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Enrique Wulff Barreiro. Historia del descubrimiento del origen de la formación de los tumores: el programa del Dr. Barbacid en los albores de los estudios sobre oncogenes. LLULL : boletín de la Sociedad Española de Historia de las Ciencias, 1996, 19 (37), pp.525-549. <hal-01244232>

HAL Id: hal-01244232

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Submitted on 23 Jun 2022

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HISTORY OF THE DISCOVERY OF THE ORIGIN OF THE FORMATION OF TUMORS: THE PROGRAM OF DR. BARBACID AT THE DAWN OF STUDIES ON ONCOGENES

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ABSTRACT

In recent History of Science a controversy has been developed on the origins of the research on oncogenes, as a new discipline, due to the concession of the Dr. Josef Steiner Cancer Research Foundation Award, in 1988, to Dr. Barbacid, in view of the winners of the 1989 Nobel Prize in Medicine or Physiology. The history of this case is approached through a sociological view, namely the professional anticipationism. The documentary method, always present in cancer research (as it was the case when the Li-Fraumeni syndrome was determined), is able to recognize the new ideas and its degree of elaboration, from a historical perspective.

We supply a periodization of the discovery of the scientific fact that initiates the tumor formation. And we afford the phases of the elementary discoveries encapsulated in the history of the scientific program, using a historiographical typology own to citation analysis. We understand the natural history of the case studying theoretically the demographic structure of the population of the Spanish scientific authors participating in this scientific research.

Keywords: Genetics, Historiography, Medicine, Bibliometry Spain, 20th century

INTRODUCTION

Discovery in medicine often presents priority problems; Barbacid and Pellicer were anticipated in the 1989 Nobel Prize in Physiology or Medicine by other US scientists who were also working on oncogenes [1].

Mariano Barbacid received the award from the Dr Josef Steiner Foundation of the University of Bern, considered by the scientific community as the highest award in cancer research, in 1988. Verbatim can be read in the book that the Institute publishes in order to point out the merits of its laureates that Dr. Barbacid is rewarded for "providing evidence that the interaction of a carcinogen with a ras proto-oncogene causes the event that leads to initiation of tumor formation" [2].

In 1989 the Nobel Prize in Physiology or Medicine was awarded for the discovery that animal tumor oncogenes are derived from cellular genes (proto-oncogenes) [8]. In short, due to the discovery that normal cells contain genes that can cause cancer if they are altered [16]. This statement contrasts with the fact that the first experimental evidence indicating that human proto-oncogenes could be activated as oncogenes in certain human tumor cell lines was obtained by Weinberg, Cooper and colleagues [21, 27].

The Nobel committee credited the article (Stéhelin, 1976) [23] published in the journal *Nature*, where the prize winners reported the presence of DNA closely related to the *src* oncogene of avian sarcoma viruses as part of the total genetic endowment of chickens [8]. In one of his few mentions of this work, M. Barbacid understands that this understanding of the cellular origin of some of the viral oncogenes alerted scientists to the possibility that related oncogenes also existed in non-viral induced neoplasms [22].

It is an anecdote but it is worth remembering that D. Stéhelin [23] led a loud discussion with the winners of the 1989 Nobel Prize. This scientist, of French nationality, while pretending to share the 1989 Nobel Prize, suffered the disavowal of the director of the CNRS [9]. M. Barbacid and A. Pellicer in 1983 and 1984 revealed the role of ras oncogene activation in human neoplasia. The first studied the activation of ras oncogenes by N-nitroso-N-methylurea chemical induction of breast cancer in rats [24]. The second one obtained a similar result using gamma irradiation of brain and thymus lymphomas also in rats [25]. Both used carcinogen-activated ras oncogenes with the same type of mutations in action as in human

tumors [26]. Both authors found that the mutation responsible for malignant activation is the replacement of glycine with aspartic acid in the exon sequence.

The Spanish team with which M. Barbacid posed the question that led him to establish the molecular basis of human neoplasia was formed by E. Santos, D. Martín Zanca, and V. Notario [See, in the bibliographical Appendix, the reference numbers 2, 3, 5, 11, 12, 13, 14 and 15]. The group of Spanish researchers who worked with A. Pellicer, involved in this deciphering of the processes of human carcinogenesis, was made up of I. Guerrero, V. Corces, P. Calzada and A. Villasante [See Bibliographic Appendix No. 4 and 17]. M. Perucho, working with a team that included, as Spanish collaborators, C. Almoguera, C. Lama and J. Jordano, proposed the characterization of human and murine cellular oncogenes and provided a method to detect mutations in transcribed genes [See Bibliographical Appendix numbers 1, 6, 8, 9, 10 and 16].

The personal relationship with Nobel Prize laureates guarantees visibility closer to that of scientific eminence [3]. M. Barbacid, A. Pellicer and M. Perucho were disciples of Severo Ochoa, and the fact of working with a Nobel laureate has meant, in the history of the award, a greater number of award concessions and a younger age in those who received it [3]. The US government owns the royalties and the licenses for the use of the scientific results of these three Spanish researchers. The winners of the 1989 Nobel Prize represent a second literature that makes its way towards the award by making use, in terms of scientific policy, of practices specific to the management of the transfer of scientific results [20]. The pioneering nature of the work of these Spanish researchers, in a highly specialized area, exposes it, in contact with the stratification of science that existed in the US at the beginning of the eighties, to the fragmentation that awaits any innovative idea, when the conditions for eponymic claim are not strong enough. And the guarantee implied by the presentation of these works to the US National Academy of Sciences by Ochoa [See Bibliographic Appendix, item N°13, and N°17], was not effective. A reference to M. Barbacid, within the US, has the character of a commemorative practice; being named in the course of speeches and official celebrations [18]. The authority of the scientist M. Barbacid, after the award of the Nobel Prize, is a thing of those laureates who both have been successively directors of the National Institutes of Health, after the award of the prize. The award-winning research program "imports" the discoveries of the program that has remained at the gates of the Nobel committee, and sets the guidelines for the dissemination of the scientific activity of M. Barbacid. The winners of the Nobel 89 anticipate the Spanish scientists [1, 19].

