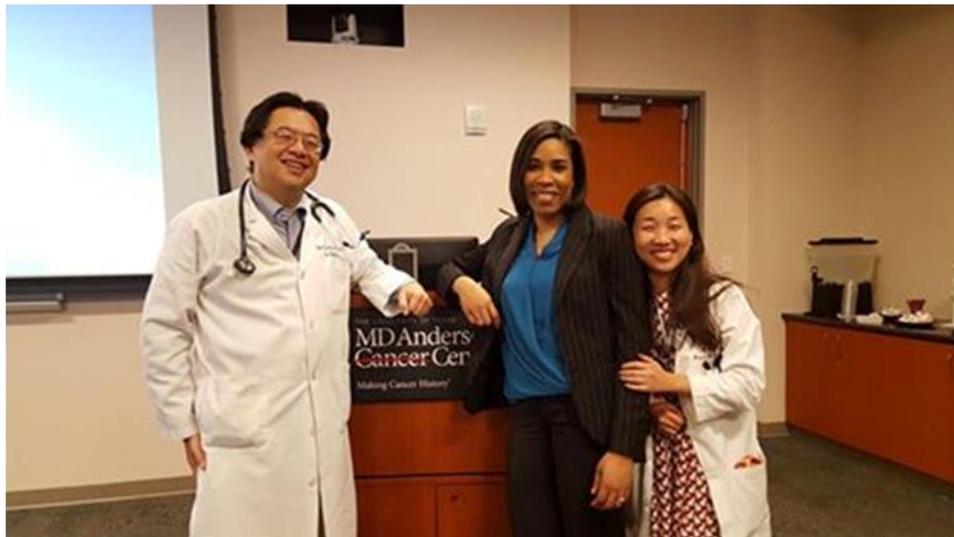


IBC Guest Speaker Series Opens Doors to New Opportunities for Collaboration



Morgan Welch Inflammatory Breast Cancer Research Program and Clinic is increasing efforts to inviting more outside guest speakers who specialize in different areas of IBC research. One of our goals is to enhance potential collaborations and new ideas that will accelerate our research, fulfilling our vision to end the suffering of patients with IBC.

Our first speaker was **Steven Van Leare**. Dr. Van Leare is a biomedical scientist who obtained his is biomedical scientist who obtained his PhD in 2009 from the University of Antwerp. Currently he is a group leader of the Translational Cancer Research Unit at the Augustinus Hospital in Antwerp. His research focuses on the molecular characterization of Inflammatory Breast Cancer (IBC) with a particular interest in cell motility, endocrine resistance and miRNA-dependent regulation of gene expression. Steven is leading an international effort, in collaboration with the MD Anderson Cancer Center (Houston, USA) and the Institut Paoli-Calmettes (Marseille,

France), to redefine the gene expression profile of tumor samples from patients with IBC. He gave an excellent talk about how cancer microenvironment and immune system impacts IBC behavior and this could be a potential targetable area to improve the outcome of patients with IBC.

Dr. **Gayathri R. Devi** came to speak to the IBC Program in early March, on Go Texan Day! Along with the day's festivities, our group was treated to an excellent presentation by Dr Devi, entitled, "Programmed Cell Death: Pathway to Translational Opportunities." Dr. Devi is an Associate Professor in the Department of Surgery and Pathology. She is also an adjunct Associate Professor in the department of Pharmaceutical Sciences at the North Carolina Central University. Dr. Devi has developed a national and internationally recognized research program and consortium toward understanding IBC. We look forward to developing exciting collaborative projects with Dr. Devi and her team.

Most recently, we had **Joan-Lewis Wambi**, Assistant Professor at the University of Kansas Medical Center, presented a wonderful lecture on her research on the role of IFITM1 in inflammatory breast cancer. Her lab group at KUMC is specifically interested in identifying novel pathways of endocrine-resistance in breast cancer and using that knowledge to help develop alternative treatment options for patients with endocrine resistant and metastatic disease.

