Integration in Europe of human genetics results obtained by Spaniards in the USA: a historical perspective

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SUMMARY

The mobility of the Spanish biochemists from Europe to the United States over the past 80 years (1927-2006) is approached from a historical perspective. The academic community on human genetics has awarded this emigrated Spanish community with the Nobel Prize as well as other awards from European foundations. The vertical/horizontal integration methodology offers an opportunity to understand the extremely satisfactory history of a small European community overseas. To piece the puzzle together, continuous reference is made to the theory of systems. To test and use this holistic history, the circulation of knowledge produced on cancer has been studied as intrinsically related to time by using algorithmic historiography.

Francisco Duran Reynals and Severo Ochoa have been selected as examples of the vertical integration. The former one because he was the director of an important collaborator, his own wife; the latter, as the founder of a Spanish specific research school in America based in his own work. The simultaneous stay of several young Spanish scientists at the Columbia University (Mariano Barbacid, Manuel Perucho and Ángel Pellicer) serves to design the horizontal integration, to create a holon hierarchy to reflect the criteria of subsidiarity and acceptability, and to focus on the Spanish discoveries and contributions to cancer research.

The transatlantic flows of knowledge generated by the Spanish elite of biochemists in the USA from 1927 on define a network of geographical displacements. As a result, the social structure thus visualizes the identity of the international mobility of scientists who leave for Europe/USA, and their return to Spain. A model of the brain drain of professionals to the USA, that retain 80% of the Spanish cancer researchers, is developed.

BACKGROUND

The little interest shown by Spanish scientists in studying and researching abroad goes back a long way. In certain historical times, the Spanish researchers and scientists in general seem to have felt a certain inferiority complex towards their colleagues from other countries, mainly from European countries – specially from Germany, France and the Scandinavian countries -, according to the information contained in several relevant documents, to the extent that this lack of self-confidence led them to allow foreign scientists to claim the credit for their own inventions and discoveries. The most shocking case was that of the Elhuyar brothers, whose discovery of Tungsten and Cesium was attributed to Scandinavian scientists.

The fact that science and technique do not appear as fundamental elements in the development of Science in Spain may be attributed to the country's poor economic level in certain historical periods, which meant that the discoveries and inventions couldn't be exploited commercially at international level. Thus, a national of another country appears as the author of a Spanish invention. That was, for example, the case of the autogyro invented by Juan de la Cierva – nowadays called helicopter – that appears as an American invention. Although it is also true that the helicopter displays certain modifications that improved the autogyro.

All this happened mainly during the 18^{th} and 19^{th} centuries. In 20^{th} century, mainly after World War II, and when Spain joined the group of countries with a more satisfactory level of development, the Spanish scientists wished to appear in the world ranking, an objective they are gradually achieving. Nowadays the causes behind the lack of that longed-for incorporation are of a different nature. The economic level plays a role in this. However there's no reason to be so pessimistic. The Historians of Science surely know that several Spanish outstanding scientists carried out research works abroad: Santiago Ramon y Cajal - Nobel prize -, Julio Palacios, Blas Cabrera, Emilio Jimeno, Augusto Pérez-Victoria, ... All these scientists have returned to Spain, where they followed their own lines of investigation and founded a school.

Later, after the publication of the agreement that established every student who obtained the Degree of Doctor had to spend two years abroad, numerous Spaniards have attended Universities abroad in order to carry out research works. Some of them, both from the historical and the current researchers, have remained in the reception countries, either for professional prestige reasons or for economic reasons. In is no yet easy to find a satisfactory job in Spain.

To prevent this paper from being too long, it focuses only on the study of those who have mainly devoted their researches to human genetics, in particular to the study of cancer.

Part I. Vertical / horizontal integration of human genetics results obtained by Spaniards in the USA.

Introduction.-

The concept of discipline can be defined by means the communication structures established by scientists in the context of the systems theory [STICHWEB, 2000]. We put forward that human genetics seem to be important for the history of the human species because inside the proteins or the nucleic acids "it exists more preserved history than in any other level of biological interaction" [ZUCKERKANDL & PAULING, 1965]. The research on it is oriented towards practical aims, mostly in the medicine domain [HOHLFELD, 1983]. The clarification of its internal scientific structure requires to solve the theoretical problems associated to its dynamics of information. These problems are concurrent with the integration of the subsystems in a general system, like the human body and its mechanisms of regulation and coordination. Similarly, the cancer tends to behave like a systemic disease at the moment of the diagnosis. The problem-oriented convergence of human genetics and medicine makes it a directed field. Although the identification of the research at the forefront of innovation considers its intrinsic ruptures a precondition.

The idea of examining the integration in Europe of the Spanish scientists' results in human genetics in the USA emphasizes the systemic aspects of the disease on human beings, for many authors point out the fact that the chronic illnesses are systemic illnesses [HOHLFELD, 1983]. The integration of the molecular event in the cell malignant transformation, its genesis and its diffusion in the organism, depends on the interaction of the different biological subsystems [KOHLER, 1973; DULBECCO, 1976; STOKER, 1975]. A holism with its own methods and techniques proves useful [ANOM, 1974]**.** This viewpoint claims that the explanation of the complex processes lies in the lower levels of organization [ALLEN, 2004]. In the context of cancer research, the (chemical and reductionist) search for the molecular basis of cancer induction is combined with the holistic vision of the close relationship between form and function in physiology [SHIMKIN, 1974; MEYER, 2004; MARRA & BOLAND, 1995].

From the information perspective, it is obvious that the research can be mapped from one vertical layer to another and through the different conceptual spaces of the several horizontal layers [CURRÁS, 2002], since information is not only the principle around which the universe organises laws but it is also the principle around which systems get organised within the laws [GORANSON, 1998].

The typical human genetics orientation towards the problem is closely related to the vertical integration type. On the other hand the empirical work among several horizontal layers results in the occurrence of new disciplines, such as biochemistry or molecular oncology [KISELEV, 1990]. Cancer research covers both information flows [MALECKI & OLSZEWSKI, 1980]. Since this is not a linear progress, determined by accumulation of results, time is not homogeneous, which means that the last moment should necessarily be favored because it would contain all the previous ones. The vertical/horizontal integration dialectics is adequate because it involves a non-linear progress [CURRÁS, 1988]**,** based on a perpetual fluctuation of the discussion. The mobility and transfer of scientists are of some advantage for their country of origin when the emigrated scientists are persuaded to communicate with their colleagues "at home" [PRICE, 1965; DEDIJER, 1964; GISH & WILSON, 1970]. The history of this

mobility is the point where the vertical/horizontal integration dialectics operates as a research method [AUBENQUE, 1972].

The fight against cancer is a distinct practical problem although there is no theoretical research programme based on it. When the integration factor is the research theme, the visibility criterion is vertical. However, when the common instruments or methods are the levellers of the integration, the organizational principles used are horizontal [MALECKI & OLSZEWSKI, 1980]. The differentiation of the conceptual spaces between vertical and horizontal levels is not a simple line but a circular enveloping one.

The brain drain from Europe to the U.S.A. [LARRAGA, 2003] dislocates the local efforts and allows the launching of new specialities. Considering these implications, this dialectical interaction is developed through research programmes called internal (fundamental theory) vs. external (practical concern, such as cancer) programmes [HOHLFELD, 1983], research strategies determined by practical aims or by theoretical results, the tackling with centripetal or centrifugal problems [MALECKI & OLSZEWSKI, 1980], and the vertical/horizontal principles around which the research integration is organised.

