

## Buenos Aires Breast Cancer Symposium 2024: Bridging Basic and Clinical Research in Breast Cancer

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### Abstract

The second edition of the Buenos Aires Breast Cancer Symposium (BA-BCS), the first to be held in person, took place from September 3rd to 6th, 2024, in Buenos Aires, Argentina. Nineteen scientists from Brazil, Canada, the United States, the United Kingdom, Denmark, Germany, and Spain, along with six Argentine experts, shared and discussed their recent findings with the audience. Young researchers had the opportunity to present their results through either mini-oral presentations or posters, facilitating one-on-one interactions and the potential for new colla-

borations. This article summarizes each talk presented at the symposium.

**Key words:** translational research, breast cancer, international symposium

### Resumen

**Simpósio de Câncer de Mama 2024: conectando a investigação básica y clínica en cáncer de mama**

Del 3 al 6 de septiembre de 2024 se llevó a cabo en Buenos Aires, Argentina, la segunda edición del Sim-

posio de Cáncer de Mama (BA-BCS), el primero que se realiza de manera presencial. Diecinueve científicos de Brasil, Canadá, Estados Unidos, Reino Unido, Dinamarca, Alemania y España, junto a seis expertos argentinos, compartieron y discutieron sus hallazgos recientes con la audiencia. Los jóvenes investigadores tuvieron la oportunidad de presentar sus resultados a través de mini-presentaciones orales o pósteres, lo que facilitó la interacción con los expertos generando un ámbito propicio para potenciar nuevas colaboraciones. Este artículo resume cada una de las charlas presentadas en el simposio.

**Palabras clave:** investigación traslacional, cáncer de mama, simposio internacional

This report aims to share the state-of-the-art topics presented at the second Buenos Aires Breast Cancer Symposium (BA-BCS 2024) which took place between the 3<sup>rd</sup> and 6<sup>th</sup> of September 2024 at IFIBYNE Institute in Buenos Aires, Argentina. This meeting was organized as a follow-up to the first one, which occurred in May 2021 online<sup>1</sup>. The first symposium was originally planned to expose young Latin American oncologists and investigators to the state of the art in breast cancer (BC) research and treatment, since the possibility of traveling abroad was, and continues to be, prohibitive for local scientists and fellows. To that goal, we invited some of the most prestigious BC researchers to participate in our first meeting in Argentina, but COVID-19 pandemic interfered with those plans. Therefore, this second edition was a great opportunity to fulfill our initial goal.

The BA-BCS 2024 began and concluded with plenary lectures and included eight mini-symposia, a special session dedicated to patient care, three poster sessions, and three roundtables conducted in Spanish. The mini-symposia highlighted specific themes in BC research. There, leading experts delivered 30-minute talks, and PhD students or post-docs, the first authors of selected abstracts chosen by the Scientific Committee, gave 15-minute oral presentations.

A total of 83 posters were displayed during the meeting, presented by graduate students, post-docs or early-career investigators from different regions of Argentina and other South American countries. These posters covered a broad spectrum of topics, i.e. analysis of the different BC

subtypes; cancer stem cells, tumor initiation and early metastasis; genomics and transcriptomics; early detection and treatment strategies; overcoming resistance and immunotherapy; experimental modeling BC and metabolism, signaling, and BC risk.

In addition, at the end of each day, roundtable discussions in Spanish addressed critical issues related to local strategies for early detection, physician training, and effective BC treatment across different regions of Argentina. They were focused on the following themes:

- “The Clinical Potential of Liquid Biopsies in Argentina”
- “The Experience of Conducting Research by Medical Professionals”
- “Navigating the Healthcare System for Patients in Different Regions of the Country”

These sessions fostered in-depth discussions, merging insights from the scientific and clinical communities. Participants shared their experiences, proposed actionable solutions, and offered recommendations aimed at benefiting patients, healthcare providers, researchers, and regulatory authorities.

A brief report of the meeting has recently been published<sup>2</sup>. Here, we provide a more extensive and complete overview of the symposium, in which the talks delivered as individual lectures, or as part of the mini-symposia are summarized. We sincerely thank all speakers and attendees who contributed to the extraordinary atmosphere created by this gathering in Buenos Aires.

