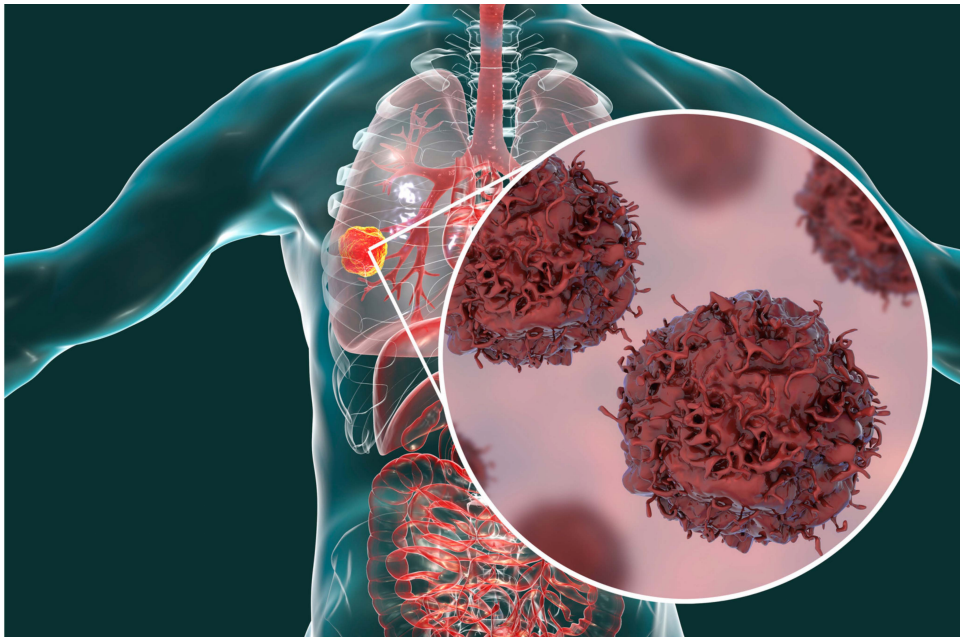
Berkeley Pharma Tech
Journal of Medicine

Exploring the Therapeutic Potential of PTPN Families in Lung and Digestive Cancers

By: Hasset Yishak, Kareem Halwah, and Jiyun Rhim



Correspondence:
hasset1@gmail.com

Keywords:
PTPN
Digestive cancer
Phosphatase
Lung cancer
Tumor promoter

Abstract

Protein phosphorylation and dephosphorylation are pivotal in regulating protein activity. Two key players, protein tyrosine kinases and protein tyrosine phosphatases (PTPN), especially non-receptor PTPNs, exert opposing influences in this process. While all PTPNs dephosphorylate substrates, their impact on different cancers varies. Some act as tumor suppressors in specific cancers, while in others, they may function as tumor promoters. This review focuses on comprehending the roles of PTPNs in lung and digestive cancers. Notably, lung cancer ranks as the third most common cancer in the US, with around 200,000 new cases reported annually. Despite declining rates in the United States, stomach cancer remains a major cause of cancer-related deaths worldwide. The objective of this review article is to elucidate the functions of PTPN1, PTPN2, PTPN3, PTPN6, PTPN11, PTPN12, and PTPN13 in lung and/or digestive cancers. Emphasis is placed on exploring their potential as prognostic markers or therapeutic targets.

Submitted: May 10, 2023
Accepted: June 30, 2023
Published: December 30, 2023

Full Open Access

Creative Commons Attribution License 4.0

1. Introduction

Cancer is a leading cause of death all over the world, and the complications associated with the disease makes it difficult to efficiently treat. Various types of cancer exist, such as lung cancer, gastric cancer, breast cancer, lymphoma, prostate cancer, and kidney cancer. Lung cancer is the second most common cancer in the United States,[1] with approximately 80% of lung cancers being non-small lung cancer (NSCLC). Furthermore, lung cancer accounts for the greatest number of deaths stemming from cancer in men with a 5-year survival rate ranging from 10 % to 20%.[2] Digestive cancer encompasses different types of cancer, such as gastric and colorectal cancer. Gastric cancer, also known as stomach cancer, significantly affects 1 in 96 men and 1 in 152 women.[1] Known as the fifth most common cancer in the world, gastric cancer's 5-year survival rate is 32%.[3] Current cancer treatments include surgery, chemotherapy, hormone therapy, radiation therapy, hyperthermia, immunotherapy, and targeted therapy.[4,5] Despite the variety of treatments, these treatments are not fully effective as millions of people continuously die from cancer annually. Thus, there is a strong drive to develop alternative treatments by exploring the molecular mechanisms of various proteins involved in the progression or inhibition of cancer.

1.1 Introduction to PTPN

With current experimentation being conducted in regards to novel therapeutics in lung and digestive cancer, this review paper explores, as well as summarizes, the existing body of scientific literature on the family of protein phosphatases known as non-receptor protein tyrosine phosphatases (PTPN). Phosphorylation and dephosphorylation are highly used mechanisms by the cell to regulate signaling within and between cells. Importantly, PTPNs affect tumor progression by dephosphorylating proteins in order to activate or inhibit potentially oncogenic pathways.[6] This creates a strong potential for PTPN families to be used as a prognosis marker and/or therapeutic target in treating lung and digestive tract cancers. Therefore, this literature review characterizes the importance of several PTPNs, PTPN 1, 3, 6, 11, 12, 13, by summarizing their roles as a tumor promoter, tumor suppressor or both as well as exploring their molecular mechanisms in digestive and/or lung cancer [Figure 1].

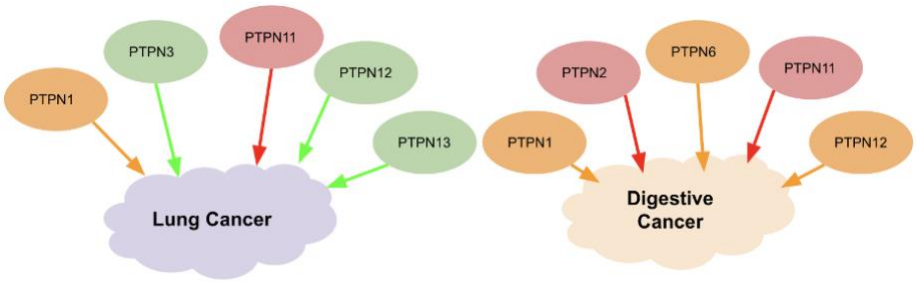


Figure 1: ***An overview of the role of each PTPN in lung or digestive cancer****. PTPNs marked in green have tumor suppressing capabilities, red as tumor promoting, and orange as having both tumor suppressing and promoting capabilities.*