We are going to approximate the natural history of M. Barbacid's scientific career that culminated in the 1988 award of the *Josef Steiner Cancer Research Foundation*, Switzerland, with a bibliometric methodology oriented to the analysis of the content of the bibliography that we consider strategic in this case.

METHODOLOGY

Nobel-eligible scientists, while having a higher proportion of co-authored papers than the average scientist, tend to emphasize their gained visibility and independence by publishing a large number, in absolute terms, of individual contributions [3].

Based on this, we located the most cited contribution of Dr. Barbacid as the sole author, taking as a date not to exceed the year 1988, when the scientist received the prize from the Steiner Foundation, from the University of Bern, Switzerland (equivalent to Nobel prize for cancer research. The contribution "Barbacid M. ras genes. *Annu. Rev. Biochem.* 56:779-827, 1987" [27] is among the most cited 1987 papers in SCI during 1987-89, with 432 citations [4]. Then we look for the article immediately after the Josef-Steiner Foundation prize was awarded, 1988, signed alone by the Spanish scientist. It turned out to be a review article, "Barbacid, M. ras oncogenes: their role in neoplasia. *20:225-235, 1990*" [22].

We analyzed these texts for relevant meanings using a singular bibliometric procedure [28]; the bibliographic coupling analysis that detects the bibliographic references shared by two articles [12]. The analysis of the bibliographic citations received as a taxonomic exposition of the articles that make up the

bibliography according to their typology from the point of view of the number of citations that they have received throughout the interval that is considered [13]. The analysis of co-citations or the study of the implicit logic in the literature according to whether or not the articles that make it up have been cited at the same time by the same author in a citation index [14]. And analysis of the dynamics of scientific authorship, or study of the population of Spanish authors to the extent that they continue to deal with the scientific problems raised or not (we will obtain a population pyramid characteristic of the research program) [15].

The bibliography is made up of 17 scientific journal articles. Its time distribution covers the period 1981-1985. See the Bibliographical Appendix.

THE HISTORY OF THE CASE FROM THE POINT OF VIEW OF INFORMATION RETRIEVAL

When a scientist considers searching the literature for relevant articles, he examines a certain number of journals over a period of time. The question in this case would focus on the history of the scientific program of Dr Mariano Barbacid, winner of the Josef Steiner Foundation (University of Bern) in 1988, within the cycle of work that determined the award of the 1989 Nobel Prize in Physiology or Medicine. The particular needs of the subject lead us to isolate 17 works signed by Spanish scientists relevant to Barbacid between 1981-1985 (Bibliographical Appendix).

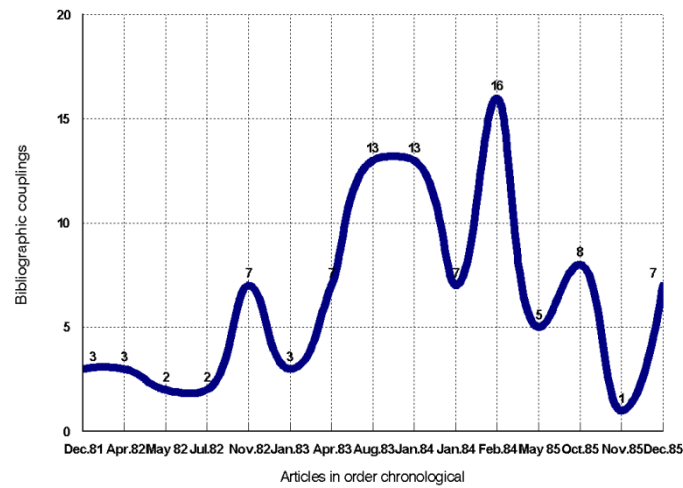
A model that reproduces the scholar communication needs of a scientist interested in the history of this case is to be constructed [12]. The group of problems that Dr. Barbacid raised and that were at the origin of the specialty of oncogene research, are to be read through it.

Figures 1 and 2 were built by using the bibliographical coupling criterion (clustering the scientific publications, over time, that used the same references in their bibliographies). To represent the search field as a two-dimensional graph, on the vertical axis the number of bibliographic couplings, and on the horizontal axis, in chronological order and by means of bibliographic coupling, all the articles with which the analyzed item is related [See Figures 1 and 2].

Pursuing to link the largest number of articles in order to have a broad fact base, which allows designing a scientific communication system, the 17 time distribution diagrams are made, one for each of the articles that appear in the bibliographic appendix. The aim is to characterize those key articles that can serve as tests. The article or articles that connect to a larger collection of articles will be called the test paper. Therefore, the temporary diagram that links the greatest number of documents will be chosen. The results are in the form of case histories.

