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A Review

Phosphodiesterase 4 as a candidate therapeutic target of cancer

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In this review, we explore the potential of cAMP-Phosphodiesterase 4 (PDE4), a key intracellular enzyme, as a therapeutic target for cancer treatment. cAMP-PDEs play a critical role in regulating intracellular levels of cyclic adenosine monophosphate (cAMP), an essential second messenger involved in cell proliferation and metastasis in a tissue-specific manner depending on the PDE isoforms present. Elevated PDE4 expression has been reported in cancers such as breast, cervical, and lung cancer. Specific PDE4 subtypes are recognized for their roles in cancer progression, making PDE4 inhibitors promising candidates for therapeutic intervention. This review examines the role of PDE4 in cancer progression and highlights the therapeutic potential of studied PDE4 inhibitors.

Keywords: cAMP, Cancer progression, Inhibitors, Metastasis, Phosphodiesterase 4, Roflumilast, Rolipram

Introduction

For decades cyclic nucleotides (cNT), cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP), have served as a candidate of great interest to the scientists due to their crucial role as intracellular signal transduction molecules, controlling several key intracellular events[1]. The term 'second messengers' has been implied to these cNTs as they serve as a mediator in the communication between an external signal or stimulus and the resulting intracellular response. Typically, an external signal typically activates a cyclase, which facilitates the conversion of the nucleotide triphosphate (NTP) precursor into the corresponding cNT. Following that the cNTs influence the functions of downstream effectors, which varies widely depending on factors like cell type, external environment, activating stimulus, signal localization, and the type of cNT generated[2].

cAMP, identified in the late 1950s, stands out as the most comprehensively researched cNT. The intracellular concentration of cAMP is modulated by the counteracting activities of two antagonistic enzymes, adenylyl cyclase (AC) and phosphodiesterase (PDE), each acting in distinct cellular pockets or compartments[3]. cAMP is synthesized from its precursor, adenosine triphosphate (ATP), through the activity of ACs[4]. These ACs are indirectly activated in response to various stimuli, such as adrenergic agonists, thereby stimulating the production of cAMP. Maintaining a balanced cAMP signaling is crucial for numerous cellular processes, including growth, differentiation, gene expression, and metabolism[5]. The amplitude and stability of a cAMP signal in most cells are largely modulated by the activity of PDE enzymes, which hydrolyze cAMP to 5'AMP, bringing the signal to an end[6] (Fig. 1).

The cyclic nucleotide phosphodiesterases

The cyclic nucleotide PDEs belong to a broad superfamily comprising 11 families, encoded by 21 different genes. Through alternative splicing and post-translational modifications, these genes can generate numerous proteins, leading to nearly 100 unique isoforms[7]. They play a crucial role in catalyzing the hydrolysis of the 3'-cyclic phosphate bond in cNT molecules, leading to their functional inactivity[8]. Structurally, these enzymes are identified by a conserved C-terminal catalytic domain and varied N-terminal regions, which consist of multiple sub-domains. The classification of PDE families is based on the homology of the C-terminal catalytic domain[8]. Each PDE family exhibits unique biochemical properties, including substrate specificity, and pharmacological sensitivity. The hydrolysis of cAMP is primarily mediated by PDE 1, 2, 3, 4, 7, 8, 10, and

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11 isozyme families. Among these, PDE4, 7, and 8 are cAMP-selective, and usually unable to hydrolyze cGMP under physiological conditions[9]. The expression patterns of various PDE families are generally wide-ranging, and these enzymes are predominantly localized intracellularly in the cytosol[7,9]. Despite the presence of relatively equal levels of AC and cAMP-dependent PDE expression in most cell types, the rate of cAMP hydrolysis surpasses the rate of synthesis in virtually all human tissues. This emphasizes the crucial role of PDE enzymes as determinants of intracellular cAMP levels, which, under basal conditions, are typically less than 5 pmol per mg of protein[10]. The individual families of PDEs play diverse roles in biological functions, encompassing processes such as myocyte contractility, development and functioning of male and female sex cells, activation of inflammatory cells, steroidogenesis, and neuronal signaling and many more[9]. The diverse physiological roles of PDEs strongly indicate their involvement in human pathology. Indeed, multiple reviews have presented evidence of PDEs to be involved in disease manifestation like in cancer[11], neurologic[12], cardiovascular[13], pulmonary[14], inflammatory[15] and paediatric diseases[16].

