CURRENT AND FUTURE CLINICAL APPLICATION - PHOSPHODIESTERASE (PDEs)-INHIBITORS

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“The article highlights some of current and future clinical application of phosphodiesterase and the potential new drug target and role of PDE Inhibitors”

KEYWORDS: PDEs- phosphodiesterases, PDEsi – phosphodiesterase inhibitor CNs – cyclic nucleotides, cAMP, cGMP, second messenger.

INTRODUCTION

“Cyclic nucleotide (CNs) phosphodiesterases (PDEs) play a critical role in intracellular signalling by selectively hydrolysing the second messengers cyclic AMP (cAMP) and cyclic GMP(cGMP) that control cAMP and cGMP regulated proteins and transcription factors.” (Keravis and Lugnier 2012, Ahmad et al 2015).

FAMILY AND ISOFORMS OF PDEs:- (Cho et al 2005, Lerner and Epstein 2006, Gresele et al 2011, García-Osta et al 2012, Zhang and Zhang 2016, Brescia and Zaccolo 2016). PDEs are the only enzymes that degrade Cyclic Nucleotides, and are grouped in a superfamily comprising 21 genes, which constitute 11 distinct PDE families, PDE1-11. (Keravis and Lugnier 2012, Brescia and Zaccolo 2016, Maurice et al 2014) "PDE1-3, 10, and 11 hydrolyse both cAMP and cGMP," (Brescia and Zaccolo 2016). "PDE1" (Brescia and Zaccolo 2016). PDE1A, PDE1B, and PDE10A have a higher affinity for cGMP over cAMP," (Brescia and Zaccolo 2016) whereas PDE1C, PDE2A, and PDE11A have equal affinity for both Cyclic nucleotide (Brescia and Zaccolo 2016).

PDE 1 INHIBITOR

PDE1 inhibitors in treating cardiovascular disease, the development of PDE1 inhibitors, specifically isoform specific inhibitors, could present a grey area of research in the
future. (Knight and Yan 2013), development of new PDE inhibitors, or other PDE-modulating drugs, to affect therapeutic strategies in cardiac failure (Knight and Yan 2013).

**PDE1 INHIBITOR AS TARGET IN VASCULAR REMODELING**

Pathological vascular remodeling is a hallmark of most vascular disorders such as atherosclerosis, postangioplasty restenosis, allograft vasculopathy, and pulmonary hypertension" (Chan and Yan 2011). PDE1 isozymes in pathological vascular remodeling." (Chan and Yan 2011), PDE1 - potential drug target to prevent vascular remodelling. PDE1 was reported to offer a new target for therapeutic intervention in pulmonary hypertension" (Keravis and Lugnier 2012).

**POTENTIAL OF PDE1 INHIBITOR**

"pan-PDE1 inhibitor" (Knight and Yan 2013)"cardiac hypertrophy" (Knight and Yan 2013) decreased myocardial hypertrophy and fibrosis" (Knight and Yan 2013), "Vinpocetine, a PDE1 inhibitor" (Levy et al 2011), PDE1 inhibitors in controlling cell malignancy" (Levy et al 2011), nimodipine, a dihydropyridine Ca2+ antagonist, selectively inhibits PDE1" (Keravis and Lugnier 2012) PDE1C a good target to inhibit proliferating smooth muscle cells (SMCs) in lesions of atherosclerosis or restenosis" (Keravis and Lugnier 2012), 8-methoxymethyl-IBMX (PDE 1 inhibitor)," (Eskandari et al 2004) MIMX -PDE1 inhibitor (Verde et al 1999).

**HYPERTENSION AND VASOSPASM**

"PDE1 inhibitors induce vasodilation and lower BP, suggesting a potential use of these vasodilators in the treatment of hypertension and vasospasm.(Laursen et al 2017).

**PDE1 INHIBITOR FAILURE**

"PDE1 INHIBITOR failed to block of heart hypertrophy, pathological vascular remodelling and cardiac remodelling in preclinical model (Maurice et al 2014).

**PDE2**

PDE2 is able to hydrolyze both cAMP and cGMP" (Knight and Yan 2013). PDE2 appears to play a vital role in multiplication of cells and invasion of the human malignant melanoma PMP cell line. Selectively hindering PDE2 might possibly inhibit growth and invasion of other malignant tumor cell lines" (Hiramoto et al 2014).
PDE2A is also expressed in regions associated with cognitive function (Richter et al 2013), including the cortex, striatum, hippocampus, amygdala, and habenula" (García-Osta et al 2012).