2. PTPN1

PTP1B, also known as protein tyrosine phosphatase non-receptor 1B, is encoded by the PTPN1 gene. Its uncontrolled growth is shown to be correlated with growth of digestive cancer, demonstrating PTPN1B's potential oncogenic role in digestive cancer.[7] For CRC (colorectal cancer), PTP1B was associated with CRC patients' low overall survival; additional studies also support the relationship of PTP1B overexpression and late stage tumors.[8] Therefore, PTP1B expression level can be utilized as a possible biomarker for prognosis of late stage tumors, including CRC.[9]

2.1 Gastric Cancer

Likewise, according to the RT-PCR assay, PTP1B was found to be overexpressed in gastric cancer tissues relative to normal gastric cells. Amplification of PTP1B was associated with poor survival of gastric cancer patients.[9] Therefore, the amplification of PTP1B can be both used as a biomarker for gastric cancer and indicative for poor survival rate, revealing PTP1B's oncogenic role as a tumor promoter in gastric carcinogenesis.[10] Furthermore, inhibition of PTP1B in gastric cells was associated with hindrance of gastric cancer cell growth in both *vitro* and *vivo*. Furthermore, its inhibition changed genome-wide expression of genes related to cell growth; thus, PTP1B can be directly used as cancer therapy to slow down digestive cancer growth.[11]

Despite there being evidence of PTP1B functioning as a tumor promoter, contrasting ideas in the literature suggest it can also function as a tumor suppressor depending on the cellular context.[12] For example, when EGF (Epidermal Growth Factor) binds to its receptor EGFR, it activates the Shc-Grb2-SOS interaction. At the end of interaction, Ras activates MEK/Erk pathway's Raf and ends with Erk

entering the nucleus to activate FGF2 (Fibroblast Growth Factor 2) which causes uncontrolled growth of the cancer.[13] If PTP1B does not interfere in the process, FGF2 promotes cancer growth. However, PTP1B can inhibit the process by interacting at the beginning or end of the Shc pathway and/or prohibiting the entry of Erk into the nucleus PTP1B's inhibition of signaling pathways leads to decrease in cancer growth[13] [Figure 2].

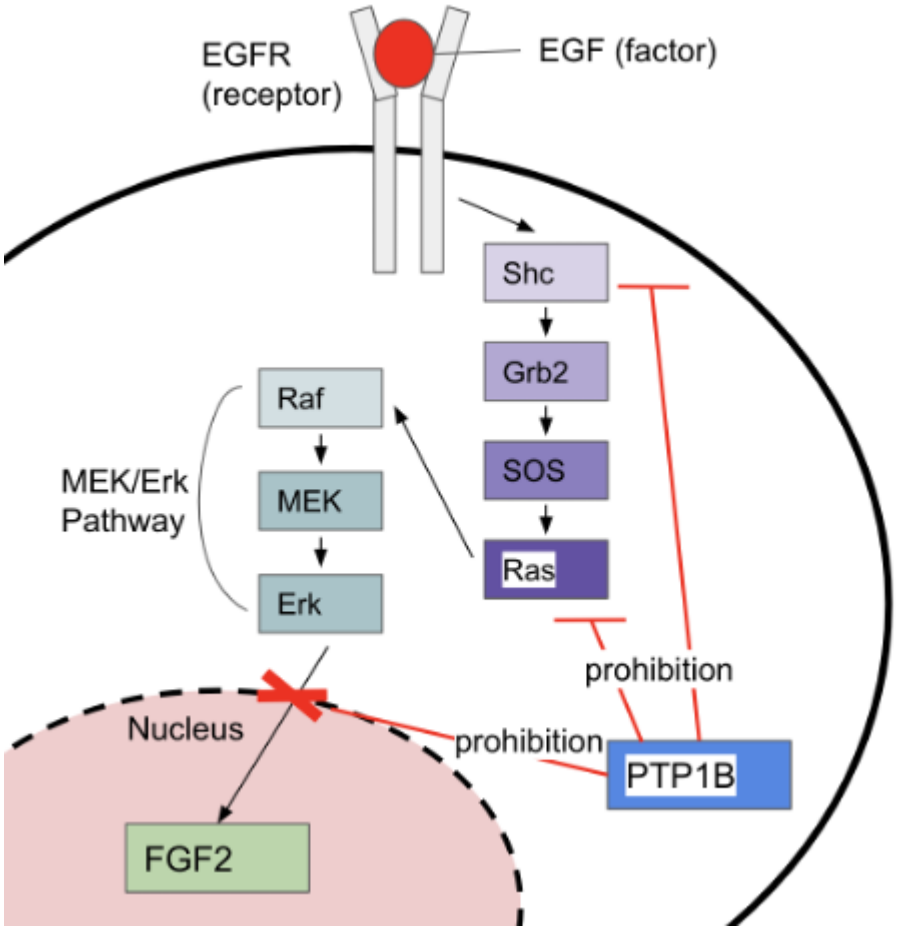


Figure 2: Effect of PTP1B on the pathway of cancer growth. *When PTP1B prohibits Shc-Grb2-SOS interaction, the growth of cancer is prohibited due to a decreased expression of FGF2. Oppositely, when PTP1B does not stop the pathway, the cancer cells will be able to proliferate and duplicate itself.*

2.2 Non-Small Cell Lung Cancer (NSCLC)

In regards to NSCLC, PTP1B levels increase with the progression of the cancer, highlighting how increased PTP1B levels are associated with poor survival of patients with NSCLC.[14] Additionally, when PTP1B expression was downregulated,

there was a decrease in cell proliferation and metastasis in *vitro*. Likewise, downregulation of PTP1B in mice transfected with NSCLC cells showed a significant decrease in tumor size compared to control mice that had unaltered PTP1B levels. These results provide evidence for PTP1B's role as a tumor promoter in lung cancer. Mechanistically, PTP1B activates the oncogene, Src (Proto-Oncogene c-Src), which promotes NSCLC proliferation and metastasis. Therefore, designing an inhibitor of PTP1B could be promising in treating NSCLC due to its suggested tumor suppressing capabilities.[14]

In Lung Adenocarcinoma (LUAD), PTPN1 is downregulated according to comprehensive bioinformatics analysis. Its upregulation has been conferred with overall higher survival rates in patients, demonstrating the overexpression of PTPN1 as a potential therapeutic target for treating LUAD patients. As well, decreased expression can be a prognostic biomarker for lung cancer progression.[15]