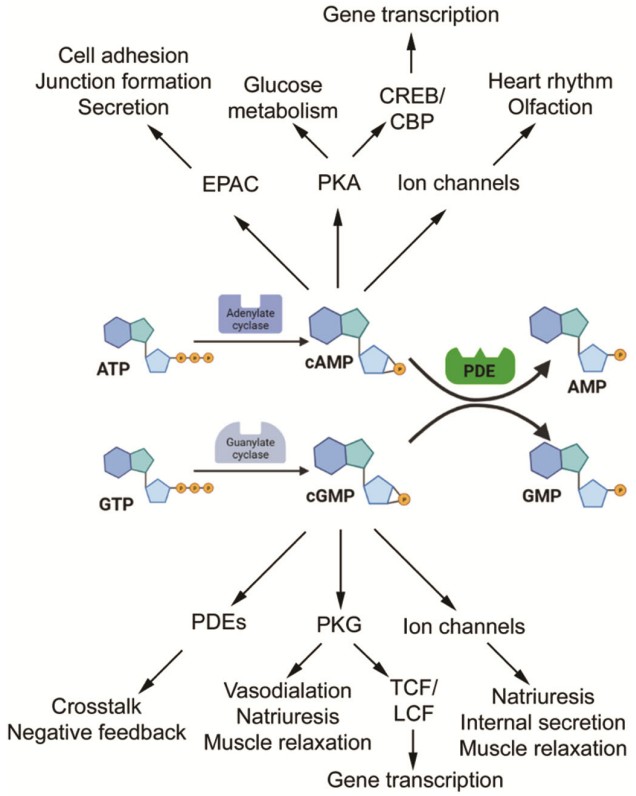

Fig. 1 — Schematic representation of synthesis and hydrolysis of cyclic nucleotides by adenylate cyclase and phosphodiesterase and the functions modulated by cyclic nucleotides

PDE4 inhibitors in therapeutics

PDE inhibitors, according to studies dating back to 1972, are largely composed of different nitrogen-containing chemical classes[17]. The initial class of PDE inhibitors identified is the group of xanthine derivatives, which played a pivotal role in advancing the development of this therapeutic category, involving PDE inhibitors. Functioning as competitive inhibitors, these compounds possess structural features reminiscent of the purine moiety found in cyclic nucleotides. This structural makeup involves a six-membered pyrimidine ring connected to a five-membered ring containing nitrogen atoms[18] (Fig. 2).

As of 2022, a total of 35 PDE inhibitors have been recognized as approved and authorized for marketing by either the Food and Drug Administration (FDA) or other drug regulatory authorities, among which there are several selective and non-selective PDE4

