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ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии

საქართველოს სამედიცინო სიახლენი

GEORGIAN MEDICAL NEWS

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GMN: Georgian Medical News is peer-reviewed, published monthly journal committed to promoting the science and art of medicine and the betterment of public health, published by the GMN Editorial Board since 1994. GMN carries original scientific articles on medicine, biology and pharmacy, which are of experimental, theoretical and practical character; publishes original research, reviews, commentaries, editorials, essays, medical news, and correspondence in English and Russian.

GMN is indexed in MEDLINE, SCOPUS, PubMed and VINITI Russian Academy of Sciences. The full text content is available through EBSCO databases.

GMN: Медицинские новости Грузии - ежемесячный рецензируемый научный журнал, издаётся Редакционной коллегией с 1994 года на русском и английском языках в целях поддержки медицинской науки и улучшения здравоохранения. В журнале публикуются оригинальные научные статьи в области медицины, биологии и фармации, статьи обзорного характера, научные сообщения, новости медицины и здравоохранения. Журнал индексируется в MEDLINE, отражён в базе данных SCOPUS, PubMed и ВИНИТИ РАН. Полнотекстовые статьи журнала доступны через БД EBSCO.

GMN: Georgian Medical News – საქართველოს სამედიცინო სიახლენი – არის ყოველთვიური სამეცნიერო სამედიცინო რეცენზირებადი ჟურნალი, გამოიცემა 1994 წლიდან, წარმოადგენს სარედაქციო კოლეგიისა და აშშ-ის მეცნიერების, განათლების, ინდუსტრიის, ხელოვნებისა და ბუნებისმეტყველების საერთაშორისო აკადემიის ერთობლივ გამოცემას. GMN-ში რუსულ და ინგლისურ ენებზე ქვეყნდება ექსპერიმენტული, თეორიული და პრაქტიკული ხასიათის ორიგინალური სამეცნიერო სტატიები მედიცინის, ბიოლოგიისა და ფარმაციის სფეროში, მიმოხილვითი ხასიათის სტატიები.

ჟურნალი ინდექსირებულია MEDLINE-ის საერთაშორისო სისტემაში, ასახულია SCOPUS-ის, PubMed-ის და ВИНИТИ РАН-ის მონაცემთა ბაზებში. სტატიების სრული ტექსტი ხელმისაწვდომია EBSCO-ს მონაცემთა ბაზებიდან.

WEBSITE

www.geomednews.com

К СВЕДЕНИЮ АВТОРОВ!

При направлении статьи в редакцию необходимо соблюдать следующие правила:

1. Статья должна быть представлена в двух экземплярах, на русском или английском языках, напечатанная через **полтора интервала на одной стороне стандартного листа с шириной левого поля в три сантиметра**. Используемый компьютерный шрифт для текста на русском и английском языках - **Times New Roman** (**Кириллица**), для текста на грузинском языке следует использовать **AcadNusx.** Размер шрифта - **12**. К рукописи, напечатанной на компьютере, должен быть приложен CD со статьей.

2. Размер статьи должен быть не менее десяти и не более двадцати страниц машинописи, включая указатель литературы и резюме на английском, русском и грузинском языках.

3. В статье должны быть освещены актуальность данного материала, методы и результаты исследования и их обсуждение.

При представлении в печать научных экспериментальных работ авторы должны указывать вид и количество экспериментальных животных, применявшиеся методы обезболивания и усыпления (в ходе острых опытов).

4. К статье должны быть приложены краткое (на полстраницы) резюме на английском, русском и грузинском языках (включающее следующие разделы: цель исследования, материал и методы, результаты и заключение) и список ключевых слов (key words).

5. Таблицы необходимо представлять в печатной форме. Фотокопии не принимаются. **Все цифровые, итоговые и процентные данные в таблицах должны соответствовать таковым в тексте статьи**. Таблицы и графики должны быть озаглавлены.

6. Фотографии должны быть контрастными, фотокопии с рентгенограмм - в позитивном изображении. Рисунки, чертежи и диаграммы следует озаглавить, пронумеровать и вставить в соответствующее место текста **в tiff формате**.

В подписях к микрофотографиям следует указывать степень увеличения через окуляр или объектив и метод окраски или импрегнации срезов.

7. Фамилии отечественных авторов приводятся в оригинальной транскрипции.

8. При оформлении и направлении статей в журнал МНГ просим авторов соблюдать правила, изложенные в «Единых требованиях к рукописям, представляемым в биомедицинские журналы», принятых Международным комитетом редакторов медицинских журналов - http://www.spinesurgery.ru/files/publish.pdf и http://www.nlm.nih.gov/bsd/uniform_requirements.html
В конце каждой оригинальной статьи приводится библиографический список. В список литературы включаются все материалы, на которые имеются ссылки в тексте. Список составляется в алфавитном порядке и нумеруется. Литературный источник приводится на языке оригинала. В списке литературы сначала приводятся работы, написанные знаками грузинского алфавита, затем кириллицей и латиницей. Ссылки на цитируемые работы в тексте статьи даются в квадратных скобках в виде номера, соответствующего номеру данной работы в списке литературы. Большинство цитированных источников должны быть за последние 5-7 лет.

9. Для получения права на публикацию статья должна иметь от руководителя работы или учреждения визу и сопроводительное отношение, написанные или напечатанные на бланке и заверенные подписью и печатью.

10. В конце статьи должны быть подписи всех авторов, полностью приведены их фамилии, имена и отчества, указаны служебный и домашний номера телефонов и адреса или иные координаты. Количество авторов (соавторов) не должно превышать пяти человек.

11. Редакция оставляет за собой право сокращать и исправлять статьи. Корректура авторам не высылается, вся работа и сверка проводится по авторскому оригиналу.

12. Недопустимо направление в редакцию работ, представленных к печати в иных издательствах или опубликованных в других изданиях.

При нарушении указанных правил статьи не рассматриваются.

REQUIREMENTS

Please note, materials submitted to the Editorial Office Staff are supposed to meet the following requirements:

1. Articles must be provided with a double copy, in English or Russian languages and typed or compu-ter-printed on a single side of standard typing paper, with the left margin of **3** centimeters width, and **1.5** spacing between the lines, typeface - **Times New Roman** (**Cyrillic**), print size - **12** (referring to Georgian and Russian materials). With computer-printed texts please enclose a CD carrying the same file titled with Latin symbols.

2. Size of the article, including index and resume in English, Russian and Georgian languages must be at least 10 pages and not exceed the limit of 20 pages of typed or computer-printed text.

3. Submitted material must include a coverage of a topical subject, research methods, results, and review.

Authors of the scientific-research works must indicate the number of experimental biological species drawn in, list the employed methods of anesthetization and soporific means used during acute tests.

4. Articles must have a short (half page) abstract in English, Russian and Georgian (including the following sections: aim of study, material and methods, results and conclusions) and a list of key words.

5. Tables must be presented in an original typed or computer-printed form, instead of a photocopied version. **Numbers, totals, percentile data on the tables must coincide with those in the texts of the articles.** Tables and graphs must be headed.

6. Photographs are required to be contrasted and must be submitted with doubles. Please number each photograph with a pencil on its back, indicate author's name, title of the article (short version), and mark out its top and bottom parts. Drawings must be accurate, drafts and diagrams drawn in Indian ink (or black ink). Photocopies of the X-ray photographs must be presented in a positive image in **tiff format**.

Accurately numbered subtitles for each illustration must be listed on a separate sheet of paper. In the subtitles for the microphotographs please indicate the ocular and objective lens magnification power, method of coloring or impregnation of the microscopic sections (preparations).

7. Please indicate last names, first and middle initials of the native authors, present names and initials of the foreign authors in the transcription of the original language, enclose in parenthesis corresponding number under which the author is listed in the reference materials.

8. Please follow guidance offered to authors by The International Committee of Medical Journal Editors guidance in its Uniform Requirements for Manuscripts Submitted to Biomedical Journals publication available online at: http://www.nlm.nih.gov/bsd/uniform_requirements.html
http://www.icmje.org/urm_full.pdf
In GMN style for each work cited in the text, a bibliographic reference is given, and this is located at the end of the article under the title "References". All references cited in the text must be listed. The list of references should be arranged alphabetically and then numbered. References are numbered in the text [numbers in square brackets] and in the reference list and numbers are repeated throughout the text as needed. The bibliographic description is given in the language of publication (citations in Georgian script are followed by Cyrillic and Latin).

9. To obtain the rights of publication articles must be accompanied by a visa from the project instructor or the establishment, where the work has been performed, and a reference letter, both written or typed on a special signed form, certified by a stamp or a seal.

10. Articles must be signed by all of the authors at the end, and they must be provided with a list of full names, office and home phone numbers and addresses or other non-office locations where the authors could be reached. The number of the authors (co-authors) must not exceed the limit of 5 people.

11. Editorial Staff reserves the rights to cut down in size and correct the articles. Proof-sheets are not sent out to the authors. The entire editorial and collation work is performed according to the author's original text.

12. Sending in the works that have already been assigned to the press by other Editorial Staffs or have been printed by other publishers is not permissible.

Articles that Fail to Meet the Aforementioned Requirements are not Assigned to be Reviewed.

ავტორთა საყურადღებოდ!

რედაქციაში სტატიის წარმოდგენისას საჭიროა დავიცვათ შემდეგი წესები:

1. სტატია უნდა წარმოადგინოთ 2 ცალად, რუსულ ან ინგლისურ ენებზე,დაბეჭდილი სტანდარტული ფურცლის 1 გვერდზე, 3 სმ სიგანის მარცხენა ველისა და სტრიქონებს შორის 1,5 ინტერვალის დაცვით. გამოყენებული კომპიუტერული შრიფტი რუსულ და ინგლისურენოვან ტექსტებში - **Times New Roman (Кириллица)**, ხოლო ქართულენოვან ტექსტში საჭიროა გამოვიყენოთ **AcadNusx.** შრიფტის ზომა – 12. სტატიას თან უნდა ახლდეს CD სტატიით.

2. სტატიის მოცულობა არ უნდა შეადგენდეს 10 გვერდზე ნაკლებს და 20 გვერდზე მეტს ლიტერატურის სიის და რეზიუმეების (ინგლისურ, რუსულ და ქართულ ენებზე) ჩათვლით.