3. PTPN2

In CRC tumor cells, PTPN2 levels are enhanced, with greater PTPN2 gene expression correlated with reduced T cell activity, recruitment, and cytotoxicity.[16] It is also inversely correlated with low immune checkpoint molecule expression.[16] PTPN2 negatively regulates IFN-γ signaling, a pathway involved in the upregulation of immunity related genes, by dephosphorylating proteins involved in the signaling pathway. Mouse models with tumors deficient in PTPN2 had increased activation of the IFN-γ receptors by the cytokine, IFN- γ, which resulted in the phosphorylation of the signal transducer and transcription protein, STAT1 [Figure 3]. STAT1 is able to homodimerize and enter the nucleus to drive transcription of genes involved in immunity related processes such as MHC-1, possibly PD-1, and others [16-8]. This results in the activation of CD4+ Th1 cells and increases the cytotoxicity of CD8+ T cells, which inhibits the growth of the tumor.[16] CD4+ Th1 cells is a type of T helper cell that releases cytokines in response to inflammation and is also involved in the activation and growth of CD8+ T cells, otherwise known as killer T-cells. Therefore, tumors deficient in PTPN2 have increased IFN-γ signaling, which results in a significant reduction of tumor size as well as greater mRNA expression of chemokines, like cxcl9/10/11 and ccl5.[16] This suggests that the inhibition of PTPN2 through a small molecule might prove to be an effective potential therapeutic drug. While additional experimentation would need to be conducted to better understand the kinetics involved with the inhibitors, a recent paper by Zhu et al.[19] has identified various small noncytotoxic molecule inhibitors that were able to inhibit PTPN2. This resulted in successful upregulation

of genes involved in IFN-γ signaling, and the sensitization of the CRC tumor to treatment.

3.1 KRAS Gene

Approximately 40% of patients with CRC have a missense mutation in the KRAS (Kirsten rat sarcoma viral oncogene homologue) gene.[20] Those with the mutation in the KRAS gene tend to have a relatively poorer prognosis compared to CRC patients with wild type KRAS.[20] KRAS encodes for the protein K-ras, which is part of the signaling pathway of RAS/MAPK, a pathway that induces cellular proliferation, migration, and cell growth. Mutations in KRAS are thought to be the most common oncogenic gene driver in human cancer, especially in pancreatic cancer, CRC, and NSCLC.[21] These mutations lead to a continued active state of KRAS that result in continuous proliferation of tumor cells by upregulating the RAS/MAPK pathway. PTPN2 has been identified as a key regulator of KRAS due to its ability to dephosphorylate KRAS, activating the KRAS-mediated MAPK pathway.[22] Therefore, it is hypothesized that inhibition of PTPN2 could suppress cancer by no longer activating KRAS, presenting itself to be a novel therapeutic target.[22]

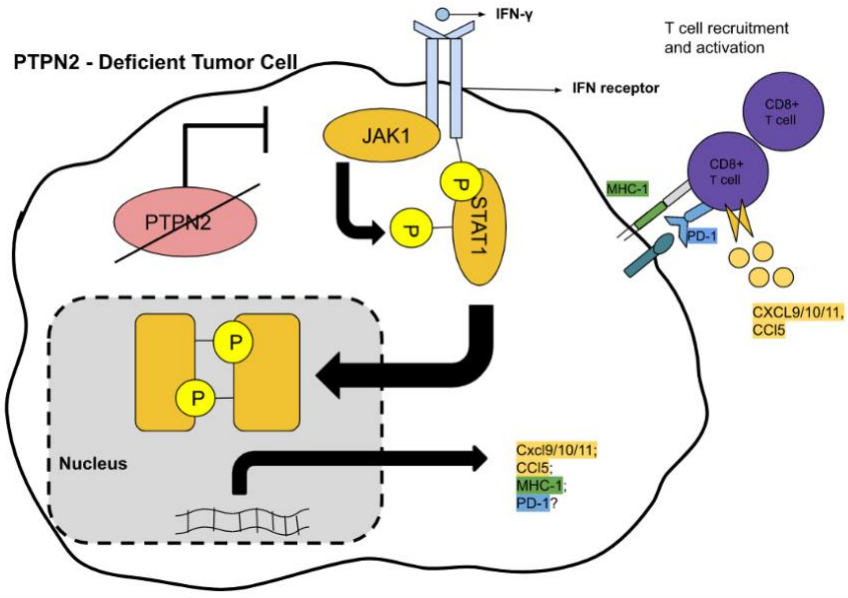


Figure 3: IFN-γ signaling pathway in PTPN2 deficient tumor cell. *STAT1 remains phosphorylated and homodimerizes in order to enter the nucleus and induce the transcription of immune related genes. This ultimately leads to an increase in chemokines as well as CD8+ cells that reduce the size of the tumor.*

4. PTPN3

Nonsense and frameshift mutations in PTPN3 that hinder its phosphatase activity have been found in lung cancer tissue.[23] Consequently, overexpression of PTPN3 results in reduced lung cancer cell growth and migration, indicating that it might have tumor suppressor capabilities.[24,25] PTPN3 is capable of suppressing lung cancer cell invasion by dephosphorylating the protein, Src, at Tyr416, which inhibits Src-mediated phosphorylation of Tyr652 on another protein known as Dishevelled Associated Activator of Morphogenesis 1 (DAAM1).[24] Tyrosine phosphorylation of DAAM 1 at Tyr652 by Src is needed for DAAM1 dimerization.[24] In the absence of PTPN3, DAAM1 is able to dimerize, leading to long and thick actin, which improves cancer cell migration. PTPN3 knockdown cells moved 30% faster than the control which had normal expression of PTPN3.[24]

4.1 EGFR

Additionally, PTPN3 is able to target EGFR for lysosomal degradation inhibiting proliferation of cancer cells. PTPN3 is capable of dephosphorylating EPS 15, which promotes the endocytosis of EGFR, given that EGFR is bound to its ligand, EGF.[25] When EGFR is internalized via lipid raft-mediated endocytosis, it is either recycled back to the cell surface, targeted to the lysosome for degradation, or internalized to subcellular compartments.[25] Thus, since PTPN3 is capable of causing EGFR to be degraded via its effects on Eps 15, PTPN3 functions as a tumor suppressor. Overexpression of PTPN3 resulted in a decrease of EGFR levels when stimulated by EGF.[25] This confirmed dephosphorylation of Eps15 by PTPN3 is capable of suppressing tumor growth.

5. PTPN6

5.1 CRC Tissue

PTPN6 was highly expressed in CRC tissue as demonstrated by qPCR, CCK-8, clone formation assay, and other assessments.[26] The overexpression of PTPN6 in malignant colon cancer cells was associated with poor prognosis in colon cancer patients. Conversely, the inhibition of PTPN6 restrained migration, invasion, and clonogenics of CRC tissues.[26] Therefore, PTPN6 amplification can potentially be used as a biomarker for CRC and its progression. PTPN 6 is a possible tumor promoter due to its ability to promote proliferation and migration of tumor cells. Additionally, PTPN6 interacts with EGFR, a receptor known to induce pathways

involved in proliferation, migration, and adhesion. Increased expression of both PTPN6 and EGFR resulted in the greatest cancerous proliferation as compared to cells with only PTPN6 or EGFR overexpressed. Thus, either targeting PTPN6 or the PTPN6-EGFR complex with an inhibitor could be a potential therapeutic.

