SPANISH NATIONAL CANCER RESEARCH CENTRE
CNIO - "LA CAIXA" FOUNDATION
FRONTIERS MEETINGS 2016

Madrid 13-16th November 2016

CANCEROMATICS III — TUMOR HETEROGENEITY

Organisers

Fátima Al-Shahrour
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CANCEROMATICS III — TUMOR HETEROGENEITY

Summary

Madrid 13-16th November 2016

CANCEROMATICS III — TUMOR HETEROGENEITY

Programme

Madrid 13-16th NOVEMBER 2016

CANCEROMATICS III — TUMOR HETEROGENEITY

Venue:
Spanish National Cancer Research Centre – CNIO Auditorium,Madrid, Spain

Chairpersons and organising committee:

Fátima Al-Shahrour, Translational Bioinformatics Unit, Clinical Research and Structural and Biocomputing Programmes, CNIO, Spain

Nuria Malats, Genetic & Molecular Epidemiology Group, Human Cancer Genetics Programme, CNIO,Spain

Chris Sander, cBio Center at Dana-Farber Cancer Institute and Computational Biology Collaboratory at Harvard Medical School, US

Alfonso Valencia, Structural Biology and Biocomputing Programme Director, CNIO, Spain

Rationale:
Cancer is a heterogeneous disease at multiple levels (patient, cellular and molecular levels) being an important clinical determinant of patient outcomes. This conference will focus on recent progress in cancer genome analysis for understanding the causes, consequences of cancer heterogeneity and its implications for cancer treatment.

Sunday November 13th, 2016

19:30-21:00 *Welcome Cocktail for all participants*
(venue: Don Pio Hotel Avenida Pío XII, 25 28016. Madrid ph: +34 913530780 http://www.hoteldonpio.com/en/)

Monday November 14th, 2016

(venue: CNIO AUDITORIUM Melchor Fernandez Almagro street- Madrid www.cnio.es)

09:00 - 09:15 Welcome address
09:15 - 10:55 **Session I: Pan-Cancer analysis**

09:15 - 09:50 Changing landscape of data and tools available for reproducible cancer genomics workflows: report from the ICGC trenches
Francis Ouellette
Ontario Institute for Cancer Research (OICR), Toronto, Canada

09:50 - 10:25 From genomic variation to molecular mechanism
Jan Korbel
EMBL, Heidelberg, Germany

10:25 - 10:55 Learning about individual tumor types through a pan-cancer analysis approach
Katherine A Hoadley
University of North Carolina, North Carolina, USA

10:55 - 11:25 Coffee break and poster session

11:25 - 13:00 **Session II: Analysis of mutations and functional impact**

11:25 - 12:00 From genotype to phenotype using evolutionary couplings
Chris Sander
Dana-Farber Cancer Institute, Boston, US

Monday November 14th, 2016

12:00 - 12:35 Tumour genomes shed light into mutational processes and cancer vulnerabilities
Núria López-Bigas
Pompeu Fabra University (UPF), Barcelona, Spain

12:35 - 13:10 Evaluating the Evaluation of Cancer Driver Genes
Rachel Karchin
Johns Hopkins University (JHU), Baltimore, US

13:10 - 14:30 *Lunch and poster session*

14:30 - 15:30 Open discussion: **Challenges in the interpretation of cancer genomes**
Chair: ***Chris Sander***

15:30 - 15:45 *Short Talk:* Evolution and timing of somatic mutations in human tumours
Santi González Rosado
EMBL-EBI, Hinxton, UK

15:45 - 16:00 *Short Talk:* Rational Design of Cancer Gene Panels with OncoPaD
Carlota Rubio-Pérez
UPF, Barcelona, Spain

16:00 - 16:30 *Coffee break and poster session*

Monday November 14th, 2016

16:30 - 17:40 **Session III: Consequences of mutations on pathway and network**

16:30 - 17:05 Modeling pharmacogenomic interactions in cancer
Lodewyk Wessels
Netherland Cancer Institute, Amsterdam, The Netherlands

17:05 - 17:40 Computational drug discovery and repositioning by “networking” genes and drugs
Diego di Bernardo
TIGEM, Naples, Italy

Tuesday November 15th, 2016

09:00 - 10:45 **Session IV: Tumor heterogeneity**

09:00 - 09:35 Dissecting intra-tumor epigenetic and expression heterogeneity: statistical challenges and solutions.
Andrew Teschendorff
UCL Cancer Institute, London, UK

09:35 - 10:10 Assessment and prognostic implications of tumor heterogeneity: a pathology prospective
Massimo Loda
HMS, Boston, US

10:10 - 10:45 Modeling cancer evolution from genomic data
Niko Beerenwinkel
ETH, Zurich, Switzerland

Tuesday November 15th, 2016

10:45 - 11:15 *Coffee break and poster session*

11:15 - 12:25 **Session IV: Tumor heterogeneity (part II)**

11:15 - 11:50 Tracking clonal evolution and intra-tumour heterogeneity in lung cancer
Charles Swanton
The Francis Crick Institute (CRICK), London, UK

11:50 - 12:25 Measuring clonal dynamics in individual cancer patients from next-generation sequencing data.
Andrea Sottoriva
The Institute of Cancer Research (IRC), London, UK

12:25 - 12:40 *Short Talk:* Estimating the population abundance of tissue-infiltrating immune and stromal cell populations using gene expression
Aurélien de Reyniès
Ligue Nationale Contre le Cancer, Paris, France

12:40 - 12:55 *Short Talk:* Intratumour heterogeneity in primary tumour and metastasis of a small cell lung carcinoma patient assessed by single cell sequencing
Paranita Ferronika
University Medical Center Groninge, The Netherlands

12:55 - 14:30 *Lunch*

Tuesday November 15th, 2016

14:30 - 15:30 Open discussion II:
From basic research to clinical practice
Chair: ***Fabien Calvo***

15:30 - 15:45 *Short Talk:* The Resistant Cancer Cell Line (RCCL) collection: cell lines with acquired drug resistance
Martin Michaelis
University of Kent, Canterbury, UK

15:45 - 16:00 *Short Talk:* Exploring gene expression variability in immune cell types and CLL
Vera Pancaldi
CNIO, Madrid, Spain

16:00 - 16:30 *Coffee break and poster session*

16:30 - 17:40 **Session V: Drug prediction and repurposing**

16:30 - 17:05 **Tudor I Oprea**
The University of New Mexico (UNM), New Mexico, US

17:05 - 17:40 Integrating computational and experimental methods in proteomics and drug discovery
Philip M. Kim
University of Toronto, Canada

Wednesday November 16th, 2016

09:00 - 10:10 **Session V: Drug prediction and repurposing (part II)**

09:00 - 09:35 Integrative computational biology for drug discovery, drug reuse and overcoming drug resistance
Bissan AlLazikani
The Institute of Cancer Research (IRC), London, UK

09:35 - 10:10 **Chris Evelo**
Maastricht University, The Netherlands

10:10 - 10:45 **Session VI: Translational Genomics**

10:10 - 10:45 Genomic classification of benign and malignant liver tumors refines the nosology and will modify patient care
Jessica ZucmanRossi
Inserm, Ille de France, France

10:45 - 11:25 The Three Prostate Cancer Genomes: Germline, Somatic, Mitochondrial
Paul Boutros
Ontario Institute for Cancer Research (OICR), Toronto, Canada

11:25 - 11:45 *Coffee break*

Wednesday November 16th, 2016

11:45 - 13:35 **Session VI: Translational Genomics (part II)**

11:45 - 12:25 International collaborative projects for genomics and clinics to address metastatic cancer treatment
Fabien Calvo
Chief Scientific Officer Cancer Core Europe, France

12:25 - 13:00 Virtualized drug development for (truly) personalized drug therapy
Hans Lehrach
Max Planck Institute for Molecular Genetics, Berlin, Germany

13:00 - 13:35 Data sharing, the beauty of recycling
Jordi Rambla
EGA, Barcelona, Spain

13:00 - 13:15 Closing remarks

Madrid 13-16th November 2016

CANCEROMATICS III — TUMOR HETEROGENEITY

Session I: Pan-Cancer analysis

Monday November 14th

Changing landscape of data and tools available for reproducible cancer genomics workflows: report from the ICGC trenches

Francis Ouellette
Senior Scientist, and Associate Director, Informatics & Biocomputing,
Associate Professor, Cell and Systems Biology,
University of Toronto Ontario Institute for Cancer Research,
Toronto, Ontario, Canada

Cancer genomics is offering a critical insight on the state of tumour genome mutations and structural alterations. The International Cancer Genomics Consortium (ICGC.org) is an International effort to sequence and characterize 25,000 tumours (50,000 tumour & normal genomes) and related clinical metadata. Within this project we are also developing a number of analyses on whole genome sequence analysis where we have developed robust methods to test and ensure reproducibility of the many tools used for mapping and identification of "true" positive genomic variants. This will be presented in the context of the work we have done in the International Cancer Genomics Consortium, which is involving more than 1 thousand researchers worldwide.

From genomic variation to molecular mechanism

Jan O. Korbel
EMBL,
Heidelberg, Germany

My presentation will cover research from our group on polymorphic genome structural variation, and on genomic somatic DNA rearrangements in cancer. I will provide an update on our efforts to reconstruct patterns of polymorphic genome structural variation through analysis of DNA sequencing data from the 1000 Genomes Project. Chromothripsis scars the cancer genome when localized chromosome shattering and repair occurs in a one-off catastrophe. While recent findings suggest a crucial role of chromothripsis in cancer development, the reproducible inference of this process has remained challenging, requiring that cataclysmic one-off rearrangements can be distinguished from localized genetic lesions that occur in a step-wise fashion. We have developed a set of conceptual criteria for the inference of complex DNA rearrangements suitable for rigorous statistical analyses, based on ruling out the alternative hypothesis that DNA rearrangements have occurred in a stepwise (progressive) fashion, and are developing in vitro models to study this striking DNA alteration process. We are further in the process of using approaches developed in our group to perform an analysis of >2,800 deeply sequenced tumor/normal paired genomes in the context of the Pan Cancer Analysis of Whole Genomes (PCAWG) project, to search for commonalities and differences in molecular processes leading to cancer in different tumor entities. I will highlight aims and preliminary results of the PCAWG Germline Cancer Genome working group, which is currently reconstructing the germline genomes of >2,800 cancer patients to examine whether somatic mutation patterns associate with germline genotypes, and to characterize these regions by cis expression quantitative trait locus mapping.

Learning about individual tumor types through a pan-cancer analysis approach

Katherine A. Hoadley
University of North Carolina,
North Carolina, USA

The Cancer Genome Atlas (TCGA) genomically characterized over 33 tumor types. With multiple data platforms analyzed including DNA, RNA and miRNA sequencing, copy number, DNA methylation, and protein analyses, we have a wealth of data to start looking at similarities across tumor types. While there is plenty of analyses within tumor types, understanding how genomic alterations and signatures are shared across is still an ongoing process. In the first pancancer analysis of TCGA, we analyzed ~3500 tumors from 12 tumor types and noted a number of commonalities and differences. Many of the features we noticed in the earlier analysis were reinforced in our larger analysis, including tumors with squamous histology grouping together and the early separation of basal-like breast cancer from other breast cancers. Many tumors still classify by tissue of origin, but often with distinctive DNA alterations that suggest that it is independent of the surrounding tissue contamination. The observances of both convergence of tumors across different tissue sites and divergence within tissue sites suggests that the cell of origin is an important feature. Considering that the major determining factor for treatment decision is the tissue of origin of a cancer, understanding these relationships will be incredibly useful in the clinic. Integration of all of the data types from TCGA strengthens these observations suggesting that the cell of origin, which is not necessarily coincident with the tissue of origin, plays and important role in the disease behavior.

Madrid 13-16th November 2016

CANCEROMATICS III — TUMOR HETEROGENEITY

Session II:
Analysis of mutations and functional impact

Monday November 14th

From genotype to phenotype using evolutionary couplings

Chris Sander
cBio Center at Dana-Farber Cancer Institute and Computational Biology Collaboratory at Harvard Medical School, US

Part 1: **Evolutionary Couplings from Maximum Entropy**. Collaborative efforts combining computational biology, structural biology and statistical physics expertise provide a partial solution to the computational protein folding problem: getting 3D structures from sequence information alone. Genomic sequences contain rich evolutionary information about functional constraints on macromolecules such as proteins. This information can be efficiently mined to detect evolutionary couplings between residues in proteins and address the long-standing challenge to compute protein and RNA three-dimensional structures from sequences alone. Substantial progress on the evolutionary couplings approach, since the initial attempts in 1994, has become possible because of the explosive growth in available sequences and the application of global statistical methods, such as maximum entropy distillation of correlated mutation patterns. In addition to proteins and RNA 3D structure, this powerful analysis of covariation helps identify functional residues involved in ligand binding, complex formation and conformational changes. We expect computation of evolutionary covariation patterns to help elucidate the full spectrum of protein and RNA structures, their functional interactions and evolutionary dynamics. Collaboration between the Sander and Marks (Harvard Medical School) groups, as well as initially with Martin Weigt, Andrea Pagnani and Riccardo Zecchina at Politecnico di Torino. Use the http://evfold.org server to compute EVcouplings and to predict 3D structure for large sequence families. Ref: **Protein 3D Structure from high-throughput sequencing** http://bit.ly/tob48p . Ref: **3D RNA and Functional Interactions from Evolutionary Couplings** http://bit.ly/3D_RNA . Ref: **Structured States of Disordered Proteins from Genomic Sequences** http://bit.ly/EC_disorder.

Part 2: **Domain hotspots in cancer**. In cancer genomics, recurrence of mutations in independent tumor samples is a strong indicator of functional impact. However, rare functional mutations can escape detection by recurrence analysis owing to lack of statistical power. We enhance statistical power by extending the notion of recurrence of mutations from single genes to gene families that share homologous protein domains. Domain mutation analysis also sharpens the functional interpretation of the impact of mutations, as domains more succinctly embody function than entire genes.

