List of gene targets predicted for miR-320a, miR-361-5p, miR-21-5p and miR-103a-3p.						
miRNA of	Potential	Alternative	Relevant Literature (With Emphasis on	P-values for miRNA-		
Interest	Gene	Name of Gene	Cancer)	gene (<0.05		
	Targets			Threshold)		
miR-361-5p	ARCN1	Archain 1	In a screen to identify genes that control 2-	HiSeq_V1		
_			deoxyglucose (2DG) sensitivity, ARCN1	$P_1 = 0.000544$		
			knockdown was found to sensitize cells to	HiSeq_V2		
			the glycolytic inhibitor. [1]	$P_2 = 7.72E-13$		
	CREG1	Cellular	There is conflicting literature for the role of	$P_1 = 0.002726$		
		Repressor of	<i>CREG1</i> in cancer. <i>CREG1</i> has been found to	$P_2 = 4.39E-07$		
		E1A stimulated	be overexpressed in non-small cell lung			
		Genes 1	carcinoma cell lines with KRAS mutations			
			and has also been found to be upregulated in			
			gastric cancer tissues. [2,3] However,			
			<i>CREG1</i> has also been found to be involved			
			in cell senescence, to reduce cell			
			proliferation, and to promote differentiation.			
			[4-6]			
	ELL3	Elongation	In the breast cancer cell line MCF-7, <i>ELL3</i>	$P_1 = 0.002395$		
		Factor For RNA	expression has been found to promote cell	$P_2 = 1.51E-07$		
		Polymerase II 3	proliferation and to increase cancer stem cell			
			populations. [7] On the other hand, <i>ELL3</i> has			
			been implicated in the stabilization process			
			of p53, which ultimately results in increased			
			cell apoptosis. [8]			
	NCEH1	Arylacetamide	NCEH1 plays an important role in lipid	$P_1 = 0.002849782$		
		Deacetylase-	metabolism and has been found to be	$P_2 = 2.01E-08$		
		Like 1	overexpressed in numerous invasive cancer			
			cell lines. [9-12] Knockdown of NCEH1 in			
			prostate cancer cells results in reduced cell			
			migration, invasion, and survival. [13]			
miR-320a	GSG2	Germ Cell	GSG2 plays a critical role in cell mitosis and	HiSeq_V1		
		Associated 2	has been found to be overexpressed in a	$P_1 = 0.003303893$		
		(Haspin)	number of neoplasms. GSG2 has been	HiSeq_V2		
			suggested to be a potential therapeutic target	$P_2 = 3.71E-06$		
			for cancer. [14-16]			
	RAD51	RAD51	In breast cancer, <i>RAD51</i> has been found	$P_1 = 0.000993014$		
		Recombinase	to be overexpressed and to be associated	$P_2 = 3.35E-07$		
			with poor prognosis. [17] Another study			
			has also shown that <i>RAD51</i> drives			
			genomic instability in multiple breast			
			cancer cell lines. [18] Additionally,			
			downregulation of <i>RAD51</i> is associated			
			with increased chemo-sensitivity. [19-20]			
	RRP1B	Ribosomal RNA	In one study, <i>RRP1B</i> was found to interact	$P_1 = 0.002623317$		
		Processing 1B	with metastasis modifier gene SIPA1 to	$P_2 = 6.55 E-07$		

List of gene targets predicted for miR-320a, miR-361-5p, miR-21-5p and miR-103a-3p.