On Tuesday afternoon, the Opening Session of the meeting was delivered by **Dr. Robert Clarke**, Director of the Manchester Breast Centre at the University of Manchester, UK. His presentation covered two distinct topics. First, he discussed the analysis of micro-environmental signals that drive BC metastatic colonization in the bone. Dr. Clarke demonstrated that proteomic analyses comparing metastatic and non-metastatic human breast tumors revealed a significant enrichment of osteomodulin in those that metastasize to bone. Furthermore, they demonstrated that osteomodulin induces migration of estrogen receptor-positive (ER+) and negative (ER-) BC cells and its overexpression promotes metastasis of MDA-MB 231 cells to mouse bone marrow

*in vivo*. Interestingly, they have also found that cyclin-dependent kinase 1 is relevant in the effect caused by osteomodulin since inhibition of this kinase prevents metastasis of BC cells overexpressing this factor in mouse bone marrow<sup>3</sup>. In the second part of his talk, Dr. Clarke referred to his studies about the possibility of targeting progesterone signaling to reduce the risk of developing ER- BC. He indicated that it has been shown that inhibiting the progesterone receptor (PR) pathway reduces hallmarks of BC risk and that this hormone is a paracrine regulator of luminal progenitor cells. It is up-regulated in the breast epithelium of premenopausal high-risk women and anti-estrogens reduce ER+, but not ER- BC. He proposed that progesterone increases the risk of BC more than estrogen alone. His data support the hypothesis that antiprogestins may target the luminal progenitor cell population, reducing the risk of ER- BC better than anti-estrogens. However, it is still unknown how this treatment may lower luminal progenitor numbers and what are the transcriptional changes in different breast cell types after antiprogestin exposure.

The following day, in the mini-symposium focused on **Luminal BC**, we heard from **Dr. Todd Miller** from Medical College of Wisconsin Cancer Center, USA. Dr. Miller's lab investigates mechanisms related to recurrence after endocrine therapy in ER+ disease. There are drug-tolerant persister cancer cells that can survive for years during endocrine therapy; targeting these cells is an attractive therapeutic approach to prevent cancer recurrence. Through a CRISPR/Cas9-based genome-wide knock-out screen they identified mitochondrial s function and oxidative phosphorylation as pathways responsible for survival during estrogen deprivation. Inhibition of mitochondrial complex I synergized with endocrine therapy and prevented tumor re-growth in preclinical models. GPX4 inhibition, which would drive lipid peroxidation, enhanced the anti-tumor effects of endocrine therapy. The Miller lab also shared findings on the use of 17 $\beta$ -estradiol as a therapeutic estrogen. They proposed that tumor adaptation to post-menopausal estrogen depletion sensitizes cancer cells to estrogen therapy and that anti-estrogens may accelerate this process. Their

POLLY clinical trial was designed to investigate the role of 17 $\beta$ -estradiol treatment in alternation with aromatase inhibitors; this treatment regimen provided clinical benefit in 8/19 (42%) patients with metastatic disease<sup>4</sup>. In preclinical models, they found that ER overexpression sensitized cancer cells to 17 $\beta$ -estradiol toxicity and hormone-induced DNA damage occurred in proliferating cells. The PARP inhibitor olaparib synergized with 17 $\beta$ -estradiol in cell lines and xenografts<sup>5</sup>, prompting clinical testing of this drug combination in the ongoing PHOEBE trial.

The second speaker was **Dr. Joseph Jerry** from the University of Massachusetts, Amherst, USA. First, he summarized his research showing that replication-associated DNA damage and repair play key roles in defining differences in susceptibility to mammary tumors among strains of mice. In addition, he showed that levels of estrogen-stimulated DNA double-strand breaks differed in these strains. Then, the talk focused on methods to immortalize normal human breast cells from women differing in BC risk. Cells were obtained from 17 donors that included individuals carrying germline mutations in BRCA1, BRCA2, and TP53 (high risk) as well as individuals without a familial history of BC (average risk). Co-expression of CDK4 and TERT yielded cell lines from 100% of donors compared to only 30% using TERT alone. The immortalized cells retained p53 function and became senescent when CDK4 was inhibited. The methods preserve populations of cells expressing both luminal and basal cell markers, with a subset retaining expression of ER-alpha and functional estrogen signaling. Therefore, Dr. Jerry's lab has shown that combined expression of CDK4+TERT provides a robust method to obtain immortalized breast cells from genetically diverse donors. These cells represent invaluable tools for investigating key mechanisms that regulate the transition from normal to cancer, pathogenic actions of hormonal exposures, and the genetic mechanisms underlying fidelity of DNA replication and repair.

The session concluded with the oral presentation of **Yamil D. Mahmoud** from IBYME-CONICET, Buenos Aires, Argentina. Mahmoud presented bioinformatics analyses based on public databases, revealing a strong correlation

between RUNX2 expression and tumor progression in luminal BC patients. These findings emphasize the importance of RUNX2 in tumor progression and suggest its potential as both a prognostic marker and a predictive indicator of therapy outcomes<sup>6</sup>.

