



PROJECT

Supervisor: Alessandro Larcher

Title: Cytostatic and Citotoxic effect of common non cancerous medications in patients with small renal masses

Curriculum: Molecular Medicine - Experimental and Clinical Medicine

Link to the personal page of the University or relevant hospital site website: <https://research.hsr.it/en/institutes/urological-research-institute/renal-cancer.html>

Description of the Project (max 3,000 characters including spaces)

Background/gap of knowledge

Renal cell carcinoma (RCC) is responsible for more than 130,000 deaths worldwide each year. Small Renal Masses (SRM) represent more than 70% of all diagnoses (Bukavina 2022). SRM can be either benign, malignant but clinically indolent or aggressive. Current treatment options include surveillance, watchful waiting, surgical extirpation, cryoablation, stereotactic body radiation therapy (SBRT) or thermal ablation (Bex 2025). Surgery, which is currently performed in most of the cases and causes long-term sequelae (renal function impairment, cardiovascular events, other-cause mortality etc.) (Capitanio 2020). An inverse association between cancer risk and administration of some common medications for chronic conditions others than cancer such as Biguanides (Coyle 2016), Statins (Alfaqih 2017), and Glucagon-Like Peptide 1 Receptor (GLP-1R) agonists (Wang 2024) has been described. However, no information at all is available about the potential benefit of therapies aimed at slowing the development of an already diagnosed cancer.

Rationale and hypothesis

The rationale of the study is grounded in the existing evidence of intricate intracellular interactions between Biguanides, Statins, and GLP-1R agonists and the progression of renal cell carcinoma (RCC) (Woodard 2010, Matuszewicz 2015, Arvanitakis 2022). The hypothesis to test is whether in patients with SRMs, the use of common medications for chronic conditions others than cancer is associated with a slower progression of tumor growth, a reduced need for surgical intervention or has an impact on renal cancer aggressiveness and prognosis compared to patients not using these medications.

Objectives and specific aims



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Aim 1 – To evaluate the cytotoxic/cytostatic effect of extremely common medications for chronic conditions others than cancer on patients-derived organoids (PDO) such as Biguanides, GLP-1 agonists and Statins.

Aim 2 – To retrospectively analyze the impact of common medications for chronic conditions others than cancer on renal cancer aggressiveness and prognosis relying on a prospectively maintained institutional dataset including more than 4000 patients elected for surgery for a renal mass.

Expected outcomes

Aim 1 - We expect that treatment of PDOs with Biguanides, GLP-1 agonists and Statins will demonstrate measurable cytostatic and/or cytotoxic effects. These effects will be quantified through dose-response assays, apoptosis markers, and proliferation indices. We also anticipate observing variability in drug responsiveness among PDOs, reflecting the heterogeneity of small renal masses and potentially identifying molecular markers predictive of treatment sensitivity.

Aim 2 - We expect to demonstrate that these medications are independently associated with renal cancer aggressiveness and prognosis after adjusting for relevant clinical confounders.

Skills that the student should acquire (max. 600 characters including spaces):

The PhD student involved in this project will acquire a diverse and interdisciplinary skillset. On the experimental side, the student will gain hands-on experience in tissue processing, PDO culture, and in vitro drug testing, including cytotoxicity and proliferation assays. She/he will also learn to interpret drug response profiles and explore mechanisms of action of repurposed agents in renal cancer models. On the clinical side, she/he will develop skills in retrospective cohort analysis using large-scale, prospectively maintained clinical databases. This includes data cleaning, survival and time-to-event analysis, multivariate regression modelling, and handling of clinical confounders. Additional skills will include data interpretation, scientific writing, and results disseminations.

References (max. 15)

- 1) Bukavina L, Bensalah K, Bray F, Carlo M, Challacombe B, Karam JA, Kassouf W, Mitchell T, Montironi R, O'Brien T, Panebianco V, Scelo G, Shuch B, van Poppel H, Blosser CD, Psutka SP. Epidemiology of Renal Cell Carcinoma: 2022 Update. Eur Urol. 2022 Nov;82(5):529-542. doi: 10.1016/j.eururo.2022.08.019. Epub 2022 Sep 10. PMID: 36100483.



- 2) Bex A, Ghanem YA, Albiges L, Bonn S, Campi R, Capitanio U, Dabestani S, Hora M, Klatte T, Kuusk T, Lund L, Marconi L, Palumbo C, Pignot G, Powles T, Schouten N, Tran M, Volpe A, Bedke J. European Association of Urology Guidelines on Renal Cell Carcinoma: The 2025 Update. *Eur Urol.* 2025 Mar 10:S0302-2838(25)00139-3. doi: 10.1016/j.eururo.2025.02.020. Epub ahead of print. PMID: 40118739.
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- 4) Coyle C, Cafferty FH, Vale C, Langley RE. Metformin as an adjuvant treatment for cancer: a systematic review and meta-analysis. *Ann Oncol.* 2016 Dec;27(12):2184-2195. doi: 10.1093/annonc/mdw410. Epub 2016 Sep 28. PMID: 27681864; PMCID: PMC5178140.
- 5) Alfaqih MA, Allott EH, Hamilton RJ, Freeman MR, Freedland SJ. The current evidence on statin use and prostate cancer prevention: are we there yet? *Nat Rev Urol.* 2017 Feb;14(2):107-119. doi: 10.1038/nrurol.2016.199. Epub 2016 Oct 25. PMID: 27779230; PMCID: PMC5830185.
- 6) Wang L, Xu R, Kaelber DC, Berger NA. Glucagon-Like Peptide 1 Receptor Agonists and 13 Obesity-Associated Cancers in Patients With Type 2 Diabetes. *JAMA Netw Open.* 2024 Jul 1;7(7):e2421305. doi: 10.1001/jamanetworkopen.2024.21305. PMID: 38967919; PMCID: PMC11227080.
- 7) Woodard J, Joshi S, Viollet B, Hay N, Plataniias LC. AMPK as a therapeutic target in renal cell carcinoma. *Cancer Biol Ther.* 2010 Dec 1;10(11):1168-77. doi: 10.4161/cbt.10.11.13629. Epub 2010 Dec 1. PMID: 20948309; PMCID: PMC3018677.
- 8) Matuszewicz L, Meissner J, Toporkiewicz M, Sikorski AF. The effect of statins on cancer cells--review. *Tumour Biol.* 2015 Jul;36(7):4889-904. doi: 10.1007/s13277-015-3551-7. Epub 2015 May 23. PMID: 26002574.
- 9) Arvanitakis K, Koufakis T, Kotsa K, Germanidis G. How Far beyond Diabetes Can the Benefits of Glucagon-like Peptide-1 Receptor Agonists Go? A Review of the Evidence on



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