			regulate tumor suppressor genes. [21] <i>RRP1B</i> has also been found to interact with splicing regulator <i>SRSF1</i> to repress metastasis. [22]	
	SYNGR2	Synaptogyrin 2	Expression of <i>SYNGR2</i> was included in a six-gene signature for thyroid tumors that could differentially diagnose malignant tumors and benign tumors. [23]	$P_1 = 0.000122781 P_2 = 0.026343543$
	TDG	Thymine DNA Glycosylase	Deletion of <i>TDG</i> along with <i>PMS2</i> alterations contributes to a supermutator phenotype in both breast cancer and	P ₁ = 0.001831776 P ₂ = 7.25E-08
			rectal cancer. [24-25]	
miR-21-5p	ATXN10	Ataxin 10	This gene has been found to be elevated in human cachectic cancer patients, and inducing <i>ATXN10</i> in cardiomyocytes proved to be sufficient in producing cachexia phenotypes. [26] On the other hand, it has also been found that <i>ATXN10</i> is associated with cell senescence in human fibroblasts, and that knockdown of <i>ATXN10</i> promoted cell senescence avoidance. [27]	HiSeq_V1 $P_1= 0.002806202$ HiSeq_V2 $P_2= 7.05E-09$
	GATAD2B	GATA Zinc Finger Domain Containing 2B	In human fibroblasts, combinatorial knockdown of <i>GATAD2B</i> along with <i>ELAVL2</i> and <i>TEAD1</i> produced CD105+ cell populations, demonstrating increased differentiation. [28] Another study found that the stabilization of <i>GATAD2B</i> from <i>LRRC42</i> induction helps to promote cell growth in lung cancer cells. [29]	P ₁ = 0.002524675 P ₂ = 2.19E-10
	MSH2	MutS Homolog 2	<i>MSH2</i> appears to play multiple roles in breast cancer, producing research suggesting that <i>MSH2</i> possesses a dual role as oncogene and tumor suppressor depending on the context. <i>MSH2</i> expression has been observed to have increased expression in breast cancer tissues compared to normal tissues, and has been observed to have a negative correlation with histological grade. [30, 31] In contrast, <i>MSH2</i> has also been reported to be a tumor suppressor for its role in the TGF- β pathway. [32, 33]	P ₁ = 0.000321851 P ₂ = 1.88E-12
	NKIRAS1	NFKB Inhibitor Interacting Ras- Like 1	In breast cancer and non-small cell lung cancer, <i>NKIRAS1</i> upregulation has been associated with the methylation of regulatory genes, potentially contributing to the	$\begin{array}{c} P_1 = 0.004336416 \\ P_2 = 9.59E10 \end{array}$

	PELI1 RMND5A	Pellino E3 Ubiquitin Protein Ligase 1 Required For Meiotic Nuclear Division 5 Homolog A	dysregulation of cell processes. [34, 35]However, NKIRAS has been found to bedeleted or methylated in renal cancer. [36,37]In leukemia, the constitutive expression ofPELI1 results in the development oflymphoid tumors. [38]In HeLa cells, the targeting of RMND5Athrough miR-138 dramatically reducescell migration. [39] On the other hand,RMND5A expression has been found toincrease after paclitaxel and carboplatin	$P_{1}= 0.001309759$ $P_{2}= 6.90E-06$ $P_{1}= 0.001820747$ $P_{2}= 6.80E-14$
	STAG2	Stromal Antigen 2	treatment for leukocyte gene expression. [40] STAG2 is believed to play a tumor suppressing role for its function in the cohesion complex for both leukemia and pancreatic cancer. [41, 42] However, complete loss of STAG2 in bladder cancer predicts good prognosis. [43]	P ₁ = 0.003000074 P ₂ = 1.93E-14
	UBE2D3	Ubiquitin Conjugating Enzyme E2 D3	UBE2D3 appears to act as a tumor suppressor in breast cancer because knockdown of UBE2D3 in breast cancer cells augments cell proliferation and invasion. [44, 45] Additionally, inhibition of UBE2D3 leads to radio-resistance. [44, 46]	P ₁ = 0.003901447 P ₂ = 2.03E-07
	USP15	Ubiquitin Specific Peptidase 15	USP15's role in enhancing TGF- β signaling has been found to be significant in glioblastomas, ovarian, and breast cancer. [47, 48] It has also been highlighted the USP15 stabilizes MDM2, a negative regulator of p53, in cancer cells. [49]	P ₁ = 0.003470684 P ₂ = 3.27E-08
miR-103a-3p	AMMECR1	Alport Syndrome, Mental Retardation, Midface Hypoplasia And Elliptocytosis Chromosomal Region Gene 1	In ER+ breast cancer cells, miR-26 overexpression was found to inhibit estrogen-stimulated cell proliferation and tumor growth; <i>AMMECR1</i> was highlighted as a potential target of miR-26 as an estrogen responsive gene. [50]	HiSeq_V1 $P_1= 0.004118655$ HiSeq_V2 $P_2= 2.55E-13$

