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PI3KΓ: A KEY PLAYER IN CANCER SIGNALLING PATHWAYS AND THERAPEUTIC TARGET FOR CANCER TREATMENT

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ABSTRACT: Phosphoinositide 3-kinase gamma (PI3Kγ) plays a vital role in cell signaling pathways essential for various physiological processes, including cell growth, differentiation, and survival. Dysregulation of PI3K signaling is implicated in the development and progression of several cancers. Activation of PI3K leads to the phosphorylation of critical proteins such as protein kinase B (PKB), ribosomal protein S6 kinase (RSK), and extracellular signal-regulated kinases 1 and 2 (ERK1/2), facilitated by the presence of phosphatidylinositol 3,4,5-triphosphate (PIP3). PI3K is involved in regulating immune responses, including thymocyte growth, neutrophil migration, and T cell activation. Numerous malignancies, including melanoma, lung cancer, prostate cancer, and breast cancer, have been linked to PI3K activity. For instance, PI3K activation is known to enhance breast cancer cell migration and invasion by stimulating the Akt/mTOR signaling pathway. Structurally, PI3Kγ consists of a catalytic subunit (P110γ) and regulatory subunits that modulate its activity. The P110γ domain architecture includes a C2 domain, helical domain, Ras-binding domain, and catalytic domain, which are critical for its function. The ATP binding pocket of P110γ is organized into distinct regions that influence substrate affinity and interactions, providing potential targets for inhibitor design.The PI3K pathway is activated through a multi-step process involving G protein-coupled receptors (GPCRs) and receptor tyrosine kinases (RTKs), resulting in the conversion of phosphatidylinositol (4,5)-bisphosphate (PIP2) to PIP3. This activation is tightly regulated by the phosphatase PTEN, which dephosphorylates PIP3 back to PIP2. PI3Kγ also influences cancer stem cell dynamics and immune modulation in the tumor microenvironment, presenting opportunities for novel therapeutic strategies.

INTRODUCTION: The enzyme PI3K, also known as phosphoinositide 3-kinase gamma, is crucial for cell signalling pathways that are involved in several physiological activities, including cell development, cell differentiation, and proliferation, and survival.

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Many forms of cancer are known to arise and advance because of PI3K signalling dysregulation [1]. The phosphorylation of protein kinase B (PKB), ribosomal protein S6 kinase (RSK), and extracellular signal-regulated kinases 1 and 2 (ERK1/2) is one of the signalling pathways that are activated in response to activating a GPCR. Presence of phosphatidylinositol 3,4,5-triphosphate (PIP3) makes this activation possible. which is connected to via PI3K. As a result, PI3K controls the growth of thymocytes, neutrophil migration, oxidative burst, and T cell activation. According to studies, many malignancies, including melanoma,

lung cancer, prostate tumors, & breast cancer, have been linked to PI3K. For instance, it's been demonstrated that PI3K activates the Akt/mTOR signalling, enhancing breast cancer cell invasion and migration [2]. PI3K has been discovered to control androgen receptor signalling and support cancer cell survival and proliferation in prostate cancer.PI3Kγ has been demonstrated to support tumour development and treatment resistance in lung cancer. By stimulating the Akt signalling pathway in melanoma, PI3Kγhas been demonstrated to improve the survival and multiplication of cancer cells.

Although p110 γ isoform is activated by both the Ras and GPCR pathways, current research has revealed a complicated interplay between these pathways. Reduced signalling downstream of GPCRs in neutrophils is the result of mutations in p110 γ that inhibit binding to Ras [3].

The PIK3CG gene produces the phosphoinositide 3-kinase gamma (PI3Kγ) enzyme, which belongs to the class I PI3K family. It is a lipid kinase that catalyses the production of second messenger molecules by phosphorylating phospha-tidylinositol's 3'-hydroxyl group on the inositol ring (PIs), which in turn activates signalling pathways that are crucial for cell growth, survival, and metabolism.

