The antibody molecule is modular and separate domains can be extracted through biochemical or genetic means. It is clear from review of the literature that a wave of novel, antigen-specific molecular forms may soon enter clinical evaluation. This report examines the developmental histories of therapeutics derived from antigen-specific fragments of antibodies produced by recombinant processes. Three general types of fragments were observed: antigen-binding fragments (Fab), single chain variable fragments (scFv) and “third generation” (3G), each representing a successive wave of antibody fragment technology. In parallel, drug developers have explored multi-specificity and conjugation with exogenous functional moieties in all three fragment types. Despite high hopes and an active pipeline, enthusiasm for differentiating performance of fragments should, perhaps, be tempered as there are yet few data that suggest these molecules have distinct clinical properties due only to their size.

Introduction

Antibody drug designers have long hypothesized that the modular nature of immunoglobulins could be exploited to engineer “customized” therapeutics, with pharmacologic properties optimized for specific applications. Thus, half-life and distribution, valency, affinity and avidity, tissue penetration and bioactivities could each be controlled by selection of appropriate molecular domains or defined genetic features, thereby theoretically allowing developers control over both safety and efficacy of antibody products. It is tempting to further speculate that the properties of designed antibodies could confer additional benefits for biomanufacturing, such as improved purity, quality and quantity of goods, and homogeneity of molecular species produced. This is a remarkable vision, and one might be tempted to see the beginnings of this revolution in antibody fragment products such as the marketed therapeutic certolizumab pegol (Cimzia).

This report focuses on therapeutics derived from antigen-specific fragments of antibodies produced by recombinant processes of any derivation and discusses 54 of these molecules that entered clinical study sponsored by a commercial firm, as well as candidates in preclinical development. Fusion proteins such as etanercept (Enbrel), which is composed of the ligand binding portion of TNFα receptor fused to an antibody Fc domain, were therefore excluded. Due to the extensive literature describing the technologies and specific antibody drug candidates, only selected references are provided.

Three technologies—antigen-binding fragments (Fab), single chain variable fragments (scFv), and “third generation” (3G) molecules—represent successive waves of antibody fragment technologies (Fig. 1). Fabs are clearly the most thoroughly explored; knowledge and experience was generated during the development of three US Food and Drug Administration (FDA) approved therapeutics (Table 1), six agents in active clinical development, and 20 discontinued programs, which collectively account for 49% of 54 identified antibody fragments that entered the commercial development process.
clinical pipeline. scFvs are a less mature, but significantly progressed set of technologies, with multiple agents in Phase 3 testing and a growing diversity of morphologies. The antibody fragment pipeline is expanding, with 10 scFvs accounting for 40% of the active clinical pipeline, and many in preclinical research. Least mature are the “3G” fragment technologies, including single domain and “miniaturized” antibody therapeutic molecules. These classes have few representatives in clinical study (6%), but account for at least half of the identified preclinical pipeline. Moreover, strong interest in exploring multi-specificity and conjugation with exogenous functional moieties continues. Therefore, it is clear that a wave of novel, antigen-specific molecular forms is now entering clinical evaluation; various trends in their development are considered here.

Enthusiasm for differentiating performance of fragments should, perhaps, be tempered as there are yet few data that suggest these molecules have distinct clinical properties due only to their size. Of the three fragments approved by the FDA, only certolizumab pegol has competitors for the same clinical indications (Crohn disease, rheumatoid arthritis, ankylosing spondilitis). Although no head-to-head comparative trials have yet been conducted, certolizumab pegol offers no clear advantages with regard to efficacy or safety over infliximab, adalimumab or golimumab. Perhaps the most direct, conclusive data regarding comparison of an antibody fragment with a full-length form will come from trials directly comparing ranibizumab (Lucentis) with bevacizumab (Avastin) for the treatment of age-related macular degeneration. Concern over the high price of ranibizumab and the molecular similarity between the antigen-binding domains of both molecules have been used to justify several trials (clinicaltrials.gov identifiers NCT00593450, NCT00710229), despite the fact that the FDA has not approved bevacizumab for this indication. Only in biomanufacturing may there be significant differences between fragments and full-sized molecules, e.g., the smaller size of fragments may permit cheaper, faster production in microbial systems, although tests of this contention have not yet been described in the public literature.