3. სტატიაში საჭიროა გაშუქდეს: საკითხის აქტუალობა; კვლევის მიზანი; საკვლევი მასალა და გამოყენებული მეთოდები; მიღებული შედეგები და მათი განსჯა. ექსპერიმენტული ხასიათის სტატიების წარმოდგენისას ავტორებმა უნდა მიუთითონ საექსპერიმენტო ცხოველების სახეობა და რაოდენობა; გაუტკივარებისა და დაძინების მეთოდები (მწვავე ცდების პირობებში).

4. სტატიას თან უნდა ახლდეს რეზიუმე ინგლისურ, რუსულ და ქართულ ენებზე არანაკლებ ნახევარი გვერდის მოცულობისა (სათაურის, ავტორების, დაწესებულების მითითებით და უნდა შეიცავდეს შემდეგ განყოფილებებს: მიზანი, მასალა და მეთოდები, შედეგები და დასკვნები; ტექსტუალური ნაწილი არ უნდა იყოს 15 სტრიქონზე ნაკლები) და საკვანძო სიტყვების ჩამონათვალი (key words).

5. ცხრილები საჭიროა წარმოადგინოთ ნაბეჭდი სახით. ყველა ციფრული, შემაჯამებელი და პროცენტული მონაცემები უნდა შეესაბამებოდეს ტექსტში მოყვანილს.

6. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრამების ფოტოასლები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალების შეღებვის ან იმპრეგნაციის მეთოდი და აღნიშნოთ სურათის ზედა და ქვედა ნაწილები.

7. სამამულო ავტორების გვარები სტატიაში აღინიშნება ინიციალების თანდართვით, უცხოურისა – უცხოური ტრანსკრიპციით.

8. სტატიას თან უნდა ახლდეს ავტორის მიერ გამოყენებული სამამულო და უცხოური შრომების ბიბლიოგრაფიული სია (ბოლო 5-8 წლის სიღრმით). ანბანური წყობით წარმოდგენილ ბიბლიოგრაფიულ სიაში მიუთითეთ ჯერ სამამულო, შემდეგ უცხოელი ავტორები (გვარი, ინიციალები, სტატიის სათაური, ჟურნალის დასახელება, გამოცემის ადგილი, წელი, ჟურნალის №, პირველი და ბოლო გვერდები). მონოგრაფიის შემთხვევაში მიუთითეთ გამოცემის წელი, ადგილი და გვერდების საერთო რაოდენობა. ტექსტში კვადრატულ ფჩხილებში უნდა მიუთითოთ ავტორის შესაბამისი N ლიტერატურის სიის მიხედვით. მიზანშეწონილია, რომ ციტირებული წყაროების უმეტესი ნაწილი იყოს 5-6 წლის სიღრმის.

9. სტატიას თან უნდა ახლდეს: ა) დაწესებულების ან სამეცნიერო ხელმძღვანელის წარდგინება, დამოწმებული ხელმოწერითა და ბეჭდით; ბ) დარგის სპეციალისტის დამოწმებული რეცენზია, რომელშიც მითითებული იქნება საკითხის აქტუალობა, მასალის საკმაობა, მეთოდის სანდოობა, შედეგების სამეცნიერო-პრაქტიკული მნიშვნელობა.

10. სტატიის ბოლოს საჭიროა ყველა ავტორის ხელმოწერა, რომელთა რაოდენობა არ უნდა აღემატებოდეს 5-ს.

11. რედაქცია იტოვებს უფლებას შეასწოროს სტატია. ტექსტზე მუშაობა და შეჯერება ხდება საავტორო ორიგინალის მიხედვით.

12. დაუშვებელია რედაქციაში ისეთი სტატიის წარდგენა, რომელიც დასაბეჭდად წარდგენილი იყო სხვა რედაქციაში ან გამოქვეყნებული იყო სხვა გამოცემებში.

აღნიშნული წესების დარღვევის შემთხვევაში სტატიები არ განიხილება.

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MINING THE CELLMINER DATABASE TO IDENTIFY SHARED BIOMARKERS OF 5-FU AND OXALIPLATIN RESPONSE

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Abstract.

Background: 5-Fluorouracil and Oxaliplatin form backbone of colorectal cancer, yet resistance limits their efficacy. Understanding the molecular determinants of sensitivity and resistance may guide potential biomarker discovery and inform drug repurposing strategies.

Methods: We performed an integrative pharmacogenomic analysis of the NCI-60 cancer cell line panel using CellMiner Database. Pathway enrichment was performed using PANTHER. Individual drug and molecular biomarker correlations were explored to identify potential therapeutic vulnerabilities and repurposing opportunities.

Results: Genetic variants in ALDH9A1 were negatively associated with both 5-FU and Oxaliplatin. Protein function–affecting variants in CAMSAP3, LUM, and LRIG2 correlated negatively. DNA methylation of FERMT3 was negatively correlated with drug response, suggesting epigenetic silencing as a resistance mechanism. Copy number variation in COL1A1 also predicted resistance but correlated positively with statin sensitivity, highlighting repurposing potential. Transcriptomic signatures revealed cytoskeletal/adhesion genes (CNN3, ACTN1, DUSP10) as resistance markers, with pathway enrichment pointing to folate metabolism, MAPK signaling, and cytoskeletal remodeling. RNA-seq confirmed NT5E and HIF1A as resistance drivers. Several microRNAs including let-7e, miR-30a, and miR-22, were negatively correlated with drug activity, positioning them as potential biomarkers. Drug–drug correlation showed several cytotoxics positively associated with 5-FU/Oxaliplatin.

Conclusion: This integrative analysis identify potential biomarkers associated with 5-FU and Oxaliplatin response, nominating ALDH9A1, FERMT3, NT5E, HIF1A, and specific microRNAs as resistance biomarkers, while GRIN1, MTHFD2, and miR-7 emerge as sensitizers. Importantly, repurposing opportunities were identified, with statins and kinase inhibitors showing context-dependent associations that may help overcome resistance. These findings may provide a framework for potential biomarkers guided therapy optimization and may inform rational combination strategies in colorectal cancer.

Key words. CellMiner, 5-Fluorouracil, oxaliplatin, chemotherapy resistance, gene expression, drug sensitivity.

Introduction.

The development of effective therapeutic strategies for malignant disease has been a critical focus of biomedical research [1]. Cancer arises from complex genetic and molecular alterations that exploit host cellular pathways, creating opportunities for targeted therapeutic intervention [2]. The search for new treatment strategies has spurred interest in drug repurposing, which involves identifying novel applications for existing drugs. This approach not only reduces the time and cost of drug development but also leverages the extensive safety and pharmacokinetic data already available for approved medications [3].

Databases are invaluable resources in molecular medicine and pharmacology, providing extensive information that can drive research and innovation [4]. However, the sheer volume and complexity of data often hinder analysis and integration. The CellMiner platform, developed by the National Cancer Institute (NCI), provides a robust resource for evaluating drug activity and molecular profiles across the NCI-60 human tumor cell lines. This platform integrates genomic, transcriptomic, and drug activity data, enabling the systematic investigation of drug interactions and their association with molecular parameters [5]. Data driven analyses have the potential to uncover novel therapeutic relationships and shared molecular pathways between different classes of drugs [6].

In this study, we utilized CellMiner database to investigate the correlations of anticancer drugs with number of FDA-approved drugs, examining their molecular parameters, including gene expression, DNA methylation, and microRNA levels [7]. As an application example, we explored the shared biomarkers of Oxaliplatin (OX), a platinum-based chemotherapeutic agent, and 5-Fluorouracil (5-FU), an antimetabolite, which serves as a cornerstone therapy for metastatic colorectal cancer [8]. This synergistic regimen achieves response rates exceeding 50% and offers significant progression-free survival benefits [9]. However, resistance or lack of response persists in a notable proportion of patients, underscoring the need to better understand the shared molecular underpinnings of these medications [10].

There is a growing concern in both academia and industry that identifying well-validated targets will become increasingly challenging. Additionally, the often-temporary responses to new molecular therapies in many solid cancers have been associated with various mechanisms of resistance [1]. By analysing drug activity and molecular features, we aimed to identify common molecular targets or pathways shared by anticancer agents. Additionally, we explored potential repurposing opportunities for FDA-approved drugs in oncology. Furthermore, our analysis sought to uncover biomarkers predictive of drug efficacy, paving the way for the development of personalized therapeutic strategies. This research highlights the power of integrating pharmacological and molecular data to deepen our understanding of drug mechanisms and explore novel applications for existing therapies. The findings might provide insights into potential synergistic drug combinations and molecular markers, contributing to the broader goal of improving treatment outcomes in cancer.

Materials and Methods.

Drugs were selected based on their NSC numbers, representing FDA-approved anticancer agents, and analyzed using the "Drug Activity Z Scores" module within the CellMiner platform.

The "Pattern Comparison" tool was used to identify shared biomarkers of two standard agents, 5-FU and Oxaliplatin, across the NCI-60 cell lines with a wide range of molecular parameters, including genetic variant amino acid changing, protein function affecting genes, DNA copy number, gene expression, protein levels, DNA methylation, and microRNA (miRNA) expression.

The retrieved data were organized with corresponding molecular features. Correlation analysis was performed to identify simultaneous shared significant associations with individual drug activity (5-Fluorouracil and Oxaliplatin) and specific genes, proteins, or miRNAs. A filter was applied (Pearson correlation $|r| > 0.334$ and $p < 0.01$) consistent with the CellMiner correlation framework [11]. Although $|r| > 0.334$ represents a modest correlation, additional false discovery rate (FDR) adjustment was applied to reduce false positives. Positive correlations ($r > 0.334$) suggested synergistic interactions or shared molecular mechanisms, whereas negative correlations ($r < -0.334$) were interpreted as potential resistance indicators or antagonistic effects. The top positively and negatively correlated genes were selected by ordering genes according to the absolute value of the Pearson correlation coefficient ($|r|$). Pathway enrichment analysis of the significantly correlated genes was conducted using the PANTHER classification system (http://pantherdb.org/), which enables functional annotation and identification of overrepresented biological processes, molecular functions, and signaling pathways based on Gene Ontology and Reactome PANTHER databases [12]. To account for multiple testing, p-values were adjusted using the False Discovery Rate (FDR) method, and features with q-values below 0.05 were retained, acknowledging the increased difficulty of passing stricter thresholds due to large dataset.

Results.

