Advances in Biology & Earth Sciences
Vol.9, Special Issue, 2024, pp.11-34
https://doi.org/10.62476/abes9s11

CANCER SIGNALING, CELL/GENE THERAPY, DIAGNOSIS AND ROLE OF NANOBIOMATERIALS

Gvozden Rosic[1*], Dragica Selakovic[1], Sabina Omarova[2]

[1]Department of Physiology, Faculty of Medical Sciences, University of Kragujevac, Serbia
[2]Faculty of Biophysics and Biochemistry, Baku State University, Baku, Azerbaijan

Abstract. An important characteristic of cancer is aberrant metabolism. Drug resistance, cancer stem cells, metastasis and tumorigenesis are all significantly impacted by abnormal cancer metabolism, which includes enhanced anabolic pathways and aerobic glycolysis. The Hippo pathway, Myc and PI3K/AKT are recognized oncogenic signaling networks that control the expression of metabolic genes and increase the level of activity of metabolic enzymes. On the other hand, abnormal metabolic pathways result in disruptions to the internal signal transduction pathways of cells, providing energy, building blocks and redox capabilities necessary for uncontrolled cancer cell proliferation. Studies and clinical trials are being carried out to investigate the impact of minute substances or dietary modifications, such as calorie restriction, fasting and intermittent fasting, on the inhibition of metabolic enzymes. The metabolic phenotypes of malignancies are remarkably diverse, much like genetic variability. Genetic abnormalities and a variety of signals found in the tumor microenvironment contribute to this variability. Therefore, one of the main objectives of contemporary cancer therapies is to overcome metabolic plasticity. This overview explains the relationships between biochemical and pathways of signaling and emphasizes recent research on the metabolic properties of cancer. We also present fresh justifications for the upcoming class of medications that target cancer metabolism. This is an overview of our latest studies on the progress of nanomedicine and disease detection at the tiny level of nano-bio interactions between biological systems and nanoparticles. Significant progress in the field of nanomedicine has been accomplished in the last 20 years. However, the absence of a thorough knowledge of nano-bio interactions in the clinical situation makes it difficult to significantly improve overall patient survival with nanomedicine.

Keywords: *Nanomedicine, drug delivery, cancer, cancer metabolism, cell signaling, drug development.*

[*]***Corresponding Author:*** *Gvozden Rosic, Department of Physiology, Faculty of Medical Sciences, University of Kragujevac, Serbia, e-mail: grosic@fmn.kg.ac.rs*

Received: *23 January 2024;* ***Accepted:*** *16 March 2024;* ***Published:*** *8 April 2024.*

1. Introduction

Tumors must have unchecked, unending growth as a fundamental feature. As a result, current research emphasizes how cancer cells vary from normal cells in their metabolic processes. Otto Warburg discovered in the 1920s that cancer cells, in contrast to normal cells, had defective respiration pathways, particularly in the mitochondria. Consequently, oxidative phosphorylation can not be used by cancer cells (OXPHOS). Rather, they use glycolysis to produce ATP (Warburg *et al*., 1927). They rely heavily on glycolysis even in conditions with plenty of oxygen (i.e., aerobic glycolysis). Recent research, however, contends that cancer cells' mitochondria are still functional and

How to cite (APA):
Rosic, G., Selakovic, D. & Omarova, S. (2024). Cancer signaling, cell/gene therapy, diagnosis and role of nanobiomaterials. *Advances in Biology & Earth Sciences, 9*(Special Issue), 11-34 https://doi.org/10.62476/abes9s11

capable of generating energy via OXPHOS (Moreno-Sánchez *et al*., 2007; Welberg *et al*., 2014). OXPHOS can provide adequate building blocks for growth, however some tumor forms have evolved to hypoxic tumor surroundings and still depend on aerobic glycolysis (Hay, 2016). Tumors are the result of oncogene and tumor suppressor gene mutations. The expression of metabolic enzymes and their functionality are directly regulated by these genetic alterations. For instance, in cancer cells, TP53 controls lipid metabolism while c-MYC stimulates glutamine absorption (Wise *et al*., 2013; Sanchez-Macedo *et al*., 2007). Cancer cells' aberrant metabolism is more than just a result of a genetic mutation. Additionally, it has a direct impact on cellular responses and tumor signal transduction pathways. The notion underlies the targeting of cancer-specific metabolic abnormalities by next-generation anticancer treatments, which have been the subject of several studies and clinical trials. We go over the abnormal metabolic phenotypes of malignancies and how they contribute to the growth of tumors in this overview.

Our goal is to identify possible therapeutic targets for novel nanobiomaterial-based anticancer medicines by examining the interplay between metabolism and signaling networks. In this overview, we highlight the most recent developments in cancer therapies and go over the many approaches and tactics for dealing with the issues related to tumor therapy and resistance. The benefits and drawbacks of the numerous anticancer medication delivery methods, such as stimuli-responsive systems and inorganic nanoparticles, have been thoroughly discussed.

2. Signal Pathways

Research has revealed important connections between aberrant metabolic phenoty pes and oncogenic signaling. Oncogene and tumor suppressor mutations can either directly regulate the transcription of enzymes involved in metabolism or by controlling regulatory elements including feedback loops and post-translational modifiers (PTM), they can indirectly control the activity of enzymes. Cancer cells possess metabolic flexibility, which enables them to adjust to settings of acute metabolic stress, thanks to the complex relationships that exist between signaling and metabolism.

2.1. LKB1/AMPK Pathway

A well-preserved energy-sensing kinase is AMPK. AMPK stimulates catabolic cellular processes while blocking anabolic pathways. Therefore, under situations of cellular energy stress, cells may tolerate AMPK activity. In contrast to other metabolic proteins, AMPK is not regulated by other metabolic intermediates; instead, it is reliant on the amounts of AMP and ADP in the cell. AMP interaction is elicited by increases in AMP/ATP ratios and AMPK conformational changes follow. Thus, upstream kinases can phosphorylate the AMPK alpha subunit through AMPK conformational shift driven by cellular energy stress (Gowans *et al*., 2013; Hawley *et al*., 1996).

Cellular calcium levels and growth factor-mediated GPCR activation both affect AMPK. When under energy stress, the upstream kinase LKB1 phosphorylates the AMPK alpha subunit, while CAMKK does the same when it detects calcium concentrations (Shaw *et al*., 2004; Hawley *et al*., 2005). In the setting of cancer, stressors such energy deprivation, hypoxia and starvation trigger AMPK, which confers characteristics of stress tolerance in certain cancers (Dasgupta *et al*., 2016).

It is yet unknown if AMPK is a tumor-suppressive or carcinogenic protein. AICAR and the type 2 diabetes medication metformin are examples of AMPK activators that are utilized in clinical settings to prevent the growth of cancer cells (Guo *et al*., 2009; Dowling *et al*., 2007). The mechanism behind its anti-proliferative action is crosstalk between the mTOR and Hippo pathways. AMPK phosphorylates YAP directly or via LATS kinase to suppress YAP-TEAD interactions in a nutrient-poor environment. By directly phosphorylating TSC2 and RAPTOR, AMPK suppresses mTORC1, a crucial regulator of the protein translation machinery (Inoki *et al*., 2003; Gwinn *et al*., 2007). AMPK, however, also promotes anoikis resistance, migration and metastasis, which makes it an oncogenic protein. For example, AMPK promotes cell motility and metastasis in prostate cancer and enhances cell survival by activating the androgen receptor-CAMKK axis. By inhibiting mTORC1, AMPK also imparts resistance to anoikis (Park *et al*., 2009; Frigo *et al*., 2010; Leprivier *et al*., 2011).

2.2. PI3K-AKT/mTOR Pathway

External growth factors carefully control anabolic metabolism and cell division in normal cells (e.g., hormones and insulin). AKT and mTOR signal transduction pathways, among others, are triggered to result in mitogen-induced cell cycle advancement. GPCR signaling and receptor tyrosine kinases (RTKs) both stimulate the PI3K-AKT pathway. PIP2 becomes PIP3 when PI3K phosphorylates it in response to activation of RTKs or GPCRs. On the other hand, PTEN, A protein known as a tumor suppressor dephosphorylates PIP3 to PIP2, which prevents PI3K/AKT communication. Mutations with gain-of-function in PI3K and mutations that cause loss of function in PTEN are seen in a wide variety of cancer types (Hoxhaj *et al*., 2019). Once it has accumulated, PIP3 binds to AKT by phosphorylating it through PDK1 and mTORC2 (Alessi *et al*., 1997; Sarbassov *et al*., 2005).

The balance between active and inactive AKT controls the growth of cells, changes in metabolism and the development of tumors. Interestingly, AKT suppresses TSC2's phosphorylation, which raises mTORC1 activity and suppresses RHEB GTPase. mTORC1 activates the cell's protein translation machinery by phosphorylating ribosomal S6K and 4E-BP1 (Thoreen *et al*., 2012).

ElF4B-elF4A heterodimerization initiates translation by unwinding the secondary domains of mRNAs upon phosphorylation (Csibi *et al*., 2014; Thoreen *et al*., 2012; Raught *et al*., 2014).

A better translation initiation complex accessibility to the 5′ region of mRNAs is achieved through 4E-BP phosphorylation, which also dissociates 4E-BP from elF4E (Ma & Blenis, 2009). Mitogen-activated AKT, thus, promotes protein synthesis through mTORC1. Enzyme metabolism is regulated by PI3K/AKT signaling. AKT phosphorylates GSK3 to block the glycogen production pathway when it is activated by insulin (Hermida *et al*., 2012). PI3K/AKT is therefore a crucial signal transduction pathway in the cellular uptake of glucose. Directly and indirectly, through post-translational changes (phosphorylation and methylation) of metabolic enzymes, PI3K/AKT upregulates glycolysis. For example, by phosphorylating and engaging the AS160 protein, AKT improves GLUT membrane trafficking (Mîinea *et al*., 2005; Sano *et al*., 2003; Eguez *et al*., 2005).

By preventing endocytosis, AKT increases the production of GLUT1/4 membranes and directly inhibits TXNIP through inhibitory phosphorylation (Waldhart *et al*., 2005). Moreover, AKT makes glycolytic enzymes like PFK1 and HK2 more

efficient. By promoting HK2's mitochondrial integration, AKT phosphorylates and activates HK2 (Roberts *et al*., 2013; Gottlob *et al*., 2001). AKT increases the activity of PFK1, which is regulated by fructose-2,6-bisphosphate (F-2,6-BP). AKT increases the productivity of glycolysis by phosphorylating PFKFB, which catalyzes the reduction of fructose-6-phosphate to F-2,6-BP (Deprez *et al*., 1997). Glycolysis is further enhanced by AKT signaling through the transcription factor HIF-1α. Certain glycolytic components, such as GLUT, are activated by HIF-1. HIF-1 activates LDH, which promotes lactate production and aerobic glycolysis (Semenza, 2003).

