ciones Bioquímicas de Bahía Blanca (INIBIBB-UNS-CONICET), Argentina
2. Instituto de Ciencias e Ingeniería de la Computación (ICIC-UNS-CONICET), Departamento de Ciencias e Ingeniería de la Computación (UNS), Bahía Blanca, Argentina
3. Unidad de Cirugía de Cabeza y Cuello, Hospital Municipal de Agudos "Dr. L. Lucero", Bahía Blanca, Argentina.

GEF-H1 is a Rho-GTPases activator whose overexpression has been shown to be associated with tumor development. However, its role in thyroid cancer (TC) progression has not yet been studied. TC has been dramatically rising worldwide in recent decades and represents the most prevalent endocrine malignancy. For this reason, we have begun analyzing GEF-H1 expression in human thyroid biopsies. We observed higher cytoplasmic protein concentration when comparing by immunohistochemistry tumor tissue (TT) with non-malignant tissue (NMT) (n=52; p=0.0003). Similar results were obtained by Western blot in thyroid biopsies and cancer cell lines. Furthermore, clinical-histopathological data showed significant GEF-H1 overexpression in TT than NMT (p=7E-07), which correlates with a less patient survival (p=0.0088). mRNA data analysis from biopsies (Human Protein Atlas and Oncomine platforms) also showed a significant GEF-H1 overexpression in TT compared with NMT. Analyzing Gene Expression Omnibus microarray data with R language, we observed that GEF-H1 is between 2-17% of the most expressed genes in different TC histotypes. We also determined that GEF-H1 expression is significantly higher in papillary and anaplastic carcinomas than NMT ($p<0.05$) and its expression increased in papillary carcinomas with lymph node invasion and/or metastasis ($p<0.001$). Moreover, we looked for those genes whose mRNA expression correlates with GEF-H1 and we evaluated their function through gene ontology analysis (DAVID and STRING platforms) and their participation in signaling pathways (KEGG and Reactome). Genes associated with migration, mechanical signaling, cytoskeleton remodeling and focal adhesions positive correlated with GEF-H1 expression in TC ($p<0.001$). The results suggest that GEF-H1 might be a potential tumor biomarker and/or therapeutic target in TC, since it would be involved in the pro-tumorigenic signaling by coordinating changes in cell morphology, proliferation, migration and invasion.

4. (104) **OSTEOSARCOMA AND MIRNAS: COMBINING IN SILICO MIRNA ANALYSIS AND PROTEOMIC PROFILING IN SEARCH OF POTENTIAL DIAGNOSTIC PANEL**

Valenzuela Alvarez M[1]; Matos B[2]; Correa A[2]; Bolontrade M.F[1].
1) Instituto de Medicina Translacional e Ingeniería Biomédica (IMTIB) – CONICET- Hospital Italiano Buenos Aires (HIBA) – Instituto Universitario del Hospital Italiano (IUHI), Buenos Aires, Argentina
2) Instituto Carlos Chagas Fiocruz Curitiba, and Program for Technological Development in Tools for Health PDTIS-FIOCRUZ Curitiba, Brazil

Osteosarcoma (OS) is the most frequent bone tumor in pediatrics and presents two critical clinical challenges, metastasis and chemoresistance. Better diagnostic and prognostic tools for OS disease progression are in need. Here we propose the use of micro-RNAs (miRNAs) as alternative diagnostic biomarkers for OS. MiRNAs are small and stable non-coding RNAs that can be obtained from liquid biopsies of different body fluids such as plasma, which in the last years have been proposed as diagnostic and prognostic biomarkers. The aim of this work was to assess an OS miRNAs database and contrast it with our own molecular and functional profiling in an OS model with metastatic behavior, in order to propose possible miRNAs as biomarker candidates. We analyzed circulating miRNAs present in the plasma of 15 healthy donors and 20 OS patients (10 with localized OS and 10 with metastatic OS) using the miRNAs dataset GSE65071. Our analysis revealed that miR-34a-5p, -200a-3p, -582-5p, -624-5p and let-7a-3p were upregulated in OS patients plasma as compared to healthy donors (fold change: 0.43; 0.78; 0.78; 0.95; 0.5 respectively; $p < 0.0001$), while miR-27a-3p and -221-3p were found downregulated in the plasma of OS patients as compared to healthy donors (fold change: -0.73; -2.64 respectively; $p < 0.0001$). There was no difference in expression between localized and metastatic OS for these miRNAs. Bioinformatics analysis of the target genes of these miRNAs revealed that they are implicated in the regulation of different cancer-related biological pathways like ECM- receptor interaction, cell cycle control and EMT, in coincidence with our proteomic approach on metastatic and non-metastatic OS cells. These results strengthen the in-silico search and constitute a proof of concept on the use of this cross-omic approach as a tool for the identification of potential miRNAs as liquid biopsy biomarkers for diseases characterized by scarce extensive population-based data.