However, other research suggests PTPN6 might have tumor suppressing capabilities by decreasing the levels of the protein SP1 (Specificity Protein 1). MAPK pathway is typically activated by SP1; however, due to PTPN6's inhibition of SP1, MAPK pathway is consequently suppressed. PTPN6 inhibition promotes enhanced chemosensitivity within CRC cells. Yet, more research needs to be conducted in order to further understand the various effects of PTPN6 within CRC.[27]

6. PTPN11

6.1 Shp2

PTPN11 is a gene that encodes for Shp2, a protein consisting of two N-terminal Src homology (SH2) domains, a catalytic PTP domain, and a C- terminal tail with tyrosyl phosphorylation sites.[28] Shp2/PTPN11 is involved in promoting signaling pathways such as Ras/ERK, RAS/MAPK, JAK/STAT, as well as KRAS signaling within the tumor microenvironment.[28] Increased expression of Shp2/PTPN11 is associated with a 5.34 fold increase in risk for gastric cancer and a 2.95 fold increase in risk for lung cancer.[29] Furthermore, other studies have found Shp2 to be highly expressed in 60.78% of gastric cancer and 70% of NSCLC tissue samples.[29]

Patients infected with *Helicobacter pylori* are at a greater risk for gastric cancer.[30] A virulence factor of *H. pylori* known as Cytotoxin associated antigen (CagA) is able to interact with the epithelial gastric cells, leading to the Src-dependent tyrosine phosphorylation of CagA.[30] The phosphorylated CagA binds with Shp2, forming a complex that allows for the transition of Shp2 into its active form. In its active form, Shp2 is capable of inducing oncogenic properties, such as neoplasia, gastric atrophy, and increased migration of gastric epithelial cells.[30] In contrast, in many cases of lung cancer, a missense mutation in the PTPN11 gene leads to a dysfunctional Shp2 protein that results in inappropriate activation of various signal transduction pathways.[31]

Due to the proto-oncogenic nature of PTPN11, various strides have been made in developing small molecule inhibitors which are capable of binding to the catalytic site of Shp2. One potential inhibitor, SHP099, is able to bind to the N-terminal, C-

terminal and PTP domain on SHP2, resulting in increased immune system activity such as greater IFN-γ signaling. This induced greater transcription of cytotoxic T-cell related genes within a mice model for lung cancer treatment.[31] While most of Shp2 inhibitors are in the preclinical study stages, the potential of PTPN11 as a therapeutic drug target is a promising prospect in treating many types of cancers, including gastric and lung cancer.

7. PTPN12

PTPN12 is a tumor suppressor that normally has an inhibitory effect on the Ras/MEK/ERK signaling by dephosphorylating the protein Shc.[32] However, it was hypothesized that a missense mutation in PTPN12 would leave Shc phosphorylated, resulting in hallmarks of cancer, such as cellular proliferation and increased migration.[33] For example, researchers identified that a variant of PTPN12 (rs3750050 G allele) increased the risk of CRC by 19%.[33]

Conversely, upregulation of PTPN12 has been correlated with incidences of esophageal carcinoma, stomach adenocarcinoma and colorectal cancer, making it a highly favorable candidate for biomarker.[34] The researchers acknowledge that these findings are seemingly in contradiction with previous literature that suggests PTPN12 to have tumor suppressing capabilities.[34] Another study showed that PTPN12 might be a favorable prognosis marker for NSCLC in patients due to higher expression levels associated with higher 5-year survival rates, especially within the subgroup with non-squamous cell carcinoma.[35] Due to the non-definitive role of PTPN12, further research still needs to be conducted.[33-35]

8. PTPN13

Like many of the other PTPNs previously discussed, PTPN13 has been shown to have both tumor suppressive and tumor promoting roles depending on the cancer being examined.[36] PTPN13 was shown to act as a tumor suppressor in breast cancer[37] and high grade serous ovarian carcinoma.[38] Likewise, in lung cancer, PTPN13 has been shown to have tumor suppressor capabilities by acting on various pathways.[38-42]

PTPN13 is downregulated in lung cancer mainly due to a loss of at least one copy of the PTPN13 locus at chromosome 4q.[40] 40% of cases are not accounted for by this mechanism, however, and further research is needed to understand how it is downregulated in those cases.[40] Various studies have shown that PTPN13

downregulation results in increased proliferation of NSCLC [39-41] in addition to greater tumor cell size.[40] To further confirm the role of PTPN13, PTPN13 expression was restored to PTPN13 knockdown cells and this resulted in slower proliferation of NSCLC.[40]

PTPN13's tumor suppressing capabilities stem from it inhibiting various oncogenic pathways. This is explored through the use of microRNAs which are known to have different effects on LUAD proliferation. For example, miR-361[43] and miR-340[44] inhibit LUAD cell growth while miR-483[45] and miR-224[46] promote LUAD cell growth. MicroRNA-30e-5p (miR-30e) is of interest to this review paper due to its ability to downregulate PTPN13 [Figure 4B]. Knockdown of miR-30e suppresses LUAD growth, suggesting that the presence of miR-30e is indicative of poor prognosis.[39] Upregulation of PTPN13 counteracts the tumor promoting effects of miR-30e by inhibiting EGFR/AKT signaling.[39]

PTPN13 was also shown to inhibit the Src/ERK/YAP1 signaling pathway, further contributing to its tumor suppressive properties in lung cancer. YAP1 promotes the proliferation of NSCLC cells, classifying it as an oncoprotein.[42,47] YAP1 has also been shown to activate the MEK/ERK pathway by promoting the expression of FGF2[39] [Figure 4A]. Nuclear YAP1 levels were increased in PTPN13 knockdown cells, indicating that PTPN13 might act to inhibit YAP1. It is also thought that YAP1 could be upregulated via the MEK/ERK pathway when PTPN13 is suppressed.[42] Thus, another pathway by which PTPN13 acts as a tumor suppressor is by inhibiting the MEK/ERK pathway, which suppresses the upregulation of YAP1.