PI3Kγ Structure: The regulatory adaptor subunits p87/84 or p101, together with the catalytic subunit P110γ, make up the heterodimeric form of PI3Kγ. The catalytic P110γ has four domains formed from the residues 114 to 1102 namely, this includes the C2 domain, helical domain, Ras-binding domain, and catalytic. C2 domain consists of amino acid residues 357 to 522 responsible for the interaction with the membranes. RBD is formed from the residues 220 to 311 flanking next to the catalytic domain of P110γ and is known to activate the enzyme by the allosteric site mechanism. The function of helical domain containing residues from 547 to 725 is not interpreted till date. p110γ's catalytic domain comprised of amino acid residues from 726 to 1092 of which residues 726 to 883 accounts for the N lobe and the rest makes up the C-Terminal connected by a loop to the former lobe that represents the innate border of the ATP binding pocket. This structural representation is somewhat like that of numerous kinases hence making it difficult for the development of specific inhibitors of various isoforms [4].

ATP Binding Pocket: The ATP binding pocket is divided into four regions - hydrophobic region II , Hinge zone, specificity region, affinity pocket. These regions classified depending upon their affinity for the substrate binding. In the hinge region of p110γ, spanning from the N to C terminals. Adenine ring facilitates two H-bonds with Val882 & Glu880. Above and below of the ATP binding site, hydrophobic amino acid- Ile879, Ile831, lle963 & Phe961 encloses the adenine ring. The P loop interacts with the phosphate region of ATP represented by the amino acids from 803 to 811. The ribose ring faces hydrophobic region II and lacks every interaction with the protein. Three hydrogen bonds are facilitated between residues - Ser806, Asn951, Lys833 and the triphosphates of ATP [5].

The PI3Kγ Pathway: The PI3K pathway is functionally important, and it is activated in a multistep process. Activated G protein Coupled receptors and RTKs stimulate class 1 PI3Ks that are coupled to their regulatory subunits or adapter molecules. Upon activation, PI3K catalyses the conversion of phosphatidylinositol (3,4)-bisphosphate (PIP2) to phosphatidylinositol (3,4,5)-trisphosphate through its catalytic domain. The PTEN (Phosphate and tensin Homolog) dephosphorylated PIP3 to PIP2 and hence regulated the PI3K pathway. At the plasma membrane, The Akt binds to PIP3 and gets activated which triggers the beginning of numerous signaling pathway responsible for translation, cell proliferation, cell survival and apoptosis and so on [6].

Formation of cancer, growth of tumours, metastasis, and cancer recurrence are all significantly influenced by cancer stem cells (CSCs). Using mouse induced pluripotent stem cells (miPSCs) exposed to conditioned medium (CM) made from cancer cells, researchers have effectively created a model of CSCs. During this conversion process, the PI3K-Akt and EGFR signalling pathways are seen to be activated. Studies done in vivo and in vitro have revealed that inhibitors of these pathways, in particular PI3K inhibitors, significantly reduce the capacity of cells

to grow, replicate, move, and invade. These results imply that future treatment strategies against CSCs may involve targeting these pathways [7].

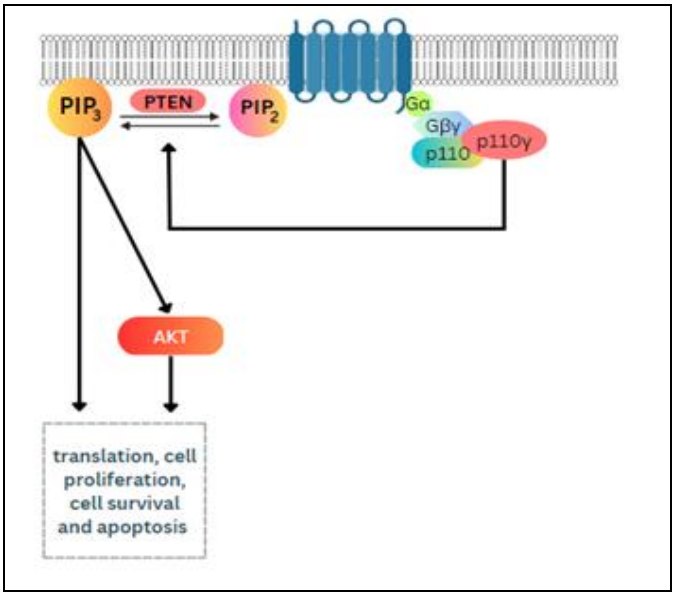

FIG. 1: ILLUSTRATION OF THE PI3KΓ SIGNALING PATHWAY

In addition, the ERK activation downstream of PI3K-γ is required for the parasite-induced, reactive oxygen species-dependent netosis.The release of parasitic neutrophil extracellular traps is greatly decreased by pharmacologically inhibiting protein kinase C [8].