2.3. p53 Pathway

One of the most renowned genes for tumor suppression, p53 regulates a range of cellular activities including as metabolism, progression of cell cycles and apoptosis. Phosphorus-regulated protein (p53) is activated in response to cellular stressors such DNA damage and hunger. Depending on the kinds and degrees of the stresses, it decides whether adaptation or cell death takes place (Kruiswijk *et al*., 2015). Three different levels of modulation affect p53: transcription, translation and post-translation. E3 ligase MDM2 controls the stability of p53 (Haupt *et al*., 1997; Kubbutat *et al*., 1997). Under energy stress, AMPK phosphorylates, acetylates and subsequently stabilizes p53. In order to preserve homeostasis, p53 creates a negative feedback loop by upregulating MDM2 to encourage p53 degradation. Research has revealed that p53 stops the cell cycle in order to fix damage to DNA before allowing the cell to proliferate again. (Lakin *et al*., 2007). Additionally, angiogenesis, carcinogenesis and the metabolic reprogramming of different malignancies are all inhibited by p53 (Kruiswijk *et al*., 2015).

OXPHOS and fatty acid oxidation (FAO) are two examples of the mitochondrial catabolic processes that are upregulated whereas aerobic glycolysis is decreased by p53. The expression of GLUT1 and GLUT4 is transcriptionally repressed by p53. Also, it suppresses PFK1, the enzyme that controls the rate of glycolysis, by lowering its allosteric activator fructose-2,6-bisphosphate and raises the TP53-inducible glycolysis and death regulator (TIGAR). (F-2,6-BP). By inhibiting LDH and activating pyruvate dehydrogenase (PDH), p53 raises TCA cycle inflow (Contractor & Harris, 2011). Furthermore, HK and glucose-6-phosphate isomerase are among the glycolytic enzymes that are indirectly inhibited by miR-34a (Kruiswijk *et al*., 2015).

2.4. Hippo Pathway

The MAPK family, transcriptional coactivators YAP and TAZ, Ste20like kinase (MST) 1/2 and the big cancer suppressing kinase (LATS) 1/2 core kinases comprise the Hippo pathway, which regulates cell proliferation, organ size and tissue homeostasis. (Harvey *et al*., 2003; Jia *et al*., 2003; Justice *et al*., 1995; Pantalacci *et al*., 2003; Tapon *et al*., 2002; Udan *et al*., 2003). Upon activation of the route, phosphorylation and activation of MST1/2 and LATS1/2 occur, leading to the phosphorylation of YAP/TAZ by upstream signals. Consequently, E3 ligase β TRCP degrades YAP/TAZ once they are trapped in the cytoplasm by 14-3-3 proteins (Zhao *et al*., 2007; 2010; Liu *et al*., 2010).

Numerous cancer forms have overactive YAP/TAZ activity (Moon *et al*., 2018; Park *et al*., 2018).

The hippocampal pathway is influenced by numerous other types of upstream regulators, including cell-to-cell contact, mechanical inputs from the environment, Wnt signaling, G protein-coupled receptor (GPCR)–ligand relationships and various types of cellular stress. On the other hand, upon deactivating Hippo signaling, YAP/TAZ translocate into the nucleus where they attach to transcription factors known as transcriptional enhanced associate domains (TEAD) to cause the activation of carcinogenic target genes.

Numerous metabolic processes are impacted by the Hippo pathway, a master regulator of cell proliferation. YAP/TAZ activity raises glycolysis by directly and indirectly increasing the activity of glycolytic enzymes. Specifically, YAP/TAZ activity stimulates FOXC2 to express HK2 and TEAD to express GLUT3. YAP/TAZ also increases the expression of the LncRNA BCAR4 and upregulates HK2 and PFKFB3 through Hedgehog signaling (Zheng *et al*., 2017). Furthermore, by increasing the level of expression of the glutamine transports SLC1A5 and SLC7A5 in cancerous breast cells, YAP/TAZ enhances glutamine metabolism. YAP/TAZ and TEAD boost the metabolism of glutamine and amino acids via expressing amino acid transporters (Park *et al*., 2015). YAP/TAZ promote the expression of glutaminase and transaminase, specifically GOT1 and PSAT1, resulting in the production of TCA cycle intermediates and NEAAs (Yang *et al*., 2018; Bertero *et al*., 2016). YAP/TAZ increases the ability of cancer cells to spread by accumulating lipids and directly modifying bile acid components (Lee *et al*., 2019).

Nutrient concentrations control both cell growth and cell cycle advancement. The Hippo pathway is greatly affected by metabolic circumstances. YAP/TAZ activity is significantly impacted by glucose metabolism. High blood sugar raises the flow of glucose to the HSP, which generates the glycosylating enzyme UDP-GlcNAc. Therefore, a high glucose environment causes YAP O-GlcNAcylation and disrupts the connection between LATS and βTrCP, which raises YAP/TAZ activity. O-GlcNAcylation causes YAP to become hyperactivated in liver and pancreatic tumors (Peng *et al*., 2017; Zhang *et al*., 2017). By interfering with the connection between LATS2 and MOB1 in breast cancer, glycosylation of LATS2 reduces its activity (Kim *et al*., 2020).

On the other hand, YAP/TAZ activity is inhibited by energy stress brought on by glucose deprivation through both Hippo-dependent and -independent processes. When ATP levels drop, the energy sensor AMPK is triggered. The YAP-TEAD interaction is prevented by AMPK's direct phosphorylation of YAP at serine 61 and serine 94 (Kim *et al*., 2020; Deran *et al*., 2014). Through AMOTL1 phosphorylation and activation, AMPK suppresses YAP indirectly (Deran *et al*., 2014). The Hippo pathway can be regulated by amounts of external hormones. GPCRs allow lipid hormones to block the pathway, such as sphingosine 1-phosphate and lysophosphatidic acid (Yu *et al*., 2013). The Hippo pathway is triggered by the peptide hormone glucagon, which raises blood glucose levels by activating PKA and cAMP (Miller *et al*., 2012; Yu *et al*., 2013). Hippo pathway kinases can also be regulated by subcellular lipid constituents. The Hippo pathway is upstream regulated by SREBP. The mevalonate pathway increases RhoA GTPase's geranylgeranylation when SREBP is engaged. RhoA is in charge of the F-actin cytoskeleton since F-actin is an established LATS kinase downstream factor. Consequently, via blocking LATS, elevated metabolism of fatty acids in cancer cells irregularly activates RhoA and increases YAP/TAZ activity (Mi *et al*., 2014; Sorrentino *et al*., 2014). It is noteworthy that YAP suppression has been demonstrated to enhance

tumor regulatory effects and that TAZ and YAP have a low prevalence in malignancies that are hematologic (Cottini *et al*., 2014; Donato *et al*., 2018). In blood malignancies such as leukemia and lymphoma, it would be crucial to elucidate the aberrant metabolic changes caused by the Hippo-YAP pathway.

3. Nanoparticles for Drug Delivery

Tumor vasculature has distinct pathophysiological characteristics, including a high percentage of rapidly angiogenizing endothelial cells. Tumor tissues grow quickly, which leads to abnormalities in cell architecture such deformed basement membranes, a rise in cell curvature and a deficiency of neovascular outer membrane cells. The accumulation of nanoparticles (NPs) that permeate tumor tissues through tumor capillary "gaps" and poor lymphatic reflux is encouraged by these abnormalities, which together result in the "enhanced permeation and retention (EPR) effect" (Jain *et al*., 2001; Gao *et al*., 2012; Liu & Lu, 2012). Passive targeting, a crucial method for the tumor accumulation of potential nanocarriers, is based on the EPR effect (Matsumura *et al*., 1986; Maeda *et al*., 2000).

Particle size has a significant impact on how nanomedicine functions within the body. For example, because of their hydrophilic nature, NPs smaller than 5 nm are amenable to rapid renal filtration. On the other hand, particles larger than 200 nm tend to accumulate quickly in organs that are in good condition or are quickly taken up by macrophages. Nanocarriers, which have particle sizes ranging from 5 to 250 nm, can accumulate over time owing to inadequate lymphatic drainage in tumor tissues. They do this by infiltrating leaky tumor capillaries and raising the total quantity of Myc protein in cells, chromatin accessibility and Myc transcriptional activity (Matsumura *et al*., 1986; Maeda *et al*., 2000). Protein photochemical changes and cellular capacity for absorption are influenced by two crucial surface properties: charge and hydrophobicity.

Hydrophobic and highly charged particles have longer in vivo circulation half-lives and higher non-specific internalization rates than neutral or oppositely charged and hydrophilic particles (Radomski *et al*., 2005; Albanese *et al*., 2012). Enough stability, another important factor influencing how long NPs circulate, is necessary for effective tumor targeting. According to studies, stable NPs frequently leak drugs before they reach their target (Letchford *et al*., 2012; Rijcken *et al*., 2007; Talelli *et al*., 2015).

This premature drug release has a big influence on how well tumors are targeted. Tumor biology, which includes elements like the degree of vascular and lymphatic vessel formation, perivascular tumor invasion and intra-tumor pressure, determines how effective passive targeting is. The effectiveness of passive nanomedicine targeting is determined by these factors as well as the physicochemical characteristics of NPs. Furthermore, targeting effectiveness is highly dependent on blood circulation time (Wen *et al*., 2023). In fact, vascular barriers that kinetically slow down transportation of systemically given nanomaterials used for drug delivery systems require a substantially longer circulation period in order to enhance the possibility of passing through the vascular wall. A significant obstacle to extended blood circulation is the reticuloendothelial system's quick clearance of nanomedicine (RES). Steric stabilizing methods like PEGylation have been developed to address this problem. This technique delays RES clearance and prolongs circulation by taking use of the steric repulsion principle. For instance, the field of nanotechnology uses PEG to produce "stealth" drug carriers that allow for longer circulation durations as well as a reduction in the

mononuclear phagocyte system (MPS) identification and clearance. PEG is now included in the majority of nanomedicines that are authorized for clinical use and it has played a key role in recent developments, including the two mRNA-based COVID-19 vaccines that are administered via PEGylated lipid nanoparticles (Shi *et al*., 2022).

Nanomedicine's cell targeting field is fast developing, as it is an integral subtype of active targeting. If certain cells, such those of the immune system, cancer or even stem cells, are specifically targeted during treatment, a number of illnesses may respond more favorably (Belfiore *et al*., 2018) NPs with specific ligands that can identify and bind to receptors specific to the target cells must be made in order to use this strategy (Mukwaya *et al*., 1998). An integral component of this strategy is the ligand-mediated recognition of the target component receptor (Gavas *et al*., 2021).

Receptor-mediated endocytosis can force NP to internalize after initiating intramembrane folding through interactions between the ligand and targeted.

When endogenous particles internalize, they are transported to the nuclear endosome where they undergo additional processing and release medicine. Because of its cell-specific delivery mechanism, the drugs are guaranteed to affect the cells of interest preferentially, potentially improving treatment outcomes and reducing side effects. Numerous researches indicate that cell targeting may be feasible and show a notable rise in NP absorption by cells in vitro. As an example, anti-HER2 monoclonal antibody-treated actively focused magnetic nanoparticles (NPs) produced tumor tissue concentrations 10–30 times higher than non-targeted NPs (Fiandra *et al*., 2013). Similar results were seen for tiny carriers loaded with cisplatin and layered double hydroxides amended with folic acid (Park *et al*., 2016; Jine *et al*., 2016).

