Cancer Biology Research Literatures

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Abstract: Cancer is the general name for a group of more than 100 diseases. Although there are many kinds of cancer, all cancers start because abnormal cells grow out of control. Untreated cancers can cause serious illness and death. The body is made up of trillions of living cells. Normal body cells grow, divide, and die in an orderly fashion. During the early years of a person's life, normal cells divide faster to allow the person to grow. After the person becomes an adult, most cells divide only to replace worn-out or dying cells or to repair injuries. This article introduces recent research reports as references in the related studies.
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1. Introduction

Cancer is the general name for a group of more than 100 diseases. Although there are many kinds of cancer, all cancers start because abnormal cells grow out of control. Untreated cancers can cause serious illness and death. The body is made up of trillions of living cells. Normal body cells grow, divide, and die in an orderly fashion. During the early years of a person's life, normal cells divide faster to allow the person to grow. After the person becomes an adult, most cells divide only to replace worn-out or dying cells or to repair injuries.

The following introduces recent reports as references in the related studies.

Altuna-Coy, A., et al. (2023). "In silico analysis of prognostic and diagnostic significance of target genes from prostate cancer cell lines derived exomicroRNAs." Cancer Cell Int **23**(1): 275.

BACKGROUND: Cancer-secreted exovesicles are important for cell-to-cell communication by altering cancer-related signalling pathways. Exovesicles-derived miRNAs (exomiRNAs)-target genes can be useful for diagnostic and prognostic purposes. METHODS: ExomiRNA from prostate cancer (PCa) cells (PC-3 and LNCaP) were quantified by qRT-PCR and compared to the healthy cell line RWPE-1 by using miRNome PCR 752 miRNAs Panel. MiRNet database was used to predict exomiRNA-target genes. ExomiRNA-target genes pathway functional enrichment was performed by using Reactome database and Enrichr platform. Protein-protein interaction analysis was carried out by using the STRING database. RNA target-gene sequencing data from The Cancer Genome Atlas Prostate Adenocarcinoma (TCGA-PRAD) database was screened out in 465 PCa patients for candidate gene expression in prostate tumour (PT) tissue and non-pathologic prostate (N-PP) tissue. Signature gene candidates were statistically analysed for diagnosis and prognosis usefulness. RESULTS: A total of 36 exomiRNAs were found downregulated when comparing PCa cells vs a healthy cell line; and when comparing PC-3 vs LNCaP, 14 miRNAs were found downregulated and 52 upregulated. Reactome pathway database revealed altered pathways and genes related to miRNA biosynthesis, miRNA-mediated gene silencing (TNRC6B and AGO1), and cell proliferation (CDK6), among others. Results showed that TNRC6B gene expression was up-regulated in PT tissue compared to N-PP (n = 52 paired samples) and could be useful for diagnostic purposes. Likewise, gene expression levels of CDK6, TNRC6B, and AGO1 were down-regulated in high-risk PT (n = 293) compared to low-risk PCa tissue counterparts (n = 172). When gene expression levels of CDK6, TNRC6B, and AGO1 were tested as a prognostic panel, the results showed that these improve the prognostic power of classical biomarkers. CONCLUSION: ExomiRNAs-targets genes, TNRC6B, CDK6, and AGO1, showed a deregulated expression profile in PCa tissue and could be useful for PCa diagnosis and prognosis.

Atiomo, W., et al. (2023). "Deciphering the Role of Insulin-Like Growth Factor 1 in Endometrial Cancer in Patients With Polycystic Ovary Syndrome: Protocol for a Methodological Approach Using Cell Culture Experiments." JMIR Res Protoc **12**: e48127.

BACKGROUND: Endometrial cancer (EC) is the most common gynecological cancer in women globally. It is linked to increasing obesity rates and longer life spans. The molecular mechanisms leading to EC are unclear; however, women with polycystic ovary syndrome (PCOS) have a 3- to 5-fold increased EC risk. According to a pilot study conducted in the

United Kingdom, insulin-like growth factor-1 (IGF-1) gene and protein were raised in the endometrium and blood of women with EC and PCOS, compared with those without PCOS (controls). Therefore, raised serum IGF-1 levels may contribute to an increased EC risk in women with PCOS, but it is necessary to test this hypothesis since not all studies have demonstrated this association. OBJECTIVE: This study aims to investigate the role of IGF-1 in mediating EC risk in PCOS. This will be achieved by evaluating the proliferative effects of PCOS serum, IGF-1, and IGF-1 antagonist on human endometrial cancer 1-A and 1-B cell lines, with a comparison to controls (using serum from women without PCOS and cell culture media). The study will also identify differentially expressed genes and pathways activated by various treatments. METHODS: We intend to recruit 20 women with PCOS and 20 women without PCOS for this cross-sectional study. All experiments will be carried out 4 times to ensure consistency. We will perform transcriptomic and phosphoproteomic profiling to identify differentially expressed genes and phosphoproteins between different treatments using RNA sequencing and phosphoproteomics. We will also perform bioinformatics pathway analysis to identify whether any unique collection of genes or phosphoproteins explains increased EC risk in PCOS. The primary outcome measure will be the cell proliferation (growth) difference measured by cell index values. Our protocol stands out due to its unique approach; no previous study has used this approach to investigate the oncogenic effect of serum from women with PCOS. Additionally, no previous study has considered the differential mutations of genes related to the insulin signaling pathway across various types of human EC cell lines and the potential impact of these variations on their experimental findings. RESULTS: Participants are currently being recruited. It is expected that preliminary findings suitable for analysis and publication will be available by the summer of 2024. CONCLUSIONS: Although we currently do not have any results to report, sharing our protocol at this stage will aid in research collaboration, provide an opportunity for early feedback, and help reduce duplication of effort by other research groups. The findings of our study will have broader implications. A deeper understanding of the mechanisms underlying the regulation of the IGF system in PCOS and EC will improve our ability to develop effective treatment modalities for EC and will be a vital step toward reducing EC in women globally. INTERNATIONAL REGISTERED REPORT IDENTIFIER (IRRID): DERR1-10.2196/48127.

Beitzen-Heineke, A., et al. (2023). "Long-term cardiotoxicity in germ cell cancer survivors after platinum-based chemotherapy: cardiac MR shows impaired systolic function and tissue alterations." Eur Radiol.

OBJECTIVES: Long-term toxicities of germ cell cancer (GCC) treatment are of particular importance in young men with a life expectancy of several decades after curative treatment. This study aimed to investigate the long-term effects of platinum-based chemotherapy on cardiac function and myocardial tissue in GCC survivors by cardiac magnetic resonance (CMR) imaging. METHODS: Asymptomatic GCC survivors >/= 3 years after platinum-based chemotherapy and age-matched healthy controls underwent CMR assessment, including left ventricular (LV) and right ventricular (RV) ejection fraction (EF), strain analysis, late gadolinium enhancement (LGE) imaging, and T1/T2 mapping. RESULTS: Forty-four survivors (age 44 [interquartile range, IQR 37-52] years; follow-up time 10 [IQR 5-15] years after chemotherapy) and 21 controls were evaluated. LV- and RVEF were lower in GCC survivors compared to controls (LVEF 56 +/- 5% vs. 59 +/- 5%, p = 0.017; RVEF 50 +/- 7% vs. 55 +/- 7%, p = 0.008). Seven percent (3/44) of survivors showed reduced LVEF (< 50%), and 41% (18/44) showed borderline LVEF (50-54%). The strain analysis revealed significantly reduced deformation compared to controls (LV global longitudinal strain [GLS] -13 +/- 2% vs. -15 +/- 1%, p < 0.001; RV GLS -15 +/- 4% vs. -19 +/- 4%, p = 0.005). Tissue characterization revealed focal myocardial fibrosis in 9 survivors (20%) and lower myocardial native T1 times in survivors compared to controls (1202 +/- 25 ms vs. 1226 +/- 37 ms, p = 0.016). Attenuated LVEF was observed after two cycles of platinum-based chemotherapy (54 +/- 5% vs. 62 +/- 5%, p < 0.001). CONCLUSION: Based on CMR evaluation, combination chemotherapy with cumulative cisplatin >/= 200 mg/m(2) is associated with attenuated biventricular systolic function and myocardial tissue alterations in asymptomatic long-term GCC survivors. CLINICAL RELEVANCE STATEMENT: Platinum-based chemotherapy is associated with decreased systolic function, non-ischemic focal myocardial scar, and decreased T1 times in asymptomatic long-term germ cell cancer survivors. Clinicians should be particularly aware of the risk of cardiac toxicity after platinum-based chemotherapy. KEY POINTS: * Platinum-based chemotherapy is associated with attenuation of biventricular systolic function, lower myocardial T1 relaxation times, and non-ischemic late gadolinium enhancement. * Decreased systolic function and non-ischemic late gadolinium enhancement are associated

with a cumulative cisplatin dose of >/= 200 mg/m(2). * Cardiac MRI can help to identify chemotherapy-associated changes in cardiac function and tissue in asymptomatic long-term germ cell cancer survivors.

Bimonte, V. M., et al. (2023). "The endocrine disruptor cadmium modulates the androgen-estrogen receptors ratio and induces inflammatory cytokines in luminal (A) cell models of breast cancer." Endocrine.

PURPOSE: Breast cancer (BC) is the most common malignancy that affects women, and it is, to date, their leading cause of death. Luminal A molecular subtype accounts for 40% of BC and is characterized by hormone receptors positive/human epidermal growth factor 2 expression and current treatment consists of surgery plus aromatase inhibitor therapy. Interestingly, several studies demonstrated that the heavy metal cadmium (Cd), classified as a group 1 human carcinogen and widely spread in the environment, exerts estrogen-like activities in several tissues and suggested an intriguing relationship between increased Cd exposure and BC incidence. Thus, aim of this study was to evaluate effects of Cd on Luminal A BC estrogen receptor (ER) positive/progesterone receptor positive cell models in vitro to characterize the mechanism(s) involved in breast cell homeostasis disruption. METHODS: T47D and MCF7 were exposed to Cd (0.5-1 microM) for 6-24 h to evaluate potential alterations in: cells viability, steroid receptors and intracellular signaling by western blot. Moreover, we evaluated the expression of inflammatory cytokines interleukin by RT-PCR. RESULTS: Our results showed a significant induction of androgen receptor (AR) and an increased AR/ER ratio. Further, Cd exposure increased pro-inflammatory cytokines interleukin (IL)6, IL8 and tumor necrosis factor alpha levels. Finally, as previously demonstrated by our group, Cd alters pathways such as mitogen-activated protein kinase family and protein kinase B. CONCLUSION: In conclusion, our study demonstrates that Cd modifies the expression and pattern of ERs and AR in BC cell lines, suggesting an alteration of BC cells homeostasis, likely predisposing to a carcinogenetic microenvironment.

Borghaei, H., et al. (2023). "Nivolumab plus chemotherapy in first-line metastatic non-small-cell lung cancer: results of the phase III CheckMate 227 Part 2 trial." ESMO Open **8**(6): 102065.

BACKGROUND: In CheckMate 227 Part 1, first-line nivolumab plus ipilimumab prolonged overall survival (OS) in patients with metastatic non-small-cell lung cancer (NSCLC) and tumor programmed death-ligand 1 (PD-L1) expression >/=1% versus chemotherapy. We report results from CheckMate 227 Part 2, which evaluated nivolumab plus chemotherapy versus chemotherapy in patients with metastatic NSCLC regardless of tumor PD-L1 expression. PATIENTS AND METHODS: Seven hundred and fifty-five patients with systemic therapy-naive, stage IV/recurrent NSCLC without EGFR mutations or ALK alterations were randomized 1 : 1 to nivolumab 360 mg every 3 weeks plus chemotherapy or chemotherapy. Primary endpoint was OS with nivolumab plus chemotherapy versus chemotherapy in patients with nonsquamous NSCLC. OS in all randomized patients was a hierarchically tested secondary endpoint. RESULTS: At 19.5 months' minimum follow-up, no significant improvement in OS was seen with nivolumab plus chemotherapy versus chemotherapy in patients with nonsquamous NSCLC [median OS 18.8 versus 15.6 months, hazard ratio (HR) 0.86, 95.62% confidence interval (CI) 0.69-1.08, P = 0.1859]. Descriptive analyses showed OS improvement with nivolumab plus chemotherapy versus chemotherapy in all randomized patients (median OS 18.3 versus 14.7 months, HR 0.81, 95.62% CI 0.67-0.97) and in an exploratory analysis in squamous NSCLC (median OS 18.3 versus 12.0 months, HR 0.69, 95% CI 0.50-0.97). A trend toward improved OS was seen with nivolumab plus chemotherapy versus chemotherapy, regardless of the tumor mutation status of STK11 or TP53, regardless of tumor mutational burden, and in patients with intermediate/poor Lung Immune Prognostic Index scores. Safety with nivolumab plus chemotherapy was consistent with previous reports of first-line settings. CONCLUSIONS: CheckMate 227 Part 2 did not meet the primary endpoint of OS with nivolumab plus chemotherapy versus chemotherapy in patients with metastatic nonsquamous NSCLC. Descriptive analyses showed prolonged OS with nivolumab plus chemotherapy in all-randomized and squamous NSCLC populations, suggesting that this combination may benefit patients with untreated metastatic NSCLC.

Brennan, K., et al. (2023). "Loss of p53-DREAM-mediated repression of cell cycle genes as a driver of lymph node metastasis in head and neck cancer." Genome Med **15**(1): 98.

BACKGROUND: The prognosis for patients with head and neck cancer (HNC) is poor and has improved little in recent decades, partially due to lack of therapeutic options. To identify effective therapeutic targets, we sought to identify molecular pathways that drive metastasis and HNC progression, through large-scale systematic analyses of transcriptomic data. METHODS: We performed meta-analysis across 29 gene expression studies including 2074 primary HNC biopsies to identify

genes and transcriptional pathways associated with survival and lymph node metastasis (LNM). To understand the biological roles of these genes in HNC, we identified their associated cancer pathways, as well as the cell types that express them within HNC tumor microenvironments, by integrating single-cell RNA-seq and bulk RNA-seq from sorted cell populations. RESULTS: Patient survival-associated genes were heterogenous and included drivers of diverse tumor biological processes: these included tumor-intrinsic processes such as epithelial dedifferentiation and epithelial to mesenchymal transition, as well as tumor microenvironmental factors such as T cell-mediated immunity and cancer-associated fibroblast activity. Unexpectedly, LNM-associated genes were almost universally associated with epithelial dedifferentiation within malignant cells. Genes negatively associated with LNM consisted of regulators of squamous epithelial differentiation that are expressed within well-differentiated malignant cells, while those positively associated with LNM represented cell cycle regulators that are normally repressed by the p53-DREAM pathway. These pro-LNM genes are overexpressed in proliferating malignant cells of TP53 mutated and HPV + ve HNCs and are strongly associated with stemness, suggesting that they represent markers of pre-metastatic cancer stem-like cells. LNM-associated genes are deregulated in high-grade oral precancerous lesions, and deregulated further in primary HNCs with advancing tumor grade and deregulated further still in lymph node metastases. CONCLUSIONS: In HNC, patient survival is affected by multiple biological processes and is strongly influenced by the tumor immune and stromal microenvironments. In contrast, LNM appears to be driven primarily by malignant cell plasticity, characterized by epithelial dedifferentiation coupled with EMT-independent proliferation and stemness. Our findings postulate that LNM is initially caused by loss of p53-DREAM-mediated repression of cell cycle genes during early tumorigenesis.

Bukva, M., et al. (2023). "Machine learning-based analysis of cancer cell-derived vesicular proteins revealed significant tumor-specificity and predictive potential of extracellular vesicles for cell invasion and proliferation - A meta-analysis." Cell Commun Signal **21**(1): 333.

BACKGROUND: Although interest in the role of extracellular vesicles (EV) in oncology is growing, not all potential aspects have been investigated. In this meta-analysis, data regarding (i) the EV proteome and (ii) the invasion and proliferation capacity of the NCI-60 tumor cell lines (60 cell lines from nine different tumor types) were analyzed using machine learning methods. METHODS: On the basis of the entire proteome or the proteins shared by all EV samples, 60 cell lines were classified into the nine tumor types using multiple logistic regression. Then, utilizing the Least Absolute Shrinkage and Selection Operator, we constructed a discriminative protein panel, upon which the samples were reclassified and pathway analyses were performed. These panels were validated using clinical data (n = 4,665) from Human Protein Atlas. RESULTS: Classification models based on the entire proteome, shared proteins, and discriminative protein panel were able to distinguish the nine tumor types with 49.15%, 69.10%, and 91.68% accuracy, respectively. Invasion and proliferation capacity of the 60 cell lines were predicted with R(2) = 0.68 and R(2) = 0.62 ($p < 0.0001$). The results of the Reactome pathway analysis of the discriminative protein panel suggest that the molecular content of EVs might be indicative of tumor-specific biological processes. CONCLUSION: Integrating in vitro EV proteomic data, cell physiological characteristics, and clinical data of various tumor types illuminates the diagnostic, prognostic, and therapeutic potential of EVs. Video Abstract.

Cai, R., et al. (2023). "The use of non-steroid anti-inflammatory drugs during radical resection correlated with the outcome in non-small cell lung cancer." World J Surg Oncol **21**(1): 358.

AIMS: The use of non-steroid anti-inflammatory drugs (NSAIDs) is conventional in management of postoperative pain in cancer patients, and further investigations have reported that some of these drugs correlated with the outcome in cancers. However, the prognostic value of the use of NSAIDs during surgery in non-small cell lung cancer (NSCLC) patients has been less addressed. METHODS: NSCLC patients staged I-III are retrospectively enrolled, and the data of the use of NSAIDs during surgery are collected. Patients are divided into two subgroups according to the use intensity (UI) (low or high) of the NSAIDs, which was calculated by the accumulate dosage of all the NSAIDs divided by the length of hospitalization. The differences of the clinical features among these groups were checked. And the disease-free survival (DFS) and overall survival (OS) differences in these groups were compared by Kaplan-Meier analysis; risk factors for survival were validated by using a Cox proportional hazards model. RESULTS: The UI was significant in predicting the DFS (AUC = 0.65, 95% CI: 0.57-0.73, P = 0.001) and OS (AUC = 0.70, 95% CI: 0.59-0.81, P = 0.001). Clinical features including type of resection (P = 0.001), N stages ($P < 0.001$), and TNM

stages (P = 0.004) were significantly different in UI low (< 74.55 mg/day) or high (>/= 74.55 mg/day) subgroups. Patients in UI-high subgroups displayed significant superior DFS (log rank = 11.46, P = 0.001) and OS (log rank = 7.63, P = 0.006) than the UI-low ones. At last, the UI was found to be an independent risk factor for DFS (HR: 0.52, 95% CI: 0.28-0.95, P = 0.034). CONCLUSIONS: The use of NSAIDs during radical resection in NSCLC patients correlated with the outcome and patients with a relative high UI has better outcome.

Chaitesipaseut, L., et al. (2023). "Outcomes of weight-based vs. fixed dose of Pembrolizumab among patients with non-small cell lung cancer." J Oncol Pharm Pract: 10781552231212926.

