International Symposium
Resolving Cancer Heterogeneity:
Drawing new horizons in precision medicine
Washington (USA), May 11-13, 2017
Highlights

Introduction

Prof. Wisturba and Prof. Pantel, chairmen of the symposium, opened the congress, by highlighting the role played by Genomics and Genetics in Cancer research. "I hope that this congress will be an opportunity to establish stable collaborations among researchers in order to work together in the future, starting from now" the speaker pointed out. The main topics discussed in this symposium were about genomics, epigenomics, genetics, personalized medicine, gene and target therapy, genome editing, basic translation and clinical research. The congress has been attended by many of the top researchers of this field coming from all the world.

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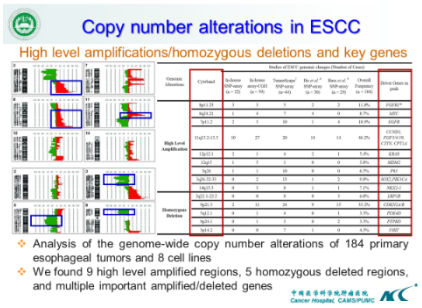
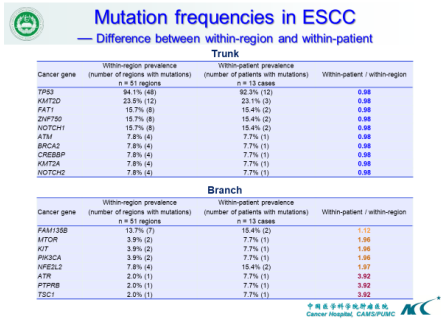
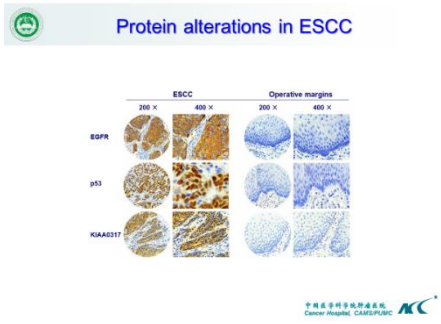
Molecular alterations and intratumor heterogeneity in esophageal squamous cell carcinoma



Molecular alterations and intratumor heterogeneity in esophageal squamous cell carcinoma (ESCC), was the topic discussed by Prof. Wang in his lecture. The speaker, coming from Beijing (CN), went deeper in his talk and presented very interesting data on this question: what important molecular alterations occurred in the ESCC. More in particular Prof. Wang talked about the genomic alterations in this type of cancer, showing that there are 9 high level amplified regions, 5 homozygous deleted regions and multiple important amplified and/or deleted genes. Speaking about the gene mutations, the speaker highlighted that in ESCC they found 609 gene mutated in at least two cases, with a mutation rate over 5% in 62 genes. In the second part of his lecture, Prof. Wang spoke about the intratumor heterogeneity and the clonal evolution and presented very interesting data on a genetic study running in ESCC patients with intratumor heterogeneity in the 36% of cases for a total of 2178 mutations of which 63 were driver mutations. Finally, the speaker talked about some issues on the study of cancer heterogeneity, like heterogeneity in early tumors and precancerous lesions, or at the RNA and protein levels and presented very interesting data on how identify significant alterations in the study of cancer heterogeneity. In conclusion, Prof. Wang pointed out that in the future there is the need for the establishment of target-based biomarker panels for the classification of ESCC and the prediction of the precancerous progression.





- What important molecular alterations and gene mutations do occur in ESCC, based on the data presented by the speaker?
- Which molecular alterations could contribute to the diagnosis and classification of ESCC, from the speaker point of view?
- Which molecular alterations could be as candidate targets for the therapy of ESCC?
- How many are the gene mutations in ESCC, based on the data presented by the speaker?
- What's about heterogeneity in early tumors and precancerous lesions, based on the data presented by the speaker?
- What are the key aspects of the heterogeneity at the RNA and protein levels, from the speaker point of view?
- How is it possible to identify significant alterations in the study of cancer heterogeneity from the speaker point of view?

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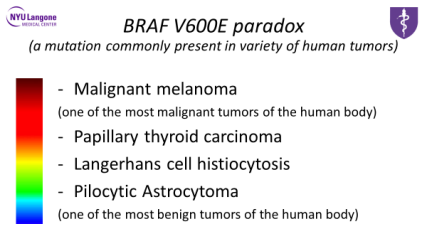
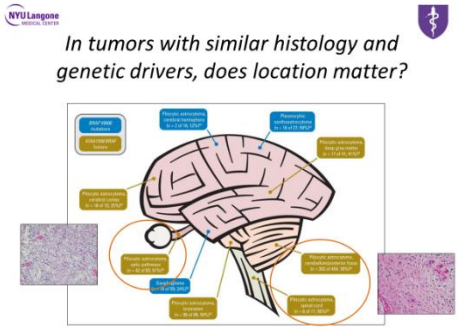
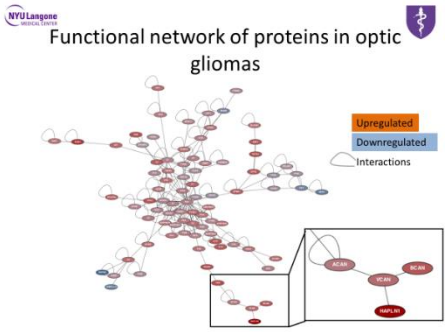
Temporospatial heterogeneity of brain tumors



Prof. Snuderl from New York (USA), spoke about temporospatial heterogeneity of brain tumors. Going deeper in his lecture, the speaker presented very interesting data on the genome-wide studies and the genetic heterogeneity in the malignant brain tumors. More in particular Prof. Snuderl talked about the BRAF V600E mutation, commonly present in many human tumors like the malignant melanoma, that is one of the most malignant tumors of the human body and the pilocytic astrocytoma, one of the most benignant tumors of the human body. In the main part of his lecture, the speaker presented very interesting data on the brain tumors and their development. More in particular Prof. Wang talked about the role of age and site in the development of pediatric brain tumors and presented very interesting data on the optic gliomas and the composition of its myxoid matrix. Finally, the speaker talked about the functional network of proteins in the optic gliomas and about the tumor development model based on the secretion of versican from the neoplastic optic pathway astrocytes, that is secreted only during the eye development in physiological conditions. In conclusion, the speaker pointed out that links between normal brain development and tumorigenesis can provide novel targets for early diagnostics and therapy.





- Why do we need to move personalized medicine beyond the DNA/RNA sequence from the speaker point of view?
- What's about mutations and the full story of tumor evolution, based on the data presented by the speaker?
- What is the role of the age and site in development of pediatric brain tumors, from the speaker point of view?
- What is the biologic role of the myxoid matrix?
- What is the composition of the myxoid matrix, based on the data presented by the speaker?

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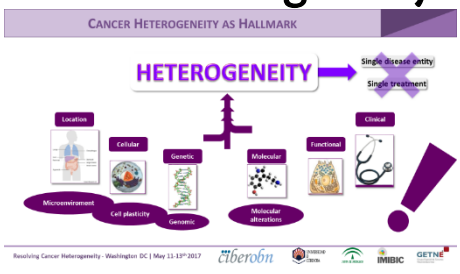
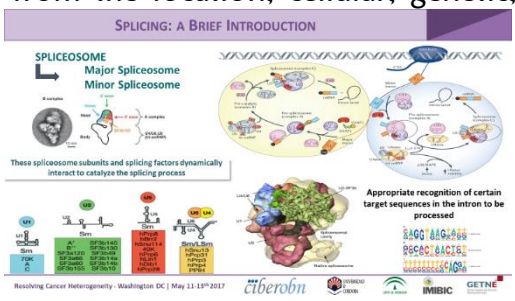
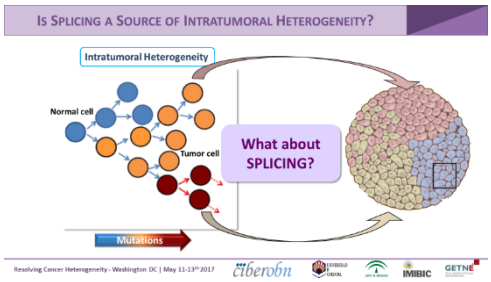
Alternative splicing: an emergent hallmark in cancer and in tumor heterogeneity



The alternative splicing: an emergent hallmark in cancer and in tumor heterogeneity, was the topic Prof. Castaño poke about in his lecture. The speaker coming from Córdoba (ES), presented very interesting data on heterogeneity as an intrinsic feature of cancer, on alternative splicing and aberrantly spliced receptors as contributors to the cancer aggressiveness and finally on the dysregulation of the splicing machinery as an oncogenic factor that contributes to cancer heterogeneity. Going deeper in his lecture, Prof. Castaño spoke about cancer heterogeneity from the location, cellular, genetic, molecular functional and clinical point of view and highlighted that genome instability and mutation is directly correlated to splicing. In the main part of his lecture, the speaker presented very interesting data on the correlation between the alternative splicing and cancer, more in particular on the alternative splicing of the somatostatin receptor 5 in the pituitary tumors and in other tumors like thyroid and breast cancer. Prof. Castaño talked also about the alternative splicing of Ghrelin related to breast, pituitary and pancreatic cancers. In the second part of his lecture, the speaker talked about the main mechanisms of splicing and the factors leading to the formation of the aberrant oncogenic splicing products. More in particular Prof. Castaño presented very interesting data on spliceosome and on the splicing machinery related to cancer. Finally, the speaker talked about splicing related to cancer and intratumoral heterogeneity. In conclusion, the speaker pointed out that the contribution of alternative splicing to cancer heterogeneity is an opportunity for the discovery of novel biomarkers and therapeutic targets to personalized medicine.





