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# Inventions shaping technological trajectories: do existing patent indicators provide a comprehensive picture?

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Since Schumpeter's seminal work on economic development (Schumpeter 1934), innovation is considered as one of the main drivers of firm performance and economic growth. At the same time, technological innovations vary considerably in terms of impact with only a minority of new inventions contributing significantly to economic growth. More recently a number of indicators derived from patent documents have been advanced to capture the nature and impact of technological inventions. Within this paper, we compare and validate these indicators within the field of biotechnology. An extensive analysis of the recent history of biotechnology allows us to identify the most important inventions (n=308) that shaped the field of biotechnology for the time period 1976 – 2001. A considerable number of these inventions have been patented between 1976 and 2001 (n= 215; 70%). For all USPTO biotech patents filed between 1976 and 2001 (n= 84,119) relevant indicators have been calculated. Within a next step, we assess which indicators allow to distinguish between most important patented inventions and their less influential counterparts by means of logistic regression models. Our findings reveal that the use of multiple, complementary, indicators provides the most comprehensive picture. In addition, it becomes clear that ex post indicators reflecting impact and value outperform ex ante indicators reflecting the nature and novelty of the invention in terms of precision and recall.

Keywords: patent indicators, important technological inventions, validation, biotechnology

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## 1. Introduction: Some technological inventions are more influential than others

While the importance of technological innovation is widely acknowledged in terms of value creation on the level of firms and economies as a whole, the nature and impact of technological inventions vary widely. Some new technologies imply a relatively small extension of prior art, while others completely disrupt or reshape the technological landscape. A large number of new technologies never end up in the commercialization phase whereas others stimulate the creation of new industries and allow companies to grow at impressive rates. For instance, Scherer and Harhoff (2000) found for 8 samples of company and university owned patents that 10% of the patents in the sample generated 48% to 93% of the total returns. A variety of concepts have been advanced to delineate important technological inventions ranging from radical to revolutionary, breakthrough, discontinuous and disruptive. Technological breakthroughs or radical inventions introduce new concepts that depart significantly from past practices, have the potential to disrupt existing markets, generate new markets and elicit follow-up innovations. As such, they can be seen as critical building blocks of a company's or a nation's creative destruction capacity and as a key determinant of long-term economic growth.

In general, the definitions used in the *management literature* tend to characterize the differential nature of inventions both in technological and in economical or financial terms. Adopting a technological perspective, radical inventions rely on a different set of science and engineering principles than previously existing technologies (Henderson and Clark 1990), and/or incorporate substantially different core technologies (Chandy and Tellis 2000). Incremental inventions in contrast, improve and extend existing technology. Henderson and Clark (1990) introduced the notion of architectural innovation in which core components remain unchanged but become related differently, in a new architecture. Radical innovations, according to their classification, are those where not only the concepts are linked together differently but the core concepts themselves are overturned. Along the economic and financial dimension, technological breakthroughs are listed as adding significant new value to the marketplace or by their impact on the competitive dynamics. For example, Tushman and Anderson (1986) defined a technological breakthrough as an order-of-magnitude improvement in the maximum achievable price versus performance frontier of an industry. Finally, breakthroughs have been defined in terms of the profound impact they have on firms, industries and markets. Utterback (1994) defined radical innovations or discontinuous change as "change that sweeps away much of a firm's existing investments in technical skills and knowledge, designs, production technique, plant and equipment," and Henderson (1993) described an innovation as being radical when it renders a firm's information filters and organizational procedures (partially) obsolete. In addition, a number of concepts closely related to radical innovations are popular in the management literature. Tushman and Anderson (1986) classified technological breakthroughs as either competence enhancing or competence-destroying, depending on whether they either reinforce or destroy established firms' existing competencies, skills, and knowledge. Technological breakthroughs are also described as inventions that serve as the basis for many subsequent technological developments (Fleming 2001; Ahuja and Lampert 2001) and as such shape the development of fields and related industries). Christensen (2003) focuses on disruptive technologies and their implications for established firms in an industry. A disruptive technology will have features that initially only a fringe market segment will value. It redefines the performance

trajectory (e.g. in the case of the disk drive industry, shrinking the size of disks). These disruptive technologies need not be radical in nature: in fact, Christensen notes that generally disruptive innovations are technologically straightforward.

In the *evolutionary economics* tradition, radical innovation is commonly evoked within typologies that attempt to characterize a product's or process' degree of innovativeness (Dosi 1982). Freeman (1992) proposed a taxonomy for technological innovation involving four levels of change: incremental innovation, radical innovation, changes of technical systems, and changes of techno-economic paradigms. Radical innovations, according to Freeman, are discontinuous as they introduce far-reaching changes in technology and affect different parts of the economy, ultimately leading to entirely new sectors.

In the last two decades, we not only witnessed the introduction of a variety of definitions; also a number of patent-based indicators have been advanced to assess the nature and value of patented technological inventions. Patents contain detailed information on the nature of the technology and leave a trail of patent citations, back citations and forward citations. This information allows to trace at least parts of the origins of technologies as well as their influence on future generations of technologies (when they directly or indirectly serve as prior art). In addition, patent citations provide indications of the economic value of patents (Griliches 1984; Jaffe & Trajtenberg 2002). Our contribution builds on most notable patent-based indicators used in the literature to assess the nature and value of patents, and aims to assess which indicators allow to identify inventive contributions that shape the development of a technological field. In order to do so, we identified major contributions within the field of biotechnology (time period: 1976 – 2001). Within a next step, the different indicators used in the literature are calculated for all granted USPTO biotech patents (time period 1976 – 2001). Finally, we rely on logistic regressions models to assess which indicators are able to identify most influential patented technologies. Our findings reveal that combining available indicators results in recall rates exceeding 55% while precision amounts to 82%. Ex post indicators measuring technological impact and economic value clearly outperform ex ante indicators reflecting the nature of an invention.

The remainder of the paper is outlined as follows. First, we introduce the data and indicators used in this analysis. Next, we discuss the descriptive statistics and results from multivariate analysis. We conclude with discussing implications as well as directions for further research.

## 2. Patent indicators that assess the nature and value of technological inventions: an overview

Different indicators relying on patent data have been used in the literature to assess the nature and impact of patented inventions.

### *2.1 Patent-indicators to assess the nature of technological inventions*

To assess the *nature* of an invention, patents can be compared in terms of backward citations, technology classes or both. Patents without backward citations to technical prior art have been labeled pioneering (Ahuja and Lampert 2001) while dissimilar patents have been defined as having a backward citation structure which is different compared to prior patents in the same field (Dahlin and Behrens 2005). The originality of a patent can be identified through a patent's backward citations with original patents relying on prior art from a broad range of technology fields (Trajtenberg et al. 1997). Finally, more creative inventions have been identified as displaying a novel pairwise combination of technology subclasses (Fleming et al. 2007).

#### *2.1.1 Dissimilar and unique backward citations*

A first way to identify technologically radical inventions was developed by Dahlin and Behrens (2005) using backward patent citations to other patents. By calculating the overlap scores between the backward citations of each patent P granted in year t with all other granted patents[1] in the same field, and averaging these overlap scores within each year relative to the grant year t, one can identify which patents have a dissimilar citation structure with respect to prior art and a unique citation structure with respect to patents granted in year t. Those patents which have low overlapping scores compared to prior art in the field are considered more novel and unique. Notice that patents without backward citations have the lowest possible overlap score and as such are considered as more novel or pioneering (Ahuja & Lampert 2001).

#### *2.1.2 New pairwise combination of technology subclasses*

The creation of new technology implies recombining and extending pre-existing technologies (Nelson and Winter 1982; Basalla 1988). Fleming (2001) conceptualizes technological invention as a recombinant search process across the technology landscape in which inventors experiment with the recombination of technological components. He argues a patent's technology subclasses capture the different components used to develop the technology. Using patent data, Fleming (2001) empirically shows breakthroughs, i.e. patents with the highest variability in forward citations, most likely originate from the recombination of familiar technology subfields, i.e. subfields with relatively more and more recent prior patents. Nevertheless, patents re-using the same combination of subfields as prior patents are found less likely to be breakthroughs. As such, breakthroughs most likely materialize from recombining disconnected but pre-existing technology subfields. To identify particularly original contributions with a potentially high impact on future technology development, Fleming et al. (2007) proposes to look at patents which are the first in history to recombine at least 2 previously disconnected technology subclasses.

#### *2.1.3 Originality*

[1] To calculate the overlap score between patent A and B, the number of overlapping backward citations of A and B is divided by the total number of backward citations of A and/or B. Only citations to patents granted in a year before the minimum grant year of A and B are taken into account.

Trajtenberg et al. (1997) develop a backward looking measure of the basicness of an invention. Originality captures the extent to which the nature of the research underlying the patent is based on technical prior art from a broad range of technology fields.

### *2.2 Patent-indicators to assess impact and value of technological inventions*

To assess the *impact* and *value* of the patent, scholars have primarily used forward citations, backward citations and technology classes. The number of citations a patent receives reflects its direct impact on future technologies as well as its private and social value (Gambardella et al. 2008). A similar backward citation structure between a patent and later patents reflects adoption by future generations of technologies (Dahlin and Behrens 2005). Patents which are cited by patents from different technology fields are considered to have a more general impact (Trajtenberg et al. 1997). Finally, technologies with a novel combination of technology subclasses are adopted by future generations of technologies in case the same combination of subclasses is frequently used by future patents (Fleming et al. 2007).

#### *2.2.1 Indicators relying on the count of forward citations*

The most popular indicator of patent impact or value is the number of forward citations received from future patents. The number of forward citations a patent receives is related to its technological importance (Albert et al. 1991; Carpenter et al. 1993; Jaffe et al. 2000) as well as its social (Trajtenberg 1990) and private value (Harhoff et al. 1999; Hall et al. 2005; Gambardella et al. 2008). The distribution of forward citations is very skewed with a large share of patents receiving no citations and a small minority of patents with a large number of forward citations. This pattern resembles the distribution of the actual value of inventions. Hence, it is likely that outliers in the distribution of forward citations pertain to more important inventions. Prior research has typically identified breakthrough patents as the top 1% or 5% in terms of citation received compared to patents with the same application year and technology class (Ahuja and Lampert 2001; Singh and Fleming 2010).

#### *2.2.2 Adoption of backward citations*

Besides having a dissimilar and unique backward citation structure, technologically radical patents should also have a backward citation structure which get adopted by future patents in the same field (Dahlin and Behrens 2005). The more similar the backward citations of a patent and future patents in the field, the more influence the patent has on future technological progress.

#### *2.2.3 Adoption of a novel pairwise combination of technology subclasses*

To assess the diffusion or adoption of a patented invention which recombines 2 disconnected technology subclasses, Fleming et al. (2007) look at the number of future patents which use the same pairwise combination of technology subclasses. The larger the number of future patents re-using the same combination of subclasses, the more impact the patent has on future technological progress.

#### *2.2.4 Generality*

Trajtenberg et al. (1997) develop a measure of generality, capturing the extent to which the patented inventions serves as prior art for a broad range of technology fields. So while originality measures the nature of the research itself, generality captures to what extent an invention is relevant for different technological fields..

## 3. Biotechnology

### *3.1 Definition and short history*

According to Bud (1993), the term biotechnology was coined as long ago as 1917, the year of the Russian revolution. Today, the best known definition is perhaps the one spelled out by the Organization for Economic Co-operation and Development (OECD 2005): "Biotechnology is the application of scientific and engineering principles to the processing of materials by biological agents to provide goods and services." Biotechnology is a complex field that emerged from agriculture and animal husbandry in ancient times through the empirical use of plants and animals which could be used as food or dyes (McGloughlin and Edward 2010). Moreover, contrary to its name, biotechnology is not a single technology. Rather it is a group of technologies that share two characteristics: working with living cells and their molecules, and having a wide range of practical uses that can improve our lives (Keener et al. 2012).

According to Buchholz and Collins (2010), 4 periods can be discerned within the history of biotechnology (before 1850, 1850 to 1890, 1890 to 1950, and the period from 1950 onwards). This paper focuses on the later period, more particularly the period from 1976 to 2001. By the 1950s, large scale production of for example beer, cheese, citric acid, pharmaceuticals and other products of social and economic relevance such as antibiotics had become well established. During that time biotechnology benefited from major public funding and realized an increasing economic impact. Major technological progress achieved during the late 1970s and 1980s, most notably due to genetic research and recombinant technologies. A milestone was the model of DNA as the molecular basis of heredity derived by Watson and Crick with the aid of data provided by Rosalind Franklin who worked in Maurice Wilkin's X-ray crystallography laboratory in 1953 (Watson and Crick 1953). However, the DNA revolution as Hotchkiss (1979) termed it, progressed or penetrated slowly into technology, initially having little effect on traditional processes and products. A significant change was triggered by the introduction of recombinant DNA (Cohen, Chang and Hsu 1972; Cohen and Boyer 1979; Cohen and Boyer 1980). The emergence of molecular biology and biochemical engineering coincides with a growing industrial interest and the range of products expanded significantly. The field's progress is reflected by the exponential rise in the number of journals devoted to biotech that were established in the late 1970s and early 1980s (Buchholz and Collins, 2010).

The integration of applied microbiology, biochemical engineering and molecular biology led to the creation of biotechnology as a scientific discipline on its own, with a common paradigm at the level of molecular research. Sub-disciplines such as genomics, transcriptomics, proteomics, metabolic flux analysis with quantitative analysis of

complex metabolic pathways and finally biochemical engineering and bioinformatics have merged to create bio-systems engineering (Sinskey 1999; Stephanopoulos 1999; Reuss 2001).

### *3.2 Identification of major contributions that shape the field of biotechnology*

In order to identify the most important technological developments that shaped the evolution of biotechnology, we relied on secondary sources including books, journal articles, websites of inventors, academics, companies and research institutes, and expert reports. Amongst those sources, we mainly relied upon scientific books that provide a consistent and exhaustive overview of major technological accomplishments in biotechnology or a particular subfield of biotechnology. Appendix 1 provides an overview of the major sources used in this respect. We verified multiple secondary sources to strengthen the overall consistency of our list of important inventions as any account might be conditioned by the personal interests or values of the authors. We concentrated on events labeled as discontinuous, pioneering, important, breakthrough, revolutionary, radical, drastic, cutting edge, fundamental, groundbreaking, dramatic, leap forward, original amongst others. In particular, we searched for those inventions which were described as contributing to the evolution of the field as a whole, highlighting fundamental leaps on certain key research trajectories or establishing new ones as clearly stated by authors.

### *3.3 Relating important contributions to patents*

After carrying out a comprehensive screening and assessment of technological contributions that shaped the field of biotechnology, we systematically searched for patents and publications associated with those contributions. Using information on the description and timing of the invention, the associated researchers, institutions and/or companies, we searched for corresponding patents and publications in the USPTO patent database and the ISI Web of Science (WOS) respectively. In some cases we found more than one corresponding patent and/or more than one corresponding publication. Of the 308 externally identified inventions, 215 (70%) were identified in the patent system while 224 (72 %) were found in the WOS database as scientific publications. For 84 (27%) of the events we only found at least one corresponding patent, for 73 (23%) we only found a publication while for 131 (43%) we found patent-paper pairs. For 9 events, we found multiple corresponding patents. Notice that for 31 contributions, neither a patent document, nor a scientific publication (present in the Web of Science) has been identified. Appendix 2 provides the reader with a detailed list of all major contributions considered within this analysis as well as the identified USPTO patents.

