retinal injury in human newborns	Wintermark P	Wintermark P	10/08/2016	10/02/2018
AU2017317575	Treatment of nonalcoholic fatty liver disease [with PDE4 inhibitors]	Takeda GMBH	Hanauer G, Nagabukuro H, Amano Y	26/08/2016	28/03/2019
AU2017330067	T cells with increased immunosuppression resistance [expressing PDEs for the treatment of cancer]	Adaptimmune Ltd	Laugel B, Skibbe K	23/09/2016	18/04/2019
WO201806070 4	Compounds and their use as PDE4 activators [for the treatment of disorders requiring a reduction of cAMP]	Mironid Ltd	Adam JM, Adams DR	28/09/2016	05/04/2018
CN108135886	PDE4 inhibitor for the treatment of diabetic nephropathy	Takeda GMBH	Hanauer G, Vollert S, Hazama M, Matsuo T	29/07/2015	08/06/2018
US2018221373	Method of treating insomnia [with PDE5 inhibitors]	Rosenberg LI	Rosenberg LI	16/09/2015	09/08/2018

WO201707029 3	PDE9 inhibitor and levodopa therapy [for treating PD or Parkinsonism]	Ironwood Pharmaceuticals Inc	Leventhal L, Townsend TM	20/10/2015	27/04/2017
WO201607554 3	Treatment of multiple sclerosis with combination of Laquinimod and a PDE4 inhibitor	Teva Pharma, Piryatinsky V, Kaye J	Piryatinsky V, Kaye J	13/11/2014	19/05/2016
AU2014307802	Treatment of cognitive impairment with combination therapy [of a PDE4 inhibitor and an Acetylcholinesterase inhibitor]	Univ Maastricht	Yamada T, Prickaerts J, Van Duinen M, Sambeth A, Blokland A	16/08/2013	10/03/2016
US2017326145	Composition comprising PDE5 inhibitor for inhibiting apoptosis of nerve cells	Aribio Inc, Sk Chemicals Co Ltd	Kim MH, Choung JJ, Ku SK	04/12/2012	16/11/2017
JP2016199574	Novel composition for the treatment of cystic fibrosis [with a PDE4 inhibitor and a prostacyclin]	Scipharm Sarl	Freissmuth M, Gloeckel C, Koenig X, Keuerleber S	07/02/2011	01/12/2016
HUE036489	PDE inhibitors for transvaginal use in the treatment of infertility	Prokrea Bcn S L	Pardina Palleja MC, Vaz-Romero Una MA	23/06/2011	30/07/2018
US2018289632	Treatment of addiction and impulse-control disorders using PDE7 inhibitors	Omeros Corp	Demopulos G, Gaitanaris G	08/11/2010	11/10/2018
JP2015212262	PDE1 inhibitors for ophthalmic disorders	Intra Cellular Therapies Inc	Davis R, Fienberg AA	25/02/2009	26/11/2015
US2017051291	RNAi-mediated inhibition of PDE4 for treatment of cAMP-related ocular disorders	Arrowhead Pharmaceuticals Inc	Yanni JM, Chatterton JE, Gamache DA, Miller ST	28/12/2005	23/02/2017
US2018185402	Use of PDE3 inhibitors for the reduction of heart size in mammals suffering from heart disease	Boehringer Ingelheim Vetmedica GMBH	Daemmgen J, Joens O, Kleemann R	25/03/2004	05/07/2018

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