By mapping mutations in 22 different tumor types to equivalent positions in multiple sequence alignments of domains, we confirm well-known functional mutation hotspots, identify uncharacterized rare variants in one gene that are equivalent to well-characterized mutations in another gene, detect previously unknown mutation hotspots, and provide hypotheses about molecular mechanisms and downstream effects of domain mutations. With the rapid expansion of cancer genomics projects, protein domain hotspot a nalysis will likely provide many more leads linking mutations in proteins to the cancer phenotype. Ref: Martin Miller, Ed Reznik, Nick Gauthier, Niki Schultz et al. **Pan-Cancer Analysis of Mutation Hotspots in Protein Domains**. http://bit.ly/domain_hotspots Ref: **MutationAligner: a resource of recurrent mutation hotspots in protein domains in cancer** http://bit.ly/MutationAligner.

Part 3: **3D hotspots in cancer**. The vast majority of somatic mutations identified in tumors occur infrequently and most are likely non-functional passenger events. Only a small subset of such rare mutations represent functional driver events and these would be overlooked by methods that rely exclusively on mutation frequency at individual amino acid positions. It is therefore critical to develop more refined methods that at genome scale identify infrequent mutations that are likely functional. Although individually rare, such mutations in aggregate are present in a significant fraction of tumors and may be important oncogenic contributors, prognostic markers and potential precision medicine therapeutic targets in a large fraction of individual patients. Method: To survey the landscape of actionable mutations in cancer, we curated a comprehensive dataset of somatic mutations, consisting of sequenced exomes and genomes of 11,119 human tumors spanning 41 cancer types. The dataset contained 1,182,802 somatic missense mutations in 18,100 protein-coding genes. We aligned the protein sequences of 7,390 genes to 32,445 protein 3D structures, and then mapped mutations in these genes onto these 3D structures for analysis. Within each structure, clusters of mutated residues were identified based on their 3D proximity. Potential functional impact was assessed statistically through a permutation-based test. Each mutated residue in an identified 3D cluster was categorized based on its association with previously identified hotspots. Results: Application of the 3Dhotspot method to 11,119 tumors identified 3,404 mutated residues that cluster in the 3D protein structures of 503 genes. The majority were infrequent mutations and many were in tumors that lacked a known driver alteration. As an example of the utility of the approach, novel mutations identified in 3D clusters in MAP2K1 (MEK1) and RAC1 were functionally validated. To facilitate widespread functional and clinical investigation, the results are available via a web resource (3dhotspots.org) and the cBioPortal for Cancer Genomics (cbioportal.org). Ref: JJ Gao, M Chang, HC Johnson, B Taylor, DB Solit, N Schultz, C Sander et al. **3D clusters of somatic mutations in cancer reveal numerous rare mutations as functional targets.**

Tumour genomes shed light into mutational processes and cancer vulnerabilities

Núria López-Bigas
Institute for Research in Biomedicine; Biomedical Genomics Laboratory,
University Pompeu Fabra,
Barcelona, Spain

Somatic mutations are the driving force of cancer genome evolution. The rate of somatic mutations appears to be greatly variable across the genome due to variations in chromatin organization, DNA accessibility and replication timing. However, other variables that may influence the mutation rate locally are unknown. We have recently demonstrated that DNA-bound proteins, such as transcription factors and histones, interfere with the NER machinery, which results in an increased rate of DNA mutations at the protein binding sites. This finding has important implications for our understanding of mutational and DNA repair processes and in the identification of cancer driver mutations. Given the evolutionary principles of cancer, one effective way to identify genomic elements involved in cancer is by tracing the signals left by the positive selection of driver mutations across tumours. We have identified 459 cancer genes with driver mutations by analyzing close to 7000 tumor exomes from 28 different cancer types, and we have search for their targeted therapeutic opportunities. Currently we are analyzing hundreds of tumor whole-genomes to identify non-coding elements, including promoters, enhances, 5' and 3' untranslated regions, microRNAs and lncRNAs, with cancer driver mutations.

Evaluating the Evaluation of Cancer Driver Genes

Rachel Karchin
Biomedical Engineering/Oncology Institute for Computational Medicine,
Johns Hopkins University (JHU),
Baltimore, US

Numerous methods have been developed to identify driver genes, but evaluation of the performance of these methods is hindered by the lack of a gold standard. I will discuss an evaluation framework that can be applied to driver gene prediction methods. Most current methods do not adequately account for heterogeneity in the number of mutations expected by chance and consequently have many false positive calls, which is acute for cancers with high mutation rates.

SHORT TALK

Evolution and timing of somatic mutations in human tumours

Lucy Yates, Moritz Gerstung and **Santiago González Rosado**

EMBL-EBI, Wellcome Genome Campus Hinxton, Cambridge, UK

The diagnosis and sequencing of a tumour occur in an advanced stage of its cell development with the cells carrying thousands of mutational events. However, copy number gains can retain developmental information about when certain mutations occurred and which mutational processes were more active in early and late tumour progression.

As part of the pan-cancer whole genomes analysis consortium (PCAWG) we have systematically analysed 3,000 whole genome patients demonstrating that whole genome duplications can occur decades before diagnosis and are preceded by mutations in a few number of cancer driver genes, including TP53, KRAS, PIK3CA and NOTCH1. We have evaluated the evolution of different mutational signatures, some of them remaining quite constant during tumour progression which can constitute useful clock markers to estimate tumour age. Our analysis also permits to establish co-occurrence of apparently independent mutational events which demonstrate that in some cases the complex copy number events observed in several tumours has been formed in a limited number of catastrophic events.

An accurate analysis in breast cancer with multiple samples per patient shows that, even the total amount of mutations can differ between patients, the increment of the mutational rate in late stages of tumour development is quite constant. It allows us to order the mutations according to copy number gains and at the same time to be able to identify at which moment the gains occurred. The obtained results demonstrate that copy number gains in breast cancer precedes tumour development several years before it was diagnosed.

The proposed abstract covers part of the results that we have obtained as members of the pan-cancer evolution and heterogeneity working group as well as other related collaborations..

SHORT TALK

Rational Design of Cancer Gene Panels with OncoPaD

Carlota Rubio-Pérez[1], Jordi Deu-Pons[1], David Tamborero[1], Nuria López-Bigas[2], Abel González-Perez[2]

[1] Biomedical Genomics Lab, Research Program on Biomedical Informatics, IMIM Hospital del Mar Medical Research Institute and Universitat Pompeu Fabra, Barcelona, Catalonia, Spain
[2] Institucio Catalana de Recerca i Estudis Avançats, Barcelona, Catalonia, Spain

Profiling somatic mutations in genes which may inform about tumor evolution, prognostic and treatment is becoming a standard tool in clinical oncology. Commercially available cancer gene panels rely on manually gathered cancerrelated genes, in a "one-size-fits-many" solution. The design of new panels requires laborious search of literature and cancer genomics resources, with no possibility to estimate their performance on cohorts of patients.

We present OncoPaD, to our knowledge the first tool aimed at the rational design of cancer gene panels. OncoPaD estimates the cost-effectiveness of the designed panel on a cohort of tumors and provides reports on the importance of individual mutations for tumorigenesis or therapy. With a friendly interface and intuitive input, OncoPaD suggests researchers relevant sets of genes to be included in the panel, because prior knowledge or analyses indicate that their mutations either drive tumorigenesis or function as biomarkers of drug response. OncoPaD also provides reports on the importance of individual mutations for tumorigenesis or therapy that support the interpretation of the results obtained with the designed panel. We demonstrate in silico that OncoPaD designed panels are more cost-effective –i.e., detect a maximum fraction of tumors in the cohort by sequencing a minimum quantity of DNA– than available panels.

With its unique features, OncoPaD will help clinicians and researchers design tailored next-generating sequencing (NGS) panels to detect circulating tumor DNA or biopsy specimens, thereby facilitating early and accurate detection of tumors, genomically-informed therapeutic decisionsand patient follow-up, with timely identification of resistance mechanisms to targeted agents. OncoPaD may be accessed through http://www.intogen.org/oncopad.

NOTES

Madrid 13-16th November 2016

CANCEROMATICS III — TUMOR HETEROGENEITY

Session III: Consequences of mutations on pathway and network

Monday November 14th

Modeling pharmacogenomic interactions in cancer

Lodewyk Wessels
Computational Cancer Biology Group,
The Netherlands Cancer Institute / Delft University of Technology,
Amsterdam, The Netherlands

Systematic studies of cancer genomes are providing unprecedented insights into the molecular nature of human cancer. Using this information to guide the development and application of therapies in the clinic is challenging. Here we report how cancer-driving alterations identified in 11,289 tumors from 29 tissues (integrating mutations, copy-number alterations, methylation and gene expression) correlate with response to 265 compounds profiled in 1,001 human cancer cell-lines. We find that cell-lines faithfully recapitulate oncogenic aberrations identified in tumors, and that many of these associate with drug sensitivity or resistance. Logic-based modeling uncovers combinations of aberrations that specifically sensitize to drugs. *For most drugs, combinations of mutations explain the drug response better than single mutations*.

Finally, projecting the identified markers back onto primary tumors captures their clinical relevance, in terms of prevalence in cancer patients. Our comprehensive analysis and associated datasets are rich resources to identify novel therapeutic options for selected cancer sub-populations.

References:

Lodewyk Wessels[1], Theo Knijnenburg[2], Francesco Iorio[3], Julio Saez Rodriguez[3], Mathew Garnett[3] and Ultan McDermott[3]

[1] The Netherlands Cancer Institute, Amsterdam, The Netherlands
[2] The Institute for Systems Biology, Seattle, Washington, USA
[3] Wellcome Trust Sanger Institute, Cambridge, United Kingdom

Computational drug discovery and repositioning by "networking" genes and drugs

Diego di Bernardo
Telethon Institute of Genetics and Medicine in Naples (TIGEM),
University of Naples Federico II,
Italy

"Big data" are a key feature of current research approaches in biomedicine, with gene expression profiles (GEPs) being one of the most commonly available data types. GEPs provide a snapshot of cell behaviour in disease or in a response to a genetic or chemical perturbation (i.e. drug). I will present our recent results in the development and application of advanced computational approaches to analyse GEPs following treatment with small molecules to elucidate drug mode-of-action and to reposition drugs with examples in Mendelian diseases and cancer. I will conclude by discussing advantages and limitations of gene expression based drug reposting and how these limitations can be tackled by including structural information on small molecules.

Madrid 13-16th November 2016

CANCEROMATICS III — TUMOR HETEROGENEITY

Session IV: Tumor heterogeneity

Tuesday November 15th

Dissecting intra-tumor epigenetic and expression heterogeneity: statistical challenges and solutions

Andrew Teschendorff
University College London & CAS-MPG Partner Institute for Computational Biology, London, UK

Intra-tumor cellular heterogeneity, in its various forms, presents one of the biggest challenges to the analysis and interpretation of cancer-omic data [1]. Of particular emerging interest is the role of epigenetic cellular heterogeneity, which is increasingly thought to play a prominent part in carcinogenesis [2-4]. In this talk I will begin by reviewing some of the strongest evidence supporting a role for epigenetic heterogeneity in the earliest stages of carcinogenesis [4-6]. I will then describe a recent study where we demonstrate and validate the existence of widespread DNA methylation field defects in the normal tissue adjacent to breast cancer [7]. In doing so, I highlight some of the statistical challenges and algorithms we developed to dissect stromal from clonal cellular heterogeneity. In particular, I demonstrate how a paradigm shift in feature selection, based on the concept of differential variability and co-variability [8], is key to the identification of such epigenetic field defects. We further demonstrate that whilst the genomic distribution of such field defects is non-random, targeting binding sites of key epigenetic regulators, that the pattern of field defects across individuals is largely stochastic. We further interpret all these findings within the context of an epigenetic stem-cell origin model of cancer and describe further evidence for this model from a pan-cancer wide multi-omic meta-analysis. In the final part of the talk I will describe our attempt to understand tumor and single-cell expression heterogeneity from a statistical mechanics perspective rooted in the concept of signaling entropy.

References:

1. Alizadeh AA, Aranda V, Bardelli A, Blanpain C, Bock C, Borowski C, Caldas C, Califano A, Doherty M, Elsner M, et al: **Toward understanding and exploiting tumor heterogeneity**. *Nat Med* 2015, **21**:846-853.
2. Feinberg AP: **Epigenetic stochasticity, nuclear structure and cancer: the implications for medicine**. *J Intern Med* 2014.
3. Issa JP: **Epigenetic variation and cellular Darwinism**. *Nat Genet* 2011, **43**:724-726.
4. Teschendorff AE, Jones A, Fiegl H, Sargent A, Zhuang JJ, Kitchener HC, Widschwendter M: **Epigenetic variability in cells of normal cytology is associated with the risk of future morphological transformation**. *Genome Med* 2012, **4**:24.
5. Jones A, Teschendorff AE, Li Q, Hayward JD, Kannan A, Mould T, West J, Zikan M, Cibula D, Fiegl H, et al: **Role of DNA methylation and epigenetic silencing of HAND2 in endometrial cancer development**. *PLoS Med* 2013, **10**:e1001551.
6. Teschendorff AE, Yang Z, Wong A, Pipinikas CP, Jiao Y, Jones A, Anjum S, Hardy R, Salvesen HB, Thirlwell C, et al: **Correlation of Smoking-Associated DNA Methylation Changes in Buccal Cells With DNA Methylation Changes in Epithelial Cancer**. *JAMA Oncol* 2015, **1**:476-485.
7. Teschendorff AE, Gao Y, Jones A, Ruebner M, Beckmann MW, Wachter DL, Fasching PA, Widschwendter M: **DNA methylation outliers in normal breast tissue identify field defects that are enriched in cancer**. *Nat Commun* 2016, **7**:10478.
8. Teschendorff AE, Liu X, Caren H, Pollard SM, Beck S, Widschwendter M, Chen L: **The dynamics of DNA methylation covariation patterns in carcinogenesis**. *PLoS Comput Biol* 2014, **10**:e1003709.