We evaluated the relationship between genetic variants resulting in amino acid substitutions and sensitivity to two widely used chemotherapy agents, Oxaliplatin and 5-Fluorouracil (5-FU), across the NCI-60 cancer cell line panel. Figure 1 summarizes the profiles of genes with significant correlations with individual agent. Genes demonstrating significant positive correlations include HIP1R, WFDC1, EVPL, SSHI. HIP1R has known roles in endocytosis and cellular signaling pathways. It is also involved in tumor development [13]. This may indicate shared sensitivity or synergistic pathways. While genes with significant negative correlations includes only ALDH9A1 that had shared significant association with 5-FU and Oxaliplatin, which is likely contribute to drug resistance. Given the established role of ALDH family enzymes in aldehyde detoxification and cancer stem cell biology [14]. These findings imply variant induced changes may contribute to reduced chemotherapeutic efficacy. Pathway enrichment analysis revealed no statistically significant GO molecular function terms after FDR correction. Importantly, number of drugs were identified with positive correlations to these negatively correlated genes, suggesting potential resistance overlaps or compensatory mechanisms. OR7G1 correlated positively with Prednisolone and INDK exhibited strong positive correlations with gefitinib and Anthranilic acid. These associations provide valuable insights into potential therapeutic strategies and pharmacological interactions worth future validation.

The impact of protein function-affecting genetic variants (Figure 2) on drug response to 5-FU and Oxaliplatin were evaluated. Three genes, CAMSAP3, LUM, and LRIG2, exhibited statistically significant negative correlations with 5-Fluorouracil sensitivity, while INSC demonstrated a significant correlation with Oxaliplatin, suggesting that these variants may contribute to resistance mechanisms against these agents. In contrast, PDE10A, ZNF560 and PTX4 displayed positive correlations with 5-FU, indicating a potential association with enhanced sensitivity. For Oxaliplatin, variants in IFT172, USP21, and SLC9A1 were significantly positively correlated implying that alterations in these genes may enhance responsiveness to Oxaliplatin-based therapies.

Further analysis identified drugs whose activity positively correlated with specific genes carrying protein function-affecting mutations. The gene INSC displayed strong positive correlations with three pharmacological agents: Gefitinib ($r = 0.348$, $p = 0.0069$), Nandrolone ($r = 0.398$, $p = 0.0018$), and Anthranilic acid ($r = 0.498$, $p = 0.0011$). These findings suggest that alterations in INSC, a gene involved in cell polarity and neurogenesis, may modulate the cellular response to agents affecting EGFR signaling (Gefitinib) or metabolic modulation (Nandrolone). Similarly, CAMSAP3, which regulates microtubule minus-end dynamics and epithelial cell architecture (15), exhibited a significant positive correlation with Rosuvastatin ($r = 0.352$, $p = 0.0063$), indicating a potential link between cytoskeletal regulation and statin-induced antitumor effects. In addition, LRIG2, a gene known to modulate receptor tyrosine kinase signaling [16], was significantly associated with Chitosan Biguanidine ($r = 0.484$, $p = 0.0008$), an antimicrobial and bioadhesive agent with emerging roles in nanomedicine and drug delivery systems. These associations provide insights into potential synergy and suggesting repurposing opportunities and novel therapeutic vulnerabilities.

The analysis of gene DNA methylation profiles (Figure 3) revealed several genes whose methylation levels significantly correlated with the activity of each drug individually. Notably, genes such as CNN3, ZNF625, IRF2BPL and MOXD1 exhibited strong positive correlations with individual agents of the combination. Conversely, FERMT3 gene displayed significant negative correlations, indicating potential roles in resistance mechanisms. Particularly, FERMT3 showed the strongest negative correlation with 5-FU and Oxaliplatin and several chemotherapeutic agent, including Carmustine, Melphalan, Vinblastine, and Mitomycin, suggesting epigenetic silencing of FERMT3 may contribute to broad drug resistance. Interestingly, we found that MIR130A methylation levels were positively correlated with targeted therapies, Erlotinib ($p = 0.0026$). These findings highlight a distinct set of methylation regulated genes with potential predictive value for chemotherapy response and drug repurposing in cancer.

The analysis of DNA gene copy number (Figure 4) revealed distinct correlations with Oxaliplatin and 5-FU activity. IL23R,

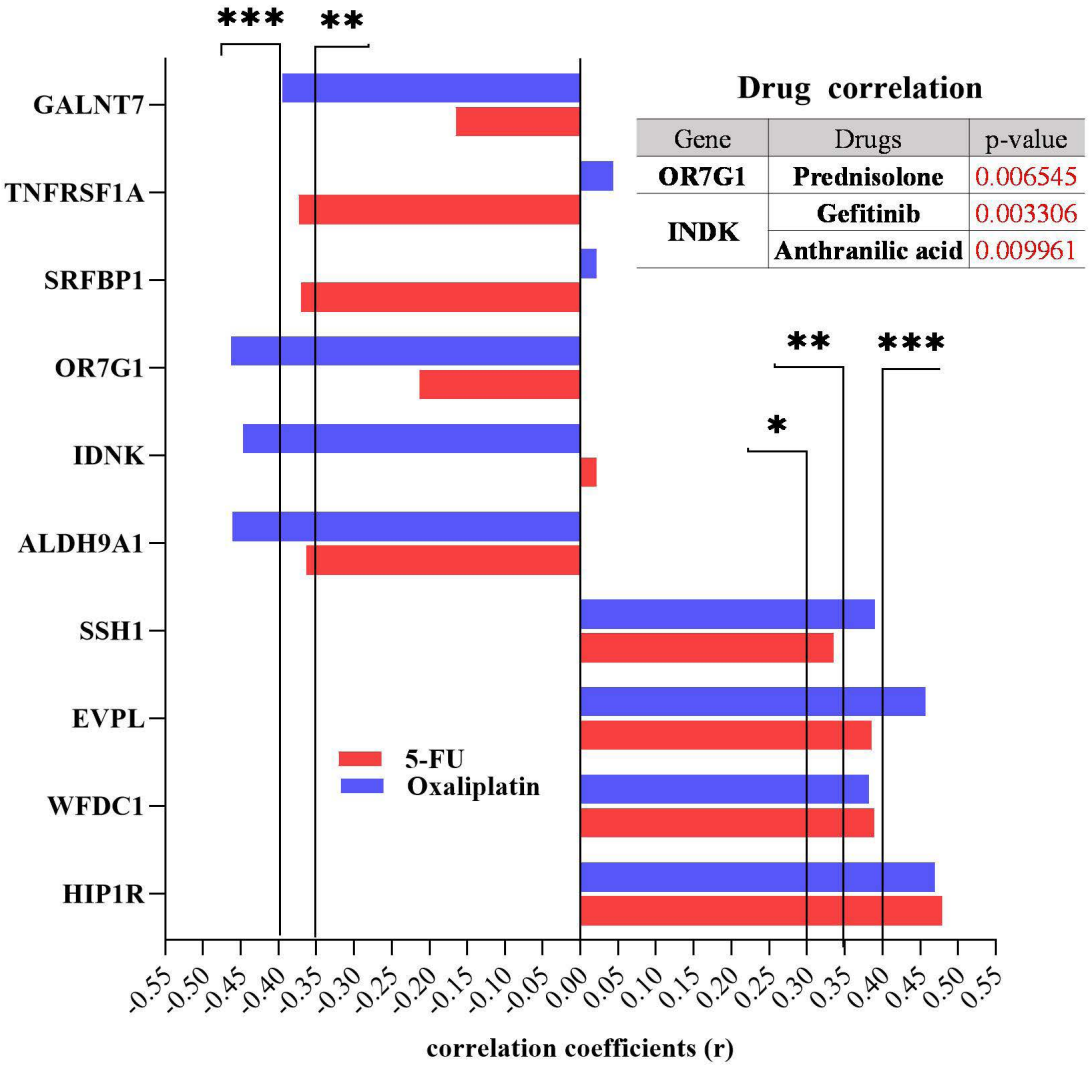


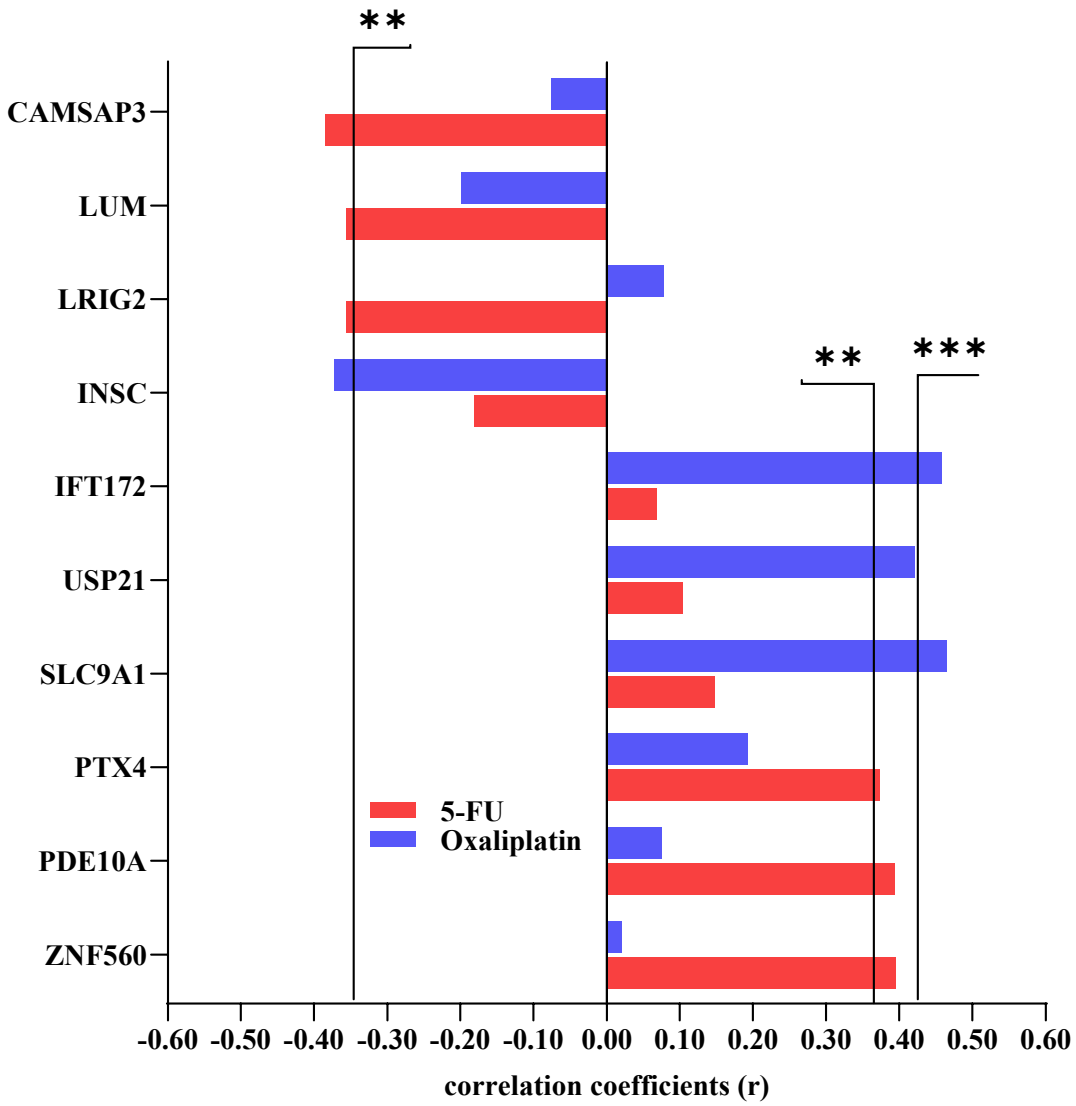
Figure 1. *Correlation of Genetic Variant Amino Acid–Changing Genes with Oxaliplatin and 5-FU.*