References

- Kobayashi H, Nishimura H, Matsumoto K, Yoshida M. Identification of the determinants of 2-deoxyglucose sensitivity in cancer cells by shRNA library screening. Biochem Biophys Res Commun. 2015 Nov 6;467(1):121–7.
- Clark DJ, Mei Y, Sun S, Zhang H, Yang AJ, Mao L. Glycoproteomic Approach Identifies KRAS as a Positive Regulator of CREG1 in Non-small Cell Lung Cancer Cells. Theranostics. 2016;6(1):65–77.
- Xu L, Wang F, Liu H, Xu X-F, Mo W-H, Xia Y-J, et al. Increased expression of cellular repressor of E1A-stimulated gene (CREG) in gastric cancer patients: a mechanism of proliferation and metastasis in cancer. Dig Dis Sci. 2011 Jun;56(6):1645–55.
- Moolmuang B, Tainsky MA. CREG1 enhances p16(INK4a) -induced cellular senescence. Cell Cycle. 2011 Feb 1;10(3):518–30.
- Veal E, Groisman R, Eisenstein M, Gill G. The secreted glycoprotein CREG enhances differentiation of NTERA-2 human embryonal carcinoma cells. Oncogene. 2000 Apr 20;19(17):2120–8.
- 6. Veal E, Eisenstein M, Tseng ZH, Gill G. A cellular repressor of E1A-stimulated genes that inhibits activation by E2F. Mol Cell Biol. 1998 Sep;18(9):5032–41.
- Ahn H-J, Kim G, Park K-S. Ell3 stimulates proliferation, drug resistance, and cancer stem cell properties of breast cancer cells via a MEK/ERK-dependent signaling pathway. Biochem Biophys Res Commun. 2013 Aug 9;437(4):557–64.
- 8. Ahn H-J, Kim K-S, Shin K-W, Lim K-H, Kim J-O, Lee J-Y, et al. Ell3 stabilizes p53 following CDDP treatment via its effects on ubiquitin-dependent and -independent

proteasomal degradation pathways in breast cancer cells. Oncotarget. 2015 Dec 29;6(42):44523–37.

- Nomura DK, Durkin KA, Chiang KP, Quistad GB, Cravatt BF, Casida JE. Serine hydrolase KIAA1363: toxicological and structural features with emphasis on organophosphate interactions. Chem Res Toxicol. 2006 Sep;19(9):1142–50.
- Jessani N, Liu Y, Humphrey M, Cravatt BF. Enzyme activity profiles of the secreted and membrane proteome that depict cancer cell invasiveness. Proc Natl Acad Sci U S A. 2002 Aug 6;99(16):10335–40.
- Chiang KP, Niessen S, Saghatelian A, Cravatt BF. An enzyme that regulates ether lipid signaling pathways in cancer annotated by multidimensional profiling. Chem Biol. 2006 Oct;13(10):1041–50.
- Shreder KR, Lin ECK, Wu J, Cajica J, Amantea CM, Hu Y, et al. Synthesis and structureactivity relationship of (1-halo-2-naphthyl) carbamate-based inhibitors of KIAA1363 (NCEH1/AADACL1). Bioorg Med Chem Lett. 2012 Sep 1;22(17):5748–51.
- Chang JW, Nomura DK, Cravatt BF. A potent and selective inhibitor of KIAA1363/AADACL1 that impairs prostate cancer pathogenesis. Chem Biol. 2011 Apr 22;18(4):476–84.
- 14. Higgins JMG. Haspin: a newly discovered regulator of mitotic chromosome behavior. Chromosoma. 2010 Apr;119(2):137–47.
- Cuny GD, Ulyanova NP, Patnaik D, Liu J-F, Lin X, Auerbach K, et al. Structure-activity relationship study of beta-carboline derivatives as haspin kinase inhibitors. Bioorg Med Chem Lett. 2012 Mar 1;22(5):2015–9.
- 16. Cuny GD, Robin M, Ulyanova NP, Patnaik D, Pique V, Casano G, et al. Structure-activity

relationship study of acridine analogs as haspin and DYRK2 kinase inhibitors. Bioorg Med Chem Lett. 2010 Jun 15;20(12):3491–4.