Various cancers, including lung cancer, have been shown to have higher than normal levels of HER2, indicating that upregulation of HER2 leads to tumor growth and poor prognosis**.** PTPN13 downregulates HER2 activity by dephosphorylating the cytoplasmic domain of HER2, possibly decreasing the metastasis associated with HER2-overactive NSCLC tumor cells.[41] PTPN13 was also found to dephosphorylate EGFR.[40] Downregulation of PTPN13 increased EGF-stimulated EGFR and HER2 phosphorylation, leading to increased activation of MAPK and Akt dependent pathways.[40]

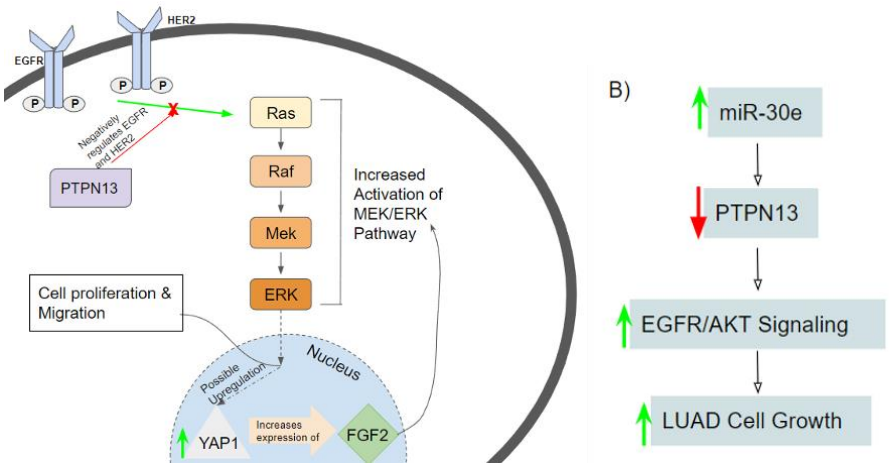


Figure 4: Overview of PTPN13's effect on various pathways. *PTPN13 has been shown to work by affecting the MEK/ERK pathway in different ways. A) PTPN13 can downregulate EGFR and HER2 receptors by dephosphorylating them [40]. YAP1 levels decrease in the presence of PTPN13, which could be due to PTPN13 inhibiting the MEK/ERK pathway. B) miR-30e is capable of downregulating PTPN13, resulting in increased cell growth in LUAD by promoting EGFR/AKT signaling.*

9. Current Clinical Trials

There are ongoing clinical trials exploring the efficacy of small molecule inhibitors on PTPN11, like JAB-3068 and JAB-3312, in patients with advanced solid tumors. It is hypothesized that these small molecules will prevent various oncogenic phenotypes associated with hyperactivation of Shp2 mediated signal transduction pathways. JAB-3068 is currently in Phase 1/2a and is recruiting patients with advanced solid tumors of NSCLC, head and neck cancer, esophageal cancer, and other metastatic solid tumors.[49] The experiment will consist of oral administration of JAB-3068 every morning after a six hour fast.[49] A pharmacokinetics (PK) analysis will be taken which will be used to monitor the drug as it reacts with the body. Similarly, the small molecule inhibitor JAB-3312 is in Phase 1 Study and is also recruiting patients with advanced solid tumors of NSCLC, CRC, pancreatic ductal carcinoma, esophageal squamous cell carcinoma, head and neck squamous cell carcinoma, breast cancer, and other solid tumors. The experiment will consist of daily oral administration of the drug in treatment cycles of 21 days.[50]

9.1 Matched Targeted Therapy

Another ongoing clinical trial is utilizing Matched Targeted Therapy (MTT) in order to test the efficacy of Trametinib on PTPN11 and other proteins involved in

cancer progression. Specifically, Trametinib is a kinase inhibitor that blocks the abnormal protein signals that cause cancer cell multiplication. The drug will be consumed orally with two mg per day. The trials are expected to be completed by 2026. Some measures that researchers will be noting are short-term and long-term progression, duration of response, survival, adverse effects, and more.[51]

10. Future Directions & Conclusion

This article provided a review of various PTPN protein families in regards to lung and digestive cancer with the goal of providing researchers foundational information in their efforts to develop therapeutics that target PTPNs. Many studies have investigated the roles of PTPNs in tumor progression, outlining how PTPNs act on different pathways and thus affect tumor progression differently. This review paper focuses on the molecular mechanisms that underlie the effects of PTPNs, as it could aid in determining if PTPN therapeutics are worth exploring. Many of these PTPNs can be used as biomarkers and/or prognosis markers as overexpression or underexpression of certain PTPNs are associated with each cancer [Figure 5]. In regards to digestive cancer, PTPN2 and PTPN11 were shown to have tumor promoting capabilities while PTP1B, PTPN6, and PTPN12 were shown to have both tumor promoting and tumor suppressing capabilities. In lung cancer, PTPN3, PTPN12, and PTPN13 were shown to have tumor suppressing capabilities while PTPN11 had tumor promoting capabilities. PTP1B was seen to have both tumor suppressing and tumor promoting capabilities depending on the cellular substrate.

Given these PTPNs and their varying effects on each cancer, therapeutic targets that act to either promote or suppress various PTPN have great potential for cancer treatment. To suppress PTPNs with tumor promoting capabilities, researchers could look into developing inhibitors that bind to the PTPN proteins. In contrast, in order to promote PTPNs with tumor suppressing capabilities, researchers could look at developing transcription factors that enhance PTPN gene expression. Therefore, additional clinical trials and research need to be conducted in order to better understand how to mechanistically target PTPNs to develop effective treatments for lung and digestive cancer.

PTPN Member	Lung Cancer	Digestive Cancer
PTPN1/PTP1B	**Biomarker**: Increased levels of PTP1B in NSCLC; decreased levels of PTPN1 in LUAD **Therapeutic**: Inhibition of PTP1B in NSCLC	**Biomarker**: Increased levels of PTP1B in CRC, gastric cancer **Therapeutic**: Inhibition of PTP1B blocks Shc-Grb2-SOS pathway and MEK/Erk pathway **Contrasting**: Tumor suppressor qualities based on cellular context
PTPN2	**Insufficient Research**	**Biomarker**: Increased levels of PTPN2 across all stages of CRC **Therapeutic**: Inhibition of PTPN2 which could increase IFN-γ signaling pathway and suppress KRAS-mediated MAPK pathway
PTPN3	**Biomarker:** Decreased levels of PTPN3 in lung cancer tissue **Therapeutic:** Upregulation of PTPN3 to allow for the dephosphorylation of Src and targeting of EGFR for lysosomal degradation	**Insufficient Research**
PTPN6	**Insufficient Research**	**Biomarker**: Increased levels of PTPN6 in CRC **Therapeutic**: Inhibition of PTPN6-SP1-MAPK pathway to increase chemosensitivity of tumor cells; Inhibition of PTPN6-EGFR complex

