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An overview of FDA-approved biologics medicines

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Recombinant DNA technologies revolutionized medicine. Herein, the approvals and mechanistic basis of biologics-based medicines are analyzed. The overall and relative rate of FDA approvals for recombinant proteins grew from the 1980s through the first half-decade of the new millennium. Over time, the number of biologics gaining approval for an orphan indication has climbed to more than 50% in the current decade. The field has been dynamic in terms of the types of biologics, indications targeted and the mechanistic basis of drug activity. Despite impressive increases in recombinant-protein-based medicine, the rate of new biologics approvals could have leveled out.

Current analysis

Recombinant DNA technology fundamentally changed the way medicines are discovered and developed. In a remarkable convergence of timing and talent, Stanford University was the epicenter of a revolution in the early 1970s, which first led to the concept, and rapidly thereafter the successful demonstration, that genes from one organism could be isolated and cloned into vectors for expression in unrelated organisms [1,2]. The resulting scientific knowledge and its commercial applications gave rise to the modern biopharmaceutical industry.

This revolution almost did not happen. Worries about the consequences of utilizing tumor-derived DNA components raised concerns about transmitting cancer among individuals working with DNA vectors or recombinant proteins. Compounding this, popular culture at the time was highly critical of the potential for science gone awry. Books and films such as *The Biological Time Bomb* (1968), *The Andromeda Strain* (1969) and *Future Shock* (1970) had primed public concerns that science would outpace society's ability to control new technology safely.

Research of more-controversial aspects of recombinant DNA research was voluntarily suspended shortly after the publication of the first papers on recombinant DNA technology. This self-imposed curtailment was an impressive demonstration of the potential impact associated with biotechnology, as was the decision of prominent scientists to request that The National Academy of Science evaluated the implications of the emerging new field of biotechnology [3]. The resulting Asilomar Conference on Recombinant DNA (1975) provided guidelines, many of which persist today, and gave rise to the ever-accelerating use of recombinant DNA technologies [4].

Within seven years of the Asilomar Conference, the first recombinant medicine had been developed and approved by the FDA. Within this time frame, a key pioneer of recombinant DNA research (Herbert Boyer) had founded Genentech (1976), developed a recombinant form of human insulin (1978) partnered with an established pharmaceutical company (Eli Lilly) and gained FDA approval for the first recombinant DNA product (Humulin®; 1982) [5,6]. This aggressive timeline set a standard that continues to be associated with the biotechnology industry today.

An assessment of biologics drugs over time was achieved by compiling a list of all recombinant biologics-based medicines approved by the FDA from 1982 through 2013. Information was gleaned initially from the FDA Orange Book and supplemented with data regarding withdrawn products using the same approaches detailed previously [7]. These results have also been verified against well-established resources such as Citeline®, PubMed and additional online resources [8]. Please note that recombinant products approved outside the USA were not included nor were products (including proteins) purified from sera and other human and non-human sources.

Since the approval of Humulin®, a total of 91 recombinant-protein-based new molecular entities (NMEs) have been approved by the FDA as

TABLE 1

Comparison of small molecule and biologic-based NMEs (1982–2013).

NME type	Total	IND to approval (years)	Withdrawn because of safety concerns (%)
Small molecule	777	8.5 ($n = 200$)	26 (3.3%)
Biologic	91	7.4 ($n = 30$)	2 (2.2%)
-Monoclonal antibody	34	7.8 ($n = 18$)	2 (5.9%)
-Enzyme modulator	26	5.9 ($n = 8$)	0
-Receptor modulator	31	8.3 ($n = 4$)	0

The total number of new molecular entities (NMEs) approved from 1982 through 2013 is indicated, as are the average times from investigational new drug (IND) to approval and the number and fraction of the molecules approved that were subsequently withdrawn for reasons of safety (noninclusive of withdrawals because of obsolescence or lack of sales). Please note that IND submission dates were available only for a relative small proportion of NMEs approved in this time period as indicated in parentheses.

therapeutics (Table 1, Fig. 1a). These biologics can be almost evenly divided into three categories: monoclonal antibodies, replacement or modulators of enzymes and replacement or modulators of cell surface receptor function. The first five approvals within each category are shown in Table 2.

