Colossal Facet
Innovation.. Research.. Science

Organizing Scientific Committee and Keynote Speakers

Ciro Isidoro
Head of the Organizing Committee
Università del Piemonte Orientale (Italy)

Omar M. Amin *Parasitology Center Inc. (USA)*
Danny Dhanasekaran *University of Oklahoma Health Sciences Center (USA)*
Marc Diederich *Seoul National University (South Korea)*
John DiGiovanni *University of Texas at Austin (USA)*
Richard Eckert *University of Meryland School of Medicine (USA)*
Judita Kinkorová *University Hospital Pilsen (Czech Republic)*
Tao Lu *Indiana University School of Medicine (USA)*
Yong-Sang Song *Seoul National University (South Korea)*
Gloria Su *Columbia University (USA)*
Young-Joon Surh *Seoul National University (South Korea)*
Stefano Tiziani *University of Texas (USA)*

Honorary Lecture

Thomas N. Seyfried
Biology Department at Boston College (USA)

Info and Registration

at **http://colossalfacet.com/cancer-conference/**

Proceedings will be published in:

Journal of Cancer Metastasis and Treatment
JCMT

Invited Speakers

Luca Colucci-D'Amato, *University of Campania "L. Vanvitelli", (I)*
Michael Firer, *Ariel University (Israel)*
Noriko Gotoh, *Kanazawa University (Japan)*
Bernd Kaina, *Institut für Toxikologie, Universitätsmedizin (Germany)*
Seong-Jin Kim, *Seoul National University (South Korea)*
Jung Weon Lee, *Seoul National University (South Korea)*
Carol Y. Lin, *Centers for Disease Control and Prevention (USA)*
Jinsong Liu, *MD Anderson Cancer Center (USA)*
Beverly A. Mock, *National Cancer Institute (USA)*
Hye-Kyung Na, *Sungshin Women's University (South Korea)*
Agarwal Rajesh, *University of Colorado Cancer Center (USA)*
Yi Sun, *University of Michigan (USA)*
Yang (Ted) D. Teng, *Harvard Medical School (USA)*

Special Awards for 3 best Oral Communication and 3 best Poster for young presenters (< 35 years old)

Conference Venue

TOP HOTEL Praha & Congress Centre
Prague, Czech Republic

FINAL Program
3rd World Congress on Cancer **"New strategies to prevent, diagnose and treat Cancer based on Precision Medicine"**
September 23-25, 2019, **TOP HOTEL Praha & Congress Centre, Prague, Czech Republic**

The program schedule at a glance

Sunday 22nd (suggested arrival date)

1st Day Monday 23rd	2nd Day Tuesday 24th	3rd Day Wednesday 25th
08.30-REGISTRATION	08.00-REGISTRATION	08.00-REGISTRATION
10.15-10.35 Opening Ceremony 10.40-12.40 1st Session	08.30-10.15 3rd Session 10.20-10.40 Coffee break 10.40-12.45 4th Session	08.50-10.30 7th Session 10.35-10.55 Coffee break 11.00-12.50 8th Session Short/Flash communications
12.45-14.00 Lunch	12.50-14.00 Lunch	12.50-14.00 Lunch
14.05-15.15 Second session	14.05-16.25 5th Session	14.05-15.35 9th Session
15.20-16.15 Honorary Lecture (group photo)	16.25-16.40 Coffee break	15.40-16.15 AWARD CEREMONY CLOSING CEREMONY (group photo)
16.15-17.00 Welcome Cocktail	16.45-19.05 6th Session	16.15-17.30 Farewell Party
17.00 --- free time	19.05-20.10 free time	
City tour (on booking)	20.15-22.30 GALA DINNER	20.00-22.00 Management meeting and Dinner
Dining down-town (at leisure)	Free cocktail time	

NOTES

Honorary Lecture (HL) 40+5 minute
Keynote Lecture (KL) 20+4 minute

Invited Lecture (IL) 17+2 minute
Invited Oral Communication (OC) 12+2 minute
Short Communication (SC) 10 minute (replaces Poster presentation)
Flash Communication (FC) 5 minute (replaces Poster presentation)
(No Poster hanging)
Please, make sure to keep in time
Special Awards for Young Presenters (< 35y)
for best (3) Short and (3) Flash Communications

Proceedings: Abstract and Full papers will be published free of charge in Journal of Cancer Metastasis and Treatment

HONORARY LECTURE (Monday 23rd, 15.20-16.15)
Chairs: Jinsong Liu (USA) – Omar M Amin (USA)
Thomas N. Seyfried (USA)
Title: Metabolic Management of Glioblastoma
Introduced by Ciro Isidoro (Italy)

SESSION CHAIRS

1. **Lauren L Mayo (USA) - Young-Joon Surh (South Korea)**
2. **Yong-Sang Song (South Korea) – Bernd Kaina (Germany)**
3. **Noriko Gotoh (Japan) – Marc Diederich (South Korea)**
4. **Josette William (USA) – John DiGiovanni (USA)**
5. **Tao Lu (USA) – Stefano Tiziani (USA)**
6. **Rajesh Agarwal (USA) – Jung Weon Lee (South Korea)**
7. **Luca Colucci D'Amato (Italy) – Richard Eckert (USA)**
8. **Gloria Su (USA) – Danny Dhanasekaran (USA) – Weronika Lucas Grzelczyk (Poland)**
9. **Judita Kinkorovà (Czech R) – Michael Green (USA)**

Gala Dinner on Tuesday 24th (purchase the ticket at Registration desk)

City Tour, Transportation, Wellness Centre (Registration desk or Hotel reception)

MONDAY 23RD SEPTEMBER

10.15-10.35 OPENING CEREMONY

SESSION 1	CHAIRS **Lauren L Mayo (USA) - Young-Joon Surh (South Korea)**
10.40-11.05	**Title: Amino Acid Depleting Enzymes Alone or in Combinations as a Therapeutic Strategy for Cancer Treatment** **John DiGiovanni, The University of Texas at Austin, USA**
11.05-11.30	**Title: Investigating Metabolic Cancer Vulnerabilities by High-Content Metabolomic Screening** **Stefano Tiziani, The University of Texas, USA**
11.30-11.55	**Title: Clinical Application of Artificial Intelligence in Ovarian Cancer** **Yong Sang Song, Seoul National University, South Korea**
11.55-12.20	**Title: Genetic and Epigenetic Regulation of Therapy Resistance in Ovarian Cancer by LncRNAs** **Danny Dhanasekaran, University of Oklahoma Health Sciences Center, USA**
12.20-12.40	**Title: Radiotherapy and Immunotherapy promote tumoral lipid oxidation and Ferroptosis IL** **Michael Green, University of Michigan, USA**

12.45 – 14.00 **LUNCH**

SESSION 2	CHAIRS **Young-Sang Song (South Korea) – Bernd Kaina (Germany)**
14.05-14.25	**Title: Polyploidy and Origin of Human Tumors IL** **Jinsong Liu, The University of Texas MD Anderson Cancer Center, USA**
14.25-14.40	**Title: Ketogenic diet as a cancer treatement: *In vitro* Quantification OC** **Edward Henry Mathews, North West University, South Africa**
14.40-14.55	**Title: Axl and autophagy LC3 expression in tumors is strongly associated with clinical prognosis of hepatocellular carcinoma patients after curative resection OC** **Chih-Wen Lin, E-Da hospital, Taiwan**
14.55-15.15	**Title: Dna Repair and Damage Response in Personalized Brain Cancer Chemotherapy IL** **Bernd Kaina, University Medical Center, Germany**

HONORARY LECTURE	**Chairs: Jinsong Liu (USA) – Omar M Amin (USA)** **Introduced by Ciro Isidoro (Italy)**
15.20-16.15	**Metabolic Management of Glioblastoma** **Thomas N. Seyfried (USA)**

16.15 GROUP PHOTO

16.15-17.00 WELCOME COCKTAIL

FREE TIME for visiting/dining downtown

TUESDAY 24TH SEPTEMBER

SESSION 3	CHAIRS **Noriko Gotoh (Japan) – Marc Diederich (South Korea)**
08.30-08.45	**Title: Novel Perspectives on the Immune Environment of Acute Myeloid Leukemia Using Multiomyxtm OC**
08.45-09.00	**Josette William, NeoGenomics Laboratories, USA**
	Title: Radiation Oncology updates in treatment of Prostate Cancer OC
09.00-09.15	**Lauren L. Mayo, The University of Texas MD Anderson Cancer Center, USA**
	Title: Novel DNA Modification in Cancer OC
09.15-09.30	**Tao Wu, Baylor College of Medicine, USA**
	Title: Evaluation of undiagnosed liver masses do not exhibit typical imaging features, but HCC even with stage C OC
09.30-09.45	**Metin Basaranoglu, Bezmialem Vakif University, Turkey**
	Title: Therapeutic effects of trehalose liposomes against tumors along with Apoptosis OC
09.45-10.00	**Yoko Matsumoto, Sojo University, Japan**
	Title: The effect of interactions between temozolomide and dexamethasone on the profile of 84 selected proteins in *glioblastoma multiforme* cells OC
10.00-10.15	**Anna Bielecka-Wajdman, Medical University of Silesia, Poland**
	Title: Sensitive detection of metabolic abnormalities in adult T-cell leukemia/lymphoma and induction of specific leukemic cell death using photodynamic therapy OC
	Takashi Oka, Okayama University, Japan

10.20 -10.40 COFFEE BREAK

SESSION 4	CHAIRS **Josette William (USA) – John DiGiovanni (USA)**
10.40-10.55	**Title: Preoperative Localization of Breast Lesions: Analysis of Current Techniques OC**
	Ray Cody Mayo, The University of Texas MD Anderson Cancer Center, USA
10.55-11.10	**Title: Managing metastatic brain disease: Stereotactic Radiosurgery alone, with radiotherapy, pre or post-microsurgery? OC**
	Leonardo Frighetto, Hospital Moinhos de Vento, Brazil
11.10-11.25	**Title: Elucidating the mechanisms underlying mitochondrial dysfunction in cancer cachexia also observed in other pathologies as well as in normal aging OC**
11.25-11.40	**Loukas, G. Astrakas, University of Ioannina Medical school, Greece**
	Title: Innovative technologies for cancer diagnosis and management Metal–organic framework encapsulation for biospecimen and biotherapeutic preservation OC
	Jeremiah Morrissey, Washington University in St. Louis, USA
11.40-11.55	**Title: Microrna-335-5p as a suppressor of metastasis and invasion in Gastric Cancer OC**
	Polakovicova Iva, Pontifícia Universidad Católica de Chile, Chile
11.55-12.05	**Title: RANBP9 as Potential Target in Non-Small Cell Lung Cancer OC**
	Vincenzo Coppola, OSU-Comprehensive Cancer Center, USA
12.05-12.20	**Title: The efficacy of targeting peptides for hepatopancreatic cancer therapy OC**
	Chin-Tarng Lin, National Taiwan University Hospital, Taiwan
12.20-12.45	**Title: One Carbon Metabolic Enzymes Play Important Roles for Cancer Cells and Cancer Stem-Like Cells IL**
	Noriko Gotoh, Kanazawa University, Japan

12.50 – 14.00 LUNCH

TUESDAY 24TH SEPTEMBER

SESSION 5	CHAIRS **Tao Lu (USA) – Stefano Tiziani (USA)**
14.05-14.30	**Title: Differential roles of the redox-sentitive transcription factor, NRF2 in multistage carcinogenesis**
14.30-14.55	**Young-Joon Surh, Seoul National University, South Korea**
	Title: The Importance of Sequential Mutations in Pancreatic Tumorigenesis
14.55-15.10	**Gloria Su, Columbia University, USA**
15.10-15.25	**Title: Serum expression of selected miRNAs in patients with laryngeal squamous cell carcinoma (LSCC) OC**
	Weronika Lucas Grzelczyk, Medical University of Lodz, Poland
	Title: Cyr61 promotes tip cell activity through VEGFR2-Hippo pathway in tumor angiogenesis OC
15.25-15.45	**You Mie Lee, Kyungpook National University, South of Korea**
15.45-16.05	**Title: Silibinin Targets Bone Morphogenic Protein 2 In Its Efficacy Against Ultraviolet B Radiation-Induced Promotion/Progression of Microscopic Basal Cell Carcinoma Formation IL**
16.05-16.25	**Rajesh Agarwal, University of Colorado Cancer Center, USA**
	Title: A Novel Sulforaphane-Regulated Gene Network in Prevention of Breast Cancer-Induced Osteolytic Bone Resorption IL
	Shivendra V. Singh, University of Pittsburgh, USA
	Title: Targeting of TM4SF5-mediated regulation of metabolic functions to overcome hepatic cancer IL
	Jung Weon Lee, Seoul National University, South Korea

16.25 – 16.40 COFFEE BREAK

SESSION 6	CHAIRS **Rajesh Agarwal (USA) – Jung Weon Lee (South Korea)**
16.45-17.10	**Title: Targeting cancer stem cells in malignant mesothelioma**
	Richard Eckert, University of Maryland School of Medicine, USA
17.10-17.35	**Title: Forward genetics to discover tumor suppressor in colorectal cancer**
	Tao Lu, Indiana University School of Medicine, USA
17.35-18.00	**Title: Immunogenic cell death in Myeloid Leukemia**
	Marc Diederich, Seoul National University, South Korea
18.00-18.25	**Title: The role of Autophagy in inflammatory cytokines-induced Epithelial to Mesenchymal Transition in Cancer**
	Ciro Isidoro, Università del Piemonte Orientale, Italy
18.25-14.45	**Title: Vasculogenic mimicry in glioblastoma and melanoma IL**
	Luca Colucci-D'Amato L, University of Campania "L. Vanvitelli", Italy
18.45-19.05	**Title: Mouse Tumor Susceptibility Alleles Identify Pathways for Intervention in Multiple Myeloma IL**
	Beverly A. Mock, National Cancer Institute, USA

20.15 – 22. 30 GALA DINNER

22.30 – 00.00 Free cocktail time

WEDNESDAY 25TH SEPTEMBER

SESSION 7	CHAIRS **Luca Colucci D'Amato (Italy) – Richard Eckert (USA)**
08.50-09.10	**Title: Mitochondrial protein VDAC1 as new target: From Concepts to Cancer Therapy IL** **Varda Shoshan-Barmatz, Ben-Gurion University of the Negev, Israel**
09.10-09.25	**Title: tRNA-derived fragment AS-tDR-007333 promotes cell proliferation in NSCLC through interacting with HSPB-1 OC** **Rihong Zhai, Shenzhen People's Hospital, China**
09.25-09.40	**Title: Breast tumor-on-chip OC** **Subia Bano, Elvesys Microfluidics Innovation Centre, France**
09.40-09.55	**Title: Tomosynthesis-Guided and Upright Stereotactic Biopsy OC** **Sarah Martaindale, The University of Texas MD Anderson Cancer Center, USA**
09.55-10.10	**Title: Giant Mediastinal Mixed Germ cell tumor, a rare case report and review of literature OC** **Abdulrahman Hakami, Jazan University, KSA**
10.10-10.25	**Title: Fungal infection and chemotherapeutic response and dose relationship OC** **Amany Nafeh, Assiut University, Egypt**

10.35 -10.55 COFFEE BREAK

SESSION 8	CHAIRS **Gloria Su (USA) – Danny Dhanasekaran (USA) – Weronika Lucas Grzelczyk (Poland)**
	Short Communication (10 min)
11.00	**Title: MGMT, BRCA1 And MEG3 methylation status in triple-negative breast cancer** **Sylwia Paszek, University of Rzeszow, Poland**
11.10	**Title: Cyr61 promotes tip cell activity in tumor angiogenesis: the role of VEGFR2-Hippo pathway** **Hyeonha Jang, Uttam Ojha, You Mie Lee, Kyungpook National University, South Korea**
11.20	**Title: Sphingosine Kinase-2 in oral squamous cell carcinoma** **Lais Brigliadori Fugio, University of São Paulo, Brazil**
11.30	**Title: DNA Methylation Markers for Noninvasive Detection of Early Stage Colorectal Cancer** **Yanqun Liu, Singapore General Hospital, Singapore**
11.40	**Title: Quantification of HER2 protein Using Multiple Reaction Monitoring-Mass Spectrometry in Formalin-Fixed Paraffin-Embedded (FFPE) Breast Cancer Tissue Specimens** **Youngsoo Kim, Seoul National University, South Korea**
11.50	**Title: Role of autophagy in nanoparticle toxicity in ovarian cancer cells** **Alessandra Ferraresi, Università del Piemonte Orientale, Italy**
12.00	**Title: Glucose-dependent autophagy control of cancer cell migration** **Chiara Vidoni, Università del Piemonte Orientale, Italy**
	Flash Communication (5 min)
12.10	**Title: A typical bronchial carcinoid with postobstructive mycobacterial** **Abdulrahman Hakami, Jazan University, KSA**
12.15	**Title: Trousseau's Syndrome in association with Lung Adenocarcinoma** **Abdulrahman Hakami, Jazan University, KSA**
12.20	**Title: Delphinidin Chloride and its hydrolytic metabolite Gallic Acid Promote Differentiation of Regulatory T cells and have an Anti-inflammatory effect on the Allograft Model** **Kwang Woo Hwang, Chung-Ang University, South Korea**
12.25	**Title: Association between heavy metal cadmium and the Warburg Effect in Breast Cancer – preliminary results** **Jablońska Ewa, Nofer Institute of Occupational Medicine, Poland**
12.30	**Title: The oyster can adapt to a harsh environment in the marine coast: Does it Mimick cancer cells?**

	Charlotte Corporeau, Ifremer, France
12.35	**Title: Resveratrol-induced modulation of Non-coding RNA in ovarian cancer cells** **Letizia Vallino, Università del Piemonte Orientale, Italy**
12.40-12.45	**Title: The microbiota-derived metabolite Butyrate inhibits colorectal cancer cell migration via modulation of autophagy** **Eleonora Secomandi, Università del Piemonte Orientale, Italy**

12.50 – 14.00 LUNCH

SESSION 9	CHAIRS **Judita Kinkorovà (Czech R) – Michael Green (USA)**
14.05-14.30	**Title: Parasites and cancer** **Omar M. Amin, Parasitology Center, Inc., USA**
14.30-14.55	**Title: Role of Biobanks in Cancer Research** **Judita Kinkorová, University Hospital Pilsen, Czech Republic**
14.55-15.15	**Title: Cancer chemoprevention with mitochondria-targeted compounds IL** **Ming You, Medical College of Wisconsin, USA**
15.15-15.30	**Title: Numerical chromosomal abnormalities are indicative of malignant biliary stricture OC** **Eman Mosaad, Assiut University, Egypt**
15.30-15.40	**The Efficacy of Ketogenic Diet with Concomitant Intranasal Perillyl Alcohol as a Novel Strategy for Therapy of Recurrent Glioblastoma OC** **Clovis O. Da Fonseca, Fluminense Federal University, Brazil**

15.40-16-00 AWARD CEREMONY (G Su, D Dhansekaran, WL Grzelczyk)

16.00-16.15 CLOSING CEREMONY (YJ Surh, D Dhanasekaran, J DiGiovanni, YS Song, C Isidoro)

GROUP PHOTO

16. 15– 17.30 FAREWELL PARTY

KEYNOTE SPEAKERS (Lecture=24 min)

SESSION 1 (Monday 23rd, 10.40-12.40)
Title: Amino Acid Depleting Enzymes Alone or in Combinations as a Therapeutic Strategy for Cancer Treatment
John DiGiovanni, The University of Texas at Austin, USA
Title: Investigating Metabolic Cancer Vulnerabilities by High-Content Metabolomic Screening
Stefano Tiziani, The University of Texas, USA
Title: Clinical Application of Artificial Intelligence in Ovarian Cancer
Yong Sang Song, Seoul National University, South Korea
Title: Genetic and Epigenetic Regulation of Therapy Resistance in Ovarian Cancer by LncRNAs
Danny Dhanasekaran, University of Oklahoma Health Sciences Center, USA

SESSION 5 (Tuesday 24th, 14.05-16.25)
Title: Differential Roles of the Redox-Sensitive Transcription Factor, Nrf2 in Multistage Carcinogenesis
Young-Joon Surh, Seoul National University, South Korea
Title: The Importance of Sequential Mutations in Pancreatic Tumorigenesis
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Title: The role of Autophagy in inflammatory cytokines-induced Epithelial to Mesenchymal Transition in Cancer
Ciro Isidoro, Università del Piemonte Orientale, Italy

SESSION 9 (Wednesday 25th, 14.05-15.35)
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Omar M. Amin, Parasitology Center, Inc., USA
Title: Role of Biobanks in Cancer Research
Judita Kinkorová, University Hospital Pilsen, Czech Republic

INVITED SPEAKERS (Invited Lecture=19 min; Invited Oral Communication=14 min)

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Title: Radiotherapy and Immunotherapy promote tumoral lipid oxidation and Ferroptosis IL
Michael Green, University of Michigan, USA

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Title: Axl and autophagy LC3 expression in tumors is strongly associated with clinical prognosis of hepatocellular carcinoma patients after curative resection OC
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Title: Dna Repair and Damage Response in Personalized Brain Cancer Chemotherapy IL
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Title: The effect of interactions between temozolomide and dexamethasone on the profile of 84 selected proteins in *glioblastoma multiforme* cells OC
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Takashi Oka, Okayama University, Japan

SESSION 4 (Tuesday 24th, 10.40-12.45)
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Title: Managing metastatic brain disease: Stereotactic Radiosurgery alone, with radiotherapy, pre or post-microsurgery? OC
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Title: Elucidating the mechanisms underlying mitochondrial dysfunction in cancer cachexia also observed in other pathologies as well as in normal aging OC
Loukas, G. Astrakas, University of Ioannina Medical school, Greece
Title: Innovative technologies for cancer diagnosis and management Metal–organic framework encapsulation for biospecimen and biotherapeutic preservation OC
Jeremiah Morrissey, Washington University in St. Louis, USA
Title: Microrna-335-5p as a suppressor of metastasis and invasion in Gastric Cancer OC
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Title: RANBP9 as Potential Target in Non-Small Cell Lung Cancer OC
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Title: The efficacy of targeting peptides for hepatopancreatic cancer therapy OC
Chin-Tarng Lin, National Taiwan University Hospital, Taiwan
Title: One Carbon Metabolic Enzymes Play Important Roles for Cancer Cells and Cancer Stem-Like Cells IL
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Title: Cyr61 promotes tip cell activity through VEGFR2-Hippo pathway in tumor angiogenesis OC
You Mie Lee, Kyungpook National University, South of Korea
Title: Silibinin Targets Bone Morphogenic Protein 2 In Its Efficacy Against Ultraviolet B Radiation-Induced Promotion/Progression of Microscopic Basal Cell Carcinoma Formation IL
Rajesh Agarwal, University of Colorado Cancer Center, USA
Title: A Novel Sulforaphane-Regulated Gene Network in Prevention of Breast Cancer-Induced Osteolytic Bone Resorption IL
Shivendra V. Singh, University of Pittsburgh, USA
Title: Targeting of TM4SF5-mediated regulation of metabolic functions to overcome hepatic cancer IL
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Beverly A. Mock, National Cancer Institute, USA

