WPD Pharmaceuticals

OCTOBER 2020 | WPD101

CSE:WBIO

Disclaimer

All statements contained herein other than statements of historical fact, including statements regarding our future results of operations and financial position, our business strategy and plans, and our objectives for future operations, are forward-looking statements. The words "believe", "may", "will", "estimate", "continue", "anticipate", "intend", "could", "expect" and similar expressions are intended to identify forward looking statements. We have based these forward-looking statements largely on our current expectations and projections about future events and trends that we believe may affect our financial condition, results of operations, business strategy, short-term and long-term business operations and objectives, and financial needs. Other statements may contain expressions of past results, studies or data owned or licensed by WPD Pharmaceuticals, Inc. (the "Company").

Such results, studies or data may not be duplicable in the future. Certain expressions of results, studies or past discoveries may also be anecdotal and non-reproducible in future studies designed specifically to test the robustness, strength or veracity of such results, studies or data. No representation herein is designed to convey any claim regarding the safety or efficacy of any compound owned or licensed by the Company. Moreover, we operate in a very competitive and rapidly changing environment. New risks emerge from time to time. It is not possible for our management to predict all risks, nor can we assess the impact of all factors on our business or the extent to which any factor, or combination of factors, may cause actual results to differ materially from those contained in any forward-looking statements we may make. In light of these risks, uncertainties and assumptions, the future events and trends may not occur and actual results could differ materially and adversely from those anticipated or implied in the forward-looking statements.

Company Overview

WPD Pharmaceuticals is a diverse biotech company that has 10 novel drug candidates with 4 in clinical development stage via its development partners. WPD drug candidates are in collaboration via its development partners with institutions including MD Anderson Cancer Center, Mayo Clinic, Emory University, Wake Forest University and leading hospitals and academic centers in Poland.

Alongside direct and indirect investment of $71 million, over $29 million of grant funding (total of $100 million USD) has gone towards the development of our robust drug development pipeline with a focus on melanoma, brain cancer, leukemia and pancreatic cancer. Notably, add to this investment figure $14 million USD in grants recently awarded to WPD Pharmaceuticals from The National Centre for Research and Development in Poland.

With a groundswell of multi-continental grant support and a diverse portfolio of potentially breakthrough drug technologies, WPD Pharmaceuticals, we believer, is now strategically positioned to enter the market with blockbuster potential.

Investment **Highlights**

Experienced Management & Advisors

Team of scientists with extensive pharmaceutical experience

Robust Drug Portfolio

10 novel drug candidates across 5 indications

Strategic Collaborations

Wake Forest University Health Sciences, Moleculin Biotech Inc. and CNS Pharmaceuticals, Inc.