We extend our deepest appreciation to Drs. Van Leare, Devi, and Lewis-Wambi for visiting our program and discussing their research. We hope to have continued success with the IBC Guest Speaker Series throughout 2016.

March EPIC Rollout – Update

As we are all well aware, the institution transitioned to a new electronic health record system, EPIC/OneConnect on March 4th. As we approach a month working within this new system, we wanted to briefly reflect. Physicians and staff have worked diligently to meet the challenge of adapting to the new EHR, and we'd like to thank everyone for their efforts. While the One Connect Onsite Command Center closed as of March 25th, 2016, help is still available by calling the CONNX line at 713-792-6669. And, as usual, for critical issues reported outside of normal business hours; 4INFO will be your best resource.

IBC to Form Fundraising Team for MD Anderson's 1st Annual Boot Walk to End Cancer

MD Anderson's Inaugural Fundraising Event, the Boot Walk to #endcancer, The MD Anderson Morgan Welch IBC Research Program and Clinic is currently working to form a team for you to sign up and join the movement to end Inflammatory Breast Cancer!

But, first, we would like to reach out the group collectively for ideas on a team name for IBC. You can place your vote for two choices: "Stomp IBC", or "IBC Wranglers" at the following link. Please place your vote by **Sunday, April 3rd, 2016!**

<https://www.surveymonkey.com/r/8K8DT7P>

IBC thanks Terry Arnold/IBC Network Foundation, Mr. And Mrs. Charles H. Cotros, and Zeta Tau Alpha Houston Alumnae Association for their generous donations



Issue 8: March 2016

A big thank you to The IBC Network Foundation/Terry Arnold, and all the donors including Bradford Range, for raising \$150,000 for a new statin trial for IBC.

Sincerest thanks to Mr. and Mrs. Charles H. Cotros for their generous gift of \$132,500 directed to support Inflammatory Breast Cancer (IBC) research under the direction of Dr. Wendy Woodward.

We'd also like to thank Zeta Tau Alpha Houston Alumnae Association for their donation of \$24,000 to the Morgan Welch IBC Research Program and Clinic.

Recent Awards and Grants:

Congratulations to our FY16 Research Match Winners!

1. **Xiaoping Wang, Jun Zhao, Rajagopal Appavu** – Determination of the efficacy of TIG1-targeted therapy using nanoparticle-delivered siRNA in inflammatory breast cancer
2. **Gita Jayachandran, Evan Cohen, Hui Gao** – Novel proximity extension assay technology for serum/plasma protein biomarker characterization of inflammatory breast cancer

An award of \$40,000 for each of the two winning projects. Thank you and appreciate your hard work and team spirit!

Pitner, Mary Kathryn, PhD, Postdoctoral Fellow in Breast Medical Oncology-Research, has been awarded the AACR-Triple Negative Breast Cancer Foundation Scholar-In-Training Award by the American Association for Cancer Research (AACR) for her abstract, "Silencing of ERKs reverses EMT and suppressed the SCS phenotype, inhibiting lung metastasis in triple-negative breast cancer." The Scholar-In Training Awards are highly competitive and are presented to those with best scored abstracts from a large applicant pool. The award recognizes outstanding young investigators for their meritorious work in triple negative breast cancer research.

IBC Program Brochure Award: Our IBC Program's "Understanding Inflammatory Breast Cancer" brochure won the bronze award from the National Health Information Awards. This Awards Program, the most comprehensive of its kind, annually recognizes the Nation's best consumer health information.

Recent Publications:

MMP2 and MMP9 serum levels are associated with favorable outcome in patients with inflammatory breast cancer treated with bevacizumab-based neoadjuvant chemotherapy in the BEVERLY-2 study.