5. (130) **REGULATORY CIS-ELEMENTS AND TRANSCRIPTION FACTOR ANALYSIS BEHIND MRP4/ABCC4 EPIGENETIC AND TRANSCRIPTIONAL PROFILE IN PANCREATIC CANCER**

Samanta Gancedo *(Instituto de Investigaciones Farmacológicas ININFA-UBA-CONICET)*, Ana Sahores *(Instituto de Biología y Medicina Experimental IByME-CONICET)*, Natalia Gómez *(Instituto de Investigaciones Farmacológicas ININFA-UBA-CONICET)*, Camila Pérez Luján *(Instituto de Investigaciones Farmacológicas ININFA-UBA-CONICET)*, Maximiliano De Sousa - Ferro *(Instituto de Investigaciones Farmacológicas ININFA-UBA-CONICET)*, Carlos Davio *(Instituto de Investigaciones Farmacológicas ININFA-UBA-CONICET)*, Betina González *(Instituto de Investigaciones Farmacológicas ININFA-UBA-CONICET)*

The multidrug resistance-associated protein 4 MRP4/ABCC4 is a xenobiotic transporter highly expressed in pancreatic ductal adenocarcinoma (PDAC), thas was found linked to increased proliferation and poor prognosis. We queried ChIP-seq and RNA-seq data from PDAC cell lines available at public repositories including the Gene Expression Omnibus (GEO) and the Encyclopedia of DNA Elements (ENCODE), analyzing Abcc4 mRNA levels and the associated epigenetic landscape of histone marks with clear functions in gene expression: H3K27ac/H3K4me for cis-regulatory elements indicative of active clusters of transcription factors (TFs), H3K4me3 for active promoters, H3K9me3 for silenced heterochromatin, and the TFs reported bound at those genomic locations. All cell lines presented H3K4me3 enrichment at the Abcc4 promoter and were depleted of H3K9me3. The high Abcc4-expressing cell lines, such as PANC1, consistently showed H3K27ac/H3K4me enrichment at specific locations of intron1, which were not detected in low Abcc4-expressing cell lines, such as HPAF2. We overlapped these regions with the TFs peaks reported in high Abcc4-expressing CFPAC1 cell line and defined three TFs clusters for further analysis. We generated HPAF2, BxPC3 and PANC1 xenografted tumors in NGS mice and evaluated Abcc4 mRNA expression (RT-PCR) and chromatin enrichment (ChIP-PCR) of H3K27ac, FoxA1 and GATA2 at the intron1 clusters. We found Abcc4 mRNA levels as expected: low in HPAF2 and increased in BxPC3 and PANC1. H3K27ac showed enrichment at the three clusters in all tumors, indicative of active/poised state, but only high Abcc4-expressing BxPC3 and PANC1 showed enrichment of FoxA1/GATA2 at these genomic locations. FoxA1 was found enriched at all clusters only in BxPC3. GATA2 showed enrichment at clusters 2 and 3 in BxPC3 and PANC1, and at cluster 1 only in PANC1. These findings suggest that FoxA1 and GATA2 may contribute to aberrant Abcc4 expression, PDAC aggressiveness and progression.

6. (150) **B2-BRADYKININ RECEPTOR NON-PEPTIDIC LIGANDS AS NEW DRUG-REPURPOSING STRATEGY AGAINST COVID-19 AND OTHER ARDS-INDUCING LUNG INFLAMMATORY INFECTIONS.**

Gómez MC[1], Luna Paez G[1], Wiebke L[1], Casco VH[1,2], Schierloh LP[1,2].
1. Facultad de Ingeniería. Universidad Nacional de Entre Ríos (UNER).
2. Instituto de I+D en Bioingeniería y Bioinformática (IBB)-UNER-CONICET.

