Targeting MDM2 for Neuroblastoma Therapy

Subjects: Oncology

Contributor: Wei Wang, Ruiwen Zhang

Neuroblastoma is an aggressive pediatric solid tumor with an overall survival rate of <50% for patients with high-risk disease. There is a highly unmet medical need for identifying and developing more effective and safer therapy for high-risk neuroblastoma. We and others have proposed that mouse double minute 2 (MDM2) represents novel molecular target for the treatment of cancer, including neuroblastoma. In the present study, we found that SP141, a unique MDM2 inhibitor, has significant in vitro activity, in vivo efficacy, and minimal host toxicity in neuroblastoma tumor models. These results provide the proof-of-principle data for targeting MDM2 to treat high-risk neuroblastoma.

Keywords: neuroblastoma,MDM2,p53,SP141

1. Introduction

Neuroblastoma is a pediatric extracranial tumor of the sympathetic nervous system and contributes to about 15% of all pediatric cancer deaths[1][2][3][4]. A hallmark of neuroblastoma is high genetic, biological, clinical, and morphological heterogeneity, which can lead to an uneven response to treatment[5]. The International Neuroblastoma Risk Group (INRG) has classified neuroblastoma into very low-risk, low-risk, intermediate-risk, and high-risk groups [6][7]. Treatment for high-risk neuroblastoma is intense and includes multimodal chemotherapy, autologous stem cell transplant, radiation, and immunotherapy [8]. However, the survival rate for children with high-risk neuroblastoma is less than 50%, and nearly half of patients develop drug resistant tumors and suffer relapse[9][10][11][12][13][14]. Thus, it is prudent to identify and develop novel non-toxic treatment strategies for neuroblastoma.

In recent years, research has focused on investigating the genetic and epigenetic changes involved in the tumorigenesis of neuroblastoma. High-throughput genome analyses have identified several genetic aberrations that contribute to neuroblastoma development. Intrinsic alterations at the genetic and epigenetic levels both suggest strategies for molecular targeted therapies, and also impose limitations to the use of such treatment for neuroblastoma[15]. Among the genetic aberrations, amplification of oncogenes and loss of tumor suppressor activity play a significant role in tumorigenesis[16][17]. One of these oncogenes is the human homolog of murine double minute 2 (MDM2, sometimes called HDM2), a negative regulator of p53, which has been found to be amplified in several human malignancies, including neuroblastoma[18][19]. In addition, MDM2 protein overexpression is often present even in neuroblastomas without MDM2 gene amplification, and is linked to a poorer prognosis of patients [18][19]. It has been suggested that the presence of T to G single nucleotide polymorphism (SNP) (SNP309; rs2279744) in the promoter region of MDM2[20] may increase the MDM2-associated malignant activity and contribute to the development of neuroblastoma[21]. Enhanced MDM2 activity leads to inhibition of the p53 pathway and contributes to tumor formation. Under normal conditions, MDM2 binds to p53 and ubiquitinates it. A study by Slack et al. showed that transcriptional activation of MDM2 via MYCN contributes to the decreased p53 activity in neuroblastoma[22]. However, abnormally post-translated p53 has been found to be resistant to MDM2-mediated degradation in neuroblastoma cells, indicating the presence of impairment of p53 function regardless of high levels in the cells[23]. Therefore, MDM2 targeting rather than p53 would be an effective strategy in neuroblastoma cells[19].

MDM2 has also been found to exhibit non-canonical p53-independent functions that contribute to neuroblastoma growth, progression, and development. In particular, MDM2 stabilizes mRNA of vascular endothelial growth factor (VEGF) by binding directly to 3’ UTR of the mRNA, thus in turn causes the increased translation of VEGF, contributing to the growth of neuroblastoma under hypoxia condition[24]. The ring domain of MDM2 binds to the MYCN mRNA adenylate/uridylate-rich elements (AREs) within the 3’UTR, and thereby increases the MYCN mRNA stability and translation in neuroblastoma cells[25]. In addition, elevated MDM2 expression has also been found to promote multidrug resistance in neuroblastoma cells[26]. Overall, these studies suggest MDM2 is a potential target for anticancer therapy in neuroblastoma[19].

