DAY 1 SESSIONS
MAY 22, 2019

Immunological Disorders | Auto Immune Diseases | Innate Immunity and Inflammation | Cancer Stem Cells | Tumor Immunology | Neuro Immunology

SESSION CHAIR

Irene Athanassakis
University of Crete, Greece

SESSION INTRODUCTION

Title: Development of a heat shock protein (HSP) neo-antigen vaccine for the treatment of diffuse intrinsic pontine glioma (DIPG)

Ashley S Plant, Children's Hospital Orange County, USA

Title: Neurometabolic evidences for diabetes and intermittent explosive disorder: A case report

Ahmet Mithat Tavli, Istanbul University, Turkey

Title: Histone deacetylase inhibition restores expression of hypoxia-inducible protein NDRG1 in pancreatic cancer

Céline Tiffon, National Cancer Institute, France

Title: Citrate export pathway and upregulation of SLC25A1 and ACLY genes in endotoxin/cytokine-induced macrophages

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Title: Traumatic brain injury as a risk factor for dementia: Literature review

Sela Ervina-Anastasia, National and Kapodistrian University of Athens, Greece

Title: Experience of the use of NSC-631570 (UKRAIN) in the treatment of malignant melanoma

Wassil Nowicky, Ukrainian Anti-Cancer Institute, Austria

Title: Effective *in vivo* therapeutic IgG antibody against VP3 of enterovirus 71 with receptor-competing activity

Fang He, Zhejiang University, China

Ashley S Plant et al., Immunol Case Rep 2019, Volume 3

DEVELOPMENT OF A HEAT SHOCK PROTEIN (HSP) NEO-ANTIGEN VACCINE FOR THE TREATMENT OF DIFFUSE INTRINSIC PONTINE GLIOMA (DIPG)

Ashley S Plant[1, 2], Uduman M[3], Castle J[3], Bruell J[3], Taylor T[2], Filbin M[4], Kieran M[4] and **Chi S[4]**
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[2]University of California, USA
[3]Agenus Biotechnologies, USA
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Diffuse intrinsic pontine glioma (DIPG) is a rare and devastating type of brainstem glioma in children which has <1% five year overall survival. Recent molecular studies have shown 80% of these tumors harbor either a histone 3.3 or histone 3.1 K27M mutation. These histone mutations occur predictably with other secondary genetic aberrations including K27M H3.3 with PDGFRA amplifications and K27M H3.1 with ACVR1 mutations. Using NetMHCpan 4.0 and NetMHCpan 3.2 binding algorithms and predictions of immunogenicity, author has identified five shared 27-mer sequences for inclusion in a heat shock neo-antigen vaccine for the treatment of DIPG. Prediction algorithms suggest sequences will cover 96.5% of the class I MHC molecules and 83.9% of the class II MHC molecules in the North American population resulting in 99.5% combined class I and II coverage in the population. The phase I clinical trial for pediatric DIPG is now underway.

BIOGRAPHY

Ashley S Plant is Director of Neuro-Oncology at Children's Hospital Orange County (CHOC) and Associate Professor of Pediatrics at University of California, Irvine, USA. She completed her medical training at Stanford University School of Medicine and her Pediatric residency training at University of California, Los Angeles, USA. She completed her hematology/oncology fellowship at Boston Children's/Dana Farber Cancer Institute in Boston and remained on as a clinical instructor at Harvard Medical School and Neuro-Oncology attending at Dana Farber before becoming Director of Neuro-Oncology at CHOC. Her previous research was under Dr. Glenn Dranoff and Dr. Jerome Ritz in the area of immuno-oncology and her current research focus is in understanding the immunophenotype of pediatric brain tumors and how to extrapolate this information into future early immunotherapy trials for children.