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Title: Giant Mediastinal Mixed Germ cell tumor, a rare case report and review of literatureOC
Abdulrahman Hakami, Amsterdam University Medical Center, The Netherlands
Title: Fungal infection and chemotherapeutic response and dose relationship OC
Amany Nafeh, Assiut University, Egypt

SESSION 8 (Wednesday 25th, 11.00-12.50) **(replace Poster presentation) Special Awards for <35y Presenters**

Short Communication (10 min)

Title: MGMT, BRCA1 and MEG3 methylation status in triple-negative breast cancer
Sylwia Paszek, University of Rzeszow, Poland

Title: Cyr61 promotes tip cell activity in tumor angiogenesis: the role of VEGFR2-Hippo pathway
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Title: Sphingosine Kinase-2 in oral squamous cell carcinoma
Lais Brigliadori Fugio, University of São Paulo, Brazil

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Title: Quantification of HER2 protein Using Multiple Reaction Monitoring-Mass Spectrometry in Formalin-Fixed Paraffin-Embedded (FFPE) Breast Cancer Tissue Specimens
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Flash Communication (5 min)

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Kwang Woo Hwang, Chung-Ang University, South Korea

Title: Association between heavy metal cadmium and the Warburg Effect in Breast Cancer – preliminary results
Jabłońska Ewa, Nofer Institute of Occupational Medicine, Poland

Title: The oyster can adapt to a harsh environment in the marine coast: Does it Mimick cancer cells?
Charlotte Corporeau, Ifremer, France

Title: Resveratrol-induced modulation of Non-coding RNA in ovarian cancer cells
Letizia Vallino, Università del Piemonte Orientale, Italy

Title: The microbiota-derived metabolite Butyrate inhibits colorectal cancer cell migration via modulation of autophagy
Eleonora Secomandi, Università del Piemonte Orientale, Italy

SESSION 9 (Wednesday 25th, 14.05-15.35)

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Ming You, Medical College of Wisconsin, USA

Title: Numerical chromosomal abnormalities are indicative of malignant biliary stricture OC
Eman Mosaad, Assiut University, Egypt

The Efficacy of Ketogenic Diet with Concomitant Intranasal Perillyl Alcohol as a Novel Strategy for Therapy of Recurrent Glioblastoma OC
Clovis O. Da Fonseca, Fluminense Federal University, Brazil

DAY 1

FIRST SESSION

CHAIR PERSONS

Lauren L Mayo and Young-Joon Surh

SESSION 1	CHAIRS **Lauren L Mayo (USA) - Young-Joon Surh (South Korea)**
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11.30-11.55	**Stefano Tiziani, The University of Texas, USA** **Title: Clinical Application of Artificial Intelligence in Ovarian Cancer**
11.55-12.20	**Yong Sang Song, Seoul National University, South Korea** **Title: Genetic and Epigenetic Regulation of Therapy Resistance in Ovarian Cancer by LncRNAs**
12.20-12.40	**Danny Dhanasekaran, University of Oklahoma Health Sciences Center, USA** **Title: Radiotherapy and Immunotherapy promote tumoral lipid oxidation and Ferroptosis IL** **Michael Green, University of Michigan, USA**

Amino Acid Depleting Enzymes Alone or in Combinations as a Therapeutic Strategy for Cancer Treatment

John DiGiovanni, Ph.D.,

Division of Pharmacology & Toxicology, College of Pharmacy and Livestrong Cancer Institutes, Dell Medical School, The University of Texas at Austin, Austin, TX

Background and Aim: Significant differences exist between the metabolism and antioxidant requirements of normal and malignant cells. Tumor cells depend on exogenous nutrients in their microenvironment to fulfill the elevated energy requirements and for maintaining appropriate intracellular antioxidant levels. Deprivation of amino acids results in growth inhibition or death of tumor cells by the modulation of various signaling cascades and in some cases redox balance. We have been evaluating potential therapeutic enzymes that degrade critical amino acids required for tumor growth. These engineered human enzymes include one that degrades either L-cysteine and one that degrades methionine.

Experimental Procedures

- In vitro cell culture experiments to evaluate cell survival using MTT and crystal violet assays
- Metabolomics analyses of amino acids and metabolites
- Analyses of oncogenic cell signaling, ROS levels and DNA damage as well as cell cycle changes using flow cytometry
- In vivo allograft and xenograft tumor experiments with various cancer cell lines.

Results: Depletion of extracellular L-cys/cystine led to depletion of intracellular L-cys, decreased levels of intracellular glutathione (GSH) and increases in intracellular ROS leading to activation of cellular signaling pathways, oxidative DNA damage and ultimately cancer cell death. Cyst(e)inase, given i.p., significantly reduced serum levels

of L-cys and significantly inhibited tumor growth in vivo of both prostate and pancreatic cancer xenograft and allograft tumor models. Notably, targeting a second antioxidant pathway together with cyst(e)inase (i.e., the thioredoxin pathway) using a thioredoxin reductase inhibitor, led to synergistic cancer cell killing and also sensitized tumor cells found to be more resistant to cyst(e)inase alone. These and other studies on the mechanisms associated with the potential anticancer activity of Cyst(e)inase will be presented. In addition, we have also studied the potential therapeutic application of a human engineered methionine (L-met) degrading enzyme called methionine gamma lyase (hMGL). Both mechanistic studies as well as in vivo preclinical therapeutic studies demonstrate significant efficacy against several cancers with hMGL.

Conclusions: Depletion of amino acids such as L-cys and L-met using human engineered enzymes offer novel approaches for treating cancer either given alone or more likely in combination with other agents.

Key words: cysteine, methionine, ROS, cell signaling, DNA damage, tumor growth inhibition

Research supported by NIH NCI grant CA189623.

John DiGiovanni received his B.S degree in Pharmacy and his Ph.D degree in Pharmacology from the University of Washington, Seattle, Washington. He did his postdoctoral work at the McArdle Laboratory for Cancer Research, University of Wisconsin, Madison, WI in carcinogenesis and cancer biology. Dr. DiGiovanni is currently Professor in the Division of Pharmacology and Toxicology, College of Pharmacy at the University of Texas at Austin. He holds the Coulter R. Sublett Endowed Chair in Pharmacy. He also has adjunct appointments in the Department of Nutritional Sciences (College of Natural Sciences) and the Department of Pediatrics (Dell Medical School). In addition, Dr. DiGiovanni is Director of the Center for Molecular Carcinogenesis and Toxicology (CMCT) and Associate Director for Basic Research in the LiveSTRONG Cancer Institutes, Dell Medical School at the University of Texas at Austin. Dr. DiGiovanni has published more than 260 research articles in prestigious peer-reviewed journals and more than 50 invited reviews/book chapters. Dr. DiGiovanni is also an elected Fellow of the American Association for the Advancement of Science.

Investigating Metabolic Cancer Vulnerabilities by High-Content Metabolomic Screening

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BACKGROUND AND AIM: The important role of cell metabolism in furthering cancer development and growth is increasingly recognized [1, 2]. Recent advances in high-throughput metabolomics technology are leading to its growing role during the development of new drugs targeting metabolic vulnerabilities in multiple cancer diseases [3, 4]. However, the drug discovery is limited by the unsuitability of animal models for high-throughput drug screening. Moreover, animal studies may not adequately predict the clinical efficacy of therapeutics in humans. These limitations motivated researchers to develop new three-dimensional (3D) in vitro models to better mimic the *in vivo* tumor microenvironment [5].

EXPERIMENTAL PROCEDURE: Here, we introduce a novel high-content metabolomics screen based on high-resolution direct infusion mass spectrometry (DIMS) technology capable to monitor the metabolic response of drug-treated mammalian cells in 3D 96-well format. This rapid and systematic metabolomic method was validated on multiple cancer and normal cells, cultured either in individual or in co-culture cell systems using ^{13}C- ^{15}N labeled tracer analysis.

RESULTS: Novel synergistic combination of drugs were identified utilizing the metabolic profiling obtained using DIMS. These include chemotherapies targeting the metabolic reprogramming of cancer cells, including mitochondrial oxidative phosphorylation and glutaminolysis.

CONCLUSION: Overall, the rapid data acquisition and improved detection limits of mass spectrometry are paving the way for applications of metabolomics in preclinical

screening [5, 6], opening new opportunities in drug discovery and personalized medicine.

KEYWORDS: drug discovery, metabolomics, cancer metabolism

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Dr. Stefano Tiziani is an Associate Professor in the Department of Nutritional Sciences at UT at Austin; in addition, he currently hold a courtesy appointment at the UT Austin Dell Medical School (Department of Oncology and Department of Pediatrics) and an adjunct position at the Medical School of UT Health Science Center at San Antonio. Research interests in his laboratory focus on translational chemical biology using a cutting edge metabolomics-based systems biology approach for metabolic biomarker discovery. His laboratory combines i) high-throughput screening measurements, ii) magnetic resonance spectroscopy and mass spectrometry-based metabolomics, iii) metabolic flux analysis and iv) other omic data to gain a better bio-mechanistic understanding of the effects of combined drug treatment and nutrient modulation in cancer and non-cancer conditions. His current research is actively devoted on developing, integrating and correlating high-throughput screening and untargeted metabolomics data to identify cancer vulnerabilities and accelerate identification of novel synergistic combinatorial treatment for more precise controlled of complex biological systems.

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Clinical Application of Artificial Intelligence in Ovarian Cancer

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Among several types of gynecologic cancer, ovarian cancer is the most lethal type. Due to the absence of specific symptom and effective biomarkers, survival rate of ovarian cancer is poor. Moreover, platinum resistance is a major obstacle in ovarian cancer treatment. Thus, accurate biomarkers associated with chemoresistance and recurrence of the cancer are necessitated. To establish personalized therapeutic strategies for ovarian cancer patients, a prediction model that precisely predict patient responses to chemotherapy and diagnosis could be computed and incorporated. Although many prediction models for cancer have been suggested, only a few number of prediction models specific for ovarian cancer has been proposed. So we performed integrative analysis incorporating both clinico-pathologic and multi-omics data and developed prediction models for diagnosis and prognosis of ovarian cancer. Also, we conducted metagenome analysis of patients with benign tumors and ovarian cancer to construct an early detection model of ovarian cancer. Gene expression data from TCGA database have been analyzed using the deep neural network model (DNN) to develop a model for predicting platinum-sensitivity in high-grade serous ovarian cancer. Lastly, we integrated clinico-pathologic and multi-omics data to reveal multiple factors associated with ovarian cancer progression.

KEYWORDS: Ovarian cancer; Multi-omics; Metagenome; TCGA; DNN

Yong Sang Song is currently the professor at Seoul National University, College of Medicine. He received his medical doctor's degree and Ph.D at the Seoul National University, Korea in 1983 and 1994 respectively. His major research interests are molecular mechanisms of tumors, especially the role of tumor microenvironment in cancer cell metabolism, chemoresistance and precision medicine in gynecologic cancer. He is particularly interested in the impact of components of tumor microenvironment and molecular markers associated with ovarian cancer progression. He is also the editor-in-chief, senior editor and the member of editorial board of several scientific journals such as *International Journal of Clinical Medicine*, *Journal of Cancer Prevention*, *Cancer Letters*, *Scientific Reports* and *Molecular Carcinogenesis*.

Genetic and Epigenetic Regulation of Therapy Resistance in Ovarian Cancer by Long Non-Coding RNAs

Danny N. Dhanasekaran[1], Ji Hee Ha[1], Ranagasudhagar Radhakrishanan[1], Muralidharan Jayaraman, Ciro Isidoro[2], Yong Sang Song[3]

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BACKGROUND AND AIM: Ovarian cancer remains the most fatal gynecological cancer in the world, with a five-year survival rate of only 46% for the localized disease and 29% for the distant-stage disease. With the recent analysis of cancer genome, LncRNAs are emerging as critical players in the pathobiology of many cancers, thus identifying them as new genomic targets for precision cancer medicine. Therefore, we sought to identify the critical lncRNA(s) involved in ovarian cancer genesis, progression, therapy resistance, and disease recurrence.

EXPERIMENTAL PROCEDURE: To identify the lncRNAs critically involved in ovarian cancers, we carried out a global analysis of mRNAs as well as lncRNAs that are differentially expressed in patient-derived ovarian cancer cells, using a series of biased and unbiased transcriptome analyses.

RESULTS: Results indicated that a total of 1351 lncRNAs and 1591 mRNAs were significantly dysregulated in patient derived cancer cells compared to normal fallopian tube-derived epithelial control cells. Co-expression network analysis of coding and noncoding RNAs identified the etiological role for several, thus far, unidentified lncRNAs and mRNAs in ovarian cancer. Further analyses indicated that the lncRNA-regulated gene expression network in ovarian cancer involves both genetic and epigenetic mechanisms. **CONCLUSION:** Our findings with representative lncRNAs

indicate that they can serve as a novel diagnostic as well as prognostic biomarkers. In addition, the findings that the silencing of specific lncRNAs inhibits xenograft tumor growth identify them as new therapeutic targets in ovarian cancer.

KEYWORDS: Ovarian cancer; precision cancer medicine, non-coding RNAs

Dr. Danny N. Dhanasekaran is the Director of NIH Center of Biomedical Research Excellence and Deputy Director for Basic Research, Stephenson Cancer Center as well as Professor and Samuel Roberts Noble Foundation Endowed Chair in Cancer Research at the Stephenson Cancer Center, University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma. He received his Ph.D. in Biochemistry from the Indian Institute of Science, Bangalore, India. Dr. Dhanasekaran is a pioneer in defining the oncogenic signaling network in ovarian cancers. His present research focuses on targeting noncoding RNAs for therapy in different cancers.

Representative Publications:

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Radiotherapy and Immunotherapy Promote Tumoral Lipid Oxidation and Ferroptosis

Michael Green[1], Weimin Wang[1], Xueting Lang[1], Jiali Yu[1], Jae Eun Choi[1], Ilona Kryczek[1], Everett Stone[2], George Georgiou[2], Marcin Cieslik[1], Daniel Wahl[1], Meredith Morgan[1], Arul Chinnaiyan[1], Theodore Lawrence[1], Weiping Zou[1]

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BACKGROUND AND AIM: Cancer immunotherapy restores or enhances the effector function of $CD8^+$ T cells in the tumor microenvironment. Radiotherapy can indirectly stimulate $CD8^+$ T cell function through innate immune signaling. Direct connections between radiotherapy and adaptive $CD8^+$ T cell function remain undefined. Ferroptosis is a recently discovered form of cell death and results from iron-dependent accumulation of lipid peroxides. It is unclear whether, and how, ferroptosis is involved in T cell immunity, cancer immunotherapy, and radiotherapy efficacy.

EXPERIMENTAL PROCEDURE: To understand the importance of ferroptosis in immunotherapy and radiotherapy efficacy, we have used genetic deletion of key ferroptosis effector genes and pharmacologic agonists and antagonists. Lipid oxidation was quantified using C11-BODIPY. A wide variety of *in vivo* and *ex vivo* analysis was performed in tumor and immune cells.

RESULTS: We show that immunotherapy-activated $CD8^+$ T cells and radiotherapy enhance ferroptosis-specific lipid peroxidation in tumor cells, and that increased ferroptosis contributes to the anti-tumor efficacy of immunotherapy and radiotherapy. Mechanistically, interferon gamma (IFNγ) released from $CD8^+$ T cells downregulates the expression of SLC7A11, a subunits of the glutamate–cystine

antiporter system x_c^-, impairs the uptake of cystine by tumor cells, and as a consequence, promotes tumor cell lipid peroxidation and ferroptosis.

CONCLUSIONS: This work establishes a novel mechanism through which $CD8^+$ T cells function. This work expands our understanding of the interactions between immunotherapy and radiotherapy.

KEYWORDS: Ferroptosis, Programmed cell death, Immune checkpoint blockade, Radiotherapy

Dr. Michael D. Green is an Assistant Professor at the University of Michigan in Ann Arbor Michigan. He received his Ph.D. from Mount Sinai, New York, and completed his postgraduate training in radiation oncology at the University of Michigan. His lab focuses on harnessing inflammation to improve anti-tumoral immunity.

Representative Publications:

1. Wang W, Green MD, Kryczek I, Sell A, Xia H, Zhou J, Li G, Li J, Li W, Wei S, Vatan L, Szeliga W, Gu W, Liu R, Lawrence TS, Stone E, Georgiou G, Chan T, and Zou W Immunotherapy promotes cancer cell ferroptosis by targeting the glutamate-cystine antiporter system xc- via IFNγ signaling pathway, Nature, May 2019
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DAY 1

SECOND SESSION

CHAIR PERSONS

Young-Sang Song and- Bernd Kaina

SESSION 2	CHAIRS **Young-Sang Song (South Korea) – Bernd Kaina (Germany)**
14.05-14.25	**Title: Polyploidy and Origin of Human Tumors IL** **Jinsong Liu, The University of Texas MD Anderson Cancer Center, USA**
14.25-14.40	**Title: Ketogenic diet as a cancer treatement: *In vitro* Quantification OC** **Edward Henry Mathews, North West University, South Africa**
14.40-14.55	**Title: Axl and autophagy LC3 expression in tumors is strongly associated with clinical prognosis of hepatocellular carcinoma patients after curative resection OC** **Chih-Wen Lin, E-Da hospital, Taiwan**
14.55-15.15	**Title: Dna Repair and Damage Response in Personalized Brain Cancer Chemotherapy IL** **Bernd Kaina, University Medical Center, Germany**

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Polyploidy and the Origin of Human Tumors

Jinsong Liu

The University of Texas MD Anderson Cancer Center, USA

Polyploid giant cancer cells (PGCCs) have long been observed in cancer and were thought originally to be nondividing. Surprisingly, the formation of blastomere by cleavage division after the formation of the zygote, with progressive decrease in cell size and increase in nuclear to cytoplasmic ratio, is the first step in embryogenesis, also shows abundant polyploidy. The evidence from our laboratories demonstrated that the stress-induced PGCCs can divide by endoreplication (endocycle and endomitosis), that leads to increased nuclear to cytoplasmic ratio which leads to dedifferentiation of somatic cells and acquisition of embryonic stemness. Therefore, formation of PGCCs in somatic cells may represent a previously overlooked endogenous embryonic program that can be activated to dedifferentiate somatic cells into stem cells of various potencies for tumor initiation. Based on these data, I propose that human tumors originate from stem cells at a specific developmental hierarchy, which can be achieved by dualistic origin: dedifferentiation of the zygote (sexual) via the blastomeric-mediated cleavage division during normal development, or transformation from damaged or aged mature somatic cells via a blastomeric-like embryonic program (asexual) via formation of PGCCs. Initiation of the tumor begins with stem cells that have uncoupled the differentiation from the proliferation program which results in stem cell maturation arrest. Thus, the birth of a tumor can be viewed as a triad that originates from stem cells via dedifferentiation through a blastomeric or blastomeric-like program, differentiation along Waddington's landscape, and arrested at a specific developmental hierarchy. The significance of polyploid blastomere-like cancer stem cells in cancer therapy will be discussed.

Ketogenic Diet as a Cancer Treatment : *in Vitro* Quantification

Edward Henry Mathews, George Edward Mathews and Albertus Abram Meyer

CRCED, North West University, South Africa

BACKGROUND: The glucose deprivation Restricted Ketogenic diet (KD-R) in combination with Metformin use, is a non-toxic broad-spectrum approach that targets the important metabolic differences between normal and cancer cells. The optimal use of this approach for cancer treatment is investigated using *in vitro* tests.

METHOD: Tests were carried out at 3mmol/L blood glucose (BG) to mimic the BG effect of KD-R in combination with Metformin. Two breast and one cervical cancer as well as one non-tumorigenic cell were used.

RESULTS: The different cell lines were affected differently. This suggests that glucose deprivation via KD-R and Metformin will not equally affect different cancers. All cell lines were most adversely affected after three weeks. Cell growth decreased to 32% for the most glucose avid cancer cell line.

Partial recovery occured after three months. Full cancer extinction can thus not be reached with only the KD-R and Metformin. Adjuvant treatments are needed. These treatments should be done when the cancer cells are at their most vulnerable, i.e. three weeks after reaching a BG level of 3mmol/L.

FUTURE WORK: Future work will entail adjuvant treatments such as chemotherapy together with KD-R and Metformin. Results should be available before the conference. Focus of our conference presentation will be on the latest results.

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Axl and Autophagy LC3 Expression in Tumors Is Strongly Associated with Clinical Prognosis of Hepatocellular Carcinoma Patients after Curative Resection

Chih-Wen Lin

E-Da hospital, Taiwan

Abstract: not provided

Dna Repair and Damage Response in Personalized Brain Cancer Chemotherapy

Bernd Kaina, Yang He, Oliver Switzeny, Wynand P.Roos, Markus Christmann, Thomas Hofmann

Institute Of Toxicology, University Medical Center, Mainz, Germany

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BACKGROUND AND AIM: First-line chemotherapeutic for malignant glioma is the DNA methylating agent temozolomide. The mechanism of cell death triggered by the minor DNA lesion, O^6-methylguanine, induced by the agent is well described. It rests on conversion of the lesion through mismatch repair into DNA double-strand breaks (DSB) that trigger downstream pathways including apoptosis and senescence[1]. Consequently, corresponding repair pathways are expected to have a great impact on temozolomide resistance, and evidence was provided for the involvement of MGMT, mismatch repair, DSB repair by homologous recombination through BRCA2 and Rad51[2] as well as XRCC3[3]. However, only MGMT found the way into the clinique, being used as predictor for therapy outcome[4].

EXPERIMENTAL PROCEDURE: A battery of cell und molecular biological methods have been applied, including apoptosis, senescence and autophagy measurements.

RESULTS: We compared methods of determining the MGMT promoter methylation status, which corresponds to MGMT silencing and therapy, and showed that MS-HRM is superior compared to MS-PCR[5]. We also show that downstream of O^6-methylguanine derived DSBs are ATR/ATM triggered pathways that activate apoptosis and senescence. Thus, data will be shown demonstrating that the SIAH1-HIPK2-p53ser46 pathway plays a key role in regulating temozolomide-induced apoptosis[6]. The question of

temozolomide threshold doses in activating survival and death pathways will also be addressed[7].

CONCLUSION: MGMT, mismatch repair and the SIAH1-HIPK2-p53ser46 pathway are key elements in personalized glioblastoma therapy with DNA-alkylating drugs.