Since the majority of neuroblastomas harbor high levels of MDM2, it is critical to develop MDM2 inhibitors for neuroblastoma treatment. The ideal MDM2 inhibitor should exert anticancer activity in neuroblastoma cells, independent of their p53 status (wild-type, null, or mutated). Other research groups have identified nutlin-3[27], MI-77301[28], MI-63[29], RITA [30], and RG7112[31] as MDM2 inhibitors that exhibit anticancer activity in neuroblastoma cells. In addition, a study by Giustiniano et al. has identified 'compound 12' as a dual inhibitor of MDM2/p53 and MDMX (MDM4)/p53 complexes, which increases p53 gene expression and induces apoptosis in SH-SY5Y neuroblastoma cells [32]. However, none of these previously-identified agents has yet been accepted as a clinical treatment for neuroblastoma.

2. SP141 is a Potent MDM2 Inhibitor

MDM2 is amplified in a variety of malignancies, including neuroblastoma[18][19][28]. The overexpression of MDM2 is linked to a poor prognosis for patients with cancer[18][19][28]. Enhanced MDM2 expression leads to inhibition of the p53 pathway and tumor growth acceleration. In addition, MDM2 has been found to exhibit p53-independent roles in the growth and progression of neuroblastoma. Our lab has a long history of developing novel strategies to target MDM2 for cancer therapy and prevention[33][34][35]. In the past, we have identified natural product MDM2 inhibitors such as genistein[36], curcumin[37], and ginsenosides[38][39][40][41][42][43][44][45], and also discovered small-molecule synthetic MDM2 inhibitors such as the SP series[46][47][48][49][50][51][52][53] and synthetic iminoquinones [54][55][56][57][58][59], which have proven effective against several different malignancies. The present study is the first to report the in vitro and in vivo anti-neuroblastoma effects of SP141, a potent and selective MDM2 inhibitor discovered in our lab. Our previous studies demonstrated that SP141 inhibits cell growth, induces apoptosis and cell cycle arrest, inhibits cell migration and invasion, and induces tumor regression without observable toxicity in models of breast cancer[46], pancreatic cancer[47], hepatocellular carcinoma[48], and glioblastoma[49]. It is most likely SP141 is a target-specific anticancer agent that may have a broad-spectrum of activity against MDM2-overexpressing cancers/tumors. Mechanistically, SP141 inhibits MDM2's oncogenic functions via both p53-dependent and -independent mechanisms. These effects are believed to be due to the fact that SP141 directly binds to MDM2 with high affinity and induces its autoubiquitination and proteasomal degradation[46][47][48][49].

SP141 significantly reduced neuroblastoma cell viability, inhibited cancer colony formation, induced apoptosis, and arrested the cancer cells in the G2/M phase, and all these effects were independent of p53 status. SP141 effectively downregulated MDM2 expression, as well as MDMX expression, in neuroblastoma tumor cells, regardless of the p53 status of the cells. SP141 treatment also increased p21 expression in neuroblastoma cells, irrespective of their p53 status. This was consistent with the findings of previous reports showing that MDM2 interacts with p21 and acts as a negative regulator of p21 by reducing its protein stability, independent of p53[60][61]. It has been demonstrated that MDM2 plays a p53-independent role in the regulation of MYCN mRNA stabilization and translation in neuroblastoma cells[25]. Our results showed that SP141 treatment decreased the MYCN expression in both p53 wild-type and p53 null neuroblastoma cells, and this may explain how SP141 inhibits the MDM2 expression in neuroblastoma cells. Our in vitro studies also showed that SP141 exhibits anti-metastatic effects, as evidenced by the results of the wound healing assay and decreases in the expression of EMT-related proteins such as β-catenin, vimentin, and Twist.

