



Mapping Collaborative Work and Innovation in Biomedicine: A Computer-Assisted Analysis of Antibody Reagent Workshops

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ABSTRACT This paper analyses a major episode in contemporary biomedical research using a new semi-quantitative approach. In the late 1970s, immunologists began producing new kinds of antibodies targeting molecules on the surface of normal and malignant blood cells. These tools quickly transformed biomedical research in immunology and oncology-hematology. Laboratories worldwide produced thousands of these new reagents and reorganized the classification, diagnosis, and prognosis of diseases such as leukemia and the lymphomas. The rapid development of these reagents initially generated considerable confusion. To avoid the impending chaos, researchers in the field, officially supported by the World Health Organization and the International Union of Immunological Societies, launched an ongoing series of distributed workshops that led to the establishment of a nomenclature of antibody reagents and cell surface molecules. The First Workshop (1981-82) mobilized 54 research groups from 14 countries and resulted in the establishment of 15 antibody/molecule categories. By the late 1990s the number of these categories had increased to more than 247 and the number of participating laboratories had risen to more than 500. Sociological analyses of this kind of large-scale collaborative research usually adopt one of two equally unsatisfactory alternatives: either they provide thick descriptions of selected sites, thus missing the figural dimension of the collaborative network, or they attempt to account for figural complexity by reducing it to a few quantitative indicators, thus destroying for all practical purposes the very phenomena under investigation. To avoid these two alternatives, we opted for a combination of ethnographic methods (interviews, content analysis) and a computer-based analysis of the more than 6000 antibodies examined during the first six workshops, using Réseau-Lu, a software program specifically designed for the treatment of heterogeneous relational data.

Keywords antibody reagents, biomedical networks, cluster designation nomenclature, cluster designation workshops, network analysis, Réseau-Lu

Mapping Collaborative Work and Innovation in Biomedicine:

A Computer-Assisted Analysis of Antibody Reagent Workshops

Alberto Cambrosio, Peter Keating and Andrei Mogoutov

Sociological analyses of large-scale collaborative research usually adopt one of two equally unsatisfactory alternatives: either they provide thick ethnographic descriptions of selected sites, thus overlooking the 'figural' dimension (the interdependency patterns) of the collaborative network, or

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they reduce figural complexity to a few quantitative indicators, thus disfiguring for all practical purposes the very phenomena under investigation.¹ We faced this problem when we decided to analyze the development of the large-scale collaborative endeavor that led to the establishment of the 'cluster of differentiation or cluster designation (CD) nomenclature' of cell-surface markers and reagents.² In the late 1970s immunologists produced new antibody tools targeting molecules on the surface of normal and malignant cells. Within a few years, these tools transformed biomedical research in immunology and oncology-hematology. Laboratories worldwide produced thousands of these new reagents and reorganized the classification, diagnosis, and prognosis of diseases such as leukemia and the lymphomas. The rapid development of these reagents initially generated considerable confusion. To avoid the impending chaos, researchers in the field, officially supported by the World Health Organization and the International Union of Immunological Societies, launched an ongoing series of distributed 'Leukocyte Typing' (or Human Leukocyte Differentiation Antigens, HLDA) workshops that led to the establishment of a nomenclature according to which equivalent reagents produced by different laboratories under different names were assigned to a same antibody set or 'cluster' with a distinctive CD number (CD1, CD2, and so on).

In order to avoid misunderstanding, let us immediately point out that although the term 'workshop' normally refers to a group of individuals sitting in the same room, in the present case the meaning has been stretched. Borrowing a metaphor from computing, we can describe the CD workshops as more 'virtual' than real and consisting of a network of laboratories. How was the network put together? The organizers of the First Workshop selected participating laboratories on the basis of two criteria. First, the laboratories had produced antibodies that the organizers then distributed anonymously to the other participants. Second, each participating laboratory had agreed to test the antibodies. The organizers then centralized the results of these blind tests for statistical analysis. The First Workshop (1981–82) mobilized 54 research groups from 14 countries and resulted in the establishment of 15 CD categories. By the seventh workshop (HLDA VII) that ended in the year 2000, the number of CDs had increased to more than 247 and the number of participating laboratories had risen to more than 500.

To analyze this process without confining ourselves to one of the aforementioned alternatives, we opted for a combination of ethnographic methods (interviews, literature analysis) and semi-quantitative methods, namely a computer-based analysis of the approximately 6000 antibodies categorized during the first six workshops (1982–96). The computer analysis was performed using Réseau-Lu (RL), a software program specifically designed for the treatment of heterogeneous relational data. After providing readers with some background information on the CD workshops and briefly introducing the software and the antibody database, we discuss the software-generated networks and clusters of researchers, cells and CD.

Before going any further, a few comments on the nature – methodological and/or substantive – of this text are in order. Our main message is methodological. As indicated by the rise in the number of co-authors of scientific papers (Cronin, 2001; Glanzel, 2002) contemporary research has become increasingly collaborative and its conduct relies, implicitly or explicitly, on the development of collaborative networks.³ As stated at the beginning of this paper, this new reality calls for the development of analytical methods able to portray a degree of complexity that is inadequately captured by traditional qualitative and quantitative methods by themselves. An obvious candidate for such a task, social network analysis, is *a priori* unsuited because, as argued in detail by actor-network theorists, techno-scientific networks cannot be reduced to social relations.⁴ We thus introduce a methodology designed to analyze *heterogeneous* networks and that configures, for instance, institutions and molecules on the same map.

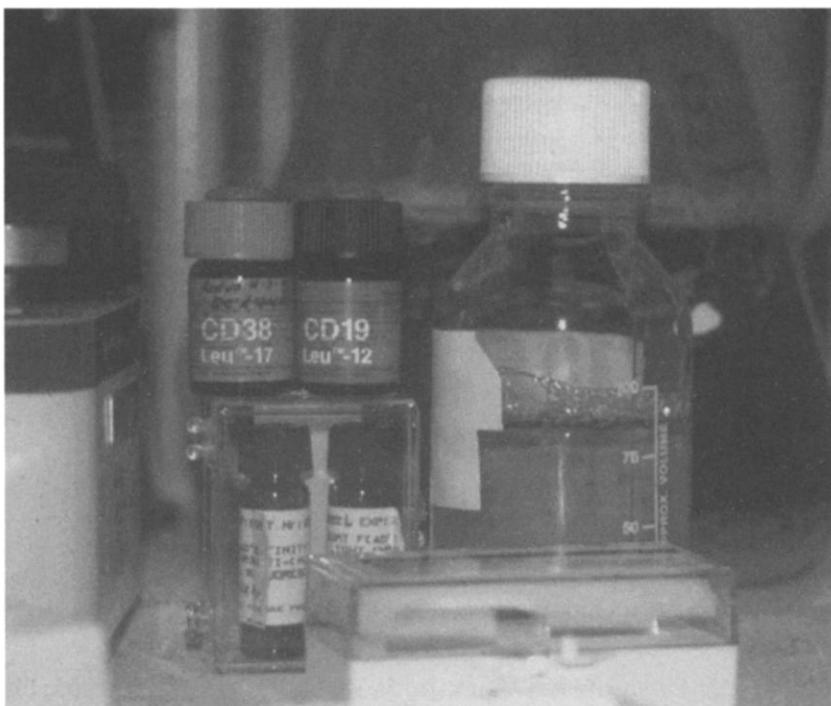
While concerned with methodology, we also believe that a convincing demonstration of the value of our approach can only be provided by a detailed case study. Indeed, by embedding our methodological argument in a case study we hope to show how network mapping of the kind we advocate can be successfully blended with, and used as an input for more traditional ethnographic research which, in turn, can be recursively used to interpret network patterns. Readers are thus also invited to view our contribution as a substantive analysis of a major episode in recent biomedical research. Accordingly, the next section will consist of a short socio-historical introduction to the area under examination.

The Cluster Designation Workshops as Collaborative Research

To most of our readers, the acronym ‘CD’ will evoke the image of the small, shiny ‘compact disk’ that is used to record music and store computer data and programs. To contemporary immunologists and hematologists, however, the acronym refers to something else, namely the expanding nomenclature of molecules on the surface of white blood cells (or leukocytes). CD designations also categorize the antibody reagents used to detect these molecular structures or ‘markers’. As we will see, historically the antibodies came first and the cell surface molecules were consequently a product of the antibody detection technique; only later were antibodies triangulated with other, independent means of molecular detection until finally, through molecular biological techniques, the process was inverted and the molecule itself used as the starting point for the production of the antibodies. Figures 1 and 2 illustrate this terminological double meaning: Figure 1 shows two bottles of antibody reagents on a laboratory bench, defined by their CD number; Figure 2 shows a schematic representation of a CD surface molecule. The referential ambiguity of the term CD bears the imprint of this historical and epistemic inversion whereby molecules whose existence was entirely due to the activity of the antibodies were turned, first conceptually and then materially, into the origin and cause of the antibody’s production.

FIGURE 1

Two bottles of CD antibody reagents on a laboratory bench. Under the CD designation, the labels mention, in smaller print, the trademark name originally given to the reagents. Photograph: AC; reprinted with permission from Keating and Cambrosio (2003: 156).

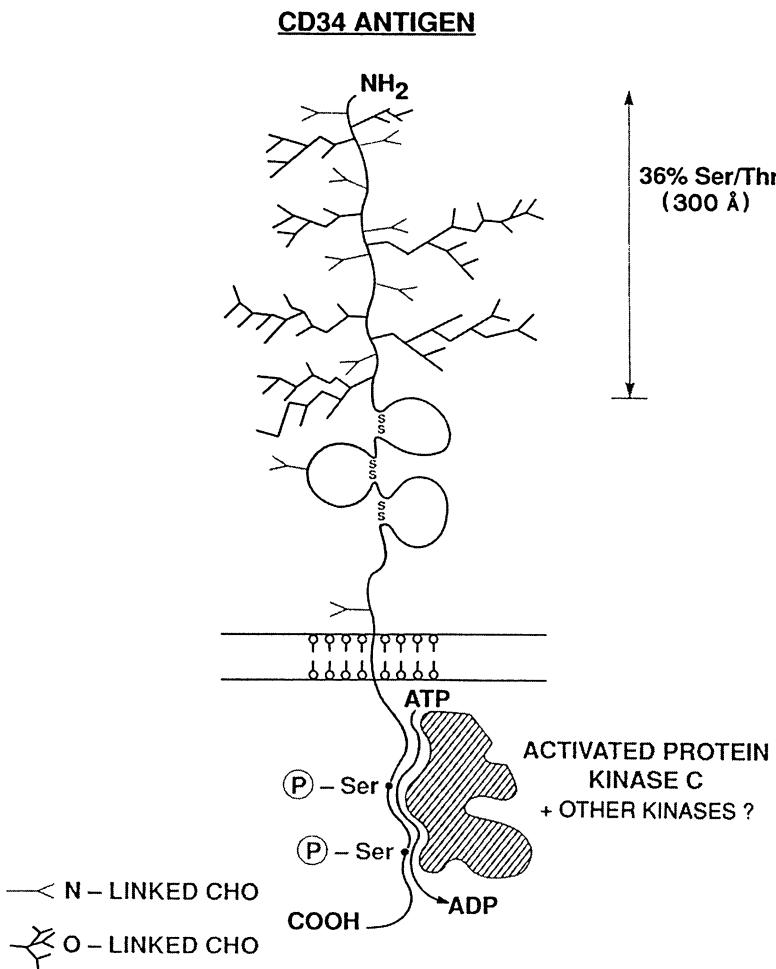


CD4 is the most (in)famous of the CD markers, because of its connection with AIDS. CD4-positive ($CD4^+$) leukocytes are specifically targeted by HIV: their decline in the bloodstream defines the onset and progress of the disease and their increase following, for instance, triple therapy signals the latter's success in keeping the virus in check. The CD4 marker, however, is quite peculiar insofar as, like CD8, its presence alone suffices to define a specific population of leukocytes called CD4 cells. Other markers, of which more than 200 are presently listed in the CD nomenclature, are held to occur in various combinations on a variety of cells and researchers attribute different roles to them, such as signaling, communication, and cell-adhesion functions. Practitioners have coined the term phenotyping or, more precisely, immunophenotyping to label the activity of defining a given cell population (and diseases related to that population) by listing the presence or absence of a set of relevant markers on its constituent cells.

