# The Lipidome: A Case Study of Treatment-Resistance in Clear Cell Renal Cell Carcinoma using Patient Derived Organoids

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## Summary

**Purpose:** To investigate the effects of three anti-cancer drugs on the lipidome of clear cell renal cell carcinoma (ccRCC) and identify lipids associated with treatment resistance and/or susceptibility
**Rationale:** ccRCC is extremely resistant to treatment; 1 in 2 patients will not survive 5 years post-diagnosis. Lipids are known to contribute to treatment resistance in other cancers yet their role in ccRCC remains poorly understood.
**Method:** Patient-derived organoids were treated with three anti-cancer drugs. The lipidomes of treated and untreated (control) PDOs were identified and compared
**Main finding:** Glycerophospholipids may contribute to treatment resistance in ccRCC.
**Significance**: Identified glycerophospholipids as potential targets for new generation anti-cancer drugs, which could bypass ccRCC resistance thus improving patient survival in the future.

## Introduction

**Background:**

- Clear Cell Renal Cell Carcinoma (ccRCC) is the predominant type of Kidney Cancer, the 8th most common cancer globally
- Characterised by high lipid abundance
- Lipids contribute to pathways in various cancers that **protect tumour cells from treatment**[1]
- However, lipid changes associated with treatment resistance in ccRCC remain **poorly characterized**[2,3]

**Objectives:**

1. Uncover effects of NUC-7738 (novel anti-cancer drug), Nivolumab and Ipilimumab on the lipidome (lipid composition) of ccRCC
2. Identify lipids associated with treatment resistance and/or susceptibility

## Methods

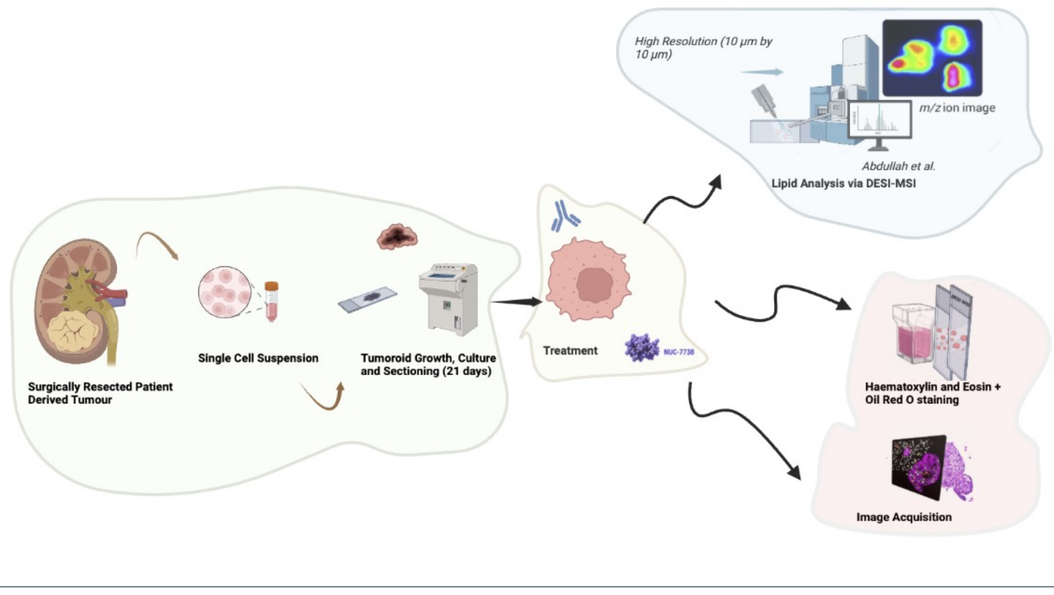


**Fig. 1**: Diagram outlining the harvesting, preparation, treatment and subsequent analysis of ccRCC organoids

1. ccRCC cells taken from patient tumours (Fig. 2)
2. Isolated patient ccRCC cells cultured to create **Patient Derived Organoids** (PDOs) (Fig. 3)
   - PDOs are 3D models of cancer cells which imitate the **structure and behaviour** of cancer in the human body
3. Lipidome of each PDO was captured using **mass spectrometry** (Fig 4)

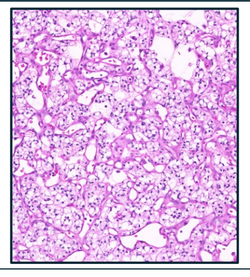

**Fig. 2** ccRCC Patient Tissue

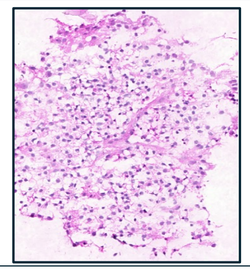

**Fig. 3** structure of a ccRCC PDO

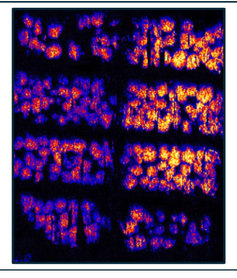

**Fig. 4** Lipidomes of PDOs

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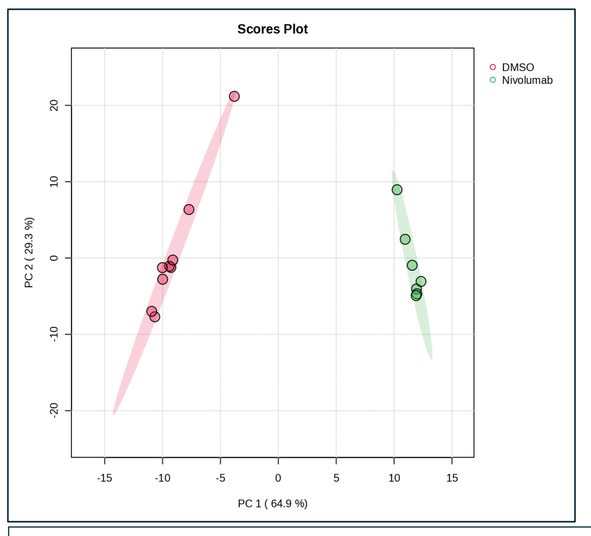
## Results



