# Research update from the MCM team (January 2024)

We continue our work on characterizing lung cancer biomarkers identified in the MCM1 project. This update focuses on PCSK5, a gene associated with lung cancer survival and which shows differential expression across various cancer types.

Project: Mapping Cancer Markers

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#### Terminology

- Proprotein: An inactive protein that can be modified to become an active protein.

- VACTERL association: A complex condition characterized by multiple congenital anatomical defects, including vertebral defects, anal atresia, cardiac defects, tracheo-esophageal fistula, renal anomalies, and limb abnormalities (VACTERL).

- Herlyn-Werner-Wunderlich syndrome: A rare congenital disorder characterized by anatomical defects in the urogenital tract.

#### Background

Precision medicine is enabled by using molecular markers (signatures) that identify disease early, and stratify patients into subgroups with different disease progression patterns, leading to potentially different treatment strategies. The Mapping Cancer Markers project analyzes data sets with millions of data points collected from patients with cancers and sarcomas to find such diagnostic, prognostic and predictive signatures.

Since November 2013, World Community Grid volunteers have donated over 875,900 CPU years to the project, helping analyze data on lung and ovarian cancer and sarcoma, much more thoroughly than otherwise possible. We are immensely grateful for the volunteers who continue to donate to this project.

Further characterising the 26 top-scoring genes in lung cancer, we have already discussed VAMP1, FARP1, GSDMB, ADH6, and IL13RA1 (in our <u>March</u>, <u>April</u>, <u>July</u>, <u>September</u>, and <u>November</u> 2023 updates). Here, we outline information on PCSK5.

## **PCSK5 Research**

PCSK5 encodes proprotein convertase subtilisin/kexin type 5, a serine endoproteinase that processes different proproteins (Uniprot). PCSK5 has been implicated in diverse biological processes. Studies in mice have revealed that it is involved in early heart development<sup>III</sup> and ovarian follicle development<sup>III</sup>. Another study suggested that it may facilitate SARS-CoV-2 entry into myocardial tissue<sup>III</sup>. Genetic variation in PCSK5 has been demonstrated to modulate high-density lipoprotein (HDL) cholesterol levels<sup>III</sup>. In addition to its association with cancer, links have been identified between PCSK5 and other diseases. For example, mutations in PCSK5 have been identified in patients with the VACTERL association<sup>III</sup> and Herlyn-Werner-Wunderlich syndrome<sup>III</sup>. PCSK5 has also been identified as a diagnostic biomarker for endometriosis<sup>III</sup> and inflammatory skin disease<sup>III</sup>.

As with the other genes we have presented, we found that PCSK5 has a protective role in lung cancer (Figure 1).



P value: 3.5e-11

Figure 1. Survival curves for patients with high and low expression of PCSK5 (KMplot).

We investigated further to see if this finding is seen in other cancers. As shown in Figure 2, PCSK5 is differentially expressed in normal tissue compared with cancer tissue across most cancer types (red labels). In most of the cases, it is the loss of PCSK5 expression that is associated with cancer, except liver, renal, stomach and testicular cancers. The literature also supports this observation, as associations have been documented between PCSK5 expression and colorectal cancer<sup>14</sup>, brain cancer<sup>14</sup>.



*Figure 2. Expression of PCSK5 in normal and cancer tissue for multiple cancer types. Red text represents a significant difference between expression in cancer tissue compared with normal tissue (TNMplot).* 

If you have any questions or comments, please leave them in <u>this thread</u> for us to answer. Thank you for your support!

## WCG Team

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