OBJECTIVE: This study aims to assess outcomes among patients with non-small cell lung cancer (NSCLC) who received treatment with pembrolizumab on a weight-based dose (WBD) or fixed-dose (FD) regimen using a non-inferiority (NI) analysis. MATERIAL AND METHODS: This retrospective cohort study included adult patients with NSCLC weighing under 100 kg who received pembrolizumab between 1 January 2015 and 31 December 2020. Patients were grouped into either WBD or FD cohort based on the initial pembrolizumab dose and dosing regimen. The primary effectiveness outcome was overall survival (OS), analyzed using NI analysis with a lower margin of 10% comparing WBD to FD. Safety outcomes were all-cause emergency room visits or hospitalizations and incidence of selected immune-related adverse events (irAEs) and analyzed using NI analysis with an upper margin of 10%. All patients were followed until the end of health plan membership, death, or 30 June 2022, whichever occurred first. RESULTS: A total of 1413 patients were evaluated. OS was observed in 36.6% of the FD group, and 37.7% in the WBD group (rate difference: 1%, 90% CI: -6%-8%, NI p-value < 0.01). NI was met in all three safety outcomes: proportion of all-cause emergency room visits (rate difference: 1.1%, NI p-value < 0.01); proportion of hospitalizations (rate difference: 2%, NI p-value < 0.01); and composite incidence of irAEs (rate difference: -2.2%, NI p-value = 0.03). CONCLUSION: These findings suggest that WBD of pembrolizumab may be as appropriate as FD for the treatment of lung cancer.

Cheng, C., et al. (2023). "[A Novel Chinese Medicine Formula Inhibits Non-small Cell Lung Cancer by Triggering Oxidative Stress Dependent on Pentose Phosphate Pathway]." Zhongguo Fei Ai Za Zhi **26**(9): 639-649.

BACKGROUND: Non-small cell lung cancer (NSCLC) is one of the most lethal malignancies worldwide. A novel Chinese medicine formula-01 (NCHF-01) has shown significant clinical efficacy in the treatment of NSCLC, but the mechanism of this formula in the treatment of NSCLC is not fully understood. The aim of this study is to investigate the molecular mechanism of NCHF-01 in inhibiting NSCLC. METHODS: Lewis lung cells (LLC) tumor bearing mice were established to detect the tumor inhibitory effect of NCHF-01. The morphological changes of tissues and organs in LLC tumor-bearing mice were detected by hematoxylin-eosin (HE) staining. NSCLC cells were treated by NCHF-01. The effects of cell viability and proliferation were detected by MTT and crystal violet staining experiment. Flow cytometry was used to detect cell cycle, apoptosis and reactive oxygen species (ROS). Network pharmacology was used to predict the mechanism of its inhibitory effect of NSCLC. Western blot and immunohistochemistry (IHC) were used to detect the expression of related proteins. RESULTS: NCHF-01 can inhibit tumor growth in LLC tumor-bearing mice, and has no obvious side effects on other tissues and organs. NCHF-01 could inhibit cell viability and proliferation, induce G2/M phase arrest and apoptosis, and promote the increase of ROS level. Network pharmacological analysis showed that NCHF-01 exerts anti-NSCLC effects through various biological processes such as oxidative stress and central carbon metabolism. NCHF-01 can reduce the protein expression and enzyme activity of the key enzymes 6-phosphate glucose dehydrogenase (G6PD) and 6-phosphogluconate dehydrogenase (6PGD) in the pentose phosphate pathway (PPP). CONCLUSIONS: NCHF-01 can inhibit NSCLC through oxidative stress dependent on the PPP.

Chiang, C. L., et al. (2023). "Treatment and survival of patients with small cell lung cancer and brain metastasis." J Neurooncol.

PURPOSE: To elucidate treatment patterns and their outcomes in patients with small cell lung cancer (SCLC) and brain metastasis (BM). METHODS: In this retrospective study, patients with SCLC and BM were stratified by treatment modality into three groups: those treated with systemic therapy only, those treated with stereotactic radiosurgery (SRS) and systemic therapy, and those treated with whole-brain radiotherapy (WBRT) and systemic therapy. The primary outcomes were overall survival (OS) and time to central nervous system progression (TTCP). RESULTS: The analysis included 149 patients. After BM diagnosis, 48 patients (32.2%) received systemic therapy alone, 33 received SRS

with systemic therapy, and 68 received WBRT with systemic therapy. The median OS and TTCP were 7.2 months and 8.7 months, respectively. Patients receiving WBRT with systemic therapy exhibited better intracranial control, but not better OS, than did the other patients. Key prognostic factors affecting OS were age, BM lesion count, chemotherapy, and immunotherapy. Notably, the Eastern Cooperative Oncology Group performance status and BM lesion count significantly influenced intracranial control in patients treated with SRS and systemic therapy. CONCLUSION: Although WBRT combined with systemic therapy offer better intracranial control in patients with SCLC and BM, this approach is not superior to the other approaches in terms of OS benefits. Emerging systemic therapies, such as immunotherapy, may be used as alternative or adjunctive treatments for specific patient populations. Further studies are warranted to refine treatment selection.

Craig, A. J., et al. (2023). "Genome-wide profiling of transcription factor activity in primary liver cancer using single-cell ATAC sequencing." Cell Rep **42**(11): 113446.

Primary liver cancer (PLC) consists of two main histological subtypes; hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (iCCA). The role of transcription factors (TFs) in malignant hepatobiliary lineage commitment between HCC and iCCA remains underexplored. Here, we present genome-wide profiling of transcription regulatory elements of 16 PLC patients using single-cell assay for transposase accessible chromatin sequencing. Single-cell open chromatin profiles reflect the compositional diversity of liver cancer, identifying both malignant and microenvironment component cells. TF motif enrichment levels of 31 TFs strongly discriminate HCC from iCCA tumors. These TFs are members of the nuclear/retinoid receptor, POU, or ETS motif families. POU factors are associated with prognostic features in iCCA. Overall, nuclear receptors, ETS and POU TF motif families delineate transcription regulation between HCC and iCCA tumors, which may be relevant to development and selection of PLC subtype-specific therapeutics.

Ding, H. P., et al. (2023). "Effects of nutritional indices and inflammatory parameters on patients received immunotherapy for non-small cell lung cancer." Curr Probl Cancer **48**: 101035.

OBJECTIVE: This research explored the relationship between a patient's nutritional state and inflammatory markers and the prognosis of their non-small cell lung cancer (NSCLC) treatment while receiving a combination of chemotherapy and immunotherapy. METHOD: This retrospective and single-center analysis included NSCLC patients who received a combination of chemotherapy and immunotherapy at the Department of Oncology at Shanghai Lung Hospital. Patients were categorized based on malnutrition, sarcopenia, sarcopenic obesity, and advanced-lung-cancer-inflammation-index (ALI) scores after collecting nutritional and inflammatory indices. Kaplan-Meier and the Cox models were utilized to analyze survival. RESULTS: There was a significant correlation between malnutrition, sarcopenia, sarcopenic obesity, and low ALI scores with lower overall survival (OS) and progression-free survival (PFS) ($p < 0.05$). Low ALI score and malnutrition were independent factors influencing patient survival in terms of both OS and PFS ($p < 0.01$). CONCLUSION: The nutritional and inflammatory indices of immunotherapy-treated NSCLC patients substantially affect their prognosis. Assessing these variables could aid in optimizing treatment strategies and improving patient outcomes. Additional research is required to comprehend the intricate relationship between nutrition, inflammation, and cancer progression and to develop individualized therapies.

Dyas, A. R., et al. (2023). "Analyzing the Impact of the COVID-19 Pandemic on Initial Oncologic Presentation and Treatment of Non-Small Cell Lung Cancer in the United States." J Thorac Cardiovasc Surg.

BACKGROUND: Significantly lower rates of NSCLC screening, healthcare avoidance, and changes to oncologic recommendations were some consequences of the medical environment during the COVID-19 pandemic. We sought to determine how the healthcare environment during the COVID-19 pandemic affected the oncologic treatment of patients diagnosed with non-small cell lung cancer (NSCLC). METHODS: This was a retrospective cohort study evaluating patients with NSCLC in the National Cancer Database (2019-2020). Patients were divided into pre-pandemic (2019) and pandemic (2020) cohorts. Patient, oncologic, and treatment variables were compared. Multivariable logistic regression was performed to control for the impact of demographic characteristics on oncologic variables and the impact of oncologic variables on treatment variables. RESULTS: There were 250,791 patients included: 114,533 patients (45.7%) were in the pandemic cohort. There were 15% fewer new NSCLC diagnoses during the pandemic. Patients diagnosed during the pandemic had more advanced clinical TNM stage on presentation ($p<0.0001$) and were more likely to have tumors in overlapping lobes or in a main bronchus ($p=0.0002$). They were less likely to

receive cancer treatment (p<0.0001), to undergo primary resection (p<0.0001), and more likely to receive adjuvant systemic therapy (p=0.004), and a combination of palliative treatment regimens (p<0.0001). After risk-adjustment, these differences remained statistically significant (p-values<0.05). CONCLUSION: The COVID-19 pandemic was associated with increased clinical stage at presentation for patients with NSCLC, which impacted subsequent treatment strategies. However, treatment differed minimally when controlling for cancer stage. Future studies will examine the impact of these differences on overall and cancer-free survival.

Esfahanian, N., et al. (2023). "Presentation and outcomes of KRAS(G12C) mutant non-small cell lung cancer patients with stage IV disease at diagnosis (de novo) versus at recurrence." Cancer Treat Res Commun **37**: 100774.

Close monitoring after diagnosis of patients with stage I-III non-small cell lung cancer (NSCLC) may result in fitter patients with lower disease burden at the time of metastatic recurrence or progression compared to patients diagnosed initially as stage IV (de novo). We compared the presentation, treatments, and outcomes of patients with KRAS(G12C)-mutated NSCLC with de novo versus recurrent stage IV disease. Of 109 patients, 94% had a smoking history. When compared to patients with KRAS(G12C)-mutated NSCLC who developed stage IV disease at recurrence (n = 38), de novo stage IV patients (n = 71) had worse ECOG performance status (p = 0.007), greater numbers of extra-thoracic metastatic sites (p = 0.001), and were less likely to receive 2nd/3rd line systemic therapy (p = 0.05, p = 0.002) or targeted therapy (p = 0.001). De novo metastatic patients had shorter overall survival than metastatic patients at recurrence (9.1 versus 24.2 months; adjusted-hazard-ratio=1.94 (95% CI: 1.14-3.28; p = 0.01)). There is a critical need for well-tolerated targeted therapies in the first-line setting for metastatic patients with de novo, high-burden, stage IV KRAS(G12C)-mutated NSCLCs.

Fan, X., et al. (2023). "Development of [(89)Zr]Zr-hCD103.Fab01A and [(68)Ga]Ga-hCD103.Fab01A for PET imaging to noninvasively assess cancer reactive T cell infiltration: Fab-based CD103 immunoPET." EJNMMI Res **13**(1): 100.

BACKGROUND: CD103 is an integrin specifically expressed on the surface of cancer-reactive T cells. The number of CD103+ T cells significantly increases during successful immunotherapy and might therefore be an attractive biomarker for noninvasive PET imaging of immunotherapy response. Since the long half-life of antibodies preclude repeat imaging of CD103+ T cell dynamics early in therapy, we therefore here explored PET imaging with CD103 Fab fragments radiolabeled with a longer ((89)Zr) and shorter-lived radionuclide ((68)Ga). METHODS: Antihuman CD103 Fab fragment Fab01A was radiolabeled with (89)Zr or (68)Ga, generating [(89)Zr]Zr-hCD103.Fab01A and [(68)Ga]Ga-hCD103.Fab01A, respectively. In vivo evaluation of these tracers was performed in male nude mice (BALB/cOlaHsd-Foxn1nu) with established CD103-expressing CHO (CHO.CD103) or CHO-wildtype (CHO.K1) xenografts, followed by serial PET imaging and ex vivo bio-distribution. RESULTS: [(89)Zr]Zr-hCD103.Fab01A showed high tracer uptake in CD103+ xenografts as early as 3 h post-injection. However, the background signal remained high in the 3- and 6-h scans. The background was relatively low at 24 h after injection with sufficient tumor uptake. [(68)Ga]Ga-hCD103.Fab01Ashowed acceptable uptake and signal-to-noise ratio in CD103+ xenografts after 3 h, which decreased at subsequent time points. CONCLUSION: [(89)Zr]Zr-hCD103.Fab01A demonstrated a relatively low background and high xenograft uptake in scans as early as 6 h post-injection and could be explored for repeat imaging during immunotherapy in clinical trials. (18)F or (64)Cu could be explored as alternative to (68)Ga in optimizing half-life and radiation burden of the tracer.

Feng, B., et al. (2023). "Chemoimmunotherapy combined with consolidative thoracic radiotherapy for extensive-stage small cell lung cancer: A systematic review and meta-analysis." Radiother Oncol: 110014.

INTRODUCTION: This study aimed to evaluate the efficacy and safety of chemoimmunotherapy combined with consolidative thoracic radiation therapy (cTRT) in patients with extensive-stage small cell lung cancer (ES-SCLC). METHODS: A meta-analysis was conducted. PubMed, Embase, Web of Science, and the Cochrane Library were searched. The study was registered in PROSPERO (registration no. CRD42023410344). RESULTS: A total of 4677 studies were initially screened and 15 studies encompassing a total of 1033 patients were included. Chemoimmunotherapy combined with cTRT significantly improved survival (HR=0.52, 95% CI: 0.39, 0.68) with favorable 6-month (0.89, 95% CI: 0.77, 1.00) and 1-year (0.77, 95% CI: 0.72, 0.82) OS, without affecting >=3 grade TRAEs (RR=1.29, 95% CI: 0.85, 1.98). Pooled 6-month and 1-year PFS were 0.67 (95% CI: 0.47, 0.86) and 0.38 (95% CI: 0.22, 0.55), respectively.

Incidence of >=3 grade TRAEs was 0.24 (95% CI: 0.08, 0.39) and radiation pneumonitis was 0.03 (95% CI: 0.01, 0.06). CONCLUSIONS: Chemoimmunotherapy combined with cTRT improves survival and shows favorable outcomes in ES-SCLC patients, with manageable adverse events. Further research with larger samples is needed to confirm these findings.

Flashner, S., et al. (2023). "ALDH2 dysfunction and alcohol cooperate in cancer stem cell enrichment." Carcinogenesis.

The alcohol metabolite acetaldehyde is a potent human carcinogen linked to esophageal squamous cell carcinoma (ESCC) initiation and development. Aldehyde dehydrogenase 2 (ALDH2) is the primary enzyme that detoxifies acetaldehyde in the mitochondria. Acetaldehyde accumulation causes genotoxic stress in cells expressing the dysfunctional ALDH2E487K dominant negative mutant protein linked to ALDH2*2, the single nucleotide polymorphism highly prevalent amongst East Asians. Heterozygous ALDH2*2 increases the risk for the development of ESCC and other alcohol-related cancers. Despite its prevalence and link to malignant transformation, how ALDH2 dysfunction influences ESCC pathobiology is incompletely understood. Herein, we characterize how ESCC and preneoplastic cells respond to alcohol exposure using cell lines, three dimensional organoids, and xenograft models. We find that alcohol exposure and ALDH2*2 cooperate to increase putative ESCC cancer stem cells with high CD44 expression (CD44H cells) linked to tumor initiation, repopulation, and therapy resistance. Concurrently, ALHD2*2 augmented alcohol-induced reactive oxygen species and DNA damage to promote apoptosis in the non-CD44H cell population. Pharmacological activation of ALDH2 by Alda-1 inhibits this phenotype, suggesting that acetaldehyde is the primary driver of these changes. Additionally, we find that Aldh2 dysfunction affects the response to cisplatin, a chemotherapeutic commonly used for the treatment of ESCC. Aldh2 dysfunction facilitated enrichment of CD44H cells following cisplatin-induced oxidative stress and cell death in murine organoids, highlighting a potential mechanism driving cisplatin resistance. Together, these data provide evidence that ALDH2 dysfunction accelerates ESCC pathogenesis through enrichment of CD44H cells in response to genotoxic stressors such as environmental carcinogens and chemotherapeutic agents.

Foy, R., et al. (2023). "Oncogenic signals prime cancer cells for toxic cell overgrowth during a G1 cell cycle arrest." Mol Cell **83**(22): 4047-4061 e4046.

CDK4/6 inhibitors are remarkable anti-cancer drugs that can arrest tumor cells in G1 and induce their senescence while causing only relatively mild toxicities in healthy tissues. How they achieve this mechanistically is unclear. We show here that tumor cells are specifically vulnerable to CDK4/6 inhibition because during the G1 arrest, oncogenic signals drive toxic cell overgrowth. This overgrowth causes permanent cell cycle withdrawal by either preventing progression from G1 or inducing genotoxic damage during the subsequent S-phase and mitosis. Inhibiting or reverting oncogenic signals that converge onto mTOR can rescue this excessive growth, DNA damage, and cell cycle exit in cancer cells. Conversely, inducing oncogenic signals in non-transformed cells can drive these toxic phenotypes and sensitize the cells to CDK4/6 inhibition. Together, this demonstrates that cell cycle arrest and oncogenic cell growth is a synthetic lethal combination that is exploited by CDK4/6 inhibitors to induce tumor-specific toxicity.

Gao, L., et al. (2023). "[SWI/SNF Complex Gene Mutations Promote the Liver Metastasis of Non-small Cell Lung Cancer Cells in NSI Mice]." Zhongguo Fei Ai Za Zhi **26**(10): 753-764.

BACKGROUND: The switch/sucrose nonfermentable chromatin-remodeling (SWI/SNF) complex is a pivotal chromatin remodeling complex, and the genomic alterations (GAs) of the SWI/SNF complex are observed in several cancer types, correlating with multiple biological features of tumor cells. However, their role in liver metastasis of non-small cell lung cancer (NSCLC) remains unclear. Our study aims to investigate the role and potential mechanisms underlying NSCLC liver metastasis induced by the GAs of SWI/SNF complex. METHODS: The GAs of SWI/SNF complex in NSCLC cell lines (H1299, H23 and H460) were identified by whole-exome sequencing (WES). ARID1A knockout H1299 cell was constructed with the CRISPR/Cas9 technology. The mouse model of liver metastasis from NSCLC was established to simulate lung cancer liver metastasis and observe the metastasis rate under different gene mutation conditions. RNA sequencing and Western blot were conducted for differential gene expression analysis. Immunohistochemistry (IHC) analysis was used to assess protein expression levels of SWI/SNF-regulated target molecules in mouse liver metastases. RESULTS: WES analysis revealed intracellular gene mutations. The animal experiments demonstrated a correlation between the GAs of SWI/SNF complex and a higher liver metastasis rate in immunodeficient mice. Transcriptome sequencing and Western blot analysis showed upregulated expression of

ALDH1A1 and APOBEC3B in SWI/SNF-mut cells, particularly in ARID1A-deficient H460 and H1299 sgARID1A cells. IHC staining of mouse liver metastases further demonstrated elevated expression of ALDH1A1 in the H460 and H1299 sgARID1A group. CONCLUSIONS: This study underscores the critical role of the GAs of SWI/SNF complex, such as ARID1A and SMARCA4, in promoting liver metastasis of lung cancer cells. The GAs of SWI/SNF complex may promote liver-specific metastasis by upregulating ALDH1A1 and APOBEC3B expression, providing novel insights into the molecular mechanisms underlying lung cancer liver metastasis.

Garcia-Fernandez, J., et al. (2023). "Chemical conjugation of aptamer-sphingomyelin nanosystems and their potential as inhibitors of tumour cell proliferation in breast cancer cells." Nanoscale.

