

Commentary on “The Gene Master Regulators (GMR) Approach Provides Legitimate Targets for Personalized, Time-Sensitive Cancer Gene Therapy”

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For decades, the scientific community tried hard to identify the gene biomarkers whose mutations or regulations cause (better say are associated with) specific forms of cancer. For instance, the September 17th 2019 release of the Genomic Data Commons Data Portal [1] includes 3,142,246 mutations detected in 22,872 genes sequenced from 37,075 cases of cancers localized in 67 primary sites. The hope was (and still is) to treat cancer by restoring the normal sequence or/and expression level of the biomarker(s). The biomarkers are selected from the most frequently and broadly altered genes in large cohorts of patients affected by the same form of cancer. Problem is that the frequent alteration indicates that the biomarkers are not in the high priorities of the cell to maintain their normal sequence or/and expression, and, as minor players, their restoration might not be of much consequence.

Despite the very rich literature and the ambitious (and very well-funded) Cancer Genome Atlas Program (TCGA [2]), there is not yet a comprehensive explanation of cancer development, nor a perfect therapeutic solution. Most cancers occur from nowhere, without being genetically inherited or directly caused by a steady deficient diet (affecting the microbiome), exposure to ionizing radiation or carcinogenic toxins, or bad habit (like smoking), although such risk factors increase the chances of the “bad luck” [3,4]. Tumors are heterogeneous, composed of regions with distinct characteristics, some of them malignant, some others preserving the normal features of the tissue. On top of these, with all similarities, each human is unique and has a unique lifeline, so, although a trained pathologist

can recognize the cancer type, the tumors are not identical, nor develop identically or respond identically to treatment.

Therefore, instead of targeting the SAME alleged gene biomarker for all humans with a particular cancer form, we devised a method by which the cancer of the ACTUAL patient itself indicates what genes are NOW commanding it. We call these commanders “gene master regulators” (GMRs) and identify them by profiling the transcriptomes of tumor biopsies or blood samples (pending on the suspected cancer type) using RNA sequencing or microarray platforms. The method, consistent with our Genomic Fabric Paradigm [5], relies on original mathematical algorithm and software that establish the gene hierarchy based on their Gene Commanding Height (GCH). GCH is a composite measure of gene expression control and coordination with major functional pathways. The GMR tops the most controlled genes by the homeostatic mechanisms (because they are critical for the cell survival and phenotypic expression) whose expression regulates most functional pathways through coordination with the expression of many other genes. The GMR approach provides the most legitimate targets for cancer gene therapy. It is also personalized and time-sensitive because the GMR hierarchy is unique for each patient and changes slowly during cancer development.

In the commented [6] and other recent papers [7,8], we proved that cancer nuclei and surrounding normal tissue are governed by distinct GMRs (illustrated in Figure 1 for a case of prostate cancer). We have

also tested on standard human cancer cell lines that manipulation of the expression of a gene has transcriptomic consequences consistent with its GCH

score. As such, it is expected that targeting the GMRs of cancer nuclei from a tissue will selectively destroy the cancer cells with little consequences on the normal ones.