PI3Kγ as Therapeutic Target:

PI3Kγ in Hematologic Malignancies: Because PI3K isoforms have a great deal in common in terms of sequence homology, it is challenging to inhibit PI3K specifically to reduce inflammation and immunosuppression in the cancer microenvironment. IC_{50} = 0.064 M upon the THP-1 cell line revealed >700-fold isoform selectivity for PI3K by a novel family of potent PI3K inhibitors with high isoform selectivity produced by divergent projection of substituents into ATP binding site pockets. Increased -selectivity is achieved by inhibitors with bicyclic hinge-binding motifs and the capacity to make numerous hydrogen bonds to the PI3Kγ hinge region [9]. Because molecular switch PI3K γ regulates immune suppression, its blockage regulates the activation of macrophages and changes them into immunological responses which leads to anticancer activity. Although the AS-605 PI3K inhibitor effectively biochemically inhibited PI3K-Akt signalling in T-ALL cell lines, it had no detectable impact in preclinical studies utilising animals that had T-ALL cell transplants or *in-vitro*. Although PI3K inhibition alone does not seem to be adequate for T-ALL therapy, it may be a beneficial therapeutic approach in other clinical settings, such as cancer immune therapy [10]. Treatment options for T-cell acute lymphoblastic leukaemia (T-ALL) are few. Ras signalling is common in T-ALL, and PI3K inhibitors appear to be effective. However, in T-ALL cell lines, single-agent therapy is ineffective in causing cell death. Even though the combination of pan-PI3K and PI3K-specific inhibitors exhibits strong synergistic effect in vitro, preclinical testing in a cancer model called T-ALL that replicates genetic heterogeneity has been unsuccessful. For logical design, combination treatment may need techniques for resolving biochemical signals in different cell populations.

Macrophage PI3Kγ regulates immune response in inflammation and cancer, with therapeutic potential in controlling immune suppression. Inhibiting PI3Kγ promotes immunostimulant, restoring T cell activation and synergizing with checkpoint inhibitors for tumor regression and improved survival. Targeting PI3Kγ-mediated gene expression predicts survival in cancer patients [11]. Duvelisib works by inhibiting PI3Kδ/γ, which is also used to treat relapsed/refractory chronic lymphocytic leukaemia (CLL) and small lymphocytic lymphoma tumours (SLL). Duvelisib boosted autophagy inhibition and according to dose decreased lung fibroblast activation by inhibiting PI3K, Akt, and mTOR phosphorylation. Findings show that Duvelisib can lower the pulmonary fibrosis immunological severity and provide potential drugs for the therapy [12].

JN-PK1 inhibits a few cancer cell lines, especially those connected to blood cancer. Cell-free enzymatic tests show that this enzyme selectively targets PI3K and spares other PI3K isoforms at low micromolar doses. JN-PK1's interactions with the PI3K system's Ile881, Ile963, and Ile879 residues were important and were discovered by *in-silico* study. Additionally, the stable placement of JN-PK1 inside the active site may be impacted by an H-bond that forms between one of the acetyl groups in JN-PK1 and Lys833 in PI3K as well as steric hindrance brought on by Lys833's side chain [13].

PI3K-γ in Diet-induced Obesity and Insulin Resistance: PI3K-γ enzyme has been demonstrated to reduce conventional macrophage activation by promoting the production of immunosuppressive genes during acute inflammation. PI3K-γ has a large impact on both obesities brought on by diet and insulin resistance. In an effort to understand the behind molecular mechanisms, researchers found that the action of PI3K-γ in the control of adiposity, which was brought on by PI3K-γ function in a nonhematopoietic cell type, was largely dependent on its role in the regulation of inflammation and insulin resistance. Leukocyte PI3K-γ activity is nevertheless necessary for efficient neutrophil attraction to adipose tissue. PI3K-γ activity in leukocytes encourages early-onset insulin resistance and adipose tissue inflammation during obesity [14].