Historically, it is worth recalling that the development of the CD nomenclature followed a profound transformation of the immunologists' understanding of the cells of the immune system that began several

FIGURE 2

Schematic representation of the CD34 receptor; the illustration shows the tree-like structure of the molecule, rooted in the cell surface. The CD34 molecule will be 'recognized' by CD34 antibody reagents available in bottles such as those shown in Figure 1. CD34 thus refers to both the molecules and the reagent used to determine the presence of the molecule. Original in black, red and white. Illustration courtesy of Mary Ann Liebert Inc., Publishers. Original artwork kindly provided by Dr. D.R. Sutherland. Source: Sutherland & Keating (1992: 120).



decades ago. On the eve of his retirement in 1991, N.A. Mitchison, a leading UK immunologist who headed the Tumour Immunology Unit of the Imperial Cancer Research Fund, summarized the work carried out under his direction since 1971 thus:

The twenty years of this Unit have seen an exciting time in immunology. At the start, one could picture the cells of the immune system as billiard balls, bouncing off one another with a minimum of interaction. At the end

they seem softer and gentler to one another, touching and feeling and transmitting signals full of meaning, for purposes that we can begin to understand. (Mitchison, 1990)

Mitchison's metaphor resonates with a more recent one:

The surface of a cell is not smooth and flat, like a ball bearing; it is more like a microscopic garden tended in darkness, bathed by warm salty fluid, a rounded and shaggy convex landscape with cellular vegetation waving like seaweed above the cell membrane . . . It is constantly changing. New vegetation shoots up and old vegetation collapses as in a time-lapse film . . . Certain receptors, like perennial flowers, grow on the surface, so permanent and unchanging a fixture that they can in essence serve as a reliable molecular landmark, or fingerprint, that reveals the identity of the cell itself. Indeed, they are known as clusters of differentiation (CD), or 'markers', and were first reported in mice by Lloyd Old in the early 1960s. (Hall, 1997: 265)

Whether described as a 'garden tended in darkness' or as the means through which anthropomorphic cells touch and feel each other and exchange meanings, the cell surface has certainly captured the imagination of scientists.

Early work on cell surface markers was carried out with traditional antibody reagents known as antisera: typically, researchers or technicians would immunize rats or rabbits with the antigen of interest and subsequently harvest specific reagents from their blood serum. This approach was largely replaced after the mid-1970s by a Nobel-Prize winning (1984) technology for the production of monoclonal antibodies, that is, exquisitely specific reagents that, at least in principle, can be produced *in vitro* in unlimited quantities.⁵ Researchers still have to immunize animals but, subsequently, having harvested the antibody-producing cells from the animal's spleen, they 'immortalize' them by fusing them with tumor cells. Once properly conserved, the cloned progeny of each individual cell can be used indefinitely for the production of a single, well defined type of antibody molecule (as opposed to mixtures of antibodies). Retrospectively, researchers have faulted the old antisera technique for its limited inter-laboratory standardizing power. The making of an antiserum was a 'black art', their quality differed from rabbit to rabbit and researchers could not produce them in large quantities: their circulation was thus limited. In contrast, since monoclonal antibodies are derived from small 'cell factories', their quality is uniform and stable. They can be produced in large quantities and widely distributed: in short, they embody the promise of 'worldwide standardization'.

The consequences of the development of the new reagents differed from field to field. In fields such as bacterial or viral diagnosis, well-established antisera were already available. In younger fields such as leukocyte markers, however, for reasons too numerous to detail here,⁶ antisera had made limited inroads. One can thus confidently argue that the use of monoclonal antibodies sparked and shaped the development of that field as we know it today. Interestingly enough, from the very outset,

commercial companies, several of which produced sophisticated computer and laser-based hardware for use with the antibody-reagents, played a crucial role in the field's development. Chief among them was Ortho Diagnostics, the first to step into the leukocyte marker field with so-called OKT-reagents (O for Ortho, K for Patrick Kung, the scientist who developed the reagents, and T for T cells, the specific subset of leukocytes targeted by the reagents). Other companies soon followed suit: Becton Dickinson (BD) with their Leu series of reagents (Leu for leukocytes) and Coulter with reagents simply labeled with the letter T (for T cells). All these reagents were produced in collaboration with university researchers. The scientists at Ortho worked initially with researchers from Harvard University's Dana (back then: Sidney) Farber Cancer Center. Following disagreements between the two groups, the Dana Farber team became the main supplier of antibody-producing clones for Coulter (now Beckman Coulter). As for BD, they had established a close relation with other institutions, including a leading immunogenetics team at Stanford University, which had played an active role in convincing the company to invest in the field.

We will return to the issue of university-industry relations later in the paper. For now, the important point is that the promise of 'worldwide standardization' offered by monoclonal antibodies was soon threatened by the very success of the new technology. Both public or university-based laboratories and private commercial companies began circulating a growing number of antibodies under, in the case of 'home made' reagents, obscure, idiosyncratic names (such as SS-2/36, VILA1, WCMH15.14 or 148-2D12) or, in the case of commercial products, different brand names (such as OKT4 or Leu3). At the beginning of the 1980s researchers began wondering, for instance, whether Leu3 was really the same as OKT4, as was generally assumed. Initial attempts to remedy the situation led to dubious solutions, such as using the term L3T4 as a mnemonic conflation of the two commercial designations (Herzenberg et al., 2000: 386). More importantly, because the antibodies defined the markers they detected, there was no way of knowing the exact correspondence between two antibodies allegedly targeting a similar marker but developed by independent laboratories. Confronted with putatively identical antibodies whose reactivity patterns nonetheless varied, researchers faced the task of ascertaining whether those differences were due to procedural reasons (differences in technique), biological causes (for example, the peculiar 'strength' with which each antibody binds to its target), socio-cognitive mechanisms (scientists' 'interpretation'), or some combination of the foregoing (Zola, 1999: 226). Only by first agreeing on the 'functional equivalence' of two antibodies could cumulative knowledge about a given cellular antigen and the processes in which it was involved be produced. To sum up the situation, in the scientists' own words:

It was felt that the lack of an exact correspondence between the specificities of the various [monoclonal antibodies] in use might act as a brake on this major technological advance. It was also thought that the elaboration

of a plethora of individual systems of nomenclature would create complete confusion, render impossible any coherent dialog between those concerned, discourage others from joining in this work, or simply prevent people from being able to understand it. (Bernard, Boumsell & Hill, 1984: 9)

If the development of a common nomenclature for the establishment of equivalences between the expanding number of marker antibodies was thus perceived as a condition of possibility for further developments in the field,⁷ researchers also felt that the nomenclature should not follow one of the existing systems insofar as this would unduly favor a given commercial brand or one of the competing laboratories. This is why the task of organizing the first CD workshop fell to two relatively junior INSERM researchers from Paris, Laurence Boumsell from the St Louis Hospital and Alain Bernard from the Gustave-Roussy Institute, who were quick to seize the opportunity of leading an international endeavor.

Boumsell and Bernard had come of age scientifically in the shadow of Jean Dausset. Dausset, a St Louis hematologist and immunogeneticist, and a Nobel Prize winner (1980) for his research on the human leukocyte (HLA) system used in tissue matching for transplantation, had been instrumental in the establishment of a previous series of workshops begun in the 1960s in the USA and devoted to the systematization of the HLA system and reagents. The idea of the leukocyte typing workshops, thus, did not come out of the blue: rather, the HLA workshops acted as a model for the HLDA workshops, since both sought to domesticate recalcitrant work materials by collating, confronting and correlating results from different and often competing laboratories to generate collective results more robust than the original findings.⁸

To put this project into practice, however, Boumsell and Bernard had to garner support from key players in the field. To this end, they traveled to the USA where, with the informal but active support of National Institutes of Health officials, they visited and managed to enroll the most important laboratories (interview with Alain Bernard, Nice, 26 September 2001). The organizing committee of the First Workshop, led by Boumsell and Bernard, included researchers from New York (Sloan-Kettering), Seattle (Fred Hutchinson), and the following universities: Duke, Vienna, Oxford and Harvard (Sidney/Dana Farber Institute). The committee was put under the joint (honorary) presidency of Jean Dausset, Stuart Schlossman, and César Milstein. Milstein, an immunogeneticist at the UK Medical Research Council, was soon to share the 1984 Nobel Prize for his role in the development of the technique for producing monoclonal antibodies. Schlossman's laboratory at Harvard's Sidney/Dana Farber Institute had played a pioneering role in the analysis of the subset of human leukocytes known as T cells.

Although its practical application entailed complex shipping operations and procedural controls, the organizational principle behind the initial CD-workshop scheme was relatively simple. Basically, antibody producers were asked to submit samples of their reagents to a central

location. The samples were subsequently redistributed to all participating laboratories to blind-test them on a set of pre-defined cell types (normal and pathological) and return the results, namely each sample's 'reactivity pattern' (that is, whether a given antibody reacted or not with a given cell type and, in case of positive reaction, to what degree). The results were then statistically analyzed with a clustering algorithm that measured the 'distance' between reactivity patterns: simply put (that is, leaving aside the discussion of the scheme's distinctive statistical features),⁹ two antibodies with an overlapping pattern of positive and negative reactions were considered to be more or less close depending on the statistically measured degree of the overlap. Clusters of closely related antibodies could be assumed to consist of antibodies directed against the same molecule and thus tentatively assigned the same CD number, thus entrenching the existence of the molecule that was presumably at the origin of their specificity. These results were then reviewed and discussed at a closing general meeting held approximately two years after the initiation of the workshop operation.