## 4. Data and findings

### *4.1 Sample Selection*

To identify all USPTO biotechnology patents, we made use of the OECD classification scheme which relies on IPC codes (OECD 2005). Data have been extracted from the Patstat patent database (version October 2011) and include all patents filed at the USPTO between 1976 and 2001 and granted before 2004 which fall into at least one of these IPC classes. The final sample used for analysis consists of 84,119 patents. Out of the 84,119 patents, 198 have been identified as an important contribution. Notice that 17 'important' patents were not classified as biotech according to the OECD definition based on IPC codes. This 17 patents are not included in the analysis as comparing with biotechnology patents might yield misleading results.

For the calculation of citation related indicators, we made use of the updated NBER patent database[2].

### *4.2 Variables*

#### *4.2.1 Dissimilar, unique and adopted backward citations*

We follow the methodology of Dahlin and Behrens (2005) and calculate for each patent P granted in year t the average annual overlap scores between the backward citations of P with respectively all other patents filed in the same field (main US technology class) within a time window of 5 years before and 5 years after the grant year of P (i.e. patents granted between t-n and t+n with 0<=n<=5). We extent their methodology by comparing a patent to all other US granted patents with at least one similar main technology class. So for each of a patent's main technology classes, we follow the methodology as outlined in Dahlin and Behrens (2005). First, we label P as being dissimilar compared to prior art in case the average annual overlap score is 0 or in case the average standardized annual overlap score is smaller than or equal to the $10^{th}$ percentile of all patents for each year t-n with n>0 and n<=5. Due to truncation, not all patents have a time window of 5 years before (and after) grant. For patents which we can only observe 3 or 4 years before grant, we require the patent's average overlap score to be 0 or it standardized average annual overlap score to be equal to or smaller than the 10th percentile threshold for each of the observed years before grant. Patents which can't be observed at least 3 years before and after the grant are not taken into account during the analysis. Following this methodology, 38% of the patents in our sample have a dissimilar citation structure. Second, a patent is labeled as unique in case the average standardized overlap score in the year of grant is below or equal to the 10 percentile threshold. We find 66% to pass the uniqueness criteria. Third, a patent is labeled as adopted in case the annual overlap score passes the $90^{th}$ percentile threshold for each year after grant. 7% of the patents is our sample pass the adoption criteria. Finally, 2.1% of the patents pass all 3 criteria.

#### *4.2.2 New and adopted pairwise combination of technology subclasses*

To identify patents which recombine 2 technology subclasses for the first time in history, we use the 2008 US technology subclass concordance to go through all technology subclass assignments of all US granted patents in order to generate all first pairwise subclass combinations. For each new subclass combination, we count the number of future patents re-using the same pairwise combination. In our sample of biotech patents, we find 44% of all

[2]see https://sites.google.com/site/patentdataproject/Home

patents displaying a new combination of technology subclasses with on average 54 future patents re-using the same combination.

#### *4.2.3 Originality and generality*

In line with Trajtenberg et al. (1997) and Hall et al. (2001), we calculate originality and generality using a measure reflecting the concentration of respectively backward and forward citations within technology classes. Originality is calculated as 1- bias-corrected[3] Herfindahl index of the technological classes (main) of all cited patents. Generality is calculated as 1- bias-corrected Herfindahl index of technological classes (main) of all citing patents.

#### *4.2.4 Indicators relying on the distribution of forward citation counts*

To identify patents with the largest impact on future technologies, we calculate for all granted US patents the count of forward citations as the number of US patents citing the patent (citations from patents granted until 2006 inclusive) and the truncated count of forward citations as the number of citations received within 5 years after application. Prior research has typically identified breakthrough patents as the top 1% or 5% in terms of citations received compared to patents within the same application year and technology class (e.g. Ahuja and Lampert 2001; Singh and Fleming 2010). This definition assumes each technology field to have a fixed share of high impact inventions each year and does not compare patents across years. To avoid a definition that forces a fixed proportion of breakthroughs every year in each class while allowing similar patents to be compared across years, we consider the distribution of both forward citations received within 5 years and the distribution of forward citations received from all future patents. We use the full count of forward citations to compare all patents sharing at least one 3-digit US technology class filed within the same year and the truncated citation count to compare all patents sharing at least one main technology class irrespectively of their time of filing. For each of the distributions, we calculate the mean and standard deviation of (truncated) forward citation counts. A patent is labeled as having a big impact in case both its truncated and full count of forward citations are larger than the mean plus n times the standard deviation in at least one of its technology classes. So for each technology class of a patent, the patent is compared with 2 distributions: the distributions of full and truncated forward citation counts. Using a 1, 2, 3, 5 and 10 standard deviation rule to identify outliers in the distribution of forward citations, we respectively find 6%, 3%, 1%, 0.5% and 0.09% of biotechnology patents in our sample to be labeled as having a disproportionate impact on future patents.

### *4.3 Descriptive statistics*

Table 1 gives an overview of descriptive statistics for the set of major technological inventions and for the control patents including a mean-comparison T-test between the two groups.

In terms of indicators reflecting the nature of the patented invention, we do not observe significant differences in the proportion of patents without citations to technical prior art. By contrast, important contributions seem to more frequently cite other patents compared to the control group (14 backward patent citations compared to 6 on average).

[3] A bias correction is necessary because not all patents have the same number of technology classes.

Furthermore, major contributions have more dissimilar backward citations (54% of dissimilar patents compared to 46% for the control group) and rely on more recent technical prior art with an average backward citation lag of 6.14 years versus 7.5 years for the control group. Both groups are not different in terms of originality indicating that important biotech patents do not rely on prior art stemming from a broader range of technology fields. Nevertheless, patent documents associated with important technological contributions contain a larger number of technology main and subclasses so they seem to cover a larger part of the technology landscape (2.65 main classes and 7.96 subclasses on average compared to 2.19 and 6.25 for the control group respectively). Finally, important contributions display a much larger number of citations to non-patent literature (45 versus 22 on average), are more likely to have a novel pairwise combination of technology subclasses (63% versus 45% on average) and contain a larger number of claims (22 versus 15 on average). In conclusion, patents associated with major technologies cite more patents, cite more recent technical prior art, contain more references to non-patent literature, have dissimilar backward citations compared to prior art in the same field but do not rely on prior art from a broader range of technology fields. Nonetheless, major patents seem to serve themselves a more general purpose by covering more technology fields, subfields and claims, and are more likely to combine previously disconnected technology subfields.

Besides being based on a different set of science and engineering principles and/or incorporating substantially different core technologies, most important technological contributions are expected to have a higher and broader impact on future technology trajectories. In line with expectations, patents associated with important contributions receive significantly more forward citations on average (105 citations and 27 citations within 5 years compared to 7 citations and 3 citations within 5 years for the control group). Accordingly, looking at outliers in the distributions of forward citations we observe 60% of the radical patents to be a 1 standard deviation outlier compared to 7% for non-radical patents and 20% to be a 10 standard deviation outlier compared to only 0.05% for the control group. Besides serving more extensively as prior art for future generations of inventions, they also tend to remain cited for a longer time with an average forward citation lag of 7.46 years compared to 5.87 for the control group. Furthermore, patents associated with important contributions seem to serve as prior art for a broader range of technology fields, reflected by an average generality score of 0.71 (compared to 0.51 for the control group). Likewise, for patents which make at least one new pairwise combination of previously disconnected technology subfields, the pairwise combination of important contributions becomes adopted by a much larger number of future patents. On average, 1,511 future patents will use the same component configuration compared to 44 future patents for the control group. Also, the backward citations of major patents are more likely to be adopted by future patents with 38% of important contributions having adopted backward citations compared to only 7% for the control group.

Finally, Dahlin and Behrens (2005) suggest to use a composite measure to identify technologically radical inventions. Besides having a citation structure which is dissimilar with prior art and gets adopted by future patents, they add an additional uniqueness criteria, i.e. having a backward citation structure which is different from patents granted in the same year in the same technology field. We find important contributions to display a backward citation structure which is less unique with 59% of the radical patents satisfying the uniqueness criteria compared to

67% for the control patents. According to the authors, technologically radical inventions should satisfy all 3 criteria. We find 17% of our important contributions to satisfy all 3 criteria compared to 2% for the control group.

Table 2 presents the correlation coefficients between most notable indicators. The dummies representing outliers in the distribution of forward citations coincide most with being an important contribution to the field. Also, the number of future patents re-using the same pairwise combination of subclasses displays a strong correlation.

In conclusion, the descriptive results suggest both backward looking measures reflecting novelty with respect to prior art as well as forward looking measures of value and impact signal important inventions within a field. Particularly measures reflecting impact on future technological progress seem to reveal discriminatory power.

### *4.3 Multivariate analysis*

Given that our dependent variable indicating whether the patent was identified as being a major contribution to the field is binary (0/1), we use logit models to assess the discriminatory power of the different indicators under study. All models include technology dummies for each of a patent's main technology classes (3digit) as well as a set of additional control variables including the number of assignees, the number of inventors, the number of citations to other patents and to the non-patent literature, the number of claims, the number of technology main and subclasses and patent age. Notice that patents in a main technology class without important contributions are dropped from the analysis during estimation. To assess the discriminatory power of the different indicators, we provide a number of statistics below each regression model in table 3. We are particularly interested in the sensitivity of the model: the % of important contributions which are predicted as such (so–called recall), as well as in the proportion of patents predicted to be important and which actually are (so-called precision).

Table 3 presents the results obtained for the full set of patents. Notice that important contributions only represent 0.24% of the total sample which seriously hampers the assessment of precision and recall rates of the different models (any model that would predict all patents as not important/radical would classify over 99% of all patents correctly). Therefore, we present parallel results for a reduced sample of matched patents in table 4. Using coarsened-exact matching (Iacus et al. 2009), we generate a more balanced sample of patents. We only retain control patents with exactly the same combination of technology classes, application year and grant year as at least one of the patents associated with an important technological contribution. Treatment and control patents for which no proper match is found are excluded from the analysis. For each remaining important contribution, we randomly sample 4 control patents among those which match and rerun the model on the reduced sample.

In terms of the indicators capturing the nature and novelty of the patented invention, we find recombining previously disconnected technology subclasses does not make a patent more likely to be important (column 3). Column 4 presents the findings for the different measures suggested by Dahlin and Behrens (2005). We find patents dissimilar to prior art in terms of backward citations are 37% more likely to be a major contribution to the field. Surprisingly, the uniqueness dummy has a negative impact suggesting that important contributions have more similar backward citations to patents filed in the same year and field. This might indicate that similar attempts building on the same

prior art are conducted during the same time period. Furthermore, we find major patents are not more original, i.e. do not rely on technical prior art from a broad range of technology fields. However, in line with the descriptive statistics, the number of backward patent citations, citations to non-patent literature, claims and technology main classes all have a positive and significant impact. The number of subclasses surprisingly becomes negative and significant in the column 7 and 8.

For the indicators reflecting impact and value, we find the dummies indicative of being an outlier in the distribution of forward citations have the most predictive power of all indicators. In column 2 of table 4, we find patents which are a one standard deviation outlier in the distribution of forward citations are 146% more likely to be important while 10 standard deviation outliers are 627% more likely to be important[4]. The stricter the criteria of being an outlier, the better the discriminative performance[5]. While a new pairwise subclass combination is not significant, the number of future patents adopting the same subclass combination is positive and significant. An increase in 100 future patents adopting the same pairwise combination is associated with a predicted increase of 8% in the likelihood of being a technological breakthrough. Also, important contributions have a backward citation structure which gets adopted by future patents. This effect is strong, patents whose backward citations strongly overlap with future patents are predicted 116 % more likely to be a breakthrough while we don't find support for a significant impact of combining dissimilarity, uniqueness and adoption (column 4). Column 5 present results for the originality and generality measures. While important contributions clearly serve a general purpose as technical prior art, they don't seem to rely themselves on technical prior art from a broad range of fields. An increase of 0.1 in generality is associated with an expected increase of 60% in terms of likelihood of being important. Finally, we present the results for all ex ante indicators reflecting dissimilarity or novelty with respect to prior art (column 6), ex post indicators reflecting impact (column 7) and both combined (column 8). The results clearly signal the superior performance of ex post indicators. Measures reflecting direct use as prior art through forward citations, indirectly reflecting adoption through subclass combination and backward citations display considerable more predictive power.

Table 4 presents the regression results for the matched sample of patents. The obtained results are in line with the overall findings. Notice that being a 10 standard deviation outlier in the distribution of forward citations is a perfect predictor of importance; not a single control patent belongs to this category. Therefore, 21 of the important contributions are dropped from the analysis. These patents have been included when calculating the discriminatory power of the models. In contrast to the results for the full sample, having a dissimilar backward citation structure is not significant anymore. The full model (column 8) combining all indicators is able to identify 55% of the radical patents (recall) while 83% of the patents predicted to be radical are indeed important (precision). Note again, that ex post indicators account for the lion share of both recall and precision.

[4] Marginal effects are calculated as the % change with respect to the average likelihood to be an important contribution, i.e. 0.2354%.
[5] Notice that more conservatively defined outliers are also less conservatively defined outliers. For instance, a patent which is a 3SD outlier is also a 2 and 1 SD outlier.

## 5. Discussion and conclusion

Technological innovation is an important constituent of economic growth. At the same time, technological inventions vary widely in terms of nature and impact. While there has been a great interest in the development of new technologies and their commercialization, only a minority of these new technologies will contribute significantly to private and social welfare in the future. As such, analyzing and understanding both the discovery and the exploitation phases of technological inventions, including their differentiated nature and impact, is important for companies and countries alike. While there has been a big interest in the competitive dynamics after the commercialization of inventions, large scale empirical research on the actual discovery of important technological contributions is scarce. As noticed by Dahlin and Behrens (2005) this is mainly due to the lack of reliable indicators that allow such a large scale quantitative assessment.