The first monoclonal antibody, muromab CD3, gained approval in 1982 as a murine protein approved for use in acute organ transplant rejection [9]. The mechanistic basis of suppressive immune function minimized the risk of immunogenicity. However, broad

application of monoclonal antibodies was hampered by the need to minimize immunogenicity and thus required new breakthroughs. A pioneering Cambridge University study demonstrated replacement of murine antibody complementarity-determining regions with human versions and thereby provided a means to decrease immunogenicity [10]. Such breakthroughs facilitated approval of the second monoclonal antibody, abciximab (1993), and thereafter ignited a revolution in protein engineering technology. The advances continue today and include fully human antibodies and

emerging technologies to enhance drug safety and efficacy.

The proportion of biologics-based approvals (relative to small molecules) generally increased through the 1980s and 1990s and represented one-third of all NME approvals in the early 2000s (Fig. 1b) and again during 2009–2010. Although the absolute number of biologics approvals has remained relatively stable (with the exceptions noted below), the relative fraction of approvals, as compared with small molecules, declined over the past three years (2011–2013). One potential explanation is that these changes
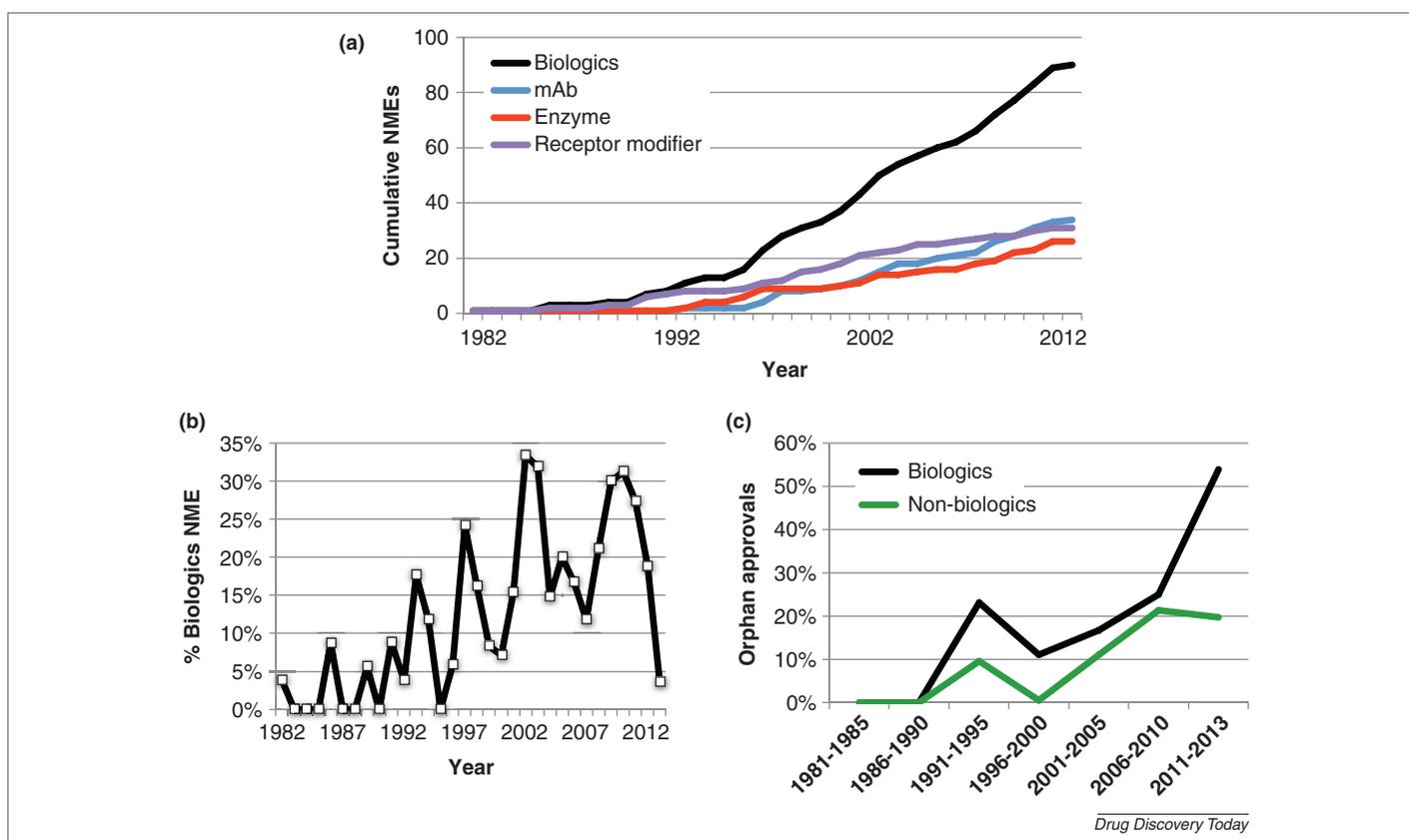

