Breast cancer continues to register one of the most common incidence and deaths among female cancers. However, during the last three decades, breast cancer treatment benefited from a sea-change for specific subtypes. These successes led to increases in the period of cancer remission, reduced therapeutic resistance, inhibition of drug toxicity, and resulting in almost life-long remission in some cases. These gains in prolonging the life of patients with breast cancer are largely attributed to targeted therapies and ever-evolving combination modalities by the bold effort of basic and clinical scientists and practicing oncologists (1–3). The records of these advances in clinical cancer research and combination targeted therapeutics would be sketchy in the absence of untiring and transforming scientific effort of our colleague Dr. José Baselga, who died on March 21, 2021 in Cerdanya, Spain. To illustrate a fulfilling career in cancer medicine and his contributions to clinical cancer research, here we will attempt to bring out a few, less-known features of José’s journey in clinical cancer research and treatment, and how these advances shaped the field of combination cancer therapeutics with a direct impact on the life of patients with breast cancer. We will begin with José’s early formative years and decisive turning point(s) along his expedition in cancer medicine and accentuate how José maintained a two-way flow of meaningful scientific questions between the laboratory and clinical settings, with a singular motive to improve the treatment of breast cancer.

Early Years

A Catalan by birth, José Baselga was born on July 3, 1959 in a family with long roots in medicine. His grandfather was a rural physician in Cardona, Spain, and his father an occupational physician in Barcelona. José completed his basic degree in Medicine at the Universitat Autònoma de Barcelona in 1982. Soon after, he started his residency training in Internal Medicine at the Hospital Vall d’Hebron in the same city. During this time, José’s desire to excel in oncology made it evident that he planned to seek advanced training abroad. One of his childhood friends and a colleague in medicine residency, Antonio González Fernandez, remembers José, “as a good student among the top ten. However, by far he was the one with a clear plan to advance his career in oncology.” Passionate about it, José did not hesitate to drop his residency in Barcelona to restart at the Kings County Hospital Center in Brooklyn, New York City. His partial residency in Spain was an advantage to José among internal medicine residents coming from their training in medical school. This advantage, along with his intelligence and tireless capacity to work, led to an appointment as a chief resident. At the time this was significant because José was the first non-American to hold such a position at the Kings County Hospital.

The Turning Point – Memorial-Sloan Kettering Cancer Center Years

After completing his residency training in 1989, José was admitted to the Medical Oncology fellowship training program at Memorial-Sloan Kettering Cancer Center (MSKCC, New York, NY). During his fellowship, José immensely benefited from the joint mentorship provided by Larry Norton and the late John Mendelsohn, as well as working in the Mendelsohn’s Research Laboratory of Receptor Biology. At that time, the laboratory was intensively pursuing the hypothesis that the growth of tumor cells with high epidermal growth factor receptor (EGFR) with an extracellular autocrine loop could be effectively inhibited by anti-EGFR–blocking antibodies (1, 4–6). These research questions caught José’s attention and imagination, leading to his intense integration in basic science and preclinical research projects with Rakesh Kumar and Hideo Masui, respectively (7–9). José’s training in translational oncology began while he worked with John Mendelsohn in the laboratory, and Larry Norton in the clinic. José recognized two concepts—more widely deprecated than appreciated at the time. These concepts became the motivation of much of his groundbreaking work over the next decades. The first concept learned by José was an understanding that the molecules responsible for...
growth regulation were more suitable targets for anticancer therapy than the subsequent downstream processes of mitoses. The second was that recombinant monoclonal antibodies (mAbs) could be useful agents for this purpose. Soon, Jose, along with his mentors, demonstrated superior antitumor activity of EGFR-blocking mAbs and doxorubicin in experimental models (8), further catalyzing his determination for several forward-looking clinical trials. Moreover, the notion of sequential blockade emerged from this work: that simultaneously attacking growth factor receptors (and, later, signal transduction therefrom) and mitosis itself could be synergistic. This idea, motivated by studies of feedback loops and alternative pathways in the laboratory of Neal Rosen at MSKCC (New York, NY), was neither obvious in those days nor popular, but Jose was not of the type to be dismayed. In 1993, he first authored a prescient paper on this topic, showing synergy between doxorubicin and an anti-EGFR mAb (9). This work continued in the demonstration in a phase I trial: that anti-EGFR chimeric antibody cetuximab combined productively with cisplatin (10). In addition, with his characteristic enthusiasm, Jose was deeply involved in germinal studies of the taxanes and dose-dense sequential therapy, both of which evolved further to good effect (11–13).