Therefore, it could be assumed that the historical reconstruction of this moment in Dr. Barbacid's scientific program can be approached in 17 ways. And we chose as test paper number 1 the one that retrieves all the others based on common bibliographical references. This is the article published on December 15, 1983 in Nature entitled "Induction of malignant activation of H-ras-1 locus by single point mutations", whose authors were S. Sukumar, V. Notario, D. Martín-Zanca and M. Barbacid [24] (See Number 3 in the Bibliographic Appendix). Their time distribution is plotted in Figure 1

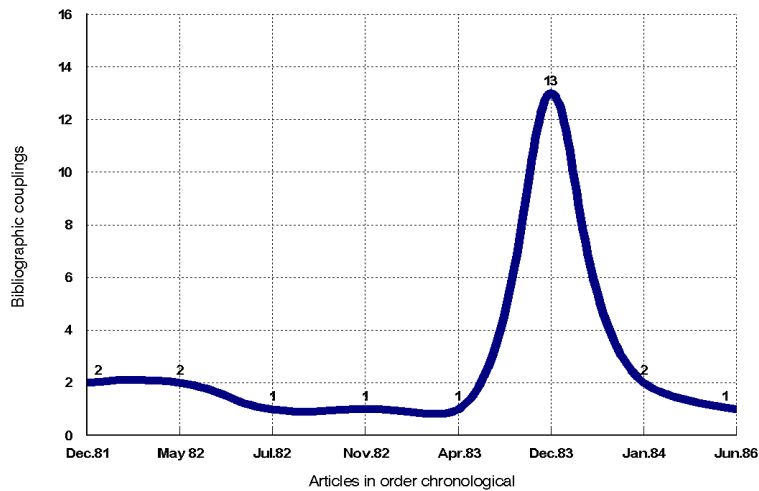
Figure 1. Time distribution of articles retrieved with test paper N° 1



[500 citations to (*Nature*, 306, 15/12/83, 658-61)]

A crucial actor in the scenario that is introduced was Severo Ochoa, to the extent that he communicated in August 1983 and in November 1985 two of the articles considered here to the US National Academy of Sciences (NAS) (See Numbers 13 and 17 in the bibliographical Appendix). To translate the centrality of this fact, a second test paper was chosen. In other words, to contribute to the story of the logic of the connection between bibliographical references, the works presented by Severo Ochoa are added. To choose between the two possible ones, Figure 1 is pointed out, which corresponds to the time distribution of the articles retrieved by test paper number 1. Among the two articles presented by Severo Ochoa, the one with the most bibliographic links was selected [13 units against 1]. In other words, test paper number 2 is the one entitled "Spontaneous activation of a human proto-oncogene" published in the Proc Natl Acad Sci USA in August 1983, the authors being E. Santos, E.P. Reddy, S. Pulciani, R.J. Feldmann and M. Barbacid [29] (See Number 13 in the Bibliographical Appendix). Time distribution of articles retrieved by test paper number 2 is plotted in Figure 2.

Figure 2. Time distribution of articles retrieved with test paper N° 2



[Proc. Natl. Acad. Sci. USA, 80, 8/83, 4679-83]

SUMMARY OF THE CASE HISTORY ACCORDING TO THE COUPLING UNITS

Test paper 1 = 'Induction of mammary carcinomas in rats by nitroso-methylurea involves malignant activation of H-ras-1 locus by single point mutations' (Nature,306,15/12/83,658-61)

Test paper 2 = 'Spontaneous activation of a human proto-oncogen'
(Proc.Natl.Acad.Sci.USA.,80,08/83,4679-83)

Based on Figure 1, it is verified that by means of the bibliographic coupling units at test paper 1, 8 articles with 7 or more shared references in their bibliographies are retrieved (Bibliographical Appendix). Thus, to tell the story of the case, according to the coupling units, the number of items available in the bibliographical Appendix is reduced to 8. The operation that is allowing it consists in the substitution of the real references of the articles, by their logical references [12]. It is understood that the logic of the scientific communication model is that of the aforementioned method.

In test paper 1 [Article N°3 Bibliographical Appendix], the molecular characterization of one of the mammary carcinoma genes is applied in a well-defined animal system to reveal that a mutation in codon 12 is enough to activate its malignancy and, therefore, tumor development. This study on animal tumors induced by carcinogenesis, reports that in rats the induction of mammary carcinomas by a single dose of nitrous methylurea (NMU) during puberty leads to the activation of H-ras-1 oncogenes in 86% of the tumors.

Of the 8 articles retrieved by test paper N°1, the one with the highest number of bibliographic units, 16 units [Article No. 16 Bibliographical Appendix], was accepted by *Science* in December 1983 and published in February 1984. This work estimated 42 mutation points that can generate a human ras gene with transforming properties. The article highlights the absence of tumor lines of the normal allele of the activated ras gene. It also discussed the possibility that ras oncogenes do not belong to the class of genes from which predisposition to cancer is followed, on the basis that ras oncogenes are activated in somatic

cell lines and not in germ lines. The following year, 1985, a population study showed, however, that this predisposition was correct [30].

In descending order of coupling units, with 13 units, another article [Article N°10 Bibliographical Appendix] is the first cloning and sequencing study of the c-K-ras gene in humans. This is a comparative analysis of the mechanisms by which the c-K-ras oncogene was activated independently in two naturally occurring human breast carcinomas. The other article with 13 connecting units is witness article N°2 [Article N°13 Bibliographical Appendix] (see below).

The following article [Article N°14 Bibliographical Appendix], with 8 coupling units, reports on the malignant transformation of mouse NIH3T3 cells, due to the combined effect of multiple copies of a normal human proto-oncogene H-ras-1.

The titles of the 4 articles with 7 coupling units, stand out for their variety of meanings, which intensifies the communicative expressiveness of the method that is being applied. In descending chronological order, this wealth of expression can be identified, in the scientific interests defended by each article, as follows.

An article (November 1982) [Article N°12 Bibliographical Appendix] reports the location of a single point (codon 12) mutation, naturally occurring, responsible for the activation of the T24 oncogene of human bladder carcinoma. This is the most cited article in the bibliography (934 citations), and the one with the highest number of co-citations (140). Another (April 1983) [Article N°6 Bibliographical Appendix] identifies a third member of the ras gene family as the human neuroblastoma cell line transforming gene and names it the N-ras-1 gene. The following work (January 1984) [Article N°4 Bibliographical Appendix] determines the existence of dominant oncogenes in human tumors induced by carcinogens. The latest work (December 1985) [Article N°11 Bibliographical Appendix] noted for overcoming the threshold of 7 bibliographical coupling units, reports on the intron/exon structure of an activated mouse N-ras gene and on the sequence of its four coding exons. Ángel Pellicer is a co-author of these last two works.