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Ahmet Mithat Tavli, Immunol Case Rep 2019, Volume 3

NEUROMETABOLIC EVIDENCES FOR DIABETES AND INTERMITTENT EXPLOSIVE DISORDER: A CASE REPORT

Ahmet Mithat Tavli
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Background: Despite studies suggesting that increased insulin resistance and higher fasting glucose levels may secondary lead to glucose hypo metabolism in specific brain regions which may contribute to the development of cognitive disturbances during diabetes I-II, the underlying mechanism of diabetes associated impulse control disorders is still unclear. Interestingly, a very recent study has demonstrated that impulse control disorders (especially intermittent explosive disorder) were significantly associated with the diabetes diagnosis. Thus, studies have reported that intermittent explosive disorder and borderline personality are associated with an increase of glucose metabolism in the limbic system and a decrease in prefrontal regions supporting the role of dynamically interacting cortico-subcortical networks. Besides their key role as a pacemaker for cortical centres via purely motoric coordination, lentiform nucleus and pons have been also shown to play a significant role in emotional process in also involving reflexive emotional reactions. This is in line with previous evidences showing that gray matter volume reductions in neocortical regions may be specific to psychiatric disorders. These findings together suggest that a disturbance in connectivity between different brain regions, rather than abnormalities within the separate regions themselves may be responsible for the clinical symptoms of intermittent explosive disorder.

Case: Here author describe a 36 year old man, experience the aggressive outburst symptoms one year after he was diagnosed as type II DM.

BIOGRAPHY

Ahmet Mithat Tavli completed his PhD in Selçuk University, Turkey. He is the Director of Neurology Department of Milas Government Hospital, Turkey. He studied for two years in Florance Nightingale Hospital and studied for two years in Medipol Experimental Laboratory in İstanbul. He has over 20 publications in various journals.

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Céline Tiffon, Immunol Case Rep 2019, Volume 3

HISTONE DEACETYLASE INHIBITION RESTORES EXPRESSION OF HYPOXIA-INDUCIBLE PROTEIN NDRG1 IN PANCREATIC CANCER

Céline Tiffon
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Pancreatic ductal adenocarcinoma affects both men and women and is highly aggressive, with a five-year survival rate of only about 5%. N-Myc downstream regulated gene-1 (NDRG1) is a hypoxia-inducible and differentiation-related protein and candidate biomarker in pancreatic cancer. As NDRG1 expression is lost in high-grade tumors, the effects of the differentiating histone deacetylase inhibitor trichostatin A (TSA) were examined in human pancreatic cancer cell lines representing different tumor grades. Panc-1 (poorly differentiated) and Capan-1 (moderately- to well-differentiated) cells were treated with TSA. Effects were assessed *in vitro* by microscopic analysis, colorimetric assays, cell counts, real-time polymerase chain reaction and western blotting. Treatment of Panc-1 cells over four days with 0.5 μM TSA restored cellular differentiation, inhibited proliferation and enhanced p21Cip1 protein expression. Trichostatin A upregulates NDRG1 mRNA and protein levels under normoxia from day one and by six-fold by day four ($p<0.01$ at all-time points). After 24hrs under hypoxia, NDRG1 expression was further increased in differentiated cells ($p<0.01$). Favorable changes were identified in the expression of other hypoxia-regulated genes. HDAC inhibitors offer a potential novel epi-drug approach for pancreatic cancer by reversing the undifferentiated phenotype and allowing patients to overcome resistance and better respond to conventional treatments. Restoration of NDRG1 expression may represent a biomarker of malignant pancreatic tumors undergoing re-differentiation and redirecting toward a lower tumor grade. The use of the human ductal Panc-1 cell line treated with TSA represents a useful tool to study cellular differentiation through epigenetic mechanisms. Furthermore, lifestyle and environmental factors especially nutrition and chemical exposure, induce effects on human health from gestation and beyond via epigenetic modifications.

BIOGRAPHY

Céline Tiffon obtained her PhD in Tumor Biology from the University of Bern, Switzerland and working on the subject of liver and pancreatic cancers. She carried out Postdoctoral Research at the Cancer Science Division of the University of Southampton, United Kingdom. Her research interests focused on the molecular mechanisms triggered by two licensed HDAC inhibitors in cutaneous T-cell lymphoma with a particular emphasis on cytokine expression. She continued with Postdoctoral Research at the University of Burgundy, France and working on the topic of endocrine disruptors. Currently, she is working as a Scientific Officer at the National Cancer Institute, France.