Chronic Rejection is Defended against PI3K Deletion: In clinical solid organ transplants, chronic rejection continues to be a significant factor in graft failure [15]. AA heart transplant model using class II MHC-mismatched hearts (specifically B6.H-2bm12 donor hearts into C57BL/6 recipients) to examine the role of PI3K inhibition in chronic rejection. When compared to WT receivers, heart allografts retrieved from PI3Kγ$^{-/-}$ recipients on day 28 had considerably less infiltration, fibrosis, and intimamedial thickness [16].

PI3Kγ Inhibition to Immune Suppression and Promotes Cancer Regression: PI3Kγ thought Akt and mTOR activation inhibits NFκB activation and C/EBPβ activation promotes immune suppression. Selectively inhibiting PI3Kγ reverses the activity. PI3Kγ and checkpoint inhibitor therapy give synergistic effects that promote tumour regression and increases the survival of the mouse model [17].

PI3Kγ Subunit Responsible for Regression in Tumour: In MDA MB-231 cells, PI3K subunits were knocked down separately (p84, p101, and p110γ), which lowered the cell lines' in vitro migration. In SCID animals, p110c or p101 knockdown prevented lung colonisation, Akt phosphorylation, and apoptosis. Like this, the suppression in 4T1.2 murine epithelial carcinoma cells of subunits p101 and p110γ prevented lung colonisation, spontaneous metastasis, and development of the main tumour. In contrast, Akt phosphorylation and lung colonisation were increased in MDA MB-231 cells with p84 knockdown. These results mark the first time that the two regulatory subunits of PI3Kγ have distinct roles in developing cancer, and they show the same degree as p110γ can be inhibited *in-vivo* cancer growth and metastasis by p101 deletion [18].

PI3K in Breast Cancer: Vascular disrupting agents (VDAs) have emerged as promising cancer treatments. A new VDA called poly(l-glutamic acid)-combretastatin A4 conjugate (PLG-CA4) shows significant antitumor activity. However, PLG-CA4 can trigger immune responses that promote tumor growth. In this study, researchers discovered that inhibiting phosphoinositide 3-kinase gamma (PI3Kγ) reduces the immunosuppressive effects of PLG-CA4 treatment. By inhibiting PI3Kγ, the number of M2-like tumor-associated macrophages (TAMs) decreased, potentially enhancing the presence of cytotoxic T lymphocytes (CTLs). Furthermore, the combination of a PI3Kγ inhibitor with PLG-CA4 resulted in prolonged survival and improved therapeutic effects when combined with an immune checkpoint inhibitor. These findings highlight the potential of PI3Kγ inhibition to enhance the efficacy of VDAs and overcome immune resistance in tumors [19]. Studies have shown out of multiple mechanism of immune resistance myeloid cells plays major role in tumour immunity by high filtration of immune suppressive cells and Immune checkpoint blocking (ICB). Selective pharmacological blocking of PI3Kγ overexpresses in myeloid cells restores ICB sensitivity. Which results in tumour reduction without a direct attack on cancer cells [20].

Neointimal Formation and Phenotypic Modification of Vascular Smooth Muscle Cells: Through controlling the production of YAP and the activation of the transcription factor CREB, PI3Kγ governs the phenotypic modification of VSMCs. A novel treatment strategy to treat proliferative vascular disease may involve modulating PI3Kγ signaling on the local vascular wall [21].

Bone Cancer Pain: This study investigated the role of PI3Kγ/Akt in bone cancer pain (BCP). Researchers found that PI3K and pAkt were increased in astrocytes, spinal neurons, even a tiny portion of microglia in rats that had cancer cells

transplanted. Spinal PI3Kγ inhibition reduced pAkt up-regulation and repressed BCP behaviour. These findings suggest that PI3Kγ/Akt regulation may be a potent BCP treatment approach [22].

Combination Therapy: Oncolytic viruses (OVs) show promise in anticancer immunotherapy, but treatment resistance remains a challenge. Tumor-Associated Myeloid Cells (TAMCs) the anticancer action is diminished of oncolytic virus M1 (OVM) by inhibiting $CD8^+$ T cells. OVM-induced TAMCs infiltrate and strengthen their immunosuppressive phenotype via IL-6 activation of PI3K-γ/Akt axis. Targeting PI3K-γ improves OVM efficacy by relieving TAMC-mediated immunosuppression, and checkpoint antibodies eliminate solid tumours that are resistant to treatment and activate a durable antitumor immunological memory. OVM's antitumor activity is double-edged, and TAMC-mediated immunosuppression must be abolished for T cell-mediated antitumor activity to prevail [23].