The following session was dedicated to **New Treatments for Luminal and Her2+ BC**. The first speaker, **Dr. Jennifer Richer** from the University of Colorado, Aurora, USA, talked about androgen receptor (AR) action in ER+ BC. Dr. Richer's presentation showed the results of clinical trials they have performed that demonstrate the benefit of adding the anti-androgen enzalutamide in ER+ BC treatment. They have previously shown that fulvestrant combined with enzalutamide was beneficial for women with heavily pretreated metastatic ER+/HER2- BC. She also indicated that the combination given for 4 months before surgery showed reduced residual tumor at the time of surgery compared with fulvestrant alone. Interestingly, invasive lobular cancer (ILC) patients showed better response than invasive cancer of no special type (IC-NST). The decrease in AR and phospho-AR (pS650AR) from baseline to the end of the fourth week of treatment was even more pronounced in ILC than IC-NST. In addition, combination-treated tumors showed significant enrichment of immune activation gene sets. The stronger immune response in this arm was detected by the number of tertiary lymphoid structures per area surrounding the resected tumor, as well as the reduction of T regs, tumor-associated macrophages and myeloid-derived suppressor cells. Therefore, Dr. Richer's group concluded that AR inhibition combined with fulvestrant activates the immune system in ER+ BC. In addition, they have also observed that this effect is more pronounced in ILC compared to IC-NST subtype.

The next speaker was **Dr. Federico Waisberg** from Instituto Alexander Fleming, Buenos Aires, Argentina. He referred to the treatment decisions that need to be taken for patients with advanced luminal BC. He particularly referred to the scenario of disease progression in patients treated with CDK4/6 inhibitors. He indicated the various treatment options available, including PI3K inhibitors, AKT inhibitors, and new drug designs including the ER, PARP inhibitors, and

antibody-drug conjugates. He used an example to show the options for this kind of patients in Argentina, pointing out to the fact that more clinical trials should be offered to these women and that only a few patients have access to precision medicine in this country.

Then, the session was closed by an abstract selected for oral presentation delivered by **Virginia Judith Wolos**, a fellow from the Instituto de Oncología "Ángel H. Roffo" of the Universidad de Buenos Aires, Argentina. She showed that Rac1 inhibition enhances the efficacy of HER2-blockade with trastuzumab antibody in trastuzumab-sensitive and resistant HER2+ BC cells. Specifically, she observed that the combined treatment significantly decreases cell viability and reduces tumor spheroid volume compared with trastuzumab as a single agent. Rac1 inhibition appears to contribute to the G1 cell cycle arrest mediated by trastuzumab.

The following mini-symposium was dedicated to the **Detection and Treatment of Triple Negative BC (TNBC)**. The first speaker was **Dr. Roger Chammas** from the Center for Translational Research in Oncology, University of São Paulo, Brazil. He talked about microRNAs (miRNAs), which can be found as cell-free (cf-miRNAs) or secreted into extracellular vesicles (vesicular miRNAs, EV-miRNAs) in plasma of BC patients. They can be used as biomarkers to distinguish between different subtypes and their onset (early vs. late). Dr. Chammas reported that both cf-miRNA and EV-miRNA, proved to be informative in discerning miRNA expression differences among BC subtypes (based on immunohistochemistry features or age at diagnosis). However, EV-miRNA shows advantages such as high-yield purification with low protein contamination using plasma samples and the possibility to separate EV subpopulations regarding the cell of origin and their biogenesis. Interestingly, both the cell-free and vesicular version of hsa-miR-197-3p distinguished TNBC patients. Nevertheless, Dr. Chammas's group found a collection of EV-miRNA that proved to be consistently expressed in early-onset TNBC patients. Therefore, as future perspectives, they propose using this set of EV-miRNA to distinguish early-onset TNBC from other non-TNBC patients and monitoring patient status according to their treatment.



The following talk by **Dr. Paolo Ceppi** from University of Southern Denmark, Odense, Denmark addressed the possibility of targeting metabolic pathways for controlling epithelial to mesenchymal transition (EMT), which determines tumor aggressiveness by causing metastasis and chemoresistance although no drug is approved to specifically inhibit it. Therefore, Ceppi's group aims to identify metabolic pathways with a potential regulatory role on EMT. They have analyzed patients with non-small cell lung cancer and found that EMT can be inhibited by metabolites belonging to the class of short chain fatty acids propionate and butanoate, which are produced by commensal microbiota and are potentially safe for therapeutic use. Dr. Ceppi indicated that treatment of lung cancer cell lines with sodium propionate reduced EMT markers and *in vitro* migration, impaired their metastatic ability and sensitized towards cytotoxic chemotherapy in advanced-stage patients. Mechanistically, they have found that EMT attenuation would be due to chromatin remodeling via p300-mediated histone acetylation. Therefore, they propose that this class of metabolites could be tested for chemoprevention of metastasis and for breaking EMT and chemotherapy resistance of other tumor types as BC.

