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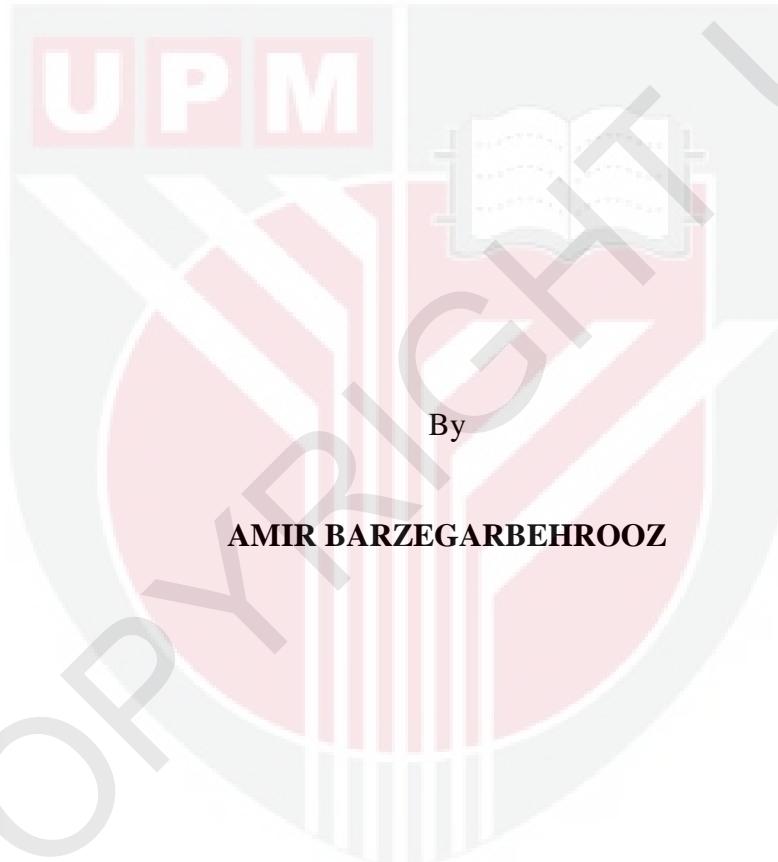
**CO-DELIVERY OF PACLITAXEL AND TEMOZOLOMIDE BY CD133-B19
APTAMER CONJUGATED POLYAMIDOAMINE DENDRIMER TO U87
STEM CELLS**

AMIR BARZEGARBEHROOZ

FBSB 2021 9



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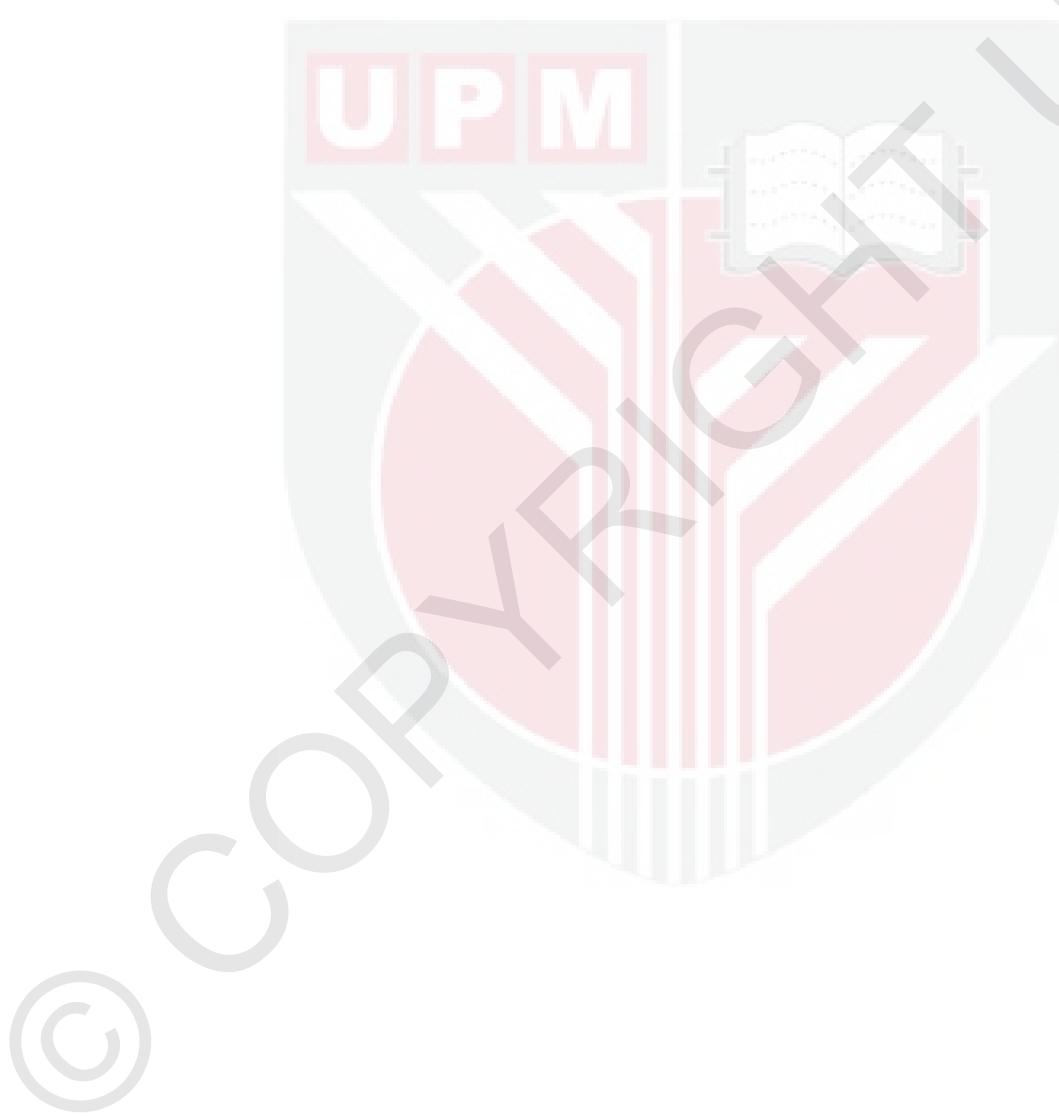
**Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia,
in Fulfilment of the Requirements for the Degree of Doctor of Philosophy**

December 2020

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Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfilment
of the requirement for the degree of Doctor of Philosophy

**CO-DELIVERY OF PACLITAXEL AND TEMOZOLOMIDE BY
CD133-B19 APTAMER CONJUGATED POLYAMIDOAMINE
DENDRIMER TO U87 STEM CELLS**

By

AMIR BARZEGARBEHROOZ

December 2020

Chairman : Associate Professor Amir Syahir bin Amir Hamzah, PhD
Faculty : Biotechnology and Biomolecular Science

Glioblastoma multiforme (GBM) is 57% of all gliomas, and 48% of the primary central nervous system (CNS) tumors. Despite multimodal treatment, based on surgery, radiotherapy, and chemotherapy, and advancements in each approach, GBM remains characterized by a poor prognosis, with an estimated overall survival of less than 6% at 5 years post-diagnosis. The first-line systemic therapy is currently represented by temozolomide (TMZ), but the majority of patients relapse after 6 months. According to consensus, recurrence of the tumor and chemotherapy resistance acquisition are two distinguishing features of GBM that originating from glioblastoma stem cells (GSCs). To overcome the problems inherent in GBM chemotherapy, targeting GSCs through an intelligent drug delivery system has come to the forefront of GBM therapeutics. In this study, B19 aptamer, RNA aptamer with high sensitivity for recognizing the AC133 epitope and the CD133 protein, (Apt)-conjugated polyamidoamine (PAMAM) dendrimer nanoparticles (NPs), called Apt-NPs, were formulated for the co-delivery of paclitaxel (PTX) and TMZ to U87 stem cells. One of the most well-known TMZ-sensitive GBM cell lines is U87. The physicochemical properties of Apt-NPs such as size, zeta potential, and polydispersity index (PDI) were analyzed by dynamic light scattering (DLS). The conjugation of NPs with the B19 aptamer was confirmed by Fourier-transform infrared spectroscopy (FTIR) and 2,4,6-trinitrobenzene sulfonic acid (TNBSA) assay. Furthermore, the spherical morphology and core-shell structures of the Apt-NPs were evaluated by Field emission scanning electron microscopes (FE-SEM), atomic force microscopy (AFM), and high-resolution transmission electron microscopy (HR-TEM). In vitro cellular uptake of the BODIPY-labeled Apt-NPs was determined using confocal microscopy. The drugs were loaded with a double emulsification solvent evaporation method. Drug-loaded Apt-NPs significantly inhibited the tumor growth of U-87 stem cells by initiation of apoptosis and cell cycle arrest in G2/M and S via the down-regulation of autophagic and multi drug resistance

(MDR) genes. Additionally, by their down-regulation by qPCR of CD133, CD44, SOX2, and Wnt/β-catenin, PI3K/AKT/mTOR (PAM) pathway, cell proliferation has substantially decreased. Addedly, simultaneous shortened telomere length with down-regulation of DKC1 and TERT subunits of telomerase by drug-loaded Apt-NPs increased apoptosis. Taken together, this dendrimer-based pharmaceutical drug delivery system along with B19 aptamer is capable of effectively transferring PTX and TMZ to U87 stem cells in consistent and without toxic effects.



Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Doktor Falsafah

**PENGHANTARAN SAMA PACLITAXEL DAN TEMOZOLOMIDE OLEH
CD133-B19 APTAMER POLIAMIDOAMIN DENDRIMER KE U87 STEM
SEL**

Oleh

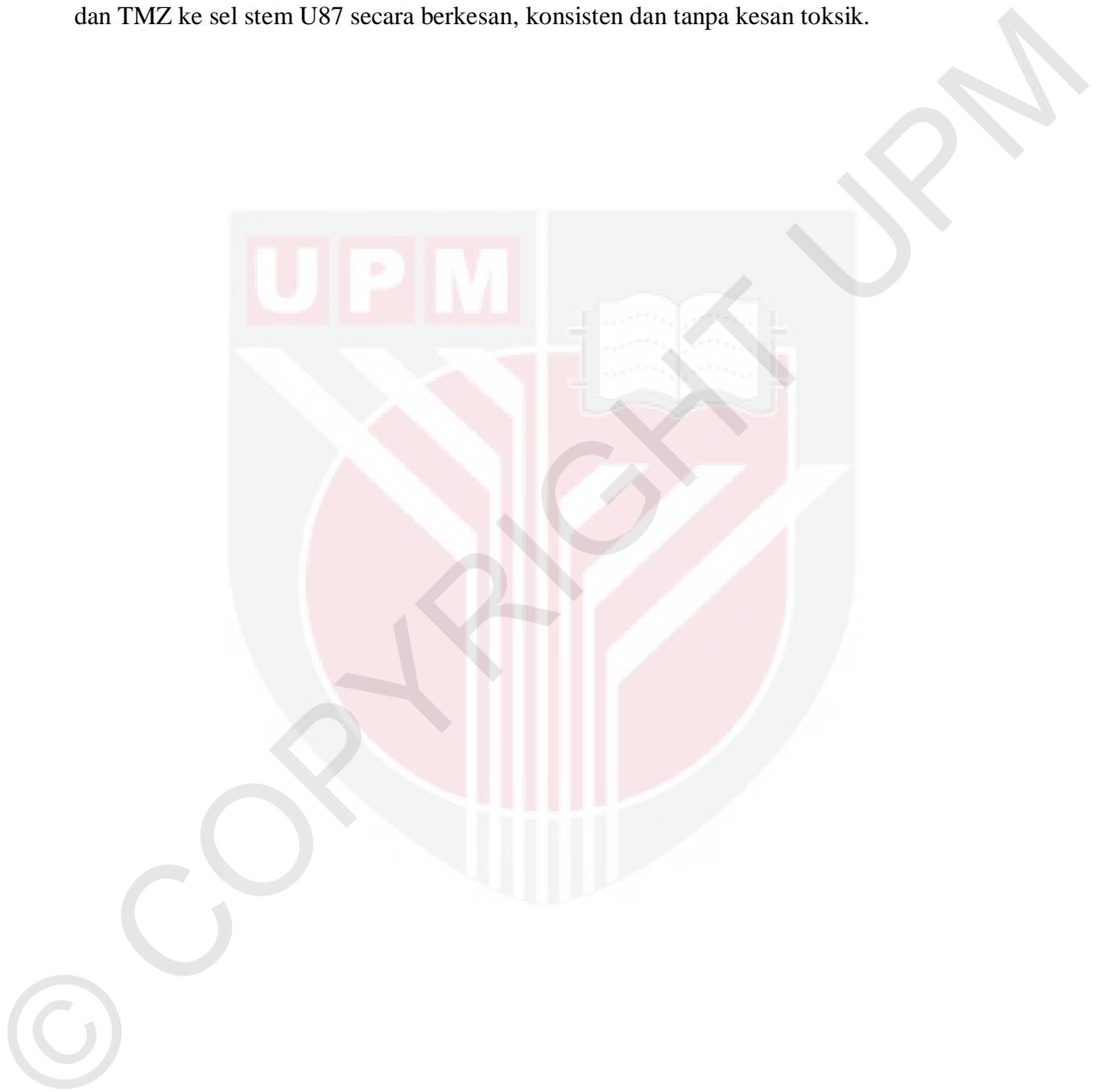
AMIR BARZEGARBEHROOZ

Disember 2020

Pengerusi : Profesor Madya Amir Syahir bin Amir Hamzah, PhD
Fakulti : Bioteknologi dan Sains Biomolekul

Glioblastoma multiforme (GBM) adalah 57% daripada kesemua glioma, dan 48% daripada tumor sistem saraf pusat utama (CNS). Walaupun terdapat rawatan multimodal, berdasarkan pembedahan, radioterapi, dan kemoterapi, serta kemajuan dalam setiap pendekatan, GBM masih mengekalkan prognosis yang buruk, dengan jangkaan kelangsungan hidup keseluruhan kurang dari 6% pada 5 tahun selepas diagnosis. Terapi sistemik utama kini adalah dengan menggunakan temozolomide (TMZ), tetapi majoriti pesakit kambuh selepas 6 bulan. Menurut kata sepakat, pengulangan tumor dan ketahanan terhadap kemoterapi adalah dua ciri khas GBM yang berasal dari sel stem glioblastoma (GSC). Untuk mengatasi masalah yang wujud dalam kemoterapi GBM, mensasarkan GSC melalui sistem penyampaian ubat pintar telah terkehadapan dalam terapi GBM. Dalam kajian ini, aptamer B19, aptamer RNA dengan kepekaan tinggi untuk mengenali epitop AC133 dan protein CD133, nanopartikel dendrimer (NP) poliamidoamin (PAMAM) terkonjugasi, dirumuskan untuk pengiriman bersama paclitaxel (PTX) dan TMZ ke U87 sel stem. Salah satu jenis sel GBM sensitif TMZ yang paling terkenal adalah U87. Sifat fizikokimia Apt-NP seperti ukuran potensi zeta, dan indeks polidispersiti (PDI) dianalisis dengan penyerakan cahaya dinamik (DLS). Konjugasi NP dengan aptamer B19 disahkan oleh spektroskopi inframerah transformasi Fourier (FTIR) dan ujian asid sulfonik 2,4,6-trinitrobenzena (TNBSA). Selanjutnya, morfologi sfera dan struktur cengkerang dari Apt-NP dinilai oleh mikroskop elektron pengimbas pelepasan medan (FE-SEM), mikroskop daya atom (AFM), dan mikroskop elektron transmisi resolusi tinggi (HR-TEM). Pengambilan sel in-vitro dari Apt-NP berlabel BODIPY ditentukan menggunakan mikroskopi konfokal. Ubat itu dimuatkan dengan kaedah penyejatan pelarut pengemulsi berganda. Apt-NP yang dimuatkan dengan ubat secara signifikan menghalang pertumbuhan tumor sel stem U87 dengan permulaan apoptosis dan penangkapan kitaran sel pada G2/M dan S melalui pengawalan turun gen ketahanan autofagik dan multidrug (MDR). Selain itu, melalui

peraturan penurunan oleh qPCR CD133, CD44, SOX2, dan jalur Wnt/β-catenin, PI3K/AKT/mTOR (PAM), percambahan sel telah menurun dengan ketara. Selain itu, panjang telomere yang dipendekkan secara serentak dengan pengunduran subunit DKC1 dan TERT oleh telomeres oleh Apt-NP yang dimuatkan ubat meningkatkan apoptosis. Secara bersama, sistem penyampaian ubat farmaseutikal berasaskan dendrimer ini bersama dengan aptamer B19 mampu memindahkan PTX dan TMZ ke sel stem U87 secara berkesan, konsisten dan tanpa kesan toksik.



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This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfilment of the requirement for the degree of Doctor of Philosophy. The members of the Supervisory Committee were as follows:

Amir Syahir bin Amir Hamzah, PhD

Associate Professor

Faculty of Biotechnology and Bimolecular Science

Universiti Putra Malaysia

(Chairman)

Asilah Binti Ahmad Tajudin, PhD

Associate Professor

Faculty of Biotechnology and Bimolecular Science

Universiti Putra Malaysia

(Member)

Mas Jaffri bin Masarudin, PhD

Associate Professor

Faculty of Biotechnology and Bimolecular Science

Universiti Putra Malaysia

(Member)

ZALILAH MOHD SHARIFF, PhD

Professor and Dean

School of Graduate Studies

Universiti Putra Malaysia

Date: 12 August 2021

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Amir

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Name and Matric No: Amir Barzegar Behrooz, GS49721

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LIST OF ABBREVIATIONS

GBM	Glioblastoma Multiforme
MGMT	O6-methylguanine-DNA methyltransferase
TMZ	Temozolomide
PTX	Paclitaxel
MDR	Multi Drug Resistance
PI3K	Phosphoinositide 3-kinase
AKT	Protein kinase B
mTOR	Mechanistic Target of Rapamycin
EMT	Epithelial Mesenchymal Transition
GSCs	Glioblastoma Stem Cells
IDH	Isocitrate dehydrogenase genes
OS	Overall survival
PFS	Progression-free survival
CDKN2A	Cyclin-dependent kinase inhibitor 2A
PDGFRA	platelet derived growth factor receptor A
EGFR	Epithelial growth factor receptor
BBB	Blood-brain barrier
SVZ	Sub-Ventricular Zone
SGZ	Sub-Granular Zone
MTIC	monomethyl triazene 5-(3-methyltriazen-1-yl)- imidazole-4-carboxamide
AIC	5-aminoimidazole-4-carboxamide
ER	Endoplasmic reticulum
Lamp1	Lysosomal-associated membrane protein 1

INFG	Interferon-gamma
Perk	PKR-like endoplasmic reticulum kinase
P62	Nucleoporin p62
LC3	Microtubule-associated protein 1A/1B-light chain 3
Wtx	Wilms tumor gene on X chromosome
GSK3 β	Glycogen synthase kinase 3 β
APC	Adenomatous polyposis coli
ABCB1	Adenosine triphosphate binding cassette sub-family B member 1
MVP	Major vault protein
v-PARP	Vault poly (ADP-ribose) polymerase
TEP-1	Telomerase-associated protein-1
ABCG2	ATP-binding cassette super-family G member 2
TWIST1	Twist-related protein 1
ZEB1	Zinc Finger E-Box Binding Homeobox 1
ZEB2	Zinc Finger E-Box Binding Homeobox 2
MB	Medulloblastoma
MDM2	Mouse double minute 2 homolog
VEGF	Vascular endothelial growth factor
IGF1	Insulin-like growth factor-1
ANG	Angiopoietin
MMP-2	Matrix metalloprotease-2
OXPHOS	Oxidative phosphorylation
GLUT	Glucose transporter

PPP	Pentose phosphate pathway
LDHA	Lactate dehydrogenase A
ROS	Reactive oxygen species
PFKFB4	Phosphofructo-2-kinase/fructose-2,6-biphosphatase 4
TRF	Telomeric Repeat Factor
POT1	Protection of telomeres protein 1
TINF2	TERF1-interacting nuclear factor 2
Rap1	Ras-proximate-1
MRN	Mre11-Rad50-Nbs1
TERT	Telomere reverse transcriptase
DKC1	Dyskerin1
TEP1	Telomerase protein component 1
DLS	Dynamic light scattering
FTIR	Fourier-transform infrared spectroscopy
HR-TEM	High-resolution transmission electron microscopy
AFM	Atomic force microscopy
TNBSA	2,4,6-Trinitrobenzene Sulfonic Acid
PAMAM	Poly (amidoamine)
PEG	Polyethylene glycol
DMSO	Dimethyl sulfoxide
FPLC	Fast protein liquid chromatography
BSA	Bovine serum albumin
diH ₂ O	Deionized water
LSCM	Laser scanning confocal microscope
ICC	Immunocytochemistry

PI	Propidium iodide
DAPI	4',6-diamidino-2-phenylindole
DMEM	Dulbecco's Modified Eagle's Medium
BLAST	Basic Local Alignment Search Tool
FPLC	Fast protein liquid chromatography
FE-SEM	Field emission scanning electron microscope
TNBSA	2,4,6-trinitrobenzene sulfonic acid
CTCF	Total cell fluorescence
TL	Telomere length
BODIPY	2,4,6-Trinitrobenzene Sulfonic Acid
MTT	3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide
XTT	3,3'-[1(phenylamino)carbonyl]-3,4-tetrazolium]-3is(4-methoxy-6-nitro) benzene sulfonic acid hydrate
PDI	Polydispersity index
Apt-NPs	CD133 B19 aptamer-PAMAM-PEG
DOX	Doxorubicin
VP-16	Etoposide
ANGs	Angiopoietins
ESCC	Esophageal squamous cell carcinoma
CSCC	Cervical squamous cell carcinomas
DSBs	Double-strand break
bp	Base pairs
cDNA	Complementary DNA
Cm	Centimetre
CNS	Central Nerve System

DNA	Deoxyribonucleic acid
ECM	Extracellular matrix
EDTA	Ethylenediaminetetraacetic acid
FC	Fold Change
GH	Growth hormone
IGF1	Insulin-like growth factor-1
kDa	Kilo Dalton
mRNA	Messenger RNA
PCR	Polymerase chain reaction
RNA	Ribonucleic acid
RNase	Ribonuclease
rpm	Revolutions per minute

CHAPTER 1

INTRODUCTION

The most common malignant primary brain tumor is glioblastoma multiforme (GBM), affecting about 57 % of all gliomas and 48 % of all cancers of the primary malignant central nervous system (CNS). It is classified by the World Health Organization (WHO) as a grade IV diffuse astrocytic and oligodendroglia tumor (Tan et al. 2020). Glioblastoma ranges from 0.59 to 5 per 100,000 population and is on the rise in many countries. Incidence varies according to age and sex, and the median survival is about 14.6 months (Grech et al. 2020). There is a slight predominance in males, and occurrence rises with age. These tumors appear to occur in people between the ages of 45 and 70 years, with a median age between the mid-60s (Jiang et al. 2017). Compared with females, glioblastoma is 1.58 times more frequent in males. Globally, the prevalence of glioblastoma is higher in North America, Australia, and Northern and Western Europe (Tan et al. 2020). The study found that brain cancer accounted for 1.95 % of all cancers in Malaysia (Goh et al. 2014). Despite recent advancements in multimodality treatment for GBM, including surgery, radiotherapy, chemotherapy and supportive care, overall prognosis remains low and long-term survival is rare. In addition, correlated morbidity with a gradual deterioration in neurological activity and quality of life may have a detrimental effect on patients, relatives and families alike (Grech et al. 2020; Tan et al. 2020).