Tabouret E, Bertucci F, Pierga JY, Petit T, Levy C, Ferrero JM, Campone M, Gligorov J, Lerebours F, Roché H, Bachelot T, van Laere S, Ueno NT, Toiron Y, Finetti P, Birnbaum D, Borg JP, Viens P, Chinot O, Gonçalves A.

Oncotarget. 2016 Feb 23. doi: 10.18632/oncotarget.7612. [Epub ahead of print]

Addition of bevacizumab to trastuzumab-based neoadjuvant chemotherapy in HER2-positive inflammatory breast cancer (IBC) was associated with favorable outcome in the BEVERLY-2 phase II trial. Circulating levels of matrix metalloproteinases (MMP) 2 and 9 were correlated to high response rate and prolonged survival in high-grade glioma treated with bevacizumab. The prognostic impact of MMP2 and MMP9 serum levels in BEVERLY-2 patients was examined. High bMMP2 and low bMMP9 serum levels were associated with better survival in HER2-positive IBC patients treated with bevacizumab- and trastuzumab-based neoadjuvant chemotherapy. Their predictive value of bevacizumab benefit needs to be further evaluated in a randomized trial.



MicroRNA expression profiling identifies decreased expression of miR-205 in inflammatory breast cancer.

Huo L, Wang Y, Gong Y, Krishnamurthy S, Wang J, Diao L, Liu CG, Liu X, Lin F, Symmans WF, Wei W, Zhang X, Sun L, Alvarez RH, Ueno NT, Fouad TM, Harano K, Debeb BG, Wu Y, Reuben J, Cristofanilli M, Zuo Z.

Mod Pathol. 2016 Feb 26. doi: 10.1038/modpathol.2016.38.

Identifying new biomarkers to be used as therapeutic targets is in urgent need for IBC. Messenger RNA expression profiling studies have indicated that inflammatory breast cancer is a transcriptionally heterogeneous disease, and specific molecular targets for inflammatory breast cancer have not been well established. In this study, microRNA expression profiling in inflammatory breast cancer in comparison with locally advanced non-inflammatory breast cancer was performed. Although many microRNAs were differentially expressed between normal breast tissue and tumor tissue, most of them did not show differential expression between inflammatory and non-inflammatory tumor samples. However, by microarray analysis, quantitative reverse transcription PCR, and in situ hybridization, we showed that microRNA-205 expression was decreased not only in tumor compared with normal breast tissue, but also in inflammatory breast cancer compared with non-inflammatory breast cancer. Lower expression of microRNA-205 correlated with worse distant metastasis-free survival and overall survival in this cohort. A small-scale immunohistochemistry analysis showed coexistence of decreased microRNA-205 expression and decreased E-cadherin expression in some ductal tumors. This study indicates that microRNA-205 may serve as a therapeutic target in advanced breast cancer including inflammatory breast cancer.

Epidemiological risk factors associated with inflammatory breast cancer subtypes.

Atkinson RL, El-Zein R, Valero V, Lucci A, Bevers TB, Fouad T, Liao W, Ueno NT, Woodward WA, Brewster AM.

Cancer Causes Control. 2016 Mar;27(3):359-66. doi: 10.1007/s10552-015-0712-3. Epub 2016 Jan 21.

In this single-institution case-control study, risk factors associated with inflammatory breast cancer (IBC) subtypes based on staining of estrogen receptor (ER), progesterone receptor (PR) and expression of human epidermal growth factor 2 (HER2neu) to determine distinct etiologic pathways, were identified.

In multivariable analysis, compared with women age ≥ 26 at first pregnancy, women age < 26 had a higher risk of triple-negative IBC. Women with a history of breast-feeding had a lower risk of triple-negative and luminal IBC. A history of smoking was associated with an increased risk of luminal IBC. Compared with normal-weight women, those who were overweight or obese (body mass index ≥ 25 kg/m) had a higher risk of all three tumor subtypes. Overweight or obese status is important modifiable risk factor for IBC of any subtype.

