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Translational medicine in Catalonia: the case of liver oncology

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Abstract. Biomedical research has improved during the last decade in Catalonia, which is currently a well-recognized international biomedical scientific hub. The policy of head-hunting and attraction of talent fostered by the Catalan Government through the ICREA Professorship initiative has been successful. In 2006, I was appointed as ICREA Professor and started a research group in Translational research in liver oncology at IDIBAPS-Hospital Clínic in Barcelona. This appointment was possible due to a suitable environment in this institution, both regarding liver and translational medical research. This article summarizes some of the major advancements in translational medicine, liver research and translational hepatic oncology achieved during the last decade.

Resum. La recerca biomèdica ha millorat notablement a Catalunya durant la darrera dècada de tal manera que el nostre país es considera un pol de recerca internacionalment reconegut. Les polítiques endegades pel Govern de la Generalitat amb la creació del programa ICREA per a l'atracció de talent internacional han estat molt exitoses. En el meu cas, vaig tornar l'any 2006 de Nova York per organitzar un grup de recerca translacional en oncologia hepàtica al IDIBAPS-Hospital Clínic de Barcelona. Els avenços del nostre grup han estat possibles atès l'entorn científic que ofereix la institució pel que fa a recerca en malalties hepàtiques i en recerca translacional. El present article analitza alguns dels avenços en recerca translacional, recerca hepàtica i recerca translacional en oncologia hepàtica assolits al nostre país en la darrera dècada.

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Translational medicine in Catalonia

Translational medicine has achieved major goals during the last decade in Catalonia. We understand translational medicine as the branch of the biomedical field aimed to translate discoveries from basic research to the clinical setting in order to benefit patients[1]. Originally, the concept of translational medicine was captured by the motto *from bench to bedside*, but I rather prefer to describe it as *from the patient to the lab and back to the patient*[2]. In most ins-

tances, translational medicine equals to the modern clinical research. In order to put this concept in context in Catalonia, we need to take into account the following facts:

a) Advancements produced in translational medicine represent, in my view, the most substantial and critical research produced in biomedical centers in Catalonia, particularly by those centers associated with clinical hospitals, such as IDIBAPS (associated to Hospital Clínic of Barcelona), IDIBELL (associated to Hospital Bellvitge) and VHIR/ VHIO (associated to Hospital Vall d'Hebrón).

b) Recent data from the Catalan Government – reported in *Science* on Sept 29th,2017- between 2007 and 2015 Catalonia has obtained 210 *European Research Council* (ERC) projects, with a total of 334M€ of funding. Some awarded projects are substantially translational in nature.

c) Most of the so called *Top 1% cited investigators* worldwide working in Catalan institutions are conducting translational research in medicine.

d) At least 3 Universities in Barcelona are offering studies in biomedical translational research. Among those, I am directing the *Official Master in Translational Medicine*, in the Faculty of Medicine, University of Barcelona.

To further understand the depth of the achievements in translational medicine in our country, I am summarizing some of the ones that have been generated in my own institution, IDIBAPS-Hospital Clínic.

a) Autoimmune encephalitis: Discovery of this new entity -autoimmune encephalitis- and characterization of the NMDA receptor as the target of the immune system. This advancement has re-defined the molecular basis of some mental disorders, thus providing the rationale for a novel therapeutic approach[3].

b) Chronic lymphocytic leukemia (CLL): Novel classification of CLL and discovery of the landscape of oncogenic mutations as potential targets for therapies[4].

c) Cancer of unknown origin: This entity is causing thousands of deaths worldwide. A recent study from IDIBELL/IDIBAPS demonstrates that by exploring the methylome of the neoplastic cells it is possible to identify the primary origin of the neoplasm and optimize the treatment[5].

d) Alzheimer disease: Identification of amyloid-related biomarkers in the asymptomatic phase of Alzheimer's disease. This discovery paves the path towards primary prevention of this devastating disease[6].

e) Bipolar disorder: By genome-wide analysis the authors identified a DNA polymorphism able to predict response to lithium for prevention of recurrence of bipolar disorder[7].