- What generates the aberrant oncogenic splicing products, based on the data presented by the speaker?
- What are the main splicing factors presented by the speaker?
- Is Splicing a Source of Cancer Heterogeneity?
- Is Splicing a Source of Intratumoral Heterogeneity?

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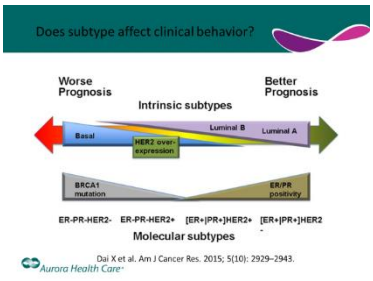
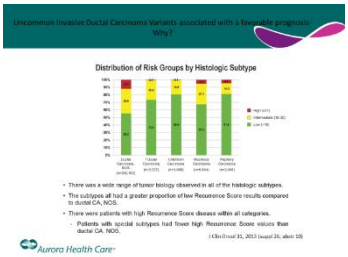
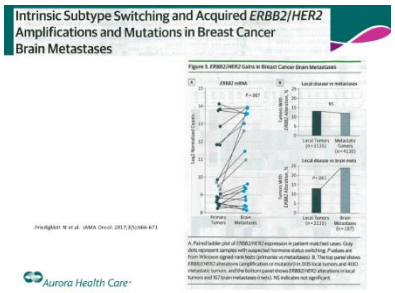
Breast cancer: genomic heterogeneity. A clinician's perspective



Breast cancer: genomic heterogeneity. A clinician's perspective, was the topic discussed by Prof. Bomzer. The speaker, coming from Milwaukee (USA), spoke about the breast cancer from the clinician point of view. Going deeper in his lecture, Prof. Bomzer presented very interesting data on the features of the molecular subtypes of the breast cancer and their impact on the tumor clinical behaviour. In the main part of his presentation, Prof. Bomzer talked about some breast cancer molecular subtypes like the uncommon invasive ductal carcinoma variants and the lobular carcinoma and its classic and variant forms. Finally, the speaker presented very interesting data on the intratumoral heterogeneity in the breast cancer brain metastasis, by highlighting that this tumor acquires alterations which have immediate clinical implications and supports comprehensive profiling of metastases to inform clinical care.





- Does subtype affect the clinical behaviour of the breast cancer, based on the data presented by the speaker?
- What are the differences in Risk Factors for Breast Cancer Molecular Subtypes based on the data presented by the speaker?
- Why the uncommon invasive ductal carcinoma variants are associated with a favorable prognosis, based on the data presented by the speaker?
- What are the classic and variant forms of the lobular carcinoma presented by the speaker?

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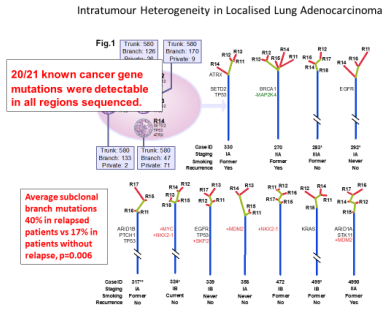
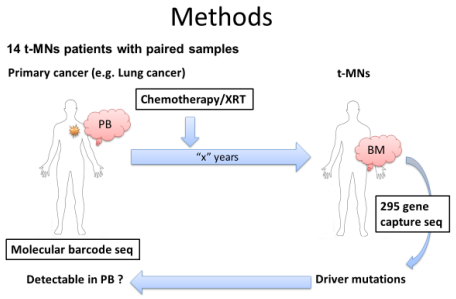
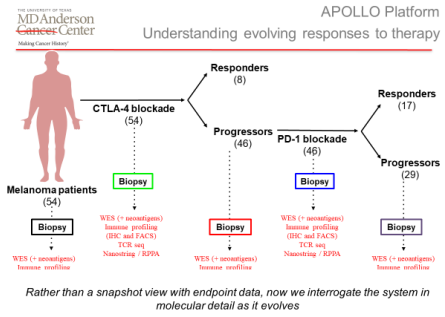
Implications of intra-tumor heterogeneity for therapy



The implications of intra-tumor heterogeneity (ITH) for therapy, was the topic discussed by Prof. Futreal in his keynote lecture. The speaker, coming from Houston (USA), talked about heterogeneity as the variable response of tumors to therapy and the variable outcomes in patients with equivalent diagnosis. Going deeper in his lecture, Prof. Futreal presented very interesting data on the intra-tumor heterogeneity in the early stage non-small-cell lung cancer (NSCLC). In the main part of his presentation, the speaker talked about the copy number variation ITH in stage 1 relapse NSCLC and about the therapy-related myeloid neoplasms (t-MNs). More in particular Prof. Futreal presented very interesting data on the clonal hematopoiesis of indeterminate potential, by highlighting that CHIP increases the risk of hematologic malignancies. The speaker presented also the data given by a clinical study running on 14 patients with t-MNs compared to 54 lymphoma pts without t-MNs, demonstrating that the incidence of t-MNs was significantly higher in primary cancer patients with clonal hematopoiesis. In the second part of his lecture Prof. Futreal talked about the immune checkpoint therapy in metastatic melanoma and presented very interesting data on the APOLLO platform study, starting from its longitudinal sampling and profiling till the evolving responses to therapy and highlighted that signatures in on-treatment biopsies were highly predictive of the response to the PD-1 blockade. In conclusion, the speaker pointed out that there is substantial opportunity for heterogeneity analyses to have clinical impact.





- What's about therapy-related myeloid neoplasms, based on the data presented by the speaker?
- What's about the clonal hematopoiesis of indeterminate potential based on the data presented by the speaker?
- What are the main clonal hematopoiesis mutation and t-MNs presented by the speaker?
- What are the future directions of the cancer heterogeneity research, from the speaker point of view?
- What's about the Apollo platform presented by the speaker?

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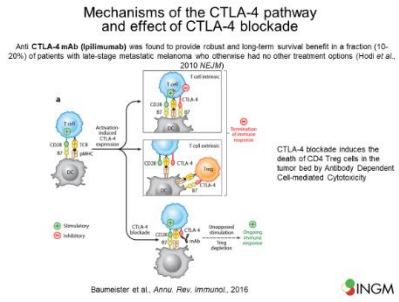
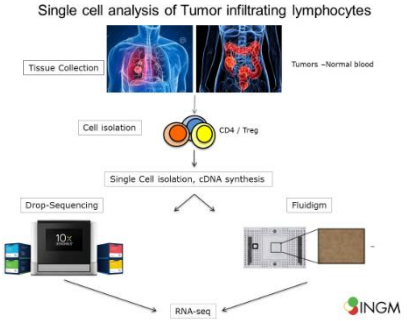
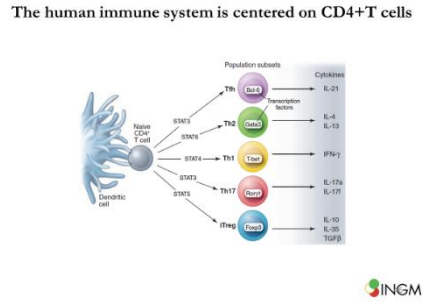
Heterogeneity of intratumoral T lymphocytes



Heterogeneity of intratumoral T lymphocytes, was the topic of Prof. Abrignani presentation. The speaker, coming from Milan (IT), talked about the paradigm shift of immunotherapy. Going deeper in his lecture, Prof. Abrignani presented very interesting data on the adaptive immune system and his response to diversity, heterogeneity and promiscuity, by highlighting that the immune response plays a key role in cancer growth. In the main part of his lecture, the speaker talked about the main problems with immunotherapy, like its efficacy in a minority of patients and the autoimmune adverse events leading to therapy discontinuation in a sizeable fraction of patients. More in particular Prof. Abrignani presented very interesting data on the immune checkpoint blockade therapies and their correlation with the immune system starting from a comprehensive analysis of human CD4 T cells present in different tumors. Finally, the speaker talked also about the intratumoral T cell flexibility and plasticity. In conclusion, Prof. Abrignani pointed out that Treg specific signature genes correlate with patients' survival in both colorectal cancer and in non-small-cell lung cancer.





