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Beyond new chemical entities

Advancing drug development based on functional versatility of antibodies

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Antibody-type agents (i.e., antibodies and derivatives thereof) may be produced as clinically valuable antidotes, which conceivably could be developed in tandem with prospective new pharmaceutical products so as to render the risks of clinical trials more acceptable from a regulatory standpoint. Yet, this is but a relatively narrow view of the full potential utility associated with antibody-type agents, the significance of which is appreciated upon reconsidering key aspects of early modern biomedical research (notably major contributions thereto by Nobel Laureate Paul Ehrlich) in light of much more recent advances (e.g., application of immunity-oriented approaches to diseases in general, epitope-specific targeting, abzyme-mediated catalysis, antibody-mediated sustained-release buffering of unbound-ligand concentrations, and enhanced thermal and metabolic stability of deuterated chemical species via the kinetic isotope effect), as conditioned by health-related concerns (e.g., current and anticipated epidemiologic transitions vis-a-vis environmental changes) especially with regard to sustainable development (e.g., emphasizing more efficient resource utilization toward increased global resilience based on greater independence from high-maintenance technological infrastructure). The broader view that thus emerges highlights the urgent need to rebalance the health-research agenda, which presently reflect an overemphasis on small-molecule candidate-drug discovery, in order to advance health based on a comprehensive fundamental synthesis of immunity and pharmacology.

Keywords: drugs, drug development, new chemical entities, antibodies, abzymes, antidotes, antibody buffering, deuteration, kinetic isotope effect, drug repurposing

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Introduction

Contemporary drug development is dominated by small-molecule new chemical entities (NCEs) traditionally distinguished from macromolecular agents (e.g., proteins such as antibodies) regarded as biologicals,[1] although the distinction may well become one of mainly historical interest given the sustained advances in synthetic chemistry.[2] Approval of a NCE for clinical use entails an increasingly expensive regulatory process reflecting high risk of failure to satisfactorily demonstrate both safety and efficacy.[3] The consequent crisis of limited therapeutic options may be mitigated by more safety-oriented development of novel pharmaceutical products together with corresponding antidotes in the form of antibody-type agents (i.e., antibodies and derivatives thereof, including proteolytically generated antigen-binding [Fab] and recombinant single-chain [scFv] fragments) that, for example, bind[4] candidate drugs with high affinity. Furthermore, antibody-type agents conceivably can contribute to greatly enrich the repertoire of therapeutic and prophylactic approaches to diseases in general through synergy with small-molecule drugs, according to the general framework outlined in this commentary.

Origins of Current Crisis in Drug Development

Premodern societies devised systems of traditional knowledge encompassing medicinal preparations derived from

naturally-occurring materials, especially plant products (e.g., as seen in the materia medica of Indian Ayurvedic and traditional Chinese medicine).[5] Eventually, drugs were manufactured on an industrial scale primarily as synthetic products, including replacements or analogs of known natural products and even exotic chemical species without any known natural counterparts.[5]

Early modern biomedical research efforts complemented drug development with studies on immunity, as exemplified by the work of German physician-scientist Paul Ehrlich: he developed the first modern chemotherapeutic agent (arsphenamine, for syphilis and trypanosomiasis) yet also conducted groundbreaking studies on antibody-mediated humoral immunity (notably with antisera against diphtheria), for which he shared the 1908 Nobel Prize in Physiology or Medicine (with Elie Metchnikoff, who pioneered the study of cell-mediated immunity).[7] Ehrlich envisioned highly specific ligand-receptor binding interactions as the chemical basis for rational design of novel therapeutic agents as, in his own words, "magic bullets" against disease.