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Vittoria Infantino et al., Immunol Case Rep 2019, Volume 3

CITRATE EXPORT PATHWAY AND UPREGULATION OF SLC25A1 AND ACLY GENES IN ENDOTOXIN/CYTOKINE-INDUCED MACROPHAGES

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In response to proinflammatory triggers, macrophages undergo metabolic shift to support the bioenergetic and biosynthetic requirements of the cell. Metabolite level changes are largely due to a rewiring of the Krebs cycle following immune cell stimulation. Activated macrophages show an altered Krebs cycle, one consequence of which is the accumulation of citrate. In this context most of citrate is diverted from Krebs cycle and channelled into the "citrate export pathway" consisting in the increase of the export of citrate into cytosol by the mitochondrial citrate carrier (CIC)-encoded by the SLC25A1 gene-followed by its cleavage into acetyl-CoA and oxaloacetate by ATP citrate lyase (ACLY). Citrate export is a consequence of SLC25A1 and ACLY genes upregulation in LPS as well as in TNFα and IFNγ activated macrophages. Remarkably, TNFα and LPS exert their effect via NF-kB sites located in SLC25A1 and ACLY gene promoters. STAT1 is responsible for IFNγ-induced SLC25A1 and ACLY upregulation, as demonstrated by its binding to STAT responsive elements in both gene promoters. What is the fate of exported citrate? Citrate-derived acetyl-CoA is used to synthesize PGE2 and oxaloacetate to produce NADPH needed for NO and ROS. SLC25A1 and ACLY gene silencing or inhibition of CIC or ACLY by different synthetic and natural molecules results in reduction of NO, ROS and PGE2 levels suggesting that the citrate pathway can be a new target to be addressed in inflammation.

BIOGRAPHY

Vittoria Infantino has completed her PhD in Cell Biochemistry and Pharmacology in 2005 studying the transcriptional regulation of the human mitochondrial carrier genes. Further she focused on the mitochondrial carrier gene regulation mechanisms as Post-Doc in the laboratory of Prof. Iacobazzi, Bari. She moved to University of Basilicata in 2008 where she is now Research Scientist in Cellular Biology. Currently, her research is focused on the "Relationship between gene regulation and metabolism in physiological and pathological conditions, with particular interest in cancer and inflammatory diseases". To deepen these topics, she performed a stay at the Trinity College Dublin-Biomedical Science Institute- School of Biochemistry-laboratory of Professor Luke O'Neill. She has 36 publications in peer reviewed international journals with H-index 19 and has been serving as an Editorial Board Member to reputed Journals.

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Sela Ervina-Anastasia, Immunol Case Rep 2019, Volume 3

TRAUMATIC BRAIN INJURY AS A RISK FACTOR FOR DEMENTIA: LITERATURE REVIEW

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National and Kapodistrian University of Athens, Greece

Dementia is one of the most serious complications of Traumatic Brain Injury. This disease can be mainly caused by road accidents and falls, clearly because the effect of the force on the brain is stronger and the changes in brain function are more radical. A retrospective cohort study which was approved by the University of California, San Francisco and Human Research Committee and was performed from January 1, 2005, through December 31, 2011 (follow-up, 5-7 years), found that among 51799 patients with trauma, 4361 developed dementia compared with 6610 patients with non-TBI trauma. The correlation of traumatic brain injury and dementia is evident especially in the larger age groups of the population. In addition, several epidemiological studies suggest that traumatic brain injury (TBI) is a risk factor for dementia, particularly for Alzheimer's disease (AD), although a significant association has not always been detected. There is evidence that in mild and severe traumatic brain injuries most patients have emerged after year's dementia in contrast to those patients who just had a minor injury. In conclusion, traumatic brain injury can be associated to a significant degree with the risk of developing dementia especially to the people with increased risk. Given the high rates of TBI to the general population serious dementia prevention measures should be taken in such incidents and clearly to carry out more studies and even longer in order to fully understand the mechanisms that affect between traumatic brain injury and dementia.