The prerequisites for the holistic conceptualization of the cellular growth cover a hierarchical relationship between research in basic cellular biology and cancer research. A vertical integration between the study of the disrupted conditions of the cellular differentiation and the normal behavior can be assumed. Interpreted in terms of the molecular genetics the tumor induction is a special subject within the cellular growth regulation [WITKOWSKI, 1986].

Likewise, the molecular developmental biology explains the cancer cells as a matter of loss of cell information, if it includes the mutagenic mechanisms [HOHLFELD, 1983]. The programme of molecular biology of the developmental processes is the interaction between the epigenetic and the genetic factors to explain the cascade of the genetics expression. The vertical opening [BONSACK, 1990] serves to interpret the cancer cells as a loss of information content or as a disruption of the biochemical specificity [SMITH & WATERMAN, 1981].

The sphere of interdisciplinary integration [BRAUN & SCHUBERT, 2003] involves a search for methods and information from different fields considering the implications for the description and the level of understanding. One discipline can prevail in the frontier level while the contribution of the other one be complementary. Or else the implication in one field can serve as a method for the other. This horizontal flow can make different fields of basic research coincide. The carriers of genetic information, in the systemic interaction of procaryotic and eucaryotic cells occurs at this level of abstraction [HOHLFELD, 1983]. And both contributions, that of cell biology and that of developmental biology, are equally relevant for the research in molecular genetics, as the history of the theories on cancer confirms.

The strong nonlinearities, the dissipative structure [CURRÁS, 1988] of many of the interdependencies typical of the disciplinary elements in cancer research allow to appreciate the quality of the unified approach. A continuous and homogenous basis seems advisable for the 230 years elapsed since Percival Pott first identified the tumoral lesion, on the basis of the effects of soot on sweat [PELLICER, 2004]. The Spanish studies on the genetic control on the mechanism of biochemical reactions carried out in the USA constitute, from 1927 on, a chapter of these historical vicissitudes [PELLICER, 2005; RODRÍGUEZ OCAÑA, 2005]. The experience of the Spanish Society of Biochemistry and Molecular Biology (SEBBM) is important as a model of organization for many outstanding experts since 1963 [TRIOLO & RIEGEL, 1961].

The *ethos* in the foundation of this group of Spanish biochemists in the USA [CASEY & AL., 2001] seems to have an impact even nowadays in the national groups of biochemical research in Spain. But there is a difference: while nowadays the stress is placed on the appeal of the institutions, the conditions of the Spanish local research from the twenties up to Spain's integration in Europe in 1986 was based on the appeal of the individuals [BOURRET & AL., 2006].

Vertical integration - horizontal integration.-

The study of the development of Science, in itself and in a broad perspective, requires a special dedication and an adequate methodology. And both methods, the vertical integration of science [CURRÁS, 2002], and its horizontal classification, appear to be suitable.

Let's see: The following aspects should be considered in Science

Science, split into basic or "pure" science, applied science and Development-oriented science, results in basic research, practical research and socioeconomic research (Figure 1).

If we consider Science as a unit, an interrelationship could be established among the three types of Science, approached here from a vertical integration viewpoint [CURRÁS, 2002]. That means three columns should be established, each of them made up of each established division, which leads to the fact that a modification in basic science means a modification in basic research. The same thing would apply to the other two columns (Figure 2).

Basic science, in its turn, has an influence on applied science and, as a result, influences development-oriented science. Therefore, a network of joint and mutual interactions is established, studied by the Sistemic Science or Theory of Systems [ATLAN, 1992; BERTALANFFY, 1934].

The horizontal integration of Science can be applied to this particular division of Science carried out by Spanish researchers taking into account its development. In this case they would be considered as superimposed layers, variably positioned, that is, some time basic or fundamental science would occupy the upper part and some other time each of the others would occupy the upper part (Figure 3).

Now, the relationship among these divisions occur horizontally as well as diagonally, which means a repercussion of one's eventual modifications on the others' eventual modifications. Likewise, the rules of the Systemic Science can be applied here to carry out a detailed study of the whole and of each of its parts.

Application to our case study.-

As mentioned in the title of this paper, our study case refers to Spanish scientists that have carried out abroad, focused on those who went to the USA. Among them, those whose researches have been mostly focused on cancer, its variants and characteristics, have been selected.

Three categories have been established: a) those who emigrated and have remained abroad; b) those who left impelled by their wish to innovate, most of whom have returned to Spain; c) those who went abroad in order to carry out their post-doctoral studies, who are the younger ones. Most of them have not returned yet.

The chosen group of 40 researchers has been classified in four categories: 1) Precursors; 2) Founders; 3) Directors (or former directors) of laboratories in the USA; 4) Researchers in their period of post-doctoral studies. Table 1 shows the list of Spanish researchers, distributed in accordance to the classification originally formulated by Ángel Pellicer, New York University School of Medicine [PELLICER, 2005].

When closely studied, Table 1 shows a breakdown into 4 columns, out of which the vertical integration can be built and the relationships among them be established as well. No doubt, there has been a mutual influence among the different categories of researchers. Considering that these types arise as a consequence of the passage of time, the classification itself is the consequence of that very passage of time. The precursors were chronologically previous to the founders, and these ones were previous to those who have been directors of laboratories, who in their turn, are chronologically previous to the post-doc researchers. Consequently, this attempt to establish a vertical integration among the four categories shown in the columns should consider an integration from bigger to minor, which implies introducing the time factor; time factor that implies a path from the oldest to the most recent.

Undoubtedly the researchers who left for the USA in early times have influenced those who went abroad later. Some of the former have become the models to be followed, while others became their senior research fellows, directors of their scientific works or outstanding collaborators.

This suggests the establishment of vertical relationships among the Spanish scientists who have performed their research in the USA, but, logically, not all those chronologically previous have had an influence on all the subsequent scientists. It would be necessary to study case by case. Some examples of direct influence that could be mentioned are Maria Luisa de Ayala, who followed her husband's – Francisco Duran Reynals[a] – lines of research and the outstanding case of Severo Ochoa – Nobel Prize 1959 – who had many followers and was the leading authority for many Spanish researchers internationally renowned nowadays, such as Margarita Salas and Santiago Grisolía.

Should we wish to establish each group's collateral relationships of influence on the other one(s), we should resort to an horizontal mutual integration among the groups. It seems understandable that the horizontal relationships must imply a mutual and reciprocal interaction, so these influences are represented by a two-direction arrow. In practical cases indeed, we know some Spanish scientists were together at the same time at the same laboratory or University, and worked on related subjects, consulted each other and discussed their respective results. This is the case of Mariano Barbacid and Ángel Pellicer at the Columbia University (USA) in 1979; Manuel Perucho coincided with Mariano Barbacid at Columbia University in 1979 as well.

Whether the vertical integration or the horizontal integration of interrelationships among Spanish scientists is applied, the results from the researches performed are always positive. In cancer studies – among others – Joan Massagué must not be forgotten**.** He studied the molecular mechanisms of inhibition or stimulation of cellular growth and was elected as a member of the United States National Academy of Sciences in 2001**.** Carlos Cordón Cardo, whose studies on molecular pathology led to the molecular study of the urinary bladder cancer**,** must also be mentioned. It should be noted that these are only a few examples drawn out of a range of different cases. Table 2

[a] See: T. F. Glick, A. Roca Rosell. Francesco Duran Reynals (Barcelona, 1899 – New Haven, USA, 1958). Virus and cancer : a controversial theory. In: Contributions to science. 1, 1999, pp. 87–98. http://www.cat-science.com/admin/articles/pdf_990101/07_Virus_and_Cancer.pdf

shows the researches performed and the results obtained [CASACUBERTA & ESTANY, 2003; PELLICER, 2004; MORANGE, 1997; WULFF, 1996A; WULFF, 1996B].