In this contribution, we rely on secondary sources to identify most important technological contributions in the field of biotechnology and relate these to patent data. As such it becomes feasible to examine whether and to what extent patent-based indicators advanced in the literature are able to identify these distinctive technological contributions. Indicators advanced so far can be labeled as ex ante to the extent that the indicator can be calculated as soon as the invention appears as a patent publication (e.g. novelty of backward citation patterns, new technology subclass combination). Available ex ante indictors reflect – at least partly - the nature and novelty of the patented invention. At the same time, a number of indicators can only be assessed ex post, i.e. after an invention's impact becomes visible (e.g. number of received citations, number of patents displaying similar citation patterns afterwards). Available, ex post, indicators reflect – at least partly – the impact and value of inventions. Our results reveal that relying on ex post indicators allows to identify important contributions on a larger scale (55,32%) and more accurately (81 % of important contributions are correctly classified) compared to ex ante indictors (27,16% and 77,19% respectively in the matched sample). The ex post indictors clearly outperform the ex post indictors in terms of precision and recall. As such, some of the recent proposed indicators, relying heavily on novelty do not qualify as accurate predictors of important contributions to the field. In addition, our findings clearly signal potential for future research aiming to identify more precisely the nature of inventions. As currently available indicators do not take into account directly the technical *content* of the inventions under study (e.g. by engaging in a textual analysis of the abstracts or claims), novel, complementary, indicators might rely on text mining algorithms to arrive at better results (e.g. Magerman, Song & Van Looy 2010; Kaplan & Vakili 2012). In terms of impact, the deployment of more sophisticated, network oriented, indicators might result in additional added value. Finally, the role of patent and non-patent references seems to do deserve further attention. While included as a control variable, the number of non-patent references consistently predicts important contributions in a positive manner. While precision and recall rates for the control variables only, are modest, it seems worthwhile to further investigate to what extent non-patent references might be relevant. We do hope our contributions inspires colleagues to engage in such endeavors.

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**TABLE 1: Descriptive Statistics**

| | | Final sample 198 Important Contributions (0.2354%) | | | |
|---|---|---|---|---|---|
| | Important Contribution | n | Mean | SD | Pr(\|T\| > \|t\|) |
| Forward Citation Count | 0 | 83921 | 6.90 | 13.98 | 0.0000 |
| | 1 | 198 | 104.96 | 183.60 | |
| Forward Citation Count 5y | 0 | 83921 | 2.80 | 5.40 | 0.0000 |
| | 1 | 198 | 26.97 | 40.42 | |
| Outlier 1SD class & class year | 0 | 83921 | 0.07 | 0.25 | 0.0000 |
| | 1 | 198 | 0.60 | 0.49 | |
| Outlier 2SD class & class year | 0 | 83921 | 0.03 | 0.17 | 0.0000 |
| | 1 | 198 | 0.49 | 0.50 | |
| Outlier 3SD class & class year | 0 | 83921 | 0.01 | 0.12 | 0.0000 |
| | 1 | 198 | 0.36 | 0.48 | |
| Outlier 4SD class & class year | 0 | 83921 | 0.01 | 0.09 | 0.0000 |
| | 1 | 198 | 0.30 | 0.46 | |
| Outlier 5SD class & class year | 0 | 83921 | 0.00 | 0.07 | 0.0000 |
| | 1 | 198 | 0.28 | 0.45 | |
| Outlier 10SD class & class year | 0 | 83921 | 0.00 | 0.02 | 0.0000 |
| | 1 | 198 | 0.20 | 0.40 | |
| No Forward Citations | 0 | 83921 | 0.26 | 0.44 | 0.0000 |
| | 1 | 198 | 0.04 | 0.20 | |
| Forward Citation Lag | 0 | 62230 | 5.87 | 3.54 | 0.0000 |
| | 1 | 190 | 7.46 | 3.62 | |
| Generality | 0 | 83921 | 0.51 | 0.28 | 0.0000 |
| | 1 | 198 | 0.71 | 0.12 | |
| Count Claims | 0 | 83895 | 15.42 | 15.18 | 0.0000 |
| | 1 | 197 | 21.98 | 20.05 | |
| Count main technology classes | 0 | 83921 | 2.19 | 1.04 | 0.0000 |
| | 1 | 198 | 2.65 | 1.25 | |
| Count technology subclasses | 0 | 83921 | 6.25 | 4.42 | 0.0000 |
| | 1 | 198 | 7.96 | 6.54 | |
| First Subclass Combi Dummy | 0 | 83921 | 0.45 | 0.50 | 0.0000 |
| | 1 | 198 | 0.63 | 0.48 | |
| First Subclass Combi Count Re-Use | 0 | 37931 | 43.97 | 188.39 | 0.0000 |
| | 1 | 125 | 1510.59 | 4654.71 | |
| Count Backward Citations | 0 | 83921 | 5.86 | 12.71 | 0.0000 |
| | 1 | 198 | 14.18 | 42.60 | |
| No Backward Citations | 0 | 83921 | 0.19 | 0.39 | 0.1948 |
| | 1 | 198 | 0.16 | 0.36 | |
| Backward Citation Lag | 0 | 67515 | 7.51 | 4.05 | 0.0000 |
| | 1 | 167 | 6.14 | 3.08 | |
| Originality | 0 | 83921 | 0.52 | 0.27 | 0.2591 |
| | 1 | 198 | 0.54 | 0.30 | |
| Count Non-Patent References | 0 | 83921 | 22.42 | 39.43 | 0.0000 |
| | 1 | 198 | 44.93 | 53.54 | |
| Dahlin and Behrens dissimilarity (before grant) | 0 | 82893 | 0.46 | 0.50 | 0.0474 |
| | 1 | 198 | 0.54 | 0.50 | |
| Dahlin and Behrens uniqueness (year grant) | 0 | 83921 | 0.67 | 0.47 | 0.0221 |
| | 1 | 198 | 0.59 | 0.49 | |
| Dahlin and Behrens adoption (after grant) | 0 | 83921 | 0.08 | 0.26 | 0.0000 |
| | 1 | 198 | 0.38 | 0.49 | |
| Dahlin and Behrens composite | 0 | 82893 | 0.02 | 0.14 | 0.0000 |
| | 1 | 198 | 0.17 | 0.38 | |

**TABLE 2: Correlation Matrix**

| | | (1) | (2) | (3) | (4) | (5) | (6) | (7) | (8) | (9) | (10) | (11) | (12) | (13) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| (1) | Important Contribution | 1 | | | | | | | | | | | | |
| (2) | Outlier 1SD class & class year | 0.0983* | 1 | | | | | | | | | | | |
| (3) | Outlier 2SD class & class year | 0.1303* | 0.6399* | 1 | | | | | | | | | | |
| (4) | Outlier 5SD class & class year | 0.1771* | 0.2690* | 0.4204* | 1 | | | | | | | | | |
| (5) | Outlier 10SD class & class year | 0.2967* | 0.1179* | 0.1843* | 0.4383* | 1 | | | | | | | | |
| (6) | First Subclass Combi Dummy | 0.0192* | 0.0852* | 0.0653* | 0.0333* | 0.0203* | 1 | | | | | | | |
| (7) | First Subclass Combi Count Re-Use | 0.2300* | 0.0436* | 0.0451* | 0.0424* | 0.0716* | 0.0892* | 1 | | | | | | |
| (8) | D&B dissimilarity (before grant) | 0.0087* | 0.0269* | 0.0154* | 0.0074 | 0.0038 | 0.1214* | 0.0263* | 1 | | | | | |
| (9) | D&B uniqueness (year grant) | -0.0078 | -0.0408* | -0.0324* | -0.0164* | -0.0075 | 0.1155* | 0.0252* | 0.4826* | 1 | | | | |
| (10) | D&B adoption (after grant) | 0.0563* | 0.1136* | 0.0959* | 0.0542* | 0.0328* | -0.0095* | 0.0432* | -0.0895* | -0.1543* | 1 | | | |
| (11) | D&B composite | 0.0503* | 0.0540* | 0.0448* | 0.0185* | 0.0158* | 0.0634* | 0.0804* | 0.1597* | 0.1054* | 0.5145* | 1 | | |
| (12) | Generality | 0.0334* | 0.1696* | 0.1145* | 0.0552* | 0.0295* | 0.1028* | 0.0202* | 0.1155* | -0.0495* | 0.0725* | 0.0431* | 1 | |
| (13) | Originality | 0.003 | 0.0606* | 0.0468* | 0.0257* | 0.0161* | 0.0341* | -0.0163* | -0.2810* | -0.2272* | 0.0923* | -0.0168* | 0.1067* | 1 |

* $p<0.01$

**TABLE 3: Identifying Important Contributions: Full Sample USPTO Biotechnology Patents**

| VARIABLES<br>Model | (1)<br>BT<br>Logit | (2)<br>BT<br>Logit | (3)<br>BT<br>Logit | (4)<br>BT<br>Logit | (5)<br>BT<br>Logit | (6)<br>BT<br>Logit<br>Ex ante | (7)<br>BT<br>Logit<br>Ex post | (8)<br>BT<br>Logit |
|---|---|---|---|---|---|---|---|---|
| outlier FC 1SD | | 1.8050*** | | | | | 1.4781*** | 1.4830*** |
| | | [0.273] | | | | | [0.273] | [0.278] |
| outlier FC 2SD | | 1.3160*** | | | | | 1.1465*** | 1.1345*** |
| | | [0.286] | | | | | [0.289] | [0.289] |
| outlier FC 5SD | | 0.9630*** | | | | | 0.9249*** | 0.9243*** |
| | | [0.334] | | | | | [0.339] | [0.345] |
| outlier FC 10SD | | 3.6375*** | | | | | 3.4846*** | 3.4944*** |
| | | [0.417] | | | | | [0.433] | [0.437] |
| First Subclass Combi Dummy | | | 0.1788 | | | 0.2261 | | -0.0285 |
| | | | [0.175] | | | [0.163] | | [0.195] |
| First Subclass Combi Count Re-Use | | | 0.0008*** | | | | 0.0006*** | 0.0006*** |
| | | | [0.000] | | | | [0.000] | [0.000] |
| D&B dissimilarity | | | | 0.3835* | | 0.3517** | | 0.0671 |
| | | | | [0.197] | | [0.176] | | [0.235] |
| D&B uniqueness | | | | -0.7819*** | | -0.9182*** | | -0.4239* |
| | | | | [0.217] | | [0.195] | | [0.256] |
| D&B adoption | | | | 1.1961*** | | | 0.8241*** | 0.6590** |
| | | | | [0.253] | | | [0.207] | [0.269] |
| D&B composite | | | | 0.3838 | | | | 0.3487 |
| | | | | [0.331] | | | | [0.382] |
| Generality | | | | | 6.2803*** | | 3.4719*** | 3.6142*** |
| | | | | | [0.992] | | [0.828] | [0.874] |
| Originality | | | | | -0.0794 | 0.1159 | | -0.6440* |
| | | | | | [0.301] | [0.324] | | [0.359] |
| Count assignees | -0.0930 | -0.1178 | -0.1469 | -0.0686 | -0.1049 | -0.0688 | -0.1573 | -0.1456 |
| | [0.147] | [0.121] | [0.152] | [0.130] | [0.145] | [0.143] | [0.118] | [0.118] |
| Count inventors | 0.0535 | 0.0462 | 0.0552 | 0.0538 | 0.0526 | 0.0516 | 0.0396 | 0.0422 |
| | [0.034] | [0.041] | [0.035] | [0.033] | [0.033] | [0.034] | [0.043] | [0.043] |
| Count PRS | 0.0052* | 0.0086*** | 0.0051* | 0.0008 | 0.0043 | 0.0030 | 0.0074*** | 0.0073*** |
| | [0.003] | [0.002] | [0.003] | [0.005] | [0.003] | [0.004] | [0.002] | [0.002] |
| Count NPRS | 0.0045*** | 0.0027*** | 0.0044*** | 0.0037*** | 0.0040*** | 0.0043*** | 0.0018** | 0.0019** |
| | [0.001] | [0.001] | [0.001] | [0.001] | [0.001] | [0.001] | [0.001] | [0.001] |
| Count claims | 0.0086*** | 0.0068*** | 0.0091*** | 0.0085*** | 0.0075*** | 0.0086*** | 0.0066*** | 0.0070*** |
| | [0.002] | [0.002] | [0.002] | [0.002] | [0.002] | [0.002] | [0.002] | [0.002] |
| Count tech. classes | 1.3601** | 1.2121* | 1.3607** | 1.4463** | 1.1134* | 1.5160** | 1.1107* | 1.2185* |
| | [0.618] | [0.706] | [0.638] | [0.614] | [0.608] | [0.664] | [0.655] | [0.666] |
| Count tech. subclasses | 0.0229 | -0.0132 | -0.0263 | 0.0181 | 0.0192 | 0.0159 | -0.0446** | -0.0426** |
| | [0.017] | [0.020] | [0.023] | [0.017] | [0.017] | [0.017] | [0.022] | [0.021] |
| Patent age | -0.1096*** | -0.1078*** | -0.0779*** | -0.1159*** | -0.1001*** | -0.1169*** | -0.0794*** | -0.0827*** |
| | [0.013] | [0.015] | [0.012] | [0.013] | [0.013] | [0.013] | [0.016] | [0.016] |
| Technology dummies | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Log Pseudolikelihood | -1189.0416 | -902.00573 | -1137.1608 | -1148.5955 | -1132.8989 | -1170.4729 | -848.21002 | -842.45801 |
| Pseudo $R^2$ | 0.1212 | 0.3333 | 0.1595 | 0.1498 | 0.1627 | 0.1336 | 0.3731 | 0.3764 |
| **Exp. Pr. >=0.5 as cut off** | | | | | | | | |
| Recall Pr( + \| BT ) | 1.03% | 17.95% | 6.15% | 1.03% | 1.03% | 1.03% | 23.08% | 24.10% |
| Specificity Pr( - \| NBT ) | 100.00% | 99.98% | 100.00% | 100.00% | 100.00% | 100.00% | 99.98% | 99.98% |
| PrecisionPr( BT \| + ) | 66.67% | 71.43% | 80.00% | 100.00% | 100.00% | 66.67% | 75.00% | 74.60% |
| Neg. pred. value Pr( NBT \| - ) | 99.74% | 99.78% | 99.75% | 99.74% | 99.74% | 99.74% | 99.80% | 99.80% |
| False + for NBT Pr( + \| NBT ) | 0.00% | 0.02% | 0.00% | 0.00% | 0.00% | 0.00% | 0.02% | 0.02% |
| False - for BT Pr( - \| BT ) | 98.97% | 82.05% | 93.85% | 98.97% | 98.97% | 98.97% | 76.92% | 75.90% |
| False + for BT Pr( NBT \| + ) | 33.33% | 28.57% | 20.00% | 0.00% | 0.00% | 33.333% | 25.00% | 25.40% |
| False - for NBT Pr( BT \| - ) | 0.26% | 0.22% | 0.25% | 0.26% | 0.26% | 0.26% | 0.20% | 0.20% |
| Correctly classified | 99.74% | 99.77% | 99.75% | 99.74% | 99.74% | 99.74% | 99.78% | 99.78% |