This general scheme underwent adjustments and major modifications in the course of the subsequent workshops. We will discuss these developments later when analyzing the maps produced with the RL software. Let us, however, emphasize right now that the initial CD scheme involved a major shift with respect to previous immunological practices. As noted by the organizers of the First Workshop, scientists could legitimately question the value of a classification based on reactivity patterns instead of 'more precise concepts, such as the definition of ... molecules or the functions exerted by the biochemical structures' (Bernard, Boumsell & Hill, 1984: 121). While admitting that the more traditional approach was ideal in principle for understanding leukocyte markers, the organizers countered, on pragmatic grounds, that it would take too long to follow that safer path but also, more substantively, that 'a total reliance on the definition of molecular entities may well prove very difficult in practice and may, paradoxically, give ambiguous results' (*ibid*). The reliance on antibody reactivity patterns against unknown cell surface components signaled an 'important departure' from the traditional approach according to which one proceeded from function to molecule: that is, having defined a phenomenon of interest, one would proceed to isolate the molecules participating in the function (Milstein, 2000: 359). The CD workshops inverted the epistemological order, so that 'the definition of a new CD [became] the starting point of the definition of its function, and not the other way around' (Milstein, 1989: 1).¹⁰ As a result, within a few years researchers found themselves confronted with 'dozens of CD antigens ... waiting for a function to be defined' (Milstein, 1989: 2, 2000: 359).

Methodology

We first investigated the CD workshops in the early 1990s using traditional qualitative methods, namely interviews with participating scientists and

analysis of the relevant publications, such as workshop proceedings and journal reports (Camberosio & Keating, 1992). We recently decided to revisit the topic by expanding on the early qualitative approach (interview and literature review updates) and by capitalizing on the available semi-quantitative information concerning the antibodies and their producers. To analyze the latter, we turned to RL, a software program for the analysis of heterogeneous relational data. The two approaches, qualitative methods and software analysis, were used as mutually informing rather than stand-alone techniques: the results of the computer-based treatment provided valuable inputs for interview questions that would otherwise not have occurred to us, and the patterns produced by the software-generated maps were interpreted with the use of the information provided by interviews and literature analysis.

The Human Leukocyte Differentiation Antigens Antibody Database

The proceedings of the first six HLDA workshops contain lists of all the antibodies submitted to each workshop (Bernard, Boumsell, Dausset et al., 1984; Reinherz et al., 1986; McMichael et al., 1987; Knapp, Dörken et al., 1989; Schlossman et al., 1995; Kishimoto et al., 1997). These data were compiled and posted on the Web in 1998 by Martin R. Hadam from the Hanover Medical School in Germany.¹¹ Hadam's database features, for each CD number, the list of related antibodies detailing the name given to each antibody by its producer (clone name) and the code attributed to it by the workshop (workshop code), the workshop (HLDA I–VI) as well as the workshop section (T, B, and so on) to which the antibody was submitted, and the name of the researcher who submitted it (the 'originator'). The same information is available for the antibodies that, for reasons to be discussed later, were submitted to a workshop but failed to cluster and thus have no assigned CD number ('unclustered antibodies'). Unfortunately, the database does not contain institutional or geographical information about the originators. After downloading the data sets for each CD and pasting them in a single Excel file, we were thus left with the task of adding this missing information.

The process turned out to be rather tedious, since the workshop proceedings often neglected to mention the originators' institutional affiliation and the list of participants to the final meeting did not necessarily contain their name, given, for instance, that a different member from the same laboratory may have attended the meeting. Sometimes the proceedings cited original papers where we were able to find the necessary information, but in many other cases we had to search Medline/PubMed and/or actual publications to obtain it. Several other problems that cannot be discussed here (such as those related to the mobility of researchers and the timing of their submissions) complicated our task. In short, we often had to make decisions and it is thus possible that errors have crept into the database. We are, however, confident that we managed to keep them to a

minimum and that they did not affect the overall patterns. After eliminating double entries,¹² the database we used for RL analysis consisted of 5552 antibodies and related information.

A few additional explanations about the database are necessary. First, different antibody originators often belonged to the same laboratory or, to put it the other way, a single laboratory often submitted several antibodies under the names of different researchers. In principle, the person listed as the originator had actually produced the antibody and/or was the first author of the paper reporting the production of the antibody, and thus not necessarily the senior member of the team. The main reason for identifying the institutional affiliation of each originator was to use the laboratory, rather than the individual researcher, as our basic analytical unit: we consider the former – understood as a specific configuration of equipment, skills, projects, and so on – as the relevant antibody production unit (Keating et al., 1999). This raises a few problems, since, for instance, it can be asked whether a small laboratory with fewer than ten researchers can be compared with a big laboratory divided into relatively autonomous sections, each about the size of a smaller laboratory. We decided, however, that rather than imposing our own definition of the appropriate institutional unit, we would follow actors' usage and accept their own definition: to build and run a large or a small laboratory is, after all, an accomplishment (rather than a structural constraint) whose outcome can be visualized on the RL-generated maps.¹³

Laboratories exchange research reagents and research reagents are thus available in laboratories other than the ones where they were initially produced. We were, however, assured that with the exception of industrial submissions, the person or, at least, the laboratory submitting a given antibody was the original producer of that antibody. To submit an antibody produced elsewhere would be contrary to professional ethics (interview with Alain Bernard, Nice, 26 September 2001). Our database, in other words, provides an inventory of the producers of the new reagents and it is thus more than, say, a list of conference participants. But is the inventory comprehensive? For the initial workshops this was certainly the case. There are two main reasons why the initial workshops attracted the overwhelming majority of antibodies produced. First, because the workshops offered the only way of ascertaining the reactivity pattern of a given antibody and thus of using it in the production of collectively sanctioned results. Second, because scientific journals soon began requiring scientists to mention the CD number of the reagents featured in their papers. Following the de facto endorsement of the CD designations by the World Health Organization,¹⁴ by the end of the 1980s the major scientific journals had imposed the CD nomenclature as standard¹⁵ and the nomenclature had similarly become a standard feature in major immunology and hematology textbooks. There was thus a compelling reason for researchers to transit their antibodies through the workshops: the workshops freighted CD with a number of conventions that transformed antibodies produced in different laboratories into mutually equivalent substances. Accordingly, journal referees would

question the use of an antibody that ‘ha[d] not been officially “blessed” by one of the Workshops’ (Zola, 1999: 227).¹⁶ Workshops, in other words, provided both truth and trust: they defined the true target of the antibody and produced confidence in the process through which this fact (open to revision) had been established. With the subsequent development of molecular biology techniques, it is now no longer necessary to submit an antibody to a workshop in order to define its reactivity. A map of the laboratories involved in the early workshops, however, provides for all practical purposes a comprehensive map of the laboratories that established the new field of human leukocyte immunophenotyping.

As far as the submission of antibodies by industrial companies is concerned, the organizers of the First Workshop decided to reject industrial submissions: only researchers from non-commercial laboratories would be allowed to present their reagents. This rule, however, was soon abandoned since, as we will see later, commercial antibodies were most often produced by outside researchers who could easily submit them to the workshop under their own names, although everybody was aware that they were available commercially (interview with Alain Bernard, Nice, 26 September 2001). Moreover, with the expansion of the workshops the task of producing and submitting the necessary quantity of a given reagent soon became expensive and time-consuming. A growing number of researchers preferred to license their antibodies to a company with the expectation that the latter submit them to a workshop (interview with Andreas van Agthoven, Marseilles, 27 November 2001). Sometimes antibodies initially submitted by a researcher were re-submitted at the following workshop by a company. For a large number of antibodies (especially for later workshops) the originator listed in the database was not the actual producer but, rather, a company production manager. To deal with this situation we decided to use the name of the company in the workshop maps, thus adopting the solution chosen by the workshop organizers. But we also generated additional maps of the institutional affiliation of the originators of the antibodies featured on the catalogue of two major companies, most of which had indeed been submitted to a workshop.

A final remark concerns a certain degree of ‘anachronism’ that is built into the database. The following list of the first six HLDA workshops gives the year and location of their closing meeting as well as the range of CD that were defined at each meeting:

HLDA I	1982	Paris	CD1–w15 ¹⁷
HLDA II	1984	Boston	CD16–26
HLDA III	1986	Oxford	CD27–45
HLDA IV	1989	Vienna	CD46–w78
HLDA V	1993	Boston	CD79–130
HLDA VI	1996	Kobe	CD131–166

In a few cases, antibodies submitted during, say, HLDA I were later reassigned to another CD designation. The specificities listed in Hadam’s

database have been accordingly corrected so that, for instance, an HLDA I reagent is listed as CD80, a designation that was established 11 years later, during the HLDA V. It would have been possible to revise the database and re-instate the original CD designations using the printed proceedings. We decided, however, that given the rarity of this occurrence the cost–benefit ratio made the enterprise pointless. It is easy to recognize on each map the anachronistic CD designations. Moreover, by keeping things as they were, we also gain some sense of the process of redefinition that was built into the workshop scheme.

Mapping Relational Data: The Réseau-Lu Software Program

Thanks to the development of the World Wide Web and related technologies, researchers in the field of science and technology studies have increasing access to large amounts of ‘qualitative–quantitative’ information about biomedical entities and activities (clinical trials, human gene and protein databases, and so on). The HLDA antibody database is an example of this new kind of resource. But how should we deal with this information? Purely qualitative inspection of the data is likely to produce fragmented information, while statistical treatment of the aggregate data will result in the production of a few quantitative indicators that can hardly do justice to the information content of the data. RL has been developed to answer this problem by constructing a visual representation of the original data that, by translating rows and columns into pictures, allows researchers to get, ‘at a glance’, a sense of the figural pattern of the data. RL also includes statistical algorithms that enable further treatment of the resulting pictures, for instance by producing maps featuring only the most significant links. The main purpose of the software, however, remains to map large amounts of complex data so that they can be visually inspected and interpreted.¹⁸

As pointed out by Dodier & Barbot (2000) in their pioneering application of RL to the analysis of biomedical data,¹⁹ the maps produced by RL share a key premise with those produced by social network analysts, namely that entities related to each other by some sort of connection of interest to the analyst can be represented on a two-dimensional plane as symbols connected by lines, and that by examining these links one can draw meaningful sociological conclusions.²⁰ As previously noted, however, social network analysis has major limitations from a science and technology studies’ point of view, namely that it takes into account only relations between humans, often defined by informal interactions (Callon, 2001). RL allows one to investigate *heterogeneous* relational data, that is, links between human and non-human entities such as researchers, molecules, and laboratories. In our case, as in the one analyzed by Dodier and Barbot (2000), these links are defined by formal relations, namely the submission of antibodies to a (temporary) central organization in charge of the coordination of a collective, distributed endeavor. Rather than further discussing the general characteristics of the maps generated by RL here, we

proceed to the next section where we will examine them in connection with the analysis of the results.

The Cluster Designation Workshops: A Computer-Assisted Analysis

In order to examine the evolution of the HLDA meetings, we analyzed each workshop separately and generated two main kinds of maps. First were maps featuring the antibody-submitting institutions (or the cities or countries where they were located) and the workshop sections to which they submitted their reagents. Second were maps of the antibody-submitting institutions (or the cities or countries where they were located) and of individual CDs. We will discuss each in turn.