Tumours of the Pancreas: Blocking PI3Kγ and the colony-stimulating factor-1 receptor (CSF-1R) together has a synergistic impact that increases the anti-tumor effect by increasing M1 tumor-associated macrophages (TAM), improving M2 TAM, and decreasing the migration by myeloid-derived suppressor cells (MDSCs) into the tumour. Dual blockage gives an approach to alternate therapy for pancreatic cancer [24].

In macrophages found in pancreatic ductal adenocarcinoma (PDAC), PI3Kγ is highly expressed In murine of PDAC, PI3Kγ inhibition slows tumour development and progression and increases survival. Inhibiting PI3K prevents fibroblast-induced pancreatic desmoplasia and tumour cell migration by increasing lymphocyte T CD8 recruitment and decreasing macrophage production of Platelet Derived Growth Factor-BB (PDGF-BB). These results imply that PI3Kγ targeting in macrophages may be a possible PDAC treatment approach [25] in tumor-associated B cells PI3Kγ was also found to be substantially elevated. The only PI3Kγ inhibitors in clinical development, IPI-549, is a cutting-edge strategy for enhancing the anti-tumor immune response. polymeric nanoparticles (NP) of encapsulated IPI-549 investigated for its efficacy in melanoma models and pancreatic cancer in mice. In both cases, IPI-549 NP dramatically reduced tumour development and increased host survival. IPI-549 NP therapy significantly reduced the tumour's+suppressive microenvironment of both plasma and cells repressive myeloid in the tumour. This way IPI-549 NP administration might be an effective treatment for Tumours of the pancreas and similar immune-suppressive malignancies [26].

Breast cancer-In this study using mice models of breast cancer, Nano-PI and -PD1 together produced long-lasting tumour remission and eradicated lung metastases. The use of Nano-PI increased medication delivery to lymph nodes and tumours, whereas the use of PTX and IPI-549 promoted macrophage repolarization. According to immune cell profiling, CD8+ and CD4+T cells, dendritic cells and B cells increased whereas T cell and regulatory T cellsfatigue decreased. According to this research, combining Nano-PI and -PD1 can change the immunological milieu in tumours and lymph nodes, leading to the long-term remission of mice with metastatic breast cancer. As a possibility for further development, this combination offers bright future promise [27].

To alter the tumour immunological microenvironment, a nanoregulator incorporating MnO_2 particle and small molecules IPI-549 is created. It alleviates hypoxia along with inhibits PI3Kγ on MDSCs, resulting in PD-L1 downregulation, TAMs polarization, enhanced infiltration of Tc and Th cells also suppressed Treg cells infiltration of gives adequate tumor immunotherapy. This nanoregulator also allows tumor-specific MRI and effectively inhibits metastasis and tumor re-growth in an animal study [28].

Colitis Associated Cancer: Recurring flare-ups of damage to tissue characterise a chronic inflammatory disease of the colon, ulcerative colitis. In people with susceptible genes, it is thought to be brought on by an aberrant immunological response to the intestinal microbes. Colorectal cancer can occur because of ulcerative colitis's chronic colon inflammation. Recent research has demonstrated that PI3K regulates the innate immune response in the gut and that deregulation of this pathway can lead to the onset of ulcerative colitis & colorectal cancer.

By regulating the actions of innate immune cells like macrophages, PI3K inhibition has been demonstrated to lessen colon inflammation & tumor development in a mouse model of ulcerative colitis [29].

Chemical Language Models: CLM-based bioactivity prediction was used to refine a virtual chemical library. CLM that has been fine-tuned using known PI3Kγ ligands. Experimentation verified computer-generated designs. There has been the discovery of a novel PI3Kγ ligand having sub-micromolar activity, showing scaffold-hopping potential.

