

**Functional Characterization of Hypoxia  
associated long non-coding RNAs and anti-  
cancer drug development for Glioblastoma  
treatment**

**GARIMA YADAV**



**DEPARTMENT OF BIOCHEMICAL ENGINEERING AND  
BIOTECHNOLOGY**

**INDIAN INSTITUTE OF TECHNOLOGY DELHI**

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**by**

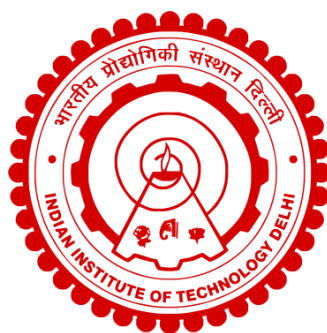
**GARIMA YADAV**

**DEPARTMENT OF BIOCHEMICAL ENGINEERING AND  
BIOTECHNOLOGY**

**submitted**

**in fulfilment of the requirements of the degree of Doctor of Philosophy**

**to the**



**INDIAN INSTITUTE OF TECHNOLOGY DELHI**

**FEBRUARY 2025**

***Dedicated to my loved ones***

# CERTIFICATE

This is to certify that the thesis entitled — **Functional Characterization of Hypoxia associated long non-coding RNAs and anti-cancer drug development for Glioblastoma treatment**, being submitted by **Ms. Garima Yadav** to the Indian Institute of Technology Delhi, for the award of degree of Doctor of Philosophy, is a record of bonafide research work carried out by her, which has been prepared under my supervision and guidance of conformity with the rules and regulations of Indian Institute of Technology Delhi. The research reports and the results presented in this thesis have not been submitted in part or full to any other University/ Institute for the award of any degree or diploma.

**Prof. Ritu Kulshreshtha**

**Professor and Head**

**Department of Biochemical Engineering and Biotechnology**

**Indian Institute of Technology Delhi**

**New Delhi- 110016. Date:**

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## ABSTRACT

Glioblastoma (GBM), a highly aggressive brain tumor is marked by the presence of pseudopalisading region and necrotic areas (PAN), which are closely linked to the tumor's increased malignancy, invasiveness, and poor prognosis. This study investigates the involvement of long non-coding RNAs (lncRNAs) in these hallmark regions of GBM, providing insights into their potential role in driving tumor progression. Using RNA-seq data from the IVY Glioblastoma Atlas Project, we identified 40 differentially expressed lncRNAs in PAN compared to Peripheral Tumor (PT) regions, implicating pathways such as mTOR, MAPK, and NF- $\kappa$ B signaling. Co-expression network analysis revealed MIR210HG as a key lncRNA, that is positively correlated with hypoxia-inducible genes like VEGFA and CA9. MIR210HG is a hypoxia-inducible lncRNA, and its induction was found to be mediated by hypoxia-inducible factor 1 and 2 (HIF-1/HIF-2). The expression of MIR210HG is significantly upregulated in GBM tissues compared to normal brain tissues across various datasets, with the highest levels observed in GBM Grade IV, correlating with poor prognosis. Functional analysis demonstrated that MIR210HG promotes cell proliferation and regulates the cell cycle, enhancing G1/S progression in GBM cells. Additionally, MIR210HG was found to promote cell migration and regulate epithelial-mesenchymal transition (EMT) markers, potentially contributing to GBM invasiveness. The downstream target prediction indicated a potential role of MIR210HG in the collagen synthesis, as silencing MIR210HG resulted in reduced COL5A1 expression. The miRNA-lncRNA interaction analysis revealed miR-503 as a potential regulator of MIR210HG and COL5A1 in GBM. Additionally, The Pan cancer expression analysis of MIR210HG through various tumor datasets demonstrated that MIR210HG is significantly upregulated in most cancers and increased with the tumor stage in a subset of them. The prognostic analysis revealed high MIR210HG expression is associated with poor overall and disease-free survival in specific cancer types. Genetic alteration analysis showed minimal alterations in the MIR210HG locus, indicating that overexpression in cancers is not due to gene amplification. The correlation of MIR210HG with promoter methylation was found to be significantly negative in nature in majority of cancers depicting the possible

