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REPORT

The BA-BCS 2021: An Initial "Trial" for Integrating Basic Science and Medical Progress on Breast Cancer in a Latin-American Country

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Abstract

The first Buenos Aires Breast Cancer Symposium (BA-BCS) was held in a virtual format, between the 17th and the 21st of May 2021. The main goal of the meeting was to facilitate the interaction among physicians and basic researchers from South America and with peers from the rest of the world. To embrace their different interests and concerns, the congress included not only talks on basic, translational and clinical research, but also round tables to discuss diagnostic methods, research financing and biobank management, as well as virtual poster sessions in which the youngest fellows presented their recent findings. This report provides a brief overview of the talks delivered during the meeting, which addressed a wide variety of vital issues for breast cancer research mostly focused on the accurate diagnosis, prevention and treatment of this illness. The presentations included a wide spectrum of themes including hormone receptors and the relevance of their mutations, immunotherapy, cancer stem cells, mouse models, environmental hazards, genetics and epigenetics, local and systemic therapies, liquid biopsies, the metastatic cascade, therapy resistance and dormancy, among others.

Keywords Breast cancer · Clinical trials · Experimental models · Advances in diagnosis and treatments

Abbreviations

BCSC	Breast cancer stem cell
ER	Estrogen receptor
MIND	Mammary intraductal model
PDX	Patient-derived xenograft
PR	Progesterone receptor
SERM	Selective ER modulator
TNBC	Triple-negative breast cancer

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The first Buenos Aires Breast Cancer Symposium was planned to be held on May 2020 at the *Usina de Arte*, a beautiful, huge historical building in the traditional *La Boca* district in Buenos Aires, capital city of Argentina. The main goal of the meeting was to expose young Latin American oncologists and investigators to the state of the art in breast cancer research and treatment. In the last years, the possibility of travelling abroad to participate in meetings has been almost prohibitive for local scientists and fellows, even before the pandemic. So we thought, if our scientists cannot travel abroad, we have to take the international research community to Argentina, and that was the leitmotif of our project. But, between February and March 2020 the COVID-19 pandemic spread around the world. In April we were optimistic enough to postpone our meeting to October. Almost all speakers agreed on the new date, but of course we had to cancel once again. By November, we decided that we had to move to a virtual format. Once more, we wrote to all our original speakers and most of them accepted this new format.

During the virtual meeting we enjoyed 2 lectures, 27 talks from invited speakers in 13 thematic mini-symposia, 3 round tables and 81 posters, from which 11, all unpublished when submitted, were selected by the Scientific Committee integrated by Omar Coso and Albana Gattelli from

IFIBYNE-UBA-CONICET, Buenos Aires, Argentina; Maria Roque (IHEM-CONICET, University of Cuyo, Mendoza, Argentina), Gaston Soria (CIBICI-CONICET, UNC, Córdoba, Argentina), Alfredo Molinolo and J. Silvio Gutkind (both from Moores Cancer Center, UCSD, San Diego, USA) to be discussed in the mini-symposia. The other accepted abstracts were presented in 4 sessions, each of which had between 85 to 110 attendees from different institutions from Argentina and other countries including Chile, Portugal, USA and UK. They were one of the meeting highlights, in which PhD students and postdoctoral fellows presented their unpublished results to the general audience in 4 min talks, with the possibility to continue the discussions with smaller groups in "private" google-meet "rooms" assigned to each poster.

