



Katedra/Zavod za molekularnu medicinu i biotehnologiju

Prof. dr. sc. Siniša Volarević

Sveučilište u Rijeci • Medicinski fakultet

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27. lipnja 2016.

PREDMET: Poziv na predavanje

Poštovani,

Zadovoljstvo nam je pozvati Vas i Vaše suradnike na predavanje koje će održati:

Dr. Jonathan D. Ashwell

Laboratory of Immune Cell Biology

National Cancer Institute

National Institutes of Health, Bethesda, Maryland, U.S.A.

Naslov predavanja:

T cell p38: a therapeutic target in autoimmunity, inflammation, and cancer

Predavanje će se održati u **utorak, 05. srpnja 2016.** u **Vijećnici** Medicinskog fakulteta Sveučilišta u Rijeci s početkom u **15.00 sati**.

Organizatori:

- doc. dr. sc. Ivana Munitić, Odjel za biotehnologiju, Sveučilište u Rijeci
- prof. dr. sc. Siniša Volarević, Zavod za molekularnu medicinu i biotehnologiju, Medicinski fakultet Sveučilišta u Rijeci

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Kratak životopis predavača:

Dr. Ashwell received his M.D. from Columbia University College of Physicians and Surgeons. He trained in internal medicine at Presbyterian Hospital in New York City. Following a postdoctoral fellowship in immunology in the laboratory of Dr. Ronald Schwartz (National Institute of Allergy and Infectious Diseases/NIH), Dr. Ashwell joined the NCI as a principal investigator. He was named Chief of the Laboratory of Immune Cell Biology in 1992.

Dr. Ashwell's laboratory focuses on areas in immunology and cell biology that fall broadly in the category of signal transduction. These include protein modifications and interactions downstream of the T cell antigen receptor (TCR), TNFR superfamily members, and Toll-like receptors, and the role of endogenous glucocorticoids in regulating thymocyte development and innate immune responses.

Dr. Ashwell's laboratory recently established that T cells possess a unique mechanism for TCR-mediated activation of p38. This alternative pathway is required for normal pro-inflammatory cytokine production, and is activated in tumor-infiltrating T cells in certain inflammatory neoplasms. Efforts are being made to characterize and target this pathway for therapeutic benefit.

Sažetak predavanja:

Pancreatic ductal adenocarcinoma (PDAC) is a highly aggressive neoplasm characterized by a marked fibro-inflammatory microenvironment, the presence of which can promote both cancer induction and growth. Therefore, selective manipulation of local cytokines is an attractive if unrealized therapeutic approach. T cells possess a unique mechanism of activation of p38 MAPK downstream of T cell receptor (TCR) engagement by phosphorylation of Tyr-323 (pY323). This alternative p38 activation pathway is required for pro-inflammatory cytokine production. Here we show in human PDAC that a high percentage of infiltrating pY323+ T cells was associated with large numbers of TNF α and IL-17-producing CD4+ tumor-infiltrating lymphocytes (TIL) and aggressive disease. The growth of murine pancreatic tumors was inhibited by genetic ablation of the alternative p38 pathway, and transfer of wild type CD4+ T cells but not those lacking the alternative pathway enhanced tumor growth in T cell-deficient mice. Strikingly, a plasma membrane-permeable peptide derived from Gadd45 α , the naturally-occurring inhibitor of p38 pY323+, reduced CD4+ TIL production of TNF α , IL-17A, IL-10, and secondary cytokines, halted growth of implanted tumors, and inhibited progression of spontaneous K-ras-driven adenocarcinoma in mice. Thus, TCR-mediated activation of CD4+ TIL results in alternative p38 activation and production of pro-tumorigenic factors, and can be targeted for therapeutic benefit.