- Le Scodan R, Cizeron-Clairac G, Fourme E, Meseure D, Vacher S, Spyratos F, et al. DNA repair gene expression and risk of locoregional relapse in breast cancer patients. Int J Radiat Oncol Biol Phys. 2010 Oct 1;78(2):328–36.
- Parplys AC, Seelbach JI, Becker S, Behr M, Wrona A, Jend C, et al. High levels of RAD51 perturb DNA replication elongation and cause unscheduled origin firing due to impaired CHK1 activation. Cell Cycle. 2015;14(19):3190–202.
- Huang F, Mazin A V. A small molecule inhibitor of human RAD51 potentiates breast cancer cell killing by therapeutic agents in mouse xenografts. PLoS One. 2014;9(6):e100993.
- Hong K-J, Hsu M-C, Hung W-C. RECK impedes DNA repair by inhibiting the erbB/JAB1/Rad51 signaling axis and enhances chemosensitivity of breast cancer cells. Am J Cancer Res. e-Century Publishing Corporation; 2015;5(8):2422–30.
- Nanchari SR, Cingeetham A, Meka P, Damineni S, Tipirisetti N, Padala C, et al. Rrp1B gene polymorphism (1307T>C) in metastatic progression of breast cancer. Tumour Biol. 2015 Feb;36(2):615–21.
- Lee M, Dworkin AM, Gildea D, Trivedi NS, Moorhead GB, Crawford NPS. RRP1B is a metastasis modifier that regulates the expression of alternative mRNA isoforms through interactions with SRSF1. Oncogene. Nature Publishing Group; 2014 Apr 3;33(14):1818– 27.
- 23. Rosen J, He M, Umbricht C, Alexander HR, Dackiw APB, Zeiger MA, et al. A six-gene model for differentiating benign from malignant thyroid tumors on the basis of gene

expression. Surgery. 2005 Dec;138(6):1050-6-7.

- 24. Vasovcak P, Krepelova A, Menigatti M, Puchmajerova A, Skapa P, Augustinakova A, et al. Unique mutational profile associated with a loss of TDG expression in the rectal cancer of a patient with a constitutional PMS2 deficiency. DNA Repair (Amst). 2012 Jul 1;11(7):616–23.
- Dalton SR, Bellacosa A. DNA demethylation by TDG. Epigenomics. NIH Public Access;
 2012 Aug;4(4):459–67.
- Schäfer M, Oeing CU, Rohm M, Baysal-Temel E, Lehmann LH, Bauer R, et al. Ataxin-10 is part of a cachexokine cocktail triggering cardiac metabolic dysfunction in cancer cachexia. Mol Metab. Elsevier; 2016 Feb;5(2):67–78.
- 27. Rovillain E, Mansfield L, Lord CJ, Ashworth A, Jat PS. An RNA interference screen for identifying downstream effectors of the p53 and pRB tumour suppressor pathways involved in senescence. BMC Genomics. BioMed Central; 2011;12:355.
- Ishihara Y, Tsuno S, Kuwamoto S, Yamashita T, Endo Y, Hasegawa J, et al. Hsa-miR 520d converts fibroblasts into CD105+ populations. Drugs R D. 2014 Dec;14(4):253–64.
- 29. Fujitomo T, Daigo Y, Matsuda K, Ueda K, Nakamura Y. Identification of a nuclear protein, LRRC42, involved in lung carcinogenesis. Int J Oncol. 2014 Jul;45(1):147–56.
- 30. Lira D, Teodoro TR, Pinhal MA da S, Fonseca FLA, Gehrke F de S, Azzalis LA, et al. Profile of hMSH2 expression in breast tumors and lymph nodes: a preliminary study. Eur Rev Med Pharmacol Sci. 2015 Sep;19(17):3229–33.
- 31. Chintamani, Jha BP, Bhandari V, Bansal A, Saxena S, Bhatnagar D. The expression of mismatched repair genes and their correlation with clinicopathological parameters and response to neo-adjuvant chemotherapy in breast cancer. Int Semin Surg Oncol. 2007;4:5.