In the opening conference, "Advances in Estrogen Receptor (ER) Targeted Approaches to Breast Cancer", Dr. Geoffrey Greene (University of Chicago, Chicago, USA) took us on a journey of his pioneering discoveries, starting with the purification of the ER protein, the development of the first antibodies against ERα [1], the cloning of the ER gene [2], and the use of x-ray crystallography to understand how agonists and antagonists work [3]. He then moved on to his recent and novel discoveries of ESR1 mutations in metastatic breast cancers [4] and the use of new selective estrogen receptor modulators (SERMs) to target them. He also showed data from the mammary intraductal model (MIND), a variant of the patient-derived xenograft (PDX) animal model that has led to new clinical trials of lasofoxifene [5]. In addition, he is currently studying the potential protective benefit of a recently approved hormone replacement therapy that combines an estrogen with a SERM. In summary, Dr. Greene showed not only that he has played a fundamental role in pivotal discoveries, but that he is still carrying out cutting edge research in the field.

The first minisymposium was focused on tumor heterogeneity and breast cancer therapy. Our invited speakers were Dr. Mohamed Bentites-Alj (University of Basel, Basel, Switzerland), Dr. Jorge Reis Filho (Memorial Sloan Kettering Cancer Center, New York City, USA) and Dr. Catalina Lodillinsky, a young scientist working at Ángel H. Roffo Institute, Buenos Aires, Argentina, whose abstract was selected by the scientific committee. Dr. Bentires-Alj gave a very interesting presentation showing the effect of the oxidoreductase ERO1A, which enhances HIF1α-VEGFA-mediated angiogenesis and metastatic colonization [6]. He also showed that the increase in stress hormones during breast cancer progression resulted in the activation of the glucocorticoid receptor, increased lung metastases and reduced overall survival in preclinical models [7]. Next, Dr. Reis Filho clearly showed how triple negative breast cancer (TNBC) is actually a diverse group of diseases. He emphasized that a subset of rare low-grade TNBCs, such as secretory carcinomas, adenoid cystic carcinomas or adenomyoepitheliomas, harbor recurrent genetic alterations and lack TP53 mutations. The correlations between histological features in this subset of tumors, and their genomic alterations, open the door to tailor the treatment decisions for patients with TNBC according to the histological type [8, 9]. Finally, Dr. Lodillinsky referred to the kinase NME1 as a potent inhibitor of breast cancer progression and her research on the molecular mechanisms involved in its activity [10].

In the second session, Dr. Carol Lange, from University of Minnesota, Minneapolis, USA, highlighted the importance of progesterone receptor (PR) and glucocorticoid receptor phosphorylation in ligand-independent transcriptional regulation of target genes required for breast cancer stem cell expansion, which may open the way to new treatments [11, 12]. The next three presentations addressed the impact of modulating the tumor microenvironment in breast cancer progression. Dr. Jennifer Richer from University of Colorado, Aurora, USA, showed that targeting enzymes involved in tryptophan catabolism may reduce tumor progression by enhancing the anti-tumor immune response. She also emphasized the similarities between the mechanisms of immune suppression during pregnancy that ensure fetal tolerance and the immune suppressive mechanisms utilized by breast cancer. The hope is that further understanding of the hormonal regulation and reversible nature of the former can lead to ways to control the process during cancer [13]. Dr. Mariana Salatino (IBYME-CONICET, Buenos Aires, Argentina) focused on a new role for the antiprogestin mifepristone that reduced tumor growth and induced immunogenic cell death in a luminal mouse breast cancer model showing higher levels of isoform A than isoform B of PR [14]. Finally, the post-doctoral fellow Dr. Andrés Marcos Castellaro, from Dr. Germán Gil´s lab at National University of Córdoba, Córdoba, Argentina, provided further evidence, based on their previous studies [15], on how conditioned macrophages may induce tumor growth and endocrine resistance through ER hyperphosphorylation and activation of the NF-κB pathway.