Breast cancer is a complex and heterogeneous disease with a high mortality rate due to non-specific cytotoxicity, low intratumoral accumulation and drug resistance associated with the ineffectiveness of chemotherapy. In recent years, all efforts have been focused on finding new markers and therapeutic targets, protein kinase MNK1b being a promising candidate. Recently, an aptamer known as apMNK2F showed a highly specific interaction with this protein kinase, leading to a significant reduction in tumour cell proliferation, migration and colony formation. However, as aptamers are unable to penetrate the cell membrane and reach the target, these small biomolecules need to be conjugated to suitable vectors that can transport and protect them inside the cells. In this work, covalent conjugation between biocompatible and non-harmful nanoemulsions of vitamin E and sphingomyelin and the aptamer was performed to facilitate intracellular delivery of the therapeutic aptamer apMNK2F. All strategies employed were based on 2-step bioconjugation and optimized to get the simplest and most reproducible vehicle with the highest association efficiency (about 70% in all cases). The ability of the nanosystems to successfully deliver the conjugated therapeutic aptamer was demonstrated and compared to other commercial transfection agents such as Lipofectamine 2000, leading to an effective decrease of breast cancer cell proliferation in the MDA-MB-231 cell line. The proliferation inhibition of the aptamer nanoconjugates compared to the non-conjugated aptamer provides evidence that the antitumoral capacity derived from kinase interaction is improved in a dose-dependent manner. Furthermore, various experiments including cell migration and colony formation assays, along with apoptosis induction experiments, emphasize the significant antitumoral potential. Overall, the obtained results indicate that the developed formulation could be a promising therapy for the treatment of breast cancer.

Gastelum-Lopez, M. L. A., et al. (2023). "Organotypic 3D Cell-Architecture Impacts the Expression Pattern of miRNAs-mRNAs Network in Breast Cancer SKBR3 Cells." Noncoding RNA **9**(6).

BACKGROUND: Currently, most of the research on breast cancer has been carried out in conventional two-dimensional (2D) cell cultures due to its practical benefits, however, the three-dimensional (3D) cell culture is becoming the model of choice in cancer research because it allows cell-cell and cell-extracellular matrix (ECM) interactions, mimicking the native microenvironment of tumors in vivo. METHODS: In this work, we evaluated the effect of 3D cell organization on the expression pattern of miRNAs (by Small-RNAseq) and mRNAs (by microarrays) in the breast cancer SKBR3 cell line and analyzed the biological processes and signaling pathways regulated by the differentially expressed protein-coding genes (DE-mRNAs) and miRNAs (DE-microRNAs) found in the organoids. RESULTS: We obtained well-defined cell-aggregated organoids with a grape cluster-like morphology with a size up to 9.2 x 10(5) mum(3). The transcriptomic assays showed that cell growth in organoids significantly affected (all $p < 0.01$) the gene expression patterns of both miRNAs, and mRNAs, finding 20 upregulated and 19 downregulated DE-microRNAs, as well as 49 upregulated and 123 downregulated DE-mRNAs. In silico analysis showed that a subset of 11 upregulated DE-microRNAs target 70 downregulated DE-mRNAs. These genes are involved in 150 gene ontology (GO) biological processes such as regulation of cell morphogenesis, regulation of cell shape, regulation of canonical Wnt signaling pathway, morphogenesis of epithelium, regulation of cytoskeleton organization, as well as in the MAPK and AGE-RAGE signaling KEGG-pathways. Interestingly, hsa-mir-122-5p (Fold Change (FC) = 15.4), hsa-mir-369-3p (FC = 11.4), and hsa-mir-10b-5p (FC = 20.1) regulated up to 81% of the 70 downregulated DE-mRNAs. CONCLUSION: The organotypic 3D cell-organization architecture of breast cancer SKBR3 cells impacts the expression pattern of the miRNAs-mRNAs network mainly through overexpression of hsa-mir-122-5p, hsa-mir-369-3p, and hsa-mir-10b-5p. All these findings suggest that the interaction between cell-cell and cell-ECM as well as the change in the culture architecture impacts gene expression, and, therefore, support the pertinence of migrating breast cancer research from conventional cultures to 3D models.

Gawlik, C., et al. (2023). "Tumor-to-tumor spread: a case report and literature review of renal cell carcinoma metastasis into thyroid cancer." World J Surg Oncol **21**(1): 362.

Tumor-to-tumor metastasis is a rare, yet important entity. Patients with a history of renal cell carcinoma (RCC) may have tumor deposits to the thyroid gland preceding or following their initial cancer diagnosis for many years. The diagnosis can be challenging, and clinicians must remain suspicious of a newly found thyroid nodule in a patient with a history of RCC. In this review, we report a case of a patient with RCC who was incidentally found to have a thyroid nodule on surveillance imaging found to be consistent with tumor-to-tumor metastasis from RCC into papillary thyroid carcinoma. It is imperative to consider this diagnosis as the thyroid is the most common site of spread, and treatment with partial or total thyroidectomy has led to improved survival.

Gong, Q., et al. (2023). "B-cell lymphoma-2 family proteins in the crosshairs: Small molecule inhibitors and activators for cancer therapy." Med Res Rev.

The B-cell lymphoma-2 (BCL-2) family of proteins plays a crucial role in the regulation of apoptosis, offering a dual mechanism for its control. Numerous studies have established a strong association between gene disorders of these proteins and the proliferation of diverse cancer cell types. Consequently, the identification and development of drugs targeting BCL-2 family proteins have emerged as a prominent area in antitumor therapy. Over the last two decades, several small-molecules have been designed to modulate the protein-protein interactions between anti- and proapoptotic BCL-2 proteins, effectively suppressing tumor growth and metastasis in vivo. The primary focus of research has been on developing BCL-2 homology 3 (BH3) mimetics to target antiapoptotic BCL-2 proteins, thereby competitively releasing proapoptotic BCL-2 proteins and restoring the blocked intrinsic apoptotic program. Additionally, for proapoptotic BCL-2 proteins, exogenous small molecules have been explored to activate cell apoptosis by directly interacting with executioner proteins such as BCL-2-associated X protein (BAX) or BCL-2 homologous antagonist/killer protein (BAK). In this comprehensive review, we summarize the inhibitors and activators (sensitizers) of BCL-2 family proteins developed over the past decades, highlighting their discovery, optimization, preclinical and clinical status, and providing an overall landscape of drug development targeting these proteins for therapeutic purposes.

Gray, J. E., et al. (2023). "Pan-tumor analytical validation and osimertinib clinical validation in EGFR mutant non-small cell lung cancer, supporting the first next generation sequencing liquid biopsy in vitro diagnostic." J Mol Diagn.

Comprehensive genotyping is necessary to identify therapy options for patients with advanced cancer; however, many are not tested, partly due to tissue limitations. Next generation sequencing (NGS) liquid biopsies overcome limitations but clinical validity is not established and adoption, limited. Clinical bridging studies used pre-treatment plasma samples and data from FLAURA (NCT02296125; n=441) and AURA3 (NCT02151981; n=450) pivotal studies to demonstrate clinical validity of Guardant360 CDx (NGS LBx) to identify patients with advanced EGFR mutant NSCLC who may benefit from osimertinib. Primary endpoint was progression-free survival (PFS). Patients EGFR mutant by NGS LBx had significant PFS benefit with first-line osimertinib over standard of care (15.2 vs 9.6 months, HR 0.41, p<0.0001) and with later-line osimertinib over chemotherapy (8.3 vs 4.2 months, HR 0.34, p<0.0001). PFS benefit were similar to the original trial cohorts selected by tissue-based EGFR testing. Analytical validation included accuracy, precision, limit of detection (LOD), and specificity. Analytical validity was established for EGFR mutation detection and pan-tumor profiling. Panel-wide LOD was 0.1%-0.5%, with 98-100% per-sample specificity. Patients with EGFR mutant NSCLC by NGS LBx had improved PFS with osimertinib, confirming clinical validity. Analytical validity was established for guideline-recommended therapeutic targets across solid tumors. The resulting FDA-approval of NGS LBx demonstrates safety and effectiveness for its intended use and is expected to improve adherence to guideline-recommended targeted therapy use.

Guan, M. C., et al. (2023). "Metformin as a booster or obstacle of immunotherapy in patients with non-small cell lung cancer and diabetes mellitus." Cancer.

Guneidy, R. A., et al. (2023). "Adverse effect of Tamarindus indica and tamoxifen combination on redox balance and genotoxicity of breast cancer cell." J Genet Eng Biotechnol **21**(1): 131.

BACKGROUND: Breast cancer is the most significant threat to women worldwide. Most chemotherapeutic drugs cause cancer cell death and apoptosis by inducing oxidative stress and producing reactive oxygen species (ROS). Cancer cells have a higher rate of metabolic activity than normal cells and thus produce more ROS. Glutathione and its related enzymes are the most significant antioxidant

defense mechanisms that protect cells from oxidative and chemotherapeutic impacts. The anticancer actions of phenolic compounds were greatly confirmed. Using phenolic compounds as drugs in combination with chemotherapy may improve health, improve treatment outcomes, and reduce dose and damage. The goal of the study was to treat breast cancer cell lines (MCF-7) with Tamarindus indica extract individually and in combination with the anticancer drug tamoxifen (TAM) to improve therapeutic efficacy. RESULTS: After 48 h of incubation at IC(25) concentrations of T. indica extract (47.3 g/mL), tamoxifen (0.8 g/mL), and their co-treatments, the biochemical and genotoxic effects on MCF-7 cell lines were investigated. In MCF7 cell lines, T. indica extract increased reduced glutathione levels as well as glutathione transferase, glutathione peroxidase, and glutathione reductase activities. The same was true for oxidative state indicators, where higher levels of catalase and lactate dehydrogenase activity were associated with higher levels of malondialdehyde. T. indica has almost no effect on the DNA damage parameters. All of these variations can produce alterations in cancer cell genotoxicity and apoptotic pathways, explaining the restoration of DNA moment to normal levels and enhanced survival. CONCLUSION: Cytotoxic and genotoxic effect of treatment with T. indica extract could be attributed to the dynamic interaction of glutathione cycle and antioxidant enzymes to combat oxidative stress, which can be considered as a positive therapeutic effect. On the other hand, the negative response of tamoxifen efficacy when co-treated with T. indica reversed tamoxifen's genotoxicity and enhanced survival.

Guo, W., et al. (2023). "circ_0006528 promotes nonsmall cell lung cancer progression by sponging miR-892a and regulating NRAS expression." Anticancer Drugs.

Micro-RNAs play essential roles in developing and progressing nonsmall cell lung cancer (NSCLC) and drug resistance. Nevertheless, the functions and mechanisms are partly explored. Therefore, the present study analyzes the effect of circ_0006528 and the mechanism of regulation of NSCLC cell progression by sponging miR-892a to regulate neuroblastoma rat sarcoma viral oncogene (NRAS) expression. Initially, circ_0006528 is identified using divergent primers-based PCR and RNase R exonuclease treatments. After administration of the designed circ_0006528-specific siRNA, the RT-qPCR analysis is used to determine the interference efficiency of siRNA. At the same time, cell growth, invasion, and migration are assessed by 3-[4,5-dimethylthiazol-2-yl]-2,5 diphenyl tetrazolium bromide (MTT), Transwell, and scratch assays in the NSCLC cell lines (secretory pathway Ca2+-ATPase isoform 1 [SPCA-1] and A549) in vitro, respectively. Further, miR-892a inhibitor is added to the cells for functional recovery assay. Finally, the xenograft mouse model is constructed to explore the effect of circ_0006528 on tumor growth in vivo. The RT-qPCR analysis in 66 pairs of NSCLC cancer and noncancerous tissues revealed that circ_0006528 is highly expressed in NSCLC patient tissues. The RNase R experiments revealed that HSA_circ_0006528 is unaffected by RNase R exonuclease. MTT assay showed that knockdown of hsa_circ_0006528 by siRNA significantly decreased cell proliferation and viability in A549 and SPCA-1 cells. The luciferase reporter assay showed direct binding of hsa_circ_0006528 to miR-892a, and miR-892a targets binding NRAS. In addition, the miR-892a inhibitor terminated the hsa_circ_0006528 siRNA, triggering inhibition of proliferation, invasion, and migration of NSCLC cells. In summary, the study revealed that the knockout of hsa_circ_0006528 downregulation of NRAS expression by sponging miR-892a inhibited NSCLC cell growth and invasion.

He, J., et al. (2024). "Multidrug resistance protein 5 affects cell proliferation, migration and gemcitabine sensitivity in pancreatic cancer MIA Paca-2 and PANC-1 cells." Oncol Rep **51**(1).

Gemcitabine-based chemotherapy has been widely adopted as the standard and preferred chemotherapy regimen for treating advanced pancreatic cancer. However, the contribution of multidrug resistance protein 5 (MRP5) to gemcitabine resistance and pancreatic cancer progression remains controversial. In the present study, the effect of silencing MRP5 on gemcitabine resistance and cell proliferation and migration of human pancreatic cancer MIA Paca-2 and PANC-1 cells was investigated by using short-hairpin RNA delivered by lentiviral vector transduction. The knockdown of MRP5 was confirmed on both mRNA and protein levels using qPCR and surface staining assays, respectively. MRP5-regulated gemcitabine sensitivity was assessed by MTT, PrestoBlue and apoptosis assays. The effect of MRP5 on pancreatic cancer cell proliferation and migration was determined using colony-formation, wound-healing and Transwell migration assays. The interaction of gemcitabine and cyclic guanosine monophosphate (cGMP) with MRP5 protein was explored using molecular docking. The results indicated that the MRP5 mRNA and protein levels were significantly reduced in all the MIA Paca-2 and PANC-1 clones. MRP5 affected gemcitabine cytotoxicity and the rate

of gemcitabine-induced apoptosis. Silencing MRP5 decreased cell proliferation and migration in both MIA Paca-2 and PANC-1 cells. Docking studies showed high binding affinity of cGMP towards MRP5, indicating the potential of MRP5-mediated cGMP accumulation in the microenvironment. In conclusion, MRP5 has an important role in cancer proliferation and migration in addition to its drug efflux functions in two widely available pancreatic tumour cell lines (MIA Paca-2 and PANC-1).

Huang, C., et al. (2023). "CKAP4 and mutant p53 cooperatively abrogate cell cycle checkpoint to induce genotoxic resistance in ovarian cancer." Clin Transl Med **13**(11): e1476.

Huang, J., et al. (2023). "Rationale and Design of a Phase II Trial of Combined Serplulimab and Chemotherapy in Patients with Histologically Transformed Small Cell Lung Cancer: a Prospective, Single-arm and Multicentre Study." Clin Oncol (R Coll Radiol).

AIMS: Transformed small cell lung cancer (T-SCLC) is a highly aggressive clinical disease with a notably poor prognosis. It most often arises from epidermal growth factor receptor (EGFR)-mutant non-small cell lung cancer (NSCLC) following treatment. To date, no standard treatment has been established for T-SCLC. Platinum-etoposide was the most commonly used regimen, but progression-free survival remains unsatisfactory. Therefore, there is an urgent unmet need to develop novel and effective strategies for this population. Our study, a multicentre, open-label, single-arm phase II clinical trial (NCT05957510), aims to evaluate the efficacy and safety of serplulimab plus chemotherapy in untreated T-SCLC patients after histological transformation. MATERIALS AND METHODS: In total, 36 eligible participants experiencing SCLC transformation from EGFR-mutant NSCLC will be enrolled to receive combination therapy of serplulimab, etoposide and carboplatin for four to six cycles, followed by maintenance therapy with serplulimab for up to 2 years. The primary endpoint is progression-free survival; secondary endpoints include objective response rate, overall survival and safety. RESULTS: Enrolment started in July 2023 and is ongoing, with an estimated completion date of December 2025. CONCLUSIONS: This study aims to provide valuable insights into the efficacy and safety of combining serplulimab with chemotherapy for treating patients with T-SCLC originating from EGFR-mutant NSCLC.

Kazmierczak-Siedlecka, K., et al. (2023). "Pharmacomicrobiomics of cell-cycle specific anti-cancer drugs - is it a new perspective for personalized treatment of cancer patients?" Gut Microbes **15**(2): 2281017.

Intestinal bacteria are equipped with an enzyme apparatus that is involved in the active biotransformation of xenobiotics, including drugs. Pharmacomicrobiomics, a new area of pharmacology, analyses interactions between bacteria and xenobiotics. However, there is another side to the coin. Pharmacotherapeutic agents can significantly modify the microbiota, which consequently affects their efficacy. In this review, we comprehensively gathered scientific evidence on the interplay between anticancer therapies and gut microbes. We also underlined how such interactions might impact the host response to a given therapy. We discuss the possibility of modulating the gut microbiota to increase the effectiveness/decrease the incidence of adverse events during tumor therapy. The anticipation of the future brings new evidence that gut microbiota is a target of interest to increase the efficacy of therapy.

Ke, D., et al. (2023). "Inhibition of UFM1 expression suppresses cancer progression and is linked to the dismal prognosis and immune infiltration in oral squamous cell carcinoma." Aging (Albany NY) **15**.

BACKGROUND: Ubiquitin fold modifier 1 (UFM1) overexpression is associated with cancer cell proliferation, migration and invasion. However, the roles and pathways of UFM1 in oral squamous cell carcinoma (OSCC) has remained undefined. METHODS: The expression of UFM1 and the relationship between UFM1 expression and prognosis were investigated using data of OSCC patients from The Cancer Genome Atlas (TCGA) database. The UFM1 co-expressed genes, and the association between the UFM1 expression and immune cells and ubiquitination were explored. The effects of UFM1 expression on the growth and migration of OSCC cells were investigated by siRNA interference, Cell Counting Kit-8 (CCK-8), Transwell, Western blotting, and wound healing experiments. RESULTS: UFM1 was highly expressed in OSCC. UFM1 overexpression was associated with short overall survival, disease-specific survival, and progression-free interval, and was an adverse factor for prognosis in OSCC. UFM1-related nomograms were significantly associated with poor prognosis in OSCC patients. Decreased UFM1 expression could inhibit the proliferation, migration, and invasion of OSCC cells. UFM1 was associated with the immune cells (such as the Th17 cells, T helper cells, and cytotoxic cells) and ubiquitination. CONCLUSION: Elevated UFM1 expression was associated with poor prognosis, ubiquitination and immune infiltration in

OSCC, and inhibition of UFM1 expression delayed OSCC progression, showing that UFM1 could be a biomarker for prognosis and treating OSCC patients.

Kim, G., et al. (2023). "Application of Small Cell Lung Cancer Molecular Subtyping Markers to Small Cell Neuroendocrine Carcinoma of the Cervix: NEUROD1 as a Poor Prognostic Factor." Am J Surg Pathol.