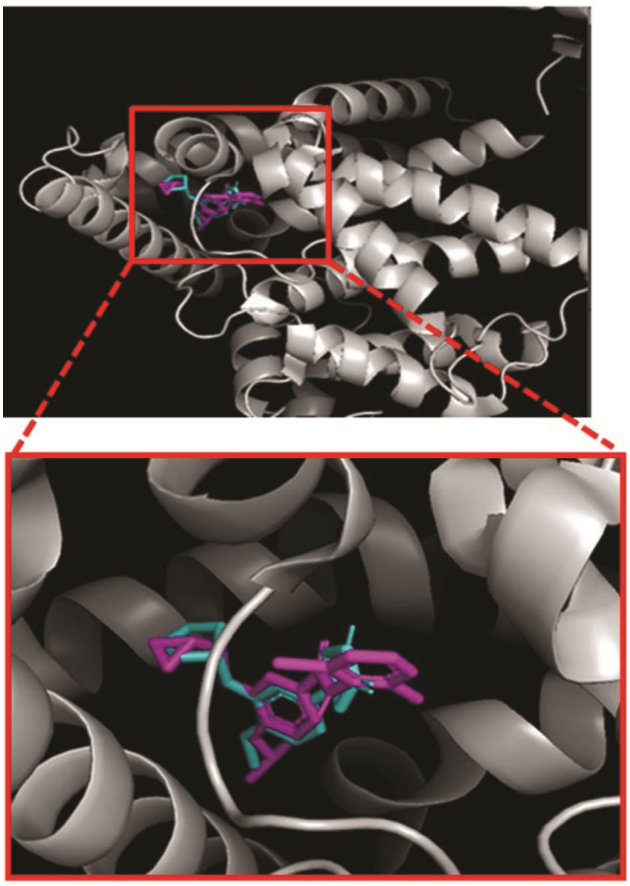

Fig. 2 — PDE 4 inhibitor rolipram and roflumilast bound to PDE4

inhibitors. The approval statuses were verified using records from databases such as DrugBank[19], Drugs-FDA[20], and European Medicines Agency (EMA)-Medicines[21], supplemented by information obtained through Google search engine and references provided by Baillie *et al*.[22] and Bondarev *et al*.[23]. The selective and non-selective PDE4 inhibitors, already approved for using as therapeutic agents against various diseases, are listed on (Table 1) and the ones under clinical trial are listed in (Table 2).

Intricate relation between cancer and PDE4

Till date several studies have explored the relationship of PDE4 with different types of cancers, focusing on its pivotal relationship with cellular growth and proliferation, as well as tissue specificity. Several researches attest to the fact that PDE4B was significantly increased in a diverse range of organs during inflammation of colorectal areas, liver and other organs[24,25].Among the several subfamilies of PDE4, PDE4A has been found to be abundant in brain along with its widespread distribution in several other tissues. PDE4D4 and PDE4D6, on the other hand, were observed to be brain-specific. PDE4C was reported to be low in lung and absent in blood. Moreover, it is one of the largest and most widely studied PDE families[26].

PDE4 in brain tumors

PDE4 have been observed to be highly expressed in brain tumor cell lines, which contributes greatly to the growth and proliferation of brain tumors such as glioblastoma, meningioma, and medulloblastoma[26]. PDE4 is also known to be associated with several central nervous system disorders along with brain tumors. Scientists have shown that forced expression of PDE4A1 in the cortex region of neurofibromatosis-1 genetically modified mouse formed ectopic tumors, which resembled low-grade optic pathway glioma. Similarly, a catalytically inactive form of PDE4A1 failed to form such tumor[27] indicating towards the fact that cAMP inhibition was tumorigenic. Lihua *et al.* have shown that selective inhibition of PDE4 with rolipram caused intracranial growth retardation in

Table 1 — List of PDE4 inhibitors approved by drug regulatory authorities

Drug Name	Disease
Ibudilast	Pulmonary disease
	Nervous system disorder
Roflumilast	Pulmonary disease
Dipyridamole	Cardiovascular disorder
Amrinone	Nervous system disorder
Milrinone	
Anagrelide	
Cilostazol	
Papaverine	
Amlexanox	
Apremilast	
Caffeine	
Crisaborole	
Difamilast	
Drotaverine	
Tofisopam	