**Dr. Pablo Mandó** from CEMIC Hospital in Buenos Aires, Argentina, presented innovative approaches to controlling the immune system in managing TNBC. He highlighted recent clinical trials demonstrating the effectiveness of immune checkpoint inhibitors targeting PD-1/PD-L1, especially when combined with chemotherapy. Dr. Mandó also emphasized the potential of PARP inhibitors for patients with BRCA1/2 mutations, describing them as a promising therapeutic strategy. Additionally, antibody-drug conjugates are emerging as an advance in TNBC treatment, offering a targeted approach that maximizes the delivery of potent drugs to cancer cells. Dr. Mandó also emphasized the importance of next-generation sequencing to personalize therapies and identified key challenges, including the need for novel biomarkers, combination therapies, and new therapeutic targets. He concluded that integrating clinical trials and real-world data is vital to improving TNBC management and outcomes.

This session was closed by a short talk by **Roman Nicolas Vilarullo** from Universidad Nacional de Quilmes, Argentina, who presented his studies about enhancing paclitaxel treatment efficacy in TNBC patients by inhibiting dyskerin pseudouridine synthase 1 (DKC1). Using docking-based virtual screening Vilarullo and his group developed R1D2-10, a novel DKC1 inhibitor. Since DKC1 is highly expressed in paclitaxel-treated TNBC, they evaluated the effects of combining R1D2-10 and paclitaxel in TNBC cell lines. Their findings demonstrated a synergistic effect on cell proliferation inhibition, cell cycle arrest and increase in apoptosis. Thus, combining chemotherapy with R1D2-10 treatment may result in a successful therapeutic strategy for TNBC reducing paclitaxel doses and its associated side effects.

Session 4 was about **Cancer Stem Cells (CSC) and Tumor Initiation**. **Dr. Fariba Behbod** from the University of Kansas Medical Center, Kansas City, USA presented her research on the progression of ductal carcinoma in situ (DCIS) to invasive ductal carcinoma (IDC). Despite existing treatments, DCIS poses diagnostic and therapeutic challenges, with a persistent BC-specific mortality rate of approximately 3%. Dr. Behbod's team performed single-cell ATAC/RNA sequencing and spatial transcriptomics on DCIS and DCIS with associated IDC. They identified epithelial cell clusters with high stemness scores and elevated FOXA1 expressions, particularly in HER2+ DCIS samples. Open chromatin regions in these stem-like clusters were also enriched for FOXA1 binding motifs, suggesting a link between FOXA1 expression and cellular stemness properties in DCIS. Her results revealed that CEACAM6 was upregulated on luminal hormone receptor positive cells with the highest stemness scores. In addition, the data indicate a potential interaction between CEACAM6-positive epithelial stem-like cells and EGFR-positive stromal cells within the tumor microenvironment. CEACAM6 is a cell adhesion protein that is upregulated in several types of cancer, including BC and its expression is associated with poor survival, tumor progression, invasion and metastasis<sup>7</sup>. Then, Dr. Behbod proposed that targeting FOXA1 activity, potentially by lysine-specific demethylase 1 (LSD1) inhibitors<sup>8</sup>, could block cellular stemness

and prevent the invasive and potentially metastatic progression of DCIS, offering a targeted strategy for aggressive DCIS subtypes.

In the following talk, **Dr. Jochen Maurer** from the University Hospital RWTH Aachen of Germany discussed the role of CSCs in breast and ovarian cancers, emphasizing their contribution to tumor behavior, metastasis, and therapy resistance. His team focused on culturing and characterizing primary human CSCs from patient's tumors, developing organoid models that simulate *in vivo* conditions. These CSC-based models allow the study of molecular mechanisms underlying tumorigenic processes such as self-renewal, differentiation, invasion, and metastasis. Focusing on TNBC, his group isolated and characterized BC stem cells (BCSCs) that closely resemble original patient tumors *in vitro* and *in vivo*. Through limiting-dilution xenograft assays, they demonstrated that BCSCs could replicate the tumor of origin in animal models, validating their use as representative models of patient tumors<sup>9</sup>. Dr. Maurer highlighted how these models are used to identify novel therapeutic options and study resistance mechanisms, and understand immune escape processes. He discussed the interactions between CSC and the tumor microenvironment, particularly stromal cells, which influence CSC behavior and therapeutic resistance<sup>10</sup>. He acknowledged the challenges of using CSC as disease models but underscored the opportunities they provide for the development of targeted treatments against aggressive cancers like TNBC.