INTRO: Dysregulation of kallikrein-bradykinin pathway has been linked to hyperinflammatory phase of several lung infections causing adult respiratory distress syndrome (ARDS) including COVID-19,

SARS, MERS and Hantavirus Respiratory Syndrome. The injectable synthetic decapeptide Icatibant (Firazyr) is the only currently approved antagonist for B2-bradykinin receptor (B2-bkR), but its high cost makes it prohibitive for most healthcare systems of the region, particularly in the current pandemic context. AIM: To find small oral bioavailable, non-peptidic repurposing drug candidates for competitive inhibition of B2-bkR. M&M: By using 3 refined atomic models of B2-bkR obtained by homology and threading methods (SWISS-model/FG-MD and GPCR-I-TASSER) a high-throughput molecular docking (AutoDockVina) virtual screening was performed against all 2893 FDA-Approved, 3153 Investigational, 2414 in-trials and 440 harmless natural compounds (Drug Bank). Strong binders ($\Delta G_{binding} \leq$ -11kcal/mol) were later scored by integrating the ligand-receptor contact forces (AutoDock tools, LigPlus) with the available toxicity, pharmacokinetic (FK) and pharmacodynamic (FD) data. By means of a high performance computing system (FIUNER cluster: 10 nodes, with 24 cores each), 20 nanoseconds molecular dynamics simulations (MDS) were run for top-10 ranked ligand-receptor complexes (NAMD/VMD). MDS trajectories were analysed by uni- and multivariate statistics using RMSD, RMSF, H-bonding and 2D-PCA as reaction coordinates (R). RESULTS & DISCUSSION: Starting from a large library of compounds, virtual screening achieved 41 putative ligands which, after filtering by FD, FK and thermodynamic criteria lead us to 6 oral-bioavailable and cost-effective promissory repurposing drugs. In order to experimentally test these candidates, a live cell imaging Ca^{2+} mobilization inhibition bioassay is under implementation.

7. (166) **IDENTIFICATION OF NON-CODING RNAs WITH CLINICAL IMPLICATIONS IN MOLECULAR SUBTYPES OF COLORECTAL CANCER. AN IN-SILICO APPROACH.**

Saulnier D[1], Zwenger A[2], Croce MV[1], Abba MC[1], Lacunza E[1]
1. Centro de Investigaciones Inmunológicas Básicas y Aplicadas (CINIBA) Facultad de Ciencias Médicas, UNLP.
2. Servicio de Oncología. Hospital Provincial Neuquén "Dr. Castro Rendón".

Colorectal cancer (CRC) is a frequently lethal disease with heterogeneous outcomes and drug responses. Multiomics studies have revealed the molecular landscape of CRC, enabling the classification of patients according to 4 consensus molecular subtypes (CMS1-4). CMS1-immune comprises most tumors with MSI. CMS2-canonical and CMS3-metabolic both show epithelial characteristics. CMS4 comprises the more mesenchymal-like cancers, with poor patient prognosis. CMS1 and CMS4 also show poor response to standard therapies. Non-coding RNAs (ncRNAs) constitute more than 70% of the transcriptome. Two main classes have been largely associated with cancer; miRNAs and lncRNAs. Since some of these ncRNAs can be detected in human body fluid and have good specificity and accessibility, they have been suggested to be used as novel potential biomarkers for CRC diagnosis and prognosis as well as in the prediction of the response to therapy. In this study, we performed a classification of 688 CRC tumors obtained from TCGA into the 4 CMS employing the CMScaller bioinformatics tool. We characterized each subtype according to its main features. We then conducted an exhaustive gene expression profile analysis to identify the top upregulated lncRNAs and mature miRNAs in each subtype (CMSk) compared to the rest of the groups (CMSk-1; pvalue<0.01), defining a CRC-CMS signature of ncRNAs. Applying different filtering criteria, we look for those ncRNAs with potential clinical implications. We identified two lncRNAs, AFAP1-AS1 and MIR99AHG, overexpressed in CMS1 and CMS4 ($p<0.01$), respectively, and associated to poor prognosis ($p<0.05$); and three miRNAs: miR-99a-5p, let-7c-5p, and miR-125b-5p, all upregulated in CMS4 and associated to bad prognosis ($p<0.05$). Overall, we defined the most relevant CMS specific lncRNAs and miRNAs in CRC, and selected a group of candidates with clinical implications to further evaluate in-vitro in CRC cell lines and ex-vivo in blood and tumors patient samples.