Institutions and Workshop Sections

Each workshop was divided into a growing number of sections, whose definition was modified over time. Researchers sending antibodies to a given HLDA workshop submitted them to a given section, and the protocols for the testing and handling of these reagents, as well as the statistical treatment of testing results, were section-specific. Since institutions could, and several actually did, submit antibodies to more than one section, the RL maps help us to visualize these distinctive submission patterns. Before proceeding any further, we need to briefly explain the principles and practices defining the division of each workshop into separate sections.

The First Workshop was organized into three sections each corresponding to one of the three major leukocyte cell types (or 'lineages'), namely B cells, T cells and myeloid cells (M). To understand this decision, readers should recall that part of the increased importance of immunology in the post-World War II period resulted from a change in emphasis from antibodies (soluble substances) and their serological reactions to immune cells. The beginnings of 'the rise of cellular immunology' have been located in the new theories and techniques of skin grafting according to which lymphocyte cells and not antibodies caused the rejection of skin grafts (Silverstein, 1989; Moulin, 1991: 199–200). At the time, however, little was known about those cells.²¹ A whole new series of investigations in the 1960s led to the dissection of what became known as the immune system (Moulin, 1989) into 'compartments' corresponding to distinct cell types (namely B, T and M) each carrying out a different function. The starting point of the First Workshop, in other words, was *functionally* defined subsets of cells.

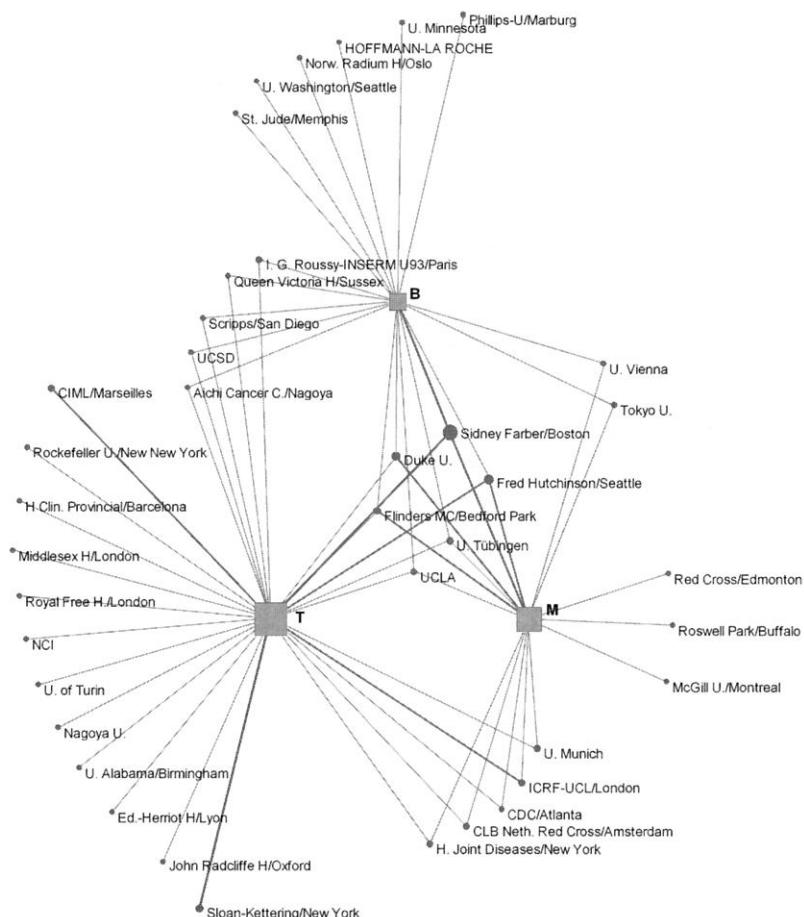
Organizers of the subsequent workshops expanded the CD nomenclature to include any surface molecule that could be detected by monoclonal antibodies rather than only the molecules that were initially thought to characterize distinct cell lineages, thus severing the link between the definition of a new CD and the existence of functional cell subsets. Some workshop participants brazenly suggested that the traditional division of

lymphocytes into B, T, and M no longer reflected a ‘biological outlook’. And indeed, while maintaining ‘for organizational reasons’ the classical subdivision of the workshop into T, B, and M sections, the organizers of the 1989 Vienna workshop quickly added that ‘the borders between these cell types are no longer as rigid as originally thought’ (Knapp, Rieber et al., 1989: 253). In addition to the cell surface structures that marked out different immunological functions,²² researchers found that some cell-surface structures participated in the ‘normal’ non-developmental functioning of non-immune cells such as cell adhesion, while others, such as cytokine receptors, were involved in the biochemical regulation of immune cell activities. Cell-based divisions could thus be deemed, from a ‘radical’ immunophenotypic point of view, as ‘completely arbitrary, without biological basis’, insofar as similar or identical structures appeared on different cells (interview with Laurence Boumsell, Paris, 18 December 1990). The upshot of the transformation of the cell surface markers was a reorientation from molecules directly related to immunology and pathology to a more physiological focus on the multifarious surface structures of the cells of the blood-cell forming (hematopoietic) system (Kersey & LeBien, 1984).²³

Let us now proceed, without any further delay, to the discussion of the first RL map, which represents the institutions that submitted reagents to the three sections of the HLDA I (see Figure 3). Institutions are represented by circles, and each institution appears only once in the map. Workshop sections (in the present case: B, T, and M) are represented by squares. The size of the circles and squares is proportional to the number of antibodies submitted by each institution or to each section. So, for instance, one can easily see that the largest number of antibodies was submitted to the T section, followed by the M and the B sections. Similarly, the Sidney Farber Institute was by far the largest reagent submitter, followed by the Fred Hutchinson Institute in Seattle and Duke University. The lines connect institutions to the section(s) to which they submitted antibodies. Figure 3 indicates that only six institutions submitted antibodies to all three sections of the First Workshop, while five other institutions, including Boumsell and Bernard’s laboratories (I.G. Roussy/INSERM U93), submitted to both the T and B sections, five to the T and M sections and two to the B and M sections. Several other institutions submitted to only one section.

We can make sense of this pattern by resorting to an analogy with the notion of a National Innovation System (NIS) developed in the mid-1980s to analyze the network of institutions responsible for the development and circulation of innovative technologies (see, for example, Lundvall, 1992). Each NIS is said to consist of three main components, namely of institutions, their relations and the strategies they display. Figure 3, from such a perspective, shows the institutions involved in the production and regulation of an innovative set of reagents as well as the relations between these institutions as mediated by their common participation in one or several workshop sections. The regulatory dimension of the HLDA workshops, with its full load of interlaboratory conventions and agreements (Keating &

FIGURE 3
HLDA I: institution/section map.



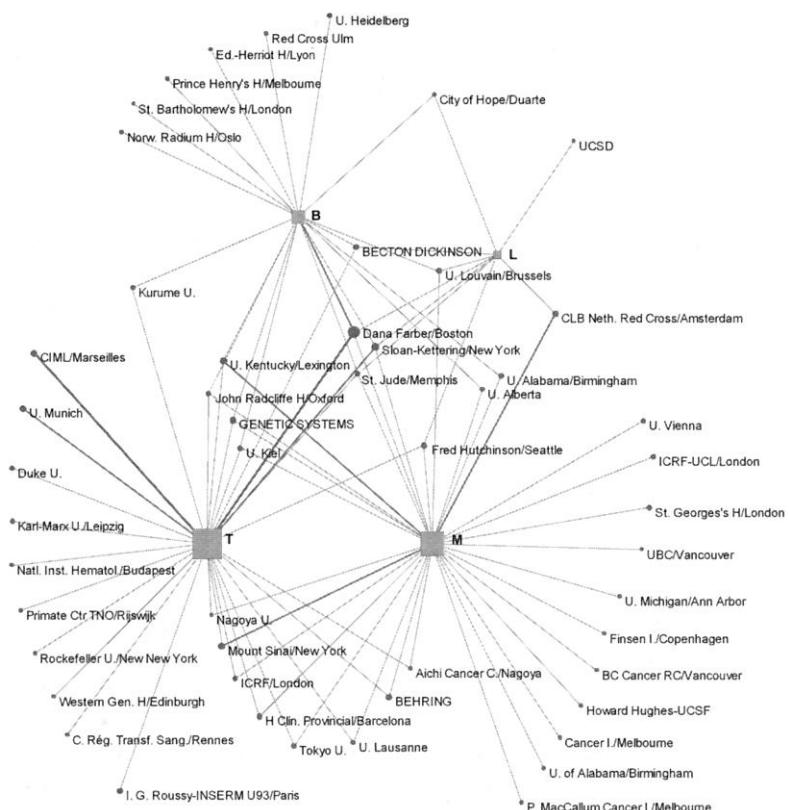
Cambrosio, 1997), is obviously central to the overall endeavor. Yet a look at the participating institutions, especially those occupying a central position on the map, shows that the workshops have been established and managed by laboratories at the research front. For these laboratories, the production of common measures for the reagents at the center of their practices provided a way of working around the uncertainties surrounding the coordination of these practices, and thus also of validating their results. As for the institutional strategies, they can also be easily read from the map: a few institutions, chiefly among them the Sidney Farber team in Boston, adopted the strategy of covering the entire field. A subsequent interview confirmed that the Boston team leader had indeed assigned individual researchers the task of producing reagents for each of the three functional cell lineages in order ensure the Institute's presence in all subfields (interview with Alain Bernard, Nice, 26 September 2001).²⁴ At the opposite

pole, several institutions chose to focus on specific domains. The analysis of this kind of strategic investment can be pursued at a finer level by looking at maps featuring the links between institutions and specific CD numbers, rather than workshop sections. By, so to speak, increasing instead of decreasing the resolution, one can furthermore produce city/section maps, in order to take into account the concentration of several institutions in a single location, or country/section maps, to show the relative weight of different national systems (maps not shown here for reasons of space).²⁵

For the moment, however, let us look at the institutions/sections maps of the subsequent workshops. Figure 4 corresponds to HLDA II. The pattern is broadly similar to that of HLDA I, with a few institutions (including the now renamed Dana Farber, still the largest antibody-submitter) occupying the central position corresponding to the laboratories active in all or at least most subfields. In addition to the increasing number of participating institutions, there are, however, two main differences with regard to HLDA I. First, commercial institutions (in capitals; for example, BECTON DICKINSON, GENETIC SYSTEMS, BEHRING) are now officially represented. They tend, in this map, to occupy a central position. One might surmise that this reflects the fact that commercial enterprises seek to produce a large spectrum of reagents, but this is not always the case as companies can position themselves differently in the field. A second development is that a new section, termed L for Leukemia, makes a (short-lived) appearance and corresponds to the transient belief that one could identify molecules that are specific to or at least strongly associated with leukemia. We have examined this episode in detail elsewhere (Keating & Cambrosio, 2003: Ch. 4). Here, let us note that the new section signals a departure from the original 'lineage' scheme and opens the door to a more pragmatic approach whereby, as previously noted, separate sections were created on an 'opportunistic' basis with molecules no longer fitting into the traditional functional lineage scheme.