*Pearson correlation coefficients (r) are shown for genes with each individual agent (5-FU or Oxaliplatin). Statistical significance is marked as follows *p < 0.05; ** p < 0.01; *** p < 0.001.*

and FAF1 genes exhibited significant negative correlations, suggesting that higher mutation burden in these genes may contribute to chemotherapy resistance. In particular, COL1A1, which encodes a collagen subunit involved in the extracellular matrix and tumor microenvironment modulation [17], showed a strong inverse correlation with 5-FU response ($r = -0.44$, $p < 0.01$), implicating structural ECM remodelling in mediating drug insensitivity. Interestingly, COL1A1 positively correlated with multiple statins, including Lovastatin, Atorvastatin, Rosuvastatin, and Simvastatin, suggesting that statin may be enhance tumors sensitivity, which is harbouring these changes. This opens the possibility for drug repurposing of statins in tumors resistant to chemotherapy. In contrast, genes such as MIR4518, ITGAL, TAGLN, and SIDT2 showed positive correlations with either 5-FU or oxaliplatin drug response. These findings reinforce the relevance of specific non-coding elements in dictating chemosensitivity and highlight opportunities for molecularly guided therapy using non-oncologic agents such as statins.

Transcriptomic microarray analysis (Figure 5) identified widespread significant gene expression correlations with 5-FU and Oxaliplatin. We found 1.472 genes correlated with 5-FU, comprising 989 positively and 483 negatively correlated genes. For Oxaliplatin, 1.861 genes showed significant correlation, with 1.161 positive and 700 negative correlations. These large-scale associations reflect broad transcriptional responses underlying variability in drug sensitivity.

To focus on the most biologically relevant candidates, we selected the ten most significant positively and negatively correlated genes with each individual agent of the combination for the presentations in the figure, based on correlation strength and statistical significance. Among the most significant positively correlated genes include NPM3, RPS7P4, MTHFD2, DDX28, ANP32A, DDN, HNRNPA1P4, RPL26P4, BTF3P12 and RSL24D1. These genes are enriched in RNA processing, ribosome assembly, and cell proliferation pathways, consistent with a role in chemosensitization. Conversely, the most significant negatively correlated genes includes CNN3,



Drug correlations			
Gene	**Drug**	**r**	**p-value**
INSC	Gefitinib	0.348	0.006948
	Nandrolone	0.398	0.001821
	Anthranilic acid	0.498	0.001121
CAMSAP3	Rosuvastatin	0.352	0.00628
LRIG2	Chitosan Biguanidine	0.484	0.000766

Figure 2. *Correlation of Genetic Variant Protein Function–Affecting Genes with 5-FU and Oxaliplatin.*

*Pearson correlation coefficients (r) are shown for genes with each individual agent (5-FU or Oxaliplatin). Statistical significance is marked as follows: ** $p < 0.01$; *** $p < 0.001$. The tables embedded shows drugs positively correlated with indicated gens.*

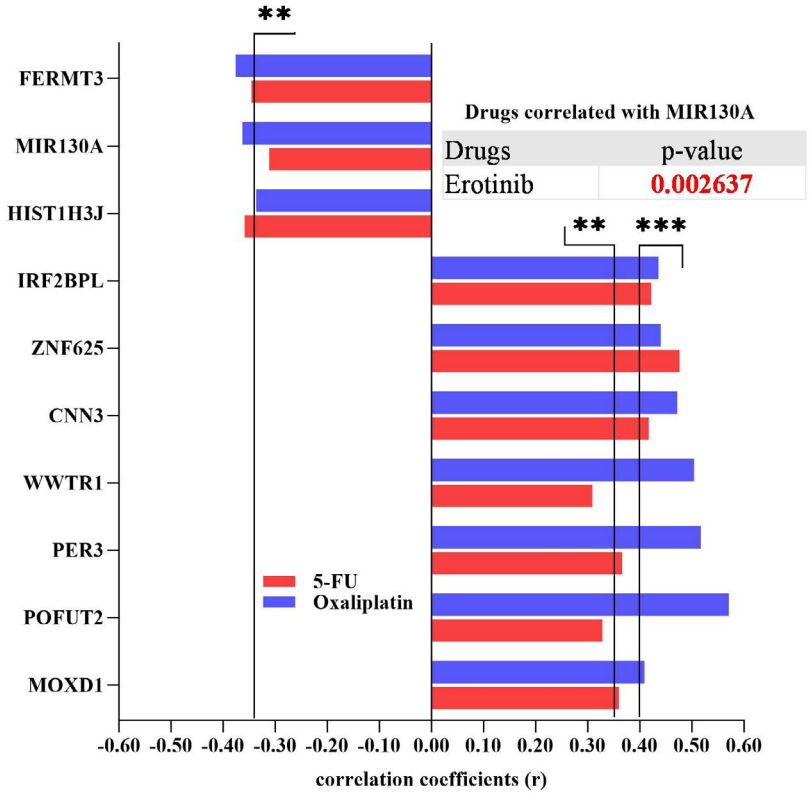


Figure 3. *Correlation of Gene DNA Methylation with 5-Fluorouracil and Oxaliplatin.*
*Pearson correlation coefficients (r) are shown for each gene with each individual agent (5-FU or Oxaliplatin). Statistical significance is marked as follows: ** p < 0.01; *** p < 0.001. the tables embedded shows positively correlated drugs with indicated genes.*

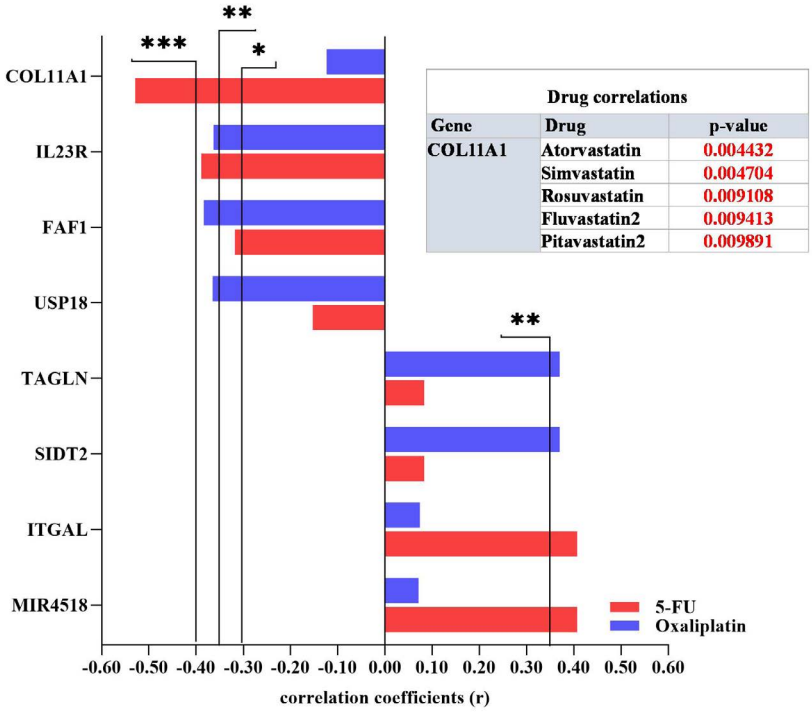


Figure 4. *Correlation of Gene DNA Copy Number with 5-FU and Oxaliplatin.*
*Pearson correlation coefficients (r) are shown for genes with each individual agent (5-FU or Oxaliplatin). Statistical significance is marked as follows: * p < 0.05; ** p < 0.01; *** p < 0.001. the tables embedded shows positively correlated drugs with indicated genes.*