KEYWORDS: Temozolomide, glioblastoma, drug resistance, apoptosis, senescence

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Dr. Bernd Kaina, Professor of Toxicology at the University Medical Center in Mainz, Germany, holds a doctoral degree from the University of Halle and worked as a postdoc and group leader at various institutions, including the German Cancer Research Center in Heidelberg. In 1993, he was appointed head of the Department of Applied Toxicology at the University of Mainz, and from 2004 to 2018 he served as group leader and director of this institute at the Medical Center in Mainz. His field of work includes the effects of environmental carcinogens as well as anticancer drugs, the mechanisms of cell death, mutagenesis and carcinogenesis with special emphasis on DNA repair. He published more than 300 papers in peer-reviewed journals and book chapters.

DAY 1

HONORARY LECTURE

CHAIR PERSONS

Jinsong Liu and Omar M Amin

HONORARY LECTURE	**Chairs: Jinsong Liu (USA) – Omar M Amin (USA)** **Introduced by Ciro Isidoro (Italy)**
15.20-16.15	**Metabolic Management of Glioblastoma** **Thomas N. Seyfried (USA)**

Metabolic Management of Glioblastoma

Seyfried, Thomas N.

Glioblastoma multiforme (GBM) remains among the most aggressive and difficult to manage primary brain tumours in humans. Abnormalities in the number, structure, and function of GBM mitochondria compromise energy metabolism through OxPhos. Glucose and glutamine are recognized as the major fermentable fuels that drive GBM growth through glycolysis and glutaminolysis, respectively. The glutamine antagonist, 6-diazo-5-oxo-L-norleucine (DON), was administered together with a calorically restricted ketogenic diet (KD-R) to treat late-stage orthotopic growth in two syngeneic mouse models of GBM; the highly invasive mesenchymal tumour, VM-M3, and the high-grade stem cell glioma, CT-2A. DON targets glutaminolysis while the KD-R reduces glucose and, at the same time, elevates neuroprotective and non-fermentable ketone bodies. The diet/drug therapeutic strategy caused massive tumour cell death or mitotic arrest, while reversing disease symptoms and improving overall survival without toxicity. The therapeutic strategy also reduced edema, hemorrhage, and inflammation associated with rapid tumour growth. Moreover, the KD-R diet facilitated DON delivery to the brain and allowed a lower nontoxic dosage to achieve therapeutic effect. Data from human case reports will also be presented. These findings support the importance of glucose and glutamine in driving GBM growth and provide a plausible therapeutic strategy for the non-toxic metabolic management of GBM and any cancer with mitochondrial defects.

Thomas N. Seyfried is Professor of Biology at Boston College, and received his Ph.D. in Genetics and Biochemistry from the University of Illinois, Urbana, in 1976. He did his undergraduate work at the University of New England where he recently received the distinguished Alumni Achievement Award. He also holds a Master's degree in Genetics from Illinois State University, Normal, IL. Thomas Seyfried served with distinction in the United States Army's First Cavalry Division during the Vietnam War, and received numerous medals and commendations. He was a Postdoctoral Fellow in the

Department of Neurology at the Yale University School of Medicine, and then served on the faculty as an Assistant Professor in Neurology. Other awards and honors have come from such diverse organizations as the American Oil Chemists Society, the National Institutes of Health, The American Society for Neurochemistry, and the Ketogenic Diet Special Interest Group of the American Epilepsy Society. Dr. Seyfried previously served as Chair, Scientific Advisory Committee for the National Tay-Sachs and Allied Diseases Association. He has received a Lifetime Achievement Award from the Academy of Complimentary and Integrative Medicine, the Mercola Recognition Award, and the Uncompromising Science Award from the American College of Nutrition for his work on cancer for his work on cancer. He presently serves on several editorial boards, including those for Nutrition & Metabolism, Neurochemical Research, the Journal of Lipid Research, Frontiers in Nutrition, Frontiers in Oncology, and ASN Neuro, where his is a Senior Editor. Dr. Seyfried has over 185 peer-reviewed publications and is author of the book, Cancer as a Metabolic Disease: On the Origin, Management, and Prevention of Cancer (Wiley Press). His book was recently translated into Chinese, and his full list of peer-reviewed publications can be found on PubMed (www.ncbi.nlm.nih.gov/pubmed/?term=Seyfried+TN)

DAY 2

THIRD SESSION

CHAIR PERSONS

Noriko Gotoh and Marc Diederich

SESSION 3	CHAIRS **Noriko Gotoh (Japan) – Marc Diederich (South Korea)**
08.30-08.45	**Title: Novel Perspectives on the Immune Environment of Acute Myeloid Leukemia Using Multiomyxtm OC** **Josette William, NeoGenomics Laboratories, USA**
08.45-09.00	**Title: Radiation Oncology updates in treatment of Prostate Cancer OC** **Lauren L. Mayo, The University of Texas MD Anderson Cancer Center, USA**
09.00-09.15	**Title: Novel DNA Modification in Cancer OC** **Tao Wu, Baylor College of Medicine, USA**
09.15-09.30	**Title: Evaluation of undiagnosed liver masses do not exhibit typical imaging features, but HCC even with stage C OC** **Metin Basaranoglu, Bezmialem Vakif University, Turkey**
09.30-09.45	**Title: Therapeutic effects of trehalose liposomes against tumors along with Apoptosis OC** **Yoko Matsumoto, Sojo University, Japan**
09.45-10.00	**Title: The effect of interactions between temozolomide and dexamethasone on the profile of 84 selected proteins in *glioblastoma multiforme* cells OC** **Anna Bielecka-Wajdman, Medical University of Silesia, Poland**
10.00-10.15	**Title: Sensitive detection of metabolic abnormalities in adult T-cell leukemia/lymphoma and induction of specific leukemic cell death using photodynamic therapy OC** **Takashi Oka, Okayama University, Japan**

Novel Perspectives on the Immune Environment of Acute Myeloid Leukemia using MultiOmyx

Josette William MD, PhD[1], Nicholas Hoe[1], Mate Nagy[1], Raghav Padmanabhan[1], and Qingyan Au[1],

[1]NeoGenomics, Aliso Viejo, CA, USA

BACKGROUND AND AIM: Acute myeloid leukemia (AML) is a clinically and molecularly heterogeneous disorder. Despites its poor prognosis, the treatment of AML remains largely unchanged over the past several decades with high dose chemotherapy remaining the mainstay of therapy. This has led to an interest to explore novel therapeutic approaches, such as bispecific antibodies, chimeric antigen receptor T cells, tumor vaccines, and immune checkpoint inhibitors

The BM constitutes the home niche for leukemic cells. TME is defined as the cellular environment in which the tumor exists. This environment is made up of endothelial, stromal, and immune cells and plays a key role in the development, propagation, and survival of cancer cells. The immune microenvironment has been well described in several hematologic malignancies, including Hodgkin lymphoma (HL), acute lymphoblastic leukemia, chronic myeloid leukemia (CML), and chronic lymphocytic leukemia, but less is known about the microenvironment in AML

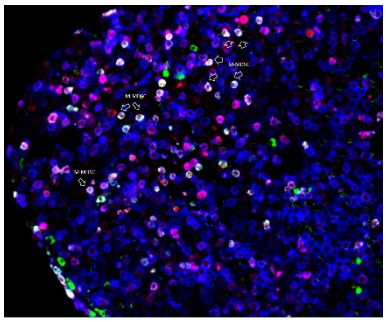
We studied the myeloid subsets in bone marrow tissues of normal and AML patients using MultiOmyx technique. We aimed to clarify the clinical significance of these cells in the AML patients.

EXPERIMENTAL PROCEDURE: MultiOmyx is an exclusive proprietary multiplex immunofluorescent technology that overcome the challenges for Immuno-Oncology Biomarker Profiling. It enables detection and visualization of up to 60 biomarkers on a single FFPE slide and Co-expression analysis of up to 25 Stains on a single cell, which is unattainable with the conventional IHC technique. Other advantages include: quantitative

Single Cell Classification, measures of marker intensity (Mean, Median & Total), and full spatial context for measuring the distances between cells with different immunophenotypes.

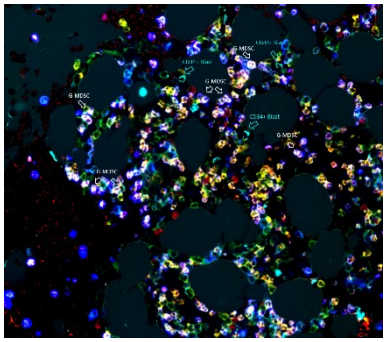
RESULTS: Myeloid subsets present in tumors are heterogeneous and play a crucial role in promoting cancer development and metastasis. Tumor associated macrophages (TAMs) and myeloid-derived suppressor cells (MDSCs) all contribute to an immunologically permissive microenvironment for cancer cells. On basis of surface markers expression, MDSC can be further subdivided into granulocytic MDSC (G-MDSC, polymorphonuclear MDSC) and monocytic MDSC (M-MDSC).). MDSC have also been shown to express immune checkpoint ligands such as PD-L1 that can suppress T cell responses *in vitro*. There is little information regarding MDSCs in AML. Tumor associated mmacrophages (TAMs) can be polarized by signals from their environment into two major subsets, called M1 and M2 macrophages. Acute myeloid leukemia blasts have been shown to differentiate monocytes from healthy donors into an M2-like phenotype in transwell coculture assays. In our study we were able to highlights the immune landscape of AML, and compared it with the landscape for normal bone marrow. We observed that both M-MDSC and G-MDSC accumulated within the TME in AML BM samples, with higher frequency of G-MDSCs over M- MDSCs. The data also revealed an abundant M2 macrophages present in the TME of the AML samples. The detection of both MDSCs and M2 macrophages in these samples supports the hypothesis that these cells contribute to the establishment of an immunosuppressive TME. Using the MultiOmyx proprietary algorithm, which takes into account the staining patterns, we quantified the counts and density of different tumor-resident myeloid subsets and measured the spatial distance from the different subsets of tumor-resident myeloid cells to CD34+ blasts in AML samples. We highlighted the correlations between the immunosuppressive myeloid cells and the different subsets of T cells including T-regulatory cells in AML clinical biopsy samples. TAMs and MDSCs are emerging as potential biomarkers for diagnosis and prognosis of cancer as well as therapeutic targets of many immunomodulating agents. As demonstrated in this study, MultiOmyx

multiplexed panel has the potential to monitor the changes of immunosuppressive myeloid cells in response to immune modulating drugs such as MDSC- targeting drugs (e.g. PDE-5 inhibitors, COX-2 inhibitors), TAM-targeting agents (e.g. anti-CSF1R) and combination therapy in treatment of AML.



The CD33+CD11b+CD15+ G-MDSCs are in white

The white arrows indicate examples of G-MDSCs



The CD33+CD11b+CD14+ M-MDSCs are in white

The white arrows indicate examples of M-MDSCs

Dr. Josette William joined NeoGenomics as Medical Director, Pharma Services and Hematopathologist in 2017. She previously served as a general pathologist for multiple laboratories and hospitals, including Quest Diagnostics Nichols Institute. In addition, Dr. William worked as a Hematopathology Consultant for DAKO/Agilent, and has extensive experience in clinical trials as a researcher for Northwestern University Feinberg School of Medicine. She completed her Hematopathology Fellowship and Anatomic and Clinical Pathology Residency at Northwestern University Feinberg School of Medicine in Chicago, Illinois. Dr. William obtained her medical degree from Ain Shams University and her PhD in Clinical Pathology, Immunology from Cairo University. In addition, Dr. William has spoken nationally and internationally, and has contributed toward several publications.

Radiation Oncology updates in treatment of Prostate Cancer

Lauren L. Mayo

The University of Texas MD Anderson Cancer Center, USA

I am a radiation oncologist at MD Anderson Cancer Center with a large proportion of my practice dedicated to prostate cancer. I would like to update the audience with the basic algorithms of radiation, hormonal and systemic therapy for low, intermediate and high risk. This talk would include information on active surveillance, definitive radiation treatment, brachytherapy as single modality and boost treatment, adjuvant and salvage (post-operative) radiation therapy, and hypofractionation and Stereotactic body radiation therapy. I understand the audience is a variety of clinicians in the medical field. I would tailor the talk to provide an overview so all can understand what is available to all prostate cancer patients and the updated studies to support these recommendations.

Colossal Facet
Innovation. Research. Science

Novel DNA Modification in Cancer

Tao P. Wu[2,6,*], Qi Xie[1,*], Ryan C. Gimple[1,3,*], Zheng Li[2], Qiulian Wu[1], Yang Yu[4], Yinsheng Wang[4], Shideng Bao[5], Andrew Z. Xiao[2,#], and Jeremy N. Rich[1,#]

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Genetic drivers of cancer can be dysregulated through epigenetic modifications of DNA. Although the critical role of DNA 5-methylcytosine (5mC) in the regulation of transcription is recognized, the functions of other non-canonical DNA modifications remain obscure.

We report the identification of novel DNA N6-methyladenine (N6-mA) modifications in human tissues and implicate this epigenetic mark in human disease, specifically the highly malignant brain cancer glioblastoma. Glioblastoma markedly upregulated N6-mA levels, which co-localized with heterochromatic histone modifications, predominantly H3K9me3. N6-mA levels were dynamically regulated by the DNA demethylase ALKBH1, depletion of which led to transcriptional silencing of oncogenic

pathways through decreasing chromatin accessibility. Targeting the N6-mA regulator ALKBH1 in patient-derived human glioblastoma models inhibited tumor cell proliferation and extended the survival of tumor-bearing mice, supporting this novel DNA modification as a potential therapeutic target for glioblastoma.

Furthermore, ALKBH1 controls the hypoxia responding genes in glioblastoma. Collectively, our results uncover a novel epigenetic node in cancer through the DNA modification N6-mA. The regulators of this new modification could serve as novel therapeutic targets in cancer therapy.

Tao Wu has completed his Ph.D. from the Chinese Academy of Sciences (Institute of Biophysics), Beijing, China. He is the Assistant Professor of Baylor College of Medicine, in the Department for Human and Molecular Genetics. He has published more than 15 papers in reputed journals and has been serving as a peer reviewer of several journals. Tao has presented his work on Cell Symposium, Gordon Conference, and Keystone Meeting. His Nature Article (2016) in which N6-mA was discovered and confirmed in mammalian cells for the first time has been cited around 200 times.

Colossal Facet
Innovation. Research. Science

Evaluation of undiagnosed liver masses not exhibit typical imaging features, but HCC even with stage C

Metin Basaranoglu

Bezmialem Vakif University, Turkey

Background and aim: Sometimes, despite of all blood examinations, transabdominal ultrasound, and computerized tomography with or without magnetic resonance imagings by multidiciplinary approach, we can not reach a strict diagnosis in patients with liver masses. In this study, we aimed to evaluate of undiagnosed liver masses, not exhibit typical imaging features.

Material and Methods: In this study, we retrospectively evaluated 140 patients with undiagnosed liver mass (es) without any typical imaging features. Then, percutaneous liver biopsy by transabdominal ultrasound guiding performed in 121 patients to obtain a liver specimen. A single gastroenterologist who is very well experienced on radiologic biopsies performed all biopsies in this study. This study icluded the years 2011, 2012, and 2013. A single experienced radiologist reevaluated imagings from the records in 2014.

Results: Pathologist evaluated 121 patients'liver specimens. Distribution of the diagnosis as follows: 45 patients with metastasis, 24 patients with HCC, 16 patients with nothing, advanced stage chronic liver disease in 8 patients, 5 patients with NET, 5 patients with dysplastic nodule or well-differentiated HCC, 4 patients with cholangiocarcinoma, 4 pts with pseudotumor (secondary to infections), 2 patients with steatosis, 2 patients with hemangioma, 1 patient with steatohepatitis, 1 patient with extramedullar hematopoesis, 1 patient with necrotising graanuloma, 1 patient with biliary cirrhosis (sistozomiazis), 1 patient with cyst hydatid, 1 patient with mixed tumor (hcc +cholangiocarcinoma). Radiologist reevaluated the radiologic records of 70

patients. The distribution of these patients as follows: 27 patients with HCC; 11 patients with chronic liver disease findings without any mass, 12 patients with metastasis, 6 patients with cholangiocarcinoma, 3 patients with hemangioma, 5 patients with abscess (one with fasciola and one with cyst hidatid), 2 cases without any liver abnormality, 1 with dysplastic nodule, 1 patient with angiomyolipom, 1 patient with gallbladder tumor, 1 patient with FNH. Further distribution of the 27 patients with HCC was shown in Table 1 according to the BCLC Staging System.

Discussion: Our results showed that HCC, even with Stage C, was one of the major cause of the liver masses not exhibit typical imaging features. HCC due to none B and none C was also a significant portion in this group of patients. More than half of the patients with HCC had normal serum α-FP level even in HCC patients with Stage C. As expected, life expectancy was in a relation with the stage of the disease.

Table 1.

Stage	HCC (A)	HCC (B)	HCC (C)		No of the pts
Number of the pts	8 pts	9 pts	10 pts	HBV	6
α-FP (↑) in	4 pts (7.4-181)	4 pts (9.5-300)	4 pts (14-300)	HCV	2
HBV	4 pts	2 pts	5 pts	HBV; α-FP (↑)	6
HCV	2 pts	3 pts	none	HCV; α-FP (↑)	2
Seronegative:	2 pts	4 pts	5 pts	HBV (-), HCV (-)	4
Exitus	2 pts	5 pts	7 pts	HBV (-), HCV (-); α-FP (↑)	6
				HBV (-), HCV (-); α-FP: un-known	1

Colossal Facet
Innovation.. Research.. Science

Therapeutic Effects of Trehalose Liposomes against Tumors along with Apoptosis

Yoko Matsumoto

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BACKGROUND AND AIM: Trehalose stabilizes membranes and proteins in cells most likely by hydrogen bonding. In this study, inhibitory effects of trehalose liposomes (DMTre) composed of L-α-dimyristoylphosphatidylcholine (DMPC) and trehalose micelles (TreC14) on the growth of tumors along with apoptosis were obtained in vitro and in vivo.

EXPERIMENTAL PROCEDURE: DMTre were prepared by the method of sonication of a mixture of DMPC and TreC14 in a buffer solution with no organic solvent.[1,2] The thickness of fixed aqueous layer (TFAL) of DMTre was evaluated from the zeta potential by an electrophoretic light scattering measurement. The fusion and accumulation of DMTre in tumor cell membrane including a fluorescence probe was observed using confocal laser microscopy. Activation of caspases for tumor cells induced by DMTre was analyzed using a flow cytometer. Assessment of therapeutic effects of DMTre aganist xenograft mice and orthotropic graft bearing mice model of carcinoma was performed.

RESULTS: Hydrodynamic diameter (d_{hy}) of DMTre composed of 30 mol% DMPC and 70 mol% TreC14 was 100 nm with single and narrow range of size distribution, which can avoid reticular endotherial system in vivo. Increase in TFAL values of DMTre was obtained in a dose-dependent manner. DMTre inhibited the growth of breast and lung tumor cells leading to apoptosis with the activation of caspases. The suppression of tumor weight of xenograft mice model of carcinoma treated with DMTre after

inoculation with breast tumor cells was obtained along with apoptosis. The remarkable reducton of volume and weight in subcutaneous tumors on subcutaneous lung carcinoma-bearing mice administered with DMTre were obtained.

CONCLUSION: Anti-tumor activities of DMTre against carcinoma-bearing mice along with apoptosis were obtained. The results of this study could contritute to the development of therapeutic agens for patients with carcinoma in future clinical application.

KEYWORDS: Trehalose, Liposome, Apoptosis, Caspase

References

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2) Y. Matsumoto et al., *Bioorg. Med. Chem. Lett.*, **26**, 301 (2016).

Prof. Yoko Matsumoto is a Professor of Department of Life Sciences at Sojo University, Japan. She received her PhD in Pharmacy from Kyushu University, Japan. She was a visiting researcher in Colorado University at Boulder with Prof. Tom Cech, USA. Yoko Matsumoto has received Outstanding Female Researcher Award from the Society of Chemical Engineering, Japan. She is one of Director for Japan Nanomedicine Society and Councilor for Japanese Association for Molecular Target Therapy of Cancer. Her current research interest focuses on liposomes for therapeutic applications. She has published more than 130 original papers.

The effect of interactions between temozolomide and dexamethasone on the profile of 84 selected proteins in *glioblastoma multiforme* cells

Anna Bielecka-Wajdman (PhD), Tomasz Ludyga, Ewa Obuchowicz (Prof.)

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BACKGROUND AND AIM: In patients with glioblastoma multiforme (GBM), standard chemotherapy with temozolomide (TMZ) is always supplemented with dexamethasone (DXM). However, for years DXM is applied as a "gold standard" in therapy of vasogenic edema, intracranial pressure and mass effect, the recent controversial results have challenged the widely accepted dogma concerning its using in therapy of GBM. The results of experimental studies emphasize that DXM may increase the aggressiveness of GBM by promoting the proliferation and invasiveness of cancer cells.

The aim of our study conducted on two primary glioblastoma lines obtained from patients and on the commercial line T98G was to assess the effect of TMZ, DXM and their interaction on the profile of 84 proteins involved in process of carcinogenesis. The tests were performed using the Proteome Profiler Human XL Oncology Array Kit (R & D) in cells cultured under two oxygen conditions: physiological for tumor hypoxia (2.5% oxygen) or in standard laboratory conditions (20% oxygen) frequently used in *in vitro* studies.

RESULTS: Our results confirmed the pro-tumorogenic properties of DXM but they have also shown that the response of GBM commercial and primary cell lines to DXM given to culture medium with or without TMZ is variable and depends on oxidation of the microenvironment.

CONCLUSION: It can be concluded that DXM and TMZ administered together or separately may induce different effects which depend on the degree of hypoxia prevailing in the malignant brain tumor.

Colossal Facet
Innovation. Research. Science

Sensitive detection of metabolic abnormalities in adult T-cell leukemia/lymphoma and induction of specific leukemic cell death using photodynamic therapy

Takashi Oka[1,2,*], Hajime Mizuno[3,#], Masumi Sakata[3], Hirofumi Fujita[4], Tadashi Yoshino[1], Yoshihisa Yamano[5], Kozo Utsumi[4], Tsutomu Masujima[3], and Atae Utsunomiya[6]

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Adult T-cell leukemia/lymphoma (ATL) is an aggressive T-cell neoplasm caused by human T-cell leukemia virus type I (HTLV-I). Therapeutic interventions have not been associated with satisfactory outcomes. We showed that the porphyrin metabolic pathway preferentially accumulates the endogenous photosensitive metabolite, protoporphyrin IX (PpIX) in ATL, after a short-term culture with 5-aminolevulinic acid (ALA). PpIX accumulated 10–100-fold more in ATL leukemic cells when compared to

healthy peripheral blood mononuclear cells (PBMCs). Patient specimens showed dynamic changes in flow cytometry profiles during the onset and progression of ATL. Furthermore, 98.7% of ATL leukemic cell death in the ATL patient specimens could be induced with 10 min of visible light exposure, while 77.5% of normal PBMCs survived. Metabolomics analyses revealed that a specific stage of the metabolic pathway progressively deteriorated with HTLV-I infection and at the onset of ATL. Therefore, this method will be useful for diagnosing and identifying high-risk HTLV-I carriers and high-risk indolent ATL who appeared to have developed or were likely to develop the aggressive subtypes with single cell resolutions. Photodynamic therapy in the circulatory system may be a potential treatment due to its highly-specific, non-invasive, safe, simultaneous, and repeatedly-treatable modalities.