Indeed, HLDA III established three new sections, one for 'non-lineage antigens' (NL), obviously a broad, somewhat sketchy category embodying the primacy of phenotypical over immediate functional concerns, and two additional categories for activation (A) and platelet (P) antigens. HLDA V saw the establishment of three additional sections for adhesion structures (AS), cytokine/chemokine receptors (C), and natural killer cell antigens (NK), whereas HLDA VI inaugurated a separate section for endothelial cell antigens (E). In order to save space, we will jump to the institution/section map of HLDA IV (Figure 5). The map shows, once again, a central core of institutions defined by their presence in all or most workshop sections, and a periphery of institutions specializing in submissions to a single section; the left side of the map also shows an intermediary ring of institutions that are present in two or three sections. The NL section has grown to a size similar or greater than the traditional T, B and M sections, thus supporting the hypothesis of a 'phenotypic turn'. Furthermore, RL has located the two new sections A and P slightly outside of the central

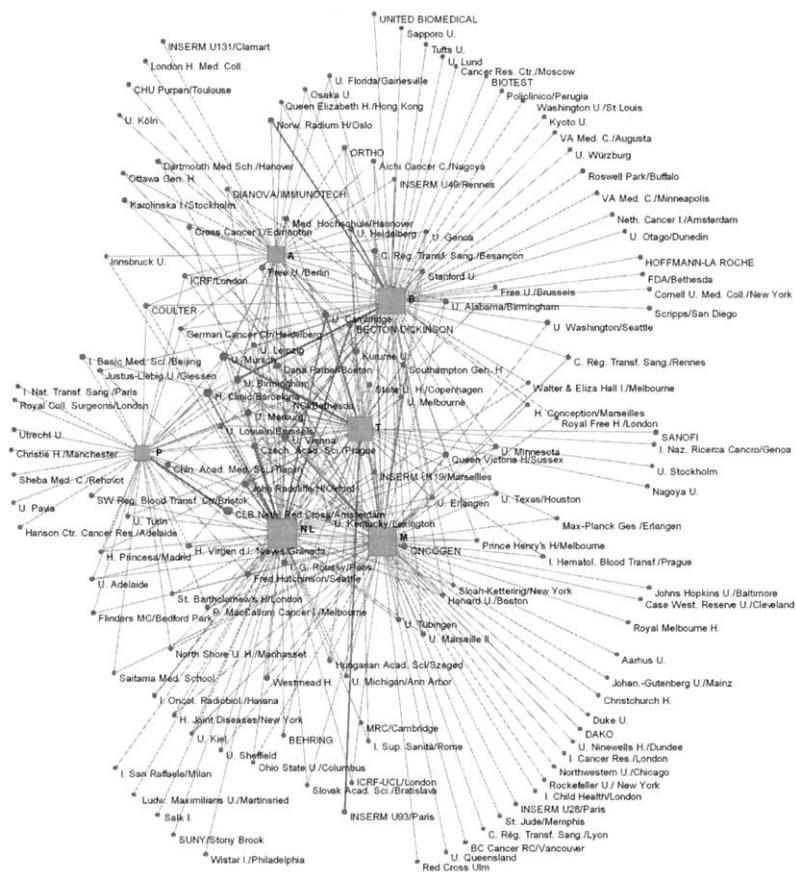
FIGURE 4
HLDA II: institution/section map.



core of the map; we can hypothesize that these sections contain, in addition to a few core institutions, a majority of laboratories that, compared to other workshop participants, pursue a more specialized strategy.

Given the growing number of institutions and links represented on the map, we can improve our interpretation by resorting to another feature of RL, namely the production of maps showing only a user-defined percentage of more specific links. In order to avoid confusion, it is important to emphasize that the notion of a specific link is relative, rather than absolute. Thus, this kind of map must be interpreted by referring simultaneously to the corresponding full-link map. If we look, for instance, at Figure 6, showing only the more specific links (50%-link map), we see that Dana Farber is connected only to the B section, whereas on Figure 5 it is one of the core institutions linked to all sections. This means that while this institution, as shown by the full-link map, continued to follow its strategy of ensuring its presence in all the workshop sections, its contribution to HLDA IV, statistically speaking, targeted the B section. Figure 6, in other words, is not a simplified version of Figure 5: for sure, it is more readable insofar as the nodes and links are 'spread out' on the two-dimensional

FIGURE 5
HLDA IV: institution/section map.

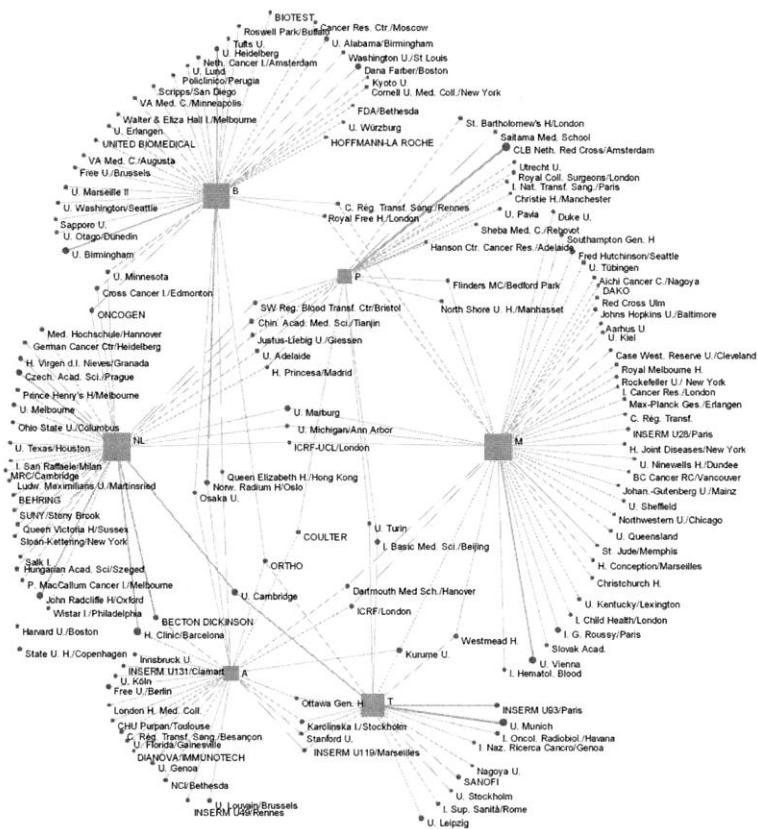


plane. But the information it provides is complementary to that to be found on the latter: it tells us, namely, about the special focus of institutions that are large reagent producers.

To conclude, let us examine in parallel the maps of HLDA V (Figure 7) and HLDA VI (Figure 8). Apart from a larger number of institutions and sections, Figures 7 and 8 share with representations of previous HLDA meetings the 'core-periphery' pattern. There is, however, an interesting difference between Figures 7 and 8: the latter is far more fragmented than the former: this pattern is clearly visible on the top of the figure, where the E section and related institutions form a semi-autonomous satellite, but it also applies to other sections of the figure. Confirmation of the pattern came from an interview in which the respondent noted that while the early meetings, in spite of the existence of sections, were largely a communal affair, with all participants sitting together at one moment or the other, the most recent ones had been characterized by a further specialization, with participants sitting in the separate rooms devoted to

FIGURE 6

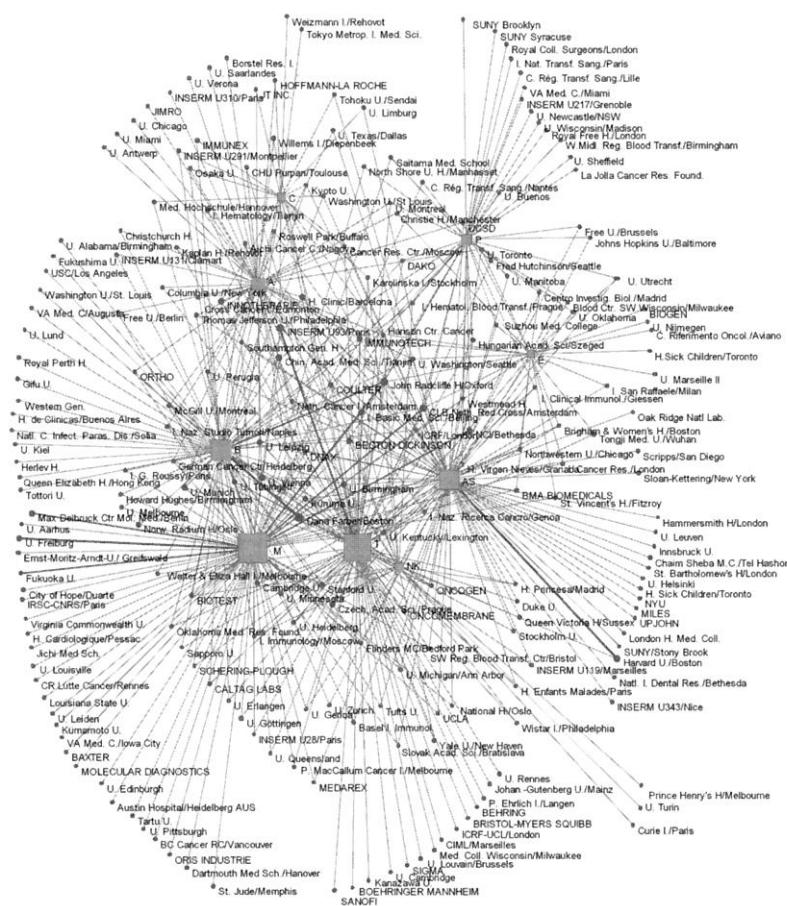
HLDA IV: institution/section map showing only the more specific links (50%).



their section (interview with Claude Mawas, Marseilles, 22 October 2001).

This increasing fragmentation can be linked to a basic transformation of the technological basis on which the HLDA workshops were based and, simultaneously, of their substantive focus, from antibodies to the cell surface molecules themselves. As readers will recall, statistical analysis was initially the only criterion for classifying an antibody within a particular cluster, even though antibody originators were also asked to submit 'some molecular data'. In more recent workshops, molecular data, that is, data obtained from gene cloning and experiments with recombinant proteins, have begun to play an increasingly important role, to the point that 'solid molecular data' have now gained the upper hand. For instance, based on the assumption that molecules coded by similar genes may have different cellular expressions, it is now deemed appropriate to assign genetically related molecules to the same cluster even when their expression pattern is dissimilar (Zola, 1999: 227–28; Mason, undated; interview with David Y. Mason, Oxford, 20 May 1997). In this sense, one could argue that the

FIGURE 7
HLDA V: institution/section map.