Rapidly Growing Operations

4 drugs in clinical development

Tightly Held Share Structure

Management and Insiders hold ~ 36%

Attractive Valuation

Discount to industry peers

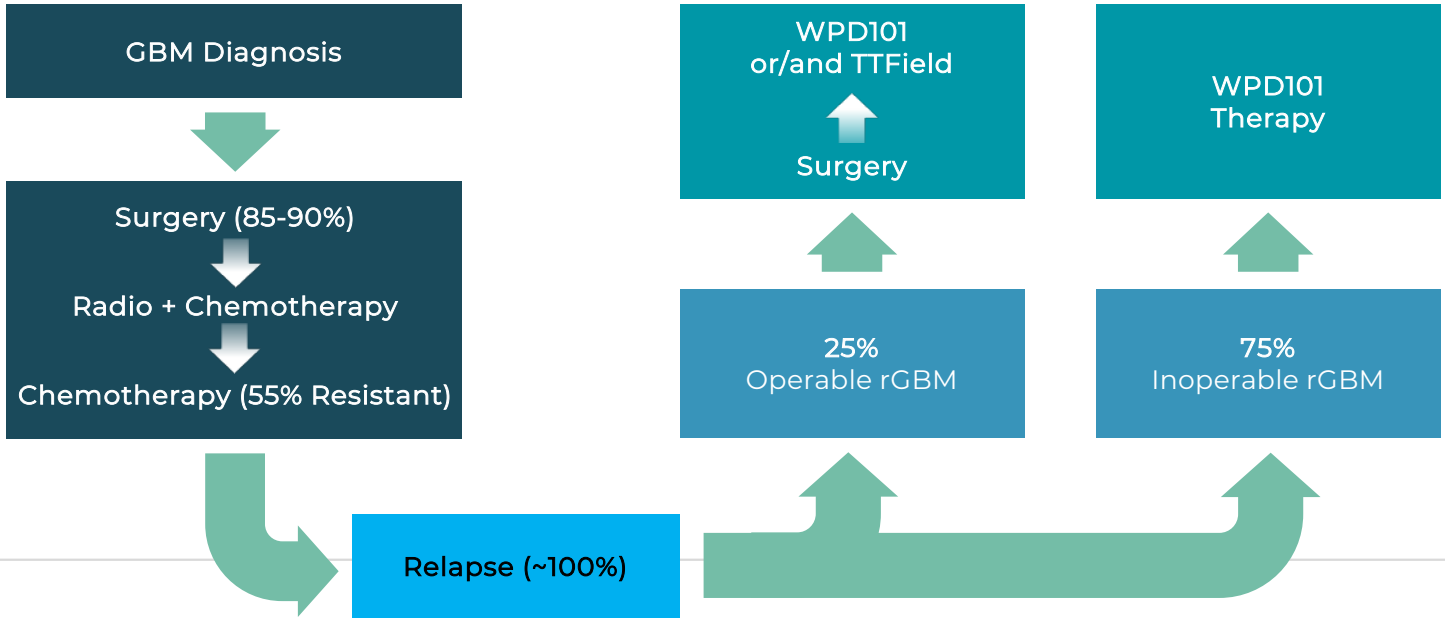
	Discovery	Pre-Clinical	Regulatory	Clinical I / II
Brain Cancers		WPD101		Berubicin
				WP1066
Pancreatic Cancers		WP1122	WP1066	
		WP1234	WP1732	
Other Cancers	WPD103			Annamycin
				WP1220
Melanoma	WPD102			

WPD101

Indications to Treat Brain Cancers
including **Glioblastoma**

WPD101

Glioblastoma also known as glioblastoma multiforme (GBM) is one of the most common and aggressive types of brain tumors, causing about 50% of all gliomas. GBM spreads insidiously through the brain without a clear border, making it difficult if not impossible to completely remove surgically. The average time from first symptoms to death is approximately 14 to 16 months. GBM is aggressive and resists most treatments. Often the goal of these treatment is more about reducing symptoms and prolonging life rather than completely curing the disease. Treatment for GBM usually includes three components: surgery, chemotherapy (tomozolomide or a combination of procarbazine, lomustine and vincristine) and radiotherapy. Almost in all cases, GBM recures after 6 months from diagnosis.



WPD101

OVERVIEW

The breakthrough of the solution is based on the use of GBM-targeted therapy against IL-13RA2 and EphA2 - brain tumor-specific receptors conjugated with bacterial cytotoxins. It is well known, that interluekin-13 receptor alpha 2 (IL13RA2) is a glioblastoma receptor that is abundantly overexpressed in over 75% of GBMs but absent in normal brain tissue. In is estimated that IL-13RA2 overexpression is reported in >50% of GBM cases. Similarly, EphA2 is cancer specific receptor recognized by ephrin A1 cytokine. Its overexpression is also a hallmark of GBM cells, thus EphA2 receptors are proposed targets (Wykosky et al., 2005, 2007, Ferluga et al., 2016). Its overexpression is confirmed in the majority of GBM specimens. It is assumed that more than 90% of GBM overexpressed at least of the receptors (Wykosky et al., 2008).