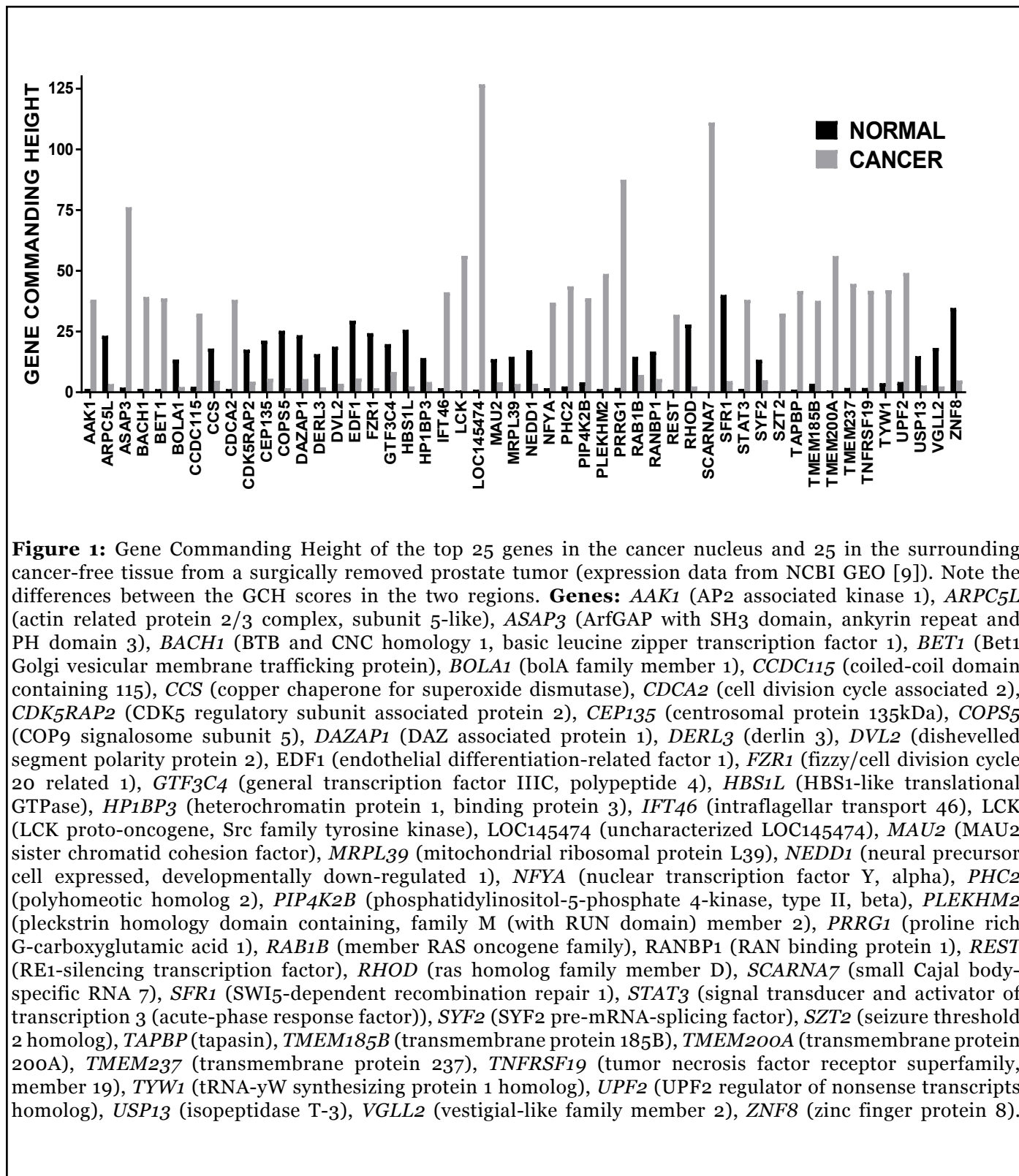


Figure 1: Gene Commanding Height of the top 25 genes in the cancer nucleus and 25 in the surrounding cancer-free tissue from a surgically removed prostate tumor (expression data from NCBI GEO [9]). Note the differences between the GCH scores in the two regions. **Genes:** *AAK1* (AP2 associated kinase 1), *ARPC5L* (actin related protein 2/3 complex, subunit 5-like), *ASAP3* (ArfGAP with SH3 domain, ankyrin repeat and PH domain 3), *BACH1* (BTB and CNC homology 1, basic leucine zipper transcription factor 1), *BET1* (Bet1 Golgi vesicular membrane trafficking protein), *BOLA1* (bola family member 1), *CCDC115* (coiled-coil domain containing 115), *CCS* (copper chaperone for superoxide dismutase), *CDCA2* (cell division cycle associated 2), *CDK5RAP2* (CDK5 regulatory subunit associated protein 2), *CEP135* (centrosomal protein 135kDa), *COPS5* (COP9 signalosome subunit 5), *DAZAP1* (DAZ associated protein 1), *DERL3* (derlin 3), *DVL2* (dishevelled segment polarity protein 2), *EDF1* (endothelial differentiation-related factor 1), *FZR1* (fizzy/cell division cycle 20 related 1), *GTF3C4* (general transcription factor IIIC, polypeptide 4), *HBS1L* (HBS1-like translational GTPase), *HP1BP3* (heterochromatin protein 1, binding protein 3), *IFT46* (intraflagellar transport 46), *LCK* (LCK proto-oncogene, Src family tyrosine kinase), *LOC145474* (uncharacterized LOC145474), *MAU2* (MAU2 sister chromatid cohesion factor), *MRPL39* (mitochondrial ribosomal protein L39), *NEDD1* (neural precursor cell expressed, developmentally down-regulated 1), *NFYA* (nuclear transcription factor Y, alpha), *PHC2* (polyhomeotic homolog 2), *PIP4K2B* (phosphatidylinositol-5-phosphate 4-kinase, type II, beta), *PLEKHM2* (pleckstrin homology domain containing, family M (with RUN domain) member 2), *PRRG1* (proline rich G-carboxyglutamic acid 1), *RAB1B* (member RAS oncogene family), *RANBP1* (RAN binding protein 1), *REST* (RE1-silencing transcription factor), *RHOD* (ras homolog family member D), *SCARNA7* (small Cajal body-specific RNA 7), *SFR1* (SWI5-dependent recombination repair 1), *STAT3* (signal transducer and activator of transcription 3 (acute-phase response factor)), *SYF2* (SYF2 pre-mRNA-splicing factor), *SZT2* (seizure threshold 2 homolog), *TAPBP* (tapasin), *TMEM185B* (transmembrane protein 185B), *TMEM200A* (transmembrane protein 200A), *TMEM237* (transmembrane protein 237), *TNFRSF19* (tumor necrosis factor receptor superfamily, member 19), *TYW1* (tRNA-yW synthesizing protein 1 homolog), *UPF2* (UPF2 regulator of nonsense transcripts homolog), *USP13* (isopeptidase T-3), *VGLL2* (vestigial-like family member 2), *ZNF8* (zinc finger protein 8).

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