The last speaker of the session was **Dr. William Muller** from Rosalind and Morris Goodman Cancer Centre, McGill University, Montreal, Canada who presented his research on how oncogenes regulate the tumor immune microenvironment in TNBC. His team investigated the role of Chi3l1, a cytokine implicated in T-cell exclusion within tumors, in creating an immunosuppressive environment. Studying murine mammary tumors lacking the transcription factor Stat3, they observed decreased expression of Chi3l1, which is elevated in human TNBCs exhibiting T-cell stromal restriction. Their findings revealed that Chi3l1 promotes immunosuppression by recruiting neutrophils and inducing neutrophil extracellular trap formation, which

impedes CD8+ T-cell infiltration into the tumor. Ablation of Chi3l1 in mouse models led to increased T-cell infiltration, delayed tumor onset, and enhanced response to immune-checkpoint blockade therapies. Moreover, overexpression of Chi3l1 in Stat3-deficient models re-established an immunosuppressive microenvironment, confirming its role in tumor progression. Additionally, Dr. Muller identified ENPP1 as a regulator of the immune-cold microenvironment in aggressive HER2+ BC. Knockdown of Enpp1 resulted in decreased tumor growth and increased T-cell infiltration. These findings suggest that targeting Chi3l1 to reduce neutrophil-mediated T-cell exclusion, along with ENPP1 inhibition, could enhance anti-tumor immunity. Therefore, his results provide promising therapeutic strategies for TNBC and aggressive HER2+ BC.

Session 5 was focused on **BC Genomics and Transcriptomics**. **Dr. Martín Abba** from Universidad Nacional de La Plata, Buenos Aires, Argentina discussed the transformative impact of oncogenomics in BC research and clinical practice. He highlighted the evolution of functional genomics tools –from early microarrays to advanced next-generation sequencing (NGS) and spatial omics technologies– that enable comprehensive multi-omics analyses at both bulk and single-cell levels. Emphasizing recent advancements, Dr. Abba showcased how transcriptomic profiling can uncover gene expression patterns across different cell types within tumors, providing insights into cancer development, progression, and therapeutic response. He compared bulk RNA sequencing, single-cell RNA sequencing, and spatial transcriptomics, which retain the spatial context of gene expression in tissue samples. Spatial omics technologies facilitate mapping cellular heterogeneity and tumor microenvironments at unprecedented resolution. Dr. Abba underscored the importance of integrating multi-omics approaches –including chromatin accessibility, immune profiling, and protein expression– to unravel the complexities of BC. His presentation highlighted how these methods aid in identifying mutational processes, signaling pathways, and predictive biomarkers, paving the way for precision oncology. Ultimately, this integration holds promise for advancing early detection,

screening, and personalized treatment strategies for BC.

In the next talk, **Dr. Pedram Razavi** from Memorial Sloan Kettering Cancer Center, New York City, USA, focused on understanding the genomic mechanisms underlying resistance to CDK4/6 inhibitors in ER+ BC. Despite the success of CDK4/6 inhibitors in combination with endocrine therapy, resistance ultimately develops in many patients, leading to disease progression. Dr. Razavi's research employs tumor sequencing and liquid biopsies to identify genomic alterations contributing to therapeutic resistance. He discussed the emergence of mutations in cell cycle regulators, gene fusions, and copy number aberrations during treatment, which can affect drug targets and signaling pathways, diminishing the efficacy of CDK4/6 inhibitors. Understanding these alterations is critical for developing strategies to overcome resistance, such as combination therapies or next-generation inhibitors. Dr. Razavi emphasized the importance of continuous genomic monitoring to personalize treatment and improve outcomes for patients with advanced ER+ BC.

**Dr. Gonzalo Gómez Abuín** from Hospital Alemán, Buenos Aires, Argentina, highlighted the clinical applications and challenges of implementing next generation sequencing (NGS) in BC management. He discussed how NGS enables comprehensive genomic profiling, allowing the identification of actionable mutations and facilitating personalized therapy. Dr. Gómez Abuín emphasized the role of NGS in detecting genetic alterations associated with treatment resistance, prognosis, and potential targets for novel therapies, including PIK3CA mutations and BRCA1/2 alterations. He addressed the practical challenges of integrating NGS into routine clinical practice, such as interpreting complex genomic data, ensuring cost-effectiveness and overcoming logistical barriers. His presentation highlighted the importance of multidisciplinary collaboration to interpret NGS results effectively and apply them in clinical decision-making to improve patient outcomes.

The abstract selected from posters for this session was presented by Pedro J. Salaberry from Instituto de Fisiología, Biología Molecular y Neurociencias (IFIBYNE), Buenos Aires, Argen-

tina, who talked about the oncogenic potential of non-coding somatic mutations in TNBC. His team focused on the role of the BAF (mSWI/SNF) chromatin remodeling complex, which exhibited frequent mutations in regulatory regions across TNBC samples, potentially driving tumor progression. By analyzing gene expression data from isogenic TNBC cell lines with varying metastatic abilities, they identified the BAF complex as a major regulatory hub. Their study suggests that BAF dysregulation could serve as a therapeutic target, with potential for intervention through epigenetic modulation strategies to address malignancy at its regulatory core.