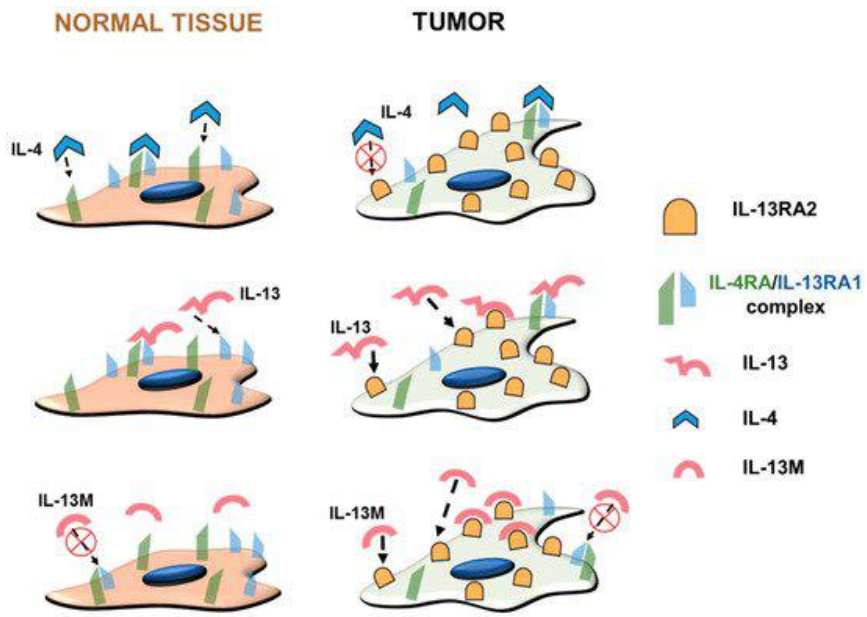


Figure 1. A schematic of the IL13 receptor system. Normal and tumor cells express IL4RA/IL13RA1. IL4 first binds to IL4RA, then to the IL13RA1 in normal cells. On the other hand, IL13RA2 is expressed by tumor cells. IL4 binds to IL4RA/IL13RA1 but not IL13RA2. IL13 binds more readily to IL13RA2 compared to IL4/IL13RA1. By introducing mutations in the IL13 ligand – IL13M, the ligands binds mostly on the IL13RA2 (https://www.mdpi.com/1422-0067/19/11/3326).

WPD101

STRATEGY

Immunotoxins are fusion proteins comprised of a toxic moiety and a targeting moiety. That allows concentration of the fusion protein at the plasma membrane of specific cell types.

WPD101 is a unique drug cocktail composed of two immunotoxins targeting simultaneously IL-13RA2 and EphA2 receptors. This strategy guarantees specific drug administration to the majority of GBM cells. Furthermore, to increase tissue distribution, minimize possible side-effects and overcome BBB difficulties, convection-enhanced delivery (CED) of WPD101, directly to the brain tumor will be applied (Debinski and Tatter, 2009)