Cervical small cell neuroendocrine carcinoma (CSCNEC) is a rare, aggressive type of cervical cancer. The treatment for CSCNEC follows the chemotherapeutic regimens used for small cell lung cancer (SCLC), with which it shares similar clinical and histologic features. For the first time, we applied neuroendocrine (NE) and SCLC molecular subtyping immunohistochemical markers [achaete-scute homolog 1 (ASCL1), neurogenic differentiation factor 1 (NEUROD1), POU class 2 homeobox 3 (POU2F3), and yes-associated protein 1] in 45 patients with CSCNEC. For the combined NE score, 51.1% of NE-high and 48.9% of NE-low subtypes were identified. The NE-high subtype tended to show worse progression-free survival and overall survival (OS) than the NE-low subtype (P=0.059 and P=0.07, respectively). Applying the SCLC molecular subtyping, 53.3% of cases were identified as NEUROD1-dominant, 17.8% as ASCL1-dominant, 13.3% as YAP-dominant, and 4.4% as POU2F3-dominant, while 11.1% of cases showed negative expression for all markers; the distribution was different from that of SCLC. The NEUROD1-dominant subtype exhibited the worst OS, while the POU2F3 subtype exhibited the best OS (P=0.003), similar to SCLC. In addition, the ASCL1-dominant and NEUROD1-dominant subtypes showed high NE scores, while yes-associated protein 1-dominant and POU2F3-dominant subtypes showed low NE scores (P=0.008). In multivariate analysis, the NEUROD1 expression was further identified as the independent prognostic factor for worse OS, together with the high FIGO stage. CSCNEC was revealed to be a heterogeneous disease with different biological phenotypes and to share some similarities and differences with SCLC. Regarding the ongoing development of tailored treatments based on biomarkers in SCLC, the application of biomarker-driven individualized therapy would improve clinical outcomes in patients with CSCNEC.

Kwon, Y. J., et al. (2023). "Prognostic significance of body mass index in small-cell lung cancer: Exploring the relationship with skeletal muscle status." J Cachexia Sarcopenia Muscle.

BACKGROUND: We investigated the prognostic significance of body mass index in small-cell lung cancer and explored whether skeletal muscle status affects the body mass index-survival relationship. METHODS: This retrospective study evaluated data from patients who underwent platinum-etoposide chemotherapy for small-cell lung cancer between March 2010 and December 2021. Skeletal muscle status was assessed using non-contrast computed tomography images of baseline positron-emission tomography-computed tomography, with the skeletal muscle index defined as the cross-sectional area of skeletal muscle divided by height squared, and the average attenuation values of skeletal muscle. Cox proportional hazards regression analysis was used to determine the correlations of body mass index, skeletal muscle metrics, and overall survival. RESULTS: We analysed the data of 1146 Asian patients (1006 men and 140 women, with a median age of 67 years [interquartile range: 61-72 years]), including 507 and 639 patients with limited and extensive disease, respectively. Being underweight, defined as a body mass index <18.5 kg/m(2) , was associated with shorter overall survival, independent of clinical covariates in both the limited-disease (hazard ratio, 1.77; 95% confidence interval, 1.01-3.09) and extensive-disease (hazard ratio, 1.71; 95% confidence interval, 1.18-2.48) groups. The prognostic value of being underweight remained significant after additional adjustment for skeletal muscle index and attenuation in both limited-disease (hazard ratio, 1.96; 95% confidence interval, 1.09-3.51) and extensive-disease (hazard ratio, 1.75; 95% confidence interval, 1.17-2.61) groups. CONCLUSIONS: Being underweight is an independent poor prognostic factor for shorter overall survival in Asian patients with small-cell lung cancer, regardless of skeletal muscle status.

Leshem, Y., et al. (2023). "Reply to "Metformin as a booster or obstacle of immunotherapy in patients with non-small cell lung cancer and diabetes mellitus"." Cancer.

Li, C., et al. (2023). "An immunogenic cell death-related signature for prediction of prognosis and response to immunotherapy in breast cancer." Chin Med J (Engl).

Li, S. and X. Zhang (2023). "[Drug Resistance Mechanism and Therapeutic Strategy of Targeted Therapy of Non-small Cell Lung Cancer with MET Alterations]." Zhongguo Fei Ai Za Zhi **26**(9): 684-691.

Mesenchymal to epithelial transition factor (MET) gene alterations involve in the proliferation, invasion, and metastasis of non-small cell lung

cancer. MET-tyrosine kinase inhibitors (TKIs) have been approved to treat non-small cell lung cancer with MET alterations, and resistance to these TKIs is inevitable. Molecular mechanisms of resistance to MET-TKIs are completely unclear. The review focused on potential mechanisms of MET-TKIs resistance and therapeutics strategies to delay and prevent resistance.[P][SEP].

Li, Y., et al. (2023). "Engrailed 2 serves as a master regulator of the super-enhancer in the TNC gene locus in non-small cell lung cancer." Environ Toxicol.

Engrailed 2 (EN2) is a homeodomain-containing protein that is dysregulated in many types of cancer. However, the role of EN2 in non-small cell lung cancer (NSCLC) and the mechanism underlying its biological function are largely unclear. Here, we showed that EN2 played an oncogenic function in NSCLC and greatly enhanced the malignant phenotype of NSCLC cells. Meanwhile, EN2 was able to boost the expression of a well-studied oncogenic Tenascin-C (TNC) gene, which in turn activated the AKT signaling pathway. Interestingly, we found that EN2 directly bound to the super-enhancer (SE) region in the TNC locus. The histone marker H3K27ac was also enriched in the region, indicating the activation of the SE. Treatment of the cells with JQ1, an inhibitor of SE activity, abrogated the effect of EN2 on the expression of TNC and phosphorylation of AKT-Ser473. Collectively, our work unveils a novel mode of EN2 function, in which EN2 governs the SE in the TNC locus, consequently activating the oncogenic TNC-AKT axis in NSCLC.

Li, Y., et al. (2023). "Effect of initial recurrence site on the prognosis of different tissue types of non-small cell lung cancer: a retrospective cohort study." World J Surg Oncol **21**(1): 360.

PURPOSE: To explore the correlation between the initial recurrence site and survival after recurrence (PRS) in non-small cell lung cancer (NSCLC). METHODS: We collected 588 stages I-III NSCLC patients with recurrence after radical resection in Yunnan Cancer Hospital from January 2013 to December 2018. We used Kaplan-Meier survival curves to compare PRS in patients with different site recurrences. The univariate and multivariate Cox proportional hazard models were used to analyze the impact of the initial recurrence site on PRS. RESULTS: The recurrence site included the lung (n = 109), brain (n = 113), bone (n = 79), abdomen (n = 28), pleura (n = 24), lymph node (n = 81), and multisite (n = 154). In the total population, patients with multisite recurrence had substantially worse PRS (24.8 months, 95% confidence interval [CI]: 17.46-32.20) than that of patients without multiple sites recurrence (42.2 months, 95% CI 32.24-52.10) (P = 0.026). However, patients with lung recurrence had better RFS (63.1 months, 95% CI 51.13-74.00) than those who did not (31.0 months, 95% CI 25.10-36.96) (P < 0.001). In adenocarcinoma, patients with pleural recurrence had substantially worse PRS (21.3 months, 95% CI 15.07-27.46) than that of patients without pleural recurrence (46.9 months, 95% CI 35.07-58.80) (P = 0.031). Multivariate Cox proportional hazards regression analysis revealed that lung recurrence (HR 0.58, 95% CI 0.40-0.82; P = 0.003) was independent protective prognostic factor for PRS in the total population, while pleural recurrence (HR 2.18, 95% CI 1.14-4.17; P = 0.018) was independent adverse prognostic factors for PRS in adenocarcinoma patients. CONCLUSION: The initial recurrence site was associated with PRS in NSCLC patients. Identification of recurrence sites could guide the subsequent treatment.

Li, Y., et al. (2023). "EphA2 as a phase separation protein associated with ferroptosis and immune cell infiltration in colorectal cancer." Aging (Albany NY) **15**.

Colorectal cancer is one of the most common malignant tumors in the digestive system, and its high incidence and metastasis rate make it a terrible killer that threatens human health. In-depth exploration of the targets affecting the progression of colorectal cancer cells and the development of specific targeted drugs for them are of great significance for the prognosis of colorectal cancer patients. Erythropoietin-producing hepatocellular A2 (EphA2) is a member of the Eph subfamily with tyrosine kinase activity, plays a key role in the regulation of signaling pathways related to the malignant phenotype of various tumor cells, but its specific regulatory mechanism in colorectal cancer needs to be further clarified. Here, we found that EphA2 was abnormally highly expressed in colorectal cancer and that patients with colorectal cancer with high EphA2 expression had a worse prognosis. We also found that EphA2 can form liquid-liquid phase separation condensates on cell membrane, which can be disrupted by ALW-II-41-27, an inhibitor of EphA2. In addition, we found that EphA2 expression in colorectal cancer was positively correlated with the expression of ferroptosis-related genes and the infiltration of multiple immune cells. These findings suggest that EphA2 is a novel membrane protein with phase separation ability and is associated with ferroptosis and immune cell infiltration, which further suggests that malignant progression of colorectal cancer may be inhibited by suppressing the phase separation ability of EphA2.

Li, Y. Q., et al. (2023). "Prediction and validation of common targets in atherosclerosis and non-small cell lung cancer influenced by atorvastatin." BMC Complement Med Ther **23**(1): 415.

BACKGROUND: Cardiovascular disease and cancer are the main causes of morbidity and mortality worldwide. Studies have shown that these two diseases may have some common risk factors. Atorvastatin is mainly used for the treatment of atherosclerosis in clinic. A large number of studies show that atorvastatin may produce anti-tumor activities. This study aimed to predict the common targets of atorvastatin against atherosclerosis and non-small cell lung cancer (NSCLC) based on network pharmacology. METHODS: The target genes of atherosclerosis and NSCLC were obtained from The Cancer Genome Atlas (TCGA) and Gene Expression Omnibus (GEO) databases. The disease-target-component model map and the core network were obtained using Cytoscape 3.7.1. The MTS and wound healing assay were used to detect the effect of atorvastatin on cell viability and migration of A549 cells. The expression of potential common target genes of atorvastatin against atherosclerosis and NSCLC were confirmed in A549 cells and lung cancer tissues of patients. RESULTS: We identified 15 identical pathogenic genes, and four of which (MMP9, MMP12, CD36, and FABP4) were considered as the key target genes of atorvastatin in anti-atherosclerosis and NSCLC. The MTS and wound healing assays revealed that atorvastatin decreased A549 cells migration significantly. Atorvastatin markedly decreased the expression of MMP9, MMP12, CD36, and FABP4 in A549 cells and patients were treated with atorvastatin. CONCLUSIONS: This study demonstrated 15 common pathogenic genes in both atherosclerosis and NSCLC. And verified that MMP 9, MMP 12, CD 36 and FABP 4 might be the common target genes of atorvastatin in anti-atherosclerosis and NSCLC.

Liao, H., et al. (2023). "IL-17A promotes tumorigenesis and upregulates PD-L1 expression in non-small cell lung cancer." J Transl Med **21**(1): 828.

BACKGROUND: The tumor microenvironment plays a key role in non-small cell lung cancer (NSCLC) development and also influences the effective response to immunotherapy. The pro-inflammatory factor interleukin-17A mediates important immune responses in the tumor microenvironment. In this study, the potential role and mechanisms of IL-17A in NSCLC were investigated. METHODS: We detected IL-17A by immunohistochemistry (IHC) in 39 NSCLC patients. Its expression was correlated with the programmed cell death-ligand1 (PD-L1). IL-17A knockdown and overexpression in A549 and SPC-A-1 cell models were constructed. The function of IL-17A was examined in vitro by wound healing, migration, invasion, plate colony formation and T cell killing assay. Western blot analysis, immunofluorescence assay and IHC were performed to investigate the regulation effects of IL-17A on autophagy in A549 and SPC-A-1. The effect of IL-17A on ROS/Nrf2/p62 signaling pathway was detected. Subcutaneous tumor models were established to examine the tumor-promoting effect of IL-17A in vivo and its effect on immunotherapy. RESULTS: We found a prevalent expression of IL-17A in NSCLC tumor tissues and it was positively correlated with PD-L1 expression ($r = 0.6121$, $p < 0.0001$). In vitro, IL-17A promotes lung cancer cell migration, invasion and colony formation ability. Moreover, IL-17A upregulated N-cadherin, Twist, and Snail, and downregulated E-cadherin in NSCLC cells. IL-17A enhanced cell survival in the T cell killing assay. Mechanistically, IL-17A induced ROS production and increased Nrf2 and p62 expression, thereby inhibiting autophagy and reducing PD-L1 degradation. In vivo experiments, anti-IL-17A monoclonal antibody alone slowed the growth of subcutaneous tumors in mice. When combined with anti-PD-L1 monoclonal antibody, tumor tissue expression of PD-L1 was reduced and the therapeutic effect was diminished. CONCLUSION: We found that IL-17A promoted NSCLC progression and inhibited autophagy through the ROS/Nrf2/p62 pathway leading to increased PD-L1 expression in cancer cells. Modulation of IL-17A may affect the therapeutic efficacy of immunotherapy.

Lin, Y., et al. (2023). "A prognostic model based on tumor microenvironment and immune cell in colorectal cancer." Scand J Gastroenterol: 1-12.

BACKGROUND: Colorectal cancer (CRC) is the second leading cause of cancer-related death. Immunotherapy is one of the new options for cancer treatment. This study aimed to develop an immune-related signature associated with CRC. METHODS: We performed differential analysis to screen out the differentially expressed genes (DEGs) of The Cancer Genome Atlas-Colorectal Cancer (TCGA-CRC) datasets. Weighted gene co-expression network analysis (WGCNA) was performed to obtain the key module genes associated with differential immune cells. The candidate genes were obtained through overlapping key DEGs and key module genes. The univariate and multivariate Cox regression analyses were adopted to build a CRC prognostic signature. We further conducted immune feature estimation and chemotherapy analysis between two risk subgroups.

Finally, we verified the expression of immune-related prognostic genes at the transcriptional level. RESULTS: A total of 61 candidate genes were obtained by overlapping key DEGs and key module genes associated with differential immune cells. Then, an immune-related prognostic signature was built based on the three prognostic genes (HAMP, ADAM8, and CD1B). The independent prognostic analysis suggested that age, stage, and RiskScore could be used as independent prognostic factors. Further, we found significantly higher expression of three prognostic genes in the CRC group compared with the normal group. Finally, real-time polymerase chain reaction verified the expression of three genes in patients with CRC. CONCLUSION: The prognostic signature comprising HAMP, ADAM8, and CD1B based on immune cells was established, providing a theoretical basis and reference value for the research of CRC.

Liu, B. W., et al. (2023). "The p53/ZEB1-PLD3 feedback loop regulates cell proliferation in breast cancer." Cell Death Dis **14**(11): 751.

Breast cancer is the most prevalent cancer globally, endangering women's physical and mental health. Phospholipase D3 (PLD3) belongs to the phosphodiesterase family (PLD). PLD3 is related to insulin-mediated phosphorylation of the AKT pathway, suggesting that it may play a role in the occurrence and development of malignant tumors. This study may further explore the molecular mechanism of PLD3 inhibiting breast cancer cell proliferation. In this study, we demonstrated that PLD3 and miR-6796 are co-expressed in breast cancer. PLD3 can bind with CDK1 and inhibit its expression, leading to mitotic arrest and inhibiting breast cancer proliferation. Wild-type p53 regulates PLD3 and miR-6796 expression by competitively binding to the PLD3 promoter with ZEB1. DNMT3B, as the target gene of miR-6796, is recruited into the PLD3 promoter by combining with ZEB1 to regulate the DNA methylation of the PLD3 promoter and ultimately affect PLD3 and miR-6796 expression. In conclusion, we revealed the role and molecular mechanism of PLD3 and its embedded miR-6796 in breast cancer proliferation, providing clues and a theoretical foundation for future research and development of therapeutic targets and prognostic markers for breast cancer.

Lucia, F., et al. (2023). "Multicentric development and evaluation of [(18)F]FDG PET/CT and CT radiomic models to predict regional and/or distant recurrence in early-stage non-small cell lung cancer treated by stereotactic body radiation therapy." Eur J Nucl Med Mol Imaging.

PURPOSE: To develop machine learning models to predict regional and/or distant recurrence in patients with early-stage non-small cell lung cancer (ES-NSCLC) after stereotactic body radiation therapy (SBRT) using [(18)F]FDG PET/CT and CT radiomics combined with clinical and dosimetric parameters. METHODS: We retrospectively collected 464 patients (60% for training and 40% for testing) from University Hospital of Liege and 63 patients from University Hospital of Brest (external testing set) with ES-NSCLC treated with SBRT between 2010 and 2020 and who had undergone pretreatment [(18)F]FDG PET/CT and planning CT. Radiomic features were extracted using the PyRadiomics toolbox(R). The ComBat harmonization method was applied to reduce the batch effect between centers. Clinical, radiomic, and combined models were trained and tested using a neural network approach to predict regional and/or distant recurrence. RESULTS: In the training (n = 273) and testing sets (n = 191 and n = 63), the clinical model achieved moderate performances to predict regional and/or distant recurrence with C-statistics from 0.53 to 0.59 (95% CI, 0.41, 0.67). The radiomic (original_firstorder_Entropy, original_gldm_LowGrayLevelEmphasis and original_glcm_DifferenceAverage) model achieved higher predictive ability in the training set and kept the same performance in the testing sets, with C-statistics from 0.70 to 0.78 (95% CI, 0.63, 0.88) while the combined model performs moderately well with C-statistics from 0.50 to 0.62 (95% CI, 0.37, 0.69). CONCLUSION: Radiomic features extracted from pre-SBRT analog and digital [(18)F]FDG PET/CT outperform clinical parameters in the prediction of regional and/or distant recurrence and to discuss an adjuvant systemic treatment in ES-NSCLC. Prospective validation of our models should now be carried out.

Makran, M., et al. (2023). "Ethylcoprostanol modulates colorectal cancer cell proliferation and mitigates cytotoxicity of cholesterol metabolites in non-tumor colon cells." Food Funct.

Sterols can be metabolized by gut microbiota. The cholesterol metabolites have been proposed as promoters of colorectal cancer (CRC), while the effect of plant sterol metabolites is unknown. This study aimed to evaluate the cytotoxicity of metabolites from cholesterol (coprostanol, cholestanol, coprostanone and cholestenone) and beta-sitosterol (ethylcoprostanol) on human colon tumor (Caco-2) and non-tumor (CCD-18Co) cells at physiological concentrations (9-300 muM) and exposure time (24 h). Ethylcoprostanol reduced the tumor cell proliferation

(MTT), showing in flow cytometry assays induction of apoptosis via production of reactive oxygen species (ROS) and ceramide. Transcriptomic analysis (qPCR) showed activation of the intrinsic apoptosis pathway (BAX/BCL2 ratio and CASP9 increased), accompanied by downregulation of the p21 gene. Cholesterol metabolites, mainly the most hydrophobic, induced apoptosis and G(0)/G(1) phase arrest in non-tumor cells through overproduction of ROS. Both the intrinsic and extrinsic (CASP8 increased) apoptosis pathways occurred. In turn, a reduction in the expression of the cyclin E(1) gene confirmed the cell cycle arrest. In addition, ethylcoprostanol protected non-tumor cells from the most cytotoxic cholesterol metabolite (cholestenone). In conclusion, ethylcoprostanol is a promising candidate as a therapeutic adjuvant in CRC, while cholesterol metabolites could act as CRC promoters through their cytotoxicity.

Mander, E. S., et al. (2023). "Pembrolizumab monotherapy for non-small cell lung cancer (NSCLC): can patient stratification be improved in the UK Tayside population? A retrospective cohort study." BMJ Open **13**(11): e076715.