Nonetheless, drug developers continue to tinker with an increasingly diverse series of molecular modules, permitting the creation of ever smaller highly-specific binding domains and the selection of diverse functional modifications. In addition, it is likely that clinical evaluation of many bispecific and multimeric molecules will expand, creating additional opportunities for clinical benefit. Given the coming diversification of fragment types, it is possible that antibody fragments, or modular therapeutics incorporating antibody domains, with efficacy and safety profiles superior to full-sized mAbs will be approved in the coming decade. Alternatively, fragments, as a class, may never empirically out-perform full-sized mAbs generally, but drug developers and clinicians might identify select applications for which fragment-derived molecules have unique utility.

**Pros and Cons**

Fragmentation of antibodies results in altered physiochemical features of these therapeutic molecules. For instance, the smaller size of fragments permits penetration into tissues inaccessible to full-size mAbs. As previously noted, antibody fragments may prove easier and less costly to manufacture due to the lack of glycosylation and relatively small size, which permits use of prokaryotic expression systems. However, fragments lack the Fc domain that serves to both stabilize full-size antibodies and allow FcR-mediated recycling. As a consequence, fragments are rapidly degraded in humans and have short circulating half-lives. Several strategies have been developed to extend the half-life of fragments, including conjugation to proteins such as albumin and PEGylation, which was applied to the FDA approved anti-TNFα Fab, certolizumab pegol. However, biomanufacturing advantages of fragment production may be lost if PEGylation is required because the process can prove expensive and technically challenging.

Lack of an Fc domain and the absence of in vivo processes that select against B cell production of unstable antibody species can increase the risk of aggregation during production or purification of antibody fragments, which in turn might increase the possibility of immunogenicity in patients. The lack of an Fc domain has additional consequences because fragments can effect therapeutic action only by binding either ligand or receptor; they do not induce Fc-mediated functions such as antibody-dependent cell-mediated

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**Figure 1. Antibody fragment types.** Depiction of a full size antibody and various antibody fragment types. CH, constant heavy chain; CL, constant light chain; IgG, immunoglobulin; Fab, antigen binding fragment; scFv, single chain variable fragment, V\_H, variable heavy chain; V\_L, variable light chain. Source: Michael Hust, Technical University of Braunschweig. Figure used with permission.
cytotoxicity or complement-dependent cytotoxicity unless specifically conjugated to an effector moiety.\(^8\)

### Overview of Fragments in Development

As part of ongoing studies of therapeutic antibody development, Tufts Center for the Study of Drug Development recently reviewed the progress of 54 fragment therapeutic candidates in clinical development and 38 molecules in preclinical research described in public literature.\(^1\) Fragments have, to date, collectively performed similarly to their full-sized brethren in the clinic; the two types of molecules demonstrate comparable cumulative success rates and both must overcome a primary barrier to progression at Phase 2 (Fig. 2). Moreover, most fragments have been developed with the intent to treat neoplastic and immunological conditions, matching broader trends also observed in full-sized mAbs. A high fraction of fragments in clinical development were conjugated to functional moieties, an unsurprising finding given that most fragments lack Fc effector domains. That said, a subtle, but notable, shift in therapeutic indications selected for fragment development was identified, indicating that drug developers may be increasingly interested in immunomodulation, rather than antineoplastic activities. Finally, successive waves of fragment therapeutics that entered clinical development were observed, with Fabs followed by second generation scFvs, and the initial representatives of a third generation of fragment therapeutics, including “miniaturized” mAbs and single antigen-binding domain molecules.

Although Fabs are discussed, the focus of this article is on second- and third-generation fragment technologies, including scFvs, “miniaturized” and single domain antibodies, as these approaches are the current focus of the industry. Development trends that are woven through diverse fragment classes, such as the advent of multi-specific and functionally conjugated molecules, are additionally considered, and highlighted molecules therefore may be discussed in multiple sections.