DAY 2

FOURTH SESSION

CHAIR PERSONS

Josette William and John DiGiovanni

SESSION 4	CHAIRS **Josette William (USA) – John DiGiovanni (USA)**
10.40-10.55	**Title: Preoperative Localization of Breast Lesions: Analysis of Current Techniques OC** **Ray Cody Mayo, The University of Texas MD Anderson Cancer Center, USA**
10.55-11.10	**Title: Managing metastatic brain disease: Stereotactic Radiosurgery alone, with radiotherapy, pre or post-microsurgery? OC** **Leonardo Frighetto, Hospital Moinhos de Vento, Brazil**
11.10-11.25	**Title: Elucidating the mechanisms underlying mitochondrial dysfunction in cancer cachexia also observed in other pathologies as well as in normal aging OC** **Loukas, G. Astrakas, University of Ioannina Medical school, Greece**
11.25-11.40	**Title: Innovative technologies for cancer diagnosis and management Metal–organic framework encapsulation for biospecimen and biotherapeutic preservation OC** **Jeremiah Morrissey, Washington University in St. Louis, USA**
11.40-11.55	**Title: Microrna-335-5p as a suppressor of metastasis and invasion in Gastric Cancer OC** **Polakovicova Iva, Pontifícia Universidad Católica de Chile, Chile**
11.55-12.05	**Title: RANBP9 as Potential Target in Non-Small Cell Lung Cancer OC** **Vincenzo Coppola, OSU-Comprehensive Cancer Center, USA**
12.05-12.20	**Title: The efficacy of targeting peptides for hepatopancreatic cancer therapy OC** **Chin-Tarng Lin, National Taiwan University Hospital, Taiwan**
12.20-12.45	**Title: One Carbon Metabolic Enzymes Play Important Roles for Cancer Cells and Cancer Stem-Like Cells IL** **Noriko Gotoh, Kanazawa University, Japan**

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Preoperative Localization of Breast Lesions: Analysis of Current Techniques

Ray Cody Mayo

The University of Texas MD Anderson Cancer Center, USA

Image-guided preoperative localization of breast lesions is a relatively common procedure. This presentation describes the most common localization options available commercially—wire localization, radioactive seed localization, radiofrequency reflector localization, and magnetic seed localization—and outlines the advantages and disadvantages of each. This information may help radiologists, surgeons, pathologists, and hospital administration as they seek to add value and provide patient-centered care.

Managing metastatic brain disease: Stereotactic Radiosurgery alone, with radiotherapy, pre or post-microsurgery?

Leonardo Frighetto

Hospital Moinhos de Vento, Brazil

Abstract: not provided

Colossal Facet
Innovation. Research. Science

Elucidating the mechanisms underlying mitochondrial dysfunction in cancer cachexia also observed in other pathologies as well as in normal aging

Loukas, G. Astrakas

University of Ioannina Medical School, Greece

Abstract: not provided

Innovative Technologies for Cancer Diagnosis and Management
Metal–Organic Framework Encapsulation for Biospecimen and Biotherapeutic Preservation

Jeremiah Morrissey, PhD and Srikanth Singamaneni, PhD

Washington University in St. Louis Departments of Anesthesiology and Mechanical Engineering and Materials Science

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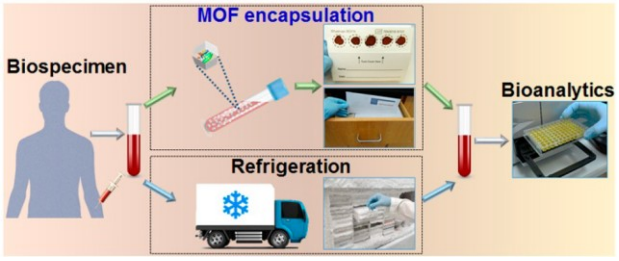
BACKGROUND AND AIM: Handling, transport, and storage of biospecimens such as blood and urine without refrigeration are extremely challenging. This formidable challenge leads to an inevitable reliance on a "cold chain" for shipping, handling, and storage of biospecimens throughout the world. The cold chain requirement impedes biospecimen procurement from under-served populations and resource-limited settings where refrigeration and electricity are not reliable or even available.

EXPERIMENTAL PROCEDURE: Here, we introduce a universal biospecimen preservation approach based on nanoporous material encapsulation for preserving protein biomarkers in biofluids under non-refrigerated storage conditions. Here we used urinary NGAL and plasma CA-125 as the model protein biomarkers and measured their concentrations before and after encapsulation by ELISA.

RESULTS: We found that encapsulation in a zeolitic imidazolate framework-8 (ZIF-8), a nanoporous material, can preserve protein biomarkers in urine and plasma for weeks at room temperature and 40 °C. The preservation efficacy for ELISA assay was greater than 85%; comparable to freezing liquid samples at −20 °C. The protein biomarkers in the relevant biofluids were first encapsulated within the nanoporous ZIF-8 crystals and then dried on paper substrates via a dry spot sample collection method and later reconstituted for analysis. This technology also preserves the biologic activity of insulin in liquid form for therapy.

CONCLUSION: This eco-friendly technology greatly improves biospecimen and biotherapeutic handling in resource-limited settings. The technology may be applicable to vaccine preservation, storage and transport at ambient temperature. Overall, this environmentally friendly and energy-efficient approach will alleviate huge financial and environmental burdens associated with "cold chain" facilities and extends biomedical research and treatment benefits to underserved populations from regions/populations currently inaccessible.



KEYWORDS: Biospecimen/Biotherapeutic Preservation, Biospecimen/Biotherapeutic Transport, Green Technology, Biomarker Integrity. MOF Encapsulation

Jeremiah is a Research Professor in the Department of Anesthesiology, Division of Clinical and Translational Research, Washington University in St. Louis School of Medicine, St. Louis, Missouri, USA since 2007. He received his Ph. D in Biochemistry from St. Louis University in 1974. After postdoctoral work he became a member of the Department of Medicine, Renal Division at Washington University in 1980 before switching to Anesthesiology. His research interests include acute and chronic kidney diseases, and kidney cancer. More recently, through collaboration with Dr. Srikanth Singamaneni in the Department of Mechanical Engineering and Material Science at Washington University, his interests have branched into nanotechnology means of measuring biomarkers of health and disease, and stabilizing biospecimen/assay components by metal organic frameworks.

1) Metal-Organic Framework as a Protective Coating for Biodiagnostic Chips, Adv. Mater. DOI: 10.1002/adma.201604433.
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Microrna-335-5p as a Suppressor of Metastasis and Invasion in Gastric Cancer

Polakovicova Iva[1, 2], Alejandra Sandoval-Borquez[3, 4], Nicolas Carrasco-Veliz[1, 2], Lorena Lobos-González[3, 4, 5], Paulina González-Villarroel[6], Alejandro Gottlieb-Riquelme[6], Edison Salas-Huenuleo[4, 7], Manuel Varas-Godoy[8], Alejandro Corvalán[1, 2].

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[7]Laboratory of Nanobiotechnology and Nanotoxicology, Facultad de Ciencias Químicas y Farmacéuticas, Universidad de Chile, Santiago, Chile.

[8]Centro de Biología Celular y Biomedicina (CEBICEM) Campus Los Leones, Universidad San Sebastian, Santiago, Chile.

BACKGROUND AND AIM: Gastric cancer is the fifth most common cancer worldwide. It is mainly diagnosed via endoscopic examination, unsuitable for screening, and patient follow-up. A deeper knowledge of its development and progression can contribute to discover effective preventive strategies. To understand this complex process, we focus on microRNAs and exosomes and their metastatic and invasive potential on gastric cells.

EXPERIMENTAL PROCEDURE: We evaluated the expression of several candidate miRNAs in 38 gastric cancer tissues and 22 plasma samples from gastric cancer patients and compared them to adjacent not-tumor tissues or plasma from symptomatic patients without cancer, respectively. We performed an association analysis of the expression of microRNA-335-5p with clinicopathological features and survival curves. For in vivo study, we injected intravenously microRNA-335-5p-loaded exosomes into immunodeficient mice with intraperitoneal tumors.

RESULTS: MicroRNA-335-5p is downregulated in advanced GC tissues relative to their paired non-tumor tissues. This downregulation is associated with worse survival rates of patients. We also demonstrated decreased levels of microRNA-335-5p in total plasma and exosomes isolated from plasma samples from GC patients, when compared to symptomatic patients without cancer. In our in vivo model of intraperitoneal carcinogenesis, we observed less metastasis but more necrosis in organs of mice that microRNA-335-5p-loaded exosomes and all mice lacked ascites.

CONCLUSION: MicroRNA-335-5p is downregulated in both types of gastric cancer samples. The difference in expression of this microRNA in plasma of gastric cancer patients versus patients without cancer is so profound that it can be considered as a possible candidate for non-invasive diagnosis of gastric cancer and the in vivo results may suggest a therapeutic role for miRNA-335.

KEYWORDS: gastric cancer, exosomes, microRNA-335-5p, metastasis, plasma

FUNDING: FONDECYTs 11181330, 1191928, 1190928, 3180783, and CONICYT-FONDAP 15130011.

Iva Polakovicova, Ph.D.

I studied at Charles University in Prague where I obtained my Master degree in Biochemistry and Ph.D. in Immunology in the field of signal transduction in mast cells in 2014. I am a molecular biologist with the background in immunology and biochemistry, expanding my area of interest in clinical research. This year, I finished my postdoctoral investigation dedicated to the role of exosomes in gastric cancer in the Laboratory of Oncology at Pontificia Universidad Católica in Santiago in Chile. Currently, I work in the same laboratory as an associated investigator on my research project funded by the government of Chile. I focus on microRNAs, extracellular vesicles/exosomes, and organoids prepared from tumor biopsies, as a model of gastric cancer. I am also a collaborator of the Advanced Center for Chronical Diseases (ACCDiS).

3 representative publications:

- Polakovicova I, Jerez S, Wichmann IA, Sandoval-Bórquez A, Carrasco-Véliz N, Corvalán AH. **Role of microRNAs and Exosomes in Helicobacter pylori and Epstein-Barr Virus Associated Gastric Cancers.** doi: 10.3389/fmicb.2018.00636.
- Sandoval-Bórquez A, Polakovicova I, Carrasco-Véliz N, Lobos-González L, Riquelme I, Carrasco-Avino G, Bizama C, Norero E, Owen GI, Roa JC, Corvalán AH. **MicroRNA-335-5p is a potential suppressor of metastasis and invasion in gastric cancer.** doi: 10.1186/s13148-017-0413-8.
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Colossal Facet
Innovation. Research. Science

RANBP9 as Potential Target in Non-Small Cell Lung Cancer

Vincenzo Coppola, MD

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Non-Small Cell Lung Cancer (NSCLC) is by far the number one cause of cancer related death in the Western world. Despite the progress made with targeted therapies and immuno-checkpoint inhibitors, the vast majority of patients still undergo treatment with genotoxic drugs such as platinum-based compounds. Studies testing whether DNA damaging agents sensitize NSCLC tumors to targeted- or immuno-therapies are ongoing. However, only a better understanding of the mechanisms of the DNA Damage Response (DDR) can lead to the validation of biomarkers predictive of response to genotoxic agents and the discovery of novel targets.

We have found that overexpression of the scaffold protein Ran Binding Protein 9 (RANBP9) is pervasive in NSCLC. Most importantly, patients with higher levels of RANBP9 have a worst treatment outcome (Tessari et al., 2018). Mechanistically, not only RANBP9 is a target (Matsuoka *et al.*, 2007) but also, surprisingly, an enhancer of the Ataxia Telangiectasia Mutated (ATM) kinase signaling (Palmieri *et al.*, 2016). Indeed, the depletion of RANBP9 in NSCLC cells abates ATM activation and its downstream targets such as p53, for example. Predictably, RANBP9 KO cells are more sensitive than controls to inhibition of the Ataxia and Telangiectasia-Related (ATR) kinase, but not ATM. Interestingly, the absence of RANBP9 renders cells more sensitive to drugs inhibiting the Poly(ADP-ribose)-Polymerase (PARP) (Tessari et al., 2018).

We will present results of our *in vitro* and *in vivo* investigation aimed to revealing the mechanisms responsible for increased sensitivity to specific genotoxic drugs when RANBP9 is absent. For this purpose, we have generated human NSCLC cell lines and new mouse models of NSCLC in which endogenous RANBP9 can be specifically ablated

in cancer cells or, alternatively, is tagged with V5-HA for its unequivocal detection. Tumors of this latter group will enable proteomic studies to identify unknown RANBP9 interactions upon DNA damaging treatment.

Colossal Facet
Innovation. Research. Science

The efficacy of targeting peptides for hepatopancreatic cancer therapy

Chin-Tarng Lin

National Taiwan University Hospital, Taiwan

Abstract: not provided

One Carbon Metabolic Enzymes Play Important Roles for Cancer Cells and Cancer Stem-Like Cells

Noriko Gotoh

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BACKGROUND AND AIM: Emerging evidence suggests that cancer stem-like cells (CSCs) are responsible for drug resistance tumor recurrence [1-6]. One-carbon (1C) metabolism incorporates carbons as building blocks of purine and pyrimidine that are used for DNA replication and RNA transcription. In the mitochondria, there are 4 major enzymes in 1C metabolism. These enzymes are strongly expressed in cancer cells, while it is scarcely expressed in normal cells. We investigated the role of MTHFD2 and MTHFD1L among them in cancer cells and CSCs.

EXPERIMENTAL PROCEDURE: We depleted expression of MTHFD2 and MTHFD1L in lung cancer cells and breast cancer cells by using siRNAs or shRNAs. By using these cells, we examined cell proliferation, sphere forming ability in vitro and in vivo. We also examined expression levels of stemness markers.

RESULTS: We showed that MTHFD2 and MTHFD1L play important roles for cancer cell proliferation, stem-like properties and drug resistance. Knockdown of *MTHFD2* led to accumulation of 5-aminoimidazole carboxamide ribonucleotide (AICAR), an intermediate of the purine synthesis pathway, in association with reduced stem-like properties.

CONCLUSION: MTHFD2 or MTHFD1L-mediated mitochondrial 1C metabolism appears critical for survival of CSCs through consumption of AICAR, leading to depletion of the intracellular pool of AICAR. Because CSCs are dependent on MTHFD2 and MTHFD1L, therapies targeting MTHFD2 may eradicate tumors.

KEYWORDS: cancer stem-like cells, lung cancer, breast cancer

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Noriko Gotoh, MD, PhD, is Professor of Cancer Research Institute, Kanazawa University in Japan. Until 2013, she was Associate Professor in Institute of Medical Science (IMSUT), The University of Tokyo in Japan. Her laboratory studies cancer stem cells and tumor heterogeneity focusing on breast cancer and lung cancer, molecular mechanisms how cancer stem cells are maintained through interaction with cancer stem cell niche, and growth factor signaling.

DAY 2

FIFTH SESSION

CHAIR PERSONS

Tao Lu and Stefano Tiziani

SESSION 5	CHAIRS **Tao Lu (USA) – Stefano Tiziani (USA)**
14.05-14.30	**Title: Differential roles of the redox-sentitive transcription factor, NRF2 in multistage carcinogenesis**
14.30-14.55	**Young-Joon Surh, Seoul National University, South Korea** **Title: The Importance of Sequential Mutations in Pancreatic Tumorigenesis**
14.55-15.10	**Gloria Su, Columbia University, USA** **Title: Serum expression of selected miRNAs in patients with laryngeal squamous cell carcinoma (LSCC) OC**
15.10-15.25	**Weronika Lucas Grzelczyk, Medical University of Lodz, Poland** **Title: Cyr61 promotes tip cell activity through VEGFR2-Hippo pathway in tumor angiogenesis OC** **You Mie Lee, Kyungpook National University, South of Korea**
15.25-15.45	**Title: Silibinin Targets Bone Morphogenic Protein 2 In Its Efficacy Against Ultraviolet B Radiation-Induced Promotion/Progression of Microscopic Basal Cell Carcinoma Formation IL**
15.45-16.05	**Rajesh Agarwal, University of Colorado Cancer Center, USA** **Title: A Novel Sulforaphane-Regulated Gene Network in Prevention of Breast Cancer-Induced Osteolytic Bone Resorption IL**
16.05-16.25	**Shivendra V. Singh, University of Pittsburgh, USA** **Title: Targeting of TM4SF5-mediated regulation of metabolic functions to overcome hepatic cancer IL** **Jung Weon Lee, Seoul National University, South Korea**

Differential Roles of the Redox-Sensitive Transcription Factor, Nrf2 in Multistage Carcinogenesis

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BACKGROUND AND AIM: Nuclear factor E2-related factor 2 (Nrf2) is a redox-sensitive transcription factor regulating the expression of a battery of genes encoding antioxidant and carcinogen detoxifying enzymes. In contrast to its tumor suppressive functions in normal cells, Nrf2 facilitates tumor growth and progression through metabolic reprograming in some cancer cells. Our previous study has demonstrated that 15-deoxy-$\Delta^{12,14}$-prostaglandin J_2 and 4-hydroxyestradiol induce overactivation of Nrf2 and consequently overexpression of its target protein, heme oxygenase-1 (HO-1), in human breast cancer cells.

EXPERIMENTAL PROCEDURE: In this study, we investigated the involvement of Nrf2 in experimentally induced hepatocarcinogenesis by utilizing Nrf2 null mice as well as wild type animals. The liver tumor was induced by intraperitoneal injection of diethylnitrosamine (DEN). The expression of Nrf2 and its target genes and proteins were measured by RT-PCR and Western blot analyses. The cell proliferation was determined by immunohistochemical analysis of PCNA expression.

RESULTS: Nrf2 expression, nuclear translocation, and transcriptional activity were enhanced in liver tumors. Overactivated Nrf2 was required for hepatoma growth in DEN-induced HCC. Following DEN treatment, *Nrf2* genetic disruption reduced expression of pentose phosphate pathway-related enzymes, the depletion of which

has been associated with an amelioration of HCC incidence. *Nrf2*-deficient mice resisted DEN-induced hepatocarcinogenesis.

CONCLUSION: The cellular stress response or cytoprotective signaling mediated via the Nrf2 is often hijacked by cancer cells. This may facilitate the remodeling of the tumor microenvironment making it advantageous for the autonomic growth of cancer cells, metastasis, angiogenesis, tolerance to anticancer therapy, and self-renewal activity of stem-like cells. Notably, Nrf2 overactivation upregulate antioxidant gene expression in breast cancer stem cells, which contribute to the manifestation and maintenance of stemness.

KEYWORDS: Nrf2, multi-stage carcinogenesis, hepatocarcinogenesis, diethylnitrosamine, heme oxygenase-1

Professor **Young-Joon Surh** currently serves as Director of Tumor Microenvironment Global Core Research Center, Seoul National University. He graduated from College of Pharmacy, Seoul National University with Bachelor's and Master's degrees. Prof. Surh earned a PhD degree at the University of Wisconsin-Madison and had postdoctoral training at MIT. After spending 3.5 years as a tenure-track Assistant Professor at Yale University School of Medicine, Prof Surh relocated to Seoul National University in 1996, Prof. Surh has been investigating the molecular mechanisms of cancer chemoprevention with anti-inflammatory and antioxidative natural products, with focus on intracellular signaling molecules as prime targets. He is currently Associate Editor of *Molecular Carcinogenesis*, *Toxicology & Applied Pharmacology*, *Free Radical Research*, and Editorial Board member of more than 10 international journals. He currently serves as President of Korean Society for Molecular and Cellular Biology (KSMCB) and President-Elect of Society for Free Radical Research (SFRR)-Asia.

3 Representative publications (out of 350):

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The Importance of Sequential Mutations in Pancreatic Tumorigenesis

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BACKGROUND AND AIM: Genetically engineered animal models (GEMMs) are established robust platforms for exploring the molecular mechanisms underlying the progression of pancreatic precancerous lesions to invasive PDA (pancreatic ductal adenocarcinoma). For example, using Pdx1-Cre to activate mutant *Kras^{G12D}* allele in the pancreas induces full spectrum of premalignant PanIN (pancreatic intraepithelial neoplasias) lesions that can eventually progress to invasive PDA [Reviewed in 1]. We and others have reported that concomitant inactivation of the *tumor suppressors p16, p19*, *p53, or* TGF-β receptor type 2 (*Tgfβ*R2*)* can synergize with oncogenic *Kras^{G12D} in promoting* the progression of the non-invasive PanINs to invasive cancer *in vivo* [1, 2]. In contrast, the inactivation of *Smad4* or *Acvr1b* in the context of mutant *Kras^{G12D}* preferentially promotes the development of pancreatic IPMNs (intraductal papillary mucinous neoplasms) but not PanINs [1, 3]. Collectively these data suggest that the order in which tumor-suppressor genes are inactivated may influence the development of pancreatic tumor subtypes. To further investigate the importance of sequential mutations in pancreatic tumorigenesis, we generated double heterozygous *Smad4$^{flox/+}$;p16$^{+/-}$;LSL-KRAS G12D;Pdx1-Cre* GEMM and asked how spontaneous inactivation of the second allele might impact the development pancreatic precancerous lesions. **EXPERIMENTAL PROCEDURE:** *Smad4$^{flox/+}$;p16$^{+/-}$;LSL-KRAS G12D;Pdx1-Cre* mice were examined and characterized in comparison to *p16$^{+/-}$;LSL-KRAS G12D;Pdx1-Cre* and *Smad4$^{flox/+}$;p16$^{+/-}$; Pdx1-Cre* GEMMs. **RESULTS:** *Smad4$^{flox/+}$;p16$^{+/-}$;LSL-KRAS G12D;Pdx1-Cre* mice shared similar medium survival and

tumor progression to *p16$^{+/-}$;LSL-KRAS G12D;Pdx1-Cre* mice (PanIN to PDA). Molecular analyses showed that biallelic inactivation only occurred at the *p16* locus in the PanINs and PDA from *Smad4$^{flox/+}$;p16$^{+/-}$;LSL-KRAS G12D;Pdx1-Cre* GEMM. **CONCLUSION:** Our results support the previous observations that the sequential inactivation of tumor-suppressor genes in the context of oncogenic *Kras^{G12D}* can dictate the development of pancreatic precancerous lesions. More importantly, the sequential mutations observed in mice mirror those detected in human patient specimens and thus illustrating that the order of genetic mutations is as critical as the mutated genes themselves in influencing tumor development and progression.