Assessment and prognostic implications of tumor heterogeneity: a pathology prospective

Massimo Loda
HMS, Pathology Department, Dana Farber Cancer Institute,
Boston, US

Morphologic, epigenetic, genetic, clinical and molecular heterogeneity is a hallmark of cancer. In multifocal cancers such as prostatic adenocarcinoma, multiple genetically distinct clones co-exist in individual foci. The search for epigenetic or genetic "driver" events that, when targeted, will affect the entire tumor, is therefore challenging. However, heterogeneity itself may indeed be informative.

Genetic heterogeneity among tumor clones provides the raw material for cellular innovation. Just as in evolution, the greater the diversity, the higher the likelihood there will be clones that can survive and evolve under selective pressure. Indeed, it had been shown that increased genetic heterogeneity of esophageal dysplasia is associated with substantially increased risk of developing invasive tumors.

Measuring genetic heterogeneity in tissue sections is challenging. In addition, it is limiting because of the restriction to one mechanism of carcinogenesis (somatic genomic alterations), ignoring epigenetics, post-translational modifications, non genetic activation of pathways etc. Another major limitation is the restriction of the analysis to the epithelial compartment, not taking into account the significant role of the microenvironment.

We studied heterogeneity in prostate cancer at the protein level utilizing a high throughput multiplex immunohistochemical assay which enables sequential staining with fluorescence detection of formalin-fixed paraffin embedded (FFPE) tissue samples with many antibodies and the production of comprehensive profiles for biomarker expression. A single section from each tumor was used for consecutive cycles of staining, image acquisition, destaining, image reacquisition, and restaining. In a different dataset we determined diversity in the microenvironment in prostate specimen via the assessment of gene expression in laser capture microdissected epithelium and adjacent stroma in normal, prostate intraepithelial neoplasia and invasive cancer.

These studies show that 1) heterogeneity is associated with aggressive clinical behavior of prostate cancer; 2) there is significant heterogeneity in the microenvironment surrounding benign and malignant prostate epithelium; 3) amount and molecular characteristics of stromal cells affect biologic behavior of prostate tumors.

Modeling cancer evolution from genomic data

Niko Beerenwinkel
ETH Zürich, Department of Biosystems Science and Engineering,
Basel, Switzerland

Cancer progression is an evolutionary process characterized by the accumulation of mutations and responsible for tumor growth, clinical progression, and drug resistance development. Evolutionary theory can be used to describe the dynamics of tumor cell populations and to make inference about the evolutionary history of a tumor from molecular profiling data. We present recent approaches to modeling the evolution of cancer, including population genetics models of tumorigenesis, phylogenetic methods of intra-tumor subclonal diversity, and probabilistic graphical models of tumor progression, and we discuss their relevance for personalized medicine in general and for precision oncology in particular.

Madrid 13-16th November 2016

CANCEROMATICS III — TUMOR HETEROGENEITY

Session IV:
Tumor heterogeneity (part II)

Tuesday November 15th

Tracking clonal evolution and intra-tumour heterogeneity in lung cancer

Charles Swanton
Translational Cancer Therapeutics Department, Francis Crick Institute & Ucl Cancer Institute
The Francis Crick Institute (CRICK),
London, UK

Increasing evidence supports complex subclonal relationships in solid tumours, manifested as intratumour heterogeneity. Parallel evolution of subclones, with distinct somatic events occurring in the same gene, signal transduction pathway or protein complex, suggests constraints to tumour evolution that might be therapeutically exploitable. Drivers of tumour heterogeneity will be presented that change during the disease course and contribute to the temporally distinct origins of lung cancer driver events. APOBEC driven mutagenesis appears to be enriched in subclones in multiple tumour types. Oncogene, tumour suppressor gene and drug induced DNA replication stress are found to drive APOBEC mutagenesis. Genome doubling, occurring early or late in tumour evolution, exacerbates chromosomal instability contributing to intercellular heterogeneity and poor outcome. On going chromosomal instability, is found to be a major driver of ongoing intratumour heterogeneity in non-small cell lung cancer, contributing to parallel evolution and selection. The finding of subclonal driver events combined with genome instability driving cell to cell variation is likely to limit the efficacy of targeted monotherapies, suggesting the need for new approaches to drug development and clinical trial design and integration of cancer immunotherapeutic approaches. Emerging data from TRACERx, a longitudinal lung cancer evolution study will be presented and the use of the clonal neo-antigenic architecture of tumours to develop precision immune-oncology will be discussed.

Measuring clonal dynamics in individual cancer patients from next-generation sequencing data

Andrea Sottoriva
The Institute of Cancer Research, Centre for Evolution and Cancer, London, UK

Despite extraordinary efforts to profile cancer genomes on a large scale, interpreting the vast amount of genomic data in the light of cancer evolution remains challenging. This is complicated by the pervasive inter-patient variation and extensive intra-tumour heterogeneity. Here we present a novel model-based framework founded on evolutionary theory and population genetics to interpret cancer genomic data and measure clonal dynamics in individual patients. In particular, we will present a null model of genomic intra-tumour heterogeneity that can be applied to next-generation sequencing data from human malignancies. This mathematical framework is based on neutral evolution and allows identifying those tumours that are characterized by complex evolutionary dynamics, such as clonal selection, and which ones are not. We also extend this model to further dissect the dynamics of malignant populations under selection. Importantly, reanalysing cancer genomic data within a quantitative modelling framework allows the measurement, in each individual patient, of novel parameters of somatic evolution that are not directly accessible in humans.

SHORT TALK

Estimating the population abundance of tissue-infiltrating immune and stromal cell populations using gene expression

Etienne Becht[1,2,3,4], Nicolas A. Giraldo[1,2,3], Laetitia Lacroix[1,2,3], Bénédicte Buttard[1,2,3], Nabila Elarouci[4], Florent Petitprez[1,2,3,4], Janick Selves[5], Pierre Laurent-Puig[6], Catherine Sautès-Fridman[1,2,3], Wolf Herman Fridman[1,2,3] and **Aurélien de Reyniès[4]**

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[2] Université Paris Descartes, Paris, France
[3] Université Pierre et Marie Curie, Paris, France
[4] Programme Cartes d'Identité des Tumeurs, Ligue Nationale Contre le Cancer, Paris, France
[5] Centre de Recherche en Cancérologie de Toulouse, Unité Mixte de Recherche, 1037 INSERM - Université Toulouse III, Toulouse, France; Department of Pathology, Centre Hospitalier Universitaire de Toulouse, Toulouse, France
[6] INSERM, UMR_S1147, Paris, France

Transcriptomic measurements of cellularly heterogeneous tissues –such as tumor samples– are influenced by the frequencies and genes' expression levels of each present cell populations. The deconvolution of these measurements can thus yield to estimates of the abundance of various immune and other stromal cell populations. Such a technique enables to leverage the large amount of publically available transcriptomic profiles of human tumors to better understand the interactions of tumor cells and their microenvironments.

For this purpose, we developed the Microenvironment Cell Populations-counter (MCP-counter) method, available as an R package. It relies on the identification of Transcriptomic Markers (TM), defined as genes with a non-null expression in one and only one cell population. These markers were identified and validated on three large series (n>6,000 in total) of pure immune, other stromal, and malignant cell populations' transcriptomic profiles. TM were selected following an unbiased and conservative procedure, suitable for their restrictive definition and the high-dimensional setting of the data. From transcriptomic data, MCP-counter produces 10 abundance estimates, one for each of 8 immune and two non-immune stromal cell populations.

We show that our approach either complement or outperforms previouslypublished methods. We validated that these estimates predict the abundance of the corresponding cell populations in three settings: i) they identify pure populations with a high sensitivity and specificity, ii) strongly correlate with known proportions in controlled mRNA mixture experiments and iii) correlate with immunohistochemical measurements' of cell populations' densities.

We illustrate its application to assess tissue-infiltration in 47 healthy tissue types, and in 32 non-hematological malignancies. We show that our method is able to reproduce immunological and stromal prognostic classifications in lung adenocarcinoma, colorectal and breast cancers.

MCP-counter method has just been accepted for publication in Genome Biology (Becht et al – in press). We applied it to analyze colon cancers (Becht et al . Clin Cancer Res 2016) and showed that analyzing the qualitative composition of the microenvironment is very informative for prognosis and therapeutic options.

SHORT TALK

Intratumour heterogeneity in primary tumour and metastasis of a small cell lung carcinoma patient assessed by single cell sequencing

Paranita Ferronika[1,5*], Hilda van den Bos[2*], Diana C.J. Spierings[2], Ali Saber[3], T. Jeroen N. Hiltermann[4], Aaron Taudt[2], David Porubsky[2], Anthonie J. van der Wekken[4], Wim Timens[3], Floris Foijer[2], Maria Colomé Tatché[2], Harry J.M. Groen[4], Anke van den Berg[3], Peter M. Lansdorp[2,6] and Klaas Kok[1]

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[2] European Research Institute for the Biology of Ageing,
[3] Department of Pathology & Medical Biology,
[4] Department of Pulmonary Diseases, University of Groningen, University Medical Centre Groningen, The Netherlands
[5] Department of Pathology, Gadjah Mada University, Faculty of Medicine, Indonesia,
[6] Terry Fox Laboratory, BC Cancer Research Centre, Vancouver, Canada
* These authors contributed equally

Background: The study of tumour evolution has been challenged by intratumour heterogeneity which is present in primary tumours and at metastatic sites. Our study aims to identify the pattern of tumour heterogeneity by assessing copy number variations (CNVs) of small cell lung cancer at the single cell level.

Method: Single cell low coverage sequencing was performed on 586 single nuclei sorted from frozen tissue specimens of two primary tumour regions, and three metastatic tumour sites in lymph node, liver, and adrenal gland. Single nuclei isolated from frozen tissue sections were flow sorted and scWGS libraries were prepared without upfront whole genome amplification to reduce PCR amplification biases and maintain a direct correlation between sequence reads and genome content. The bioconductor package called AneuFinder was used to select good quality cells (n=341) and analyze them for CNVs. As an overall quality check merged CNVs were compared to traditional arrayCGH data obtained from each of the tissue samples.

Result: Merged CNV plots were identical to the arrayCGH based CNV plots of the matched tumour samples, thus excluding bias in selection of cells. Heterogeneity was present in each area of primary and metastatic tumour, with the highest heterogeneity score in primary tumour. Individual cells with a CNV pattern similar to metastatic tumour samples were present in the primary tumour.

Conclusion: Single cell sequencing facilitates a detailed view of intratumour heterogeneity at the single cell level and allows unbiased identification of cells contributing to tumour metastasis.

Keywords: single cell sequencing, copy number variation, intratumour heterogeneity.

SHORT TALK

The Resistant Cancer Cell Line (RCCL) collection: cell lines with acquired drug resistance

Martin Michaelis[1]; Wass, M.N.[1]; Cinatl, J. jr.[2]

[1] Centre for Molecular Processing and School of Biosciences, University of Kent, Canterbury, UK
[2] Institut für Medizinische Virologie, Klinikum der Goethe-Universität, Frankfurt am Main, Germany

The heterogeneity and individuality of cancer diseases is tremendously high. Recent genomic investigations revealed a tremendous genetic complexity in the cells from solid cancer diseases. Cancer cell (sub) populations may differ substantially between primary tumours and metastases as well as within primary tumours. This heterogeneity is a consequence of cancer clonal evolution processes. Among other models, comprehensive cancer cell line collections will be required to address this wide complexity. Resistance acquisition to anti-cancer therapies represents a major obstacle to the development of effective anti-cancer therapies. Major cancer cell drug resistance mechanisms have been discovered in drug-adapted cancer cell lines including the ABC transporters ABCB1 (also known as P-glycoprotein or MDR1) and ABCC1 (also known as MRP1) and clinically relevant resistance mechanisms to so-called "targeted therapeutics" (e.g. EGFR tyrosine kinase inhibitors, oncogenic BRAF inhibitors, anti-androgens). The Resistant Cancer Cell Line (RCCL) collection is a unique collection of approx. 1300 cancer cell lines from 15 different cancer entities that represents 125 different parental cell lines 67 cytotoxic and targeted anti-cancer drugs (www.kent.ac.uk/stms/cmp/RCCL/RCCLabout.html). Initially chemosensitive cancer cell lines are adapted to growth in the presence of clinical concentrations of anti-cancer drugs. In conclusion, the RCCL collection is a readily available tool for the studying of drug-induced cancer cell resistance mechanisms, the investigation of anti-cancer agents, and the examination of drug-induced clonal evolution processes.

SHORT TALK

Exploring gene expression variability in immune cell types and CLL

Vera Pancaldi[1], Simone Ecker[2], Daniel Rico[1,3], Dirk S. Paul[4], Alfonso Valencia[1]
and the BLUEPRINT consortium

[1] Spanish National Cancer Research Centre (CNIO), Madrid, Spain
[2] UCL Cancer Institute, University College London, London, UK
[3] Newcastle University, Newcastle, UK
[4] Cambridge University, Cambridge, UK

Tumour heterogeneity has been associated with cancer aggressiveness and prognosis. Traditionally, the origin of the heterogeneity has been attributed to the different genetic clones present. However, differences in gene expression profiles in isogenic populations can potentially add further phenotypic variability. We developed methods to assess expression variability across cancer patients. First, we investigated variability in the context of chronic lymphocytic leukemia (CLL). The disease presents two subtypes defined by the mutational status of immunoglobulin genes, which show severely different clinical outcomes, M-CLL (mutated, 70 patients) and U-CLL (unmutated, 52 patients). Only a few genes are differentially expressed between the two subtypes, despite significant differences in their genome sequence and methylation patterns.