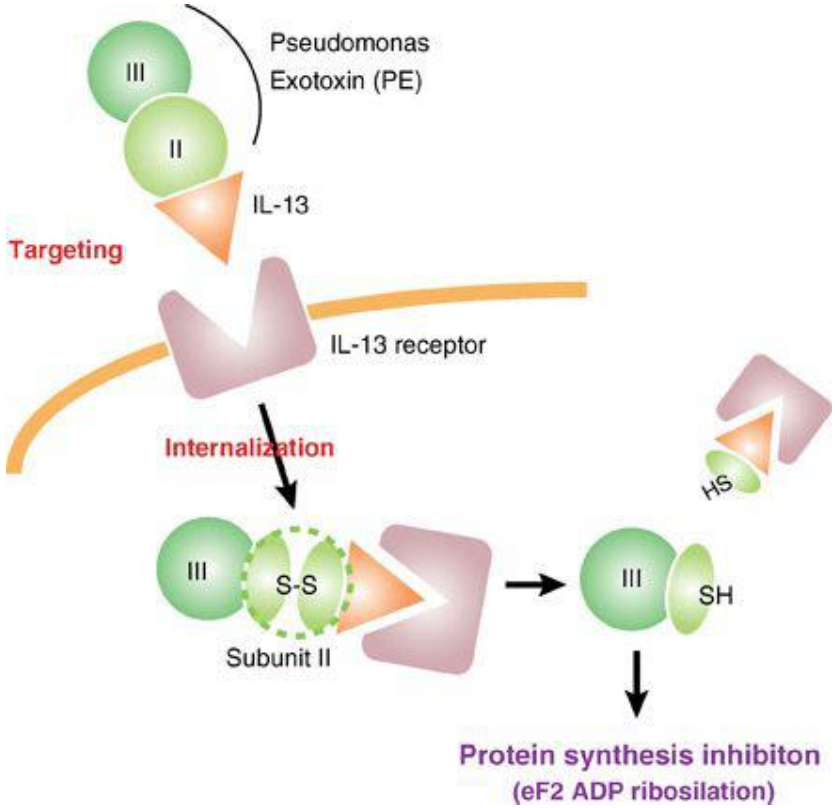


Figure 2. A schematic of the IL13 cytotoxins action. IL13 conjugated to bacteria toxin specifically recognizes and binds to its IL13RA2 receptor. Receptor-ligand complex is internalized and transported within the cell. Further, bacteria toxin is released and inhibits protein synthesis, leading to intrinsic cell death induction. (https://doi.org/10.1007/978-3-540-4748-1_1476).

WPD101

CURRENT STATUS

WPD101 is currently in the preclinical stage of development. Its consistent anticancer properties are demonstrated and validated in dogs with spontaneous GBM closely resembling GBM in human patients. Canine model of spontaneous gliomas represents the closest translational model to human diseases and provides potentially more clinicaly relevant assessment of potential efficacy in human trials regarding biological and technological aspects of treatment (Figure 3). Canine gliomas, as well as human GBM cells, overexpress tumor-associated IL-13RA2 and EphA2 receptors that are not present in normal brain cells. IL-13RA2 and EphA2 are conjointly present in >90% of patient and dogs with GBM.

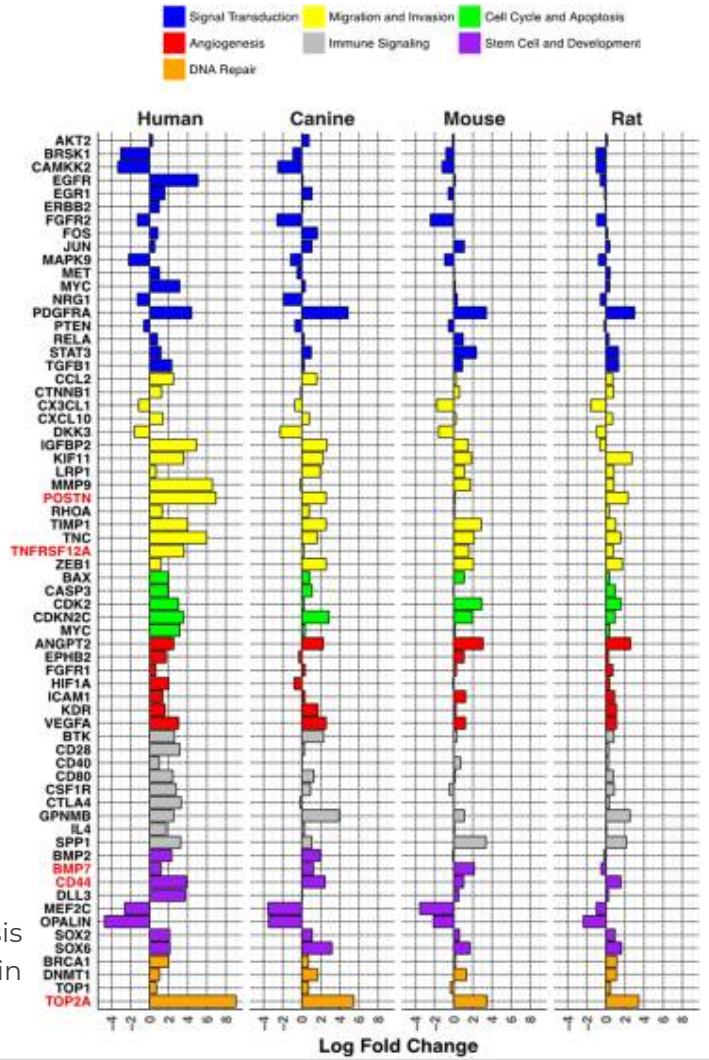


Figure 3. Comparative transcriptional analysis of GBM signature gene expression patterns in human, canine, mouse and rat samples.

