Screening Novel Drug Candidates for Kidney Renal Clear Cell Carcinoma Treatment: A Study on Differentially Expressed Genes through the Connectivity Map Database

Bin Gao  Lijuan Wang  Na Zhang  Miaomiao Han  Yubo Zhang  Huancai Liu  Dongli Sun  Yifei Liu

Department of Urology, Tangshan Central Hospital, Tangshan, China

Keywords
Kidney renal clear cell carcinoma · Connectivity map · Drug screening · The Cancer Genome Atlas

Abstract
Objective: Kidney renal clear cell carcinoma (KIRC) is a common cancer with high morbidity and mortality in renal cancer. Thus, the transcriptome data of KIRC patients in The Cancer Genome Atlas (TCGA) database were analyzed and drug candidates for the treatment of KIRC were explored through the connectivity map (CMap) database. Methods: The transcriptome data of KIRC patients were downloaded from TCGA database, and KIRC-associated hub genes were screened out through differential analysis and protein-protein interaction (PPI) network analysis. Afterward, the CMap database was used to select drug candidates for KIRC treatment, and the drug-targeted genes were obtained through the STITCH database. A PPI network was constructed by combining drug-targeted genes with hub genes that affected the pathogenesis of KIRC to obtain final hub genes. Finally, combining hub genes and KIRC-associated hub genes, the pathways affected by drugs were explored by pathway enrichment analysis. Results: A total of 2,312 differentially expressed genes were found in patients, which were concentrated in immune cell activity, cytokine, and chemokine secretion pathways. Drug screening disclosed 5 drug candidates for KIRC treatment: fedratinib, Ly344864, geldanamycin, AS-605240, and luminespib. Based on drug-targeted genes and KIRC-associated hub genes, 16 hub genes were screened out. Pathway enrichment analysis revealed that drugs mainly affected pathways such as neuroactive ligand pathways, cell adhesion, and chemokines. Conclusion: The above results indicated that fedratinib, LY 344864, geldanamycin, AS-605240, and luminespib could be used as candidates for KIRC therapy. The findings from this study will make contributions to the treatment of KIRC in the future.

Introduction
Kidney renal clear cell carcinoma (KIRC) is a common type of renal cell carcinoma, with the highest morbidity rate among renal cell carcinomas. According to statistics from the National Cancer Institute, the morbidity of KIRC accounts for 80% of all renal cell carcinoma cases...
KIRC is a disease with a high mortality rate and the 5-year survival rate of advanced KIRC patients is only 10%. According to statistics from National Cancer Institute, if treatment is carried out when the tumor is small, the 5-year survival rate of patients can rise to 50%–69%. Accordingly, early diagnosis and treatment are critical to the prognosis of KIRC patients.

There are many treatments for KIRC, including surgical resection, drug therapy, and immunotherapy. The surgical treatment is to remove the tumor tissue from patients. Because the tumor tissue of KIRC patients grows slowly, tumor tissue removal can effectively treat KIRC patients when the diameter of the tumor is 3–4 cm and before the tumor metastasis occurs [2]. In addition to surgical treatment, medication is also one of the most effective treatments for KIRC. There are many drugs used to treat KIRC such as cabozantinib, axitinib, sunitinib, sorafenib, and pazopanib [3, 4]. Cabozantinib is a small molecule tyrosine kinase inhibitor with 9 targeted sites and the inhibitory properties of vascular endothelial growth factor (VEGF) as well as MET [5]. Cabozantinib can bind and restrain tyrosine kinase, thereby suppressing tumor angiogenesis [6]. Axitinib, sunitinib, sorafenib, and pazopanib are inhibitors of VEGF and VEGF receptors, which can suppress the growth of cancer tissue by inhibiting tumor tissue angiogenesis [7]. Apart from the above-mentioned drugs that can achieve antitumor effects by inhibiting angiogenesis, mTOR pathway has been a therapeutic target of novel drugs, such as everolimus and temsirolimus [8, 9]. With the continuous development of drugs, the survival rate as well as the survival status of KIRC patients has been conspicuously improved [7]. Nevertheless, these drugs still have shortcomings such as the low drug response rate and strong side effects. Therefore, it is necessary to develop more therapeutic drugs clinically for KIRC to prolong the survival period and improve the life quality of patients.