PTPN11	**Biomarker**: Increased levels of PTPN11/Shp2 in 70% of NSCLC tissue samples **Therapeutic**: Small molecule inhibition of PTPN11/Shp2 which prevents Shp2 mediated signal transduction pathways that are hyperactivated	**Biomarker**: Increased levels of PTPN11/Shp2 in 60.78% of gastric cancers **Therapeutic**: Small molecule inhibition of PTPN11/Shp2 which prevents Shp2 mediated signal transduction pathways that are hyperactivated
PTPN12	**Prognosis Marker**: Increased levels of PTPN12 are associated with higher 5-year survival rates in NSCLC	**Biomarker**: Increased levels of PTPN12 are correlated with incidences of digestive cancers **Contrasting**: Other research has shown PTPN12 as a tumor suppressor that normally has an inhibitory effect on the Ras/MEK/ERK signaling by dephosphorylating the protein Shc
PTPN13	**Biomarker:** Decreased levels in NSCLC **Therapeutic:** Upregulation of PTPN13 to inhibit the Src/ERK/YAP1 signaling pathway, counteract the effects of miR-30e, and to downregulate HER2 activity	**Insufficient Research**

Figure 5: Summary of PTPN families and their potential as a biomarker, prognosis marker, and or/ therapeutic target in lung and digestive cancer. *Green represents PTPN as a tumor suppressor. Red represents tumor promoter. Orange represents both tumor suppressor and promoter capabilities. "Contrasting" refers to conflicting research regarding the role of the PTPN. "Insufficient Research" refers to not enough publications on the topic to include in the review.*

References

1. Lung cancer statistics: How common is lung cancer? Lung Cancer Statistics | How Common is Lung Cancer? (n.d.). Retrieved March 22, 2023, from https://www.cancer.org/cancer/lung-cancer/about/key-statistics.html

2. Sung, H., Ferlay, J., Siegel, R. L., Laversanne, M., Soerjomataram, I., Jemal, A., & Bray, F. (2021). Global cancer statistics 2020: Globocan estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: A Cancer Journal for Clinicians*, *71*(3), 209–249. https://doi.org/10.3322/caac.21660

3. Stomach cancer - statistics. Cancer.Net. (2022, August 18). Retrieved March 22, 2023, from https://www.cancer.net/cancer-types/stomach-cancer/statistics

4. Centers for Disease Control and Prevention. (2022, June 9). *Cancer treatments*. Centers for Disease Control and Prevention. Retrieved March 22, 2023, from https://www.cdc.gov/cancer/survivors/patients/treatments.htm#:~:text=Surgery%3A%20An%20operation%20where%20doctors,hormones%20they%20need%20to%20grow.

5. *Types of cancer treatment*. National Cancer Institute. (n.d.). Retrieved March 22, 2023, from https://www.cancer.gov/about-cancer/treatment/types

6. Tang, X., Qi, C., Zhou, H., & Liu, Y. (2022). Critical roles of PTPN family members regulated by non-coding RNAS in tumorigenesis and immunotherapy. *Frontiers in Oncology*, *12*. https://doi.org/10.3389/fonc.2022.972906

7. Xu, Q., Wu, N., Li, X. et al. Inhibition of PTP1B blocks pancreatic cancer progression by targeting the PKM2/AMPK/mTOC1 pathway. Cell Death Dis 10, 874 (2019). https://doi.org/10.1038/s41419-019-2073-4

8. Hoekstra E, Das AM, Swets M, et al. Increased PTP1B expression and phosphatase activity in colorectal cancer results in a more invasive phenotype and worse patient outcome. *Oncotarget*. 2016;7(16):21922-21938. doi:10.18632/oncotarget.7829

9. Zhou J, Guo H, Zhang Y, Liu H, Dou Q. The role of PTP1B (PTPN1) in the prognosis of solid tumors: A meta-analysis. *Medicine (Baltimore)*. 2022;101(40):e30826. doi:10.1097/MD.0000000000030826

10. Wang N, She J, Liu W, et al. Frequent amplification of PTP1B is associated with poor survival of gastric cancer patients. *Cell Cycle*. 2015;14(5):732-743. doi:10.1080/15384101.2014.998047

11. Wang J, Chen X, Liu B, Zhu Z. Suppression of PTP1B in gastric cancer cells in vitro induces a change in the genome-wide expression profile and inhibits gastric cancer cell growth. *Cell Biol Int*. 2010;34(7):747-753. doi:10.1042/CBI20090447

12. Lessard L, Stuible M, Tremblay ML. The two faces of PTP1B in cancer. *Biochim Biophys Acta*. 2010;1804(3):613-619. doi:10.1016/j.bbapap.2009.09.018

13. Harmer SL, Defranco AL. SHC contains two grb2 binding sites needed for ... - researchgate. ResearchGate. https://www.researchgate.net/profile/Anthony-D

efranco/publication/14020657_Shc_contains_two_Grb2_binding_sites_needed_for_efficient_formation_of_complexes_with_SOS_in_B_lymphocytes/links/00b49517194a617a09000000/Shc-contains-two-Grb2-binding-sites-needed-for-efficient-formation-of-complexes-with-SOS-in-B-lymphocytes.pdf. Published August 1997. Accessed May 5, 2023.

14. Liu H, Wu Y, Zhu S, et al. PTP1B promotes cell proliferation and metastasis through activating src and ERK1/2 in non-small cell lung cancer. *Cancer Lett*. 2015;359(2):218-225. doi:10.1016/j.canlet.2015.01.020

15. Wang C-C, Shen W-J, Anuraga G, Khoa Ta HD, Xuan DTM, Chen S-T, Shen C-F, Jiang J-Z, Sun Z, Wang C-Y, Wang W-J. Novel Potential Therapeutic Targets of PTPN Families for Lung Cancer. *Journal of Personalized Medicine*. 2022; 12(12):1947. https://doi.org/10.3390/jpm12121947

16. Katkeviciute, E., Hering, L., Montalban-Arques, A., Busenhart, P., Schwarzfischer, M., Manzini, R., Conde, J., Atrott, K., Lang, S., Rogler, G., Naschberger, E., Schellerer, V. S., Stürzl, M., Rickenbacher, A., Turina, M., Weber, A., Leibl, S., Leventhal, G. E., Levesque, M., Spalinger, M. R. (2021). Protein tyrosine phosphatase nonreceptor type 2 controls colorectal cancer development. *Journal of Clinical Investigation*, *131*(1). https://doi.org/10.1172/jci140281

17. Ivashkiv, L. B. (2018). IFNΓ: Signalling, epigenetics and roles in immunity, metabolism, disease and cancer immunotherapy. *Nature Reviews Immunology*. 18(9), 545–558. https://doi.org/10.1038/s41577-018-0029-z