Considerable interest in the discovery that a wide variety of tumor cells contain activated ras genes, detectable by gene transfer in NIH 3TE cells, is organized by the work of Barbacid [29] published in the August 1983 Proc Natl Acad Sci USA, which presented Severo Ochoa to the scientific community. We know it as test paper n°. 2. It reports on the spontaneous activation of the human proto-oncogene c-has/bas during the transfection of NIH/3T3 cells, an event that occurred without the involvement of known carcinogens. The explanation of the event was hindered by the limited knowledge of the biochemical properties of the secondary and tertiary structures of the protein p21. This protein, encoded by the spontaneously activated c-has/ras gene, will incorporate aspartic acid as its 12th amino acid residue. Furthermore, the proper coupling of the alpha-helical structure of the amino terminal domain of ras proteins is altered by a conformational change after the replacement of the 12th amino acid residue (Gly) by any other amino acid residue (except proline). This mechanism of malignant activation of ras oncogenes is later supplemented by the discovery, also by Barbacid, of the mechanics of ras gene amplification as an alternative pathway by which ras genes can participate in the development of human neoplasms [Article N°14 Bibliographic Appendix, as noted above].

Test paper number 2 [Article N°13 Bibliographical Appendix] also reports that the computer analysis explains how the structural alteration of the products of the p21 protein that is observed, after the substitution of glycine for any amino acid residue, is always the same: the disappearance, in transforming p21, of a flexible transition region that allows the amino-terminal domain of the normal p21 protein to dock in the central core of the molecule, leading to a more rigid tertiary structure. Its greatest link through bibliographic links is with test paper N°1 [Article N°3 bibliographical appendix]. This connection is expressive of results illustrating the strong evolutionary pressure towards conservation of the amino acid sequence of the amino terminal domain in p21 proteins.

CITATION HISTORIES

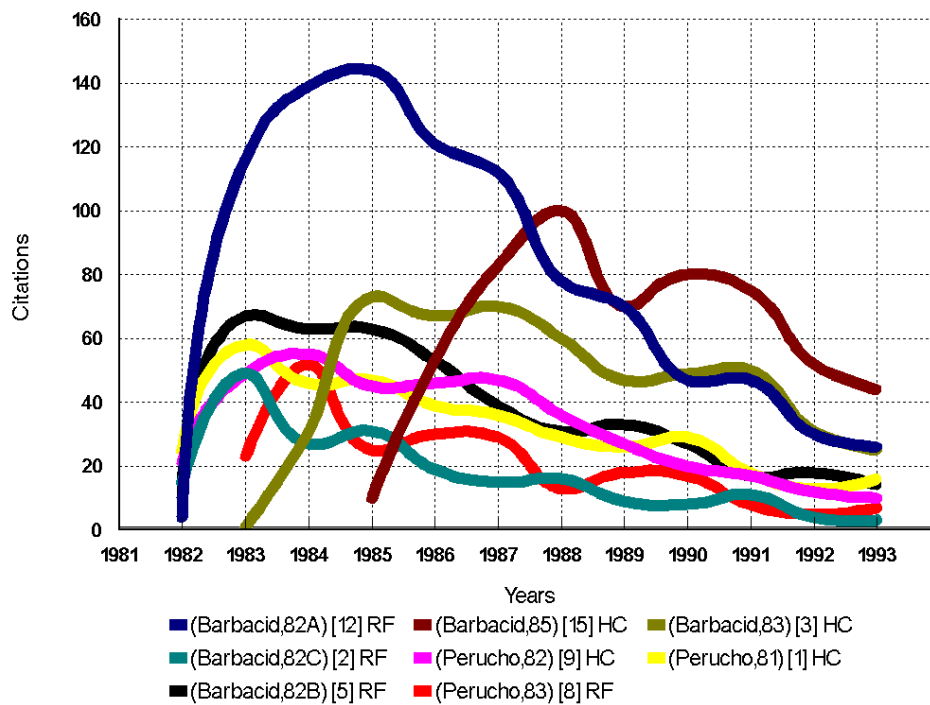
Starting from the fact that historiometric criteria facilitate opportunities to detect the creativity and leadership of a scientific program. Here plots of time series are interpreted based on the Weibull distribution [31]. That is why we distinguish the various types of citation histories from a group of publications in our bibliography [13]. This group is chosen through the historiographical criteria of bibliometrics, that is, the determination of the research front.

The historiography of research fronts (or groups of research articles closely related by scientists, as they are cited together very frequently) [6,16], 1983-1988, highlights 5 articles from our bibliography (see Numbers 2,5 ,6,8 and 12). It should be remembered that bibliographic collections follow the 20/80 rule [17], and that the bibliography is made up of 17 entries. The small size makes, perhaps, that the rule is slightly violated, considering a 30/70 (segment of maximum relevance vs. rest of the collection).

The temporal graphs of the number of citations that allude to the 5 articles included above are analyzed. Six more articles are added to study them as well. In the first place, four for being heavily cited (according to the accumulation of citations in successive numbers of SCI) (See Numbers 15, 3, 9 and 1 in the Bibliographic Appendix) and, secondly, the two articles presented by Severo Ochoa (See Numbers 13 and 17 in the Bibliographical Appendix).

