SYNERGISTIC ACTION OF 9-CIS RETINOIC ACID AND MITOTANE IN A H295R ADRENOCORTICAL CANCER XENOGRAFT MODEL

Zoltán Nagy[1], Kornélia Baghy[2], Peter M. Szabó[3], Ilona Kovalszky[2], Pál Perge[1], Attila Patócs[4], Károly Rácz[1], Peter Igaz[1]

[1]2nd Department of Medicine, Semmelweis University, H-1088 Budapest, Hungary, [2]1st Department of Pathology and Experimental Cancer Research, Semmelweis University, H-1088 Budapest, Hungary, [3]Biometric Research Branch, Division of Cancer Treatment and Diagnosis, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA, [4]"Lendület-2013" Hereditary Endocrine Tumours Research Group, Hungarian Academy of Sciences and Semmelweis University, H-1088 Budapest, Hungary

INTRODUCTION

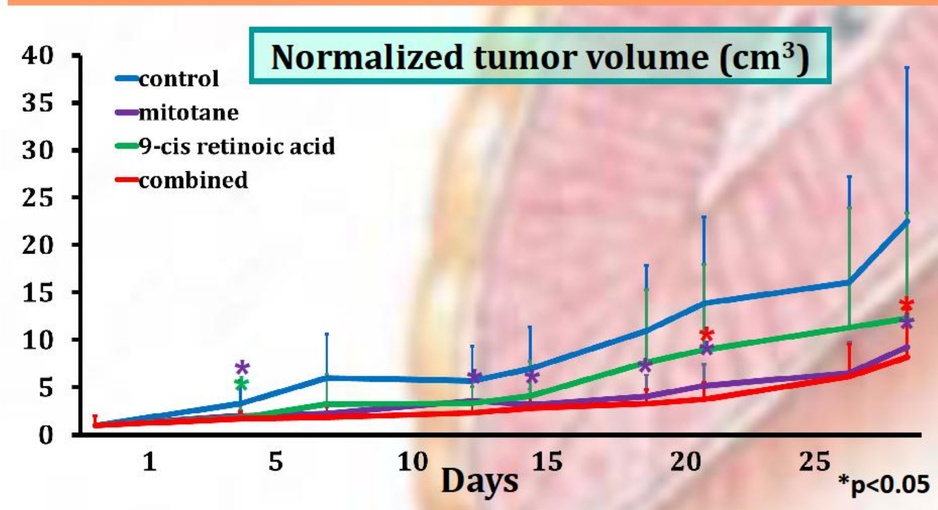
Current drug treatment options for adrenocortical carcinoma (ACC) are rather limited and intensive efforts are going on to find novel effective agents. In our previous functional genomics study, retinoid signaling via the retinoid X receptor (RXR) was identified as a major pathogenic pathway in ACC and we have demonstrated the *in vitro* activity of 9-cis retinoic acid (9-cisRA) acting via the RXR on NCI-H295R cells and also found that 9-cisRA has antitumoral effects in a small pilot xenograft study.