At present, the method of screening drug candidates based on the connectivity map (CMap) database is undoubtedly the most promising one among numerous ways to screen cancer drugs. The CMap database is a small molecule and gene-phenotype association database established by analyzing the difference in gene expression of human cells after treating with various small molecule drugs [10]. Researchers can use the database to calculate and screen possible therapeutic drugs based on differential disease expression profiles [11]. To date, several studies have carried out the screening of drugs through the CMap database. For instance, Yu et al. [12] compared the expression differences in cancer tissue of liver cancer patients in The Cancer Genome Atlas (TCGA) database and screened out 3 potential liver cancer treatment drugs: mercaptopurine, reserpine, and rifabutin. After the ability of CMap in drug screening has been proved, various drug screening databases are developed, such as DMAP [13]. The application of these drug screening databases provides great convenience for tumor drug screening.

This study calculated and analyzed the difference in gene expression between tumor tissue of KIRC patients and normal tissue based on the data of KIRC patients in TCGA database. In addition, this study researched the biological pathways that affected the pathogenesis of KIRC and analyzed KIRC-associated hub genes affecting KIRC pathogenesis through the protein–protein interaction (PPI) network analysis. Besides, differentially expressed genes (DEGs) were also entered into CMap database to further screen drug candidates for the treatment of KIRC. Finally, the association between target genes of drug candidates and KIRC-associated hub genes was analyzed, and the biological processes affected by drug candidates were further explored. Through bioinformatics methods and jointly using multiple bioinformatics databases, this study screened therapeutic drugs for KIRC, which provided a theoretical basis for clinical treatment of KIRC.

**Materials and Methods**

**Data Resource**

Gene expression data (count) of patients with KIRC and corresponding clinical information were downloaded from TCGA database (https://portal.gdc.cancer.gov/) to obtain a total of 530 cancer tissue samples and 72 adjacent tissue samples.

**Differential Analysis**

Differential analysis was performed on the expression data of cancer tissue and adjacent tissue samples using the R package “edgeR,” with |Log2FC| ≥2 and FDR <0.05 as thresholds to select DEGs.

**Functional Enrichment Analysis**

The Kyoto Encyclopedia of Genes and Genomes (KEGG) and Gene Ontology (GO) functional enrichment analyses were performed on DEGs using the R package “clusterProfiler.” KEGG enrichment analysis could be used to judge the difference in biological pathways and biological functions, while GO enrichment analysis could also be used to judge differences in cell structure and molecular function. The pathways with p adjusted <0.05 were considered to be significantly enriched pathways, and the R package “enrichplot” was used for visualizing the enrichment results.

**Construction and Analysis of PPI Network**

PPI network analysis was carried out on STRING website (https://string-db.org/). The data were first uploaded to the STRING website and built a PPI network, with the credibility
threshold set to 0.9. After the PPI network was constructed, the results were visualized using Cytoscape software and the connectivity of the nodes was calculated. Eventually, the nodes with a connectivity >50 were selected as KIRC-associated hub genes for subsequent analysis.

**Screening of Potential Drug Molecules**

CMap is a database of the association between drug bioactive small molecules and gene expression, which could predict small molecule compounds to treat specific diseases via gene expression characteristics. This study utilized the online tool of the CMap website (https://broadinstitute.org/CMap) to predict the possibility of drug treatment of KIRC and gave a prediction score then potential drug molecules were screened based on the score. Subsequently, 150 upregulated DEGs and 150 downregulated DEGs with the most significant expression differences were entered into the website for drug screening. The CMap prediction score represented the correlation between the drug and DEGs, and the negative correlation indicated that the drug was suitable for the treatment of KIRC. In this study, −85 was selected as the threshold of prediction score to screen drug candidates for KIRC treatment.

**Association Analysis of Drug-Targeted Genes**

After obtaining the drug candidates, the drug-targeted genes were inquired through STITCH (http://stitch.embl.de/) database. A PPI network was constructed based on drug-targeted genes and
KIRC-associated hub genes to screen for drug candidates-target genes-KIRC-associated hub genes. Subsequently, GO and KEGG enrichment analyses were conducted on the selected hub genes and KIRC-associated hub genes.