Targeting cancer cells and the cells that line tumor blood arteries (angiogenic endothelial cells, for example) can reduce the blood delivery to cancer cells, leading to hypoxia and necrosis. Furthermore, the efficiency of nanocarriers containing conventional chemotherapeutic drugs can be improved by this method. However, the NPs used for cell targeting must fulfill the conditions for passive targeting, such as having a steady, long-lasting blood flow, a suitable particle size and efficient drug retention (Arranja *et al*., 2017). Cell targeting is not without its difficulties, though. The intricacy of biological systems presents formidable obstacles. Proteins are drawn to the surfaces of nanocarriers when they are injected into biological fluids, creating an adsorption layer known as the protein corona (Xiao *et al*., 2022). This protein layer modifies the physicochemical characteristics of nanocarriers, which in turn affects their biological behavior and eventually determines their fate in vivo. The pharmacokinetics, toxicity, targeting ability and stability of nanocarriers are all greatly impacted by this process. Thus, a critical factor in the physiological activity of nanoparticles is the characterization of the protein that comprise the corona (Xiao *et al*., 2022).

3.1. Drug Release

After being ingested, the nanomedicine is delivered to the nuclear endosome, where it undergoes additional processing and is released. At the point where the nanocarrier breaks down or disintegrates, the drug that has been enclosed is released. Active release mechanisms are triggered by specific triggers within the cell or TME, whereas passive release mechanisms depend on the drug's diffusion or breakdown. A number of pertinent research in the field of stimuli-responsive nanomedicine should be taken into consideration, in addition to the conclusions previously presented in our work. Stimuli-responsive nanomedicines are a novel way to improve the efficiency of

drug delivery. They work by reacting to certain physical or biological stimuli and then controlling the amount, timing and location of drug release patterns (Mura *et al*., 2013).

The release of medications contained in nanoparticles (NPs) can be triggered by both internal and external stimuli, including as pH, redox processes, light, magnetic fields, temperature and ultrasound (Lu *et al*., 2016). According to Mura et al. (2013), these methods can improve targeted medicine delivery to ill areas and regulate drug biodistribution. This contributes to the resolution of non-specific biodistribution of cells and tissues, which frequently alters the effectiveness of treatment. These nanoreactors are inactive in healthy tissues, but they activate in the presence of an acidic TME. This leads to the generation of reactive species, which oxidatively stress cells and reduce their antioxidant capacity. Ultimately, this leads to synergistic tumor ablation (Li *et al*., 2017).

Thermoresponsive liposomes were investigated in a research to improve their anti-cancer effectiveness (Shah *et al*., 2023).

In accordance with the increasing temperature at tumor locations, they noticed that thermoresponsive liposomes loaded with cisplatin exhibited more cytotoxicity at higher temperatures. Recent work (Afzalipour *et al*., 2021) has created a technique that greatly suppresses tumor development and increases survival rates by combining an alternating magnetic field with magnetic nanoparticles coated with temozolomide. Furthermore, substantial advancements in the treatment of cancer have been demonstrated by studies on pH-responsive nanoparticles. pH-responsive nanovesicles have been shown to be effective in drug administration, particularly when loaded with doxorubicin, which has been shown to have strong anti-cancer effects in both in vitro and in vivo settings by and A kind of colloidal nanocarrier called niosomes has a pH sensitivity that may be modulated by surfactants, as Marianecci et al. have out. Moreover, Li et al. (2017) have built the novel ROS-responsive nanomedicine platform (Swetha *et al*., 2023; Di Francesco *et al*., 2017; Marianecci *et al*., 2016; Li *et al*., 2016).

The need for effective treatment options is driven by the rise in cancer cases worldwide. The therapeutic potential of immunity cell-derived nanomedicine, specifically macrophage-derived nanomedicine, has been shown by recent studies. Since these nanovesicles originate from immune system cells that readily recognize and kill tumor cells, they have inherent long-circulation qualities and a natural affinity for cancer tissues (Barone *et al*., 2022; Yan *et al*., 2023).

To fully use these nanovesicles' therapeutic potential, a variety of tactics have been used. Extracellular vesicles (EVs) produced from macrophages, for example, have been found to be essential in the TME mostly due to their capacity to transfer proteins and nucleic acids across cells and organs (Barone *et al*., 2022).

Nevertheless, there are drawbacks to EVs as well, including limited yield, inadequate targeting and very inefficient components, all of which may be lessened with engineering (Yan *et al*., 2023). GBM was given a new lease of life when extracellular vesicles (M1EVs) generated from M1-like macrophages developed. Chemiexcited photodynamic treatment (CDT) and hypoxia-activated chemotherapy were two goals synergistically achieved by functionalizing M1EVs, which were engineered to overcome several challenges (Wang *et al*., 2022).

This suggests that immune cell-derived nanovesicles could be used for customized, multimodal therapy. The possibility that EV-based systems could improve the effectiveness of RNA disruption therapies is raised by additional data that combining the characteristics of EVs and the liposomes to generate hybrid NPs boosts

siRNA dispersion for particular cells (Evers *et al*., 2022). Previous results indicate that immune cell-generated nanovesicles, particularly those derived from macrophages, can be used to create effective, personalized anti-cancer nanomedicines. To improve engineering techniques for treatment of cancer, future research should focus on increasing the ability to select and potency of these nanovesicles. The application of folate-targeted nanotechnology in active targeting is a successful illustration of an engaged targeting technique. Since folate is overexpressed on the surface of many tumor cells, folate is a perfect ligand for changing nanocarriers to make them more attractive to tumor cells (Lin *et al*., 2020; Paolino *et al*., 2012). Folate-targeted nanosystems have shown promise in anti-cancer applications, as numerous studies have shown.

3.2. Application of nanomedicine in treatments of cancer

The exceptional qualities and capabilities of nanomaterials have aided in the advancement of research on tumor therapy. Liposomes, micelles made of polymers (PMs), dendrimers in quantum dots (QDs), nanotubes made of carbon (CNTs), mesoporous nanoparticles made of silica (MSNs), metallic/magnetic nanoparticles and quantum dots (QDs) are only a few of the nanomaterials that are showing promise as novel cancer therapies (NPs). These fascinating nanomaterials offer customized drug delivery, controlled release, improved stability and increased penetration into tumor tissues. They also make tailored medication, photothermal therapy and multimodal imaging possible. As such, the field of nanomedicine presents a great opportunity to advance the development of tumor medicines and tackle the challenges related to traditional cancer treatments. In the parts that follow, we will go into the precise roles that nanocrystals play in several elements of cancer treatment, like chemotherapy and surgery.

3.2.1. Surgery

In contrast to traditional surgery, which frequently involves the removal of sick tissues and may endanger nearby healthy ones, nanomaterials provide an invaluable tool for quick and effective hemostasis, enhancing patient protection during surgical operations. Furthermore, tiny cancers pose a serious barrier to the efficiency of surgery since they are frequently impossible to detect with the human eye. On the other hand, nanotechnology can be used to map sentinel lymph nodes, efficiently mark remaining tumor cells and micrometastases and highlight tumor borders and surrounding essential structures.

This offers helpful advice for tumor excision and significantly raises the detection resolution. Image-guided an operation (IGS) for metastatic ovarian cancer was considerably improved, for example, by Zhang et al.'s studies on the in vivo generation of NIR-II-emitting NPs that used lanthanide-doped NaGdF4. Moreover, Moritz et al. designed CLIO-Cy5.5, a dual-purpose nanoparticle that serves as both an MRI contrast compound and an in the near-in fluorescence optical probe (Kircher *et al*., 2003) and has been shown to be useful in defining the margins of orthotopic malignancies in hosts. Beyond these advantages, NPs have also been used to increase the effectiveness of cryosurgery by controlling the freezing range, guiding the production of ice balls and improving the freezing temperature distribution, all of which lessen the risk of injury to nearby healthy tissues (Hou *et al*., 2018). Recent research indicates that the addition of

magnesium oxide nanoparticles to tumor cells greatly enhanced their thermal conductivity, improving the freezing effect (Deng *et al*., 2005)

3.2.2. Chemotherapy

Chemotherapy with conventional methods is commonly utilized, however it can cause discomfort to patients since it damages tissue that is healthy in addition to the tumor. Its rapid excretion from the body means that it must be administered often and may lead to drug resistance, both of which decrease the likelihood of patient survival (Sivak *et al*., 2017). NPs, on the other hand, may be designed to stick to cancer cells specifically and to gather at the tumor site. This would provide a very effective, low-toxicity treatment strategy that can defeat tumor drug resistance.

Targeted drug delivery and localized drug release can be accomplished by NPs through the use of TME properties such as pH, redox fluctuations, enzyme activity, hypoxia, or particular cell surface receptors (Zhang *et al*., 2023). The preferential binding of desialylated glycoprotein receptors to hepatocellular carcinoma cells has been demonstrated by mesoporous silicon nanoparticles (NPs) infused with lactic acid, which may provide an alternative to non-specific chemotherapy treatments. To optimize therapeutic efficacy, nanocarriers can also carry many drugs at once, regardless of their specific properties. In contrast to (Sivak *et al*., 2017) who reported a forming itself, nanocapsule structure for simultaneous drug administration, (Lin *et al*., 2016) developed a method to treat brain cancers with vincristine and chemotherapy in tandem. These combination methods, which take into account all of vincristine's various processes (including anti-angiogenesis, TME modulation and apoptotic induction), often result in improved

3.2.3. Immunotherapy

Even with all of the potential that cancer immunotherapies have, only around 10 percent of patients show meaningful benefits. Combining immunotherapy and nanotechnology may offer new approaches to overcome this obstacle. NPs have shown promise in improving tumor immunotherapy through TME modulation to promote anti-tumor immune responses and tumor vaccination effectiveness enhancement. For example, co-delivery of adjuvants and antigens is made possible by nanoparticle-based vaccinations or “nano vaccines”, which overcome the drawbacks of traditional cancer vaccines. Antigen-presenting cells (APCs) have been shown to respond better to antigen delivery and to be activated. Tumor immunotherapy has also shown promise for novel nanoparticle-based medications, especially those that include metals like iron, zinc and copper. Iron nanoparticles, for example, can trigger a potent adaptive immune response and induce death in tumor cells by eliciting Fenton reactions. It has been discovered that zinc nanoparticles cause immunogenic cell death, which stimulates the systemic immune response. Adjuvants such as copper nanoparticles (NPs) have been used in cancer vaccines to enhance dendritic cell maturation and antigen presentation. Combination therapy employing nanotechnologies in medicine as a basis further offers the synergistic approach of co-delivering immune modulators or chemotherapy medications with PD-1/PD-L1 inhibitors to prevent tumor immune evasion. Combining nanomedicine with immunotherapy may therefore provide novel and efficient ways to boost the immune system's defenses against cancer.

3.2.4. Radiotherapy

High-energy X-rays are used in radiotherapy, a common clinical cancer treatment, to kill cancer cells that divide quickly and stop tumor development (Fan *et al*., 2015). However, solid tumors due to limited oxygen flow, they are hypoxic, making them several times more radioresistant than regular tissues, which reduces the efficacy of therapy. Moreover, weak radiation is received by tumor cells that are far from the radiation source (Fan *et al*., 2017). In order to counteract radioresistance, oxygen delivery carriers have been created using nanotechnology. For example, fluorocarbon has been investigated in this context; it is a temperature-sensitive molecule with great affinity for oxygen adsorption and delivery. High-energy X-rays are used in radiotherapy, a common clinical cancer treatment, to kill cancer cells that divide quickly and stop tumor development however, solid tumors have two to three times the radioresistance of normal tissues due to their hypoxic nature from low oxygen delivery, which reduces the efficacy of therapy. Moreover, weak radiation is received by tumor cells that are far from the radiation source (Fan *et al*., 2017). In order to counteract radioresistance, oxygen delivery carriers have been created using nanotechnology. For instance, fluorocarbon, a temperature-sensitive compound with strong oxygen adsorption and delivery affinity, has been explored in this context (Song *et al*., 2017).