Table 2 — List of PDE4 inhibitors under clinical trial

Disease	Drug name	Phase of clinical trial
Alzheimer's disease	Etazolate	Phase 2
	MEM1414	Phase 2
	BPN14770	Phase 2
Allergic rhinitis	BLX-028914	Phase 2
	GSK256066	Phase 2
	OX914	Phase 2
Tuberculosis	OC-11050	Phase 2
	CI 1044	Phase 2
Asthma	GSK256066	Phase 2
	IPL,512,602	Phase 2
	IPL,576,092	Phase 2
	MEM1414	Phase 2
	Oglemilast	Phase 2
	OX914	Phase 2
	Revamilast	Phase 2
	Ensifentrine	Phase 3
	Tanimilast	Phase 3
Chronic obstructive pulmonary disorder	CI 1044	Phase 1
	GSK256066	Phase 2
	Oglemilast	Phase 2
	Ronomilast	Phase 2
	Tetomilast	Phase 2
	Ensifentrine	Phase 3
	Tanimilast	Phase 3
Fragile X syndrome	BPN14770	Phase 2
Cutaneous lupus erythematosus	CC-11050	Phase 2
Diabetic nephropathy	CTP-499	Phase 2
Cystic fibrosis	Ensifentrine	Phase 3
Huntington's disease	Rolipram	Phase 2
Major depressive disorder		
Multiple sclerosis		
Lung cancer	Exisulind	Phase 3
Prostate cancer		
Breast cancer		
GI tumors		

model glioblastoma multiforme and medulloblastoma xenografts[28]. PDE4B has also been found to be up-regulated in medulloblastoma[29]. PDE4D was also observed to be upregulated in brain tumors. There are enough scientific reasons for targeting PDE4 in brain tumors. Though no clinical trials with market available PDE4 inhibitors are in plan right now, it might be an effective option for targeting brain tumors in the future. One weak PDE inhibitor, pentoxiphylline was in trial as a part of a combination drug therapy (Protocol ID NCI-95-C-0069)[30]. Unfortunately, the clinical trial result was not promising as the combination therapy caused side effects like gastrointestinal problems and CNS toxicities. Thus, specific PDE4 inhibitors which have already been tested in animal models like rolipram might be a better choice for the future clinical trials.

PDE4 in prostate, pancreatic and colorectal cancer

PDE4B has been considered as a prognostic marker in colorectal cancers, as scientists have reported that oncogenic KRAS can up-regulate the intracellular PDE4B level in HCT116 cell line[31]. Also, in patients suffering from colorectal cancer, expression of PDE4B was found to be increased significantly[32]. Likewise, PKA-mediated phosphorylation of the N-terminus of PDE4 has also been implicated to the growth and proliferation of prostate cancer cells[33]. PDE4D, another subtype of PDE4 was also reported by seven different groups to be a major player in androgen sensitive prostate cancer. It was also established that PDE 4 inhibition can reverse the conditions associated with prostate cancer by initiating the process of apoptosis, decreased cell proliferation and decreased cell migration of the prostate cells[34,35]. Another article have also reported that PDE4D inhibitors can limit cell growth in prostate cancer cells by altering the signaling of sonic hedgehog, MAPK, and androgen receptor mediated pathways[34]. Jeong *et al.* reported that PDE4D is responsible for pancreatic cancer growth through mTORC1 signaling[36]. Relations between suppressed expression of a specific p53 induced microRNA, miR-129-5p was also shown to be associated with the increased expression of PDE4D in colon cancer cells[37].

PDE4 in lung cancer

A study made made by Pullamsetti*et al.* revealed that lung cancer cells showed higher expression of PDE4 compared to normal lung cells and inhibiting the same with siRNA or small molecule inhibitors hampered the proliferation and colony formation of human lung cancer cells[38]. PDE4A and PDE4D were also observed to hinder the growth and proliferation of lung cancer cell lines through hypoxia-inducible factors[39]. Moreover, the up-regulation of PDE4A and PDE4D by TGF-β1 stimulation was shown to promote epithelial-to-mesenchymal transition in alveolar epithelial cells[40].