The last session of the second day, Session 6, was about **Immunotherapy and Fighting Treatment Resistance**. **Dr. Adrian Lee** from the University of Pittsburgh, USA discussed the evolution and adaptation of BC during progression, focusing on endocrine resistance in hormone-receptor positive (HR+) metastatic disease. His team analyzed alterations in the ER gene (ESR1), observing key mechanisms such as gene fusions, copy number variations and point mutations that drive resistance. By examining tissue and liquid biopsies during treatment and conducting rapid autopsies, their research revealed the acquisition of ESR1 mutations in hormone-refractory metastatic BC. Their findings indicated that ESR1 mutations not only confer endocrine resistance, but also enhance metastatic capabilities, with mutant ESR1 cells exhibiting increased cell-cell adhesion and forming larger circulating tumor cell clusters. These alterations have significant clinical implications, affecting disease progression and response to therapy. Dr. Lee introduced the BCRF AURORA program, which performs comprehensive molecular profiling of primary and metastatic BC. This program aims to elucidate the natural history of the disease, providing insights into resistance mechanisms and guiding the development of targeted treatments, such as the use of Elacestrant for ESR1-mutant cases. Dr. Lee research highlights novel dependencies and therapeutic vulnerabilities, which display implications for improving strategies against metastatic endocrine-resistant BC.

**Dr. Dejan Juric** from the Massachusetts General Hospital, Boston, USA, presented advancements in the use of PI3K inhibitors for BC treat-

ment, particularly addressing challenges linked to HR+, HER2- advanced BC with PIK3CA mutations. He highlighted the importance of targeting the PI3K pathway, a critical driver of tumor progression and resistance mechanisms in BC. Dr. Juric emphasized the development of isoform-selective inhibitors, such as Alpelisib and inavolisib<sup>11</sup>, which specifically inhibits the PI3K-alpha isoform, reducing toxicity compared to earlier, broader PI3K inhibitors. He detailed ongoing research on mutant-selective PI3K inhibitors like RLY-2608 and STX-478, which bind allosterically, effectively targeting mutant PI3K-alpha while minimizing side effects like hyperinsulinemia. This selective approach promises enhanced efficacy in tumors with PIK3CA mutations while preserving patient quality of life. Additionally, Dr. Juric discussed combining PI3K inhibitors with CDK4/6 inhibitors and ER blockers, which had shown improved outcomes in PIK3CA-mutant BC<sup>12</sup>. He concluded by underscoring the potential of these novel inhibitors to provide a precision medicine approach, targeting genetic mutations directly linked to cancer progression, with implications for refining BC treatment protocols and addressing endocrine resistance.

The third talk of the session was presented by **Dr. María Vivanco** from CIC bioGUNE, Basque Research and Technology Alliance, Derio, Spain, who focused on the role of cancer heterogeneity in hormone therapy resistance in BC, emphasizing the influence of estrogen and tamoxifen on CSC. Her research revealed that estrogen reduces the stem cell pool in breast tissue, whereas tamoxifen often fails to exert this effect on BC CSC due to the emergence of resistant populations. The development of tamoxifen-resistant cancer cells with high Sox2 and low PR expression correlates with poor patient prognosis. These resistant cells exhibit elevated self-renewal and tumorigenic potential, driven by Sox2-dependent signaling pathways. Dr. Vivanco highlighted her team's efforts to target these resistant CSCs pharmacologically. By using polyoxometalates (POMs) to inhibit Sox2, they observed reduced CSC content, impaired cell migration, and re-sensitization to tamoxifen. *In vivo* studies showed that Sox2 inhibition reduced tumor growth and recurrence. Her findings support Sox2 as a biomarker for resistance

and a potential therapeutic target. Dr. Vivanco's research points out to the need for targeted therapies against CSC-driven resistance in hormone-refractory BC, aiming to enhance treatment efficacy and decrease recurrence.

For this session, the abstract selected for oral exposition was presented by **Florencia Mauro** from IBYME-CONICET, Buenos Aires, Argentina. Her group investigated the role of the TNF/MUC4 axis in TNBC progression. Her team demonstrated that blocking TNF with etanercept or a dominant-negative protein reduced MUC4 expression in TNBC cell lines and impaired their invasive capabilities. In mouse models, the dominant-negative and anti-PD-1 immunotherapy prevented lung metastasis and increased survival rates. In TNBC patients treated with chemotherapy, high MUC4 expression inversely correlated with tumor-infiltrating lymphocytes and PD-L1 expression. Thus, TNF blockade and immunotherapy could be an effective treatment strategy for TNBC patients, and MUC4 could serve as a predictive biomarker to guide therapy.