**Statistical Analysis**

All data in this study were completed using R 4.0.2 (https://cran.r-project.org/) and Cytoscape. Unless otherwise specified, FDR <0.05 was considered statistically significant.

**Results**

**Differential Gene Expression Analysis and Functional Pathway Enrichment Analysis of DEGs in KIRC**

In this study, the expression matrices of cancer tissue and adjacent tissue of TCGA-KIRC patients were downloaded for differential analysis. It could be seen from the data in Figure 1A that a total of 2,312 DEGs were found including 1,533 upregulated genes and 779 downregulated genes in cancer tissue. Subsequently, KEGG and GO enrichment analyses were carried out on these DEGs (Fig. 1B, C). The results of KEGG enrichment analysis showed that DEGs were mainly enriched in several major pathways such as neuroactive ligand-receptor interaction pathway, cytokine-cytokine receptor interaction pathway, and cell adhesion molecules (CAMS) (Fig. 1B), indicating that the differences between KIRC cancer tissue and adjacent tissue were mainly manifested in neurotransmitter transmission, immune cell recruitment, and CAMS pathways. Figure 1C provided the results of GO enrichment analysis showed that the differences in biological pathways between cancer tissue and adjacent tissue were mainly manifested in T cell activation, lymphocyte activation, and CAMS pathways. Besides, the differences in cell structure were mainly concentrated in the extracellular matrix, side of membrane, and cell surface receptors. Moreover, the differences in molecular functions were mainly concentrated in the activities of cation channel and transmembrane channel. Overall, the results of GO enrichment analysis demonstrated that cancer tissue might have differences in immune cell activity, cell surface receptors, and cell channel activities compared with the adjacent tissue.
Fig. 3. KIRC drug candidates and drug-targeted genes. A KIRC drug candidates, colors represent the prediction scores. The red means positively correlated and the blue means negatively correlated. B–F Correlation between predicted drugs and their target genes, the red dot in the center represents the predicted drugs, and other dots represent targeted genes. KIRC, kidney renal clear cell carcinoma.
Selection of KIRC-Associated Hub Genes

In order to analyze KIRC-associated hub genes, a PPI network was established using the STRING website as presented in Figure 2A. After the construction of the PPI network, the connectivity of each node gene was calculated by Cytoscape software to select genes with connectivity >50 as the KIRC-associated hub genes (Fig. 2B). After screening, a total of 16 KIRC-associated hub genes with high node degrees were obtained, namely CCR5, CCL4, CXCR4, AGTR2, ADCY2, ADCY8, CASR, LPAR5, MICHR1, PMCH, NMUR2, NMU, SAA1, C3, KNG1, and GNGT1.

Screening of KIRC Therapeutic Drugs

First, 150 upregulated genes and 150 downregulated genes from the differential analysis were uploaded to CMap and then the scores of drug candidates that could be used for KIRC treatment in different KIRC cell lines were obtained from the detailed results. A total of 6 drug candidates for KIRC treatment were screened out with the scores < −85 (Fig. 3A), including fedratinib, LY 344864, geldanamycin, PI-3Ky inhibitor AS-605240, luminespib, and verrucarin-A. Afterward, the drug-targeted genes of 5 drugs were obtained through STITCH database. Verrucarin-A was excluded since verrucarin-A was not included in the STITCH database and its target was unknown. The other results were categorized and prepared for subsequent bioinformatics analysis (Table 1). Figure 3B–F illustrated that these drug candidates had a total of 46 target genes.

Association between Drug-Targeted Genes and KIRC-Associated Hub Genes

To study the relationship between drug candidates and KIRC, the relationship between the drug-targeted genes and KIRC-associated hub genes was calculated through the STRING website. Combining the relationship between drug-targeted genes and drugs along with the calculation results of the STRING website, a PPI network was constructed to identify the interactions between these genes (Fig. 4A). Screening of drug-targeted genes that were correlated with KIRC-associated hub genes revealed that there were associations between 16 drug candidates-target genes-KIRC-associated hub genes and KIRC-associated hub genes (Fig. 4B). Further analysis demonstrated that the 5 drug candidates all targeted the 16 hub genes, suggesting that the 5 drug candidates had an impact on KIRC-associated hub genes. Finally, the correlation between KIRC-associated hub genes and 16 hub genes was sorted out as detailed in Tables 2 and 3. The results exhibit-

