

Quantum Insights: Dynamic Quantum Clustering (DQC) used for drug repurposing

Executive Summary:

A potential, less costly, alternative to the classical drug discovery pipeline is drug repurposing. Repurposing - the process of identifying an already approved drug that can work on a disease other than that the disease it was designed to attack – can increase the market for an existing drug. But, from a human point of view, there is another virtue of this approach. It can save lives by identifying drug candidates for treating rare or orphan diseases. Namely, diseases that – for economic reasons – do not get much attention from large pharmaceutical companies.

Quantum Insights (QI) has developed a method that uses RNAseq data from TCGA (and other possible sources) to identify drugs most likely to be successfully repurposed to treat new diseases. The method leverages DQC's ability to identify diagnostic signatures - using a density mapping approach driven by quantum mechanics principles¹ - to create a *similarity distance* between the diseases for which TCGA RNAseq data is available. We then focus on a specific drug – or disease - in question and use the *similarity distance* map to find the diseases that are closest to this disease. Finally, we determine which genes play the most important role in defining the *similarity distance* and examine whether there is evidence if any of these genes are known targets of the drug to be repurposed. If we find a match between a drug and a disease candidate for which that drug can be repurposed, then we look for clinical evidence that our prediction is correct. Clearly the same approach can be used to find candidate drugs to treat a disease for which there is no known current treatment.

A Case Study: KIRP – an orphan kidney cancer

Kidney renal papillary cell carcinoma (KIRP or PRCC) is a renal cell cancer with poor prognosis under current treatments. It comprises about 10-15% of all kidney cancers. At present there are not good treatments for KIRP. Our challenge was to find an existing drug that is likely to help treat a patient diagnosed with KIRP using the RNAseq expression data for the patient's tumor. We began by analyzing RNAseq data – obtained from TCGA (40 cancers, n=10,000, 60,000 genes) - and restricted the genes to the 18,000 genes present in a patient's poor quality KIRP sample. Our *similarity distance* analysis identified several non-kidney cancers closest to KIRP. These were:

- Liver hepatocellular carcinoma (LIHC)
- Thyroid carcinoma (THCA)

¹ The technical paper on the method is available here: <http://quantuminsights.io/wp-content/uploads/2019/03/Dyanamic-Quantum-Clustering.pdf>

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- Cholangiocarcinoma (CHOL)
- Uveal melanoma (UVM)
- Adrenocortical carcinoma (ACC)

We next identified existing, FDA-approved, drugs to treat each disease.

- CHOL, UVM and ACC did not have FDA-approved drugs and were excluded from the rest of the analysis.
- LIHC and THCA have, in total, 10 FDA-approved drugs. (Listed in Appendix A)

Next, using the Open Targets website (<https://www.targetvalidation.org>), we identified the target gene for each approved drug, resulting in 47 target genes (listed in Appendix B).

- Three genes (Programmed Cell Death 1; *PDCD1*, Immunoglobulin Heavy Constant Epsilon; *IGHE*, and Epherin Receptor B6; *EPHB6*) were not included in the TCGA list of 18,000 genes and were excluded from the rest of the analysis.
- We calculated the gene expression difference for KIRP vs “healthy kidney” samples as defined in the TCGA.
- There are 30 genes where the difference was significant, but only 4 genes that were overexpressed in KIRP relative to healthy kidney cells: *Proto-Oncogene Receptor Tyrosine Kinase (MET)*, *Transmembrane Protein 4 (TMEM43 – aka Luma)*, *Sarcoma gene (SRC)*, *Erb-B2 Receptor Tyrosine Kinase (ERBB3)*.

We focused on overexpressed genes because the action of these four drugs is to inhibit their targets.