OBJECTIVE: Pembrolizumab is a programmed cell death protein-1 (PD-1) inhibitor used to treat advanced patients with non-small cell lung cancer (NSCLC) with a programmed cell death ligand-1 (PD-L1) tumour proportion score (TPS) >/=50. Further sub-division of TPS-based stratification has not been evaluated in the UK, although smoking-induced tumour mutational burden and the immunogenic effects of prior radiotherapy are suggested to improve response. AIMS: To investigate if PD-L1 TPS >/=80%, smoking status or radiotherapy before or within 2 months of treatment influenced progression-free survival (PFS) in patients with NSCLC treated with pembrolizumab monotherapy. METHODS: PD-L1 TPS, smoking status and radiotherapy exposure were compared in patients with NSCLC in National Health Service (NHS) Tayside (n=100) treated with pembrolizumab monotherapy between 1 November 2017 and 18 February 2022. Survival estimates were compared using log-rank analysis, and Cox proportional hazards analysis was used to investigate the influence of potential confounding factors, including tumour stage and performance status. RESULTS: PFS was not significantly different (log-rank HR=0.330, p=0.566) comparing patients with PD-L1 TPS 50-79% and PD-L1 TPS >/=80%. Smokers had significantly improved PFS (log-rank HR=4.867, p=0.027), while patients receiving radiotherapy had significantly decreased PFS (log-rank HR=6.649, p=0.012). A Cox regression model confirmed that both radiotherapy (p=0.022) and performance status (p=0.009) were independent negative predictors of PFS. CONCLUSIONS: More rigorous PD-L1 TPS stratification did not influence survival outcomes. Smoking history improved PFS, although it was not an independent response predictor, while radiotherapy and performance status independently influenced clinical response. We suggest that further stratification of PD-L1 TPS is not warranted, while performance status and radiotherapy treatment may be additional clinically useful biomarkers of response to pembrolizumab in patients with NSCLC.

McEvoy, A. M., et al. (2023). "Merkel cell carcinoma recurrence risk estimation is improved by integrating factors beyond cancer stage: a multivariable model and web-based calculator." J Am Acad Dermatol.

BACKGROUND: Merkel cell carcinoma (MCC) recurs in 40% of patients. In addition to stage, factors known to affect recurrence risk include: sex, immunosuppression, unknown primary status, age, site of primary tumor, and time since diagnosis. PURPOSE: Create a multivariable model and web-based calculator to predict MCC recurrence risk more accurately than stage alone. METHODS: Data from 618 patients in a prospective cohort were used in a competing risk regression model to estimate recurrence risk using stage and other factors. RESULTS: In this multivariable model, the most impactful recurrence risk factors were: AJCC stage ($p<0.001$), immunosuppression (hazard ratio 2.05; $p<0.001$), male sex (1.59; $p=0.003$) and unknown primary (0.65; $p=0.064$). Compared to stage alone, the model improved prognostic accuracy (concordance index for two-year risk, 0.66 vs. 0.70; $p<0.001$), and modified estimated recurrence risk by up to 4-fold (18% for low-risk stage IIIA vs. 78% for high-risk IIIA over five years). LIMITATIONS: Lack of an external data set for model validation. CONCLUSION: / Relevance: As demonstrated by this multivariable model, accurate recurrence risk prediction requires integration of factors beyond stage. An online calculator based on this model (at merkelcell.org/recur) integrates time since diagnosis and provides new data for optimizing surveillance for MCC patients.

Meng, Q., et al. (2023). "Prognostic hub gene CBX2 drives a cancer stem cell-like phenotype in HCC revealed by multi-omics and multi-cohorts." Aging (Albany NY) **15**.

Hepatocellular carcinoma (HCC) is a malignant tumor with a high prevalence and fatality rate. CBX2 has been demonstrated to impact the development and advancement of various cancers, albeit it has received limited attention in relation to

HCC. In this study, CBX2 and CEP55 were screened out with the refined triple regulatory networks constructed by total RNA-seq datasets (TCGA-LIHC, GSE140845) and a robust prognostic model. Aberrantly higher expression levels of CBX2 and CEP55 in HCC may be caused by CNV alterations, promoter hypo-methylation, open chromatin accessibility, and greater active marks such as H3K4me3, H3K4me1, and H3K27ac. Functionally, CBX2, which was highly correlated with CD44, shaped a cancer stem cell-like phenotype by positively regulating cell-cycle progression, proliferation, invasion, metastasis, wound healing, and radiation resistance, revealed by combining bulk RNA-seq and scRNA-seq datasets. CBX2 knockdown validated its role in affecting the cell cycle. Importantly, we revealed CBX2 could activate gene by cooperating with co-regulators or not rather than a recognizer of the repressive mark H3K27me3. For instance, we uncovered CBX2 bound to promoter of CTNNB1 and CEP55 to augment their expressions. CBX2 showed a highly positive correlation with CEP55 at pan-cancer level. In addition, CBX2 and CEP55 may enhance extracellular matrix reprograming via cancer-associated fibroblast. Surprisingly, patients with high expression of CBX2 or CEP55 exhibited a higher response to immunotherapy, indicating that CBX2 and CEP55 may be promising therapeutic targets for HCC patients.

Mi, J., et al. (2023). "lncRNA MIAT promotes luminal B breast cancer cell proliferation, migration, and invasion in vitro." J Appl Genet.

Long noncoding RNAs (lncRNAs) play a role in the emergence and progression of several human tumors, including luminal B breast cancer (BC). The biological functions and potential mechanisms of lncRNA myocardial infarction-associated transcripts (MIAT) in luminal B BC, on the contrary, are unknown. In this work, we used UALCAN database analysis to find high expression of lncRNA MIAT in luminal BC tissues and also confirmed high levels of lncRNA MIAT expression in luminal B BC tissues and cells. In vitro knockdown of MIAT inhibited the proliferation, migration, and invasion of BT474 cells. In addition, we found that miR-150-5p levels were significantly reduced in luminal B BC specimens and cells, and miR-150-5p levels were significantly increased when MIAT was knocked down. And TIMER database analysis showed that MIAT was positively associated with PDL1. Through bioinformatic tools and in vitro experiments, lncRNA MIAT could function as a competitive endogenous RNA (CeRNA) to further regulate programmed cell death ligand 1 (PDL1) expression by directly sponging miR-150-5p. In conclusion, our data suggest that MIAT, an oncogene, may sponge miR-150-5p to regulate PDL1 expression and affect proliferation, migration, and invasion in luminal B BC in vitro.

Miao, D., et al. (2023). "Management of locally advanced non-small cell lung cancer: state of the art and future directions." Cancer Commun (Lond).

Lung cancer is the second most common and the deadliest type of cancer worldwide. Clinically, non-small cell lung cancer (NSCLC) is the most common pathological type of lung cancer; approximately one-third of affected patients have locally advanced NSCLC (LA-NSCLC, stage III NSCLC) at diagnosis. Because of its heterogeneity, LA-NSCLC often requires multidisciplinary assessment. Moreover, the prognosis of affected patients is much below satisfaction, and the efficacy of traditional therapeutic strategies has reached a plateau. With the emergence of targeted therapies and immunotherapies, as well as the continuous development of novel radiotherapies, we have entered an era of novel treatment paradigm for LA-NSCLC. Here, we reviewed the landscape of relevant therapeutic modalities, including adjuvant, neoadjuvant, and perioperative targeted and immune strategies in patients with resectable LA-NSCLC with/without oncogenic alterations; as well as novel combinations of chemoradiation and immunotherapy/targeted therapy in unresectable LA-NSCLC. We addressed the unresolved challenges that remain in the field, and examined future directions to optimize clinical management and increase the cure rate of LA-NSCLC.

Motono, N., et al. (2023). "Relative efficacies of EGFR-TKIs and immune checkpoint inhibitors for treatment of recurrent non-small cell lung cancer after surgery." Oncology.

INTRODUCTION: The relative efficacies of epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) and immune checkpoint inhibitors (ICIs) for the treatment of recurrent non-small cell lung cancer (NSCLC) after surgery remain unclear. METHODS: Among 801 patients with NSCLC who underwent pulmonary resection at Kanazawa Medical University between 2017 and 2021, 64 patients had recurrence. We retrospectively compared the efficacies of EGFR-TKIs and ICIs in these patients with recurrent NSCLC who underwent pulmonary resection. RESULTS: The 3-year overall survival rates after recurrence were 79.3% in patients who received EGFR-TKIs, 69.5% in patients who received ICIs, and 43.7% in patients who received cytotoxic agents. There was no significant difference

in overall survival between patients treated with EGFR-TKIs and ICIs (p=0.14) or between patients treated with ICIs and cytotoxic agents (p=0.23), but overall survival was significantly higher in patients treated with EGFR-TKIs compared with cytotoxic agents (p<0.01) The probabilities of a 2-year response were 88.5%, 61.6%, and 25.9% in patients treated with EGFR-TKIs, ICIs, and cytotoxic agents, respectively. There was no significant difference in response periods between patients treated with EGFR-TKIs and ICIs (p=0.18), but the response period was significantly better in patients treated with EGFR-TKIs (p<0.01) or ICIs (p=0.03) compared with cytotoxic agents. Percent-predicted vital capacity (p=0.03) and epidermal growth factor receptor gene mutation (p<0.01) were significant factors affecting the overall response to chemotherapy in multivariate analysis. CONCLUSION: EGFR-TKIs and ICIs are effective for treating recurrent NSCLC after surgery. Although adjuvant chemotherapy for completely resected pathological stage II to IIIA NSCLC, atezolizumab or Osimertinib, has also been recently approved as adjuvant chemotherapy, there is a risk that patients who relapse after adjuvant chemotherapy will have less choice.

Nagaoka, Y., et al. (2023). "Activation of the TGF-beta1/EMT signaling pathway by claudin-1 overexpression reduces doxorubicin sensitivity in small cell lung cancer SBC-3 cells." Arch Biochem Biophys: 109824.

Small-cell lung cancer (SCLC), which accounts for about 15 % of all lung cancers, progresses more rapidly than other histologic types and is rarely detected at an operable early stage. Therefore, chemotherapy, radiation therapy, or their combination are the primary treatments for this type of lung cancer. However, the tendency to acquire resistance to anticancer drugs is a severe problem. Recently, we found that an intercellular adhesion molecule, claudin (CLDN) 1, known to be involved in the migration and invasion of lung cancer cells, is involved in the acquisition of anticancer drug resistance. In the present study, we investigated the effect of CLDN1 on the anticancer-drug sensitivity of SCLC SBC-3 cells. Since epithelial-mesenchymal transition (EMT), which is involved in cancer cell migration and invasion, is well known for its involvement in anticancer-drug sensitivity via inhibition of apoptosis, we also examined EMT involvement in decreased anticancer-drug sensitivity by CLDN1. Sensitivity to doxorubicin (DOX) in SBC-3 cells was significantly decreased by CLDN1 overexpression. CLDN1 overexpression resulted in increased TGF-beta1 levels, enhanced EMT induction, and increased migratory potency of SBC-3 cells. The decreased sensitivity of SBC-3 cells to anticancer drugs upon TGF-beta1 treatment suggested that activation of the TGF-beta1/EMT signaling pathway by CLDN1 causes the decreased sensitivity to anticancer drugs and increased migratory potency. Furthermore, treatments with antiallergic agents tranilast and zoledronic acid, known EMT inhibitors, significantly mitigated the decreased sensitivity of CLDN1-overexpressing SBC-3 cells to DOX. These results suggest that EMT inhibitors might effectively overcome reduced sensitivity to anticancer drugs in CLDN1-overexpressing SCLC cells.

Nakamichi, S., et al. (2023). "A Phase II Study of Ubenimex Combined With Pembrolizumab, Nab-Paclitaxel, and Carboplatin for Previously Untreated Advanced Squamous Non-Small-Cell Lung Cancer: TORG2241 (UBE-Q)." Clin Lung Cancer.

BACKGROUND: According to the results of the KEYNOTE-407 trial, pembrolizumab plus platinum-based chemotherapy is the standard of care for patients with previously untreated advanced squamous non-small-cell lung cancer (NSCLC). Ubenimex, a potent aminopeptidase inhibitor, is an oral drug with immunostimulatory and antitumor activities. We aim to assess the safety and efficacy of ubenimex in combination with pembrolizumab, nab-paclitaxel, and carboplatin in patients with previously untreated advanced squamous NSCLC. PATIENTS AND METHODS: This prospective, single-arm, multicenter, phase II clinical trial is conducted to confirm the tolerability and efficacy of the tested drugs. Patients with previously untreated advanced squamous NSCLC will receive a predetermined daily dose of ubenimex orally plus 4 cycles of pembrolizumab, nab-paclitaxel, and carboplatin, followed by continuous administration of ubenimex and pembrolizumab for a maximum of 2 years. To confirm tolerability, the daily dose of ubenimex will begin at level 1 (30 mg), which will be increased to levels 2 (60 mg) and 3 (120 mg) according to the escalation criteria, with a standard 3 + 3 design for achieving the target dose-limiting toxicity rate of 33%. The efficacy, safety, and tolerability of ubenimex at the determined dose level will be analyzed. The primary endpoint of the efficacy evaluation will be the objective response rate assessed by an independent review committee. CONCLUSIONS: This is the first study to evaluate the efficacy and safety of ubenimex combined with pembrolizumab, nab-paclitaxel, and carboplatin in patients with previously untreated advanced squamous NSCLC. The results will help devise future treatment strategies.

Nasuh, S., et al. (2023). "ARID3A and ARID3B exert direct regulatory control over the long non-coding RNAs (lncRNAs) MALAT1 and NORAD within the context of non-small cell lung cancer (NSCLC)." Pathol Res Pract **252**: 154948.

Lung cancer, known for its high mortality rates and poor prognosis, remains one of the most prevalent cancer types. Early detection and effective treatment methods are crucial for improving survival rates. Non-small cell lung cancer (NSCLC) accounts for approximately 85 % of all lung cancer cases. Long non-coding RNAs (lncRNAs), which play vital roles in various biological processes, have been implicated in the development of cancer and can impact key therapeutic targets in different cancer types. In NSCLC, the dysregulation of specific lncRNAs, such as MALAT1 and NORAD, has been associated with neoplastic initiation, progression, metastasis, tumor angiogenesis, chemoresistance, and genomic instability. Both MALAT1 and NORAD directly regulate the expression of the transcription factor E2F1, thereby influencing cell cycle progression. Additionally, MALAT1 has been reported to affect the expression of p53 target genes, leading to cell cycle progression through the repression of p53 promoter activity. NORAD, on the other hand, is indirectly regulated by p53. The AT-rich interaction domain (ARID) family of DNA-binding proteins, particularly ARID3A and ARID3B, are involved in various biological processes such as cell proliferation, differentiation, and development. They also play significant roles in E2F-dependent transcription and are transcriptional targets of p53. The intricate balance between promoting cellular proliferation through the pRB-E2F pathway and inducing growth arrest through the p53 pathway underscores the crucial regulatory role of ARID3A, ARID3B, and their interaction with lncRNAs MALAT1 and NORAD. In this study, we aimed to investigate the potential interactive and functional connections among ARID3A, ARID3B, MALAT1, and NORAD in NSCLC, considering their involvement in the pRB-E2F and p53 pathways. Our findings strongly suggest that ARID3A and ARID3B play a regulatory role in controlling MALAT1 and NORAD in NSCLC. Specifically, our study demonstrates that the activities of MALAT1 and NORAD were markedly increased upon the overexpression of ARID3A and ARID3B. Therefore, we can conclude that ARID3A and ARID3B likely contribute significantly to the oncogenic functions of MALAT1 and NORAD in NSCLC. Consequently, targeting ARID3A and ARID3B could hold promise as a therapeutic approach in NSCLC, given their direct control over the expression of MALAT1 and NORAD.

Nath, J., et al. (2023). "Definitive Radiotherapy in Locally Advanced Head and Neck Squamous Cell Cancer with Clinical Extranodal Extension." Indian J Otolaryngol Head Neck Surg **75**(4): 3519-3529.

PURPOSE: The extranodal extension (ENE) in head and neck squamous cell carcinoma (HNSCC) is a potential poor prognostic factor. Clinical ENE (cENE) was incorporated in the HNSCC staging system in the 8th edition of AJCC. There is not much evidence to support the treatment of HNSCC with cN3b with radiotherapy in radical intent. This study aims to assess the treatment outcome in patients of HNSCC with cN3b disease treated with definitive radiotherapy. METHOD: Forty-five HNSCC patients with cN3b disease treated with definitive radiotherapy with or without concurrent chemotherapy between January 2018 to December 2018 were retrospectively evaluated. RESULTS: The median age of the study patients was 60 years (40-75years). Only 35 patients (77.8%) could complete the prescribed course of treatment, and the leading common cause of non-completion was treatment-related toxicities. After a median follow-up period of 9.3 months (range 2-33), the median OS and PFS were 22.6 months and 7.2 months, respectively. Fourteen patients (31.1%) in our study developed grade III/IV mucositis, and 11 (24.4%) developed severe grade III/IV dermatitis. The locoregional failure constituted 24 patients (53.3%). CONCLUSION: The treatment outcome of HNSCC with cN3b disease is inferior. A personalized and subjective approach should be undertaken before choosing radiotherapy with a radical intent in this group of patients.

Nayak, A. L., et al. (2023). "Survival of Patients With Head and Neck Merkel Cell Cancer: Findings From the Pan-Canadian Merkel Cell Cancer Collaborative." JAMA Netw Open **6**(11): e2344127.

IMPORTANCE: Merkel cell carcinoma (MCC) is an aggressive cutaneous neuroendocrine carcinoma. Due to its relatively low incidence and limited prospective trials, current recommendations are guided by historical single-institution retrospective studies. OBJECTIVE: To evaluate the overall survival (OS) of patients in Canada with head and neck MCC (HNMCC) according to American Joint Committee on Cancer 8th edition staging and treatment modalities. DESIGN, SETTING, AND PARTICIPANTS: A retrospective cohort study of 400 patients with a diagnosis of HNMCC between July 1, 2000, and June 31, 2018, was conducted using the Pan-Canadian Merkel Cell Cancer Collaborative,

a multicenter national registry of patients with MCC. Statistical analyses were performed from January to December 2022. MAIN OUTCOMES AND MEASURES: The primary outcome was 5-year OS. Multivariable analysis using a Cox proportional hazards regression model was performed to identify factors associated with survival. RESULTS: Between 2000 and 2018, 400 patients (234 men [58.5%]; mean [SD] age at diagnosis, 78.4 [10.5] years) with malignant neoplasms found in the face, scalp, neck, ear, eyelid, or lip received a diagnosis of HNMCC. At diagnosis, 188 patients (47.0%) had stage I disease. The most common treatment overall was surgery followed by radiotherapy (161 [40.3%]), although radiotherapy alone was most common for stage IV disease (15 of 23 [52.2%]). Five-year OS was 49.8% (95% CI, 40.7%-58.2%), 39.8% (95% CI, 26.2%-53.1%), 36.2% (95% CI, 25.2%-47.4%), and 18.5% (95% CI, 3.9%-41.5%) for stage I, II, III, and IV disease, respectively, and was highest among patients treated with surgery and radiotherapy (49.9% [95% CI, 39.9%-59.1%]). On multivariable analysis, patients treated with surgery and radiotherapy had greater OS compared with those treated with surgery alone (hazard ratio [HR], 0.76 [95% CI, 0.46-1.25]); however, this was not statistically significant. In comparison, patients who received no treatment had significantly worse OS (HR, 1.93 [95% CI, 1.26-2.96)]. CONCLUSIONS AND RELEVANCE: In this cohort study of the largest Canada-wide evaluation of HNMCC survival outcomes, stage and treatment modality were associated with survival. Multimodal treatment was associated with greater OS across all disease stages.