We found that the more aggressive subtype of CLL shows significantly increased variability of gene expression across patients. Genes with increased variability in U-CLL are enriched in processes related to cell cycle, signalling, cell differentiation, and development. These observations indicate an important relation between the more heterogeneous gene expression patterns and the faster progression of U-CLL. Strikingly, a classifier based solely on gene expression variability measurements was able to correctly predict the disease subtype of CLL patients. However, we could not ascertain whether the variability just reflected genetic variation across individuals.

We then applied a similar approach to analyse variability in gene expression of monocytes, neutrophils and T cells from 125 fully sequenced healthy individuals, as part of the BLUEPRINT project. With this dataset, we estimated what proportion of the expression variability is due to genetic variants. This allowed us to suggest an important role for non-genetic variability in immunity. To conclude, expression variability is an important phenotype of biological and clinical interest.

Reference:

Simone Ecker, Vera Pancaldi, Daniel Rico and Alfonso Valencia, Higher gene expression variability in the more aggressive subtype of chronic lymphocytic leukemia, Genome Medicine20157:8

Madrid 13-16th November 2016

CANCEROMATICS III — TUMOR HETEROGENEITY

Session V:
Drug prediction and repurposing

Tuesday November 15th

Tudor I. Oprea
Department of Internal Medicine, Translational Informatics Division,
The University of New Mexico,
Albuquerque, US

Integrating computational and experimental methods in proteomics and drug discovery

Philip M. Kim
Donnelly Centre, University of Toronto,
Canada

I will present our advances in combining computational and experimental techniques to develop novel inhibitors. We have developed an integrated pipeline that first computationally designs large libraries of potential inhibitors and can then screen these for either cellular phenotype or high affinity binding. I will showcase this pipeline on two example applications, first for developing inhibitors to protein-protein interactions and second for developing novel high-affinity biologics.

I will also present work on alternative splicing and updates to transcription factor recognition codes.

NOTES

Madrid 13-16th November 2016

CANCEROMATICS III — TUMOR HETEROGENEITY

Session V: Drug prediction and repurposing (part II)

Wednesday November 16th

Integrative computational biology for drug discovery, drug reuse and overcoming drug resistance

Bissan Al-Lazikani
The Institute of Cancer Research (IRC),
London, UK

Despite our successes in curing 50% of cancer patients with existing therapies, many patients remain with limited treatment options. Moreover, patients often relapse on previously effective drugs due to tumour evolution under the selective pressure of the drug. These challenges require that we build our armoury of smart mechanistic drugs, and apply data-driven approaches to optimising therapy for patients. In this talk I will illustrate the application of computational technologies to select novel targets for cancer drug discovery, explore drug resistance through pathway remodelling and optimise drug combination therapy for patients.

Chris Evelo
Maastricht University,
The Netherlands

Madrid 13-16th November 2016

CANCEROMATICS III — TUMOR HETEROGENEITY

Session VI: Translational Genomics

Wednesday November 16th

Genomic classification of benign and malignant liver tumors refines the nosology and will modify patient care

Jessica Zucman-Rossi
Directrice de l'unité Inserm U674/1162, Université Paris Descartes,
Hopital Européen Georges Pompidou, Department of Oncology,
Paris, France

Hepatocellular carcinoma (HCC) is one of the leading causes of death by cancer worldwide. It is mainly developed on cirrhosis due to chronic hepatitis B and C, metabolic and alcoholic liver diseases in western countries. In contrast, hepatocellular adenomas are rare benign liver tumors frequently developed in women after oral contraception. Recent advances in molecular classification and dissection of genetic and epigenetic drivers have increased our knowledge of the molecular diversity of benign and malignant liver tumors. Using genomic approaches, we identified several new oncogenes and tumor suppressor genes and we described a molecular classification of hepatocellular adenomas that is used in clinical routine. Recently, using sequencing, we identified TERT promoter mutations activating telomerase as the most important mechanism of malignant transformation of both adenoma in carcinoma and of cirrhotic nodules in carcinoma. We also found new etiological factors predisposing to liver tumor development with the finding of recurrent AAV2 insertions in cancer driver genes but also mutational signatures as the result of exposure to specific genotoxic agents. Finally, next generation sequencing was particularly fruitful to identify new drug targets in hepatocellular carcinoma and these finding open new avenues to develop genome based clinical trials.

The Three Prostate Cancer Genomes: Germline, Somatic, Mitochondrial

Paul Boutros
Ontario Institute for Cancer Research (OICR), Informatics and Biocomputing, Toronto, Canada

Prostate cancer remains the most frequently diagnosed non-skin tumour type in men, and the gradual aging of the population is only increasing its frequency. Current clinical criteria used to identify which patients are in need of receiving therapy, or of which therapy they should take are coarse and inaccurate. To try to address this challenge, the Canadian Prostate Cancer Genome Network (CPC-GENE) has sequenced the germline, somatic nuclear and somatic mitochondrial genomes of prostate cancer patients. Each of these three genomes has yielded surprising mechanistic and clinical insights into the underlying etiology and aggression of prostate cancer.

NOTES

Madrid 13-16th November 2016

CANCEROMATICS III — TUMOR HETEROGENEITY

Session VI: Translational Genomics (part II)

Wednesday November 16th

International collaborative projects for genomics and clinics to address metastatic cancer treatment

Fabien Calvo
Chief scientific officer Cancer Core Europe,
France

Several US-based and global initiatives such as The Cancer Genome Atlas and the International Cancer Genome Consortium have led to an increase in the use of genomics to inform treatment decisions and opened the way for more personalized medicine. These initiatives sought to describe the molecular events associated with the development of various types of cancer, and used DNA and RNA-seq, methylation profiling… to identify mutations, deletions, amplifications, viral insertions, microRNA variations, epigenetic modifications, and other important genomic events in cancer formation.

This large body of work [with contributions from many researchers from various countries] led to the identification of coding driver mutations that occurred at a frequency of greater than 5%, as well as noncoding driver mutations in cis-regulatory regions and non-coding RNAs. This work also uncovered novel mechanisms of mutations, including environmental exposures (*e.g.* aristolochic acid), prognostic biomarkers that can be used to stratify aggressive versus indolent tumours, defined mutation signatures linked with specific tumors, and revealed new mechanisms of carcinogenesis related to genomic rearrangement; it has also brought to light new biological pathways that contribute to the formation of cancer and how these pathways can targeted by drugs.

The major impact on cancer discovery has been to illustrate the limitations of precision medicine, since responses to targeted therapies are not universal (around 50-80% at best), are of limited duration (from 6-12 months) and patients often develop resistance (especially for B-RAF, EGFR TKI, and ALKi). Furthermore, most of these therapies do not have a significant impact on overall survival, except in hematological malignancies, and in some solid tumors, although second and third generation drugs can overcome resistance.

ICGCmed is pursuing the goal of collecting genomic and clinical data on 200,000 patients with different cancer types including information on patient outcomes. Linking extensive genomic information obtained by sequencing tumors, together with information on the particular clinical environment that tumors developed in, and patient's response to therapy, will enable clinicians to better define who to treat—thereby increasing the number of patients who can truly benefit from targeted drugs, especially if clinically-validated biomarkers are available.

Virtualized drug development for (truly) personalized drug therapy

Hans Lehrach
Max Planck Institute for Molecular Genetics
Dahlem Center for Genome Research and Medical Systems Biology
Alacris Theranostics GmbH,
Berlin, Germany

Every patient is different. In particular, every tumor is different. Even subgroups of tumor cells can react differently to specific therapies, due to the heterogeneity of many tumors. Drug therapies therefore typically only help a fraction of patients; many patients do not respond, with some suffering sometimes severe side effects of ineffective treatments.

The ability to identify effects and possible side effects of different drugs on individual patients will, in our view, require highly detailed molecular analyses of every individual patient and his/her individual disease; data that is integral to generating individualized computer models, which can then be used to test the effects of drugs (or other therapies) on the individual.

This will, on one hand, provide a basis for a truly personalized selection of therapies optimal for the individual patient, first in cancer patients, but increasingly also in other areas of medicine and prevention. It will, however, also open the way to an increasing virtualization of the drug development process, by e.g. virtual clinical trials of drug candidates carried out throughout the development process.

Data sharing, the beauty of recycling

Jordi Rambla
EGA Project Group, Bioinformatics and Genomics Programme,
CRG-Centre for Genomic Regulation,
Barcelona, Spain

When the research project has finished and the paper is out, data could still enjoy an enviable health and life.However, some decisions taken before and during project life cycle could have a great impact on it. This lecture will review such aspects and mention the initiatives that the community is gathering to overcome them.

Madrid 13-16th November 2016

CANCEROMATICS III — TUMOR HETEROGENEITY

Speakers' Biographies

Bissan Al-Lazikani

Chief scientific officer Cancer Core Europe,
France

Bissan Al-Lazikani trained in computational biology and computer science. She leads computational biology and chemogenomics at the Institute's of Cancer Research's leading Cancer Research UK Cancer Therapeutics Unit. She led the development of integrative computational approaches to inform drug discovery that are now internationally adopted and provided to the community via the canSAR knowledgebase. She is Head of Data Science at the ICR where she is applying computational biology and broad informatics for optimising and adapting cancer therapy.

Fátima Al-Shahrour
Translational Bioinformatics Unit, Clinical Research and Structural and Biocomputing Programmes, CNIO, Madrid, Spain

Fatima Al-Shahrour (Madrid, 1975) obtained her PhD from *Universidad Autónoma de Madrid* (UAM) in 2006. During her PhD she worked at the Bioinformatics Unit at *Spanish National Cancer Research Center* (CNIO, Madrid, Spain) and *Centro de Investigaciones Príncipe Valencia* (Valencia, Spain) under Dr. Joaquín Dopazo supervision. During this period, her research work dealt with the development of new Bioinformatics tools for microarray gene expression analysis, with a particular focus on computational methods for the functional interpretation of high-throughput experiments.

In 2007, she joined the Computational Biology and Bioinformatics group at Cancer Program under supervision of Prf. Dr. Jill P. Mesirov at *Broad Institute of Massachusetts Institute of Technology (MIT) and Harvard* (Cambridge, USA). In 2008, she got a staff position at *Broad Institute of MIT and Harvard* as a Computational Biologist working at Dr. MD. Benjamin L. Ebert's lab at *Brigham Women's Hospital* (BWH, Boston). During this period, her research was focused on the study the biology and treatment of cancer under a genomic perspective using hematopoiesis as a model system.

In 2012, she joined the CNIO to lead the Translational Bioinformatics Unit in the Clinical Research Programme and Structural and Biocomputing Programme. Her research interests are focused on the development of computational genomic-based to transform the available cancer genomic data into models that allows mechanistic understanding of cancer processes, followed by the application of comprehensive computational approaches to cancer diagnostics and treatment.

Niko Beerenwinkel
ETH Zürich, Department of Biosystems Science and Engineering,
Basel, Switzerland

Associate Professor, ETH Zürich
Visiting Scientist
Program: Algorithmic Challenges in Genomics

Niko Beerenwinkel was trained in mathematics and biology at the University of Bonn, and received his PhD in computer science from Saarland University in 2004. He served as a postdoctoral researcher at the UC Berkeley and Harvard University before joining ETH Zurich in 2007, where he has been an associate professor of computational biology since 2013. Beerenwinkel's research is at the interface of mathematics, statistic and computer science with biology and medicine. His interests range from the mathematical foundations of biostatistical models to clinical applications in cancer and infectious diseases. He has developed methods for inferring the genetic composition of virus populations, analyzing HIV drug resistance, and predicting the outcome of antiviral combination therapy. In cancer research, he is interested in multi-omics data integration and the genomic diversity and evolutionary dynamics of tumors. In addition, Beerenwinkel's group has developed probabilistic graphical models for network reconstruction from observational and interventional data, such as RNA interference screens.

Paul C. Boutros
Ontario Institute for Cancer Research, Informatics and Biocomputing,
Toronto, Canada

Dr. Paul Boutros pursued his undergraduate education at the University of Waterloo in Chemistry, with co-op training ranging from water-purification to petrochemicals. But he found his true calling during a work term at Michigan State University developing computer models of drug response. His undergraduate thesis on modeling DNA damage received first place at the National Undergraduate Chemistry Conference. In 2004, he started a PhD at the Ontario Cancer Institute, where he received the CIHR/Next Generation First Prize and an Invitrogen Canada Young Investigator Silver Award. He received his PhD in 2008 and started his independent research career at the Ontario Institute for Cancer Research, where he remains today. Dr. Boutros co-leads the Canadian Prostate Cancer Genome Network and leads an international consortium optimizing algorithms for genomic data analysis. He is a Terry Fox Research Institute New Investigator, and has been named Prostate Cancer Canada Rising Star in Prostate Cancer Research.

Diego Di Bernardo
Telethon Institute of Genetics and Medicine in Naples (TIGEM),
University of Naples Federico II,
Italy

Diego Bernardo was born in Naples on June 26, 1972. He received the "Laurea cum laude" in Electronic Engineering in January 1997 by the University of Naples "Federico II". In 2001, thanks to a Marie Curie Fellowship awarded by the European Commission, he received the title of (PhD) from the University of Newcastle School of Medicine, UK, in the laboratory of Prof. Alan Murray. Until April 2002 he was a postdoctoral researcher at the Wellcome Trust Sanger Center in Cambridge (United Kingdom) in the laboratory of Dr Tim Hubbard. From May 2002 to December 2002 he was a postdoctoral researcher in the laboratory of Prof. Jim Collins in the Department of Bioengineering at the University of Boston, USA. Since January 2003 he is an independent researcher (Principal Investigator) at the Telethon Institute of Genetics and Medicine in Naples (TIGEM) where he runs his own lab. In November 2007 he became Assistant Professor at the University of Naples "Federico II" and in November 2015 Associate Professor in Biomedical Engineering in the same University. In July 2011 he was appointed Director of the research program in Systems Biology of TIGEM. His research interests are strongly interdisciplinary topics in the field of bioengineering and its applications in the field of biotechnology and biomedicine.