Connolly et al., 2018

WPD**101a**

The Phase I clinical trial in dogs with spontaneous malignant gliomas

ACCEPTED MANUSCRIPT

Phase I trial of convection-enhanced delivery of IL13RA2 and EPHA2 receptor targeted cytotoxins in dogs with spontaneous intracranial gliomas

John H Rossmeisl ✉, Denise Herpai, Mindy Quigley, Thomas E Cecere, John L Robertson, Ralph B D'Agostino, Jonathan Hinckley, Stephen B Tatter, Peter J Dickinson, Waldemar Debinski ✉

Neuro-Oncology, noaa196, https://doi.org/10.1093/neuonc/noaa196

Published: 19 August 2020 **Article history** ▾

In the published study, 17 dogs diagnosed with glioma and immunohistochemically positive for IL-13RA2 (17/17) or/and EphA2 (11/17) receptors were treated with escalating doses of IL-13- and ephrinA1-based cytotoxins. Cytotoxins were delivered through the Convention Enhanced Delivery (CED) method. CED allowed consistent intratumoral delivery of the cocktail with a median coverage of 70% (range 40-94%) of the tumor. No dose-limiting toxicities were observed. At 42 days of treatment, volumetric tumor reductions were observed in 15/16 dogs, with median reduction of 42% (range 5-94%). Objective tumor responses were observed in 8/16 (50%) dogs, and the median tumor volume reduction was 79% (range 65-94% of tumor volume regression).

The authors conclude that the CED of IL-13RA2/EphA2 targeting cytotoxins at concentrations ranging from 0.05-1.6 ug/mL was safe and resulted in clinically relevant responses in 50% of dogs with gliomas.

WPD101

Scientific Advice in MHRA

In July 2020, WPD consulted MHRA in Scientific Advice procedure to discuss quality, non-clinical and regulatory aspects of WPD101a for the treatment of glioblastoma multiforme. MHRA accepted WPD drug development plan.

LICENSE

On November 28, 2017, WPD signed a license agreement (the “Wake Forest License Agreement”) with Wake Forest University of Health Sciences (WFUHS) granting WPD an exclusive, worldwide, royalty-bearing license under certain patented and patent-pending technologies for the diagnosis and treatment of glioblastoma multiforme (GBM), to make, use, import, offer for sale and sell licensed pharmaceutical products, including the right to sublicense its rights under the Wake Forest License Agreement, subject to WFUHS’ retained right to make, have made, and use licensed products solely for non- commercial, educational, academic, and research purposes. The term of the Wake Forest License Agreement is for the life of the licensed patents.

WPD101

FUNDING

In February 2018, WPD received a grant from the European Union, under the European Regional Development Fund, the Smart Growth Operational Program 2014-2020, implemented under the National Center for Research and Development in Poland (NCBiR) for the development of WPD101 that would include Phase I clinical studies in GBM tumors. Management expects this grant to cover 70 – 80% of all research and development costs for the next 2-3 years. Total estimated costs associated with the WPD101 phase I clinical trials are 33,699,206 PLN (CDN$11,457,730), comprised of pre-clinical costs of 6,992,609 PLN (CDN$2,377,487), clinical costs of 17,724,943 PLN (CDN$6,026,480), and lab development/manufacturing costs of 8,982,653 PLN (CDN$3,054,102).

Corporate **Overview**

WPD Pharmaceuticals Inc.