Liu et al. (2010) created tantalum oxide nanoparticles (NPs) with absorbed perfluorocarbon to boost tumor oxidation. As the adsorbed perfluorocarbon continuously released oxygen, the NPs focused the radiation towards the tumor. NPs may also function as radiosensitizers. As an example, Swanner et al.'s work (Swanner *et al*., 2015) demonstrated that both in vitro and in vivo, silver nanoparticles (AgNPs) dramatically decreased the vitality and radiosensitized triple- Negative breast cancer cells. Increased DNA damage (Zheng *et al*., 2013) elevated Bax/caspase-3 expression resulting in cell death, lower Bcl-2 expression and lower levels of catalaseAmong the effects of AgNPs on cancer of the liver in human HepG2 cells are total GSH and the antioxidant superoxide dismutase.

3.2.5. Photothermal/Photodynamic therapy

Two novel light-based cancer treatment techniques are photothermal therapy (PTT) and photodynamic therapy (PDT). Through the application of light-activated photosensitive molecules (PSs), PDT generates harmful reactive oxygen species (ROS) within tumor cells, ultimately leading to the tumor cells' destruction (Yuan *et al*., 2012). However, PDT has problems from tumor hypoxia, tissue penetration of short-wavelength light, aggregation-induced PS cooling and possible damage to cells from systemic PS dispersion (Ji *et al*., 2022; Yang *et al*., 2018; Tian *et al*., 2020; Wang *et al*., 2019). Nanophotosensitizers, which offer improved photophysical characteristics and enable regulated PS distribution, can help with these problems (Liang *et al*., 2018).

Liang et al. (2018) have developed a TME-responsive AuNC@MnO2 (AM) nanoplatform for oxygen-enhanced photodynamic treatment (PDT) that may effectively suppress tumor development and metastasis in metastatic breast cancer patients. Analogously, it has been shown that a TME-responsive nanoplatform might potentially alleviate PDT tumor hypoxia (Xu *et al*., 2017). Conversely, photothermal therapy (PTT) induces intratumoral harm by converting ultraviolet light into heat using the tumor cells' high heat sensitivity (Hussein *et al*., 2018). This method makes use of many near-infrared (NIR) nanomaterials, such as carbon nanotubes and gold nanorods (Wei *et al*.,

2021). Heat shock proteins (HSPs) generate thermal resistance in tumor cells, which limits PTT and calls for the development of materials that absorb NIR more efficiently (Li *et al*., 2017). In these areas, there have been interesting advancements. A porphyrin-based micelle, for instance, has shown to be successful.

3.2.6. Diagnosis and Imaging

It is commonly known that early tumor diagnosis improves prognosis and survival rates. Conventional non-invasive imaging modalities, including MRI, CT, PET, OI, SPECT and PET, are essential, but their sensitivity and specificity might be problematic, making a thorough assessment of the illness more difficult. Through the use of nanoparticles (NPs) including QDs, liposomes and AuNPs, nanotechnology opens up new possibilities in biomedical imaging by offering multifunctional, tumor-specific devices. By combining with optical, magnetic and acoustic imaging methods, these NPs improve multimodal imaging and offer thorough diagnostic data. QDs are especially remarkable as remarkable optical imaging nanoprobes because of their special optical characteristics and capacity to increase the specificity of cancer diagnosis.

The selection of efficient targeted drugs is aided by photographic proof of liposome formation in malignant tissues. Because of their minuscule nature and their biocompatibility AuNPs are excellent contrast agents which make it feasible to monitor the proliferation of tumor cells by X-ray irradiation and find malignancies in an early stage. Additionally, while avoiding iodine damage, image quality is improved by NPs encapsulated with iodine, a CT contrast agent. SPECT/CT and nanoparticle-enhanced CT imaging have shown promise in melanoma as breast cancer models and they remain a promising means of diagnosing cancer early (Lee *et al*., 2013; Mojarrad *et al*., 2020).

4. Gene therapy

When cancers initially appear, they are localized disorders, but they frequently spread to other parts of the body, making them incurable (Gao *et al*., 2020; Hu *et al*., 2021; Pan *et al*., 2022; Zhao *et al*., 2023). Cancer treatments nowadays are based on clinical and pathological staging, which is determined by morphological diagnostic methods such as histology and conventional radiography. The only cancer treatments now available are radiation, chemotherapy and surgery (Singhal *et al*., 2010). But the state of technology still makes it difficult to identify cancer early and cure it.

Although there have been significant breakthroughs in conventional medicines such as radiation and chemotherapy, cancer therapy is still not perfected due to various challenges. Some of these include the establishment of various types of drug resistance, extreme cytotoxicity, insufficient doses of medicines reaching the tumor area, general prevalent dispersion of anti-tumor medicines and the difficulty to monitor treatment responses (Lan *et al*., 2021; Xu *et al*., 2021; 2023; Das et al., 2009); Parveen & Sahoo, 2006). To predict successful therapies and patient outcomes, the diagnostic and prognostic classes used today are inadequate (Wang *et al*., 2016).

Thus, given their great potential, it is imperative to address pressing demands such defining tumor margins, detecting recurring tumor cells and micro-metastases and figuring out total tumor removal.

Through the introduction of foreign genetics into the DNA composition of tumor cells, gene therapy seeks to produce deadly effects. Research on cancer is expanding

quickly on this area in both the clinical and preclinical phases. Genetic therapy is a powerful cancer treatment technique that includes introducing therapeutic protein-producing genes, controlling the synthesis and release of tumor-associated genes and converting benign substances into deadly medications. In the context of cancer treatment, gene therapy can offset the diminished effectiveness and side effects of chemotherapy.

Genetic therapy techniques have been created for the treatment of cancer as a result. The employment of transgenes that stop tumor growth upon insertion into tumor cells is also one of these tactics, along with hairpin hairpin RNA (shRNA), interrupting RNA (siRNA) and miRNA-mediated gene silence (Wang *et al*., 2016). With siRNA and shRNA, specific the oncogene and mutation tumor suppressor genes can be targeted, minimizing damage to the system microenvironment (Li *et al*., 2021). Through an enzymatic process, ribonuclease has reduced a type of double-stranded RNA called siRNA to lesser molecules with 20–25 nucleotides.

When siRNA interacts with the versatile protein Argonaute (RISC), the RNA Inspired Silencing Complex is produced". The targeted matching mRNA is bound by this complex, eliminating the passenger RNA strand. According to Bader et al. (2011), tumor-associated microRNA (tuRNA) is essential for the growth, spread and metastasis of cancers. Therefore, the cornerstone of miRNA-based cancer therapies is the inhibition or activation of this miRNA. Further research has been done on a number of suicide genes in different tumor cell types. These genes include cytosine deaminase (CDK), BCL-2 type protein (BAX2), human tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), truncated Bid, carboxyl esterase/irinotecan and a couple of others (Wang *et al*., 2016).

Getting genes or siRNA/miRNA to malignant cells is one of the main challenges in the technique of employing gene therapy for cancer. Gene therapy has several benefits; however, unmodified siRNA has trouble passing cell membranes because of its size and vulnerability to serum nuclease breakdown. Moreover, targeted RNA interference (RNAi) via miRNA confronts electrostatic repulsion induced by the anionic charge shared by the cell membrane. Although viruses have historically been the primary means of transferring genes to their intended cells, they carry the risk of seriously triggering the host's immune system and inflammatory processes. Important problems with viral vectors include toxicities, immunological and inflammatory responses and difficulties with gene regulation and targeting.

Another concern is the potential for the virus to reactivate and transmit illness. Non-viral driven gene delivery methods have garnered significant attention as a work around. Since non-viral vectors are harmless, they can be employed frequently for relatively little money and cause fewer immune responses. Catalytic polymers and nanoparticles delivered by liposomes are the most often employed non-viral vectors. The dimensions, density of charge, shape and colloidal stability of nanoparticles determine their potential utility as virus-free gene delivery vehicles. Jere et al. (2009) successfully delivered an Akt1 siRNA-loaded biodegradable nano-polymeric carrier, thereby silencing the Akt1 protein and reducing cancer cell survival, proliferation, malignancy and metastasis.

5. Future perspective of nanobiomedicine-based tumor therapeutics

Although nanotechnology has great promise to cure tumors by offering specific molecular features for targeted and less toxic treatments, there are a few obstacles that need to be overcome before the full benefits of nanotechnology in cancer therapy can be realized. Biological barriers that prevent nanomedicine from building up and penetrating tumors from blood and tissue to the cellular level are a major barrier (Kim *et al*., 2017).

Endothelial cells that line blood arteries are strongly linked to the main obstacles to medication delivery at the blood level. Diseases like cancer and inflammation can cause poor blood flow, which may restrict the administration of medications. The vascular endothelial growth factor-dependent nature of tumor vasculature and its permeability can also severely impair drug delivery (VEGF) (Urbanczyk *et al*., 2022).

Barriers at the tissue level can include inadequate vascularization, which can lead to hypoxic (low-oxygen) regions that may impair the efficacy and delivery of medications. Increased TME interstitial fluid pressures may make it more difficult for medications to enter tissues. The different tissue characteristics found inside and between tumors further complicate drug delivery. Various cell types, genetic abnormalities or alterations in the endothelium can all be examples of this heterogeneity, which can impact the efficacy and delivery of medications (Kim *et al*., 2017; Nagy *et al*., 2010).

The primary barrier at level of cell is the passive nature of the majority of drug delivery methods, which rely on diffusion and concentration gradients to move drugs from regions of high concentration (blood) to regions of low concentration (tumor interstitium), thereby limiting the amount of medication that reaches tumor cells (Kim *et al*., 2017).

As an alternative, active transport mechanisms enable the selective passage of molecules across a barrier against the direction of the density gradient. Cellular energy saved as ATP or GTP is used by these systems to function. Despite their size, these obstacles are not insurmountable. To address these problems, a number of approaches are being developed, including vascular promotion treatment, vessel normalization and iRGD-based medication delivery. However, more research is required to move these promising ideas toward practical reality for patients with cancer and other disorders.

Furthermore, for long-term therapeutic uses, worries about the toxicity and safety of nanomedicine—including its effects on reproductive systems and organs—are essential. Furthermore, for the best possible therapeutic outcome, the drug loading and release control of nanocarriers need to be improved. Adoption barriers include difficult synthesis, expensive prices, low biocompatibility and limited stability of nanomaterials, which prevent their wider use in medical contexts. Additionally, transferring preclinical discoveries into therapeutic trials is complicated by the lack of appropriate animal models that closely resemble human tumor disorders. Unlocking the full potential of nanotechnology to transform tumor therapies and provide tailored, efficacious cancer treatments requires overcoming these challenges by creative thinking and thorough investigation.

While there is great potential for early cancer detection and treatment with nanomedicine, the field is still in its infancy and has several unresolved issues that must be addressed before gaining regulatory approval for commercial use. To progress nanomedicine in tumor therapy, a number of important avenues should be explored.

First and foremost, it is critical to reduce nanomaterial toxicity and provide safety assessment guidelines. Secondly, particular tumor types should be targeted and biological barriers should be overcome in order to increase delivery efficiency through the development of precise nanodrug delivery techniques.