PDE4 in breast cancer

Several recent researches have also linked PDE4 to breast cancer progression and metastasis. PDE4 was observed to be cancer enhanced isoform of phosphodiesterse (PDE). It was also reported that increased expression of this PDE isoform was the reason behind decreased cAMP levels in breast tumor environment. A study made by Mukherjee *et al.* have not only demonstrated that PDE4 inhibitor was able to hinder the growth of triple negative human breast cancer cell line MDAMB231, but also reported that small molecule PDE4 inhibitor was able to alter the fate of breast cancer stem cells *via* cAMP/PKA/mTOR signaling pathway[41] thereby significantly increasing autophagy-dependent apoptotic potential of the breast cancer cells. Moreover, a recent report from Bagchi *et al.* suggested that PDE4 inhibitor rolipram was able to modulate the hedgehog signaling pathway in both hormone-responsive and triple negative breast cancer cell lines and retarded the growth of tumor in mice model. The PDE4 inhibitor rolipram was observed to modulate the Hh pathway transcription factors increasing the repressor functions of the GLI transcription factors[42]. Scientists have also demonstrated that vehicle-encapsulated small molecule selective inhibitor of PDE4 was able to affect breast cancer cells antagonistically[43].

PDE4 in blood cancer

Serrels and group have explored the FAK/RACK1/PDE4D5/Rap1 signaling pathway in cancer cells and reported the control of cell polarization and integrin adhesion formation[44]. Scientists have also reported that PDE4 inhibitors could activate a protein phosphatase 2A mediated mitochondrial pathway in chronic lymphocytic leukemia cells[45]. Reports have also demonstrated key role of PDE4 in diffuse large B-cell lymphoma as well as melanoma and liver cancer[46].

PDE4 inhibitors in cancer therapeutics

The correlation between the development of tumors and interference with the cAMP signaling pathway has been demonstrated by scientists throughout the world (Figure 3). It has been observed that elevated levels of PDE4 in certain tumor cells lead to reduced compared to normal cells[47]. Increased level of intracellular cAMP has been identified as a protective mechanism against tumor progression, suggesting that inhibiting PDE4, which are responsible for cAMP hydrolysis, could be a promising strategy for preventing tumor growth. This has brought attention to PDE4 inhibitors as potential agents with anticancer properties[48]. Till date, several successful attempts have been made by the scientists to put PDE4 inhibitors forward as therapeutic agents against cancer, some of which are discussed here.

A well-established PDE4 inhibitor, rolipram, has been shown to be able to overcome resistance in tumors, leading to a reduction in the survivability of human glioblastoma cells. Additionally, combining rolipram with bevacizumab treatment has also been effective against the same[26]. Moon *et al*. demonstrated that rolipram controlled glioblastoma cell density by utilizing two pathways: PKA- and Epac1/Rap1-mediated cell death and cell cycle arrest[49]. Studies in breast cancer showed that PDE4 inhibitor rolipram not only functioned via cAMP/PKA/ mTOR signaling pathway and via hedgehog signaling pathway but could directly inhibit matrix metalloproteinases like MMP2 and MMP9, important proteins associated with cancer metastasis[50]. PDE4 inhibitor roflumilast and prednisone were also successfully tested against B cell malignancies[51]. Roflumilast has also been exploited against lung carcinogenesis[52]. Exisulind, a dual inhibitor of PDE4 and PDE5, was also observed to be against colon, pancreatic and bladder cancer cell lines[53,54]. Combinatorial application of exisulind and chemotherapeutic drug docetaxel has been observed to be potent against orthotopic tumors[55]. Apremilast, another PDE4 inhibitor, has been found to be effective against colorectal cancer cells[56]. Theobromine has been found to be able to prevent proliferation of malignant glioblastoma by regulating PDE4 negatively[57].