CSE: WBIO

Capital Structure	
Issued and Outstanding	111,520,388
Warrants	3,949,997
Fully Diluted	115,470,385
Management and Insider holdings	36%

Contact

Vancouver Office

Suite 1080
789 West Pender St
Vancouver, BC V6C 1H2

Warsaw Office

Żwirki i Wigury 101
02-089 Warszawa
Poland

wpdpharmaceuticals.com

CSE:WBIO

Appendix / References:

1. Bojkova D., Klann K., Koch B., Widera M., Krause D., Ciesek S., Cinatl J., Munch C. Proteomics of SARS-CoV-2-infected host cells reveals therapy genes. Nature 2020, 583:469-472.
2. Brooks TA, O'Loughlin KL., Minderman H., Bundy BN., Ford LA., Vredenburg MR., Bernacki RJ., Priebe W., Baer MR. The 4'-O-benzylated doxorubicin analog WP744 overcomes resistance mediated by P-gp multidrug resistance protein and breast cancer resistance protein in cell lines and acute myeloid leukemia cells. Invest New Drugs 2007, 25:115-22.
3. Cheng CC., Shi LH., Wang XJ., Wang SH., Wan SQ., Liu SR., Wang YF., Lu Z., Wang LH., Ding Y. Stat3/Oct-4/c-Myc signal circuit for regulating stemness-mediated doxorubicin resistance of triple-negative breast cancer cells and inhibitory effect of WP1066. Int J Oncol 2018; 53:339-348.
4. Connolly NP., Shety AC., Stokum JA., Hoeschele I., Siegel MB., Miller CR., Kim AJ., Ho CY., Davila E., Simard JC., Devine SE., Rossmeisl JH., Holland EC., Winkles JA., Woodworth GF. Cross-species transcriptional analysis reveals conserved and host-specific neoplastic proccesses in mammalian glioma. Sci Rep 2018, 1180.
5. Debinski W., Dickinson P., Rossmeisl JH., Robertson J., Gibo DM. New agents of targeting of IL-13RA2 expressed in primary human and cacine brain tumors. PloS One 2013, 16:e77719.
6. Debinski W., Tatter SB. Convention-enhanced delivery for the treatment of brain tumors.
7. Debinski W., Thompson JP. Retargeting interleukin 13 for radioimmunodetection and radioimmunotherapy of human high-grade gliomas. Clin Cancer Res 1999, 5:3143s-3147s.
8. Debinski W., Gibo DM., Obiri NI., Kealiher A., Puri RK. Novel anti-brain tumor cytotoxins specific for cancer cells. Nat Biotechnol 1998; 16:449-53.
9. Federl S., Estrov Z., Kantarjian HM., Harris D., Van Q., Fokt I., Przewloka C., Godlewski J., Woynarowski JM., Priebe W. WP744, a novel anthracycline with enhanced proapoptotic and antileukemic activity. Anticancer Res 2001, 21:3777-84.
10. Ferluga S., Lema Tome CM., Herpai Mazess D., D-Agostino R., Debinski W. Simultaneous targeting of Eph receptors in glioblastoma. Oncotarget 2016; 7:59860-59876.
11. Geng L., Li X., Zhou X., Fang X., Yuan D., Wang X. WP1066 exhibits antitumor efficacy in nasal-type natural killer/T-cell lymphoma cells through downregulation of the STAT3 signaling pathway. Oncol Rep 2016, 36:2868-2874.
12. Gruber BM. Anuszewska EL., Bubko I., Goździk A., Fokt I., Priebe W. Effect of structural modification at the 4, 3', and 2' positions of doxorubicin on topoisomerase II poisoning, apoptosis and cytotoxicity in human melanoma cells. Arch Immunol Ther Exp (Warsz) 2007, 55:193-8.
13. Gruber BM., Anuszewska EL., Bubko I., Kasprzycka-Guttman T., Misiewicz I., Skupińska K., Fokt I., Priebe W. NFkappaB activation and drug sensitivity in human neoplastic cells treated with anthracyclines. Acta Pol Pharm. 2008, 65: 267-71
14. Hussain SF., Kong LY., Jordan J., Conrad C., Madden T., Fokt I., Priebe W., Heimberger AB. A novel small molecule inhibitor of signal transducers and activators of transcription 3 reverses immune tolerance in malignant glioma patients. Cancer Res 2007, 15:9630-6.