Robust standard errors in brackets
*** p<0.01, ** p<0.05, * p<0.1

**TABLE 4: Identifying Important Contributions: Matched Sample USPTO Biotechnology Patents**

| VARIABLES | (1) BT | (2) BT | (3) BT | (4) BT | (5) BT | (6) BT | (7) BT | (8) BT |
|---|---|---|---|---|---|---|---|---|
| Model | Logit | Logit | Logit | Logit | Logit | Logit Ex ante | Logit Ex post | Logit |
| outlier FC 1SD | | 1.8581*** | | | | | 1.5067*** | 1.5762*** |
| | | [0.420] | | | | | [0.479] | [0.474] |
| outlier FC 2SD | | 1.4375*** | | | | | 1.4981** | 1.4307** |
| | | [0.553] | | | | | [0.593] | [0.598] |
| outlier FC 5SD | | 0.8176 | | | | | 0.4734 | 0.5706 |
| | | [0.798] | | | | | [0.785] | [0.799] |
| outlier FC 10SD | | | | | | | | |
| First Subclass Combi Dummy | | | 0.3054 | | | 0.3743 | | 0.0445 |
| | | | [0.249] | | | [0.245] | | [0.317] |
| First Subclass Combi Count Re-Use | | | 0.0006*** | | | | 0.0005*** | 0.0005*** |
| | | | [0.000] | | | | [0.000] | [0.000] |
| D&B dissimilarity | | | | 0.3679 | | 0.2982 | | -0.0618 |
| | | | | [0.307] | | [0.298] | | [0.383] |
| D&B uniqueness | | | | -0.6405** | | -0.8339*** | | -0.3543 |
| | | | | [0.318] | | [0.316] | | [0.427] |
| D&B adoption | | | | 0.9331*** | | | 0.4368 | 0.1576 |
| | | | | [0.341] | | | [0.406] | [0.462] |
| D&B composite | | | | 0.1826 | | | | 0.7930 |
| | | | | [0.588] | | | | [0.625] |
| Generality | | | | | 7.6696*** | | 4.7156*** | 4.8108*** |
| | | | | | [1.466] | | [1.313] | [1.338] |
| Originality | | | | | -0.0812 | -0.1211 | | -0.4837 |
| | | | | | [0.409] | [0.416] | | [0.517] |
| Count assignees | -0.1453 | -0.3485 | -0.1318 | -0.1509 | -0.2373 | -0.1512 | -0.4080 | -0.4106 |
| | [0.148] | [0.287] | [0.153] | [0.145] | [0.203] | [0.158] | [0.312] | [0.300] |
| Count inventors | 0.0098 | 0.0026 | 0.0036 | 0.0126 | -0.0066 | 0.0174 | -0.0043 | 0.0122 |
| | [0.058] | [0.067] | [0.059] | [0.058] | [0.061] | [0.060] | [0.071] | [0.071] |
| Count PRS | 0.0086 | 0.0286 | 0.0096 | -0.0008 | 0.0081 | 0.0047 | 0.0211 | 0.0211 |
| | [0.020] | [0.022] | [0.020] | [0.021] | [0.013] | [0.020] | [0.017] | [0.017] |
| Count NPRS | 0.0137*** | 0.0115*** | 0.0136*** | 0.0127*** | 0.0129*** | 0.0131*** | 0.0112*** | 0.0112*** |
| | [0.003] | [0.003] | [0.003] | [0.003] | [0.003] | [0.003] | [0.003] | [0.003] |
| Count claims | 0.0254*** | 0.0065 | 0.0269*** | 0.0223*** | 0.0253*** | 0.0251*** | 0.0084 | 0.0084 |
| | [0.008] | [0.011] | [0.008] | [0.008] | [0.008] | [0.008] | [0.010] | [0.010] |
| Count tech. classes | 0.5599 | 0.4741 | 0.6639 | -0.0763 | 0.6584 | 0.7871 | 0.3870 | 0.2156 |
| | [0.500] | [0.647] | [0.528] | [0.642] | [0.490] | [0.504] | [0.704] | [0.747] |
| Count tech. subclasses | -0.0036 | 0.0279 | -0.0518 | 0.0073 | 0.0189 | -0.0239 | 0.0153 | 0.0113 |
| | [0.036] | [0.044] | [0.043] | [0.037] | [0.039] | [0.042] | [0.052] | [0.059] |
| Patent age | -0.0501** | -0.0332 | -0.0196 | -0.0432** | -0.0441** | -0.0424** | 0.0001 | 0.0041 |
| | [0.021] | [0.027] | [0.021] | [0.021] | [0.022] | [0.021] | [0.029] | [0.028] |
| Technology dummies | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Log Pseudolikelihood | -304.49303 | -220.40988 | -295.04756 | -295.80042 | -267.94068 | -299.96087 | -201.37105 | -200.03016 |
| Pseudo R2 | 0.0944 | 0.2734 | 0.1225 | 0.1202 | 0.2031 | 0.1079 | 0.3361 | 0.3405 |
| **Exp. Pr. >=0.5 as cut off** | | | | | | | | |
| Recall Pr( + \| BT ) | 14.18% | 51.06% | 31.48% | 30.86% | 37.04% | 27.16% | 55.32% | 55.32% |
| Specificity Pr( - \| NBT ) | 97.77% | 95.95% | 97.37% | 96.96% | 95.14% | 97.37% | 96.36% | 96.76% |
| Precision Pr( BT \| + ) | 64.52% | 78.26% | 79.69% | 76.92% | 71.43% | 77.19% | 81.25% | 82.98% |
| Neg. pred. value Pr( NBT \| - ) | 79.97% | 87.29% | 81.25% | 81.05% | 82.17% | 80.30% | 88.31% | 88.35% |
| False + for NBT Pr( + \| NBT ) | 2.23% | 4.05% | 2.63% | 3.04% | 4.86% | 2.63% | 3.64% | 3.24% |
| False - for BT Pr( - \| BT ) | 85.82% | 48.94% | 68.52% | 69.14% | 62.96% | 72.84% | 44.68% | 44.68% |
| False + for BT Pr( NBT \| + ) | 35.48% | 21.74% | 20.31% | 23.08% | 28.57% | 22.81% | 18.75% | 17.02% |
| False - for NBT Pr( BT \| - ) | 20.03% | 12.71% | 18.75% | 18.95% | 17.83% | 19.70% | 11.69% | 11.65% |
| Correctly classified | 79.21% | 85.98% | 81.10% | 80.64% | 80.79% | 80.03% | 87.24% | 87.56% |
| Observations | 635 | 614 | 635 | 635 | 635 | 635 | 614 | 614 |

Robust standard errors in brackets, outlier FC 10SD is dropped because it predicts important contributions perfectly in the matched sample, 21observations are dropped from the analysis

*** p<0.01, ** p<0.05, * p<0.1

**APPENDIX 1: Overview of major sources used to map the evolution of biotechnology**

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**APPENDIX 2: technologically radical biotechnology patents 1976-2001**

| YEAR | PATENTS |
|---|---|
| **1976** | |
| A Southern blot is a method routinely used in molecular biology for detection of a specific DNA sequence in DNA samples. Southern blotting combines transfer of electrophoresis-separated DNA fragments to a filter membrane and subsequent fragment detection by probe hybridization. The method is named after its inventor, the British biologist Edwin Southern. It is directly relevant to PCR. | |
| J. Michael Bishop and Harold Varmus, virologists at UCSF, showed that oncogenes appear on animal chromosomes, and alterations in their structure or expression can result in cancerous growth. | |
| **1977** | |
| **Genentech, Inc.**, reports the production of the first human protein manufactured in a bacteria: somatostatin (also known as growth hormone-inhibiting hormone (GHIH) or somatotropin release-inhibiting factor (SRIF)) , a human growth hormone-releasing inhibitory factor. For the first time, a synthetic, recombinant gene was used to clone a protein. Many consider this to be the advent of the Age of Biotechnology. | |
| Frederick Sanger's DNA sequencing method predominated in the early work on the sequencing of entire genomes of the bacteriofage, φX174 (5368 bp) and in 1982 coliphage λ (48 502 bp). | |
| W.J. Rutter and Howard Goodman isolated the gene for rat insulin. | |
| Walter Gilbert and Allan Maxam at **Harvard University** devised a method for sequencing DNA using chemicals rather than enzymes. | |
| Prior to the advent of molecular biology, microorganisms were treated with radiation or mutagens to alter their DNA in a random manner, with the hope of isolating survivors with a unique (or enhanced) propensity to produce a desired end product. The Rut C30 fungal strain of Trichoderma reesei, developed by Montencourt, was obtained in this manner to produce cellulases for hydrolysis of cellulose. | |
| **1978** | |
| The Cohen-Boyer technology for recombinant DNA is a path-breaking one by any standard, 'arguably the defining technology of modern molecular biology' (National Research Council, 1997, p.40). There are in fact three Boyer and Cohen patents: 4740470, 4468464, 4237224. All patents are continuations or continuations-in-part of patents originally filed in 1974, 1976, 1978. | US 4468464 |
| Recombinant nucleic acid and gene transfer technologies have dramatically increase the pace of biological research and drastically altered fundamental concepts in biology, genetics, cloning and medicine. […] The impact of this rapid rate of gene transfer vector development has given rise to a wide range of vectors with very different characteristics with little coordinated or assembled information on which to base containment and safety assessment. | US 4363877 |
| Products such as film, sheet, paper, fiber, coating material, binder, and molded materials e.g. capsules, cups et al are disclosed by using alpha-glucan | US 4306059 |
| One of the first patents on a molecular gene as such, patent number 4,322,499 (entitled 'Adrenocorticotropin-lipotropin precursor gene'), was filed in December 1978. This patent is identified by Warren Kaplan (2001) as the first true 'gene' patent. It deserves to be identified as a molecular gene patent because it specifies the gene sequence precisely in molecular terms by listing the As, Ts, Cs and Gs of the sequence in the claims | US 4322499 |
| Genentech, Inc. and The City of Hope National Medical Center announced the successful laboratory production of human insulin using recombinant DNA technology. This was achieved by a team of scientists led by Robert Crea, Keichi Itakura, David Goeddel, Dennis Kleid, and Arthur Riggs. Insulin thus became the first genetically manufactured drug to be approved by the FDA. | |
| Studies by David Botstein and others found that when a restrictive enzyme is applied to DNA from different individuals, the resulting sets of fragments sometimes differ markedly from one person to the next. Such variations in DNA are called restriction fragment length polymorphisms, or RFLPs, and they are extremely useful in genetic studies. | |
| **1979** | |
| The efficient cloning of longer fragments, up to 40 kb, was first made possible by the development of the cosmid cloning system by Collins and Hohn in 1978. They used small plasmids packaged in vitro into lambda bacteriophage coates. | US 4304863 |
| Dr. Arthur Riggs, Ph.D, is a geneticist who worked with Genentech to express the first artificial gene in bacteria. His work was critical to the modern biotechnology industry because it enabled the large-scale manufacturing of protein drugs, including insulin. Along with fellow City of Hope researcher Keiichi Itakura, Riggs collaborated with Genentech scientist Herbert Boyer, and used recombinant DNA technology to become the first to produce a human protein in E. | US 4366246 |

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| coli. Following the advice of Riggs and Itakura, the group successfully produced the hormone Somatostatin in 1977 as a proof of concept before they attempted to work with the more complicated insulin molecule. The group succeeded in producing insulin in 1978, and in 1979, Riggs received the Juvenile Diabetes Foundation Research Award for this work. | |
| One of the major strategies in genetic engineering technology was ligation of DNA fragments to a cloning vehicle. | US 4356270<br>US 4704362 |
| **Cetus** had begun research on one promising immune regulator, the interferons, that led to a joint agreement with **Shell Oil Company** on 1 July 1980. Cetus took responsibility for the scientific work and Shell for product development (regulatory affairs, clinical programs, and market research). | US 4262090 |
| The Cohen-Boyer patent "Process for producing biologically functional molecular chimeras" Dec 2, 1980 "The most-successful patent in university licensing, in The entire history of university licensing, is the Cohen-Boyer patent". As of February 13, 1995, licensing agreements had generated $139 million in royalties, which have shown an exponential increase in value since their beginning. In 1990–1995 alone, the licensing fees earned $102 million" Also, "The Cohen-Boyer patent is considered by many to be the classic model of technology transfer envisaged by supporters of the Bayh-Dole Act, which was intended to stimulate transfer of university-developed technology into the commercial sector. " | US 4237224 |
| Microorganisms play a fundamental role in the global re cycling of matter by re leasing carbon, nitrogen, phosphorus, and sulfur from an immense variety of complex organic compounds for reuse by living organisms and in generating energy. | US 4247543 |
| Carba decapeptide derivatives of $TYR^6$ are disclosed. They are useful as agents for the treatment of acromegaly and the management of diabetes in a mammal. | US 4244947 |
| Other important discoveries included the purification of DNA polymerase and RNA polymerase. | US 4283489 |
| Process for producing antibodies to hepatitis virus and cell lines is disclosed. | US 4271145 |
| In 1979 the first human interferon gene was cloned and during the next 18 months more successes followed. | US 4530901 |
| It was Michael (Mike) Smith in 1979 who had been the first to show that site-specific mutation with synthetic oligonucleotides was feasible. He was awarded the Nobel Prize for this in 1993. In the opening remarks of his lecture on that occasion in Stockholm, he pointed out that he had '... had the good fortune to arrive in the laboratory of Gobind Khorana, in September 1956, just one month after he had made the accidental discovery of the phosphodiester method for the chemical synthesis of e oligodeoxyribonucleotides, a synthetic approach whose full exploitation led to elucidation of the genetic code and the first total synthesis of a gene. | |
| **1980** | |
| Considerable effort has been put into the development of vector systems for cloning genes in animal cells. These vectors are needed in biotechnology for synthesis of recombinant protein from genes that are not expressed correctly when cloned in E.coli or yeast, and methods for cloning in humans are being sought by clinical molecular biologists attempting to devise techniques for gene therapy, in which a disease is treated by introduction of a cloned gene into the patient. | US 4394443 |
| At the end of the 1970s, researchers in molecular biology, immunology, and related fields began to develop additional strategies, moving away from knon molecules, such as insulin or growth hormone, to focus on unexplored domains, the biological molecules that seemed to have important regulatory roles but whose precise function, or range of functions, remained unknown. This new focus was above all on the immune system, particularly on the interleukins - proteins secreted by one component of the immune system that stimulate other components of the immune system activity. | US 4390623 |
| The potential usefulness of urokinase in fibrinolytic therapy for myocardial infarction and other conditions was studied since a decade ago. Activators of the plasminogen are present in small amounts in urine and tissues, the expense of purification and their low abundance have made large-scale clinical studies very difficult. Investigators in Europe, US and Japan have cloned complete sequence of cDNA for urokinase and other plasminogen activators and have their reported expression in microorganisms. | US 4370417 |
| Another approach is the utilization of monoclonal antibodies to identify a protein antigen in a given organism. This approach has yielded remarkable results when applied to the development of an antimalarial vaccine […] The gene for this antigen was cloned using monoclonal antibodies to screen a recombinant DNA E.coli expression library […] The nucleotide sequence of this isolated recombinant cDNA clone enabled the synthesis of peptides which mimicked the immunodominant epitope. | US 4362867 |
| Influenza viruses type A, B and C cause flu in mammals and birds. The influenza virus type A has been the cause of several pandemics in the past. […] Two of these proteins are located on the surface of the viral particles and define their antigenecity: a hemmaglutinin (H or HA) and a neuraminidase (N or NA). […] As the hemmaglutinin is the most rapidly evolving gene product and is crucial for viral attachment and evasion from the immune system recombinant influenza virus vaccines are developed using gene coding this protein. | US 4357421 |
| The ultimate blend of molecular genetics and clinical microbiology, however, was to be found in the development of diagnostic DNA probes for the identification of pathogenic bacteria directly from clinical specimens. Steve Moseley, a graduate student in Stan's laboratory, used a colony DNA hybridization technique and | US 4358535 |