epigenetic regulation of expression of MIR210HG. Notably, MIR210HG showed negative correlations with immune cells and thus may have strong impact on the tumor microenvironment. Functional analysis indicates its association with hypoxia, angiogenesis, metastasis, and DNA damage repair processes. MIR210HG was found to interact with several proteins and potentially regulate chromatin modifications and transcriptional regulation. These findings highlight the oncogenic role of MIR210HG and suggest its potential as a diagnostic and therapeutic target in many cancers. In addition, coumarin derived triazole compounds were screened for their anti-cancer properties. The candidate compounds showed anti-proliferative and migration inhibitory properties along with an increase in cell apoptosis. The candidate compounds were further shown to downregulate the levels of MIR210HG and miR-210-3p in GBM. Overall, this research identifies lncRNA signature in the GBM tumor microenvironment and its association with cancer pathways and disease prognosis. We further demonstrate pro-oncogenic role of MIR210HG in GBM and provide a mechanistic insight. Additionally, we identify new drug compounds with a potential to target MIR210HG in GBM.

## सारांश

ग्लियोब्लास्टोमा (GBM) एक अत्यधिक आक्रामक मस्तिष्क ट्यूमर है, जो हाइपोक्सिक क्षेत्रों और नेक्रोसिस की उपस्थिति से विशेष रूप से छद्मपलिसेडिंग क्षेत्र और नेक्रोटिक क्षेत्रों (PAN) में चिह्नित होता है। ये क्षेत्र ट्यूमर की बढ़ती घातकता, आक्रामकता, और खराब पूर्वानुमान से निकटता से जुड़े होते हैं। इस अध्ययन में GBM के इन महत्वपूर्ण क्षेत्रों में लंबी गैर-कोडिंग RNA (lncRNA) की भागीदारी की जांच की गई है, जो ट्यूमर की प्रगति में इनकी संभावित भूमिका पर अंतर्दृष्टि प्रदान करता है। IVY Glioblastoma Atlas Project से प्राप्त RNA-seq डेटा का उपयोग करके, हमने PAN की तुलना में पेरिफेरल ट्यूमर (PT) क्षेत्रों में 40 भिन्न रूप से व्यक्त lncRNAs की पहचान की, जो mTOR, MAPK, और NF- $\kappa$ B सिग्नलिंग जैसी पथों से जुड़े हैं। सह-अभिव्यक्ति नेटवर्क विश्लेषण में MIR210HG को एक प्रमुख lncRNA के रूप में पहचाना गया, जो हाइपोक्सिया-प्रेरित जीन जैसे VEGFA और CA9 के साथ सकारात्मक रूप से सहसंबद्ध है। MIR210HG एक हाइपोक्सिया-प्रेरित lncRNA है, और इसका प्रेरण हाइपोक्सिया-प्रेरित फैक्टर 1 और 2 (HIF-1/HIF-2) द्वारा मध्यस्थित पाया गया। विभिन्न डेटा सेटों में सामान्य मस्तिष्क ऊतकों की तुलना में GBM ऊतकों में MIR210HG का अभिव्यक्ति स्तर काफी अधिक पाया गया, विशेष रूप से ग्रेड IV GBM में, जो खराब पूर्वानुमान से सहसंबद्ध था। कार्यात्मक विश्लेषण ने दिखाया कि MIR210HG कोशिका प्रसार को बढ़ावा देता है और GBM कोशिकाओं में G1/S प्रगति को बढ़ाते हुए कोशिका चक्र को नियंत्रित करता है। इसके अलावा, MIR210HG ने कोशिका प्रवासन को बढ़ावा दिया और एपिथेलियल-मेसेंकाइमल ट्रांज़िशन (EMT) मार्करों को नियंत्रित किया, जिससे GBM की आक्रामकता में संभावित योगदान हुआ। डाउनस्ट्रीम टारगेट प्रेडिक्शन ने कोलेजन संश्लेषण में MIR210HG की संभावित भूमिका का संकेत दिया, क्योंकि MIR210HG को साइलेंस करने पर COL5A1 अभिव्यक्ति में कमी देखी गई। miRNA-lncRNA इंटरैक्शन विश्लेषण ने miR-503 को GBM में MIR210HG और COL5A1 का संभावित नियामक बताया। इसके अतिरिक्त, विभिन्न ट्यूमर डेटा सेटों के माध्यम से किए गए पैन-कैंसर अभिव्यक्ति विश्लेषण ने दिखाया कि MIR210HG अधिकांश कैंसरों में काफी अधिक अभिव्यक्त होता है और कुछ कैंसरों के एक उपसमूह में ट्यूमर के चरण के साथ बढ़ता है। पूर्वानुमान विश्लेषण से पता चला कि MIR210HG की उच्च अभिव्यक्ति कुछ कैंसर प्रकारों में खराब समग्र और रोग-मुक्त जीवन प्रत्याशा से जुड़ी है। आनुवंशिक परिवर्तन विश्लेषण ने MIR210HG लोकेस में न्यूनतम परिवर्तन दिखाए, जो इंगित करता है कि कैंसर में इसकी ओवरएक्सप्रेशन जीन एम्पलीफिकेशन के कारण नहीं है। MIR210HG का प्रमोटर मिथाइलेशन के