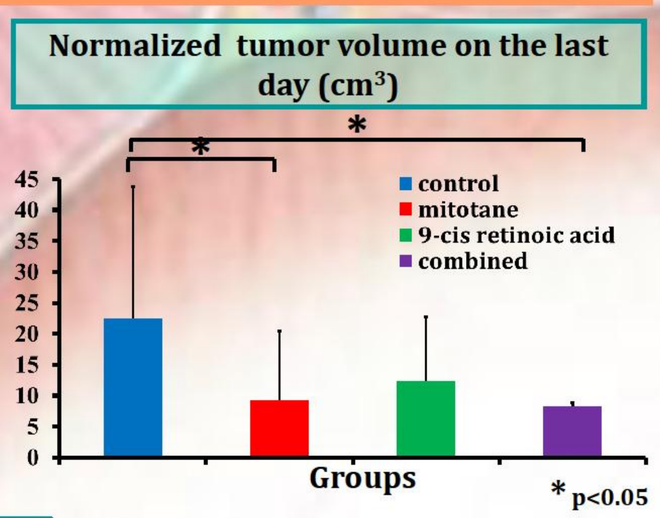
OBJECTIVES

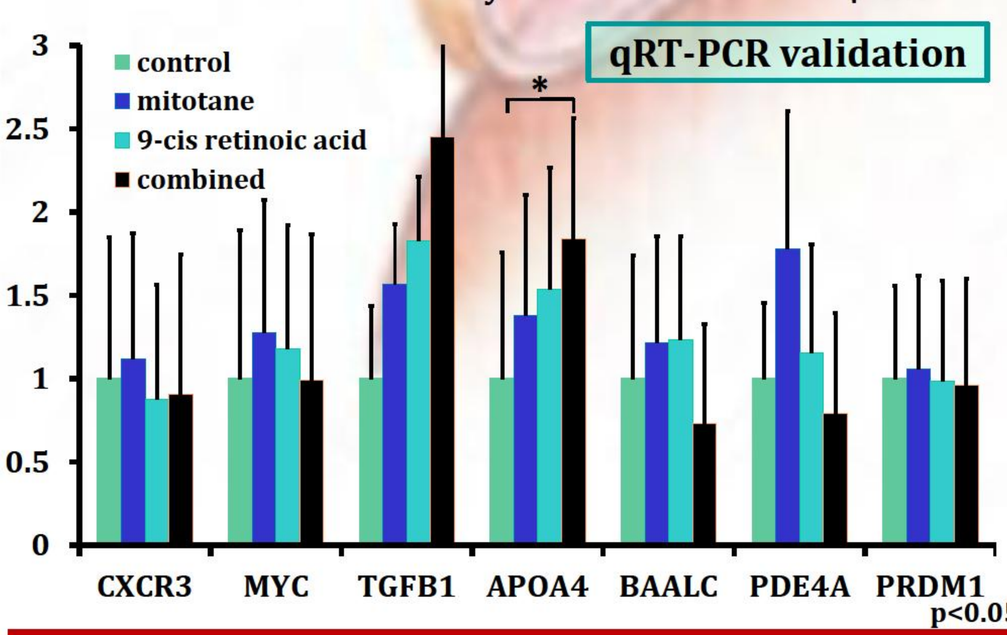
To investigate the antitumoral effect of 9-cisRA and its combination with mitotane in a large-scale xenograft study.

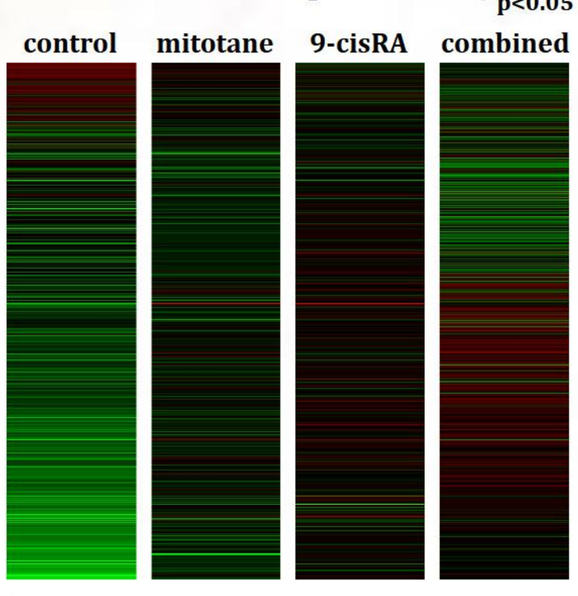
MATERIALS AND METHODS

- **H295R xenografted SCID mice in four group (i. control, corn oil; ii. mitotane, 200 mg/kg; iii. 9-cisRA, 5 mg/kg; iv. combined, 200 mg/kg mitotane + 5mg/kg 9-cisRA)**
- **histology (HE) and immunohistochemistry (Ki-67)**
- **whole genome microarray (Agilent 4x44K)**
- **bioinformatical (Genespring) and pathway analysis (IPA)**
- **validation of genes and miRNAs (qRT-PCR)**









RESULTS

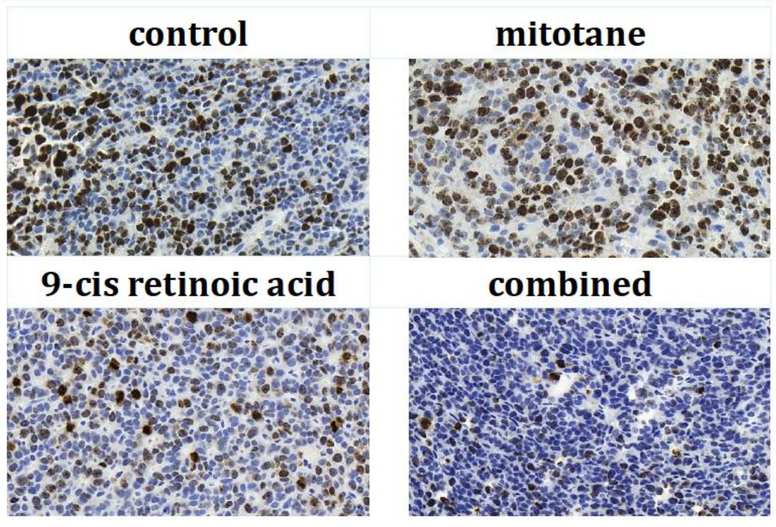
- **The normalized tumor volumes were smaller in each treated groups, but only in the mitotane and the combined treated group reached significant values**
- **Ki-67 index decreased significantly in the 9-cisRA, and combined treatment groups**
- **We have found 483 significant geneexpressional differences between the groups, but only without Benjamin-Hochberg correction**
- **Only APOA4 could be validated by qRT-PCR**
- **From circulating microRNAs selected based on previous studies, *hsa-miR-483-5p* was significantly reduced in the group receiving combined treatment**