Modifiable risk factors, age at first pregnancy (≥ 26), breast-feeding, and smoking may be associated with specific IBC subtypes. These results highlight the importance of evaluating epidemiologic risk factors for IBC for the identification of subtype-specific prevention strategies.

Inflammatory Breast Cancer: A Distinct Clinicopathological Entity Transcending Histological Distinction.

Raghav K, French JT, Ueno NT, Lei X, Krishnamurthy S, Reuben JM, Valero V, Ibrahim NK.

PLoS One. 2016 Jan 11;11(1):e0145534. doi: 10.1371/journal.pone.0145534. eCollection 2016.

Although well recognized in breast oncology literature, histologic subtypes have not been previously described in inflammatory breast cancer (IBC). The purpose of this study was to describe lobular subtype in IBC and assess the impact of histology on patient outcomes. A total of 30, 37, and 592 patients were seen to have invasive lobular, mixed, or ductal histology, respectively. Grade 3 tumors were more common in the ductal group (78%) than in the lobular (60%) or mixed (61%) group. The 3-year overall survival rates were 68%, 64%, and 62% in the lobular, mixed, and ductal groups, respectively. After adjustment, histology did not have a significant effect on death in the lobular group or mixed group compared with the ductal group. In this cohort of IBC patients, lobular histology was seen in 4.5% cases. Histology does not appear to have a significant effect on survival outcomes in IBC patients, unlike in patients with non-inflammatory breast cancer, indicating the distinct biological behavior of the IBC phenotype.



High HER2/Centromeric Probe for Chromosome 17 Fluorescence In Situ Hybridization Ratio Predicts Pathologic Complete Response and Survival Outcome in Patients Receiving Neoadjuvant Systemic Therapy With Trastuzumab for HER2-Overexpressing Locally Advanced Breast Cancer.

Kogawa T, Fouad TM, Liu DD, Wu J, Shen Y, Masuda H, Fujii T, Chavez-MacGregor M, Alvarez RH, Hortobágyi GN, Valero V, Ueno NT.

Oncologist. 2016 Jan;21(1):21-7. doi: 10.1634/theoncologist.2015-0101. Epub 2015 Dec 9.

This study was performed to determine whether the human epidermal growth factor receptor-related 2 (HER2)/centromericprobe for chromosome 17 fluorescence in situ hybridization (FISH) ratio is a predictor of a pathologic complete response (pCR), recurrence-free survival (RFS), and/or overall survival (OS) in patients receiving neoadjuvant systemic treatment (NST) with trastuzumab (NST-T) for HER2+ locally advanced breast cancer (LABC). The pCR group's median HER2 FISH ratio was significantly higher than that of the non-pCR group (6.4 vs. 5.2; $p = .003$) suggesting that a high HER2 FISH ratio is a potential indicator for a high pathologic complete response rate and a better prognosis when patients are treated with NST-T.

Comprehensive Two- and Three-Dimensional RNAi Screening Identifies PI3K Inhibition as a Complement to MEK Inhibitor AS703026 for Combination Treatment of Triple-Negative Breast Cancer.

Lee J, Galloway R, Grandjean G, Jacob J, Humphries J, Bartholomeusz C, Goodstal S, Lim B, Bartholomeusz G, Ueno NT, Rao A.

J Cancer. 2015 Oct 28;6(12):1306-19. doi: 10.7150/jca.13266. eCollection 2015.