In addition, SP141 effectively inhibited the growth of neuroblastoma xenograft tumors in vivo and inhibited MDM2 expression in the tumor tissues and increased the Caspase 3 expression in both NB-1643 and LA1-55n xenograft models, independent of the p53 status. It is also important to note that SP141 exhibited no significant toxicity in mice at the relatively high dose of 40 mg/kg, as indicated by the results of organ specific histopathological examination and tracking of body weight. Overall, our results clearly suggest that SP141 exerts antitumor activity in models of neuroblastoma, and the antitumor activity may mechanistically be due to its targeting MDM2 and inhibiting MDM2 expression, which occurs regardless of the p53 status of the cancer cells.

Previous research has identified several dual inhibitors of the MDM2/p53 complex and MDM4/p53 complex in cancer cells. For instance, RITA inhibited cells growth, induced apoptosis, and disrupted the interaction between p53 and MDM2/MDMX in neuroblastoma cells, and also inhibited the growth of SK-N-DZ xenograft tumors in mice[30]. Compound 12 is another molecule found to be a dual inhibitor of MDM2/p53 and MDM4/p53 complexes, which also increases p53 protein levels and enhances the levels of p53 target genes (MDM2, p21, PUMA), and inhibits the proliferation of SHSY-5Y neuroblastoma cells[32]. Likewise, SP141 has also been found to reduce the protein levels of both MDM2 and MDMX in neuroblastoma cells. Thus, SP141 appears to act as a dual inhibitor of both MDM2 and MDMX in neuroblastoma cells, irrespective of their p53 status.

SP141 warrants further investigation as an MDM2 antagonist, particularly in combination with other agents currently used to treat neuroblastoma, such as mTOR or ALK inhibitors, to provide improved anticancer activity against neuroblastomas with different genetic backgrounds. In addition, although the anti-neuroblastoma activities of SP141 have been

demonstrated in this study, further studies are necessary to confirm the efficacy and safety of SP141 using other models of neuroblastoma, including primary tumor-derived models with different genetic backgrounds.