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| cloned genes encoding the heat-stable and heat-labile enterotoxins of ETEC to detect homologous sequences in E.coli isolated from patients with diarrhea. This technique revolutionized the identification of bacterial pathogens, since laborious and expensive phenotypic tests such as animal toxin assays could be replaced by a simple colony hybridization. | |
| Many plasmid vectors in current use carry the origin of DNA replication from the genome of a single-stranded filamentous bacteriophage such as M13 or f1. Such vectors, which are sometimes called phagemids, combine the best features of plasmids and single-stranded bacteriophage vectors and have the advantage of two separate modes of replication: as a conventional double-stranded DNA plasmid and as a template to produce single-stranded copies of one of the phagemid strands. […] since their introduction in the early 1980s, phagemids have eliminated much of the need to subclone segments of foreign DNA from plasmids into conventional single-stranded bacteriophage vectors. | US 4349629 |
| A method is provided so that mature proteins or polypeptides can be produced, free of signal sequences or other chemical substituents, such as an f-met, on the proteins or polypeptides. | US 4338397 |
| A fundamental limitation of competitive immunoassays is that the signal levels at zero and very low concentrations of analyte are relatively high, causing a low signal: noise ration and impaired sensitivity. Since micro- and nanoscale immunoassays produce very low levels of signal it is advantageous to use the immunometric format to maximize the signal:noise ratio. The ambient analyte assay format offers 2 additional advantages. First, it is unique in that the exact volume of sample does not need to be known, as the antibodies sample the analyte providing an estimate of concentration around the antibody spot. Second, this assay involves small microspots of antibody, typically less than 100 micron in diameter and spaced less than 50 micron apart, which lends itself to manufacture at the microscale. | US 4376110 |
| In 1980 Mario R. Capecchi developed the methodology for microinjection of DNA and other molecules, directly into the cell nucleus. This considerably increased the efficiency of producing recombinant cell lines compared to just allowing uptake of DNA into the cells or injecting it into the cytoplasm. About 30% of the cells, injected at a rate of nearly a 1000 per hour, incorporated foreign DNA. | |
| **1981** | |
| Researchers describe and review protocols for protoplast fusion for microbial species found to be generally applicable for industrial strain development | |
| Major processes that use immobilized enzymes are for isomerization of glucose to fructose (HFCS production) and the modification of 6APA (i.e. aminopenicillic acid). In vitro, immobilized enzymes (i.e. enzymes attached to an insoluble matrix) act on homogeneous substrates where both substrate and product are dissolved in a liquid. in this case, an immob. enz. enables ease of processing and the ability to reuse the enzyme. | US 4379171 |
| Steven Rosenberg and his colleagues at the National Cancer Institute were reporting promising results using crude interleukin 2 prepared from human cell lines. These results indicated that IL-2 might well play a role in strengthening the immune system and might be a potent anticancer agent. IL-2 was becoming the "molecule of choice". | |
| Landmark Diamond v. Chakrabarty case leads to first patent of genetically engineered microorganism. The U.S. Supreme Court ruled in that genetically altered life forms can be patented. This Supreme Court decision allowed the Exxon oil company to patent an oil-eating microorganism. This ruling opened up enormous possibilities for commercially exploiting genetic engineering. | US 4259444 |
| Genentech, Inc. cloned interferon gamma. | US 5582824<br>US 5096705<br>US 4925793<br>US 4727138<br>US 4762791 |
| W.J. Rutter and Pablo Valenzuela published a report in Nature on a yeast expression system to produce the hepatitis B surface antigen. | |
| In a relatively simple procedure, two human urinary kallikreins can be purified to apparently homogeneous forms. Results of studies underway at present indicate that our purification procedure can be made simpler still. Concentration of urinary proteins by ultrafiltration eliminates the need for precipitation of proteins with (NH4)2SO4 and for decolorizing with charcoal. In contrast with the human urinary protein(s) purified by Hial et al. (1974), the kallikreins obtained by our method possess strong arginyl esterase activities (fraction A-1-2, 76,umol/min per mg of protein; fraction A-2, 100,umol/min per mg of protein). | US 4327178 |
| Octapeptides lowering growth hormone are disclosed. | US 4328135 |
| The paper describes our recent studies on the selection of a suitable acyl group for attachment to the hydrazide moiety and an active sied chain for the 2-position of the tetrapeptide hydrazide. In general analogs synthesized with these considerations in mind have been found to be potent analgesics when administered i.v. and s.c. Among the analog prepared, H-Tyr-D-Met(O)-Gly-Phe-NHNHCOCH2CH3, has been found to have extraordinarily high activity is the hot-plate assay after | US 4382923 |

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| either s.c. or i.v. administration. | |
| In vivo experiments suggest that treatment of chronic renal failure patients with a rennin inhibitor might result in a significant improvement of the disease status. | US 4384994 |
| Scientists at **Ohio University** produced the first transgenic animals by transferring genes from other animals into mice. | |
| Mouse embryonic stem cells are derived from the inner cell mass by scientists Martin Evans, Matthew Kaufman, and Gail R. Martin. Gail Martin is attributed for coining the term "Embryonic Stem Cell". | |
| The worldwide sales of monoclonal antibodies was around 3.5 billion US dollars in 2001, and grew to an estimated 5 billion US dollars in 2003. […] Monoclonal antibodies as weapons in the battle against cancer. […] a number of therapeutics based on m.a. are now on the market after yielding promising results in clinical studies. | US 4474893 |
| New and useful intermediate nucleotides bound to an inorganic polymer support and processes for the conversion to oligonucleotides which are especially useful for the synthesis of polynucleotides, particularly ribonucleic (RNA) and deoxyribonucleic acids (DNA). | US 4458066 |
| **Eli Lilly** received a license to make insulin. | US 4421685 |
| **1982** | |
| The incorporation of a bacterial gene from Bacillus thurigiensis (Bt) gene, into cotton (Bollguard®) enabled the cotton to produce proteins that are toxic to cotton bolloworm and budworm. Another genetically altered product by Monsanto, introduced in 1996, was cotton seed that contained a gene from cacterium, Bt. the gene enables the bacterium - and now the cotton plants - to make a protein that is toxic to bollworms ad tobacco budworms, thereby reducing the need for pesticides that are otherwise used to control insect infestations. | US 4467036 |
| **Applied Biosystems, Inc**. introduced the first commercial gas phase protein sequencer, dramatically reducing the amount of protein sample needed for sequencing. | US 5273715 |
| Michael Smith at the University of British Columbia, Vancouver, developed a procedure for making precise amino acid changes anywhere in a protein. | US 5118800 |
| Cetus, Immunex, and Genentech were about to lose that race to the Japanese researcher Tadatsugu Taniguchi, who isolated the gene for IL-2 in late 1982. | US 5399669 |
| A novel non-allelic human growth hormone variant is disclosed. It is prepared by a new method of obtaining cDNA from the genomic sequences of a eukaryotic organism. | US 4446235 |
| Rosenberg sought to assess the ability of recombinant IL-2 to make T cells grow, to measure its effects in in vistro sensitization of T cells against foreign cells, and to use it to make more lymphokine-activated killer (LAK) cells. These are so-called cytoxic, or "killer", T cells, which, when activated by IL-2, destroy a variety of types of tumor cells. | US 4690915 |
| The clinical progress with conjugates of MAbs and cytotoxic drugs has been rather slow. An important factor that has limited the use of this approach for treatment of cancer is the relatively low potency of standard chemotherapeutic agents. The potency of these compounds is further reduced by their conjugation with MAbs. A recent report that such a conjugate, BR96-dexorubicin is highly effective in curing xenografted human carcinoma-bearing mice, has rejuvenated great interest in MAb-drug conjugates. | US 4671958 |
| Frederick Sanger's DNA sequencing method predominated in the early work on the sequencing of entire genomes of the bacteriofage, φX174 (5368 bp) and in 1982 coliphage λ (48 502 bp). | |
| **1983** | |
| Mullis' own version of how he came to the concept of PCR. | |
| A landmark paper announced a successful diagnostic test for sickle-cell anemia that used two probes to distinguish the normal-betaglobin allele from the mitation. This was the first timean allele-specific oligonucleotide proble had been successfully used on human genomic DNA. | US 4395486 |
| **Stanford Research Institute International** filed for a patent for an E. coli expression vector. | US 4393064 |
| Nucleoside medications contribute an astonishing array of chemistries and structures to nucleic acids. The importance of these chemistries and structures to DNA and RNA function is only beginning to be understood. | US 4711955 |
| Recombinant immunoglobin preparations are disclosed. | US 4816567 |
| Jay Levy's lab at **UCSF** isolated the AIDS virus at almost the same moment it was isolated at the **Pasteur Institute** in Paris and at the **NIH.** | |
| That particular award was given to Dr. Mark for his work in obtaining a patent for Human Recombinant Interleukin-2 Muteins, which is used to treat cancer of the kidney and skin, and is still marketed internationally. | US 4518584 |
| A study of an extended family in Venezuela with Huntington's chorea demonstrated that family members with the disease show a distinct and characteristic pattern of restriction fragment lengths, leading to a new screening test. The same methods of investigation revealed patterns for cystic fibrosis, adult polycystic | |

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| kidney disease, Duchenne muscular dystrophy, and others. | |
| Processes for inserting DNA into eucaryotic cells and for producing proteinaceous materials are disclosed. | US 4634665 |
| **1984** | |
| The incorporation of a bacterial gene from Bacillus thurigiensis (Bt) gene, into cotton (Bollguard®) enabled the cotton to produce proteins that are toxic to cotton bollworm and budworm. | US 4683194 |
| Monoclonal antibodies that recognize a stage-specific antigen on immature human marrow cells are provided. These antibodies are useful in methods of isolating cell suspensions from human blood and marrow that can be employed in bone marrow transplantation. Cell suspensions containing human pluripotent lympho-hematopoietic stem cells are also provided, as well as theraputic methods employing the cell suspensions. | US 4714680 |
| Method for transporting substances into living cells and tissues and apparatus has been disclosed. The process can be used to mark cells or tissue or to biochemically affect tissues or tissue in situ as well as single cells in vitro. | US 4945050 |
| Cal Bio scientists described in Nature the isolation of a gene for anaritide acetate, which helps to regulate blood pressure and control salt and water excretion. | |
| Charles Cantor and David Schwartz developed pulsed-field gel electrophoresis. | US 4695548 |
| Method for identification and isolation of DNA encoding a desired protein. | US 4675285 |
| […] molecular biologist […] will be tempted to buy a completely automated machine. Several such very sophisticated pieces of equipment are now available on the market. […] they give excellent results. | US 4668476 |
| This invention provides a method for diagnosis of genetic abnormalities or other genetic conditions which can be readily automated. The method is used to determine the presence or absence of a target sequence in a sample of denatured nucleic acid and entails hybridizing the sample with a probe complementary to a diagnostic portion of the target sequence (the diagnostic probe), and with a probe complementary to a nucleotide sequence contiguous with the diagnostic portion (the contiguous probe), under conditions wherein the diagnostic probe remains bound substantially only to the sample nucleic acid containing the target sequence. | US 4883750 |
| **Harvard** molecular geneticists Philip Leder and Timothy Stewart awarded the first patent for a genetically altered animal, a mouse that is highly susceptible to breast cancer. It became known as the "oncomouse". | US 4736866 |
| Methods and compositions for detecting human tumors are disclosed. | US 4699877 |
| One year after Mullis conceived of PCR, he returned to the 58-base-pair region of the human beta-globin gene containing the sickle-cell mutation that Elrich's group had been working on. By june 1984 Mullis was satisfied that he had succeeded in achieving some amplification. | US 4617261 |
| Major limitations to treatment with synthetic peptides […] and include the cost of production, the short in vivo half-life, and the lack of oral bioavailability. Each of these limitations could potentially be overcome by employing gene therapeutic procedures.[…] Several types of antiviral proteins have been used in gene therapeutic approaches. | US 4626524 |
| The genesis of the antibiotic industry that preceded the current era of engineered organisms was catalyzed by government incentives and support during World War II. The motivation was the discovery of the beneficial effects of penicillin and the difficulty of producing penicillin through chemical synthesis. | US 4626525 |
| R. Gallo and L. Montagnier announced the identification of retrovirus involvement in AIDS. | |
| **1985** | |
| Axel Ullrich reported the sequencing of the human insulin receptor in Nature. | |
| W.J. Rutter's **UCSF** team described the sequencing in Cell two months later | |
| Since the discovery of tumor necrosis factor TNF alfa […], TNF superfamily has grown to a large family of related proteins consisting of over 20 members that signal through over 30 receptors. Members of this superfamily have wide tissue distribution and play important roles ranging from regulation of the normal biological processes such as immune responses, hematopoiesis and morphogenesis to their role in tumorigenesis, transplant rejection, septic shock, viral replication, bone resorption and autoimmunity. | US 4677063 |
| One of the major achievements in the peptide fields is related to the tumor imaging (somatostatin). | US 4812554 |
| The forerunner of combinatorial chemistry using solid-phase synthesis became known as the 'tea-bag' technique, and was developed by Richard A. Houghten in 1985 for peptides. | US 4631211 |
| The summary of valuable products derived from plant materials by Balandrin et al. (1985) is as valid to day as it was in 1985. their analysis shows that the recovery of bioactive compounds, classified as secondary metabolites, will continue to be an important source of medicines, pesticides, and specialty chemicals. | |
| Kary Mullis and others at Cetus Corporation in Berkeley, California, invented a technique for multiplying DNA sequences in vitro by, the polymerase chain reaction (PCR). PCR has been called the most revolutionary new technique in molecular biology in the 1980s. Cetus patented the process, and in the summer of | US 4683202 |

