PAX8 Small molecule inhibitors for the treatment of ovarian cancer (Ramot)

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OUTLINE

The PAX8 transcription factor is essential for ovarian cancer proliferation, and its silencing in ovarian cancer cells leads to senescence and apoptosis. We propose a novel anti-ovarian cancer therapy based on small molecule binders of PAX8 that stabilize it in a conformation that cannot bind DNA. The approach could be applicable also to other transcription factors that are involved in other types of cancers.

UNMET NEED

Ovarian cancer is the deadliest gynecologic malignancy in the western world, with 30-40% 5-year overall survival. The mainstay of treatment is surgery and chemotherapy, and most patients initially respond, but in 80% of the cases the disease eventually relapses and the patients succumb to their illness. Targeted therapies are scarce and mostly effective in a small percentage of patients. Therefore, novel ovarian cancer therapies are a significant unmet need.

OUR SOLUTION

A wide variety of DNA-binding transcription factors are linked to cancer, and are considered top targets for anti-cancer therapy. However, in spite of intensive research, there are no known clinically-approved transcription factor inhibitors, leading to the notion that transcription factors are “undrugable" [2]. We suggest this is because the effort to inhibit transcription factor activity has been focused only on the DNA-bound conformation, which is difficult to inhibit, because it does not have a drugable binding pocket. Here, we examine for the first time an alternative approach, using the transcription factor PAX8: We conducted a virtual screen of small molecules that would stabilize PAX8 conformations that cannot bind DNA. Stabilizers molecules cause a shift in the PAX8 protein population towards a non-DNA binding conformation, thereby reducing PAX8 transcriptional activity.

OUR PRODUCT

Our preliminary in-silico screen resulted in 22 compounds that were tested in-vitro. Of the 22 compounds, 11 blocked PAX8 transcriptional activity and 5 of these inhibited ovarian cancer cell proliferation in-vitro by 2-10 fold, some with IC50 of about 1-3 M. Novel chemical entities, designed based on our current hits, and optimized for improved activity and ADME-Tox properties, could be used as antiovarian cancer drugs.

DIFFERENTIATION

Up to date our solution is the first that allow a direct treatment of ovarian cancer via targeting of Pax8. Due to predicted specificity, we vision a very low rate of side effects if any

REFERENCES

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