KEYWORDS: sequential mutations, tumor-suppressor genes, PanIN, IPMN, pancreatic tumor subtypes

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Dr. Gloria Su received her B.A. from Northwestern University and her Ph.D. from the University of Chicago. She is a Professor in the Departments of Pathology & Cell Biology and Otolaryngology/Head & Neck Surgery at Columbia University Irving Medical Center. Dr. Su's laboratory has developed multiple genetically-engineered mouse models (GEMMs) that recapitulate human pancreatic cancer at both genetic and histologic levels. These GEMMs and 3D organoids derived from them are powerful tools for interrogating the processes of pancreatic tumorigenesis and metastasis, and platforms for biomarker and drug discoveries. Notably, Dr. Su's team has reported that the loss of the wild-type *KRAS* is associated with pancreatic cancer metastasis in mice and in humans. They have also demonstrated that the inactivation of different tumor-suppressor genes following *Kras* activation may influence the dichotomy of PanIN and IPMN (precancerous lesions of pancreatic ductal adenocarcinoma) development and progression. In addition to mouse modeling, Dr. Su and her team have contributed to the cancer genetics of human IPMN and head and neck squamous carcinoma (HNSCC) by identifying the dysregulation of the PI3K-PTEN signaling axis in IPMN and HNSCC patients. Dr. Su currently serves on the editorial boards of Scientific Reports, Cancer Letters, PLOS One, and Genes & Diseases.

Serum expression of selected miRNAs in patients with laryngeal squamous cell carcinoma (LSCC)

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Abstract: not provided

Cyr61 promotes tip cell activity through VEGFR2-Hippo pathway in tumor angiogenesis

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Cyr61 stimulates active angiogenesis in various tumours, although the mechanism is fairly unknown. Here, we report that Cyr61 enhances the activity of tip cells during angiogenesis by regulating VEGFR2-Hippo pathway. Microvessel networks and directional vascular cell migration patterns were deformed in Cyr61-knockdown zebrafish embryos. Moreover, Cyr61 promoted the endothelial sprouting activity in angiogenesis. Cyr61 induced the interaction of integrin αvβ3 with VEGFR2 which activated downstream MAPK/PI3K signalling pathways, YAP/TAZ, as well as Rho effector mDia1 to enhance tip cell activity and Cyr61 itself. Integrin αvβ3 inhibitor repressed tip cell number and sprouting in postnatal retinas from endothelial cell-specific Cyr61 transgenic mice (*VE-Cadherin:Cyr61*), and also allograft tumours in Cyr61 transgenic mice showed hyperactive vascular sprouting. Cancer patients with high *Cyr61* expression have poor survival outcomes and positive correlation with *integrin αvβ3* and high *YAP/TAZ*. Thus, our data underscore the positive feedback regulation of tip cells by Cyr61 through integrin αvβ3/VEGFR2 and YAP/TAZ activity, suggesting a promising therapeutic intervention for pathological angiogenesis.

Silibinin Targets Bone Morphogenic Protein 2 in Its Efficacy against Ultraviolet B Radiation-Induced Promotion/Progression of Microscopic Basal Cell Carcinoma Formation

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BACKGROUND AND AIM: Non-melanoma skin cancers (NMSCs) account for about half of all malignancies diagnosed annually in the United States. Around 80% of NMSCs are basal cell carcinoma (BCC) and 20% are squamous cell carcinoma (SCC). Whereas the efficacy of several chemopreventive agents has been examined and reported against both BCC and SCC, a majority of these studies have focused on the test agent's activity in a long-term setting to determine the amount of tumors formed. Notably, the studies evaluating the efficacy of chemopreventive agents during early stage/s of BCC development are lacking. Accordingly, utilizing the well-established patched (Ptch)+/- mouse model of UVB-induced BCC formation, we excised skin samples from UVB exposed mice prior to tumor formation to study the promotion/progression of BCC and to determine the target/s of silibinin, a well-known skin cancer (SCC) chemopreventive agent, in BCC tumor growth inhibition.

EXPERIMENTAL PROCEDURE: We use a multifactor approach:

- long-term ultraviolet B radiation-induced mouse skin tumorigenesis in Ptch heterozygous mice focusing on BCC;

- investigating and quantifying expression of molecular regulators and cyclobutane pyrimidine dimers by immunohistochemistry and/or immunoblotting;

- and real-time PCR with mouse signal transduction pathway finder PCR array.

RESULTS: As early as one month, we found that UVB exposure significantly increased the number of mast cells in Ptch+/- mice by about 48% (P<0.05), which was completely inhibited (to control levels) by silibinin topical treatments. In Ptch+/+ mice, which do not develop BCC tumors, we did not observe any increase in mast cells following UVB exposure, suggesting this could be a specific pathway in the development of BCC. To decipher the molecular mechanism of these findings, we performed a PCR profiler array analysis of several genes involved in signal transduction pathways which showed strong differences between Ptch+/+ and Ptch+/- mice that were unexposed, UVB irradiated, and silibinin treated. Most notably, following UVB exposure for 1 month, in Ptch+/- mice the expression of Bone morphogenetic protein 2 (BMP-2), Hairy/enhancer-of-split related with YRPW motif 1 (Hey1), and Inhibitor of DNA binding 1 (Id1) was significantly upregulated when compared to Ptch+/+ mice. Additional studies focusing on BMP-2 found that silibinin strongly inhibits UVB-induced expression of BMP-2 in Ptch+/- mouse skin. Consistent with these results, we also found that silibinin strongly attenuates UVB-induced BMP-2 expression and DNA damage in Ptch+/- mouse skin ex vivo. Regarding BCC formation, silibinin treatment inhibited UVB-induced microscopic BCC formation in Ptch+/- mice; microscopic tumor number and size were reduced by 73% and 84%, respectively. Together, our results suggest a possible role of BMP-2 in early stages of BCC development and that silibinin plausibly acts through BMP-2 to inhibit microscopic BCC formation.

CONCLUSION: Our current findings in BCC model, together with previous studies in SCC model, suggest that silibinin could be a multi-target agent capable of being a chemopreventive agent for both types of NMSCs.

KEYWORDS: Basal cell carcinoma; Silibinin; Bone morphogenetic protein 2

Prof. Rajesh Agarwal, a Cancer Pharmacologist, graduated from the chemistry department, Lucknow University, India in 1981 with Ph.D. degree. He worked at several positions in India from 1981 to 1988, and then moved to Case Western Reserve University, Cleveland, OH, USA as Research Associate where he grew to the Position of Assistant Professor in Dermatology Department in 1992. He moved to Colorado in 1998 and is Full Professor and Vice Chair, Department of Pharmaceutical Sciences, University of Colorado School of Pharmacy. He has over 380 peer-reviewed publications and has been an invited speaker across the globe. He is an active member of several National Institutes of Health grant review committee, and is an editorial board member of several lead cancer journals. He is an elected fellow of the American Association for the Advancement of Science (AAAS) in Pharmaceutical Sciences in 2009; recipient of outstanding achievement award from Society of American Asian Scientists in Cancer Research in 2009, and several other national and international awards.

A Novel Sulforaphane-Regulated Gene Network in Prevention of Breast Cancer-Induced Osteolytic Bone Resorption

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Bone is the most preferred site for colonization of metastatic breast cancer cells for each subtype of the disease. The standard of therapeutic care for breast cancer patients with bone metastasis include bisphosphonates (e.g., zoledronic acid), which have poor oral bioavailability, and a humanized antibody (denosumab). However, these therapies are palliative and a subset of patients still develop new bone lesions and/or experience serious adverse effects. Therefore, a safe and orally bioavailable intervention for prevention/therapy of osteolytic bone resorption is still a clinically unmet need. This study demonstrates prevention of breast cancer-induced bone resorption by small molecule (sulforaphane, SFN) that is safe clinically and orally bioavailable. *In vitro* osteoclast differentiation was inhibited in a dose-dependent manner upon addition of conditioned media from SFN-treated breast cancer cells representative of different subtypes. Targeted microarray coupled with interrogation of TCGA dataset revealed a novel SFN-regulated gene signature involving cross-regulation of runt-related transcription factor 2 (RUNX2) and nuclear factor-κB and their downstream effectors. Both RUNX2 and p65/p50 expression were higher in human breast cancer tissues compared to normal mammary tissue. RUNX2 was recruited at the promotor of *NFKB1*. Inhibition of osteoclast differentiation by SFN was augmented by doxycycline-inducible stable knockdown of RUNX2. Oral SFN administration significantly increased the percentage of bone volume/total volume of affected bones in the intracardiac MDA-MB-231-Luc model indicating *in vivo*

suppression of osteolytic bone resorption by SFN. These results indicate that SFN is a novel inhibitor of breast cancer induced osteolytic bone resorption *in vitro* and *in vivo*. These findings necessitate clinical investigations to determine the effect of SFN administration on osteolytic bone resorption in women with metastatic breast cancer.

This study was supported by the grant CA225716 awarded by the National Cancer Institute.

Targeting of TM4SF5-Mediated Regulation of Metabolic Functions to Overcome Hepatic Cancer

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BACKGROUND AND AIM: Liver is an organ that diverse nutrient can be metabolized and its cancer show arginine auxotroph which involve arginine delivery from extracellular diet sources and lysosomal protein degradation products. Among genes involved in hepatic cancer, transmembrane 4 L six family member 5 (TM4SF5) structurally similar to the tetraspanins with 4 transmembrane domains, is shown to be highly expressed in cancerous liver tissues and correlated with many hepatic metabolism genes. However, it is unknown whether and how TM4SF5 is involved in arginine metabolism in livers.

EXPERIMENTAL PROCEDURE: To explore it, we examined if TM4SF5 expression could be involved in mTORC1 signaling pathway, since mTORC1 signaling is a central hub of various cellular metabolism processes.

RESULTS: First, we found shuttling of TM4SF5 between plasma membrane and lysosomal (late endosomal) membrane, depending on availability of amino acids. Further, upon resupply of arginine to arginine-starved cells, lysosomal TM4SF5 associated with mTOR, leading to an increased S6K phosphorylation. The association between TM4SF5 and mTOR appeared to require the C-terminal regions of TM4SF5 and kinase activity of mTOR. In addition, an endosomal arginine transporter SLC38A9 and a cytosolic arginine sensor Castor1 was found to be associated with TM4SF5, indicating TM4SF5 as an arginine sensor on late endosomal (lysosomal) membrane. Interestingly, the association of Castor1 with TM4SF5 was negatively regulated by L-

arginine, but concomitantly the association between mTOR and TM4SF5 increased. Further interestingly, certain residues in the extracellular loop 2 of TM4SF5 bound to arginine. Thus association of TM4SF5 with mTOR, SLC38A9, and arginine on lysosomal membrane might allow TM4SF5 to propagate arginine response to mTORC1 by directly sensing arginine in the lysosome and also to elevate cytosolic arginine pool for cellular homeostasis.

CONCLUSION: Therefore, all these observations suggest TM4SF5 as an arginine sensor on late endosomal membrane and as a promising therapeutic target candidate for the arginine auxotroph of hepatic cancers.

KEYWORDS: Amino acid metabolism; Arginine auxotroph; arginine transporter; hepatic cancer; molecular modeling; lysosome; mTOR; S6K1; TM4SF5.

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Dr. Jung Weon Lee is a Professor at Dept. of Pharmacy, Seoul National University (SNU), Korea. He got Ph.D. in Pharmacology, University of North Carolina at Chapel Hill, NC, USA. He had a postdoc period at Memorial Sloan-Kettering Cancer Center, NY, USA. In 2001, He came back to Korea, and in 2009 moved to Dept. of Pharmacy, SNU. His researches focus on how cellular functions occur at the molecular levels. His researches focuses on the roles of a tetraspanin, TM4SF5, in metabolic disorders, inflammation, fibrosis, tumorigenesis and metastasis, and on the anti-TM4SF5 reagents to block TM4SF5-mediated diseases (Lab homepage: http://jwl.snu.ac.kr).

DAY 2

SIXTH SESSION

CHAIR PERSONS

Rajesh Agarwal and Jung Weon Lee

SESSION 6	CHAIRS **Rajesh Agarwal (USA) – Jung Weon Lee (South Korea)**
16.45-17.10	**Title: Targeting cancer stem cells in malignant mesothelioma** **Richard Eckert, University of Maryland School of Medicine, USA**
17.10-17.35	**Title: Forward genetics to discover tumor suppressor in colorectal cancer** **Tao Lu, Indiana University School of Medicine, USA**
17.35-18.00	**Title: Immunogenic cell death in Myeloid Leukemia** **Marc Diederich, Seoul National University, South Korea**
18.00-18.25	**Title: The role of Autophagy in inflammatory cytokines-induced Epithelial to Mesenchymal Transition in Cancer** **Ciro Isidoro, Università del Piemonte Orientale, Italy**
18.25-14.45	**Title: Vasculogenic mimicry in glioblastoma and melanoma IL** **Luca Colucci-D'Amato L, University of Campania "L. Vanvitelli", Italy**
18.45-19.05	**Title: Mouse Tumor Susceptibility Alleles Identify Pathways for Intervention in Multiple Myeloma IL** **Beverly A. Mock, National Cancer Institute, USA**

Targeting Cancer Stem Cells in Malignant Mesothelioma

Richard L. Eckert[1,2,4], Gautam Adhikary[1], Daniel Grun[1], Joseph S. Friedberg[3,4], Wen Xu[1], Jeffrey Keillor[5], Sivaveera Kandasamy[3], H. Richard Alexander[5]

Department Of Biochemistry And Molecular Biology[1], Department Of Dermatology[2], Department Of Surgery And Division Of General And Surgical Oncology[3], Greenebaum Comprehensive Cancer Center[4], University Of Maryland School Of Medicine, Baltimore Usa; Department Of Surgery[5], Robert Wood Johnson Medical School, New Brunswick, New Jersey; Department Of Chemistry[5], University Of Ottawa, Ottawa, Ontario

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BACKGROUND AND AIM: Mesothelioma is an aggressive, treatment resistant and fatal cancer of the mesothelial lining of the pleural and peritoneal cavities that is initiated by exposure to asbestos or nanotubes. Surgical reduction and chemotherapy are first line treatments, but recurrence of highly aggressive and drug-resistance disease is common. Disease recurrence is associated with expansion of mesothelioma cancer stem cells (MCS cells). Thus, new treatments are needed for this disease that target the cancer stem cell population.

EXPERIMENTAL PROCEDURE: We use genetic gene expression and knockdown approaches, signaling studies, xenograft tumor studies, transcriptome analysis and protein structure studies to characterize the role of the transglutaminase 2 (TG2) cancer stem cell survival factor in enhancing MSC cell survival and function.

RESULTS: We show that tissue transglutaminase (TG2), a cancer stem cell survival and drug-resistance protein, is highly enriched in human mesothelioma tumors and in mesothelioma cancer stem cells (MCS cells), and drives MCS cell spheroid formation, invasion and migration. TG2 knockdown or TG2 inhibitor treatment, reduces MCS cell survival, spheroid formation, matrigel invasion, migration and tumor formation. These

are important observations as, MCS cells comprise a highly aggressive subpopulation of tumor that form rapidly growing and aggressive tumors. In addition, transcriptome analysis reveals that TG2 loss is associated with reduced levels of mRNA encoding a wide range of cancer stem cell and epithelial-mesenchymal transition proteins, and that TG2 knockdown reduces expression of transcripts and proteins encoding pro-cancer matrix proteins including collagens COL1A2 and COL3A1 that are involved in metastasis. Mesothelin, a mesothelioma cell-specific MCS cell survival protein and attachment factor, is also reduces in TG2 knockdown cells.

CONCLUSIONS: These studies indicate that TG2 is highly overexpressed in MCS cells and drives the cancer stem cell phenotype to enhance MCS cell stemness, survival and invasion, and suggests that TG2 is an important candidate mesothelioma cancer stem cell therapy target.

KEYWORDS: mesothelioma, cancer stem cells, tumor formation, stem cell therapy, transglutaminase 2

Dr. Richard L. Eckert, PhD is the John F.B. Weaver Distinguished Professor and the Chair of the Department of Biochemistry and Molecular Biology and Deputy Director of the Greenebaum Comprehensive Cancer Center at the University of Maryland School of Medicine, Baltimore, Maryland. He received his PhD in Biochemistry from the University of Illinois-Urbana/Champaign and extensive additional training at M.I.T and Harvard Medical School. Dr. Eckert is internationally recognized as a pioneer in defining the factors that control normal cell differentiation and confer oncogenic traits on cancer stem cells in squamous cell carcinoma and mesothelioma.

Representative Publications:

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Forward genetics to discover tumor suppressor in colorectal cancer

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The nuclear factor κB (NF-κB) plays pivotal roles in inflammatory and immune responses and in cancer. Therefore, understanding its regulation holds great promise for disease therapy. Using validation-based insertional mutagenesis (VBIM), a powerful technique established by us, we discovered a novel negative regulator of NF-κB (named NNRN1) in colorectal cancer (CRC). We showed that NNRN1 overexpression downregulated the expression of NF-κB-dependent genes, many of which are related to cancer. Additionally, compared to the vector control group, overexpression of NNRN1 in HEK293 cells or CRC HT29, DLD1, and HCT116 cells dramatically reduced NF-κB activity, cellular proliferation, anchorage-independent growth, and migratory ability *in vitro*, and unsurprisingly, significantly decreased xenograft tumor growth *in vivo*. In contrast, shNNRN1 knockdown cells showed quite opposite effect. Furthermore, co-immunoprecipitation (Co-IP) experiment confirmed that NNRN1 may form a complex with the p65 subunit of NF-κB. Importantly, immunohistochemistry (IHC) data exhibited much lower NNRN1 expression level in CRC patient tumor tissues compared to normal tissues, indicating that NNRN1 may function as a tumor suppressor in CRC. To conclude, our findings for the first time uncovered the negative regulatory function of NNRN1 in NF-κB signaling, and present NNRN1 as an innovative therapeutic target in CRC treatment.

Dr. Tao Lu is a tenured Associate Professor and principle investigator at Department of Pharmacology and Toxicology, and a member of Simon Cancer Center at Indiana University School of Medicine. She obtained her Ph.D. degree from University of Toledo, School of Medicine, and finished her postdoctoral training at Cleveland Clinic in Ohio with the world renowned cancer biologist Dr. George Stark, who is the member of National Academy of Sciences and National Academy of Medicine in U.S., as well as a Fellow of the Royal Society in London, UK. Dr. Lu's research focuses on the discovery of novel regulators of NF-κB, particularly, on the epigenetic regulation of NF-κB and its role in cancer therapeutics. She won multiple awards at international scientific meetings. Dr. Lu has published over 50 papers with 2 were highlighted by *F1000 Prime.* She currently holds several ongoing patent applications regarding NF-κB regulation and serves as the grant reviewer at the National Cancer Institute (NCI) study section in U.S., and a guest scientific grant reviewer for several countries internationally. She also serves as the editorial board member of multiple scientific journals.

Colossal Facet
Innovation. Research. Science

Immunogenic Cell Death in Myeloid Leukemia

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BACKGROUND AND AIM: We investigate the effect of pharmacologically active compounds that act as immunoadjuvants able to trigger a cancer stress response and release of damage-associated molecular patterns (DAMPs) in myeloid leukemia [1]. These processes result in a chemotherapeutic response with a potent immune-mediating reaction. Several parameters determine whether a compound can act as an ICD inducer including the nature of the inducer, the premortem stress pathways, the cell death pathways, the intrinsic antigenicity of the cell, and the potency and availability of an immune cell response [2].

EXPERIMENTAL PROCEDURE: We use a multifactor approach:

- detecting ER stress markers;
- investigating and quantifying caspase-dependent or independent cell death;
- measuring the release of danger associated molecular patterns;
- quantifying phagocytosis of compound-treated cells by both murine and human monocyte-derived macrophages;
- perform colony formation assays and in vivo zebrafish xenografts;
- and perform vaccination assays with immunocompetent mice.

RESULTS: We identified ICD-inducing capacities of old (coumarinics) and novel (stemphol, cardiac glycoside UNBS1450) inducers of immunogenic cell death together with venetoclax and experimental BH3 mimetics. We detected their capacity to trigger synergistic cell death in myeloid leukemia in an attempt to overcome apoptosis-resistant myeloid leukemia alone or in combination with other chemotherapeutic compounds.

CONCLUSION: The identification of hallmarks of ICD is important in determining the prognostic biomarkers for new therapeutic approaches and combination treatments [3]. In myeloid leukemia, combination treatments of ICD-inducing pharmacological agents [4] with Venetoclax showed positive synergistic effects [5] allowing to confer immunogenicity to otherwise cytotoxic non-immunogenic treatments.

KEYWORDS: Cell death; personalized medicine; Bcl-2

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Dr. Marc Diederich was appointed associate Professor of Biochemistry at the College of Pharmacy of Seoul National University in 2012. In 2017, he was tenured and promoted to full professor at SNU. Prof. Diederich's research focuses on the development of novel anticancer drugs. As an example, natural marine compounds represent an interesting source of novel leads with potent chemotherapeutic or chemo-preventive activities. He and his collaborators investigated compounds that exhibit anti-microbial, anti-inflammatory and anti-cancer activities. More recently, he investigated the effects of natural compounds that induce immunogenic cell death via the release of alarmins and the activation of corresponding signaling pathways, eventually improving immune recognition of cancer cells as a promising source for novel anti-cancer agents.

The role of Autophagy in inflammatory cytokines-induced Epithelial to Mesenchymal Transition in Cancer

Chiara Vidoni, Alessandra Ferraresi, Eleonora Secomandi, Letizia Vallino, Suyanee Thongchot, Danny Dhanasekaran§, **Ciro Isidoro**

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§ Stephenson Cancer Center, Oklahoma University Health Science Center (Oklahoma City, US)

The peculiar hallmark distinguishing malignant from bening tumors is the capability of the former to invade the extracellular matrix and metastasize to near and distant organ. This process implies an epigenetic change in the expression of genes that leads to a reversible phenotypic change of the cancer cells from epithelial-like to mesenchymal-type known as Epithelial-to-Mesenchymal Transition (EMT). The tumor microenvironment plays a pivotal role in this process, the major players being the pro-inflammatory cytokines IL-6 and IL-8 released by Cancer Associated Fibroblasts (CAFs), immune cells (M2 macrophages) and cancer cells themselves.

Autophagy, a lysosome-driven catabolic process for degradation of self-constituents, participates in the stress response for maintaining cell homeostasis. It has been shown that autophagy is down-regulated during cell locomotion, while it is induced when cells arrest their migration.