### Antigen Binding Fragments

Fab agents are the oldest class of monoclonal antibody (mAb) fragment therapeutics, demonstrated by the fact that all eight fragment therapeutics that entered clinical development before 1995 were Fabs.\(^1\) This class of fragments is also arguably the most successful, accounting for 49% of fragments to have entered clinical development and three FDA approved clinical applications. Abciximab (Reopro, Centocor/Johnson & Johnson) is a Fab fragment of a chimeric antibody against platelet glycoprotein IIb/IIIa, approved in 1994 as an adjunct to prevent thrombosis during to coronary artery catheterization for ST-elevation myocardial infarction. Ranibizumab (Lucentis, Genentech) is a humanized Fab directed against vascular endothelial growth factor A, approved in 2004 as a treatment for neovascular (wet) age-related macular degeneration. Certolizumab pegol (UCB) is a pegylated anti-TNF\(\alpha\) Fab approved in 2008 for treatment of Crohn disease. Beyond these monoclonal fragments, polyclonal Fab agents are also marketed, including CroFab, DigiFab and Digibind. The corollary to successful experiences with Fab technology is the large number of failed projects. Failure and success alike are learning experiences, and provide knowledge that can be applied in pharmacology, regulatory concerns and biomanufacturing, which may explain why numerous companies continue to test Fabs in clinical development.

### Single-Chain Variable Fragments

Single-chain variable fragments (scFvs) are recombinant molecules in which the variable regions of light and heavy immunoglobulin chains encoding antigen-binding domains are engineered into a single polypeptide. Generally, the \(V_h\) and \(V_l\) sequences are joined by a flexible linker sequence, and a series of variants are generated for optimizing binding affinity and stability.\(^9\) Molecular engineers have continued to diversity the fundamental scFv molecule, resulting in paired scFvs that bind to one another through complementary regions to form bivalent molecules (diabodies), complementary scFvs themselves produced as a single chain (tandem scFvs or tascFvs), and bispecific tandem scFvs (bis-scFvs), among others. Nearly as many scFv therapeutics have entered clinical development (19) as Fabs (23), accounting for 40% of clinically evaluated fragments.\(^1\) These candidates include 12 active and nine discontinued agents, most in early development, with all having entered clinical study after 1995. With at least 11 scFv publicly described in preclinical research,\(^1\) interest in this technology remains strong. From these data, scFvs appear to be a promising technology that, while as yet unproven, will have many opportunities to achieve clinical success in the future.

Five monovalent, monospecific scFvs were developed, only two of which remain active projects in early development. ESBA-105 is an anti-TNF\(\alpha\) scFv in Phase 1 development by ESBAtech for ophthalmic indications. Efungumab (Mycograb), an scFv that binds to the heat shock protein of \textit{Candida albicans}, is in Phase 2 development by NeuTec, a wholly-owned subsidiary of Novartis. Novomab-G2 is an anti-cancer scFv discontinued in Phase 2 by Viventia after the company decided to pursue a formulation that included a

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**Table 1. Monoclonal antibody fragments approved in the US**

| Generic (brand) names | Description | Indication of 1st approval | Date of 1st approval | Sponsor |
|-----------------------|-------------|---------------------------|----------------------|---------|
| abciximab (Reopro)    | Anti-GP\(\beta\)IIIa chimeric Fab | Clot prevention in angioplasty | 12/22/94 | Centocor |
| ranibizumab (Lucentis) | Anti-VEGF-A humanized Fab | Macular degeneration | 06/30/06 | Genentech |
| certolizumab pegol (Cimzia) | Anti-TNF\(\alpha\) pegylated humanized Fab | Moderate to severe Crohn disease | 04/22/08 | UCB |

Fab, antigen binding fragment; GP, glycoprotein; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor.

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\[1\] www.landesbioscience.com mAbs

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cytotoxic conjugate. Pexelizumab is an anti-CD20 SMIP discontinued in 2007 by Alexion Pharmaceuticals and Proctor & Gamble after primary outcomes were not met in two Phase 3 trials. Aurograb, an scFv that binds to a surface protein of methicillin-resistant Staphylococcus aureus, was discontinued in 2008 after Phase 2 trials failed to show efficacy.

Diabodies, composed of non-covalent dimers of scFvs, are bivalent antigen-binding molecules. Few, if any, diabodies have entered clinical development, and, to my knowledge, none have commercial sponsorship. An iodine-123-labeled diabody version of the anti-CEA chimeric antibody cT84.66 is being evaluated for pre-surgical immunoscintigraphic detection of colorectal cancer in a study sponsored by the Beckman Research Institute of the City of Hope (ClinicalTrials.gov NCT00647153).