Thirdly, to prevent systemic toxicity and improve the effectiveness of medication delivery, it is essential to guarantee the stability and regulated release of carriers. By addressing complexity issues, simplifying nano-design is also essential to enabling clinical translation. The large-scale production of nanomedicine can benefit greatly from novel manufacturing tools and technologies including non-infiltrating template microprinting and microfluidic technology. Last but not least, developing in vivo and ex vivo evaluation models—such as microarrays, tumor-like organs and models of human-derived tumor xenografts—is essential for a thorough assessment and for improving the correlation between experimental results. Future work on novel nanomaterial-based drug delivery systems and the application of cutting edge methods like 3D-printed living tumor models can improve target identification, medication development and treatment effectiveness prediction even more.

6. Conclusions

In summary, nanomedicine has the potential to transform cancer therapy by addressing the shortcomings of conventional medicines. It finds uses in a range of therapies by using nanoparticle-mediated medication delivery for improved tumor targeting and therapeutic effectiveness. Although there are still issues to be resolved, including improving biocompatibility, controlling drug release, streamlining nano-design and creating appropriate assessment models, the use of nanomedicine in cancer treatments has bright prospects. Its full promise will only be realized with further innovation, which will open the door to more individualized and powerful therapies that will greatly enhance patient outcomes and advance the battle against cancer.

References

Afzalipour, R., Khoei, S., Khoee, S., Shirvalilou, S., Raoufi, N.J., Motevalian, M. & Karimi, M.Y. (2021). Thermosensitive magnetic nanoparticles exposed to alternating magnetic field and heat-mediated chemotherapy for an effective dual therapy in rat glioma model. *Nanomedicine: Nanotechnology, Biology and Medicine,* 31. https://doi.org/10.1016/j.nano.2020.102319

Albanese, A., Tang, P.S. & Chan, W.C. (2012). The effect of nanoparticle size, shape and surface chemistry on biological systems. *Annual Review of Biomedical Engineering,* 14, 1–16. https://doi.org/10.1146/annurev-bioeng-071811-150124

Alessi, D.R., James, S.R., Downes, C., Holmes, A.B., Gaffney, P.R., Reese, C.B. & Cohen, P. (1997). Characterization of a 3-phosphoinositide-dependent protein kinase, which phosphorylates and activates protein kinase Bα. *Current Biology,* 7, 261–269. https://doi.org/10.1016/s0960-9822(06)00122-9

Alexis, F., Pridgen, E., Molnar, L.K. & Farokhzad, O.C. (2008). Factors affecting the clearance and biodistribution of polymeric nanoparticles. *Molecular Pharmaceutics,* 5, 505–515. https://doi.org/10.1021/mp800051m

Arranja, A.G., Pathak, V., Lammers, T. & Shi, Y. (2017). Tumor-targeted nanomedicines for cancer theranostics. *Pharmacological Research,* 115, 87–95. https://doi.org/10.1016/j.phrs.2016.11.014

Barone, A., d'Avanzo, N., Cristiano, M.C., Paolino, D. & Fresta, M. (2022). Macrophage-derived extracellular vesicles: A promising tool for personalized cancer therapy. *Biomedicines,* 10. https://doi.org/10.3390/biomedicines10061252

Belfiore, L., Saunders, D.N., Ranson, M., Thurecht, K.J., Storm, G. & Vine, K.L. (2018). Towards clinical translation of ligand-functionalized liposomes in targeted cancer therapy: Challenges and opportunities. *Journal of Controlled Release,* 277, 1–13. https://doi.org/10.1016/j.jconrel.2018.02.040

Bertero, T., Oldham, W.M., Cottrill, K.A., Pisano, S., Vanderpool, R.R., Yu, Q. & Chan, S.Y. (2016). Vascular stiffness mechanoactivates YAP/TAZ-dependent glutaminolysis to drive pulmonary hypertension. *Journal of Clinical Investigation,* 126, 3313–3335. https://doi.org/10.1172/JCI86387

Bertrand, N., Leroux, J.C. (2012). The journey of a drug-carrier in the body: An anatomo-physiological perspective. *Journal of Controlled Release,* 161, 152–163. https://doi.org/10.1016/j.jconrel.2011.09.098

Contractor, T., Harris, C.R. (2011). p53 negatively regulates transcription of the pyruvate dehydrogenase kinase Pdk2. *Cancer Research,* 72, 560–567. https://doi.org/10.1158/0008-5472.CAN-11-1215

Cosset, E., Ilmjärv, S., Dutoit, V., Elliott, K., Von Schalscha, T., Camargo, M.F. & Cheres, D.A. (2017). Glut3 addiction is a druggable vulnerability for a molecularly defined subpopulation of glioblastoma. *Cancer Cell,* 32, 856–868. https://doi.org/10.1016/j.ccell.2017.10.016

Cottini, F., Hideshima, T., Xu, C., Sattler, M., Dori, M., Agnelli, L., Hacken, E.T. & Tonon, G. (2014). Rescue of Hippo coactivator YAP1 triggers DNA damage–induced apoptosis in hematological cancers. *Nature Medicine,* 20, 599–606. https://doi.org/10.1038/nm.3562

Csibi, A., Lee, G., Yoon, S.O., Tong, H., Ilter, D., Elia, I. & Blenis, J. (2014). The mTORC1/S6K1 pathway regulates glutamine metabolism through the eIF4B-dependent control of c-Myc Translation. *Current Biology,* 24, 2274–2280. https://doi.org/10.1016/j.cub.2014.08.007

Das, M., Mohanty, C. & Sahoo, S.K. (2009). Ligand-based targeted therapy for cancer tissue. *Expert Opinion on Drug Delivery,* 6, 285-304. https://doi.org/10.1517/17425240902780166

Dasgupta, B., Chhipa, R.R. (2016). Evolving lessons on the complex role of AMPK in normal physiology and cancer. *Trends in Pharmacologicl Sciences,* 37, 192–206. https://doi.org/10.1016/j.tips.2015.11.007

Deng, Z.S., Liu, J. (2005). Numerical simulation of selective freezing of target biological tissues following injection of solutions with specific thermal properties. *Cryobiology,* 50, 183–192. https://doi.org/10.1016/j.cryobiol.2004.12.007

Deprez, J., Vertommen, D., Alessi, D.R., Hue, L. & Rider, M.H. (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,* 272, 17269–17275. https://doi.org/10.1074/jbc.272.28.17269

DeRan, M., Yang, J., Shen, C.H., Peters, E.C., Fitamant, J., Chan, P. & Wu, X. (2014). Energy stress regulates Hippo-YAP signaling involving AMPK-Mediated Regulation of Angiomotin-like 1 Protein. *Cell Reports,* 9, 495–503. https://doi.org/10.1016/j.celrep.2014.09.036

Di Francesco, M., Celia, C., Primavera, R., D'Avanzo, N., Locatelli, M., Fresta, M. & DiMarzio, L. (2017). Physicochemical characterization of pH-responsive and fusogenic self-assembled non-phospholipid vesicles for a potential multiple targeting therapy. *Internetional Journal of Pharmaceutics,* 528, 18–32. https://doi.org/10.1016/j.ijpharm.2017.05.055

Donato, E., Biagioni, F., Bisso, A., Caganova, M., Amati, B. & Campaner, S. (2018). YAP and TAZ are dispensable for physiological and malignant haematopoiesis. *Leukemia,* 32, 2037–2040. https://doi.org/10.1038/s41375-018-0111-3

Dowling, R.J., Zakikhani, M., Fantus, I.G., Pollak, M. & Sonenberg, N. (2007). Metformin inhibits mammalian target of rapamycin–dependent translation initiation in breast cancer cells. *Cancer Research*, 67, 10804–10812. https://doi.org/10.1158/0008-5472.CAN-07-2310

Eguez, L., Lee, A., Chavez, J.A., Miinea, C.P., Kane, S., Lienhard, G.E. & McGraw, T.E. (2005). Full intracellular retention of GLUT4 requires AS160 Rab GTPase activating protein. *Cell Metabolism*, 2, 263–272. https://doi.org/10.1016/j.cmet.2005.09.005

Evers, M.J., van de Wakker, S.I., de Groot, E.M., de Jong, O.G., Gitz-François, J.J., Seinen, C.S. & Vader, P. (2022). Functional siRNA delivery by extracellular vesicle-liposome hybrid nanoparticles. *Advanced Healthcare Materials*, 11. https://doi.org/10.1002/adhm.202101202

Fan, W., Bu, W., Zhang, Z., Shen, B., Zhang, H., He, Q. & Shi, J. (2015). X-ray radiation-controlled no-release for on-demand depth-independent hypoxic radiosensitization. *Angewandte Chemie International Edition*, 54, 14026–14030. https://doi.org/10.1002/anie.201504536

Fan, W., Yung, B., Huang, P. & Chen, X. (2017). Nanotechnology for multimodal synergistic cancer therapy. *Chemical Reviews*, 117, 13566–13638. https://doi.org/10.1021/acs.chemrev.7b00258

Fiandra, L., Mazzucchelli, S., De Palma, C., Colombo, M., Allevi, R., Sommaruga, S. & Corsi, F. (2013). Assessing the in vivo targeting efficiency of multifunctional nanoconstructs bearing antibody-derived ligands. *ACS Nano*, 7, 6092–6102.

Frigo, D.E., Howe, M.K., Wittmann, B.M., Brunner, A.M., Cushman, I., Wang, Q. & McDonnell, D.P. (2010). CaM kinase kinase beta-mediated activation of the growth regulatory kinase AMPK is required for androgen-dependent migration of prostate cancer cells. *Cancer Resarch*, 71, 528–537. https://doi.org/10.1158/0008-5472.CAN-10-2581

Gao, Y., Zhang, H., Lirussi, F., Garrido, C., Ye, X.Y. & Xie, T. (2020). Dual inhibitors of histone deacetylases and other cancer-related targets: a pharmacological perspective. *Biochemical Pharmacology*, 182. https://doi.org/10.1016/j.bcp.2020.114224

Gao, Z., Zhang, L. & Sun, Y. (2012). Nanotechnology applied to overcome tumor drug resistance. *Journal of Controlled Release*, 162, 45–55. https://doi.org/10.1016/j.jconrel.2012.05.051

Gavas, S., Quazi, S. & Karpi´nski, T.M. (2021). Nanoparticles for cancer therapy: Current progress and challenges. *Nanoscale Research Letters*, 16, 173. https://doi.org/10.1186/s11671-021-03628-6

Gottlob, K., Majewski, N., Kennedy, S., Kandel, E., Robey, R.B. & Hay, N. (2001). Inhibition of early apoptotic events by Akt/PKB is dependent on the first committed step of glycolysis and mitochondrial hexokinase. *Genes & Development*, 15, 1406–1418. https://doi.org/10.1101/gad.889901

Gowans, G.J., Hawley, S.A., Ross, F.A. & Hardie, D.G. (2013). AMP is a true physiological Regulator of AMP-activated protein kinase by both allosteric activation and enhancing net phosphorylation. *Cell Metabolism*, 18, 556–566. https://doi.org/10.1016/j.cmet.2013.08.019

Guo, D., Hildebrandt, I.J., Prins, R.M., Soto, H., Mazzotta, M.M., Dang, J. & Mischel P.S. (2009). The AMPK agonist AICAR inhibits the growth of EGFRvIII-expressing glioblastomas by inhibiting lipogenesis. *Proceedings of National Academy Academy Science*, *106*, 12932–12937. https://doi.org/10.1073/pnas.0906606106

Gwinn, D.M., Shackelford, D.B., Egan, D.F., Mihaylova, M.M., Mery, A., Vasquez, D.S. & Shaw, R.J. (2008). AMPK Phosphorylation of Raptor Mediates a Metabolic Checkpoint. *Molecular Cell*, 30, 214–226. https://doi.org/10.1016/j.molcel.2008.03.003

Harvey, K.F., Pfleger, C.M. & Hariharan, I.K. (2003). The Drosophila Mst Ortholog, hippo, restricts growth and cell proliferation and promotes apoptosis. *Cell*, 114, 457–467. https://doi.org/10.1016/s0092-8674(03)00557-9

Haupt, Y., Maya, R., Kazaz, A. & Oren, M. (1997). Mdm2 promotes the rapid degradation of p53. *Nature,* 387, 296–299.