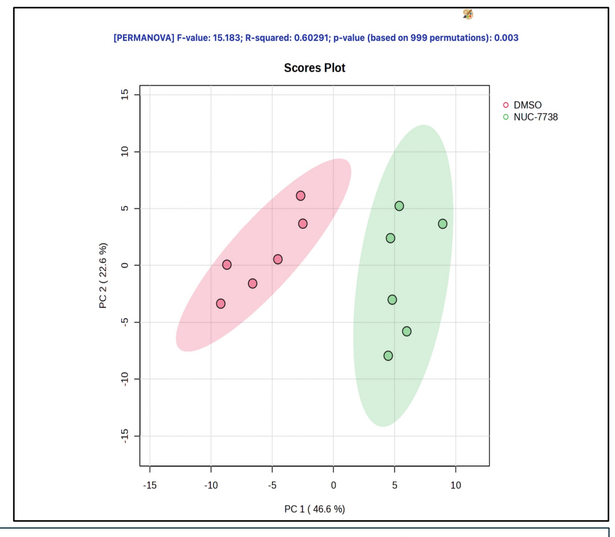




**Fig. 5a** (left) and **5b** (right): Principal Component Analysis (PCA) , a pattern-finding statistical tool. PCA compares the lipid profiles of control (red) and treated (green) samples. Each circle represents **one sample.** (Images above highlight examples of PCA for two of the tested drugs)

- All tested anti-cancer drugs induced **changes in the lipidome** of ccRCC PDOs compared to control

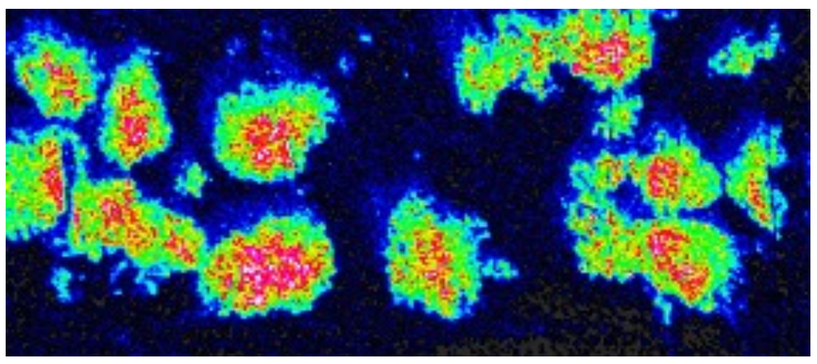
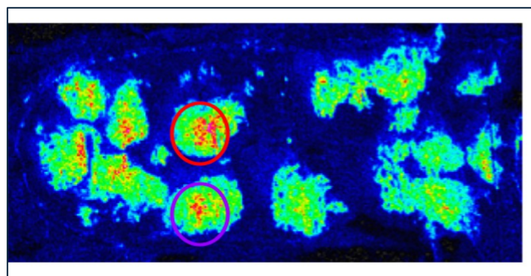
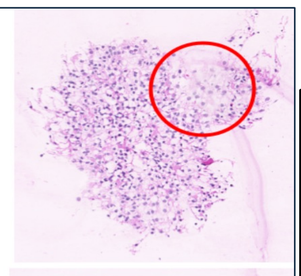


**Fig. 6** Heatmap image showing **high concentrations** of a specific phospholipid (bright red zones) present within a **treatment-resistant** organoid cluster

- **Glycerophospholipids** were present in higher abundance within PDOs that did not respond to treatment





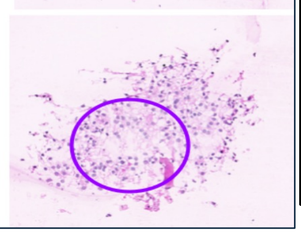


**Fig. 7 High concentrations** of fatty acids (circled) **align with regions** of cell death visible on the tissue stains of PDOs structure

- **Fatty acids** were present in higher abundance within treatment responsive PDOs
- Fatty acids were associated with areas of cell death

## Discussion

- The findings suggest that glycerophospholipids may play a role in treatment resistance and that fatty acids might be associated with treatment susceptibility
- Glycerophospholipids influence cellular signalling, cancer progression, and immune-cell function which **contribute to treatment resistance** in other cancers[4,5]
- **Drugs** targeting glycerophospholipids given in tandem with current treatments can potentially help **counter resistance** in ccRCC
- Fatty acids are known to drive and accumulate as byproducts of cell death[6]
- Therefore, the confinement of fatty acids to areas of cell death in our samples can confound their influence in ccRCC treatment susceptibility
- Future studies should **expand the sample size** beyond N=1 to improve generizability
- Use of PDOs is a **strength** as it allows accurate bridging of relevant scientific findings to patients

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