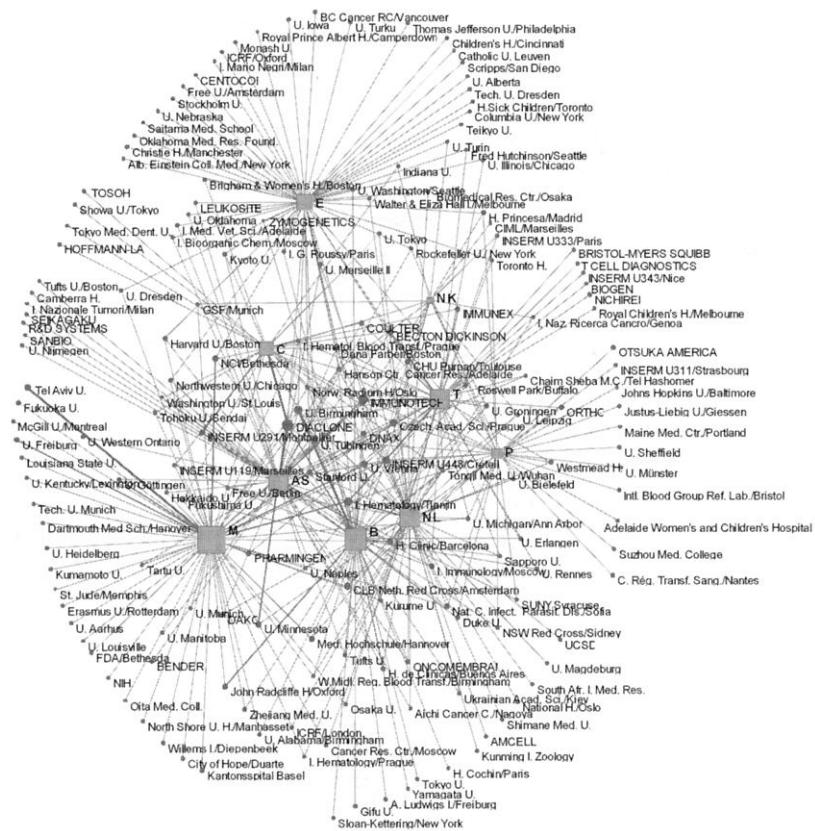
system has freed itself from its original antibody-based technology. In turn, problems linked to specific molecules have now taken the upper hand. As noted by Zola (1999: 228), paraphrasing David Mason (undated), the Chair of HLDA VI:

The primary focus ... should be on the functional molecules (the 'antigens'); the antibodies are merely tools used in their study. Whereas in the late 70s and early 80s the question behind many studies was 'What does my antibody react with?', we are now able to focus on much more fundamental questions about intercellular interactions and cell-molecule interactions.

Institutions and Cluster Designation

As we hinted in the previous sections, maps connecting institutions to individual CDs can be used to 'fine-tune' the analysis of the strategic investments displayed by specific laboratories. Figure 9 shows such a map

FIGURE 8
HLDA VI: institution/section map.



for HLDA I. The graphical conventions are similar to those used in the previous set of maps: squares denote institutions, circles the CD categories, and the relative size of the symbols corresponds to the number of antibodies submitted by a given institution or assigned to a given CD.

Before analyzing Figure 9, however, we must deal with a methodological issue. We generated the institutions/sections maps using data for all the antibodies that had been submitted to a given section, regardless of whether they ended up as members of a CD cluster or, for a variety of reasons,²⁶ they remained ‘unclustered’. In so doing, we followed the approach chosen by the Editors of the Workshop Proceedings: they had similarly listed all the antibodies submitted to each section, regardless of their final destination. In the case of the institutions/CD maps, however, we had to exclude the unclustered reagents since, by definition, they had no CD number. We did so after verifying that there was no such thing as ‘good’ and ‘bad’ submitters, that is, institutions that, for instance, systematically submitted reagents that remained unclustered.

FIGURE 9
HLDA I: institution/section map.



This raised, however, another problem: since the reagents were assigned to a CD only after they had been sent to a particular section and had undergone blind testing, we could not claim that a laboratory had chosen to submit a reagent to a given CD. Well . . . not quite, but almost, since, as noted by an interviewee, submitting institutions very often had a very good idea of the CD targeted by their reagents (interview with Claude Mawas, Marseilles, 22 October 2001). In other words, institutions/CD maps can also be interpreted ‘strategically’, albeit with some caution. Workshop results did not always correspond to expectations. In the course of generating a reagent, a laboratory ended up, through the vagaries of the immunization process, producing other reagents that did not correspond

to the intended specificity domain and decided to submit them anyway to a workshop in case they were useful to other laboratories with which they could subsequently exchange reagents. Finally, in interpreting these maps we must not forget the 'anachronistic' CDs, as explained earlier.

Figure 9 confirms many of the conclusions that follow inspection of Figure 1; for instance, the major role played by a few institutions as antibody producers. The novel information to be found in the new kind of map is, of course, related to the CDs themselves. We can see, for instance, that CD15, followed by CD8, is by far the CD to which the largest cluster of antibodies was assigned by the workshop. This configuration prompted us to look for an explanation. While, as sociologists, we were immediately tempted to investigate the possible strategic role (scientific, clinical and/or commercial) played by CD15, the answer, as offered by scientists, turned out to be biological, namely that CD15 is a surface molecule that easily elicits the production of antibodies (it has a high immunogenic power) so that many laboratories, through no choice of their own, ended up with anti-CD15 antibodies.

CD8 is quite different. The Marseille-Luminy Immunology Centre (CIML/Marseilles on the centre top of Figure 9), for instance, submitted a relatively large number of antibodies, but they all targeted CD8, a fact related to their research program on cytotoxicity, an immune function mediated by CD8 molecules. Thus, contrary to traditional social network analysis, RL-generated maps do not pre-judge matters by displaying only social links: they leave the 'ontological' issue of the nature of the links open for further inquiry. By doing so, they also leave open the question whether, for instance, the intermediary role played by molecules is what links a given institution to other institutions (and molecules) or, vice versa, whether the molecules are connected by the intermediary role played by institutions.²⁷ In this specific sense, RL maps are ontologically neutral (they do not pre-empt nor pre-determine the results of further inquiry into the source of the displayed patterns) and thus also heuristically flexible.

Institution/CD maps, as compared with institution/section maps, are, so to speak, truer to the phenotypic shift of the workshops: they portray the workshops as focused on the molecules rather than on the broader, functional cell lineages. They also bring us closer to the actual content of scientific activities insofar as they display new scientific entities (the CD molecules) as opposed to organizational structures (the workshop sections). They do so by linking the entities to the institutions that, for all practical purposes, entrench their existence as bona fide biomedical entities. From this point of view, not all CDs are born equal: some are more robust in the sense that they can rely on the support of a larger number of institutions, while others exist only because of a few institutions (the definition of a CD required the existence of at least two antibodies). This is clearly visible from Figure 10, corresponding to HLDA III, where one can easily contrast a relatively small number of 'strong' CDs at the core at the map with a periphery of 'weak' CDs. If we compare Figure 10 with Figures 11 and 12, corresponding to HLDA IV and VI respectively, we see a

progressive transformation of this pattern. On Figure 11, the 'old' CDs, that is, those corresponding to early-defined specificities (and thus also those that have acquired a well-defined biomedical status), have migrated to the bottom of the map, where they co-exist with a majority of the large antibody-producing institutions, while a second cluster of institutions and CDs has appeared towards the top of the map; both are surrounded by a periphery of fragmented CDs and institutions. In Figure 12, the fragmentation pattern is quite advanced: only a few large CDs now stand out. Unsurprisingly, the large producers of reagents, located at the center-top of the figure, are mostly commercial companies (Coulter, Pharmingen, BD, Diaclone, Immunotech).

More specific interpretations could be offered by focusing on a given set of CD and institutions, following their evolution through the workshops and examining in parallel the related scientific and commercial literature.

FIGURE 10
HLDA III: institution/section map.

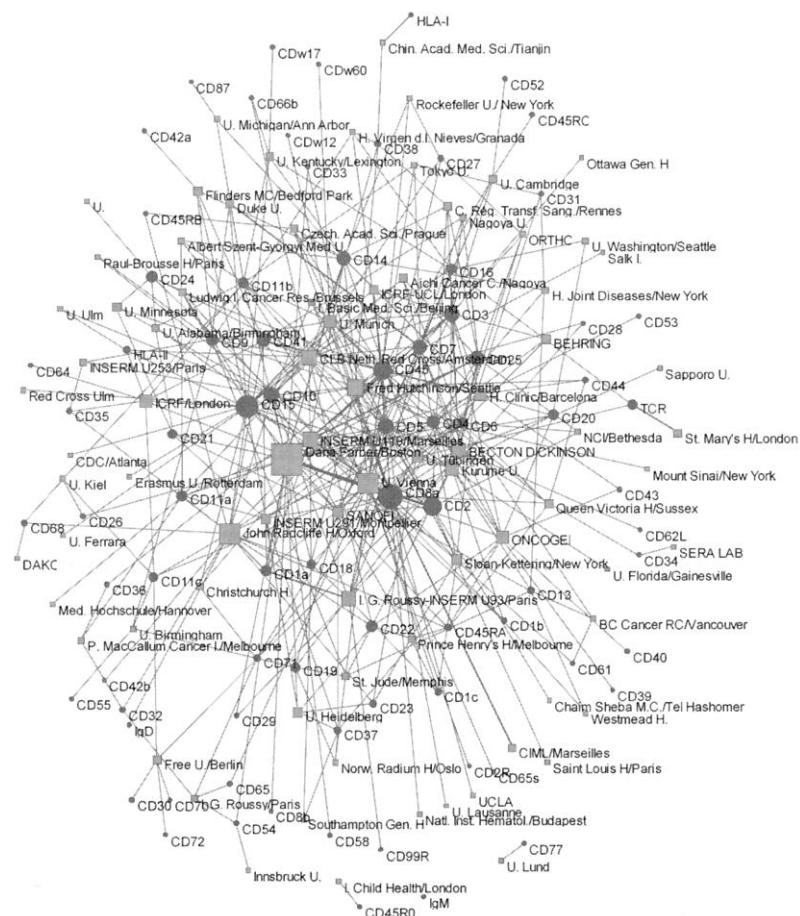
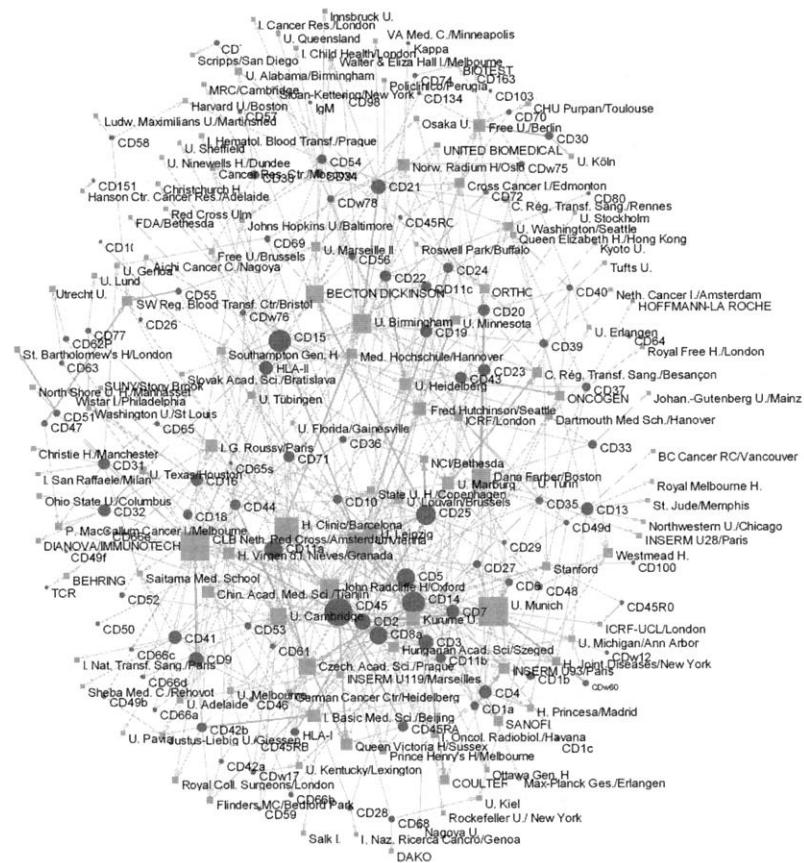


FIGURE 11
HLDA IV: institution/section map.