At the time that Jose was getting involved in translational oncology, the significance of a second member of the EGFR family, the HER2/c-Neu/ErbB-2 oncogene was emerging. HER2 was beginning to be at the forefront of a surface oncogene that is upregulated in breast and many other solid tumors (14, 15). One of these studies was from Marc J. Van de Vijver (14) – who subsequently came to MSKCC on a sabbatical in John Mendelsohn’s laboratory. During this time, Marc J. Van de Vijver, along with Rakesh Kumar and John Mendelsohn, defined the details of EGFR trafficking and activation by an extracellular autocrine pathway, providing an additional rational for using anti-EGFR-blocking antibodies to interrupt an autocrine growth stimulatory loop (6). As the scientific community was aware of John Mendelsohn’s inhibitory anti-EGFR studies, a similar approach was attempted for HER2 by many laboratories, even though there was no known HER2 ligand. This led to the development of growth-inhibitory anti-HER2 mAbs against an extracellular region of HER2 receptor in breast tumor cells with upregulated HER2 (16, 17). One such antibody, mAb4D5, was developed by Genentech (17) and later humanized as rhHuAb HER2/trastuzumab (Herceptin) to treat patients with breast cancer with HER2 upregulation (18). At the time, the mechanism of action of mAb4D5 was not fully understood. Because of the scientific interests of the laboratory and informal discussions with Marc J. Van de Vijver, Rakesh Kumar, and John Mendelsohn, in collaboration with H. Michael Shepard from Genentech, demonstrated the effectiveness of mAb4D5 to inhibit the phosphorylation of HER2 on tyrosine residues as well as HER2 downregulation from the cell surface in breast cancer cells with upregulated HER2 (19). As Jose was working with patients at MSKCC’s breast cancer program in the early to mid-1990s and because Mendelsohn’s laboratory was also studying certain aspects of HER2 biology in breast tumor cells, it was natural that he was interested in the emerging evidence that HER2, not uncommonly overexpressed in breast cancer, was potentially a therapeutic target as well as a prognostic biomarker. Working clinically in the breast cancer program in the early to mid-1990s and due to Jose’s involvement with anti-EGFR mAbs with Larry Norton and John Mendelsohn, the concept of blocking cell surface receptor-tyrosine kinases by anti-receptor mAbs encouraged the young Baselga to explore strategies to inhibit HER-2 in patients with breast cancer along with his mentors. In 1996, Jose was the first author of the first phase II trial of single-agent trastuzumab (20). While the response rate was modest - one complete remission and four partial remissions in 45 patients with HER2-overexpressing metastatic breast cancer - and average response durations were only a few months, this was a critical publication because it demonstrated some activity of mAb as an emerging class of drugs. The pharmacokinetic assays mastered during this trial were important in designing subsequent dose schedules, which formed the basis for further investigation. This seminal publication confirmed that a biomarker could be used to stratify patients for a given study. More importantly, the publication provided a pathway for the development of anti-HER2 therapy in conjunction with antimitic chemotherapy. There was evidence of profound synergy with this combination treatment rather than the modest benefit as a single-agent targeted treatment. In fact, Jose’s collaborative laboratory work documented the power of combination treatment (21). Simultaneously, he showed that HER2 overexpression was a predictive marker for paclitaxel sensitivity (22) This, together with the demonstration that HER2-directed therapy enhances the effect, was the basis for inclusion of paclitaxel in the pivotal trial first-authored by Denis Slamon that put trastuzumab on the map and established the foundation for its clinical applications up to the present day (23). Through these seminal studies, Jose became one of the early leaders in the development of trastuzumab, leading to one of the earliest clinical trials of this life-saving antibody, in combination with cisplatin (24). The concept was enormously successful and trastuzumab became one of the major contributors to prolonging the lives of patients with HER2-positive metastatic breast cancer. More importantly, the combination of trastuzumab with cytotoxic therapy led to decreased recurrence rates and significantly increased survival rates for patients with nonmetastatic HER2-positive disease (25, 26). Jose’s work also contributed to the clinical development of pertuzumab, another HER2-directed mAb, becoming the current standard treatment for HER2-positive breast cancer. The collaboration among Jose, Larry Norton, and John Mendelsohn represented one of the earliest examples of targeted therapy in breast oncology and catapulted Jose into a position of prominence as one of the leading translational investigators in breast cancer treatment. A significant outcome of Jose’s work is the notion of sequential blockade therapies.