Systems science implications.-

The study of the interrelationships among Spanish scientists has been presented considering, on the one hand, a vertical integration among them and, on the other hand, applying the principles of horizontal integration among them as well. But nothing has been said on how to establish these interrelationships and how to proceed. It's here that the Systemic Science, based on the Systems theory but with a greater degree of complexity, plays a role, when a definitely scientific nature is attached to the Theory.

In order neither to complicate nor to make this paper long, and assuming that the principles of the Systemic Science are well-known, it is postulated that the Systemic Science involves the mutual and pluridirectional relationship of all its components. First, the reference system has to be built and the first holon must be established, in other words, the foundation stone or element on which to base the System. In this case we have set the holon at a Spanish scientist, the Nobel Prize Severo Ochoa. Since different groups of scientists have been established, we build as many systems as groups have been formed (data are not shown; operated by HistCite software). Then, by means of the interactions, vectors, flows and refluxes that influence the System, its evolution can be studied, resulting in the holon hierachy shown in Figure 4. The coherence relationships inside it are guaranteed by Severo Ochoa's autonomy and capability, who used his executive capability to present to the United States National Academy of Sciences articles written by authors placed in the holons developed at levels 3 and 4 (two articles, by Santos & Barbacid in 1983, and by Perucho in 1985) and cowriting articles with authors of the holon at the second level (8 articles with M. Salas between 1965 and 1967). Therefore, the acceptability of the results at the 4 holarchical levels, which expresses the capability for coordinated actions and mutual agreement, develops the definition of holon in terms of autonomy and ability to cooperate. The three members of the second holon were trained at Ochoa's laboratory, the five members of the third holon at Salas's and the three members of the fourth holon at Barbacid's. The criterion of subsidiarity among holons at different levels would be, so, the results acceptability.

Table 2 shows the results of the researches performed by Spanish scientists who have developed their scientific task in the USA, on subjects related to cancer. This table cannot be exhaustive, if not for other reason because of the lack of exhaustive data. Nevertheless it shows the efficiency of the Spanish scientists who went to the USA, whose importance should not be disregarded (Figure 4).

Part II. Transatlantic flows of knowledge: Evidence from citations

Introduction.-

The triumphant growth of American science after 1940 has greatly accelerated the importation of scholars from Europe. The emigration history of the Spanish elite in biochemistry towards the USA begins in 1927, when Francisco Duran Reynals moved from the Institut Pasteur in Paris to the Rockefeller Institute in New York, and it became outstanding after Severo Ochoa left the Marine Biological Laboratory in Plymouth and joined the Washington University School of Medicine in 1941. The

departure from Spain of all the other biochemists, founders and developers of the Spanish elite of cancer researchers can only be explained by these precursor personalities' appeal (see Table 1 and Figure 6).

The history of the Spanish biochemists' bastion in the country with the highest scientific development is the history defined by the knowledge circulation it produces, as well as that of this community's stratification, its social structure [COLE & COLE, 1973]. For the purposes of this paper we define "social structure" as the strong ties created throughout the research career (obtention of the Bachelor and Doctorate degrees, post-doctorate options) and the mobility dynamics (departure from Spain towards Europe/USA and return to Spain). Figure 6 shows the network of geographical displacements, a general image of this social structure.

Occasionally, the "older" scientists' first publications are not in the databases, and their C.V. are not always available on the internet. That's why the use of bibliometric methods seems to be appropriate to identify a scientist's international mobility in the first instance [LAUDEL, 2003; PIERSON & COTGREAVE, 2000]**.** Table 3 shows the citations data for the whole universe of the 40 elite scientist studied.

Two recent contributions [PELLICER, 2005; PELLICER, 2004] highlight the importance of Spanish biochemists who moved to the USA in order to attend regular university courses there**.** The first one was Marino Martínez Carrión in 1959. Other Spanish doctorates at the universities of Bolonia (Izpisúa in 1987) and Heidelberg (Muñoz in 1995) also moved to the USA after the integration of Spain in Europe in 1986.

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Our analysis starts with two questions: who exactly have been the Spanish elite biochemists in the USA over the last 80 years (1927–2006)? what is the knowledge circulation on cancer they have produced like? In this specific historical case we have built our work upon a recent contribution on the history of the SEBBM (Spanish Society of Biochemistry and Molecular Biology) **[**PELLICER, 2005], a prosopographical description written with a close knowledge of the basis of the Spanish biochemists network in the USA which codes a set of 40 biographies in four types of relations: (a) the initiation relationship type – the precursors (five biographies); (b) the basical relationship type – the founders (five biographies); (c) the "political" relationship type –heading laboratories in the USA (twenty biographies); (d) the "developmental" relationship type – the young researchers who are at the initial stage of their careers in the USA (ten biographies).

Quantitative evidences.-

The 40 emigrated Spanish biochemists have produced a total of 7,187 pieces of work (see Table 1) in the period 1927–2006. Their professional careers have been

brilliant enough to produce a great number of citable publications. The best pattern to get to the historical background of these documents is to arrange the citations that each article has got chronologically in descending order, from most recent to oldest. For the long-term study [TRIST, 1973] this method highlights the most recent usefulness of the information stored in the library of the Spanish scholars and offers a broader basis for the retrospective vision. A span of the present in order to detect the roots in the past.

A total of 194131 citations quoted by 70711 authors can be ascribed to these 40 scientists and researchers between 1927 and 2006. The average number of citations was 725 (see Table 3) and the median was 1173 per member of Group I (the precursors, who arrived in the U.S. between 1927 and 1953) The average number of citations for Group II (the founders, 1945–1959) is 1812 and a median of 2275, while for Group III, heads of laboratory (1971–1993), the average number of citations was 1999.7 and the median 2429. Lastly, for Group IV, made up of scientist in the initial stages of their careers (1988–1996), the average was 1829 and the median 1659.

Although both the number of journals on biochemistry and the number of biochemists have increased fast between 1945 and 1988, the average number of citations ascribed to each author remains almost unalterable. The association among Groups II, III and IV is significant, with F= 69. These three adjacent time intervals (1945–1959), (1971–1993), (1988–1996) are very much alike. The prolific perseverance in publishing and the acknowledgement through the citations reflect the steady encouragement that research and publication are given in the North American universities.

A substantial difference exists for the initial period (1927–1953), because F = 0.2 for the four groups. The emigrated scholars, precursors of the biochemistry research carried out by Spaniards in the U.S., were born between 1899 and 1911 (see Figure 5). The production frontier, defined by the fitting line, reveals two of the precursors as "outliers" on the right side of the graph. One (Grande Covián) suffered political reprisals until 1950, hence the isolation effect shown on the lower right part of Figure 5 [LLAVONA & BANDRÉS, 2003]**.** The other one, Nobel Prize Severo Ochoa, appears on the right upper side emphasizing the strength of his intellectual contribution in terms of citations and his slower depreciation through time (Figure 5).

Table 3 shows that the percentage scheme of acknowledgement follows the same model for the four groups as far as the origin of the citations is concerned. The U.S.A. acknowledge the Spaniards in 42% of the occurrences, Spain acknowledges them in 4.5%, and the rest of Europe in 33%. Similarly, the difference in the acknowledgement patterns[b] between the authors who returned to Spain (647/67/449) and those who remained in the U.S.A. (848/63/669) is not statistically significant (F = 0.21). For cancer research the knowledge circulation is as follows: 831/54/586. This pattern seems to be very similar to the one identified for the authors that remained in the USA Indeed, 80% of the Spanish cancer researchers have not returned to Spain.