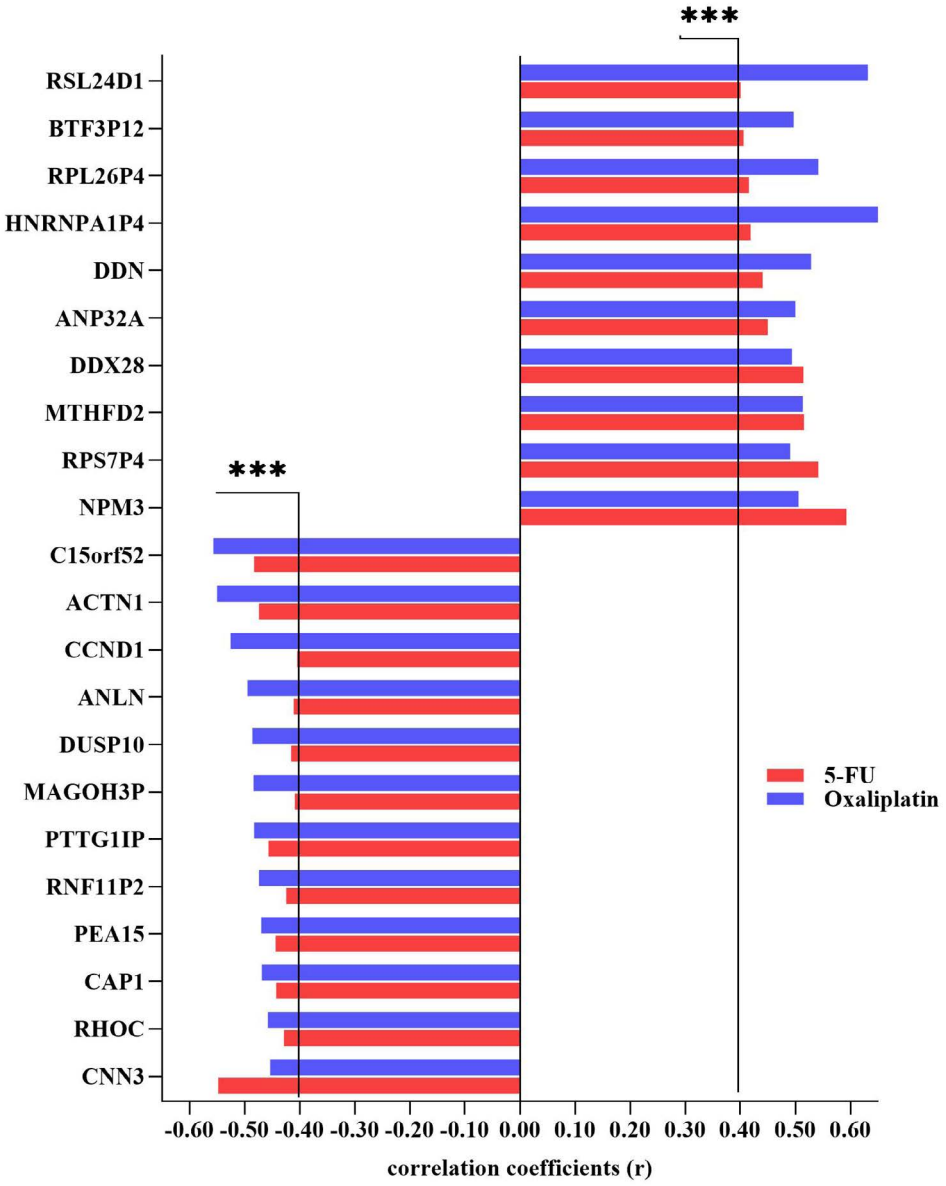


Figure 5. *Correlation of Gene transcript microarray with oxaliplatin and 5-FU.*
*Pearson correlation coefficients (r) are shown for genes with each individual agent (5-FU or Oxaliplatin). Statistical significance is marked as follows: *** $p < 0.001$.*

C15orf52, ACTN1, PTTG1IP, PEA15, CAP1, RHOC, RNF11P2, DUSP10, ANLN, MAGOH3P and CCND1. These are associated with cytoskeletal integrity, ubiquitin signaling, and cell adhesion features that may support drug resistance through mechanical stabilization, reduced drug uptake, or enhanced survival signaling.

Gene ontology enrichment analysis was performed using the PANTHER Overrepresentation Test on negatively correlated microarray genes with drug response. The analysis identified several overrepresented molecular functions (FDR < 0.05), Pathway Enrichment of the 5-FU/Oxaliplatin agents were significantly enriched in molecular functions involved in MAPK signaling regulation, folate metabolism, cell adhesion, and cytoskeletal regulation, which are consistent with mechanisms of drug resistance (Figure 6).

Several negatively correlated genes identified via microarray transcription showed statistically significant positive association with numerous FDA-approved drugs, suggesting their potential utility in resistant phenotypes (Table S1). For example, C15orf52 demonstrated strong positive correlation with Lovastatin, Simvastatin, and Rosuvastatin, as well as Dasatinib, indicating that statins and multi-kinase inhibitors may exert synthetic lethality in tumors. Similarly, RNF11 was negatively correlated with multiple statins and Zoledronate, a bisphosphonate, suggesting possible lipid metabolism linked vulnerabilities. Notably, DUSP10, another gene, showed strong positive correlation with BRAF/MEK pathway inhibitors: Dabrafenib and Vemurafenib, potentially indicating a MAPK-dependence in DUSP10-low cells. Other notable associations include PEA15 with multiple statins (e.g., Lovastatin, Atorvastatin) and

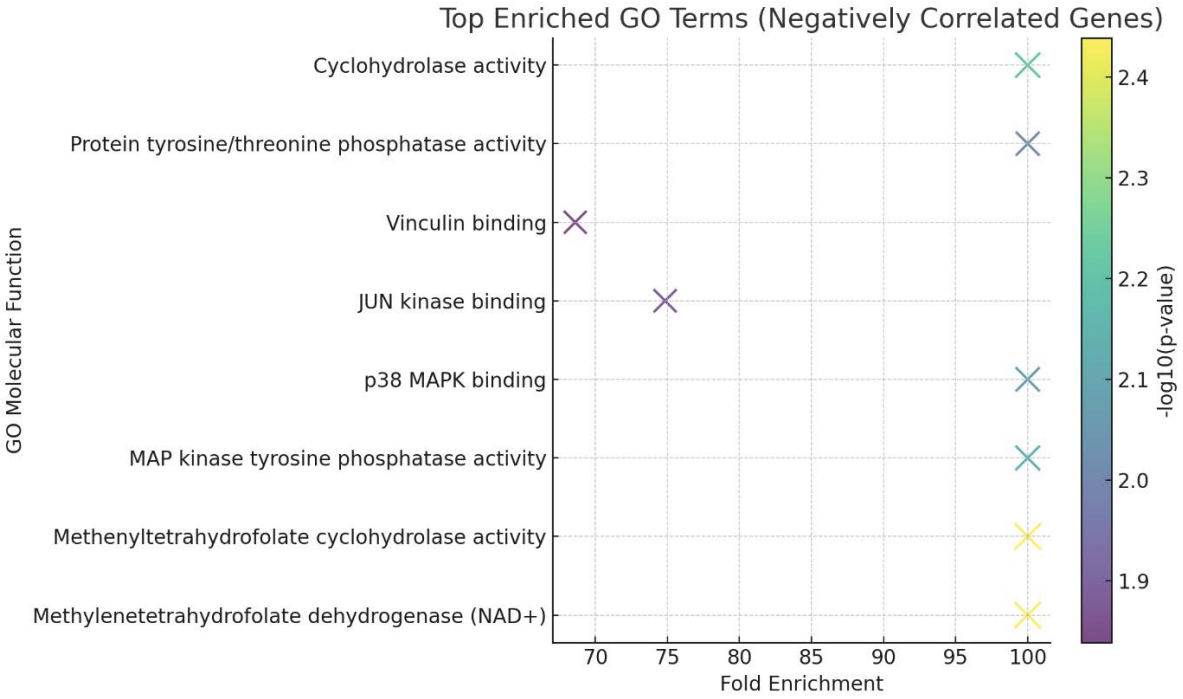


Figure 6. *Enriched Gene Ontology (GO) molecular functions for negatively correlated genes from microarray. GO term enrichment was performed using PANTHER database with fold enrichment on the x-axis and $-\log_{10}$ (p-value) represented by the color scale. The size of the points reflects the number of genes mapped to each term.*

kinase inhibitors like Lenvatinib and Dasatinib. Additionally, MGST3 and UTRN were significantly correlated with Afatinib, Erlotinib, and Zoledronate, indicating EGFR-pathway inhibitors may be effective in tumors expressing these genes. These findings suggest that statins, EGFR/BRAF inhibitors, and bisphosphonates could be viable adjunct therapies in tumors where these downregulated transcripts are detected. Such inverse transcript-drug activity patterns support a strategy for repurposing existing agents to target resistant cancers.

Transcriptome-wide correlation analysis using RNA-seq data (Figure 7) revealed differential gene expression patterns significantly associated with 5-FU and oxaliplatin response. For 5-FU, a total of 605 genes demonstrated statistically significant correlations ($p < 0.01$), of which 153 were positively correlated and 452 negatively correlated with drug activity. In contrast, oxaliplatin exhibited a broader impact, with 2,843 genes significantly correlated with drug response. Among these, 2,023 genes showed positive correlations, and 820 genes were negatively correlated.

This distinct disparity in the direction and magnitude of shared correlations between the individual drug highlights their differential molecular mechanisms of action. Notably, genes such as NT5E, LEPROT, C15orf52, GNG12, EPAS1, HIF1A and DUSP10 were the most significant negatively correlated, while genes such as DDN, PALD1 and KLK1 were the most significant positively correlated with individual chemotherapeutic agents. The convergence of expression patterns for some genes across both drugs supports their potential roles as shared regulatory mediators or biomarkers of therapy responsiveness.

Importantly, several genes were consistently identified across both microarray and RNA-seq platforms, thereby strengthening their candidacy as robust biomarkers. For example, DDN and NPM3 emerged as positively correlated in both datasets, while DDX28, DUSP10, and C15orf52 were consistently negatively correlated. The recurrence of these associations across independent transcriptomic platforms reduces the likelihood of false positives and suggests that these genes may represent more reliable biomarkers of 5-FU and Oxaliplatin response. In contrast, genes unique to either microarray or RNA-seq may reflect platform-specific detection sensitivity or context-dependent regulation, and thus should be interpreted with caution.