Researchers are trying to establish new treatment regimens for cancer due to the short-comings posed by the existing chemotherapeutic agents. Chemoresistance and ineffectiveness against cancer stem cell population are also reasons behind the lookout for new anti-cancer drugs. Drug repurposing seemed to be one of the options to provide for a solution to the present lack of new options. Moreover, study of the pharmacokinetic properties has revealed that there is a

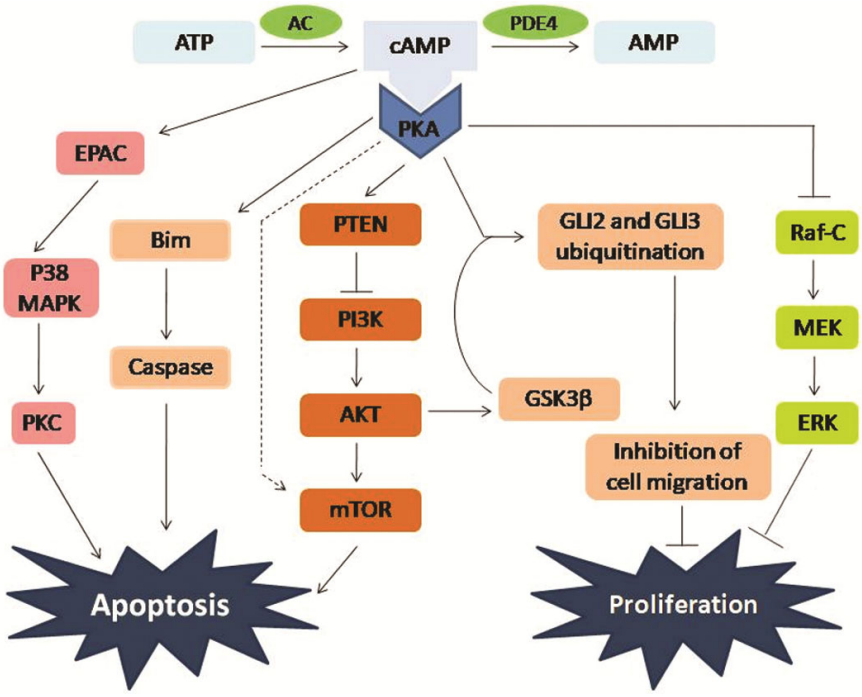

Fig. 3 — Schematic representation of the functioning of cAMP-dependent PDE4, which have been utilized by researchers against several types of cancers

Rolipram			
Physiochemical Properties		Lipophilicity	
Molecular Weight	275.34 g/mol	WLOGP	2.24
No. of heavy atoms	20	Water solubility	
No. of H-bond acceptors	3	Log S (ESOL)	-2.90
No. of H-bond donors	1	Class	Soluble
Molar refractivity	80.73	Pharmacokinetics	
TPSA	47.56 Å^2	GI absorption	High
Druglikeliness		B-B-B permeant	Yes
Lipinski	0 violation	P-gp substrate	Yes

Roflumilast			
Physiochemical Properties		Lipophilicity	
Molecular Weight	403.21 g/mol	WLOGP	5.62
No. of heavy atoms	12	Water solubility	
No. of H-bond acceptors	6	Log S (ESOL)	-5.04
No. of H-bond donors	1	Class	Moderately Soluble
Molar refractivity	93.86	Pharmacokinetics	
TPSA	60.45 Å^2	GI absorption	High
Druglikeliness		B-B-B permeant	No
Lipinski	0 violation	P-gp substrate	No

Paclitaxel			
Physiochemical Properties		Lipophilicity	
Molecular Weight	853.91 g/mol	WLOGP	3.41
No. of heavy atoms	62	Water solubility	
No. of H-bond acceptors	14	Log S (ESOL)	-6.66
No. of H-bond donors	1	Class	Poorly Soluble
Molar refractivity	218.96	Pharmacokinetics	
TPSA	221.29 Å^2	GI absorption	Low
Druglikeliness		B-B-B permeant	No
Lipinski	2 violations	P-gp substrate	Yes

Doxorubicin			
Physiochemical Properties		Lipophilicity	
Molecular Weight	543.52 g/mol	WLOGP	-0.32
No. of heavy atoms	39	Water solubility	
No. of H-bond acceptors	12	Log S (ESOL)	-3.91
No. of H-bond donors	6	Class	Soluble
Molar refractivity	132.66	Pharmacokinetics	
TPSA	206.07 Å^2	GI absorption	Low
Druglikeliness		B-B-B permeant	No
Lipinski	3 violation	P-gp substrate	Yes