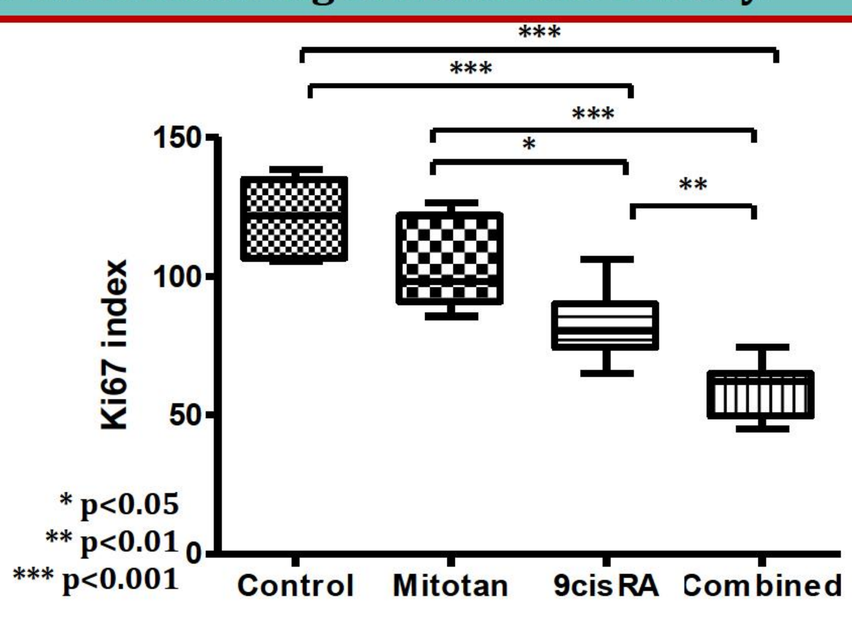
DISCUSSION

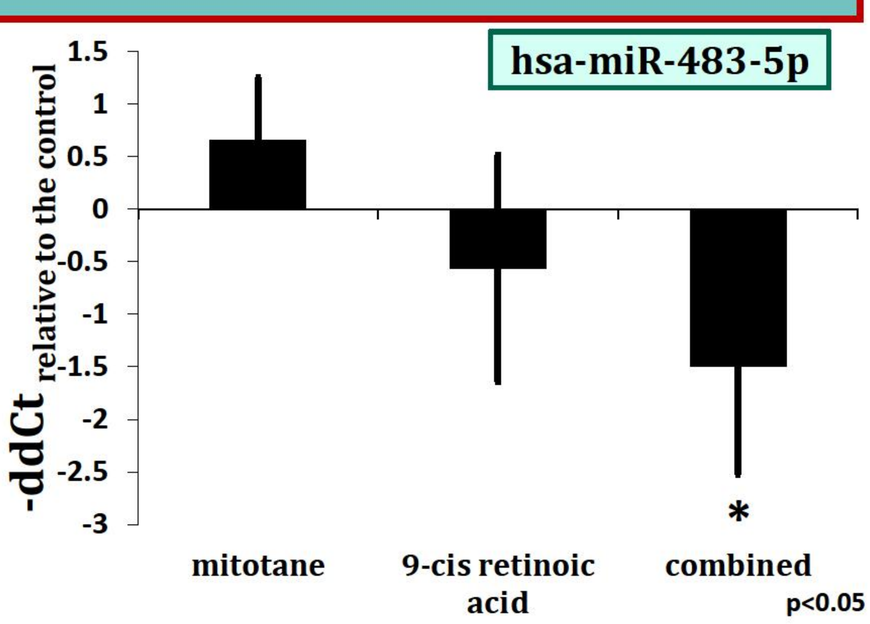
1. Our results show that 9-cisRA might be a helpful additive in the treatment of ACC in combination with mitotane, but its mechanism of action awaits further investigations. Proteomics studies are under way.

2. Circulating microRNAs can be used for the monitoring of treatment efficacy.

Ki-67 proliferation index







17 ECE 4--GP-29
Endocrine tumours
Zoltan Nagy
DOI: 10.3252/pso.eu.17ece.2015
Poster presented at: ECE2015 16-20 May 2015 DUBLIN, IRELAND 17th EUROPEAN CONGRESS OF ENDOCRINOLOGY