We found that pro-inflammatory cytokines promotes cancer cell migration following down-regulation of autophagy in the migratory cells. We have also investigated at molecular level the mechanisms through which the cytokines modulate autophagy.

Our data highlight the role of autophagy in cancer cell EMT and migration, offering opportunities for therapeutical interventions to prevent invasion and metastasization.

Ciro Isidoro is Professor of Pathology at the School of Medicine of Università del Piemonte Orientale (Novara, Italy). He received his doctoral degree in Biological Sciences from the University of Torino (Italy) and his doctoral degree in Medicine and Surgery from the University of Piemonte Orientale (Novara, Italy). He is Visiting Professor at the Faculty of Medicine, Siriraj Hospital, of Mahidol University (Bangkok, Thailand), Visiting Professor at the Department of Cell Biology of the Oklahoma City University Health Sciences Center (US), and Professeur Honoraire at the Faculté de Medecine et de Pharmacie de l'Université de Franche-Comté, Besancon (France). He is member of the Scientific board of the « Integrative Cancer Research Center of the Georgia Institute of Technology » (Atlanta, US). Ciro Isidoro has co-authored > 140 peer-reviewed original articles published in international journals. He serves as Co-Editor in Chief of the Journal of Traditional and Complementary Medicine and Associate Editor of Autophagy, Int J of Molecular Scuinces, Molecular Carcinogensis, BMC Cancer, and other journals. His fields of expertise include the subjects "autophagy regulation in cancer" and "mechanisms of anticancer activity of dietary products".

Colossal Facet
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Vasculogenic Mimicry in Glioblastoma and Melanoma

Luca Colucci-D'Amato, Maria Teresa Gentile, Olga Pastorino

Laboratory of Molecular and Cellular Neuropathology
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University of Campania "L. Vanvitelli"
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BACKGROUND AND AIM: Neo-angiogenesis is the most studied mechanism of vascularization in tumors and refers to sprouting of new blood vessels from pre-existing one and it may be inhibited by natural compounds. Vasculogenic mimicry (VM) is an alternative mechanisms of tumor vascularization providing a mean by which some tumors can escape anti-angiogenetic therapy. VM occurs in glioblastoma (GBM) and melanoma, both tumors of neuroepithelial derivation. We investigated the role of REST/NRSF gene in the pathophysiology of VM as well as the effects of compounds such as the histone deacetylase inhibitors (HDACis) to interfere with VM.

EXPERIMENTAL PROCEDURE. To measure tube formation, cell migration and invasion we used: in vitro tube formation assay on matrigel, Boyden chamber migration assay, wound healing assay, invasion test, Real-Time Migration Monitoring. To measure cell viability: MTT and trypan blue exclusion test. To transfect cells: Lipofectamine standard protocol.

RESULTS. We analyzed a number of GBM and melanoma cell lines. We found that the expression of REST parallels the ability to migrate and to form tubes on matrigel. Upon genetic or chemical down-regulation of REST (via siRNA or dominant negative mutant or HDACi), we observed a decrease of migration ability as well as of tube formation. Finaly , we found that different Histone deacetylase inhibitors impair vasculogenic mimicry from glioblastoma cells.

Conclusions. Our findings show that REST/NRSF gene is an important molecular player in the pathophysiology of vasculogenic mimicry in GBM and melanoma and show that HDAC inhibitors alone can impair the formation of tubes from GBM cells.

Keys words: vasculogenic mimicry, REST/NRSF, glioblastoma, melanoma, HDAC inhibitors.

Luca Colucci-D'Amato is Associate Professor of General Pathology, University of Campania Luigi Vanvitelli, after having been Researcher at National Research Council (Cnr), until 2005. He has obtained a medical doctor degree summa cum laude at University of Naples "Federico II" where he also got a PhD in Molecular and Cellular Pathology. Then he was certified summa cum laude Resident in Neurology at II University of Naple. He spent training periods abroad, at the National Cancer Institute, N.I.H., (Bethesda, USA), in the Department of Molecular Biology, Bristol-Myers Squibb Pharmaceutical Research Institute, (Princeton, USA) and at the Centre de Genetique Moleculaire, CNRS, (Gif-sur-Yvette, Francia)

His work focuses on the mechanisms underlying proliferation and differentiation in neural cells, including brain tumors and neurodegenerative diseases. Current interests: Natural compounds active on neural tumors, Vasculogenic mimicry in neural tumors; mechanisms of neurodegeneration.

Recent representative publications:

1. HUVEC Tube-formation Assay to Evaluate the Impact of Natural Products on Angiogenesis. Gentile MT, Pastorino O, Bifulco M, Colucci-D'Amato L. J Vis Exp. 2019 doi: 10.3791/58591.
2. Histone Deacetylase Inhibitors Impair Vasculogenic Mimicry from Glioblastoma Cells. Pastorino O, Gentile MT, Mancini A, Del Gaudio N, Di Costanzo A, Bajetto A, Franco P, Altucci L, Florio T, Stoppelli MP, Colucci-D'Amato L. Cancers (Basel). 2019. doi: 10.3390/cancers11060747.
3. Ruta graveolens L. induces death of glioblastoma cells and neural progenitors, but not of neurons, via ERK 1/2 and AKT activation.Gentile MT, Ciniglia C, Reccia MG, Volpicelli F, Gatti M, Thellung S, Florio T, Melone MA, Colucci-D'Amato L. PLoS One. 2015 doi: 10.1371/journal.pone.0118864. eCollection 2015.

Mouse Tumor Susceptibility Alleles Identify Pathways for Intervention in Multiple Myeloma

Beverly A. Mock

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BACKGROUND AND AIM: Multiple Myeloma (MM) is a clonal proliferation of neoplastic plasma cells in the bone marrow. Despite recent therapeutic advances, drug resistance and MM progression is common. Mouse plasma cell tumors model these antibody producing neoplasms. Long-term genetic studies utilizing backcross, and congenic strain analyses coupled with positional cloning strategies and functional studies identified *Cdkn2a, Mtor* and *Mndal* as plasmacytoma susceptibility genes. Tumor incidence data in congenic strains carrying resistance alleles of *Cdkn2a* and *Mtor* led us to *hypothesize* that drug combinations affecting these pathways are likely to have an additive, if not synergistic effect in inhibiting tumor cell growth.

EXPERIMENTAL PROCEDURE: Drug combination (mTOR and HDAC inhibitors) activity and synergy was measured in B cell neoplasms and NCI-60 cell lines. *In vivo* activity was assessed in xenograft experiments. Co-expression network analyses of microarray data from *in vitro* drug treatment delineated the cooperative mTORi/HDACi transcriptional response. Selectivity of the response for genes differentially regulated in MM was determined by GSEA of datasets from healthy controls and MM patients. The combination's potential clinical utility was evaluated by developing a multivariate survival prediction model from the response signature in a MM patient dataset. Functional enrichment and transcription factor activity testing of the response signature delineated the combination's biological activities.

RESULTS: The combination was active and synergistic in 90% of cell lines and controlled *in vivo* tumor growth for 12 weeks. Combination response signature genes were correlated with improved survival and the signature was functionally enriched for cell cycle, apoptosis, antigen presentation, and DNA damage response. The combination is predicted to repress oncogenic factors and activate tumor suppressors (RB1, CDKN2A). **CONCLUSION:** The traditional and novel systems-level genomic approaches used to assess combination activity, disease specificity, and clinical potential demonstrate the efficacy of combined mTORi/HDACi, and warrant further investigation in clinical trials.

KEYWORDS: Mtor, p16, HDAC, rapamycin, entinostat, systems pharmacology

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As a Senior Investigator in the Center for Cancer Research at the National Cancer Institute, **Dr. Mock** leads a research team in the areas of complex genetic traits associated with cancer and systems pharmacology approaches to develop drug combinations. Dr. Mock's research translates basic research findings into hypothesis-driven preclinical evaluations in cell lines and animal models to inform the potential for clinical trial design. She collaborates with scientists and clinicians within and outside of the NIH and serves as a Deputy Laboratory Chief for the Laboratory of Cancer Biology and Genetics and one of the CCR's Deputy Directors.

DAY 3

SEVENTH SESSION

CHAIR PERSONS

Luca Colucci D'Amato and Richard Eckert

SESSION 7	CHAIRS **Luca Colucci D'Amato (Italy) – Richard Eckert (USA)**
08.50-09.10	**Title: Mitochondrial protein VDAC1 as new target: From Concepts to Cancer Therapy IL** **Varda Shoshan-Barmatz, Ben-Gurion University of the Negev, Israel**
09.10-09.25	**Title: tRNA-derived fragment AS-tDR-007333 promotes cell proliferation in NSCLC through interacting with HSPB-1 OC** **Rihong Zhai, Shenzhen People's Hospital, China**
09.25-09.40	**Title: Breast tumor-on-chip OC** **Subia Bano, Elvesys Microfluidics Innovation Centre, France**
09.40-09.55	**Title: Tomosynthesis-Guided and Upright Stereotactic Biopsy OC** **Sarah Martaindale, The University of Texas MD Anderson Cancer Center, USA**
09.55-10.10	**Title: Giant Mediastinal Mixed Germ cell tumor, a rare case report and review of literature OC** **Abdulrahman Hakami, Jazan University, KSA**
10.10-10.25	**Title: Fungal infection and chemotherapeutic response and dose relationship OC** **Amany Nafeh, Assiut University, Egypt**

Mitochondrial protein VDAC1 as new target: From Concepts to Cancer Therapy

Varda Shoshan-Barmatz

Ben-Gurion University of the Negev, Israel

Abstract: not provided

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tRNA-derived fragment AS-tDR-007333 promotes cell proliferation in NSCLC through interacting with HSPB-1

Wenyan Yang[1], Lin Yang[2], Qihan He[1], Peikun Ding[2], Zheng Wang[2], Lijuan Ling[2], Yi Song[1], **Rihong Zhai**[1]

[1]Shenzhen University School of Medicine, Shenzhen, China; [2]Shenzhen People's Hospital, Shenzhen, China

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Background： tRNA derived-fragments (tRFs) is a new class of non-coding small-molecule RNA. Recent studies suggest that tRFs are involved in the development and progress of several cancers. But the impact of tRFs in non-small cell lung cancer (NSCLC) remains elusive.

Methods: NSCLC-related tRFs were determined by RNA-seq. Expression of tRF in tumor tissues， plasma, and in NSCLC cell lines was analyzed with qRT-PCR. The effect of tRF on NSCLC malignancy was evaluated *in vitro* by loss- and gain-of-function assays. RNA-seq was conducted to screen for the target genes of tRF. The mechanism of action of tRF was explored with RNA pulldown, RNA immunoprecipitation (RIP), and qRT-PCR.

Results: RNA-seq identified 7 differentially expressed tRFs between pre-and post-operation plasmas in patients with NSCLC. Among them, the expression of a novel tRF termed AS-tDR-007333 was significantly upregulated in pre-operative plasma, in NSCLC tissues, and in NSCLC cell lines. Overexpression of AS-tDR-007333 promoted NSCLC cell (PC9, HCC827, A549) proliferation, while knockdown of AS-tDR-007333 inhibited cell growth. RNA-seq showed that up-regulation of AS-tDR-007333 led to the activation of oncogenes such as *MED29, AL049829.1, SCHIP1, SAMD12, MRFAP1*, and *SHISA5*. RNA pulldown and RIP analyses revealed that AS-tDR-007333 can bine directly with the heat shock protein beta-1 (HSPB-1). Rescue assays demonstrated that HSPB1 was involved in AS-tDR-007333 mediated NSCLC cell proliferation.

Conclusion: Our study reveals an oncogenic role of AS-tDR-007333 in NSCLC, suggesting that it may be a novel target for diagnosis and the treatment of NSCLC.

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Breast tumor-on-chip

Subia Bano

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Elvesys Microfluidics Innovation Centre Paris, France- 75011

Back ground and Aim: Breast cancer is the most common invasive cancer among women. There are several chemotherapeutic and radiotherapeutics approaches are available but they have certain limitations. Over the past few years, improved understanding of the microenvironment heterogeneity of breast cancer has allowed the development of more effective treatment strategy. However, researchers have still not been able to recapitulate the entire tumor microenvironment to study the tumor progression and invasion. In this way, more complex 3D *in vitro* cancer models have been developed. These 3D tumor models still lack the cell-cell, cell-tissue interactions, and more balanced interstitial fluidic flow that are present within living system. Furthermore, mimicking of different physiological condition and collection of samples from tumor microenvironment is also difficult. In this direction, breast tumor-on-chip model has emerged as an alternative system to study the tumor microenvironment and deciphering its role in metastasis. In this work microfluidics system is integrated to 3D breast tumor to bridge the gap between 2D and animal model effectively, to evaluate the efficacy of anti-cancerous drug. These microfluidic systems contain small chambers for cell culture, enabling control over local gradients and maintain the interstitial fluidic flow of the local breast tumor microenvironment.

Experimental Procedure: In this work the multi-compartment microfluidics platform is generated by designing a specific PDMS chip with three channels which are separated by specific barriers (50 µm). The cancerous and fibroblast cells (cocultures) are suspended with collagen hydrogel and loaded into central channel, one of the side

channels are used to grow the endothelial cells to make this system vascularized. The barriers inside the chips will allow to exchange the signaling molecules.

Results: The cancer cells in presence of fibroblast cells are growing very well into these microchannels and this result is confirmed with live/dead assay. At this stage we got the preliminary data, we are still working in this area.

Conclusion: Integration of microfluidics system into breast tumor will add as another toolset that can make a more efficient testing platform in the current therapeutic development pipeline.

Keywords: Microfluidics, breast tumor, hydrogels, spheroids, coculture

Myself **Subia Bano**, have completed my PhD from Department of Biotechnology, Indian Institute of Technology Kharagpur. I have worked on Cancer Research, Stem cells, Biomaterials, Tissue Engineering and Drug/Gene delivery system. During my PhD, I was working on the efficiency of drug/growth factor loaded silk fibroin-folate nanoparticles in 2D and 3D tumor model. Meanwhile I also check the efficacy of growth factor loaded nanoparticles for the chondrogenic differentiation of rat and human mesenchymal stem cells. I did my Post doctorate from School of Pharmacy, University of Eastern Finland, I was working on peptide mediated gene delivery to the differentiated retinal cell line and *in vivo* rat model. Currently I am working at Elvesys Microfluidic Innovation Centre, Paris as a Marie Curie Individual Fellow. I am working here on multicompartment breast tumor-on-chip system to study the tumor microenvironment and deciphering its role in metastasis.

Selected Publications**:**

- Subia B, Reinisalo M, Dey N, Tavakoli S, Subrizi A, Ganguli M, Ruponene M (2019). Nucleic acid delivery to differentiated retinal pigment epithelial cells using cell-penetrating peptide as a carrier. European Journal of Pharmaceutics and Biopharmaceutics 140; 91-99.
- Subia B, Dey T, Sharma S, Kundu SC (2015).Target specific delivery of anticancer drug in silk fibroin based 3D distribution model of bone–breast cancer cells. ACS Applied Materials and Interfaces 7,4,2269-2279.
- Subia B, Chandra S, Talukdar S, Kundu SC (2014). Folate conjugated silk fibroin nanocarriers for targeted drug delivery. Integrative Biology 6;2, 203-214.

Tomosynthesis-Guided and Upright Stereotactic Biopsy

Sarah Martaindale, MD

The University of Texas MD Anderson Cancer Center, USA

This lecture will cover technical components of tomosynthesis-guided and upright stereotactic biopsy, such as biopsy unit set-up and patient preparation, as well as clinical components, including benefits, pitfalls, and lesions types which are especially benefit from this type of biopsy.

Objectives:
At the end of this session attendees will be able to:

1) Know the basics of patient positioning and unit set-up for tomosynthesis-guided and upright stereotactic biopsy

2) Understand the benefits of tomosynthesis-guided biopsy

3) Understand the pitfalls of tomosynthesis-guided and upright stereo biopsy

4) Review lesion types that may benefit from tomosynthesis-guided biopsy

Outline:

I: Introduction

II. Tomosynthesis-guided biopsy unit set-up and patient preparation

III. Benefits of tomosynthesis-guided and upright stereotactic biopsy

IV. Pitfalls of tomosynthesis-guided and upright biopsy

V. Examples of lesion types which may benefit from tomosynthesis-guided and upright biopsy

VI. Conclusion

VII. Questions

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Giant Mediastinal Mixed Germ cell tumor, a rare case report and review of literature

Abdulrahman Hakami

Jazan University , USA

Introduction: Germ cell tumors are relatively rare, embryologically derived from reproductive cells usually arise in the gonads. Mediastinal germ cell tumor estimated about 1-3 % of all germ cell tumors, generally seen in the anterior mediastinum and the metastatic lesions are mostly seen in the posterior mediastinum. The most aggressive germ cell tumor subtypes are choriocarcinoma, embryonal carcinoma and yolk-sac tumors. While seminomas only very rarely spread distantly. The presentations vary ranging from accidental findings on routine radiography to life-threatening respiratory and cardiovascular compromise, can also present as gigantic big intrathoracic germ cell tumor like our case.

Case report: 30 years old male patient, not known to have any chronic illness, referred from TB hospital center because history of dyspnea, cough and loss of appetite with weight loss for more than 4 months, no history of chest pain or hemoptysis. Chest x-ray done and showed complete obliteration of the right side of thorax, was suspected pleural effusion and diagnosed as case of pleural TB and empyema, started on ant tuberculosis drugs, antibiotics and received chest drain with a little bloody fluid. Patient not improved and referred to our hospital, Computed hospital of chest with contrast revealed a very big mas obliterating the right side of chest, pushing the trachea and mediastinum to the left side with minimal effusion in both sides. Pleural US revealed mass and effusion but no empyema. Differential diagnosis was mediastina mass, adenocarcinoma, thymic carcinoma, lymphomas, fibroma or fibrosarcoma. US guided transthoracic fine needle biopsy from the right side mass revealed mixed germ cell tumor. The patient's condition had rapidly deteriorated prior the confirming the

diagnosis or starting with treatments and died because of difficult airway breathing due to deviated and compressed airway and possible pneumothorax after transthoracic biopsy.

Conclusion: Germ cell tumors are aggressive and rapidly growing cancers, the previous literature reported the nature of the extragonadal mediastinal germ cell tumor can appear as Giant mass occlude whole lung, compressing the great vessels, adherent to chest wall, pericardium, and lung, like our case and this make a worse prognosis, The estimated event-free survival at 10 years after combined treatment is 80.4%. Chemotherapy, debulking and pneumoctomy are the treatment for such cases.

Dr. **Abdulrahman Hakami** Assistant professor of Medicine in Jazan University, Saudi Arabia Researcher in Amsterdam University, The Netherlands. He did the speciality of internal medicine and respiratory diseases in Sweden and has completed a clinical and research fellowship in interventional pulmonology and interstitial lung diseases at Amsterdam University, the Netherlands. He interested in research about lung cancer, Mycobacterial tuberculosis and Interstitial lung diseases. He has reviewed a lot of manuscripts in different journals. Editors in BMC and BMJ journals.

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Fungal infection and chemotherapeutic response and dose relationship

Amany Nafeh

Assiut University, Egypt

Abstract: not provided

DAY 3

EIGHTH SESSION

CHAIR PERSONS

Gloria Su , Danny Dhanasekaran and Weronika Lucas Grzelczyk

SESSION 8	CHAIRS **Gloria Su (USA) – Danny Dhanasekaran (USA) – Weronika Lucas Grzelczyk (Poland)**
	Short Communication (10 min)
11.00	**Title: MGMT, BRCA1 And MEG3 methylation status in triple-negative breast cancer** **Sylwia Paszek, University of Rzeszow, Poland**
11.10	**Title: Cyr61 promotes tip cell activity in tumor angiogenesis: the role of VEGFR2-Hippo pathway** **Hyeonha Jang, Uttam Ojha, You Mie Lee, Kyungpook National University, South Korea**
11.20	**Title: Sphingosine Kinase-2 in oral squamous cell carcinoma** **Lais Brigliadori Fugio, University of São Paulo, Brazil**
11.30	**Title: DNA Methylation Markers for Noninvasive Detection of Early Stage Colorectal Cancer** **Yanqun Liu, Singapore General Hospital, Singapore**
11.40	**Title: Quantification of HER2 protein Using Multiple Reaction Monitoring-Mass Spectrometry in Formalin-Fixed Paraffin-Embedded (FFPE) Breast Cancer Tissue Specimens** **Youngsoo Kim, Seoul National University, South Korea**
11.50	**Title: Role of autophagy in nanoparticle toxicity in ovarian cancer cells** **Alessandra Ferraresi, Università del Piemonte Orientale, Italy**
12.00	**Title: Glucose-dependent autophagy control of cancer cell migration** **Chiara Vidoni, Università del Piemonte Orientale, Italy**
	Flash Communication (5 min)
12.10	**Title: A typical bronchial carcinoid with postobstructive mycobacterial** **Abdulrahman Hakami, Jazan University, KSA**
12.15	**Title: Trousseau's Syndrome in association with Lung Adenocarcinoma** **Abdulrahman Hakami, Jazan University, KSA**

12.20	**Title: Delphinidin Chloride and its hydrolytic metabolite Gallic Acid Promote Differentiation of Regulatory T cells and have an Anti-inflammatory effect on the Allograft Model** **Kwang Woo Hwang, Chung-Ang University, South Korea**
12.25	**Title: Association between heavy metal cadmium and the Warburg Effect in Breast Cancer – preliminary results** **Jabłońska Ewa, Nofer Institute of Occupational Medicine, Poland**
12.30	**Title: The oyster can adapt to a harsh environment in the marine coast: Does it Mimick cancer cells?** **Charlotte Corporeau, Ifremer, France**
12.35	**Title: Resveratrol-induced modulation of Non-coding RNA in ovarian cancer cells** **Letizia Vallino, Università del Piemonte Orientale, Italy**
12.40-12.45	**Title: The microbiota-derived metabolite Butyrate inhibits colorectal cancer cell migration via modulation of autophagy** **Eleonora Secomandi, Università del Piemonte Orientale, Italy**

DAY 3

SHORT COMMUNICATION

MGMT, *BRCA1* and *MEG3* Methylation Status in Triple-Negative Breast Cancer

Sylwia Paszek[1], Agnieszka Kołacińska[2,3], Marcin Braun[4], Ewa Kaznowska[1], Dorota Jesionek-Kupnicka[4], Edyta Barnaś[1], Izabela Zawlik[1#]

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[2] Department of Head and Neck Cancer Surgery, Medical University of Lodz, Paderewskiego 4, 93-509 Lodz, Poland

[3] Breast Unit, Cancer Center, Copernicus Memorial Hospital, Pabianicka 62, 93-513 Lodz, Poland

[4] Department of Pathology, Chair of Oncology, Medical University of Lodz, Paderewskiego 4, 93-509 Lodz, Poland

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BACKGROUND AND AIM: Breast cancer is one of the most common cancer in women worldwide. The most severe type of breast cancer is triple-negative breast cancer (TNBC) due to unfavorable clinical course and poor prognosis. The development of cancer is often associated with dysregulation of epigenetic mechanisms, including DNA methylation. The aim of our study was to evaluate *MGMT* (O6-methylguanine DNA methyltransferase), *BRCA1* (breast cancer 1) and *MEG3 (*maternally expressed 3) methylation in TNBC.

