здібностей усіх керівників, менеджерів та фахівців установ і організацій. Однак подібні тренінги та курси не можуть вирішити проблему, оскільки для розвитку стійких навичок креативності необхідно використовувати спеціальні програми з підготовки викладачів, тренерів та керівників організацій з високим рівнем розвитку креативності і запроваджувати їх у навчальні плани ВНЗ.

У зв'язку з чим виникає необхідність розвивати креативність як основу професійних компетенцій на протязі всього періоду професійної діяльності менеджерів,та результатом успішного стане нова організаційна модель креативної організації, яка постійно модернізується, самонавчається та продукує інновації на основі управління креативною діяльністю і тим самим забезпечує собі успіх у жорсткій конкурентній боротьбі при несподіваних змінах зовнішнього середовища.

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# МЕДИЧНІ НАУКИ

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## HEDGEHOG PATHWAY SIGNALING IS ASSOCIATED WITH SURVIVAL IN BREAST CANCER

Hedgehog pathway is one of the major developmental pathways in a variety of multicellular organisms from flies to humans [1]. Though its components are also involved in a number of postnatal developmental processes, the hedgehog pathway is mostly inactive in the adult organism. However, aberrant Hedgehog signaling has been linked to numerous types of cancers and several components of the pathway are either proto-oncoproteins or tumor suppressors [1].

We studied effect of differential expression of genes involved in Hedgehog signaling on survival in breast cancer patients. We performed the Kaplan-Meier survival analysis using an online Kaplan-Meier plotter at https://kmplot.com/ that is capable to assess the effect of 54k genes on survival in 21 cancer types. The tool is used for discovery and validation of gene biomarkers of survival in cancer based on meta-analysis of massive cancer databases [2]. Sources for the databases include GEO, EGA, and TCGA. We performed the analysis of 2032 patients with breast cancer for whom clinical data was available for analysis in the databases.

We found, that change of gene expression of a number of components of the Hedgehog pathway is associated with an alteration in survival in breast cancer patients. STK36 is a serine/threonine protein kinase which plays an important role in the Hedgehog pathway by positively regulating activity of zinc-finger GLI transcription factors GLI1, GLI2 and GLI3 [3]. GLI transcription factors have important roles in intracellular signaling cascade, acting as the main mediators of the Hedgehog signaling pathway [4]. GLI1 could act as transcriptional inhibitor as well as an activator [4].

We found that high expression of STK36 promotes survival in breast cancer (Fig. 1), with upper quartile survival 25 months in the low expression cohort vs. 69 months in the high expression cohort.

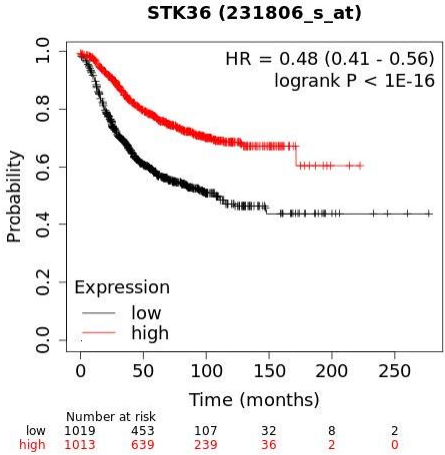


*Figure 1*. **Effect of the expression of STK36 gene on the survival in breast cancer patients.**

Similarly, high expression of GLI2 increases survival (Fig. 2), with 29 months in the low expression cohort vs 52 months in the high expression cohort in the upper quartile.

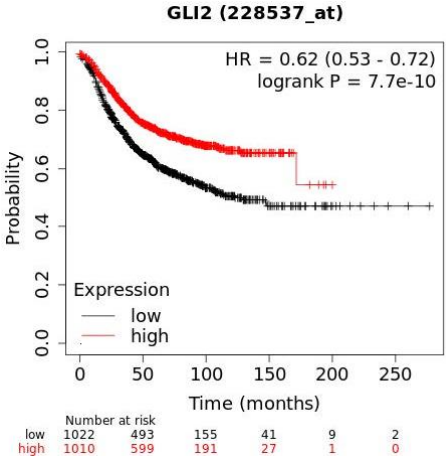


*Figure 2*. **Effect of the expression of GLI2 gene on the survival in breast cancer patients.**

Interestingly, low or high expression of GLI1 or GLI3 did not have a significant effect on the survival of the patients with breast cancer (Fig. 3).