BIOGRAPHY

Sela Ervina–Anastasia studied Nursing at the University of Western Attica, Greece and now she is a postgraduate student in the postgraduate program of the National Kapodistrian University of Athens, Greece. Her specialization is Surgical Nursing. She has two publications in international journals and has participated in three world medical conferences.

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Wassil Nowicky et al., Immunol Case Rep 2019, Volume 3

EXPERIENCE OF THE USE OF NSC-631570 (UKRAIN) IN THE TREATMENT OF MALIGNANT MELANOMA

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Introduction: Malignant melanoma is one of the most deadly skin cancers. At the early stages of melanoma development the patients are treated surgically, but the advanced disease is virtually incurable. Numerous clinical investigations have been conducted to improve efficiency of melanoma treatment. Nevertheless, biologists and clinicians continue working on new possible methodology of treatment and keep up to search new therapeutic agents as drug resistance is a commonly observed problem. NSC-631570 is an anti-cancer agent created on the basis of alkaloids from the plant *Chelidonium majus*. For more than 20 years NSC-631570 had been used for cancer treatment. Monotherapy and combined application of NSC-631570 are successfully used for the treatment of malignant melanoma since 1996.

Aim: The purpose of this study is to describe the experience of the use of NSC-631570 in the treatment of malignant melanoma and to disclose of some mechanisms of the preparation action.

Materials & Methods: B-16 melanoma cells of C57BL/6 mice were kindly supplied by the Bank of Cell Cultures and Transplantable Experimental Tumors of R.E. Kavetsky Institute of Experimental Pathology, Oncology and Radiobiology (Kyiv, Ukraine) MM-4 cells, exhibiting a relatively low metastatic potential, were established from the primary lesion of subcutaneously injected B16 cells. MM-4M2 cell lines established by two sequential passages of lung metastases of MM-4 cells after intravenous injection are highly metastatic. Cells were cultured *in vitro* in Dulbecco's Modified Eagle Medium (DMEM; Sigma, St. Louis, MO, USA) supplemented with 10% fetal calf serum (FCS), penicillin (100 U/ml) and streptomycin (100 µg/ml) at 37°C in 5% CO2. To determine the effects of NSC-631570 on cell viability, cells were treated with NSC6-31570 at the different concentrations (1.6, 3.2, 6.4, 12.5, 25, 50, 100 and 200 µg/ml) for 24hrs and 48hrs periods. Cell viability was determined by MTT test. HMGB1 level in conditioned medium was evaluated by ELISA. TAP mRNA was examined by RT-PCR and TAP protein in ELL Lysates was determined by Western blot.

Results: Treatment of B16 melanoma cells with NSC-631570 at apoptogenic concentrations induced dose-dependent tumor cell death accompanied by dose dependent release of HMGB1, more in high-metastasizing cells. The levels of HMGB1 in the cell probes treated with the drug exhibited strong correlation with the levels of cell death. Author found a significant increase in the number of mRNA for TAP1 in melanoma B16 cells after treatment with NSC-631570 at the non-apoptogenic concentration, whereas only a trace quantity of the TAP1 mRNA was found in untreated cells: Treatment of melanoma B16 cells with NSC-631570 increased expression of mRNA encoding TAP2 by ~3-fold ($p < 0.05$); increase of TAP1-proteins expression was confirmed by Western blot analysis. It is known that correction of TAP1 and/or TAP2 defects in B16 mouse melanoma enhances the cell surface expression of MHC class I molecules and significantly reduces the rate of subcutaneous tumor growth and pulmonary metastatic burden.