Hawley, S.A., Davison, M., Woods, A., Davies, S.P., Beri, R.K., Carling, D. & Hardie, D.G. (1996). Characterization of the AMP-activated protein kinase kinase from rat liver and identification of threonine 172 as the major site at which it phosphorylates AMP-activated protein kinase. *Journal of Biological Chemistry,* 271, 27879–27887. https://doi.org/10.1074/jbc.271.44.27879

Hawley, S.A., Pan, D.A., Mustard, K.J., Ross, L., Bain, J., Edelman, A.M. & Hardie, D.G. (2005). Calmodulin-dependent protein kinase kinase-β is an alternative upstream kinase for AMP-activated protein kinase. *Cell Metabolism,* 2, 9–19. https://doi.org/10.1016/j.cmet.2005.05.009

Hay, N. (2016). Reprogramming glucose metabolism in cancer: Can it be exploited for cancer therapy? *Nature Reviews Cancer,* 16, 635–649. https://doi.org/10.1038/nrc.2016.77

Hermida, M.A., Kumar, J.D. & Leslie, N.R. (2017). GSK3 and its interactions with the PI3K/AKT/mTOR signalling network. *Advances in Biological Regulation,* 65, 5–15. https://doi.org/10.1016/j.jbior.2017.06.003

Hou, Y., Sun, Z., Rao, W. & Liu, J. (2018). Nanoparticle-mediated cryosurgery for tumor therapy. *Nanomedicine,* 14, 493–506. https://doi.org/10.1016/j.nano.2017.11.018

Hoxhaj, G., Manning, B.D. (2019). The PI3K–AKT network at the interface of oncogenic signalling and cancer metabolism. *Nature Reviews Cancer,* 20, 74–88. https://doi.org/10.1038/s41568-019-0216-7

Hu, S., Hui, Z., Lirussi, F., Garrido, C., Ye, X.Y. & Xie, T. (2021). Small molecule DNA-PK inhibitors as potential cancer therapy: A patent review (2010-present). *Expert Opinion on Therapeutic Patents,* 31, 435-452. https://doi.org/10.1080/13543776.2021.1866540

Hussein, E.A., Zagho, M.M., Nasrallah, G.K. & Elzatahry, A.A. (2018). Recent advances in functional nanostructures as cancer photothermal therapy. *International Journal of Nanomedicine*, 13, 2897–2906. https://doi.org/10.2147/IJN.S161031

Inoki, K., Zhu, T. & Guan, K.-L. (2003). TSC2 mediates cellular energy response to control cell growth and survival. *Cell,* 115, 577–590. https://doi.org/10.1016/s0092-8674(03)00929-2

Jain, R. (2001). Delivery of molecular medicine to solid tumors: Lessons from in vivo imaging of gene expression and function. *Journal of Controlled Release,* 74, 7–25. https://doi.org/10.1016/s0168-3659(01)00306-6

Jere, D., Jiang, H.L., Kim, Y.K., Arote, R., Choi, Y.J., Yun, C.H. & Cho C.S. (2009). Chitosan-graft-polyethylenimine for Akt1 siRNA delivery to lung cancer cells. *International Journal of Pharmaceutics*, 378, 194-200. https://doi.org/10.1016/j.ijpharm.2009.05.046

Ji, B., Wei, M. & Yang, B. (2022). Recent advances in nanomedicines for photodynamic therapy (PDT)-driven cancer immunotherapy. *Theranostics*, 12, 434–458. https://doi.org/10.7150/thno.67300

Jia, J., Zhang, W., Wang, B., Trinko, R. & Jiang, J. (2003). The Drosophila Ste20 family kinase dMST functions as a tumor suppressor by restricting cell proliferation and promoting apoptosis. *Genes and Development,* 17, 2514–2519. https://doi.org/10.1101/gad.1134003

Jin, Z., Lv, Y., Cao, H., Yao, J., Zhou, J., He, W. & Yin, L. (2016). Core-shell nanocarriers with high paclitaxel loading for passive and active targeting. *Scientific Reports,* 6. https://doi.org/10.1038/srep27559

Justice, R.W., Zilian, O., Woods, D.F., Noll, M. & Bryant, P.J. (1995). The Drosophila tumor suppressor gene warts encodes a homolog of human myotonic dystrophy kinase and is required for the control of cell shape and proliferation. *Genes & Development*, 9, 534–546. https://doi.org/10.1101/gad.9.5.534

Kim, E., Kang, J.G., Kang, M.J., Park, J.H., Kim, Y.J., Kweon, T.H. & Cho, J.W. (2020). O-GlcNAcylation on LATS2 disrupts the hippo pathway by inhibiting its activity. *Proceedings of the National Academy of Science,* 117, 14259–14269. https://doi.org/10.1073/pnas.1913469117

Kim, S.M., Faix, P.H. & Schnitzer, J.E. (2017). Overcoming key biological barriers to cancer drug delivery and efficacy. *Journal of Controlled Release*, 267, 15–30. https://doi.org/10.1016/j.jconrel.2017.09.016

Kircher, M.F., Mahmood, U., King, R.S., Weissleder, R. & Josephson, L. (2003). A multimodal nanoparticle for preoperative magnetic resonance imaging and intraoperative optical brain tumor delineation. *Cancer Research*, 63, 8122–8125.

Kruiswijk, F., Labuschagne, C.F. & Vousden, K.H. (2015). p53 in survival, death and metabolic health: A lifeguard with a licence to kill. *Nature Reviews Molecular Cell Biology*, 16, 393–405. https://doi.org/10.1038/nrm4007

Kubbutat, M.H.G., Jones, S.N., & Vousden, K.H. (1997). Regulation of p53 stability by Mdm2. *Nature*, 387, 299–303. https://doi.org/10.1038/387299a0

Lakin, N.D., Jackson, S.P. (1999). Regulation of p53 in response to DNA damage. *Oncogene*, 18, 7644–7655.

Lee, C.K., Jeong, S.H., Jang, C., Bae, H., Kim, Y.H., Park, I. & Koh, G.Y. (2019). Tumor metastasis to lymph nodes requires YAP-dependent metabolic adaptation. *Science*, 363, 644–649. https://doi.org/10.1126/science.aav0173

Lee, N., Choi, S.H. & Hyeon, T. (2013). Nano-sized CT contrast agents. *Advanced Materials*, 25, 2641–2660. https://doi.org/10.1002/adma.201300081

Letchford, K., Burt, H.M. (2012). Copolymer micelles and nanospheres with different in vitro stability demonstrate similar paclitaxel pharmacokinetics. *Molecular Pharmaceutics*, 9, 248–260. https://doi.org/10.1021/mp2002939

Li, C., Lin, L., Zhang, L., Xu, R., Chen, X., Ji, J. & Li, Y. (2021). Long noncoding RNA p21 enhances autophagy to alleviate endothelial progenitor cells damage and promote endothelial repair in hypertension through SESN2/AMPK/TSC2 pathway. *Pharmacological Research*, 173. https://doi.org/10.1016/j.phrs.2021.105920

Li, J., Dirisala, A., Ge, Z., Wang, Y., Yin, W., Ke, W. & Anraku, Y. (2017). Therapeutic vesicular nanoreactors with tumor-specific activation and self-destruction for synergistic tumor ablation. *Angewandte Chemie International Edition*, 129, 14213–14218. https://doi.org/10.1002/anie.201706964

Li, J., Ge, Z., Toh, K., Liu, X., Dirisala, A., Ke, W. & Kataoka K. (2021). Enzymatically transformable polymersomebased nanotherapeutics to eliminate minimal relapsable cancer. *Advanced Materials*, 33. https://doi.org/10.1002/adma.202105254

Li, J., Ke, W., Wang, L., Huang, M., Yin, W., Zhang, P. & Ge, Z. (2016). Self-sufficing H_2O_2-responsive nanocarriers through tumor-specific H_2O_2 production for synergistic oxidation-chemotherapy. *Journal of Controlled Release*, 225, 64-74.

Li, R., Zhang, L., Shi, L. & Wang, P. (2017). MXene Ti3C2: An effective 2D light-to-heat conversion material. *ACS nano*, *11*(4), 3752-3759. https://doi.org/10.1021/acsnano.6b08415

Liang, R., Liu, L., He, H., Chen, Z., Han, Z., Luo, Z. & Cai, L. (2018). Oxygen-boosted immunogenic photodynamic therapy with gold nanocages@manganese dioxide to inhibit tumor growth and metastases. *Biomaterials*, 177, 149–160. https://doi.org/10.1016/j.biomaterials.2018.05.051

Lin, T., Zhao, P., Jiang, Y., Tang, Y., Jin, H., Pan, Z. & Huang, Y. (2016). Blood-brain-barrier-penetrating albumin nanoparticles for biomimetic drug delivery via albumin-binding protein pathways for antiglioma therapy. *ACS Nano*, 10, 9999–10012. https://doi.org/10.1021/acsnano.6b04268

Lin, Y.H., Chen, C.Y. (2020). Folate-targeted curcumin-encapsulated micellar nanosystem for chemotherapy and curcumin-mediated photodynamic therapy. *Polymers*, 12. https://doi.org/10.3390/polym12102280

Liu, C.Y., Zha, Z.Y., Zhou, X., Zhang, H., Huang, W., Zhao, D. & Guan, K.L. (2010). The Hippo Tumor Pathway Promotes TAZ Degradation by Phosphorylating a Phosphodegron and Recruiting the SCFβ-TrCPE3 Ligase. *Journal of Biological Chemistry*, 285, 37159–37169. https://doi.org/10.1074/jbc.M110.152942

Liu, Y., Lu, W. (2012). Recent advances in brain tumor-targeted nano-drug delivery systems. *Expert Opinion on Drug Delivery*, 9, 671–686. https://doi.org/10.1517/17425247.2012.682726

Lu, Y., Aimetti, A.A., Langer, R. & Gu, Z. (2016). Bioresponsive materials. *Nature Reviews Materials*, 2, 1–17. https://doi.org/10.1038/natrevmats.2016.75

Ma, X.M., Blenis, J. (2009). Molecular mechanisms of mTOR-mediated translational control. *Nature Reviews Molecular Cell Biology*, 10, 307–318. https://doi.org/10.1038/nrm2672

Maeda, H., Wu, J., Sawa, T., Matsumura, Y. & Hori, K. (2000). Tumor vascular permeability and the EPR effect in macromolecular therapeutics: A review. *Journal of Controlled Release*, 65, 271–284. https://doi.org/10.1016/s0168-3659(99)00248-5

Marianecci, C., Di Marzio, L., Del Favero, E., Cantù, L., Brocca, P., Rondelli, V. & Carafa, M. (2016). Niosomes as drug nanovectors: Multiscale pH-dependent structural response. *Langmuir*, 32, 1241–1249. https://doi.org/10.1021/acs.langmuir.5b04111

Matsumura, Y., Maeda, H. (1986). A new concept for macromolecular therapeutics in cancer chemotherapy: Mechanism of tumoritropic accumulation of proteins and the anti-tumor agent smancs. *Cancer Research*, 46, 6387–6392.