Ohri, N., et al. (2023). "Selective Personalized Radioimmunotherapy for Locally Advanced Non-Small-Cell Lung Cancer Trial." J Clin Oncol: JCO2300627.

PURPOSE: Standard therapy for locally advanced non-small-cell lung cancer (LA-NSCLC) is concurrent chemoradiotherapy followed by adjuvant durvalumab. For biomarker-selected patients with LA-NSCLC, we hypothesized that sequential pembrolizumab and risk-adapted radiotherapy, without chemotherapy, would be well-tolerated and effective. METHODS: Patients with stage III NSCLC or unresectable stage II NSCLC and an Eastern Cooperative Oncology Group performance status of 0-1 were eligible for this trial. Patients with a PD-L1 tumor proportion score (TPS) of >/=50% received three cycles of induction pembrolizumab (200 mg, once every 21 days), followed by a 20-fraction course of risk-adapted thoracic radiotherapy (55 Gy delivered to tumors or lymph nodes with metabolic volume exceeding 20 cc, 48 Gy delivered to smaller lesions), followed by consolidation pembrolizumab to complete a 1-year treatment course. The primary study end point was 1-year progression-free survival (PFS). Secondary end points included response rates after induction pembrolizumab, overall survival (OS), and adverse events. RESULTS: Twenty-five patients with a PD-L1 TPS of >/=50% were enrolled. The median age was 71, most patients (88%) had stage IIIA or IIIB disease, and the median PD-L1 TPS was 75%. Two patients developed disease progression during induction pembrolizumab, and two patients discontinued pembrolizumab after one infusion because of immune-related adverse events. Using RECIST criteria, 12 patients (48%) exhibited a partial or complete response after induction pembrolizumab. Twenty-four patients (96%) received definitive thoracic radiotherapy. The 1-year PFS rate is 76%, satisfying our efficacy objective. One- and 2-year OS rates are 92% and 76%, respectively. The most common grade 3 adverse events were colitis (n = 2, 8%) and esophagitis (n = 2, 8%), and no higher-grade treatment-related adverse events have occurred. CONCLUSION: Pembrolizumab and risk-adapted radiotherapy, without chemotherapy, are a promising treatment approach for patients with LA-NSCLC with a PD-L1 TPS of >/=50%.

Orozco-Leal, G., et al. (2023). "Considerations for the Cure Assumption in an NICE Single Technology Appraisal of Nivolumab with Chemotherapy for Neoadjuvant Treatment of Resectable Non-Small Cell Lung Cancer: Evidence Assessment Group Perspective." Pharmacoeconomics.

Orsburn, B. C. (2023). "Metabolomic, Proteomic, and Single-Cell Proteomic Analysis of Cancer Cells Treated with the KRAS(G12D) Inhibitor MRTX1133." J Proteome Res.

Mutations in KRAS are common drivers of human cancers and are often those with the poorest overall prognosis for patients. A recently developed compound, MRTX1133, has shown promise in inhibiting the activity of KRAS(G12D) mutant proteins, which is one of the main drivers of pancreatic cancer. To better understand the mechanism of action of this compound, I performed both proteomics and metabolomics on four KRAS(G12D) mutant pancreatic cancer cell lines. To obtain increased granularity in the proteomic observations, single-cell proteomics was successfully performed on two of these lines. Following quality filtering, a total of 1498 single cells were analyzed. From these cells, 3140 total proteins were identified with approximately 953 proteins quantified per cell. At 48 h of treatment, two distinct populations of cells can be observed based on the level of effectiveness of

the drug in decreasing the total abundance of the KRAS protein in each respective cell, with results that are effectively masked in the bulk cell analysis. All mass spectrometry data and processed results are publicly available at www.massive.ucsd.edu at accessions PXD039597, PXD039601, and PXD039600.

Pan, H., et al. (2023). "Immunogenic cell stress and death in the treatment of cancer." Semin Cell Dev Biol **156**: 11-21.

The successful treatment of oncological malignancies which results in long-term disease control or the complete eradication of cancerous cells necessitates the onset of adaptive immune responses targeting tumor-specific antigens. Such desirable anticancer immunity can be triggered via the induction of immunogenic cell death (ICD) of cancer cells, thus converting malignant cells into an in situ vaccine that elicits T cell mediated adaptive immune responses and establishes durable immunological memory. The exploration of ICD for cancer treatment has been subject to extensive research. However, functional heterogeneity among ICD activating therapies in many cases requires specific co-medications to achieve full-blown efficacy. Here, we described the hallmarks of ICD and classify ICD activators into three distinct functional categories namely, according to their mode of action: (i) ICD inducers, which increase the immunogenicity of malignant cells, (ii) ICD sensitizers, which prime cellular circuitries for ICD induction by conventional cytotoxic agents, and (iii) ICD enhancers, which improve the perception of ICD signals by antigen presenting dendritic cells. Altogether, ICD induction, sensitization and enhancement offer the possibility to convert well-established conventional anticancer therapies into immunotherapeutic approaches that activate T cell-mediated anticancer immunity.

Pashootan, P., et al. (2023). "Metal-based Nanoparticles in Cancer Therapy: Exploring Photodynamic Therapy and its Interplay with Regulated Cell Death Pathways." Int J Pharm: 123622.

Photodynamic therapy (PDT) represents a non-invasive treatment strategy currently utilized in the clinical management of selected cancers and infections. This technique is predicated on the administration of a photosensitizer (PS) and subsequent irradiation with light of specific wavelengths, thereby generating reactive oxygen species (ROS) within targeted cells. The cellular effects of PDT are dependent on both the localization of the PS and the severity of ROS challenge, potentially leading to the stimulation of various cell death modalities. For many years, the concept of regulated cell death (RCD) triggered by photodynamic reactions predominantly encompassed apoptosis, necrosis, and autophagy. However, in recent decades, further explorations have unveiled additional cell death modalities, such as necroptosis, ferroptosis, cuproptosis, pyroptosis, parthanatos, and immunogenic cell death (ICD), which helps to achieve tumor cell elimination. Recently, nanoparticles (NPs) have demonstrated substantial advantages over traditional PSs and become important components of PDT, due to their improved physicochemical properties, such as enhanced solubility and superior specificity for targeted cells. This review aims to summarize recent advancements in the applications of different metal-based NPs as PSs or delivery systems for optimized PDT in cancer treatment. Furthermore, it mechanistically highlights the contribution of RCD pathways during PDT with metal NPs and how these forms of cell death can improve specific PDT regimens in cancer therapy.

Pirzadeh, M., et al. (2023). "Barriers to Timely Lung Cancer Care in Early Stage Non-Small Cell Lung Cancer and Impact on Patient Outcomes." Clin Lung Cancer.

BACKGROUND: Optimal time to treatment for early-stage lung cancer is uncertain. We examined causes of delays in care for Veterans who presented with early-stage non-small cell lung cancer (NSCLC) and whether workup time was associated with increased upstaging or all-cause mortality. METHODS: We performed a retrospective analysis of Veterans referred to our facility with radiographic stage I or II NSCLC between January 2013 to December 2017, with follow-up through October 2021. Patient demographics, tumor characteristics, time intervals of care, and reasons for delays were collected. Guideline concordance (GC) was defined as treatment within 14 weeks of abnormal image. Multivariable analyses were performed to determine association between delays in care, survival, and upstaging. RESULTS: Data from 203 Veterans were analyzed. Median time between abnormal imaging to treatment was 17.7 weeks (IQR 12.7-26.6). Only 33% of Veterans received GC care. Most common patient-related delays were: intercurrent hospitalization/comorbidity (23%), no-shows (16%) and inability to reach Veteran (17%). Most common system-related delay: lack of scheduling availability (25%). Delays associated with upstaging: transportation issues, request for coordination of appointments, and unforeseen appointment changes. Rates of upstaging did not differ between GC and discordant groups (P = .6). GC care was not an independent predictor of mortality. Post-hoc,

treatment within 8 weeks was associated with lower rates of upstaging (P = .05). CONCLUSION: Although GC care did not impact survival or upstaging for early-stage NSCLC, shorter timeframes may be beneficial. Modifiable delays in care exist which may be addressed at an institutional level to improve timeliness of care.

Qin, A., et al. (2023). "A Phase II Trial of Pevonedistat and Docetaxel in Patients With Previously Treated Advanced Non-Small-Cell Lung Cancer." Clin Lung Cancer.

BACKGROUND: Postimmunotherapy (IO) treatment options for stage IV non-small-cell lung cancer (NSCLC) remain limited. Docetaxel alone or in combination with ramucirumab remains a standard of care, but response rates and survival benefit are suboptimal. Cullin-RING ligases (CRL) catalyze degradation of tumor suppressor proteins and are overactivated in NSCLC. Neddylation, which is catalyzed by the NEDD8 activating enzyme (NAE), is required for the activation of CRLs. Pevonedistat, a first-in-class small molecule NAE inhibitor, exerted antitumor activity when combined with docetaxel in preclinical studies. METHODS: We conducted a phase II, single-arm, investigator-initiated study evaluating the efficacy of pevonedistat plus docetaxel in patients with relapsed/refractory stage IV NSCLC. Patients received docetaxel 75 mg/m(2) on day 1 and pevonedistat 25 mg/m(2) on days 1, 3 and 5 of a 21-day cycle. The primary endpoint was objective response rate (ORR). RESULTS: From March 5, 2018 to January 26, 2021, we enrolled 31 patients. The ORR was 22% (1 CR, 5 PR), median PFS was 4.1 months, and median OS was 13.2 months. The incidence of Grade >/=3 adverse events (AE) was 53% in patients (n = 30) who received at least 1 dose of both drugs, with the most frequent being neutropenia and AST/ALT elevation. One patient was taken off study for a Grade 4 transaminase elevation. There were no Grade 5 toxicities. CONCLUSION: Our data suggest that the combination of docetaxel and pevonedistat is safe and exerts activity in patients with relapsed NSCLC. These encouraging results suggest that the neddylation pathway is an antitumor pathway that should be further studied.

Ramesh, S., et al. (2023). "MET Inhibitor Capmatinib Radiosensitizes MET Exon 14-Mutated and MET-Amplified Non-Small Cell Lung Cancer." Int J Radiat Oncol Biol Phys.

PURPOSE: The objective of this study was to investigate the effects of inhibiting the MET receptor with capmatinib, a potent and clinically relevant ATP-competitive tyrosine kinase inhibitor, in combination with radiation in MET exon 14-mutated and MET-amplified non-small cell lung (NSCLC) cancer models. METHODS AND MATERIALS: In vitro effects of capmatinib and radiation on cell proliferation, colony formation, MET signaling, apoptosis, and DNA damage repair were evaluated. In vivo tumor responses were assessed in cell line xenograft and patient-derived xenograft models. Immunohistochemistry (IHC) was used to confirm in vitro results. RESULTS: In vitro clonogenic survival assays demonstrated radiosensitization with capmatinib in both MET exon 14-mutated and MET-amplified NSCLC cell lines. No radiation-enhancing effect was observed in MET wild-type NSCLC and human bronchial epithelial cell line. Minimal apoptosis was detected with the combination of capmatinib and radiation. Capmatinib plus radiation compared to radiation alone resulted in inhibition of DNA double-strand break repair as measured by prolonged expression of gammaH2AX. In vivo, the combination of capmatinib and radiation significantly delayed tumor growth compared to vehicle control, capmatinib alone, or radiation alone. IHC indicated inhibition of phospho-MET and phospho-S6 and a decrease in Ki67 with inhibition of MET. CONCLUSIONS: Inhibition of MET with capmatinib enhanced the effect of radiation in both MET exon 14-mutated and MET-amplified NSCLC models.

Ren, J., et al. (2024). "Copy number variations in esophageal squamous cell carcinoma: Emerging cancer drivers and biomarkers (Review)." Oncol Rep **51**(1).

The morbidity and mortality of esophageal squamous cell carcinoma (ESCC) remains high in China. ESCC is significantly influenced by a complex interplay of environmental and genetic factors. Copy number variations (CNVs) are a major form of genome-scale changes in ESCC and are closely related to tumorigenesis and development. Genome-wide detection and analysis allow the identification of important CNV-affected genes with potential clinical applications. In both coding and non-coding regions, CNVs have been identified frequently in certain segments of chromosomes. CNV-impacted genes have crucial roles in multiple cellular processes, including proliferation, apoptosis, metastasis, and metabolic pathways. More importantly, they may serve as potential therapeutic targets for patients with ESCC. Therefore, studying the role of CNVs in ESCC is helpful to explore the pathogenesis of ESCC and to find effective treatment targets, which have profound implications for the diagnosis and therapy of ESCC.

Rist, D., et al. (2023). "Cancer Cell Targeting, Magnetic Sorting, and SERS Detection through Cell Surface Receptors." ACS Sens.

Integrins are cellular surface receptors responsible for the activation of many cellular pathways in cancer. These integrin proteins can be specifically targeted by small peptide sequences that offer the potential for the differentiation of cellular subpopulations by using magnetically assisted cellular sorting techniques. By adding a gold shell to the magnetic nanoparticles, these integrin-peptide interactions can be differentiated by surface-enhanced Raman spectroscopy (SERS), providing a quick and reliable method for on-target binding. In this paper, we demonstrate the ability to differentiate the peptide-protein interactions of the small peptides CDPGYIGSR and cyclic RGDfC functionalized on gold-coated magnetic nanoparticles with the integrins they are known to bind to using their SERS signal. SW480 and SW620 colorectal cancer cells known to have the integrins of interest were then magnetically sorted using these functionalized nanoparticles, suggesting differentiation between the sorted populations and integrin populations among the two cell lines.

Rudin, C. M., et al. (2023). "SKYSCRAPER-02: Tiragolumab in Combination With Atezolizumab Plus Chemotherapy in Untreated Extensive-Stage Small-Cell Lung Cancer." J Clin Oncol: JCO2301363.

PURPOSE: The phase III SKYSCRAPER-02 study determined whether the benefits of atezolizumab plus carboplatin and etoposide (CE) could be enhanced by the addition of tiragolumab in untreated extensive-stage small-cell lung cancer (ES-SCLC). We report final progression-free survival (PFS) and overall survival (OS) analyses. METHODS: Patients received tiragolumab 600 mg/placebo, plus atezolizumab 1,200 mg and CE (four cycles), then maintenance tiragolumab/placebo plus atezolizumab. Primary end points were investigator-assessed PFS and OS in patients without history/presence of brain metastases (primary analysis set [PAS]). Additional end points included PFS and OS in all patients regardless of brain metastases status (full analysis set [FAS]), response, and safety. RESULTS: Four hundred ninety patients were randomly assigned (FAS): 243 to tiragolumab arm and 247 to control arm. At the cutoff date (February 6, 2022; median duration of follow-up, 14.3 months [PAS] and 13.9 months [FAS]), final analysis of PFS in the PAS (n = 397) did not reach statistical significance (stratified hazard ratio [HR], 1.11; P = .3504; median, 5.4 months tiragolumab v 5.6 months control). At the cutoff date (September 6, 2022; median duration of follow-up, 21.2 months [FAS]), median OS in the PAS at final OS analysis was 13.1 months in both arms (stratified HR, 1.14; P = .2859). Median PFS and OS in the FAS were consistent with the PAS. The proportion of patients with immune-mediated adverse events (AEs) in the tiragolumab and control arms was 54.4% and 49.2%, respectively (grade 3/4: 7.9% and 7.7%). AEs leading to treatment withdrawal occurred in 8.4% and 9.3% of tiragolumab- and control-treated patients, respectively. CONCLUSION: Tiragolumab did not provide additional benefit over atezolizumab and CE in untreated ES-SCLC. The combination was well tolerated with no new safety signals.

Shi, C., et al. (2023). "Correction: Dendritic cell hybrid nanovaccine for mild heat inspired cancer immunotherapy." J Nanobiotechnology **21**(1): 438.

Skorda, A., et al. (2023). "Quantification of cell death and proliferation of patient-derived ovarian cancer organoids through 3D imaging and image analysis." STAR Protoc **4**(4): 102683.

Patient-derived organoids (PDOs) are ideal ex vivo model systems to study cancer progression and drug resistance mechanisms. Here, we present a protocol for measuring drug efficacy in three-dimensional (3D) high-grade serous ovarian cancer PDO cultures through quantification of cytotoxicity using propidium iodide incorporation in dead cells. We also provide detailed steps to analyze proliferation of PDOs using the Ki67 biomarker. We describe steps for sample processing, immunofluorescent staining, high-throughput confocal imaging, and image-based quantification for 3D cultures. For complete details on the use and execution of this protocol, please refer to Lahtinen et al. (2023).(1).

Society of Cancer Precision Medicine of Chinese Anti-Cancer, A., et al. (2023). "[Chinese Expert Consensus on the Clinical Practice of Non-small Cell Lung Cancer □Fusion Gene Detection Based on RNA-based NGS]." Zhongguo Fei Ai Za Zhi.

RNA-based next-generation sequencing (NGS) has been recommended as a method for detecting fusion genes in non-small cell lung cancer (NSCLC) according to clinical practice guidelines and expert consensus. The primary targetable alterations in NSCLC consist of gene mutations and fusions, making the detection of gene mutations and fusions indispensable for assessing the feasibility of targeted therapies. Currently, the integration of DNA-based NGS and RNA-based NGS allows for simultaneous detection of gene mutations and fusions and has been partially implemented in clinical practice. However, standardized guidelines and

criteria for the significance, application scenarios, and quality control of RNA-based NGS in fusion gene detection are still lacking in China. This consensus aims to provide further clarity on the practical significance, application scenarios, and quality control measures of RNA-based NGS in fusion gene detection. Additionally, it offers guiding recommendations to facilitate the clinical implementation of RNA-based NGS in the diagnosis and treatment of NSCLC, ultimately maximizing the benefits for patients from fusion gene detection.

Tamiya, A. (2023). "Long-term survival of patients with advanced non-small cell lung cancer treated using immune checkpoint inhibitors." Respir Investig **62**(1): 85-89.

Lung cancer is the leading cause of cancer-related deaths worldwide and has a high incidence of metastasis. For patients with advanced non-small cell lung cancer (NSCLC) without targetable genomic driver mutation, the development of specific antibodies called immune checkpoint inhibitors (ICIs) against the programmed death-1 receptor, its partner programmed death ligand-1, and the cytotoxic T-lymphocyte-associated protein 4 receptor have proved more effective than standard therapies in phase III trials and have led to unprecedented prolonged survival in the first-line setting. Long-lasting effects of ICI treatment have also been recorded and reported to persist even after the treatment is discontinued. Therefore, almost all patients with advanced NSCLC without driver mutation are treated with ICIs, such as PD-1 or PD-L1 therapy, in the first-line setting to achieve long-term response. However, a review summarizing the long-term survival of patients from different phase III trials is lacking to date. In this review, we aim to summarize data on the long-term survival of patients who received ICIs as first-line treatment.

