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趙瑞益 教授

研究興趣

趙瑞益老師實驗室有三個主要研究方向包括：1) 癌症生長基因的分子調控及藥物開發、2) 奈米鑽石的分子作用及生醫應用、3) 選擇性自噬作用接受體在癌症及奈米藥物運送的角色。目前癌症是台灣和世界人類致死率與醫藥照護花費最高的疾病之一，發展新穎有效治療癌症的策略與藥物是非常迫切需要。我們發現癌細胞中 Survivin 與 EGFR 會調控癌細胞的生長與產生抗藥性，進一步探索尋找能控制癌細胞生長基因的新穎化合物，期望能改善治療惡性腫瘤的效果。我們開發出一種新型化合物 SP101，具有抑制 Survivin 表現、EGFR 突變與癌幹性所產生的抗藥作用，並能克服臨床 EGFR-TKI 標靶藥物的抗藥性 (Yin et al., 2014 *Bioorg Med Chem Lett*; 2016 *US patent and 2017 Taiwan patent*)。我們也開發出新型白蛋白結合 EGFR-TKI 複合體，可作為標靶藥物的運送 (Boobalan, 2017 *Bioorg Med Chem Lett*; 2019 *Taiwan and US patents*)。此外，我們研究團隊在奈米鑽石之生物醫學的研究已有十年以上經驗，發表超過 15 篇奈米鑽石研究成果的國際期刊論文，在奈米鑽石相關的研究論文已被引用次數 > 1,200 次，平均每篇被引用 ~ 80 次，研究貢獻主要在奈米鑽石的生物相容性評估、生物標定、藥物運送及對生物體的影響。我們發現奈米鑽石是一種含碳的奈米材料，在體內及體外具有高度生物相容性 (Lien et al., 2012 *Biomaterials*; Vijayanthimala et

al., 2012 *Biomaterials*; Huang et al., *Sci Rep* 2014)。奈米鑽石可作為癌細胞與幹細胞的標定及追蹤 (Lien et al., 2012 *Biomaterials*; Hsu et al., 2014 *Sci Rep*)。我們進一步開發奈米鑽石同時結合紫杉醇與 EGFR 抗體標靶藥物，此新型奈米藥物複合體能有效抑制腫瘤並增加療效 (Lin et al., 2017 *Sci Rep*; Liao et al., 2019, *Acta Biomater*)。近幾年我們的研究重點在探討選擇性自噬作用接受體在癌症及奈米藥物運送的角色。選擇性自噬作用是人類細胞處理外來病原體與代謝細胞內含物及受損胞器的重要恆定機制，自噬作用也是目前研發癌症新療法的方向。自噬作用接受體是調控選擇性自噬作用的關鍵蛋白，同時具有連接泛素與 LC3 的結合位，可控制選擇性自噬作用路徑的進行。我們首次發現藥物載體在細胞中會結合自噬作用受體 (SQSTM1, OPTN and NDP52) 進入選擇性自噬路徑 (Liu et al., 2017 *Autophagy*)。我們提出新的觀點為泛素包覆的奈米顆粒會與自噬作用受體結合而進入選擇性自噬路徑，促進其運送至溶小體，我們研究闡述自噬作用受體在細胞內進行奈米藥物運送及釋放的功能。我們實驗室的長期目標為研發出有效治療癌症的新策略與藥物。



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Research Interests

The Chao laboratory has three major research topics: 1) molecular regulation and new drug development of cancer growth genes, 2) molecular reaction and biomedical applications of nanodiamonds, and 3) role of selective autophagy receptors in cancers and nanodrug delivery. Cancers are the most mortality and highest cost of medicine care in Taiwan and worldwide. Development of novel strategies and drugs for cancer therapy is highly desired. Our previous studies contributed the roles of Survivin and EGFR in regulating tumor growth and drug resistance. We seek to translate insights in inhibiting cancer growth genes by novel compounds into improved therapies for malignant tumors. We develop a novel compound, SP101, that can overcome the drug resistance of Survivin expression, EGFR mutations and cancer stemness in human lung cancer (Yin et al., 2014 *Bioorg Med Chem Lett*; 2016 *US* patent and 2017 *Taiwan* patent). We also create a new albumin-EGFR-TKI composite for targeted drug delivery (Boobalan, 2017 *Bioorg Med Chem Lett*; 2019 *Taiwan and US* patents). In addition, our research team has studied nanodiamond, a carbon-based nanomaterial, for over 10 years. We have published over 15 papers related to nanodiamonds and total cited number was over 1,200 times (average ~80 times/paper). Our studies contributed nanodiamonds on biocompatible evaluation, bio-labeling, drug delivery and biological impacts. We demonstrated that nanodiamond is a promising carbon nanomaterial with biocompatibility *in vitro* and *in vivo* (Lien et al., 2012 *Biomaterials*; Vijayanthimala et al., 2012 *Biomaterials*;

Huang et al., *Sci Rep* 2014). Nanodiamond can be used for cancer and stem cell labeling and tracking (Lien et al., 2012 *Biomaterials*; Hsu et al., 2014 *Sci Rep*). We further developed that co-delivery of paclitaxel and cetuximab enhanced tumor inhibition and therapeutic efficacy (Lin et al., 2017 *Sci Rep*; Liao et al., 2019, *Acta Biomater*). In recent years, we focus on the investigation of selective autophagy receptors in cancers and nanodrug delivery. Selective autophagy plays a pivotal role in the processing of foreign pathogens, cellular components, and damaged organelles to maintain homeostasis in human cells. Currently, autophagy is an important target for developing novel cancer therapeutics. Selective autophagy receptors contain an Ub-associated domain and an LC3-interacting region, which can recruit LC3-containing autophagosomes to ubiquitinated cargos into selective autophagy pathway. We found for the first time that ubiquitin-coated nanodiamonds bind to selective autophagy receptors (SQSTM1, OPTN and NDP52) for entry into the selective autophagy pathway (Liu et al., 2017 *Autophagy*). Our study provides novel insight that ubiquitin-coated nanoparticles bind to autophagy receptors for entry into the selective autophagy pathway, facilitating their delivery to lysosomes. We illustrate the biological impacts and pivotal roles of autophagy receptors in transportation and drug delivery by those nanomaterials. The long-term goal of our laboratory is to discover of novel targets and potential therapeutic compounds for cancer therapy.