Fabien Calvo

Chief scientific officer Cancer Core Europe, France

Fabien Calvo is Chief Scientific Officer for Cancer Core Europe, a consortium of six Comprehensive Cancer Centres including Cambridge Cancer Centre, the German Cancer Research Centre (DKFZ) and the National Centre for Tumour Diseases (NCT) in Heidelberg, the Val d'Hebron Institute of Oncology in Barcelona, The Karolinska Insttitute in Stockholm, Gustave Roussy Cancer Campus Grand Paris, and the National Cancer Institute (NKI) in Amsterdam.

His role as CSO is to organize and coordinate medical research and scientific activities and assist the consortium in developing a global vision and planning and delivering the implementation of the strategy. Fabien Calvo is currently Professor of Pharmacology at University of Paris-Denis Diderot. From April 2007 to September 2014, Fabien Calvo was Deputy Director General of the National Cancer Institute of France, in charge of Research and Innovation Programs. He launched with the USA, Canada, UK and Germany, the International Cancer Genome Consortium for which he chairs the Scientific Planning Committee of ICGCmed.

Chris Evelo
Maastricht University,
The Netherlands

Prof. Dr. Chris Evelo leads an enthusiastic group of 14 researchers at BiGCaT and is a PI at MaCSBio. Prof. Evelo is experienced in the training of young international scientists (10 PhD candidates since 2008, 4 completed). As a Professor in "Bioinformatics for Integrative Systems Biology" his research aims at better interpretation of experimental data through integration in data models that build on structured knowledge. One main focus of his group lies on interoperability approaches underlying such integrative efforts: standards, ontologies, mapping tools and provenance of the data and methods used. He participates in several related European projects including Elixir, ODEX4All, FAIR Data Project and DiXA. In May 2016, he has been appointed as the new co-leader of the European Elixir Interoperability Platform. As a co-founder of the WikiPathways project, he is involved in supporting research communities to structure biological knowledge in biological pathways and sharing them on WikiPathways. Furthermore, he is in the Open PHACTS consortium which focuses on large-scale semantic web based knowledge structuring of relations between chemicals, gene-products and diseases. In this project, he collaborates closely with pharmaceutical companies like GlaxoSmithKline (GSK) and Janssen Pharmaceuticals. Prof. Evelo's group is also known for the development of open source bioinformatics tools. Those range from graphical, stand-alone applications like PathVisio, a tool for pathway editing, analysis and visualization, to advanced software libraries like BridgeDb, a framework for database identifier mapping. As part of the NUTRIM research school, Prof. Evelo is especially interested in the application of bioinformatics and systems biology approaches in nutritional and metabolic health research, and he is involved in several large European projects in the field (NuGO, Microgennet, Micronutrient Genomics Project, EuroDISH).

Contribution to Science
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Katherine A. Hoadley
University of North Carolina,
North Carolina, USA

Dr. Katherine Hoadley is an Assistant Professor at the University of North Carolina at Chapel Hill. Her research interests include integrative genomic analyses to better understand cancer, particularly the aggressive basal-like subtype of breast cancer. She was one of the lead scientists for gene expression-based analyses and oversaw UNC's RNA sequencing contribution to The Cancer Genome Atlas (TCGA) Project. She helped lead TCGA's effort to genomically characterize breast cancer (Nature 2012) and was co-first author for TCGA's pancancer subtype analysis which was listed by ASCO as one of the Clinical Cancer Advances of 2015 and selected by the Clinical Research Forum as one of the Top Ten Clinical Research Achievements Awards of 2015. She is currently co-chairing the Testicular Germ Cell Analysis Working Group and is on the Steering Committee for the Pan-cancer Atlas project in TCGA. In addition, Dr. Hoadley is involved in several other large international genomics projects including the International Cancer Genomics Consortium.

Rachel Karchin
Biomedical Engineering/Oncology Institute for Computational Medicine,
Johns Hopkins University,
Baltimore, US

Rachel Karchin, Ph.D. is an Associate Professor in the Departments of Biomedical Engineering and Oncology at Johns Hopkins University. She received a Ph.D. in Computer Science from the University of California, Santa Cruz in 2003, spent three years as a postdoctoral fellow in the Department of Biopharmaceutical Sciences at University of California, San Francisco, and joined the Hopkins faculty in 2006. Her lab develops algorithms and tools to interpret and model genomic data, with a focus on translational applications for cancer diagnosis and prognosis. She is currently the William R. Brody Faculty Scholar at Johns Hopkins Whiting School of Engineering.

Philip M. Kim
Donnelly Centre, University of Toronto,
Canada

Philip M. Kim is an Associate Professor at the University of Toronto. His main expertise is in the identification, analysis and perturbation of protein interactions. His lab is developing novel methods to dissect and inhibit interactions of modular protein domains, which involve a combination of experimental and computational methods. He holds a Ph.D. from the Massachusetts Institute of Technology and a B.S. in Biochemistry and Physics from the University of Tuebingen.

Jan O. Korbel
EMBL,
Heidelberg, Germany

Jan Korbel is a Group Leader at the European Molecular Biology Laboratory (EMBL) in Heidelberg, Germany, in the Genome Biology Unit. Prior to his position at EMBL, Jan co-developed the paired-end mapping technique enabling the characterization of genomic structural variants by massively-parallel DNA sequencing, at Yale University. With expertise in Human Genetics and Computational Biology, Jan's research focuses on structural variation of the genome in the germline and in cancer. His group has developed several approaches for the characterization of structural variation and applied these to identify the extent, origin, and functional consequences of different genomic alteration processes in the germline and in cancers, including in pediatric brain tumors and prostate cancer. He is particularly interested in understanding determinants of structural variation processes, including catastrophic DNA rearrangement and DNA regulatory context-altering rearrangement processes. Jan has a leading role in the 1000 Genomes Project and the Pan-Cancer Analysis of Whole Genomes (PCAWG) Initiative, which is organized within the International Cancer Genome Consortium (ICGC). Since 2015, he is an elected member of the German Academy of Sciences Leopoldina and in 2016, he became a member of EMBO.

Hans Lehrach
Max Planck Institute for Molecular Genetics
Dahlem Center for Genome Research and Medical Systems Biology
Alacris Theranostics GmbH,
Berlin, Germany

Professor Hans Lehrach is director (em.) of the Max Planck Institute for Molecular Genetics in Berlin. He has held positions at Harvard University (USA), EMBL (Germany) and the Imperial Cancer Research Fund, UK. Prof. Lehrach is author of more than 1000 publications and 24 patents, is a fellow of the AAAS, he holds the Ján Jessenius SAS Medal of Honour (2003), the Karl Heinz Beckurts Award (2004) and the Gusi Prize (2015) in recognition of his achievements in medical sciences. He was co-ordinator of 'ITFoM: IT Future of Medicine' (www.itfom.eu), a finalist of the FET Flagship Call, which has established a strong technological roadmap and network of partners from 33 countries.

Dr. Lehrach has founded several biotechnology companies such as Sequana Therapeutics, GPC Biotech, Scienion, Prot@gen, PSF Biotech, Atlas Biolabs. Dr. Lehrach is founder of the Berlin-based company Alacris Theranostics GmbH, specialising in the development of new approaches for personalised medicine for cancer patient diagnosis, treatment and drug stratification. He is chairman of the Supervisory Board and scientific advisor of the company since 2008. In 2010 he founded the non-for-profit research institute The Dahlem Centre for Genome Research and Medical Systems Biology (DCGMS).

Massimo Loda

HMS, Pathology Department, Dana Farber Cancer Institute,
Boston, US

Dr. Loda received his M.D. *summa cum laude* at the University of Milan, Italy in 1980, trained in anatomic pathology at the Deaconess Hospital, Harvard Medical School and subsequently in molecular pathology at New England Medical Center, Tufts University. He set up and directed in the early '90s one of the first diagnostic molecular pathology labs at Beth Israel Deaconess Medical Center in Boston. Dr. Loda joined the Dana-Farber Cancer Institute in 1998 as an independent investigator. He started and directed the experimental pathology cores for the Dana-Farber/Harvard Cancer Center, and the Center for Molecular Oncologic Pathology, an experimental molecular pathology unit at Dana-Farber Cancer Institute. He is currently Chair of the newly formed department of Oncologic Pathology at Dana-Farber Cancer Institute, Professor of Pathology at Harvard Medical School, Associate Member of the Broad Institute and a senior surgical and molecular pathologist at the Brigham & Women's Hospital in Boston. His laboratory is focused on the study of prostate cancer pathogenesis and progression, with a specific interest in metabolic alterations associated with cancer.

Núria López-Bigas
Institute for Research in Biomedicine; Biomedical Genomics Laboratory,
University Pompeu Fabra,
Barcelona, Spain

Núria López-Bigas is an ICREA Research Professor at the Institute for Research in Biomedicine and associate professor at the University Pompeu Fabra. She leads the Biomedical Genomics lab (http://bg.upf.edu).

She has a PhD in Biology from the University of Barcelona and has expertise in Medical Genetics and in Computational Biology and Bioinformatics. During her PhD work, she studied the molecular causes of hereditary deafness at the group of Xavier Estivill. Next she moved to the European Bioinformatics Institute in Hinxton (Cambridge, UK) to work on Computational Genomics at the group of Christos A. Ouzounis and then at the Center for Regulatory Genomics (Barcelona) at the group of Roderic Guigó. Nuria joined the University Pompeu Fabra in April 2006, was appointed ICREA Research Professor in October 2011 and her lab moved to Institute for Research in Biomedicine in November 2016.

Her research is focused on the study of cancer from a genomics perspective. She is particularly interested in the identification of cancer driver mutations, genes and pathways across tumor types and in the study of their targeted opportunities.

Among the most important achievements obtained by Lopez-Bigas' lab are the development of pioneer methods to identify driver genes (Oncodrive methods), the creation of IntOGen (http://www.intogen.org), a discovery tool for cancer research, the obtention of a landscape of driver events and their therapeutic opportunities across close to 7000 tumours of 28 different cancer types (Rubio-Perez et al, 2015), and the discovery that protein-bound DNA impairs nucleotide excision repair (Radhakrishnan et al., 2016).

Núria Malats
Genetic & Molecular Epidemiology Group, Human Cancer Genetics Programme,
CNIO,
Madrid, Spain

Dr. Núria Malats is currently the head of the Genetic and Molecular Epidemiology Group at the Spanish National Cancer Research Centre (CNIO), Madrid, Spain. She has a broad expertise in these fields of research by focusing mainly on pancreas and bladder cancer. She coordinates several large national and international studies integrating different levels of information, including omics data, in both disease development and progression. She has over 200 publications and is external reviewer of national and international funding agencies and first rank scientific journals. Dr. Malats is the chair of the EUPancreas COST Action "An integrated European platform for pancreas cancer research: from basic science to clinical and public health interventions for a rare disease".

Tudor I. Oprea
Professor, Department of Internal Medicine, Chief, Translational Informatics Division,
The University of New Mexico,
Albuquerque, US

Tudor Oprea, MD PhD, is a health informatics scientist with interests in knowledge management applied to lead and drug discovery, target and drug repurposing, translational informatics and health-record analytics. Dr. Oprea has contributed to conceptual developments for lead-likeness, systems chemical biology, and the identification of selective, potent compounds for the G-protein estrogen receptor, the formyl peptide receptors FPR1 and FPR2, the small GTP-ases Rac1 and Cdc42, and GLUT5, a fructose-only transporter. His work led to clinical trials for Raltegravir and Ketorolac, both evaluated as anti-cancer agents. To date, he has co-authored over 160 publication and 7 granted US patents. He serves as PI for the NIH project "Illuminating the Druggable Genome Knowledge Management Center".

Francis Ouellette
Senior Scientist, and Associate Director, Informatics & Biocomputing,
Associate Professor, Cell and Systems Biology,
University of Toronto, Ontario Institute for Cancer Research,
Toronto, Ontario, Canada

B.F. Francis Ouellette is the associate director of the Informatics and Biocomputing platform as well as a Senior Scientist at the Ontario Institute for Cancer Research (OICR) in Toronto, Ontario. Before his move to Toronto in 2007, Francis was an Associate Professor in the department of Medical Genetics at UBC, and Director of the UBC Bioinformatics Centre (UBiC). Francis was trained at McGill University (Montreal) (undergraduate and graduate studies), as well as the University of Calgary and Simon Fraser University. After working on the yeast genome sequencing project (McGill) he took a position at the NCBI as GenBank coordinator. He currently also holds a position of Associate Professor in the department of Cell and Systems Biology at the University of Toronto.

His work at the OICR involves bioinformatics training, as well as biocuration and management of cancer genomic data. Since his work at the NIH, coordinating GenBank, an open DNA sequence database, Francis has been dedicated to ensuring openness of Science: the data it generates, and the publications that report them. Francis is a PLOS Computational Biology Education Editor; Associate Editor for DATABASE, an OUP Open Access journal. Francis also serves on the scientific advisory board on a number of NIH-funded projects, as well as Genome Canada, H3ABionet (in Africa) and Elixir Europe.

Jordi Rambla
EGA Project Group, Bioinformatics and Genomics Programme,
CRG-Centre for Genomic Regulation,
Barcelona, Spain

Jordi Rambla is a member of the European Genome-phenome Archive (EGA – https://ega-archive.org) management team and is coordinating the Barcelona site. The EGA is a worldwide repository of human genomic studies that are consented to be shared only when specific criteria are matched.