However, some outstanding differences appear when the demography of the scientific authorship is considered. If the university where they have written their PhD (doctoral dissertation) is the criterion, the maximum citation rate corresponds to those authors who have presented their dissertations in European, non-Spanish universities (866/69/635), followed by those whose dissertations have been presented in Spain**,** while those who presented their dissertations in the USA come last (649/44/588).

[b] The acknowledgment pattern is expressed as the average number of citations per sample member; the USA, Spain and the rest of Europe, respectively.

Therefore, the Spanish biochemists' research crystallizes in a professional brain drain model towards the USA. This brain drain model favors the circulation of Doctors in Europe and gives precedence to national doctoral diplomas obtained in Spain**,** while preference to the USA framework for the obtention of the Doctorate degree is only given last. It must be noted that the first member of this group of Spanish biochemists to present his dissertation in the USA was Joan Oró in 1956 at the Houston University, and the first biochemist ever to attend regular university courses there was Marino Martínez Carrión in 1959.

It must also be emphasized that the results in the USA of a Spanish scientist's work (Mariano Barbacid, 1021/118/730) have obtained the highest European award for cancer studies in 1988[c] (the Dr. Josef Steiner Cancer Research Foundation Award, University of Basel, Switzerland). Later, in the course of the 'European Neuroscience Association' 17th annual meeting in Vienna 1994, Barbacid was awarded the 'Neuronal Plasticity Prize' of 'La Fondation Ipsen' for being the first to identify and clone the trk oncogene [WULFF, 2006].

It seems quite natural to try and single out the scientists exiled and purged after the Spanish Civil War (1936–1939) when studying this period. Their average citation rates are the lowest (432/21/401). In all the cases Spain's loss of scientific relevance did have an influence on all of these authors. The reasons for their international mobility did not prevent them from returning to Spain (Francisco Grande Covián) nor from becoming members of prestigious groups like the U.S. National Academics of Science (Pedro Cuatrecasas).

The election to this honorary position (the U.S. National Academics of Science membership) of two of these Spanish emigrated scientists (Pedro Cuatrecasas, Joan Masssagué) is remarkable because number of citations they receive is indeed out of the ordinary: a quarter of the total acknowledgement obtained by the emigrated biochemists. These high productivities – which suggest that the displacement to a new environment develops the abilities they previously had – affect equally both a scientist coming from the exile (Cuatrecasas) and one who received his degree at a Spanish university in the seventies (Massagué).

The number of American institutions that have hosted them over these 80 years 1927–2006, grew to reach at least 27. As Figure 6 shows, there were eight Spanish Centres able to project their post-doctoral training in the USA (on the left side of Figure 6) for the studied sample of biochemists over this period. And the percentage expression [NALIMOV, 1981] ascribes 40% of that creativity to the Barcelona campus, 22% to the Valencia campus and 14% to the Madrid campus. At least 11 Spanish institutions receive the influence of the biochemistry research carried out by these emigrated scientists in the United States (in Figure 6 from right to left). Only in 35% of the cases is recorded the return of the scientists to Spain. The rest of the data merely indicate incidental cooperations conducted by Spanish biochemists in the U.S.A. with Spain. The CSIC, a separate body independent from the Universities, appears interested in favoring the access abroad and facilitates the return mobility (Figure 6).

Conclusions.-

Throughout this paper we have advanced that the Spanish scientific emigration to the USA has been segmented by economic and innovation reasons, as well as by the

[c] Dr. Josef Steiner Krebsstiftung. Laureates 1988.
http://www.steinerstiftung.unibe.ch/pdf/krebsforschungspreis1988.aspx

continuation of post-doctoral studies. The available empirical work [SZELÉNYI, 2003; GARCÍA-ROMERO & MODREGO, 2001] indicates that about 30% of the Life Sciences doctorates in the USA were awarded to candidates from other countries. Furthermore, 47% of those who received their doctorate either in 1972 or in 1990 were still in the USA in 1995, which means these are long-term migratory flows.

The first part of this paper considers the homology among the cancer research object, the mobility organization of the Spanish scientists working on it in the USA and the visibility of the results that they obtain. The history of this mobility has been developed using the vertical/horizontal integration of science from the systemic point of view [CURRÁS, 2002].

A group of 40 emigrated biochemists has been split into four columns, vertically displayed in order to introduce the time factor. This vertical influence has allowed to differentiate chronologically among precursors, founders, directors and post-doctoral researchers. The interest of the horizontal integration has been highlighted in the case of the Spanish research on oncogenes, because the same scientists have coincided in the same laboratories in Spain and in the USA. The holon-hierarchical identity of the Spanish research on cancer in the USA has been studied with systemic estimation criteria and the main discoveries and contributions over the period 1927–2006 have been pointed out.

In the second part we have studied in depth the scientific careers of 40 European scientists who emigrated to the USA, some of whom eventually returned to their country of origin, Spain. The recount of average citations received by the Spanish biochemists arrived in the USA between 1927 and 1953, 1945 and 1959, 1971 and 1993, 1988 and 1996 has been made. The geographical origin of the citations (USA, Spain, Rest of Europe, Rest of America, Asia, Oceania, and Africa) and the emigration have been the parameters considered. The effects of isolation and centrality of the emigrated scholars' scientific production have been analyzed (as a function of their age) and the topography of the knowledge circulation on cancer produced by them has been paid special attention. The demography of the scientific authorship and the model of professional brain drain towards the USA, on the basis of the universities where they had presented their dissertations (in Spain, in the rest of Europe or in the USA), has been highlighted. The election of emigrated scientists to outstanding positions (such as the membership of the US National Academy of Sciences) has also been considered. Lastly, the relationship between the research institutions involved in the USA and in Spain has been outlined and the most creative Spanish campuses in terms of mobility and the return of the scientists to their home country have been described.