Surgery is the standard therapy for GBM, although often it is not necessary to eliminate the whole tumor and surviving tumor cells activate again due to the proliferation of tumors to other tissues in the brain, leading to GBM relapse (Kim et al. 2015). Therefore, tumor resection by surgery is associated with chemotherapy and radiotherapy (Alifieris and Trafalis 2015). Furthermore, invasive glioblastoma tumor growth reduced the effectiveness of radiotherapy and caused recurrence of the tumor (Yang et al. 2020). The current standard in treatment chemotherapy, the oral alkylating agent temozolomide (TMZ), is effective only in a subset of patients and prolongs patients' median survival by only 3 months and TMZ resistance is one of the obstacles ahead in its application (Sachamitr et al. 2021). Though O6-methylguanine-DNA methyltransferase (MGMT) repair activity is the most well-known contributors to TMZ resistance, many other key molecular pathways have come to light in recent years. Main evolving mechanisms include the autophagy, multi drug resistance (MDR), Wnt/β-catenin pathway, PI3K/AKT/mTOR pathway, and epithelial mesenchymal transition (EMT) (Singh et al. 2020). In addition, at least in part, the poor outcome of GBM to treatment may be attributed to the presence of a population of tumor-initiating cells known as cancer stem cells (CSCs) that have been shown to drive tumor growth and therapy resistance (Shergalis et al. 2018; Yang et al. 2020). Efficient tumor eradication would therefore require novel therapeutic approaches targeting CSCs in addition to bulk tumor cells.

Chemotherapy has been the most common treatment for glioblastoma. Single chemotherapy promoted the drug resistance of the tumor after a certain period, which substantially hampered the effective treatment of GBM. Combination with diverse of anticancer mechanisms is expected to enhance GBM therapy and several attempts have been made in clinical trials (Lun et al. 2016; Mangraviti et al. 2015; Sita et al. 2017; Taal et al. 2014). Several previous studies have demonstrated the inhibitory effects of PTX-NPs (PAMAM) and TMZ-NPs (PAMAM) on glioma cells (Fana et al. 2020; Singh et al. 2019; Sun et al. 2017). Experimentally, synergistic antitumor effects of PTX and TMZ on C6 and U-87 GBM cells were observed (Xu et al. 2016a). However, owing to physiological barriers of glioblastoma, several clinical trials on the combination chemotherapies have demonstrated little survival gain and have not been able to produce favorable outcomes. As a result, multiple delivery systems have been developed to address these difficulties and have enhanced therapeutic results (Galanis et al. 2013; Lee et al. 2015; Lundy et al. 2019; Verreault et al. 2015; Wick et al. 2017).

1.1 Problem Statement

GBM is an aggressive, high-grade brain tumor with a substantial clinical burden. Patients are also seriously affected by complications leading to and after diagnosis of GBM. Popular signs include headache, seizures, cognitive or personality changes, and numerous focal neurological deficits. Treatment for newly diagnosed GBM is aggressive and usually requires surgical resection, radiation therapy, and TMZ chemotherapy, but despite advancements in these treatments, outcomes are low in most cases (Ostrom et al. 2013; Schwartzbaum et al. 2006). The released study analyzed the direct medical costs of GBM in the US private insurance market, including patients receiving Medicare coverage from employer-sponsored commercial health plans. The estimated net expense (including both the patient paying and the plan paid) per patient in the 6 and 12 months following GBM-related surgery was \$138,767 and \$184,107, respectively (Jiang et al. 2017). The troubling mechanism of TMZ resistance is believed to be powered mainly by a special group of undifferentiated and highly tumorigenic cancer stem cells known as glioma stem cells (Singh et al. 2020). Previous findings have shown that PTX has the potential to be useful as an adjunct to TMZ chemotherapy for C6 (Magaña-Maldonado et al. 2014; Xu et al. 2016a) and U87 (Xu et al. 2016a) gliomas. The findings of the investigations revealed that PTX and TMZ administration alone constitute a potentially effective chemotherapy strategy against GSCs (U251-CD133^{pos}) (Sun et al. 2018) and (MU028-CD133^{pos}) (Brown et al. 2017). However, thus far, the effectiveness of combination therapy of PTX and TMZ on U-87 stem cells has not been reported. It is therefore essential to develop novel therapeutic nanosystem that deliver effectively PTX-TMZ into U87 stem cells to improve GBM treatment outcomes.

In the current study, the B19 aptamer (Apt)-conjugated polyamidoamine (PAMAM) dendrimer nanoparticles (NPs), called Apt-NPs, were designed to deliver a combination of PTX and TMZ directly to U87 stem cells. This study investigated the *in vitro* co-delivery efficiency of PTX and TMZ by Apt-NPs, as well as, its effect on

U87 stem cells growth, signaling pathways and/or biomarkers, which are critically involved in the development and maintenance of GBM.

Based on this, the research questions are:

1. Can the co-administration of PTX-TMZ reduce the number of cancer stem cells in the U87 cell line?
2. Can drugs-loaded Apt-NPs lead to greater reduction in the number of cancer stem cells in the U87 cell line?
3. Is the drugs-loaded Apt-NPs complex capable of binding directly to cancer stem cells in the U87 cell line?
4. Can the Apt-NPs drugs complex change the function of signaling pathways and/or biomarkers of cancer stem cells in the U87 cell line?

1.2 Research objectives

1.2.1 General objective

To develop of co-delivery nanosystems for anti-glioma stem cells therapy in U87 cell line

1.2.2 Specific objectives

The specific objectives of the study were:

1. To synthesis and characterize of PTX-TMZ-loaded Apt-NPs
2. To isolate and characterization of cancer stem cells from a human glioblastoma cell line U87
3. To determine the effect of co-administration of PTX and TMZ on the change in the number of cancer stem cells in the U87 cell line
4. To determine the effect of the Apt-NPs alone and Apt-NPs drugs on the change in the number of cancer stem cells in the U87 cell line
5. To determine the effect of the Apt-NPs drugs on the modulation of signaling pathways and/or biomarkers of cancer stem cells in the U87 cell line
6. To determine the effect of the Apt-NPs drugs on the telomere length and telomerase activity of cancer stem cells in the U87 cell line

REFERENCES

- Murat Anastasia, Eugenia Migliavacca, Thierry Gorlia, Wanyu L Lambiv, Tal Shay, Marie-France Hamou, Nicolas De Tribolet, Luca Regli, Wolfgang Wick, Mathilde Kouwenhoven M.C., Johannes A Hainfellner, Frank L Heppner, Pierre-Yves Dietrich, Zimmer Yitzhak, Cairncross J.Gregory, Janzer Robert-Charles, Domany Eytan, Mauro Delorenzi, Roger Stupp, and Monika E Hegi. 2008. "Stem Cell-Related 'Self-Renewal' Signature and High Epidermal Growth Factor Receptor Expression Associated with Resistance to Concomitant Chemoradiotherapy in Glioblastoma." *Journal of Clinical Oncology*. 20:26 (18):3015-24.
- Affinito Alessandra, Cristina Quintavalle, Carla Lucia Esposito, Giuseppina Roscigno, Catello Giordano, Silvia Nuzzo, Lucia Ricci-Vitiani, Iolanda Scognamiglio, Zoran Minic, Roberto Pallini, Maxim V. Berezovski, Vittorio de Francisis, and Gerolama Condorelli. 2020. "Targeting Ephrin Receptor Tyrosine Kinase A2 with a Selective Aptamer for Glioblastoma Stem Cells." *Molecular Therapy - Nucleic Acids* 5:20:176-185.
- Aghajani Marjan, Behzad Mansoori, Ali Mohammadi, Zahra Asadzadeh, and Behzad Baradaran. 2019. "New Emerging Roles of CD133 in Cancer Stem Cell: Signaling Pathway and MiRNA Regulation." *Journal of Cellular Physiology*. 234(12):21642-21661.
- Ahmad Zaheer, Afzal Shah, Muhammad Siddiq, and Heinz Bernhard Kraatz. 2014. (2014). Polymeric micelles as drug delivery vehicles. *RSC Adv.*, 4(33), 17028–17038.
- Ahmed Syed Ijlal, Gohar Javed, Altaf Ali Laghari, Syeda Beenish Bareeqa, Saba Farrukh, Shajeeah Zahid, Syeda Sana Samar, and Kashif Aziz. 2018. "CD133 Expression in Glioblastoma Multiforme: A Literature Review." *Cureus*. 11;10(10):e3439
- Airley Rachel E. and Ali Mobasheri. 2007. "Hypoxic Regulation of Glucose Transport, Anaerobic Metabolism and Angiogenesis in Cancer: Novel Pathways and Targets for Anticancer Therapeutics." *Chemotherapy*. 53(4):233-56.
- Alexis Frank, Eric Pridgen, Linda K. Molnar, and Omid C. Farokhzad. 2008. "Factors Affecting the Clearance and Biodistribution of Polymeric Nanoparticles." in *Molecular Pharmaceutics*. 5, 4, 505–515
- Alifieris Constantinos and Dimitrios T. Trafalis. 2015. "Glioblastoma Multiforme: Pathogenesis and Treatment." *Pharmacology and Therapeutics*. 152:63-82.

- Alves Ana Laura V, Izabela N. F. Gomes, Adriana C. Carloni, Marcela N. Rosa, Luciane S. Silva, Adriane F. Evangelista, Rui Manuel Reis, and Viviane Aline O. Silva. 2021. "Role of Glioblastoma Stem Cells in Cancer Therapeutic Resistance : A Perspective on Antineoplastic Agents from Natural Sources and Chemical Derivatives." *Stem Cell Research & Therapy*. 24;12(1):206.
- Amen Alexandra M, Christof Fellmann, Katarzyna M. Soczek, Shawn M. Ren, J. Lew, Gavin J. Knott, Jesslyn E. Park, Andrew M. Mckinney, Andrew Mancini, and A. Jennifer. 2020. "Cancer-specific loss of TERT activation sensitizes glioblastoma to DNA damage." *PNAS*. 30;118(13):e2008772118.
- Amero Paola, Carla Lucia Esposito, Anna Rienzo, Fortunato Moscato, Silvia Catuogno, and Vittorio De Franciscis. 2016. "Identification of an Interfering Ligand Aptamer for EphB2/3 Receptors." *Nucleic Acid Therapeutics* 26 (2):102–10.
- Angelastro James M. and Michael W. Lamé. 2010. "Overexpression of CD133 Promotes Drug Resistance in C6 Glioma Cells." *Molecular Cancer Research*. 8(8):1105-15.
- Anido Judit, Andrea Sáez-Borderías, Alba Gonzàlez-Juncà, Laura Rodón, Gerard Folch, Maria A. Carmona, Rosa M. Prieto-Sánchez, Ignasi Barba, Elena Martínez-Sáez, Ludmila Prudkin, Isabel Cuartas, Carolina Raventós, Francisco Martínez-Ricarte, M. Antonia Poca, David García-Dorado, Michael M. Lahn, Jonathan M. Yingling, Jordi Rodón, Juan Sahuquillo, José Baselga, and Joan Seoane. 2010. "TGF- β Receptor Inhibitors Target the CD44high/Id1high Glioma-Initiating Cell Population in Human Glioblastoma." *Cancer Cell*. 18(6): 655-668.
- Appel Eric A, Matthew J. Rowland, Xian Jun Loh, Richard M. Heywood, Colin Watts, and Oren A. Scherman. 2012. "Enhanced Stability and Activity of Temozolomide in Primary Glioblastoma Multiforme Cells with Cucurbit[n]Uril." *Chemical Communications*. 48(79):9843-5.
- Arifin Davis Yohanes, Kam Yiu Timothy Lee, and Chi Hwa Wang. 2009. "Chemotherapeutic Drug Transport to Brain Tumor." *Journal of Controlled Release*. 137(3):203-10.
- Arora Anjali and Kumaravel Somasundaram. 2019. "Glioblastoma vs Temozolomide: Can the Red Queen Race Be Won?" *Cancer Biology and Therapy* 20(8):1083–90.
- Arya Kesavan R, Ramachandran P. Bharath Chand, Chandran S. Abhinand, Achuthsankar S. Nair, Oommen V. Oommen, and Perumana R. Sudhakaran. 2021. "Identification of Hub Genes and Key Pathways Associated with Anti-Vegf Resistant Glioblastoma Using Gene Expression Data Analysis." *Biomolecules* 11(3):1–20.

- Ashraf Muhammad Aqeel, Wanxi Peng, Yasser Zare, and Kyong Yop Rhee. 2018. "Effects of Size and Aggregation/Agglomeration of Nanoparticles on the Interfacial/Interphase Properties and Tensile Strength of Polymer Nanocomposites." *Nanoscale Research Letters* 13: 214
- Azzabi A, A. N. Hughes, P. M. Calvert, E. R. Plummer, R. Todd, M. J. Griffin, M. J. Lind, A. Maraveyas, C. Kelly, K. Fishwick, A. H. Calvert, and A. V. Boddy. 2005. "Phase I Study of Temozolomide plus Paclitaxel in Patients with Advanced Malignant Melanoma and Associated in Vitro Investigations." *British Journal of Cancer*. 92(6):1006-12.
- Bae So Hyun, Min Jung Park, Min Mi Lee, Tae Min Kim, Se Hoon Lee, Sung Yun Cho, Young Hoon Kim, Yu Jung Kim, Chul Kee Park, and Chae Yong Kim. 2014. "Toxicity Profile of Temozolomide in the Treatment of 300 Malignant Glioma Patients in Korea." *Journal of Korean Medical Science*. 29(7): 980–984.
- Bae Yoonhee, Eric S. Green, Goo Young Kim, Su Jeong Song, Ji Young Mun, Sunray Lee, Jong Il Park, Jong sang Park, Kyung Soo Ko, Jin Han, and Joon Sig Choi. 2016. "Dipeptide-Functionalized Polyamidoamine Dendrimer-Mediated Apoptin Gene Delivery Facilitates Apoptosis of Human Primary Glioma Cells." *International Journal of Pharmaceutics*. 515(1-2):186-200.
- Bae Yoonhee, Su Jeong Song, Ji Young Mun, Kyung Soo Ko, Jin Han, and Joon Sig Choi. 2017. "Apoptin Gene Delivery by the Functionalized Polyamidoamine (PAMAM) Dendrimer Modified with Ornithine Induces Cell Death of HepG2 Cells." *Polymers*. 9(6):197.
- Bai Cheng Zhe, Sunghyun Choi, Kihoon Nam, Songhie An, and Jong Sang Park. 2013. "Arginine Modified PAMAM Dendrimer for Interferon Beta Gene Delivery to Malignant Glioma." *International Journal of Pharmaceutics*. 445(2):79-87
- Bai Jin, Yan Su Chen, Peng Jin Mei, Qing Hua Liu, Ying Du, and Jun Nian Zheng. 2015. "Pinx1 Is Up-Regulated and Associated with Poor Patients' Survival in Gliomas." *International Journal of Clinical and Experimental Pathology*. 8(6):6952-9.
- Baker Sharyn D, Mark Wirth, Paul Statkevich, Pascale Reidenberg, Kevin Alton, Susan E. Sartorius, Margaret Dugan, David Cutler, Vijay Batra, Louise B. Grochow, Ross C. Donehower, and Eric K. Rowinsky. 1999. "Absorption, Metabolism, and Excretion of 14C-Temozolomide Following Oral Administration to Patients with Advanced Cancer." *Clinical Cancer Research*. 5(2):309-17.
- Bao Shideng, Qilian Wu, Roger E. McLendon, Yueling Hao, Qing Shi, Anita B. Hjelmeland, Mark W. Dewhirst, Darell D. Bigner, and Jeremy N. Rich. 2006. "Glioma Stem Cells Promote Radioresistance by Preferential Activation of the DNA Damage Response." *Nature*. 444(7120):756-60.

- Barzegar Behrooz Amir, Fatemeh Nabavizadeh, Jamal Adiban, Mehdi Shafiee Ardestani, Rouhollah Vahabpour, Mohammad Reza Aghasadeghi, and Hamid Sohanaki. 2017. "Smart Bomb AS1411 Aptamer-Functionalized/PAMAM Dendrimer Nanocarriers for Targeted Drug Delivery in the Treatment of Gastric Cancer." *Clinical and Experimental Pharmacology and Physiology* 44(1):41–51.
- Barzegar Behrooz Amir, Amir Syahir, and Syahida Ahmad. 2018. "CD133: Beyond a Cancer Stem Cell Biomarker." *Journal of Drug Targeting*. 27(3):257-269
- Batchelor Tracy T, David A. Reardon, John F. De Groot, Wolfgang Wick, and Michael Weller. 2014. "Antiangiogenic Therapy for Glioblastoma: Current Status and Future Prospects." *Clinical Cancer Research*. 20(22):5612-9.
- Bayraç Abdullah Tahir, Oya Ercan Akça, Füsün İnci Eyidoğan, and Hüseyin Avni Öktem. 2018. "Target-Specific Delivery of Doxorubicin to Human Glioblastoma Cell Line via SsDNA Aptamer." *Journal of Biosciences* 43(1):97–104.
- Behzadi Shahed, Vahid Serpooshan, Wei Tao, Majd A. Hamaly, Mahmoud Y. Alkawareek, Erik C. Dreaden, Dennis Brown, Alaaldin M. Alkilany, Omid C. Farokhzad, and Morteza Mahmoudi. 2017. "Cellular Uptake of Nanoparticles: Journey inside the Cell." *Chemical Society Reviews*. 46, 4218-4244
- Ben-Porath Ittai, Matthew W. Thomson, Vincent J. Carey, Ruping Ge, George W. Bell, Aviv Regev, and Robert A. Weinberg. 2008. "An Embryonic Stem Cell-like Gene Expression Signature in Poorly Differentiated Aggressive Human Tumors." *Nature Genetics*. 40(5):499-507.
- Benitez Jorge A, Jianhui Ma, Matteo D'Antonio, Antonia Boyer, Maria Fernanda Camargo, Ciro Zanca, Stephen Kelly, Alireza Khodadadi-Jamayran, Nathan M. Jameson, Michael Andersen, Hrvoje Miletic, Shahram Saberi, Kelly A. Frazer, Webster K. Cavenee, and Frank B. Furnari. 2017. "PTEN Regulates Glioblastoma Oncogenesis through Chromatin-Associated Complexes of DAXX and Histone H3.3." *Nature Communications* 8 (4):1–14.
- Bera Binoy. 2015. "Nanoporous Silicon Prepared by Vapour Phase Strain Etch and Sacrificial Technique." *International Journal of Computer Applications Micro* (2015):42–45.
- De Berardinis Ralph J. and Navdeep S. Chandel. 2016. "Fundamentals of Cancer Metabolism." *Science Advances* 2(5).
- Bharadwaj Rajnish and Hongtao Yu. 2004. "The Spindle Checkpoint, Aneuploidy, and Cancer." *Oncogene*. 23(11):2016-27.