Tan, K., et al. (2023). "Construction of an anoikis-associated lncRNA-miRNA-mRNA network reveals the prognostic role of beta-elemene in non-small cell lung cancer." Sci Rep **13**(1): 20185.

beta-Elemene is the main active ingredient in Curcumae Rhizoma that exerts antitumour effects. Anoikis affects tumour development through various biological pathways in non-small cell lung cancer (NSCLC), but the regulation between beta-elemene and anoikis remains to be explored. First, we explored the molecular expression patterns of anoikis-associated genes (AAGs) using consensus clustering and characterized the impact of AAGs on patient prognosis, clinical characteristics, and genomic instability. In addition, we revealed that AAG regulatory genes have rich interactions with beta-elemene targets, and established a lncRNA-miRNA-mRNA network to explain the effect of beta-elemene on anoikis. Finally, to reveal the prognostic effect of their correlation, the prognostic scoring model and clinical nomogram of beta-elemene and anoikis were successfully established by least absolute shrinkage and selection operator (LASSO) and random forest algorithms. This prognostic scoring model containing noncoding RNA (ncRNA) can indicate the immunotherapy and mutational landscape, providing a novel theoretical basis and direction for the study of the antitumour mechanism of beta-elemene in NSCLC patients.

Tomassini, S., et al. (2023). "On-cloud decision-support system for non-small cell lung cancer histology characterization from thorax computed tomography scans." Comput Med Imaging Graph **110**: 102310.

Non-Small Cell Lung Cancer (NSCLC) accounts for about 85% of all lung cancers. Developing non-invasive techniques for NSCLC histology characterization may not only help clinicians to make targeted therapeutic treatments but also prevent subjects from undergoing lung biopsy, which is challenging and could lead to clinical implications. The motivation behind the study presented here is to develop an advanced on-cloud decision-support system, named LUCY, for non-small cell LUng Cancer histologY characterization directly from thorax Computed Tomography (CT) scans. This aim was pursued by selecting thorax CT scans of 182 LUng ADenocarcinoma (LUAD) and 186 LUng Squamous Cell carcinoma (LUSC) subjects from four openly accessible data collections (NSCLC-Radiomics, NSCLC-Radiogenomics, NSCLC-Radiomics-Genomics and TCGA-LUAD), in addition to the implementation and comparison of two end-to-end neural networks (the core layer of whom is a convolutional long short-term memory layer), the performance evaluation on test dataset (NSCLC-Radiomics-Genomics) from a subject-level perspective in relation to NSCLC histological subtype location and grade, and the dynamic visual interpretation of the achieved results by producing and analyzing one heatmap video for each scan. LUCY reached test Area Under the receiver operating characteristic Curve (AUC) values above 77% in all NSCLC histological subtype location and grade groups, and a best AUC value of 97% on the entire dataset reserved for testing, proving high generalizability to heterogeneous data and robustness. Thus, LUCY is a clinically-useful decision-support system able to timely, non-invasively and reliably provide visually-understandable predictions on

LUAD and LUSC subjects in relation to clinically-relevant information.

Tong, F., et al. (2023). "FKBP5 associated CD8 T cell infiltration is a novel prognostic biomarker in luminal B breast cancer." J Int Med Res **51**(11): 3000605231211771.

OBJECTIVE: To investigate the relationship between FKBP prolyl isomerase 5 (FKBP5) gene expression and CD8 T cells in tumour progression and immunology of the luminal B subtype of breast cancer (LBBC) using bioinformatics analyses. METHODS: The Gene Expression Profiling Interactive Analysis 2, Human Protein Atlas and breast cancer gene-expression miner v4.5 databases were used for data mining and analysing FKBP5, its co-expressed genes and CD8 T cell-related markers. The Tumor IMmune Estimation Resource 2.0 database was used for analysing the correlation and prognosis of FKBP5 and CD8 T cell infiltration level in LBBC. RESULTS: Upregulated FKBP5 expression was correlated with improved survival in LBBC. Upregulated FKBP5-related CD8 T cell markers were also demonstrated to be significantly correlated with better survival in LBBC and might play a role in the biological activity of FKBP5. CONCLUSION: These findings suggest that FKBP5 and its associated CD8 T cell infiltration are potential benign prognostic indicators for LBBC.

Uong, T. N. T., et al. (2023). "Direct tumor irradiation potentiates adoptive NK cell targeting against parental and stem-like cancer in human liver cancer models." Int J Radiat Oncol Biol Phys.

BACKGROUND: Radiotherapy (RT) has been shown to effectively induce the expression of intercellular adhesion molecule-1 (ICAM-1) which is recognized by lymphocyte function-associated antigen 1 (LFA-1) expressed on NK cells. However, the potential synergistic antitumor immune response of tumor irradiation and administered NK cells has not been explored in intractable human liver cancers. Furthermore, NK cell targeting against both parental and cancer stemness has never been investigated. METHODS: Highly activated ex vivo NK cells were administered into the human liver tumor bearing mice. Tumor direct RT was optimized according to tumor bearing site. HepG2 and Hep3B ICAM-1 knockout cells were generated using CRISPR/CAS9. Stemness tumor spheres were generated. NK cell cytolysis against parental and tumorsphere was evaluated using flow cytometry and real-time cytotoxicity assay. RESULTS: A combination of adoptive NK cell therapy with RT significantly improved therapeutic efficacy over monotherapies against subcutaneous, orthotopic, and metastatic human liver tumor models. Direct tumor irradiation potentiated NK cell recognition and conjugation against liver cancer through the LFA-1/ICAM-1 axis. Suppression of immune synapse formation on NK cells using high-affinity LFA-1 inhibitors or ICAM-1 knockout liver cancer induced "outside-in" signal blocking in NK cells, resulting in failure to eliminate liver tumor despite the combination therapy. NK cells effectively recognized and targeted triple-high EPCAM(+)CD133(+)CD24(+) liver cancer expressing upregulated ICAM-1 in the irradiated tumor microenvironment, which led to prevention of the initiation of metastasis, improving survival in a metastatic model. In addition, the LFA-1/ICAM-1 axis interruption between NK cells and stemness liver tumorspheres significantly diminished NK cell cytolysis. Consistent with our preclinical data, the LFA-1/ICAM-1 axis correlated with survival outcomes in metastatic cancer patients from the TCGA databases. CONCLUSIONS: NK cells in combination with tumor irradiation can provide synergistic therapeutic effects for NK cell recognition and elimination against both parental and stem-like liver cancer through LFA-1/ICAM-1.

Urban, L., et al. (2024). "Unravelling heterogeneous effects of cancer-associated fibroblasts on poor prognosis markers in breast cancer EM-G3 cell line: In vitro-targeted treatment (anti-IL-6, anti-VEGF-A, anti-MFGE8) based on transcriptomic profiling." Oncol Rep **51**(1).

Breast cancer is the most frequently diagnosed cancer in women worldwide. Although dramatically increased survival rates of early diagnosed cases have been observed, late diagnosed patients and metastatic cancer may still be considered fatal. The present study's main focus was on cancer-associated fibroblasts (CAFs) which is an active component of the tumor microenvironment (TME) regulating the breast cancer ecosystem. Transcriptomic profiling and analysis of CAFs isolated from breast cancer skin metastasis, cutaneous basal cell carcinoma, and squamous cell carcinoma unravelled major gene candidates such as IL6, VEGFA and MFGE8 that induced co-expression of keratins-8/-14 in the EM-G3 cell line derived from infiltrating ductal breast carcinoma. Western blot analysis of selected keratins (keratin-8, -14, -18, -19) and epithelial-mesenchymal transition-associated markers (SLUG, SNAIL, ZEB1, E-/N-cadherin, vimentin) revealed specific responses pointing to certain heterogeneity of the studied CAF populations. Experimental in vitro treatment using neutralizing antibodies against IL-6, VEGF-A and MFGE8 attenuated the modulatory effect of CAFs on EM-G3 cells. The present study provided novel data in

characterizing and understanding the interactions between CAFs and EM-G3 cells in vitro. CAFs of different origins support the pro-inflammatory microenvironment and influence the biology of breast cancer cells. This observation potentially holds significant interest for the development of novel, clinically relevant approaches targeting the TME in breast cancer. Furthermore, its implications extend beyond breast cancer and have the potential to impact a wide range of other cancer types.

Vyas, D. and S. Wairkar (2023). "Effect of variables on exemestane-loaded albumin nanoparticles: Statistical optimization and anti-cancer activity in MCF-7 cell lines." Pharm Dev Technol: 1-13.

This research aimed to evaluate the effect of variables on exemestane-loaded bovine serum albumin nanoparticles (EXE-BSA NPs) to improve anti-breast cancer activity. EXE-BSA NPs were optimized using 3(2) factorial design wherein the concentration of BSA (X1) and sonication time (X2) were independent variables and particle size (Y1) and %w/w entrapment efficiency (Y2) were dependent variables. The statistical optimization revealed a significant effect of BSA concentration on both variables, whereas sonication time affected only particle size. The optimized EXE-BSA NPs were spherical with 124.1 +/- 2.62 nm particle size, 83.95 +/- 1.06% w/w drug entrapment and exhibited a biphasic release of 100% (w/w) drug over 72 h. The optimized formulation induced cytotoxicity in MCF-7 cell lines with an IC50 value of 21.46+/-microg/mL by MTT assay, almost half the free drug (54.87 microg/mL). Thus, statistically optimized EXE-BSA NPs were effective in MCF-7 cell lines and can be explored to treat estrogen receptor-positive breast cancer.

Wang, J., et al. (2023). "Single-cell and bulk transcriptomics identifies a tumor-specific CD36(+) cancer-associated fibroblast subpopulation in colorectal cancer." Cancer Commun (Lond).

Wang, T. W., et al. (2023). "Radiomics of metastatic brain tumor as a predictive image biomarker of progression-free survival in patients with non-small-cell lung cancer with brain metastasis receiving tyrosine kinase inhibitors." Transl Oncol **39**: 101826.

BACKGROUND AND OBJECTIVE: Epidermal growth factor receptor (EGFR)-targeted tyrosine kinase inhibitors (TKIs) are the first-line therapy for EGFR-mutant non-small-cell lung cancer (NSCLC). Early prediction of treatment failure in patients with brain metastases treated with EGFR-TKIs may help in making decisions for systemic drug therapy or local brain tumor control. This study examined the predictive power of the radiomics of both brain metastasis tumors and primary lung tumors. We propose a deep learning based CoxCC model based on quantitative brain magnetic resonance imaging (MRI), a prognostic index and clinical data; the model can be used to predict progression-free survival (PFS) after EGFR-TKI therapy in advanced EGFR-mutant NSCLC. METHODS: This retrospective single-center study included 271 patients receiving first-line EGFR-TKI targeted therapy in 2018-2019. Among them, 72 patients who had brain metastases before receiving first-line EGFR-TKI treatment. Three radiomic features were extracted from pretreatment brain MRI images. A CoxCC model for the progression risk stratification of EGFR-TKI treatment was proposed on the basis of MRI radiomics, clinical features, and a prognostic index. We performed time-dependent PFS predictions to evaluate the performance of the CoxCC model. RESULTS: The CoxCC model based on a prognostic index, clinical features, and radiomic features of brain metastasis exhibited higher performance than clinical features combined with indexes previously proposed for determining the prognosis of brain metastasis, including recursive partitioning analysis, diagnostic-specific graded prognostic assessment, graded prognostic assessment for lung cancer using molecular markers (lung-molGPA), and modified lung-molGPA, with c-index values of 0.75, 0.67, 0.66, 0.65, and 0.65, respectively. The model achieved areas under the curve of 0.88, 0.73, 0.92, and 0.90 for predicting PFS at 3, 6, 9 and 12 months, respectively. PFS significantly differed between the high- and low-risk groups ($p < 0.001$). CONCLUSIONS: For patients with advanced-stage NSCLC with brain metastasis, MRI radiomics of brain metastases may predict PFS. The CoxCC model integrating brain metastasis radiomics, clinical features, and a prognostic index provided reliable multi-time-point PFS predictions for patients with advanced NSCLC and brain metastases receiving EGFR-TKI treatment.

Wang, X., et al. (2023). "[Evaluation of Efficacy and Prognosis Analysis of Stage III-IV SMARCA4-deficient Non-small Cell Lung Cancer Treated by PD-1 Immune Checkpoint Inhibitors plus Chemotherapy and Chemotherapy]." Zhongguo Fei Ai Za Zhi **26**(9): 659-668.

BACKGROUND: The SMARCA4 mutation has been shown to account for at least 10% of non-small cell lung cancer (NSCLC). In the present, conventional radiotherapy and targeted therapy are difficult to improve outcomes due to the highly aggressive and refractory nature of SMARCA4-deficient NSCLC (SMARCA4-DNSCLC) and the

absence of sensitive site mutations for targeted drug therapy, and chemotherapy combined with or without immunotherapy is the main treatment. Effective SMARCA4-DNSCLC therapeutic options, however, are still debatable. Our study aimed to investigate the efficacy and prognosis of programmed cell death 1 (PD-1) immune checkpoint inhibitors (ICIs) in combination with chemotherapy and chemotherapy in patients with stage III-IV SMARCA4-DNSCLC. METHODS: 46 patients with stage III-IV SMARCA4-DNSCLC were divided into two groups based on their treatment regimen: the chemotherapy group and the PD-1 ICIs plus chemotherapy group, and their clinical data were retrospectively analyzed. Efficacy assessment and survival analysis were performed in both groups, and the influencing factors for prognosis were explored for patients with SMARCA4-DNSCLC. RESULTS: Male smokers are more likely to develop SMARCA4-DNSCLC. There was no significant difference in the objective response rate (76.5% vs 69.0%, P=0.836) between chemotherapy and the PD-1 ICIs plus chemotherapy or the disease control rate (100.0% vs 89.7%, P=0.286). The one-year overall survival rate in the group with PD-1 ICIs plus chemotherapy was 62.7%, and that of the chemotherapy group was 46.0%. The difference in median progression-free survival (PFS) between the PD-1 ICIs plus chemotherapy group and the chemotherapy group was statistically significant (9.3 mon vs 6.1 mon, P=0.048). The results of Cox regression analysis showed that treatment regimen and smoking history were independent influencing factors of PFS in patients with stage III-IV SMARCA4-DNSCLC, and family history was an individual influencing factor of overall survival in patients with stage III-IV SMARCA4-DNSCLC. CONCLUSIONS: Treatment regimen may be a prognostic factor for patients with SMARCA4-DNSCLC, and patients with PD-1 ICIs plus chemotherapy may have a better prognosis.

Wang, Z., et al. (2023). "TRIM3 facilitates ferroptosis in non-small cell lung cancer through promoting SLC7A11/xCT K11-linked ubiquitination and degradation." Cell Death Differ.

Ferroptosis, a unique form of regulated necrotic cell death, is caused by excessive iron-dependent lipid peroxidation. However, the underlying mechanisms driving ferroptosis in human cancers remain elusive. In this study, we identified TRIM3, an E3 ubiquitin-protein ligase, as a key regulator of ferroptosis. TRIM3 is downregulated in lung adenocarcinoma (LUAD) and lung squamous cell carcinoma (LUSC), two major types of non-small cell lung cancer (NSCLC). Forced expression of TRIM3 promotes cell death by enhancing the cellular level of ROS and lipid peroxidation. Moreover, our in vivo study determined that TRIM3 overexpression diminishes the tumorigenicity of NSCLC cells, indicating that TRIM3 functions as a tumor suppressor in NSCLC. Mechanistically, TRIM3 directly interacts with SLC7A11/xCT through its NHL domain, leading to SCL7A11 K11-linked ubiquitination at K37, which promotes SLC7A11 proteasome-mediated degradation. Importantly, TRIM3 expression exhibits a negative correlation with SCL7A11 expression in clinical NSCLC samples, and low TRIM3 expression is associated with a worse prognosis. This study reveals that TRIM3 functions as a tumor suppressor that can impede the tumorigenesis of NSCLC by degrading SLC7A11, suggesting a novel therapeutic strategy against NSCLC.

Wilson, G. A., et al. (2023). "Active growth signaling promotes senescence and cancer cell sensitivity to CDK7 inhibition." Mol Cell **83**(22): 4078-4092 e4076.

Tumor growth is driven by continued cellular growth and proliferation. Cyclin-dependent kinase 7's (CDK7) role in activating mitotic CDKs and global gene expression makes it therefore an attractive target for cancer therapies. However, what makes cancer cells particularly sensitive to CDK7 inhibition (CDK7i) remains unclear. Here, we address this question. We show that CDK7i, by samuraciclib, induces a permanent cell-cycle exit, known as senescence, without promoting DNA damage signaling or cell death. A chemogenetic genome-wide CRISPR knockout screen identified that active mTOR (mammalian target of rapamycin) signaling promotes samuraciclib-induced senescence. mTOR inhibition decreases samuraciclib sensitivity, and increased mTOR-dependent growth signaling correlates with sensitivity in cancer cell lines. Reverting a growth-promoting mutation in PIK3CA to wild type decreases sensitivity to CDK7i. Our work establishes that enhanced growth alone promotes CDK7i sensitivity, providing an explanation for why some cancers are more sensitive to CDK inhibition than normally growing cells.

Xia, T., et al. (2023). "IGF2BP2 Drives Cell Cycle Progression in Triple-Negative Breast Cancer by Recruiting EIF4A1 to Promote the m6A-Modified CDK6 Translation Initiation Process." Adv Sci (Weinh): e2305142.

IGF2BP2 is a new identified N6-methyladenosine (m6A) reader and associated with poor prognosis in many tumors. However, its role and related mechanism in breast cancer, especially in triple-negative breast cancer (TNBC), remains

unclear. In this study, it is found that IGF2BP2 is highly expressed in TNBC due to the lower methylation level in its promoter region. Functional and mechanical studies displayed that IGF2BP2 could promote TNBC proliferation and the G1/S phase transition of the cell cycle via directly regulating CDK6 in an m6A-dependent manner. Surprising, the regulation of protein levels of CDK6 by IGF2BP2 is related to the changes in translation rate during translation initiation, rather than mRNA stability. Moreover, EIF4A1 is found to be recruited by IGF2BP2 to promote the translation output of CDK6, providing new evidence for a regulatory role of IGF2BP2 between m6A methylation and translation. Downregulation of IGF2BP2 in TNBC cell could enhance the sensitivity to abemaciclib, a CDK4/6 inhibitor. To sum up, our study revealed IGF2BP2 could facilitate the translation output of CDK6 via recruiting EIF4A1 and also provided a potential therapeutic target for the diagnosis and treatment of TNBC, as well as a new strategy for broadening the drug indications for CDK4/6 inhibitors.

Xiao, P. and D. Zhong (2023). "[Research Progress of BRAF Fusion in Non-small Cell Lung Cancer]." Zhongguo Fei Ai Za Zhi **26**(10): 782-788.

In advanced non-small cell lung cancer (NSCLC), V-Raf murine sarcoma viral oncogene homolog B1 (BRAF) mutation is highly malignant and has poor prognosis, and currently Dabrafenib in combination with Trametinib is approved for first-line treatment of patients with BRAF V600 mutation. In addition to mutations, BRAF fusion can also occur. With the development of gene detection, the detection of BRAF fusion is gradually increasing, but there is a lack of effective therapeutic strategies for BRAF fusion. In this paper, we review the clinical characteristics, mechanism of action, and clinical treatment of BRAF fusion to provide a basis for the treatment of BRAF fusion in NSCLC patients.

Xiao, Q., et al. (2023). "Overexpression of ZNF488 supports pancreatic cancer cell proliferation and tumorigenesis through inhibition of ferroptosis via regulating SCD1-mediated unsaturated fatty acid metabolism." Biol Direct **18**(1): 77.

