Our project was focusing to clarify the potential biological role of epidermal growth factor receptor (EGFR) in human colorectal and lung adenocarcinoma as well as in human melanoma. According to the workplan, we applied cell lines with different molecular background that represent the most common alterations of EGFR-pathway. We applied different in vitro and in vivo models to measure antitumor activity of target based modalities alone and in combinations.

In the first year we served a proof that BRAF-mutant melanoma cells proved to be sensitive against EGFR-specific tyrosine-kinase inhibitor (TKI) treatment, while NRAS-mutant and wild type NRAS-BRAF-expressing showed relative resistance. Moreover, EGFR-TKI-strategy could enhance the effect of vemurafenib in BRAF-mutant melanoma. Our preclinical data suggest that EGFR is a potential target in the therapy of BRAF-mutant malignant melanoma; however, more benefits could be expected from irreversible EGFR-TKIs and combined treatment settings. Our paper is recently under review; however it is not yet accepted.

In another closely related study we investigated the response to prenylation inhibition (zoledronic acid) in thirteen human melanoma cell lines with known BRAF, NRAS and PTEN mutational status. This paper was accepted for publication, with fellow researcher as a co-author (Garay T, Kenessey I, Molnár E, Juhász É, Réti A, László V, Rózsás A, Dobos J, Döme B, Berger W, Klepetko W, Tóvári J, Tímár J, Hegedűs B. Prenylation inhibition-induced cell death in melanoma: reduced sensitivity in BRAF mutant/PTEN wild-type melanoma cells. PLoS One. 2015 Feb 3;10(2):e0117021. doi: 10.1371/journal.pone.0117021. eCollection 2015.).

We examined the potential role of prenylation inhibition in the treatment of non-small cell lung cancer (NSCLC), we detected genotype-dependent response: in proliferation cell lines with wild type KRAS proved to be sensitive, while KRAS-mutant cells were resistant. Nevertheless, zoledronic acid inhibited the migration of all cell line, which suggests the role of non-KRAS small G-proteins in the signalization of cell migration. Our paper was accepted for publication (Kenessey I, Kói K, Horváth O, Cserepes M, Molnár D, Izsák V, Dobos J, Hegedűs B, Tóvári J, Tímár J. KRAS-mutation status dependent effect of zoledronic acid in human non-small cell cancer preclinical models. Oncotarget. 2016 Oct 21. doi: 10.18632/oncotarget.12806.) with the participation of the applicant as a first author.

As a co-author we have an accepted paper, which analyzed bone metastasis of NSCLC with known KRAS-status. (Lohinai Z, Klikovits T, Moldvay J, Ostoros G, Raso E, Timar J, Fábián K, Kovalszky I, Kenessey I, Aigner C, Renyi-Vamos F, Klepetko W, Hegedus B, Dome B. KRAS-mutation incidence and prognostic value are metastatic site-specific in lung adenocarcinoma: poor prognosis in patients with KRAS-mutation and bone metastasis. Scientific Reports; accepted for publication in 16th of November, 2016).

In our colorectal panel we tested the in vitro anti-proliferative effect of gefitinib: except one cell line with wild type KRAS-BRAF, significant inhibition was appeared. Note that in our assay this was the only cell line that showed sensitivity against EGFR-specific monoclonal antibody. In combination, zoledronic acid increased the effect of gefitinib. Similarly to NSCLC, zoledronic acid did not induce significant apoptosis, rather the blockade of cell cycle caused the anti-cancer effect. Only one cell line migrated in Boyden-chamber. However, neither gefitinib nor zoledronic acid influenced migratory capacity of that line.

In a side project we analyzed the expression of p16 in 67 oral squamous cancers, and compared to routine clinicopathologic parameters. From surgical samples tissue microarray blocks were prepared and expression of p16 as well as other molecular markers (p53, Ki67, EGFR) were studied. In contrast to previous studies on HNSCC, with the exception of recurrence, the expression of p16 was not found associated to clinicopathologic parameters. The expression of p53 and EGFR significantly correlated to each other. We concluded that traditional molecular categorization of HNSCC could not be completely adaptable to Hungarian samples. Potential coexposition of common etiological factors (e.g. HPV, smoking, alcohol) could blur borders between distinct categories. This paper is accepted for publication in Hungarian, with fellow researcher as a senior author (Vánkos JB, Piurkó V, Suba Z, Németh Z, Tímár J, Kenessey I. The prognostic role of expression of p16 tumor suppressor gene in Hungarian patients with oral squamous cell carcinoma. Magy Onkol. 2015 Dec 10;59(4):352-359. Epub 2015 Oct 25.).

Summarizing our publication activity, we have four accepted papera, and two papers are under review. In the department three gradual students and a PhD-student associated with this project, and one of them will perform her results in the annual conference of student researchers (TDK) in the Semmelweis University.