He is also coordinating and participating in several ELIXIR (https://www.elixir-europe.org/use-cases/human-data) and Global Alliance for Genomics and Health (GA4GH – http://genomicsandhealth.org) initiatives related to human data management.

Chris Sander
Dana-Farber Cancer Institute,
Boston, US

Chris Sander started as a theoretical physicist and switched to theoretical biology after a first postdoc, in part inspired by the first completely sequenced genome.

He founded two departments of computational biology, one at the EMBL in Heidelberg, and one at MSKCC Cancer Center in New York. He co-founded the research branch of the European Bioinformatics Institute in Cambridge and a biotech startup with Millennium in Boston.

Chris joined the Harvard community in 2016 as Professor-in-Residence of Cell Biology at HMS, Director of the cBio Center at Dana-Farber and advisor to the Ludwig Center at Harvard.

With his group and collaborators, he would like to beat drug resistance in cancer using systems biology methods, develop the next generation cBioPortal for Cancer Research & Therapy, obtain biomolecular structures and functional interactions on a large scale using evolutionary information - and do cool computations with 10 million human genomes.

Andrea Sottoriva
The Institute of Cancer Research, Centre for Evolution and Cancer,
London, UK

"Andrea Sottoriva obtained his BSc in computer science from the University of Bologna in 2006 and his MSc in computational modelling from the University of Amsterdam in 2008. While attending his master's he worked in neutrino physics at the Institute for Nuclear and High Energy Physics (NIKHEF) in the Netherlands. He then specialised in computational biology and bioinformatics and became interested in mathematical modelling of cancer. In 2012 he completed his PhD in cancer genomics and modelling at the University of Cambridge, focusing on the integration of computational models with cancer genomic data. He then conducted postdoctoral research at the University of Southern California, investigating the use of multiple sampling genomic data from human malignancies to understand tumour evolution. Andrea joined the Centre for Evolution and Cancer at The Institute of Cancer Research, London, in 2013, where his research focuses on using multi-disciplinary approaches based on high-throughput genomics and mathematical modelling to understand cancer as a complex system driven by evolutionary principles. The goal of his group is to identify those patient-specific rules that regulate the development and progression of the disease, to inform prognosis and novel therapeutic options that are tailored to the need of the individual cancer patient."

Charles Swanton
Translational Cancer Therapeutics Department, Francis Crick Institute & Ucl Cancer Institute
The Francis Crick Institute (CRICK),
London, UK

Professor Charles Swanton (FRCP PhD FMedSci) completed his MDPhD in 1999 at the Imperial Cancer Research Fund Laboratories and Cancer Research UK clinician/scientist medical oncology training in 2008. Charles combines his laboratory research at the Francis Crick Institute with clinical duties focussed on biological mechanisms of cancer drug resistance. Charles was made Fellow of the Royal College of Physicians in April 2011 and Chair in Personalised Cancer Medicine and Consultant Thoracic Medical Oncologist at UCL Hospitals in November 2011. Charles is the Chief Investigator of the CRUK TRACERx lung cancer evolution study and was awarded the Royal College of Physicians Goulstonian lecture and Graham Bull Prize for Clinical Sciences in 2013, Fellow of the European Academy of Cancer Sciences in 2013, and Fellow of the Academy of Medical Sciences in 2015. Charles was awarded the Jeremy Jass Prize (2014), Stand up to Cancer Translational Cancer Research Prize (2015), Glaxo Smithkline Biochemical Society Prize in recognition of distinguished research leading to new advances in medical science and the Ellison-Cliffe Medal and Lecture, Royal Society of Medicine (2016). Charles was appointed Napier Professor in Cancer by the Royal Society in 2016.

Andrew Teschendorff
University College London & CAS-MPG Partner Institute for Computational Biology, London, UK

Prof. Andrew Teschendorff trained as a Theoretical Physicist at the University of Edinburgh and Cambridge University, where in May 2000 he obtained his PhD in Theoretical Particle Physics. He entered the field of Statistical Cancer Genomics in 2003, joining first the Breast Cancer Functional Genomics Lab at the University of Cambridge and later the UCL Cancer Institute at University College London. He currently holds a dual appointment as a PI in Computational Systems Genomics at the CAS-MPG Partner Institute for Computational Biology in Shanghai and the Department of Women's Cancer at UCL, as well as holding a Newton Royal Society Fellowship at the UCL Cancer Institute. His broad research interest is in Statistical Cancer Epigenomics and Cancer System-omics. He has published over 90 papers in peer-reviewed journals, is Associate Editor for Epigenomics, BMC Systems Biology and Scientific Reports, and reviews regularly for many journals including *Nature, JAMA, Nature Methods, Genome Research, Genome Biology, PLoS Computational Biology, and Bioinformatics*. He is the recipient of various academic awards, including the Tait Medal and Robert Schlapp Prize in Physics (1995), the Jennings Prize (1996), a Cambridge-MIT Initiative Fellowship (2003-2005), an Isaac Newton Trust Award (2006), the Heller Research Fellowship (2008-2013), a Wellcome Trust VIP Award (2009-2010), and a CAS Visiting Professorship (2013-2014). He is co-PI on the Horizon 2020 FORECEE program and holds 2 patents on Risk Prediction in Cancer.

Alfonso Valencia

Structural Biology and Biocomputing Programme Director,
CNIO, Spain

Alfonso Valencia is a Computational Biologist / Bioinformatician interested in the analysis of large collection of genomic information with particular emphasis in the study of protein families and protein interaction networks applied to (epi)genomics, cancer biology and precision medicine.

He is a biologist with formal training in population genetics and biophysics which he received from the Universidad Complutense de Madrid. He was awarded his PhD in 1988 at the Universidad Autónoma de Madrid. He was a Visiting Scientist at the American Red Cross Laboratory in 1987 and from 1989-1994 was a Postdoctoral Fellow at the laboratory of Chris Sander at the European Molecular Biology Laboratory (EMBL), Heidelberg, Germany.

In 1994 Alfonso Valencia set up the Protein Design Group at the Centro Nacional de Biotecnología, Consejo Superior de Investigaciones Cientificas (CSIC) in Madrid where he was appointed as Research Professor in 2005.

Prof. Valencia is now Vice-Director of Basic Research and Director of the Structural Biology and Biocomputing Programme at the Spanish National Cancer Research Centre (CNIO). He is also Director of Spanish Bioinformatics Institute (INB-ISCIII) a node of the European Bioinformatics Infrastructure ELIXIR.

During this period Alfonso Valencia served on the Scientific Advisory Board of the European Molecular Biology Laboratory; Biozentrum, Basel; the Swiss Institute for Bioinformatics, he INTERPRO database; the EBI chemical Databases, the IRB in Barcelona. He has participated in a number of review committees, including ERC, German excellence program, Spanish Grant Evaluation Agency (ANEP); as well as the Steering Committee of the European Science Foundation Programme on Functional Genomics (2006-2011).

Alfonso Valencia is Co-Executive Editor of Bioinformatics (OUP), the main journal in the field. He is Associate Editor of FEBS lett and has been in the Editorial Board of EMBO Journal and EMBO Reports, among others.

Alfonso Valencia has published more than 300 articles with Google Scholar profile has an h-index of 83, i10 of 265). His group participates in various international consortiums including GENCODE/ENCODE, BLUEPRINT/IHEC (epigenomics), RDConnect/ IRDiRC (rare diseases), CLL/ICGC (cancer genomics).

Prof. Valencia is Executive Editor of the main journal in the field since 2006 ("Bioinformatics" OUP) and Professor Honoris Causa of the Danish Technical University - DTU.

Lodewyk Wessels
Computational Cancer Biology Group,
The Netherlands Cancer Institute / Delft University of Technology,
Amsterdam, The Netherlands

Lodewyk Wessels is the head of the Computational Cancer Biology group at the Netherlands Cancer Institute in Amsterdam, The Netherlands. His group focuses on developing novel computational approaches to exploit a wide variety of data sources to map out the cancer landscape, unravel its regulation and employ this knowledge the develop strategies for personalized treatment. Dr Wessels received his M.Sc. and Ph.D. both from the Department of Electronic and Computer Engineering, University of Pretoria, South Africa. From 1993 to 1997 he was a member of the Center for Spoken Language Understanding at the Oregon Graduate School of Science and Technology, initially as graduate student and later as post-doctoral fellow. In 1997 he joined the Faculty of Electrical Engineering, Mathematics and Computer Science at the Delft University of Technology and was appointed assistant professor in 2002. In 2006 he became a faculty member at the Netherlands Cancer Institute in Amsterdam, The Netherlands. He was appointed chair of Computational Cancer Biology at the Delft University of Technology in April 2012 and heads the Cancer Systems Biology Center at the Netherlands Cancer Institute.

Jessica Zucman-Rossi

Directrice de l'unité Inserm U674/1162, Université Paris Descartes,
Hopital Européen Georges Pompidou, Department of Oncology,
Paris, France

Jessica Zucman-Rossi is Professor of Medicine at University Paris Descartes, within the depatment of Oncology at the European Hospital Geaorges Pompidou (AP-HP). She leads an INSERM laboratory in "Functional Genomics of Solid Tumors", with a focus on liver, mesothelial and renal tumors. Her team aims to develop basic genomic approaches based on human tumors analyses to identify new mechanisms of tumorigenesis and to transfer this knowledge into biomarkers that could be introduced in clinical care. In particular, the group was pioneer in the elucidation of the molecular classification of benign and malignant liver tumors. Prof Zucman-Rossi was the PI of the French liver tumor project in the International Cancer Genome Consortium (ICGC). Currently, she is executive secretary of the ILCA (International Liver Cancer Association) and she acts as co-Editor for Journal of Hepatology.

NOTES

Madrid 13-16th November 2016

CANCEROMATICS III — TUMOR HETEROGENEITY

Poster Sessions

Changes in Genome-wide and Chromosome Arm-wise Ploidy are Dependent on Tumour Type and Can be Used to Predict Common Mutations in Kidney Clear Cell Renal Cell Carcinoma Tissue

Graeme Benstead-Hume[1], Sarah K Wooller[1], Jessica A Downs[2] and Frances M G Pearl[1]

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Identifying gene mutations that correlate to changes in ploidy may provide clues for loci of driver mutations, especially those in areas of loss of heterozygosity. Furthermore identifying alterations in chromosome arms that are correlated to these mutations may provide insight into how specific genes interact with the karyotype as a whole.

Here we have used a systematic approach to estimate the overall ploidy status of a cancer cell, and to identify the correlation of mutations in specific genes with losses or gains of individual chromosome arms. In order to maximise the sensitivity and utility of the analyses, we evaluated each chromosome arm separately. Consequently, an altered signal could reflect changes in chromosome number or karyotypic aberrations such as non-reciprocal translocations. For simplicity, we refer to these as changes in ploidy.

Using pan-cancer data from The Cancer Genome Atlas (TCGA), we investigate how ploidy in cancer cells varies both by tissue type and through mutations in specific genes and how suitable this data is for use in machine learning classifiers.

We find that the change in both genome-wide ploidy and individual arm ploidy is dependent on tumour type. We highlight, for example, the significant loss in ploidy in chromosome arm 3p and gain of ploidy in 5q in kidney clear cell renal cell carcinoma (KIRC) tissue samples.

We find that certain gene mutations are closely associated with genome-wide ploidy change in certain cancers. Again focusing on KIRC, we show mutations in VHL and PBRM1 to be associated with significant changes in both genome-wide and chromosome arm-wise ploidy.

Finally, utilising a set of machine learning classifiers, we find that patterns of loss and gain in individual chromosome arms can be used with varying success to predict specific gene mutations. Using these same classifiers, we finally highlight which arms are most associated with each mutated genes in KIRC tissue using machine learning importance metric.

A Machine Learning pipeline to infer causal models of cancer progression from an ensemble of cross-sectional tumors

Giulio Caravagna[1], Alex Graudenzi[2,6], Daniele Ramazzottis[3] and Rebeca Sanz-Pamplona[4], Luca De Sano[5,6], Giancarlo Mauri[6], Victor Moreno[4,6], Marco Antoniotti[5], Bud Mishra[8]

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The quest for an extensive etiology of tumor heterogeneity (TH) and for the identification of cancer evolutionary trajectories is central to devise effective personalized treatment strategies (McGranahan et al, Cancer Cell 27(1), 2015). NGS data allow us to develop inference techniques that extract evolutionary progression models (EPMs) recapitulating how (epi)genomic events orchestrate cancer initiation and development (Beerenwinkle et al, Systematic Biology 64(1), 2015). Such models can quantify the extent of TH, and explain the emergence of drug-resistant and metastatic phenotypes. We can infer EPMs from sequencing of single-biopsies collected from multiple tumors, or from multiple biopsies/cells of a single tumor. These formulations elucidate orthogonal aspects of the progression, namely evolution in an ensemble of patients with the same tumor subtype, or in an individual patient. Individual-level inference is becoming increasingly popular, but it requires NGS data types (multi-region bulk, or single-cell) that are not yet commonly available. Ensemble-level inference, instead, can exploit the voluminous amount of single-sample bulk NGS data collected in repositories such as TCGA. Here, I will present the open-source Machine Learning "Pipeline for Cancer Inference" (PiCnIc) that infers the underlying somatic evolution of ensembles of tumors (Caravagna et al, PNAS 113(28), 2016). PiCnIc combines custom techniques for sample stratification, driver selection and identification of fitness-equivalent exclusive alterations to exploit a state-oftheart algorithm for causal inference of EPMs. PiCnIc allows to combine prior biological knowledge with computational predictions, and computes multiple measures of statistical confidence for a model. An application to process MSI and MSS colorectal tumors is shown that demonstrate its ability to reproduce relevant knowledge on CRC progression, as well as to suggest novel experimentally verifiable hypotheses.