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References.-

ALLEN, G.E. (2004), A pact with the embryo : Viktor Hamburger, holistic and mechanistic philosophy in the development of neuroembryology, 1927–1955, *Journal of the History of Biology*, 37 : 421–475.
ANON. (1974), Does cancer research have realistic aims?, *Nature*, 249 : 299–300.
ATLAN, H. (1992), *L'organisation Biologique et la Théorie de l'Information.* Hermann, Paris.
AUBENQUE, P. (1972), *Le Problème de l'Être chez Aristote : Essai sur la Problématique Aristotélicienne*, Presses Universitaires de France, Paris.
BERTALANFFY, L. VON. (1934), *Teoría del Desarrollo Biológico: Introducción a la Biología Teórica*, Universidad Nacional de La Plata, Buenos Aires.
BONSACK, F. (1990), Ouverture vertical et ouverture horizontale, *Bulletin de l'Association Ferdinand Gonseth*, 55 : 4–5.
BOURRET, P., MOGOUTOV, A., JULIAN-REYNIER, C., CAMBROSIO A. (2006), A new clinical collective for French cancer genetics: A heterogeneous mapping analysis, *Science, Technology, & Human Values*, 31 (4) : 431–464.
BRAUN, T., SCHUBERT, A. (2003), A quantitative view on the coming of age of interdisciplinarity in the sciences 1980–1999, *Scientometrics*, 58 (1) : 183–189.
CASACUBERTA, D., ESTANY, A. (2003), *¿Eureka?: El Trasfondo de un Descubrimiento sobre el Cáncer y la Genética Molecular*, Tusquets, Barcelona.
CASEY, T., MAHROUM, S., DUCATEL, K., BARRÉ, R. (2001), *The Mobility of Academic Researchers: Academic Careers & Recruitment in ICT and Biotechnology*, IPTS, Seville.http://www.jrc.es/home/pages/detail.cfm?prs=728
COLE, J. R., COLE, S. (1973), *Social Stratification in Science*, University of Chicago, Chicago,
CONI, N. (2002), Medicine and the Spanish Civil War, *Journal of the Royal Society of Medicine*, 95 : 147–150.
CURRÁS, E. (1988), Implicaciones de la teoría de sistemas. In: E. CURRÁS, *La Información en sus Nuevos Aspectos: Ciencias de la Documentación*. Madrid, Paraninfo, 1988, pp.140–169.
CURRÁS, E. (2002), Vertical integration of sciences: an approach to a different view of knowledge organization, *Journal of Information Science*, 28 (5) : 417–426.
DEDIJER, S. (1964), Migration of scientists: a world-wide phenomenon and problem, *Nature*, 201 (4923) : 964–967.
DULBECCO, R. (1976), From the molecular biology of oncogenic DNA viruses to cancer, *Science*, 192 : 437–440.
GARCÍA-ROMERO, A., MODREGO, A. (2001). *Research Training in Spain: An Assessment Exercise*. European Commission. ftp://ftp.cordis.europa.eu/pub/improving/docs/ser_conf_bench_garcia-Romero.Pdf
GISH, O., WILSON, J. A. (1970). Emigrating British physicians, *Social Studies & Medicine*, 3 : 495–511.
GORANSON, T. (1998), Mailing Received on Sat Sep 26 17:54:41. http://fis.icts.sbg.ac.at/mailings/0148.html
HOHLFELD, R. (1983). Cancer research. A study of praxis-related theoretical developments in chemistry, the biosciences and medicine. In: W. SCHÄFER (Ed.), *Finalization in Science: The Social Orientation of Scientific Progress*, D. Reidel Publishing Company, pp. 93–126.
KISELEV, F. L. (1990), Molecular oncology. In: R. V. PETROV (Ed.), *Medical Dimensions of Molecular Biology*, Nauka, 1990.

KOHLER, R. E. (1973), The enzyme theory and the origin of biochemistry, *Isis*, 64 (222) : 181–196.
LARRAGA, V. E. (2003), La pérdida de talentos científicos en. España, DT 22/2003, Fundación Alternativas, Madrid, 2003. http://www.falternativas.org/base/download/07b2_08-09-05_22_2003.pdf
LAUDEL, G. (2003), Studying the brain drain : can bibliometric methods help?, *Scientometrics*, 57 (2) : 215–237.
LLAVONA, R., BANDRÉS, J. (2003), Francisco Grande Covián y la psicología, *Psicothema*, 15 (3) : 345–351. http://www.psicothema.com/psicothema.asp?ID=1071
MALECKY, I., OLSZEWSKI, E. (1980), Regularities in the development of contemporary science. In: B. BARNES (Ed.), *Estudios Sobre Sociología de la Ciencia: Regularidades en el Desarrollo de la Ciencia Contemporánea*. Alianza, 1980. (originally published by: *Organon*, vol 13, pp. 193–212.)
MARRA, G., BOLAND, C. R. (1995), Hereditary nonpolyposis colorectal cancer: the syndrome, the genes, and historical perspectives, *Journal of the National Cancer Institute*, 87 (15) : 1114–1125.
MEYER, S. C. (2004), The origin of biological information and the higher taxonomic categories, *Proceedings of the Biological Society of Washington*, 117 (2) : 213–239.
MORANGE, M. (1997), From the regulatory vision of cancer to the oncogene paradigm, 1975–1985, *Journal of the History of Biology*, 30 : 1–29.
NALIMOV, V. V. (1981), *Faces to Science*, ISI Press, Philadelphia, p.250.
PELLICER, À. (2005), Bases moleculars del càncer. In: Díssetè Congrés de Metges i Biòlegs de Llengua Catalana. Fundació Alsina i Bofill, pp. 15–28. http://taller.iec.cat/cmibllc/fons/17/17.01.005.pdf
PELLICER, Á. (2004), Contribución de los científicos españoles n Estados Unidos a la bioquímica. In: E. MUÑOZ (Dir.), *Cuarenta Años de la Sociedad Española de Bioquímica y Biología Molecular*. Sociedad Estatal de Conmemoraciones Culturales, pp. 227–248.
PIERSON, A. S., COTGREAVE, P. (2000), Citation figures suggest that the UK brain drain is a genuine problem, *Nature*, 407 (6800) : 13.
PRICE, D. J. S. (1965), The scientific foundations of science policy, *Nature*, 206 (4981) : 233–238.
RODRÍGUEZ-OCAÑA, E. (2005), E. MUÑOZ (dir.), M. J. SANTESMASES, A. ROMERO, J. ÁVILA (Eds). Cuarenta años de la Sociedad Española de Bioquímica y Biología Molecular (1963–2003), Madrid, Sociedad Estatal de Conmemoraciones Culturales, S.A., 2004, 362 pp. ISBN: 84-95486-79-02., *Dynamis. Acta Hisp. Med. Sci. Hist. Illus.*, 25 : 576–578. (Review.)
SCHERER, F. M. (2000), The emigration of German-speaking economists after 1933, *Journal of Economic Literature*, XXXVIII : 614–626.
SHIMKIN, M. B. (1974), History of cancer research : a starter reading list and guide, *Cancer Research*, 34 : 1519–1520.
SMITH, T. F., WATERMAN, M. S. (1981), Overlapping genes and information theory, *Journal of Theoretical Biology*, 91 : 379–380.
STICHWEH, R. (2000), Systems theory as an alternative to action theory? The rise of ‘communication’ as a theoretical option, *Acta Sociologica*, 43 (1) : 5–13.
STOKER, M. (1975), Limits to oncology, *Nature*, 254 : 547–548.
SZELÉNYI, K. (2003), Explaining the migration and settlement of foreign graduate students : global integration theory and the theory of cumulative causation, UCLA Center for Comparative and Global Research. http://www.international.ucla.edu/cms/files/katipaper.doc

TRIOLO, V. A., RIEGEL, I. L. (1961), The American Association for Cancer Research, 1907–1940. Historical review, *Cancer Research*, 21 (2) : 137–167.
TRIST, E. (1973), *Organizaçao e Financiamento da Investigaçao*, Livraria Bertrand, Lisboa.
WITKOWSKI, J. A. (1986), Somatic cell hybrids : a fusion of biochemistry, cell biology and genetics, *Trends in Biochemistry Sciences*, 11 : 149–152.
WULFF, E. (1996A), Historia del descubrimiento del orígen de la formación de los tumores : el programa del Dr. Barbacid en los albores de los estudios sobre oncogénesis, *Llull*, 19 : 525–549.
WULFF, E. (1996B), The natural history of the discovery of hereditary carcinogenesis of the colon – Scientific dynamics in information flow, *Arbor*, CLIV (608) : 9–31. [In Spanish.]
WULFF, E. (2006), La familia trk de receptores de las neurotrofinas y el receptor p75, un caso de caracterización de hipótesis múltiples en la historia del factor de crecimiento nervioso (NGF). In: Actas IX Congreso de la Sociedad Española de Historia de las Ciencias y de las Técnicas. Cádiz.
ZUCKERKANDL, E., PAULING, L. (1965), Molecules as documents of evolutionary history, *Journal of Theoretical Biology*, 8 (2) : 357–366. http://profiles.nlm.nih.gov/MM/B/B/N/V/_/mmbbnv.pdf

FIGURES AND TABLES

Figure 1. Science as unity.