Table 1. Information of drug candidates

| CMap         | STITCH      | Score  | SMILES                                      |
|--------------|-------------|--------|---------------------------------------------|
| TG-101348    | Fedratinib  | −85.71 | CC1=CN=C(N=C1NC2=CC(=CC=C2)S(=O)=O)NC(C(C)C)NC3=C(C=C3)OCCN4CCCC4 |
| Ly 344864    | Ly 344864   | −85.94 | CN(C1CCCC2=C(C1)C3=C(N2)C=CC(=C3)NC(=O)C4=CC=CC(C=C4)F |
| Geldanamycin | Geldanamycin| −88.26 | CC1CC(C(C=C(C(C=C(C(C=C(O)NC2=CC=C=C(C(=O)NC(=O)C(=C(C1)C2=O)OC)OC)OC(=O)N(C)C)O)OC |
| AS-605240    | PI-3Ky Inhi | −91.64 | C1=CC2=NC=CN=C2=C1=C3C(=O)NC(=O)S3 |
| NVP-AUY922   | Luminespib  | −95.11 | CCNC(=O)C1=NOC=C2=C2=C=C(C=C2)CN 3CCOC3C4=CC(=C(C=C4)O)O(C(C)C |

CMap, connectivity map.

Fig. 4. PPI network of drug-targeted genes and KIRC-associated hub genes. A PPI network shows the correlation between drug-targeted genes and KIRC-associated hub genes. Lines represent the interaction between nodes. Nodes at left represent predicted drugs, nodes at right represent KIRC-associated hub genes, and nodes in the middle represent drug candidates-target genes. B Drug candidates-target genes-KIRC-associated hub genes which correlate with KIRC-associated hub genes. The blue rectangle presents the predicted drugs, the yellow rectangle represents the drug candidates-target genes-KIRC-associated hub genes, and the red rectangle represents the KIRC-associated hub genes. KIRC, kidney renal cell carcinoma; PPI, protein-protein interaction.

(For figure see next page.)
ited that drug candidates were all associated with KIRC-associated hub genes, and these drug candidates were all related to KIRC.

**Analysis of Pathways That May Be Affected by Drugs**

After confirming that the drug candidates were associated with KIRC, the hub genes and KIRC-associated hub genes were merged to investigate the pathways that might be affected by drugs. The results of KEGG enrichment analysis denoted that the above genes were mainly enriched in the neuroactive ligand-receptor interaction pathway, chemokine signaling pathway, cyclic adenosine monophosphate (cAMP) signaling pathway, and PI-3k-Akt signaling pathway (Fig. 5A). The results of GO analysis presented that the above genes were mainly enriched in biological processes such as serotonin signaling pathway and calcium channel protein, in cell structures such as cell ion channels and G protein-coupled receptor, and in molecular functions such as G protein-coupled receptor (Fig. 5B). These results exhibited that drug candidates mainly affected cell ion channels and G protein-coupled receptor pathway. Taken together, 5 drug candidates were screened out and pathways affected by these drugs were explored to reveal that these drug candidates mainly affected the pathways of neuroactive ligands, cell adhesion, and chemokines.

**Discussion**

Kidney cancer is a common cancer in modern times, with a morbidity of 3–5% in the population. In the US, about 60,000 people suffer from kidney cancer each year, which has created a major burden on society [14]. There are 2 variants of kidney cancer, namely KIRC and renal nonclear cell carcinoma, and the morbidity of KIRC accounts for 80% of all renal cancer cases, which is the main type of renal cancer [15]. Many risk factors can lead to KIRC including gender, age, genetic factors, lifestyle, diet, occupation, and environmental factors, which may also influence the risk of developing KIRC. In terms of age, according to the results of epidemiological surveillance, the age of the first diagnosis of KIRC is normally distributed, with a median of 64 years [16]. In terms of gender, studies believe that KIRC mutations are related to gender and can further affect the incidence of different genders, generally speaking, the incidence of men is higher than that of women [17]. Genetic factors are considered to be one of the main factors affecting the risk of KIRC, and there have been several studies on gene mutations that affect the pathogenesis of KIRC, which conclude that the genes that affect the onset of KIRC mainly include mutations of genes such as VHL, BAP1, SDHB, SDHC, and SDHD [18, 19]. Besides, lifestyle can also affect the onset of KIRC and researchers have found that moderate drink-
ing and increased physical exercise can reduce the risk of KIRC [7]. In this study, 1,533 upregulated genes and 779 downregulated genes were screened by bioinformatics methods. The enrichment analysis of these genes clarified that changes in several key pathways such as immune cell activity, secretion of cytokines and chemokines, and CAMS were the main reasons for the pathogenesis of KIRC. Then a PPI network was established for further screening of genes. Finally, 16 hub genes that affected the pathogenesis of KIRC were discovered.