For instance, with the passage of time, a number of new institutions have joined the original group of laboratories in the role of major antibody contributors to the workshops. Some of these institutions, such as the John Radcliffe Hospital in Oxford or the Immunology Institute of the University of Vienna, have had their visibility confirmed by becoming the organizers of one of the workshops. Other institutions, such as the Hospital Clinic in Barcelona or the Central Laboratory of the Netherlands's Red Cross (CLB), have also become consistently high submitters.

We can advance the hypothesis that for some of these institutions, antibody submission has been a spin-off of specific research programs (situated somewhere along the basic-clinical continuum of biomedical research), while for others it has become a self-contained endeavor, linked, for instance, to routine diagnostic activities. Moreover, the research programs of all major and minor contributors have shifted in the 20 years since the First Workshop was launched, and these shifts can be read, at least partly, from the links entertained with specific CDs. And, along with

FIGURE 12
HLDA VI: institution/section map.



these transformations, and with the transformation of both the technical basis for defining CDs and of their market economy, the role and structure of the workshops have also shifted. In this sense, and although space limitations prevent us from reporting here on additional investigations, the RL maps are a tool for generating and investigating new research questions.

Commercial Companies

In this final section, we would like to explore another intriguing possibility offered by the maps generated by RL. Several antibodies, initially submitted at a given workshop, were resubmitted at a later one, either because they had not been clustered during the early workshop, because they were

later deemed to target new specificities, or because they could be used as controls for the workshop testing procedures. Since antibodies generally have a distinctive 'clone name' that was listed in our database, we were able to generate maps displaying the transfer of antibodies from one originator (the person or company submitting the antibody to a previous workshop) to another (the one submitting the same reagent to a subsequent workshop). Such maps thus show links between those institutions among which some sort of property transfer (for example, licensing of the antibody) has occurred. To produce the map shown in Figure 13 we eliminated those antibody clones with common names such as A1, A2, B1, B2, T1, T2, and so on: by doing so, we certainly lost a few genuine links, but we also eliminated a large number of (potential) artifacts.

The bottom left side of Figure 13 features, in addition to a few small company networks (DAKO, Nichirei), links connecting only two institutions that can probably be accounted for by the fact that originators moved

FIGURE 13
Institutions that submitted the same antibody to different workshops.



to another laboratory bringing their reagents with them. Far more interesting are the links between academic laboratories and major commercial companies. Among the commercial producers we see, on the top left and right side, Coulter and Immunotech and, at the center right side, BD and Pharmingen. In more recent years, their neighbors on the map bought Immunotech and Pharmingen. The networks within which these companies operate, as shown on the map, are quite distinct (although some links between them do exist), and some are larger than others.

Florida-based Coulter, a major producer of clinical equipment, including automatic cell counters, initially sold only a few major CD reagents with well-established clinical value. Immunotech adopted a different strategy. The French Medical Research Council (INSERM) supported Immunotech – created in 1982 as a spin-off of the publicly funded Centre d'Immunologie de Marseille-Luminy (CIML) – by signing a 10-year contract giving first-right-of-refusal for all antibodies produced by INSERM laboratories (interviews with Michel Delaage and Michel Hirn, Immunotech, Marseille-Luminy, 24 February 1997).²⁸ In 1983 Immunotech began selling specialized monoclonal antibodies for cell analysis. By the end of 1984, Immunotech's catalog featured 70 reagents including a large selection of leukocyte markers, thus placing the firm in competition with Ortho, BD and Coulter for a share of the French market estimated at 5–10 million French francs. The company soon began selling on the international market and established several foreign subsidiaries. By the mid-1990s, a major part of the company's catalog consisted of anti-leukocyte reagents. In 1996 Coulter acquired Immunotech. The rationale for this merger has been explained as follows by a Coulter marketing official:

The Immunotech type mindset is very different from Coulter's. Where Coulter has to justify things, everything has to stand on its own financially. It's difficult to justify a CD123b, we don't even know what it's going to be used for and we don't know what the return on that is. The time that it takes to develop that is the same as it takes to develop CD4 which brings in millions of dollars . . . We wanted a company that was focused on doing CD123b's and had no trouble justifying that, and that was Immunotech. They can really go out much further into the future. In this field you have to develop enough products that don't turn out to be big winners in order to find the ones that do. You may have 50 or 100 products of which one or two become real clinically relevant and highly profitable, but if you're not there, then just having the one that's the winner is not good enough. (Interview with William Gutierrez, Hialeah, Florida, 7 May 1996)

Figure 13 makes this strategy visible. By acquiring Immunotech, Coulter, whose supply of reagents appears to be provided to a large extent by the Sidney/Dana Farber Institute, obviously bought into a larger antibody-producer network that included laboratories located in Immunotech's home town of Marseilles (the CIML and one of its subsequent spin-offs, the INSERM Unit 119) but also other INSERM and European laboratories.

Figure 13, however, only shows a limited number of links, namely those corresponding to antibodies re-submitted by a company after initial submission by their initial producer. To gain more information about the origin of commercial antibodies we took the 2000 catalog of Beckman-Coulter-Immunotech that provides, for each of the CD reagents sold by the company, the clone name and references to selected papers. As expected, given the regulatory role played by the CD nomenclature, most of these reagents were submitted to a HLDA workshop and this information was mentioned in the catalog. We could thus easily locate them in our database. As previously noted, only recent reagents have been given a CD number without necessarily transiting through a workshop. We found the origin of these latter reagents by examining the scientific literature and through collaboration with Immunotech's antibody production manager in Marseilles who, with additional help from his Florida counterpart, agreed to verify and complete our database. We were thus able to create a new database similar to the HLDA database but including only the company's reagents. Figure 14 shows the resulting network.

Compared with Figure 13, Figure 14 shows the situation after the acquisition of Immunotech by Coulter, that is, after the merging of the two networks. The initial version of Figure 14 displayed ten different INSERM laboratories separately (for example, INSERM U448/Créteil, INSERM U211/Nantes, and so on); in the final version, shown here, we decided to treat them as a single unit, in order to visualize the role of this national research network. Figure 14 thus shows, to the right, a large bi-polar network, featuring two major hubs – INSERM and the Dana/Sidney Farber Institute – with connections to a few smaller poles, such as, on the US side, the Fred Hutchinson Institute in Seattle and, on the European site, the Hospital Princesa in Madrid. The left side of the figure features a series of small, isolated links. Obviously, the two companies, before their fusion, had counted on a few major producers for a large part of their catalog, occasionally resorting to additional producers when reagents against specific CD molecules were needed to complete the catalog.

We thought it would be interesting to compare Coulter-Immunotech with BD-Pharmingen. We proceeded in a similar way, using the company's 2000 catalog. We were able to trace the origin of 85% of the antibodies (168 out of 198). While some caution is needed in interpreting the results because of the incomplete data, the resulting map (not shown here) displays a larger degree of fragmentation than the one to be found in the Coulter-Immunotech map despite the fact that, as in the latter, a few institutions are major contributors (for example, the University of Munich and a laboratory of the Chinese Academy of Medical Sciences, whose presence is due to the fact that a Chinese researcher working for Pharmin-gen subsequently returned to his home country). The institution/CD map, however, by focusing attention on the German and Chinese contributions may be somewhat deceptive. Indeed, after generating the corresponding country/CD map (not shown here), we immediately noticed that by far the

FIGURE 14
Originators of the human CD antibodies featured in the year 2000 catalog of Beckman-Coulter-Immunotech.



largest contributing cluster was US-based. A similar map for Coulter-Immunotech (not shown here) shows, unsurprisingly, a bi-polar pattern with two large US and French clusters at the center of the map. In both cases, the large central cluster(s) are surrounded by smaller national satellite clusters (12 countries for Coulter-Immunotech and 14 countries for BD-Pharmingen, a noteworthy difference here being Australia, present in the latter but absent from the former). Beyond their single versus bi-national bases, both companies rely on the national network of the company's country of origin, with the difference, however, that whereas Coulter-Immunotech, as far as the USA is concerned, has relied on a smaller number of key contributors within that network (namely the Dana Farber Institute: see Figure 13), BD-Pharmingen has developed a diversified network of national suppliers.

Concluding Remarks

We opened this paper with a reference to the notion of ‘figuration’ developed by Norbert Elias (1978: 128–33) as an antidote to both methodological individualism, and its mirror image, deterministic, macro-structural approaches. Sociology, he argued, could only blossom by rejecting the artificial opposition between ‘individuals’ and ‘society’. Designed to take into account only individuals’ interdependencies, the notion can be fruitfully extended to include the tools, objects, and the material and conceptual entities without which individuals could hardly entertain relations. Figurations, then, turn into heterogeneous networks of the kind analyzed by the actor-network theory (Callon, 2001).

One of the properties of figurations as sociological objects is that they vary widely in scale, and the study of these variations, that is, of shifting configurational patterns, is an important element of their analysis. The latter, as is often the case when we confront new objects of inquiry, calls for the development of new analytical methods: Elias (1978: 132), for instance, explicitly mentioned the need for new statistical tools that were not predicated on the premise that each individual is an independent unit. The analysis presented in the present paper is a contribution in this broad direction. Unlike other statistical or network analysis software, RL, because of its minimalist ‘parti pris’ (Mogoutov, 1998), does not introduce any *a priori* assumption about the nature of the entities and of the links connecting them: it simply displays large amounts of information by following graphical conventions that allow researchers to inspect and interrogate the data without reducing them to a few indicators.

Our case study focused on a collaborative endeavor of the kind that is becoming increasingly common in the biomedical field. In this case the hybrid, heterogeneous nature of the collaborative networks is apparent from the dual referent of the acronym CD used to designate the entities on which the whole enterprise is centered. As noted by a major immunology textbook:

The term CD (cluster designation) was derived by computer analysis of monoclonal antibodies raised in different laboratories worldwide against human leukocyte antigens Monoclonal antibodies with similar specificity characteristics were grouped together and given a CD number. This number is now also used to indicate the specific molecule recognized by a group of monoclonal antibodies. (Roitt et al., 1989: 2–4)

The point, here, is not simply that the acronym ‘CD’ refers both to the tools targeting the leukocyte molecules and to the molecules themselves, thus conflating representation and intervention,²⁹ but also that the phrase ‘computer analysis of monoclonal antibodies raised in different laboratories worldwide against human leukocyte antigens’ refers to a complex socio-technical undertaking whose distinctive collaborative patterns shifted with the evolution of the technical platforms mobilized to perform the work and the changing market for its products. As shown in the present

paper, this collaborative undertaking can be analyzed by combining traditional and computer-assisted methods that do justice to its figural complexity and heterogeneous nature. In turn, the results of this kind of analysis can be used as starting points for further, more specific inquiries into different aspects of the overall endeavor.