- What's about the Immune checkpoints, based on the data presented by the speaker?
- What can immune responses adapt to, based on the data presented by the speaker?
- What are the main problems with immunotherapy, based on the data presented by the speaker?
- What's about the single cell analysis of tumor infiltrating lymphocytes, based on the data presented by the speaker?

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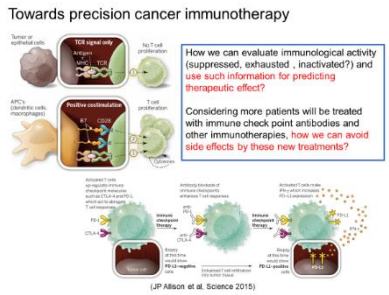
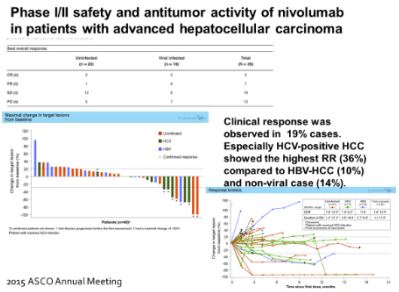
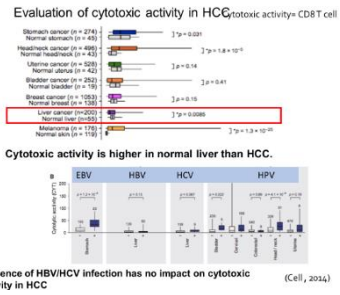
Inter-patient heterogeneity in tumor microenvironment



Prof. Shibata coming from Tokyo (Ja) spoke about inter-patient heterogeneity in tumor microenvironment and presented very interesting data on the different level of heterogeneity in the tumor development. Going deeper in his lecture, the speaker talked about the precision cancer immunotherapy and presented very interesting data on three interpatient heterogeneous components of the personalized cancer immunotherapy like somatic, germline genome and the immune environment composition, given by studies running in patients affected by biliary tract cancer and patients with hepatocellular carcinoma. Finally, Prof. Shibata presented very interesting data given by phase I/II study on the safety and antitumor activity of nivolumab in patients with advanced hepatocellular carcinoma.





- What are the different levels of heterogeneity in tumor and in immuno-environment development, presented by the speaker?
- What are the three interpatient heterogeneous components to consider for personalized cancer immunotherapy, based on the data presented by the speaker?
- What's about the pipeline of neo-antigen analysis, based on the data presented by the speaker?
- What is the correlation between TCR diversity and immune gene expression?

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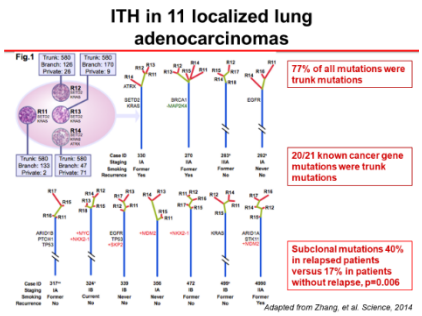
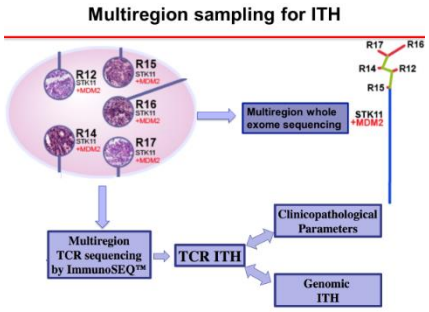
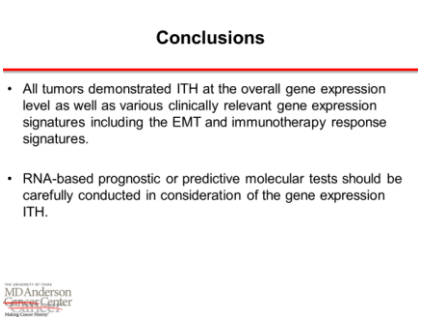
Intra-tumor heterogeneity of lung cancer: beyond genomics



Prof. Zhang from Houston (USA), spoke about "intra-tumor heterogeneity of lung cancer: beyond genomics" and presented very interesting data starting from the concept heterogeneity and tumor microenvironment. More in particular, the speaker talked about genomic intra-tumor heterogeneity (ITH), tumor infiltrating T lymphocyte ITH, methylation and gene expression ITH. Speaking about genomic ITH, Prof. Zhang presented very interesting data on the multi-region whole exome sequencing and the detection of ITH in 11 localized lung adenocarcinomas. In the second part of his presentation, the speaker talked about tumor infiltrating T lymphocyte ITH and presented very interesting data starting from the observation that ITH is present in T cell density and clonality and that the majority of T cell clones are restricted to individual tumor regions. Finally, Prof. Zhang talked about methylation and gene expression ITH and presented very interesting data on DNA methylation heterogeneity and their association with clinical characteristics and on gene expression heterogeneity, their molecular subtypes present in different tumor regions and the correlation with the different immune therapy response signatures in different tumor regions.





- Why is ITH associated with risk of postsurgical recurrence in localized lung adenocarcinomas, from the speaker point of view?
- What is the survival benefit of the adjuvant chemotherapy, based on the data presented by the speaker?
- What's about DNA methylation ITH and their association with clinical characteristics, based on the data presented by the speaker?
- What is the intratumoral and inter-individual gene expression heterogeneity, based on the data presented by the speaker?

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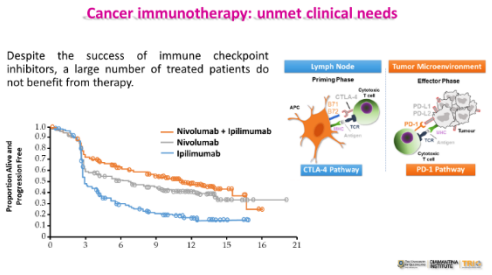
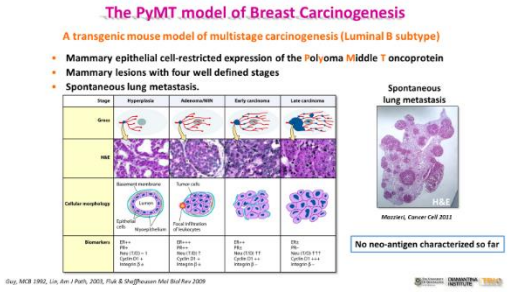
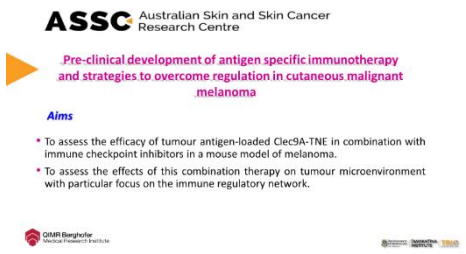
Personalized immunotherapy to overcome cancer heterogeneity



Prof. Dolcetti from Brisbane (AUS), spoke about personalized immunotherapy to overcome cancer heterogeneity. More in particular, the speaker talked about the unmet clinical need of the cancer immunotherapy. Going deeper in his lecture, Prof. Dolcetti presented very interesting data on the present challenges linked with cancer immunotherapy and more in particular on the pathways towards personalized immunotherapy for cancer, with particular attention to neo-antigen-based vaccines. In the main part of his presentation, the speaker talked about dendritic cells targeting, new technologies for targeting proteins like murine CD8+, human CD141+and murine and human CLEC9A+ and finally about the therapeutic nanocarrier emulsion (TNE) as a flexible system for antigen encapsulation and targeting. Speaking about Clec9A, Prof. Dolcetti presented very interesting data on the complex OVA-Clec9A-TNE that targets CD8+DCs in the spleen and its intracellular trafficking. More in particular the speaker presented other data on the mechanism promoted by the complex Clec9A-TNE inducing the antigen-specific- T-cell response and on the Polyoma Middle T oncoprotein (PyMT) model of breast cancer. In the last part of his presentation, Prof. Dolcetti spoke about another model developed in collaboration with ASSC that is the Australian Skin and Skin Cancer Research Center on the pre-clinical development of antigen specific immunotherapy and strategies to overcome regulation in cutaneous malignant melanoma and presented very interesting preliminary data obtained in mice on the immunogenicity of the B16 model. Finally, the speaker talked about the antigen formulations to be used in cancer vaccines for poorly immunogenic tumors.