**PDE2 INHIBITORS**

Erythro-9-(2-hydroxy-3-nonyl) adenine (EHNA) (Verde et al 1999), an inhibitor of adenosine deaminase (ADA), was shown to act as a selective PDE2 inhibitor" (Gresele et al 2011).

**PDE2 INHIBITOR AS ANTI-ANXIETY**

**POTENTIAL FOR CLINICAL USE**

"PDE2 may be a novel pharmacological drug target for the the treatment of anxiety disorders" (Masood et al 2009, Keravis and Lugnier 2012).

**PDE3-** PDE3 hydrolyzes cAMP with a much higher affinity than cGMP (Knight and Yan 2013) endothelial dysfunction had a major effect on PDE3 function (Hubert et al 2014).

**PDE3 LOCATION** - PDE3A is mainly present in heart, platelet, vascular smooth muscle and oocytes, whereas PDE3B is mainly associated with fat cells (adipocytes), hepatocytes and spermatocytes." (Keravis and Lugnier 2012).

**PDE3 ENZYME INHIBITORS**

cilostamide (Verde et al 1999) Dipyridamole (Maurice et al 2014) and cilostazol" (Gresele et al 2011), Vinpocetine, IC86340" (Gresele et al 2011) vesnarinone, lixazinone, anagrelide" (Gresele et al 2011) PDE3 enzyme inhibitors, including amrinone, milrinone and enoximone, have been used to treat congestive cardiac failure (Knight and Yan 2013) PDE3 enzyme inhibitors were discovered to exhibit cardiotonic, inotropic, bronchodilatory and vasodilatory activities" (Maurice et al 2014), siguazodan (PDE3 enzyme inhibitor) (Eskandari et al 2004).

**POTENTIAL FOR CLINICAL USE**

**ANTI-PLATELET:** Anagrelide (Gresele et al 2011) is a potent enzyme inhibitor of PDE3 and a potent and broad-spectrum enzyme inhibitor of platelet aggregation" (Gresele et al 2011), Cilostazol inhibits both primary and secondary platelet aggregation induced by collagen, ADP, arachidonic acid and adrenaline with" (Gresele et al 2011), cilostazol over conventional antiplatelet therapy is the relatively short recovery time of platelet function" (Gresele et al 2011).
CARDIAC FAILURE –(Gresele et al 2011, Knight and Yan 2013).

ROLE OF CYCLIC NUCLEOTIDE IN CARDIAC FAILURE: - Chronic stimulation of β-adrenergic receptors is associated with development of maladaptive cardiac remodeling, fibrosis and cardiac myocyte apoptosis, while chronic cGMP signaling can attenuate these same effects and preserve cardiac function (Knight and Yan 2013).

Milrinone, a specific PDE3A enzyme inhibitor, inhibits arachidonic acid-induced platelet shape change and platelet aggregation (Gresele et al 2011), inhibition of PDE3 results in a dramatic increase in heart rate and cardiac contractile function (Knight and Yan 2013), PDE3 inhibition is associated with increased cardiac contractility and cardiac output, as well as decreased peripheral vascular resistance, thereby relief of many symptoms of cardiac failure(Knight and Yan 2013). PDE3 enzyme inhibitors provide acute inotropic, lusitropic and vasodilatory (Maurice et al 2014).

SIDE EFFECT OF PDE3 INHIBITION IN CARDIAC FAILURE :- chronic treatment with PDE3 enzyme inhibitors in cardiac failure patients is associated with increased mortality due to irregular rhythms and sudden death (Knight and Yan 2013).

Cancer metastasis -Cilostazol, a dual enzyme inhibitor of PDE3 and adenosine uptake, is used for the treatment of intermittent claudication, due to its anti-aggregant and vasodilator properties. Cilostazol has been tested as a tool for the inhibition of breast cancer metastasis" (Levy et al 2011), block human colon cancer cell motility, and might be effective as an antimetastasis drug" (Levy et al 2011).