Conclusion: Thus, NSC-631570 exhibits powerful therapeutic effect in the treatment of malignant melanoma. The drug not only selectively kills tumor cells but also recovers the role of the dying primary tumor as an effective immunogenic hub.

Recent Publications:

1. Funel N, Costa F, Pettinari L, Taddeo A, Sala A, Chiriva-Internati M and Dalle-Donne I (2010) Ukrain affects pancreas cancer cell phenotype *in vitro* by targeting MMP-9 and intra-/extracellular SPARC expression. Pancreatology, 10(5): 545-552.
2. M Skivka L, G Fedorchuk O, M Susak Y, Y Susak M, M Malanchuk O, P Rudyk M and Nowicky W (2015) Physical activity interferes with the immunomodulatory effect of the antineoplastic drug NSC631570. Current pharmaceutical biotechnology 16(1): 49-59.
3. Rudyk M, Fedorchuk O, Susak Y, Nowicky Y and Skivka L (2016) Introduction of antineoplastic drug NSC631570 in an inpatient and outpatient setting: Comparative evaluation of biological effects. Asian Journal of Pharmaceutical Sciences 11(2): 308-317.
4. Jesionek W, Fornal E, Majer-Dziedzic B, Móricz Á M, Nowicky W and Choma I M (2016) Investigation of the composition and antibacterial activity of Ukrain™ drug using liquid chromatography techniques. Journal of Chromatography A 1429: 340-347.

BIOGRAPHY

Wassil Nowicky is the Director of Nowicky Pharma and President of the Ukrainian Anti-Cancer Institute, Austria. He is the Inventor of the anti-cancer preparation on the basis of celandine alkaloids "NSC-631570". He is the author of over 300 scientific articles dedicated to cancer research. He is a real member of the New York Academy of Sciences, member of the European Union for applied immunology and of the American Association for scientific progress. He is the Honorary Doctor of the Yanka Kupala State University in Grodno, Doctor Honoris Causa of the Open International University on Complex Medicine in Colombo, Honorary Member of the Austrian Society. He has received the award for Merits of National Guild of Pharmacists of America, the award of Austrian Society of Sanitary, Hygiene and Public Health Services and others.

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Fang He et al., Immunol Case Rep 2019, Volume 3

EFFECTIVE *IN VIVO* THERAPEUTIC IGG ANTIBODY AGAINST VP3 OF ENTEROVIRUS 71 WITH RECEPTOR-COMPETING ACTIVITY

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Passive immunization is an effective option for treatment against hand, foot and mouth disease caused by EV71, especially with cross-neutralizing IgG monoclonal antibodies. In this study, an EV71-specific IgG2a antibody designated 5H7 was identified and characterized. 5H7 efficiently neutralizes the major EV71 genogroups (A, B4, C2 and C4). The conformational epitope of 5H7 was mapped to the highly conserved amino acid position 74 on VP3 capsid protein using escape mutants. Neutralization with 5H7 is mediated by the inhibition of viral attachment, as revealed by virus-binding and post-attachment assays. In a competitive pull-down assay with SCARB2, 5H7 blocks the receptor-binding site on EV71 for virus neutralization. Passive immunization of chimeric 5H7 protected 100% of two-week-old AG129 mice from lethal challenge with an EV71 B4 strain for both prophylactic and therapeutic treatments. In contrast, 10D3, a previously reported neutralizing antibody that takes effect after virus attachment, could only confer prophylactic protection. These results indicate that efficient interruption of viral attachment is critical for effective therapeutic activity with 5H7. This report documents a novel universal neutralizing IgG antibody for EV71 therapeutics and reveals the underlying mechanism.

BIOGRAPHY

Fang He is from Institute of Preventive Veterinary Medicine, College of Animal Sciences of Zhejiang University, China. Her research mainly focuses on vaccine and antibody development against multiple human and animal infectious diseases, including influenza, HFMD and major swine diseases. She has published over 40 research articles in SCI top journals mostly as first or corresponding author in Journal of Virology and Journal of Proceedings of the National Academy of Sciences of the United States of America.

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