EXPERIMENTAL PROCEDURE: In this study 44 TNBC patients were included. The methylation status of the *MGMT*, *BRCA1* and *MEG3* promoter regions were analysed by methylation-specific PCR.

RESULTS: *MGMT*, *BRCA1* and *MEG3* promoters methylation was found in 70.4%, 61.3% and 61.3% of TNBC patients, respectively. Moreover, we have shown that the frequency of *MGMT* and *BRCA1* methylation is higher in older patients compared to younger patients (p-value for *MGMT* is p=0.0194 and for *BRCA1* is p=0.0188).

Additionally, in one of TNBC patient with glandular and squamous histopathological components, it was shown that the promoters status of all analysed genes, changed from methylated to unmethylated after chemotherapy of this patient.

CONCLUSION: The high frequency of *MGMT*, *BRCA1* and *MEG3* methylation indicates that epigenetic changes are important mechanisms in breast cancer. Moreover, our results indicates that *MGMT* and *BRCA1* methylation may have greater impact in the development of breast cancer in older patients compared to younger patients.

FUNDING SOURCE: This study was supported by the University of Rzeszow.

KEYWORDS: TNBC, DNA methylation, *MGMT*, *BRCA1*, *MEG3*.

Professor Izabela Zawlik is a Head of Department of Genetics at University of Rzeszow in Poland since 2013. She worked as a Postdoctoral Fellow (2006-2008) at The International Agency for Research on Cancer (WHO) in Lyon in France. She worked at Department of Molecular Pathology and Neuropathology at Medical University of Lodz in Poland from 2003 to 2013. She has got experience with research work on field of molecular biology of cancers and neurodegenerative diseases. Her whole bibliography includes 50 scientific publications with total Impact Factor 110 and h-index 15.

Age of Presenter: 29 years

In 2014 **Sylwia Paszek** has graduated in Biotechnology at the University of Rzeszow, Poland and obtained the title of M.Sc. Since 2016 she has been working as an assistance at the University of Rzeszow. Since 2018 she is also a PhD student at the University of Rzeszow. She involved in many scientific projects concerning molecular biology of cancers.

The most representative publications are as follows:

1. Paszek S, Gabło N, Barnaś E, Szybka M, Morawiec J, Kołacińska A, Zawlik I. Dysregulation of microRNAs in triple-negative breast cancer. *Ginekol Pol*. 2017;88(10):530-536. doi:10.5603/GP.a2017.0097.

2. Kołacińska A, Herman K, Morawiec J, Paszek S, Zawlik I, Śliwczyński A. Improvement in outcomes of breast cancer patient treatment in Poland in the 21st century. *Breast J*. 2019;25:474-478. doi:10.1111/tbj.13245

3. Chaber R, Gurgul A, Wróbel G, Haus O, Tomoń A, Kowalczyk J, Szmatoła T, Jasielczuk I, Rybka B, Ryczan-Krawczyk R, Duszeńko E, Stąpor S, Ciebiera K, Paszek S, Potocka N, Arthur CJ, Zawlik I. Whole-genome DNA methylation characteristics in pediatric precursor B cell acute lymphoblastic leukemia (BCP ALL). *PLoS* One. 2017:10;12(11):e0187422. doi:10.1371/journal.pone.0187422

Cyr61 promotes tip cell activity in tumor angiogenesis: the role of VEGFR2-Hippo pathway

Hyeonha Jang

Uttam Ojha, You Mie Lee, Kyungpook National University, South Korea

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Abstract: not provided

Sphingosine Kinase 2 in Oral Squamous Cell Carcinoma

Lais Brigliadori Fugio1*, Andréia Machado Leopoldino1

1 Department of Clinical Analysis, Toxicology and Food Sciences,
School of Pharmaceutical Sciences of Riberião Preto, University of São Paulo, Ribeirão Preto, SP, Brazil.

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Background and aim: sphingosine kinase 2 (SK2) is one of the enzymes responsible for producing sphingosine-1-phosphate (S1P)1. Recently, SK2 has been associated with protective autophagy and survival, and regulation of p21 in breast and colon cancer cells2; 3. However, the role of SK2 in oral squamous cell carcinoma (OSCC) is still unclear. Thus, our study aims to investigate the involvement of SK2 in autophagy and proliferation in OSCC cells.

Experimental procedure: HN13 and HN12 (OSCC) cell lines were transduced with short hairpin RNA interference against SK2 and a lentiviral vector containing cDNA for SK2, respectively. Cell cycle analyses were performed by propidium iodide staining and flow cytometry. Western blotting and
immunofluorescence assays were adopted to analyze protein levels and cellular distribution.

Results: HN13 cells with SK2 knockdown showed a decrease of pAkt, c-MYC, and LC3 levels (an autophagy marker) while p21 was increased. Besides that, the SK2 knockdown in HN13 cells caused cell arrest in S phase with reduction of the cells in G2/M. SK2 overexpression in HN12 cells leads to an increase of pAkt, c-Myc, and LC3 levels.

Conclusion: Our work is the first to demonstrate the role of SK2 in proliferation and autophagy in OSCC cells. Other studies are in progress to understand the molecular

mechanism underlying the role of SK2 and its potential as a target. Financial support: FAPESP (grant: 2016/19103-2; scholarship: 2018/14225-8, CAPES, CNPq- Brazil.

Keywords: sphingosine-1-phosphate, autophagy, proliferation, oral cancer, sphingosine kinase.

References:

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Lais Brigliadori Fugio completed her graduation in Chemistry from University of São Paulo (2015), Brazil. Currently, she is a Ph.D. candidate in Biotechnology and Biosciences at the School of Pharmaceutical Sciences of Ribeirão Preto, University of São Paulo, Brazil. She is working on the project focusing on the involvement of SK2 regulation of oral cancer cell metabolism.

DNA Methylation Markers for Noninvasive Detection of Early Stage Colorectal Cancer

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BACKGROUND AND AIM: Colorectal cancer (CRC) is the most common cancer in Singapore. Earlier detection enhances chances of a cure and facilitates reducing CRC mortality rates. Colonoscopy is currently the gold standard for CRC diagnosis, but a somewhat troublesome and invasive procedure makes its acceptance not high in the general public as a screening tool. Epigenetic silencing of tumor-related genes by promoter methylation is common in CRC, but no biomarker has been proven to be individually of sufficient sensitivity or specificity in routine clinical practice. Aim of this study is to identify tumor-derived methylated genes in the serum of stage IIA CRC and assessed their diagnostic potentials for early stage of colorectal cancer.

EXPERIMENTAL PROCEDURE: In this prospective study, DNA methylation levels were measured by quantitative methylation-specific PCR (QMSP). Two genes (*PPP1R3C* and *ADHFE1*) were first investigated in serum samples of an exploratory set of stage IIA CRC case-controls. Methylation results were verified in the sera of a test set compromising 50 stage IIA cases and 50 age-gender-matched healthy controls. Receiver operating characteristic curve (ROC) was constructed for assessment of assay performance.

RESULTS: Serum methylation levels of *PPP1R3C* and *ADHFE1* were significantly higher in stage IIA patients as compared to healthy controls (both $P<0.001$, Mann-Whitney *U* test). Areas under the receiver operating curve (AUCs) using serum methylation levels of *PPP1R3C* and *ADHFE1* were 0.60 [95% confidence interval (CI), 0.48-0.71] and 0.73

(95% CI, 0.62-0.83), respectively. At a specificity of 80%, the assay sensitivities of methylated *PPP1R3C* and *ADHFE1* were 26% and 56%, respectively.

CONCLUSION: Serum methylation levels of *ADHFE1* might be useful for minimally invasive detection of early stage II colorectal cancer. Validation study in larger and independent cohorts and identification of additional markers are necessary.

KEYWORDS: Early Diagnosis, Colorectal Cancer, Cell-free DNA, Blood Biomarkers, DNA Methylation,

Yanqun Liu was initially trained in Medicine. Later on, she acquired a PhD in National University of Singapore. She is currently a Senior Principal Scientist in Singapore General Hospital. Her research interests include biomarker studies for early diagnosis or recurrence monitoring of sporadic colorectal cancer, as well as riddle-solving hereditary colorectal cancer syndromes including Lynch Syndrome. Representative publications are as below.

1) **Y Liu**, MH Chew, CK Tham, CL Tang, SYK Ong, Y Zhao. Methylation of serum *SST* gene is an independent prognostic marker in colorectal cancer. *Am J Cancer Res*. 2016;6(9):2098-2108
2) CK Tham, MH Chew, R Soong, JF Lim, MK Ang, CL Tang, Y Zhao, SYK Ong, **Y Liu**. Postoperative Serum Methylation Levels of *TAC1* and *SEPT9* Are Independent Predictors of Recurrence and Survival of Patients with Colorectal Cancer. *CANCER*. 2014; 120: 3131-41. Doi: 10.1002/cncr.28802.
3) **Y Liu**, MH Chew, XW Goh, SY Tan, et. al. Systematic Study on Genetic and Epimutational Profile of a Cohort of Amsterdam Criteria-Defined Lynch Syndrome in Singapore. *PLOS ONE*. 2014; 9: e94170. Doi: 10.1371/journal.pone.0094170.

Colossal Facet
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Quantification of HER2 protein Using Multiple Reaction Monitoring-Mass Spectrometry in Formalin-Fixed Paraffin-Embedded (FFPE) Breast Cancer Tissue Specimens

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Human epidermal growth factor receptor 2 (HER2) protein is often overexpressed in breast cancer and is correlated with a worse prognosis and thus accurate detection of HER2 by using optimum techniques is crucial to provide appropriate cares for patients. However, none of the techniques are the universal gold standard to detect accurate HER2 status. In this context, we established a multiple reaction monitoring (MRM) assay to quantitate HER2 protein that improves upon existing methods in differentiating between each HER2 status in FFPE tissue specimens. We developed a targeted proteomic assay based on multiple reaction monitoring mass spectrometry (MRM-MS) and quantified levels of HER2-MRM protein in breast cancer FFPE tissues.

We analyzed a total of 210 breast cancer FFPE tissue specimens which were comprised of HER2 0 (n=30), HER2 1+ (n=30), HER2 2+FISH- (n=61) HER2 2+FISH+ (n=59), and HER2 3+ (n=30). We applied normalization factors that can represent the tumor size to simplify the overall experimental work-flow and raise the accuracy and precision of the results of HER2 quantification. In this context, the ratio between the quantification data of HER2 peptides by MRM assay and the normalization factor can be a new factor for determining HER2 status.

In order to select the most suitable normalization factor that can differentiate ambiguous IHC results of HER2 (HER2 2+FISH- versus HER2 2+FISH+) which cannot be

distinguished by IHC, area under the receiver operating curve (AUROC) values were calculated by using each normalized value of 120 HER2 2+ samples. In order to determine whether the data generated by MRM matched with the data obtained by IHC and FISH scores, the quantitative data of a HER2 peptide normalized by a Junctional adhesion molecule A (JAM1) peptide with the highest AUROC values were used. The Mann Whitney U test determined that significant differences were found in all the HER2 and FISH groups, and especially the MRM data can distinguish between HER2 2+FISH- and HER2 2+FISH+ ($p < 0.000$), which cannot be differentiated by IHC. In addition, the MRM data distinguished the HER2 positive group that was expected to benefit from trastuzumab therapy and HER2 negative group ($p < 0.000$).

We developed an experimental work-flow that are simple and clear enough to automation by introducing normalization factors for accurate HER2 status determination through MRM assay. The MRM assay that we developed clearly distinguished the equivocal HER2 status that could not be classified by the conventional method, IHC, as well as the overall HER2 classification. Our developed assay using MRM for determining HER2 status would provide clinicians with valuable diagnostic information and ensure that all patients whose breast cancers express HER2 proteins have the opportunity to receive proper treatment.

Keywords: Breast cancer, HER2, Formalin-Fixed Paraffin-Embedded (FFPE), Normalization factor, Multiple Reaction Monitoring (MRM), Trastuzumab

Amino-functionalized Nanoparticles Promote Toxicity in Ovarian Cancer Cells by Impinging on Autophagy

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BACKGROUND In the last decades, nanotheranostics has obtained great attention for its potential application in biomedical field by combining multimodal imaging along with selective targeting therapy in the same nanoplatforms.[1] However, the contribution of metabolic, genetic or epigenetic features of tumor cells and tumor microenvironment in the cellular response to the nanoparticles have not fully addressed.[2]

AIM We investigated the cellular stress response to polystyrene nanoparticles (PS-NPs) functionalized with amino groups in two ovarian cancer cell models differing in the expression, among others, of relevant proteins involved in endocytosis (caveolin-1, CAV-1) and in pro-survival/pro-death pathways (PTEN and TP53).

RESULTS NH_2-PS-NPs were toxic in both cell lines, leading to primary necrosis which was time- and dose-dependent, yet with different mechanisms of toxicity. In OVCAR3 cells, which are PTEN and TP53 mutated and CAV-1 deficient, autophagy was insufficient to protect the cells from NH_2-PS-NPs toxicity. Autophagy inducers prevented while autophagy gene silencing exacerbated NH_2-PS-NPs-induced cell death. By contrast, in OAW42 cells, which express wild-type PTEN, TP53 and CAV-1, NH_2-PS-NPs strongly impaired autophagosome formation, along with an increased production of the mitochondrial anion superoxide resulting in ATG4 inactivation.

Accordingly, resveratrol, a nutraceutical known to inhibits the formation of anion superoxide, rescued ATG4-mediated autophagy and reduced NH_2-PS-NPs toxicity.

CONCLUSIONS Taken together, our findings point out the relevance of the genetic background of target cells, that determine the type and consequences of the stress response elicited by the NPs. Our data outline the necessity of a better assessment of the genetic/epigenetic and metabolic status of the target cells when designing theranostics for cancer therapy, in fully agreement with the principle of personalized medicine.

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KEYWORDS Autophagy, Cell Death, Nanotheranostics, Polystyrene, Stress Response.

Age of presenter: 30

Alessandra Ferraresi received her PhD degree in Medical Sciences and Biotechnology at Università del Piemonte Orientale (Novara, Italy) in 2019 under the mentorship of Prof. Ciro Isidoro. From then, she is postdoctoral fellow in the Laboratory of Molecular Pathology and Nanobioimaging. She completed her Master's degree in Pharmaceutical Biotechnologies at Università di Bologna in 2014. She received her Bachelor's degree in Biotechnology at Università di Parma in 2011. Her current research mainly focused on cancer cell dormancy, the crosstalk between cancer cells and tumor microenvironment and the applications of nanotheranostics in cancer.

She has co-authored eleven articles published in peer-reviewed journals.

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Glucose-Dependent Autophagy Control of Cancer Cell Migration

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BACKGROUND and AIM: Because of its aggressiveness and of its diagnosis at the very late stage, remains Ovarian Cancer (OC)[1] one of the main leading cause of death among women[2]. IL-6 is an inflammatory cytokine over-expressed in serum and ascitic liquid of ovarian cancer affected patients[3]. One of the hallmarks of cancer is the so-called Warburg effect, which consists in an alteration of glucose metabolism[4]. The goal is to investigate the mechanisms underlying the involvement of glycolysis and its mechanistic link with autophagy in cancer cell migration.

EXPERIMENTAL PROCEDURE: To mimic a pro-inflammatory tumor microenvironment, we treated ovarian cancer cells with IL-6, in absence or presence of glucose. To examine the molecular pathways linking glycolysis and autophagy in cell motility, we employed the metabolically inert glucose analogues 2-Deoxy Glucose (2-DG). Additionally, we used RV, a nutraceutical with anti-cancer properties, known to interfere with the utilization of glucose.

RESULTS: We found that glucose is necessary for cell migration, with IL-6 promoting glucose uptake and cell motility. On the contrary, inhibiting the glucose uptake or its utilization blocks cancer cell migration while up-regulating autophagy.

CONCLUSION: Our data indicate that the up-regulation of autophagy promoted by glucose deprivation hampers ovarian cancer cell migration.

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KEYWORDS: glucose, mTORC1, migration, autophagy, HK2

Age of presenter: 32

Chiara Vidoni received her PhD degree in Medical Sciences and Biotechnology at Università del Piemonte Orientale (Novara, Italy) in 2017. She performed her PhD studies under the mentorship of Prof. Ciro Isidoro in the Laboratory of Molecular Pathology. She completed her Master's degree in Medical Biotechnologies at Università del Piemonte Orientale in 2012. She received her Bachelor's degree in Biotechnologies at Università del Piemonte Orientale in 2009. From 2017, she is postdoctoral fellow in Prof. Isidoro's Laboratory. Her current research focused on the role and regulation of autophagy in neurodegenerative diseases, cancer, cancer metabolism and regenerative medicine.

She has co-authored twelve articles published in peer-reviewed journals.

Publications:

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DAY 3

FLASH COMMUNICATION

Colossal Facet
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A typical bronchial carcinoid with postobstructive mycobacterial

Abdulrahman Hakami

Jazan University, USA

Abstract: not provided

Colossal Facet
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Trousseau's Syndrome in association with Lung Adenocarcinoma

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Background: Trousseau's syndrome (TS) is a hypercoagulability manifestation of the paraneoplastic syndrome (PNS), known as a variant of cancer-associated thrombosis and defined as a migratory thrombophlebitis found typically in patients with an underlying malignancy. TS commonly occurs in pancreatic cancer (24%), lung cancer (20%), prostate cancer (13%), stomach cancer (12%) then breast and colon cancer.

Case presentation: Here, we describe the case of 50 years old male patient, nonsmoker, he was doing checkup for his job, found to have mantoux test (TBT) highly positive so ordered for him chest x-ray. He has a previous chronic history of burning sensation of both feet, respond to analgesic drugs. No history of shortness of breath or cough. No history of fever, night sweating, weight loss, loss of appetite and fatigue. Auscultation of Chest x-ray revealed a mass in left upper lobe of lung. Computed Tomography chest showed left lingual superior segment lobulated mass 5.5 x 4.3 cm with left hilar and mediastinal lymph node enlargement. Also in the CT reported bone metastasis in vertebra that confirmed with bone sacn. Tumor markers were negative. CT guided biopsy for this lesion in the left upper chest done and the histopathology result showed poorly differentiated adenocarcinoma, molecular studies: EGFR, ALK, ROS, PD-1 were negative. Patient referred to the oncology center as case of lung adenocarcinoma with distant metastasis, stage T4bN2bM1 and started in chemotherapy Cisaplatin and Alimta. Spirat CT revealed incidental finding of multiple filling defect indicate segmental pulmonary embolism, because of legs pain done also Doppler of lower limb and showed deep venous thrombosis in the left limb. Started with Enoxaparin full dose. This case report indicate a Trousseau's syndrome (TS)

Cancer- associated thrombosis. The patient after receiving first cycle chemotherapy, was discharged on Enoxaparin and was stable and return to his job.

Conclusions: TS is a paraneoplastic manifestation must consider in patients with advanced stages of cancer regardless of the primary site of the cancer. In lung cancer, the paraneoplastic syndrome presented more frequently with small cell carcinoma in 10% but regarding TS in the literature, previous cases reported adenocarcinoma was the most prevalent histology associated thrombosis.

Keywords: Trousseau syndrome, adenocarcinoma, Cancer-associated thrombosis

Dr. **Abdulrahman Hakami** Assistant professor of Medicine in Jazan University, Saudi Arabia Researcher in Amsterdam University, The Netherlands. He did the speciality of internal medicine and respiratory diseases in Sweden and has completed a clinical and research fellowship in interventional pulmonology and interstitial lung diseases at Amsterdam University, the Netherlands. He interested in research about lung cancer, Mycobacterial tuberculosis and Interstitial lung diseases. He has reviewed a lot of manuscripts in different journals. Editors in BMC and BMJ journals.

Delphinidin Chloride and Its Hydrolytic Metabolite Gallic Acid Promote Differentiation of Regulatory T cells and Have an Anti-inflammatory Effect on the Allograft Model

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Regulatory T cells (Tregs) control the reactivity of other T cells to prevent excessive inflammatory responses. They also plays a role in preventing autoimmune diseases; but when they are overproduced, they decreased vital immunity, which can lead to invasion of external pathogens. Therefore, it is most important in preventing the development of immune diseases to maintain the homeostasis of these cells. Delphinidin chloride is an anthocyanidin and known to have anti-oxidant activities. However, its structure is very unstable and easily decomposed. One of these degradation products is gallic acid, which also has anti-oxidant effects. In this study, we examined the effect of these materials on Tregs in controlling immune response. It was found that these materials further promote differentiation into Tregs, and TGF-*β* and IL-2 related signals are involved in this process. Furthermore, it was verified that a variety of immunosuppressive proteins were secreted more, and the function of induced Tregs was also increased. Finally, in the allograft model, we could find a decrease in activated T cells when these materials were treated because they increased differentiation into Tregs. Therefore, these two materials are expected to become new candidates for the treatment of diseases caused by excessive activation of immune cells, such as autoimmune diseases.

Practical Application: Delphinidin, a kind of anthocyanin rich in pigmented fruits, and its hydrolytic metabolite, gallic acid, are known to have antimicrobial and anti-oxidant properties. In this experiment, it was shown that delphinidin and gallic acid had an

effect of increasing the differentiation of regulatory T cells, and the effect of suppressing the function of memory T cells was also observed. Due to these functions, delphinidin and gallic acid might have the potential to be used as immune suppressive agents in organ transplant and autoimmune disease patients or be a model for food development associated with the immune system.

Keywords: delphinidin, gallic acid, Treg, allograft model

Association between Heavy Metal Cadmium and the Warburg Effect in Breast Cancer – Preliminary Results

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BACKGROUND AND AIM: Warburg effect is a cancer hallmark described as reprogramming of energy metabolism, in which cells produce energy mainly due to glycolysis instead of oxidative phosphorylation. The Warburg effect is extremely important for the survival of tumor cells, particularly under hypoxia, but it may also occur under aerobic conditions (hence it is called the aerobic glycolysis). Although Warburg effect was discovered almost 100 years ago, it is still not known whether it is a cause or a consequence of cancer. Interestingly, there are few studies investigating the association between the known carcinogenic factors and the Warburg effect. The aim of this study was to analyze the association between carcinogenic metal **cadmium (Cd)** and the Warburg effect in **breast cancer**.