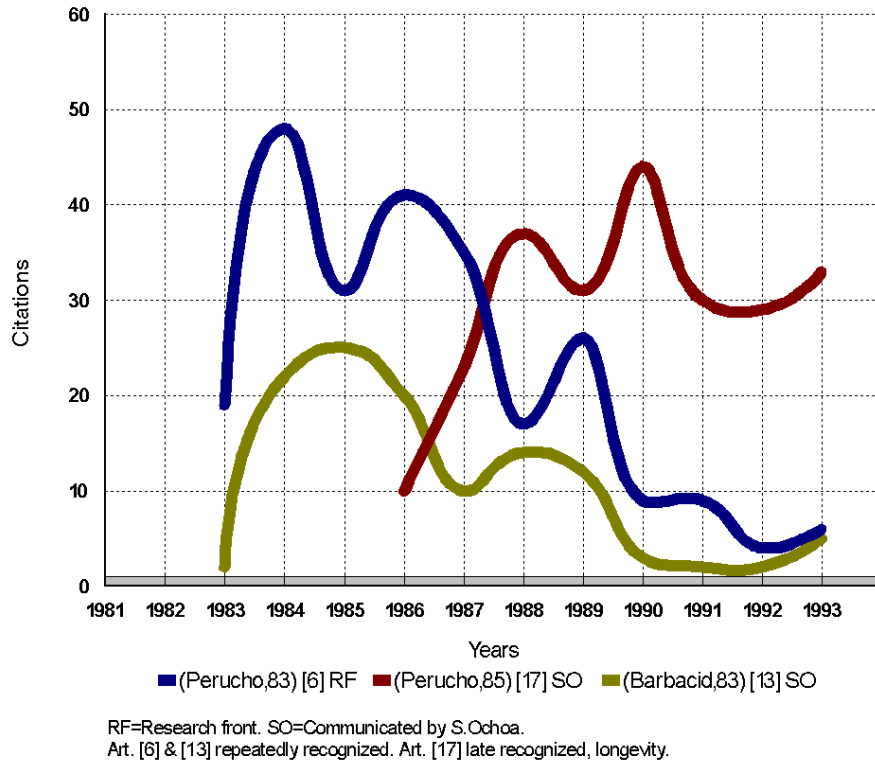
It is understood that the citations that an article obtains are like the votes that a candidate obtains in, for example, the European elections. History is then interpreted in terms of recognition. Before the graphs, the articles that include basic discoveries will be distinguished (Figure 3), as well as the works repeatedly or finally recognized (Figure 4).

Figure 3. Citation histories of articles – basic discoveries



HC=Highly cited. RF=Research front.

Figure 4. Citation histories of articles – other typologies



Of the 11 scientific publications, 8 can be said to be recognized as basic. As the average life of a scientific publication is shorter as a literature grows faster, and as oncogene studies have grown to the point of discouraging new researchers [18], the number of relevant documents stands out in basic science terms.

In descending order of accumulated citations, the results considered basic are: the simple substitution of an amino acid is enough to confer malignant properties to the gene product of the oncogenes of human bladder carcinoma T24, mutations have been located in ras oncogenes of natural development in the codon 12 (934 citations, Article N°12 in the bibliographical Appendix); H-ras-1 oncogenes are directly activated by the carcinogen NMU during the initiation of mammary tumors (564 citations, Article N°15 in the bibliographical Appendix); chemical carcinogenesis represents a suitable model to study the role of transforming ras genes in human neoplasias (500 citations, Article N°3 in the bibliographical Appendix); demonstration that the T24 oncogene is a mutated allele of an activated human ras cellular gene analogous to a retroviral onc gene (433 citations, Article No. 5 in the Bibliographical Appendix); report on the cloning and preliminary characterization of the transforming gene of the human bladder carcinoma cell line, T24 (387 citations, Article N°9 in the bibliographical Appendix); rediscovery of the ras genes, overlapping pathways leading to tumorigenesis may arise independently (381 citations, Article No. 1 in the bibliographical Appendix); preliminary identification and characterization, in the mammary genome, of the N-ras gene responsible for oncogenic transformation, present in the human neuroblastoma cell line (225 citations, Article No. 8 in the bibliographical Appendix); determination of the existence of dominant oncogenes in human tumors, in the course of gene transfection assays, molecular cloning of a biologically active oncogene present in T24 human bladder carcinoma cells, rediscovery of ras genes (206 citations, Article No. 2 in the bibliographical appendix).

For the other three articles, the formalization of the regularities revealed in the number of citations received over time offers the following aspect. Two of them are repeatedly recognized works (Articles N°6 and N°13 in the bibliographical Appendix). Respectively one coins the term N-ras for the third member of the ras gene family whose isolation and transformation is mentioned above, and identifies its malignant properties with a mutated allele of the cellular ras gene in question (246 citations, Article No. 6); the other work (communicated by S. Ochoa) reports on the mutation point, at the 12th codon, that activates the malignant transformation of the human c-has/bas protooncogene (116 citations, Article N°13). Lastly, one of the 11 publications (also communicated by Severo Ochoa), Article N°17 in the bibliographical Appendix, can be understood as finally recognized, with signs of presenting a certain longevity; reports a diagnostic method to detect and characterize single point mutations in transcribed genes, entails a technique that can identify most base substitutions, and provides useful information regarding the expression levels of ras oncogenes in human tumors, analyzing the relative expression of the normal alleles and of the transformants.

LOGICAL CONTENT OF THE BIBLIOGRAPHY BASED ON CO-CITATION ANALYSIS

The intense activity of the research program in question gave rise to a new specialty based on the study of oncogenes and carcinogenesis. It is conceivable that the systematic exploration of the structure of these beginnings can be based on a technique that identifies highly interactive document clusters. This technique is the analysis of co-citations [5].

Here it is understood that co-citation is a form of interaction between two articles based on the fact that they are cited together by one or more other items [33]. The idea will be to determine, through the analysis of co-citations, the role, in the conformation of the specialty, of those articles that are more interactive, according to the examination of the map of co-citations - not reproduced due to size problems.