FIGURE 1

Accumulation of FDA-approved biologics. **(a)** The accumulation of the three major categories of biologics-based new molecular entities (NMEs) is shown over time since the initial approval of Humulin® in 1982. **(b)** The proportion of biologics-based NMES (relative to all NMEs) is shown on a half-decade basis. **(c)** The proportion of biologics-based and non-biologics-based orphan approvals is shown over time.

TABLE 2

First five biologics approved in major categories.

Monoclonal antibody	Receptor modulator	Enzyme modulator
Muromonab CD3 (Ortho, 1982)	rhInsulin (Eli Lilly, 1982)	Dornase alfa Genentech (1993)
Abciximab (Centocor, 1993)	Interferon alpha-2a (Roche, 1986)	Pegaspargase (Enzon, 1994)
Rituximab IDEC (1997)	Epoetin alfa (Amgen, 1989)	Imiglucerase (Genzyme, 1994)
Basiliximab (Novartis, 1998)	Filgrastim (Amgen, 1991)	Alteplase (Genentech, 1996)
Palivizumab (MedImmune, 1998)	Sagramostim (Immunex, 1991)	Reteplase (Boehringer-Mannheim, 1996)

reflect capacity levels within the regulatory agency (e.g. FDA Center for Biologics Evaluation and Research; CBER). At this early stage, it cannot be excluded that this recent trend simply reflects random chance and it remains to be seen whether such findings will persist over the coming years.

To identify factors relevant to the growing popularity of biologics, the development and regulatory histories of FDA-approved, small-molecule- and biologics-based medicines were compared. A commonly held view is that biologics are generally safer and have shorter approval times (and, by inference, costs) for clinical development [11,12]. With this in mind, the average time of clinical development [the time from investigational new drug (IND) submission until FDA approval] for all NMEs approved since 1982 (the year Humulin® was approved) was analyzed. Note: FDA reviewer packages did not always provide IND submission dates and the availability of information is included in the parentheses of Table 1 (middle column).

Clinical development times were indeed generally shorter for biologics than for small molecule therapeutics (Table 1). Whereas the average small molecule product had an average time interval of 8.5 years from the time of IND submission until final approval, the average for all biologics was 7.4 years. Looking more closely, the three categories of biologics fared differently. Recombinant enzymes and their modulators tended to have relatively short clinical development times (5.9 years), whereas monoclonal antibody drugs averaged 7.8 years. Likewise, the average development time of 8.3 years for non-antibody receptor modulators was virtually indistinguishable from small molecules. Thus, the idea that all biologics are subject to a shorter clinical development time often relates to the type of biologic drug under investigation.