References

1. Colon, N.C.; Chung, D.H. Neuroblastoma. Adv. Pediatr. 2011, 58, 297–311.
2. Louis, C.U.; Shohet, J.M. Neuroblastoma: Molecular pathogenesis and therapy. Annu. Rev. Med. 2015, 66, 49–63.
3. Schwab, M.; Westermann, F.; Hero, B.; Berthold, F. Neuroblastoma: Biology and molecular and chromosomal patholog y. Lancet Oncol. 2003, 4, 472–480.
4. Lakoma, A.; Barbieri, E.; Agarwal, S.; Jackson, J.; Chen, Z.; Kim, Y.; McVay, M.; Shohet, J.M.; Kim, E.S. The MDM2 sm all-molecule inhibitor RG7388 leads to potent tumor inhibition in p53 wild-type neuroblastoma. Cell Death Discov. 201 5, 1, 15026.
5. Ngan, E.S.-W. Heterogeneity of neuroblastoma. Oncoscience 2015, 2, 837–838.
6. Cohn, S.L.; Pearson, A.D.J.; London, W.B.; Monclair, T.; Ambros, P.F.; Brodeur, G.M.; Faldum, A.; Hero, B.; Iehara, T.; Machin, D.; et al. The international neuroblastoma risk group (INRG) classification system: An INRG task force repor t. J. Clin. Oncol. 2009, 27, 289–297.
7. Sokol, E.; Desai, A.V. The Evolution of Risk Classification for Neuroblastoma. Children 2019, 6, 27.
8. Smith, V.; Foster, J. High-Risk Neuroblastoma Treatment Review. Children 2018, 5, 114.
9. Mlakar, V.; Jurkovic-Mlakar, S.; Lopez, G.; Maris, J.M.; Ansari, M.; Gumy-Pause, F. 11q deletion in neuroblastoma: A re view of biological and clinical implications. Mol. Cancer 2017, 16, 114.
10. Gatta, G.; Botta, L.; Rossi, S.; Aareleid, T.; Bielska-Lasota, M.; Clavel, J.; Dimitrova, N.; Jakab, Z.; Kaatsch, P.; Lacour, B.; et al. Childhood cancer survival in Europe 1999–2007: Results of EUROCARE-5—a population-based study. Lancet Oncol. 2014, 15, 35–47.
11. Tonini, G.P.; Capasso, M. Genetic predisposition and chromosome instability in neuroblastoma. Cancer Metastasis Re v. 2020, 39, 275–285.
12. Matthay, K.K.; Maris, J.M.; Schleiermacher, G.; Nakagawara, A.; Mackall, C.L.; Diller, L.; Weiss, W.A. Neuroblastom a. Nat. Rev. Dis. Primers 2016, 2, 16078.
13. Park, J.R.; Kreissman, S.G.; London, W.B.; Naranjo, A.; Cohn, S.L.; Hogarty, M.D.; Tenney, S.C.; Haas-Kogan, D.; Sha w, P.J.; Kraveka, J.M.; et al. Effect of Tandem Autologous Stem Cell Transplant vs Single Transplant on Event-Free Sur vival in Patients With High-Risk Neuroblastoma: A Randomized Clinical Trial. Jama 2019, 322, 746–755.
14. Zage, P.E. Novel Therapies for Relapsed and Refractory Neuroblastoma. Children 2018, 5, 148.
15. Domingo-Fernandez, R.; Watters, K.; Piskareva, O.; Stallings, R.L.; Bray, I. The role of genetic and epigenetic alteratio ns in neuroblastoma disease pathogenesis. Pediatr. Surg. Int. 2013, 29, 101–119.
16. Nicolai, S.; Pieraccioli, M.; Peschiaroli, A.; Melino, G.; Raschellà, G. Neuroblastoma: Oncogenic mechanisms and thera peutic exploitation of necroptosis. Cell Death Dis. 2015, 6, e2010.
17. Lee, E.Y.H.P.; Muller, W.J. Oncogenes and Tumor Suppressor Genes. Cold Spring Harb. Perspect. Biol. 2010, 2, a003 236.
18. Corvi, R.; Savelyeva, L.; Breit, S.; Wenzel, A.; Handgretinger, R.; Barak, J.; Oren, M.; Amler, L.; Schwab, M. Non-synte nic amplification of MDM2 and MYCN in human neuroblastoma. Oncogene 1995, 10, 1081–1086.
19. Zafar, A.; Wang, W.; Liu, G.; Xian, W.; McKeon, F.; Zhou, J.; Zhang, R. Targeting the p53-MDM2 pathway for neuroblast oma therapy: Rays of hope. Cancer Lett. 2021, 496, 16–29.
20. Cattelani, S.; Defferrari, R.; Marsilio, S.; Bussolari, R.; Candini, O.; Corradini, F.; Ferrari-Amorotti, G.; Guerzoni, C.; Pec orari, L.; Menin, C.; et al. Impact of a Single Nucleotide Polymorphism in the MDM2 Gene on Neuroblastoma Developm ent and Aggressiveness: Results of a Pilot Study on 239 Patients. Clin. Cancer Res. 2008, 14, 3248–3253.
21. Cattelani, S.; Ferrari-Amorotti, G.; Soliera, A.R.; Manzotti, G.; Raschellà, G.; Calabretta, B. Neuroblastoma: Role of MD M2 and SNP309 as Markers; Springer: Dordrecht, The Netherlands, 2013.
22. Slack, A.; Chen, Z.; Tonelli, R.; Pule, M.; Hunt, L.; Pession, A.; Shohet, J.M. The p53 regulatory gene MDM2 is a direct t ranscriptional target of MYCN in neuroblastoma. Proc. Natl. Acad. Sci. USA 2005, 102, 731–736.
23. Zaika, A.; Marchenko, N.; Moll, U.M. Cytoplasmically “Sequestered” Wild Type p53 Protein Is Resistant to Mdm2-media ted Degradation. J. Biol. Chem. 1999, 274, 27474–27480.

24. Zhou, S.; Gu, L.; He, J.; Zhang, H.; Zhou, M. MDM2 Regulates Vascular Endothelial Growth Factor mRNA Stabilization in Hypoxia. Mol. Cell. Biol. 2011, 31, 4928–4937.

25. Gu, L.; Zhang, H.; He, J.; Li, J.; Huang, M.; Zhou, M. MDM2 regulates MYCN mRNA stabilization and translation in hu man neuroblastoma cells. Oncogene 2012, 31, 1342–1353.