Bhat Krishna P. L, Veerakumar Balasubramaniyan, Brian Vaillant, Ravesanker Ezhilarasan, Karlijn Hummelink, Faith Hollingsworth, Khalida Wani, Lindsey Heathcock, Johanna D. James, Lindsey D. Goodman, Siobhan Conroy, Lihong Long, Nina Lelic, Suzhen Wang, Joy Gumin, Divya Raj, Yoshinori Kodama, Aditya Raghunathan, Adriana Olar, Kaushal Joshi, Christopher E. Pelloski, Amy Heimberger, Se Hoon Kim, Daniel P. Cahill, Ganesh Rao, Wilfred F. A. DenDunnen, Hendrikus W. G. M. Boddeke, Heidi S. Phillips, Ichiro Nakano, Frederick F. Lang, Howard Colman, Erik P. Sulman, and Kenneth Aldape. 2013. "Mesenchymal Differentiation Mediated by NF-KB Promotes Radiation Resistance in Glioblastoma." *Cancer Cell.* 24(3):331-46.

Bhattacharjee Sourav. 2016. "DLS and Zeta Potential - What They Are and What They Are Not?" *Journal of Controlled Release* 235:337–51.

Binello Emanuela and Isabelle M. Germano. 2011. "Targeting Glioma Stem Cells: A Novel Framework for Brain Tumors." *Cancer Science.* 102(11):1958-66.

Bisson Isabelle and David M. Prowse. 2009. "WNT Signaling Regulates Self-Renewal and Differentiation of Prostate Cancer Cells with Stem Cell Characteristics." *Cell Research.* 19(6):683-97.

Bonnet Dominique and John E. Dick. 1997. "Human Acute Myeloid Leukemia Is Organized as a Hierarchy That Originates from a Primitive Hematopoietic Cell." *Nature Medicine.* 3(7):730-7.

Bonomi Arianna, Daniela Lisini, Stefania Elena Navone, Simona Frigerio, Marta Dossena, Emilio Ciusani, Paolo Rampini, Giovanni Marfia, Valentina Coccè, Loredana Cavicchini, Francesca Sisto, Eugenio Parati, Renato Mantegazza, Marco Rimoldi, Manuela Rizzetto, Giulio Alessandri, and Augusto Pessina. 2015. "Human CD14+ Cells Loaded with Paclitaxel Inhibit in Vitro Cell Proliferation of Glioblastoma." *Cyotherapy.* 17(3):310-9.

Boutou Effrossyni, Dimitris Vlachodimitropoulos, Vassiliki Pappa, Horst-Werner Sturzbecher, and Constantinos E. 2013. "DNA Repair and Telomeres — An Intriguing Relationship." *New Research Directions in DNA Repair.* 6(8):56-79

Brito Daniela A, Zhenye Yang, and Conly L. Rieder. 2008. "Microtubules Do Not Promote Mitotic Slippage When the Spindle Assembly Checkpoint Cannot Be Satisfied." *Journal of Cell Biology.* 7(8)-65-98

Brown Daniel V, Paul M. Daniel, Giovanna M. D'Abaco, Andrew Gogos, Wayne Ng, Andrew P. Morokoff, and Theo Mantamadiotis. 2015. "Coexpression Analysis of CD133 and CD44 Identifies Proneural and Mesenchymal Subtypes of Glioblastoma Multiforme." *Oncotarget.* 6(8): 6267–6280.

Brown Daniel V, Gulay Filiz, Paul M. Daniel, Frédéric Hollande, Sebastian Dworkin, Stephanie Amiridis, Nicole Kountouri, Wayne Ng, Andrew P. Morokoff, and Theo Mantamadiotis. 2017. "Expression of CD133 and CD44 in Glioblastoma Stem Cells Correlates with Cell Proliferation, Phenotype Stability and Intratumor Heterogeneity." *PLoS ONE.* 5(8):76-89

Bryukhovetskiy Igor, Arina Ponomarenko, Irina Lyakhova, Sergey Zaitsev, Yulia Zayats, Maria Korneyko, Marina Eliseikina, Polina Mischenko, Valerie Shevchenko, Hari Shanker Sharma, Aruna Sharma, and Yuri Khotimchenko. 2018. "Personalized Regulation of Glioblastoma Cancer Stem Cells Based on Biomedical Technologies: From Theory to Experiment (Review)." *International Journal of Molecular Medicine*. 42(2):691-702.

Buccarelli Mariachiara, Matteo Marconi, Simone Pacioni, Ivana De Pasqualis, Quintino Giorgio D'Alessandris, Maurizio Martini, Barbara Ascione, Walter Malorni, Luigi Maria Larocca, Roberto Pallini, Lucia Ricci-Vitiani, and Paola Matarrese. 2018. "Inhibition of Autophagy Increases Susceptibility of Glioblastoma Stem Cells to Temozolomide by Igniting Ferroptosis." *Cell Death and Disease*. 9(4):65-78

Buscemi Giacomo, Camilla Savio, Laura Zannini, Francesca Micciche, Debora Masnada, Makoto Nakanishi, Hiroshi Tauchi, Kenshi Komatsu, Shuki Mizutani, Kumkum Khanna, Phil Chen, Patrick Concannon, Luciana Chessa, and Domenico Delia. 2001. "Chk2 Activation Dependence on Nbs1 after DNA Damage." *Molecular and Cellular Biology*. 21(15): 5214–5222.

le Calvé Benjamin, Michal Rynkowski, Marie le Mercier, Céline Bruyère, Caroline Lonez, Thierry Gras, Benjamin Haibe-Kains, Gianluca Bontempi, Christine Decaestecker, Jean Marie Ruysschaert, Robert Kiss, and Florence Lefranc. 2010. "Long-Term in Vitro Treatment of Human Glioblastoma Cells with Temozolomide Increases Resistance in Vivo through up-Regulation of GLUT Transporter and Aldo-Keto Reductase Enzyme AKR1C Expression." *Neoplasia*. 12(9):727-39.

Campos Benito, Lingcheng Zeng, Philip H. Daotrong, Volker Eckstein, Andreas Unterberg, Heimo Mairbäurl, and Christel Herold-Mende. 2011. "Expression and Regulation of AC133 and CD133 in Glioblastoma." *GLIA*. 59 (12): 1974-1986

Carroll Veronica A. and Margaret Ashcroft. 2006. "Role of Hypoxia-Inducible Factor (HIF)-1 α versus HIF-2 α in the Regulation of HIF Target Genes in Response to Hypoxia, Insulin-like Growth Factor-I, or Loss of von Hippel-Lindau Function: Implications for Targeting the HIF Pathway." *Cancer Research* 66(12):6264–70.

Ceña Valentín and Pablo Játiva. 2018. "Nanoparticle Crossing of Blood–Brain Barrier: A Road to New Therapeutic Approaches to Central Nervous System Diseases." *Nanomedicine*. 13(13):1513-1516.

Chakravarti Arnab, Gary Zhai, Yoshiyuki Suzuki, Sormeh Sarkesh, Peter M. Black, Alona Muzikansky, and Jay S. Loeffler. 2004. "The Prognostic Significance of Phosphatidylinositol 3-Kinase Pathway Activation in Human Gliomas." *Journal of Clinical Oncology*. 12(6): 45-57

- Cheng Wei Yi, Jessica J. Kandel, Darrell J. Yamashiro, Peter Canoll, and Dimitris Anastassiou. 2012. "A Multi-Cancer Mesenchymal Transition Gene Expression Signature Is Associated with Prolonged Time to Recurrence in Glioblastoma." *PLoS ONE*. 7(4):e34705.
- Chithrani B. Devika and Warren C. W. Chan. 2007. "Elucidating the Mechanism of Cellular Uptake and Removal of Protein-Coated Gold Nanoparticles of Different Sizes and Shapes." *Nano Letters*. 7, 6, 1542–1550
- Chithrani B. Devika, Arezou A. Ghazani, and Warren C. W. Chan. 2006. "Determining the Size and Shape Dependence of Gold Nanoparticle Uptake into Mammalian Cells." *Nano Letters*. 6, 4, 662–668
- Chithrani Devika B, Michael Dunne, James Stewart, Christine Allen, and David A. Jaffray. 2010. "Cellular Uptake and Transport of Gold Nanoparticles Incorporated in a Liposomal Carrier ." *Nanomedicine: Nanotechnology, Biology, and Medicine* 6(1):161–69.
- Choe Gheeyoung, Steve Horvath, Timothy F. Cloughesy, Katherine Crosby, David Seligson, Aarno Palotie, Landon Inge, Bradley L. Smith, Charles L. Sawyers, and Paul S. Mischel. 2003. "Analysis of the Phosphatidylinositol 3'-Kinase Signaling Pathway in Glioblastoma Patients in Vivo." *Cancer Research*. 63(11):2742-6.
- Choi Jason, Alexandre Moquin, Enzo Bomal, Li Na, Dusica Maysinger, and Ashok Kakkar. 2017. "Telodendrimers for Physical Encapsulation and Covalent Linking of Individual or Combined Therapeutics." *Molecular Pharmaceutics*. 14, 8, 2607–2615.
- Choudhary Om Prakash. 2017. "Scanning Electron Microscope : Advantages and Disadvantages in Imaging Components." *Int.J.Curr.Microbiol.App.Sci* 6(5):1877–82.
- Cj Padmakrishnan, Easwer Hv, Vinod Vijayakurup, Girish R Menon, Suresh Nair, and Srinivas Gopala. 2019. "High LC3/Beclin Expression Correlates with Poor Survival in Glioma: A Definitive Role for Autophagy as Evidenced by In Vitro Autophagic Flux." *Pathology and Oncology Research*. 25(1):137–48.
- Clayton Katherine N, Janelle W. Salameh, and Steven T. Wereley. 2016. "Physical Characterization of Nanoparticle Size and Surface Modification Using Particle Scattering Diffusometry." *BIOMICROFLUIDICS*. 054107(10):1–14.
- Colgin Lorel M and Roger R. Reddel. 1999. "Telomere Maintenance Mechanisms and Cellular Immortalization." *Current Opinion in Genetics and Development*. 9(1):97-103.
- Contini Claudia, Matthew Schneemilch, Simon Gaisford, and Nick Quirke. 2018. "Nanoparticle–Membrane Interactions." *Journal of Experimental Nanoscience*. 13 (1) 62-81

- Crespo Silvia, Marcus Kind, and Alexandre Arcaro. 2016. "The Role of the PI3K/AKT/MTOR Pathway in Brain Tumor Metastasis." *Journal of Cancer Metastasis and Treatment*. 2016;2:80-89.
- Danaei M, M. Dehghankhold, S. Ataei, F. Hasanzadeh Davarani, R. Javanmard, A. Dokhani, S. Khorasani, and M. R. Mozafari. 2018. "Impact of Particle Size and Polydispersity Index on the Clinical Applications of Lipidic Nanocarrier Systems." *Pharmaceutics*. 10(2):57.
- Daniele Simona, Barbara Costa, Elisa Zappelli, Eleonora Da Pozzo, Simona Sestito, Giulia Nesi, Pietro Campiglia, Luciana Marinelli, Ettore Novellino, Simona Rapposelli, and Claudia Martini. 2015. "Combined Inhibition of AKT/MTOR and MDM2 Enhances Glioblastoma Multiforme Cell Apoptosis and Differentiation of Cancer Stem Cells." *Scientific Reports* 5:1–14.
- Dausend Julia, Anna Musyanovych, Martin Dass, Paul Walther, Hubert Schrezenmeier, Katharina Landfester, and Volker Mailänder. 2008. "Uptake Mechanism of Oppositely Charged Fluorescent Nanoparticles in Hela Cells." *Macromolecular Bioscience*. 8(12):1135-43.
- DeCarvalho Ana C, Kevin Nelson, Nancy Lemke, Norman L. Lehman, Ali S. Arbab, Steven Kalkanis, and Tom Mikkelsen. 2010. "Gliosarcoma Stem Cells Undergo Glial and Mesenchymal Differentiation in Vivo." *Stem Cells*. 28 (2): 181-190
- Deng Danni, Kaiming Luo, Hongmei Liu, Xichen Nie, Lian Xue, Rong Wang, Yuan Xu, Jun Cui, Naiyuan Shao, and Feng Zhi. 2019. "P62 Acts as an Oncogene and Is Targeted by MiR-124-3p in Glioma." *Cancer Cell International* 19(1):1–13.
- Deprez Johan, Didier Vertommen, Dario R. Alessi, Louis Hue, and Mark H. Rider. 1997. "Phosphorylation and Activation of Heart 6-Phosphofructo-2-Kinase by Protein Kinase B and Other Protein Kinases of the Insulin Signaling Cascades." *Journal of Biological Chemistry*. 4(4):78-98
- Dubrovska Anna, Sungeun Kim, Richard J. Salamone, John R. Walker, Sauveur Michel Maira, Carlos García-Echeverría, Peter G. Schultz, and Venkateshwar A. Reddy. 2009. "The Role of PTEN/Akt/PI3K Signaling in the Maintenance and Viability of Prostate Cancer Stem-like Cell Populations." *Proceedings of the National Academy of Sciences of the United States of America*. 6;106(1):268-73.
- Düvel Katrin, Jessica L. Yecies, Suchithra Menon, Pichai Raman, Alex I. Lipovsky, Amanda L. Souza, Ellen Triantafellow, Qicheng Ma, Regina Gorski, Stephen Cleaver, Matthew G. Vander Heiden, Jeffrey P. MacKeigan, Peter M. Finan, Clary B. Clish, Leon O. Murphy, and Brendan D. Manning. 2010. "Activation of a Metabolic Gene Regulatory Network Downstream of MTOR Complex 1." *Molecular Cell*. 39(2):171-83.

- Eaton P, P. Quaresma, C. Soares, C. Neves, M. P. de Almeida, E. Pereira, and P. West. 2017. "A Direct Comparison of Experimental Methods to Measure Dimensions of Synthetic Nanoparticles." *Ultramicroscopy* 9(182):179–90.
- Mansfield Edward D. H, Katy Sillence, Patrick Hole, Adrian C. Williamsa and and Vitaliy V. Khutoryanskiy. 2015. "POZylation: A New Approach to Enhance Nanoparticle Diffusion through Mucosal Barriers." *Nanoscale* 7(10):13671–79.
- Ekonomou Antigoni, SH Cedar, Clive G. Ballard, and Stephen L. Minger. 2008. "Stem-Cells: Prospects for Treating Dementia." *British Journal of Neuroscience Nursing*. 4(5):56-76
- Elias Maria C, Kathleen R. Tozer, John R. Silber, Svetlana Mikheeva, Mei Deng, Richard S. Morrison, Thomas C. Manning, Daniel L. Silbergeld, Carlotta A. Glackin, Thomas A. Reh, and Robert C. Rostomily. 2005. "TWIST Is Expressed in Human Gliomas and Promotes Invasion." *Neoplasia*. 7(9):824-37.
- Elliott Amicia D. 2020. "Confocal Microscopy: Principles and Modern Practices." *Curr Protoc Cytom* 92(2):e68.
- Esposito Carla L, Silvia Nuzzo, Swati A. Kumar, Anna Rienzo, Clare L. Lawrence, Roberto Pallini, Lisa Shaw, Jane E. Alder, Lucia Ricci-Vitiani, Silvia Catuogno, and Vittorio de Franciscis. 2016. "A Combined MicroRNA-Based Targeted Therapeutic Approach to Eradicate Glioblastoma Stem-like Cells." *Journal of Controlled Release* 238:43–57.
- Esposito Carla Lucia, Silvia Nuzzo, Silvia Catuogno, Simona Romano, Filomena de Nigris, and Vittorio de Franciscis. 2018. "STAT3 Gene Silencing by Aptamer-SiRNA Chimera as Selective Therapeutic for Glioblastoma." *Molecular Therapy - Nucleic Acids* 10(March):398–411.
- Fana Michael, John Gallien, Bhairavi Srinageshwar, Gary L. Dunbar, and Julien Rossignol. 2020. "Pamam Dendrimer Nanomolecules Utilized as Drug Delivery Systems for Potential Treatment of Glioblastoma: A Systematic Review." *International Journal of Nanomedicine*. 2020:15 Pages 2789—2808
- Feldkamp Matthias M, Prateek Lala, Nelson Lau, Luba Roncari, and Abhijit Guha. 1999. "Expression of Activated Epidermal Growth Factor Receptors, Ras-Guanosine Triphosphate, and Mitogen-Activated Protein Kinase in Human Glioblastoma Multiforme Specimens." *Neurosurgery*. 45(6):1442-53.
- Feliu Neus, Pekka Kohonen, Jie Ji, Yuning Zhang, Hanna L. Karlsson, Lena Palmberg, Andreas Nyström, and Bengt Fadeel. 2015. "Next-Generation Sequencing Reveals Low-Dose Effects of Cationic Dendrimers in Primary Human Bronchial Epithelial Cells." *ACS Nano*. 9, 1, 146–163

Fidoamore Alessia, Loredana Cristiano, Andrea Antonosante, Michele D'Angelo, Erica Di Giacomo, Carlo Astarita, Antonio Giordano, Rodolfo Ippoliti, Elisabetta Benedetti, and Annamaria Cimini. 2016. "Glioblastoma Stem Cells Microenvironment: The Paracrine Roles of the Niche in Drug and Radioresistance." *Stem Cells International*. 6(8):87-97

Filippi-Chiela Eduardo Cremonese, Mardja Manssur Bueno Silva, Marcos Paulo Thomé, and Guido Lenz. 2015. "Single-Cell Analysis Challenges the Connection between Autophagy and Senescence Induced by DNA Damage." *Autophagy*. 11(7):1099-113.

Flamant Lionel, Annick Notte, Noelle Ninane, Martine Raes, and Carine Michiels. 2010. "Anti-Apoptotic Role of HIF-1 and AP-1 in Paclitaxel Exposed Breast Cancer Cells under Hypoxia." *Molecular Cancer*. 13;9:191.

Foroozandeh Parisa and Azlan Abdul Aziz. 2018. "Insight into Cellular Uptake and Intracellular Trafficking of Nanoparticles." *Nanoscale Research Letters*. 10 (7):54-69.

Fruehauf John P, Henry Brem, Steven Brem, Andrew Sloan, Geoffrey Barger, Weidong Huang, and Ricardo Parker. 2006. "In Vitro Drug Response and Molecular Markers Associated with Drug Resistance in Malignant Gliomas." *Clinical Cancer Research*. 12(15):4523-32.

Fu Jun, Qun Ying Yang, Ke Sai, Fu Rong Chen, Jesse C. S. Pang, Ho Keung Ng, Aij Lie Kwan, and Zhong Ping Chen. 2013. "TGM2 Inhibition Attenuates ID1 Expression in CD44-High Glioma-Initiating Cells." *Neuro-Oncology*. 15 (10): 1353–1365

Fu Wei, Chao You, Lu Ma, Hao Li, Yan Ju, Xi Guo, Sirong Shi, Tao Zhang, Ronghui Zhou, and Yunfeng Lin. 2019. "Enhanced Efficacy of Temozolomide Loaded by a Tetrahedral Framework DNA Nanoparticle in the Therapy for Glioblastoma." *ACS Applied Materials and Interfaces* 11(43):39525–33.

Fung Lawrence K, Matthew G. Ewend, Allen Sills, Eric P. Sipos, Reid Thompson, Mark Watts, O. Michael Colvin, Henry Brem, and W. Mark Saltzman. 1998. "Pharmacokinetics of Interstitial Delivery of Carmustine, 4-Hydroperoxycyclophosphamide, and Paclitaxel from a Biodegradable Polymer Implant in the Monkey Brain." *Cancer Research*. 15;58(4):672-84.

Furuta Takuya, Hemragul Sabit, Yu Dong, Katsuyoshi Miyashita, Masashi Kinoshita, Naoyuki Uchiyama, Yasuhiko Hayashi, Yutaka Hayashi, Toshinari Minamoto, and Mitsutoshi Nakada. 2017. "Biological Basis and Clinical Study of Glycogen Synthase Kinase- 3 β -Targeted Therapy by Drug Repositioning for Glioblastoma." *Oncotarget*. 4;8(14):22811-22824.