Gene ontology enrichment analysis (Figure 8) was performed using the PANTHER overrepresentation test on genes negatively correlated with drug response. The analysis identified several overrepresented molecular functions (FDR < 0.05), indicating a strong enrichment in biological activities related to cytoskeletal dynamics, signaling, and membrane transport. Key molecular functions enriched include structural constituent of ribosome, actin binding, cadherin binding, and cell adhesion molecule binding, implicating structural and adhesion-related mechanisms in mediating drug responses. Additionally, protein tyrosine phosphatase activity and co-receptor activity were significantly overrepresented, suggesting involvement of intracellular signaling regulators. Several transmembrane transporter activities including sodium ion transmembrane transporter activity and metal ion transporter activity were also enriched, indicating potential roles in ionic homeostasis and drug transport. These findings suggest that drug sensitivity and resistance may be modulated by genes involved in ribosomal structure, actin cytoskeleton regulation, G protein-coupled signaling, and ion transport, providing insight into the biological

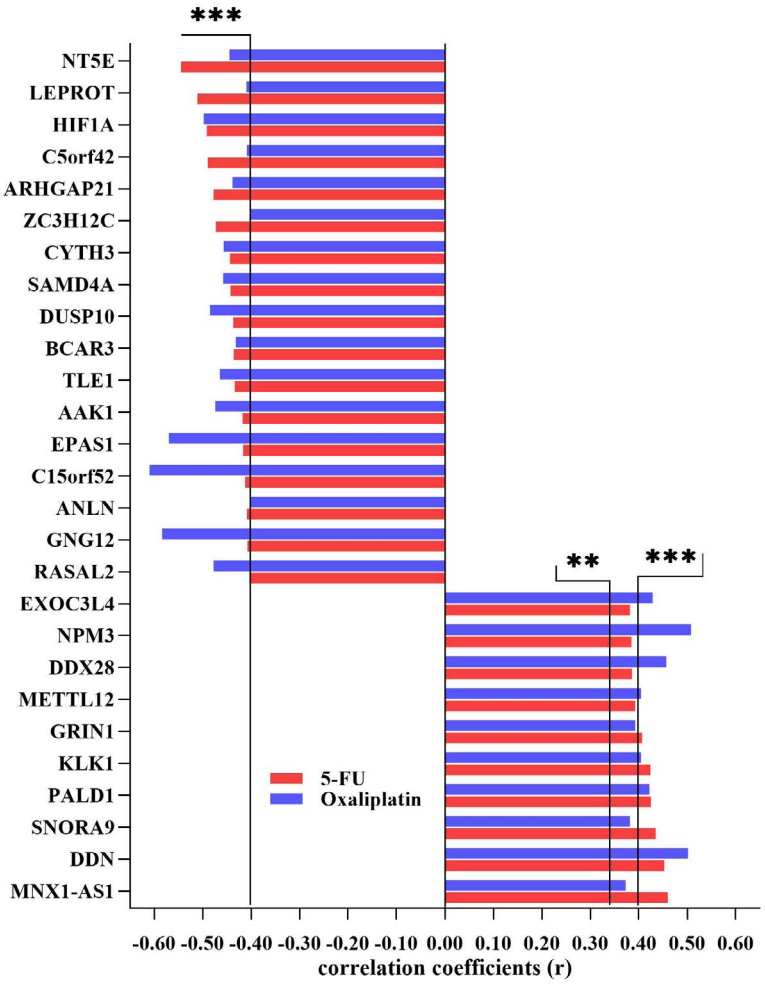


Figure 7. *Correlation of Gene Composite Transcription Level (RNAseq) with 5-FU and Oxaliplatin Sensitivity.*
*Pearson correlation coefficients (r) are shown for genes with each individual agent (5-FU or Oxaliplatin). Statistical significance is marked as follows: ** p<0.01; *** p < 0.001.*

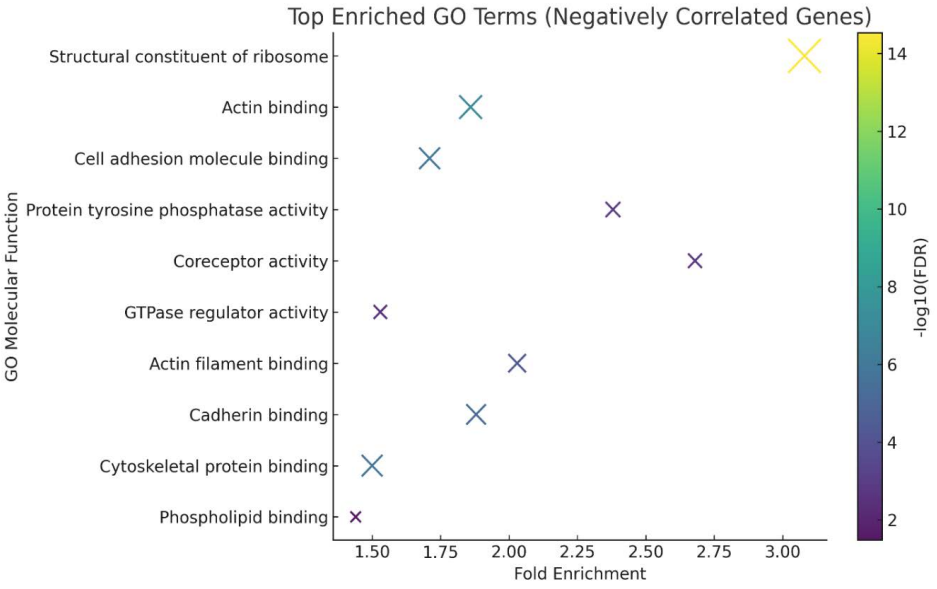


Figure 8. *Enriched GO molecular functions for negatively correlated genes from the RNAseq dataset.*
Gene Ontology enrichment was performed using the PANTHER Classification System. The x-axis represents fold enrichment, while the color scale indicates $-\log_{10}$ (p-value). Point size corresponds to the number of mapped genes.

basis for variability in chemotherapeutic response.

Further drug-gene interaction analysis revealed that several negatively correlated genes were positively associated with number of FDA approved drugs (Table S2). For instance: NT5E was positively correlated with multiple statins (Simvastatin, Pitavastatin, Lovastatin), suggesting a possible metabolic or membrane transport mechanism influencing drug response. LEPROT, HIF1A, and C5orf42 showed strong positive correlations with kinase inhibitors such as Erlotinib, Gefitinib, and Lenvatinib, indicating roles in EGFR or VEGF-related signaling. TLE1 was associated with Afatinib and Lenvatinib, hinting at possible MAPK or tyrosine kinase–driven pathways. These findings suggest that some genes downregulated or antagonistic to 5-FU/oxaliplatin response may be targetable by other approved agents, particularly statins, EGFR inhibitors, and multi-kinase inhibitors. This opens the possibility for repurposing or combination strategies to overcome resistance and improve therapeutic outcomes.

MicroRNA expression profiles (Figure 9) were analyzed for significantly shared correlations with sensitivity to 5-FU and Oxaliplatin. A total of 22 microRNAs showed significant correlation with 5-FU, evenly split into 11 positively and 11 negatively correlated, indicating potential dual roles in chemosensitization and resistance. In contrast, 49 microRNAs

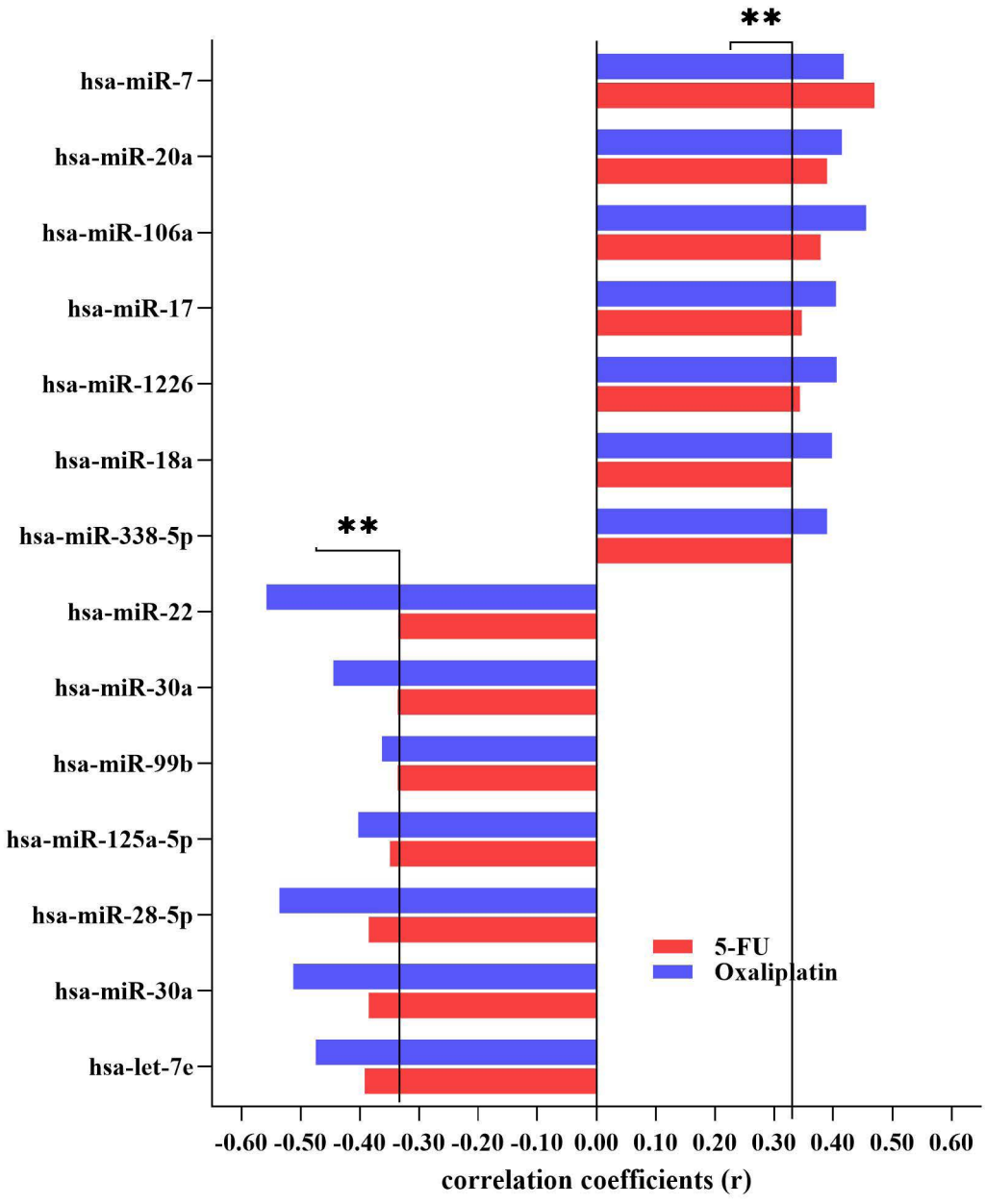


Figure 9. *Correlation of Micro-RNA Level with Oxaliplatin and 5-FU Sensitivity.*
*Pearson correlation coefficients (r) are shown for genes with each individual agent (5-FU or Oxaliplatin). Statistical significance is marked as follows: ** $p < 0.01$.*

were significantly correlated with Oxaliplatin, with a skewed distribution: 31 positive and 18 negative associations, suggesting broader microRNA involvement in oxaliplatin response pathways.