Using molecular genetics, two scFvs can be engineered in tandem into a single polypeptide, separated by a linker domain, called a "tandem scFv" (tascFv). TascFvs have been found to be poorly soluble and require refolding when produced in bacteria, or they may be manufactured in mammalian cell culture systems, which avoids refolding requirements but may result in poor yields. Construction of a tascFv with genes for two different scFvs yields a "bispecific single-chain variable fragments" (bis-scFvs). Only two tascFvs have been developed clinically by commercial firms; both are bispecific agents in active early phase development by Micromet for oncologic indications, and are described as "Bispecific T-cell Engagers (BiTE)." Blinatumomab is an anti-CD19/anti-CD3 bispecific tascFv that potentiates T-cell responses to B-cell non-Hodgkin lymphoma in Phase 2. MT110 is an anti-EP-CAM/anti-CD3 bispecific tascFv that potentiates T-cell responses to solid tumors in Phase 1. Bispecific, tetravalent "TandAbs" are being researched by Affimed, but none have yet reached clinical development.

**Third Generation Molecules**

Another approach to reducing the size of antigen-binding immunoglobulin-derived recombinant proteins has been to "miniaturize" full-sized mAbs by removing domains deemed non-essential for function. Miniaturized mAbs were included in the "3G" fragment category due to the relatively recent advent of this approach, in contrast to scFvs, which were described as early as 1988. Only a handful of "miniaturized" antibodies have entered clinical development.

Among the best examples of mAb miniaturization are the small modular immunopharmaceuticals (SMIPs) from Trubion Pharmaceuticals. These molecules, which can be monovalent or bivalent, are recombinant single-chain molecules containing one V_Ig, one V_H Ig, antigen-binding domain, and one or two constant "effector" domains, all connected by linker domains. Presumably, such a molecule might offer the advantages of increased tissue or tumor penetration claimed by fragments while retaining the immune effector functions conferred by constant domains. At least three "miniaturized" SMIPs have entered clinical development. TRU-015, an anti-CD20 SMIP developed in collaboration with Wyeth, is the most advanced project, having progressed to Phase 2 for rheumatoid arthritis (RA). Earlier attempts in systemic lupus erythematosus (SLE) and B cell lymphomas were ultimately discontinued. Trubion and Facet Biotechnology are collaborating in the development of TRU-016, an anti-CD37 SMIP, for the treatment of CLL and other lymphoid neoplasias, a project that has reached Phase 2. Wyeth has licensed the anti-CD20 SMIP SBI-087 for the treatment of autoimmune diseases, including RA, SLE and possibly multiple sclerosis, although these projects remain in the earliest stages of clinical testing.

Gemab is research application of their "Unibody" technology, in which the hinge region has been removed from IgG4 molecules. While IgG4 molecules are unstable and can exchange light-heavy chain heterodimers with one another, deletion of the hinge region prevents heavy chain-heavy chain pairing entirely, leaving highly specific monovalent light/heavy heterodimers, while retaining the Fc region to ensure stability and half-life in vivo. This configuration may minimize the risk of immune activation or oncogenic growth, as IgG4 interacts poorly with FcRs and monovalent unibodies fail to promote intracellular signaling complex formation. These contentions are, however, largely supported by laboratory, rather than clinical, evidence. Biotecnol is also developing a "miniaturized" mAb, CAB051, which is a "compacted" 100 kDa anti-HER2 antibody in preclinical research.

Recombinant therapeutics composed of single antigen-binding domains have also been developed, although they currently account for only 4% of the clinical pipeline. These molecules are extremely small, with molecular weights approximately one-tenth of those observed for full-sized mAbs. Arana and Domantis engineer molecules composed of antigen-binding domains of human immunoglobulin light or heavy chains, although only Arana has a candidate in clinical testing, ART-621, an anti-TNFα molecule in Phase 2 study for the treatment of psoriasis and rheumatoid arthritis. Ablynx produces "nano-bodies" derived from the antigen-binding variable heavy chain regions (V_HH) of heavy chain antibodies found in camels and llamas, which lack light chains. Two Ablynx anti-von Willebrand Factor nano-bodies have advanced to clinical development, including ALX-0081, in Phase 2 development as an intravenous therapy to prevent thrombosis in patients undergoing percutaneous coronary intervention for acute coronary syndrome, and ALX-0681, a Phase 1 molecule for subcutaneous administration intended for both patients with acute coronary syndrome and thrombotic thrombocytopenic purpura.

