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Therapeutic Targets in Ovarian Cancer: Proliferative (C1) Vs Differentiated (C4) Subtypes

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Project mentor: Dr. Lajos Kalmar

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Project Title

Therapeutic Targets in Ovarian Cancer: Proliferative (C1) vs Differentiated (C4) Subtypes

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Project lead:

- **Shaden Almohawwes:** I completed this project individually, handling all stages from data analysis to the final report and poster.

Project Mentor

- **Dr. Lajos Kalmar (University of Cambridge, Dept. of Genetics):** Provided technical guidance on analysis strategy.

Project Objectives and Goals

1. Compare proteomic profiles between ovarian cancer clusters **C1 (proliferative/mesenchymal-like)** and **C4 (differentiated/epithelial-like)**.
2. Identify significantly altered proteins between the two clusters.
3. Perform pathway enrichment to understand biological differences.
4. Map differentially expressed proteins to known or potential drug targets.
5. Explore implications for personalized therapy in ovarian cancer.

Current Progress and Milestones Achieved

- Dataset from **Tan et al., 2024 (CPTAC)** successfully obtained (MOESM8–9).
- Samples filtered for **C1 and C4 clusters, primary tumors only**.
- Preprocessing completed (zero-to-NA conversion, log transformation).
- QC done using PCA and clustering heatmaps.
- Differential expression performed using **limma**.
- GO and Reactome enrichment analyses completed.
- Drug–target mapping finalized with DrugBank and Open Targets cross-referencing.
- Poster prepared and presented at the Cambridge Bioinformatics Summer Programme, awarded **Highly Commended Poster recognition**.

Methodology and Approach

- **Data preprocessing:** MSnbase in R for handling proteomic data.
- **Differential expression:** Limma (adjusted p-value < 0.05).
- **Visualization:** PCA plots, heatmaps, bubble plots.
- **Functional enrichment:** clusterProfiler for GO and Reactome pathways.
- **Drug mapping:** Cross-checked proteins with DrugBank and Open Targets.

Preliminary Results or Findings

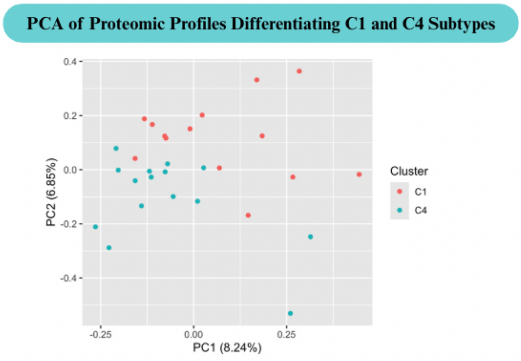


Figure 1. PCA plot of proteomic profiles distinguishing C1 and C4 clusters.
Samples show separation along PC1 and PC2, highlighting distinct molecular signatures between the two groups.

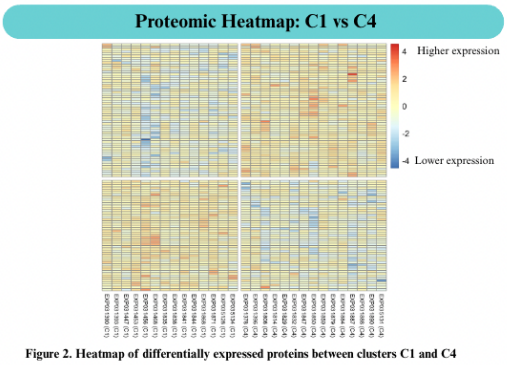


Figure 2. Heatmap of differentially expressed proteins between clusters C1 and C4
Displays the expression patterns of significantly altered proteins across ovarian cancer clusters C1 and C4, and highlights clear separation of expression profiles between the two clusters, reflecting their distinct molecular characteristics.

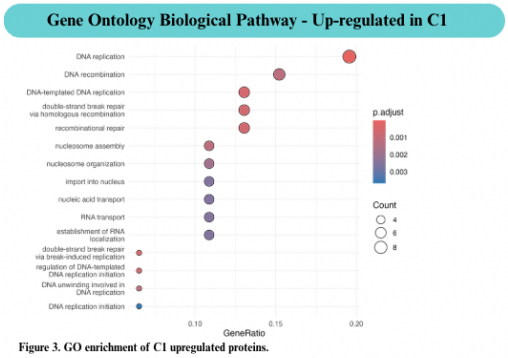


Figure 3. GO enrichment of C1 upregulated proteins.
C1 cluster proteins are enriched in DNA replication, recombination, and repair processes, suggesting active cell proliferation and genomic maintenance pathways.