- What are the unmet clinical needs of the cancer immunotherapy, from the speaker point of view?
- What are the present challenges of the cancer immunotherapy, based on the data presented by the speaker?
- How do Clec9A-TNE induce antigen-specific T-cell responses?
- What is the PyMT model of Breast Carcinogenesis, based on the data presented by the speaker?
- What are the aims of the Australian skin and skin-cancer research center, based on the data presented by the speaker?
- Which antigen formulations can be used in cancer vaccines for poorly immunogenic tumours?

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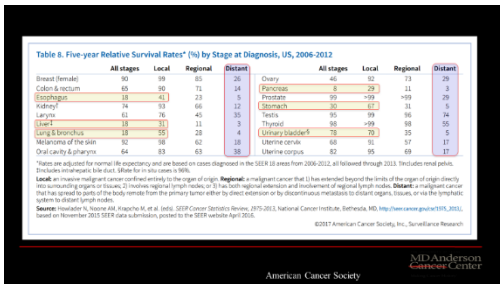
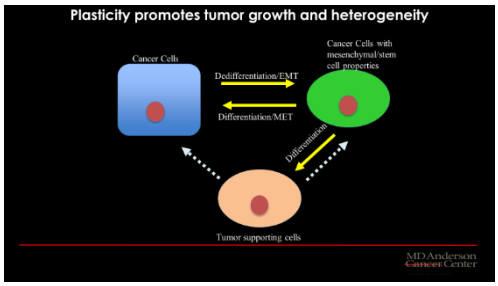
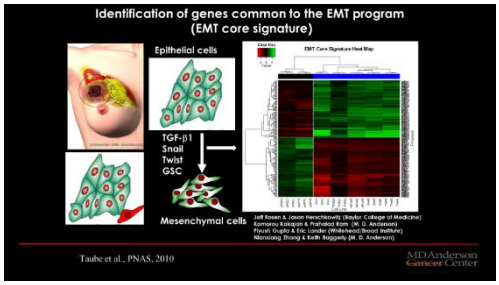
Role of cancer cell plasticity in tumor heterogeneity



The role of cancer cell plasticity in tumor heterogeneity, was the topic discussed by Prof. Mani from Houston (USA), more in particular the speaker talked about metastatic cancer, by highlighting that more than 90% cancer related death are due to metastases. Going deeper in his lecture, Prof. Mani presented very interesting data on the mechanisms leading to the development of metastases, starting from the concept that tumors are not equals due to their heterogeneity. In the main part of his presentation, the speaker talked about inter and intra heterogeneity and about the role played by the cellular plasticity in promoting metastases and therapy resistance and presented very interesting data on the complex process leading to the development of metastases starting from the epithelial mesenchymal transition (EMT) induction. More in particular Prof. Mani talked about the role played by EMT in promoting the stem cell properties and how plasticity induced by EMT can promote metastases together with tumor growth and heterogeneity. In the last part of his lecture, the speaker presented very interesting data on the methods for identifying and targeting plasticity and plasticity induced heterogeneity. More in particular he talked about the transcription factor FOXC2 and the effects of its inhibition leading to the reduction of metastases. Finally, the speaker talked about the application of the multispectral imaging for the identification of cancer cells with increased plasticity.





- How many are the cancer related death due to metastasis, based on the data presented by the speaker?
- Why 30% of the women develop metastasis and not the 70% of the women diagnosed with breast cancer, based on the data presented by the speaker?
- What is the role of the cellular plasticity in promoting metastasis and therapy resistance, based on the data presented by the speaker?
- How to identify and target plasticity and plasticity induced heterogeneity, from the speaker point of view
- Can we predict clinical outcome by analyzing Circulating Tumor Cells (CTCs)?

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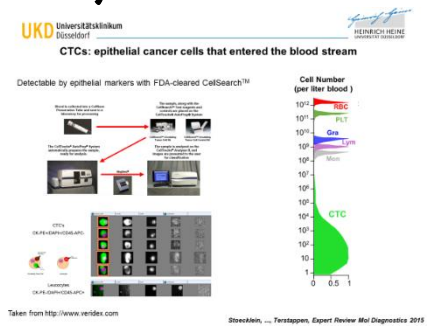
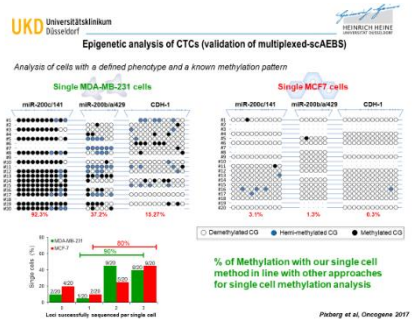
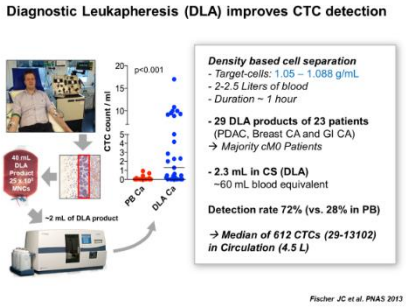
CTC-analysis: new insights through molecular single cell analysis



Prof. Stoecklein from Düsseldorf (IT), presented very interesting data on CTC-analysis: new insights through molecular single cell analysis. More in particular the speaker talked about CTCs and the CellSearch ™ able to perform CTC count and molecular characterization. Going deeper in his lecture, Prof. Stoecklein presented very interesting experimental data on the epigenetic analysis of EMT associated genes in CTCs. More in particular he spoke about the main mechanisms of the EMT process related to specific gene expressions like miR200 and E-cadherin and their regulation through DNA methylation. In the main part of his lecture, Prof, Stoecklein presented very interesting data on another experiment on the genomic profiling of CTCs in metastatic castration resistant prostate cancer during therapy with the aim to identify genetic mechanisms for therapeutic resistance. Finally, the speaker talked about the CTC detection through the diagnostic leukapheresis and presented very interesting data demonstrating that diagnostic leukapheresis improves the CTC detection.





- Can CS-CTCs inform on EMT-state, based on the data presented by the speaker?
- What is the genomic profiling of CTCs in metastatic castration resistant prostate cancer (mCRPC), based on the data presented by the speaker?
- What is the major challenge of CTC-based Liquid biopsy from the speaker point of view?

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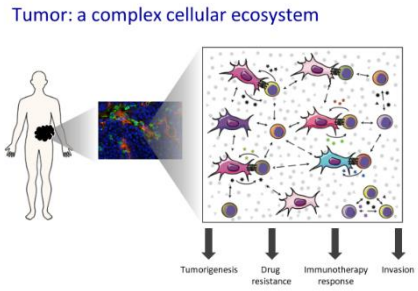
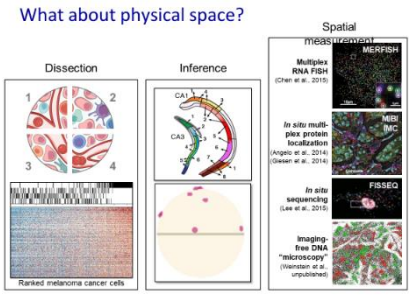
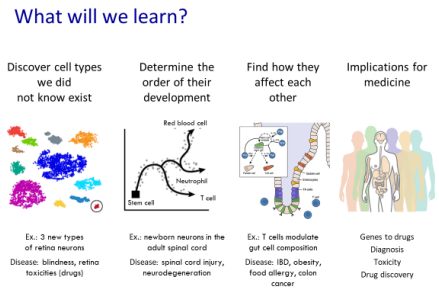
Dissecting the tumor ecosystem with single cell RNA-Seq



Dissecting the tumor ecosystem with single cell RNA-Seq was the topic of Prof. Rozenblatt-Rosen presentation. The speaker, coming from Cambridge (USA), presented very interesting data starting from the concept that tumors present a complex cellular ecosystem. Going deeper in her lecture, Prof. Rozenblatt-Rosen talked about the use of genomics for studying tumors and more in particular about single cell genomics and its capacity to dissect the tumor ecosystem and presented a case study on metastatic melanomas with more than 4600 cells from 19 patients aimed to the selection of the malignant cells and their molecular status. In the main part of her lecture, Prof. Rozenblatt-Rosen talked about the clinical outcomes the growing scale involving other cells coming from many other tumors and about the epithelial tumors, very important to study also if very difficult to do. Finally, the speaker talked about the development of a 3D tumor cell atlas and about the Human Cell Atlas aimed to create a comprehensive reference map of the types and properties of all the human cells as a basis for understanding, diagnosing, monitoring and treating health and disease and presented the main initiatives and the centers involved in this project.





- How to use genomics to study tumors, from the speaker point of view?
- What would single cell genomics teach us, based on the data presented by the speaker?
- What are the main challenges with MBC biopsies, from the speaker point of view?
- What about physical space, based on the data presented by the speaker?
- What is the scope of the Tumor Cell Atlas presented by the speaker?
- What is the Mission of the Human Cell Atlas, from the speaker point of view?