In addition, at least 16 domain molecules are being researched in preclinical studies, accounting for nearly half of the identified preclinical research pipeline, with Ablynx responsible for 5 and Domantis responsible for the remaining 11 candidate. Domantis, a wholly-owned subsidiary of GlaxoSmithKline since 2007, produces single-domain molecules based on human immunoglobulin sequences, which may or may prove advantageous in the clinic.

These data are consistent with the relative novelty of individual antibody domain molecules, and demonstrate how little is known about the clinical efficacy of agents derived from these binding domains, despite encouraging pre-clinical research and great commercial interest.
Multi-Specificity

Although multi-specific molecules were described in the previous sections, this approach is sufficiently important to warrant separate, parallel consideration when evaluating trends in the development of antibody fragment therapeutics.

Natural antibodies express two identical antigen-binding domains, and are therefore mono-specific, but bivalent. In contrast, bispecific molecules possess two different antigen-binding domains, each with different target specificity. Bispecific antibodies were initially described in the mid 1980s, and were generated by the fusion of two antibody-producing cells, each with distinct specificity. These “quadromas” produced multiple molecular species, as the two distinct light chains and two distinct heavy chains were free to recombine in the quadromas in multiple configurations. Since these early efforts, bispecific Fabs, scFvs and full-size mAbs have been generated and tested using a variety of technologies. Six bispecific fragments have entered development, including four discontinued bispecific Fabs, three of which were from Domantis, and two bispecific tscFvs in active development by Micromet. At least 11 bispecific fragments therapeutics in preclinical research have been described in public documents, including two Fabs from Immunomedics, five scFvs including four from Affimed and one from Targa, as well as four bispecific human “domain” antibodies from Domantis. Nine of those fragments are intended for development in oncologic indications, and the remaining two for immunological disorders. The Immunomedic compounds are each trimeric, with two arms specific for one target, and a third arm specific to a second target. These molecules function for the most part by potentiating B cell, T cell or natural killer cell responses to tumor cells.

Although not clearly an antibody fragment, Trion Pharma has sought to develop “trispecific” molecules by expressing bispecific antibodies with two distinct Fabs and an Fc, demonstrating highly potent macrophage activation properties. This was first described for a mouse IgG2a anti-Ep-CAM, rat IgG2b anti-CD3 quadroma, called BiUII. The authors propose that BiUII permits the co-localization of tumor cells expressing Ep-CAM, T cells expressing CD3, and macrophages expressing FcγRI, potentiating the costimulatory and anti-tumor functions of the immune cells.

Trion has three trispecific full-length mAbs that have entered clinical development, including catumaxomab (Removab), an anti-EpCAM rat-human hybrid molecule approved in the EU, and in Phase 3 study in the US, for malignant ascites.

Conjugation

Similar to multi-specificity, the conjugation of exogenous effector moieties to antibody fragment molecules is an important approach taken by drug designers. For this reason, although conjugated molecules were described in previous sections, separate consideration is given to this topic.

Full-length antibodies have biological functions conferred by both antigen binding and the complement fixation and cellular activation capacity of the Fc domain. The biological function of the three approved Fab fragment therapeutics, however, is strictly limited to the capacity of the single binding domain molecule to bind the target. Nearly half of fragments in clinical development were conjugated to exogenous functional moieties and all of these were intended for the treatment of cancer. This constitutes a higher proportion than that observed for all anti-cancer mAbs, of which approximately 44% are immunoconjugates. These data demonstrate that drug developers are well aware of the functional limitation of fragments that lack effector domains or see fragments as an opportunity to more precisely control the functional properties of therapeutic candidates.

A total of 24 conjugated antibody fragments have entered clinical study, with eight active projects and one molecule approved in China. Metuximab-I131 (Licartin) is a murine IgG1 anti-CD147 F(ab), conjugated to iodine-131 produced by Chengdu Hoist Hitech and approved by the Chinese State FDA for the treatment of liver cancer; this molecule has not met regulatory approval in any other country. The remaining eight projects in active development are well-distributed throughout the phases of clinical development, with two in Phase 3 and two in Phase 2. Of the 24 conjugated fragments, 12 are fragments conjugated to cellular toxins, seven are conjugated to radioisotopes, three to cytokines and one to an enzyme to target toxic metabolites; the type of moiety conjugated to 1 is unknown.