- Galanis Evanthisia, S. Keith Anderson, Jackie M. Lafka, Joon H. Uhm, Caterina Giannini, Shaji K. Kumar, Teresa K. Kimlinger, Donald W. Northfelt, Patrick J. Flynn, Kurt A. Jaeckle, Timothy J. Kaufmann, and Jan C. Buckner. 2013. "Phase II Study of Bevacizumab in Combination with Sorafenib in Recurrent Glioblastoma (N0776): A North Central Cancer Treatment Group Trial." *Clinical Cancer Research*. 19(17): 4816-4823
- Galifianakis Nataliya V, Dimitris G. Placantonakis, and Mitchell Chesler. 2018. "Intracellular PH Measurements in Glioblastoma Cells Using the PH-Sensitive Dye BCECF." *Methods in Molecular Biology*. 2018;1741:103-109.
- Gallicchio Lisa, Shahinaz M. Gadalla, John D. Murphy, and Naoko I. Simonds. 2018. "The Effect of Cancer Treatments on Telomere Length: A Systematic Review of the Literature." *Journal of the National Cancer Institute*. 110(10):1048-1058.
- Gang Wang, Jun Jie Wang, Xing Li Fu, Guang Rui, and Shing Shun Tony To. 2017. "Advances in the Targeting of HIF-1 α and Future Therapeutic Strategies for Glioblastoma Multiforme (Review)." *Oncology Reports*. 37(2):657-670.
- Gao Song, Xue Jun Yang, Wen Gao Zhang, Yan Wei Ji, and Qiang Pan. 2009. "Mechanism of Thalidomide to Enhance Cytotoxicity of Temozolomide in U251-MG Glioma Cells in Vitro." *Chinese Medical Journal*. 5;122(11):1260-6.
- Garros-Regulez Laura, Paula Aldaz, Olatz Arrizabalaga, Veronica Moncho-Amor, Estefania Carrasco-Garcia, Lorea Manterola, Leire Moreno-Cugnon, Cristina Barrena, Jorge Villanua, Irune Ruiz, Steven Pollard, Robin Lovell-Badge, Nicolas Sampron, Idoia Garcia, and Ander Matheu. 2016. "MTOR Inhibition Decreases SOX2-SOX9 Mediated Glioma Stem Cell Activity and Temozolomide Resistance." *Expert Opinion on Therapeutic Targets*. 20(4):393-405.
- Garros-Regulez Laura, Idoia Garcia, Estefania Carrasco-Garcia, Aquilino Lantero, Paula Aldaz, Leire Moreno-Cugnon, Olatz Arrizabalaga, Jose Undabeitia, Sergio Torres-Bayona, Jorge Villanua, Irune Ruiz, Larraitz Egaña, Nicolas Sampron, and Ander Matheu. 2016. "Targeting SOX2 as a Therapeutic Strategy in Glioblastoma." *Frontiers in Oncology*. 24;6:222.
- Geng Yan, Paul Dalheimer, Shenshen Cai, Richard Tsai, Manorama Tewari, Tamara Minko, and Dennis E. Discher. 2007. "Shape Effects of Filaments versus Spherical Particles in Flow and Drug Delivery." *Nature Nanotechnology*. 2, 249-255(2007)
- Germer Katherine, Marissa Leonard, and Xiaoting Zhang. 2013. "RNA Aptamers and Their Therapeutic and Diagnostic Applications." *International Journal of Biochemistry and Molecular Biology* 4(1):27-40.

- Gerson S. L. and J. K. V. Willson. 1995. "O6-Alkylguanine-DNA Alkytransferase: A Target for the Modulation of Drug Resistance." *Hematology/Oncology Clinics of North America*. 9(2):431-50.
- Gerson Stanton L. 2004. "MGMT: Its Role in Cancer Aetiology and Cancer Therapeutics." *Nature Reviews Cancer*. 4(4):296-307.
- Giancotti Filippo G. 2013. "Mechanisms Governing Metastatic Dormancy and Reactivation." *Cell*. 7;155(4):750-64.
- Glaser Talita, Inbo Han, Liquan Wu, and Xiang Zeng. 2017. "Targeted Nanotechnology in Glioblastoma Multiforme." *Frontiers in Pharmacology*. 2017; 8: 166.
- Glumac Paige M. and Aaron M. LeBeau. 2018. "The Role of CD133 in Cancer: A Concise Review." *Clinical and Translational Medicine*. 9;7(1):18.
- Goh Chin Hwee, Yeow Yen Lu, Bik Liang Lau, Jacqueline Oy Leng Wong, Hock Keong Lee, Donald Ngian San Liew, and Albert Sii Hieng Wong. 2014. "Brain and Spinal Tumour." *Medical Journal of Malaysia*. 69(6):261-7.
- Goidts V J. Bageritz, L. Puccio, S. Nakata, M. Zapatka, S. Barbus, G. Toedt, B. Campos, A. Korshunov, S. Momma, E. Van Schaftingen, G. Reifenberger, C. Herold-Mende, P. Lichter, and B. Radlwimmer. 2012. "RNAi Screening in Glioma Stem-like Cells Identifies PFKFB4 as a Key Molecule Important for Cancer Cell Survival." *Oncogene*. 31(2012):3235–3243
- Gong Aihua and Suyun Huang. 2012. "FoxM1 and Wnt/β-Catenin Signaling in Glioma Stem Cells." *Cancer Research*. 15;72(22):5658-62.
- Goodman Catherine M, Catherine D. McCusker, Tuna Yilmaz, and Vincent M. Rotello. 2004. "Toxicity of Gold Nanoparticles Functionalized with Cationic and Anionic Side Chains." *Bioconjugate Chemistry*. 15(4):897-900.
- Gratton Stephanie E. A, Patricia A. Ropp, Patrick D. Pohlhaus, J. Christopher Luft, Victoria J. Madden, Mary E. Napier, and Joseph M. DeSimone. 2008. "The Effect of Particle Design on Cellular Internalization Pathways." *Proceedings of the National Academy of Sciences of the United States of America*. 105 (33) 11613-11618
- Grech Neil, Theresia Dalli, Sean Mizzi, Lara Meilak, Neville Calleja, and Antoine Zrinzo. 2020. "Rising Incidence of Glioblastoma Multiforme in a Well-Defined Population." *Cureus*. 12(5): e8195.
- Greider Carol W. and Elizabeth H. Blackburn. 1985. "Identification of a Specific Telomere Terminal Transferase Activity in Tetrahymena Extracts." *Cell*. 43(2):405-13.

- Grouchko Michael, Polina Roitman, Xi Zhu, Inna Popov, Alexander Kamyshny, Haibin Su, and Shlomo Magdassi. 2014. "Corrigendum: Merging of Metal Nanoparticles Driven by Selective Wettability of Silver Nanostructures." *Nature Communications* 3994(11):4213.
- Guan Ding Guo, Han Min Chen, Sheng Fang Liao, and Tian Zhi Zhao. 2015. "Combination of Temozolomide and Taxol Exerts a Synergistic Inhibitory Effect on Taxol-Resistant Glioma Cells via Inhibition of Glucose Metabolism." *Molecular Medicine Reports*. 4(6): 7705-7711.
- Guda Maheedhara R, Collin M. Labak, Sara Ibrahim Omar, Swapna Asuthkar, Subra Airala, Jack Tuszyński, Andrew J. Tsung, and Kiran K. Velpula. 2019. "GLUT1 and TUBB4 in Glioblastoma Could Be Efficacious Targets." *Cancers* 11(9):1–18.
- Haar Catherine P, Preetha Hebbar, Gerald C. Wallace, Arabinda Das, William A. Vandergrift, Joshua A. Smith, Pierre Giglio, Sunil J. Patel, Swapan K. Ray, and Naren L. Banik. 2012. "Drug Resistance in Glioblastoma: A Mini Review." *Neurochemical Research*. 37(6):1192-200.
- Hägerstrand Daniel, Xiaobing He, Maja Bradic Lindh, Saskia Hoefs, Göran Hesselager, Arne Östman, and Monica Nistér. 2011. "Identification of a SOX2-Dependent Subset of Tumor-and Sphere-Forming Glioblastoma Cells with a Distinct Tyrosine Kinase Inhibitor Sensitivity Profile." *Neuro-Oncology*. 13(11):1178-91.
- Hamidi Mehrdad, Amir Azadi, and Pedram Rafiei. 2006. "Pharmacokinetic Consequences of Pegylation." *Drug Delivery* 13(6):399–409.
- Han Feng, Rong Hu, Hua Yang, Jian Liu, Jianmei Sui, Xin Xiang, Fan Wang, Liangzhao Chu, and Shibin Song. 2016b. "PTEN Gene Mutations Correlate to Poor Prognosis in Glioma Patients: A Meta-Analysis." *OncoTargets and Therapy*. 9:3485-92
- Hanahan Douglas and Robert A. Weinberg. 2011. "Hallmarks of Cancer: The next Generation." *Cell*. 144(5):646-74.
- Haruta Kazuhiko, Natsuki Otaki, Masakazu Nagamine, Tomoyoshi Kayo, Asako Sasaki, Shinsuke Hiramatsu, Masayuki Takahashi, Kuniyoshi Hota, Hideaki Sato, and Hiroaki Yamazaki. 2017. "A Novel PEGylation Method for Improving the Pharmacokinetic Properties of Anti-Interleukin-17A RNA Aptamers." *Nucleic Acid Therapeutics* 27(1):36–44.
- Hawe Andrea, Wendy L. Hulse, Wim Jiskoot, and Robert T. Forbes. 2011. "Taylor Dispersion Analysis Compared to Dynamic Light Scattering for the Size Analysis of Therapeutic Peptides and Proteins and Their Aggregates." *Pharm Res* 28(5):2302–10.

- Hayashi Takuro, Kazuhide Adachi, Shigeo Ohba, and Yuichi Hirose. 2013. "The Cdk Inhibitor Flavopiridol Enhances Temozolomide-Induced Cytotoxicity in Human Glioma Cells." *Journal of Neuro-Oncology*. 115(2):169-78.
- He Chunbai, Yiping Hu, Lichen Yin, Cui Tang, and Chunhua Yin. 2010. "Effects of Particle Size and Surface Charge on Cellular Uptake and Biodistribution of Polymeric Nanoparticles." *Biomaterials*. 31(13): 3657-3666
- He Jie, Zhengnan Shan, Lihua Li, Fen Liu, Zhihui Liu, Mingxu Song, and Haiqing Zhu. 2011. "Expression of Glioma Stem Cell Marker CD133 and O6-Methylguanine-DNA Methyltransferase Is Associated with Resistance to Radiotherapy in Gliomas." *Oncology Reports*. 26(5):1305-13.
- He Lu, Hong Zhou, Zhiqing Zeng, Hailun Yao, Weiping Jiang, and Hongtao Qu. 2019. "Wnt/β-Catenin Signaling Cascade: A Promising Target for Glioma Therapy." *Journal of Cellular Physiology*. 234(3):2217-2228.
- Heiden Matthew G. Vande, Lewis C. Cantley, and Craig B. Thompson. 2009. "Understanding the Warburg Effect: The Metabolic Requirements of Cell Proliferation." *Science*.324(5930):1029-33.
- Her Nam Gu, Jeong Woo Oh, Yun Jeong Oh, Suji Han, Hee Jin Cho, Yeri Lee, Gyu Ha Ryu, and Do Hyun Nam. 2018. "Potent Effect of the MDM2 Inhibitor AMG232 on Suppression of Glioblastoma Stem Cells." *Cell Death and Disease* 9(8):1–12.
- Hermission Mirjam, Andrea Klumpp, Wolfgang Wick, Georg Nagel, Wynand Roos, Bernd Kaina, and Michael Weller. 2006. "O 6 -Methylguanine DNA Methyltransferase and P53 Status Predict Temozolomide Sensitivity in Human Malignant Glioma Cells." *Journal of Neurochemistry* 96(3):766-76.
- Herrmann Markus, Irene Pusceddu, Winfried März, and Wolfgang Herrmann. 2018. "Telomere Biology and Age-Related Diseases." *Clinical Chemistry and Laboratory Medicine*. 26;56(8):1210-1222.
- Ho Maria Y. and John R. Mackey. 2014. "Presentation and Management of Docetaxel-Related Adverse Effects in Patients with Breast Cancer." *Cancer Management and Research*. 27;6:253-9.
- Hocking Kyle M., Brian C. Evans, Padmini Komalavilas, Joyce Cheung-Flynn, Craig L. Duvall, and Colleen M. Brophy. 2019. "Nanotechnology Enabled Modulation of Signaling Pathways Affects Physiologic Responses in Intact Vascular Tissue." *Tissue Engineering - Part A* 25(5–6):416–26.

- Hombach-Klonisch Sabine, Maryam Mehrpour, Shahla Shojaei, Craig Harlos, Marshall Pitz, Ahmed Hamai, Krzysztof Siemianowicz, Virginia Likus, Emilia Wiechec, Brian D. Toyota, Reyhane Hoshyar, Amir Seyfoori, Zahra Sepehri, Sudharsana R. Ande, Forough Khadem, Mohsen Akbari, Adrienne M. Gorman, Afshin Samali, Thomas Klonisch, and Saeid Ghavami. 2018. "Glioblastoma and Chemoresistance to Alkylating Agents: Involvement of Apoptosis, Autophagy, and Unfolded Protein Response." *Pharmacology and Therapeutics*. 184:13-41.
- Hoshyar Nazanin, Samantha, Gray, Hongbin Han, & Gang, and Bao. 2016. "The Effect of Nanoparticle Size on in Vivo Pharmacokinetics and Cellular Interaction." *Nanomedicine* 11(6):673–92.
- Hou Helei, Dantong Sun, and Xiaochun Zhang. 2019. "The Role of MDM2 Amplification and Overexpression in Therapeutic Resistance of Malignant Tumors." *Cancer Cell International*. 7(6):98-112
- Hou Xu, Yaohua Liu, Huailei Liu, Xin Chen, Min Liu, Hui Che, Fei Guo, Chunlei Wang, Daming Zhang, Jianing Wu, Xiaofeng Chen, Chen Shen, Chenguang Li, Fei Peng, Yunke Bi, Zhuowen Yang, Guang Yang, Jing Ai, Xin Gao, and Shiguang Zhao. 2015. "PERK Silence Inhibits Glioma Cell Growth under Low Glucose Stress by Blockage of P-AKT and Subsequent HK2's Mitochondria Translocation." *Scientific Reports* 5:1–9.
- Hu Bo, Ping Guo, Quan Fang, Huo Quan Tao, Degui Wang, Motoo Nagane, Hui Jein Su Huang, Yuji Gunji, Ryo Nishikawa, Kari Alitalo, Webster K. Cavenee, and Shi Yuan Cheng. 2003. "Angiopoietin-2 Induces Human Glioma Invasion through the Activation of Matrix Metalloprotease-2." *Proceedings of the National Academy of Sciences of the United States of America* 100(15):8904–9.
- Hu Che Ming Jack and Liangfang Zhang. 2012. "Nanoparticle-Based Combination Therapy toward Overcoming Drug Resistance in Cancer." *Biochemical Pharmacology*. 15;83(8):1104-11.
- Huang Xin, Qiangqian Qi, Xuming Hua, Xinyuan Li, Wenchuan Zhang, Hui Sun, Shiting Li, Xiaoqiang Wang, and Bin Li. 2014. "Beclin 1, an Autophagy-Related Gene, Augments Apoptosis in U87 Glioblastoma Cells." *Oncology Reports* 31(4):1761–67.
- Iacopino Fortunata, Cristiana Angelucci, Roberto Piacentini, Filippo Biamonte, Annunziato Mangiola, Giulio Maira, Claudio Grassi, and Gigliola Sica. 2014. "Isolation of Cancer Stem Cells from Three Human Glioblastoma Cell Lines : Characterization of Two Selected Clones." 9(8): e105166.
- Ignatova Tatyana N, Valery G. Kukekov, Eric D. Laywell, Oleg N. Suslov, Frank D. Vrionis, and Dennis A. Steindler. 2002. "Human Cortical Glial Tumors Contain Neural Stem-like Cells Expressing Astroglial and Neuronal Markers in Vitro." *GLIA*. 39(3):193-206.

- Islam Mohammed M. and Chun Li Zhang. 2015. "TLX: A Master Regulator for Neural Stem Cell Maintenance and Neurogenesis." *Biochimica et Biophysica Acta - Gene Regulatory Mechanisms*. 54(7):34-47
- Iwadate Yasuo. 2016. "Epithelial-Mesenchymal Transition in Glioblastoma Progression." *Oncology Letters*. 11(3):1615-1620.
- J Rossignol, Munro N.M., Fana M., Srinageshwar B., Malkowski C., Climie S., Gallien J., Swanson D., and Sharma A. 2019. "Use of Dendrimer Nanoparticles Encapsulated Curcumin as a Potential Therapy for Glioblastoma in Mice." *Cell Transplantation*. 4(5):56-76
- Jain Aviral and Sanjay K. Jain. 2008. "PEGylation: An Approach for Drug Delivery. A Review." *Critical Reviews in Therapeutic Drug Carrier Systems*. ;25(5):403-47.
- Jain Keerti, Prashant Kesharwani, Umesh Gupta, and N. K. Jain. 2010. "Dendrimer Toxicity: Let's Meet the Challenge." *International Journal of Pharmaceutics*. 1(2):122-142.
- Jaiswal Ritu, Frederick Luk, Penelope V. Dalla, Georges Emile Raymond Grau, and Mary Bebawy. 2013. "Breast Cancer-Derived Microparticles Display Tissue Selectivity in the Transfer of Resistance Proteins to Cells." *PLoS ONE*. 12;8(4):e61515.
- Jaiswal Ritu and Lisa M. Sedger. 2019. "Intercellular Vesicular Transfer by Exosomes, Microparticles and Oncosomes - Implications for Cancer Biology and Treatments." *Frontiers in Oncology*. 45(4): 67-79
- Jani Rupalben Kaushalkumar and Gohil Krupa. 2019. "Active Targeting of Nanoparticles: An Innovative Technology for Drug Delivery in Cancer Therapeutics." *Journal of Drug Delivery and Therapeutics*. 9(1): 54-65
- Janiszewska Jolanta, Inmaculada Posadas, Pablo Jativa, Marta Bugaj-Zarebska, Zofia Urbanczyk-Lipkowska, and Valentín Ceña. 2016. "Second Generation Amphiphilic Poly-Lysine Dendrons Inhibit Glioblastoma Cell Proliferation without Toxicity for Neurons or Astrocytes." *PLoS ONE*. 31(5):98-112
- Janiszewska Michalina, Mario L. Suvà, Nicolo Riggi, Riekelt H. Houtkooper, Johan Auwerx, Virginie Clément-Schatlo, Ivan Radovanovic, Esther Rheinbay, Paolo Provero, and Ivan Stamenkovic. 2012. "Imp2 Controls Oxidative Phosphorylation and Is Crucial for Preservin Glioblastoma Cancer Stem Cells." *Genes and Development*. 26(27):1926-44
- Jansson Lina, Grace S. Kim, and Alan G. Cheng. 2015. "Making Sense of Wnt Signaling—Linking Hair Cell Regeneration to Development." *Frontiers in Cellular Neuroscience* 9 (March):1–12.

- Jiang B. H, G. Jiang, J. Z. Zheng, Z. Lu, T. Hunter, and P. K. Vogt. 2001. "Phosphatidylinositol 3-Kinase Signaling Controls Levels of Hypoxia-Inducible Factor 1." *Cell Growth and Differentiation*. 12(7):363-9.
- Jiang Shan, Kala Hill, Dipen Patel, A. Reginald Waldeck, Marc Botteman, Abdalla Aly, and Andrew D. Norden. 2017. "Direct Medical Costs of Treatment in Newly-Diagnosed High-Grade Glioma among Commercially Insured US Patients." *Journal of Medical Economics*. 20(12):1237-1243.
- Jiapaer Shabierjiang, Takuya Furuta, Shingo Tanaka, Tomohiro Kitabayashi, and Mitsutoshi Nakada. 2018. "Potential Strategies Overcoming the Temozolomide Resistance for Glioblastoma." *Neurologia Medico-Chirurgica*. 58(10):405-421.
- Jin Feng, Guang Kui Han, Hao Zhang, Ran Zhang, Gen Hua Li, Song Feng, Xian Yun Qin, Ling Sheng Kong, Quan Min Nie, Hua Rong Li, and Lei Zhao. 2017. "Difference in the Inhibitory Effect of Temozolomide on TJ905 Glioma Cells and Stem Cells." *Frontiers in Neurology*. 13;8:474.
- Jin Hong, Daniel A. Heller, Richa Sharma, and Michael S. Strano. 2009. "Size-Dependent Cellular Uptake and Expulsion of Single-Walled Carbon Nanotubes: Single Particle Tracking and a Generic Uptake Model for Nanoparticles." *ACS Nano*. 3(1):149-158
- Jonge Niels de and and Stephen J. Pennycook , Rachid Sougrat,, Brian M. Northan4. 2010. "Three-Dimensional Scanning Transmission Electron Microscopy of Biological Specimens." *Microsc Microanal*. (1):54–63.
- Joo Kyeung Min, Shi Yean Kim, Xun Jin, Sang Yong Song, Doo Sik Kong, Jung Ii Lee, Ji Won Jeon, Mi Hyun Kim, Bong Gu Kang, Yong Jung, Juyoun Jin, Seung Chyul Hong, Woong Yang Park, Dong Sup Lee, Hyunggee Kim, and Do Hyun Nam. 2008. "Clinical and Biological Implications of CD133-Positive and CD133-Negative Cells in Glioblastomas." *Laboratory Investigation*. 7(8):99-116
- Kampan Nirmala Chandalega, Mutsa Tatenda Madondo, Orla M. McNally, Michael Quinn, and Magdalena Plebanski. 2015. "Paclitaxel and Its Evolving Role in the Management of Ovarian Cancer." *BioMed Research International*. 2015:413076.
- Kang Sang Sun, Taegun Kwon, Do Yoon Kwon, and Su Il Do. 1999. "Akt Protein Kinase Enhances Human Telomerase Activity through Phosphorylation of Telomerase Reverse Transcriptase Subunit." *Journal of Biological Chemistry*. 274(19):13085-90.
- Kanzawa T, I. M. Germano, Y. Kondo, H. Ito, S. Kyo, and S. Kondo. 2003. "Inhibition of Telomerase Activity in Malignant Glioma Cells Correlates with Their Sensitivity to Temozolomide." *British Journal of Cancer*. 89(5):922-9.