Vaccines and antibody-containing preparations were thus developed against many infectious diseases; but further success was limited by inadequate knowledge of immunity.[8] Hence, attention shifted toward small-molecule anti-infective agents (e.g., sulfa drugs, penicillins, and other antibiotics) known for their potentially dramatic curative effects upon introduction into clinical practice but invariably rendered ineffective by the emergence of resistant pathogen strains, in a vicious circle of drug development negated by drug resistance.[9] More generally, small-molecule drugs pose the challenge of accurately predicting their adverse effects;[10] yet, acquisition of the requisite empirical data to improve prediction of the said adverse effects is hindered by prevailing regulatory regimes, which mandate evaluation of drug safety using animal models of questionable scientific and ethical validity.[11]

Drug development is thus constrained by risk aversion born of uncertainty as regards safety, reflecting a conservative attitude deeply rooted in the premodern origins of medicine, as evident in the Hippocratic directive to abstain from causing harm and echoed in the modern bioethical principle of nonmaleficence.[12] This is compounded further by the perception of drugs as inherently harmful, which at least partly derives from a fundamental dictum of toxicology, attributed to Swiss-German physician-alchemist Paracelsus and predicated on the assertion that "all things are poison"; but the entire dictum itself may be succinctly restated as "the dose makes the poison," which points to dose dependence as the basis for framing drug safety.[13]

From Antidotes to Dosage Regulators

Dose dependence of pharmacologic effects calls for regulation of drug dosage to balance safety with efficacy, as typically accomplished by adjusting the dose and dosing interval. Where drug toxicity occurs, it may be mitigated by administration of specific antidotes, notably antibody-type agents that bind drugs to either sequester them (e.g., with Fab fragments to cardiac glycosides such as digoxin[14]) or catalyze their chemical transformation into less harmful products (e.g., with abzymes that catalyze hydrolysis of cocaine[15]), thereby decreasing concentrations of active drug below toxic levels. More generally, antibody-type agents may serve as dosage regulators that maintain concentrations of active drug within a desired range, as can be understood with regard to the kinetics of ligand-receptor interactions including biochemical catalysis.

Typical antigen-antibody interaction occurs as reversible (i.e., purely noncovalent) ligand-receptor binding, toward a dynamic equilibrium between unbound (i.e., free) and bound species as characterized by the binding affinity (quantified as the equilibrium association constant K_A, such that $K_A = k_{on}/k_{off}$ where k_{on} and k_{off} are the respective on- and off-rate constants), which is often expressed as the equilibrium dissociation constant K_D (such that $K_D = 1/K_A$). For a given ligand-receptor pair, K_D is the concentration of ligand (e.g., antigen) at which half the receptor (e.g., antibody) ligand-binding sites are occupied by ligand. In cases of irreversible binding due to stable covalent linkage, affinity is virtually infinite (i.e., practically with infinite K_A and zero K_D), as may be realized by engineering complementary reactive groups between antibody and antigen.[16] For reversible binding wherein the receptor (e.g., an abzyme) catalyzes the chemical transformation of the ligand, classical Michaelis–Menten kinetics may be used to describe steady-states at which the concentration of ligand-receptor complex remains essentially fixed over time, as characterized by the Michaelis–Menten constant $K_m = (k_{off} + k_{cat})/k_{on}$, where k_{cat} is the catalytic constant (i.e., turnover number). K_m is the ligand concentration for half-maximal catalysis and reduces to K_D where k_{cat} vanishes.

Hence, the use of antibody-type agents as antidotes that merely sequester drugs (i.e., without catalysis) is clearly limited by both stoichiometry and affinity, as the number of drug-binding sites represents a physical upper limit on the amount of drug that can be sequestered, and only a fraction of the said sites actually can be occupied by drug given finite binding affinity (e.g., unless irreversible binding occurs due to covalent linkage). Although the number of the said sites might be increased by adding more antidote to sequester more drug, this is physically plausible only up to a certain point (e.g., the solubility limit of the antidote), and undesirable biological effects almost certainly would be encountered before that point is reached in vivo (e.g., due to hyperviscosity syndrome associated with excessive circulating antibody concentration[17]). Moreover, protein engineering conceivably is necessary to achieve infinite affinity via covalent linkage or even maximal affinity via purely noncovalent binding, in view of the affinity ceiling associated with affinity maturation in vivo (except perhaps in cases where rearrangement of germline antibody genes fortuitously yields paratopes that bind with affinity above the said ceiling).[18] Catalysis by antibody-type agents is thus a potential means for transcending the stoichiometric and affinity limits of noncatalytic ligand-receptor binding as basis for antidote activity.