26. Keshelava, N.; Zuo, J.J.; Chen, P.; Waidyaratne, S.N.; Luna, M.C.; Gomer, C.J.; Triche, T.J.; Reynolds, C.P. Loss of p5 3 function confers high-level multidrug resistance in neuroblastoma cell lines. Cancer Res. 2001, 61, 6185–6193.

27. Van Maerken, T.; Ferdinande, L.; Taildeman, J.; Lambertz, I.; Yigit, N.; Vercruysse, L.; Rihani, A.; Michaelis, M.; Cinatl, J.; Cuvelier, C.A.; et al. Antitumor Activity of the Selective MDM2 Antagonist Nutlin-3 against Chemoresistant Neuroblas toma with Wild-Type p53. J. Natl. Cancer Inst. 2009, 101, 1562–1574.

28. Lu, J.; Guan, S.; Zhao, Y.; Yu, Y.; Wang, Y.; Shi, Y.; Mao, X.; Yang, K.L.; Sun, W.; Xu, X.; et al. Novel MDM2 inhibitor SA R405838 (MI-773) induces p53-mediated apoptosis in neuroblastoma. Oncotarget 2016, 7, 82757–82769.

29. Gamble, L.D.; Kees, U.R.; Tweddle, D.A.; Lunec, J. MYCN sensitizes neuroblastoma to the MDM2-p53 antagonists Nut lin-3 and MI-63. Oncogene 2012, 31, 752–763.

30. Burmakin, M.; Shi, Y.; Hedström, E.; Kogner, P.; Selivanova, G. Dual Targeting of Wild-Type and Mutant p53 by Small Molecule RITA Results in the Inhibition of N-Myc and Key Survival Oncogenes and Kills Neuroblastoma Cells In Vivo a nd In Vitro. Clin. Cancer Res. 2013, 19, 5092–5103.

31. Al-Ghabkari, A.; Narendran, A. In Vitro Characterization of a Potent p53-MDM2 Inhibitor, RG7112 in Neuroblastoma Ca ncer Cell Lines. Cancer Biother. Radiopharm. 2019, 34, 252–257.

32. Giustiniano, M.; Daniele, S.; Pelliccia, S.; La Pietra, V.; Pietrobono, D.; Brancaccio, D.; Cosconati, S.; Messere, A.; Giu ntini, S.; Cerofolini, L.; et al. Computer-Aided Identification and Lead Optimization of Dual Murine Double Minute 2 and 4 Binders: Structure–Activity Relationship Studies and Pharmacological Activity. J. Med. Chem. 2017, 60, 8115–8130.

33. Rayburn, E.; Zhang, R.; He, J.; Wang, H. MDM2 and Human Malignancies: Expression, Clinical Pathology, Prognostic Markers, and Implications for Chemotherapy. Curr. Cancer Drug Targets 2005, 5, 27–41.

34. Nag, S.; Qin, J.; Srivenugopal, K.S.; Wang, M.; Zhang, R. The MDM2-p53 pathway revisited. J. Biomed. Res. 2013, 27, 254.

35. Qin, J.-J.; Li, X.; Hunt, C.; Wang, W.; Wang, H.; Zhang, R. Natural products targeting the p53-MDM2 pathway and muta nt p53: Recent advances and implications in cancer medicine. Genes Dis. 2018, 5, 204–219.

36. Li, M.; Zhang, Z.; Hill, D.L.; Chen, X.; Wang, H.; Zhang, R. Genistein, a Dietary Isoflavone, Down-Regulates the MDM2 Oncogene at Both Transcriptional and Posttranslational Levels. Cancer Res. 2005, 65, 8200–8208.

37. Li, M.; Zhang, Z.; Hill, D.L.; Wang, H.; Zhang, R. Curcumin, a Dietary Component, Has Anticancer, Chemosensitization, and Radiosensitization Effects by Down-regulating the MDM2 Oncogene through the PI3K/mTOR/ETS2 Pathway. Canc er Res. 2007, 67, 1988–1996.