साथ सहसंबंध अधिकांश कैंसरों में नकारात्मक पाया गया, जो MIR210HG की अभिव्यक्ति के संभावित एपिजेनेटिक नियमन को दर्शाता है। विशेष रूप से, MIR210HG ने प्रतिरक्षा कोशिकाओं के साथ नकारात्मक सहसंबंध दिखाया और इस प्रकार इसका ट्यूमर माइक्रोएनवायरनमेंट पर मजबूत प्रभाव हो सकता है। कार्यात्मक विश्लेषण इसके हाइपोक्सिया, एंजियोजेनेसिस, मेटास्टेसिस और डीएनए क्षति मरम्मत प्रक्रियाओं के साथ जुड़ाव का संकेत देता है। MIR210HG को कई प्रोटीनों के साथ इंटरैक्ट करते हुए पाया गया और यह संभावित रूप से क्रोमैटिन संशोधनों और ट्रांसक्रिप्शनल नियमन को नियंत्रित कर सकता है। ये निष्कर्ष MIR210HG की ओंकोजेनिक भूमिका को उजागर करते हैं और इसे कई कैंसरों में नैदानिक और चिकित्सीय लक्ष्य के रूप में सुझाते हैं। इसके अतिरिक्त, क्यूमारिन से व्युत्पन्न ट्रायाज़ोल यौगिकों को उनके एंटी-कैंसर गुणों के लिए स्क्रीन किया गया। उम्मीदवार यौगिकों ने GBM में MIR210HG और miR-210-3p के स्तर को कम करने के साथ-साथ कोशिका अपोप्टोसिस में वृद्धि, कोशिका प्रसार और प्रवासन को रोकने वाले गुण दिखाए। कुल मिलाकर, यह शोध GBM ट्यूमर माइक्रोएनवायरनमेंट में lncRNA हस्ताक्षर की पहचान करता है और इसके कैंसर पथों और रोग के पूर्वानुमान से संबंध को दर्शाता है। हम GBM में MIR210HG की प्रो-ओंकोजेनिक भूमिका को प्रदर्शित करते हैं और यांत्रिक अंतर्दृष्टि प्रदान करते हैं। इसके अलावा, हम GBM में MIR210HG को लक्षित करने की क्षमता वाले नए औषध यौगिकों की पहचान करते हैं।

# Table of Contents

	<b>Page No.</b>
Certificate	i
Acknowledgment	ii
Abstract	iv
List of Figures	xiii
List of Tables	xv
Abbreviations	xvi
1. Introduction	1 - 5
2. Review of Literature	6 - 37
2.1. Glioblastoma	6
2.2. Epidemiology and Etiology (Morbidity and mortality)	6
2.3. Classification	7
2.4. Cellular States in GBM	10
2.5. Treatment	12
2.5.1. Surgery	13
2.5.2. Radiation	13
2.5.3. Chemotherapy	13
2.5.4. Immunotherapy	14
2.6. Challenges to GBM therapy	15
2.6.1. Invasive growth pattern	15
2.6.2. Limited penetration of drugs beyond Blood Brain Barrier	15
2.6.3. Resistance to conventional therapy	16
2.6.4. Long Non Coding RNAs (lncRNAs)	16
2.7. A brief history	17
2.8. Biogenesis of lncRNA	18
2.9. Cellular functions of lncRNAs	19
2.10. Mechanism of Action	21
2.11. Characterizing lncRNAs: Assessing Coding Potential,	23