PDE 4
The PDE4 family is highly specific for cAMP," (Knight and Yan 2013).PDE4 isoforms associate with β1 and β2 adrenergic receptors" (Knight and Yan 2013) PDE4D may play an important role in human atrial function and susceptibility to arrythmias" (Knight and Yan 2013) The PDE4 subfamily of PDEs (García-Osta et al 2012) &isoform-selective enzyme inhibitor (García-Osta et al 2012) play important role in pathogenesis. PDE4 family is composed of 4 different genes, 4A, B, C, and D and" (Oliva et al 2012), PDE4A and 4B are, in particular, implicated in several neurological disorders such as schizophrenia, depression, and bipolar disorder" (Oliva et al 2012), PDE4B and 4D are upregulated after experimental
autoimmune encephalomyelitis, acute ischemic stroke, or spinal cord injury" (Oliva et al 2012).

Phosphodiesterase (PDE)4 enzyme inhibitors are novel anti-inflammatory (Boswell-Smith and Spina 2009, Kumar et al 2013), inhibit neutrophil activation (Boswell-Smith and Spina 2009, Souza et al 2001), PDE 4 Enzyme inhibitor act on immune cell and thus suppress immune response (Coon et al 2014). Concentrations of IL-10 rose significantly in the lung and serum and these increases were blocked by rolipram" (Souza et al 2001) IL-10 have been shown to limit the inflammatory injuries following reperfusion of several ischaemic tissues" (Souza et al 2001). PDE4D in cognition, memory and antidepressive behaviour (Maurice et al 2014) PDE4 subtypes are expressed in a number of cell types that are considered suitable drug targets for the treatment of human airway system diseases such as asthma and COPD" (Keravis and Lugnier 2012) PDE4 subtypes are expressed in a number of cell types that are considered suitable drug targets for the treatment of human airway system diseases such as asthma and COPD" (Keravis and Lugnier 2012), inhibition of PDE4 can regulate the generation of cytokines from human basophils." (Eskandari et al 2004) Type 4 phosphodiesterase (PDE4) enzyme inhibitors mimic the pharmacological actions of alpha2-adrenoceptor antagonists." (Robichaud et al 2002) effective enzyme inhibitors of PDE-4 may lead to new myorelaxant and anti-inflammatory drugs" (Muñoz-Pérez et al 2017) Phosphodiesterase (PDE) 4 enzyme inhibitors have been shown to inhibit eosinophil PDE4" (Cooper et al 1999) Non-selective enzyme inhibitors of cyclic nucleotide phosphodiesterase (PDE) block allergen-induced contraction of passively sensitized human airways" (Schmidt et al 2000).

**PDE4 LOCATION**- PDE4s are present in brain, smooth muscle, heart, kidney, endothelial cells and immunocytes" (Keravis and Lugnier 2012) PDE4 family is comprised of 4 primary gene products (PDE4A, PDE4B, PDE4C, PDE4D) and is highly expressed in neutrophils and monocytes, CNS tissue and smooth muscles of the lung" (Skoumbourdis et al 2009).

once-daily treatment of severe chronic obstructive lung disease (COPD)" (Kumar et al 2013). Flavonoids have been reported to inhibit PDE4, and also elicit additional anti-inflammatory effects through other pathways." (Kumar et al 2013). Inhaled PDE4 enzyme inhibitor GSK256066 (Maurice et al 2014), denbufylline (PDE4 enzyme inhibitor) (Eskandari et al 2004), substituted 7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazines as potent PDE4 enzyme inhibitors" (Skoumbourdis et al 2009), thalidomide analogs on the contractions of pregnant human myometrium tissue may be due to their PDE-4 enzyme inhibitory effect" (Fernández-Martínez et al 2016) East Indian sandalwood oil has significant anti-inflammatory, it suppressed total cellular PDE activity, PDE4, and 7 transcript levels, nuclear factor kappa B (NF-kB) activation, and pro-inflammatory cytokines/chemokine synthesis (Sharma et al 2018), apremilast & crisaborole were approved for the treatment of inflammatory airway diseases, psoriatic arthritis, and atopic dermatitis, respectively" (Li et al 2018).

POTENTIAL CLINICAL USE


PDE ENZYME INHIBITORS reduce cytokines-PDE enzyme inhibitors prevent cAMP hydrolysis in 1β immune cells, decreasing synthesis of pro-inflammatory cytokines such as interleukin-α and tumor necrosis factor-" (Oliva et al 2012) thus help in treating autoimmune diseases.

