BIOGRAPHICAL SKETCH

NAME **SOTIRIOU, Christos, MD, PhD**	**POSITION TITLE** • Research director at the FNRS, Université Libre de Bruxelles (ULB), Brussels, Belgium • Full Professor at the Medical Oncology Unit, Jules Bordet Institute, Université Libre de Bruxelles (ULB), Brussels, Belgium • Director of the J.-C. Heuson Breast Cancer Translational Research Laboratory, Université Libre de Bruxelles (ULB), Brussels, Belgium

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	YEAR(S)	FIELD OF STUDY
Université Libre de Bruxelles (ULB), Belgium	MD	1986 - 1993	Medicine
Université Libre de Bruxelles (ULB), Belgium	Postgraduate diploma in Internal Medicine/ Oncology	1993 - 1999	Internal Medicine and Medical Oncology
National Institutes of Health (NIH), Bethesda, USA	Research Fellow	1999 - 2001	Breast Cancer Genomics
Université Libre de Bruxelles (ULB), Belgium	PhD thesis	1999 - 2004	Breast Cancer Genomics

Personal statement

The BCTL headed by Prof Sotiriou is an academic laboratory from the faculty of Medicine of the Université Libre de Bruxelles (ULB) located at the Jules Bordet Institute (IJB). The main research focus of my laboratory consists in improving the molecular understanding of breast cancer biology, disease dissemination and progression using state-of-the art "omics" technologies as well as in developing prognostic and predictive biomarkers for breast cancer (BC). My group, composed of 20 persons, is a well-diversified multidisciplinary team integrating translational research post-docs, clinical research fellows, bioinformatic and wet lab PhD students. The ultimate goal is to accelerate the translation of basic science discoveries dedicated to breast cancer into the clinic.

Main achievements

1) Gene expression profiles associated with prognosis and response to therapy in breast cancer

My group was among the first to adopt gene expression profiling for prognostic and predictive studies in Europe. This led to the development of the Genomic Grade Index- GGI **(Sotiriou et al. J Natl Cancer Inst. 2006)**, a gene expression signature of which the prognostic value has recently been validated using material from the BIG 1-98 trial **(Ignatiadis et al. JAMA Oncol. 2016)**. The results of this research were validated in a prospective randomized III clinical trial in Europe (ASTER 70s) assessing the benefit of adjuvant chemotherapy for estrogen receptor (ER)-positive, HER2-negative breast cancer (BC) in women over 70 years old according to GGI. We were the first to demonstrate that the common denominator driving the prognostic performance of almost all prognostic gene signatures is proliferation, which was shown to be mostly informative in ER-positive, HER2-negative disease **(Sotiriou et al. Nat Rev Cancer 2007; Sotiriou et al. N Engl J Med. 2009; Haibe-Kains et al. J Natl Cancer Inst. 2012)**. These findings influenced patient recruitment in the phase III MINDACT trial in which our group was actively involved **(Cardoso et al. N Engl J Med. 2016, Piccart et al. Lancet Oncol 2021)**. Indeed, this study was initially designed to include all patients under 70 years old irrespective of ER and HER2 status.

2) Investigating primary breast cancer heterogeneity

Within the context of the International Cancer Genome Consortium, my group was involved in the first reporting of the mutational landscape of BCs using whole exome and genome sequencing (**Stephens et al. Nature 2012, Nik-Zainal et al. Nature 2016**).

These studies demonstrated that the number of somatic point mutations varied markedly between patients and highlighted the substantial genetic diversity underlying BC. Through a collaborative effort, my group, together with the Sanger Institute, investigated the subclonal architecture of primary BCs using whole genome/targeted sequencing of multiple samples (n=303) from 50 patients (**Yates et al. Nat Med. 2015**). This study showed that the extent of intra-tumor heterogeneity varied substantially among different patients and that alterations affecting key genes involved in BC, including PIK3CA, TP53, PTEN, BRCA2 and MYC, occurred early (clonal) in some tumors and relatively late (subclonal) in others. We found similar results in multifocal BCs, which represent about 25% of BCs (**Desmedt et al. J Pathol. 2015**). In another study combining whole exome and RNA sequencing analyses, my group produced the largest survey so far of A-to-I RNA editing in breast and other cancers. This is the first time that A-to-I editing is shown to be a major source of mRNA sequence variability in breast and potentially other cancers highlighting another layer of tumor complexity which may potentially affect prognosis and response to therapy (**Fumagalli et al. Cell Rep. 2015**). These results provide new insights into the molecular alterations that drive BC tumorigenesis and highlight the presence of substantial genomic inter- and intra-patient heterogeneity.