	Localization and Structure	
2.12.	lncRNA and their role in cancer	24
2.13.	The diagnostic, prognostic and therapeutic potential of lncRNAs	27
2.14.	An overview of the status and role of lncRNAs in GBM	29
2.15.	Hypoxia and lncRNAs in Glioblastoma	31
2.16.	Anti-cancer small molecules	33
3.	Objectives	38
4.	Identification and characterization of long non-coding RNAs associated with hypoxia in glioblastoma	39-89
4.1.	Background	39
4.2.	Material and Methods	40 - 46
4.2.1.	lncRNA and mRNA data source and analysis	40
4.2.2.	Cell lines and culture conditions	41
4.2.3.	Gene Expression and Prognostic Value Analysis	41
4.2.4.	Gene expression quantitation using Real-time qPCR (qRT-PCR)	41
4.2.5.	Patients Samples	42
4.2.6.	shRNA or siRNA mediated knockdown of MIR210HG	42
4.2.7.	Stable cell line generation	42
4.2.8.	Azacytidine demethylation and HDAC inhibitor treatment	43
4.2.9.	Cell proliferation Assay	43
4.2.10.	Colony Formation Assay	43
4.2.11.	Cell Cycle Analysis using FACS	43
4.2.12.	Scratch Assay	44
4.2.13.	Transwell Assay	44
4.2.14.	Western Blotting	44
4.2.15.	Cellular Fractionation	44
4.2.16.	Immunofluorescence Microscopy	45
4.2.17.	Confocal Microscopy	45
4.2.18.	Relative Luciferase Assay	45

4.2.19.	Statistical analysis	46
4.3.	Results	46 - 83
4.3.1.	Differentially expressed lncRNAs and mRNAs in pseudopalisading region of GBM	46
4.3.2.	Pathway enrichment of differentially expressed lncRNAs	47
4.3.3.	GO Pathway enrichment analysis of differentially expressed mRNAs.	48
4.3.4.	Transcription factor regulating differentially expressed mRNAs and lncRNAs	51
4.3.5.	Co-expression network analysis of differentially expressed lncRNAs and mRNAs	52
4.3.6.	Determining the Hypoxia Regulatory Elements on the promoter of lncRNAs and their expression analysis in response to hypoxia	55
4.3.7.	Preliminary Characterization of MIR210HG	57
4.3.8.	Functional Characterization of MIR210HG	61
4.3.9.	MIR210HG and molecular signature of Glioma	65
4.3.10.	Epigenetic Regulation of MIR210HG	67
4.3.11.	Role of MIR210HG in proliferation and cell cycle distribution	68
4.3.12.	Cell cycle regulators contributed to the growth promotion by MIR210HG	70
4.3.13.	Role of MIR210HG in the EMT and migration	73
4.3.14.	Mechanists Insight into MIR210HG Function	76
4.3.15.	Role of MIR210HG in regulating NFkB and collagen synthesis	77
4.3.16.	COL5A1 is overexpressed in GBM and is associated with poor prognosis	79
4.3.17.	COL5A1 promotes GBM proliferation	82
4.3.18.	Role of COL5A1 in altering F-actin distribution of GBM cells	83
4.3.19.	miR-503 regulates MIR210HG and COL5A1	84
4.4.	Discussion	87
4.5.	Conclusion	89
5.	Pan cancer analyses of the candidate lncRNA	90 - 119

5.1.	Background	90
5.2.	Material and Methods	91 - 93
5.2.1.	Gene Expression Analysis of MIR210HG	91
5.2.2.	Genetic Alterations in MIR210HG	92
5.2.3.	Single Nucleotide Polymorphism (SNP) in MIR210HG	92
5.2.4.	Methylation of MIR210HG	92
5.2.5.	Transcription Factor Binding	92
5.2.6.	Prognostic Value of MIR210HG in pan cancer	93
5.2.7.	Immune cells correlation	93
5.2.8.	Functional Aspect of MIR210HG	93
5.2.9.	Regulatory Mechanism	93
5.3.	Results	93 - 119
5.3.1.	MIR210HG is overexpressed in several cancers	93
5.3.2.	Prognostic significance of MIR210HG	97
5.3.3.	MIR210HG locus shows minimal genetic alteration in cancer patients	99
5.3.4.	Regulation of MIR210HG	101
5.3.5.	MIR210HG and immune cells correlation and its association with cancer cell immunity	105
5.3.6.	Functional Role of MIR210HG	108
5.3.7.	MIR210HG interacting protein partners	112
5.3.8.	Role of MIR210HG in epigenetic regulation	114
5.4.	Discussion	116
6.	To evaluate the small molecules for their anti-cancer activity and their ability to inhibit candidate lncRNA expression.	120 - 133
6.1.	Background	120
6.2.	Material and Methods	121 - 123
6.2.1.	Design, synthesize and characterization of small molecules	121
6.2.2.	Particle size characterization of small molecules	121
6.2.3.	Cell culture & treatment	121
6.2.4.	Cytotoxicity analysis & IC50 determination	122