- Karar Jayashree and Amit Maity. 2011. "PI3K/AKT/MTOR Pathway in Angiogenesis." *Frontiers in Molecular Neuroscience*. 5(8):234-341
- Karmakar Surajit, Naren L. Banik, and Swapan K. Ray. 2008. "Combination of All-Trans Retinoic Acid and Paclitaxel-Induced Differentiation and Apoptosis in Human Glioblastoma U87MG Xenografts in Nude Mice." *Cancer*. 112(3):596-607.
- Kaur Balveen, Fatima W. Khwaja, Eric A. Severson, Shannon L. Matheny, Daniel J. Brat, and Erwin G. Van Meir. 2005. "Hypoxia and the Hypoxia-Inducible-Factor Pathway in Glioma Growth and Angiogenesis." *Neuro-Oncology*. 7(2):134-154
- Kaur Navjot, Sivarajan Chettiar, Sachin Rathod, Phalguni Rath, Dattatraya Muzumdar, M. L. Shaikh, and Anjali Shiras. 2013. "Wnt3a Mediated Activation of Wnt/β-Catenin Signaling Promotes Tumor Progression in Glioblastoma." *Molecular and Cellular Neuroscience* 54:44–57.
- Kawagoe Jun, Masahide Ohmichi, Toshifumi Takahashi, Chika Ohshima, Seiji Mabuchi, Kazuhiro Takahashi, Hideki Igarashi, Akiko Mori-Abe, Maki Saitoh, Botao Du, Tsuyoshi Ohta, Akiko Kimura, Satoru Kyo, Masaki Inoue, and Hirohisa Kurachi. 2003. "Raloxifene Inhibits Estrogen-Induced Up-Regulation of Telomerase Activity in a Human Breast Cancer Cell Line." *Journal of Biological Chemistry*. 278(44):43363-72.
- Ke Weilun, Kun Shao, Rongqin Huang, Liang Han, Yang Liu, Jianfeng Li, Yuyang Kuang, Liya Ye, Jinning Lou, and Chen Jiang. 2009. "Gene Delivery Targeted to the Brain Using an Angiopep-Conjugated Polyethyleneglycol-Modified Polyamidoamine Dendrimer." *Biomaterials*. 30(36):6976-85.
- Kelf T. A, V. K. A. Sreenivasan, J. Sun, E. J. Kim, E. M. Goldys, and A. V. Zvyagin. 2010. "Non-Specific Cellular Uptake of Surface-Functionalized Quantum Dots." *Nanotechnology*. 21(28):285105.
- Kerbel Robert S. 1991. "Inhibition of Tumor Angiogenesis as a Strategy to Circumvent Acquired Resistance to Anti- cancer Therapeutic Agents." *BioEssays*. 13(1):31-6.
- Kim Injune, Hwan Gyu Kim, June No So, Joo Heon Kim, Hee Jin Kwak, and Gou Young Koh. 2000. "Angiopoietin-1 Regulates Endothelial Cell Survival through the Phosphatidylinositol 3'-Kinase/Akt Signal Transduction Pathway." *Circulation Research*. 7-21;86(1):24-9.
- Kim Jung Whan, Irina Tchernyshyov, Gregg L. Semenza, and Chi V. Dang. 2006. "HIF-1-Mediated Expression of Pyruvate Dehydrogenase Kinase: A Metabolic Switch Required for Cellular Adaptation to Hypoxia." *Cell Metabolism*. 3(3):177-85.

- Kim Sang Soo, Joe B. Harford, Kathleen F. Pirolo, and Esther H. Chang. 2015. "Effective Treatment of Glioblastoma Requires Crossing the Blood-Brain Barrier and Targeting Tumors Including Cancer Stem Cells: The Promise of Nanomedicine." *Biochemical and Biophysical Research Communications*. 18;468(3):485-9.
- Kim Young Jeon and Chong Rae Park N. 2001. "Principle of Field Emission-Scanning Electron Microscopy (FE-SEM) and Its Application to the Analysis of Carbon Nanostructures." *Carbon Science* 2(3):202–11.
- Kimura Akiko, Masahide Ohmichi, Jun Kawagoe, Satoru Kyo, Seiji Mabuchi, Toshifumi Takahashi, Chika Ohshima, Emi Arimoto-Ishida, Yukihiro Nishio, Masaki Inoue, Hirohisa Kurachi, Keiichi Tasaka, and Yuji Murata. 2004. "Induction of HTERT Expression and Phosphorylation by Estrogen via Akt Cascade in Human Ovarian Cancer Cell Lines." *Oncogene*. 3;23(26):4505-15.
- Kingston David G. I, G. Samaranayake, and C. A. Ivey. 1990. "The Chemistry of Taxol, A Clinically Useful Anticancer Agent1." *Journal of Natural Products*. 5(6):143-164
- Kleffel Sonja and Tobias Schatton. 2013. "Tumor Dormancy and Cancer Stem Cells: Two Sides of the Same Coin?" *Advances in Experimental Medicine and Biology*. 45(32):89-110.
- Knizhnik Anna V, Wynand P. Roos, Teodora Nikolova, Steve Quiros, Karl Heinz Tomaszowski, Markus Christmann, and Bernd Kaina. 2013. "Survival and Death Strategies in Glioma Cells: Autophagy, Senescence and Apoptosis Triggered by a Single Type of Temozolomide-Induced DNA Damage." *PLoS ONE*. 8(1):e55665.
- Kolhar Poornima, Aaron C. Anselmo, Vivek Gupta, Kapil Pant, Balabhaskar Prabhakarpandian, Erkki Ruoslahti, and Samir Mitragotri. 2013. "Using Shape Effects to Target Antibody-Coated Nanoparticles to Lung and Brain Endothelium." *Proceedings of the National Academy of Sciences of the United States of America*. 22(3):90-115.
- Kominsky Scott, Howard M. Johnson, Gail Bryan, Taishi Tanabe, Amy C. Hobeika, Prem S. Subramaniam, and Barbara Torres. 1998. "IFN γ Inhibition of Cell Growth in Glioblastomas Correlates with Increased Levels of the Cyclin Dependent Kinase Inhibitor P21(WAF1/CIP1)." *Oncogene* 17(23):2973–79.
- Konecny Gottfried, Michael Untch, Dennis Slamon, Małgorzata Beryt, Steffen Kahlert, Margret Felber, Elena Langer, Sandra Lude, Hermann Hepp, and Mark Pegram. 2001. "Drug Interactions and Cytotoxic Effects of Paclitaxel in Combination with Carboplatin, Epirubicin, Gemcitabine or Vinorelbine in Breast Cancer Cell Lines and Tumor Samples." *Breast Cancer Research and Treatment*. 7(12):77-90

- Konno Tomohiro, Junji Watanabe, and Kazuhiko Ishihara. 2003. "Enhanced Solubility of Paclitaxel Using Water-Soluble and Biocompatible 2-Methacryloyloxyethyl Phosphorylcholine Polymers." *Journal of Biomedical Materials Research - Part A*. 1;65(2):209-14.
- Koul Dimpay. 2008. "PTEN Signaling Pathways in Glioblastoma." *Cancer Biology and Therapy*. 5(6):78-98
- Kreso Antonija and John E. Dick. 2014. "Evolution of the Cancer Stem Cell Model." *Cell Stem Cell*. 54(6):67-99
- Kreso Antonija, Catherine A. O'Brien, Peter Van Galen, Olga I. Gan, Faiyaz Notta, Andrew M. K. Brown, Karen Ng, Ma Jing, Erno Wienholds, Cyrille Dunant, Aaron Pollett, Steven Gallinger, John McPherson, Charles G. Mullighan, Darryl Shibata, and John E. Dick. 2013. "Variable Clonal Repopulation Dynamics Influence Chemotherapy Response in Colorectal Cancer." *Science*. 339(6119):543-8.
- Kuen Cha, Sharida Fakurazi, Siti Othman, and Mas Masarudin. 2017. "Increased Loading, Efficacy and Sustained Release of Silibinin, a Poorly Soluble Drug Using Hydrophobically-Modified Chitosan Nanoparticles for Enhanced Delivery of Anticancer Drug Delivery Systems." *Nanomaterials*. 8;7(11):379.
- Kumari Sudha, Swetha Mg, and Satyajit Mayor. 2010. "Endocytosis Unplugged: Multiple Ways to Enter the Cell." *Cell Research*. 20(5):543-600.
- Labak Collin M, Paul Y. Wang, Rishab Arora, Maheedhara R. Guda, Swapna Asuthkar, Andrew J. Tsung, and Kiran K. Velpula. 2016. "Glucose Transport: Meeting the Metabolic Demands of Cancer, and Applications in Glioblastoma Treatment." *American Journal of Cancer Research* 6(8):1599–1608.
- Lamarche Brandon J, Nicole I. Orazio, and Matthew D. Weitzman. 2010. "The MRN Complex in Double-Strand Break Repair and Telomere Maintenance." *FEBS Letters*. 584 (17): 3682-3695.
- Langhans Julia, Lukas Schneele, Nancy Trenkler, Hélène Von Bandemer, Lisa Nonnenmacher, Georg Karpel-Massler, Markus D. Siegelin, Shaoxia Zhou, Marc Eric Halatsch, Klaus Michael Debatin, and Mike Andrew Westhoff. 2017. "The Effects of PI3K-Mediated Signalling on Glioblastoma Cell Behaviour." *Oncogenesis*. 6(11):398.
- Lara Pedro C, Martin Prusky, Martina Zimmermann, and Luis A. Henríquez-Hernández. 2011. "MVP and Vaults: A Role in the Radiation Response." *Radiation Oncology*. 56(3):32-56.
- Lee Chooi Yeng. 2017. "Strategies of Temozolomide in Future Glioblastoma Treatment." *OncoTargets and Therapy*. 10: 265–270.

- Lee Eudocia Q, David A. Reardon, David Schiff, Jan Drappatz, Alona Muzikansky, Sean A. Grimm, Andrew D. Norden, Lakshmi Nayak, Rameen Beroukhim, Mikael L. Rinne, Andrew S. Chi, Tracy T. Batchelor, Kelly Hempfling, Christine McCluskey, Katrina H. Smith, Sarah C. Gaffey, Brendan Wrigley, Keith L. Ligon, Jeffrey J. Raizer, and Patrick Y. Wen. 2015. "Phase II Study of Panobinostat in Combination with Bevacizumab for Recurrent Glioblastoma and Anaplastic Glioma." *Neuro-Oncology*. 17(6):862-7.
- Lee Sang Y. 2016. "ScienceDirect Temozolomide Resistance in Glioblastoma Multiforme." *Genes & Diseases* 3(3):198–210.
- Lee Yeri, Jin Ku Lee, Sun Hee Ahn, Jeongwu Lee, and Do Hyun Nam. 2016. "WNT Signaling in Glioblastoma and Therapeutic Opportunities." *Laboratory Investigation*. 96(2):137-50.
- Lesniak Wojciech G, Nikita Oskolkov, Xiaolei Song, Bachchu Lal, Xing Yang, Martin Pomper, John Laterra, Sridhar Nimmagadda, and Michael T. McMahon. 2016. "Salicylic Acid Conjugated Dendrimers Are a Tunable, High Performance CEST MRI NanoPlatform." *Nano Letters*. 65(7):110-125.
- Li Lei, Dongxi Xiang, Sarah Shigdar, Wenrong Yang, Qiong Li, Jia Lin, Kexin Liu, and Wei Duan. 2014. "Epithelial Cell Adhesion Molecule Aptamer Functionalized PLGA-Lecithin-Curcumin-PEG Nanoparticles for Targeted Drug Delivery to Human Colorectal Adenocarcinoma Cells." *International Journal of Nanomedicine*. 9: 1083–1096.
- Li Shyh Dar and Leaf Huang. 2008. "Pharmacokinetics and Biodistribution of Nanoparticles." *Molecular Pharmaceutics*. 5, 4, 496–504.
- Li Xiaoman, Changjing Wu, Nianci Chen, Huadi Gu, Allen Yen, Liu Cao, Enhua Wang, and Liang Wang. 2016. "PI3K/Akt/MTOR Signaling Pathway and Targeted Therapy for Glioblastoma." *Oncotarget*. 7(22):33440-50.
- Lin Fan, Mark C. De Gooijer, Eloy Moreno Roig, Levi C. M. Buil, Susan M. Christner, Jan H. Beumer, Thomas WEurdinger, Jos H. Beijnen, and Olaf Van Tellingen. 2014. "ABCB1, ABCG2, and PTEN Determine the Response of Glioblastoma to Temozolomide and ABT-888 Therapy." *Clinical Cancer Research* 20(10):2703–13.
- Liou Geou Yarh. 2019. "CD133 as a Regulator of Cancer Metastasis through the Cancer Stem Cells." *International Journal of Biochemistry and Cell Biology*. 106:1-7.
- Liu Gentao, Xiangpeng Yuan, Zhaojun Zeng, Patrizia Tunici, Hiushan Ng, Iman R. Abdulkadir, Lizhi Lu, Dwain Irvin, Keith L. Black, and John S. Yu. 2006. "Analysis of Gene Expression and Chemoresistance of CD133+ Cancer Stem Cells in Glioblastoma." *Molecular Cancer*. 2;5:67.

- Liu Jian Ye, Dong Qian, Li Ru He, Yong Hong Li, Yi Ji Liao, Shi Juan Mai, Xiao Peng Tian, Yan Hui Liu, Jia Xing Zhang, Hsiang Fu Kung, Yi Xin Zeng, Fang Jian Zhou, and Dan Xie. 2013. "PinX1 Suppresses Bladder Urothelial Carcinoma Cell Proliferation via the Inhibition of Telomerase Activity and P16/Cyclin D1 Pathway." *Molecular Cancer*. 6(8):89-111.
- Liu Ying, Shifang Ren, Lili Xie, Chunhong Cui, Yang Xing, Chanjuan Liu, Benjin Cao, Fan Yang, Yinan Li, Xiaoning Chen, Yuanyan Wei, Haojie Lu, and Jianhai Jiang. 2015. "Mutation of N-Linked Glycosylation at Asn548 in CD133 Decreases Its Ability to Promote Hepatoma Cell Growth." *Oncotarget*. 6(24):20650-60.
- Liu Yongjie, Naiquan Duan, and Shibo Duan. 2017. "Amplification of PINX1 in Glioblastoma Promotes Cell Proliferation and Is Targeted by MiR-627." *International Journal of Clinical and Experimental Medicine*. 65(7):99-145.
- Livak Kenneth J. and Thomas D. Schmittgen. 2001. "Analysis of Relative Gene Expression Data Using Real-Time Quantitative PCR and the 2- $\Delta\Delta CT$ Method." *Methods*. 2(4):78-89
- Livney Yoav D, Julia Modrejewski, Johanna G. Walter, Shira Engelberg, and Yehuda G. Assaraf. 2018. "Cancer Cell-Selective, Clathrin-Mediated Endocytosis of Aptamerdecorated Nanoparticles." *Oncotarget*. 9(30):20993-21006.
- Llaguno Sheila R. Alcantar, and Luis F. Parada. 2016. "Cell of Origin of Glioma: Biological and Clinical Implications." *British Journal of Cancer*. 115(12):1445-1450.
- Lötsch Daniela, Elisabeth Steiner, Klaus Holzmann, Sabine Spiegl-Kreinecker, Christine Pirker, Juraj Hlavaty, Helga Petznek, Balazs Hegedus, Tamas Garay, Thomas Mohr, Wolfgang Sommergruber, Michael Grusch, and Walter Berger. 2013. "Major Vault Protein Supports Glioblastoma Survival and Migration by Upregulating the EGFR/PI3K Signalling Axis." *Oncotarget* 4(11):1904–18.
- Löwe J, H. Li, K. H. Downing, and E. Nogales. 2001. "Refined Structure of A β -Tubulin at 3.5 Å Resolution." *Journal of Molecular Biology*. 54(3):99-112.
- Lun Xueqing, J. Connor Wells, Natalie Grinshtein, Jennifer C. King, Xiaoguang Hao, Ngoc Ha Dang, Xiuling Wang, Ahmed Aman, David Uehling, Alessandro Datti, Jeffrey L. Wrana, Jacob C. Easaw, Artee Luchman, Samuel Weiss, J. Gregory Cairncross, David R. Kaplan, Stephen M. Robbins, and Donna L. Senger. 2016. "Disulfiram When Combined with Copper Enhances the Therapeutic Effects of Temozolomide for the Treatment of Glioblastoma." *Clinical Cancer Research*. 22(15):3860-75.

- Lundy David J, Keng Jung Lee, I. Chia Peng, Chia Hsin Hsu, Jen Hao Lin, Kun Hung Chen, Yu Wen Tien, and Patrick C. H. Hsieh. 2019. "Inducing a Transient Increase in Blood-Brain Barrier Permeability for Improved Liposomal Drug Therapy of Glioblastoma Multiforme." *ACS Nano.* 67(7):45-76.
- Lunnoo Thodsaphon, Jirawat Assawakhajornsak, and Theerapong Puangmali. 2019. "In Silico Study of Gold Nanoparticle Uptake into a Mammalian Cell: Interplay of Size, Shape, Surface Charge, and Aggregation." *Journal of Physical Chemistry C* 123(6):3801–10.
- Luo Zimiao, Zhiqiang Yan, Kai Jin, Qiang Pang, Ting Jiang, Heng Lu, Xianping Liu, Zhiqing Pang, Lei Yu, and Xinguo Jiang. 2017. "Precise Glioblastoma Targeting by AS1411 Aptamer-Functionalized Poly (L- γ -Glutamylglutamine)-Paclitaxel Nanoconjugates." *Journal of Colloid and Interface Science* 490:783–96.
- Macheda Maria L, Suzanne Rogers, and James D. Best. 2005. "Molecular and Cellular Regulation of Glucose Transporter (GLUT) Proteins in Cancer." *Journal of Cellular Physiology*. 202(3):654-62.
- Madaan Kanika, Sandeep Kumar, Neelam Poonia, Viney Lather, and Deepti Pandita. 2014. "Dendrimers in Drug Delivery and Targeting: Drug-Dendrimer Interactions and Toxicity Issues." *Journal of Pharmacy and Bioallied Sciences*. 6(3):139-50.
- Magaña-Maldonado Roxana, Karen Manoutcharian, Norma Y. Hernández-Pedro, Edgar Rangel-López, Verónica Pérez-De La Cruz, César Rodríguez-Balderas, Julio Sotelo, and Benjamín Pineda. 2014. "Concomitant Treatment with Pertussis Toxin plus Temozolomide Increases the Survival of Rats Bearing Intracerebral RG2 Glioma." *Journal of Cancer Research and Clinical Oncology*. 140(2):291-301.
- Mahmood Syed, Uttam Kumar Mandal, Bappaditya Chatterjee, and Muhammad Taher. 2017. "Advanced Characterizations of Nanoparticles for Drug Delivery : Investigating Their Properties through the Techniques Used in Their Evaluations." *Nanotechnol Rev* 6(4):355–72.
- Major Michael B, Nathan D. Camp, Jason D. Berndt, Xianhua Yi, Seth J. Goldenberg, Charlotte Hubbert, Travis L. Biechele, Anne Claude Gingras, Ning Zheng, Michael J. MacCoss, Stephane Angers, and Randall T. Moon. 2007. "Wilms Tumor Suppressor WTX Negatively Regulates WNT/ β -Catenin Signaling." *Science*. 87(8):65-79.
- Mak Anthony B, Allison M. L. Nixon, Saranya Kittanakom, Jocelyn M. Stewart, Ginny I. Chen, Jasna Curak, Anne Claude Gingras, Ralph Mazitschek, Benjamin G. Neel, Igor Stagljar, and Jason Moffat. 2012. "Regulation of CD133 by HDAC6 Promotes β -Catenin Signaling to Suppress Cancer Cell Differentiation." *Cell Reports*. 2(4):951-63.