**Fig. 5.** The results of enrichment analysis of KIRC-associated hub genes combined with drug candidates-target genes-KIRC-associated hub genes. A The result of KEGG enrichment analysis. B The result of GO enrichment analysis. KIRC, kidney renal clear cell carcinoma; KEGG, Kyoto Encyclopedia of Genes and Genomes; GO, Gene Ontology.
Subsequently, CMap was used to screen targeted drugs suitable for KIRC treatment, which was fedratinib, LY 344864, geldanamycin, AS-605240, and luminespib. Fedratinib is a JAK2 inhibitor, which is mainly used for the treatment of myelofibrosis, and due to its inhibition of TH17 activity, it is now regarded to be used to inhibit the immune storm caused by COVID-19 [20, 21]. A study denoted that JAK2 is a biomarker that affects the progression of KIRC, inhibition of JAK2 can promote cancer apoptosis through the JAK2/FOXO3 pathway, and thus, it is believed that fedratinib may be an effective drug for the treatment of KIRC [22]. LY 344864 is a kind of 5-hydroxytryptamine 1F receptor agonist, which is an experimental drug used to treat migraines, whereas the role of serotonin receptor in cancer is unclear [23]. Geldanamycin is a traditional anticancer drug and an inhibitor of Hsp90, and in vitro experiments revealed that geldanamycin has a good inhibitory effect on KIRC cell lines and is a potential KIRC therapeutic drug [24]. AS-605240 is a PI3Kγ inhibitor that is believed to reduce the chemother-apy-caused cardiotoxicity as along with tumor growth as a promising new drug [25]. Similar to geldanamycin, luminespib is also an inhibitor of Hsp90 that is now widely used in liver cancer and lung cancer, whereas no previous study has investigated the application of luminespib in the treatment of KIRC, accordingly, while this study believed that luminespib has good prospects for the treatment of KIRC [26, 27]. In summary, although this study did not define the mechanism of LY 344864, the other drugs screened in this study did suitable for cancer treatment, which has not yet been used in the treatment of KIRC. The screening results of this study were relatively accurate, which provided theoretical support for clinical drug development.

After selection, the drug-targeted genes were obtained based on the data in the STITCH database. Then the correlation between the drug-targeted genes and the KIRC-associated hub genes were calculated, and finally, 16 hub genes were screened out, including AKT1, JAK2, PIK3CB, RAF1, PIK3CG, HSP90B1, HTR7, HTR2A, HTR2B, PIK3CA, HTR2C, HTR1B, HTR1D, HTR1A, HTR1E, and HTR1F. Among them, AKT, PIK3CB, PIK3CG, and PIK3CA are all related to the mTOR signaling pathway, which can affect the occurrence of cancer through the mTOR signaling pathway [28, 29]. JAK2 can stimulate cancer migration through the JAK2/SATA3 pathway [30]. RAF1 can promote cancer migration through the RAF1/MEK/ERK pathway [31]. HSP90B1 is a heat shock protein, overexpression of which in cancer tissue is associated with dismal prognosis in patients with non-small cell lung cancer [32]. HTR7, HTR2A, HTR2B, HTR2C, HTR1B, HTR1D, HTR1A, HTR1E, and HTR1F are all serotonin receptors. Although the relationship between serotonin receptors and cancer remains an open issue, the results of this study indicated that serotonin receptors might be used as targets for cancer treatment. Afterward, research was also conducted on the pathways affected by drug candidates. Pathway enrichment analyses were performed on hub genes and KIRC-associated hub genes. The results demonstrated that drug candidates mainly affected neural signal transduction, immunity, and metabolic activity. The pathways enriched by these genes were basically the same as those enriched by DEGs of KIRC, implying that the drug screening results were reliable.

