L-21
GROUP OF CANCER IMMUNOTHERAPY AND MOLECULAR EPIDEMIOLOGY OF VIRUS INFECTIONS

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The group is composed of the team of Laboratory of Molecular and Tumor Virology (headed by Ruth Tachezy) and Laboratory of Immunotherapy (headed by Michal Šmahel). While the research of the team led by Ruth Tachezy focuses mainly on the molecular epidemiology of anelloviruses, polyomaviruses, herspesviruses, and papillomaviruses with the aim of evaluating the involvement of these viruses in different benign and malignant disorders, the research of the group of Michal Šmahel is focused on the optimization of combined cancer immunotherapy. The research of both teams complements each other. Finding the association of viruses with particular disorders opens the possibility of searching for diagnostic, therapeutic, preventive, and prognostic markers of these diseases. Therapeutic markers are being further explored in both *in vitro* and *in vivo* model systems and combined immunotherapy is further evaluated.

In the National Institute of Virology and Bacteriology, the team will explore the role of microbiome/virome in the pathogenesis of autoimmune and malignant diseases linked to human papillomaviruses and polyomaviruses. In the laboratory, the pipeline for the preparation and analysis of viromes was implemented and proved to allow the reliable detection of a wide range of viruses with different characteristics[1]. The method will be further optimized and utilized for virome analyses in patients with autoimmune disorder – psoriasis – since our previous research has shown that these patients on long-term treatment with biologics might be at increased risk of acquisition or reactivation of numerous viral infections[2].

The second direction of research will extend our recent findings where we focused on the analyses of the tumor microenvironment (TME) of head and neck squamous cell carcinomas (HNSCC; Fig. 1) in relation to their etiology to explain the prognostic advantages of patients with HPV-associated tumors. In the laboratory, mass cytometry for solid tumors[3] and multiplex multispectral fluorescent immunohistochemistry were implemented for the complex analyses of TME. In previous studies with the help of new techniques, we have analyzed TME of HNSCC of viral and non-viral etiology and detected PD1+CD8+ cells as an independent positive prognostic marker for patients with HNSCC[4]. Furthermore, we also focused on tumor-associated macrophages (TAMs), which represent the main immune population in TME with a controversial influence on the prognosis. We have observed more pro-tumorigenic M2 TAMs and higher mRNA expression of M2 markers – cluster of differentiation 163 (CD163), ARG1, and prostaglandin endoperoxide synthase 2 (PTGS2) in HPV non-associated tumors and M1 marker nitric oxide synthase 2 (NOS2) in an HPV+ group. The expression of ARG1 mRNA was revealed to be a negative prognostic factor for the overall survival of HNSCC patients[5].

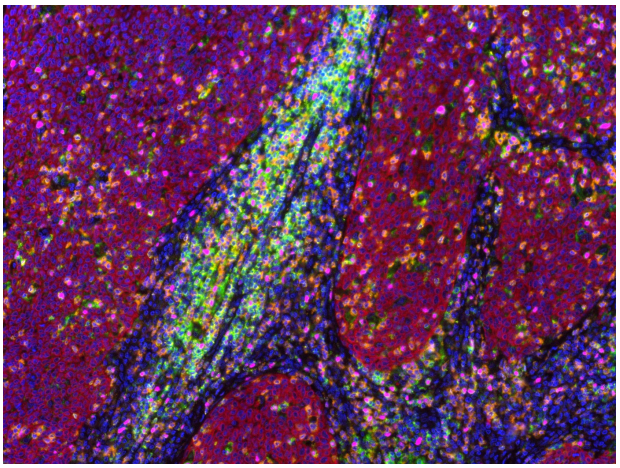

Fig. 1. **Analysis of the head and neck squamous cell carcinoma environment.** Multispectral fluorescent staining of formalin fixed paraffin embedded tumor samples (green – CD4, orange – CD8, yellow – CD3, magenta – FOXP3, red – panCytokeratin AE1/AE3, blue – DAPI).

In mouse models of HPV-induced tumors with reversible or irreversible MHC class I downregulation established in our laboratory, we studied combined immunotherapy aimed at repolarization of protumor M2 TAMs into anti-tumor M1 TAMs and found resistance to this treatment in tumors with irreversible MHC class I downregulation[6].

Within the project we will cooperate with the group of Sandra Huerfano from the Faculty of Science, Charles University on antiviral innate immune responses to human polyomaviruses; Pavel Dřevínek group from the 2nd Medical Faculty, Charles University on anelloviruses dynamics; Marián Hajdúch group at the Faculty of Medicine and Dentistry, Palacký University on the HPV-specific antibody prevalence; and Radin Nencka group from The Institute of Organic Chemistry and Biochemistry, Czech Academy of Science, on STING activation.

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