PiCnIc's implementation, example case studies and further material are available at the webpage of the TRONCO tool for Translational Oncology https://sites.google.com/site/troncopackage

Multi-sample simulation of intratumor heterogeneity

Harald Detering, David Posada

Phylogenomics, University of Vigo, Vigo, Spain

Intratumor heterogeneity (ITH) has proven to be an important medical indicator of cancer patient prognosis as well as the basis for the study of tumor evolution. Accordingly, various tools have been developed recently to reconstruct the clonal substructure of tumors from sequencing data. We are developing a computational model to generate simulated bulk and single cell sequencing data based on an evolutionary clone tree. Simulation of paired tumor/normal data including multiple tumor samples will enable the exploration of complex modes of cancer development. Knowing the underlying ancestry and cellular prevalence of clones in bulk sequencing samples it will be possible to assess the performance of clonal reconstruction methods, identify strengths and weaknesses of different approaches which may lead to improved procedures.

Heterogeneity in mitochondrial content underlies cell-to-cell variability in TRAIL induced apoptosis

Juan Díaz-Colunga[1], Silvia Márquez[1], Fernando Almazán[1], Raúl Guantes[2] and Francisco J Iborra[1]

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Variability and resistance of tumor cells to chemotherapeutic agents has been associated many times with genetic intratumoral heterogeneity. However, it is becoming increasingly clear that non-genetic differences between cells also play a prominent role in the response and resistance of tumors to treatments. One much studied case is the cell-to-cell variability observed in survival and death times following an apoptotic trigger. This variability has been linked to differences in the amounts of the proteins involved in the apoptotic pathways. Previous findings show that, due to the high energetic demands of the gene expression machinery, heterogeneity in mitochondrial content accounts for roughly 50% of the variability observed at the protein level. In addition, mitochondrial outer membrane permeabilization (leading to the realease of proapoptotic proteins to the cytosol) is a crucial step in the apoptotic signalling pathway. These observations suggest that the amount and/or functionality of mitochondria in individual cells may determine the timing and susceptibility to apoptotic stimuli, both indirectly as modulators of protein variability, and directly as key mediators of apoptosis.

References:

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OncoSimulR: genetic simulation of cancer progression with arbitrary epistasis and mutator genes

Ramon Diaz-Uriarte

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Forward genetic simulations are widely used in cancer research and population genetics to examine complex models that are mathematically intractable, to verify analytic results from mathematical models, and to generate data to assess the performance of statistical methods. Several programs and libraries are available, but none of these are well suited if we require:

- complete flexibility to specify arbitrary epistatic effects of high order;
- possibility to specify order effects between arbitrary numbers of genes; with order effects the fitness of genotype AB depends on whether A or B is acquired first, a phenomenon recently identified between JAK2 and TET2 in myeloproliferative neoplasms;
- tracking of the complete history of all clones and sampling from the population at arbitrary times and with different resolution (e.g., whole tumor vs. single-cell), both crucial features to understand heterogeneity;
- gene-specific mutation rates;
- mutator/antimutator genes (genes whose mutation leads to an increase/
- decrease in the mutation rate of other genes);
- large (> 10000) number of genes;
- large (> 10^6) asexual populations;
- varied models of growth.

These scenarios are particularly relevant for cancer progression models and also common in other evolutionary genetics studies. I have developed OncoSimulR, an R package (that uses C++ underneath for speed), to provide those features. OncoSimulR also allows specifying fitness using directed acyclic graphs to define restrictions in the order of accumulation of mutations, as is common in many cnacer progression models.

These features make OncoSimulR a unique forward genetic simulation tool, particularly well suited for examining cancer evolution models, including heterogeneity and its relation to sampling processes. OncoSimulR is available from BioConductor (http://bioconductor.org/packages/release/bioc/html/OncoSimulR.html) and github (https://github.com/rdiaz02/OncoSimul).

Measuring the impact of sequencing depth in somatic variant calling using single-cell sequencing data

João Miguel Fernandes Alves, David Posada

Department of Biochemistry, Genetics and Immunology,
University of Vigo and Institute of Biomedical Research of Vigo (IBIV), Vigo, Spain

It has long been appreciated that the large majority of cancer genomes are genetically heterogeneous despite its monoclonal origin. Quantifying this intratumor heterogeneity (ITH) remains a difficult task, as standard methods in cancer genomics generally rely on the analyses of bulk tissue samples, which can only provide an average signal from a pooled mixture of heterogeneous cell types. Because of this, single-cell sequencing (SCS) strategies are now widely viewed as a promising approach to study ITH.

However, several challenges surrounding current SCS methodologies greatly limits one's ability of obtaining reliable genomic information from single cells. For instance, the multiple rounds of whole genome amplification, required prior to genome sequencing, are known to introduce a high number of sequence artifacts that can be confounded with genuine biological variation, including false-positive (FP) signals due to amplification errors, false-negative errors due to insufficient coverage, and allelic dropout events. Moreover, since only a small number of single cells can be sequenced at high depths at a reasonable cost, sampling bias may also lead to inaccurate estimates of somatic variation. Consequently, alternative strategies are needed in order to identify and reduce the noise generated in SCS experiments.

Here, we applied the census-based variant discovery principle to assess the impact of sequencing coverage on somatic variant detection. Making use of publicly available datasets, we quantified the sensitivity and specificity of different sequencing strategies to somatic variant detection, and determined the degree to which sequencing depth affects FP contamination. Interestingly, we demonstrate that, using fairly large sample sizes, the detection of somatic mutations is maximized at moderate depths. Moreover, a high proportion of potential FPs were observed for high coverage sets (~50x), suggesting that lower depths are optimal solutions for FP avoidance.

Osteosarcoma cells tracking: tumor heterogeneity and clonal evolution

Stefano Gambera, Teresa Cejalvo Goyanes , Ana Judith Perise Barrios, Miguel Angel Rodriguez Milla, Isabel Cubillo Moreno, Alvaro Morales-Molina, Arantzazu Alfranca Gonzalez, Javier Garcia-Castro

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Osteosarcomas (OS) are the most common type of bone cancers and appear heterogeneous both histologically and radio graphically. This variability suggests the presence of cancer stem cells undergoing aberrant osteogenic differentiation. In order to characterize OS heterogeneity and tumor clonal dynamics, we have employed a lentiviral-based RGB tracking system. This tool consists of transducing tumor cells (human, murine and canine OS) with a combination of three lentiviral vectors which express respectively for red, green and blue fluorescent proteins (LeGO-vectors). The combination of these proteins at different expression levels confers a unique colour to each individual cell and its progeny, thus allowing us to identify and track cells coming from specific clones.

Our data shows that OS cell lines recapitulate radio-graphical characteristics of OS. We were able to track clonal behaviour in vivo and identify differences between clones in terms of proliferation, invasiveness and metastatic propensity, also detecting competition/ collaboration between clones. We were also able to recolour populations and retrace them in a secondary recipient. In conclusion the study shows differences in tumour clonal heterogeneity of primary tumors and metastasis, highlighting also phenomenon's of clonal evolution during time.

PhD student developing the Doctoral thesis under the supervision of Doctor Javier Garcia Castro

Epigenetic and genetic deregulation in cancer target distinct signaling pathway domains

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2 University of Chinese Academy of Sciences, Beijing, China
3 Department of Women's Cancer, University College London, London, UK
4 Statistical Genomics Group, Paul O'Gorman Building, UCL Cancer Institute, University College London, London, UK

Cancer is characterized by both genetic and epigenetic alterations. While cancer driver mutations and copy-number alterations have been studied at a systemslevel, relatively little is known about the systems-level patterns exhibited by their epigenetic counterparts. Here we perform a pan-cancer wide systems-level analysis, mapping candidate cancer-driver DNA methylation alterations onto a human interactome. We demonstrate that functional DNA methylation alterations in cancer tend to map to nodes of lower connectivity and inter-connectivity, compared to the corresponding alterations at the genomic level. We find that epigenetic alterations are relatively overrepresented in extracellular and transmembrane signaling domains, whereas cancer genes undergoing amplification or deletion tend to be enriched within the intra-cellular domain. A meta-analysis identifies WNT-signaling, as a key pathway where epigenetic deregulation preferentially targets extracellular components. These results suggest that epigenetic deregulation in cancer not only targets tissue-specific transcription factors, but also modulates signaling within the extra-cellular domain, providing novel system-level insight into the potential distinctive role of genetic and epigenetic alterations in cancer.

Rational design of non-resistant targeted cancer therapies

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[6] ICREA, Barcelona, Spain

Drug resistance is one of the major problems in targeted cancer therapy. High mutation rates and selective pressure can efficiently result in drug-resistance to therapy. Although there are many mechanisms for drug resistance, a classic mechanism is due to changes in the amino acids in the drug-target binding site. Despite of the numerous efforts made to individually understand and overcome these mutations, there is a lack of comprehensive analysis of the mutational landscape that can potentially cause resistance.

Herein, we present a framework that computationally predicts the potential of a sequence mutation to confer resistance to targeted therapies in cancer. Our model first quantifies the likelihood of mutations in the drug target using the probabilities from the mutational signatures associated to the cancer class. Next, we developed a Random Forest Classifier (RFC) that uses structural information of the drug-protein interaction to predict the resistance-likeness of the aforementioned mutations. The combination of the predicted likelihood with the resistance-likeness allows the detection of mutations with the highest chance to be responsible of resistance to a particular targeted cancer therapy. Finally, for these treatment-threatening mutations, the classifier proposes alternative therapies overcoming the resistance.

We exemplified the applicability of the model using the EGFR-gefitinib treatment for Lung Adenocarcinoma (LUAD) and Lung Squamous Cell Cancer (LSCC) and the ERK2-VTX11e treatment for melanoma and colorectal cancer. Our model correctly identified the phenotype of some of the known resistance mutations, including the EGFR-T790M or the ERK2-P58L/S/T. Moreover, the model predicted new clinically unseen mutations as potentially responsible of resistance to EGFR-gefitinib and ERK2-VTX11e targeted cancer therapies. Finally, we provided a map of the predicted sensitivity of alternative ERK2 and EGFR inhibitors, with a particular focus in two molecules with a low predicted resistance-likeness.

Targeting the retinoblastoma pathway by a new cellular viroimmunotherapy

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A high mutational heterogeneity is observed in cancer and it is recognized as a well-known hallmark. However, some genome alterations are found more frequently and constitute interesting targets to develop broad spectrum therapies for different types of tumor.

Particularly, the retinoblastoma (Rb) pathway, a key regulator in the cell cycle progression, is usually altered in cancer cells. Thus, oncolytic viruses that specifically replicate in deregulated Rb pathway cells, such as ICOVIR-5, have been designed. Our strategy, named Celyvir, uses mesenchymal stem cells (MSC) as carriers for oncolytic viruses. However, the better efficacy of syngeneic or allogenic MSC as vehicles and the role of the immune system in this therapy are still unknown.

In this study we use a murine adenocarcinoma model treated with our cellular viroimmunotherapy. Compared to the untreated group, we observed a 42% reduction in the tumor volume of the group treated with allogenic murine mesenchymal stem cells (mMSC) infected with ICOVIR-5, while the group treated with infected syngeneic mMSC presented only a 30% reduction. We also observed an intratumoral activation of the immune system and a maintenance of the immune response after adoptive transference of the treatment. Our results show that allogenic mMSC are more effective oncolytic virus carriers and tend to induce a better antitumoral response.

Decoding the intra-tumor genetic heterogeneity in endometrial cancer: implication in diagnosis and cancer progression

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In developed countries, endometrial cancer is the most common cancer that affects the female genital tract. Although the majority of endometrial cancers are diagnosed at early stages with a 5-year overall survival around 80%, advanced tumors are associated with poor outcome. Their early detection is crucial to improve the survival of patients. Additionally, a correct assessment of the pre-clinical diagnosis is decisive to guide the surgical treatment and management of the patient. In this sense, the study of intra-tumor heterogeneity is important for cancer progression understanding and proper diagnosis. Whole-exome sequencing and subsequent targeted amplification was performed in multiple samples (60 primary tumor and 37 metastasis specimen) from 11 patient diagnosed with metastatic endometrial carcinoma to understand the implication of intra-tumor heterogeneity in cancer progression. Different grade of heterogeneity was found, indicating a clonal evolution from primary tumor subclones to metastasis. Moreover patient derived xenografts (PDX) from one of the patients were analyzed to study the clonal evolution of the tumor in the animal model. The implication of intra-tumor heterogeneity in the clinical diagnosis of endometrial tumor was also analyzed by commercial targeted genetic sequencing. A total of 83 paired samples were sequenced (uterine aspirates and hysterectomy specimens), including 62 endometrioid and non-endometrioid tumors, 10 cases of atypical hyperplasia and 11 non-cancerous endometrial disorders. Notably, the genetic analysis of uterine aspirates captures this heterogeneity, solving, at least partially, the potential problem of genetic misdiagnosis when a single tumor biopsy is analyzed, even in samples that are not histologically classifiable.