The question of improved safety was also examined. The analyses reported here were restricted to FDA-approved NMEs (and thus could not address the question of how many clinical candidates had been rejected as a result of toxicity concerns). Nevertheless, one view of post-approval safety was achieved by assessing the number of NMEs later withdrawn from the market owing to concerns about toxicity (Table 1). When evaluating small molecule products approved since 1982, 3.3% (26 in total) have subsequently been withdrawn because of safety concerns. Biologics generally tended to fare better, with an average of 2.2% (2 of 90) withdrawn from the market because of safety. Both withdrawals were of monoclonal antibody drugs. Although the sample sizes are small, the rate of monoclonal antibody withdrawals as a result of safety (5.9%) is almost twice as high as with small molecules. Increased experience with these products will help clarify whether this is a durable trend or a statistical anomaly.

Another trend was an increased propensity of biologics to obtain an initial approval under the Orphan Drug Act. Since its inception in the early 1980s [13], an increasing frequency of initial FDA approvals for biologics-based NMEs has been granted to drugs targeting rare and underserved populations (Fig. 1c). Biologics-based medicines have emphasized these indications, with 54% of biologics approved in the ongoing decade approved for orphan indications. By contrast, the current rate of orphan approvals for small molecules now stands at 20%.

In evaluating the indications targeted by biologics, they largely conform to overall NME trends as reported previously [14]. Oncology and autoimmune/inflammation disorders are most commonly targeted by biologics, followed by metabolic, cardiovascular and infectious diseases (Fig. 2a). Receptor modifiers reflected the overall distribution of indications targeted with biologics (Fig. 2b). The number of new approvals for receptor modifiers rose through the 1980s and 1990s, peaking in the period from 2001 to 2006. The first enzyme replacement and modulators gained approval in the early 1990s and tended to favor metabolic disorders, including inborn genetic errors of metabolism (Fig. 2c, other data not shown). The approval rate for enzyme modifiers has been remarkably steady over time. The first monoclonal antibodies were approved in the early 1990s but were heavily weighted toward oncology and inflammatory disorders (Fig. 2d). Like enzyme modifiers, the approval rate for new monoclonal antibody products has remained relatively stable over the past 15 years.

From a mechanistic standpoint, the targets and mechanistic activities of biologics NMEs could be broadly distinguished into different groupings. In a first analysis, the functional site of drug action was assessed (Fig. 3a). Specifically, the earliest FDA approvals focused on biologics that act directly on the cell surface captured the majority of NMEs until the current decade. Starting in the early 1990s, NMEs targeting secreted proteins (e.g. cytokine traps) and mechanisms involving cell internalization (e.g. lysosomal storage enzymes) first entered the market (Fig. 3a).