Therefore, bibliographic information was extracted from the pages of the Science Citation Index (SCI) between 1981 and 1987, both from the cited documents (the 17 of the bibliographical appendix) and from the citing ones, and a computerized file was created with these data, which are ordered by citing articles. For each citing article, all pairs of cited articles are extracted. Finally, all identical pairs are counted [33].

Four articles were highly cited, numbers 3, 5, 6 and 12 of our bibliographical Appendix. The "events" that these documents represent must be seen, from the point of view of the scientists who consider them together by co-citing them, as a set of exemplars for the research area [14].

An examination of the titles of the articles suggests the following thematic characterization:

- (Santos, Jul. 1982) [Article N°5]: Discovery that the human bladder carcinoma T24 oncogene is an activated form of the human gene homologous to v-bas;
- (Reddy, Nov. 1982) [Article #12]: The transforming properties of the T24 oncogene of human bladder carcinoma are responsible for the point mutation in the amino acid;
- (Shimizu, Apr. 1983) [Article N°6]: Three transforming human genes are involved in viral ras oncogenes;
- (Sukumar, Dec. 1983) [Article N°3]: Single point mutations are the result of chemical induction of mammary carcinomas in rats.

The strongest relationship is found between the documents from the year 1982, 140 co-citations. With almost half of the co-citations are the relations of the article (Reddy, 1982) with (Shimizu, 1983), 79 co-citations, and also of the (Reddy, 1982) with (Sukumar, 1983), 76 co-citations.

So, for the point of view of the conformation of paradigms in Kuhn's style (which is the one that is handled in the analysis of co-citations [33]), the article (Reddy, 1982) has a great centrality. And together with (Santos, 1982) they would express the core of Mariano Barbacid's program, that is, the interaction of a carcinogen with a ras proto-oncogene is at the origin of tumor formation.

To end this section, here is a secondary aspect although perhaps quite visible. The SCI bibliographic instrument exposes the advancement of science through the research fronts. Well, in this analysis of cocitations we have had to do with two research fronts: "oncogenes and the genetics of human cancer: viral transformation genes and their DNA structure" (case of (Santos, 1982) and of (Reddy, 1982)), and "Characterization of human and murine cellular oncogenes" (Shimizu, 1983).

ANALYSIS OF SCIENTIFIC AUTHORSHIP

The natural history of the scientific career of Dr. Barbacid, in this period, 1981-1988, whose achievements are recognized by the 1988 prize for cancer research of the Dr Josef Steiner Foundation (University of Bern), can be approximated by means of the study of the demographic structure of the population of the 11 Spanish scientific authors that appear in the registry of scientific authors of articles in the bibliographical appendix [15].

The aim is to deduce a perspective of survival on the research front that records, in terms of statistics of the scientific community, the distribution of productivity of the authors with criteria of continuity or transience in the research effort. Seeking thus to obtain a population pyramid characteristic of the research program. The reason is that perhaps the comparison between the pyramid obtained and the one considered normal for the entire normal scientific community [15] approximates what has been called, in the introduction, the fragmentation that awaits any innovative idea.

The idea of the demographic pyramid consisted in discriminating between those who remain "alive" throughout the duration of the analysis, 1982-1986, that is, the "continuants" of the nucleus, those who continue to publish and those who are cited all the time, those that are "dying" or continuants that do not belong to the core, and finally those that only "live" one year, the transient ones. They are the demographic groups (a), (b) and (c) that are at the end of this section.

What happens in the current demographic model, average of all the data from the scientific community (data from 1976)? [15]. Well, the core would be 13% of the authors (from the point of view of citations). And here the core is made up of 18% of the authors (there is a typo, in 1986 these authors do not "publish", for the purposes of our bibliographical Appendix, but all the analysis indicates that this detail can be omitted). That is, standard pyramid is obtained. Let's go see how it was achieved.

What we want is to find frequency parameters and probability of publication. For this reason, we want to determine the relationship between the demographic groups of authors, according to what they have published, and the extent of their inspiration in the rest of the scientific community, according to what they have been cited (See Table). We will be using the Science Citation Index; in the case of authorship, the Source Index for 1982-1986, and in the case of citations, the Citation Index for 1984-1986.

Table. Relationships between the authors as sources and the authors as they cite them. Spanish authors as listed in the bibliographical appendix. Mentions of authorship in the selected articles (1982-1986), v. occurrences in the Science Citation Index (1984-1986).

Auth Cit/Pub	No Cit	84	85	86	84/5	84/6	85/6	84/5/6	Tot.
82									
83								1	1
84								1	1
85				2					2
86									
82/3									
82/4									
82/5									
82/6									
83/4									
83/5									
83/6									
84/5			1						1
84/6									
85/6									
82/3/4									
82/3/5									
82/3/6									
82/4/5									
82/4/6									
82/5/6									
83/4/5								1	1
83/5/6									
84/5/6								2	2
82/3/4/5								1	1
82/3/4/6									
82/3/5/6									
82/4/5/6									
83/4/5/6									
82/3/4/5								2	2
82/3/4/5/6									
Total			1	2				8	11

There are 11 Spanish scientific authors in the statements of responsibility of our 17 articles (in the bibliographical Appendix). The 11 authors are in the five source indices and in the three citation indices in question.

In the core of authors who continue to publish for all five years and receive citations for the three years considered, there are two authors, Mariano Barbacid and Manuel Perucho.

Of the transient authors on the research front, that is, those who only appear in the authorship mention of a single article (four people), 50% are cited as transient in a single index, and 50% continue in the citing research front.

Lastly, the behavior of those who continue at the front with two, three and four years in the mentions of authorship of the articles, is in general continuous in terms of citations, receiving 80% citations in the three years.