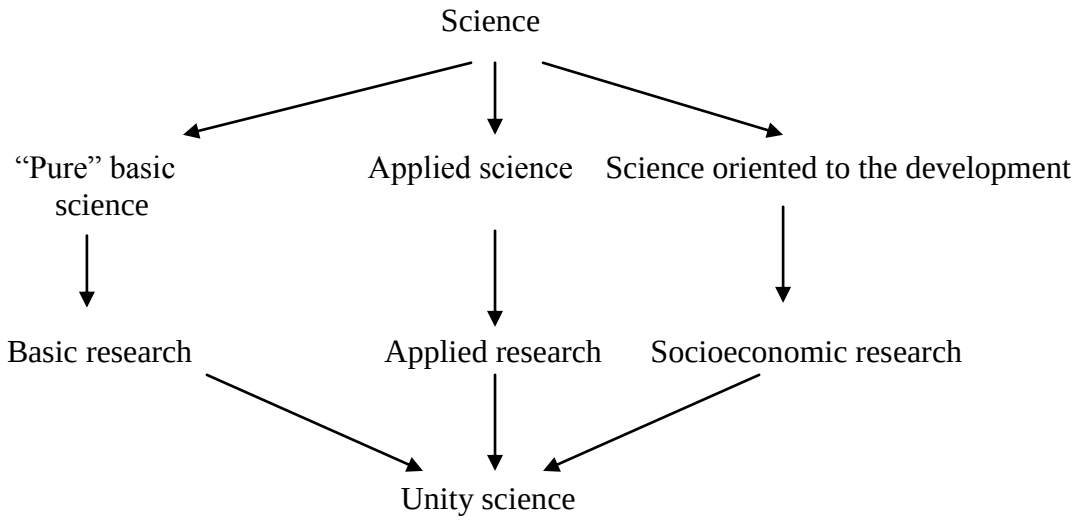


Figure 2. Vertical integration of science.

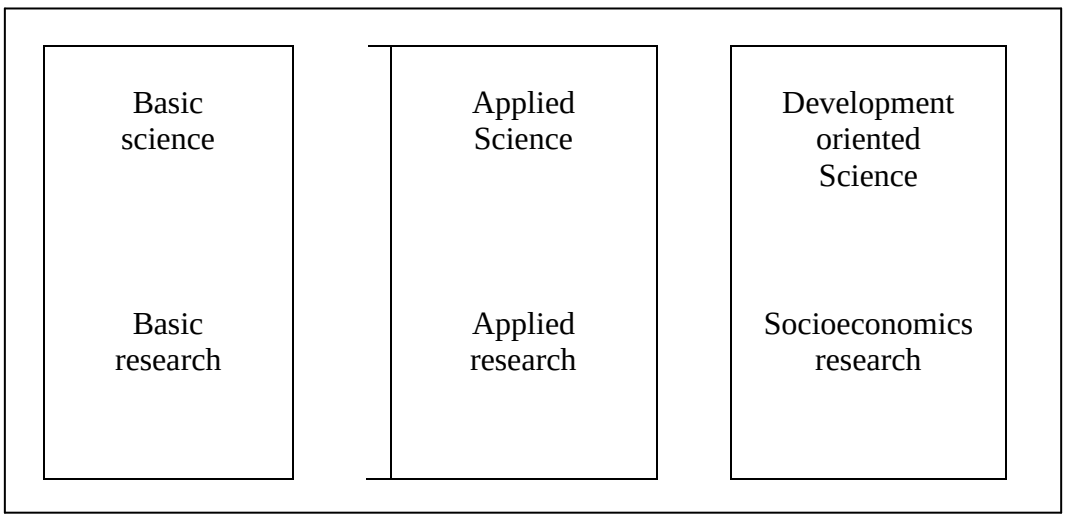


Figure 3. Horizontal integration of the science.

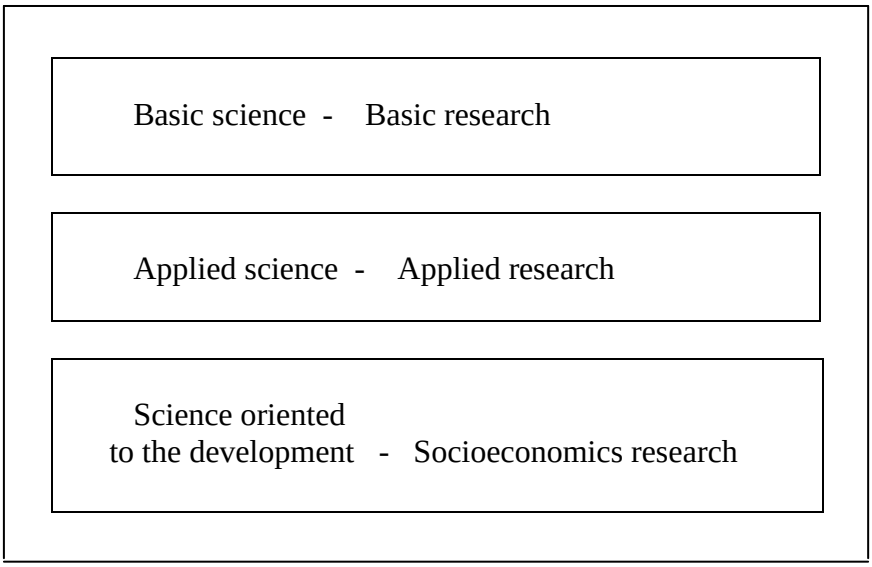
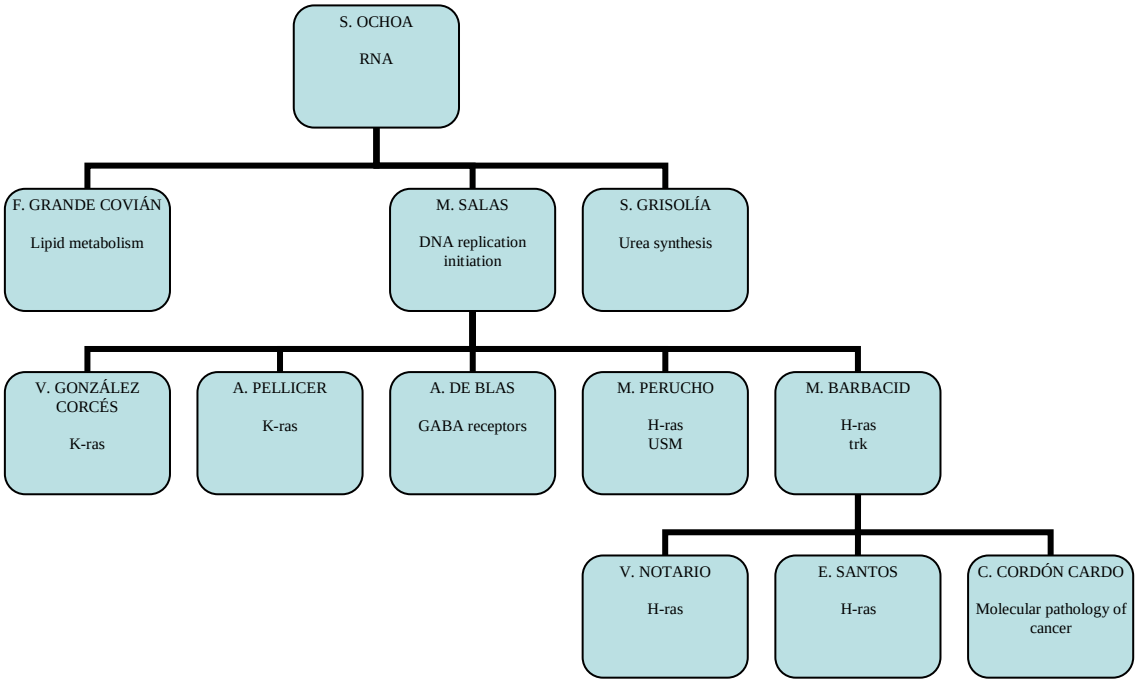


Figure 4. Holon-hierarchical identity of the cancer research, by spanish scientists in the USA. [d]



[d] Abbreviations: RNA.- ribonucleic acid; ADN.- deoxyribonucleic acid; K-ras.- Kirsten rat sarcoma 2 viral oncogene homolog; GABA.- gamma-aminobutyric acid; USM.- Ubiquitous somatic mutations; H-ras.- Harvey rat sarcoma viral oncogene homolog; trk.- tyrosine kinase.