Among the shared microRNAs, hsa-let-7e, hsa-miR-30a, hsa-miR-28-5p, hsa-miR-125a-5p, hsa-miR-99b, hsa-miR-30a*, and hsa-miR-22 were negatively correlated with both drugs, potentially representing tumor suppressor miRNAs involved in resistance mechanisms. Conversely, hsa-miR-338-5p, hsa-miR-18a, hsa-miR-1226*, hsa-miR-17*, hsa-miR-106a, hsa-miR-20a*, and hsa-miR-7 displayed positive correlations with 5-FU and Oxaliplatin, suggesting roles in enhanced drug sensitivity. The most prominent examples include hsa-miR-22, which had the strongest negative correlation with Oxaliplatin, and hsa-miR-7, which showed the strongest positive correlation with 5-FU.

To further explore therapeutic relevance, we identified FDA-approved drugs whose activity levels were positively correlated with these negatively correlated miRNAs, indicating potential synergistic or compensatory sensitivity in resistant phenotypes (Table S3). For example, hsa-miR-30a showed strong positive correlation with Erlotinib, Afatinib, Gefitinib, Lapatinib, and Dasatinib. hsa-let-7e was positively associated with Lenvatinib. hsa-miR-99b and hsa-miR-30a* were both linked to enhanced response to Lenvatinib, Dasatinib, and Gefitinib. Lastly, hsa-miR-22, another suppressive miRNA, showed positive drug correlation with Lovastatin, Pitavastatin, Dasatinib, and Lenvatinib.

Collectively, these observations highlight distinct and overlapping microRNA regulatory patterns associated with chemosensitivity to 5-FU and Oxaliplatin and may inform future biomarker or therapeutic targeting strategies. In addition, These findings suggest that tumors exhibiting high levels of these miRNAs and hence resistance to 5-FU or Oxaliplatin may still be vulnerable to targeted kinase inhibitors (e.g., EGFR/VEGFR inhibitors) or statins, providing a rational basis for combination or sequential therapy strategies.

We performed a correlation analysis to identify compounds with activity patterns similar or antagonistic to 5-FU and oxaliplatin individually (Figure 10). Several drugs, including methotrexate, nitrogen mustard, trimetrexate glucuronate, melbex, trifluridine, cytarabine, idarubicin, and etoposide, exhibited strong positive correlations ($r > 0.5$, $p < 0.001$) with both 5-FU and oxaliplatin, suggesting shared molecular or mechanistic properties. These agents are antimetabolites or DNA-damaging agents, may potentially act synergistically or reflect similar susceptibility mechanisms in colorectal cancer models. In contrast, a subset of targeted agents such as vandetanib, acalabrutinib, zanubrutinib, irolfufen, and copanlisib demonstrated negative correlations, particularly with oxaliplatin ($r < 0$, $p < 0.05$), while showing

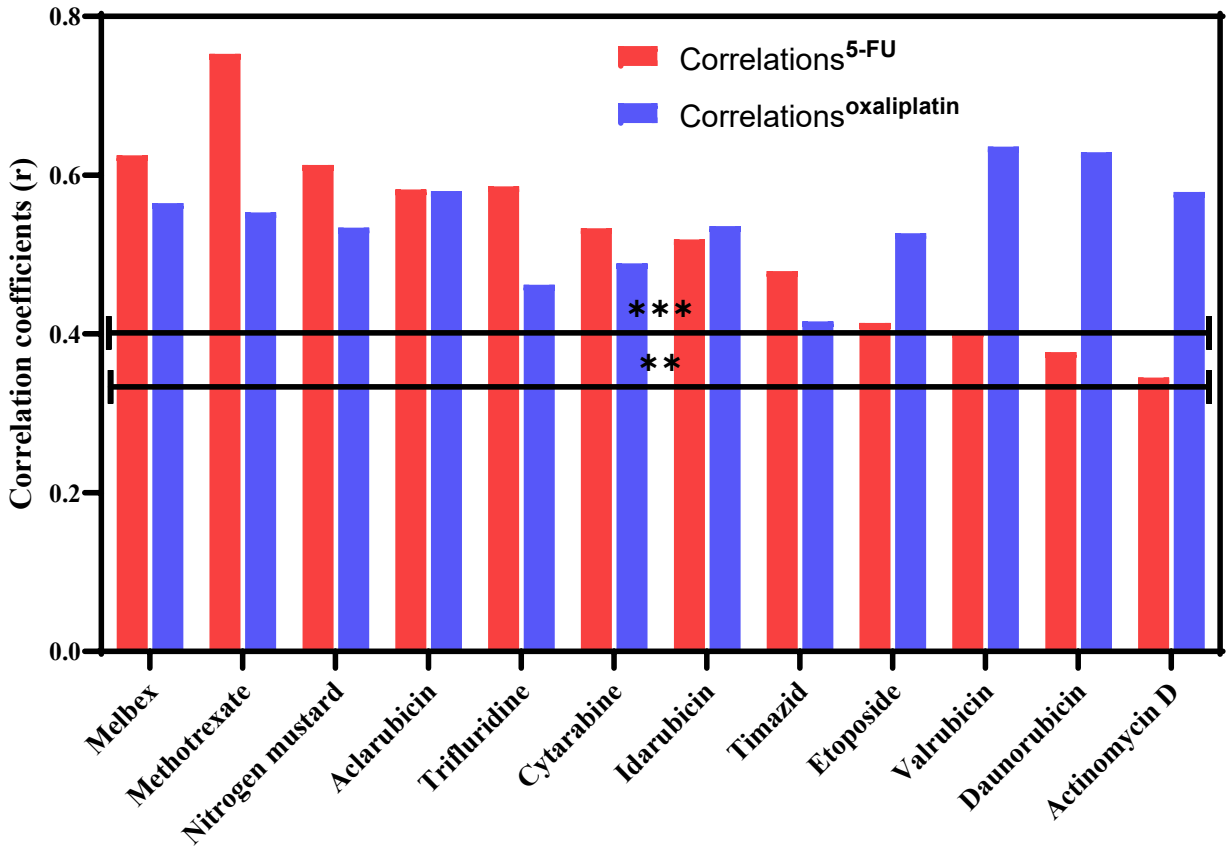


Figure 10. *Correlation of selected FDA-approved drugs with 5-Fluorouracil (5-FU) and Oxaliplatin activity.*
*Bar plot showing Pearson correlation coefficients for drug activity profiles with with each individual agent (5-FU or Oxaliplatin). Statistical significance is indicated by asterisks (**p < 0.01, ***p < 0.001).*

weaker or non-significant associations with 5-FU. These findings suggest potential antagonistic interactions or differing mechanisms of action, which may influence treatment selection or contraindicate their concomitant use with platinum-based therapy. This comparative correlation profiling highlights candidate drugs that may synergize with or oppose 5-FU/oxaliplatin activity and offers a foundation for prioritizing agents in combination regimens or repurposing efforts.

Discussion.

The present integrative multi-omics analysis of the NCI-60 panel highlights a complex molecular landscape shaping colorectal cancer responses to 5-Fluorouracil (5-FU) and Oxaliplatin. In this study, we analyzed overlapping molecular correlates of each drug separately, rather than directly evaluating their synergistic interactions. By applying significant statistical thresholds ($|r| > 0.3$, $p < 0.01$, FDR < 0.05), our findings may provide a refined and biologically grounded view of candidate biomarkers, resistance mediators, and drug repurposing opportunities.

Several amino acid–changing variants (HIP1R, WFDC1, EVPL, SSHI) shared a significant positive correlation with chemosensitivity of individual agent, while ALDH9A1 correlated negatively with both 5-FU and Oxaliplatin (Figure 1). Overexpression of aldehyde dehydrogenase (ALDH) drives chemotherapy resistance by detoxifying cytotoxic aldehydes, thereby reducing oxidative stress, DNA damage, and apoptosis [18,19]. This is consistent with the detoxifying role of ALDH enzymes in resistance. At the protein function level, variants in CAMSAP3, LUM, and LRIG2 were negatively correlated, while INSC, IFT172, USP21, and SLC9A1 correlated positively (Figure 2). These results suggest that disruption of cytoskeletal

Table S1. *list of drug–gene associations identified from transcriptomic microarray analysis.*

Gene	Drug	p-value	Gene	Drug	p-value
C15orf52	Lovastatin	0.00101	**DUSP10**	Pazopanib	0.003606
	Simvastatin	0.004039		Dabrafenib	0.000027
	Rosavastatin	0.000117		Vemurafenib	0.000005
	Dasatinib	0.007447	**PEA15**	Lovastatin	0.00017
MAGOH3P	Dasatinib	0.005437		Simvastatin	0.000563
RNF11	Lovastatin	0.002087		Lenvatinib	0.000756
	Simvastatin	0.002434		Mevastatin	0.00558
	Pitavastatin	0.005693		Pitavastatin	0.002419
	Fluvastatin	0.004074		Atorvastatin	0.001988
	Zoledronate	0.00989		Bleomycin	0.005106
RHOC	Lovastatin	0.000251		Zoledronate	0.005727
	Fluvastatin	0.003629	**CNN3**	Lovastatin	0.002586
	Dasatinib	0.002344		Pitavastatin	0.001505
	Mevastatin	0.009142		Fluvastatin	0.009953
	Pitavastatin	0.005899		Dasatinib	0.008678
	Atorvastatin	0.004806		Lenvatinib	0.002363
	Rosavastatin	0.003839		Erotinib	0.002727

Table S2. *list of drug–gene associations identified from RNA-seq composite transcriptional analysis.*

Gene symbol	Drug	p-value	Gene symbol	Drug	p-value
HIF1A	Erotinib	0.00919	AAK1	Bleomycin	0.00091
C5orf42	Fluvastatin	0.00646	EPAS1	Dasatinib	0.00013
	Rosavastatin	0.00473		Erotinib	0.00475
	Lapatinib	0.00422		Lenvatinib	0.00579
	Gefitinib	0.00408	ANLN	Simvastatin	0.00229
	Simvastatin	0.00376		Pitavastatin	0.00273
	Pitavastatin	0.00316		Lovastatin	0.00281
	Afatinib	0.00306		Fluvastatin	0.00637
	Erotinib	0.00059		Mevastatin	0.00893
DUSP10	Vemurafenib	0.00006	RASAL2	Erotinib	1.1E-05
	Dabrafenib	0.00037		Afatinib	0.00067
	Pazopanib	0.00747		Simvastatin 1	0.00148
BCAR3	Pitavastatin	0.00112		Gefitinib	0.0021
	Fluvastatin	0.0017		Bleomycin	0.0041
	Simvastatin	0.00291		Dasatinib	0.00666
	Dasatinib	0.00306		Neratinib	0.00924
	Lovastatin	0.00425	TLE1	Afatinib	0.00809
	Zoledronate	0.00706		Gefitinib	0.00996