The last day of the meeting Session 7 started, focusing on **Early Detection and Treatment**. The first speaker was **Dr. Vanesa Gottifredi** from Instituto Leloir, Buenos Aires, Argentina who talked about targeting the chromosomal instability induced by cancer therapy. Vanesa Gottifredi's lab is interested in unraveling whether it is possible to kill cancer cells while preventing chromosomal instability, a type of genomic instability that triggers rapid adaptation to treatments. She presented data showing that certain types of cancer cells, including some from breast and ovarian origin, can be killed *in vitro* by drugs that induce cell death but not chromosomal instability<sup>13,14</sup>. Furthermore, she showed that after treatment with genotoxic agents which are currently evaluated in clinical trials, chromosomal instability can be selectively prevented without losing the killing power of such agents<sup>15</sup>.

Next, **Dr. Catherine Park** from the University of California, San Francisco, USA, presented data regarding the evolution of breast radiotherapy options for today's early-stage patients. She focused in how the era of molecular subtyping in BC has revolutionized staging, prognosis and prediction in treatment. Concomitantly, this brought an increasing ability to predict risk and more selectively choose treatments for individ-



ual patients. In this context, breast radiotherapy has also expanded to offer more directed and highly effective approaches that require less time and rads, resulting in lower exposure to normal tissues. During her talk, the latest treatment approaches were highlighted in addition to areas of continued investigation and controversy.

**Dr. Adriana de Siervi** from Oncoliq, Buenos Aires-Argentina gave a short talk focused on circulating miRNAs as biomarkers for cancer detection and predictive prognosis using liquid biopsies. Oncoliq, is a company that emerged as a spin-off from CONICET. It is developing an early cancer detection test, based on PCR-detected miRNAs and AI. Dr. De Siervi showed data indicating that their approach is highly specific and sensitive for early cancer detection (stages 0 and 1). Studies are ongoing and she proposes that it might be a useful tool for the follow-up of patients with dense breast and/or Bi Rad 3.

The abstract selected for oral presentation was exposed by **Marianela Sciacca** from Instituto de Oncología Ángel H Roffo, Buenos Aires, Argentina. Her study focused on unraveling mechanisms related to DCIS to IDC transition. Her group had previously determined that MT1-MMP is essential for the initial invasion of BC. This work compares RNA-seq data from MT1-MMP high invasive tumor cells against a set of human high-grade DCIS<sup>16</sup> and SPARC emerged as a candidate gene in early BC progression. This study identifies SPARC as a driver of early tumor progression via a TGF- $\beta$ 1-dependent mechanism, suggesting TGFRI as a target for SPARC-positive patients.

The following session, number 8, was dedicated to the **Understanding and Modeling BC Subtypes**. The first talk was presented by **Dr. Adrian Lee** from the University of Pittsburgh, Pittsburgh, USA replacing **Dr. Steffi Oesterreich**, who was unable to attend the meeting. The talk focused on characterizing ILC, which is the most common special subtype of BC, accounting for 10%-15% of all histological subtypes. He emphasized the hallmark of ILC, which is the loss of E-cadherin that results in the growth of de-cohesive cells. Differences between ILC and IC-NST were highlighted, such as increased mutations in FOXA1 in ILC, in contrast to GATA1 in IC-NST,

as well as increased involvement of AKT/PTEN pathway in the first compared to the ER+ IC-NST. In addition, ILC tumors are frequently encountered among the luminal A tumors, they are frequently multifocal and bilateral, making it more difficult to excise clear margins. Thus, women with ILC have increased rates of mastectomies. Other characteristics that were remarked included the fact that they may have lower response rates to pre-operative chemotherapy, but they are exquisitely hormone-sensitive. Also, they have less metastases to liver and lung, but more metastasis to unique sites (ovary, peritoneum) and they recur lately. Finally, since stroma is important in these tumors they may have increased growth factor signaling.

The next talk was presented by **Dr. Alana Welm** from the University of Utah, Salt Lake City, Utah, USA. Dr. Welm highlighted the relevance of patient derived xenografts (PDX) models of cancer. Based on earlier data indicating that PDX engraftment correlates with poor outcomes in BC, she showed the data of a blinded non-interventional trial with 80 patients. She found that PDX engraftment is a strong, independent prognostic factor for early relapse and death in TNBC, HER2-low and HER2- BC, and is more accurate and specific than standard assessments for recurrence risk. This study confirmed that tumor engraftment assays may be used to identify patients who present poor outcomes, are at the highest risk of relapse and may benefit from additional treatment<sup>17</sup>.