In fact, it is common to predict possible therapeutic drugs through public databases such as CMap. In 2018, Koudijs et al. [33] predict drug action of several tumor drugs on KIRC patients by the above database. Generally speaking, their research performs gene differential expression analysis in KIRC patients and analyzed signatures from tumor tissues and drugs. Then, they screen out tumor drugs sensitive to KIRC by GSEA. Our research is similar to theirs but varying in focus. Their research focuses on excavating individualized medication regimen thus using entirely different data processing with us. Recently, Pang et al. [34] also predict possible tumor drugs based on DEGs of tumors and nontumor tissues by CMap database, and they predict that vorinostat is a candidate for papillary renal cell carcinoma. Their research object is different from our study in spite of similarity in methodology. Overall, this method is widely accepted in predicting drugs for tumors.

Besides, we noticed that in drug-target gene network, HTR2C, HTR1B, HTR1D, HTR1A, HTR1E, and other serotonin receptor family genes show a high degree. Targets of Ly344864 in the network are all HTR family. We therefore speculated that Ly344864 exerted an anticancer effect by acting on a variety of serotonin receptors in KIRC. Essentially, Ly344864 is a serotonin receptor agonist and it can play a biological function similar to serotonin, a generally regarded neurotransmitter and in most cases a modulator of body’s neural network by activating receptors. Moreover, a study [35] reported that activation of some serotonin receptors is associated with tumor growth. It mentioned that activation of serotonin receptors represses activity of adenylate cyclase to block the downstream cAMP signaling pathway, and exerts an anticancer role. Ly344864 may also activate the signal pathway mentioned above and exert an anticancer effect (online suppl. Fig. 1; for all online suppl. material, see www.
A study proposed that regulating cAMP signaling pathway affects tumor cell behaviors. In 2018, Cheng et al. [36] revealed that cAMP signaling pathway activates downstream PKA and ultimately enhances invasive and metastasis potentials of prostate cancer cells. Combined analysis in this study with earlier research findings, it can be seen that Ly344864 is a hopeful targeted drug for KIRC.

Viewed in total, we studied KIRC patients through bioinformatics analysis and screened out 5 drugs that could be used for KIRC treatment. The correlation analysis between the drug-targeted genes and KIRC-associated hub genes displayed that the pathways affected by the drug candidates were basically the same as the pathways enriched by DEGs of KIRC, suggesting the reliable results of drug screening. The study was limited by the lack of experimental verification on the selected drugs since it was a pure bioinformatics article based on public databases for bioinformatics mining. Notwithstanding these limitations, verification methods used in this study such as association analysis of drug-targeted genes and hub genes and functional enrichment analyses verified the accuracy and application value of the results. Therefore, despite the lack of experimental certification, the results of the drug screening are still used as theoretical bases for further clinical investigation and research.

Statement of Ethics
An ethics statement was not required for this study type, no human or animal subjects or materials were used.

Conflict of Interest Statement
The authors declare no conflicts of interest.

Funding Sources
There was no funding for this paper.

Author Contributions
B.G. contributed to the study design, L.W. and N.Z. conducted the literature search. M.H. and Y.Z. acquired the data. B.G., H.L., and D.S. wrote the article. D.S. performed data analysis and drafted. X.T. and H.B. revised the article. Y.L. gave the final approval of the version to be submitted.

Data Availability Statement
The data used to support the findings of this study are included within the article. The data and materials in the current study are available from the corresponding author on reasonable request.