So we get three demographic groups:

- (a) The core. They are in all the articles (1982-1986) (remember the "errata" of the year 1986) and they are cited every year (1984-1986). They are Barbacid and Perucho. The 18.1% of the population

(b) Authors who continue in the research front and do not belong to the core. They appear in several successive mentions of authorship (but not in all) and, in this case, they are always cited. They are Guerrero, Martin Zanca, Pellicer and Santos. The 36.3% of the population

(c) Transient authors. They appear only one year as authors of a work. They are Almoguera, Calzada, Corces, Notario and Villasante. The 45.4% of the population.

This is a standard population pyramid for the research programs. In this way, we have demographically modeled the consistency of the research program, without changes in the perception that we obtain from the study of its history due to the fragmentation derived from the recognition of discoveries.

CONCLUSIONS

The history of the discovery by Mariano Barbacid of the scientific fact that is at the origin of the formation of a tumor, the interaction of a carcinogen with a ras proto-oncogene, is studied. This achievement earned the Josef Steiner Prize in 1988, but the following year, 1989, the Nobel Prize went to other hands.

We proceeded to make a model of scientific communication that would satisfy the needs of a possible scientist interested in this history, located at the dawn of a new specialty today of great dimensions. Utilizing the method of analyzing the bibliographic sources used by the authors of 17 articles considered key, a map of the scientific achievements towards which the authors' information needs converge over time was identified, and evaluated with an efficiency criterion that receives the name of bibliographic coupling technique.

The semantic alterations that highlight the innovation were instrumentalized by elaborating the citation histories of the considered articles. We infer a typology that includes basic scientific facts, and, on the other hand, repeatedly recognized and finally recognized works.

The logical consistency of the bibliography in its interaction with the literature of the country where the research takes place was exposed, and for this we used the analysis of co-citations.

The natural history of Dr. Barbacid's scientific career was approached, in this period, 1981-1985, through the study of the bibliographic structure of the population of 11 Spanish scientific authors that appear in the registry of scientific authors who sign the selected bibliography. .

With this research it has been tried to elucidate facts and regularities, and provide, in a certain way, a theoretical explanation.

FINAL NOTE

It cannot be shown that Nobel Prize laureates are less qualified than less distinguished scientists. And it is possible that the criteria of institutional stratification do not intervene in the bibliographically detectable phenomena on the research front. There are opportunities to detect creativity and leadership through historiometric criteria. The characteristics of creativity in a given discipline can be parameterized. The work of discovering the repeated activation of a ras oncogene by means of the repeated mutation of a specific nucleotide locus, enters into guidelines of eminence that, *noblesse oblige*, earned him the Nobel Prize for cancer research, or prize of the Josef Steiner Cancer Research Foundation Award.

ACKNOWLEDGMENT

Dra. I.M^a Gómez Caridad (CINDOC) for her explanation of the reference [15]. Dr. G. Espinosa (Dpt. Pathology, Univ. Valencia) for his scientific review. An anonymous referee for his indications.

The article was published by LLULL (ISSN 0210-8615) Vol. 19 (n° 37)

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BIBLIOGRAPHICAL APPENDIX

The list of the 17 articles selected to study the case follows below. The specifications consist of: number of citations (until 1994); articles presented by Severo Ochoa; test papers for the application of the bibliographic coupling technique, mentioning the 8 retrieved articles with these test papers, which are studied; mention of the 9 articles for which the citation histories are made, and the research fronts to which they belong, if any.

N° 1

PERUCHO, M.; GOLDFARB, M.; SHIMIZU, K.; LAMA, C.; FOGH, J. & WIGLER, M.: "Human-tumor-derived cell lines contain common and different transforming genes". *Cell*, 27 (Dec. 1981), 467-76.

[381 citations. *With citation history in Fig. 3 it is (Perucho, 81), an article that can be retrieved with test paper 2, by means of 2 bibliographic coupling units*].

N° 2

PULCIANI, S.; SANTOS, E.; LAUVER, A.V.; LONG, L.K.; ROBBINS, K.C. & BARBACID, M.: "Oncogenes in human tumor cell lines: Molecular cloning of a transforming gene from human bladder carcinoma cells". *Proc Natl Acad Sci USA*, 79 (May. 1982), 2845-9.

[206 citations. *With citation history, in Fig. 3 it is (Barbacid, 82C), an article that can be retrieved with test paper 2, through 2 bibliographic coupling units*.

Research Front, 83-1740, "Oncogenes and the genetics of human cancer; viral transforming genes and their DNA structure"].

N° 3

SUKUMAR, S.; NOTARY, V.; MARTIN-ZANCA, D. & BARBACID, M.: "Induction of mammary carcinomas in rats by nitroso-methylurea involves malignant activation of H-ras-1 locus by single point mutations". *Nature*, 306 (Dec. 1983), 658-61.

[500 citations. *With citation history, in Fig. 3 it is (Barbacid, 83). Test paper n° 1*].

N° 4

GUERRERO, I.; CALZADA, P.; MAYER, A. & PELLICER, A.: "A molecular approach to leukemogenesis: Mouse lymphomas contain an activated c-ras oncogene". *Proc Natl Acad Sci USA*, 81 (Jan. 1984), 202-5.

[175 citations. *An article that can be retrieved with test paper n°1, 7 bibliographic coupling units, through test paper n° 2 with 2 units*].

N° 5

SANTOS, E.; TRONICK, S.R.; AARONSON, S.A.; PULCIANI, S. & BARBACID, M.: "T24 human bladder carcinoma oncogene is an activated form of the normal human homologue of BALB- and Harvey- MSV transforming genes". *Nature*, 298 (Jul. 1982), 343-7.

[433 citations. *With citation history, in Fig. 3 it is (Barbacid, 82B), an article that can be retrieved with test paper n° 2 with 1 bibliographic coupling unit*.

