A spotlight on cancer researchers in Spain: new paradigms and disruptive ideas

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Introduction

Over the last years, there have been relevant advances in cancer research and in treatment based on specific genetic alterations improving survival in some tumors. Nevertheless, progress is still dismal in most carcinomas when are disseminated with metastasis; the survival is less than 30% in most cases. Then, we need to move forward looking for new paradigms which may explain the complex mechanisms involved in carcinogenesis and in new treatment approaches.

With these objectives, we met this month of July, in the Aragonian Pyrenees, a group of 15 scientists conducting research in Spain who are changing many paradigms in research and developing disruptive projects. In a 3-day meeting, we share ideas and establish an ideal framework of collaborations, where pathologists, oncologists, biologists, bioinformaticians and data scientists, altogether, looked for new approaches and synergistic teams. Most researchers are younger than 45 years, and their outstanding findings and talent made us to be optimistic for great advances in

upcoming years. This was the first one of a series of summer meetings that we are planning to organize. Other 15–20 more younger outstanding researchers will be invited to participate in the forthcoming editions.

Some of the most relevant highlights of the meeting can be summarized in the following points:

The proposal of new paradigms in cancer research

- (a) The cellular reprogramming and cellular plasticity, in biology and cancer by Dr. Maria Abad that can explain the intratumoral heterogeneity and the dynamics of tumor progression. Cellular plasticity is the ability of cells to transit between different states or cellular identities, including transitions between epithelial and mesenchymal states, or between differentiated and dedifferentiated states. The paradigm of cellular plasticity is represented by embryonic stem cells, which are

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capable of generating all the specialized cells that make up our adult organism. Dr. Yamanaka demonstrated in 2006 that we can convert specialized adult cells into embryonic stem cells (called iPS, from induced pluripotent stem cells) through a process called cell reprogramming. Later, our investigations showed that we are capable of inducing cellular reprogramming inside living organisms. Cell reprogramming has immense potential in regenerative medicine, since it opens the possibility of generating stem cells that in turn regenerate any damaged cell type. However, today we know that this process is a mechanism that tumors use to generate, maintain themselves, and survive therapies such as radio or chemotherapy.

- (b) The role of cellular metabolism in the transformation and tumor progression, as presented by Dr. Patricia Sancho, especially focused on active metabolic pathways in highly aggressive cells such as tumor stem cells, as new therapeutic strategies. The importance of mitochondrial enzymes in the development of many tumors is being key for the diagnosis of them, as IDH1 in brain tumors. Likewise, Dr. Alejo Efeyan emphasized that reprogrammed metabolism is a hallmark of tumor cells, as most mutations selected in cancer increase nutrient uptake, fuel anabolism, and even have a negative effect on the metabolism of the patient. Fortunately, the energetic demands associated with oncogenic mutations constitute a potential vulnerability that many laboratories are trying to enumerate and understand, to then exploit therapeutically. In particular, Dr. Efeyan pinpointed vulnerabilities of follicular lymphomas caused by activating mutations in the nutrient signaling cascade upstream of the mTOR kinase, a master regulator of anabolism. Dr. Efeyan described the selective sensitivity of this group of tumors to pharmacological inhibition of mTOR using genetically engineered mice.
- (c) The new approaches of inflammation and cancer by Dr. Julián Pardo, and Dr. María Abad, who contributed in presentation data that support the relationship between inflammation and the development of some tumors, as well as plasticity and change of cellular phenotype.

The most recent experimental and clinical data suggest that the relationship between inflammation and cancer is not restricted to the initiation of the carcinogenic process but, in addition, the composition of the inflammatory microenvironment affects the outcome of anticancer therapy, including traditional treatments like chemotherapy or radiotherapy as well as the most recent advances in biologicals and immunotherapies. On this basis, Dr. Pardo reviewed the new possibilities of selectively modulating the inflammatory immune response to prevent the development of cancer or to treat it, minimizing possible side effects.

- (d) The still unknown meaning of the micropeptides, presented by Dr. María Abad, in cell biology and cancer. They are derived from sequences that until recently were considered non-coding for DNA, long-non-coding RNA, which have impressive perspectives for the understanding of current biology.
- (e) The diagnosis based on liquid biopsies analyzing oncogenic mutations (e.g., BRAFV600E) with prognostic and therapeutic value. This work is based on the combination of extracellular vesicles (e.g., exosomes) and cell-free DNA (cfDNA) released by the tumor cells into the lymphatic fluid and the bloodstream. The pioneer work of Dr. Héctor Peinado in melanoma is already in the clinical setting. His findings open a new avenue of analysis of using novel biofluids currently discarded in the clinic (e.g., drainage implanted post-lymphadenectomy). His data show for the first time that exudative seroma obtained post-lymphadenectomy is a novel biofluid enriched on extracellular vesicles and DNA that can be interrogated for melanoma markers and BRAF mutation. Analysis of *BRAF*^{V600} mutation identified patients at risk of relapse with high significance. These data support a novel technique to detect residual disease right after surgery in stage III melanoma patients. This analysis could be a novel approach to aid oncologists to identify high-risk groups of patient post-lymphadenectomy and improve patient outcomes).
- (f) The realization of the virtual biopsy for the diagnosis by Dr. Alberto J. Schuhmacher that combines the target selectivity and specificity of antibodies toward a given tumor cell marker with positron emission tomography (PET) imaging to generate immuno-PET. This “virtual biopsy” is equivalent to conduct the non-invasive diagnosis and monitoring of patients over time using an in vivo, integrated, quantifiable, 3D, full body immuno-histochemistry. This approach will allow the diagnosis of tumors where access by biopsy is impossible or can lead to great morbidity to patients.
- (g) The new bioinformatic approaches and analysis of massive sequencing. Drs. Ignacio Varela and Víctor Quesada presented the tools they use for massive sequencing studies and for single-cell sequencing. Dr. Varela studies from a bioinformatic and molecular perspective the genetic and functional heterogeneity within tumors and their possible role in tumor progression and metastasis. Dr. Quesada summarized his contribution to the Spanish node of the International Cancer Genome Consortium, studying chronic lymphocytic leukemia (CLL). This contribution included the development of the *Sidró*n algorithm, which takes into account the process of high-throughput sequencing to improve genotype calling and filter out artifacts. By applying this tool to CLL/normal paired samples, this