BACKGROUND: Pancreatic cancer is a malignancy with high mortality. Once diagnosed, effective treatment strategies are limited and the five-year survival is extremely poor. Recent studies have shown that zinc finger proteins play important roles in tumorigenesis, including pancreatic cancer. However, it remains unknown on the clinical significance, function and underlying mechanisms of zinc finger protein 488 (ZNF488) during the development of pancreatic cancer. METHODS: The clinical relevance of ZNF488 and stearoyl-CoA desaturase 1 (SCD1) was examined by analyzing the data from The Cancer Genome Atlas (TCGA) and immunohistochemical staining of the tissue microarray. Gain-of-function and loss-of-function experiments were performed by transfecting the cells with overexpressing lentivirus and siRNAs or shRNA lentivirus, respectively. The function of ZNF488 in pancreatic cancer was assessed by CCK8, colony formation, EdU staining, PI/Annexin V staining and xenografted tumorigenesis. Chip-qPCR assay was conducted to examine the interaction between ZNF488 and the promoter sequence of SCD1. Transcription activity was measured by dual luciferase reporter assay. mRNA and protein expression was detected by qRT-PCR and immunoblotting experiment, respectively. Fatty acid was quantified by gas chromatography mass spectrometry. RESULTS: ZNF488 was overexpressed in pancreatic cancer samples compared with normal tissues. High expression of ZNF488 predicted the poor prognosis of the patients. In vitro, ZNF488 upregulation contributed to the EuU cooperation, proliferation and colony formation of MIAPaCa-2 and PANC-1 cells. Based on PI/Annexin V and trypan blue staining results, we showed that ZNF488 suppressed the ferroptosis and apoptosis of pancreatic cancer cells. Mechanistically, ZNF488 directly interacted with the promoter sequence of SCD1 gene and promoted its transcription activity, which resulted in enhanced palmitoleic and oleic acid production, as well as the peroxidation of fatty acid. In vivo, ZNF488 overexpression promoted the xenograted tumorigenesis of PANC-1, which was reversed by SCD1 knockdown. Importantly, combination of erastin and SCD1 inhibitors A939572 completely blunted the growth of ZNF488 overexpressed MIAPaCa-2 and PANC-1 cells. Usage of A939572 or erastin recovered the sensitivity of pancreatic cancer cells to the treatment of gemcitabine. Lastly, we found a positive correlation between ZNF488 and SCD1 in pancreatic cancer patients based on TCGA and immunohistochemical staining results. CONCLUSION: Overexpression of ZNF488 suppresses the ferroptosis and apoptosis to support the growth and tumorigenesis of pancreatic cancer through augmentation of SCD1-mediated unsaturated fatty acid metabolism. Combination of SCD1 inhibitors, ferroptosis inducers or gemcitabine could be applied for the treatment of pancreatic cancer with overexpression of ZNF488.

Xie, Z., et al. (2023). "Insights into the inhibition of stomach cancer MKN45 cell growth by Poria cocos ethanol-soluble extract based on MAPK/PI3K

signaling pathways and components cell fishing." J Ethnopharmacol **320**: 117417.

ETHNOPHARMACOLOGICAL RELEVANCE: Poria cocos F.A. Wolf is an edible fungus with forming sclerotia, which has the effects of promoting diuresis, exuding dampness, invigorating the spleen, and regulating the stomach. P. cocos has a high application in the clinic of traditional Chinese medicine, and some studies have indicated that P. cocos has a good effect on tumor diseases. According to ancient records and modern studies, P. cocos wine offers beneficial effects in terms of strengthening tendons and bones and anti-tumor effects. AIM OF THE STUDY: To understand the substance composition of P. cocos ethanol-soluble extract (PESE) and then further study the effect and potential mechanism of PESE components on gastric cancer. MATERIALS AND METHODS: In vitro and in vivo experiments were performed to detect the cell activity and apoptotic condition. Differential expression analysis and pathway enrichment were performed based on transcriptomics and were verified by real-time polymerase chain reaction and western blotting. The mice of the stomach cancer tumor model were randomly categorized into three groups. The weight and tumor volume of the mice were measured, and the pathological characteristics of tumor tissue and immunohistochemical changes were determined. Then, the main active components of PESE were detected by MKN45 cell fishing. RESULTS: In vitro experiments showed that PESE inhibited the proliferation of MKN45 cells, but it did not induce apoptosis. Based on the transcriptome and western blotting results, the inhibition of MKN45 proliferation by PESE may be influenced by mitogen-activated protein kinase (MAPK) and phosphoinositide-3-kinase-protein kinase B (PI3K-Akt) signaling pathways. In vivo experiments showed that PESE inhibited tumor growth in mice and caused partial necrosis of tumor cells but had no toxic effect on mice. Cell fishing identified nine triterpenoids of P. cocos as the major active components of PESE. CONCLUSIONS: The results indicated that PESE has a significant inhibitory effect on stomach cancer, and its mechanism probably commonly affects the MAPK and PI3K-Akt signaling pathways, which could be due to the triterpenoid components.

Xu, M., et al. (2023). "Efficacy of rechallenge immunotherapy after immune monotherapy resistance in patients with advanced non-small cell lung cancer." J Cancer Res Clin Oncol.

PURPOSE: Drug resistance inevitably occurs despite the encouraging results of immunotherapy. This study attempted to investigate immunotherapy rechallenge treatment regimens and factors associated with outcomes in patients with non-small cell lung cancer (NSCLC) according to resistance status. METHODS: A retrospective study was conducted on patients with advanced NSCLC who received immune checkpoint inhibitor (ICI) monotherapy and immune rechallenge between March 2016 and December 2022. Primary resistance (RR) was defined by an absence of response after treatment administered for less than 6 months before progression. Acquired resistance (AR) was defined as a response to immunotherapy treatment administered for more than 6 months before progression. Disease progression in as many as three lesions was defined as systemic progression, whereas disease progression in fewer than three lesions was defined as oligo-progression. RESULTS: Of 40 patients, 18 (45%) had primary resistance, and 22 (55%) developed AR. Overall survival (OS) was not reached. A significant difference in progression-free survival (PFS) was observed in individuals rechallenged with ICIs after AR and RR (7.0 months vs. 2.1 months, P = 0.003). Patients receiving interval treatment before rechallenge achieved longer PFS than those who did not (6.2 months vs. 4.0 months, P = 0.027). Multivariate analysis demonstrated that systemic progression was a risk factor significantly associated with PFS after ICI rechallenge (P = 0.006). After AR, ICI rechallenge prolonged the duration of PFS if patients developed oligo-progression (5.4 months vs. 1.1 months, P < 0.001). CONCLUSION: ICI rechallenge is likely to be an option for patients with oligo-progression during rechallenge, particularly after AR.

Xu, X., et al. (2023). "Hsa_circ_0022383 promote non-small cell lung cancer tumorigenesis through regulating the miR-495-3p/KPNA2 axis." Cancer Cell Int **23**(1): 282.

Hsa_circ_0022383 (circ_0022383) is a newly discovered circRNA. Its functions and relevant molecular mechanisms in tumorigenesis have not been reported. Here we aimed to explore how circ_0022383 regulates the tumorigenesis of non-small-cell lung cancer (NSCLC). We found thatcirc_0022383 expression was dramatically elevated in NSCLC tissues and cell lines. Upregulation of circ_0022383 was associated with poor prognosis in NSCLC patients. Silencing of circ_0022383 repressed cell proliferation and migration in vitro and inhibited oncogenesis and tumor metastasis in vivo. Moreover, our results discovered that circ_0022383 was mainly located in the cytoplasm of NSCLC cells. Mechanistically, circ_0022383 sponged miR-495-3p to modulate KPNA2 expression, thereby regulating NSCLC

tumorigenesis and progression. In conclusion, our study demonstrates that circ_0022383 facilitates NSCLC tumorigenesis by regulating the miR-495-3p/KPNA2 axis, providing new insights into NSCLC development.

Xu, Y., et al. (2023). "Single cell atlas of kidney cancer endothelial cells reveals distinct expression profiles and phenotypes." Res Sq.

Background Tumor endothelial cells (TECs) represent the primary interface between the tumor microenvironment and circulating immune cells, however their phenotypes are incompletely understood in highly vascularized clear cell renal cell carcinoma (ccRCC). Methods We purified tumor and matched normal endothelial cells (NECs) from ccRCC specimens and performed single-cell RNA-sequencing to create a reference-quality atlas available as a searchable web resource for gene expression patterns. We established paired primary TECs and NECs cultures for ex vivo functional testing. Results TECs from multiple donors shared a common phenotype with increased expression of pathways related to extracellular matrix regulation, cell-cell communication, and insulin-like growth factor signaling that was conserved in comparison to hepatocellular carcinoma associated TECs, suggesting convergent TEC phenotypes between unrelated tumors. Cultured TECs stably maintained a core program of differentially regulated genes, were inherently resistant to apoptosis after vascular endothelial growth factor removal and displayed increased adhesiveness to subsets of immune cells including regulatory T-cells. Conclusions Our studies delineate unique functional and phenotypic properties of TECs, which may provide insights into their interactions with available and emerging therapies. Functional phenotypes of cultured TECs suggest potential mechanisms of resistance to both antiangiogenic and immune-based therapies.

Yang, L., et al. (2023). "Hyperfractionated Accelerated Radiotherapy Versus Stereotactic Body Radiotherapy in the Treatment of Limited-Stage Small Cell Lung Cancer: A Matched-Pair Analysis." Am J Clin Oncol.

BACKGROUND: Concurrent chemoradiotherapy based on hyperfractionated accelerated radiotherapy (HART) is the first-line recommended regimen for the treatment of small-cell lung cancer (SCLC). However, Stereotactic Body Radiotherapy (SBRT) is also regarded as an effective treatment for limited-stage (LS) SCLC, and the efficacy and safety of HART versus SBRT stay controversial. METHODS: In this study, 188 LS-SCLC patients were retrospectively divided into two groups receiving chemotherapy combined with either HART or SBRT. In HART group, patients received 4500 cGy in 30 fractions, administered twice daily for 3 weeks. Whereas in the SBRT group, a total radiation dose of 4000-4500 cGy was delivered in 10 fractions over 2 weeks. Thirty-three pairs of patients were finally included for next analysis. RESULTS: The estimated objective response rates were 63.6 % (21/33) and 78.8 % (26/33) in HART group and SBRT group, respectively (P = 0.269). Furthermore, there was no significant difference between HART and SBRT groups in overall survival (26 months vs. 29 months, P = 0.362) and progression free survival (11 months vs. 15 months, P = 0.223). As for the adverse events, toxicity of both groups is similar and slight that no grade 4 event was observed. Grade 3 pneumonitis cases were all occurred in the HART group (9.1%, 3/33, P = 0.238), and grade 3 esophagitis cases were all occurred in the SBRT group (6.1%, 2/33, P = 0.492). CONCLUSIONS: Compared with HART, SBRT could be another effective treatment with satisfactory safety for the concurrent chemoradiotherapy in patients with LS-SCLC.

Yoo, S. S., et al. (2023). "Promoter-Specific Variants in NeuroD1 and H3K4me3 Coincident Regions and Clinical Outcomes of Small Cell Lung Cancer." J Korean Med Sci **38**(45): e381.

BACKGROUND: Neurogenic differentiation 1 (NeuroD1) is a representative small cell lung cancer (SCLC) transcription regulator involved in the carcinogenesis and behavior of SCLC. Histone modifications play an important role in transcription, and H3 lysine 4 trimethylation (H3K4me3) is primarily associated with promoter regions. METHODS: We investigated the association between single nucleotide polymorphisms (SNPs) in NeuroD1 and H3K4me3 coincident regions, selected using ChIP sequencing (ChIP-seq), and the clinical outcomes of 261 patients with SCLC. RESULTS: Among 230 SNPs, two were significantly associated with both the chemotherapy response and overall survival (OS) of patients with SCLC. RNF145 rs2043268A>G was associated with worse chemotherapy response and OS (under a recessive model, adjusted odds ratio [aOR], 0.50, 95% confidence interval [CI], 0.26-0.94, P = 0.031, and adjusted hazard ratio [aHR], 1.88, 95% CI, 1.38-2.57, P < 0.001). CINP rs762105A>G was also associated with worse chemotherapy response and OS (under a dominant model, aOR, 0.47, 95% CI, 0.23-0.99, P = 0.046, and aHR, 2.03, 95% CI, 1.47-2.82, P < 0.001). ChIP-quantitative polymerase chain reaction and luciferase assay confirmed that the two SNPs were located in the active promoter regions and influenced

the promoter activity of each gene. CONCLUSION: To summarize, among SNPs selected using ChIP-seq in promoter regions with high peaks in both NeuroD1 and H3K4me3, RNF145 rs2043268A>G and CINP rs762105A>G were associated with clinical outcomes in patients with SCLC and also affected the promoter activity of each gene.

Youssef, G., et al. (2023). "Disseminating cells in human oral tumours possess an EMT cancer stem cell marker profile that is predictive of metastasis in image-based machine learning." Elife **12**.

Cancer stem cells (CSCs) undergo epithelial-mesenchymal transition (EMT) to drive metastatic dissemination in experimental cancer models. However, tumour cells undergoing EMT have not been observed disseminating into the tissue surrounding human tumour specimens, leaving the relevance to human cancer uncertain. We have previously identified both EpCAM and CD24 as CSC markers that, alongside the mesenchymal marker Vimentin, identify EMT CSCs in human oral cancer cell lines. This afforded the opportunity to investigate whether the combination of these three markers can identify disseminating EMT CSCs in actual human tumours. Examining disseminating tumour cells in over 12,000 imaging fields from 74 human oral tumours, we see a significant enrichment of EpCAM, CD24 and Vimentin co-stained cells disseminating beyond the tumour body in metastatic specimens. Through training an artificial neural network, these predict metastasis with high accuracy (cross-validated accuracy of 87-89%). In this study, we have observed single disseminating EMT CSCs in human oral cancer specimens, and these are highly predictive of metastatic disease.

Zhang, W., et al. (2023). "AEP-cleaved DDX3X induces alternative RNA splicing events to mediate cancer cell adaptation in harsh microenvironments." J Clin Invest.

Oxygen and nutrient deprivation is a common feature of solid tumours. Although abnormal alternative splicing (AS) has been found to be a new driving force in tumour pathogenesis and progression, the regulatory mechanisms of AS underlying the adaptation of cancer cells to harsh microenvironments remain unclear. Here, we found that hypoxia- and nutrient deprivation-induced asparagine endopeptidase (AEP) specifically cleaves DDX3X in a HIF1A-dependent manner. This cleavage yields truncated carboxyl-terminal DDX3X (tDDX3X-C), which translocates and aggregates in the nucleus. Unlike intact DDX3X, nuclear tDDX3X-C complexes with an array of splicing factors and induces AS events of many pre-mRNAs; for example, enhanced exon skipping (ES) in exon 2 of the classic tumour suppressor PRDM2 leads to a frameshift mutation of PRDM2. Intriguingly, the novel isoform ARRB1 big up tri, openexon13 binds to glycolytic enzymes and regulates glycolysis. By utilizing in vitro assays, glioblastoma organoids and animal models, we revealed that AEP/tDDX3X-C promotes tumour malignancy via these isoforms. More importantly, high AEP/tDDX3X-C/ARRB1 big up tri, openexon13 in cancerous tissues was tightly associated with poor patient prognosis. Overall, our discovery of the effect of AEP-cleaved DDX3X switching on alternative RNA splicing events identifies a new mechanism in which cancer cells adapt to oxygen/nutrient shortages and provides novel diagnostic/therapeutic targets.

Zhou, J., et al. (2023). "LncRNA IDH1-AS1 sponges miR-518c-5p to suppress proliferation of epithelial ovarian cancer cell by targeting RMB47." J Biomed Res: 1-15.

Long noncoding RNA (lncRNA) IDH1 antisense RNA 1 (IDH1-AS1) is involved in the progression of multiple cancers, but its role in epithelial ovarian cancer (EOC) is unknown. Therefore, we investigated the expression levels of IDH1-AS1 in EOC cells and normal ovarian epithelial cells by quantitative real-time PCR (qPCR). We first evaluated the effects of IDH1-AS1 on the proliferation, migration, and invasion of EOC cells through cell counting kit-8, colony formation, EdU, transwell, wound-healing, and xenograft assays. We then explored the downstream targets of IDH1-AS1 and verified the results by a dual-luciferase reporter, qPCR, rescue experiments, and Western blotting. We found that the expression levels of IDH1-AS1 were lower in EOC cells than in normal ovarian epithelial cells. High IDH1-AS1 expression of EOC patients from the Gene Expression Profiling Interactive Analysis database indicated a favorable prognosis, because IDH1-AS1 inhibited cell proliferation and xenograft tumor growth of EOC. IDH1-AS1 sponged miR-518c-5p whose overexpression promoted EOC cell proliferation. The miR-518c-5p mimic also reversed the proliferation-inhibiting effect induced by IDH1-AS1 overexpression. Furthermore, we found that RNA binding motif protein 47 (RBM47) was the downstream target of miR-518c-5p, that upregulation of RBM47 inhibited EOC cell proliferation, and that RBM47 overexpressing plasmid counteracted the proliferation-promoting effect caused by the IDH1-AS1 knockdown. Taken together, IDH1-AS1 may suppress EOC cell proliferation and tumor growth via the miR-518c-5p/RBM47 axis.

Zhou, P. Y., et al. (2023). "Single-cell and spatial architecture of primary liver cancer." Commun Biol **6**(1): 1181.

Primary liver cancer (PLC) poses a leading threat to human health, and its treatment options are limited. Meanwhile, the investigation of homogeneity and heterogeneity among PLCs remains challenging. Here, using single-cell RNA sequencing, spatial transcriptomic and bulk multi-omics, we elaborated a molecular architecture of 3 PLC types, namely hepatocellular carcinoma (HCC), intrahepatic cholangiocarcinoma (ICC) and combined hepatocellular-cholangiocarcinoma (CHC). Taking a high-resolution perspective, our observations revealed that CHC cells exhibit internally discordant phenotypes, whereas ICC and HCC exhibit distinct tumor-specific features. Specifically, ICC was found to be the primary source of cancer-associated fibroblasts, while HCC exhibited disrupted metabolism and greater individual heterogeneity of T cells. We further revealed a diversity of intermediate-state cells residing in the tumor-peritumor junctional zone, including a congregation of CPE(+) intermediate-state endothelial cells (ECs), which harbored the molecular characteristics of tumor-associated ECs and normal ECs. This architecture offers insights into molecular characteristics of PLC microenvironment, and hints that the tumor-peritumor junctional zone could serve as a targeted region for precise therapeutical strategies.

Zhou, X., et al. (2023). "MHC class II regulation of CD8(+) T cell tolerance and implications in autoimmunity and cancer immunotherapy." Cell Rep **42**(11): 113452.

Major histocompatibility complex (MHC) class II-reactive CD8(+) T cells are found in humans and animals, but little is known about their identity, development, and function. In this study, we discover a group of CD8(+) T cells reactive to both MHC class I and II molecules in MHC class II-deficient mice. We clone their T cell receptors (TCRs) and analyze their development and function. In wild-type animals, thymocytes bearing those TCRs are purged by negative selection. In the absence of MHC class II, they develop into mature CD8(+) T cells. When encountering MHC class II in the periphery, they undergo robust activation and proliferation, attack self-tissues, and cause lethal autoimmune diseases. In adoptive T cell therapy, those CD8(+) T cells are able to efficiently control MHC class II-expressing tumors. This study opens the door to investigation of dual-reactive CD8(+) T cells, their development and selection in the thymus, and the perils and promises when their normal development and selection are compromised.

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