Triple-negative breast cancer (TNBC) is a major cause of death among breast cancer patients that results from intrinsic and acquired resistance to systemic chemotherapies. To identify novel targets for effective treatment of TNBC through combination strategies with MEK inhibitor (AS703026), a novel method of combining high-throughput two- and three-dimensional (2D and 3D) RNAi screening was used. TNBC cells were transfected with a kinome siRNA library comprising siRNA targeting 790 kinases under both 2D and 3D culture conditions with or without AS703026. Molecule activity predictor analysis revealed the PI3K pathway as the major target pathway in the RNAi combination studies in TNBC. It was found that PI3K inhibitor SAR245409 (also called XL765) combined with AS703026 synergistically inhibited proliferation compared with either drug alone. Reduced in vitro colony formation and migration and invasion ability were also observed with the combination treatment. The data suggests that SAR245409 combined with AS703026 may be effective in patients with TNBC. It can be concluded that novel powerful high-throughput RNAi assays were able to identify anti-cancer drugs as single or combinational agents. Integrated and multi-system RNAi screening methods can complement difference between in vitro and in vivo culture conditions, and enriches targets that are close to the in vivo condition.

Simvastatin prevents triple-negative breast cancer metastasis in pre-clinical models through regulation of FOXO3a.

Wolfe AR, Debeb BG, Lacerda L, Larson R, Bambhroliya A, Huang X, Bertucci F, Finetti P, Birnbaum D, Van Laere S, Diagaradjan P, Ruffell B, Trenton NJ, Chu K, Hittelman W, Diehl M, Levental I, Ueno NT, Woodward WA.

Breast Cancer Res Treat. 2015 Dec;154(3):495-508. doi: 10.1007/s10549-015-3645-3. Epub 2015 Nov 21.

Statins have been correlated with improved metastasis-free survival in aggressive breast cancer. The purpose of this study was to examine the effect of statins on metastatic colonization by triple-negative breast cancer (TNBC) cells. TNBC cell lines were treated with simvastatin and then studied for cell cycle progression and proliferation in vitro, and metastasis formation in vivo, following injection of statin-treated cells. Reverse-phase protein assay (RPPA) analysis was performed on statin-treated and control breast cancer cells. The prognostic value of FOXO3a mRNA expression was examined in eight public breast cancer gene expression datasets including 1479 patients. Simvastatin increased G1/S-phase arrest of the cell cycle and inhibited both proliferation and migration of TNBC cells in vitro. In vitro pre-treatment and in vivo treatment with simvastatin reduced metastases. Simvastatin inhibited in vitro endpoints associated with metastasis through a FOXO3a mechanism and



reduced metastasis formation in vivo. FOXO3a expression was prognostic for metastasis formation in patient data. This study indicates that further investigation of simvastatin as a cancer therapy is warranted.

Epidemiological risk factors associated with inflammatory breast cancer subtypes

Atkinson RL, El-Zein R, Valero V, Lucci A, Bevers TB, Fouad T, Liao W, Ueno NT, Woodward WA, Brewster AM.

In this single-institution case-control study, we identified risk factors associated with inflammatory breast cancer (IBC) subtypes based on staining of estrogen receptor (ER), progesterone receptor (PR) and expression of human epidermal growth factor 2 (HER2neu) to determine distinct etiologic pathways.

Overweight or obese status is important modifiable risk factor for IBC of any subtype. Modifiable risk factors, age at first pregnancy (≥ 26), breast-feeding, and smoking may be associated with specific IBC subtypes. These results highlight the importance of evaluating epidemiologic risk factors for IBC for the identification of subtype-specific prevention strategies.

Oral Presentation:

Xiaoping (Maggie) Wang, Ph.D., Research Scientist

Topic: "Investigating the efficacy of Panitumumab in IBC cell lines"