3) Deciphering breast cancer metastatic dissemination

The origins of metastatic disease are unclear and phylogenetic analyses can provide the opportunity to understand the intra-cancer evolution and metastatic progression of BC. From an autopsy series, my group indexed point mutations and copy number aberrations from the primary tumor and multiple matched metastases using exome sequencing and SNP arrays. Our results showed that metastases differ substantially from the primary tumor. Most intriguingly, our data revealed two different paths leading to metastatic dissemination through primary-to-metastases and daughter-to-daughter metastases dissemination, namely parallel and cascade paths, respectively **(Brown et al. Nat Commun 2017)**. In addition, recently, we showed that lymph nodes and distant metastases shared a common origin in only 25% of the cases highlighting that the predominant route of metastatic dissemination is the direct hematogenous spread of tumor cells from the primary tumor to distant organs, independently of lymph node metastasis. Noticeably, patients sharing a common origin significantly have a worse prognosis. These results shed light on the routes on which tumor cells metastasize and their role in disease progression in BC **(Venet et al. EBiomedicine 2020; Danai et al. EBiomedicine 2022)**. My group was also extensively involved in the AURORA study aiming to better uncover the processes of relapse in metastatic breast cancer by performing multi-omics profiling on paired primary tumors and early-course metastases. Our first report showed that metastases were enriched in ESR1, PTEN, CDH1, PIK3CA, and RB1 mutations as well as MDM4 and MYC amplifications and ARID1A deletions. Of interest, intrinsic subtype switching occurred in 36% of cases. We also showed that metastases had lower immune score and increased immune-permissive cells. High tumor mutational burden correlated to shorter time to relapse in HR+/HER2- cancers. ESCAT tier I/II alterations were detected in 51% of patients and matched therapy was used in 7% (**Aftimos et al. Cancer Discov 2021**). Our results highlight the intrinsic dissemination properties endowed in primary tumors, the role of tumor dormancy in metastatic progression, and the molecular differences that characterize metastatic from primary lesions.

4) Genomic profiles of early and metastatic lobular breast cancer

Despite being the second most common histological subtype of BC after invasive ductal breast (IDC) cancer, limited studies investigated the molecular landscape of invasive lobular breast cancer (ILC). We were among the first to report the genomic differences that characterize primary ILC from IDC **(Desmedt et al. J Clin Oncol. 2016)**, some of those being of immediate clinical relevance such as mutations in ERBB2, ERBB3 and genes involved in the PI3K pathway.

More recently, aiming at identifying mechanisms of cancer progression and endocrine resistance, we characterized the genomic profiles of matched primary and metastatic samples (n=279) from 80 ILC patients using targeted gene and low pass whole genome sequencing. Of interest, we reported the enrichment and/or acquisition of somatic mutations in metastatic samples, some of which with potential therapeutic implications including ERBB2, ESR1 & AKT1, CDH1, NF1, MAP3K1, as well as several copy number aberrations such as CCND1, CCNE1 and IGF1R amplifications as well as ESR1 deletions **(Richard F et al. Clin Cancer Res 2020; Desmedt C NPJ Breast 2019)**. Finally, we were the first to report the immune landscape that characterizes early and metastatic ILC showing lower TILs level as well as different immune cell composition as compared to IDC **(Desmedt C et al. J Natl Cancer Inst 2018)**.

5) Molecular characterization of Triple Negative Breast Cancer and its tumor microenvironment

During the last decade, several groups, including ours, reported the first genomic and transcriptomic profiles of triple-negative breast cancer (TNBC), highlighting the presence of six molecular subtypes associated with different prognoses and responses

to treatment. Our group further unraveled TNBC heterogeneity by mapping the genomic alterations that characterize each molecular subtype, paving the path for the development of novel targeted therapeutic approaches for TNBC patients (**Bareche et al. Annals of Oncol. 2018; highlighted by Reis-Filho in Nat Rev Clinic Oncol. 2018**). Also, we investigated TME heterogeneity within each TNBC molecular subtype, including immune infiltrate spatial localization and composition, demonstrating for the first time that each TNBC subtype is associated with specific TME profiles (**Bareche et al. J Natl Cancer Inst. 2020**). Finally, in collaboration with Pr. J. Lundeberg, our group was one of the first to use spatial transcriptomics on the largest TNBC cohort to date and identified 9 spatial archetypes, characterized by distinct molecular features, TME composition, and potentially targetable molecular pathways. Of interest, we also derived a tertiary lymphoid structure (TLS) signature whose prognostic and predictive value for treatment with ICIs were validated in external datasets (**Wang et al., Nat commun 2024**).