References:

15. Inge TH., Harris NL., Wu J., Azizkhan RG., Priebe W. WP744 is a novel anthracycline with enhanced activity against neuroblastoma. J Surg Res 2004, 121:187-96.
16. Kawakami K., Kawakami M., Joshi B., Puri RK. Interleuki-13-receptor-targeted cancer therapy in an immunodeficient animal model of human head and neck cancer. Cancer Res 2001, 61:6194-200.
17. Kawakami K., Terabe M., Kawakami M., Berzofsky JA., Puri RJ. Characterization of a novel human tumor antigen interleukin-13 receptor a2 chain. Cancer Res 2006; 66:4434-4442.
18. Kioi M., Seetharam S., Puri RK. Targeting IL-13RA2-positive cancer with a novel recombinant immunotoxin composed of a single-chain antibody and mutated *Pseudomonas* exotoxin. Mol Cancer Ther 2008, 7:1579-87.
19. Kolonias D., Podona T., Savaraj N., Gate L., Cossum P., Lampidis TJ. Comparison of annamycin to Adriamycin in cardiac and MDR tumor cell systems. Anticancer Res 1999, 19:1277-83.
20. Lee HT., Xue J., Chou PC., Zhou A., Yang P., Conrad CA., Aldape KD, Priebe W., Patterson C., Sawaya R., Xie K., Huang S. Stat3 orchestrates interaction between endothelial and tumor cells and inhibition of STAT3 suppresses brain metastasis of breast cancer cells. Oncotarget 2015, 6:10016-29.
21. Lema Tome CM., Palma E., Ferluga S., Lowther WT., Hantgan R., Wykosky J., Debinski W. Structural and functional characterization of monomeric Ephrin A1 binding site to EphA2 receptor. J Biol Chem 2012, 287:14012-22.
22. Li T., Murphy S., Kiselev B., Bakshi KS., Zhang J., Eltahir A., Zhang Y., Chen Y., Zhu J., Davis RM., Madsen LA., Morris JR., Karolyi DR., LaConte SM., Sheng Z., Dorn HC. A new interlekukin-13 amino-coated gadolinium metallofullerene nanoparticle for targeted MRI detection of glioblastoma tumor cells. J Am Chem Soc 2015, 137:7881-8.
23. Nguyen V., Conyers JM., Zhu D., Gibo DM., Hantgan RR., Larson SM., Debinski W., Mintz A. A novel ligand delivery system to non-invasively visualize and therapeutically exploit the IL-13RA2 tumor-restricted biomarker. Neuro Oncol 2012; 14:1239-1253.
24. Pandya H., Gibo DM., Garg S., Kridel S., Debinski W. An interleukin 13 receptor alpha 2-specific peptide homes to human glioblastoma multiforme xenografts. Neuro Oncol 2012, 14:6-18.
25. Rossmeisl JH., Clapp K., Pancotto TE., Emch S., Robertson JL., Debinski W. Canine butterfly glioblastomas: a neuroradiological review. Front Vet Sci 2016; 3:40.
26. Sai KKS., Sattiraju A., Almageuel FG., Xuan A., Rideout S., Krishnaswamy RS., Zhang J., Herpal DM., Debinski W., Mintz A. Peptide-based PET imaging of the tumor restricted IL13RA2 biomarker. Oncotarget 2017, 24:50997-51007.
27. Sanchez EL., Lagunoff M. Viral activation of cellular metabolism. Virology 2015, 479-480:609-18.