Research Front, 83-1740, "Oncogenes and the genetics of human cancer; viral transforming genes and their DNA structure"].

N° 6

SHIMIZU, K.; GOLDFARB, M.; SUARD, Y.; PERUCHO, M.; LI, Y.; KAMATA, T.; FERAMISCO, J.; STAVNEZER, E.; FOGH, J. & WIGLER, M.H.: "Three human transforming genes are related to the viral ras oncogenes". *Proc Natl Acad Sci USA*, 80 (Apr. 1983), 21 12-6.

[246 citations. *With citation history, in Fig. 4 it is (Perucho, 83). An article that can be retrieved with test paper n° 1, 7 bibliographic coupling units, with test paper n° 2 with 1 unit*.

Research Front, 84-4046, "Characterization of human and murine cellular oncogenes"1.

N° 7

GUERRERO, I.; WONG, H.; PELLICER, A. & BURSTEIN, D.E.: "Activated N- ras gene induces neuronal differentiation of PC12 rat pheochromocytoma cells". *J. Cell Physiol*, 129 (Jun. 1986), 71-76.

[91 citations. *An article that can be retrieved with test paper n° 2, 1 bibliographic coupling unit*].

N° 8

SHIMIZU, K.; GOLDFARB, M.; PERUCHO, M. & WIGLER, M.: "Isolation and preliminary characterization of the transforming gene of a human neuroblastoma cell line". *Proc Natl Acad Sci USA*, 80 (Jan. 1983), 383-7.

[225 citations. *With citation history, in Fig. 3 it is (Perucho, 83)*.

Research Front, 84-4046, "Characterization of human and murine cellular oncogenes"].

N° 9

GOLDFARB, M.; SHIMIZU, K.; PERUCHO, M. & WIGLER, M.: "Isolation and preliminary characterization of a human transforming gene from T24 bladder carcinoma cells". *Nature*, 296 (Apr. 1982), 404-9.

[387 citations. *With citation history, in Fig. 3 it is (Perucho, 82)*].

N° 10

NAKANO, H.; YAMAMOTO, F.; NEVILLE, C.; EVANS, D.; MIZUNO, T. & PERUCHO, M.: "Isolation of transforming sequences of two human lung carcinomas: Structural and functional analysis of the activated c-K-ras oncogenes". *Proc Natl Acad Sci USA*, 81 (Jan. 1984), 71-5.

[100 citations. *An article that can be retrieved with test paper n° 1, 13 bibliographic coupling units*].

N° 11

GUERRERO, I.; VILLASANTE, A.; CORCES, V. & PELLICER, A.: "Loss of the normal N-ras allele in a mouse thymic lymphoma induced by a chemical carcinogen". *Proc Natl Acad Sci USA*, 82 (Dec. 1985), 7810-4.

[83 citations. *An article that can be retrieved with test paper n° 1, 7 bibliographic coupling units, with test paper n° 2 with 1 unit*].

N° 12

REDDY, E.P.; REYNOLDS, R.K.; SANTOS, E. & BARBACID, M.: "A point mutation is responsible for the acquisition of transforming properties by the T24 human bladder carcinoma oncogene". *Nature*, 300 (Nov. 1982), 149-152.

[934 citations. *With citation history, in Fig. 3 it is (Barbacid, 82A)*. *An article that can be retrieved with test paper n° 1, 7 bibliographic coupling units*.

Research Front, 83-1740, "Oncogenes and the genetics of human cancer; viral transforming genes and their DNA structure".

N° 13

SANTOS, E.; REDDY, E.P.; PULCIANI, S.; FELDMANN, R.J. & BARBACID, M.: "Spontaneous activation of a human proto-oncogene". *Proc Natl Acad Sci USA*, 80 (Aug. 1983), 4679-83.

[116 citations. *Article communicated by Severo Ochoa, April 29, 1983. With citation history, in Fig. 4 it is (Barbacid, 83)*. *Test paper n° 2, 13 bibliographic coupling units with test paper n° 11*].

N° 14

PULCIANI, S.; SANTOS, E.; LONG, L.K.; SORRENTINO, V. & BARBACID, M.: "ras Gene amplification and malignant transformation". *Moll Cell Biol*, 5 (Oct. 1985), 2836-41.

[146 citations. *An article that can be retrieved with test paper n° 1, 8 bibliographic coupling units*].

N° 15

ZARBL, H.; SUKUMAR, S.; ARTHUR, A.V.; MARTIN-ZANCA, D. & BARBACID, M.: "Direct mutagenesis of Ha-ras-1 oncogenes by N-nitroso-N-methylurea during initiation of mammary carcinogenesis in rats". *Nature*, 315 (May. 1985), 382-5.

[564 citations. *With citation history, in Fig. 3 it is (Barbacid, 85)*].

N° 16

SANTOS, E.; MARTIN-ZANCA, D.; REDDY, E.P.; PIEROTTI, M.A.; DELLA PORTA, G. & BARBACID, M.: "Malignant activation of a K-ras oncogene in lung carcinoma but not in normal tissue of the same patient". *Science*, 223 (Feb. 1984), 661-4.

[215 citations. *An article that can be retrieved with test paper n° 2, 16 bibliographic coupling units*].

N° 17

WINTER, E.; YAMAMOTO, F.; ALMOGUERA, C. & PERUCHO, M.: "A method to detect and characterize point mutations in transcribed genes: Amplification and overexpression of the mutant c-Ki-ras allele in humar tumor cells". *Proc Natl Acad Sci USA*, 82 (Nov. 1985), 7575-7579.

[242 citatios. *Article communicated by Severo Ochoa, July 25, 1985. With citation history, in Fig. 4 it is (Perucho, 85). An article that can be retrieved with 1 bibliographic coupling unit through test paper n° 1*].