Biologics can be broadly distinguished based on their target types: (i) soluble cytokines acting on lymphoid cells; (ii) soluble growth factors impacting non-lymphoid cells; (iii) nonsoluble modulators of cell signaling and adhesion; (iv) proteases; and (v) other mechanisms. Almost two-thirds of biologics impacted soluble targets (cytokines, growth factors and secreted enzymes) (Fig. 3b). Like the prior analyses, the three subsets (monoclonal antibodies, enzyme modulators and receptor modulators) are compared. Unsurprisingly, receptor modifiers largely focused upon cytokines and growth factors (Fig. 3c). By contrast, enzyme-based biologics largely targeted proteases and monoclonal antibody drugs tended to be modulators of cell signaling or adhesion.
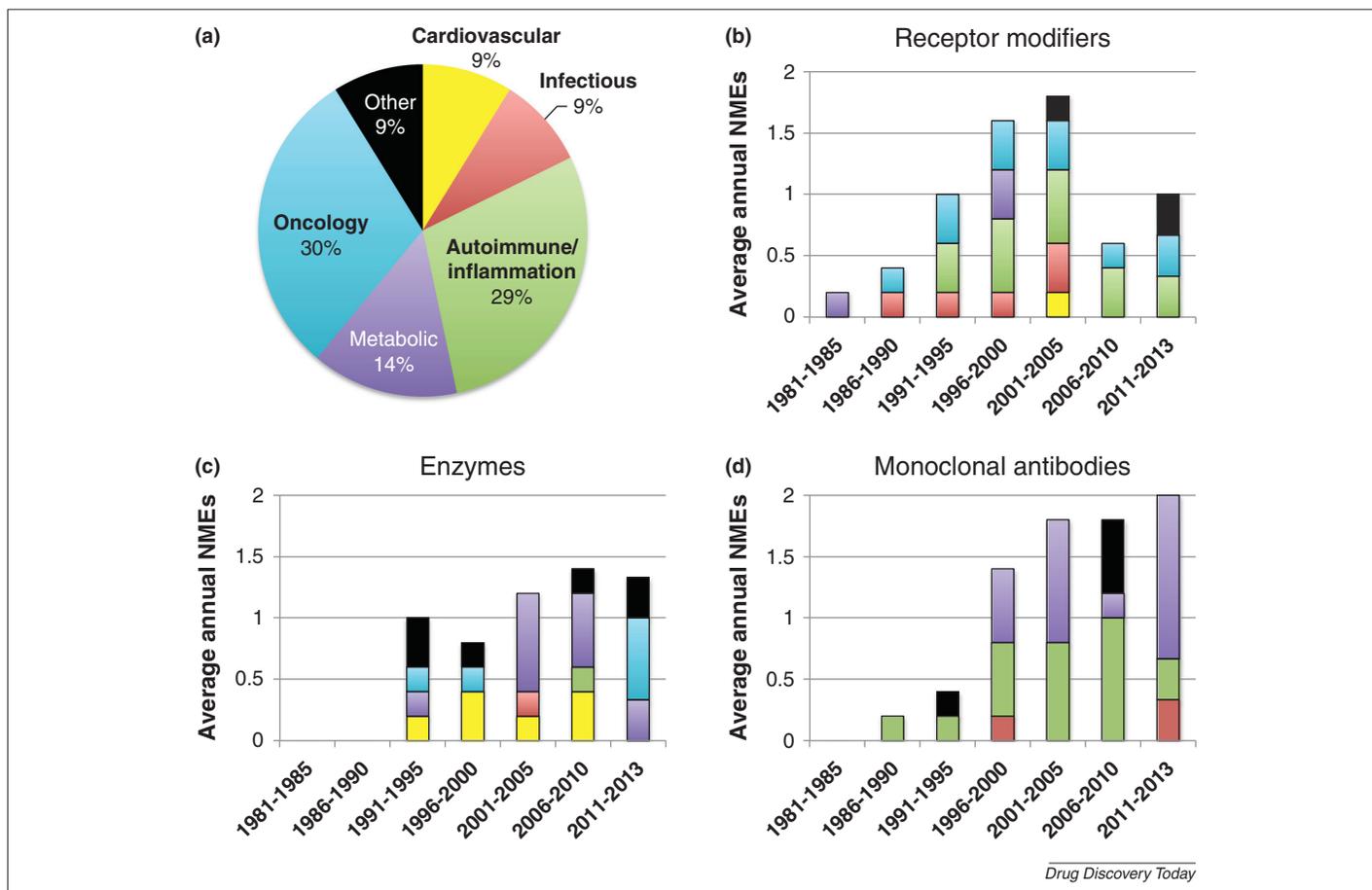
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FIGURE 2

Clinical indications targeted by biologics-based new molecular entities (NMEs). **(a)** The indications for which biologics gained their initial approval were divided into the categories shown. **(b–d)** Using the same color schema as (a) the indications targeted by the three major types of biologics-based therapeutics are indicated over time.