6) Uncovering the immune landscape of breast cancer

With the aim of developing predictive biomarkers for response to therapy, our group highlighted the key role of interferon-driven immune signatures and the levels of tumor-infiltrating lymphocytes (TILs) in predicting clinical outcome and response to neoadjuvant chemotherapy in HER2-positive and TNBC subtypes (**Desmedt C et al. Clin Cancer Res. 2007; Ignatiadis et al. J Clin Oncol. 2012; Loi S, et al. J Clin Oncol. 2013**). Furthermore, we were the first to report the immune landscape that characterizes early and metastatic lobular breast cancer (**Desmedt et al. J Natl Cancer Inst. 2018**). Also, we demonstrated an association between higher levels of TILs and immune signatures with increased benefit to anti-HER2 therapies in HER2-positive disease (**Fumagalli et al. JAMA Oncol. 2016; Ignatiadis et al. J Natl Cancer Inst. 2019**). Of interest, in collaboration with Yale investigators from the TransALTTO committee, we demonstrated that T-cell β chain variable genes were associated with benefit to dual anti-HER2 blockade beyond TILs and immune gene signatures (**Powles et al. JAMA Oncol. 2018**). More recently, investigating B-cell and T-cell receptor (BCR and TCR) repertoire complexity in the NeoALTTO and CALGB 40601 phase III trials, we generated a clinic-biologic prognostic model, including baseline stromal TILs level and BCR repertoire evenness, that was able to refine prognosis beyond residual cancer burden (RCB) (**Rediti et al. Nat Commun. 2023**). In the poorer immunogenic luminal breast cancer, we recently investigated the role of RANK signalling pathway in modulating immune activation. Pre-operative single-agent RANKL inhibition in pre-menopausal early-stage breast cancer patients, increased levels of TILs and decreased immunosuppressive cells. Thus, RANK pathway inhibitors could enhance anti-tumor immune responses in luminal BC and soluble RANKL could predict this immune-modulatory effect (**Gómez-Aleza C et al. Nat Commun. 2020**). Further analyses to characterize the TME and to better select patients that might respond to immune checkpoint inhibitors (ICI) are ongoing in the context of the EORTC's IMMUcan project (Integrated iMMUnoprofiling of large adaptive CANcer patient cohorts, https://immucan.eu) whose BC cohort is being coordinated by our group. Preliminary results of the BC cohorts were presented at the AACR 2024 and ESMO IO 2024 annual meetings (Manuscript in preparation). The above results open new avenues for developing novel immune therapeutic strategies in various breast cancer subtypes.

7) Liquid biopsy as a tool to investigate and monitor breast cancer

The use of circulating tumor DNA (ctDNA) is increasingly being advocated as an alternative to metastatic biopsies for the monitoring of the disease and treatment response assessment. We pioneered the use of ultra-high coverage NGS for mutation detection from synchronous tumor and plasma samples in patients with metastatic BC **(Rothé F et al. Ann Oncol. 2015)**. Our data showed concordant results between paired tumor and plasma samples in 78% of the patients whereas in 22% of the patients' tumor and plasma ctDNA revealed additional mutations highlighting the complementary of primary tumor and ctDNA analysis. More recently, we have studied plasma ctDNA in the context of the NeoALTTO phase 3 trial using ddPCR in collaboration with Sarah Dawson lab in Peter MacCallum Cancer Center (Melbourne, Australia). We showed that ctDNA detection before neoadjuvant anti-HER2 therapies was associated with decreased pCR rates. Interestingly, patients with HER2-enriched tumors and undetectable ctDNA at baseline had the highest pCR rates, therefore appearing as the best candidates for treatment de-escalation strategies **(Rothé F et al. Clin Cancer Res. 2019)**. Similar results were found after a neoadjuvant chemotherapy (**Cailleux et al. JCO Precis Oncol. 2022**). We are currently developing several research projects using the concept of liquid biopsy for the monitoring and early detection of recurrence of breast cancer in the adjuvant setting.

Residency internal medicine and oncology

10/1993 - 09/1994 Department of Internal Medicine and Oncology, Jules Bordet Institute, Université Libre de Bruxelles (ULB), Brussels, Belgium

10/1994 - 09/1996 Department of Internal Medicine, Etterbeek-Ixelles Center Hospital, Université Libre de Bruxelles (ULB), Brussels, Belgium
10/1996 - 09/1997 Department of Oncology, Jules Bordet Institute, Université Libre de Bruxelles (ULB), Brussels, Belgium
10/1997 - 09/1999 Research fellow of the Belgian Foundation for Scientific Research (FNRS), Department of Oncology, and Laboratory of Endocrinology, Bone Metabolism and Breast Oncology, Jules Bordet Institute, Université Libre de Bruxelles (ULB), Brussels, Belgium
10/1999 - 09/2001 Research Fellow, National Cancer Institute (NCI), Division of Clinical Sciences, National Institutes of Health (NIH), Bethesda, MD, USA