Breast Cancer Stem Cells (BCSC) and the de-differentiated phenotype were the topics of the following session, which included 3 speakers from European laboratories plus a short talk by a local PhD student. First, Dr. Jochen Maurer from University Hospital RWTH, Aachen, Germany, described his method to isolate, characterize, and propagate BCSC from triple-negative tumors after chemotherapy, and how it can be used as a tool to screen and test novel therapeutic agents [16]. Then Dr. Paolo Ceppi (University of Southern Denmark, Odense, Denmark) explained the relevance of metabolic pathways associated to the epithelial-to-mesenchymal transition and the stem cell-like phenotype [17]. Dr. Robert Clarke, from University of Manchester, UK, referred to the crucial role of bone marrow-derived cytokines for stimulating breast

cancer cell colonization in the bone. The data obtained by his group revealed that IL1β induces intracellular NFκB and CREB signaling in breast cancer cells, which lead to Wnt ligand secretion, autocrine Wnt signaling activation and CSC colony formation. Therefore, inhibiting this pathway could be an important strategy to prevent bone metastasis formation [18]. Finally, Martín García Solá from Dr. Kordon´s Laboratory (IFIBYNE-UBA-CONICET, Buenos Aires, Argentina) showed that bio-informatic integration of multiple scRNA-seq data-sets provides new insights into mammary gland development [19].

The contribution of mouse models to new breakthrough discoveries for breast cancer prevention and treatment was the theme of Session 4. The first talk by Dr. Joseph Jerry from University of Massachusetts, Amherst, USA, was focused on the identification of mechanisms by which exposure to endogenous hormones and environmental chemicals may impact on inherited breast cancer risk. To this end, Dr. Jerry mapped a locus in mouse chromosome 7 that includes a genetic modifier, which may regulate repair of estrogen-induced DNA damage and would be responsible for the variable mammary tumor risk in different mouse strains [20]. Next, Dr. Fariba Behbod (University of Kansas, Kansas City, USA) focused her talk on the MIND model that allows the in vivo analysis of ductal carcinoma in situ (DCIS) progression. She showed the relevance of the BCL9-STAT3 pathway to DCIS invasive progression [21] and discussed efforts to "humanize" the MIND model to include the study of the immune system during DCIS evolution. Dr. William Muller, from Rosalind and Morris Goodman Cancer Center, Montreal, Canada, showed that upon ablation of the canonical mTORC1 activator (*Rheb1*) in multiple transgenic mouse models, mammary tumors display *mTOR* gene mutations that allow constitutive activation of the kinase, indicating that mTORC1 activation is required for mammary tumor initiation [22]. Finally, Dr. Diego Grinman, a postdoctoral fellow at Dr. Wysolmerski's laboratory (Yale School of Medicine, New Haven, USA) showed his recent results indicating that mammary tumor expression of parathyroid hormone-related protein (PTHrP) contributes to cancer progression and causes anorexia, possibly, through a calcium dependent mechanism.

The sixth session focused on the relevance of genetic and epigenetic alterations in breast cancer progression and their relationship with environmental hazards. Dr. Adrian Lee from University of Pittsburgh, USA, described the state-of-the-art techniques for functional genomics characterization of breast cancer disease, highlighting the heterogeneity and diversity between primary breast carcinomas, local recurrent tumors, and the metastatic ones at genomics and transcriptomics levels. Evolution of changes in progression to metastasis is now well described and highlights not only mechanisms of drug resistance but also new therapeutic targets [23–25]. Next talk, by Dr. Sophie Lelièvre (Institut de Cancérologie de l'Ouest, Pays de la Loire, France) was centered on environmental challenges and cancer risk build-up. She presented an interesting risk-on-chip model to analyze the additive effects of microenvironmental stressors, such as increased reactive oxygen species and matrix stiffness, on the epigenome of the breast epithelium. Her collaborative results showed how pathways linked to oxidative stress synergize with the pesticide Glyphosate that influences the activity of TET demethylating enzymes to trigger tumor onset. She insisted on the importance of combining cell culture-based risk models and clinical data to help identify epigenetically controlled noncoding RNAs that may serve the evaluation of breast cancer risk [26–28]. Dr. Guenter Vollmer, from Technische Universität Dresden, Germany, showed that natural botanical extracts obtained from hops or honeybush, for example, may represent promising tools for a preventive strategy for hormone-dependent breast cancer. This is due to the negative impact on the activity of ERα in the breast, following the parallel activation of ERβ [29] or the aryl hydrocarbon receptor pathways by these extracts [30, 31]. Selected from poster abstracts, Santiago Madera´s talk referred to the continuity of pioneering discoveries by Dr. P. V. Elizalde´s group (IBYME-CONICET, Buenos Aires, Argentina) on the role of nuclear ErbB-2 in ErbB-2-positive breast cancer [32–34]. Using transcriptomic and preclinical approaches he provided evidence indicating that nuclear ErbB-2 can be considered a therapeutic target in trastuzumab-resistant breast cancer.