Table S3. *list of drug–microRNA associations identified from CellMiner analysis.*

MicroRNA	Drugs	p-value
hsa-let-7e	Lenvatinib	**0.008016**
hsa-miR-30a	Erotinib	**0.000003**
	Afatinib	**0.000776**
	Gefitinib	**0.001296**
	Neratinib	**0.002918**
	Lapatinib	**0.008232**
	Dasatinib	**0.000285**
	Lenvatinib	**0.005946**
hsa-miR-99b	Lenvatinib	**0.004457**
hsa-miR-30a*	Gefitinib	**0.007851**
	Lenvatinib	**0.003974**
	Lapatinib	**0.002838**
	Neratinib	**0.000250**
	Dasatinib	**0.000158**
	Gefitinib	**0.000104**
	Afatinib	**0.000015**
	Erotinib	**0.000001**
hsa-miR-22	Lovastatin	**0.007330**
	Pitavastatin	**0.006185**
	Dasatinib	**0.003331**
	Lenvatinib	**0.001862**

regulators (CAMSAP3) [20] and RTK modulators (LRIG2) [16,21] may contribute to reduced sensitivity, whereas polarity and trafficking genes (INSC, IFT172) enhance drug response [22,23].

DNA methylation of CNN3, ZNF625, IRF2BPL and MOXD1 correlated positively, while FERMT3 showed strong negative correlations with individual drug of the combination and multiple alkylating agents (Figure 3). FERMT3 has shown to play a role in chemoresistance in certain cancers, particularly glioblastoma and colorectal cancer [24]. These findings imply that epigenetic silencing of adhesion-related genes (FERMT3) may broadly confer chemoresistance [25]. Copy number alterations also showed that IL23R, FAF1, and COL1A1 were negatively correlated, while SLC35A, TAGLN, SIDT2 and others were positively correlated with each drug individually (Figure 4). Notably, COL1A1, a key collagen subunit driving extracellular matrix (ECM) remodeling and chemotherapy resistance [26], showed strong associations with statins in our analysis. Statins inhibit the mevalonate pathway and block prenylation of Rho GTPases, leading to reduced fibroblast activation and collagen deposition [27]. This mechanistic link suggests that statins could mitigate ECM-driven resistance by disrupting COL1A1-mediated remodelling, thereby enhancing tumor sensitivity to 5-FU and Oxaliplatin.

Our transcriptomic analyses highlighted two distinct molecular signatures of 5-FU and Oxaliplatin response. Cytoskeletal and adhesion-related genes (CNN3, ACTN1, DUSP10, C15orf52) were consistently negatively correlated with each drug individually, suggesting that tumors with reinforced structural integrity and adhesion signaling may resist chemotherapy by stabilizing the cellular architecture and reducing drug penetration [28-31]. Conversely, biosynthetic and ribosomal genes (MTHFD2, RPL26, BTF3P12) correlated positively, indicating that highly proliferative cells reliant on ribosome biogenesis and folate metabolism may be more vulnerable to antimetabolite and DNA-damaging agents [32-34].

Among the resistance genes, NT5E (CD73) and HIF1A stand out as clinically relevant. NT5E is a known driver of immune evasion and chemoresistance through adenosine signaling [35-37], while HIF1A mediates hypoxia adaptation, both of which can blunt chemotherapy efficacy [38,39]. On the other hand, GRIN1 and KLK1, which were positively correlated with drug sensitivity, may enhance stress signaling and apoptotic pathways, rendering cells more susceptible to cytotoxic injury [40,41].

Pathway enrichment reinforced these mechanistic insights, with MAPK regulation, folate metabolism, cytoskeletal remodeling, and adhesion emerging as dominant processes. These align directly with the pharmacology of 5-FU (thymidylate synthase inhibition/folate metabolism) [42,43] and Oxaliplatin (DNA crosslinking with cytoskeletal stress) [9], strengthening the biological plausibility of our findings.

Interestingly, several genes showed consistent associations across both microarray and RNA-seq platforms, strengthening their relevance as shared biomarkers of 5-FU and oxaliplatin response. Among the positively correlated genes, DDN and NPM3. The later are linked to ribosomal biogenesis and RNA processing, processes that typically support proliferative capacity but also confer increased vulnerability to DNA-damaging agents [44]. Conversely, negatively correlated genes such as DDX28, DUSP10, and C15orf52 have been implicated in stress adaptation and signaling regulation [30,45]. The recurrence of these associations across independent transcriptomic platforms underscores their potential as robust biomarkers. Clinically, such shared-response signatures could stratify patients more likely to exhibit sensitivity (DDN, NPM3) or resistance (DDX28,

DUSP10, C15orf52) to 5-FU/oxaliplatin–based regimens, may provide a rationale for integrating these potential markers into biomarker-driven treatment selection.

Multiple microRNAs showed shard significant correlations with 5-FU and Oxaliplatin individually. Among the positively correlated, miR-7, miR-601, miR-572, and miR-1226 were linked to enhanced chemosensitivity (Figure 9). miR-7 is known to inhibit PI3K/AKT and MAPK pathways, thereby promoting apoptosis and sensitizing cells to DNA-damaging agents [46,47]. miR-601 has been reported to regulate inflammatory and apoptotic pathways [48], potentially lowering resistance thresholds, while miR-572 modulates cell-cycle regulators and has been associated with enhanced cytotoxicity under stress conditions [49,50]. Similarly, miR-1226 has tumor-suppressive effects by downregulating oncogenic kinases such as AKT1 and HER2, consistent with its positive correlation in our dataset [51,52].

Conversely, let-7e, miR-30a, and miR-22 were negatively correlated, suggesting roles in resistance. Let-7e is a classical tumor suppressor miRNA that can repress RAS and HMGA2 signaling; its reduced expression has been linked to aggressive phenotypes and poor drug response [53,54]. miR-30a regulates epithelial–mesenchymal transition (EMT) and adhesion pathways, processes that contribute to chemoresistance [55]. miR-22 has dual roles in cancer but has been associated with resistance when upregulated, partly through modulation of p53 activity and folate cycle enzymes [56]. Taken together, these findings suggest that specific miRNA expression profiles do not merely act as passive correlates but actively regulate signaling networks central to chemotherapy outcomes. Their dual roles highlight the potential of circulating miRNAs to serve both as predictive biomarkers and as therapeutic targets to overcome 5-FU/Oxaliplatin resistance.

Across molecular layers, several resistance associated genes showed strong positive correlations with FDA-approved agents, nominating potential repurposing strategies (Figures 5,7 and 9). For instance, C15orf52 and RNF11, both negatively correlated with 5-FU and Oxaliplatin individually, displayed positive associations with statins and the multi-kinase inhibitor Dasatinib. Statins inhibit the mevalonate pathway, reducing prenylation of Rho GTPases and thereby disrupting cytoskeletal integrity and adhesion mechanisms [57] that overlap with the resistance signatures observed for C15orf52 and RNF11. Similarly, DUSP10, a MAPK phosphatase, was linked to enhanced activity of BRAF/MEK inhibitors such as Dabrafenib and Vemurafenib, suggesting that tumors with suppressed DUSP10 expression may become dependent on MAPK signaling and thus sensitized to kinase blockade [30,58].

Comparative drug–drug correlation profiling further reinforced these insights (Figure 10). Classical cytotoxics such as methotrexate, cytarabine, idarubicin, and etoposide shared strong positive correlation patterns with 5-FU and Oxaliplatin, consistent with overlapping mechanisms in DNA synthesis inhibition or DNA damage. In contrast, certain targeted kinase inhibitors (Vandetanib, Copanlisib, Zanubrutinib) showed negative correlations, particularly with Oxaliplatin, implying a potential antagonism when combined. Such findings underscore the need to carefully distinguish between agents likely to enhance versus impair efficacy when designing rational combinations.

While CellMiner enables robust hypothesis generation, the NCI-60 panel cannot fully replicate patient tumor heterogeneity [5,59,60]. In vitro sensitivity does not necessarily equate to in vivo efficacy [61,62]. Another key limitation of this study is that we examined overlapping molecular correlates of each drug independently, rather than directly assessing the molecular basis of their potential synergistic interactions. Additionally, the correlation threshold applied ($|r| > 0.334$) represents modest associations and may capture noise; this criterion was selected based on established CellMiner practice. To enhance robustness, FDR adjustment was applied and overlapping results between RNA-seq and microarray were highlighted as more dependable candidates. Finally, correlation analyses do not establish causation; experimental validation in colorectal cancer models is essential before clinical translation.

Collectively, our results identify a potential biomarkers of sensitivity (GRIN1, METTL12, SLC35A, miR-7) and resistance (HIF1A, FERMT3, NT5E, IL23R), while highlighting a promising opportunities to repurpose widely available drugs (statins, EGFR/VEGFR inhibitors) to overcome resistance and optimize therapy.

Conclusion.

This multi-omics analysis has identified a potential biomarkers associated of 5-FU and Oxaliplatin sensitivity and resistance across the NCI-60 panel. Genes such as GRIN1, METTL12, MOXD1, and SLC35A, together with microRNAs like miR-7, emerged as candidate correlated with chemosensitivity, while resistance signature were associated to HIF1A, MACF1, NT5E, FERMT3, and IL23R. Pathway enrichment proposed that folate metabolism, MAPK signaling, cytoskeletal remodeling, and adhesion are central to chemotherapy outcomes.

Importantly, resistance-associated genes showed significant positive correlations with number of FDA-approved drugs including statins and kinase inhibitors, nominating these as promising adjuncts for resistant colorectal cancers.

Future studies should validate these correlations in patient cohorts, dissect mechanisms of how these biomarkers might influence drug transport, metabolism, and repair, and translate them into clinical biomarker assays. Ultimately, this integrative framework provides a prospective foundation for biomarker guided personalization of 5-FU/oxaliplatin therapy and rational drug repurposing strategies to overcome resistance and improve patient outcomes.

Conflict of interest.

The author declares no conflict of interest.

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