References
1 Vera-Badillo FE, Templeton AJ, Duran I, Ocana A, de Gouveia P, Aneja P, et al. Systemic therapy for non–clear cell renal cell carcinoma: a systematic review and meta-analysis. Eur Urol. 2015 Apr;67(4):740–9.
2 Schuhmacher P, Kim E, Hahn F, Sekula P, Jilg CA, Leiber C, et al. Growth characteristics and therapeutic decision markers in von Hippel-Lindau disease patients with renal cell carcinoma. Orphanet J Rare Dis. 2019;14(1):235.
3 Vecchio SJD, Ellis RJ. Cabozantinib for the management of metastatic clear cell renal cell carcinoma. J Kidney Cancer VHL. 2018;5(4):1–5.
4 Yoshida K, Takagi T, Kondo T, Kobayashi H, Iizuka J, Fukuda H, et al. Efficacy of axitinib in patients with metastatic renal cell carcinoma refractory to nivolumab therapy. Int J Clin Oncol. 2019;49(6):576–80.
5 Yakes FM, Chen J, Tan J, Yamaguchi K, Shi Y, Yu P, et al. Cabozantinib (XL184), a novel MET and VEGFR2 inhibitor, simultaneously suppresses metastasis, angiogenesis, and tumor growth. Mol Cancer Ther. 2011;10(12):2298–308.
6 Yu SS, Quinn DJ, Dorff TB. Clinical use of cabozantinib in the treatment of advanced kidney cancer: efficacy, safety, and patient selection. Onco Targets Ther. 2016;9:5825–37.
7 Hisieh JF, Purdue MP, Signoretti S, Swanton C, Albíges I, Schmidinger M, et al. Renal cell carcinoma. Nat Rev Dis Primers. 2017;3:17009.
8 Hisieh JF, Chen D, Wang PI, Marker M, Redzematovic A, Chen Y-B, et al. Genomic biomarkers of a randomized trial comparing first-line everolimus and sunitinib in patients with metastatic renal cell carcinoma. Eur Urol. 2017;71(3):405–14.
9 Zhang H, Berel D, Wang Y, Li P, Browmick NA, Figlin RA, et al. A comparison of KU0063794, a dual mTORC1 and mTORC2 inhibitor, and temsirolimus in preclinical renal cell carcinoma models. PLoS One. 2013; 8(1):e54918.
10 He J, Yan H, Cai H, Li X, Guaqu Q, Zheng W, et al. Statistically controlled identification of differentially expressed genes in one-to-one cell line comparisons of the CMAP database for drug repositioning. J Transl Med. 2017; 15(1):198.
11 Chierici M, Francescato M, Bussola N, Jerman G, Furlanello C. Predictability of drug-induced liver injury by machine learning. Biol Direct. 2020;15(1):3.
12 Yu L, Xie F, Gao L. Predict new therapeutic drugs for hepatocellular carcinoma based on gene mutation and expression. Front Bioeng Biotechnol. 2020;8:88.
13 Huang H, Nguyen T, Ibrahim S, Shantharam S, Yue Z, Chen JY. DMAP: a connectivity map database to enable identification of novel drug repositioning candidates. BMC Bioinformatics. 2015;16(Suppl 13):S4.
14 Massari F, Di Nunno V, Mollica V, Graham J, Gatto L, Heng D. Adjuvant tyrosine kinase inhibitors in treatment of renal cell carcinoma: a meta-analysis of available clinical trials. Clin Genitourin Cancer. 2019;17(2):e339–e44.
15 Qian CN. Hijacking the vasculature in ccRCC: co-option, remodelling and angiogenesis. Nat Rev Urol. 2013;10(5):300–4.
16 Shuch B, Vourganti S, Ricketts CJ, Middleton L, Peterson J, Merino MJ, et al. Defining early-onset kidney cancer: implications for genetic and somatic mutation testing and clinical management. J Clin Oncol. 2014;32(5):431–7.
Screening Novel Drug Candidates for KIRC Treatment

17 Ricketts CJ, Linehan WM. Gender specific mutation incidence and survival associations in Clear Cell Renal Cell Carcinoma (CCRCC). PLoS One. 2015;10(10):e0140257.

18 Haas NB, Nathanson KL. Hereditary kidney cancer syndromes. Adv Chronic Kidney Dis. 2014;21(1):81–90.

19 Adeniran AJ, Shuch B, Humphrey PA. Hereditary renal cell carcinoma syndromes: clinical, pathologic, and genetic features. Am J Surg Pathol. 2015;39(12):e1–18.

20 Blair HA. Fedratinib: first approval. Drugs. 2019;79(15):1719–25.

21 Wu D, Yang XO. TH17 responses in cytokine storm of COVID-19: an emerging target of JAK2 inhibitor Fedratinib. J Microbiol Immunol Infect. 2020;53(3):368–70.