6.2.5.	Effect of compounds on cell proliferation	122
6.2.6.	Effect of Compounds in Cell Cycle Distribution	122
6.2.7.	Effect of Compounds on Apoptosis	123
6.2.8.	Gene expression quantitation using qRT-PCR	123
6.3.	Results	123 - 133
6.3.1.	Design, synthesize and characterization of small molecules	123
6.3.2.	Particle size characterization of small molecules	124
6.3.3.	In vitro cytotoxicity and selectivity index	125
6.3.4.	RI-16, RI-18 and RI-19 suppresses cellular proliferation of GBM cells	127
6.3.5.	RI-16, RI-18 and RI-19 leads to cell cycle arrest in GBM cells	128
6.3.6.	RI-16, RI-18 and RI-19 induces apoptosis of GBM cells	131
6.3.7.	RI-16, RI-18 and RI-19 alters the expression of MIR210HG and miR-210	132
6.4.	Discussion	134
7.	Concluding Remarks and Future Perspectives	136 - 140
8.	References	141 - 171
	Appendices	172 – 219
	Resume of the Author	220-222

# LIST OF FIGURES

<b>Figure no</b>	<b>Title</b>	<b>Page no</b>
2.1	Pictorial representation of Incidence and Mortality Ratio in cancers	7
2.2	Pictorial representation of mechanism of pseudopalisade formation	12
2.3	Mode of action of lncRNAs	23
4.1	Differentially expressed lncRNAs and mRNAs in pseudopalisading region of GBM	47
4.2	Pathway enrichment of differentially expressed lncRNAs	48
4.3	GO and pathway analysis of upregulated mRNAs	49
4.4	GO and pathway analysis of downregulated mRNAs	50
4.5	Transcription factors regulating differentially expressed lncRNAs	51
4.6	Transcription factors regulating differentially expressed mRNAs	52
4.7	Co expression network analysis of upregulated lncRNAs and mRNAs	53
4.8	Network cluster of downregulated lncRNAs and mRNAs	54
4.9	Co expression network analysis of downregulated lncRNAs and mRNAs	55
4.10	Hypoxia Regulatory Elements on the promoter of lncRNAs	56
4.11	Subcellular Localisation of MIR210HG	58
4.12	Tissue specific expression of MIR210HG.	59
4.13	MIR210HG is a hypoxia inducible lncRNA	60
4.14	HIF-1/HIF-2A regulate MIR210HG expression	61
4.15	MIR210HG expression across Glioma Grade and histopathology	62
4.16	MIR210HG expression in recurrent tumor	63
4.17	Expression of MIR210HG in GBM cell lines and patients	64
4.18	MIR210HG and survival analysis	65
4.19	Correlation of MIR210HG with the molecular pattern signature of Glioma	66
4.20	Epigenetic Regulation of MIR210HG	68
4.21	Expression of MIR210HG upon si and sh-RNA knockdown	69
4.22	Role of MIR210HG in proliferation and cell cycle distribution	70
4.23	MIR210HG regulates G1/S phase transition	72
4.24	Expression of MIR210HG in Glioblastoma subtypes	73
4.25	Role of MIR210HG in migration of Glioblastoma cells	75
4.26	Effect of MIR210HG on genes involved in EMT	76
4.27	Pathway analysis of correlated genes to MIR210HG	77
4.28	Role of MIR210HG in regulating NFkB and collagen synthesis	78
4.29	Expression of COL5A1 in Glioma	80
4.30	Expression of COL5A1 in subtype of GBM	81