COPD (Boswell-Smith and Spina 2009, Spina 2009, García-Osta et al 2012, Maurice et al 2014). selective PDE4 enzyme inhibitor, roflumilast (Boswell-Smith and Spina 2009) reduces the exacerbation and worsening of symptoms associated with severe chronic obstructive pulmonary disease, Phosphodiesterase4 enzyme inhibitors are currently under development for the treatment of human airway system diseases including asthma and chronic obstructive pulmonary disease" (Spina 2009). Also in pulmonary fibrosis and allergic rhinitis (Maurice et al 2014).
Osteoarthritis (Tenor et al 2002) nitric oxide contributes to cartilage degradation in osteoarthritis" (Tenor et al 2002), PDE4 enzyme inhibitors to reduce IL-1b-induced NO, thus PDE4 enzyme inhibitors may have chondroprotective effect " (Tenor et al 2002).


BRAIN TUMORS- abnormal regulation of cyclic AMP levels may be a possible determinant of brain tissue tumorigenesis and that among the mechanisms of its dysregulation is altered expression of PDE, enzyme inhibitors of PDE4 indicates that this may be a Potential new target to brain cancer therapy." (Sengupta et al 2011).


Improving synaptic and cognitive function (García-Osta et al 2012) PDE4 enzyme inhibitors exert a number of memory and cognition enhancing effects and have neuro-protective and neuro-regenerative properties (Richter et al 2013).

Ischemic Repurfusion Injury- the inflammatory injuries following reperfusion of several ischaemic tissues" (Souza et al 2001).

CARDIAC FAILURE -decreased PDE4D activity causes defective RyR2-channel function associated with cardiac failure and irregular rhythms." (Lehnart et al 2005).


ANTI-DEPRESSANT –PDE4 enzyme inhibitor can be used as antidepressant (Maurice et al 2014).

PDE4 ENZYME INHIBITOR IN DIABETES-Roflumilast has also recently been reported to reduce levels of glycahed haemoglobin and blood glucose in patients with newly diagnosed type 2 diabetes" (Maurice et al 2014), peripheral myopathy and cardiac dysfunction in Duchenne muscular dystrophy, as well as insulin resistance, type 2 diabetes" (Maurice et al 2014).
OBESITY, METABOLIC SYNDROME, DIABETES - PDE4 enzyme inhibitors, may be useful for treating syndrome certain metabolic diseases, including obesity, type 2 diabetes and metabolic" (Maurice et al 2014).

Side-Effects - nausea, emesis" (Robichaud et al 2002, Spina 2009, Maurice et al 2014) and diarrhea." (Boswell-Smith and Spina 2009), side effects can be decreased by shifting route of administration via the inhaled route, and/or development of non-emetic PDE4 enzyme inhibitors and mixed PDE enzyme inhibitors." (Spina 2009). PDE4 enzyme inhibitors like roflumilast are ideal for COPD and have the potential for developing nonemetic anti-inflammatory drugs" (Boswell-Smith and Spina 2009). PDE4 enzyme inhibitors lacking side effects is critical for therapeutic applications that require chronic long term treatment, such as Alzheimer's disease (García-Osta et al 2012). Isoform-specific PDE4 enzyme inhibitors could be extremely beneficial, and could help to reduce side effects associated with enzyme inhibitor treatment (Knight and Yan 2013).

"PDE5 specifically hydrolyzes cGMP" (Knight and Yan 2013, Murthy 2001, (Butrous 2014).

"Pathological conditions, PDE5 expression in the heart can be highly upregulated (Knight and Yan 2013). PDE5 expression is upregulated in experimental cardiac failure induced by myocardial infarction" (Knight and Yan 2013), PDEsI improve function, and reduce levels of inflammatory markers" (Knight and Yan 2013), PDE5 is the predominant expressed in skeletal, cardiac and smooth muscle (Murthy 2001).


POTENTIAL FOR CLINICAL USE
CLASS III CARDIAC FAILURE" (KNIGHT AND YAN 2013) -sildenafil(Zhang and Zhang 2016) treatment appeared to reduce cardiac hypertrophy" (Knight and Yan 2013). class III cardiac failure" (Knight and Yan 2013), sildenafil treated patients experienced an improvement in cardiac function, and significant reduction in New York Heart Association cardiac failure" (Knight and Yan 2013, Zhang and Zhang 2016).
PDE5 ENZYME INHIBITORS AND T2DM - Chronic use of phosphodiesterase-5 enzyme inhibitors has been demonstrated to improve insulin action on muscle cell, glucose uptake by the prolongation the nitric oxide (NO)/cyclic guanosine monophosphate (cGMP)/ protein kinase (PKG) signalling system. (Poolsup et al 2016).