group uncovered novel biochemical pathways involved in CLL tumorigenesis, such as splicing, telomere protection and proteostasis. These results illustrate how the complexity of cancer development may lead future clinical strategies to emphasize two existing concepts: personalization and transversality. Regarding personalization, mutational patterns in CLL are extremely heterogeneous; even different mutations affecting the same gene may have diverse biochemical effects. On the other hand, some of the novel mechanisms of CLL tumorigenesis play important roles in unrelated tumors, which suggests that transversal strategies may become useful.

The presentation of new approaches in cancer treatment

- (a) Based on new genetic targets, as the so-called master genes. The outstanding work of Dr. Laura Soucek, who has developed the first inhibitor against the Myc transcription factor based on a cell-penetrating peptide (Omomyc) with dominant negative action and that is already in clinical development. The Omomyc-purified mini-protein behaves as a cell-penetrating peptide and could be used as a drug. This novel and unexpected feature allowed us to treat non-small cell lung cancer (NSCLC) in vitro and in vivo, showing significant efficacy and an excellent safety profile. Finally, thanks to an ongoing effort for more than 20 years, Omomyc will reach clinical trials in 2020 for NSCLC and breast cancer, and, if proven effective, could be applied to many more oncological indications.
- (b) The presentation of a novel antitumor agent, Trabectedin, of marine origin, Dr. José Jimeno. Presented how Trabectedin, a marine-derived anticancer drug can be developed through the fusion of clinical evidence and molecular biology: the model leads to the identification of soft tissue sarcoma patients, specifically round cell mixed liposarcoma bearing the t 12;16 that lead to the CHOP FUS fusion gene: a 90% rate of long lasting responses and tumor control can be achieved, moreover, if type III translocations are excluded, the model of therapeutic intervention in this patients with Trabectedin achieves a 100% rate of tumor control including responses lasting for more than 2 years.
- (c) Based on the intratumoral heterogeneity, the new paradigm of cooperation of tumor clones and cells of the microenvironment (fibroblasts, vascular cells, glial cells, inflammatory cells). Dr. Manuel Valiente presented his work to understand the development of metastases at the cerebral level, with very novel therapeutic results based on preventing the communication of tumor cells with cells of the cerebral glia. The cells of metastasis as they grow modify the brain and transform it into an environment that, unlike what happens in the initial stages, protects metastatic cells. We have identified signaling pathways that mark this altered microenvironment that promotes metastasis, we have dissected the functional mechanisms of metastasis-microenvironment communication and we have generated a pioneering concept test of the application of this biology to a new therapy that has proved very successful only in mice but also in patients. These findings suggest that a new potential pathway to improve anti-metastatic therapies could be to take into account organ-specific survival mechanisms that cancer cells develop during the colonization of each secondary organ. This in fact might generate in the future a novel personalized therapy for metastasis in which, specific drugs would be provided to challenge the viability of cancer cells attending to key organ-specific molecular mechanisms.
- (d) Looking for targeting hubs or funnel factors, Dr. Ramón y Cajal presented the clinical data of the expression of signaling factors in human tumors. The expression was quite heterogeneous in most of them (pAKT, pmtor, pMAPK, pS6) but 4EB-P1 and specially pEIF4E that were overexpressed throughout the tumor cells. The heterogeneity of other signaling factors may be associated with local factors such hypoxia, oxidative stress, and starvation. Since pEIF4E confers resistance to many cellular stresses and anticancer drugs, he presented a new inhibitor of the kinase MNKS which phosphorylate eIF4E, developed by the group of the Sarriá Chemical Institute. A proposal of treatment based on combining anti-peIF4E plus chemotherapy was presented.
- (e) Projects based on blocking cell communication and with the microenvironment. Dr. Pilar Martín-Duque, Dr. Santiago Ramón y Cajal and Dr. Héctor Peinado presented new therapeutic approaches based on preventing the cell communication and avoiding the development of metastasis. Dr. Martín-Duque is searching for “Trojan Horses”, as vectors to transfer these and other therapies selectively to tumors, avoiding toxicity or side effects into other organs. So far, her group have identified several of these vectors using them with treatments from themselves or collaborators, such as nanoparticles, drugs or viruses. Dr. Ramón y Cajal showed that knocking down an integrin, the exosome uptake was altered and, therefore, cell communication, opening new avenues to prevent metastasis, as shown in animal models.

In summary, new paradigms and disruptive projects are coming with promising perspectives. We ask for greater

investment in science strengthening networks and research teams promoting disruptive investigations which are almost never financed by the state agencies. Proposal can be favoring fiscally the private donations that can help the works based on new paradigms and that State agencies support with about 20% its budget to disruptive ideas of researchers as most successful technological companies do.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the Institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent For this type of study informed consent is not required.

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