Concluding remarks: outcomes and implications

The major finding of the present study is that the numbers and diversity of FDA approvals of biologics NMEs accelerated from the early 1980s through the middle of the past decade. The first generation of biotechnology drugs largely consisted of recombinant growth factors and other modulators of cell surface proteins. Over time, the field has seen the emergence and growth of recombinant enzymes and monoclonal antibodies as well.

Biologics have been the subject of considerable dynamism in terms of attractiveness to the pharmaceutical industry. The attractiveness of biologics diminished in the 1980s and 1990s, perhaps due in part by the newness of the technology and concerns about safety (i.e. immunogenicity) as well as the high costs of goods (including the myriad patents required for targeting, modifying and/or producing biologics-based medicines). Increasing experience with biologics, along with advances in protein engineering, manufacturing improvements and

the expiration of key patents, overcame these concerns and increased the attractiveness of biologics. Another attractive feature of biologics has been decreased competition from generic manufacturers. Consequently, the past decade has witnessed high-profile acquisitions of biologics-based biotechnology companies (e.g. Genentech, MedImmune and others) by established pharmaceutical companies.

Although there has been considerable dynamism in the field in terms of drug type (e.g. antibodies relative to enzymes, etc.), the rate of new approvals has decreased from an annual average of 4.8 NMEs in the period spanning 2001–2005 to 4.0 per year (2006–2010). The approval rates of monoclonal-antibody- and enzyme-based biologics have remained constant and the decrease is attributable to receptor modifiers. This class of molecules includes agonists such as recombinant growth factors as well as antagonists such as decoy receptors. One possibility is that this reduction arose by chance and does not portend future decreases. When viewed in a different way, the relative proportion

of all biologics (relative to small molecules) has likewise decreased in the past three years (Fig. 1b). This outcome is unexpected given the movement of many traditional pharmaceutical companies toward biologics. Given the long time periods required for drug development, the effects of the larger industry's embrace of biopharmaceuticals could take decades to manifest in terms of increased biologics approvals.