38. Nag, S.A.; Qin, J.-J.; Wang, W.; Wang, M.-H.; Wang, H.; Zhang, R. Ginsenosides as anticancer agents: In vitro and in v ivo activities, structure–activity relationships, and molecular mechanisms of action. Front. Pharmacol. 2012, 3, 25.

39. Wang, W.; Qin, J.-J.; Li, X.; Tao, G.; Wang, Q.; Wu, X.; Zhou, J.; Zi, X.; Zhang, R. Prevention of prostate cancer by natu ral product MDM2 inhibitor GS25: In vitro and in vivo activities and molecular mechanisms. Carcinogenesis 2018, 39, 1 026–1036.

40. Wang, W.; Rayburn, E.R.; Hao, M.; Zhao, Y.; Hill, D.L.; Zhang, R.; Wang, H. Experimental therapy of prostate cancer wi th novel natural product anti-cancer ginsenosides. Prostate 2008, 68, 809–819.

41. Wang, W.; Rayburn, E.R.; Hang, J.; Zhao, Y.; Wang, H.; Zhang, R. Anti-lung cancer effects of novel ginsenoside 25-OC H3-PPD. Lung Cancer 2009, 65, 306–311.

42. Wang, W.; Rayburn, E.R.; Zhao, Y.; Wang, H.; Zhang, R. Novel ginsenosides 25-OH-PPD and 25-OCH 3 -PPD as expe rimental therapy for pancreatic cancer: Anticancer activity and mechanisms of action. Cancer Lett. 2009, 278, 241–248.

43. Wang, W.; Wang, H.; Rayburn, E.R.; Zhao, Y.; Hill, D.L.; Zhang, R. 20(S)-25-methoxyl-dammarane-3β, 12β, 20-triol, a n ovel natural product for prostate cancer therapy: Activity in vitro and in vivo and mechanisms of action. Br. J. Cancer 20 08, 98, 792–802.

44. Wang, W.; Zhang, X.; Qin, J.-J.; Voruganti, S.; Nag, S.A.; Wang, M.-H.; Wang, H.; Zhang, R. Natural Product Ginsenosi de 25-OCH3-PPD Inhibits Breast Cancer Growth and Metastasis through Down-Regulating MDM2. PLoS ONE 201 2, 7, e41586.

45. Wang, W.; Zhao, Y.; Rayburn, E.R.; Hill, D.L.; Wang, H.; Zhang, R. In vitro anti-cancer activity and structure–activity rel ationships of natural products isolated from fruits of Panax ginseng. Cancer Chemother. Pharmacol. 2007, 59, 589–60 1.