Figure 5. – (Scherer FM, 2000)
Plot of Citation Counts (Y Axis) Against the Age of 14 Spanish biochemists emigrated to the USA (X Axis), in logarithm expression.
Severo Ochoa (58, 4), Grande Covián (54,1.4), Cuatrecases (27, 4.15) y Martínez Carrión (27, 2.58) son "outliers".

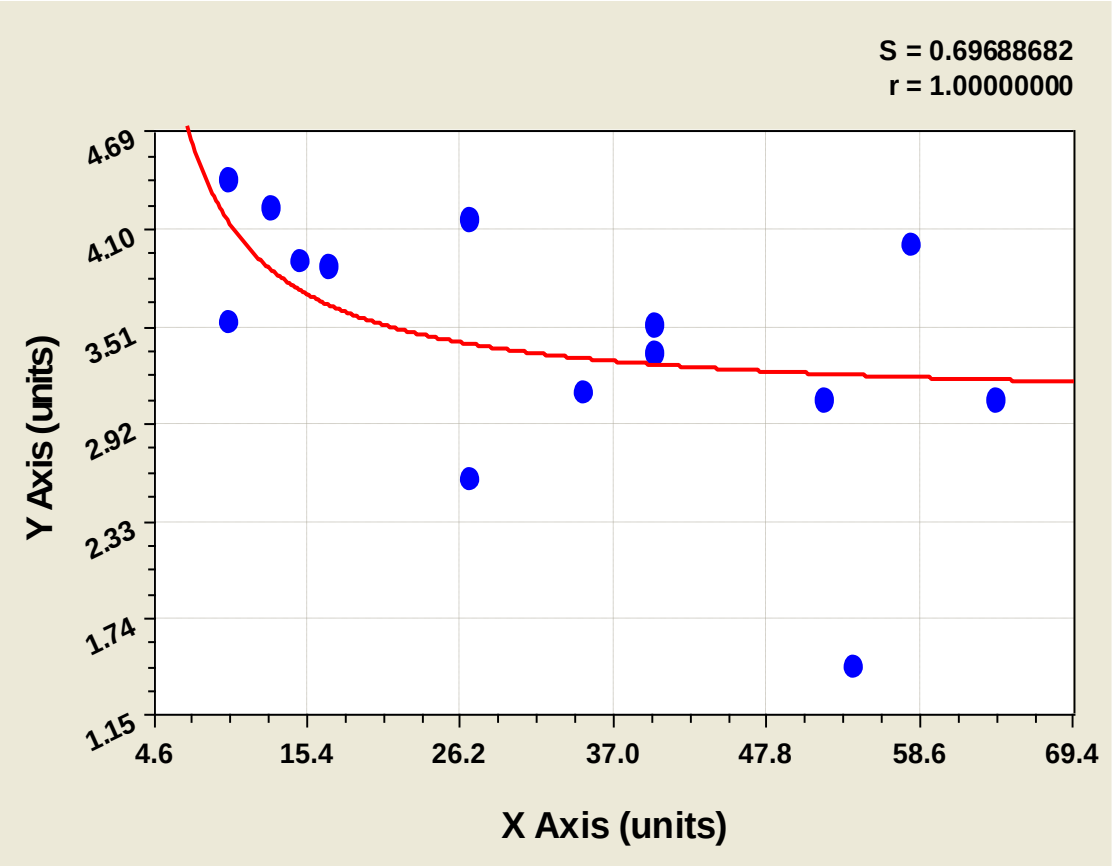


Figure 6.- Network of institutions towards the USA system and, return mobility. (1927-2006)

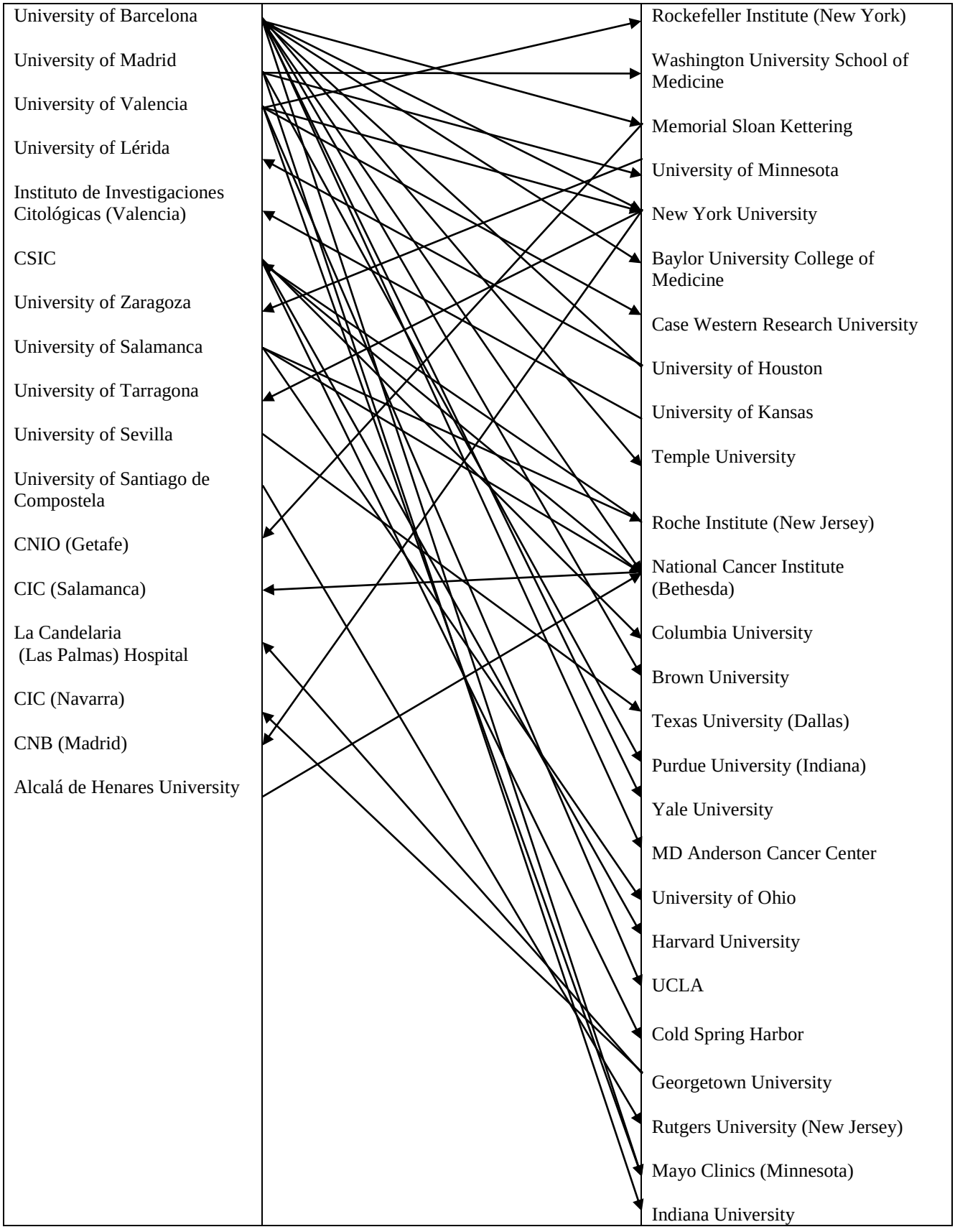


Table I. Spanish biochemists, emigrated to the USA, 1927-2006.