The epidermal growth factor receptor (EGFR) pathway is an important therapeutic target in inflammatory breast cancer (IBC). Our preliminary clinical trial of panitumumab (PmAb), a humanized anti-EGFR therapy, combined with chemotherapy showed the highest ever observed pathological complete tumor response (pCR) rate to pre-surgical treatment in patients with HER2-negative IBC. However, the mechanism behind this therapeutic effect is not well defined. To address this knowledge gap, we examined the mechanism of how PmAb treatment inhibits the aggressiveness of IBC cells. Our preclinical study showed that PmAb treatment inactivates EGFR signaling in IBC cells as indicated by the inhibition of EGFR phosphorylation upon EGF stimulation, which in turn reduces the expression of COX-2, a key molecule in the inflammatory response and whose expression positively correlates with worse outcome of IBC patients, as well as the population of cancer stem-like cells (CSC), a subpopulation of cancer cells which has competence for self-renewal and capacity to re-establish tumor heterogeneity. These results suggest that EGFR pathway may regulate CSC in IBC through a mediator of inflammation (COX-2). We further identified Nodal, a member of TGF β family involving in the regulation of stem cell pluripotency, as a key component in EGFR/COX-2-mediated CSC regulation in IBC. We will identify molecules in the EGFR/COX-2/TGF β signaling axis that could enhance the efficacy of EGFR targeted therapy in IBC.

News/Events:

IBC Multi-Team Clinic (IBC MTC): Since August 2015 when we first launched our IBC MTC led by our multidisciplinary team of IBC Specialists in the field of breast medical oncology, surgical oncology and experimental radiation, we have seen an increase in patient enrollment by 54%. The quality of care does not differ between the IBC MTC and our regular IBC Clinic, the only difference between clinics will be the timing of appointments with our IBC Specialists. Please provide us your feedback.

IBC 10th Anniversary: 2016 marks the 10th anniversary of the establishment of MD Anderson's Morgan Welch Inflammatory Breast Cancer Research Program and Clinic, with 2017 being the 10th anniversary for being recognized by the State of Texas, through "State of Texas Rare and Aggressive Cancer Research" appropriations. Starting 2016 fall, we plan to kick-off our celebration with an Ambassador Luncheon in September, followed by a Scientific Conference in February 2017. We thank all our patients, advocates, families, friends and communities for your generous and ardent support throughout the past decade!



Current Clinical Trials Open for New Patient Enrollment

- 2006-1072 IBC Registry**
- 2013-0007 Phase II study of Denosumab to define the role of bone related biomarkers in patients with breast cancer and bone metastasis**
- 2013-0139 Phase IB trial of two folate binding protein peptide vaccine (E39 and J65) in breast and ovarian cancer patients**
- 2013-0436 Combination immunotherapy with Herceptin and HER2 vaccine E75 in low and intermediate HER2 expressing breast cancer patients to prevent recurrence**
- 2014-0464 A phase II study of BIBF-1120 (Nintedanib) for patients with HER2 normal metastatic inflammatory breast cancer**
- 2014-0533 A phase II study of anti-PD1 (MK-3475) therapy in patients with metastatic inflammatory breast cancer who have received prior chemotherapy with clinical response**
- 2014-0034 A phase II study using Talimogene Laherparepvec (T-VEC) as a single agent for IBC or non-IBC patients with inoperable local recurrence**

Current Lab Studies

- PA15-0499 Tissue biomarker study of T-DM1 and/or Pertuzumab resistant or refractory breast cancer NI0000-A-U002.**
- PA12-0097 Prognostic utility of CTCs assessed by AdnaGen technology and clinical outcome of patients with stage III breast cancer**
- PA12-0728 Expansion and characterization of tumor-infiltrating and tumor-associated T cells from primary and metastatic triple-negative breast cancer and inflammatory breast cancer**
- PA12-0860 Assessing feasibility of sentinel lymph node increase dissection in IBC**
- PA14-0772 Derivation of Pt derived xenograft tumor models from isolated CTC from breast cancer pts(IBC/TNBC)**
- PA14-0778 Gene profiles in androgen receptor-positive CTC in patients with metastatic breast cancer**

If you are interested in learning more about our clinical trials, or lab studies, please email the Morgan Welch Inflammatory Breast Cancer Research Program and Clinic directly at ibcp@mdanderson.org. We are happy to provide general information and eligibility guidelines for our clinical trials and lab studies.

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