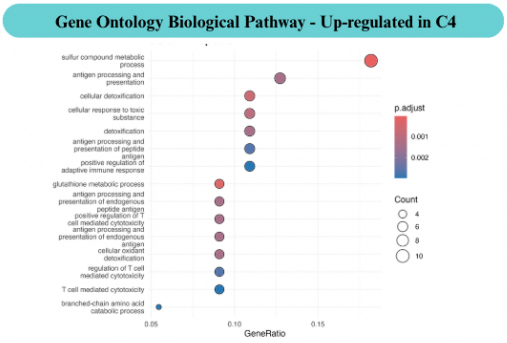


Figure 4. GO enrichment of C4 upregulated proteins.
C4 cluster proteins are enriched in detoxification, glutathione metabolism, and immune-related processes, highlighting stress response a

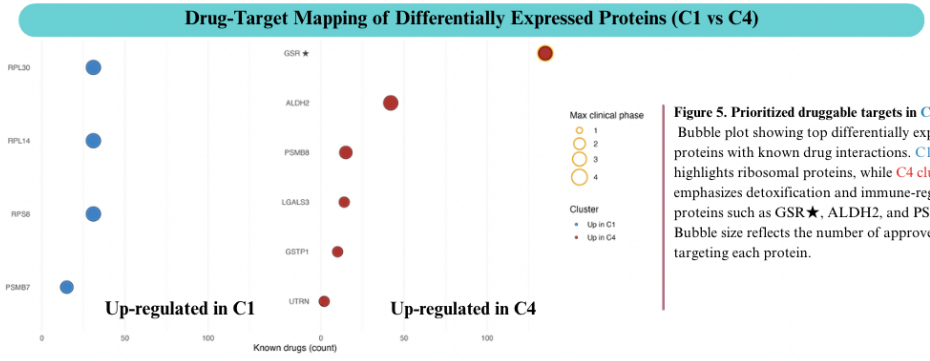


Figure 5. Prioritized druggable targets in C1 vs. C4.
Bubble plot showing top differentially expressed proteins with known drug interactions. C1 cluster highlights ribosomal proteins, while C4 cluster emphasizes detoxification and immune-regulatory proteins such as GSR★, ALDH2, and PSMB8. Bubble size reflects the number of approved drugs targeting each protein.

- **PCA & Heatmap:** Clear segregation between C1 and C4 clusters.
- **C1 tumors:** Enriched in DNA replication, ribosomal biogenesis, and ECM interactions → highly proliferative and aggressive.
- **C4 tumors:** Enriched in detoxification (glutathione metabolism), immune regulation, and epithelial differentiation → less aggressive.
- **Drug–Target Mapping:**
  - **C1:** Ribosomal proteins (RPL30, RPL14, RPS6, PSMB7).
  - **C4:** Detoxification/immune proteins **(GSR★, ALDH2, PSMB8)**.
- Key insight: **different clusters may require different therapeutic strategies** → one-size-fits-all treatment is ineffective.

Discussion

- **C1 tumors**: Showed enrichment in DNA replication and ribosomal proteins → explains their aggressive, proliferative behavior. These findings suggest that ribosome biogenesis could be explored as a therapeutic vulnerability (1).
- **C4 tumors**: Enriched in detoxification and immune-regulatory pathways (e.g., **GSR, ALDH2, PSMB8**) → indicates better stress resistance and potential sensitivity to redox- or proteasome-targeted therapies (2).
- **Clinical relevance**: These subtype differences highlight why uniform treatments often fail in ovarian cancer. For example, immune checkpoint inhibitors showed little benefit overall, but activity was seen in biomarker-defined subgroups only (3).
- **Future direction**: Proteomic subtyping could enable **precision therapy**, ensuring patients receive treatments aligned with their tumor biology, minimizing toxicity, and improving outcomes (4).

Challenges and Obstacles Encountered

- **Data complexity:** High dimensionality of proteomic datasets required extensive preprocessing.
- **Missing values:** Zeros had to be carefully treated as NA without imputation.
- **Time constraints:** Limited timeframe.
- **Interpretation:** Translating proteomic signals into actionable therapeutic insights required intensive literature integration.

Next Steps and Future Work

- Extend analysis to include **C2 (immunoreactive)** and **C3 (fallopian-like)** clusters.
- Integrate **multi-omics (genomic + transcriptomic)** with proteomic results.
- Validate candidate drug targets (e.g., GSR, ribosomal proteins) in experimental models.
- Collaborate with clinical researchers to design **subtype-guided therapeutic trials**.

Resources and Tools Used

- **Data:** CPTAC ovarian cancer proteomics dataset (Tan et al., 2024, MOESM8–9).
- **Software:** R (MSnbase, limma, clusterProfiler, ggplot2).
- **Databases:** DrugBank, Open Targets.
- **Mentorship:** University of Cambridge Genetics Department.

Acknowledgments

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