In this session, two abstracts were selected for oral presentation. **Sabrina A. Vallone** from Gattelli's group at the Instituto de Fisiología, Biología Molecular y Neurociencias (IFIBYNE), Universidad de Buenos Aires (UBA), Argentina presented data regarding the interaction between adipocytes and tumor cells. Her group identified RET receptor tyrosine kinase as a breast tumor-adipose tissue interplay regulator based on the fact that adipose stroma surrounding RET+ tumors is enriched in immature adipocytes. They showed that PDGFB is a RET signaling downstream factor in breast tumor cells that promotes pre-adipocyte commitment in favor of tumor growth. Thus, the authors unveiled the relevance of the RET/PDGFB axis driving BC progression.

The second abstract was presented by Dr. **Tomas Dalotto** from IBYME-CONICET, Buenos Aires, Argentina. He presented data showing that progesterone promotes TNBC metastasis through RANKL-expressing Treg cells. Using the 4T1 murine model the authors demonstrated that progestin treatment increased lung metastatic burden, which was reverted upon Treg cell depletion. Progestins activated progesterone membrane receptors on Tregs, enhancing their immunosuppressive activity and RANKL production inducing BC cell invasiveness. Finally, progestin-induced, Treg-mediated increase of the metastatic potential of 4T1 tumors was prevented by a RANKL antibody. Therefore, these authors describe how Tregs could directly promote a metastatic and aggressive phenotype on TNBC.

A Special Session dedicated to patient care and the **Improvement of Quality of Life** was presented by Dr. **Syril Pettit** from the Health and Environmental Sciences Institute (HESI), Washington DC, USA. Dr. Syril Pettit focused her talk on the importance of understanding how adverse effects associated with therapy can impact patient outcomes and the importance of understanding these effects from the perspective of the patient. She presented data illustrating that the improved efficacy of cancer therapeutics increases lifespan but may also rise the overall duration of cancer therapy or the years-lived post-therapy. Cancer therapeutic safety and tolerability may need to be reconsidered taking into account chronic administration and long-term survivorship. Dr. Pettit indicated that chronic therapy-related adverse events are unintended and often under-acknowledged. To address the gap in actionable research on the impact of treatment adverse effects on patient life quality and the availability of interventions to reduce these effects (while still optimizing patient outcomes) HESI launched an international research grant program called *Thrive* in 2017. This initiative supports novel research that helps to predict, reduce, or prevent adverse effects of cancer treatment. The studies funded by these grants have helped to advance science and visibility for this under-studied arena. *Thrive*-funded studies have resulted in new knowledge shared through publications, spurred new clinical trials, led to two patents, and helped catalyze approaches that will benefit patients' outcomes. Additionally, Dr.

Pettit described collaborative research programs that seek to better understand the mechanism of undesired toxicities associated with novel cancer therapies (e.g., antibody-drug conjugates, targeted protein degraders, immunotherapies, etc.). These initiatives are led by HESI staff and involve academic, clinical, government, industry and non-profit scientists.

BA-BCS 2024 concluded with a plenary lecture by Dr. **Katherine Hoadley** of the UNC Lineberger Comprehensive Cancer Center in Chapel Hill, USA. Her talk, 'Quantitative Medicine for BC Patients,' provided insightful perspectives on the future of breast cancer care. In her talk, Dr. Hoadley focused on the molecular alterations acquired in BC cells from non-metastatic to metastatic stages. Her group profiled a set of 55 paired primary and metastatic samples with detailed clinical data to uncover key molecular alterations during BC progression. Multi-platform sequencing showed subtype switching between the analyzed stages in approximately 30% of Luminal and HER2+ subtypes, but it was rare in basal subtypes. Lower expressions of immune signatures were observed in metastasis, particularly those in the liver and brain. This was associated with the downregulation of HLA-A in metastases through multiple mechanisms including deletion, mutation, or DNA methylation. Additionally, they observed ER-mediated downregulation of cell adhesion genes in metastases<sup>18</sup>. She then explained the design and partial results of the ongoing "Harnessing the Analysis of RNA Expression and Molecular Subtype to Optimize Novel Therapy for Metastatic BC" trial or HARMONY. This trial will determine if providing physicians with molecular information about the tumor improves treatment decisions for patients with metastatic BC.

Finally, the closing remarks from the organizing committee celebrated the success of the Symposium. They highlighted the high quality and generosity of the invited speakers, the active participation of attendees, and the educational spirit that extended beyond the scheduled talks and discussions to include coffee breaks, lunch, and even the *agape* and *tango* show set among dinosaur skeletons hanging from the roof of the Natural Science Museum. We, the organizers, received excellent feedback from all participants of this first "face-to-face" BA-BCS, which

has opened the channels for new collaborative endeavors that are essential for developing relevant translational research from South America to the world.

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