Pulmonary hypertension (PAH)
"Tadalafil (Cialis) -40 mg/day for arterial pulmonary hypertension" (García-Osta et al 2012). PDE-5 enzyme inhibitors significantly improved exercise capacity and decreased lung pressures." (Jeremy Feldman et al 2010). Ardenafil are currently approved for the treatment of pulmonary hypertension arterial" (Maurice et al 2014) PDE-5 enzyme inhibitors for pulmonary hypertension in adults and children" (Barnes et al 2017).


Alzheimer's disease(García-Osta et al 2012, Kumar et al 2013, Richter et al 2013) Vardenafil, sildenafil, and, more recently, tadalafil have all been used as pharmacological tools, confirming their efficacy in Alzheimer's mouse models." (García-Osta et al 2012).

PDE5 ENZYME INHIBITORS AND DIGITAL ISCHEMIA -digital ischemia" (Ng et al 2010)"vasospastic component, a marked improvement in digital blood flow may be observed with sildenafil use." (Ng et al 2010), phosphodiesterase 5 enzyme inhibitors may be used as an adjunct to improving skin flap survival (Ng et al 2010).

PDE 5 ENZYME INHIBITORS AND UROLOGY- Inhibition of PDE5 is expected to be an effective strategy in treating benign urological diseases. (Zhang and Zhang 2016).

urological diseases- urinary and genital illnesses, such as priapism, premature ejaculation, urinary tract calculi, overactive bladder, Peyronie's disease, and female sexual dysfunction" (Zhang and Zhang 2016).
PDE5 ENZYME INHIBITORS AND OSTEOPOROSIS (Ahmad et al 2015) - PDE5 enzyme inhibitors glucocorticoid-induced osteoporosis (Huyut et al 2018), markers of oxidative stress and bone atrophy were significantly decreased by treatment with the PDE-5 enzyme inhibitors, zaprinast and avanafil (Huyut et al 2018) pentoxifylline (Horiuchi et al. 2004), accelerated bone formation by BMP-stimulated osteoblast differentiation" (Ahmad et al 2015).

COLITIS & COLON TUMOR -"PDE-5 enzyme inhibitor Sildenafil inhibited colonic tumorigenesis dependent on inflammation and suppressed DSS-induced colitis." (Lin et al 2017).

Systemic sclerosis- related vasculopathy, as manifested by Raynaud's Phenomenon and digital ulcers (Impens et al 2011).

Allergy-Zaprinast was the first PDE5 enzyme inhibitor used in humans as a mast cell-stabilizer in allergy treatment. (Levy et al 2011).

CYSTIC FIBROSIS- "PDE5 enzyme inhibitors in Cystic Fibrosis." (Noel et al 2012).

SIDE-EFFECT- sildenafil (Knight and Yan 2013, Zhang and Zhang 2016)treatment was associated with a slight but significant worsening of kidney function" (Knight and Yan 2013, Zhang and Zhang 2016).

CONTRAINDICATION OF PDE5 ENZYME INHIBITORS- "PDE5 enzyme inhibitors (example, sildenafil and vardenafil) is contraindicated in patients with retinal degeneration (Maurice et al 2014, Ahmad et al 2015).

PDE6
PDE6 family is restricted to retinal rod and cone cells (Keravis and Lugnier 2012) to pineal gland" (Keravis and Lugnier 2012). PDE5 enzyme inhibitors also inhibit PDE6" (Keravis and Lugnier 2012).

PDE6 SUBTYPE POTENTIAL- PDE6 subtypes could be therapeutic targets in pulmonary hypertension" (Keravis and Lugnier 2012).
PDE 7
PDE7 enzyme inhibitors regulate pro-inflammatory and immune T-cell functions (Castaño et al 2009), thioxoquinazolines are potent PDE7 enzyme inhibitors (Castaño et al 2009). It prevents neuro-inflammation by modulating cAMP levels" (Paterniti et al 2011).

Cyclic AMP (cAMP) has been recognized as an important second messenger regulating immune and inflammatory response" (Nakata et al 2002) Agents with the ability to elevate intracellular cAMP levels have been demonstrated to possess immuno-suppressive and anti-inflammatory properties" (Nakata et al 2002).