The topics of mechano-signaling and the role of extracellular matrix stiffness by Dr. Valerie Weaver (University of California, San Francisco, USA.), the intricate functional mechanism acting at the tumor microenvironment of metastasis by Dr. John Condeelis (Albert Einstein Cancer Center, Bronx, USA) and the importance of disseminated cancer cell dormancy regulation by Dr. Julio Aguirre Ghiso (Icahn School of Medicine at Mount Sinai, New York City, USA) were addressed in Session 7. Throughout the presentations we learned about the key role that the interaction between BCSC and the microenvironment plays in the regulation of invasion and dormancy. Moreover, we saw how translational research approaches combining cutting edge technology, molecular biology and clinical research have allowed to move forward and advance to the point where several clinical trials are in progress, or about to start. This highlights the fact that, most likely, these lines of research might represent new points for therapeutic intervention to develop treatments for metastatic cancer in the near future [35–38]. In addition, we had two excellent talks also related to the metastatic process, selected from the posters, describing ongoing lines of research involving the use of the hemostatic compound desmopressin as a repurposed drug for TNBC management by the young investigator Dr. Juan Garona (National

University of Quilmes, Bernal, Argentina) and the role of hypoxia in resistance to HER2-targeted antibody therapies by the PhD student Virginia Wolos from Dr. Gabriel Fiszman´s lab at Ángel H. Roffo Institute of Oncology, University of Buenos Aires, Argentina.

In Session 9, Dr. Steffi Oesterreich, from University of Pittsburgh, USA, showed current efforts to target mutant ER in breast cancer. She highlighted the different ER mutations that are present mainly in metastatic sites, but are absent in the primary tumor, and that may be studied in liquid biopsies. The mutations, including ESR1 hotspot point mutations at Y537S and D538G [39–44] and ESR1 fusion genes [25, 45, 46] cause ligand independent activation of ER, resulting in endocrine resistant metastatic disease. In turn, Dr. Todd Miller (Dartmouth College, Lebanon, USA) focused on dormant ER + cells that start to grow after prolonged estrogen deprivation and show changes in metabolism towards fatty acid oxidation, opening the possibility of using this pathway to target dormant breast cancer cells [47].

Session 10 focused on the efforts to unveil mechanisms associated to novel targets that are important for the advancement of precision medicine. Dr. Violeta Serra from Vall d'Hebron Institut d'Oncologia (VHIO), Barcelona, Spain, reviewed the use of PARP inhibitors in BRCA1/2 mutated tumors and pointed out the relevance of using predictive biomarkers that correlate with PARPi response [48]. Dr. Santiago Bella (Sanatorio Allende and Clínica Universitaria Reina Fabiola, Córdoba, Argentina) focused on the current availability and use of CDK inhibitors for advanced breast cancer in South America. Dr. Dejan Juric (Massachusetts General Hospital, Boston, USA) conducted a journey on the use of PI3K inhibitors in clinical trials. He pointed out the importance of detecting PIK3CA mutations not only in solid tissue, but also in circulating DNA, and highlighted the relevance of combining endocrine therapies with CDK and PI3K inhibitors at early stages to avoid cross resistance [49]. Next, we had two short talks selected from posters. The PhD student Andrés Elia reported a new trial conducted by Dr. C. Lanari (IBYME-CONICET, Buenos Aires, Argentina) using the antiprogestin mifepristone in selected breast carcinomas with higher levels of isoform A than isoform B of PR. Finally, Dr. Fabiana Rossi, from Dr. M. Rossi Lab, at Austral University, Pilar, Argentina, showed promising pre-clinical data on the use of ubiquitin regulators as novel therapeutic targets [50].