Still, at the end of our methodological and substantive journey, readers may wonder: was it worth it? In particular, did the time we spent constructing the database and the computer power we mobilized to analyze it and produce maps generate results that could not have been obtained by more traditional methods? Having already argued that the mapping approach described in this paper is not meant to replace but, rather, to complement other approaches (in particular, ethnographic ones), we now specify that this complementary relation covers three different situations. First, some of the results we described could be, and have in fact been, obtained without resorting to RL mapping. We do maintain, however, that even in this case the availability of maps has allowed us to structure and add visual strength to our analytical argument. Second, some of the results could, in principle, have been obtained by, say, ethnographic analysis, but were only elicited, in practice, by the maps. This is particularly true of information that we gathered from our respondents after showing them the maps: asked to comment on a given figural pattern, they engaged in recollections that had not spontaneously occurred to them even in reply to specific questions. We thus suggest that in this era of collaborative biomedical endeavors, network maps should become an important element of the ethnographic interviewer's toolkit. Finally, it is obvious that the analysis of the overall figural pattern of each workshop, and of the evolution of these patterns from the early to the more recent workshops is predicated upon the availability of maps such as those featured in this paper. As previously argued, the maps provide a comprehensive view of the antibody producers and of the antibodies produced, and of their constitutive relations. This kind of map should be of even greater significance in situations where, unlike the CD workshops, the structure of the collaborative endeavor is less codified.

In conclusion, let us note that the existence of a striking similarity between the methods used by scientists to develop the CD nomenclature and those we used to map this process has not escaped our attention. This is by no means a unique situation. Software for visualizing three-dimensional models of molecules or analyzing the results of DNA chip experiments has been used to map social networks and to perform bibliometric analyses.³⁰ On a more general level, a group of physicists turned network analysts calls for the use of similar methods in analyzing social and biological networks.³¹ Unfortunately, while methods converge, the tendency, so far, has been to analyze each kind of network (social, biological, and so on) independently, that is, by respecting the alleged ontological distinctiveness of each domain. As argued in the present contribution, we strongly favor the opposite heuristic stance, namely the mapping and analysis of heterogeneous networks.

Notes

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1. For a related discussion of this issue, see Callon (2001). On the notion of 'figuration', and on how it avoids the macro-micro divide, see Elias (1978: 128–33). Figurations, in Elias' sense, refer to specific interdependency forms that, however, only involve human agents: here we extend it to include interdependences between humans and non-human entities such as tools or molecules.
2. For an initial, somewhat dated analysis of this episode, see Cambrosio & Keating (1992).
3. See, for example, Vinck (1992). One has only to think, in this respect, the staging of multi-center clinical trials.
4. For a recent discussion of actor-network theory, see Law & Hassard (1999); see also Callon (2001). Social network analysis is discussed later in the subsection on *Mapping relational data*.
5. For a detailed sociological analysis of this episode, see Cambrosio & Keating (1995).
6. But see Keating & Cambrosio (2003: Ch. 4) for more details.
7. Generally speaking, and as noted by Fortanier et al. (1997: 297) in their analysis of the therapeutic use of CD34, the definition and regulation of the objects at the center of a given set of practices provide a way of working around the uncertainties surrounding the coordination of these practices. The burden of agreement, in other words, is shifted from human actors to the objects themselves. This idea is borrowed from the 'economy of conventions' school: see, for example, Boltanski & Thévenot (1991).
8. A description of the HLA Workshops can be found in Dausset (1998: 79–108 and 119–41). On the HLA system, see Löwy (1986, 1987, 1990) and Moulin (1991: 208–26).
9. For more details on the statistical procedure adopted during the First Workshop see Cambrosio & Keating (1992).
10. An expression of this trend may be found in recent work on CD14 which has transformed this molecule from a mere marker used to separate cell subclasses into a molecule with significant immuno-physiological attributes; see, for example, Ziegler-Heitbrock & Ulevitch (1993).
11. <www.mh-hannover.de/aktuelles/projekte/hlda7/hldabase/select.htm> (last accessed May 2002). The database was created as part of the initiatives related to the Seventh Workshop. Further electronic information about the CD molecules and related antibody reagents is to be found in the 'CD Molecules' section of the 'Proteins on the Web' site developed by the National Institutes of Health: <www.ncbi.nlm.nih.gov/prow> .
12. For quality control purposes, a subset of antibodies was submitted twice to the 'blind panel section' of recent workshops. At the time of the first workshop, monoclonal antibodies were relatively new and uncertain reagents. Moreover, workshop participants used different techniques with the antibodies. It could thus be asked: how did the results obtained with these two different techniques compare? Furthermore, the

- reliability of the research groups participating in the workshop could not be taken for granted. Did they master the new techniques and instruments? Did they properly prepare and handle the cells against which the antibodies had to be tested? And what about the secondary reagents, that is, reagents other than monoclonal antibodies, including, for instance, traditional serological reagents (that is, reagents obtained by immunizing animals against a given substance and collecting the serum from the immunized animals) used to detect the presence of the monoclonal antibodies? Were they correctly produced and used and did laboratory differences in secondary reagents influence the outcome of the tests? If this were so, could laboratories and the results they generated be compared? Largely because of these uncertainties, the workshop organizers had to assess two kinds of reliability: the reliability of the laboratories performing the tests and the reliability of the tests. As one depended on the other, organizers of the First Workshop asked each laboratory to test the panel of 137 reagents not only against a set of cells of its own choice, but also against specific types of cells. Organizers also asked participating laboratories to indicate 'the procedures used to separate the cell populations as well as the results of local controls made to check the purity of a preparation' (Bernard et al., 1984: 15). As a result of this design, the organizers of the First Workshop categorized laboratories that were unable to implement techniques successfully used by the other research groups as unreliable.
13. A more practical issue concerned how to enter the name of the institution in the database. For graphical reasons (detailed names clutter the maps) we used shorthand denominations: for instance, Unit 93 of INSERM (the French Medical Research Council) was located at St Louis Hospital in Paris, a major French center for research on blood cancers, which is per se a relevant item of information: we opted, however, for 'INSERM U93/Paris' leaving out the information about the hospital; the latter, if necessary, can be added in our discussion of the RL maps. Similarly, if a single laboratory from, say, Duke University submitted antibodies, we simply use the shorthand 'Duke U' leaving out the name of the laboratory. The main issue, in this regard, was one of consistency: sometimes a researcher signed with the name of the university and sometimes with the name of an institute within that university: using tools provided by Excel (PivotTable Report), we have revised all the database fields to control for consistency. Finally, we also became aware of the fact that in some cases two institutions had established a long-standing collaboration leading to the joint production of antibodies, some submitted by one institution, some by another: in these rare cases we have used a joint denomination, For example, 'I.G. Roussy-INSERM U93/Paris'.
 14. The *Bulletin of the World Health Organization* published the report of the first CD Workshop (World Health Organization, 1984), thus giving the CD designations the endorsement of a major international institution that is well known for its work in the field of medical classifications.
 15. The tone was set by a short anonymous announcement stating that 'in the interest of consistency, *Nature* [would] in future use the CD nomenclature for all T-cell differentiation antigens between CD1 and CD8' (Anonymous, 1987). In order to facilitate the task, the journal included a list of the alternative, commercial designations. By restricting this initial enforcement of the CD nomenclature to the CD1–CD8 range, *Nature* adopted a pragmatic approach. Alternative designations for higher CD numbers often conveyed information about the function of the molecule. CD25, for example, was also known more tellingly as the interleukin-2 receptor.
 16. Zola (1999: 227) further notes that 'up to a third of antibodies submitted to workshops as being against known CD turn out to be wrongly assigned by their submitters', wrongly, that is, as sanctioned by the workshop. The official blessing, however, does not eliminate possible problems with individual batches of a given antibody.
 17. The workshop organizers also built into the system ways of dealing with uncertainty, such as provisional designations (so-called CDw) that have to be confirmed at the following workshop. The system is admittedly not foolproof, as 'dead CDs' and, more frequently, the splitting of CDs into sub-CDs show. But the overall scheme has turned

- out to be remarkably robust, and has been able to survive even the major change in focus from reactivity patterns to molecular analysis that, as already mentioned, has characterized the more recent workshops.
18. For additional information on (an early version of) RL, see Mogoutov (1998, 1999).
 19. For another example of the application of RL to the analysis of biomedical data, see Rabeharisoa (2001).
 20. For social network analysis see, for example, Scott (2000) and Wasserman & Faust (1994).
 21. Nor did many people, especially pathologists, seem to care: 'In those days pathologists spoke of lymphocytes and plasma cells as being similar to medical students – always there, never doing very much, but standing around looking on when important things were going on in medicine'; see Good (1994: 112).
 22. Things are actually more complex, because a distinction has to be made between 'functions' as laboratory immunologists understand them and 'functions' in the clinical sense. We would like to thank Dr Alfred I. Tauber for bringing this to our attention.
 23. An example of this reorientation can be found in a review paper by Timothy A. Springer entitled 'Adhesion Receptors of the Immune System,' which by March 1993 had received 892 citations (Veggeberg, 1993).
 24. See also two previous interviews with Stuart F. Schlossman (Boston, MA, 20 September 1988 and 30 April 1992). On maps featuring the name of originators rather than institutions, we see that different researchers from that team submitted to the three sections. For a detailed analysis of work by the Boston team in the area of leukocyte subsets, see Keating & Cambrosio (1994).
 25. We have posted a full set of maps (in color) on the following Web site:
<www.aguidel.com/ssss>, where maps can be inspected at greater magnification, zooming in and out of regions of interest.
 26. Reasons mentioned in the literature or during interviews included an unusual reactivity pattern caused by either the antibody's specificity for a rare surface molecule, the reagent's singular biochemical properties or other 'unknown reasons'.
 27. For a case study of molecular entities connecting laboratories, see Poon (2001).
 28. A joint initiative of INSERM (the French Medical Research Council) and CNRS (the French National Council for Scientific Research), the CIML had been established in 1975. On the CIML see Maurice (1993). On the creation of French biotechnology start-ups, including Immunotech, see Mustar (1997, 1998) and Walsh et al. (1996).
 29. On 'representing and intervening' in general see Hacking (1983) and, for the specific case of lymphocyte surface molecules, Cambrosio & Keating (2000).
 30. See, for example, the software suite OMNIVIZ (<www.omniviz.com>).
 31. See, for example, Girvan & Newman (2002) and, for a popularized introduction to these approaches, Barabási (2002).

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