Twelve Fab conjugates have entered clinical development, including metuximab I-131 and an active Phase 3 candidate, naptumomab estafenatox (Anyara), an anti-5T3 Fab conjugated to the staphylococcal enterotoxin A, a superantigen, being developed by Active Biotech to treat lung cancer by immune stimulation. Nine of these 12 have been discontinued. Five Fabs were conjugated to cytotoxins, including naptumomab estafenatox and three discontinued molecules also conjugated to staphylococcal enterotoxin A. The fifth cytotoxin-conjugated Fab is an active Phase 1 candidate, Viventia’s Phase 1 citatuzeumab bogatox (VB6-845), conjugated to bougain. Five Fabs have been conjugated to radioisotopes, including metuximab I131 and a bispecific Fab, Pentacea (MN14-734; IBC Pharmaceuticals), with one arm directed against a hapten molecule that can be separately conjugated to a radioisotope, thereby permitting antibody fragment delivered radiotherapy; antineoplastic development of this molecule was discontinued in Phase 2. One Fab, Medarex’s MDX-214, was genetically fused to a cytokine, epidermal growth factor, but ultimately discontinued in Phase 2. Another, AstraZeneca’s ZD-2767C, is an anti-CEA F(ab), fused to carboxypeptidase G2. Designed for antibody directed enzyme prodrug therapy of cancer, the molecule was discontinued after Phase 1 testing.

Twelve scFv conjugates have entered clinical development, six of which remain in active development. The most advanced of these is Viventia Biotech’s VB4-845, an anti-EpCAM scFv conjugated to pseudomonas exotoxin PE-38 that advanced to Phase 3 development for head and neck cancer under the trade name Proxinium. This project was discontinued, but development of VB4-845 as a treatment of bladder cancer continues. VB4-845 under the trade name Vicinium is at Phase 2 for this indication. Six additional scFvs genetically fused to PE-38 have entered clinical development. All of these were from different companies and
Antibody fragments are a heterogeneous assortment of molecules assembled by researchers inspired by the modular nature of antibodies. Those who wish to apply this diverse collection to drug development seek to maintain the high specificity and selectivity of antibodies, while offering distinct biological profiles such as cheaper and faster manufacturing, control over avidity as well as affinity and altered PK and tissue distributions.

Critics have much reason for pessimism due most prominently to the observation that fragments have remained a minority of therapeutic mAbs in development, resulting in only three molecules that have been approved by the FDA. It is not clear from the available data if the approval success rate for Fabs is significantly less than the rate observed among full-size monoclonal therapeutics (Fig. 2). However, when all fragments are considered, the success rate is clearly no better than that observed for full-sized humanized mAbs, and one would expect that if fragments possessed biological features that truly differentiated them from full-sized mAbs, the drug development community would have seized upon and exploited such advantages. This is particularly apparent for anti-cancer fragments, the most common therapeutic indication for both fragments and full-size antibody therapeutics alike. High hopes for the success of fragments in treating cancer were placed upon the theory that smaller molecules could penetrate deeper into target tissues; however, not one of 35 anti-cancer fragments that entered clinical development has yet been approved by the FDA (although ten remain in development), while one ophthalmologic, one anti-inflammatory and one cardiovascular/hematologic fragment has been approved out of cohorts of only 2, 6 and 8 candidates that entered clinical study, respectively.

Few direct comparisons between fragments and full-sized mAbs are possible, but available data suggests that certolizumab pegol is not inherently safer or more efficacious than other anti-TNFα antibodies, and it is expected by many observers that bevacizumab will approximate the efficacy of ranibizumab at significantly lower expense. Other direct comparisons will require additional data for molecules in early development, e.g., anti-CD20 SMIPs TRU-015 or SBI-087 that may compete with rituximab and ofatumumab, and CAB051, an anti-Her2 Neu “miniaturized” antibody that may compete with trastuzumab.

These conclusions are retrospective, however, and technological evolution is rapid and ambitious. The bulk of the fragments with biological features that are truly differentiated from full-sized mAbs, Fabs and scFvs—the “3G” molecules, including “nanobodies”, “minibodies” and “unibodies”, and the various bi- and trispecific molecules—are only now entering early clinical development, and the molecular engineers responsible no doubt have greater ambitions yet to come. Thus, the promise of antibody fragment therapeutics remains, as yet unfilled, but not broken.

Acknowledgements

The author thanks colleagues at Tufts University for helpful discussions and suggestions and Michael Hust for the use of Figure 1.
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