Mi, W., Lin, Q., Childress, C., Sudol, M., Robishaw, J., Berlot, C.H. & Yang, W. (2014). Geranylgeranylation signals to the Hippo pathway for breast cancer cell proliferation and migration. *Oncogene*, 34, 3095–3106. https://doi.org/10.1038/onc.2014.251

Mîinea, C.P., Sano, H., Kane, S., Sano, E., Fukuda, M., Peränen, J. & Lienhard, G.E. (2005). AS160, the Akt substrate regulating GLUT4 translocation, has a functional Rab GTPase-activating protein domain. *Biochemical Journal*, 391, 87–93. https://doi.org/10.1042/BJ20050887

Miller, E., Yang, J., DeRan, M., Wu, C., Su, A.I., Bonamy, G.M. & Wu, X. (2012). Identification of serum-derived sphingosine-1-phosphate as a small molecule regulator of YAP. *Chemistry & Biology*, 19, 955–962. https://doi.org/10.1016/j.chembiol.2012.07.005

Mo, J.S., Meng, Z., Kim, Y.C., Park, H.W., Hansen, C.G., Kim, S. & Guan, K.L. (2015). Cellular energy stress induces AMPK-mediated regulation of YAP and the Hippo pathway. *Nature Cell Biology*, 17, 500–510. https://doi.org/10.1038/ncb3111

Mojarrad, P., Zamani, S., Seyedhamzeh, M., Omoomi, F.D., Karimpourfard, N., Hadadian, S. & Ardestani, M.S. (2020). Novel radiopharmaceutical (Technetium-99m)-(DOTA-NHS-ester)-Methionine as a SPECT-CT tumor imaging agent. *European Journal of Pharmaceutical Sciences*, 141. https://doi.org/10.1016/j.ejps.2019.105112

Moon, S., Park, S.Y. & Park, H.W. (2018). Regulation of the Hippo pathway in cancer biology. *Cellular and Molecular Life Science*, 75, 2303–2319. https://doi.org/10.1007/s00018-018-2804-1

Moreno-Sánchez, R., Rodríguez-Enríquez, S., Marín-Hernández, A. & Saavedra, E. (2007). Energy metabolism in tumor cells. *FEBS Journal*, 274, 1393–1418. https://doi.org/10.1111/j.1742-4658.2007.05686.x

Mukwaya, G., Forssen, E.A., Schmidt, P. & Ross, M. (1998). DaunoXome®(Liposomal Daunorubicin) for first-line treatment of advanced, HIV-related Kaposi's Sarcoma. In *Long Circulating Liposomes: Old Drugs, New Therapeutics*, 147-163. Berlin, Heidelberg: Springer Berlin Heidelberg.

Mura, S., Nicolas, J. & Couvreur, P. (2013). Stimuli-responsive nanocarriers for drug delivery. *Nature Materials*, 12, 991–1003.

Nagy, J.A., Chang, S.H., Shih, S.C., Dvorak, A.M. & Dvorak, H.F. (2010). Heterogeneity of the tumor vasculature. *Seminars in Thrombosis Hemostasis*, 36, 321–331. https://doi.org/10.1055/s-0030-1253454

Ng, T.L., Leprivier, G., Robertson, M.D., Chow, C., Martín, M.J., Laderoute, K.R. & Sorensen, P.H.B. (2011). The AMPK stress response pathway mediates anoikis resistance through inhibition of mTOR and suppression of protein synthesis. *Cell Death & Differentiation*, 19, 501–510. https://doi.org/10.1038/cdd.2011.119

Pan, L., Feng, F., Wu, J., Fan, S., Han, J., Wang, S. & Xu K. (2022). Demethylzeylasteral targets lactate by inhibiting histone lactylation to suppress the tumorigenicity of liver cancer stem cells. *Pharmacological Research,* 181. https://doi.org/10.1016/j.phrs.2022.106270

Pantalacci, S., Tapon, N. & Léopold, P. (2003). The Salvador partner Hippo promotes apoptosis and cell-cycle exit in Drosophila. *Nature Cell Biology,* 5, 921–927. https://doi.org/10.1038/ncb1051

Paolino, D., Licciardi, M., Celia, C., Giammona, G., Fresta, M., & Cavallaro, G. (2012). Folate-targeted supramolecular vesicular aggregates as a new frontier for effective anti-cancer treatment in in vivo model. *European Journal of Pharmaceutics and Biopharmaceutics*, 82, 94–10. https://doi.org/10.1016/j.ejpb.2012.06.001

Park, D.H., Cho, J., Kwon, O.J., Yun, C.O. & Choy, J.H. (2016). Biodegradable inorganic nanovector: Passive versus active tumor targeting in siRNA transportation. *Angewandte Chemie International Edition,* 55, 4582–4586. https://doi.org/10.1002/anie.201510844

Park, H.U., Suy, S., Danner, M., Dailey, V., Zhang, Y., Li, H. & Collins, S.P. (2009). AMP-activated protein kinase promotes human prostate cancer cell growth and survival. *Molecular Cancer Therapeutics,* 8, 733–741. https://doi.org/10.1158/1535-7163.MCT-08-0631

Park, J.H., Shin, J.E. & Park, H.W. (2018). The Role of Hippo Pathway in Cancer Stem Cell Biology. *Molecules and Cells*, 41, 83–92. https://doi.org/10.14348/molcells.2018.2242

Park, Y.Y., Sohn, B.H., Johnson, R.L., Kang, M.H., Kim, S.B., Shim, J.J. & Lee, J.S. (2015). Yes-associated protein 1 and transcriptional coactivator with PDZ-binding motif activate the mammalian target of rapamycin complex 1 pathway by regulating amino acid transporters in hepatocellular carcinoma. *Hepatology*, 63, 159–172. https://doi.org/10.1002/hep.28223

Peng, C., Zhu, Y., Zhang, W., Liao, Q., Chen, Y., Zhao, X. & Pei, H. (2017). Regulation of the Hippo-YAP Pathway by Glucose Sensor O-GlcNAcylation. *Molecular Cell*, 68, 591–604. https://doi.org/10.1016/j.molcel.2017.10.010

Radomski, A., Jurasz, P., Alonso-Escolano, D., Drews, M., Morandi, M., Malinski, T. & Radomski, M.W. (2005). Nanoparticle-induced platelet aggregation and vascular thrombosis. *British Journal of Pharmacology*, 146, 882–893. https://doi.org/10.1038/sj.bjp.0706386

Raught, B., Peiretti, F., Gingras, A., Livingstone, M., Shahbazian, D., Mayeur, G.L. & Hershey, J.W.B. (2004). Phosphorylation of eucaryotic translation initiation factor 4B Ser422 is modulated by S6 kinases. *EMBO Journal,* 23, 1761–1769. https://doi.org/10.1038/sj.emboj.7600193

Rijcken, C.J.F. (2007) *Tuneable & Degradable Polymeric Micelles for Drug Delivery: From Synthesis to Feasibility in Vivo*. Utrecht University: Utrecht, The Netherlands.

Roberts, D.J., Tan-Sah, V.P., Smith, J.M. & Miyamoto, S. (2013). Akt phosphorylates HK-II at Thr-473 and increases mitochondrial HK-II association to protect cardiomyocytes. *Journal of Biological Chemistry*, 288, 23798–23806. https://doi.org/10.1074/jbc.M113.482026

Sanchez-Macedo, N., Feng, J., Faubert, B., Chang, N., Elia, A., Rushing, E.J. & Zaugg K. (2013). Depletion of the novel p53-target gene carnitine palmitoyltransferase 1C delays tumor growth in the neurofibromatosis type I tumor model. *Cell Death & Differentiation*, 20, 659–668. https://doi.org/10.1038/cdd.2012.168

Sano, H., Kane, S., Sano, E., Mîinea, C.P., Asara, J.M., Lane, W.S. & Lienhard, G.E. (2003). Insulin-stimulated phosphorylation of a rab GTPase-activating protein regulates GLUT4 translocation. *Journal of Biological Chemistry*, 278, 14599–14602. https://doi.org/10.1074/jbc.C300063200

Sarbassov, D.D., Guertin, D.A., Ali, S.M. & Sabatini, D.M. (2005). Phosphorylation and regulation of Akt/PKB by the Rictor-mTOR Complex. *Science,* 307, 1098–1101. https://doi.org/10.1126/science.1106148

Semenza, G.L. (2003). Targeting HIF-1 for cancer therapy. *Nature Reviews Cancer,* 3, 721–732. https://doi.org/10.1038/nrc1187

Shah, H., Madni, A., Filipczak, N., Jan, N., Khan, M.M., Khan, S. & Torchilin V.P. (2023). Cisplatin-loaded thermoresponsive liposomes for enhanced anti-cancer efficacy. *Journal of Drug Delivery Science and Technolpgy,* 84. https://doi.org/10.1016/j.jddst.2023.104509

Shaw, R.J., Kosmatka, M., Bardeesy, N., Hurley, R.L., Witters, L.A., Depinho, R.A. & Cantley, L.C. (2004). The tumor suppressor LKB1 kinase directly activates AMP-activated kinase and regulates apoptosis in response to energy stress. *Proceedings of National Academy Academy Science*, 101, 3329–3335. https://doi.org/10.1073/pnas.0308061100

Shi, D., Beasock, D., Fessler, A., Szebeni, J., Ljubimova, J.Y., Afonin, K.A. & Dobrovolskaia, M.A. (2022). To PEGylate or not to PEGylate: Immunological properties of nanomedicine's most popular component, polyethylene glycol and its alternatives. *Advanced Drug Delivery Reviews,* 180. https://doi.org/10.1016/j.addr.2021.114079

Singhal, S., Nie, S. & Wang, M.D. (2010). Nanotechnology applications in surgical oncology. *Annual Review of Medicine, 61*, 359-373. https://doi.org/10.1016/j.addr.2021.114079

Sivak, L., Subr, V., Tomala, J., Rihova, B., Strohalm, J., Etrych, T. & Kovar, M. (2017). Overcoming multidrug resistance via simultaneous delivery of cytostatic drug and P-glycoprotein inhibitor to cancer cells by HPMA copolymer conjugate. *Biomaterials*, 115, 65–80. https://doi.org/10.1016/j.biomaterials.2016.11.013

Song, G., Ji, C., Liang, C., Song, X., Yi, X., Dong, Z. & Liu, Z. (2017). TaOx decorated perfluorocarbon nanodroplets as oxygen reservoirs to overcome tumor hypoxia and enhance cancer radiotherapy. *Biomaterials*, 112, 257–263. https://doi.org/10.1016/j.biomaterials.2016.10.020