4.31	COL5A1 and survival analysis	82
4.32	COL5A1 promotes GBM proliferation	83
4.33	COL5A1 alters F-actin distribution of GBM cells	84
4.34	miR-503 regulates MIR210HG	85
4.35	miR-503 regulates COL5A1	86
5.1	Expression of MIR21HG (FPKM) across TCGA tumor samples	94
5.2	Expression of MIR210HG (log <sub>2</sub> (TPM+1) scale) across all tumor	95
5.3	The expression levels of MIR210HG in pancreatic cancer	96
5.4	Expression of MIR210HG across pathological stages of cancer	97
5.5	Survival analysis for the prognosis value of MIR210HG across cancer types	98
5.6	Genetic alteration frequency of MIR210HG in TCGA datasets	99
5.7	Common SNP variants	100
5.8	TF regulating MIR210HG	101
5.9	Analysis of Promoter of MIR210HG	102
5.10	The correlation between DNA methylation and MIR210HG expression	104
5.11	Correlation of T cells, CAFs with MIR210HG	106
5.12	Correlation of stromal score and immune regulators with MIR210HG	107
5.13	MIR210HG and immune related pathways.	108
5.14	Correlation of functional state and MIR210HG	109
5.15	Pathway analysis of 100 genes correlated with MIR210HG	110
5.16	Expression of MIR210HG in endothelial cells	111
5.17	Correlation of MIR210HG and hypoxia genes in TCGA cancer	112
5.18	MIR210HG interacting protein partners	113
5.19	The correlation of genes with promoter methylation and MIR210HG expression	115
6.1	Design, synthesis and characterization of compounds	124
6.2	Particle size distribution	125
6.3	In vitro cytotoxicity activities of compounds	126
6.4	Anti-proliferative effects of compounds	127
6.5	Cell cycle distribution analysis of LN229 cells after treatment with compounds	129
6.6	Cell cycle distribution analysis of LN18 cells after treatment with compounds	130
6.7	RI-16, RI-18, RI-19 induces apoptosis in LN229 cells	131
6.8	The assessment of the nuclear morphology using DAPI staining	132
6.9	Compounds inhibit MIR210HG and miR-210 expression in GBM cells	133

## LIST OF TABLES

<b>Table no</b>	<b>Title</b>	<b>Page no</b>
1	Categories of Glioma according to WHO Classification of CNS tumor 2021	8
2	A list of molecular markers recommended by WHO 2021 for diagnosis and classification of GBM.	10
3	Chemotherapeutic drugs for GBM treatment in Clinical trail	13
4	Role of lncRNAs in different types of cancer	24
5	lncRNAs as diagnostic and prognostic markers	28
6	Overview of the status and role of lncRNA in GBM	29
7	Hypoxia associated lncRNAs in GBM	32
8	Coumarin hybrid compounds and their anti-cancer properties	34
9	The coding potential score of MIR210HG transcripts as per CPC2 data tool	57
10	List of miRNAs gain and loss due to presence of SNP variants	100
11	Selectivity index of compounds in cancer cells as compared to normal cell	127

## ABBREVIATIONS

Adrenocortical carcinoma	ACC
Bladder urothelial carcinoma	BLCA
Breast invasive carcinoma	BRCA
Cervical squamous cell carcinoma and endocervical adenocarcinoma	CESC
Cholangiocarcinoma	CHOL
3-(4,5-dimethylthiazole-2-yl)-2,5-diphenyl tetrazolium bromide	MTT
Colon adenocarcinoma	COAD
Diffuse large B-cell lymphoma	DLBC
Esophageal carcinoma	ESCA
Glioblastoma	GBM
Head and Neck squamous cell carcinoma	HNSC
Kidney Chromophobe	KICH
Kidney renal clear cell carcinoma	KIRC
Kidney renal papillary cell carcinoma	KIRP
Acute Myeloid Leukemia	LAML
Brain Lower Grade Glioma	LGG
Liver hepatocellular carcinoma	LIHC
Lung adenocarcinoma	LUAD
Lung squamous cell carcinoma	LUSC
Mesothelioma	MESO
Non-small-cell lung cancer	NSCLC
Ovarian serous cystadenocarcinoma	OV
Pancreatic adenocarcinoma	PAAD
Pheochromocytoma and Paranglioma	PCPG
Prostate adenocarcinoma	PRAD
Rectum adenocarcinoma	READ

Sarcoma	SARC
Skin Cutaneous Melanoma	SKCM
Stomach adenocarcinoma	STAD
Testicular Germ Cell Tumors	TGCT
Thyroid carcinoma	THCA
Thymoma	THYM
Uterine Corpus Endometrial Carcinoma	UCEC
Uterine Carcinosarcoma	UCS
Blood brain barrier	BBB
Cellular tumor regions	CT
Infiltration into the brain tissue	IT
Microvascular proliferation	MVP
Pseudopalisades around necrosis	PAN
Bovine serum albumin	BSA
Central Brain Tumor Registry of United State	CBTRUS
Dimethyloxaloylglycine	DMOG
Central nervous system	CNS