If the trend toward decreased biologics approvals proves to be durable, there are potential explanations. For one, a recent report in this series demonstrated the number of biopharmaceutical companies gaining an approval for at least one biologics-based NME has decreased to a level not seen since the 1980s [15]. Alternative explanations could include a continuing high cost of goods (in terms of manufacturing and royalty burdens) often associated with biologics as compared with small molecule therapeutics [16–18]. Although biologics have historically conveyed important advantages over small molecules in terms of pharmacokinetics (with circulating
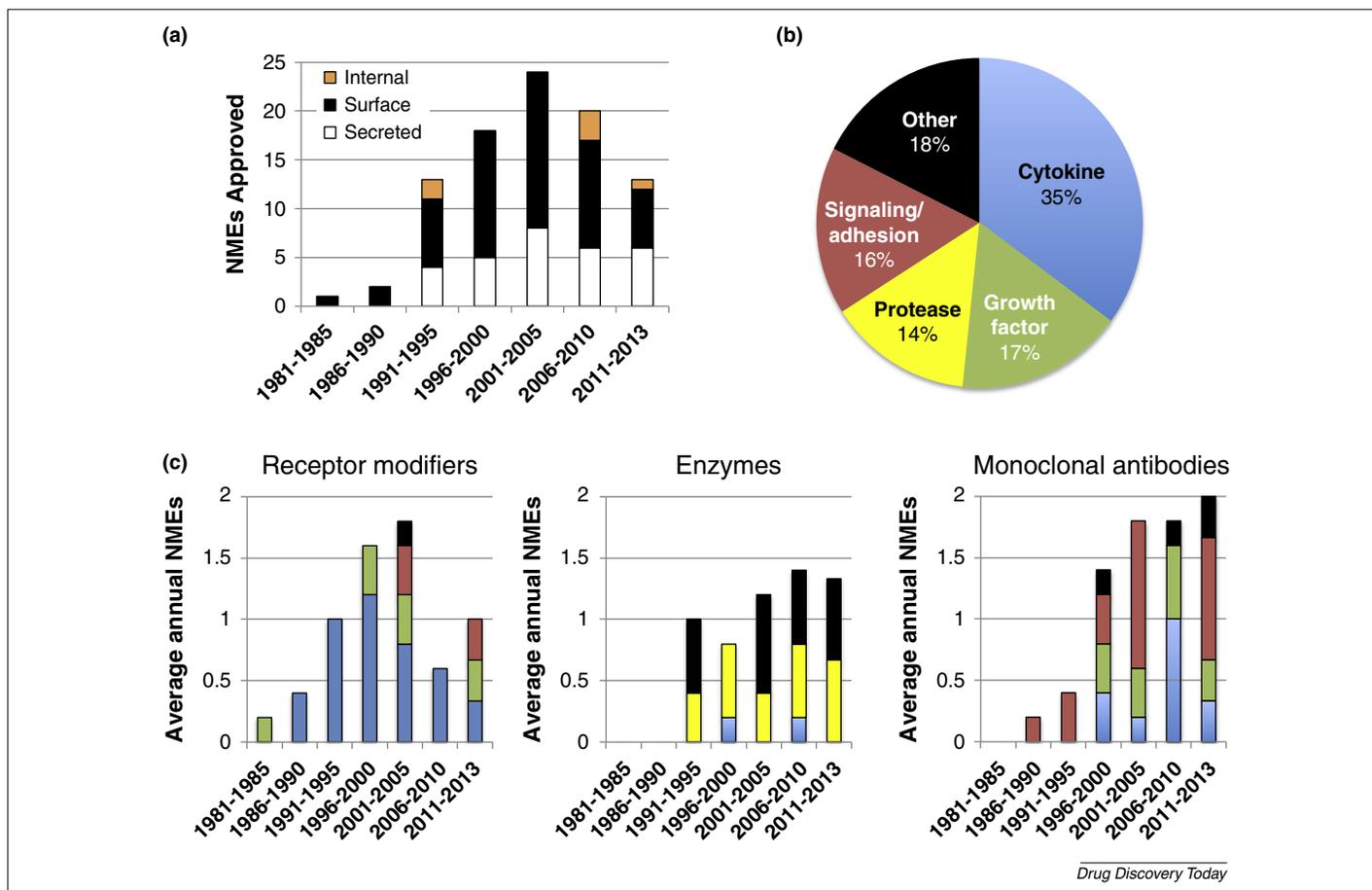
FIGURE 3

Mechanistic basis of biologics efficacy. **(a)** All biologics new molecular entities (NMEs) were categorized as acting upon secreted (soluble), surface-bound or internal targets as indicated. **(b)** Utilizing a different perspective, target molecules recognized by biologics NMEs were categorized as indicated. **(c)** Using the same color schema as (b), the three major categories of biologics NMEs were evaluated over time in reference to the types of targets recognized.

half-lives often measured in weeks rather than hours), new technologies might be increasing the relative attraction of small molecule therapeutics [19]. Thus, it is worth watching whether the observed decrease in biologics NMEs continues and, if so, understanding the causes of this reduction.

Although the present study was focused on NMEs, debate continues over how to introduce generic versions of biologics (also known as biosimilars). The lower costs of generic medicines provide strong incentives for the introduction of biosimilars and these have been successfully launched in many countries [20,21]. The Biologics Price Competition and Innovation Act was formally passed by Congress in 2009, yet questions remain regarding implementation [22–25]. The FDA is actively drafting guidelines for the introduction of biosimilars but key issues remain to be resolved regarding the vital concepts associated with bioequivalence. It will be interesting to determine how wide-scale introduction of biosimilars will impact future development of new biologics-based medicines.

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