22 Kang MA, Lee J, Ha SH, Lee CM, Kim KM, Jang KY, et al. Interleukin4Rα (IL4Rα) and IL13Rα1 are associated with the progress of renal cell carcinoma through Janus Kinase 2 (JAK2)/Forkhead Box O3 (FOXO3) pathways. Cancers. 2019 Sep 18;11(9):1394.

23 Agosti RM. 5HT1F- and 5HT7-receptor agonists for the treatment of migraines. CNS Neurol Disord Drug Targets. 2007;6(4):235–7.

24 Bohonowycz JE, Peng S, Gopal U, Hance MW, Wing SB, Argraves KM, et al. Comparative analysis of novel and conventional Hsp90 inhibitors on HIF activity and angiogenic potential in clear cell renal cell carcinoma: implications for clinical evaluation. BMC Cancer. 2011;11:520.

25 Li M, Sala V, De Santis MC, Cimino J, Cappello P, Pianca N, et al. Phosphoinositide 3-kinase gamma inhibition protects from anthracycline cardiotoxicity and reduces tumor growth. Circulation. 2018;138(7):696–711.

26 Piotrowska Z, Costa DB, Oxnard GR, Huberman M, Gainor JF, Lennes IT, et al. Activity of the Hsp90 inhibitor luminespib among non-small-cell lung cancers harboring EGFR exon 20 insertions. Ann Oncol. 2018;29(10):2092–7.

27 Augello G, Emma MR, Cusimano A, Azzolina A, Mongiovi S, Puleio R, et al. Targeting HSP90 with the small molecule inhibitor AUY922 (luminespib) as a treatment strategy against hepatocellular carcinoma. Int J Cancer. 2019;144(10):2613–24.

28 Zhang X, Wang S, Wang H, Cao J, Huang X, Chen Z, et al. Circular RNA circNRIP1 acts as a microRNA-149-5p sponge to promote gastric cancer progression via the AKT1/mTOR pathway. Mol Cancer. 2019;18(1):20.

29 Willems I, Tamburini J, Chauvin N, Lacombe C, Mayeu P, Bouscary D. PI3K and mTOR signaling pathways in cancer: new data on targeted therapies. Curr Oncol Rep. 2012;14(2):129–38.

30 Wang Y, Jing Y, Ding L, Zhang X, Song Y, Chen S, et al. Epiregulin reprograms cancer-associated fibroblasts and facilitates oral squamous cell carcinoma invasion via JAK2-STAT3 pathway. J Exp Clin Cancer Res. 2019;38(1):274.

31 Qi ZH, Xu XH, Zhang SR, Xu JZ, Li S, Gao HL, et al. RIFK4/PEBP1 axis promotes pancreatic cancer cell migration and invasion by activating RAF1/MEK/ERK signaling. Int J Oncol. 2018;52(4):1105–16.

32 Xu Y, Chen Z, Zhang G, Xi Y, Sun R, Wang X, et al. HSP90B1 overexpression predicts poor prognosis in NSCLC patients. Tumour Biol. 2016;37(10):14321–8.

33 Koudijs KKM, Terwisscha van Scheltinga AGT, Böhringer S, Schimmel KJM, Guchelaar HJ. Personalised drug repositioning for clear cell renal cell carcinoma using gene expression. Sci Rep. 2018;8(1):5250.

34 Pang JS, Li ZK, Lin P, Wang XD, Chen G, Yan HB, et al. The underlying molecular mechanism and potential drugs for treatment in papillary renal cell carcinoma: a study based on TCGA and Cmap datasets. Oncol Rep. 2019;41(4):2089–102.

35 Dizeyi N, Bjartell A, Nilsson E, Hansson J, Gdaleanu V, Cross N, et al. Expression of serotonin receptors and role of serotonin in human prostate cancer tissue and cell lines. Prostate. 2004;59(3):328–36.

36 Cheng Y, Gao XH, Li XJ, Cao QH, Zhao DD, Zhou JR, et al. Depression promotes prostate cancer invasion and metastasis via a sympathetic-cAMP-FAK signaling pathway. Oncogene. 2018;37(22):2953–66.