18. Liu, X., Ye, L., Bai, Y., Mojidi, H., Simister, N. E., & Zhu, X. (2008). Activation of the JAK/STAT-1 signaling pathway by IFN-γ can down-regulate functional expression of the MHC class I-related neonatal Fc receptor for IGG. *The Journal of Immunology*, *181*(1), 449–463. https://doi.org/10.4049/jimmunol.181.1.449

19. Zhu, Z., Tang, R., Huff, S., Kummetha, I. R., Wang, L., Li, N., & Rana, T. M. (2023). Small-molecule PTPN2 inhibitors sensitize resistant melanoma to Anti-PD-1 Immunotherapy. *Cancer Research Communications*, 3(1), 119–129. https://doi.org/10.1158/2767-9764.crc-21-0186

20. Zhu, G., Pei, L., Xia, H., Tang, Q., & Bi, F. (2021). Role of oncogenic kras in the prognosis, diagnosis and treatment of colorectal cancer. *Molecular Cancer*, *20*(1). https://doi.org/10.1186/s12943-021-01441-4

21. Huang, L., Guo, Z., Wang, F., & Fu, L. (2021). Kras mutation: From undruggable to druggable in cancer. *Signal Transduction and Targeted Therapy*, *6*(1). https://doi.org/10.1038/s41392-021-00780-4

22. Huang, Z., Liu, M., Li, D., Tan, Y., Zhang, R., Xia, Z., Wang, P., Jiao, B., Liu, P., & Ren, R. (2020). PTPN2 regulates the activation of KRAS and plays a critical role in proliferation and survival of Kras-driven cancer cells. *Journal of Biological Chemistry*, 295(52), 18343–18354. https://doi.org/10.1074/jbc.ra119.011060

23. Jung, Y., Kim, P., Jung, Y., Keum, J., Kim, S.-N., Choi, Y. S., Do, I.-G., Lee, J., Choi, S.-J., Kim, S., Lee, J.-E., Kim, J., Lee, S., & Kim, J. (2012). Discovery of alk-PTPN3 gene fusion from human non-small cell lung carcinoma cell line using next generation RNA sequencing. *Genes, Chromosomes and Cancer*, *51*(6), 590–597. https://doi.org/10.1002/gcc.21945

24. Li, M.-Y., Peng, W.-H., Wu, C.-H., Chang, Y.-M., Lin, Y.-L., Chang, G.-D., Wu, H.-C., & Chen, G.-C. (2019). PTPN3 suppresses lung cancer cell invasiveness by counteracting SRC-mediated DAAM1 activation and actin polymerization. *Oncogene*, 38(44), 7002–7016. https://doi.org/10.1038/s41388-019-0948-6

25. Li, M.-Y., Lai, P.-L., Chou, Y.-T., Chi, A.-P., Mi, Y.-Z., Khoo, K.-H., Chang, G.-D., Wu, C.-W., Meng, T.-C., & Chen, G.-C. (2014). Protein tyrosine phosphatase PTPN3 inhibits lung cancer cell proliferation and migration by promoting EGFR endocytic degradation. *Oncogene*, 34(29), 3791–3803. https://doi.org/10.1038/onc.2014.312

26. Liu G, Zhang Y, Huang Y, Yuan X, Cao Z, Zhao Z. PTPN6-EGFR Protein Complex: A Novel Target for Colon Cancer Metastasis. *J Oncol*. 2022;2022:7391069. Published 2022 Feb 11. doi:10.1155/2022/7391069

27. Fang H, Ma W, Guo X, Wang J. PTPN6 promotes chemosensitivity of colorectal cancer cells via inhibiting the SP1/MAPK signalling pathway. *Cell Biochem Funct*. 2021;39(3):392-400. doi:10.1002/cbf.3604

28. Chan, G., & Neel, B. G. (2016). Role of PTPN11 (shp2) in cancer. *Protein Tyrosine Phosphatases in Cancer*, 115–143. https://doi.org/10.1007/978-1-4939-3649-6_4

29. Li, S., Wang, X., Li, Q., & Li, C. (2022). Role of shp2/PTPN11 in the occurrence and prognosis of cancer: A systematic review and meta-analysis. *Oncology Letters*, *25*(1). https://doi.org/10.3892/ol.2022.13605

30. Goto, Y., Ando, T., Yamamoto, K., Tamakoshi, A., El-Omar, E., Goto, H., & Hamajima, N. (2005). Association between serum pepsinogens and Polymorphismofptpn11 encoding SHP-2 amonghelicobacter pylori seropositive Japanese. *International Journal of Cancer*, *118*(1), 203–208. https://doi.org/10.1002/ijc.21338

31. Nian, Q., Zeng, J., He, L., Chen, Y., Zhang, Z., Rodrigues-Lima, F., Zhao, L., Feng, X., & Shi, J. (2021). A small molecule inhibitor targeting SHP2 mutations for the lung carcinoma. *Chinese Chemical Letters*, *32*(5), 1645–1652. https://doi.org/10.1016/j.cclet.2021.01.002

32. Huo, Y.-hu, Wang, Y.-ni, Meng, L.-bing, Zhang, A.-li, & Liu, B. (2020). Progress in the correlation between PTPN12 gene expression and human tumors. *Medicine*, *99*(24). https://doi.org/10.1097/md.0000000000020445

33. Shen, N., Li, L., Xu, W., Tian, J., Yang, Y., Zhu, Y., Gong, Y., Ke, J., Gong, J., Chang, J., Zhong, R., & Miao, X. (2019). A missense variant in PTPN12 associated with the risk of colorectal cancer by modifying Ras/MEK/erk signaling. *Cancer Epidemiology*, *59*, 109–114. https://doi.org/10.1016/j.canep.2019.01.013

34. Chen, J., Zhao, X., Yuan, Y., & Jing, J.-jing. (2020). The expression patterns and the prognostic roles of PTPN family members in digestive tract cancers. https://doi.org/10.21203/rs.3.rs-19689/v1

35. Cao, X., Chen, Y.-Z., Luo, R.-Z., Zhang, L., Zhang, S.-L., Zeng, J., Jiang, Y.-C., Han, Y.-J., & Wen, Z.-S. (2015). Tyrosine-protein phosphatase non-receptor type 12 expression is a good prognostic factor in resectable non-small cell lung cancer. *Oncotarget*, *6*(13),

11704–11713.
https://doi.org/10.18632/oncotarget.3588

36. Mcheik, S., Aptecar, L., Coopman, P., D'Hondt, V., & Freiss, G. (2020). Dual role of the PTPN13 tyrosine phosphatase in cancer. *Biomolecules*, *10*(12), 1659. https://doi.org/10.3390/biom10121659