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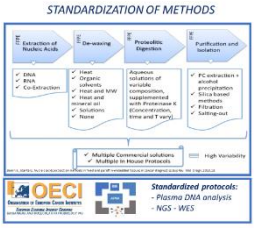
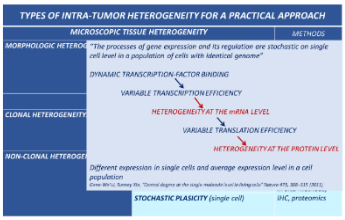
Tumor heterogeneity: a complex approach for clinical research and diagnostics



The main topic of Prof. Stanta presentation, Tumor heterogeneity: a complex approach for clinical research and diagnostics. The speaker, coming from Trieste (IT), presented very interesting data on the human tissue diagnostic flow and the methods applied for analysing heterogeneity in diagnostic and clinical research. Going deeper in his lecture, Prof. Stanta talked about the types of intra-tumor heterogeneity like the microscopic tissue and the molecular heterogeneity. More in particular the speaker presented very interesting data on the practical approach to heterogeneity and on the ATMA-Expert Center that is the archive tissue molecular analysis expert center and its projects like HERCULES aiming to the comprehensive characterization and effective combinatorial targeting of high-grade serious ovarian cancer via single-cell analysis.



- How to analyse heterogeneity in diagnostics and clinical research in patients' solid tissues and blood, from the speaker point of view?
- What are the types of intra-tumor heterogeneity for a practical approach, based on the data presented by the speaker?
- What's about the heterogeneity evaluation, from the speaker point of view?

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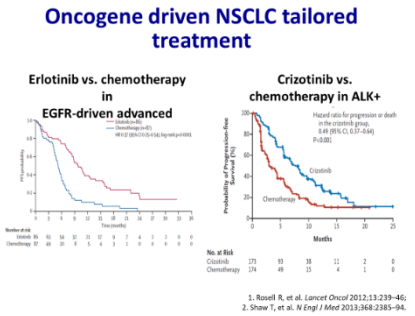
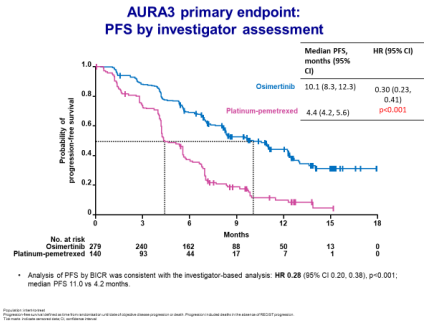
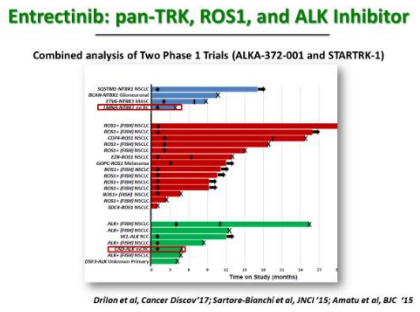
Mechanism of resistance to target therapy and treatment strategy in solid tumors: focus on lung and colorectal cancer



Prof. De Braud from Milan (IT), spoke about mechanism of resistance to target therapy and treatment strategy in solid tumors: focus on lung and colorectal cancer and presented very interesting data starting from the concept that gene mutations or rearrangements are druggable targets allowing to improve outcomes in NSCLC patients. Going deeper in his lecture, Prof. De Braud talked about the resistance to EGFR TKIs and about T790M inhibitors. In the main part of his lecture, the speaker presented very interesting data on AURA and AURA2 that are phase I and II studies of osimertinib administered in NSCLC patients. Prof. De Braud presented other very interesting data on other topics like the second generation ALK inhibitors, the resistance to ROS1 TKIs and the treatment at progression. Finally, the speaker talked about Colon Rectal Cancer and presented a huge amount of data on the mechanisms of resistance to EGFR in CRC patients. More in particular Prof. De Braud talked about the BRAF-targeting combinations, the ALK, ROS1, NTRK fusions and about MSI-high. In conclusion, the speaker pointed out that the need for continuous molecular monitoring of the disease is an essential tool to guide subsequent therapies.





- What are the druggable targets in NSCLC, based on the data presented by the speaker?
- Can we find EGFR T790M in the blood, based on the data presented by the speaker?
- What are the main mechanisms and the potential strategies to overcome acquired resistance to ALK inhibition, based on the data presented by the speaker?
- What are the main ALK next-generation inhibitors presented by the speaker?
- How to treat the progression, based on the data presented by the speaker?

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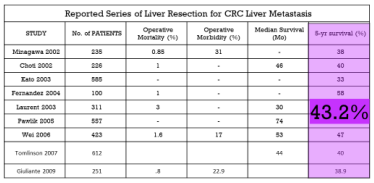
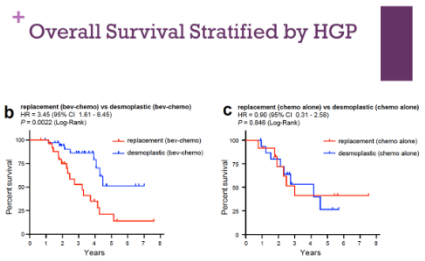
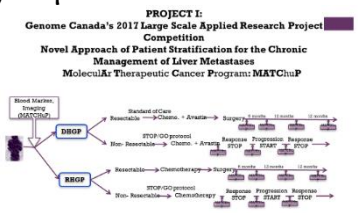
Heterogeneity in colorectal cancer metastasis and response to therapy: Vessel co-option mediates resistance to anti-angiogenic therapy in liver metastases



Reported Series of Liver Resection for CRC Liver Metastasis					
STUDY	No. of PATIENTS	Operative Mortality (%)	Operative Morbidity (%)	Median Survival (Mo)	5-yr survival (%)
Minagawa 2002	238	0.85	31	-	38
Choti 2002	226	1	-	46	40
Kato 2003	585	-	-	-	33
Fernandez 2004	100	1	-	-	58
Laurent 2003	311	3	-	30	43.2%
Fawlik 2005	557	-	-	74	58
Wei 2006	423	1.6	17	53	47
Tomlinson 2007	612			44	40
Giuliante 2009	251	.8	22.9		38.9

Heterogeneity in colorectal cancer metastasis and response to therapy: Vessel co-option mediates resistance to anti-angiogenic therapy in liver metastases, was the topic discussed by Prof. Metrakos from Montreal (CA). More in particular the speaker presented very interesting data on the colon cancer liver metastasis, its natural history characterized by a 5 years survival rate of about 43%. Going deeper in his lecture, Prof. Metrakos talked about the histological growth patterns divided into desmoplastic (DHGP) and replacement (RHGP) and presented very interesting data demonstrating that RHGP and DHGP have different amounts of vasculature and also different pathological response. In the main part of his presentation the speaker talked about survival and presented very impressive data on the overall survival stratified by HGP where treatment based on the association between Bevacizumab plus chemo was characterized by the 50% of survival at 5 years in the replacement cohort. Prof. Metrakos presented also very interesting data on other cancer types like breast cancer metastasis and the different expressions of ANG 1, 2 and 3 between D and R HGP leading to different rate of responses to therapy. Finally, the speaker talked about the application of the MRI for a better patients' stratification.





- What are the histological growth patterns of the colon cancer liver metastases, based on the data presented by the speaker?
- What's about the Overall Survival stratified by HGP, based on the data presented by the speaker?
- What are the main characteristics of the appearance of new lesions during treatment, based on the data presented by the speaker?
- What are the main characteristics of the angiopoietin (ANG)–TIE2 system, based on the data presented by the speaker?