On the last day of the meeting, in Session 12, Dr. Catherine Park (University of California, San Francisco, USA) talked about how local ablative treatment of metastasis could improve outcomes in patients with limited metastatic disease. Particularly, she made a special reference to clinical trials that test the efficacy of stereotactic ablative radiotherapy for the comprehensive treatment of oligometastatic cancers, as the SABR-COMET study [51]. In her talk, Dr. Victoria Costanzo from Alexander Fleming Institute, Buenos Aires, Argentina, indicated therapeutic approaches presently being applied in Argentina for HER2 + patients. She emphasized that many new treatments have emerged in the last 2 years for the advanced disease. She highlighted that the challenge is how to adapt them to the treatment of the early disease to cure more patients. Then, Dr. Florencia Perazzo (CEMIC, Buenos Aires, Argentina) proposed that there is enough data to establish a proof of principle for immunotherapy for both early and advanced TNBC. However, she pointed out that new combination regimens and more refined biomarkers should be established to improve the response and to better identify the patients that most likely would benefit from immunotherapy [52]. Matthew Winder from CRUK Beatson Institute, UK, was selected to present his abstract in this session. He showed evidence of a critical pro-survival role for MCL-1, a BCL-2 family protein, in TNBC [53]. The results indicate that targeting this protein has an impact on tumor progression and cancer stem-cell like behavior in breast cancer.

In the last minisymposium, Dr. Pedram Razavi, from Memorial Sloan Kettering Cancer Center, New York, USA, indicated the relevance of serial liquid biopsies for detection of minimal residual disease, monitoring treatment and following clonal evolution of breast tumors [54, 55]. He also referred to the strengths and weak points of analyzing circulating tumor DNA [56]. Next, Dr. Osvaldo Podhajcer from Leloir institute, Buenos Aires, Argentina, referred to the Breast Cancer Study initiative performed by the US-Latin America Cancer Research Network. More than 1000 tumors were characterized by gene-expression using cDNA microarrays and immunohistochemistry. Current studies, still unpublished, are presently carried on to analyze driven molecular pathways in the attempt to determine differences possibly associated to ancestry. Selected from the posters, the PhD student at IBYME-CONICET, Gabriela Pattacini referred to the establishment of patient derived xenograft (PDX) breast cancer bank in Buenos Aires, to test the efficacy of existing and novel drugs that would lead to faster development of new therapeutic approaches.

In the Closing conference, Dr. Charles Perou (UNC Lineberger Comprehensive Cancer Center, Chapel Hill, USA) started his lecture "Quantitative Medicine for Breast Cancer Patients" talking about the seminal paper that described for the first time the molecular portraits of breast cancer, highlighting the impact of that study on the understanding of breast cancer biology as well as the improvement of therapeutic decisions [57]. Then, he referred to the relevance of the "PAM50 ROR Score", which allows to accurately distinguish between luminal A and luminal B tumors. This analysis, together with tumor size, permits to quantitatively predict recurrence, and thus facilitate decision making on the appropriate length of endocrine therapy

treatments [58]. Towards the end of his talk, Dr. Perou showed data underscoring the relevance of analyzing the immune anti-tumor activity as well as T-cell and B-cell signatures [59] to predict treatment response of triple negative and HER2 + breast cancers [60]. This suggests that combined tumor and microenvironment molecular profiles may provide new predictor markers for prospective use in patients with different tumor subtypes.