- Mangraviti Antonella, Stephany Yi Tzeng, Kristen Lynn Kozielski, Yuan Wang, Yike Jin, David Gullotti, Mariangela Pedone, Nitsa Buaron, Ann Liu, David R. Wilson, Sarah K. Hansen, Fausto J. Rodriguez, Guo Dong Gao, Francesco Dimeco, Henry Brem, Alessandro Olivi, Betty Tyler, and Jordan J. Green. 2015. "Polymeric Nanoparticles for Nonviral Gene Therapy Extend Brain Tumor Survival in Vivo." *ACS Nano*. 67(8):12-32.
- Mangum Ross. 2012. "Glioma Stem Cells and Their Therapy Resistance." *Journal of Carcinogenesis & Mutagenesis*.
- Martin-Orozco Elena, Ana Sanchez-Fernandez, Irene Ortiz-Parra, and Maria Ayala-San Nicolas. 2019. "WNT Signaling in Tumors: The Way to Evade Drugs and Immunity." *Frontiers in Immunology*. 2(4):43-54.
- Martinez Paula and Maria A. Blasco. 2010. "Role of Shelterin in Cancer and Aging." *Aging Cell* 9(5):653–66.
- Mathieu Véronique, Nancy De Nève, Marie Le Mercier, Janique Dewelle, Jean François Gaussion, Mischael Dehoux, Robert Kiss, and Florence Lefranc. 2008. "Combining Bevacizumab with Temozolomide Increases the Antitumor Efficacy of Temozolomide in a Human Glioblastoma Orthotopic Xenograft Model." *Neoplasia*. 10(12):1383-92.
- Matoba Satoaki, Ju Gyeong Kang, Willmar D. Patino, Andrew Wragg, Manfred Boehm, Oksana Gavrilova, Paula J. Hurley, Fred Bunz, and Paul M. Hwang. 2006. "P53 Regulates Mitochondrial Respiration." *Science*. 16;312(5780):1650-3.
- Mattix Brandon, Thomas Moore, Olga Uvarov, Samuel Pollard, Lauren O'donnell, Katelyn Park, Devante Horne, Jhilmil Dhulekar, Laura Reese, Duong Nguyen, Jacqueline Kraveka, Karen Burg, And Frank Alexis. 2013. "Effects Of Polymeric Nanoparticle Surface Properties On Interaction With Brain Tumor Environment." *Nano LIFE*. 3(4): 1343003.
- Mayo Lindsey D, Jack E. Dixon, Donald L. Durden, Nickolas K. Tonks, and David B. Donner. 2002. "PTEN Protects P53 from Mdm2 and Sensitizes Cancer Cells to Chemotherapy." *Journal of Biological Chemistry*. 15;277(7):5484-9.
- McCord Matthew, Yoh Suke Mukouyama, Mark R. Gilbert, and Sadhana Jackson. 2017. "Targeting WNT Signaling for Multifaceted Glioblastoma Therapy." *Frontiers in Cellular Neuroscience*. 54(5):67-98.
- Mecca Carmen, Ileana Giambanco, Rosario Donato, and Cataldo Arcuri. 2018. "Targeting MTOR in Glioblastoma: Rationale and Preclinical/Clinical Evidence." *Disease Markers*. 18;2018:9230479.

Mellinghoff Ingo K, Maria Y. Wang, Igor Vivanco, Daphne A. Haas-Kogan, Shaojun Zhu, Ederlyn Q. Dia, Kan V. Lu, Koji Yoshimoto, Julie H. Y. Huang, Dennis J. Chute, Bridget L. Riggs, Steve Horvath, Linda M. Liau, Webster K. Cavenee, P. Nagesh Rao, Rameen Beroukhim, Timothy C. Peck, Jeffrey C. Lee, William R. Sellers, David Stokoe, Michael Prados, Timothy F. Cloughesy, Charles L. Sawyers, and Paul S. Mischel. 2005. "Molecular Determinants of the Response of Glioblastomas to EGFR Kinase Inhibitors." *New England Journal of Medicine*. 353(19):2012-24.

Méndez Olga, Jiri Zavadil, Mine Esencay, Yevgeniy Lukyanov, Daniel Santovasi, Shu Chi Wang, Elizabeth W. Newcomb, and David Zagzag. 2010. "Knock down of HIF-1 α in Glioma Cells Reduces Migration in Vitro and Invasion in Vivo and Impairs Their Ability to Form Tumor Spheres." *Molecular Cancer*. 10;353(19):2012-24.

Merighi Stefania, Annalisa Benini, Prisco Mirandola, Stefania Gessi, Katia Varani, Edward Leung, Stephen MacLennan, Pier Giovanni Baraldi, and Pier Andrea Borea. 2007. "Hypoxia Inhibits Paclitaxel-Induced Apoptosis through Adenosine-Mediated Phosphorylation of Bad in Glioblastoma Cells." *Molecular Pharmacology*. 72(1):162-72.

Mirzoeva O. K. and J. H. J. Petrini. 2001. "DNA Damage-Dependent Nuclear Dynamics of the Mre11 Complex." *Molecular and Cellular Biology*. 21(1):281-8.

Mishima K, M. Mishima-Kaneko, T. Kawata, H. Saya, N. Ishimaru, K. Yamada, R. Nishikawa, and N. Shigematsu. 2014. "Mre11-Rad50-Nbs1 Complex Inhibitor Mirin Enhances Radiosensitivity In Human Glioblastoma Cells." *Neuro-Oncology*. 3(4):76-98.

Mishra Prajna, Bismita Nayak, and R. K. Dey. 2016. "PEGylation in Anti-Cancer Therapy: An Overview." *Asian Journal of Pharmaceutical Sciences*. 11(3):337-348.

Mitchell Michael J, Margaret M. Billingsley, Rebecca M. Haley, Marissa E. Wechsler, Nicholas A. Peppas, and Robert Langer. 2021. "Engineering Precision Nanoparticles for Drug Delivery." *Nature Reviews Drug Discovery* 20(2):101–24.

Molinari Francesca and Milo Frattini. 2014. "Functions and Regulation of the PTEN Gene in Colorectal Cancer." *Frontiers in Oncology*. 2013 (3):326-337.

Montaldi Ana P, Paulo R. D. V Godoy, and Elza T. Sakamoto-hojo. 2015. "Mutation Research / Genetic Toxicology and Environmental Mutagenesis APE1 / REF-1 down-Regulation Enhances the Cytotoxic Effects of Temozolomide in a Resistant Glioblastoma Cell Line." *Mutation Research - Genetic Toxicology and Environmental Mutagenesis* 793:19–29.

- Morilla Maria, Perez, Cosaka, and Romero. 2011. "Uptake and Intracellular Traffic of SiRNA Dendriplexes in Glioblastoma Cells and Macrophages." *International Journal of Nanomedicine*. 6:2715-28.
- Morshed Ramin A, Yu Cheng, Brenda Auffinger, Michelle L. Wegscheid, and Maciej S. Lesniak. 2013. "The Potential of Polymeric Micelles in the Context of Glioblastoma Therapy." *Frontiers in Pharmacology*. 2013 (4):67-98.
- Munoz Jessian L, Nykia D. Walker, Kathleen W. Scotto, and Pranela Rameshwar. 2015. "Temozolomide Competes for P-Glycoprotein and Contributes to Chemoresistance in Glioblastoma Cells." *Cancer Letters*. 10;367(1):69-75.
- Murayama Takahiko and Noriko Gotoh. 2019. "Drug Resistance Mechanisms of Cancer Stem-like Cells and Their Therapeutic Potential as Drug Targets." *Cancer Drug Resistance*. 4(6):7-17.
- Nagata Yoichi, Keng Hsueh Lan, Xiaoyan Zhou, Ming Tan, Francisco J. Esteva, Aysegul A. Sahin, Kristine S. Klos, Ping Li, Brett P. Monia, Nina T. Nguyen, Gabriel N. Hortobagyi, Mien Chie Hung, and Dihua Yu. 2004. "PTEN Activation Contributes to Tumor Inhibition by Trastuzumab, and Loss of PTEN Predicts Trastuzumab Resistance in Patients." *Cancer Cell*. 6(2):117-27.
- Nager Mireia, Deepshikha Bhardwaj, Carles Cantí, Loreta Medina, Pere Nogués, and Judit Herreros. 2012. " β -Catenin Signalling in Glioblastoma Multiforme and Glioma-Initiating Cells." *Chemotherapy Research and Practice*. 2012(2012):192362.
- Naha Pratap C, Maria Davoren, Alan Casey, and Hugh J. Byrne. 2009. "An Ecotoxicological Study of Poly(Amidoamine) Dendrimers-toward Quantitative Structure Activity Relationships." *Environmental Science and Technology*. 1;43(17):6864-9.
- Nakai Eiichi, Kaechang Park, Toshio Yawata, Takahiro Chihara, Ayano Kumazawa, Hiromichi Nakabayashi, and Keiji Shimizu. 2009. "Enhanced Mdr1 Expression and Chemoresistance of Cancer Stem Cells Derived from Glioblastoma." *Cancer Investigation*. 27(9):901-8.
- Nangia Shikha and Radhakrishna Sureshkumar. 2012. "Effects of Nanoparticle Charge and Shape Anisotropy on Translocation through Cell Membranes." *Langmuir*. 5(6):98-110.
- Navarro L, R. Gil-Benso, J. Megías, L. Muñoz-Hidalgo, T. San-Miguel, R. C. Callaghan, J. M. González-Darder, C. López-Ginés, and M. J. Cerdá-Nicolás. 2015. "Alteration of Major Vault Protein in Human Glioblastoma and Its Relation with EGFR and PTEN Status." *Neuroscience* 297:243–51.

- Ni Shilei, Xiaoyong Fan, Jiangang Wang, Hongxu Qi, and Xingang Li. 2014. "Biodegradable Implants Efficiently Deliver Combination of Paclitaxel and Temozolomide to Glioma C6 Cancer Cells in Vitro." *Annals of Biomedical Engineering.* 42(1):214-21.
- Nichols, Gary, Stephen Byard, Mark J. Bloxham, Joanne Botterill, Neil J. Dawson, Andrew Dennis, Valerie Diart, Nigel C. North, and John D. Sherwood. 2002. "A Review of the Terms Agglomerate and Aggregate with a Recommendation for Nomenclature Used in Powder and Particle Characterization." *Journal of Pharmaceutical Sciences* 91(10):2103-9.
- Nikanjam Mina, Andrew R. Gibbs, C. Anthony Hunt, Thomas F. Budinger, and Trudy M. Forte. 2007. "Synthetic Nano-LDL with Paclitaxel Oleate as a Targeted Drug Delivery Vehicle for Glioblastoma Multiforme." *Journal of Controlled Release.* 124(3):163-171.
- Nuzzo Silvia, Valentina Brancato, Alessandra Affinito, Marco Salvatore, Carlo Cavalieri, and Gerolama Condorelli. 2020. "The Role of RNA and DNA Aptamers in Glioblastoma Diagnosis and Therapy: A Systematic Review of the Literature." *Cancers* 12(8):1-17.
- O'Connor Matthew S, Amin Safari, Dan Liu, Jun Qin, and Zhou Songyang. 2004. "The Human Rap1 Protein Complex and Modulation of Telomere Length." *Journal of Biological Chemistry.* 279(27):28585-91.
- Odeh F, H. Nsairat, W. Alshaer, M. A. Ismail, E. Esawi, B. Qaqish, A. A. Bawab, and S. I. Ismail. 2019. "Aptamers Chemistry: Chemical Modifications And conjugation strategies." *Molecules* 25(3):1-51.
- Okamoto Keiji and Hiroyuki Seimiya. 2019. "Revisiting Telomere Shortening in Cancer." *Cells.* 8(2):107.
- Ostrom Quinn T, Haley Gittleman, Paul Farah, Annie Ondracek, Yanwen Chen, Yingli Wolinsky, Nancy E. Stroup, Carol Kruchko, and Jill S. Barnholtz-Sloan. 2013. "CBTRUS Statistical Report: Primary Brain and Central Nervous System Tumors Diagnosed in the United States in 2006-2010." *Neuro-Oncology.* 76(8):23-45.
- Palumbo Silvia, Luigi Pirtoli, Paolo Tini, Gabriele Cevenini, Francesco Calderaro, Marzia Toscano, Clelia Miracco, and Sergio Comincini. 2012. "Different Involvement of Autophagy in Human Malignant Glioma Cell Lines Undergoing Irradiation and Temozolomide Combined Treatments." *Journal of Cellular Biochemistry.* 113(7):2308-18.
- Papandreou Ioanna, Rob A. Cairns, Lucrezia Fontana, Ai Lin Lim, and Nicholas C. Denko. 2006. "HIF-1 Mediates Adaptation to Hypoxia by Actively Downregulating Mitochondrial Oxygen Consumption." *Cell Metabolism.* 3(3):187-97.

Park Kinam. 2012. "The Role of Major Vault Protein (MVP) in Drug Resistance." *Journal of Controlled Release*. 28;163(2):266.

Peixoto Joana and Jorge Lima. 2018. "Metabolic Traits of Cancer Stem Cells." *DMM Disease Models and Mechanisms*. 6597):90-99.

Peng Li, Yanling Liang, Xinxin Zhong, Zhiman Liang, Yinghong Tian, Shuji Li, Jingxue Liang, Ransheng Wang, Yuqi Zhong, Yusheng Shi, and Xingmei Zhang. 2020. "Aptamer-Conjugated Gold Nanoparticles Targeting Epidermal Growth Factor Receptor Variant III for the Treatment of Glioblastoma." *International Journal of Nanomedicine* 15:1363–72.

Persano Luca, Elena Rampazzo, Alessandro Della Puppa, Francesca Pistollato, and Giuseppe Basso. 2011. "The Three-Layer Concentric Model of Glioblastoma: Cancer Stem Cells, Microenvironmental Regulation, and Therapeutic Implications." *TheScientificWorldJournal*. 2(8):22-43.

Phianmongkhon Aphirak and Julie Varley. 2003. "Z Potential Measurement for Air Bubbles in Protein Solutions." *Journal of Colloid and Interface Science* 260(2):332–38.

Pietras Alexander, Amanda M. Katz, Elin J. Ekström, Boyoung Wee, John J. Halliday, Kenneth L. Pitter, Jillian L. Werbeck, Nduka M. Amankulor, Jason T. Huse, and Eric C. Holland. 2014. "Osteopontin-CD44 Signaling in the Glioma Perivascular Niche Enhances Cancer Stem Cell Phenotypes and Promotes Aggressive Tumor Growth." *Cell Stem Cell*. 6;14(3):357-69.

Platet Nadine, Shi Yong Liu, Michèle El Atifi, Lisa Oliver, François M. Vallette, François Berger, and Didier Wion. 2007. "Influence of Oxygen Tension on CD133 Phenotype in Human Glioma Cell Cultures." *Cancer Letters*. 18;258(2):286-90.

Pölönen Petri, Ashik Jawahar Deen, Hanna M. Leinonen, Henna Kaisa Jyrkkänen, Suvi Kuosmanen, Mimmi Mononen, Ashish Jain, Tomi Tuomainen, Sanna Pasonen-Seppänen, Jaana M. Hartikainen, Arto Mannermaa, Matti Nykter, Pasi Tavi, Terje Johansen, Merja Heinäniemi, and Anna Liisa Levonen. 2019. "Nrf2 and SQSTM1/P62 Jointly Contribute to Mesenchymal Transition and Invasion in Glioblastoma." *Oncogene* 38(50):7473–90.

Postma T. J, J. J. Heimans, S. A. Luykx, C. J. Van Groeningen, L. F. M. Beenen, O. S. Hoekstra, M. J. B. Taphoorn, B. A. Zonnenberg, M. Klein, and J. B. Vermorken. 2000. "A Phase II Study of Paclitaxel in Chemonaive Patients with Recurrent High-Grade Glioma." *Annals of Oncology*. 11(4):409-13.

Qian Dong, Bin Zhang, Li Ru He, Mu Yan Cai, Shi Juan Mai, Yi Ji Liao, Yan Hui Liu, Marie C. Lin, Xiu Wu Bian, Yi Xin Zeng, Jun Jian Huang, Hsiang Fu Kung, and Dan Xie. 2013. "The Telomere/Telomerase Binding Factor PinX1 Is a New Target to Improve the Radiotherapy Effect of Oesophageal Squamous Cell Carcinomas." *Journal of Pathology*. 229(5):765-74.

- Rahdar Abbas, Nooshin Amini, and Faezeh Askari. 2019. "Dynamic Light Scattering: A Useful Technique to Characterize Nanoparticles." *J. Nanoanalysis* 6(2):80–89.
- Rajasekhar Vinagolu K, Agnes Viale, Nicholas D. Soccia, Martin Wiedmann, Xiaoyi Hu, and Eric C. Holland. 2003. "Oncogenic Ras and Akt Signaling Contribute to Glioblastoma Formation by Differential Recruitment of Existing MRNAs to Polysomes." *Molecular Cell*. 12(4):889-901.
- Rane Sagar S and Phillip Choi. 2005. "Polydispersity Index: How Accurately Does It Measure the Breadth of the Molecular Weight Distribution?" *Chemistry of Materials* 17(4):926.
- Régina Anthony, Michel Demeule, Alain Laplante, Julie Jodoin, Claude Dagenais, France Berthelet, Albert Moghrabi, and Richard Bélineau. 2001. "Multidrug Resistance in Brain Tumors: Roles of the Blood-Brain Barrier." *Cancer and Metastasis Reviews* 20(1–2):13–25.
- Reifenberger Guido, Lu Liu, Koichi Ichimura, Esther E. Schmidt, and V. Peter Collins. 1993. "Advances in Brief Amplification and Overexpression of the MDM2 Gene in a Subset of Human Malignant Gliomas without P53 Mutations1 Three Different Probes for WDM Were Synthesized by Reverse." *Chemistry journal* 1(5):65-78.
- Ren Yu, Xuan Zhou, Mei Mei, Xu Bo Yuan, Lei Han, Guang Xiu Wang, Zhi Fan Jia, Peng Xu, Pei Yu Pu, and Chun Sheng Kang. 2010. "MicroRNA-21 Inhibitor Sensitizes Human Glioblastoma Cells U251 (PTEN-Mutant) and LN229 (PTEN-Wild Type) to Taxol." *BMC Cancer*. 65(9):76-98.
- Riva Gabriele, Simona Baronchelli, Laura Paoletta, Valentina Butta, Ida Biunno, Marialuisa Lavitrano, Leda Dalprà, and Angela Bentivegna. 2014. "In Vitro Anticancer Drug Test: A New Method Emerges from the Model of Glioma Stem Cells." *Toxicology Reports*. 2014(1):188-199.
- Rizvi Syed A and Ayman M. Saleh. 2018. "Applications of Nanoparticle Systems in Drug Delivery Technology." *Saudi Pharmaceutical Journal*. 43(4):100-123.
- Rooj A. K, A. Bronisz, and J. Godlewski. 2016. "The Role of Octamer Binding Transcription Factors in Glioblastoma Multiforme." *Biochimica et Biophysica Acta - Gene Regulatory Mechanisms* 1859(6):805–11.
- Ruan Dong, Xin Li, Aixia Li, Baohui Liu, and Feng Xu. 2017. "Paclitaxel Inhibits Growth and Proliferation of Glioblastoma through MMP-9- Mediated P38/JNK Signaling Pathway." *Biomedical Research (India)*. 23(5):123-135.
- Ryskalina Larisa, Gloria Lazzeri, Marina Flaibani, Francesca Biagioli, Stefano Gambardella, Alessandro Frati, and Francesco Fornai. 2017. "MTOR-Dependent Cell Proliferation in the Brain." *BioMed Research International*. 6(7):77-88.

Sabourian Parinaz, Ghazaleh Yazdani, Seyed Sajad Ashraf, Masoud Frounchi, Shohreh Mashayekhan, Sahar Kiani, and Ashok Kakkar. 2020. "Effect of Physico-Chemical Properties of Nanoparticles on Their Intracellular Uptake." *International Journal of Molecular Sciences*. 28;21(21):8019.

Sachamitr Patty, Jolene C. Ho, Felipe E. Ciamponi, Wail Ba-alawi, Fiona J. Coutinho, Paul Guilhamon, Michelle M. Kushida, Florence M. G. Cavalli, Lilian Lee, Naghmeh Rastegar, Victoria Vu, María Sánchez-osuna, Jasmin Coulombe-huntington, Evgeny Kanshin, Heather Whetstone, Mathieu Durand, Philippe Thibault, Kirsten Hart, Maria Mangos, Joseph Veyhl, Wenjun Chen, Nhat Tran, Bang-chi Duong, Ahmed M. Aman, Xinghui Che, Xiaoyang Lan, and Owen Whitley. n.d. "PRMT5 Inhibition Disrupts Splicing and Stemness in Glioblastoma." *Nature Communications* (2021):1-17.

Sadekar S. and H. Ghandehari. 2012. "Transepithelial Transport and Toxicity of PAMAM Dendrimers: Implications for Oral Drug Delivery." *Advanced Drug Delivery Reviews*. 1;64(6):571-88.

Salatin Sara, Solmaz Maleki Dizaj, and Ahmad Yari Khosrourshahi. 2015. "Effect of the Surface Modification, Size, and Shape on Cellular Uptake of Nanoparticles." *Cell Biology International*. 39(8):881-90.

Saleem Azeem, Gavin D. Brown, Frank Brady, Eric O. Aboagye, Safiye Osman, Sajinder K. Luthra, Alex S. O. Ranicar, Cathryn S. Brock, Malcolm F. G. Stevens, Edward Newlands, Terry Jones, and Pat Price. 2003. "Metabolic Activation of Temozolomide Measured in Vivo Using Positron Emission Tomography." *Cancer Research*. 1(5):22-44.

Sanai Nader, Arturo Alvarez-Buylla, and Mitchel S. Berger. 2005. "Neural Stem Cells and the Origin of Gliomas." *New England Journal of Medicine*. 7(8):44-66.

Sancho Patricia, David Barneda, and Christopher Heeschen. 2016. "Hallmarks of Cancer Stem Cell Metabolism." *British Journal of Cancer*. 14;114(12):1305-12.