Catalytic antibody-type agents may be produced as abzymes elicited by

immunization with suitable transition-state analogs, such that the resulting paratopes bind the actual transition states and thereby effect catalysis via transition state stabilization (e.g., where phosphonate analogs mimic tetrahedral transition states for the hydrolysis of ester or amide linkages).[19] Alternatively, antibodies may be produced against an enzyme active site, such that abzymes may be produced as antiidiotypic antibodies bearing catalytic paratopes that mimic the original enzyme active site.[20] In addition to mimicry of transition states and enzyme active sites, appropriately placed chemically reactive (e.g., nucleophilic) groups may be engineered into paratopes; this may be facilitated through immunization with covalently reactive analogs (e.g., of a peptide or protein) bearing appropriately placed electrophilic groups, such that covalent linkage occurs between the electrophilic groups and proximate nucleophilic groups on the paratope, in which case the said linkage could favor production of antibodies wherein the said nucleophilic groups assume special catalytic roles (e.g., nucleophilic attack on the carbonyl carbon atom of a peptide bond, leading to hydrolysis of the said bond).[21] Furthermore, a plurality of amino-acid residue sidechains may be engineered into a paratope to effect catalysis (e.g., by creating a catalytic triad similar to that of a classic serine protease).[22]

Apart from serving as antidotes, antibody-type agents could also function as vehicles for sustained-release buffering of drugs in vivo for tightly controlled dosage regulation.[23] Reversible ligand-receptor binding between haptens and cognate antibodies is the basis for antibody buffering of free (i.e., unbound) hapten concentration, which is analogous to pH buffering and thus maximal at a hapten concentration of K_D (just as pH buffering is maximal at the pK_a of the conjugate acid-base pair for a given buffer system); thus, for a hapten-binding monoclonal antibody at equilibrium with free hapten concentration equal to K_D, exactly half the paratopes are occupied by hapten. This provides a robust mechanism for maintaining free-drug concentrations within relatively narrow ranges in vivo, with antibody-bound drug being released to replace free drug lost via processes of biotransformation and excretion. To maintain a steady-state with respect to free-drug concentration, lost drug could be replenished accordingly by administering additional drug to recharge the antibody (which itself might be replenished by supplying exogenous antibody). Because the free-drug concentration associated with maximal buffering would be affinity-dependent, antibodies could be engineered to customize affinity levels (e.g., by site-directed mutagenesis to decrease affinity) and thereby achieve maximal buffering at appropriate free-drug concentrations.

In all the scenarios discussed thus far, affinity levels arguably should be considered in the context of cross-reactivity conceptualized as differential affinity for multiple potential targets including various drugs and even endogenous biomolecules, especially where catalytic modification of targets is possible. Although cross-reactivity may be advantageous, for example, where this enables a paratope to bind structurally related compounds and thereby mitigate their toxicity (as in the case of anti-digoxin Fabs that also bind other structurally similar cardiac glycosides[14]), adverse effects might result from unintended cross-reactivity of antibody-type agents with particular drugs (e.g., where multiple drugs are concomitantly used, as is increasingly commonplace among geriatric patients[24]) and also with self-epitopes (e.g., where catalytic hydrolysis of peptide bonds can damage self-biomolecules[25]).