Besides these extraordinary sessions our symposium also included three round tables integrated by South American investigators that discussed issues that concern the local community of breast cancer researchers and physicians. In the first one, focused on Genomics Platforms Dr. Ernesto Korbenfeld from Hospital Británico, Buenos Aires, presented the Oncotype DX platform, showing data indicating that some postmenopausal women with ER + / PR + /HER2- node positive breast cancer may safely avoid adjuvant chemotherapy, while premenopausal women on the same condition may still likely benefit from it. Next, Dr. Fernando Petracci (Alexander Fleming Institute, Buenos Aires) showed the clinical utility of MammaPrint and BluePrint for determining prognosis and guiding decision-making with respect to the administration of adjuvant chemotherapy in patients with newly diagnosed invasive breast cancer. The following round table on Biorepositories and Sample Management included five speakers: Dr. Andrea Bosaleh (Hospital Juan P. Garrahan, Buenos Aires, Argentina), Dr. Liliana Virginia Siede (UBA-UMSA, Buenos Aires, Argentina), Dr. Alfredo Molinolo (Moores Cancer Center, UCSD, San Diego, USA), Dr. Gonzalo Ardao (Army Central Hospital (HCFFAA), Montevideo, Uruguay) and Dr. Ana Palmero (Public Health Ministry, Argentina), all with expertise in tissue banking and pathology. The talks and discussions were focused on regulatory and general management issues as well as on technical aspects of tissue processing. The participants agreed that there are still several matters to work on in the interaction between biobank administrators and institutional review boards in order to make breast cancer samples more available to the local scientific community. Finally, the roles of government and non-government agencies, as well as industry, and their interaction in supporting and promoting breast cancer research were discussed in the third round table. Dr. Andrea Llera (Leloir Institute, Buenos Aires) mentioned aspects not commonly addressed when basic researchers apply to clinical grants such as costs associated to subject (patient) transportation, follow up, nursing and care, etc. Dr. Daniel Gomez (National University of Quilmes, Bernal, Argentina) referred to the possibility of participating from Argentina in international consortiums in the context of The European Union calls. Dr. Rosana Felice (GlaxoSmithKline, Argentina) talked about the experience of GSK in collaborating with Argentinian governmental agencies for funding translational projects. Finally, Judith Najdorf (University of Buenos Aires and CONICET, Argentina) provided her vision as a social scientist dedicated to the analysis of funding and evaluation of basic and translational scientific projects on health issues.

Conclusions and Perspectives

The first Buenos Aires Breast Cancer Symposium demonstrated that building a constructive network among breast cancer basic researchers and clinicians from all around the world with a relevant participation of South American researchers, who are commonly underrepresented in most international meetings, is possible. We, the organizers, received excellent feedbacks from all participants, including students who presented their results for the first time to an international audience, and experienced investigators working in the most important institutions around the world. Several new collaborative endeavors were initiated among participants even in the absence of face-to-face poster sessions, coffee breaks, corridors, meals and drinks, which usually are the most productive moments for establishing collaborations in a scientific meeting.

We hope that this meeting represents a new step forward in the advancement of breast cancer research in Argentina, setting a milestone from which the scientific and the medical communities may further contribute towards improvements in the diagnosis, treatment and management of breast cancer. Many challenges lie ahead, many related to the fact that we are a developing country. We trust that the community, the authorities, and industry may find a way to work together with scientists to achieve this common goal. This was our first trial, and we hope to repeat and improve this experience in the near future.

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Declarations

Ethics Approval and Consent to Participate Not applicable.

Consent for Publication The manuscript has been read and approved by all authors. All participants have read and approved the content of the manuscript. All abstracts of the meeting including welcome and closing words will be published in a supplement of Medicina, Buenos Aires.

Conflict of Interest Dr. Edith C. Kordon is an Editorial board member of the Journal of Mammary Gland Biology and Neoplasia.

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