Sarafian Victoria S, Ilian Koev, Nikolay Mehterov, Maria Kazakova, and Krassimir Dangalov. 2018. "LAMP-1 Gene Is Overexpressed in High Grade Glioma." (12):1-6.

Schmitt M, M. Metzger, D. Gradl, G. Davidson, and V. Orian-Rousseau. 2015. "CD44 Functions in Wnt Signaling by Regulating LRP6 Localization and Activation." *Cell Death and Differentiation*. 22(4):677-89.

Schwartzbaum Judith A, James L. Fisher, Kenneth D. Aldape, and Margaret Wrensch. 2006. "Epidemiology and Molecular Pathology of Glioma." *Nature Clinical Practice Neurology*. 2(9):494-503

- Scudiero Dominic A, Robert H. Shoemaker, Kenneth D. Paull, Anne Monks, Siobhan Tierney, Thomas H. Nofziger, Michael J. Currens, Donna Seniff, and Michael R. Boyd. 1988. "Evaluation of a Soluble Tetrazolium/Formazan Assay for Cell Growth and Drug Sensitivity in Culture Using Human and Other Tumor Cell Lines." *Cancer Research* 48(17):4827–33.
- Sell Stewart. 2010. "On the Stem Cell Origin of Cancer." *American Journal of Pathology*. 43(3):66-79.
- Sercombe Lisa, Tejaswi Veerati, Fatemeh Moheimani, Sherry Y. Wu, Anil K. Sood, and Susan Hua. 2015. "Advances and Challenges of Liposome Assisted Drug Delivery." *Frontiers in Pharmacology*. 2015(8):99-114.
- Sharifzad Farzaneh, Saeid Ghavami, Soura Mardpour, Mahsa Mollapour, Zahra Azizi, Adeleh Taghikhani, Marek J. Łos, Javad Verdi, Esmail Fakharian, Marzieh Ebrahimi, and Amir Ali Hamidieh. 2019. "Glioblastoma Cancer Stem Cell Biology: Potential Theranostic Targets." *Drug Resistance Updates*. 42:35-45.
- She Qing Bai, David B. Solit, Qing Ye, Kathryn E. O'Reilly, Jose Lobo, and Neal Rosen. 2005. "The BAD Protein Integrates Survival Signaling by EGFR/MAPK and PI3K/Akt Kinase Pathways in PTEN-Deficient Tumor Cells." *Cancer Cell*. 8(4):287-297.
- Shergalis Andrea, Armand Bankhead, Urarika Luesakul, Nongnuj Muangsin, and Nouri Neamati. 2018. "Current Challenges and Opportunities in Treating Glioblastomas." *Pharmacological Reviews*. 65(7):32-46.
- Shi Fei, Jinying Zhang, Hongyu Liu, Liangliang Wu, Hongyu Jiang, Qiyan Wu, Tianyi Liu, Meiqing Lou, and Hao Wu. 2018. "The Dual PI3K/MTOR Inhibitor Dactolisib Elicits Anti-Tumor Activity in Vitro and in Vivo." *Oncotarget*. 9(1):706-717.
- Shibuya Keita, Masashi Okada, Shuhei Suzuki, Manabu Seino, Shizuka Seino, Hiroyuki Takeda, and Chifumi Kitanaka. 2015. "Targeting the Facilitative Glucose Transporter GLUT1 Inhibits the Self-Renewal and Tumor-Initiating Capacity of Cancer Stem Cells." *Oncotarget* 6(2):651–61.
- Shigdar Sarah, Liang Qiao, Shu Feng Zhou, Dongxi Xiang, Tao Wang, Yong Li, Lee Yong Lim, Lingxue Kong, Lianhong Li, and Wei Duan. 2013a. "RNA Aptamers Targeting Cancer Stem Cell Marker CD133." *Cancer Letters*. 54(6):31-44.
- Shigdar Sarah, Liang Qiao, Shu Feng Zhou, Dongxi Xiang, Tao Wang, Yong Li, Lee Yong Lim, Lingxue Kong, Lianhong Li, and Wei Duan. 2013b. "RNA Aptamers Targeting Cancer Stem Cell Marker CD133." *Cancer Letters*. 54(6):31-44.

- Si Daolin, Fei Yin, Jing Peng, and Guangying Zhang. 2020. "High Expression of CD44 Predicts a Poor Prognosis in Glioblastomas." *Cancer Management and Research* 12:769–75.
- Sieron P, C. Hader, J. Hatina, R. Engers, A. Wlazlinski, M. Müller, and W. A. Schulz. 2009. "DKC1 Overexpression Associated with Prostate Cancer Progression." *British Journal of Cancer*. 101(8):1410-1416.
- Singh Mayank Kumar, Madhusudana Kuncha, V. Lakshma Nayak, Akella V. S. Sarma, M. Jerald Mahesh Kumar, Abhay Singh Chauhan, and Ramakrishna Sistla. 2019. "An Innovative In Situ Method of Creating Hybrid Dendrimer Nano-Assembly: An Efficient next Generation Dendritic Platform for Drug Delivery." *Nanomedicine: Nanotechnology, Biology, and Medicine*. 32(7):66-87.
- Singh Neha, Alexandra Miner, Lauren Hennis, and Sandeep Mittal. 2020. "Mechanisms of Temozolomide Resistance in Glioblastoma - a Comprehensive Review." *Cancer Drug Resistance*. 54(2):111-120.
- Singh Sheila K, Ian D. Clarke, Mizuhiko Terasaki, Victoria E. Bonn, Cynthia Hawkins, Jeremy Squire, and Peter B. Dirks. 2003. "Identification of a Cancer Stem Cell in Human Brain Tumors." *Cancer Research*. 15;63(18):5821-8.
- Sita Timothy L, Fotini M. Kouri, Lisa A. Hurley, Timothy J. Merkel, Alexandra Chalastanis, Jasmine L. May, Serena T. Ghelfi, Lisa E. Cole, Thomas C. Cayton, Stacey N. Barnaby, Anthony J. Sprangers, Nikunjkumar Savalia, Charles David James, Andrew Lee, Chad A. Mirkin, and Alexander H. Stegh. 2017. "Dual Bioluminescence and Near-Infrared Fluorescence Monitoring to Evaluate Spherical Nucleic Acid Nanoconjugate Activity in Vivo." *Proceedings of the National Academy of Sciences of the United States of America*. 65(8):88-99.
- Snigdha Kirti, Karishma Sanjay Gangwani, Gauri Vijay Lapalikar, Amit Singh, and Madhuri Kango-Singh. 2019. "Hippo Signaling in Cancer: Lessons from Drosophila Models." *Frontiers in Cell and Developmental Biology*. 43(2):35-57.
- Song Shuzheng, Guoqing Pei, Yaqiong Du, Jugang Wu, Xiaochun Ni, Shoulian Wang, Bojian Jiang, Meng Luo, and Ji Wei Yu. 2018. "Interaction between CD133 and PI3K-P85 Promotes Chemoresistance in Gastric Cancer Cells." *American Journal of Translational Research*. 21(2):345-359.
- Song Wen Shin, Yi Ping Yang, Chi Shuan Huang, Kai Hsi Lu, Wei Hsiu Liu, Wai Wah Wu, Yi Yen Lee, Wen Liang Lo, Shou Dong Lee, Yi Wei Chen, Pin I. Huang, and Ming Teh Chen. 2016. "Sox2, a Stemness Gene, Regulates Tumor-Initiating and Drug-Resistant Properties in CD133-Positive Glioblastoma Stem Cells." *Journal of the Chinese Medical Association*. 79(10):538-45.

Spencer Caroline M. and Diana Faulds. 1994. "Paclitaxel: A Review of Its Pharmacodynamic and Pharmacokinetic Properties and Therapeutic Potential in the Treatment of Cancer." *Drugs*. 48(5):794-847.

Stevens Malcolm F. G, John A. Hickman, Simon P. Langdon, David Chubb, Lisa Vickers, Robert Stone, Ghousia Baig, Colin Goddard, Neil W. Gibson, John A. Slack, Christopher Newton, Edward Lunt, Christian Fizames, and Francois Lavelle. 1987. "Antitumor Activity and Pharmacokinetics in Mice of 8-Carbamoyl-3-Methyl-Imidazo[5, 1-d], 2, 3, 5-Tetrazin-4(3/f)-One (CCRG 81045; M & B 39831), a Novel Drug with Potential as an Alternative to Dacarbazine." *Cancer Research*. 5(8):10-23.

Suk Jung Soo, Qingguo Xu, Namho Kim, Justin Hanes, and Laura M. Ensign. 2016. "PEGylation as a Strategy for Improving Nanoparticle-Based Drug and Gene Delivery." *Advanced Drug Delivery Reviews*. 1(2):34-54.

Sun Ting, Haibin Wu, Yanyan Li, Yulun Huang, Lin Yao, Xionghui Chen, Xiaoxiao Han, Youxin Zhou, and Ziwei Du. 2017. "Targeting Transferrin Receptor Delivery of Temozolomide for a Potential Glioma Stem Cell-Mediated Therapy." *Oncotarget*. 8(43):74451-74465.

Sun Weichao and Liling Tang. 2016. "MDM2 Increases Drug Resistance in Cancer Cells by Inducing EMT Independent of P53." *Current Medicinal Chemistry*. 23(40):4529-4539.

Sun Xiyang, Ying Chen, Hui Zhao, Guanglei Qiao, Meiyang Liu, Chunlei Zhang, Daxiang Cui, and Lijun Ma. 2018. "Dual-Modified Cationic Liposomes Loaded with Paclitaxel and Survivin Sirna for Targeted Imaging and Therapy of Cancer Stem Cells in Brain Glioma." *Drug Delivery*. 25(1):1718-1727.

Sutter R, O. Shakhova, H. Bhagat, H. Behesti, C. Sutter, S. Penkar, A. Santuccione, R. Bernays, F. L. Heppner, U. Schüller, M. Grotzer, H. Moch, P. Schraml, and S. Marino. 2010. "Cerebellar Stem Cells Act as Medulloblastoma-Initiating Cells in a Mouse Model and a Neural Stem Cell Signature Characterizes a Subset of Human Medulloblastomas." *Oncogene*. 25;29(12):1845-56.

Suwala Abigail Kora, Katharina Koch, Dayana Herrera Rios, Philippe Aretz, Constanze Uhlmann, Isabella Ogorek, Jörg Felsberg, Guido Reifenberger, Karl Köhrer, René Deenen, Hans Jakob Steiger, Ulf D. Kahlert, and Jaroslaw Maciaczyk. 2018. "Inhibition of Wnt/Beta-Catenin Signaling Downregulates Expression of Aldehyde Dehydrogenase Isoform 3A1 (ALDH3A1) to Reduce Resistance against Temozolomide in Glioblastoma in Vitro." *Oncotarget*. 27;9(32):22703-22716.

Taal Walter, Hendrika M. Oosterkamp, Annemiek M. E. Walenkamp, Hendrikus J. Dubbink, Laurens V. Beerepoot, Monique C. J. Hanse, Jan Buter, Aafke H. Honkoop, Dolf Boerman, Filip Y. F. de Vos, Winand N. M. Dinjens, Roelien H. Enting, Martin J. B. Taphoorn, Franchette W. P. J. van den Berkmortel, Rob L. H. Jansen, Dieta Brandsma, Jacoline E. C. Bromberg, Irene van Heuvel, René M. Vernhout, Bronno van der Holt, and Martin J. Van Den Bent. 2014. "Single-Agent Bevacizumab or Lomustine versus a Combination of Bevacizumab plus Lomustine in Patients with Recurrent Glioblastoma (BELOB Trial): A Randomised Controlled Phase 2 Trial." *The Lancet Oncology*. 32(4):66-89.

Takahashi Hironobu, Takuro Niidome, Takahito Kawano, Sunao Yamada, and Yasuro Niidome. 2008. "Surface Modification of Gold Nanorods Using Layer-by-Layer Technique for Cellular Uptake." *Journal of Nanoparticle Research*. 43(7):167-198.

Tan Aaron C, David M. Ashley, Giselle Y. López, Michael Malinzak, Henry S. Friedman, and Mustafa Khasraw. 2020. "Management of Glioblastoma: State of the Art and Future Directions." *A Cancer Journal for Clinicians*. 43(8):678-987.

Tao Wei, Xiaowei Zeng, Jun Wu, Xi Zhu, Xinghua Yu, Xudong Zhang, Jinxie Zhang, Gan Liu, and Lin Mei. 2016. "Polydopamine-Based Surface Modification of Novel Nanoparticle-Aptamer Bioconjugates for in Vivo Breast Cancer Targeting and Enhanced Therapeutic Effects." *Theranostics*. 11;6(4):470-84.

Tao Wei, Jinxie Zhang, Xiaowei Zeng, Danny Liu, Gan Liu, Xi Zhu, Yanlan Liu, Qingtong Yu, Laiqiang Huang, and Lin Mei. 2015. "Blended Nanoparticle System Based on Miscible Structurally Similar Polymers: A Safe, Simple, Targeted, and Surprisingly High Efficiency Vehicle for Cancer Therapy." *Advanced Healthcare Materials*. 3;4(8):1203-14.

Tauriello Daniele V. F, Ingrid Jordens, Katharina Kirchner, Jerry W. Slootstra, Tom Kruitwagen, Britta A. M. Bouwman, Maria Noutsou, Stefan G. D. Rüdiger, Klaus Schwamborn, Alexandra Schambony, and Madelon M. Maurice. 2012. "Wnt/β-Catenin Signaling Requires Interaction of the Dishevelled DEP Domain and C Terminus with a Discontinuous Motif in Frizzled." *Proceedings of the National Academy of Sciences of the United States of America*. 98(87):345-369.

Teng David H. F, Rong Hu, Huai Lin, Thaylon Davis, Diana Iliev, Cheryl Frye, Brad Swedlund, Kipp L. Hansen, Vickie L. Vinson, Kathryn L. Gumpfer, Lee Ellis, Adel El-Naggar, Marsha Frazier, Samar Jasser, Lauren A. Langford, Jeff Lee, Gordon B. Mills, Mark A. Pershouse, Raphael E. Pollack, Carmen Tornos, Patricia Troncoso, W. K. Alfre. Yung, Gregory Fujii, Amy Berson, Robert Bookstein, Joseph B. Bolen, Scan V. Tavtigian, and Peter A. Steck. 1997. "MMAC1/PTEN Mutations in Primary Tumor Specimens and Tumor Cell Lines." *Cancer Research*. 1;57(23):5221-5.

- Thi Thai Thanh Hoang, Emily H. Pilkington, Dai Hai Nguyen, Jung Seok Lee, Ki Dong Park, and Nghia P. Truong. 2020. "The Importance of Poly(Ethylene Glycol) Alternatives for Overcoming PEG Immunogenicity in Drug Delivery and Bioconjugation." *Polymers*. 2;12(2):298.
- Tian Xiao Peng, Dong Qian, Li Ru He, He Huang, Shi Juan Mai, Chang Peng Li, Xiao Xia Huang, Mu Yan Cai, Yi Ji Liao, Hsiang fu Kung, Yi Xin Zeng, and Dan Xie. 2014. "The Telomere/Telomerase Binding Factor PinX1 Regulates Paclitaxel Sensitivity Depending on Spindle Assembly Checkpoint in Human Cervical Squamous Cell Carcinomas." *Cancer Letters*. 10;353(1):104-14.
- Toy Randall, Pubudu M. Peiris, Ketan B. Ghaghada, and Efstatios Karathanasis. 2014. "Shaping Cancer Nanomedicine: The Effect of Particle Shape on the in Vivo Journey of Nanoparticles." *Nanomedicine*. 9(1):98-117.
- Turner Kara, Vimal Vasu, and Darren Griffin. 2019. "Telomere Biology and Human Phenotype." *Cells*. 8(1):73.
- Ulasov I. V, G. Lenz, and M. S. Lesniak. 2018. "Autophagy in Glioma Cells: An Identity Crisis with a Clinical Perspective." *Cancer Letters*. 76(21):987-1004.
- Uram Łukasz, Aleksandra Filipowicz, Maria Misiorek, Natalia Pieńkowska, Joanna Markowicz, Elżbieta Wałajtys-Rode, and Stanisław Wołowiec. 2018. "Biotinylated PAMAM G3 Dendrimer Conjugated with Celecoxib and/or Fmoc-L-Leucine and Its Cytotoxicity for Normal and Cancer Human Cell Lines." *European Journal of Pharmaceutical Sciences*. 1;124:1-9.
- Uram Łukasz, Maria Misiorek, Monika Pichla, Aleksandra Filipowicz-Rachwał, Joanna Markowicz, Stanisław Wołowiec, and Elżbieta Wałajtys-Rode. 2019. "The Effect of Biotinylated PAMAM G3 Dendrimers Conjugated with COX-2 Inhibitor (Celecoxib) and PPAR γ Agonist (Fmoc-L-Leucine) on Human Normal Fibroblasts, Immortalized Keratinocytes and Glioma Cells in Vitro." *Molecules*.24(20):3801.
- Vaughan Catherine, Lathika Mohanraj, Shilpa Singh, Catherine I. Dumur, Mahesh Ramamoorthy, Carleton T. Garrett, Brad Windle, W. Andrew Yedull, Sumitra Deb, and Swati Palit Deb. 2011. "Human Oncoprotein MDM2 Up-Regulates Expression of NF-KB2 Precursor P100 Conferring a Survival Advantage to Lung Cells." *Genes and Cancer*. 45(7):246-259.
- Venkatesan Thiagarajan, Ali Alaseem, Aiyavu Chinnaiyan, Sivanesan Dhandayuthapani, Thanigaivelan Kanagasabai, Khalid Alhazzani, Priya Dondapati, Saad Alobid, Umamaheswari Natarajan, Ruben Schwartz, and Appu Rathinavelu. 2018. "MDM2 Overexpression Modulates the Angiogenesis-Related Gene Expression Profile of Prostate Cancer Cells." *Cells*.56(2):99-119.

- Verreault M, M. Wehbe, D. Strutt, D. Masin, M. Anantha, D. Walker, F. Chu, I. Backstrom, J. Kalra, D. Waterhouse, D. T. Yapp, and M. B. Bally. 2015. "Determination of an Optimal Dosing Schedule for Combining Irinophore C™ and Temozolomide in an Orthotopic Model of Glioblastoma." *Journal of Controlled Release*. 22(87):45-79.
- Vitucci Mark, Natalie O. Karpinich, Ryan E. Bash, Andrea M. Werneke, Ralf S. Schmid, Kristen K. White, Robert S. McNeill, Byron Huff, Sophie Wang, Terry Van Dyke, and C. Ryan Miller. 2013. "Cooperativity between MAPK and PI3K Signaling Activation Is Required for Glioblastoma Pathogenesis." *Neuro-Oncology*. 87(9):88-99.
- Vlashi Erina, Chann Lagadec, Laurent Vergnes, Tomoo Matsutani, Kenta Masui, Maria Poulou, Ruxandra Popescu, Lorenza Della Donna, Patrick Evers, Carmen Dekmezian, Karen Reue, Heather Christofk, Paul S. Mischel, and Frank Pajonka. 2011. "Metabolic State of Glioma Stem Cells and Nontumorigenic Cells." *Proceedings of the National Academy of Sciences of the United States of America*. 24(5):356-369.
- Voigt Nadine, Petra Henrich-Noack, Sarah Kockentiedt, Werner Hintz, Jürgen Tomas, and Bernhard A. Sabel. 2014. "Surfactants, Not Size or Zeta-Potential Influence Blood-Brain Barrier Passage of Polymeric Nanoparticles." *European Journal of Pharmaceutics and Biopharmaceutics* 87(1):19–29.
- Wang Baoyan, Lingyan Lv, Zhi Wang, Yan Jiang, Wei Lv, Xin Liu, Zhongyuan Wang, Yue Zhao, Hongliang Xin, and Qunwei Xu. 2015. "Improved Anti-Glioblastoma Efficacy by IL-13Ra2 Mediated Copolymer Nanoparticles Loaded with Paclitaxel." *Scientific Reports* 5(October):1–13.
- Wang Dongyang, Yuanxu Guo, Yanqing Li, Weiling Li, Xiaojing Zheng, Haibin Xia, and Qinwen Mao. 2015. "Detection of CD133 Expression in U87 Glioblastoma Cells Using a Novel Anti-CD133 Monoclonal Antibody." *Oncology Letters*. 9(6):2603-2608.
- Wang Fengfei, Zheng Zheng, Jitian Guan, Dan Qi, Shuang Zhou, Xin Shen, Fushun Wang, David Wenkert, Batool Kirmani, Touradj Solouki, Ekokobe Fonkem, Eric T. Wong, Jason H. Huang, and Erxi Wu. 2018. "Identification of a Panel of Genes as a Prognostic Biomarker for Glioblastoma." *EBioMedicine* 37:68–77.
- Wang Hsiao Han, Chen Chieh Liao, Nan Haw Chow, Lynn Ling Huei Huang, Jih Ing Chuang, Kuo Chen Wei, and Jyh Wei Shin. 2017. "Whether CD44 Is an Applicable Marker for Glioma Stem Cells." *American Journal of Translational Research*. 3(2):77-89.
- Wang Ji Long, Xiao Jiao Du, Jin Xian Yang, Song Shen, Hong Jun Li, Ying Li Luo, Shoaib Iqbal, Cong Fei Xu, Xiao Dong Ye, Jie Cao, and Jun Wang. 2018. "The Effect of Surface Poly(Ethylene Glycol) Length on in Vivo Drug Delivery Behaviors of Polymeric Nanoparticles." *Biomaterials* 182(June):104–13.