- Liu L, Zhou W, Cheng C-T, Ren X, Somlo G, Fong MY, et al. TGFβ induces "BRCAness" and sensitivity to PARP inhibition in breast cancer by regulating DNA-repair genes. Mol Cancer Res. 2014 Nov;12(11):1597–609.
- 33. Chen L, Li Y, Fu Y, Peng J, Mo M-H, Stamatakos M, et al. Role of deregulated microRNAs in breast cancer progression using FFPE tissue. PLoS One. 2013;8(1):e54213.
- 34. Pronina I V, Loginov VI, Burdennyy AM, Fridman M V, Kazubskaya TP, Dmitriev AA, et al. Expression and DNA methylation alterations of seven cancer-associated 3p genes and their predicted regulator miRNAs (miR-129-2, miR-9-1) in breast and ovarian cancers. Gene. 2016 Jan 15;576(1 Pt 3):483–91.
- 35. Braga EA, Loginov VI, Pronina I V, Khodyrev DS, Rykov S V, Burdennyy AM, et al. Upregulation of RHOA and NKIRAS1 genes in lung tumors is associated with loss of their methylation as well as with methylation of regulatory miRNA genes. Biochem Biokhimiia. 2015 Apr;80(4):483–94.
- Gerashchenko G V, Bogatyrova OO, Rudenko EE, Kondratov AG, Gordiyuk V V, Zgonnyk YM, et al. Genetic and epigenetic changes of NKIRAS1 gene in human renal cell carcinomas. Exp Oncol. 2010 Jul;32(2):71–5.
- 37. Dmitriev AA, Rudenko EE, Kudryavtseva A V, Krasnov GS, Gordiyuk V V, Melnikova N V, et al. Epigenetic alterations of chromosome 3 revealed by NotI-microarrays in clear cell renal cell carcinoma. Biomed Res Int. 2014;2014:735292.
- Park H-Y, Go H, Song HR, Kim S, Ha G-H, Jeon Y-K, et al. Pellino 1 promotes lymphomagenesis by deregulating BCL6 polyubiquitination. J Clin Invest. 2014 Nov;124(11):4976–88.
- 39. Li J, Chen Y, Qin X, Wen J, Ding H, Xia W, et al. MiR-138 downregulates miRNA

processing in HeLa cells by targeting RMND5A and decreasing Exportin-5 stability. Nucleic Acids Res. Oxford University Press; 2014 Jan;42(1):458–74.

- González-Fernández R, Morales M, Avila J, Martín-Vasallo P. Changes in leukocyte gene expression profiles induced by antineoplastic chemotherapy. Oncol Lett. Spandidos Publications; 2012 Jun;3(6):1341–9.
- Mullenders J, Aranda-Orgilles B, Lhoumaud P, Keller M, Pae J, Wang K, et al. Cohesin loss alters adult hematopoietic stem cell homeostasis, leading to myeloproliferative neoplasms. J Exp Med. 2015 Oct 19;212(11):1833–50.
- Evers L, Perez-Mancera PA, Lenkiewicz E, Tang N, Aust D, Knösel T, et al. STAG2 is a clinically relevant tumor suppressor in pancreatic ductal adenocarcinoma. Genome Med. 2014;6(1):9.
- Qiao Y, Zhu X, Li A, Yang S, Zhang J. Complete loss of STAG2 expression is an indicator of good prognosis in patients with bladder cancer. Tumour Biol. 2016 Aug;37(8):10279–86.
- 44. Wang W, Yang L, Hu L, Li F, Ren L, Yu H, et al. Inhibition of UBE2D3 expression attenuates radiosensitivity of MCF-7 human breast cancer cells by increasing hTERT expression and activity. PLoS One. 2013;8(5):e64660.
- 45. Mittal MK, Singh K, Misra S, Chaudhuri G. SLUG-induced elevation of D1 cyclin in breast cancer cells through the inhibition of its ubiquitination. J Biol Chem. 2011 Jan 7;286(1):469–79.
- 46. Yang H, Wu L, Ke S, Wang W, Yang L, Gao X, et al. Downregulation of Ubiquitinconjugating Enzyme UBE2D3 Promotes Telomere Maintenance and Radioresistance of Eca-109 Human Esophageal Carcinoma Cells. J Cancer. 2016;7(9):1152–62.

- 47. Eichhorn PJA, Rodón L, Gonzàlez-Juncà A, Dirac A, Gili M, Martínez-Sáez E, et al.
 USP15 stabilizes TGF-β receptor I and promotes oncogenesis through the activation of TGF-β signaling in glioblastoma. Nat Med. 2012 Mar;18(3):429–35.
- 48. Zhang L, Zhou F, García de Vinuesa A, de Kruijf EM, Mesker WE, Hui L, et al. TRAF4 promotes TGF-β receptor signaling and drives breast cancer metastasis. Mol Cell. 2013 Sep 12;51(5):559–72.
- Zou Q, Jin J, Hu H, Li HS, Romano S, Xiao Y, et al. USP15 stabilizes MDM2 to mediate cancer-cell survival and inhibit antitumor T cell responses. Nat Immunol. 2014 Jun;15(6):562–70.
- 50. Tan S, Ding K, Li R, Zhang W, Li G, Kong X, et al. Identification of miR-26 as a key mediator of estrogen stimulated cell proliferation by targeting CHD1, GREB1 and KPNA2. Breast Cancer Res. 2014;16(2):R40.