46. Wang, W.; Qin, J.-J.; Voruganti, S.; Srivenugopal, K.S.; Nag, S.; Patil, S.; Sharma, H.; Wang, M.-H.; Wang, H.; Buolam wini, J.K.; et al. The pyrido[b]indole MDM2 inhibitor SP-141 exerts potent therapeutic effects in breast cancer model s. Nat. Commun. 2014, 5, 5086.
47. Wang, W.; Qin, J.-J.; Voruganti, S.; Wang, M.-H.; Sharma, H.; Patil, S.; Zhou, J.; Wang, H.; Mukhopadhyay, D.; Buolam wini, J.K.; et al. Identification of a New Class of MDM2 Inhibitor That Inhibits Growth of Orthotopic Pancreatic Tumors in Mice. Gastroenterology 2014, 147, 893–902.e2.
48. Wang, W.; Hu, B.; Qin, J.-J.; Cheng, J.-W.; Li, X.; Rajaei, M.; Fan, J.; Yang, X.; Zhang, R. A novel inhibitor of MDM2 on cogene blocks metastasis of hepatocellular carcinoma and overcomes chemoresistance. Genes Dis. 2019, 6, 419–43 0.
49. Punganuru, S.R.; Arutla, V.; Zhao, W.; Rajaei, M.; Deokar, H.; Zhang, R.; Buolamwini, J.K.; Srivenugopal, K.S.; Wang, W. Targeted Brain Tumor Therapy by Inhibiting the MDM2 Oncogene: In Vitro and In Vivo Antitumor Activity and Mecha nism of Action. Cells 2020, 9, 1592.
50. Deokar, H.; Deokar, M.; Wang, W.; Zhang, R.; Buolamwini, J.K. QSAR studies of new pyrido[3,4-b]indole derivatives as inhibitors of colon and pancreatic cancer cell proliferation. Med. Chem. Res. 2018, 27, 2466–2481.
51. APatil, S.A.; Addo, J.K.; Deokar, H.; Sun, S.; Wang, J.; Li, W.; Suttle, D.P.; Wang, W.; Zhang, R.; Buolamwini, J.K. Synt hesis, Biological Evaluation and Modeling Studies of New Pyrido[3,4-b] indole Derivatives as Broad-Spectrum Potent A nticancer Agents. Drug Des. 2017, 6, 143.
52. Qin, J.-J.; Wang, W.; Li, X.; Deokar, H.; Buolamwini, J.K.; Zhang, R. Inhibiting β-Catenin by β-Carboline-Type MDM2 In hibitor for Pancreatic Cancer Therapy. Front. Pharmacol. 2018, 9, 5.
53. Qin, J.-J.; Wang, W.; Sarkar, S.; Zhang, R. Oral delivery of anti-MDM2 inhibitor SP141-loaded FcRn-targeted nanoparti cles to treat breast cancer and metastasis. J. Control. Release 2016, 237, 101–114.
54. Nadkarni, D.H.; Wang, F.; Wang, W.; Rayburn, E.R.; Ezell, S.J.; Murugesan, S.; Velu, S.E.; Zhang, R. Synthesis and In Vitro Anti-Lung Cancer Activity of Novel 1, 3, 4, 8- Tetrahydropyrrolo [4, 3, 2-de]quinolin-8(1H)-o ne Alkaloid Analogs. M ed. Chem. 2009, 5, 227–236.
55. Wang, F.; Ezell, S.J.; Zhang, Y.; Wang, W.; Rayburn, E.R.; Nadkarni, D.H.; Murugesan, S.; Velu, S.E.; Zhang, R. FBA-T PQ, a novel marine-derived compound as experimental therapy for prostate cancer. Investig. N. Drugs 2010, 28, 234–2 41.
56. Wang, W.; Cheng, J.-W.; Qin, J.-J.; Hu, B.; Li, X.; Nijampatnam, B.; Velu, S.E.; Fan, J.; Yang, X.-R.; Zhang, R. MDM2-N FAT1 dual inhibitor, MA242: Effective against hepatocellular carcinoma, independent of p53. Cancer Lett. 2019, 459, 15 6–167.
57. Wang, W.; Qin, J.-J.; Voruganti, S.; Nijampatnam, B.; Velu, S.E.; Ruan, K.; Hu, M.; Zhou, J.; Zhang, R. Discovery and C haracterization of Dual Inhibitors of MDM2 and NFAT1 for Pancreatic Cancer Therapy. Cancer Res. 2018, 78, 5656–56 67.
58. Wang, W.; Rayburn, E.R.; Velu, S.E.; Chen, D.; Nadkarni, D.H.; Murugesan, S.; Chen, D.; Zhang, R. A novel synthetic i minoquinone, BA-TPQ, as an anti-breast cancer agent: In vitro and in vivo activity and mechanisms of action. Breast C ancer Res. Treat. 2010, 123, 321–331.
59. Wang, W.; Rayburn, E.R.; Velu, S.E.; Nadkarni, D.H.; Murugesan, S.; Zhang, R. In vitro and in vivo anticancer activity o f novel synthetic makaluvamine analogues. Clin. Cancer Res. 2009, 15, 3511–3518.
60. Zhang, Z.; Wang, H.; Li, M.; Agrawal, S.; Chen, X.; Zhang, R. MDM2 Is a Negative Regulator of p21WAF1/CIP1, Indep endent of p53. J. Biol. Chem. 2004, 279, 16000–16006.
61. Jin, Y.; Lee, H.; Zeng, S.X.; Dai, M.; Lu, H. MDM2 promotes p21waf1/cip1 proteasomal turnover independently of ubiqu itylation. EMBO J. 2003, 22, 6365–6377.