- Wang Jian, Per Sakariassen, Oleg Tsinkalovsky, Heike Immervoll, Stig Ove Bøe, Agnete Svendsen, Lars Prestegarden, Gro Røslund, Frits Thorsen, Linda Stuhr, Anders Molven, Rolf Bjerkvig, and Per Enger. 2008. "CD133 Negative Glioma Cells Form Tumors in Nude Rats and Give Rise to CD133 Positive Cells." *International Journal of Cancer*. 78(8):898-926.
- Wang L. I. N, Chunhui Liu, Feng Qiao, Mingjun Li, H. U. A. Xin, Naifeng Chen, Y. A. N. Wu, and Junxing Liu. 2021. "Analysis of the Cytotoxic Effects , Cellular Uptake and Cellular Distribution of Paclitaxel - Loaded Nanoparticles in Glioblastoma Cells in Vitro." 32(8): 1-10.
- Wang Qin, Xu Li, Yu Zhu, and Ping Yang. 2014. "MicroRNA-16 Suppresses Epithelial-Mesenchymal Transition-Related Gene Expression in Human Glioma." *Molecular Medicine Reports*. 56(7):456-467.
- Wang Weikang, Yi Quan, Qibin Fu, Yu Liu, Ying Liang, Jingwen Wu, Gen Yang, Chunxiong Luo, Qi Ouyang, and Yugang Wang. 2014. "Dynamics between Cancer Cell Subpopulations Reveals a Model Coordinating with Both Hierarchical and Stochastic Concepts." *PLoS ONE*. 9(1):e84567.
- Wick Wolfgang, Thierry Gorlia, Martin Bendszus, Martin Taphoorn, Felix Sahm, Inga Harting, Alba A. Brandes, Walter Taal, Julien Domont, Ahmed Idbaih, Mario Campone, Paul M. Clement, Roger Stupp, Michel Fabbro, Emilie Le Rhun, Francois Dubois, Michael Weller, Andreas von Deimling, Vassilis Golfinopoulos, Jacoline C. Bromberg, Michael Platten, Martin Klein, and Martin J. van den Bent. 2017. "Lomustine and Bevacizumab in Progressive Glioblastoma." *New England Journal of Medicine*. 334(6):987-996.
- Wickström Malin, Cecilia Dyberg, Jelena Milosevic, Christer Einvik, Raul Calero, Baldur Sveinbjörnsson, Emma Sandén, Anna Darabi, Peter Siesjö, Marcel Kool, Per Kogner, Ninib Baryawno, and John Inge Johnsen. 2015. "Wnt/β-Catenin Pathway Regulates MGMT Gene Expression in Cancer and Inhibition of Wnt Signalling Prevents Chemoresistance." *Nature Communications*. 25;6:8904.
- Wijaya Juwina, Yu Fukuda, and John D. Schuetz. 2017. "Obstacles to Brain Tumor Therapy: Key ABC Transporters." *International Journal of Molecular Sciences*. 67(78):76-98.
- Williams Bret R, Olga K. Mirzoeva, William F. Morgan, Junyu Lin, Wesley Dunnick, and John H. J. Petrini. 2002. "A Murine Model of Nijmegen Breakage Syndrome." *Current Biology*. 16;12(8):648-53.
- Wiwatthanapatapee Rueedeekorn, Begoña Carreño-Gómez, Navid Malik, and Ruth Duncan. 2000. "Anionic PAMAM Dendrimers Rapidly Cross Adult Rat Intestine in Vitro: A Potential Oral Delivery System?" *Pharmaceutical Research*. 32(3):67-98.

- Wojtowicz Karolina, Radoslaw Januchowski, Michal Nowicki, and Maciej Zabel. 2017. "VPARP Adjusts MVP Expression in Drug-Resistant Cell Lines in Conjunction with MDR Proteins." *Anticancer Research*. 76(2):99-119.
- Woo Seon Rang, Yunhee Ham, Wonyoung Kang, Heekyoung Yang, Sujong Kim, Juyoun Jin, Kyeung Min Joo, and Do Hyun Nam. 2014. "KML001, a Telomere-Targeting Drug, Sensitizes Glioblastoma Cells to Temozolomide Chemotherapy and Radiotherapy through DNA Damage and Apoptosis." *BioMed Research International*. 2014;2014:747415.
- Wu Guikai, Wen Hwa Lee, and Phang Lang Chen. 2000. "NBS1 and TRF1 Colocalize at Promyelocytic Leukemia Bodies during Late S/G2 Phases in Immortalized Telomerase-Negative Cells. Implication of NBS1 in Alternative Lengthening of Telomeres." *Journal of Biological Chemistry*. 29;275(39):30618-22.
- Wu Xin, Baoyue Ding, Jing Gao, Huanyun Wang, Wei Fan, Xiang Wang, Wei Zhang, Xiaoyu Wang, Lihua Ye, Min Zhang, Xueying Ding, Jiyong Liu, Quangang Zhu, and Shen Gao. 2011. "Second-Generation Aptamer-Conjugated PSMA-Targeted Delivery System for Prostate Cancer Therapy." *International Journal of Nanomedicine*. 2011;6:1747-56.
- Wu Yingwei, Qi Fan, Feng Zeng, Jinyu Zhu, Jian Chen, Dandan Fan, Xinwei Li, Wenjia Duan, Qinghua Guo, Zhonglian Cao, Karen Briley-Saebo, Cong Li, and Xiaofeng Tao. 2018. "Peptide-Functionalized Nanoinhibitor Restains Brain Tumor Growth by Abrogating Mesenchymal-Epithelial Transition Factor (MET) Signaling." *Nano Letters*. 67(8):88-114.
- Xiang Dongxi, Conglong Zheng, Shu Feng Zhou, Shuxi Qiao, Phuong Ha Lien Tran, Chunwen Pu, Yong Li, Lingxue Kong, Abbas Z. Kouzani, Jia Lin, Ke Liu, Lianhong Li, Sarah Shigdar, and Wei Duan. 2015. "Superior Performance of Aptamer in Tumor Penetration over Antibody: Implication of Aptamer-Based Theranostics in Solid Tumors." *Theranostics*. 2;5(10):1083-97.
- Xie You Ke, Shao Fen Huo, Gong Zhang, Fu Zhang, Zu Ping Lian, Xiong Lin Tang, and Chuan Jin. 2012. "CDA-2 Induces Cell Differentiation through Suppressing Twist/SLUG Signaling via MiR-124 in Glioma." *Journal of Neuro-Oncology*. 110(2):179-86.
- Xu Bo, Chuanwu Jiang, Hongxing Han, Hong Liu, Ming Tang, Longxi Liu, Wenyan Ji, Xuechao Lu, Xiuli Yang, Yunxu Zhang, and Yongji Liu. 2015. "Icaritin Inhibits the Invasion and Epithelial-to-Mesenchymal Transition of Glioblastoma Cells by Targeting EMMPRIN via PTEN/AKt/HIF-1 α Signalling." *Clinical and Experimental Pharmacology and Physiology* 42(12):1296–1307.

- Xu Jing, He Huang, Renjun Peng, Xiping Ding, Bing Jiang, Xianrui Yuan, and Jian Xi. 2018. "MicroRNA-30a Increases the Chemosensitivity of U251 Glioblastoma Cells to Temozolomide by Directly Targeting Beclin 1 and Inhibiting Autophagy." *Experimental and Therapeutic Medicine* 15(6):4798–4804.
- Xu Wei, Peixue Ling, and Tianmin Zhang. 2013. "Polymeric Micelles, a Promising Drug Delivery System to Enhance Bioavailability of Poorly Water-Soluble Drugs." *Journal of Drug Delivery*. 2013;2013:340315.
- Xu Yin, Ivan Stamenkovic, and Qin Yu. 2010. "CD44 Attenuates Activation of the Hippo Signaling Pathway and Is a Prime Therapeutic Target for Glioblastoma." *Cancer Research*. 15;70(6):2455-64.
- Xu Yuanyuan, Ming Shen, Yiming Li, Ying Sun, Yanwei Teng, Yi Wang, and Yourong Duan. 2016a. "The Synergic Antitumor Effects of Paclitaxel and Temozolomide Co-Loaded in MPEG-PLGA Nanoparticles on Glioblastoma Cells." *Oncotarget*. 12;7(15):20890-901.
- Xu Yuanyuan, Ming Shen, Yiming Li, Ying Sun, Yanwei Teng, Yi Wang, and Yourong Duan. 2016b. "The Synergic Antitumor Effects of Paclitaxel and Temozolomide Co-Loaded in MPEG-PLGA Nanoparticles on Glioblastoma Cells." *Oncotarget*. 12;7(15):20890-901.
- Yan Yuanliang, Zhijie Xu, Shuang Dai, Long Qian, Lunquan Sun, and Zhicheng Gong. 2016. "Targeting Autophagy to Sensitive Glioma to Temozolomide Treatment." *Journal of Experimental and Clinical Cancer Research*. 32(87):234-246.
- Yang Jun, Zhuyan Shi, Ruiyuan Liu, Yanyue Wu, and Xin Zhang. 2020. "Combined-Therapeutic Strategies Synergistically Potentiate Glioblastoma Multiforme Treatment via Nanotechnology." *Theranostics*. 10(7):3223-3239.
- Yang Muh Hwa, Min Zu Wu, Shih Hwa Chiou, Po Min Chen, Shyue Yih Chang, Chung Ji Liu, Shu Chun Teng, and Kou Juey Wu. 2008. "Direct Regulation of TWIST by HIF-1 α Promotes Metastasis." *Nature Cell Biology*. 56(87):345-378.
- Yang Yi Ping, Yueh Chien, Guang Yuh Chiou, Jong Yuh Cherng, Mong Lien Wang, Wen Liang Lo, Yuh Lih Chang, Pin I. Huang, Yi Wei Chen, Yang Hsin Shih, Ming Teh Chen, and Shih Hwa Chiou. 2012. "Inhibition of Cancer Stem Cell-like Properties and Reduced Chemoradioresistance of Glioblastoma Using MicroRNA145 with Cationic Polyurethane-Short Branch PEI." *Biomaterials*. 23(45):878-965.

- Ye Fei, Yibei Zhang, Yue Liu, Kazunari Yamada, Jonathan L. Tso, Jimmy C. Menjivar, Jane Y. Tian, William H. Yong, Dörthe Schaeue, Paul S. Mischel, Timothy F. Cloughesy, Stanley F. Nelson, Linda M. Liau, William McBride, and Cho Lea Tso. 2013. "Protective Properties of Radio-Chemoresistant Glioblastoma Stem Cell Clones Are Associated with Metabolic Adaptation to Reduced Glucose Dependence." *PLoS ONE*.8(11):e87654.
- Yeh Jih Kai, Mei Hsiu Lin, and Chao Yung Wang. 2019. "Telomeres as Therapeutic Targets in Heart Disease." *JACC: Basic to Translational Science*.4(7):855-865.
- Yoon Sorah and John J. Rossi. 2018. "Aptamers: Uptake Mechanisms and Intracellular Applications." *Advanced Drug Delivery Reviews*. 134:22-35.
- Yoon Sorah, Xiwei Wu, Brian Armstrong, Nagy Habib, and John J. Rossi. 2019. "An RNA Aptamer Targeting the Receptor Tyrosine Kinase PDGFR α Induces Anti-Tumor Effects through STAT3 and P53 in Glioblastoma." *Molecular Therapy - Nucleic Acids* 14(March):131–41.
- Yu Shi cang, Yi fang Ping, Liang Yi, Zhi hua Zhou, Jian hong Chen, Xiao hong Yao, Lei Gao, Ji Ming Wang, and Xiu wu Bian. 2008. "Isolation and Characterization of Cancer Stem Cells from a Human Glioblastoma Cell Line U87." *Cancer Letters*. 28;265(1):124-34.
- Yu Zhiyun, Guifang Xie, Guangtong Zhou, Ye Cheng, Guangtao Zhang, Guangming Yao, Yong Chen, Yunqian Li, and Gang Zhao. 2015. "NVP-BEZ235, a Novel Dual PI3K-MTOR Inhibitor Displays Anti-Glioma Activity and Reduces Chemoresistance to Temozolomide in Human Glioma Cells." *Cancer Letters*. 10;367(1):58-68.
- Zadeh Gelareh, Keyvan Koushan, Lisa Pillo, Patrick Shannon, and Abhijit Guha. 2004. "Role of Ang1 and Its Interaction with VEGF-A in Astrocytomas." *Journal of Neuropathology and Experimental Neurology* 63(9):978–89.
- Zein Randa, Wissam Sharrouf, and Kim Selting. 2020. "Physical Properties of Nanoparticles That Result in Improved Cancer Targeting." *Journal of Oncology*. 45(87):878-998.
- Zhang Di, Huan Xu, Mei Na Hu, and Yi Hui Deng. 2015. "'PEG Dilemma' for Liposomes and Its Solving Approaches." *Yaoxue Xuebao*. 50(3):252-60.
- Zhang Jihong, Malcolm F.G. Stevens, and Tracey D. Bradshaw. 2011. "Temozolomide: Mechanisms of Action, Repair and Resistance." *Current Molecular Pharmacology*. 5(1):102-14.
- Zhang Lei, Hongwei Yu, Yuhui Yuan, John S. Yu, Zhenkun Lou, Yixue Xue, and Yunhui Liu. 2020. "The Necessity for Standardization of Glioma Stem Cell Culture: A Systematic Review." *Stem Cell Research and Therapy*. 23(3):99-132.

- Zhang Long, Yong Wang, Dejun Yang, Wenjuan Huang, Pengyan Hao, Sheng Feng, Dietmar Appelhans, Tinghong Zhang, and Xingjie Zan. 2019. "Shape Effect of Nanoparticles on Tumor Penetration in Monolayers versus Spheroids." *Molecular Pharmaceutics* 16(7):2902–11.
- Zhang Rui, Jian Zhao, Xu Wang, Li Li Wang, Jian Xu, and Chun Song. 2014. "PinX1 without the G-Patch Motif Suppresses Proliferation, Induces Senescence, but Does Not Inhibit Telomerase Activity in Colorectal Cancer SW480 Cells." *Oncology Reports*. 32(3):987-1005.
- Zhang Xiaoling, Vernon Mar, Wen Zhou, Lea Harrington, and Murray O. Robinson. 1999. "Telomere Shortening and Apoptosis in Telomerase-Inhibited Human Tumor Cells." *Genes and Development*. 15;13(18):2388-99.
- Zhang Xingmei, Li Peng, Zhiman Liang, Zhewen Kou, Yue Chen, Guangwei Shi, Xiaowen Li, Yanling Liang, Fang Wang, and Yusheng Shi. 2018. "Effects of Aptamer to U87-EGFRvIII Cells on the Proliferation, Radiosensitivity, and Radiotherapy of Glioblastoma Cells." *Molecular Therapy - Nucleic Acids* 10(1838):438–49.
- Zhao Mengnan, Elia Bozzato, Nicolas Joudiou, Sina Ghiassinejad, Fabienne Danhier, Bernard Gallez, and Véronique Préat. 2019. "Codelivery of Paclitaxel and Temozolomide through a Photopolymerizable Hydrogel Prevents Glioblastoma Recurrence after Surgical Resection." *Journal of Controlled Release*. 10;309:72-81.
- Zheng Nan, Jing Li, Cheng Xu, Lishi Xu, Sanming Li, and Lu Xu. 2018. "Mesoporous Silica Nanorods for Improved Oral Drug Absorption." *Artificial Cells, Nanomedicine and Biotechnology* 46(6):1132–40.
- Zhong Ze Huai, Wei Qin Jiang, Anthony J. Cesare, Axel A. Neumann, Renu Wadhwa, and Roger R. Reddel. 2007. "Disruption of Telomere Maintenance by Depletion of the MRE11/RAD50/NBS1 Complex in Cells That Use Alternative Lengthening of Telomeres." *Journal of Biological Chemistry*. 5;282(40):29314-22.
- Zhou Cefan, Hongxia Cheng, Wenyi Qin, Yi Zhang, Hui Xiong, Jing Yang, Huang Huang, Yefu Wang, Xing Zhen Chen, and Jingfeng Tang. 2017. "Pygopus2 Inhibits the Efficacy of Paclitaxel-Induced Apoptosis and Induces Multidrug Resistance in Human Glioma Cells." *Oncotarget*. 25;8(17):27915-27928.
- Zhou Gang, Olivier Latchoumanin, Mary Bagdesar, Lionel Hebbard, Wei Duan, Christopher Liddle, Jacob George, and Liang Qiao. 2017. "Aptamer-Based Therapeutic Approaches to Target Cancer Stem Cells." *Theranostics*.7(16):3948-3961.

- Zhou Gang, Sarah Da Won Bae, Romario Nguyen, Xiaoqi Huo, Shuanglin Han, Zhiqiang Zhang, Lionel Hebbard, Wei Duan, Mohammed Eslam, Christopher Liddle, Lawrence Yuen, Vincent Lam, Liang Qiao, and Jacob George. 2021. “An Aptamer-Based Drug Delivery Agent (CD133-Apt-Dox) Selectively and Effectively Kills Liver Cancer Stem-like Cells.” *Cancer Letters* 501:124–32.
- Zhou Xiao Zhen and Kun Ping Lu. 2001. “The Pin2/TRF1-Interacting Protein PinX1 Is a Potent Telomerase Inhibitor.” *Cell*. 23(8):789-923.
- Zhou Yunfei, Yan Zhou, Takashi Shingu, Li Feng, Zhao Chen, Marcia Ogasawara, Michael J. Keating, Seiji Kondo, and Peng Huang. 2011. “Metabolic Alterations in Highly Tumorigenic Glioblastoma Cells: Preference for Hypoxia and High Dependency on Glycolysis.” *Journal of Biological Chemistry*. 16;286(37):32843-53.
- Zhu Qinchang, Ge Liu, Masaaki Kai, and Alain O. A. Miller. 2015. “DNA Aptamers in the Diagnosis and Treatment of Human Diseases.” *Molecules* 20(12):20979–997.
- Zhu Xu Dong, Bernhard Küster, Matthias Mann, John H. J. Petrini, and Titia De Lange. 2000. “Cell-Cycle-Regulated Association of RAD50/MRE11/NBS1 with TRF2 and Human Telomeres.” *Nature Genetics*.76(8):654-789.
- Zuccarini Mariachiara, Patricia Giuliani, Sihana Ziberi, Marzia Carluccio, Patrizia Di Iorio, Francesco Caciagli, and Renata Ciccarelli. 2018. “The Role of Wnt Signal in Glioblastoma Development and Progression: A Possible New Pharmacological Target for the Therapy of This Tumor.” *Genes*. 9(2): 105.

BIODATA OF STUDENT

Amir Barzegar Behrooz was born on December 4, 1986 in Tehran, Iran's capital. He completed his primary education at a national school in his hometown before continuing his secondary education in Experimental Sciences at Kharazmi High School in Tehran, Iran. Following his high school graduation, he successfully passed the Iranian university entrance exam and was admitted to the Islamic Azad University – Medical Science Department in the field of Cellular and Molecular Biology from 2006 to 2011. In 2012, he passed the Master of Science entrance test after completing his bachelor's degree. He was rated 7th out of over 15,000 applicants. In 2016, he graduated from Tehran University of Medical Science with a Master in Medical Physiology and a CGPA of 17.63. Due to his strong interest in targeted cancer therapy research, he applied to continue his PhD studies in the Faculty of Biotechnology and Biomolecular Science at Universiti Putra Malaysia (UPM) in late 2017 and enrolled as a Philosophy of Doctorate nominee under the guidance of Associated Professor Amir Syahir Amir Hamzah.

LIST OF PUBLICATIONS

Barzegar Behrooz, Amir, Amir Syahir, Syahida Ahmad. CD133: beyond a cancer stem cell biomarker. *Journal of drug targeting*. Index, IF: 5.1, 2019, 27(3), 257-269.

Hassn Mesrati, Malak, **Amir Barzegar Behrooz**, Asma Y Abuhamad, Amir Syahir. Understanding Glioblastoma Biomarkers: Knocking a Mountain with a Hammer. *Cells*. Index, IF:6.5, 2020, (2073-4409), 9(5).

Barzegar Behrooz, Amir, Amir Syahir. Could We Address the Interplay Between CD133, Wnt/β-Catenin, and TERT Signaling Pathways as a Potential Target for Glioblastoma Therapy? *Frontiers in Oncology*. Index, IF:6.2, 2021, 11, 1049.

Barzegar Behrooz, Amir, Reza Vazifehmand, Asilah Ahmad Tajudin, Mas Jaffri Masarudin, Zamberi Sekawi, Amir Syahir. Tailoring drug co-delivery nanosystem for mitigating U-87 stem cells drug resistance. *Drug Delivery and Translational research*. Index, IF:4.6, 2021, 16, 1-17.