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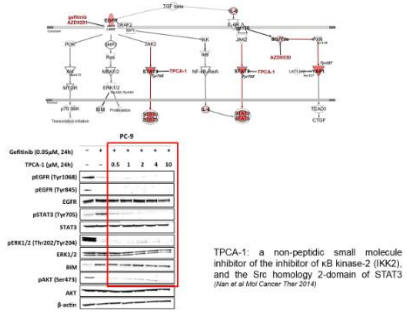
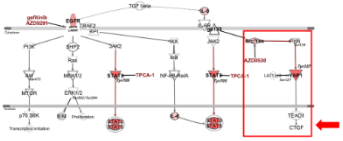
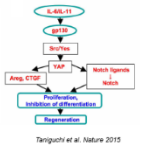
Kinome reprogramming in EGFR mutant NSCLC



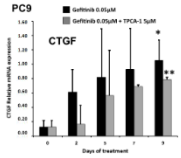
TPCA-1: a non-peptidic small molecule inhibitor of the inhibitor of κB kinase-2 (IKK2), and the Src homology 2-domain of STAT3 (Nan et al Mol Cancer Ther 2014)

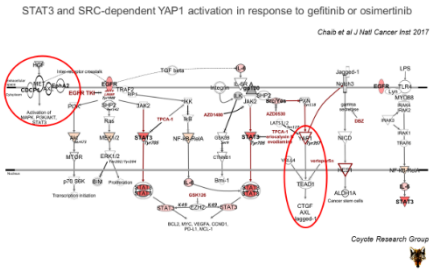
Prof. Karachaliou from Barcelona (ES), spoke about Kinome reprogramming in EGFR mutant NSCLC. More in particular, the speaker talked about the STAT3 and YAP signaling. Going deeper in her lecture Prof. Karachaliou presented very impressive data on lung cancer cells that survive after an initial EGFR inhibitor treatment through the activation of the transcriptional factors STAT3 and Src-YAP1. In the main part of his lecture, the speaker talked about her experiments running on EGFR mutant cell lines exposed to immunotherapeutic agents like gefitinib, afatinib and osimertinib and the effects of double and triple combination therapy on STAT3 and YAP signaling of EGFR mutant cell lines. Finally, the speaker talked about the preparation of a phase 1 clinical trial with the combination of osimertinib plus TPX0005 running in EGFR mutant NSCLC patients and presented very interesting data on the effects of double and triple combination therapy on PC9 and H1975 mutant cell lines.





Taniguchi et al. Nature 2015





- Why is EGFR TKI monotherapy inadequate for patients with EGFR-mutant NSCLC, based on the data presented by the speaker?
- Why are the EGFR mutations dispensable for intrinsic resistance, based on the data presented by the speaker?
- What are the main characteristics of TPCA-1 presented by the speaker?
- What is the effect of the triple combination of gefitinib, TPCA-1, and AZD0530 on STAT3, paxillin, and YAP1 phosphorylation, based on the data presented by the speaker?

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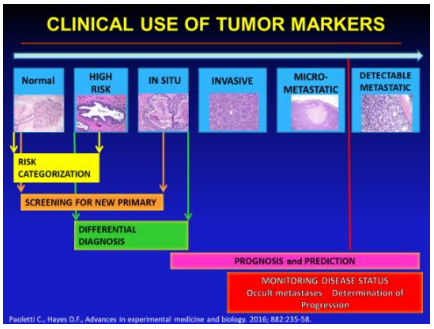
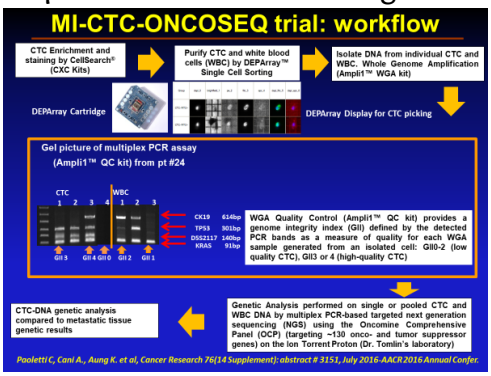
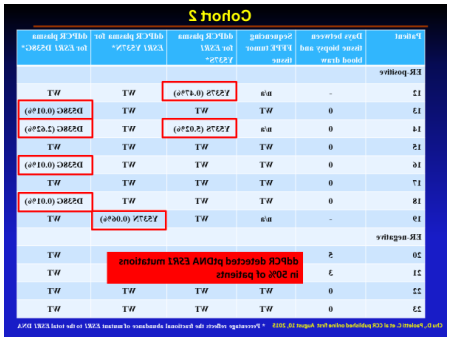
Using liquid biopsy to detect diverse mechanisms of resistance to endocrine therapy in hormone-receptor positive metastatic breast cancer



Using liquid biopsy to detect diverse mechanisms of resistance to endocrine therapy in hormone-receptor positive metastatic breast cancer (MBC), was the topic discussed by Prof. Paoletti from Ann-Arbor (USA), more in particular the speaker talked about the clinical use of tumor markers useful for the risk categorization at the beginning of the process of tumor development till the monitoring of the disease status in the metastatic phase. In the main part of her lecture, Prof. Paoletti presented very interesting data on the tests for circulating tumor cells and more in particular on liquid biopsy studies of estrogen receptor positive MBC patients, aimed to find out comprehensive answers to very important questions like the possibility to identify women with ER positive MBC who will not benefit from next endocrine treatment or the possibility to perform somatic mutation profiling on DNA derived from CTC of cancer patients participating in the MI-ONCOSEQ trial or the possibility to perform genomic analysis of CTC instead of tissue. In conclusion, the speaker pointed out that the future direction of the diagnostic protocols in patients with MBC is characterized by an integrated approach combining tissue and liquid biopsy blood tests.





- What is the clinical use of the tumor makers from the speaker point of view?
- What's about the Liquid Biopsy Studies of Estrogen Receptor Positive MBC, based on the data presented by the speaker?
- Can we identify women with ER positive metastatic breast cancer who will NOT benefit from NEXT Endocrine Treatment (ET)?
- What are the main characteristics of the COMETI P2 trial presented by the speaker?
- What's about the future plans presented by the speaker?

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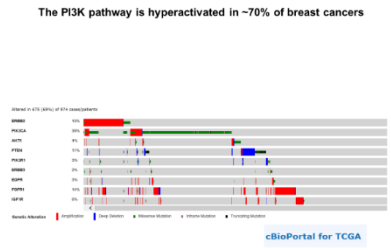
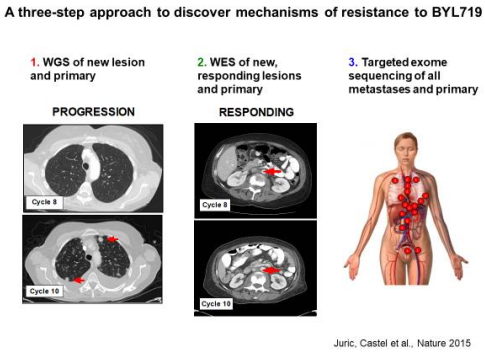
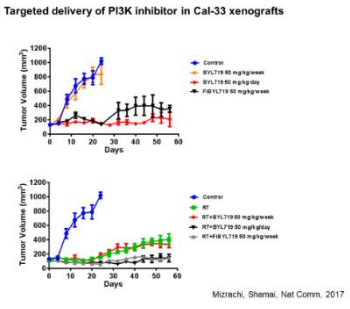
PI3K inhibitors, how to treat and who?



Prof. Scaltriti from New York (USA), presented very interesting data on "2PI3K inhibitors, how to treat and who?", starting from the concept that the P13K pathway is hyperactivated in about the 70% of breast cancer patients. Going deeper in his lecture, Prof. Scaltriti presented very interesting data on mTORC1 activity responsible for the level of response to P13K inhibition. More in particular the speaker talked about the molecular models working at the receptorial level demonstrating that the mTORC1 activity limits the sensitivity to P13K inhibition. In the main part of his presentation, Prof. Scaltriti presented very interesting experimental data on the tight correlation between PDK1 knockdown and the decrease of viability and signaling of mTORC1. In the main part of his lecture, the speaker talked about the acquired resistance to P13K inhibition and presented very interesting data on a patient clinical history and outcome with the intention to well define a correct approach for discovering the resistance to the selective P13K inhibitor BYL719. Finally, the speaker talked about new targeted delivery and presented very interesting and preliminary data produced in his laboratory on new developmental compounds.





- What's about the PI3K pathway hyperactivation and the breast cancers, based on the data presented by the speaker?
- What's about the correlation between P13K and TORC1 activity, based on the data presented by the speaker?
- What are the main characteristics of the acquired resistance to PI3Kα inhibition, based on the data presented by the speaker?
- What's about targeted delivery, based on the data presented by the speaker?