EXPERIMENTAL PROCEDURE: We conducted observational study among 100 women with breast cancer, from whom fragments of tumor tissue and tumor-adjacent tissue were collected, in order to compare Cd contents and molecular effect of the Warburg effect. In both types of tissue we determined Cd content and the expression of mRNA of HIF-1α (key driver of the Warburg effect) and other proteins associated with the

Warburg effect (including glucose transporters, glycolytic enzymes or kinases regulating glycolysis). In addition urinary Cd concentration as a marker of environmental exposure was analyzed. To investigate the effect of Cd on the Warburg effect in vitro, we analyzed molecular and metabolic markers of the Warburg effect (lactate concentration and pyruvate kinase activity) in MCF-7 cells exposed to non-toxic, environmentally relevant concentrations of Cd for 72 hours (short term exposure) and for 6 months (imitation of chronic exposure to Cd).

RESULTS: In the preliminary study of 15 patients we observed significant positive correlation between urinary Cd concentration and the expression of HIF-1α, both in tumor ($r=0.80$, $p<0.001$) and tumor-adjacent tissues ($r=0.75$, $p<0.001$). Cd content in tumor tissue was also significantly correlated with the expression of PDK1 (pyruvate dehydrogenase kinase 1; $r=0.48$, $p<0.001$). Preliminary data analysis of MCF-7 cell line showed also that HIF-1α expression was significantly increased upon Cd exposure (1 uM – 20 uM).

CONCLUSION: Preliminary results of this study may suggest a possible link between Cd exposure and the molecular effects of the Warburg effect. Complete data analysis, including metabolic markers, will allow to formulate final conclusions.

KEYWORDS: cadmium, Warburg effect, HIF-1α, glycolysis, breast cancer

Ewa Jablonska, PhD – graduated from Medical University of Lodz/Poland (Public Health Department, 2004) and Technical University of Lodz/Poland (Biotechnology, 2006). Main scientific interest: essential trace elements and heavy metals in cancer, mainly selenium and selenoproteins, genetic and epigenetic cancer markers. Representative publications:

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Colossal Facet
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The Oyster Can Adapt to a Harsh Environment in the Marine Coast: Does It Mimick Cancer Cells?

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BACKGROUND AND AIM. The tumor physical microenvironment is extreme. Interestingly, the rocky intertidal zone is among the most physically harsh environments on earth. The oyster *Crassostrea gigas*, libving in this habitat, is among the champion of physiological adaptation to extreme environments. Our hypothesis is that environemental adaptation of oyster cells can mimic cancer cells inside the tumor. **EXPERIMENTAL PROCEDURE.** Oysters were challenged to three extreme environments in the field, at high, medium and low bathymetric levels. Biochemical analysis were done to identify the environmental responses. **RESULTS** At two times during the experiment, we sampled all the organs of oysters in the field, extracted total proteins from flesh, and performed laboratory analysis, in order to obtain a rapid picture of metabolic activities linked with extreme environmental responses. First results demonstrated that challenged oysters in high/medium bathymetry exhibited a low weight gain, increased HK activity and increased mitochondrial functioning. We also quantified an up-regulation of AMPK activation, a key energy-sensor that controls glucose, lipid and protein metabolism in *C. gigas*. Interestingly, up-regulation of AMPK was initially reported as a hallmark of cancer cells, to support the high energy demand of highly proliferative cells. **CONCLUSION** We propose the oyster as a new model for cancer research, to identify mechanisms underlying the ability of cells to adapt a harsh

environment. The oyster is a marine invertebrate that evolved 500 millions years ago and we are convinced that it could help us to identify common ancestral pathways for cell adaptation to a harsh environment, for a better understanding of cancer cells functioning inside the tumor.

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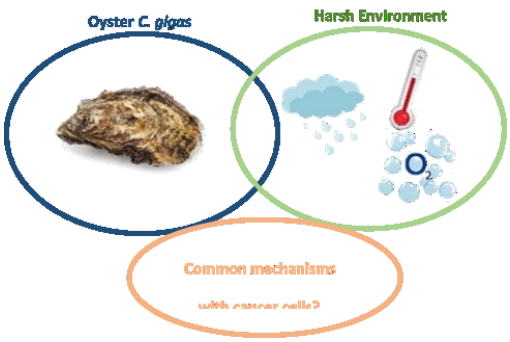
Figures.



Can the oyster be a new model for cancer research ?

KEYWORDS. *Environment, invertebrate, metabolism, biochemistry, omics*

I obtained my phD in molecular and cellular biology in Paris in 1998. During 10 years, I conducted post-doctoral research to study signaling pathways in vertebrate species. Since 2012, as a marine biologist, I am studying the impact of climate change on the functioning of marine animals, more specifically bivalve molluscs. My expertise is to quantify the physiological and metabolic state of the oyster *Crassostrea gigas* in response to changes in environmental factors (temperature, oxygen, salinity, pH, nutrients). I conduct integrative physiological approaches, from genes to phenotypes, by using experimental field approaches (on foreshore) as well as animal manipulations under laboratory conditions, combined with cellular and molecular global omics analyzes.

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Resveratrol-Induced Modulation of Non-Coding RNA in Ovarian Cancer Cells

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BACKGROUND AND AIM: The 90% of human genome is transcribed and, of this, only the 2% encodes proteins; the remaining sequences enclose non-coding genes [1; 2]. Non-coding RNAs (ncRNAs) play a crucial role in the regulation of several biological processes and their dysregulation may influence cancer development, functioning as oncogenes or tumor suppressors; ncRNAs generally are divided into two main groups based on size: long non-coding RNAs (lncRNAs) of about 200 nucleotides, acting as positive or negative transcription modulator, and microRNAs (miRNAs) of about 20-22 nucleotides, acting as post-transcriptional silencing molecules [3, 4]. The aim of our work was to investigate whether Resveratrol (RV), a polyphenolic compound with anticancer properties [5], could modulate ncRNAs in ovarian cancer cell lines.

EXPERIMENTAL PROCEDURE: Ovarian cancer cells were treated with RV (100 μM). Total RNA was isolated from the cells and mRNA was amplified and labeled. Labeled specimens were fragmented and hybridized to Human Whole Genome Oligo Microarrays. 100 ng of total RNA were treated following the miRNA microarray protocol. RNA was dephosphorylated, denaturated, ligated and labeled. Samples were hybridized to Human miRNA Microarray. DIANA TOOLS was used to retrieve predicted microRNA targets and Gene Ontology (GO) for predicting their involvement in biological processes.

RESULTS: We show that Resveratrol (RV) modulates non-coding transcripts that impact on cancer cell features.

CONCLUSION: Our data support the view that RV treatment can be effective in cancer therapy on regulating epigenetic mechanisms involved in cancer development.

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KEYWORDS: miRNA, long non-coding RNA, epigenetics, polyphenol, treatment

Age of Presenter 24

Letizia Vallino received her Bachelor's degree in Biology at Università del Piemonte Orientale in Vercelli (Italy) in July 2017. She completed her Master's degree in Biology at Università del Piemonte Orientale in Alessandria (Italy) in July 2019. In March 2018 to present, she works in Laboratory of Molecular Patology under the supervision of Prof. Ciro Isidoro. In October 2018 she was selected speaker flash communication at the "International workshop NO-CANCER 2018 – Understanding cancer cell biology to improve diagnosis and therapy" in Novara; in July 2018 she was selected speaker flash communication at the "2nd World Congress on Cancer" in Bologna (Italy). Her current research focused on cancer biology, particularly cancer-related autophagy, cancer metabolism and epigenetic control.

The Microbiota-derived Metabolite Butyrate Inhibits Colorectal Cancer Cell Migration via Modulation of Autophagy

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BACKGROUND Colorectal cancer (CRC) is the third most common cause of cancer deaths worldwide. The etiology of CRC involves host genetic predisposition and environmental factors, among them the diet plays an important role. The proportion of dietary fiber and meat assumed, influences the composition of intestinal microbiota, which get energy from ingested food [1]. One of the main metabolites produced by gut microbiota is the short chain fatty acid butyrate. Butyrate exerts a beneficial role in the maintenance of intestinal epithelium integrity through various mechanisms [1]. Autophagy is of the main cellular process which promotes a balanced macromolecular turnover and guarantees cell homeostasis [2].

AIM We studied the anti-migratory and anti-inflammatory properties of butyrate, a probiotic metabolite, in a colorectal cancer cellular model. Furthermore, we investigated the molecular pathways underlying these effects, with a particular focus on autophagy.

EXPERIMENTAL PROCEDURE HCT116 colorectal cancer cells were treated with 5mM sodium butyrate and 50 ng/ml interleukin-6. In order to study cell motility a wound healing scratch assay was performed. Cellular homogenates were employed for protein expression studies through western blot analysis. Immunofluorescence was performed on fixed cells.

RESULTS We found that butyrate counteracts colorectal cancer cell migration, even in the presence of interleukin-6 (IL-6), a well known pro-inflammatory cytokine. This

effect is accompanied with a reduced expression of activated STAT3 and Twist1. Furthermore, the probiotic metabolite prevents IL-6-induced expression of N-cadherin, a typical hallmark of epithelial-to-mesenchymal transition. In addition, butyrate strongly accelerates the autophagy flux, alone and in co-presence with IL-6, suggesting autophagy as a putative mechanism responsible for slowing down cell motility.

CONCLUSION Taken together, our findings identified anti-cancer properties of butyrate, in particular its ability to counteract IL-6-induced colon cancer cell migration, by upregulating autophagy.

KEYWORDS Colon Cancer, microbiota, butyrate, autophagy

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Age of presenter: 26

Eleonora Secomandi is a PhD student in Medical Sciences and Biotechnology at Università del Piemonte Orientale (Novara, Italy), working under the mentorship of Prof. Ciro Isidoro in the Laboratory of Molecular Pathology. She completed the Master's degree in Medical Biotechnologies with honors at Università del Piemonte Orientale di Novara in 2018. She received her Bachelor's degree in Biological Sciences at Università del Piemonte Orientale in 2016. Her current research focused on cancer biology, protein synthesis and regulation of autophagy in cancer.

She has co-authored five articles published in peer-reviewed journals.

Representative Careers:

August – September 2017 Summership at Clinical Investigative Center, Inserm 1431, University of Franche-Comté, Besançon, France.

Scientific Publications:

- Vidoni C, Ferraresi A, **Secomandi E**, Vallino L, Gardin C, Zavan B, Mortellaro C, Isidoro C. Autophagy drives osteogenic differentiation of human gingival mesenchymal stem cells. Cell Commun Signal. 2019 Aug 19;17(1):98. doi: 10.1186/s12964-019-0414-7.
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DAY 3

NINETH SESSION

CHAIR PERSONS

Judita Kinkorovà and Michael Green

SESSION 9	CHAIRS **Judita Kinkorovà (Czech R) – Michael Green (USA)**
14.05-14.30	**Title: Parasites and cancer** **Omar M. Amin, Parasitology Center, Inc., USA**
14.30-14.55	**Title: Role of Biobanks in Cancer Research** **Judita Kinkorová, University Hospital Pilsen, Czech Republic**
14.55-15.15	**Title: Cancer chemoprevention with mitochondria-targeted compounds IL** **Ming You, Medical College of Wisconsin, USA**
15.15-15.30	**Title: Numerical chromosomal abnormalities are indicative of malignant biliary stricture OC** **Eman Mosaad, Assiut University, Egypt**
15.30-15.40	**The Efficacy of Ketogenic Diet with Concomitant Intranasal Perillyl Alcohol as a Novel Strategy for Therapy of Recurrent Glioblastoma OC** **Clovis O. Da Fonseca, Fluminense Federal University, Brazil**

Parasites and Cancer

Dr. **Omar M. Amin**

Parasitology Center, Inc., USA

This Power Point presentation is based on our work at Parasitology Center, Inc. (PCI), in Scottsdale, Arizona, USA and covers the diagnosis, pathology, relationships with cancer, and treatment of human parasitic infections in the United States based on our own patient history and testing. The conceptual thesis and practical observations of extensive damage of parasites to human tissues and the initiation of host defense strategies causing out of control cell divisions leading to metastasis is emphasized. A brief introduction to laboratory procedures, misdiagnoses/mistreatment, and impact on public health, especially cancer, is made. A systematic treatment of protozoan and helminth (worm) parasites follows, emphasizing epidemiology and exposure, symptoms, and gross pathology. Herbal and allopathic remedies including our own anti-parasitic herbal product Freedom/Cleanse/Restore are presented. All topics are illustrated with labeled pictures of the various kinds of parasites and their gross pathology in human tissues, when applicable. The presentation is followed by a brief discussion of case histories and treatment of intestinal pathogenic bacteria that usually cause GI symptoms similar to those caused by intestinal parasites.

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Role of Biobanks in Cancer Research

Judita Kinkorova

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BACKGROUND AND AIM: Biobanks are an important tool for biomedical research and a pillar of personalized medicine. Biobanks are collections of biological material and the associated data and information stored in an organized system, for a population or a large subset of population (OECD definition) [1]. During last three decades the role of biobanks has increased dramatically. They act as sources for wide range of biomedical research and support the basic principles of personalized medicine. They contribute to prevention, early diagnosis, prognosis, right treatment, therapy monitoring and optimal approach to a patient [2]. Cancer was and remains as one of the main causes of mortality and morbidity worldwide. The number of cancers especially rare cancers make cancer diseases serious candidates for personalized medicine approaches.

How can biobanks contribute to the process of cancer treatment?

Biobanks as sources of various human biological material from different patients, form different regions, males or females, young or old, with other comorbidities, before and after surgery, from different social and environmental associations, different ethnic groups and others, offer wide range of samples for any type of research. Based on these characteristics, biobanks are a corn stones for new biomarkers discoveries for new drugs discoveries for new techniques and technologies applications and innovations [3]. On the other hand, data and information connected with samples are another source for modelling, data applications and artificial intelligence applications, with respect to ethical, legal and social issues. Personalized medicine principles guarantee the best possible approach to every patient it means prevention, early diagnosis,

treatment and treatment monitoring. Biobanking is a phenomenon, that is intrinsically based on international collaboration, samples and data and information exchange, no one institution all over the world can cover all challenges offering by biobanking. Biobanking requires multidisciplinary international strategy.

CONCLUSION: Biobanks are efficient tool for new biomedical research and personalized medicine approach to every patient and contribute to support health care systems, international collaboration, biomedical research and innovation.

KEYWORDS: biobanks, personalized medicine, biomarkers, cancer treatment, innovations

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3. **Kinkorova, J.,** Topolcan, O., EPMAJ, 2018, 9(4), 345 – 353.

Dr. Judita Kinkorová is the manager of international research cooperation and affairs at University Hospital in Pilsen and Charles University, Faculty of Medicine in Pilsen. She is the manager of European project from FP7 focused on biobanking infrastructures, BBMRI-ERIC in Pilsen, and she is a manager of the hospital integrated biobank at University Hospital in Pilsen. Her main areas of interest are personalized medicine, biobanking and biomarkers. She is a member of editorial board EMPA Journal (European Association for Preventive, Predictive and Personalized Medicine) for biobanks and repositories. Dr. Kinkorová is a member of EPMA, European Association for Preventive, Predictive and Personalized Medicine, ISOBM, International Society of Oncology and BioMarkers, and EGTM European Group for Tumour Markers, and ISBER, International Society for Biological and Environmental Repositories.

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Cancer chemoprevention with mitochondria-targeted compounds

Ming You

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We synthesized two mitochondria-targeted compounds, mito-honokiol (Mito-HNK) and mito-lonidamine (Mito-LND), that facilitates its mitochondrial accumulation; this dramatically increases its potency and efficacy against highly metastatic lung cancer lines in vitro, and in orthotopic lung tumor xenografts and brain metastases in vivo. Both Mito-HNK and Mito-LND are >100-fold more potent than the parent compounds in inhibiting cell proliferation, inhibiting mitochondrial complexes, stimulating reactive oxygen species generation, and oxidizing mitochondrial peroxiredoxin-3. Interestingly, Mito-HNK appears to induce apoptosis via suppressing the phosphorylation of mitoSTAT3, while Mito-LND induces autophagic cell death via inactivating AKT/mTOR/p70S6K signaling. Both Mito-HNK and Mito-LND cause no toxicity in mice even when administered for eight weeks at >20 times the effective cancer inhibitory dose. A highly synergistic effect is observed when combining the two compounds and its mechanistic basis is being vigorously pursued. Collectively, these findings show that mitochondrial targeting compounds are a promising preventive/therapeutic approach to mitigate lung cancer development and brain metastasis.

Ming You is the Joseph F Heil Jr. Professor in Molecular Oncogenesis, director of disease prevention research center, and associate provost for cancer research at Medical College of Wisconsin (Milwaukee, Wisconsin). He received his medical degree in 1982 from Beijing Medical College and his PhD in pathology from the Medical College of Ohio in 1989. He was a visiting scientist at the National Institute of Environmental Health Sciences (NIEHS, NIH) and was Visiting Professor in the UK's Medical Research Council (MRC) Toxicology Unit at University of Leicester. He was a member of the Board of Scientific Counselors of the NCI, a member of the NCI's Cancer Susceptibility Think Tank and Cancer Chemoprevention Think Tank, and the chair of the Review Panel for Chemopreventive Agent Development Research Group (CADRG), Division of Cancer Prevention at the NCI. His publications focus on work in genetics and chemoprevention of lung cancer and his bibliography includes over 250 titles. He served on editorial boards of Cancer Research, Carcinogenesis, Cancer Prevention Research, Molecular Carcinogenesis, and PLoS One. He has mentored a large number of graduate students and post-doctoral fellows. His fields of expertise include lung carcinogenesis, genetic susceptibility, lung cancer chemoprevention and immunoprevention.

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Numerical chromosomal abnormalities are indicative of malignant biliary stricture

Eman Mosaad

Assiut University, Egypt

Abstract: not provided

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The Efficacy of Ketogenic Diet with Concomitant Intranasal Perillyl Alcohol as a Novel Strategy for Therapy of Recurrent Glioblastoma

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BACKGROUND: It has been hypothesized that persistent ketotic hypoglycemia might represent a potential therapeutic strategy against high-grade gliomas. Perillyl alcohol (POH) is a non-toxic, naturally-occurring, hydroxylated monoterpene that exhibits cytotoxicity against temozolomide-resistant glioma cells, regardless of O6-methylguanine-methyltransferase promoter methylation status. This study aimed to evaluate the toxicity and therapeutic efficacy of intranasal POH administered in combination with a ketogenic diet (KD) program for the treatment of patients with recurrent glioblastoma.

PATIENTS AND METHODS: Thirty two patients were divided into two groups - KD or standard diet, both associated with intranasal POH (n=17 and n=15, respectively). The nutritional status and anthropometric parameters of patients were measured. Patients that adhered to the KD maintained a strict dietary regimen, while receiving inhalation of POH (55 mg, four times daily) in an uninterrupted administration schedule for three months. Neurological examination and imaging analysis (magnetic resonance imaging) were used to monitor disease progression. Clinical toxicity and overall survival were correlated with tumor size, topography, extent of peritumoral edema, and frequency of seizures. In the KD patient, strict compliance with the KD was confirmed by

measuring the levels of ketone bodies in the urine (9/17 patients) at three times a week.

RESULTS: After three months of well tolerated treatment, we observed a *partial response* in 77.8% (7/9 patients), *stable disease* in 11.1% (1/9) and 11.1% (1/9) presented with *progressive disease*. Among the patients assigned to the standard diet (control group), the *partial response* was 25% (2/8 patients), *stable disease* was 25% (2/8), and *progressive disease* was 50% (4/8 patients). The patients assigned to the KD group presented with: reduced frequency of seizures; a slight increase in lean muscle mass; reduced serum lipid levels; and decreased low-density lipoprotein cholesterol (LDL-C) levels.

CONCLUSIONS: These results are encouraging and suggest that KD associated with intranasal POH may represent a viable option as an adjunct therapy for recurrent GBM

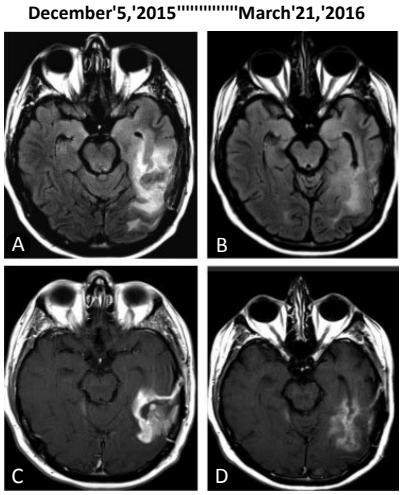

Figure 1. Effect of KD concomitant with inhalational POH in a patient with recurrent GBM. Representative brain MRI scans are shown from before the onset of treatment (left panels) and after 3 months of treatment (right panels). A,B: MRI axial fluid-attenuated inversion recovery (FLAIR); C,D: T1-weighted image (T1W) with contrast. Note marked reduction of peritumoral edema and tumor size after treatment.

DAY 3

CLOSING CEREMONY

CHAIR PERSONS

YJ Surh, D Dhanasekaran, J DiGiovanni,
YS Song, C Isidoro

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Special Issue

Papers from the 3rd World Congress Cancer 2019

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Special Issue Introduction

This Special Issue of Journal of Cancer Metastasis and Treatment is dedicated to the proceedings of the 3rd World Congress on Cancer 2019 going to be held in Prague (Czech Republic) in September 23-25 (http://colossalfacet.com/cancer-conference/).
The theme of the Conference Cancer-2019 is "New strategies to prevent, diagnose and treat Cancer based on Precision Medicine". The Conference will focus on the biomolecular mechanisms of cancer development, on the altered energetic metabolism in cancer cells, on the cancer patient's metabolic alterations, and on the diagnostic and therapeutic approaches. Major topics include: Pathogenetic mechanisms (oncogenes, oncosuppressors, DNA repair, cancer stem cells, epigenetics, inflammation, immune responses); Metabolism (Nutrition, Fasting, Obesity) and Cancer; Novel strategies for Prevention, Diagnosis and Therapy (imaging, Phytochemicals, nanotheranostics). The conference will gather academicians and young inspired scientists from all around the world with the aim to strengthen the international cooperation in the fight against Cancer. One other major goal of this Conference is, in fact, to create an atmosphere of interactions between young and senior scientists to favor novel cooperation that shall bring to new and more efficacious strategies to understand and fight cancer. The Organizing Scientific Committee is formed by renowned scientists in the field who will deliver a keynote Speech. Thomas N Seyfried will deliver the Honorary Lecture. In addition, we will have Invited Lectures and Oral Communications and Poster presentation from registered attendees from all over the World.
This Special Issue shall collect the contribution in the form of original research paper or of review article from all the participants at the Conference.

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