Presently, we have no clinical data that tells us if these drugs will work on KIRP. However, it turns out that for the drugs that target *MET*, *SRC*, *TMEM43*, and *ERBB3* (Cabozantinib, Nivolumab, and Vandetanib) there are several clinical trials testing the hypothesis that these drugs work on KIRP²:

1. 3 trials including Cabozantinib: [NCT02761057](#), [NCT03685448](#), [NCT03635892](#)
2. 2 trials including Nivolumab: [NCT03177239](#), [NCT03635892](#) (this is a duplicate trial: Cabozantinib + Nivolumab)
3. 1 trial including Vandetanib: [NCT02495103](#)

When these trials complete we will be able to assess the validity of our prediction.

² Searching Clinicaltrials.gov on “[Kidney renal papillary cell carcinoma](#)” (must target *papillary* vs other kidney cancers”

Appendix A: Drugs approved for LIHC and THCA

LIHC	liver hepatocellular carcinoma	Target Engagement
Cabometyx, Cometriq	Cabozantinib	MET, KDR, MAD2L1BP
Cyramza	Ramucirumab	KDR
Keytruda	Pembrolizumab	PDCD1, IGHE
Lenvima	Lenvatinib Mesylate	FLT4, KDR, FLT1
Nexavar	Sorafenib Tosylate	PDGFRB, RAF1, KIT, RET, BRAF, FLT1, KDR, FLT3, FLT4
Opdivo	Nivolumab	PDCD1, TMEM43
Stivarga	Regorafenib	ABL1, RAF1, KIT, BRAF, DDR2, FGFR2, PDGFRA, PDGFRB, FGFR1, RET, KDR, FLT4, TEK, FLT1, FRK, MAPK11, EPHA2, ABCB1, CYP3A4
THCA	Thyroid Cancer	
Cabometyx, Cometriq	Cabozantinib	MET, KDR, MAD2L1BP
Caprelsa	Vandetanib	ERBB3, EPHB2, SRC, EGFR, RET, EPHA3, ERBB4, EPHB4, ERBB2, EPHA7, TEK, KDR, EPHA2, PTK6, EPHA4, EPHB1, FLT4, EPHB3, EPHA10, EPHB6, FLT1, EPHA8, EPHA6, EPHA5, VEGFA, CYP3A4
Tafinlar	Dabrafenib Mesylate	BRAF, CPB2
Lenvima	Lenvatinib Mesylate	FLT4, KRD, FLT1
Mekinist	Trametinib	MAP2K1, MAP2K2, CYP3A4
Nexavar	Sorafenib Tosylate	PDGFRB, RAF1, KIT, RET, BRAF, FLT1, KDR, FLT3, FLT4

The 10 drugs approved for LIHC and THCA are:

- Cabozantinib

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- Ramucirumab
- Pembrolizumab
- Lenvatinib Mesylate
- Sorafenib Tosylate
- Nivolumab
- Regorafenib
- Vandetanib
- Dabrafenib Mesylate
- Trametinib

Appendix B: 30 Genes differentiating KIRP from Healthy Kidney

CYP3A4	FLT4
DDR2	FRK
EPHA3	KDR
EPHA4	KIT
EPHA5	MAP2K1
EPHA6	MAPK11
EPHA8	MET
EPHB1	PDGFRA
EPHB3	PDGFRB
EPHB4	RAF1
ERBB2	RET
ERBB3	SRC
ERBB4	TEK
FGFR2	TMEM43
FLT1	VEGFA

Note: Genes in **bold** are overexpressed relative to healthy kidney cells (all were $p < 0.00136$). The other genes are significantly under expressed.

Appendix C: Open Questions

- Out of 30 genes that are significantly different between KIRP our tumor adjacent “healthy” kidney cells, only 4 were over-expressed in KIRP. Many other genes were significantly suppressed, is a 1:6.5 ratio of over-to-under expression surprising?
 - Is this small number because tumor adjacent cells are not really healthy cells?
Quantum Insights is looking for “true healthy” cells in order to re-run this analysis.
- Are there other ways (besides KIRP/healthy kidney ratio) to determine if a subset of the 10 drugs will have a positive effect on KIRP?