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| 1991 sold the patent to Hoffman-La Roche, Inc. for $300 million. By the way, it took close to 4 years for specialists to appreciate the technology's potential, and longer still for a larger scientific community to begin practically exploiting its power. | |
| […] It is now critically important to develop human anti-tumor antibodies which can be used clinically in order to determine whether human monoclonal antibodies are the key to effective cancer immunodiagnosis and therapy. | US 4753894 |
| Programs to develop herbicide resistant plants have resulted in genes which can be used as selectable markers in plant […] For example, a Salmonella gene encoding the enzyme 5-enolpyruvyl-3-phosphoshikimate synthase (EPSP synthase) was produced accordingly. | US 4769061 |
| **Cal Bio** cloned the gene that encodes human lung surfactant protein, a major step toward reducing a premature birth complication. | US 4912038 |
| **1986** | |
| UC Berkeley chemist Peter Schultz described how to combine antibodies and enzymes (creating "abzymes") to create pharmaceuticals. | |
| A regiment of scientists and technicians at **Caltech and Applied Biosystems, Inc.**, invented the automated DNA fluorescence sequencer. | |
| Frederick Sanger's DNA sequencing method predominated in the early work on the sequencing of entire genomes of the bacteriofage, φX174 (5368 bp) and in 1982 coliphage λ (48 502 bp). Animal viruses followed: 1986-1990, for example the 229-kb genome of cytomegalovirus (CMV) and the 192-kb genome of Vaccinia virus (191.6 kb) as well as organelle DNA: 1986 chloroplast DNA (121 024 bp) and in 1992 mitochondrial DNA of the liverwort Marchantia polymorpha (184 kb). | |
| Since its conception by K. Mullis in 1985, the PCR 'short cut' has frequently made previously difficult or inaccessible gene sequence available for isolation, analysis, cloning and in vitro manipulation. | US 4683195 |
| The production of glyphosate-resistant crops has been the focus of much research for over a decade. | US 4940835 |
| The determination of the primary structure of proteins and peptides is a crucial step in the characterization of these molecule. […] Automated instrumentation is now used for this process, as well as for the subsequent identification of the amino acids release from the sample. | US 4811218 |
| Any separation method depends on the differences between the items to be separated. Charge and size are two properties of molecules that are frequently used for separation. One of the most widely used techniques in molecular biology, gel electrophoresis, uses both these properties. […] The cross-linking gives rise to pores, and the choice of separated – agarose for larger fragments (thousands of oligonucleotides) and polyacrylamide for smaller ones (hundreds of oligonucleotides). | US 4855225 |
| A definition of neoplasms and rules for distinguishing them from other classes of diseases could only be made after the appropriate avances had been made in microscopic anatomy and pathology, of which we may recall the description of the tissues. | US 4968603 |
| The calculation of receptor binding affinity for each newly generated derivative ligand remains the most challenging aspect of drug design. Not only is this task very difficult, it also is critical for the success of the program. […] Accurate determination of ligand-receptor binding typically involves complex, CPU-intensive quantum chemical calculations. | US 4859609 |
| Recent investigations have demonstrated that extremophilic archaea, bacteria and fungi have colonized environments that were believed to be inhospitable for survival. Their true diversity in fact, is not yet been fully explored. The thermostable enzymes isolated from these organisms have just started providing conversions under conditions that are appropriate for industrial applications. […] With the availability of thermostable enzymes a number of new applications in the future are likely. | US 4889818 |
| **1987** | |
| Alec Jeffreys introduces technique for DNA fingerprinting to identify individuals. | US 5175082 |
| **Calgene, Inc.** received a patent for the tomato polygalacturonase DNA sequence, used to produce an antisense RNA sequence that can extend the shelf-life of fruit. | US 4801540 |
| Maynard Olson and colleagues at Washington University invented "yeast artificial chromosomes," or YACs, expression vectors for large proteins. | US 4889806 |
| Surprising finding: endothelial carcinomas which over-express the 'oncogene' ras, were in fact less malignant than others with a lower level of expression. The diagnostic potential for this type of method became immediately clear. The concept that miniaturization would permit the simultaneous analysis of an ever-increasing number of samples with an increasing number of probes and with reduced material costs, drove further developments towards CHIP and other microarray technologies. | |
| Process for amplifying, detecting, and/or cloning nucleic acid sequences using a thermostable enzyme has been disclosed. | US 4965188 |
| Amplification method for polynucleotide assays was invented by researchers at Syntex | US 4994368 |
| The creation of muteins became reality. Genec loning provides the final link to close the circle. This aspect was certainly included in the work John Collins' group on the design of human PSTI mutein in 1984-85 which produced low picomolar affinity inhibitors of leukocyte elastase (patent application 1987). | US 5126322 |

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| The ability to sequence complete genomes has dramatically changed the nature of biomedical research and medicine. Genomic information on emerging pathogens and drug resistant strains is of great importance to public health policy. | US 5064754 |
| **1988** | |
| **SyStemix Inc.** receives a license on a patent application for the SCID -hu mouse, an immune deficient mouse with a reconstituted human immune system. | US 5476997<br>US 5612018 |
| **Genencor International, Inc.** received a patent for a process to make bleach-resistant protease enzymes to use in detergents. | US 5336611 |
| Nucleic acid hybridization is a fundamental technique in molecular genetics. It is a method for identifying closely related molecules within two nucleic acid populations. | US 5200313 |
| Blockade of the action of angiotensin II (AII) has long been a target for development of novel antihypertensive agents. […] The benzimidazole ring was found to be one of the most suitable templates arranging three essential components in correct direction. | US 4880804 |
| High resolution patterning on solid substrates disclosed. The solid substrate may, for example, be an insulator of the kind used for substrates in printed circuitry or may, as another example, be a semiconductor of the kind used in semiconductor microcircuitry. | US 5079600 |
| Method of detecting a predisposition to cancer by the use of restriction fragment length polymorphism of the gene for human poly (ADP-ribose) polymerase has been disclosed. | US 5272057 |
| Dideoxynucleotide DNA sequencing methods are dramatically improved by utilizing the DNA polymerase from Thermus aquaticus to catalyze the primer extension reactions. | US 5075216 |
| DNA encoding and methods of production of insulin-like growth factor binding protein BP53 are disclosed. DNA isolates coding for insulin-like growth factor binding protein may be used to produce the protein via recombinant expression systems. Insulin-like growth factor binding protein is useful as a binder to insulin-like growth factor and as a metabolic regulator. | US 5258287 |
| **1989** | |
| Epogen (Epoetin alfa) a genetically engineered protein introduced, providing a means to help patients with kidney failure. | |
| In the late 1980s Mario Capecchi and colleagues pioneered a method to target the inserted gene to a desired position in the genome. These researchers took advantage of an observation that, on rare occasions, an injected, mutated copy of a gene lines up precisely with the original form of the gene in the mouse genome. By a process called homologous recombination, the aligned DNA segments are cut and rejoined to each other. The result is a precise stitching of the introduced DNA into the targeted gene in the mouse genome. This means that scientists found they could make minor modifications to a gene before injecting it and, by homologous recombination, or "gene targeting," replace the natural gene with this transgenic version. | |
| Dabs are antibodies in which there is only one protein chain derived from only one of the 'domains' of the antibody structure, and hence are called single domain antibodies or Dabs. […] Related ideas are single-chain binding technology (SCA), patented by Genex, […]. SCAs […] are terms for antibody- binding domains in which the two binding regions from light and heavy chains are linked by a short peptide, so they can be produced by one gene. This makes them much easier to produce in bacteria from recombinant DNA, since there is no need for the two chains of the normal antibody structure to be made separately and then assembled within the cell. | US 4946778 |
| Polymer conjugation radically changes the pharmacokinetics of the bound drug, and conjugates with prolonged circulation times target tumors passively via the enhanced permeability and retention (EPR) effect. | US 5162430 |
| Physical mapping of complex genomes are provided. | US 5219726 |
| A method for the production of human tissue type plasminogen activator (tPa) using cells is disclosed. The invention provides a method for producing single-chain tPA in a high concentration and with a relatively small amount of double-chain tPA in the medium. | US 5151359 |
| **1990** | |
| Large scale photolithographic solid phase synthesis of polypeptides and receptor binding screening are provided. | US 5143854 |
| Somatotropin, commonly known as growth hormone (GH) is a polypeptide chain containing about 190 amino acid residues, produced by the pituitary gland in mammals and is responsible for a number of anabolic processes. It has two disulphide bridges, with 4 alpha helices arranged in anti-paralel distinctive manner. GH molecule binds with two receptor molecules to exhibit its full biological activity. Somatotropin (STH) refers to the growth hormone 1 produced naturally in animals, whereas the term somatropin refers to growth hormone produced by recombinant DNA technology,[1] and is abbreviated "HGH" in humans. The amino acids of helix 3 in GH were shown to have significant growth-promoting activity. | US 5310882 |
| US Patent Nos. 4,940,835 and 5,188,642 are two key patents in the area of genetically engineered crops. | US 5188642 |

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| Novel DNA-binding proteins, especially repressors of gene expression, are obtained by variegation of genes encoding known binding proteins and selection for proteins binding the desired target DNA sequence. A novel selection vector may be used to reduce artifacts. Heterooligomeric proteins which bind to a target DNA sequence which need not be palindromic are obtained by a variety of methods. | US 5198346 |
| UCSF and **Stanford University** were issued their 100th recombinant DNA patent license. By the end of fiscal 1991, both campuses had earned $40 million from the patent. | US 4973555 |
| A method for treating skeletal and other connective tissue disorders is proposed. It is one of the most dominant patents in the field of hematopoietic stem cells. | US 5226914 |
| The FDA licensed **Chiron**'s hepatitis C antibody test to help ensure the purity of blood bank products. | US 6027729 |
| Transformation vectors allowing expression of Bacillus thuringiensis endotoxins in plants are described. Transformed plant cells and their progeny exhibit stably inherited polypeptide toxin expression useful for protecting said plant cells and their progeny against certain insect pests and in controlling said insect pests. | US 5254799 |
| Methods are provided for producing plants exhibiting one or more desired phenotypic traits. | US 5231020 |
| Michael Fromm, molecular biologist at the **Plant Gene Expression Center**, reported the stable transformation of corn using a high-speed gene gun. | |
| Mary Claire King, epidemiologist at **UC-Berkeley**, reported the discovery of the gene linked to breast cancer in families with a high degree of incidence before age 45. | US 5622829 |
| First automated DNA sequencing machine developed at Caltech. | US 5171534 |
| Genetic suppressor (or enhancer) analysis has led to the identification of a large number of specific transcription factors as well as general components of the transcription machinery. | US 5217889 |
| Methods are provided for detecting the interaction between a first test protein and a second test protein, in vivo, using reconstitution of the activity of a transcriptional activator. | US 5283173 |
| Frederick Sanger's DNA sequencing method predominated in the early work on the sequencing of entire genomes of the bacteriofage, φX174 (5368 bp) and in 1982 coliphage λ (48 502 bp). Animal viruses followed: 1986-1990, for example the 229-kb genome of cytomegalovirus (CMV) and the 192-kb genome of Vaccinia virus (191.6 kb) as well as organelle DNA: 1986 chloroplast DNA (121 024 bp) and in 1992 mitochondrial DNA of the liverwort Marchantia polymorpha (184 kb). | |
| **1991** | |
| Analyzing chromosomes from women in cancer-prone families, Mary-Claire King, of the University of California, Berkeley, finds evidence that a gene on chromosome 17 causes the inherited form of breast cancer and also increases the risk of ovarian cancer. | |
| In the early 1990s two other powerful cloning methodologies were established, namely the Bacterial Artificial Chromosome (BAC) libraries developed by Hiroaki Shizuya in 1992 and Yeast Artificial Chromosomes (YAC) initially developed by Maynard Olson in 1988 to 1991. The latter methodology was effectively used in 1993 in Alan Coulson's and Sir John E. Sulston's (Nobel Laureate 2002) laboratory in Cambridge in association with R. Waterston to map the genome of Coenorhabditis elegans (the round worm) (draft genome map presented at Cold Spring Harbor in 1989). The same methodology was also used in 1993 in Jean Weissenbach's laboratories in Paris to map parts of the human genome. | |
| DNA chips have emerged as a core genomic technology that enables cost-effective gene expression monitoring, mutation detection, single nucleotide polymorphism analysis and other genomic analyses. DNA chips are manufactured through a highly scalable process, called Very Large-Scale Immobilized Polymer Synthesis (VLSIPS), that combines photolithographic technologies adapted from the semiconductor industry with combinatorial chemistry. | US 5424186 |
| Intracellular transport of different biologically active molecules is one of the key problems in drug delivery in general since many pharmaceutical agents need to be delivered intracellularly to exert their therapeutic action inside the cytoplasm or on the nucleus or other specific organelles. […] The addition of the positive charge to the nanocarrier can significantly enhance its uptake by cells, and the use of cationic lipids and cationic polymers as transfection vectors for intracellular delivery of DNA was suggested quite few years ago. | US 5264618 |
| Directed evolution and related methods have identified proteins with a variety of functionally important properties. […] Through directed evolution, protein function can be engineered if a suitable selection assay is available. | US 5223409 |
| A method of sequencing of genomes by hybridization of oligonucleotide probes is disclosed. The conditions under which oligonucleotides hybridize only with entirely homologous sequences are recognized. | US 5202231 |
| Recombinant altered antibodies and methods of making altered antibodies are disclosed. | US 5225539 |
| Glucose is the most common carbon and energy source for fermentations since it is readily available and relatively inexpensive. Glucose, which is also referred to as dextrose or an industrial sugar, is derived from hydrolysis of starch from corn that has been processed by wet milling or dry milling. at some point in the future | US 5198035 |