References:

28. Sattiraju A., Solingapuram Sai KK., Xuan A., Pandya DN., Almageul FG., Wadas TJ., Herpal DM., Debisnki W., Mintz A. IL13RA2 targeted alpha particle therapy against glioblastomas. Oncotarget 2017, 27:42997-43007.
29. Sau S., Mondal SK., Kashaw SK., Iyer AK., Banerjee R. Combination of cationic dexamethasone derivative and STAT3 inhibitor (WP1066) for aggressive melanoma: a strategy for repurposing a phase I clinical trial drug. Mol Cell Biochem 2017, 436:119-136.
30. Sau S., Mondal SK., Kashaw SK., Iyer AK., Banerjee R. Combination of cationic dexamethasone derivative and STAT3 inhibitor (WP1066) for aggressive melanoma: a strategy for repurposing a phase I clinical trial drug. Mol Cell Biochem 2017, 436:119-136.
31. Sterba M., Popelova O., Vavrova A., Jirkowvsky E., Kovarikova P., Gersl V., Simunek T. Oxidative stress, redox signaling and metal chelation in anthracycline cardiotoxicity pharmacological cardioprotection. Antioxid Redox Signal 2013, 18:899-929.
32. Trevino AV., Woynarowska BA., Herman TS., Priebe W., Woynarowski JM. Enhanced topoisomerase II targeting by annamycin and related 40demetoxy anthracycline analogues. Mol Cancer Ther 2004, 3:1403-10.
33. Thaci B., Brown CE., Binello E., Werbaneth K., Sampath P., Sengupta S. Significance of interleukin 13 receptor alpha-targeted glioblastoma therapy. Neuro Oncol 2014; 16:1304-1312.
34. Thanker SK., Chang J., Christfolk HR. Viral hijacking of cellular metabolism. BMC Biology 2019, 17:59.
35. Tsujita Y., Horiguchi A., Tasaki S., Isono M., Asano T., Ito K., Asano T., Mayumi Y., Kushibiki T. STAT3 inhibition by WP1066 suppress tumor growth and invasiveness of bladder cancer cells. Oncol Rep 2017, 38:2197-2204.
36. Wang Y., Li YR., Sun MX., Ni B., Huan C., Li C., Fan HJ., Ren XF., Mao X. Triggering unfolded protein response by 2-deoxy-D-glucose inhibits porcine epidemic diarrhea virus propagation. Antiviral Res. 2014, 106:33-41.
37. Wetzler M., Thomas DA., Wang ES., Shepard R., Ford LA., Heffner TL., Parekh S., Andreeff M., O-Brien S., Kantarjian HM. Phase I/II trial of nanomolecular liposomal annamycin in adult patients with relapse/refractory acute lymphoblastic leukemia Clin Lymphoma Myeloma Leuk 2013, 13:430-4.
38. Wu J., Harris N., Inge T. Nuclear factor-kappa B and apoptosis inducing factor activation by doxorubicin analog WP744 in SH-SY5Y neuroblastoma cells. J Surg Res 2004, 122:231-9.
39. Wykosky J., Gibo DM., Debinski W. A novel, potent and specific ephrin A1-based cytotoxin against EphA2 receptor et al. Mol Cancer Ther 2007, 6:3208-18.
40. Wykosky J., Gibo DM., Stanton C., Debinski W. EphA2 as a novel molecular marker and target in glioblastoma multiforme. Mol Cancer Ther 2005, 3:541-51.

References:

41. Wykosky J., Gibo DM., Stanton C., Debinski W. Interleukin -13-receptor alpha 2, EphA2 and Fos- related antigen 1 as molecular denominators of high-grade astrocytomas and specific targets for combinatorial therapy. Clin Cancer Res 2008; 14:199-208.
42. Yu J., Yan X., Liu Y., Zhang K., Wang J., Zhang H., Liu F. Deleayed administration of WP1066, an STAT3 inhibitor, ameliorates radiation-induced lung injury in mice. Lung 2016, 194:67-74.
43. Zielinski R., Tworowska I., Skora S., Rusin A, Venugopal R, Jayakumar A., Fokt I., Kang Y., Fleming J., Huang Y. Targeting IL13RA2 in melanoma and pancreatic cancer. Cancer Res 2018, 78(13): abstract1927.
44. Zielinski R. et al. Preclinical evaluation of WP1122, a 2-DG prodrug and inhibitor of glycolysis. Proceedings: Symposia on Cancer Research 2017, Cancer Metabolism, Houston, TX, 10/2017.