Transforming Oncology at Vall d’Hebron

Jose’s passion for translational cancer research, nurturing excellence in academic medicine and love for his native country, prompted his return to the Vall d’Hebron University Hospital with a vision in mind: creating a comprehensive cancer center in his hometown Barcelona. In 1996, he chaired the Oncology and Hematology Department at Vall d’Hebron and subsequently, became the first director of the Vall d’Hebron Institute of Oncology (VHIO, Barcelona, Spain). The mandate of the institute was to create a center wherein preclinical and translation sciences are intermingled with oncology practices. To this end, Jose quickly recruited Josep Tabernero, the current VHIO director, as well as Joaquin Arribas and Joan Albanell (both also trained at MSKCC, New York, NY), to lay the foundation in basic and translation cancer, respectively, at Vall d’Hebron. As there was no precedent of a research laboratory at Vall d’Hebron, the team started their research programs from a small empty room at the general hospital, publishing the first set of growth factor research manuscripts in 1998 (27, 28). These early successes were instrumental for the first major expansion of preclinical and translational research programs and positioned the Vall d’Hebron as a preferred site for phase I studies and a hub for international cancer clinical trials, many of which were
Based on José’s research studies at MSKCC. Examples of such studies included, the pivotal phase III trial on trastuzumab and paclitaxel in HER2-positive advanced breast cancer (23), new cetuximab trials (29), and an International phase I trial of gefitinib (also known as ZD1839; refs. 30, 31). José was also a pathbreaker in attracting large philanthropic donations for the center, the first of which was for the construction and equipment of an oncology research building. At the national level, he soon became the president of Solid Tumor Intensification (SOLTI) group and turned it into a leading consortium of international breast cancer research (29), while collaborating with other European leaders, such as the European Cooperative Trial in Operable Breast Cancer (ECTO; ref. 32). Over the next very few years, his center became one of the guiding lights of translational research in oncology in Europe. Laboratory research flourished, and the center attracted outstanding trainees that today populate many cancer centers around the world. The center also focused on multidisciplinary approaches to managing malignant disease, which resulted in improved clinical outcomes. José’s translational research team was enormously prolific, publishing basic and translational observations in leading peer-reviewed journals in Europe and North America. During his first ten years in Barcelona, José evolved from a very promising oncologist at MSKCC to an internationally acclaimed leader in cancer medicine while remained connected with his mentors, Larry Norton at MSKCC and John Mendelsohn at the University of Texas MD Anderson Cancer Center (MDACC). It is important to note that prior to José’s departure to Chair the Department of Medical Oncology at Vall d’Hebron University Hospital in Barcelona in 1996, and even after as a collaborator, José contributed meaningfully to the overall breast cancer clinical research program at MSKCC.

**Completing the Cycle to the United States**

José demonstrated his strength to master the art of establishing large oncology programs and taking laboratory findings to the bedside. He decided to continue the cycle of his international career by returning to the United States. In 2010, he became the Chief of the Division of Hematology and Oncology at the Massachusetts General Hospital in Boston, MA, and in 2013, he was recruited to its starting point at MSKCC. This 24-year span now led José as Physician-in-Chief and later, Chief Medical Officer until 2018. In 2019, José joined the multinational pharmaceutical company, AstraZeneca as Global Director of Oncology Research.