Professional Experience

- Since 10/2017 Directeur de Recherches (Research Director) at the National Foundation for Scientific Research (FNRS), Faculty of Medicine, Université Libre de Bruxelles (ULB), Brussels, Belgium (Tenured position)
- Since 10/2013 Maître de Recherches (Senior Research Faculty Member) at the National Foundation for Scientific Research (FNRS), Faculty of Medicine, Université Libre de Bruxelles (ULB), Brussels, Belgium (Tenured position)
- Since 10/2013 Full Professor, Medical Oncology Clinic, Institut Jules Bordet, Université Libre de Bruxelles (ULB), Brussels, Belgium
- Since 03/2010 Head of the J.-C. Heuson Breast Cancer Translational Research Laboratory, Faculty of Medicine, Université Libre de Bruxelles (ULB), Brussels, Belgium
- 10/2005-09/2013 Chercheur qualifié (Junior Research Faculty Member) at the National Foundation for Scientific Research (FNRS), Faculty of Medicine, Université Libre de Bruxelles (ULB), Brussels, Belgium (Tenured position)
- 10/2005-09/2013 Associate Professor, Medical Oncology Unit, Institut Jules Bordet, Université Libre de Bruxelles (ULB), Brussels, Belgium
- 10/2001-02/2010 Head of the Microarray Unit at the Institut Jules Bordet, Université Libre de Bruxelles (ULB), Brussels, Belgium
- 10/2001-09/2005 Assistant Professor, Medical Oncology Unit, Institut Jules Bordet, Université Libre de Bruxelles (ULB), Brussels, Belgium

Other Experience and Professional Memberships

- Full member of the European Society for Medical Oncology (ESMO) since 2001
- Full member of the American Association for Cancer Research (AACR) since 2001
- Full member of the American Society for Clinical Oncology (ASCO) since 2001
- Full member of the Belgian Society of Medical Oncology (BSMO) since 2015
- Associate member of the Belgian Royal Academy of Medicine since 2022
- Expert member of the editorial board for the WHO Classification of Tumours, 5th Edition, Breast Tumours, 2019 and 6th Edition, Breast Tumors 2025
- Elected Member of the Scientific Council of the International Agency for Research on Cancer for Belgium (IARC- WHO- World Health Organisation), 2012 – 2016
- Elected Fellow of the European Academy of Cancer Sciences in October 2010, which is hosted under the auspices of European CanCer Organization (ECCO)
- Associate Editor of Annals of Oncology (Breast Cancer), official journal of the European Society of Medical Oncology (ESMO) since January 2014
- Member of the editorial board of Journal of the National Cancer Institute (Breast Cancer), since December 2017
- Core Faculty Member of the European School of Oncology (ESO) since 2017
- Member of the scientific advisory board of the Lobular Breast Cancer Alliance (LBCA) since 2018
- Member of the National Foundation for Research (FNRS) evaluation committee since 2017
- Member of National Foundation for Research (FNRS) / FRIA since 2017
- Member of the Abstract Review Committee for Annual CTRC-AACR San Antonio Breast Cancer Symposium (SABCS)
- Member of the Abstract Review Committee for the Annual European Society of Medical Oncology (ESMO)
- Member of the scientific committee for the Annual European Breast Cancer Conference (EBCC) Congress
- Co-Chair of the Scientific Evaluation Committee for the French National Cancer Institute (INCa) – Translational research

Awards

- Prize "Yvonne et Thomas Rucquois" to support one-year research fellowship, at the National Cancer Institute (NCI), Bethesda, USA (2000)
- Prize Gaston Ithier in translational research (2006/2010)
- Prize Cycle for Life in translational research (2006)
- Prize "Fondation Majoie pour l'Innovation" (2008)
- Prize for the best translational scientific research paper of 2008 – Breast Journal Club – Camogli, Italy (2009)
- "Ruban Rose Grand Prix de la Recherche Prize" from the foundation "Le Cancer du Sein, Parlons-en !" – France (2010)
- 20th Raymond Bourgine Award for the achievements in cancer research – ICACT – 24th International Congress on Anticancer Treatment – France (2013)
- Joseph Maisin Scientific Prize - Clinical biomedical sciences, a Quinquennial scientific Prize awarded by the F.R.S.-FNRS (Belgian Fund for Scientific Research), Belgium (2015)
- EBCC-14 Breast Cancer Science Award: Breast cancer biology for precision medicine (2024)

Summary

Peer-reviewed publications: > 300
Book chapters: 23
Invited Speaker: > 200
Google scholar H-Index: 119
Total number of citations (Google scholar - all): 76728