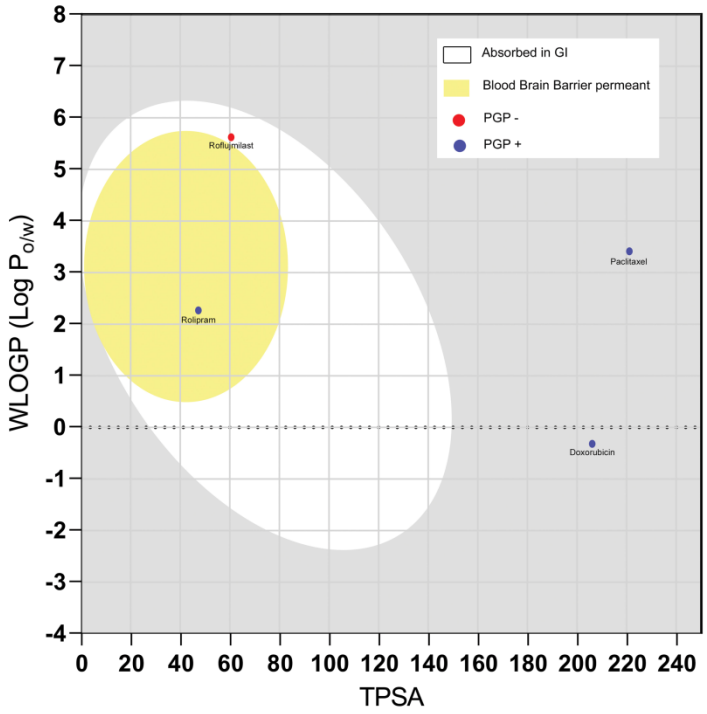

Fig. 4 — Physiochemical, toxicological and pharmacokinetic properties of rolipram, roflumilast, paclitaxel and doxorubicin as well as graphical representation of the boiled egg plot obtained from their pharmacokinetic properties

significant lack of drug likeliness of paclitaxel and doxorubicin, which are commonly used as chemotherapeutic agents against several cancers worldwide (Fig. 4). Several therapeutic agents that are developed against cancer have failed to generate desired response against triple negative breast cancer cells and other resistant cancer types. Therefore, researchers have tried to develop therapeutic models that are capable of targeting cancers which are difficult to target and track. Studies have shown that in case of breast cancer PDE4 inhibitors like rolipram can effectively regress triple negative breast cancer which is the type of breast cancer majorly associated with cancer relapse. Not only that, unlike present chemotherapeutic options like paclitaxel, PDE4 inhibitor rolipram was also effective in regressing breast cancer stem cells, responsible for tumor relapse[41,58]. In cases of several other cancer types like

lung cancer, blood cancer, brain cancer and others, PDE4 inhibitor showed promising results. Also, the pharmacokinetics of PDE4 inhibitor rolipram and roflumilast proved to have better drug likeliness than the existing chemotherapeutics. PDE inhibitors like rolipram and roflumilast were followed Lipinski's rule of 5 better than the conventional chemotherapeutic drugs like doxorubicin and paclitaxel which showed three violations and two violations respectively. It has been already shown by Mukherjee *et al*. that rolipram regresses breast cancer cells as well as the breast cancer stem cells alone and in combination with paclitaxel. Since PDE4 inhibitors have been proved to have anti-cancer activity according to the pre-clinical and clinical studies, they might be successfully repurposed with the existing rationale and tools for cancer application either in nano vesicles or in combination with the existing chemotherapeutic targets.

Conclusion

To conclude it can be said that PDE inhibitors have been studied in various cancers and their efficacies have been evaluated at various levels. It is possible to exploit them at various levels; either alone or with existing chemotherapeutic drugs to have a new generation of repurposed drugs for cost-effective cancer treatment.

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Conflict of interest

Both the author declares no conflicts of interest.

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