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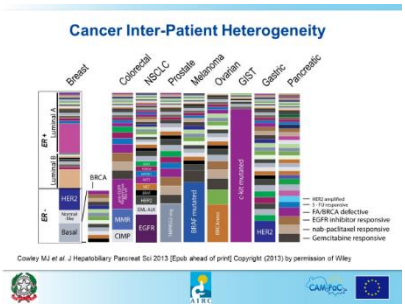
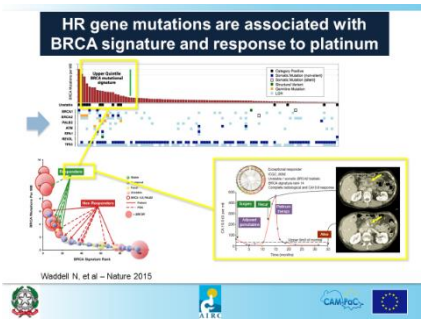
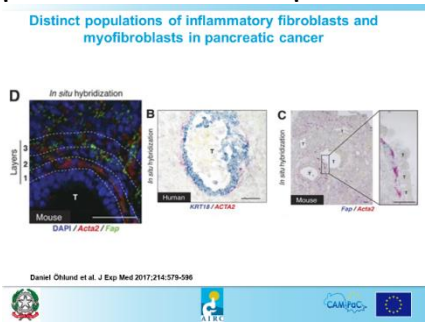
Cancer heterogeneity and molecular diagnostics



Prof. Scarpa from Verona (IT), spoke about Cancer heterogeneity and molecular diagnostics and presented very interesting data starting from the cancer inter-patient heterogeneity of the most important malignant tumors. Going deeper in his lecture Prof. Scarpa talked about the biobank materials and their use finalized to the association of morphology with genetics and presented very interesting data given by a cohort of 200 patients affected by Pancreatic ductal adenocarcinoma divided into 7 subtypes. In the main part of his presentation the speaker talked about gene mutations and presented very impressive data on the association between specific mutations and follow-up, prognosis and the prediction of drug efficacy. More in particular Prof. Scarpa talked about experimental studies running in mice driving specific gene mutations like the BRCA, TGFβ and the SWI/SNF mice. The speaker talked also about the molecular subtypes of PDAC and presented very interesting data on their immunogenic profile. In the last part of his lecture, Prof. Scarpa talked about the inter and intra-patient heterogeneity of the Pancreatic Cancer and its environment characterized by a very composite and variable stroma.





- What are the main characteristics of the Cancer Inter-Patient Heterogeneity, based on the data presented by the speaker?
- What's about the Inter- and Intra- Patient Heterogeneity in pancreatic cancer, based on the data presented by the speaker?
- What is the main environment of the pancreatic cancer, based on the data presented by the speaker?
- What's about pancreatic cancer objectives and methods, based on the data presented by the speaker?

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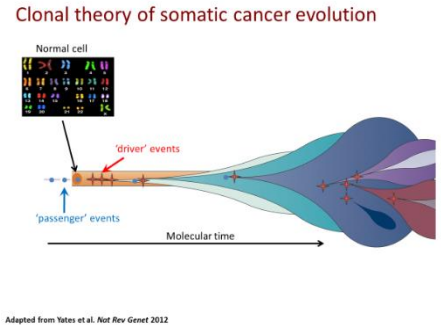
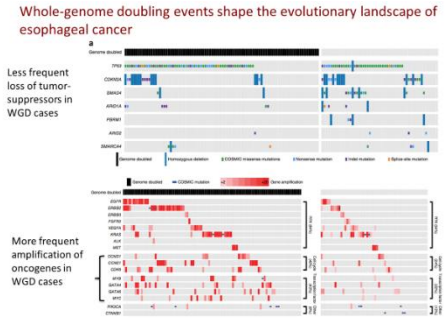
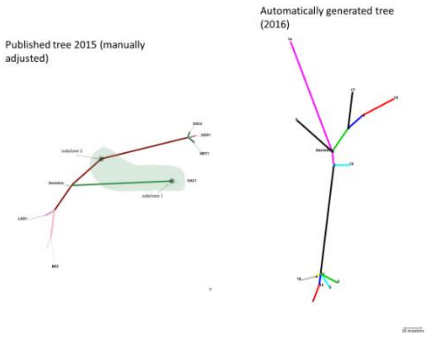
Computational dissection of intra-tumor genetic heterogeneity and applications to the study of cancer treatment, evolution, and metastasis



Computational dissection of intra-tumor genetic heterogeneity and applications to the study of cancer treatment, evolution, and metastasis, was the topic discussed by Prof. Carter from Boston (USA), more in particular the speaker talked about the cancer-tissue heterogeneity, a computational approach to the analysis of the clonal evolution and about its applications to study cancer evolution and metastasis. Going deeper in his lecture, Prof. Carter presented very interesting data on the clonal theory of the somatic cancer evolution and on ABSOLUTE that permits the deconvolution of genetic heterogeneity in cancer-tissue samples. In the main part of his lecture, the speaker talked about the evolution and impact of subclonal mutations in chronic lymphocytic leukemia patients, the application of the genome sequencing for the genetic and the clonal dissection of murine small cell lung carcinoma progression and about the evolution of the oesophageal adenocarcinoma from Barrett's oesophagus. Prof. Carter presented a huge amount of data for any of these topics with the intention to explain the role played by the computational approach in these processes. The speaker talked also about the so called "clinical actionable" mutations and presented very interesting examples of their application. Finally, Prof. Carter presented very interesting data on the use of the cerebral spinal fluid as a genetic surrogate in breast cancer patients with brain metastasis.





- What is the clonal theory of the somatic cancer evolution, based on the data presented by the speaker?
- Can we deconvolve cancer tissue samples, based on the data presented by the speaker?
- What's about Evolution and Impact of Subclonal Mutations in Chronic Lymphocytic Leukemia based on the data presented by the speaker?
- What's about the genomic characterization of brain metastases, based on the data presented by the speaker?

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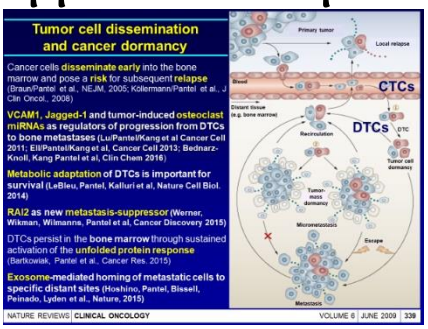
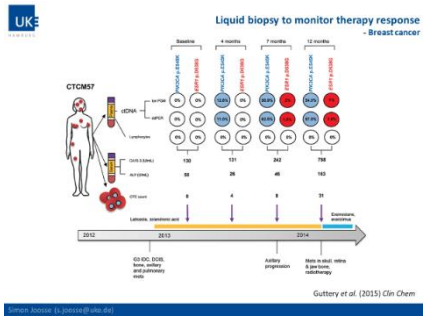
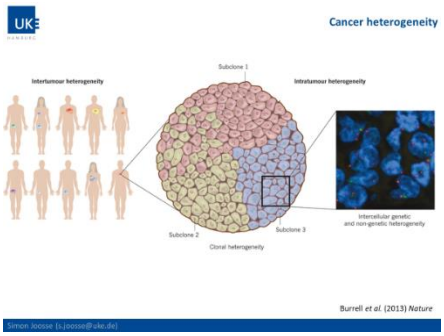
Circulating tumor cells: molecular characterization and clinical applications in patients with solid tumors



Prof. Pantel from Hamburg (DE), spoke about Circulating tumor cells: molecular characterization and clinical applications in patients with solid tumors and presented very interesting data starting from the key points of the tumor cell dissemination and the cancer dormancy. Going deeper in his lecture, the speaker talked about liquid biopsy and its aims. In the main part of his lecture, Prof. Pantel presented very interesting data on the application of liquid biopsy in early stage cancer and more in particular talked about IMENEO that is the international meta-analysis of CTCs detection in early breast cancer patients treated by neo-adjuvant chemotherapy study, that collected data in more than 2000 individual patients. The speaker presented also very interesting data given by another meta-analysis on the monitoring of therapy, through CTC application. In the last part of his lecture, Prof. Pantel talked about CTC characterization and presented very interesting data on the therapeutic targets and the resistance mechanisms. Finally, the speaker talked about the genomic characterization of single CTC.





- What are the main characteristics of the tumor cell dissemination and cancer dormancy, based on the data presented by the speaker?
- What are the aims of the liquid biopsy from the speaker point of view?
- Can CTC / ctDNA monitoring predict the efficacy of therapeutic interventions like chemotherapy or hormonal therapy, based on the data presented by the speaker?
- What's about the detection of tumor-derived exosomes, from the speaker point of view?

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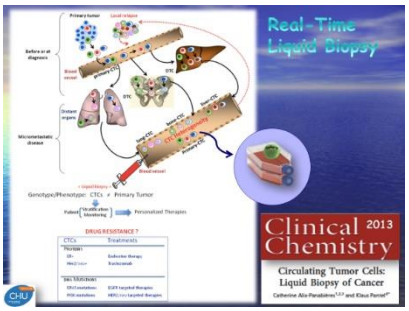
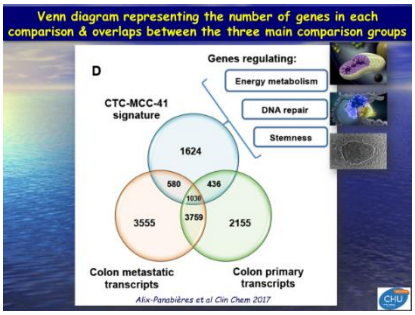
Molecular portrait of metastasis-competent CTCs in colon cancer



Molecular portrait of metastasis-competent CTCs in colon cancer was the topic discusses by Prof. Alix-Panabieres. The speaker coming from Montpellier (FR), presented very interesting data on the real time liquid biopsy. Going deeper in her lecture, Prof. Alix-Panabieres talked about CellSearch ™ system and its applications in breast, prostate, colon, lung, ovarian, rectum and pancreas cancers. In the main part of her talk, the speaker presented very interesting data on the CIRCUTEC project that is the assessment of CTCs in solid tumor including patients with inoperable recurrent and or metastatic head and neck squamous -cell carcinoma. Prof. Alix-Panabieres presented also other very impressive data on the detection of CTCs with epithelial and mesenchymal plasticity thanks to the genomic characterization of single CTCs. Finally, the speaker talked about the identification of metastasis-competent CTCs and presented very interesting data given by in vivo lab examinations running in patients affected by breast cancer, colon cancer and advanced prostate cancer.