Chemical synthesis and biological tests showed the ability to produce PI3Kγ ligands having medium to minimal nanomolar activity. In a medulloblastoma cell model, the most effective medications reduced PI3Kγ dependent Akt phosphorylation, indicating the potency of PI3K ligands in suppressing the PI3K/Akt pathway in cancer cells [30].

PI3K Signaling in PDAC: The decrease in tumour size brought on by p110 deficiency can be reversed by HFDs through compensatory increased levels of alternative p110 isoforms. Even though p110γ acts as a cell-autonomous malignancy promoter, systemic p110γ deficiency in the presence of a compromised exocrine pancreas can result in minor liver damage that can worsen in the presence of a high-fat diet. Additionally, this impairs the metabolism of lipids and glucose. These data suggest that PI3K pathway-targeting drugs may be underutilised for the treatment of Pancreatic ductal adenocarcinoma (PDAC) and may increase the risk of adverse effects, such as Non-Alcoholic fatty liver disease (NAFLD), particularly in the setting of obesity [31].

Clinical Trials Investigating PI3Kγ Inhibitors: Several clinical trials are currently underway to investigate the efficacy and safety of PI3Kγ inhibitors. These trials aim to explore the potential of targeting PI3Kγ for various medical conditions. The following table summarizes some of the ongoing clinical trials investigating PI3Kγ inhibitors, as listed on the clinicaltrials.gov website [32].

TABLE 1: CLINICAL TRIAL DATA ON PI3Kγ

Study Title	Conditions	Interventions	Phases
Safety and efficacy study of tenalisib (RP6530) in combination with pembrolizumab in relapsed or refractory CHL	Classical hodgkin lymphoma	Drug: tenalisib biological: pembrolizumab	Phase1
A study of duvelisib in combination with pembrolizumab in head and neck cancer	Head and neck squamous cell carcinoma	Drug: duvelisib biological: pembrolizumab	Phase1|phase2
A safety and efficacy study of duvelisib in relapsed/refractory follicular lymphoma	Follicular lymphoma	Drug: duvelisib	Phase2
Safety and efficacy study of a dual PI3K delta/gamma inhibitor in T-cell lymphoma	Lymphoma, T-cell, peripheral lymphoma, T-cell, cutaneous	Drug: RP6530	Phase1
Efficacy and safety of tenalisib (RP6530), a PI3K δ/γ and SIK3 inhibitor, in patients with locally advanced or metastatic breast cancer	Locally advanced breast cancer metastatic breast cancer	Drug: tenalisib drug: tenalisib	Phase2
Safety and efficacy of tenalisib (RP6530) in combination with romidepsin in patients with relapsed/refractory T-cell lymphoma	T cell lymphoma	Drug: tenalisib drug: romidepsin	Phase1|phase2
Window of opportunity study of IPI-549 in patients with locally advanced HPV+ and HPV- head and neck squamous cell carcinoma	Head and neck squamous cell carcinoma head and neck cancer head and neck carcinoma head and neck cancer stage IV head and neck cancer stage III HPV-related carcinoma HPV-related malignancy HPV-related squamous cell carcinoma	Drug: IPI-549	Phase 2
Efficacy and safety study of tenalisib (rp6530), a novel PI3Kδ/γ dual inhibitor in patients with relapsed/refractory indolent non-hodgkin's	Non hodgkin lymphoma	Drug: tenalisib	Phase 2

lymphoma (iNHL)			
A study of duvelisib in patients with relapsed or refractory peripheral t cell lymphoma (PTCL)	Peripheral t-cell lymphoma	Drug: duvelisib	Phase 2
Efficacy and safety of tenalisib (RP6530) in patients with relapsed/refractory chronic lymphocytic leukaemia (CLL)	Leukaemia, lymphocytic, chronic, B-cell	Drug: tenalisib	Phase 2

CONCLUSION: Inhibitors targeting the PI3K-Akt and EGFR signalling pathways show promise in inhibiting the growth, invasion and migration abilities of cancer stem cells (CSCs) and may be effective in future therapies. Selective inhibition of PI3Kγ has shown significant results in inhibiting cell proliferation and self-renewal. Additionally, PI3Kγ inhibition has been found to regulate immune suppression, activate macrophages, and promote anti-cancer activity. In various cancer types, including leukaemia and breast cancer, targeting PI3Kγ has shown potential in combination therapies and immune modulation.

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