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| it is probable that industrial sugars will be derived from cellulosic materials as well. advances in bioconversion technologies for fuel ethanol production from cellulose will effectively decrease costs of industrial sugars, that by virtue of their sources (wood, agricultural waste), are not suitable for food. | |
| A screening method for the selection of mutagenized proteins that are normally secreted by cells is described. The method includes the development of a cloning vector for the expression of secretory proteins as fusion proteins on the cell surface of transfected mammalian cells. | US 5223408 |
| **1992** | |
| The growth of biofuels has resulted in a new area of growth for biotechnology for the development of advanced enzymes and microorganisms. | US 5348871 |
| Annonaeous acetogenins from the Indiana banana (pawpaw) (asimina triloba) tree are compounds that have potential as chemotherapy agents against breast cancer. | US 5229419 |
| The keywords in the titles of the most important patents include: […], and "fluid handling in mesoscale analytical devices'. | US 5304487 |
| Once solid substrates replaced nylon in the 1990s, this method provided a relatively cheap, quick and reproducible way for high-throughput gene expression analysis. | US 5445934 |
| Since cytokines have pleitropic effects, their modulation has potential use in a range of diseases including inflammatory and autoimmune disorders. The so-called inflammatory cytokines IL-1 and TNF-alfa play a prominent role in sepsis, inflammatory bowel disease, RA, and IDDM. They are the focus of many biotechnology ventures such as Immunex Corp who have produced soluble ligand binding portions of IL-1 and TNF receptors to act as functional antagonists. | US 5319071 |
| **American and British scientists** unveil a technique for testing embryos in vitro for genetic abnormalities such as cystic fibrosis and hemophilia. | |
| Frederick Sanger's DNA sequencing method predominated in the early work on the sequencing of entire genomes of the bacteriofage, φX174 (5368 bp) and in 1982 coliphage λ (48 502 bp). Animal viruses followed: 1986-1990, for example the 229-kb genome of cytomegalovirus (CMV) and the 192-kb genome of Vaccinia virus (191.6 kb) as well as organelle DNA: 1986 chloroplast DNA (121 024 bp) and in 1992 mitochondrial DNA of the liverwort Marchantia polymorpha (184 kb). | |
| In the early 1990s two other powerful cloning methodologies were established, namely the Bacterial Artificial Chromosome (BAC) libraries developed by Hiroaki Shizuya in 1992 and Yeast Artificial Chromosomes (YAC) initially developed by Maynard Olson in 1988 to 1991. The latter methodology was effectively used in 1993 in Alan Coulson's and Sir John E. Sulston's (Nobel Laureate 2002) laboratory in Cambridge in association with R. Waterston to map the genome of Coenorhabditis elegans (the round worm) (draft genome map presented at Cold Spring Harbor in 1989). The same methodology was also used in 1993 in Jean Weissenbach's laboratories in Paris to map parts of the human genome. | |
| Instrument and method for the sequencing of genome are provided. | US 5288644 |
| Growth Hormone Antagonists (GHA) may play a role in the treatment of cancer. This has been supported by several experimental studies of GHA in breast, brain, and colon cancer. | US 5350836 |
| p53 is one of the most frequently mutated genes in human cancers and, as a result, is also one of the most well-studied genes in the history of cancer research. Although many functions have been ascribed to p53 over the years, one of the first activities to be characterized was the ability to bind DNA sequence-specifically through its central domain. This domain (the core) contains the most evolutionaily conserved sequences of the protein. | US 5362623 |
| **1993** | |
| An international research team, led by Daniel Cohen, of the **Center for the Study of Human Polymorphisms** in Paris, produces a rough map of all 23 pairs of human chromosomes. | |
| Nanogen Inc. has developed technology that integrates advanced microelectronics and molecular biology on proprietary semiconductor microchips. The technology has broad commercial applications in biomedical research, medical diagnostics, genomic research, genetic testing, and drug discovery. | US 5605662 |
| Viruses expressing chimeric binding proteins are detected. | US 5403484 |
| ProtoGene Laboratories Inc. of Palo Alto has received US Patent 5474796 "Method and Apparatus for conducting an Array of Chemical Reactions on a Support Surface". The technology allows custom DNA, as an example, to be synthesized in place on the surface of glass in such a way that different DNA sequences can be localized to different regions of the glass. Using this technology, the company hopes to develop an inexpensive custom DNA to be synthesized. The development of the technology was supported by Human Genome Program grant from the Department of Energy. | US 5474796 |
| Researchers at the University of Copenhagen, Denmark, have recently invented a new class of synthetic molecules which look and act like DNA, termed peptide backbone incorporating normal nucleic acid bases in the desired sequence. This molecule has a neutral rather than negative net charge, and does not contain labile phosphate-oxygen-sugar bonds. Consequently, PNAs survive much longer within cells than their conventional oligonucleotide counterparts. They have also been demonstrated to bind 50-100 times more tightly to complementary sequences than 'natural' nucleic acids. PNAs therefore look set to revolutionize some DNA- | US 5539082 |

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| based diagnostic test formats. Moreover, despite concerns about the potential in vivo side-effects of their longevity, PNAs could be immensely useful for both antisense and antigene based techniques. | |
| There are now many important patents issued under regular patent laws supplementing protection under this PBR system. A sampling is presented […] which shows the scope and force of the mesh of rights. Chart 1: some representative patents affecting wheat and wheat research: […] Chimeric genes for transforming plant cells using viral promoters, US 5352605, Fraley et al, Oct 4, 1994, Monsanto. | US 5352605 |
| The patent reproduced below represent the primary patents describing the generation and use of human ES cells. | US 5690926 |
| This paper focuses on the concept that an elevation of blood concentrations of growth hormone in meat animals markedly increases growth rate, improves feed efficiency, and dramatically increases muscle mass while decreasing adipose tissue (fat) mass. | US 5374620 |
| Double-stranded DNA is the main form of genetic storage material in living organisms. […] Any DNA-cleaving reagent can be converted into a sequence-specific one by conjugation of its active moiety to a molecule that is capable of recognizing specific sequence of double-stranded DNA. | US 5641625 |
| Recombinant retroviruses are used for almost all trials of hematopoietic gene transfer, both to mark cells and to treat diseases. Retroviruses are important in gene therapy trials for two reasons – the genome is relatively easy to manipulate, and the virally encoded genes integrate into host chromosomes. | US 5716826 |
| **1994** | |
| The first genetically engineered food product, the Flavr Savr tomato, gained **FDA** approval. | |
| A rational manipulation of the electrode surface functionality by immobilizing selected types of molecule is an essential key for the development of electrochemical sensors and devices. | US 5610287 |
| Sequencing by hybridization (SBH) is an approach whereby a collection of overlapping oligonucleotide sequences is assembled together to determine an organism's DNA sequence. Through the efficient method of SBH, scientists are able to gather information on the genomes of different species ad organisms for the future development of biological sciences, medicine, and agriculture. | US 5525464 |
| Method of identifying a stochastically-generated peptide, polypeptide, or protein having ligand binding property and compositions thereof | US 5723323 |
| Delivery of exogenous DNA sequences in a mammal is now possible so that polynucleotide sequences, comprising DNA and RNA molecules can be directly administered, for example by injection, to tissues, such as muscle, and expressed as a protein, polypeptide or polypeptide. | US 5580859 |
| W. French Anderson: father of gene therapy. | US 5399346 |
| The first breast cancer gene is discovered. The BRCA1 gene, previously implicated in the development of rare familial forms of breast cancer, also appears to play a role in much more common types of non-inherited breast cancers. | |
| A multitude of genes, human and otherwise, were identified and their functions described. These included:<br>• Ob, a gene predisposing to obesity<br>• BCR, a breast cancer susceptibility gene<br>• BCL-2, a gene associated with apoptosis (programmed cell death)<br>• hedgehog genes (so named because of their shape, these produce proteins which guide cell differentiation in advanced organisms)<br>• Vpr, a gene governing reproduction of the HIV virus.<br>Linkage studies identified genes for a variety of ailments including: bipolar disorder, cerulean cataracts, melanoma, hearing loss, dyslexia, thyroid cancer, sudden infant death syndrome, prostate cancer and dwarfism. | |
| Other recently developed tools useful in the miniaturization of biosensing devices include nanowires and nanotubes. Nanotubes are particularly promising because of their durability and extreme sensitivity to electronic transport and voltage caused by interjunction temperature differences. | US 6203814 |
| Human mesenchymal stem cells are thought to be multipotent cells, which are present in adult marrow, that can replicate as undifferentiated cells and that have the potential to differentiate to linages of mesenchymal tissues, including bone, cartilage, fat, tendon, muscle, and marrow stroma. | US 5486359 |
| The greatest progress in HER2-targeted therapies has been made using monoclonal antibodies directed towards the extracellular domain of the HER2 receptor. | US 5677171 |
| Genetic researchers successfully transferred the CFTR (cystic fibrosis transmembrane conductance regulator) gene into the intestines of mice. This appears to be a major step towards gene therapy for patients with cystic fibrosis. Researchers reported early success with a liposomal method for delivering the CFTR gene in humans. | US 5958893 |
| A group of researchers reported the first successful systemic selective inhibition of gene expression using antisense oligonucleotides. | |
| First US patent for DNA microarrays granted. Southern founded Oxford Gene Technology (OGT), a company that developed DNA microarray technology. OGT won a 1999 patent infringement lawsuit against Affymetrix based on his patent holdings in microarray technology. | US 5700637 |

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| Recombinant antibodies specific for a growth factor receptor are described. | US 5571894 |
| Methods and apparatus for the detection of an analyte utilizing mesoscale flow systems are disclosed. | US 5637469 |
| The use of long single-stranded DNA fragments enables Nanogen to increase the certainty of identification by preventing mismatch thus ensuring that bound pairs are truly complimentary. The current chip design contains a 5x5 array of 25 electrodes in an active area of 1mm2, however, the company is planning to develop larger arrays with up to 10000 test sites. […] The feasibility of engineering such high density electrically addressable microstructures is a result of exploiting advances in the semiconductor industry that have enabled the microprocessor to contain millions of switches on a single silicon chip. The combination of this complementary metal oxide semiconductor technology with the miniaturization of electrophoresis and fluorescent detection systems, that are in wide use in diagnostic laboratories, will allow Nanogen to further increase the complexity of the microchips. | US 5632957 |
| The advent of high-speed sequencing methods has changed the way we study the DNA sequences that code for proteins. […] Genomic regulation involves not only expressed genes but structural and sequence signals in the DNA where regulatory proteins may bind. […] Mapping these metabolic, regulatory, and signaling systems to the genome sequence is the goal of the field of functional genomics. | US 5614395 |
| Sequence-specific detection of nucleic acid hybrids using a DNA-binding molecule or assembly capable of discriminating perfect hybrids from non-perfect hybrids | US 5871902 |
| Coating composition having anti-reflective, and anti-fogging properties are proposed. The coating compositions are particularly useful in the manufacture of disposable surgical masks and face shields. | US 5585186 |
| The present invention relates to the cloning of the gene of a thermophilic DNA ligase, from Thermus aquaticus strain HB8, and the use of this ligase in a ligase chain reaction (LCR) assay for the detection of specific sequences of nucleotides in a variety of nucleic acid samples, and more particularly in those samples containing a DNA sequence characterized by a difference in the nucleic acid sequence from a standard sequence including single nucleic acid base pair changes, deletions, insertions or translocations. | US 5494810 |
| Since the Harvard Mouse patent was issued in 1988, hundreds of other patents pertaining to transgenic animals have been issued in the United States, including patents to chickens (US Patent No. 5,656,479), cows (US Patent No. 5,750,176), dogs (US Patent No. 6,498,791), mice (US Patent No. 6,552,246), monkeys (US Patent No. 5,489,524), pigs (US Patent No. 6,498,285), rabbits (US Patent No. 5,675,063), rats (US Patent No. 5,489,742), and sheep (US Patent No.5,763,739). | US 5656479 |
| Since the Harvard Mouse patent was issued in 1988, hundreds of other patents pertaining to transgenic animals have been issued in the United States, including patents to chickens (US Patent No. 5,656,479), cows (US Patent No. 5,750,176), dogs (US Patent No. 6,498,791), mice (US Patent No. 6,552,246), monkeys (US Patent No. 5,489,524), pigs (US Patent No. 6,498,285), rabbits (US Patent No. 5,675,063), rats (US Patent No. 5,489,742), and sheep (US Patent No.5,763,739). | US 5750176 |
| **1995** | |
| Method for liquefying starch diployed by researchers at Genencor. | US 5756714 |
| A method for preparing probes, as well as several probes for use in qualitative or quantitative hybridization assays are disclosed. | US 5840488 |
| There are several reasons for interest in preparation of interspecific hybridomas, and the exact nature of the reason is important in determining the appropriate experimental approach. The most common motivation in investigating interspecific fusion is the desire to immortalize an antibody-producing cell from a species for which appropriate drug-marked, immortal B-lymphocyte fusion partners are not available. […] antibody responses of such commonly immunized animals as hamsters, guinea pigs, rabbits, goates, sheep, and horses can presently be immortalized only by interspecific fusion. | US 5675063 |
| By exploiting the intermolecular integration reaction catalysed by Cre or Flp, a single chromosomal loxP or FRT element can serve as a landing site for the integration of exogenous DNA. Such experiments have been successfully accomplished in mammalian cells using either the Cre or Flp systems, providing a potential means to generate isogenic cell lines and mouse strains. | US 5677177 |
| In cancer, blocking the activity of the growth factors and receptor is a viable way to target this pathway. Avastin, a humanized monoclonal antibody to VEGF, is capable of blocking tumor angiogenesis and provides a survival advantage in patients with advanced colorectal cancer is demonstration that this type of approach is possible. | US 5939531 |
| It was quickly appreciated that the injected DNA functions as a source of immunogen in situ and can induce strong immune responses, particularly cellular immune responses. The DNA used in this procedure is sometimes referred to as naked DNA. | US 5589466 |
| Partitioned microelectronic device array is provided. | US 5593838 |

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| Technological advances allowed the fabrication of oligonucleotide arrays with extremely large numbers of features. At the same time, the sequencing of the entire genome has been completed for several organisms of interest, including Homo Sapiens. Given both facts above, one could envisage arrays that cover the entire genome of a given organism. In fact, Affimetrix currently manufactures and sells such arrays, called tiling arrays. Affymetrix tiling arrays use short sequences, currently 25-mer oligonucleotides, that are equally spaced across the entire genome. | US 5744305 |
| Many instruments on the market are designed to produce microarrays of biological samples, but few are capable of efficiently and precisely depositing low volumes of protein lysate as small diameter spots in a microarray format. | US 5807522 |
| Apparatus for heating a fluid-carrying compartment of reaction cuvette is described. | US 5567617 |
| A **European research team** has identified a genetic defect which appears to underlie the most common cause of deafness. | |
| Researchers at **Duke University Medical Center** transplanted hearts from genetically altered pigs into baboons, proving that cross-species operations are possible. Later, the first baboon-to-human bone marrow transplant is performed on an AIDS patient. | |
| The discovery of the conserved structure of antibodies, particular IgGs, across many species suggested the possibility of chimeric antibodies, and the realization that the homology extended to the antigen-binding site facilitated the engineering of humanized immunoglobulins. | US 5585089 |
| Hitherto unrecognized properties of RNA add further support to the idea that RNA was the central molecule in the origin of life, report researchers. | |
| It was only in 1995 that the genome of a bacterium, Haemophilus influenza, [1 830 137 bp] was sequenced in its entirety by Craig Venter's group. | |
| A new gene mapping technique, STS gene mapping, could greatly speed the work of geneticists involved in the international Human Genome Project. | |
| A single gene has been identified that appears to control the growth and development of eyes throughout the animal kingdom. | |
| A new transgenic mouse carrying a gene for human Alzheimer's disease is developed. | US 6210919<br>US 6717031 |
| A method is proposed for producing genetically modified neural cells comprises culturing cells derived from embryonic, juvenile, or adult mammalian neural tissue with one or more growth factors that induce multipotent neural stem cells to proliferate and produce multipotent neural stem cell progeny which include more daughter multipotent neural stem cells and undifferentiated progeny that are capable of differentiating into neurons, astrocytes, and oligodendrocytes. The proliferating neural cells can be transfected with exogenous DNA to produce genetically modified neural stem cell progeny. | US 5750376<br>US 5851832 |
| A method is proposed for identifying a nucleotide base pair at a point mutation site in a DNA target using a mismatch repair enzyme. | US 5683877 |
| This invention provides methods by which biologically derived DNA sequences in a mixed sample or in an arrayed single sequence clone can be determined and classified without sequencing. | US 5871697 |
| DNA shuffling is based on repeated cycles of point mutagenesis, recombination, and selection that should allow in vitro molecular evolution of complex sequences such as proteins. DNA shuffling by random fragmentation and reassembly offers several advantages over more traditional mutagenesis strategies. | US 5830721 |
| Methods are described for generating polynucleotides having desired characteristics by iterative selection and recombination. | US 5811238 |
| Macromolecular combinatorics (e.g. shuffling, RNA aptamers or mRNA-protein fusions) when combined with either high-throughput screening methods Or, better yet, intelligent selection schemes, will allow proteins and nucleic acids with a vast array of novel properties to be produced. | US 5792613 |
| **1996** | |
| Methods and compositions for cellular and metabolic engineering are proposed. Recursive sequence recombination entails performing iterative cycles of recombination and screening or selection to “evolve” individual genes, whole plasmids or viruses, or even whole genomes. | US 5837458 |
| The disclosed invention is a device for adhering cells in a specific and predetermined position. The device is used in a method for culturing cells on a surface or in a medium and also for performing cytometry. Furthermore, the device is used in immobilization of cells at a surface and for controlling the shape of a cell. | US 5776748 |
| Method of detecting nucleic acids is disclosed. | US 5800992 |
| Bioluminescence has a number of important biological and ecological functions. | US 6247995<br>US 6152358<br>US 5876995 |
| Abgenix’s XenoMouse and XenoMax are human antibody technologies using transgenic mice to create therapeutic monoclonal antibodies. Abgenix’s XenoMouse is a transgenic mouse in which the mouse’s antibody gene expression is suppressed and replaced with human antibody genes. The mice engineered though this process have approximately 80% of the human heavy-chain antibody genes as well as a significant amount of the light-chain genes. Abgenix has developed multiple strains of XenoMouse animals, each of which produces a different class of antibody to perform different class of antibody to perform different therapeutic functions. | US 6150584 |