"PDE7 enzyme inhibitors have the potential to be used to treat immunological and inflammatory disorders." (Nakata et al 2002), thereby selective PDE7 enzyme inhibitors have the potential to be used to treat immunological and inflammatory disorders. (Nakata et al 2002).

**Location and expression**- expressed simultaneously on leukocytes and on the brain" (Paterniti et al 2011).

**PDE7 ENZYME INHIBITORS** - S14 and VP1.15 (Paterniti et al 2011), TC3.6 (Mestre et al 2015) PDE7-selective enzyme inhibitors, have been reported to inhibit growth and induce apoptosis in many different human cancer cell lines (Maurice et al 2014).

**POTENTIAL CLINICAL USE**
**SPINAL CORD INJURY (SCI)** "(Paterniti et al 2011) reduces neuroinflammation which is modulated by cAMP levels" (Paterniti et al 2011).

**Primary Progressive Multiple Sclerosis (PPMS),** (Mestre et al 2015)- PDE7 enzyme inhibitors, and specifically TC3.6, as a novel class of agents with therapeutic potential for PPMS." (Mestre et al 2015).

**Chronic Lymphoid Leukemia** (CLL)- high expression of PDE7B in chronic lymphoid leukemia (CLL) cells" (Levy et al 2011), PDE7 B Specific enzyme inhibitor has a potential for treatment of CLL. PDE7 family is a pharmacological target in chronic lymphocytic leukaemia (CLL)." (Keravis and Lugnier 2012).
PDE8
PDE8 is highly specific for cAMP (Knight and Yan 2013), specific role for PDE8A regulation in cardiac pathology has not yet been reported (Knight and Yan 2013), PDE8 could play a role in protecting against cardiac irregular rhythms or other forms of cardiovascular disease" (Knight and Yan 2013).PDE8 defect leading to Cushing syndrome" (Levy et al 2011) PDE8 enzyme inhibitor will be helpful for studying the role of PDE8 in cardiovascular pathologies. (Keravis and Lugnier 2012).

PDE9- enzyme inhibitors BAY-73-6691, PF-04447943 (Keravis and Lugnier 2012) A potential new drug target to treat memory deficits associated with old age and neurodegenerative disorders diseases such as Alzheimer's disease (García-Osta et al 2012) BAY 73-6691 inhibits PDE9A" (Keravis and Lugnier 2012).

"BAY 73-6691 in rodents has demonstrated that PDE9 inhibition increases learning and memory" (Keravis and Lugnier 2012) PDE9A enzyme inhibitor that enhances synaptic plasticity and cognitive function (Keravis and Lugnier 2012) phosphodiesterase-9 (PDE9) enzyme inhibitors and biometal-chelators have received much attention as potential therapeutics for the treatment of Alzheimer's disease (AD).(Su et al 2016).

PDE10A
LOCATION- PDE10A is expressed mainly in brain (Keravis and Lugnier 2012), striatal medium spiny neurons, in pineal gland and, to a lower extent, in testis" (Keravis and Lugnier 2012).


PDE 10 A -enzyme inhibitors may also be used to treat cognitive deficits accompanied with schizophrenia. The PDE10A enzyme inhibitor TP-10 is active in a various preclinical models points towards its efficacious in the treatment of schizophrenia (García-Osta et al 2012). Papaverine is another PDE10A" (García-Osta et al 2012) PDE10 enzyme inhibitors are being considered as cognition enhancers (Maurice et al 2014).

Disorders neuropsychiatric (Maurice et al 2014) PDE10A enzyme inhibitors, which have been shown to have antipsychotic effects" (Maurice et al 2014), papaverine and MP-10 treatments act on the negative symptoms of schizophrenia" (Keravis and Lugnier 2012).
PDE 11
LOCATION- PDE11 is mainly present in prostate and to a lower amount in pituitary gland, liver and heart." (Keravis and Lugnier 2012) PDE11A is a genetic factor for the development of testicular and adrenal tumours (Libé et al., 2011).

PDE11A mutations were described in a subgroup of patients with Cushing syndrome (Maurice et al 2014). PDE11 mutations may increase susceptibility to prostate cancer or to adrenal and testicular tumours (Maurice et al 2014).