Expanding Roles of Antibody-Type Agents in Drug Development

Whereas clinical trials historically have been designed with relatively superficial regard to factors underlying the variability of health outcomes (e.g., success or failure of particular therapeutic interventions), the emerging context-dependent customization of health care (e.g., through personalized medicine) emphasizes individual circumstances as crucial determinants of the said outcomes.[26] Dose dependence of pharmacologic effects is thus subject to variation in both pharmacokinetics (e.g., reflecting genetic background and also environmental influences such as exposure to chemical modulators of drug metabolism) and pharmacodynamics (e.g., due to variability among molecular targets and pathways thereof), such that safety and efficacy may be difficult to consistently realize.[27,28] In extreme cases, idiosyncratic reactions may occur that result in severe harm even at very low dose levels (e.g., where immune mechanisms produce a greatly amplified response, as observed in drug-induced forms of anaphylaxis and toxic epidermal necrolysis).[29]

Potential adverse drug reactions may be addressed by both antidote usage and microdosing (i.e., administration of drugs at extremely low doses). As discussed in the preceding section, antibody-type agents can serve as antidotes through either catalytic chemical transformation of drugs or noncatalytic drug binding, with catalysis possibly transcending the stoichiometric and affinity limits of noncatalytic binding. As regards microdosing, it enables preliminary investigation of in-vivo drug activity (including effects on specific molecular targets) and pharmacokinetics, thus providing an opportunity for critical exploratory studies (e.g., either in Phase 0 clinical trials or for individually customized treatment regimens) that limit initial drug exposure in the interest of safety.[30,31] This might be achieved where drug effects would be due to free rather than protein-bound drug, in particular by using antibody-type agents as drug-binding vehicles to buffer free-drug concentrations in vivo. For example, microdosing might be performed using a mixture of drug and cognate drug-binding vehicle, equilibrated ex vivo prior to administration, such that local free-drug concentrations everywhere in vivo would remain below some physicochemically predetermined limit (e.g., K_D); and adverse drug reactions could be managed with prompt administration of drug-specific antidote (e.g., a drug-degrading abzyme, or additional drug-binding vehicle).

Where the results of initial microdosing would appear to be favorable as regards safety, dose escalation might be pursued toward therapeutically adequate free-drug

concentrations in vivo, with continued monitoring for possible adverse drug reactions and provision for appropriate contingency measures including antidote administration. Dose escalation could be effected by increasing the amount of administered drug relative to the drug-binding vehicle, and possibly also by replacing the drug-binding vehicle with another of lower drug-binding affinity (i.e., higher K_D), to enable efficient buffering over a higher range of free-drug concentrations. Further dose escalation might be realized by modulating pharmacokinetics, notably through interference with drug metabolism and excretion, to prolong free-drug half-life. This could be effected by administering yet other drugs (e.g., to inhibit hepatic drug metabolism or decrease renal drug clearance),[32] which themselves might be maintained at adequate concentrations using cognate drug-binding vehicles, albeit complicating safety considerations (e.g., by introducing the requirement for antidotes to the extra drugs and also the possibility of unintended drug interactions).

While certain antibody-type agents could serve as drug-binding vehicles, others might serve as antagonists (e.g., anti-idiotypic antibodies) to the said vehicles via inhibition of drug-binding activity, thereby facilitating fine regulation of free-drug concentrations; and yet other agents (e.g., anti-anti-idiotypic antibodies) might be developed in turn to antagonize the said inhibition of drug-binding activity, to enable even finer regulation of free-drug concentrations. Systems of antagonists thus might be developed (e.g., as idiotypic networks) that exhibit redundancy in the form of structurally distinct yet functionally comparable antibody-type agents appropriate for different individuals (e.g., to avoid adverse autoimmune and allergic reactions, possibly in part by avoiding repeated administration of the same agent to the same individual). Safety of the various agents thus would be defined in terms of factors including possible adverse immune reactions vis-a-vis recipient immune status (broadly construed as regards genetic background and immunization history encompassing prior exposure to the said agents) and even possible molecular mimicry of drugs (e.g., by antiidiotypic antibodies that might function as agonists or antagonists of the structurally mimicked drugs[33]).