37. Hamyeh, M., Bernex, F., Larive, R. M., Naldi, A., Urbach, S., Simony-Lafontaine, J., Puech, C., Bakhache, W., Solassol, J., Coopman, P. J., Hendriks, W. J. A. J., & Freiss, G. (2020). PTPN13 induces cell junction stabilization and inhibits mammary tumor invasiveness. *Theranostics*, *10*(3), 1016–1032. https://doi.org/10.7150/thno.38537

38. D'Hondt, V., Lacroix-Triki, M., Jarlier, M., Boissiere-Michot, F., Puech, C., Coopman, P., Katsaros, D., & Freiss, G. (2017). High PTPN13 expression in high grade serous ovarian carcinoma is associated with a better patient outcome. *Oncotarget*, *8*(56), 95662–95673. https://doi.org/10.18632/oncotarget.21175

39. Zhuang, L., Shou, T., Li, K., Gao, C.-L., Duan, L.-C., Fang, L.-Z., Zhang, Q.-Y., Chen, Z.-N., Zhang, C., Yang, S.-T., & Li, G.-F. (2017). MicroRNA-30E-5P promotes cell growth by targeting *PTPN 13* and indicates poor survival and recurrence in lung adenocarcinoma. *Journal of Cellular and Molecular Medicine*, *21*(11), 2852–2862. https://doi.org/10.1111/jcmm.13198

40. Scrima, M., De Marco, C., De Vita, F., Fabiani, F., Franco, R., Pirozzi, G., Rocco, G., Malanga, D., & Viglietto, G. (2012). The nonreceptor-type tyrosine phosphatase PTPN13 is a tumor suppressor gene in non–small cell lung cancer. *The American Journal of Pathology*, *180*(3), 1202–1214. https://doi.org/10.1016/j.ajpath.2011.11.038

41. Zhu, J.-H., Chen, R., Yi, W., Cantin, G. T., Fearns, C., Yang, Y., Yates, J. R., & Lee, J.-D. (2007). Protein tyrosine phosphatase PTPN13 negatively regulates HER2/erbb2 malignant signaling. *Oncogene*, *27*(18), 2525–2531. https://doi.org/10.1038/sj.onc.1210922

42. Wang, J., Li, S., Zhang, X., Zhu, N., Yiminniyaze, R., Dong, L., Li, C., Gulinuer, W., Xia, J., Li, J., Zhou, D., Liu, X., Zhang, Y., Zhang, Y., & Li, S. (2022). Protein tyrosine phosphatase PTPL1 suppresses lung cancer through Src/ERK/YAP1 signaling. *Thoracic Cancer*, *13*(21), 3042–3051. https://doi.org/10.1111/1759-7714.14657

43. Chen, W., Wang, J., Liu, S., Wang, S., Cheng, Y., Zhou, W., Duan, C., & Zhang, C. (2016). MicroRNA-361-3p suppresses tumor cell proliferation and metastasis by directly targeting SH2B1 in NSCLC. *Journal of Experimental & Clinical Cancer Research*, *35*(1). https://doi.org/10.1186/s13046-016-0357-4

44. Fernandez, S., Risolino, M., Mandia, N., Talotta, F., Soini, Y., Incoronato, M., Condorelli, G., Banfi, S., & Verde, P. (2014). Mir-340 inhibits tumor cell proliferation and induces apoptosis by targeting multiple negative regulators of p27 in non-small cell lung cancer. *Oncogene*, *34*(25), 3240–3250. https://doi.org/10.1038/onc.2014.267

45. Song, Q., Xu, Y., Yang, C., Chen, Z., Jia, C., Chen, J., Zhang, Y., Lai, P., Fan, X., Zhou, X., Lin, J., Li, M., Ma, W., Luo, S., & Bai, X. (2014). Mir-483-5p promotes invasion and metastasis of lung adenocarcinoma by targeting rhogdi1 and

Alcam. *Cancer Research*, *74*(11), 3031–3042. https://doi.org/10.1158/0008-5472.can-13-2193

46. Cui, R., Meng, W., Sun, H.-L., Kim, T., Ye, Z., Fassan, M., Jeon, Y.-J., Li, B., Vicentini, C., Peng, Y., Lee, T. J., Luo, Z., Liu, L., Xu, D., Tili, E., Jin, V., Middleton, J., Chakravarti, A., Lautenschlaeger, T., & Croce, C. M. (2015). MicroRNA-224 promotes tumor progression in nonsmall cell lung cancer. *Proceedings of the National Academy of Sciences*, *112*(31). https://doi.org/10.1073/pnas.1502068112

47. Vichas, A., Riley, A. K., Nkinsi, N. T., Kamlapurkar, S., Parrish, P. C., Lo, A., Duke, F., Chen, J., Fung, I., Watson, J., Rees, M., Gabel, A. M., Thomas, J. D., Bradley, R. K., Lee, J. K., Hatch, E. M., Baine, M. K., Rekhtman, N., Ladanyi, M., ... Berger, A. H. (2021). Integrative oncogene-dependency mapping identifies rit1 vulnerabilities and synergies in Lung Cancer. *Nature Communications*, *12*(1). https://doi.org/10.1038/s41467-021-24841-y

48. Zhang, Y., Wang, Y., Zhou, D., Wang, K., Wang, X., Wang, X., Jiang, Y., Zhao, M., Yu, R., & Zhou, X. (2021). Radiation-induced yap activation confers glioma radioresistance via promoting FGF2 transcription and DNA damage repair. *Oncogene*, *40*(27), 4580–4591. https://doi.org/10.1038/s41388-021-01878-3

49. A first-in-human study of Jab-3068 (SHP2 inhibitor) in adult patients with advanced solid tumors in China - full text view. Full Text View - ClinicalTrials.gov. (n.d.). Retrieved March 24, 2023, from https://clinicaltrials.gov/ct2/show/NCT03565003?term=PTPN11&cond=Non-small%2BCell%2BLung%2BCancer&draw=2&rank=3

50. A first-in-human, phase 1 study of jab-3312 in adult patients with advanced solid tumors - full text view. Full Text View - ClinicalTrials.gov. (n.d.). Retrieved March 24, 2023, from https://clinicaltrials.gov/ct2/show/NCT04045496?term=PTPN11&cond=Non-small%2BCell%2BLung%2BCancer&draw=2

51. A Study Evaluating the Activity of Anti-cancer Treatments Targeting Tumor Molecular Alterations/Characteristics in Advanced / Metastatic Tumors. (MegaMOST) - full text view. Full Text View - ClinicalTrials.gov. (n.d.). Retrieved March 24, 2023, from https://clinicaltrials.gov/ct2/show/study/NCT04116541?term=Protein+tyrosine+phosphatases+non-receptor+type&draw=2&rank=2