OTHER FUTURE POTENTIAL
CANCER, TUMOR :- abnormal regulation of cAMP levels may be a major determinant of brain tumorigenesis and altered expression of PDE (Sengupta et al 2011) enzyme inhibitors of PDE4 indicates that this may be a promising drug target to brain cancer therapy." (Sengupta et al 2011), immune-mediated disease and haematopoietic malignancies. (Lerner and Epstein 2006). PDEs in normal haematopoietic cells and the report suggest that family-specific enzyme inhibitors will be therapeutically useful in myeloid and lymphoid malignancies,(Lerner and Epstein 2006, Hiramoto et al 2014). PDEs in a variety of tumors, primarily in endocrine glands, both in tumor predisposition and as potential therapeutic targets (Levy et al 2011), PDEs are increased in prostatic cancer patients (Levy et al 2011). PDE7-selective enzyme inhibitors, have been reported to inhibit growth and induce apoptosis in many different human cancer cell lines" (Maurice et al 2014) PDE5 plays a role in cancer. In melanoma cells (Keravis and Lugnier 2012) PDE5 inhibition is responsible for the breast tumour cell growth enzyme inhibitory activity and apoptosis inducing activity of sulindac sulphite and may contribute to the chemopreventive properties of sulindac" (Keravis and Lugnier 2012) PDE-5 enzyme inhibitor use was not associated with decreased Prostate cancer (Jainnagerwalla et al 2016).

RESVERATROL AND CURCUMIN AS PDE ENZYME INHIBITOR
"PDE isozymes, including PDE3B, PDE8A, and PDE10A, which have been associated with the regulation of insulin secretion in islets of pancreas (Rouse et al 2014), Resveratrol and curcumin are polyphenols, natural-occurring polyphenols as PDE enzyme inhibitors that enhance pancreatic beta cell function (Rouse et al 2014).
PDE AS TARGET FOR T2 DM
A potential therapeutic target in the handling T2DM lies in regulating the activity of phosphodiesterases enzymes (Rouse et al 2014).

Traumatic brain injury - (Oliva et al 2012)-cyclic AMP (cAMP), a molecule involved in inflammation, is down-regulated after traumatic brain injury (Oliva et al 2012), therapies to reduce inflammation after Traumatic Brain Injury could be facilitated with targeted therapies, in particular for PDE1A, PDE4B2, PDE4D2, or PDE10A." (Oliva et al 2012) cyclic nucleotide levels to mediate neuro-protection or neurorepair (Knott et al 2017).

KIDNEY INJURY AND MITOCHONDRIAL DYSFUNCTION- PDE enzyme inhibitors that increase cGMP are inducers of Mitochondrial biogenesis in vitro and in vivo, and suggest their potential efficacy in AKI(Acute Kidney Injury) and other diseases characterized by mitochondrial dysfunction and suppressed Mitochondrial Biogenesis (Whitaker et al 2013).


PDE4 catalytic domains together support the feasibility of designing the next generation of anthelmintics/nematicides that could selectively bind to nematode PDEs." (Schuster et al 2019).

ORAL DISEASE related to hyposalivation (Ahmad et al 2015).

LIVER DISEASE- "NAFLD(Non-alcoholic fatty liver disease), ALD (alcoholic liver disease) and in other liver diseases and focus on PDE inhibition as an exceptional therapeutic target in these condition" (Wahlang et al 2018).

DUAL PDE ENZYME INHIBITORS -enzyme inhibitors of PDE10A and disease PDE4 in Huntington's" (Maurice et al 2014). KF19514, which inhibits both PDE1 and PDE4, was reported to reduce airway remodelling and inflammation asthma in a murine model (Maurice et al 2014), Inhibition of PDE7 and PDE4 could be an effective strategy to treat asthma, COPD" (Maurice et al 2014). Enzyme inhibitors with dual selectivity for PDE3 COPD and PDE4 as potential therapeutics for asthma and COPD” (Maurice et al 2014) "PDE3/4 enzyme
inhibitors are now designed as therapeutic agents for chronic obstructive pulmonary disease.” (Keravis and Lugnier 2012).

"PDE7/PDE4 dual enzyme inhibitors would represent a novel class of drugs that could regulate pro-inflammatory and immune T-cell function and be especially useful in treating a wide variety of immune and inflammatory disorders (Keravis and Lugnier 2012) Org 30029 - mixed PDE3 and 4 enzyme inhibitor (Eskandari et al 2004).

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