8. (185) **WHOLE-EXOME SEQUENCING LANDSCAPE OF A RAPIDLY-PROGRESSING CUTANEOUS MELANOMA PATIENT**

Ana Mordoh *(Centro de Investigaciones Oncológicas-Fundación Cáncer (CIO-FUCA), CABA)*, Ibel Carri *(IIBIO-UNSAM, Buenos Aires)*, María Marcela Barrio *(CIO-FUCA, CABA)*, José Mordoh *(CIO-FUCA, CABA; Fundación Instituto Leloir, IIBBA-CONICET, CABA; Instituto Alexander Fleming, CABA), Mariana Aris (CIO-FUCA, CABA)*

Cutaneous Melanoma (CM) is a skin cancer with a high Tumor Mutational Burden (TMB) and a high-risk metastatic rate; the genetic landscape of a CM patient with rapid clinical evolution is described here.
Methods: Whole-exome sequencing analyses on gDNA from germline, precursor-nevi, primary CM and lymph-node metastasis (LN-mts) microdissected-tumor biopsies were performed. Data were analyzed following GATK guidelines (GRCh37/HG19 reference). Detection algorithms: HaplotypeCaller v3.3.0 for germline SNP; Mutect2 v3.8-0 for somatic SNPs/INDELs; FACETS v0.6.0 for CNV. Differential alterations in the allelic frequency (AF) of SNP/INDELs as well as in the cellular fraction (CF) of copy-number-variation (CNV) were discerned in genes with impact on cancer hallmarks in each step of tumor transformation and progression.
Results: Germline trunk mutations with known effect on susceptibility and poor-prognosis in CM were detected, early affecting genome stability (n=60). Regarding somatic gene alterations, CNV prevailed over SNP/INDELs, both showing an increasing number of affected genes in the path from nevi to metastasis. Accordingly, TMB tripled with progression (2.875X). The main somatic trunk driver was the oncogene BRAFV600E, with an increasing AF and CF in primary and LN-mts, sustaining proliferative signaling. At CNV level, deletion prevailed over gene amplification (8.42X). Metastasis-persisting genes exhibited increasing CF variation throughout progression (1.65X), supporting a functional selection of these altered-genes. Amplified genes (n=494) mainly affected cell proliferation, invasion & metastasis, angiogenesis and metabolism hallmarks. While deleted genes (n=4161) mainly affected regulation of cell proliferation, cell death and immunity hallmarks.
Conclusion: in this gradual although rapidly-progressing CM case, WES analysis allowed us to disguised differential alterations with impact on cancer hallmarks in each step of tumor transformation and progression.

9. (276) ***SERRATIA MARCESCENS* INVOLVED IN THE EARLY RESERVOIR OF GENETIC PLATFORMS RELATED TO DISSEMINATION OF ANTIMICROBIAL RESISTANCE MECHANISMS**

Gambino AS[1],Déraspe M[2], Álvarez VE[1], Quiroga MP[1], Corbeil J[2], Roy PH[2], Centrón D[2].
[1] Instituto de Microbiología y Parasitología Médica, Universidad de Buenos Aires-Consejo Nacional de Investigaciones Científicas y Tecnológicas (IMPaM, UBA-CONICET), Buenos Aires, Argentina.
[2] Département de Médecine Moléculaire. Centre de Recherche en Données Massives. Centre de Recherche en Infectiologie. Département de Biochimie, de Microbiologie et de Bio-informatique, Université Laval, Québec, Canada.

Serratia marcescens is a Gram-negative, facultative anaerobic bacillus of the *Enterobacteriaceae* family. It has a ubiquitous distribution and is a frequent cause of hospital-acquired infections.
S. marcescens SCH909 is a multidrug-resistant strain isolated in 1988 that was sequenced by Miseq and PacBio. The chromosome (5.315.598 bp) and the pSCH909 plasmid (83.750 bp) were assembled with SPAdes 3.9.0. The genome was annotated with Prodigal and RefSeq database for the genome annotation which was completed with specific analysis by using Blast. Insertion sequences were searched by ISfinder and phages with PHASTER. Antimicrobial resistance genes were identified using RESfinder, CARD and Blastn with a cut-off e-value of e^{-10}.
Different sources of genetic platforms related to the diffusion of antibiotic resistance mechanisms were found including the IncL-type pSCH909 plasmid, a new transposon Tn*6824*, 13 insertion sequences in the genome.Also four integrons were found, one of them the class 2 integron *dfrA1-sat2-ybeA-ybfA-ybfB-ybgA*.and three class 1 integrons, two of them were "*head to head*" in pSCH909 (*dfrA1-aa-*