**Beyond Institutions**

As a key opinion leader, José had important advisory roles at several large pharmaceutical companies with concomitant development of anticancer agents. He also led some of the seminal phase III trials with new agents from early phase I, to pivotal phase III trials leading to regulatory approvals. His early interest in the HER family eventually extended into the PI3K/akt/mTOR signaling pathways that he codirected with Gabriel Hortobagyi - the definitive clinical trial of everolimus (an mTOR inhibitor), leading to regulatory approval by the European Medicines Agency (EMA) and FDA and incorporation into the standard of care for breast cancer. José had an extensive network of clinical and translational collaborations around the globe. It is worth mentioning the work that he and Luca Gianni did as outstanding leaders of the Michelangelo Foundation - a group that conducted novel and creative breast cancer clinical trials with targeted agents, such as The ECTO trial. José’s involvement in this foundation led to the concept of dual anti-HER2 antibody in the absence of chemotherapy for selected patients with HER2-positive metastatic breast cancer. He was also a leading force in SOLTI, an innovative breast cancer research organization in Spain, with links in France, the Netherlands, and Italy, with about 400 members at approximately 100 research sites. Also noteworthy, was José’s extensive collaboration with Breast International Group (BIG) where his vision, energy, and extensive connections contributed substantially to the development and conduct of multiple clinical trials that affected the practice of clinical oncology. José’s contributions to cancer medicine were enhanced by his ability to remain connected with all stakeholders. José was a very active member of the major professional societies where he served in several leadership positions: José served as the president of the European Society of Medical Oncology (ESMO) and the American Association for Cancer Research (AACR). His tenure in these societies was highly productive and accelerated the incorporation of genomic science into modern cancer investigation. In his native Catalonia, José founded the Fundació d’Estudis i recerca Oncològica (FERO). José coauthored about 400 peer-reviewed research articles and reviews in peer-reviewed journals. In addition, he was the founding co-Editor-in-Chief of Cancer Discovery, one of the flagship journals of the AACR. José was also recognized by numerous professional associations and institutions. In 1992, he received a Young Investigator Award from the American Society of Clinical Oncology and one year later, he received the prestigious Career Development Award from the same organization. Other awards were achieved in 2004 as an elected Member of the American Society of Clinical Investigation; 2007, the American Italian Cancer Foundation Prize for Scientific Excellence in Medicine; 2008, the Rei Jaume Prize in Medical Investigation from the Generalidad Valenciana y la Fundación Valenciana de Estudios Avanzados and the Rosenthal Family Foundation Award from the American Association for Cancer Research; 2010, the Gold medal from the Queen Sofia Spanish Institute in New York; 2011, the Laurea Honoris Causa (honorary doctorate) from the Universitat de Valencia (Spain); 2012, the Joseph B. Martin Award from Massachusetts General Hospital, Boston, MA; in 2014 he became a member of the National Academy of Medicine; 2016, the John Wayne Clinical Research Lecture Award at the Society of Surgical Oncology, the XXVIII Catalonia International Prize; 2017, the Lifetime Achievement Award by the European Society for Medical Oncology; and in 2021, the AACR dedicated a Clinical Symposium in his honor during the annual meeting. In addition to science and medicine, José loved life and lived intensely: he was, along with his wife Sylvia Garriga, an avid and expert skier, and enjoyed travel, outdoor sport activities, and the finer aspects of life. His passion for life and transformative capacity was manifested in everything he touched. Another asset of José was his deep involvement in mentoring students, residents, fellows, and younger colleagues, while always making a point about how to pursue the best science and bring their best version together. He was very generous to share his professional and personal experiences with his colleagues and mentees alike and served as an excellent collaborator who loved to work hard with insights about the best way to move forward in numerous team science projects. In some way, José continued the legacy of his laboratory research mentor, late John Mendelsohn, in enabling his mentees and younger colleagues to achieve their dreams in cancer medicine.

Besides clinical cancer research, it is important to emphasize José’s unmitting commitment toward the excellence in the quality of...
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patient care by bringing the most promising laboratory findings to the bedside. His legacy will remain alive at the institutions he served, and globally by the treatments he developed. José was a relentless force in translational research, who brought out the best from people around you with a human touch and respect for others. Baselga’s death has robbed the world of a great mind, and a man of vision who dedicated his professional life to the search for better understanding of the cancer problem and whose persistence contributed significantly to bringing together clinicians and scientists in their efforts to enhance cancer cure rates and quality of life.

Acknowledgments

The authors thank Prof. Pamela Rameshwar, Rutgers New Jersey Medical School (Newark, NJ) for her critical reading of the manuscript.

Received May 3, 2021; accepted May 6, 2021; published first June 11, 2021.

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In Memoriam: José Baselga's Journey in Cancer Medicine

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