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| A collaboration of scientists reports sequencing of the complete genome of a complex organism, Saccharomyces cerevisiae, otherwise known as baker's yeast. The achievement marks the complete sequencing of the largest genome to date - more than 12 million base pairs of DNA. | |
| The sequencing of the genome of ancient organisms, archaea, found in inhospitable climates deep in thermal vents under the sea should greatly advance understanding of the evolution of life on Earth. The microorganisms are neither eukaryotes nor prokaryotes. T-cell researchers determined the three-dimensional structure of these critical components of the immune system. | |
| A new inexpensive diagnostic biosensor test for the first time allow instantaneous detection of the toxic strain of E. coli strain 0157:H7, the bacteria responsible for several recent food-poisoning outbreaks. | |
| The invention provides fast and highly accurate mass spectrometer based processes for detecting a particular nucleic acid sequence in a biological sample. | US 6043031 |
| The discovery of a gene associated with Parkinson's disease provides an important new avenue of research into the cause and potential treatment of the debilitating neurological ailment. | |
| Method for achieving integration of exogenous DNA delivered by non-biological means to plant cells. | US 6051409 |
| A purified preparation of primate embryonic stem cells is disclosed. A method for isolating a primate embryonic stem cell line is also disclosed. | US 5843780<br>US 6200806 |
| Positional sequencing by hybridization (PSBH) has a number of potential advantages over conventional SBH. | US 6007987 |
| The present invention provides a miniaturized integrated nucleic acid diagnostic device and system. The device is useful in a variety of applications, and most notably, nucleic acid based diagnostic applications and de novo sequencing applications. | US 5922591 |
| A method is provided for analyzing a polynucleotide containing a variable sequence. | US 6150095 |
| The present invention provides a novel histamine H2 receptor (H2RH) and polynucleotides which identify and encode H2RH. The invention also provides genetically engineered expression vectors and host cells comprising the nucleic acid sequences encoding H2RH and a method for producing H2RH. | US 5817480 |
| **1997** | |
| This invention relates to a new nonwoven material which has very high Frazier permeability while having substantial hydrostatic head liquid barrier properties. The material is comprised of fibers which are approximately one denier and finer fibers which have sufficient strength properties so as not to need a support scrim. The fabric is quite comfortable because of its breathability, quite soft because of its construction, and protective from liquids from rain to hazardous chemicals. | US 5885909 |
| High information screening can inject new life into screening programmes for low molecular weight compounds and their semi-synthetic chemical derivatives. 'High information screening' gives better insight into the mode of action of a new drug and its potential side-effects and is expected to give a higher success rate for clinical phase I trials by greater selection during the preclinical phase. Recent breakthroughs in this area can be seen e.g. in the discovery of both Epothilon, a potential blockbuster as a replacement for the anti-cancer agent Taxol (Paclotaxel) and Agyrin A, a potential anti-cancer drug with a novel mechanism, originating from screening programmes of the secondary metabolites of the gliding bacteria (Genus Myxobacteriaceae). | US 5969145 |
| High throughput DNA sequencing essentially started with the introduction of Hunkapillar's 454 sequencing machines in 1997. This accelerated the completion of the human genome sequence of 3 billion compiled bases by 2000. This entailed collecting at least 15 times as much raw sequence data (i.e. more than 45 billion). | US 5632041 |
| In 1989, under the leadership of André Goffeau a European consortium of 74 laboratories was set up to sequence the genome of the budding yeast Saccharomyces cerevisiae (12.5 Mb). This was completed in 1997 as a result as a result of over 600 scientists in over 100 institutions working together. This was the largest collaboration that had ever taken place in molecular biology. | |
| Macromolecular combinatorics (e.g. shuffling, RNA aptamers or mRNA-protein fusions) when combined with either high-throughput screening methods Or, better yet, intelligent selection schemes, will allow proteins and nucleic acids with a vast array of novel properties to be produced. | US 6207446 |
| Researchers at **Scotland's Roslin Institute** report that they have cloned a sheep--named Dolly--from the cell of an adult ewe. Polly the first sheep cloned by nuclear transfer technology bearing a human gene appears later. | |
| Artificial human chromosomes created for the first time. | US 6716608 |
| Morphatides: novel shape and structure libraries. This invention provides a method for identifying one or more complexes from a library of complexes. | US 6838238 |
| Don P. Wolf and a team of researchers at the federally-funded Oregon National Primate Research Center announce that they have produced rhesus monkeys from cloned embryos, the first successful use of cloning-related technology in primates. They used laboratory techniques that had previously worked with frogs, cattle, and mice. | |
| Orasure, a bloodless HIV-antibody test using cells from the patient's gums approved. It provides a highly accurate alternative to blood testing, according to a study published in the Journal of the American Medical Association (JAMA). | |

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| The use of human cells as acceptors for the accessory chromosomes led to the development of human accessory chromosomes (HACs) as cloning vectors by J.J. Harrington in 1997. | |
| Clock, the first gene providing the circadian rhythm of mammalian life identified. | US 5874241 |
| Using a bit of DNA and some commonplace biological laboratory techniques, researchers have now engineered the first DNA computer "hardware" ever: logic made of DNA. | |
| Hopkins University reported the first derivation of human embryonic germ cells from an isolated population of cells in fetal gonadal tissue, known as the primordial germ cells, which are destined to become the eggs and sperm. Researchers developed pluripotent stem cell “lines”, which are not only capable of renewing themselves for long periods, but can also give rise to many types of human cells or tissues. | US 6090622<br>US 6245566 |
| **1998** | |
| Protein fragment complementation assays for the detection of biological or drug interactions has been disclosed. The invention provides a general protein-fragment complementation assays to detect biomolecular interactions in vivo and in vitro. | US 6294330 |
| **University of Hawaii** scientists, clone three generations of mice from nuclei of adult ovarian cumulus cells. | US 6641526<br>US 6331659 |
| The FDA grants marketing clearance to RemicadeTM (infliximab), a novel monoclonal antibody for treatment of Crohn’s disease. | |
| Patterned article having alternating hydrophilic and hydrophobic surface regions has been disclosed. | US 6352758 |
| Immunostimulatory polynucleotide-immunomodulatory molecule conjugate compositions are disclosed. | US 6610661 |
| **Two research teams** succeed in growing embryonic stem cells, the long sought grail of molecular biology. | |
| Scientists at Japan's **Kinki University** clone eight identical calves using cells taken from a single adult cow, a feat indicative of the increasing reliability of cloning technology. | |
| Favorable results with a new antibody therapy against breast cancer, HER2neu (Herceptin), herald a new era of treatment based on molecular targeting of tumor cells. | US 6403630 |
| Fomivirsen becomes the first approved therapeutic agent developed with antisense medical technology. | |
| Research with tumor starving biologicals including angiostatin and endostatin begins to show promise in the clinic. | |
| The first complete animal genome the C.elegans worm is sequenced. | |
| A rough draft of the human genome map is produced, showing the locations of more than 30,000 genes. | |
| A method for DNA reassembly after random fragmentation, and its application to mutagenesis of nucleic acid sequences by in vitro or in vivo recombination is described. The present invention also relates to a method of repeated cycles of mutagenesis, shuffling and selection which allow for the directed molecular evolution in vitro or in vivo of proteins. | US 6180406 |
| Advanced anticancer nanotherapeutics should contain inhibitors of both drug efflux pumps and antiapoptotic cellular defense. Several methods have been recently developed to modulate pump and nonpump resistance. The most promising are based on the suppression of the overexpression of P-glycoprotein or multidrug resistance associated proteins and antiapoptotic members of BCL2 family proteins. The two main approaches are currently being used for this purpose. […] the second approach is based on the use of antisense oligonuclotides (ASOs) directed to mRNA encoding proteins responsible for both types of cellular defense. | US 5801154 |
| Macromolecular combinatorics (e.g. shuffling7, RNA aptamers8 or mRNA-protein fusions9) when combined with either high-throughput screening methods Or, better yet, intelligent selection schemes, will allow proteins and nucleic acids with a vast array of novel properties to be produced. | |
| **1999** | |
| This invention provides methods of obtaining pest resistance genes that are improved over naturally occurring genes for use in conferring upon plants resistance to pests. The methods involve the use of DNA shuffling of pest resistance genes to produce libraries of recombinant pest resistance genes. | US 6500617 |
| Enfuvirtide originated at Duke University, where researchers formed a pharmaceutical company known as Trimeris. Trimeris began development on enfuvirtide in 1996 and initially designated it T-20. In 1999, Trimeris entered into partnership with Hoffmann-La Roche to complete the development of the drug. It was approved by the U.S. Food and Drug Administration (FDA) on March 13, 2003 as the first HIV fusion inhibitor, a new class of antiretroviral drugs. It was approved on the basis of two studies (TORO 1 and TORO 2) which compared the effect of optimized regimens of antiretroviral medication with and without the addition of enfuvirtide on serum viral load. | US 6541020 |
| Miragen, based in Irvine, Calif., has developed a technique called the Antibody Profile Assay (AbPTM) that can identify an individual by a subset of normally occurring antibodies present in his body. These antibodies, called Individual Specific Autoantibodies (ISA's), are not affected by medicines or illnesses, and with | US 4880750 |

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| very few exceptions are stable across a person's lifetime -- just like a fingerprint. | |
| A rapid scan of patient DNA for mutations or polymorphisms using microarrays has the potential to revolutionize DNA diagnostics. […] the result is a very small and uniform spot of crystallized MALDI-TOF matrix that can be entirely covered by the laser irradiation profile. This breakthrough in sample preparation allows the entire MALDI-TOF procedure to be automated, leading to a viable platform for commercial scale DNA diagnostics. Both Sequenom Inc and Brax are developing a commercial platform for DNA diagnostics based on mass spectrometry. | US 6258538 |
| Disclosed are methods of obtaining human hematopoietic cells from human pluripotent embryonic stem cells using mammalian stromal cells. Hematopoietic cells derived in this way are useful for creating cell cultures suitable for transplantation, transfusion, and other purposes. | US 6280718 |
| A new medical diagnostic test will for the first time allow quick identification of BSE/CJD a rare but devastating form of neurologic disease transmitted from cattle to humans. | |
| Inventors have performed separation of bacterial and cancer cells from peripheral human blood in microfabricated electronic chips by dielectrophoresis. Efforts towards the construction of a “laboratory-on-a-chip” system are presented which involves the selection of DNA probes, dyes, reagents and prototyping of the fully integrated portable instrument. | US 6403367 |
| Fast and highly accurate mass spectrometry-based processes for detecting particular nucleic acid molecules and sequences in the molecules are provided. | US 6277573 |
| Importance of understanding the laboratory and clinical implications of an assay’s lower limit of detection, dynamic range or range of quantification of hepatitis C virus RNA. | US 6303305 |
| To advance protein microarray analysis of clinical specimens, many technical hurdles in the fields of surface chemistries, microarray processing, large-scale production of specific recombinant binders, and detection strategies have to be overcome. | US 6524793 |
| **2000** | |
| The use of immunostimulatory DNA to provoke a TH1 phenotype has been an impetus for the development of DNA vaccines. | US 6949520 |
| Fluid handling devices including a substrate with a diamond-like film. The devices include capillaries and microfluidic articles. | US 6749813 |
| Small rods of nanometer diameter can be grown by vapor deposition or by pulsed electrochemical deposition into nanoporous membranes. By successive deposition of different metals, it is possible to produce segmented metal nanorods. Such particles are commercially available as nanobarcodes identifying individual pharmaceutical pills. | US 7045049 |
| The advantages of the reporter gene encoding chitobiase are that chitobiase and N-acetyl-beta-D-glucosaminidase activities are missing in E.coli strains and that bacterial chitobiase activity can be measured quantitatively and monitored using blue/white colony indicator plates. | US 6838239 |
| When anti-CD40 immunotherapy is combined with chemotherapy the result is an 80% cure rate. […] Humanized agonistic anti-CD40 antibodies are currently developed, and it seems clear that human clinical trials based on the synergy between CD40 activation and cytotoxic chemotherapy are warranted. | US 6843989 |
| The DNA sequence of the fruit fly Drosophila is published. | |
| The DNA sequence of the first plant Arabidopsis thaliana is completed. | |
| Pigs are cloned. | |
| Methods of evolving a polynucleotides by mutagenesis and recombination are disclosed. | US 6365408 |
| **2001** | |
| The draft of the human genome sequence is published in Science and Nature. | |
| The DNA sequence of the rice genome is completed. This is the first crop plant to be sequenced. | |
| Chinese National Hybrid researchers report developing a "super rice" that could produce double the yield of normal rice. | |
| Modifying double stranded DNA to enhance separations by matched ion polynucleotide chromatography | US 6838242 |
| Method for cell patterning is provided. The present invention provides a masking system for selectively applying cells to predetermined regions of a surface. | US 6893850 |
| This invention relates to carbon-matrix composites, such as carbon-carbon composites, and a method for forming them by forming a fabric of fusible and infusible fibers which can be processed and carbonized to form a composite. | US 6638883 |
| Transport proteins are found mostly in biological membranes where they carry material from one side to the other. Nutrients, such as sugar, must be transported into cells of all organisms, whereas waste products are deported. Multi-cellular organisms also have transport proteins to carry materials around the body. | US 6838241 |
| Decoy receptor 3 (DcR3) is a soluble decoy receptor belonging to the tumor necrosis factor receptor superfamily that is overexpressed in various malignant tumor types. DcR3 has been implicated in tumor cell survival by inhibiting apoptosis and by interfering with immune surveillance. | US 6843990 |

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| A single  gene from Arabidopsis inserted into tomato plants by UC Davis Scientist Edwardo Blumwald creates the first crop able to grow in salty water and soil. | US 6936750 |
| Instrument for monitoring polymerase chain reaction of DNA | US 6818437 |
| Biosteel - recombinant spider silk is produced in goat milk. Spider drag line silk has 80 times the tensile strength of steel. | US 6268169 |