Name	Location (Most permanent address.]	In the USA
PRECURSORS		
Francisco Duran Reynals	Yale University Department of Pathology and Bacteriology	1938-1958.
Maria Luisa de Ayala	Albert Einstein College of Medicine	? -1986
Jordi Folch i Pi	Harvard University School of Medicine	1936-1979
Severo Ochoa	New York University School of Medicine	1942-1985.
Francisco Grande Covián	University of Minnesota	1953-1979
FOUNDERS		
Santiago Grisolía	University of Kansas	1945-1976
Joan Oró	University of Houston	1952-1994
Carlos Villar-Palasí	University of Virginia	1955-2003
Pedro Cuatrecasas	Johns Hopkins University	1948-
Marino Martínez-Carrión	University of Kansas	1959? -2001
LABO. DIRECTORS		
Mariano Barbacid	Bristol Myers-Squibb Pharmaceutical Research Institute in Princeton, New Jersey	1974-1998
Ángel Pellicer	New York University School of Medicine, Dpt Pathology	1976-
Manuel Perucho	Burnham Institute La Jolla, California.	1979-
Joan Massagué **http://www.garfield.library.upenn.edu/histcomp/massague-j_auth/**	Memorial Sloan-Kettering Cancer Center, New York	1979-
Eugenio Santos	National Cancer Institute, NIH, Bethesda, Maryland	1978-1999
Vicente Notario	Georgetown University, Washington D.C.	1982-
Gabriel Núñez	University of Michigan	1978-
Álvaro Puga	University of Cincinnati	1972-
Carlos Cordón-Cardo	Memorial Sloan-Kettering Cancer Center	1980-
José Costa	Yale University, School of Medicine, New Heaven	1980-
Pedro Gastón	The State University of New Jersey (Newark), School of Medicine	1975-1999
Bernardo Nadal Ginard	Harvard University, Dpt of Cellular and	1975-

	Molecular Biology	
Miguel Coca Prados	Yale University, Ophthalmology & Visual Science Department	1977-
Víctor González Corces	Johns Hopkins University, Department of Biology.	1982-
Juan Carlos Izpisúa Belmonte	Salk Institute for Biological Studies, San Diego	1993-
Mariano Estebán	State University of New Cork (Downstate), Biochemistry Department	1975-1992
Valentín Fuster	Mount Sinai Medical Center (New York)	1971-
Juan José Badimón	Mount Sinai Medical Center (New York)	1981
Ángel Luis de Blas	University of Connecticut (Storss), Physiology & Neurobiology Dpt.	1978-
INITIAL STAGE		
Víctor Muñoz	University of Maryland, Dpt. Of Chemistry and Biochemistry	1996-
Serafín Piñol-Roma	Mount Sinai School of Medicine, Department of Biochemistry and Molecular Biology.	1990•-
Gregorio Gil	Virginia Commonwealth University-Medical College of Virginia	1988-
Xavier Graña	Temple University School of Medicine, Biochemistry Dpt.	1992•-
Áriel Ruiz i Altaba	New York University Medical Center, Department of Cell Biology (Skirball).	1989+-
Juan Botas	Baylor College of Medicine (Houston), Departments of Molecular and Human Genetics and Molecular & Cellular Biology	1986•-
Rafael Yuste	Columbia University, Dpt of Biology.	1991•-
Sofía Casares	Mount Sinai School of Medicine, Immunobiology Center	1993-
Juan Carlos de la Torre	Scripps Research Institute, Virology Division	1985•-
Adolfo García-Sastre	Mount Sinai School of Medicine, Microbiology Dpt.	1997•

• Source: internet

+ http://www.med.nyu.edu/people/A.RuiziAltaba.html

Table II. Spanish discoveries and contributions in the USA to cancer research (1927-2006)

Duran Reynals F, 1928.	Hyalurodinase discovery, or Reynals factor of infection diffusion discovery.
Duran Reynals ML, 1980.	Maternal resistance factor to the leukaemia virus.
Perucho M, 1982.	Human oncogene first isolation (T-24), nowadays called H-ras.
Santos E & Barbacid M, 1982.	ras oncogene mutation point conferring malignant properties to their genomic product identification.
De Blás AL, 1983.	Isolation of the endogenous benzodiazepines.
Pellicer A & González Corcés V, 1984.	K-ras oncogene gamma radiation activation.
Perucho M, 1985.	New diagnostical method of the expression levels of the ras oncogenes in human tumors.
Barbacid M, 1986.	Identification of the trk oncogen as the receptor for the Nerve Growth Factor (NGF).
Massagué J, 1986.	Discovery of the signallement mechanisms by TGF-beta of the cell growth and differentiation factors.
Perucho M, 1992.	Discovery of the mutator phenotype responsible of the colon cancer.
Núñez G, 1993.	Isolation of the gene gel-x, dominant regulator of the apoptodic cellular death.

Table III.- AVERAGE CITATION COUNTS FOR GROUPS. [e]

A Citations origins

	Group I	Group II	Group III	Group IV
USA	298 (41%)	719 (39.6%)	889.9 (44.5%)	814.3 (44.5%)
Spain	30 (4.1%)	75.2 (4.1%)	54.4 (2.7%)	80.1 (4.3%)
Rest of Europe	216 (29%)	635.8 (35%)	678.6 (33.9%)	628.2 (34.3%)
Rest of America	522 (7.2%)	112.8 (6.2%)	96.5 (4.8%)	83.1 (4.5%)
Asia	112 (15%)	223.2 (12.3%)	239.9 (11.9%)	190.3 (10.4%)
Australian Continent	12 (1.3%)	38 (2%)	36.6 (1.8%)	30.4 (1.6%)
África	6 (0.8%)	8.2 (0.4%)	3.7 (0.1%)	3.2 (0.1%)

B Emigration destination

	Authors who returned to Spain[f]	Authors who remained in the USA[g]
USA	647.8 (45%)	848.1 (43.5%)
Spain	67.6 (4.7%)	63.3 (3.2%)
Rest of Europe	449.8 (31.2%)	669.2 (34.3%)
Rest of America	73.5 (5.1%)	98.2 (5%)
Asia	173.1 (12%)	229.3 (11.7%)
Australian Continent	21.6 (1.5%)	35.7 (1.8%)
Africa	4.1 (0.3%)	4.75 (0.2%)

[e] Only are reckoned those citations received by the publications of the period in which the authors were in the USA.

[f] Authors who returned to Spain (Grande Covián, Grisolía, Barbacid, Santos, Esteban, Gascón).

[g] Authors who remained in the USA (Duran Reynals, Ayala, Folch i Pi, Ochoa, Oró, Villar Palasí, Cuatrecasas, Martínez Casas, Pellicer, Perucho, Massagué, Notario, Núñez, Puga, Cordón Cardo, Costa, Pérez Soler, Nadal Ginard, Coca Prados, González Corces, Izpisúa Belmonte, Fuster, Badimón, de Blas, Muñoz, Piñol Roma, Gil, Graña, Ruiz i Altaba, Botas, Yuste, Casares, de la Torre, García Sastre).