- What are the main characteristics of the real-time liquid biopsy, based on the data presented by the speaker?
- What's about the TACTIK Project, presented by the speaker?
- What's about the molecular characterization of CTCs, based on the data presented by the speaker?
- What do we need for the detection of functional CTC/DTC, based on the data presented by the speaker?

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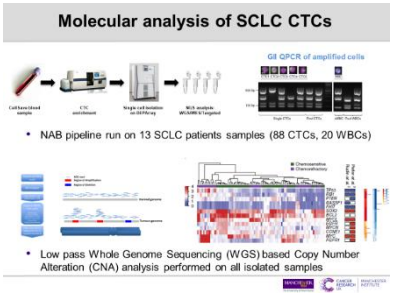
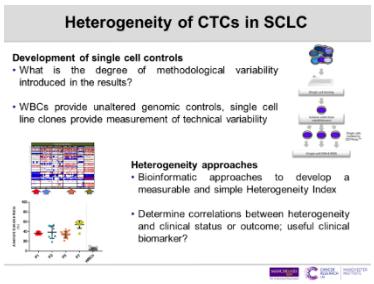
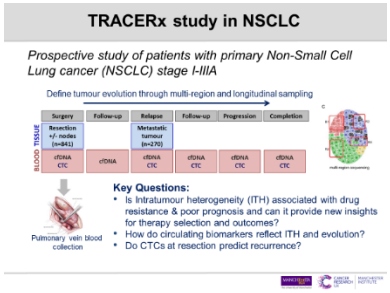
Utilising CTCs to investigate tumour molecular status and heterogeneity in small cell lung cancer



Prof. Rothwell spoke about "utilising CTCs to investigate tumour molecular status and heterogeneity in small cell lung cancer". The speaker coming from Manchester (UK), presented very interesting data starting from the description of the need for a liquid biopsy. Going deeper in his lecture, Prof. Rothwell talked about the applicability of liquid biopsy on patients affected by small-cell-lung cancer and addressed the issues about intrinsic and acquired resistance. In the main part of his lecture, the speaker presented very interesting data on molecular analysis of SCLC CTCs through the CAN-based classifier. Prof. Rothwell talked also about heterogeneity and its role from a clinical point of view and presented very interesting data given by the TRACERx study running in NSCLC patients. In conclusion, the speaker pointed out that CTCs can be used as a surrogate "tumour biopsy" in SCLC patients for the molecular characterization of the disease.





- Why do we need for liquid biopsy, from the speaker point of view?
- Can CTCs be used in place of tumour biopsies in SCLC, from the speaker point of view?
- Can CTCs be used to identify clinically relevant biomarkers, based on the data presented by the speaker?
- Can CTCs be used to investigate tumour heterogeneity, based on the data presented by the speaker?

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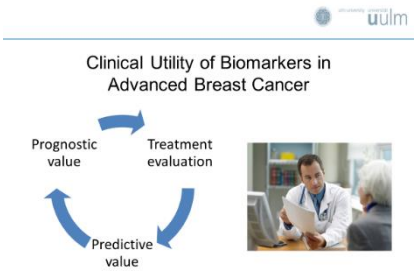
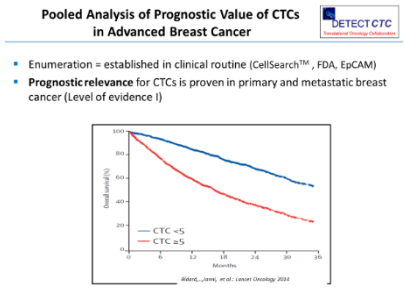
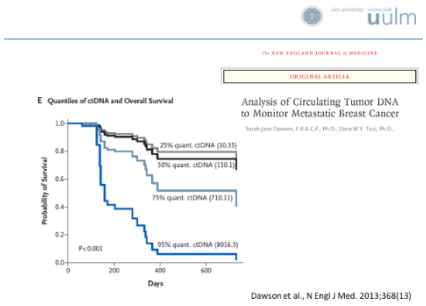
Clinical utility and perspectives of CTCs in advanced breast cancer



Clinical utility and perspectives of CTCs in advanced breast cancer was the topic of Prof. Janni. The speaker coming from Ulm (DE), talked about the prognostic value, the treatment evolution and about the predictive value of biomarkers in advanced breast cancer form the clinical point of view. Speaking about biomarkers prognostic value, Prof, Janni presented very interesting data on the detection of CTCs in peripheral blood in metastatic breast cancer patients and on its prognostic value, stating that the CTCs detection presents a level 1 of evidence from the prognostic point of view. Talking about treatment evaluation, the speaker presented very interesting data given by SWOGS0500 that is a randomized phase III trial aiming to test the strategy to change therapy vs maintaining therapy in MBC patients with elevated CTCs levels, in conclusion the speaker pointed out that from a treatment monitoring point of view, CTCs detection has a very little relevance. Finally, Prof. Janni talked about the CTCs detection predictive value and presented very impressive data given by a meta-analysis based on 48 analyses, pointing that this procedure may be inefficient, despite the advantages linked to the liquid biopsy instead of the tissue one. The speaker presented also other data given by the DETECT study running on 1123 metastatic breast cancer of which 711 were positive for CTCs detection. Inconclusion, Prof. Janni pointed out that the CTCs characterization would add significantly to predictive relevance.





- What is the clinical utility of biomarkers in the advanced breast cancer, from the speaker point of view?
- What is the pipeline of novel drugs in breast cancer, presented by the speaker?
- What are the main challenges in the treatment of metastatic breast cancer patients, based on the data presented by the speaker?
- What are the main characteristics of the DETECT study presented by the speaker?
- What are the PI3K Inhibitors in clinical development, based on the data presented by the speaker?

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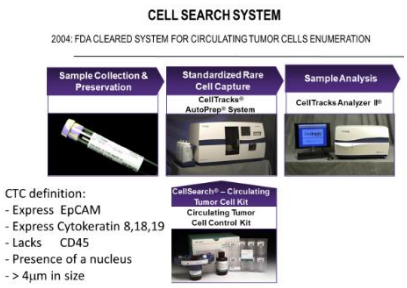
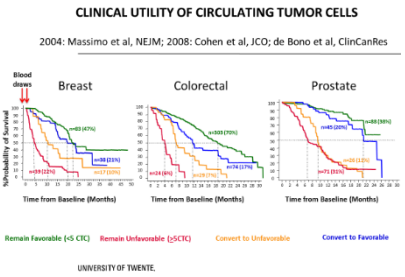
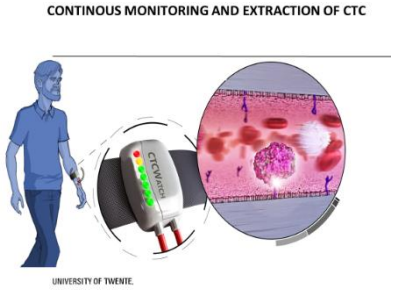
CTCs: past, present and future



CTCs: past, present and future was the topic discussed by Prof. Terstappen. The speaker coming from Enschede (NL), presented very interesting data starting from the first observations of the CTCs and the related tools for their detection. Going deeper in his lecture, Terstappen presented very interesting data on the first steps toward the automation of the CTCs enumeration till to the CellTracks analyser and the and the Cell Search Systems. In the main part of his lecture, the speaker talked about the clinical utility of the CTCs detection and presented very interesting data on the gene expression CTCs profiles and on the relationship between their definition and survival.





Prof. Terstappen talked also about the CTCs workflow for their isolation from blood and DLA and presented very interesting data ACCEPT that is an opensource image analysis program. Speaking about future opportunities Prof. Terstappen presented very interesting data on the possibility of a continuous monitoring and extraction of CTC and on charging the CTC lab on a chip for identifying the most effective therapy and loafing drug and dilution buffer.

- What is the clinical utility of circulating tumor cells, based on the data presented by the speaker?
- What are the different approaches to isolate CTC from DLA presented by the speaker?
- What's about the liquid biopsies for cancer patients, based on the data presented by the speaker?
- What's about the gene expression profiles of CTCs, based on the data presented by the speaker?

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