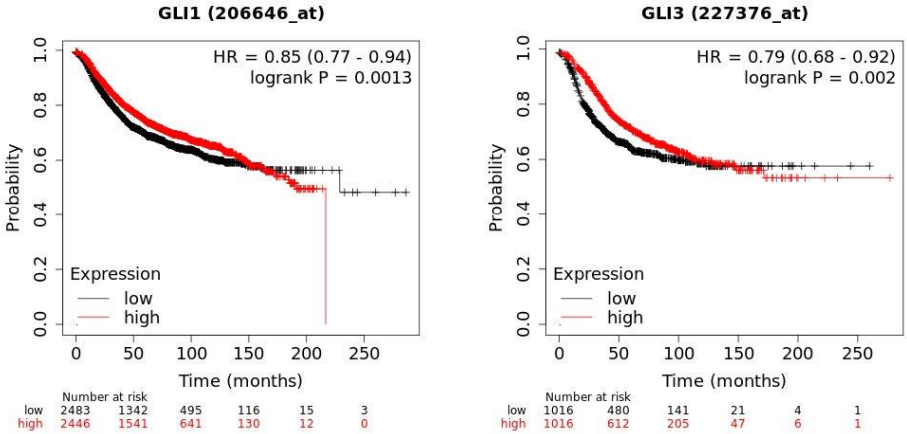


*Figure 3.* **Effect of the expression of GLI1 and GLI3 genes on the survival in breast cancer patients.**

The expression of STK36 was significantly positively correlated with the expression of each of the GLI genes (Table 1).

*Table 1.*

**Correlation between expression of STK36 and GLI1, GLI2, and GLI3.**

| Affymetrix ID | 231806_s_at | 206646_at | 228537_at | 227376_at |
|---|---|---|---|---|
| **231806_s_at** | 1 (p<1E-04) | | | |
| **206646_at** | 0.387 (p<1E-04) | 1 (p<1E-04) | | |
| **228537_at** | 0.3526 (p<1E-04) | 0.5628 (p<1E-04) | 1 (p<1E-04) | |
| **227376_at** | 0.393 (p<1E-04) | 0.2758 (p<1E-04) | 0.2687 (p<1E-04) | 1 (p<1E-04) |

GLI2 protein regulates WNT signaling pathway that consists proteins that pass signals into a cell through cell surface receptors. Of the WNT genes, high expression of WNT3 and WNT8A was favorable for survival of breast cancer patients (Fig. 4).

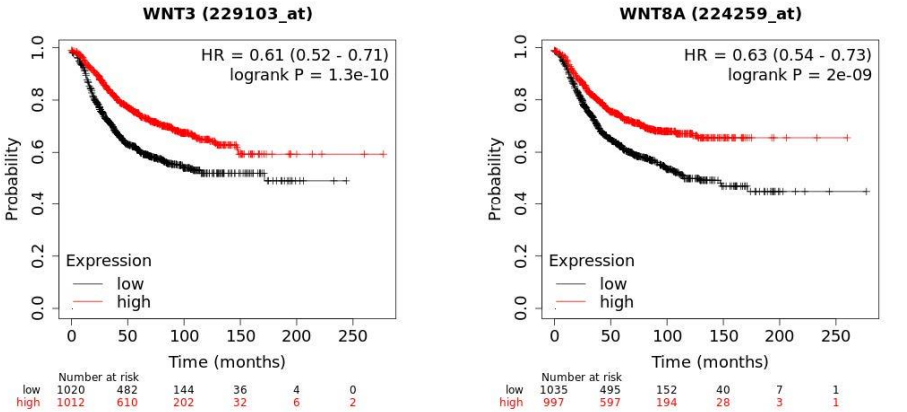


*Figure 4.* **Effect of expression of the WNT3 and WNT8A genes on the survival in breast cancer patients.**

BTRC (Beta-Transducin Repeat Containing E3 Ubiquitin Protein Ligase) is another important component of Hedgehog signaling. It is a component of the ubiquitin protein ligase complex called SCFs (SKP1-cullin-F-box), which functions in phosphorylation-dependent ubiquitination. The BTRC product protein was shown to regulate multiple cellular processes by mediating the degradation of various targets including phosphorylated NFKBIA, targeting it for degradation and thus activating nuclear factor kappa-B [5]. Cell cycle regulators constitute a major group of substrates of the BTRC product protein activity. In our analysis, the upper quartile survival in the low expression cohort was 25 months, while in the high expression cohort it was 61 months.

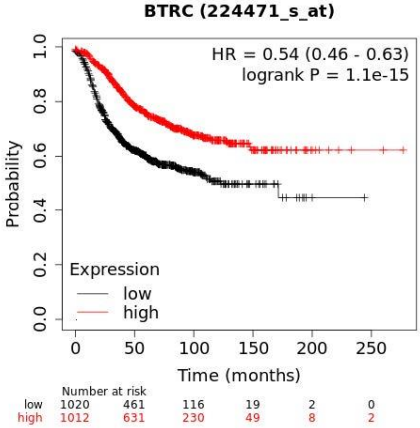


*Figure 5.* **Effect of expression of the BTRC gene on the survival in breast cancer patients.**

After correction for multiple testing, the effect of high or low expression of genes DHH, SHH, SMO, SUFU, WNT1, WNT10B, WNT2, WNT4, WNT8B on the survival in the breast cancer patients did not reach statistical significance.

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