Song, L., Tang, H., Liao, W., Luo, X., Li, Y., Chen, T. & Zhang, X. (2017). FOXC2 positively regulates YAP signaling and promotes the glycolysis of nasopharyngeal carcinoma. *Experimental Cell Research*, 357, 17-24. https://doi.org/10.1016/j.yexcr.2017.04.019

Sorrentino, G., Ruggeri, N., Specchia, V., Cordenonsi, M., Mano, M., Dupont, S. & Del Sal, G. (2014). Metabolic control of YAP and TAZ by the mevalonate pathway. *Nature Cell Biology*, 16, 357–366. https://doi.org/10.1038/ncb2936

Swanner, J., Mims, J., Carroll, D.L., Akman, S.A., Furdui, C.M., Torti, S.V. & Singh, R.N. (2015). Differential cytotoxic and radiosensitizing effects of silver nanoparticles on triple-negative breast cancer and non-triple-negative breast cells. *International Journal of Nanomedicine*, 10, 3937–3953. https://doi.org/10.2147/IJN.S80349

Swetha, K.L., Paul, M., Maravajjala, K.S., Kumbham, S., Biswas, S. & Roy, A. (2023). Overcoming drug resistance with a docetaxel and disulfiram loaded pH-sensitive nanoparticle. *Journal of Controlled Release,* 356, 93–114. https://doi.org/10.1016/j.jconrel.2023.02.023

Talelli, M., Barz, M., Rijcken, C.J., Kiessling, F., Hennink, W.E. & Lammers, T. (2015). Core-crosslinked polymeric micelles: Principles, preparation, biomedical applications and clinical translation. *Nano Today*, 10, 93–117. https://doi.org/10.1016/j.nantod.2015.01.005

Tapon, N., Harvey, K.F., Bell, D.W., Wahrer, D.C., Schiripo, T.A. & Hariharan, I.K. (2002). Salvador promotes both cell cycle exit and apoptosis in drosophila and is mutated in human cancer cell lines. *Cell*, 110, 467–478. https://doi.org/10.1016/s0092-8674(02)00824-3

Thoreen, C.C., Chantranupong, L., Keys, H.R., Wang, T., Gray, N.S. & Sabatini, D.M. (2012). A unifying model for mTORC1-mediated regulation of mRNA translation. *Nature Cell Biology*, 485, 109–113. https://doi.org/10.1038/nature11083

Tian, J., Xiao, C., Huang, B., Wang, C. & Zhang, W. (2020). Janus macromolecular brushes for synergistic cascade-amplified photodynamic therapy and enhanced chemotherapy. *Acta Biomaterialia,* 101, 495–506. https://doi.org/10.1016/j.actbio.2019.11.018

Udan, R.S., Kango-Singh, M., Nolo, R., Tao, C. & Halder, G. (2003). Hippo promotes proliferation arrest and apoptosis in the Salvador/Warts pathway. *Nature Cell Biology*, 5, 914–920. https://doi.org/10.1038/ncb1050

Urbanczyk, M., Zbinden, A. & Schenke-Layland, K. (2022). Organ-specific endothelial cell heterogenicity and its impact on regenerative medicine and biomedical engineering applications. *Advanced Drug Delivery Reviews*, 186. https://doi.org/10.1016/j.addr.2022.114323

Waldhart, A.N., Dykstra, H., Peck, A.S., Boguslawski, E.A., Madaj, Z.B., Wen, J. & Wu, N. (2017). Phosphorylation of TXNIP by AKT mediates acute influx of glucose in response to insulin. *Cell Reports*, 19, 2005–2013. https://doi.org/10.1016/j.celrep.2017.05.041

Wang, K., Kievit, F.M. & Zhang, M. (2016). Nanoparticles for cancer gene therapy: Recent advances, challenges and strategies. *Pharmacological Research*, 114, 56-66. https://doi.org/10.1016/j.phrs.2016.10.016

Wang, M., Zhai, Y., Ye, H., Lv, Q., Sun, B., Luo, C. & He, Z. (2019). High co-loading capacity and stimuli-responsive release based on cascade reaction of self-destructive polymer for improved chemo-photodynamic therapy. *ACS Nano*, 13, 7010–7023. https://doi.org/10.1021/acsnano.9b02096

Wang, X., Ding, H., Li, Z., Peng, Y., Tan, H., Wang, C. & Wei, W. (2022). Exploration and functionalization of M1-macrophage extracellular vesicles for effective accumulation in glioblastoma and strong synergistic therapeutic effects. *Signal Transduction and Targeted Therapy*, 7, 74.

Warburg, O., Wind, F. & Negelein, E. (1927). The metabolism of tumors in the body. *Journal of General Physiology*, 8, 519–530. https://doi.org/10.1085/jgp.8.6.519

Wei, G., Wang, Y., Yang, G., Wang, Y. & Ju, R. (2021). Recent progress in nanomedicine for enhanced cancer chemotherapy. *Theranostics*, 11, 6370–6392. https://doi.org/10.7150/thno.57828

Weinberg, E.S., Chandel, N.S. (2014). Targeting mitochondria metabolism for cancer therapy. *Nature Chemical Biology*, 11, 9–15.

Wen, P., Ke, W., Dirisala, A., Toh, K., Tanaka, M. & Li, J. (2023). Stealth and pseudo-stealth nanocarriers. *Advanced Drug Delivery Reviews*, 198. https://doi.org/10.1016/j.addr.2023.114895

Wise, D.R., DeBerardinis, R.J., Mancuso, A., Sayed, N., Zhang, X.Y., Pfeiffer, H.K. & Thompson C.B. (2008). Myc regulates a transcriptional program that stimulates mitochondrial glutaminolysis and leads to glutamine addiction. *Proceedings of National Academy Academy Science*, 105, 18782–18787. https://doi.org/10.1073/pnas.0810199105

Xiao, Q., Zoulikha, M., Qiu, M., Teng, C., Lin, C., Li, X. & He, W. (2022). The effects of protein corona on in vivo fate of nanocarriers. *Advanced Drug Delivery Reviews*, 186. https://doi.org/10.1016/j.addr.2022.114356

Xu, H., Li, L., Wang, S., Wang, Z., Qu, L., Wang, C. & Xu, K. (2023). Royal jelly acid suppresses hepatocellular carcinoma tumorigenicity by inhibiting H3 histone lactylation at H3K9la and H3K14la sites. *Phytomedicine*, 118. https://doi.org/10.1016/j.phymed.2023.154940

Xu, H., Van der Jeught, K., Zhou, Z., Zhang, L., Yu, T., Sun, Y. & Lu, X. (2021). Atractylenolide I enhances responsiveness to immune checkpoint blockade therapy by activating tumor antigen presentation. *Journal of Clinical Investigation*, 131. https://doi.org/10.1172/JCI146832

Xu, J., Xu, L., Wang, C., Yang, R., Zhuang, Q., Han, X. & Liu, Z. (2017). Near-infrared-triggered photodynamic therapy with multitasking upconversion nanoparticles in combination with checkpoint blockade for immunotherapy of colorectal cancer. *ACS Nano*, 11, 4463–4474. https://doi.org/10.1021/acsnano.7b00715

Yan, Y., Zhang, H., Wei, S., Xie, W., Chen, Y. & Yang, H. (2023). Engineering extracellular vesicles derived from macrophages for tumor therapy: A review. *Materials Advances*, 4, 1213–1225.

Yang, C., Stampouloglou, E., Kingston, N.M., Zhang, L., Monti, S. & Varelas, X. (2018). Glutamine-utilizing transaminases are a metabolic vulnerability of TAZ/YAP-activated cancer cells. *EMBO Reports*, 19. https://doi.org/10.15252/embr.201643577

Yang, Y., Zhu, W., Feng, L., Chao, Y., Yi, X., Dong, Z. & Chen, M. (2018). G-quadruplex-based nanoscale coordination polymers to modulate tumor hypoxia and achieve nuclear-targeted drug delivery for enhanced photodynamic therapy. *Nano Letters*, 18, 6867–6875. https://doi.org/10.1021/acs.nanolett.8b02732

Yu, F.X., Zhang, Y., Park, H.W., Jewell, J.L., Chen, Q., Deng, Y. & Guan, K.L. (2013). Protein kinase A activates the Hippo pathway to modulate cell proliferation and differentiation. *Genes & Development*, 27, 1223–1232. https://doi.org/10.1101/gad.219402.113

Yu, F.X., Zhao, B., Panupinthu, N., Jewell, J.L., Lian, I., Wang, L.H. & Guan K.L. (2012). Regulation of the Hippo-YAP pathway by G-protein-coupled receptor signaling. *Cell*, 150, 780–791. https://doi.org/10.1016/j.cell.2012.06.037

Yuan, H., Chong, H., Wang, B., Zhu, C., Liu, L., Yang, Q. & Wang, S. (2012). Chemical molecule-induced light-activated system for anti-cancer and antifungal activities. *Journal of the American Chemical Society*, 134, 13184–13187. https://doi.org/10.1021/ja304986t

Zhang, C., Liu, J., Liang, Y., Wu, R., Zhao, Y., Hong, X. & Feng, Z. (2013). Tumourassociated mutant p53 drives the Warburg effect. *Nature Communications*, 4. https://doi.org/10.1038/ncomms3935

Zhang, L., Zhang, B., Liang, R., Ran, H., Zhu, D., Ren, J. & Cai, L. (2023). A dual-biomineralized yeast micro-/nanorobot with self-driving penetration for gastritis therapy and motility recovery. *ACS Nano*, 17, 6410–6422. https://doi.org/10.1021/acsnano.2c11258

Zhang, X., Qiao, Y., Wu, Q., Chen, Y., Zou, S., Liu, X. & Sun, F. (2017). The essential role of YAP O-GlcNAcylation in high-glucose-stimulated liver tumorigenesis. *Nature Communications*, 8. https://doi.org/10.1038/ncomms15280

Zhao, B., Li, L., Tumaneng, K., Wang, C.Y. & Guan, K.L. (2010). A coordinated phosphorylation by Lats and CK1 regulates YAP stability through SCF β-TRCP. *Genes & Development*, 24, 72–85. https://doi.org/10.1101/gad.1843810

Zhao, B., Wei, X., Li, W., Udan, R.S., Yang, Q., Kim, J. & Guan, K.L. (2007). Inactivation of YAP oncoprotein by the Hippo pathway is involved in cell contact inhibition and tissue growth control. *Genes & Development*, 21, 2747–2761. https://doi.org/10.1101/gad.1602907

Zhao, H., Tang, S., Tao, Q., Ming, T., Lei, J., Liang, Y. & Xu, H. (2023). Ursolic acid suppresses colorectal cancer by down-regulation of wnt/β-catenin signaling pathway activity. *Journal of Agricultural and Food Chemistry*, 71, 3981-3993. https://doi.org/10.1021/acs.jafc.2c06775

Zheng, Q., Yang, H., Wei, J., Tong, J.L. & Shu, Y.Q. (2013). The role and mechanisms of nanoparticles to enhance radiosensitivity in hepatocellular cell. *Biomedicine & Pharmacotherapy*, 67, 569–575. https://doi.org/10.1073/pnas.0810199105

Zheng, X., Han, H., Liu, G., Ma, Y., Pan, R., Sang, L. & Lin, A. (2017). Lnc RNA wires up Hippo and Hedgehog signaling to reprogramme glucose metabolism. *EMBO Journal*, 36, 3325–3335. https://doi.org/10.15252/embj.201797609