Liver research at IDIBAPS-Hospital Clínic

The Liver Unit at Hospital Clínic-IDIBAPS is one of the 3-4 international groups with a higher impact in advancing the understanding of the pathogenesis and treatment of liver diseases during the last decades. This Unit was founded and led by Dr Joan Rodés, a giant in the world of Hepatology. He was also founder of the *European Association for the Study of the Liver* (EASL) and Editor-in-chief of Journal of Hepatology. His outstanding scientific production – *h index* of 128- was acknowledged with several national and international awards. He had the vision in 1970-80 to organize the research in liver disease according to specific areas (ascites, portal hypertension, hepatitis, liver cancer and transplant), assigning the leadership of each one to different faculties. An overview of the main contributions has been reported elsewhere[8,9], and are summarized as follows:

a) **Staging and treatment of hepatocellular carcinoma (HCC):** The proposal of the Barcelona-Clínic system (BCLC) for staging and treatment allocation[10,11], has been adopted by European and US clinical practice guidelines of management of HCC. This group has also provided the evidence for establishing chemoembolization as standard of care in intermediate HCC[12], and led the international randomized trials supporting the use of sorafenib[13] and regorafenib[14] in first and second line treatments in advanced cases.

b) **Pathogenesis and treatment of ascites:** Characterization of the mechanisms involved in the development of liver-related complications, such as ascites[15]. In addition, the authors led several studied supporting the use of albumin infusion to prevent hepato-renal syndrome after large volume paracentesis[16] and to improve survival of spontaneous bacterial peritonitis episodes[17].

c) **Treatment of portal hypertension:** The group described the pathofisiological mechanisms of portal hypertension and the efficacy of pharmacological[18] and non-pharmacological therapeutic approaches[19].

d) **Treatment of hepatitis C infection:** The treatment of hepatitis C infection has revolutionized the field during the last 5 years. Nowadays, up to 90% of patients achieve sustained virological responses with the new drug antiviral treatments. The group has contributed to the understanding and management of this infection in the context of chronic liver disease[20] and after liver transplantation[21].

Other important achievements have been reported in the areas of liver transplantation and cholestatic disorders.

Translational research in liver oncology

In 2006, and taking advantage of the outstanding research environment in the setting of the Liver Unit and the BCLC group, I created the group of *translational research in liver oncology* at the IDIBAPS- Hospital Clínic. This occurred after spending 3 years at the Mount Sinai School of Medicine in Nova York, were I created the Liver Cancer Program. Thus, after my return to Europe I retained the position of Director of this program in NYC, which is currently the only NCI recognized liver cancer program in the US. As a result of these two outstanding positions, our group has been able to produce more than 200 research articles in peer-reviewed journals (mean impact factor/article: 18 points). This research has been supported by competitive (including EU and NIH grants) and non-competitive funding of around 20M€. I can proudly say that I have been able to mentor 35 physicians and scientists interested in translational research in liver oncology. As a result of all this effort we have made the following contributions:

a) **Establishment of the molecular classification of HCC.** We proposed a molecular classification of HCC after analyzing the genome of >1000 cases[22,23]. More recently, we complemented the information by providing the characterization of the immune class of HCC, which is expected to respond to checkpoint inhibitors, and the exclusion class, which is expected to be primary resistant to immune therapies[24].

b) **Characterization of oncogenes and signaling pathways involved in the pathogenesis of HCC.** As a result of several studies we defined that the main molecular aberrations occurring in HCC are nowadays non actionable, and only around 30% could be potentially treated with effective drugs[25,26]. From a more clinical perspective, some early clinical trials are currently ongoing based upon these discoveries.

c) **Establishment of the molecular characterization of intrahepatic colangiocarcinoma (iCCA) and discovery of novel oncogenic drivers.** We proposed a novel classification of iCCA and discovered a novel oncogene resulting from a translocation leading to a fusion protein involving FGFR2[27,28]. These results have been translated in early clinical trials.

d) **Involvement in the design of clinical practice guidelines for the management of HCC.** I have participated in developing the Clinical Practice Guidelines of management of HCC supported by the EASL (2001, 2012 and 2018) and ESMO (2018).

After analyzing the research achievements described above in the area of translational medicine, liver research and translational liver oncology, it seems obvious to me that successful research is achieved by scientist with a unique fingerprint: a) **talented** leadership and group, b) adequate **environment** to facilitate conducting high-end research, c) hard **work capacity**, this is a constant in all cases, and d) focus on a specific area.

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