At any rate, elimination kinetics of antibody-type agents is a key consideration particularly where such agents would serve as drug-binding vehicles, insofar as free-drug concentrations might increase unacceptably (e.g., if the said vehicles were eliminated faster than the free drug would be). The stability of antibody-type agents varies widely; for example, antibody half-life in vivo may be on the order of weeks due to antibody recycling via Fc-receptor binding within acidified endosomes,[34] but Fab fragments and other antibody derivatives lacking an Fc component tend to be degraded much more rapidly (e.g., with a half-life of only hours) unless suitably modified (e.g., by PEGylation or PASylation[35]). Drug-binding vehicles and their cargo drugs thus should be matched as regards relative elimination kinetics. On a related note, antibody-type agents might be engineered to minimize their immunogenicity (e.g., by humanization or the introduction of regulatory T-cell epitopes also known as tregitopes[36]), so as to avoid inducing immune-mediated elimination.

Future Prospects

The use of antibody-type agents as antidotes and drug buffers opens vast opportunities for translational research. Rapid innovation might be realized first with drugs already approved for clinical use, to facilitate further enhancement of clinical outcomes using the said drugs (e.g., by maintaining in-vivo free-drug concentrations within the therapeutic window over longer dosing intervals) while better enabling subsequent application both prospectively to NCEs and even retrospectively to other chemical entities previously deemed unsuitable as drugs (e.g., due to unacceptably narrow therapeutic windows and impractically short dosing intervals). Such work initially would employ passive immunization (i.e., using exogenous antibody-type agents), although active immunization (e.g., by immunization with carrier-linked haptens to elicit endogenous drug-binding antibodies) might prove more advantageous in selected cases (e.g., where it would obviate repeated administration of exogenous antibodies during long-term therapy for chronic conditions such as hypertension).

Additionally, use of antibody-type agents as discussed thus far might be enhanced further via the kinetic isotope effect, which is the quantum-mechanical phenomenon that accounts for greater stability of chemical bonds where deuterium replaces ordinary hydrogen.[37] Relative to their nondeuterated counterparts, perdeuterated drugs typically exhibit greater thermal and metabolic stability, which might be enhanced through association with antibody-type agents used as drug-binding vehicles; likewise, perdeuterated antibody-type agents themselves might be more stable, which could complement the stability of perdeuterated drugs. Such effects could translate to longer pharmaceutical shelf life and extended in-vivo half-lives of either or both drugs and their cognate drug-binding vehicles.

Notwithstanding the aforementioned potential advantages of using antibody-type agents as drug-binding vehicles, this might be counterproductive where free-drug concentrations would be difficult to buffer at therapeutically appropriate levels, especially for anti-infective drugs due to emergence of pathogen drug resistance at subtherapeutic drug concentrations.[38] Sustainable control and prevention of infectious diseases arguably could be achieved more definitively using vaccines and other immunity-based approaches that directly target pathogens,[39] for both human and veterinary applications.

The above scheme thus could enable fuller exploitation of already approved drugs in a manner akin to drug repositioning (i.e., drug repurposing for alternative clinical indications),[40] in that regulatory barriers would be much lower than for approval of typical NCEs (considering that antibodies and other biologicals might be more readily approved than small-molecule drugs[41]). Likewise, packaging NCEs together with cognate antidotes and drug-binding vehicles could lower regulatory barriers relative to approval of NCEs per

se as drugs. New therapeutic options thus developed, particularly those with very long dosing intervals, would better support global health in the face of interrelated epidemiologic and environmental transitions such as population aging (associated with increasing incidence of geriatric conditions)[42] and climate change (characterized by severe weather disrupting health-care delivery on massive scales).[43]

Conclusions

The use of antibody-type agents as antidotes and pharmacological buffers provides means for facilitating and enhancing drug development, by better addressing safety concerns and enabling more favorable pharmacokinetics toward longer dosing intervals. This could support more balanced translational research to more fully exploit already approved drugs and other known chemical entities, as an alternative to high-risk conventional NCE-based drug discovery, in line with current and anticipated global health trends. The "magic bullet" concept of Paul Ehrlich thus may be extended to include bipartite "core-plus-vehicle" constructs, each comprising a pharmacologically active core drug coupled with a cognate drug-binding vehicle for regulating free-drug concentrations in vivo.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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