Regulation of S phase Arrest and Mitotic Catastrophe by HDAC1/HDAC2 and PP2A

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Over 3 billion base pairs of a mammalian cell have to be replicated with every cell division. Limitations in the supply of nucleotides and DNA lesions slow down replication fork speed and trigger a complex replicative stress response to prevent genomic instability and cancer development. The checkpoint kinases ataxia telangiectasia mutated (ATM), ATM and Rad3-related (ATR), checkpoint kinase-1 (CHK1), and checkpoint kinase-2 (CHK2) are at the heart of this response. These factors catalyze processes that slow down the cell cycle as well as mechanisms that stabilize the replication fork and processes that initiate DNA repair. Such pathways ensure the faithful transmission of DNA without epigenetic alterations and DNA mutations. As expected for such a pivotal mechanism, checkpoint kinase signaling is highly regulated. Posttranslational modifications including phosphorylation and acetylation regulate checkpoint kinases at multiple levels. Recent data show that class I histone deacetylases (HDACs) can affect checkpoint kinase signaling and genomic stability. How these HDACs control checkpoint kinases exactly and if they show specificity for certain checkpoint kinases and DNA repair pathways has not been resolved. Moreover, although it is known that phosphorylation triggers checkpoint kinase activation and that the trimeric phosphatase PP2A attenuates checkpoint kinase phosphorylation it is unknown how this activity of PP2A is modulated. PP2A consists of the subunits A (structural component, PPP2R1A/B), C (catalytic activity, PPP2CA/B), and B (discriminates between substrates to allow specificity of the PP2A holoenzyme). Our data illustrate that class I HDACs are required for checkpoint kinase phosphorylation in human and murine cells. We show that these enzymes suppress the expression of certain PP2A subunits and we reveal that one of the B type subunits specifically targets checkpoint kinases for dephosphorylation by the PP2A holoenzyme. With genetic and biochemical app.

Anti-metastatic treatment prescription for a highly metastatic pancreatic cancer model driven by single-cell RNA-seq analysis

Javier Perales-Patón[1], Spas Dimitrov[2], Héctor Tejero[1], Elena Piñeiro-Yáñez[1], Pedro P. Lopez-Casas[2], Alfonso Valencia[3], Manuel Hidalgo[2], and Fátima Al-Shahrour[1]

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Despite remarkable progress in understanding genetic and molecular basis in pancreatic carcinogenesis, pancreatic cancer remains a dismal scenario. The lethality of pancreatic cancer stems from a lack of therapeutic strategies and the rapid dissemination from the primary lesion to widespread metastasis. Here we have isolated single cells from the main scenarios during tumour dissemination of a highly metastatic Patient-Derived Xenograft model in order to discover a target therapy against the metastatic settings. Primary tumour, liver metastasis cells and circulating tumour cells (CTCs, in bloodstream) were sequenced by using single-cell RNAseq. Gene expression analyses have shown a strong transcriptional down-regulation in CTCs, which might be associated to a cell dormancy state. From the minor leak of genes detected as up-regulated in CTCs, many of those genes are associated to both a positive and a negative regulation of apoptosis. Interestingly, one of the most up-regulated and over-expressed genes in CTCs is related to anoikis disruption and cancer progression. We hypothesize this gene could be a potential target for a anti-metastatic treatment. According to these insights, we have proposed up to four candidate treatments of metastasis inhibition in order to being tested in a personalized pre-clinical trial.

Analysis of exome heterogeneity of B-lymphocytes from a patient with chronic lymphocytic leukemia

Tamara Prieto[1], Sonia Prado-López[1], Nuria Estévez-Gómez[1], Sandra Suárez[2], Irene Figueroa[2], Carmen Loureiro[2], João Alves[1] and David Posada[1]

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Intratumor heterogeneity has important clinical implications because renders single tumor samples not representative of the spectrum of somatic cancer mutations present in a patient. Here, we analyze exome sequencing data from two different tumor samples -peripheral blood and bone marrow- from a patient with chronic lymphocytic leukemia before and after treatment. We identify single nucleotide and copy number variants in order to reconstruct the different clones present in the tumor and their evolutionary relationships in time and space.

Analysis of structural variation in tumor genomes associated to transposase-like gene activity

Elias Rodríguez-Fos[1], Santi González[1], Montserrat Puiggròs[1], Anton G. Henssen[2], Alex Kentsis[2,4,5] and David Torrents[1,3]

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DNA Transposases are enzymes that catalyse the movement of mobile elements in the genome known as transposons. Some transposase-derived genes, such as PGBD5, keep their enzymatic activity in human cells. The expression of PGBD5 has been related to mobilisation of transposons through a motif specific cut and paste mechanism across the genome. The excision and insertion mechanism of transposable elements can cause genomic rearrangements and have a potential mutagenic activity in cancer.

In a collaborative effort with the Sloan Kettering Institute (NY, US) we have studied the role of transposase-like genes in genome variability related to cancer. Through the analysis of WGS derived for cells overexpressing PGBD5, we have identified using SMuFin a significant enrichment of 150 to 300 bp deletions that agree with a transposon activity, despite the corresponding integration of the deleted regions seems to be absent. The majority of these deletions show a characteristic motif (CACTGCA), expanding around the breakpoint. Interestingly, we also found a recurrent pattern of confronted Alu sequences flanking the borders of the deletion, that could be acting as substrate in homologous recombination events triggered by this gene. Recent analysis in a first subset of Breast cancer patients from PanCancer also show that these characterized deletions are present across different patients in a same cancer type. We also found the same pattern of confronted Alus in all the breakpoints within the deletions. Preliminary analysis of patients from other type of cancers such as Ovarian, point that these type of deletions are present also across cancer types. Understanding the mechanisms behind the role of transposase-like genes in cancer through the study of the structural alterations and the correlation with functional genomic features will contribute to the description of the underlying tumorigenic processes and potentially be used as markers for the different types of tumor progression.

Denoised perturbation signatures extracted by DART reveal biological and clinical information in single-cell setting

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Intra-tumor cellular heterogeneity presents a major challenge for precision medicine. While identification of genomic aberrations across single cells within a tumor can inform on drug treatment and resistance mechanisms, it is becoming widely appreciated that profiling activity of oncogenic pathways using mRNA expression data may be more informative. Recently, a number of algorithms (e.g. VIPER and DART) have been proposed for inferring activity of regulators and oncogenic pathways. Previously we showed how DART inferred an actionable AKT-signaling gene module, allowing identification of ER+ breast cancer patients who don't respond to endocrine treatment but who may benefit from alternative therapy targeting the AKT-pathway. DART uses large RNA-Seq datasets to denoise perturbation signatures from the literature and public databases, extracting tissue and disease specific regulons. These then allow predictions of activity of the perturbation signatures in single samples, including single-cell data. Application of DART to TCGA RNA-Seq and scRNA-Seq data of lung adenoma carcinoma patients, and to CTCs from prostate cancer patients confirm the power of DART to extract biologically and clinically relevant information in the single-cell setting.

Cancer Genome Interpreter identifies driver and actionable alterations

David Tamborero[1], Carlota Rubio-Perez[1], Jordi Deu-Pons[1], Michael Schroeder[1,2], Ana Vivancos[3], Ana Rovira[4], Ignasi Tusquets[4,5], Joan Albanell[4,6], Jordi Rodon[3], Josep Tabernero[3], Rodrigo Dienstmann[3], Abel Gonzalez-Perez[1] and Nuria Lopez-Bigas[1,7]

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The use of genomic information is key to improving the management of cancer and to increase the cost-efectiveness of available therapies. We have developed the Cancer Genome Interpreter (CGI), an online platform which supports the biological and clinical interpretation of the alterations (mutations, copy number changes and translocations) found in a tumor. Briefly, and upon reception of the list of alterations detected in the tumor and its cancer type, the CGI first identifies already validated oncogenic events. Second, it predicts the effect of the remaining alterations of uncertain significance by using an ensemble of bioinformatics methods. Third, the CGI reports the influence of these variants on the clinical response to drugs (sensitivity, resistance and toxicity) according to the current state of knowledge (ranging from pre-clinical evidences to clinical guidelines). Finally, the CGI lists the available interactions of existing chemical compounds with all genes bearing driver alterations in the tumor sample with the aim to explore novel actionable events. The output of the CGI are provided via interactive reports organized following distinct levels of clinical relevance and includes all the ancillary information on which they are based. This empowers the review of these results, and makes the platform highly versatile. We envisage that the CGI will support decisions in different pre-clinical and translational scenarios, such as the selection of the most appropriate clinical trial for patients with tumors bearing mutations of unknown significance, or the design of experimental assays aimed to evaluate the use of novel genomic guided-therapeutic strategies. We will present several results obtained by the CGI to illustrate its value in different use case scenarios.

Inferring drug sensitization in cancer using gene expression data

Héctor Tejero, Javier Perales-Patón, Miriam Rubio-Camarillo, Ángel Carro, Gonzalo Gómez-López and Fátima Al-Shahrour

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Over the recent years, it has been shown that antitumour drugs are more effective when given in combination. Thus, computational prediction of drug combinations that could act synergistically has been greatly studied in the last years.

Here we study the possibility of inferring a combinatorial treatment with a first drug which might sensitize to the immediate response of a second drug. The drug-pair relationships are established by comparing the transcriptional effects from the first drug against transcriptional biomarkers of response for the second one.

Basically, there are two types of drug-associated gene expression signatures: the ones associated to the transcriptional effect of the drug treatment and the ones associated to the phenotypic response to the drug. The first ones can be obtained from projects like Connectivity map or the LINCS L1000. The second one can be obtained from pharmacogenomic projects like the Genomic of Drug Sensitivity of Cancer (GDSC) or the Cancer Cell Line Encyclopedia (CCLE). In both cases we obtain the expression signatures by means of a differential expression analysis using Limma. A correction by cell line and cancer type was considered in the LINCS L1000 data and GDSC or CCLE data, respectively.

By looking for the drugs with the most similar transcriptional effect to the gene expression signature associated to a second drug we can propose which drugs could be used to sensitize the second one in a way that they could act synergistically. Several similarity measures have been tried as Jaccard, Xsum or the Spearman correlation coefficient.

This approach could be used to propose resensitization treatments, second-line therapies or even combinations of drugs, it also could be extended by considering not only the transcriptional effect of drugs but also the one associated to other therapeutic interventions or the transcriptional response associated to the acquired resistance to a given drug.

19

Intra-cell line heterogeneity in a neuroblastoma cell line

Miguel Julia[1,2], Emily Saintas[1,2], Georgia Walden[1,2], Jaroslav Cinatl[3], Florian Rothweiler[3], Darren K. Griffin[2], Jindrich Cinatl jr.[2], Martin Michaelis[1], **Mark N. Wass[1]**

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Cancer cell lines represent a major model for the investigation of the cancer cell biology and cancer cell response to anti-cancer drugs. In order to study the intra-cell line heterogeneity of the MYCN-amplified neuroblastoma cell line UKF-NB-3, we have established 10 single cell-derived clonal UKF-NB-3 sub-lines. UKF-NB-3 and its clonal sub-lines were characterised by whole exome sequencing, 24-chromosome fluorescence in situ hybridisation (FISH), cell growth kinetics, and determination of drug sensitivity profiles.

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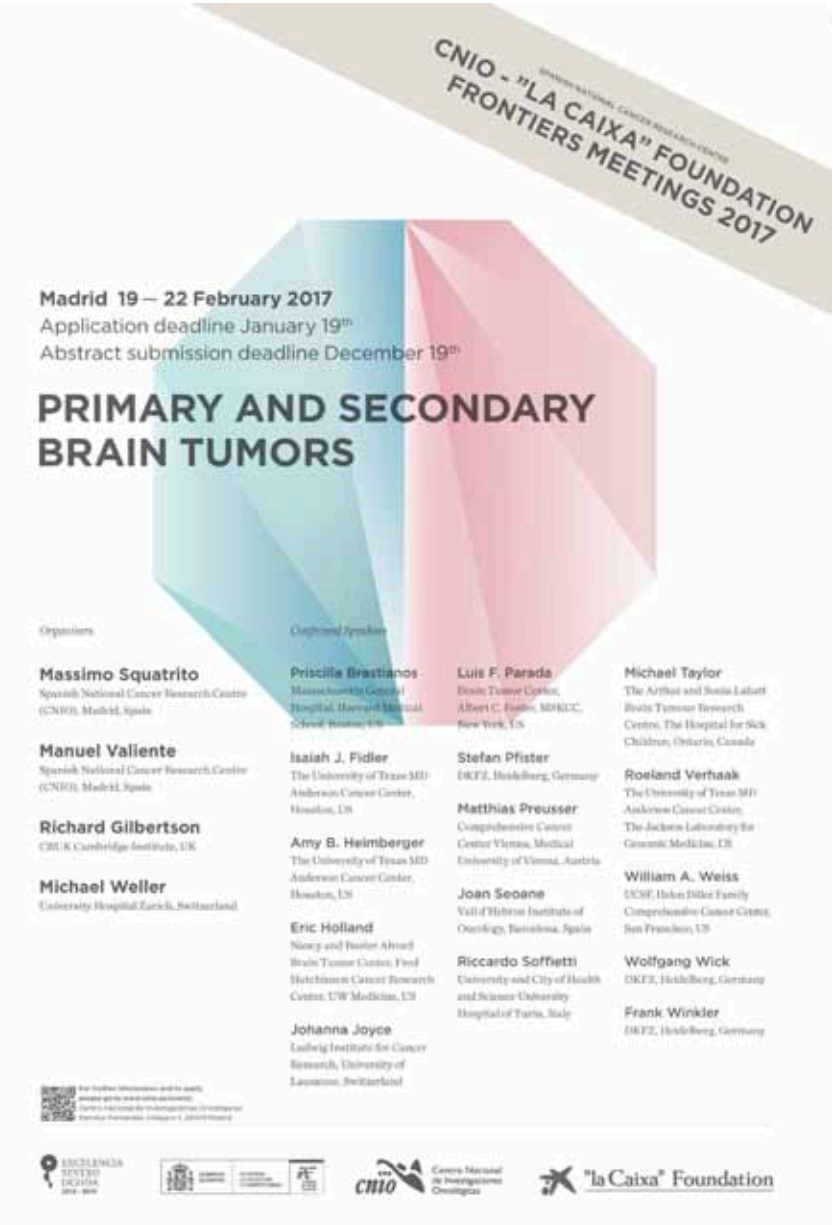

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