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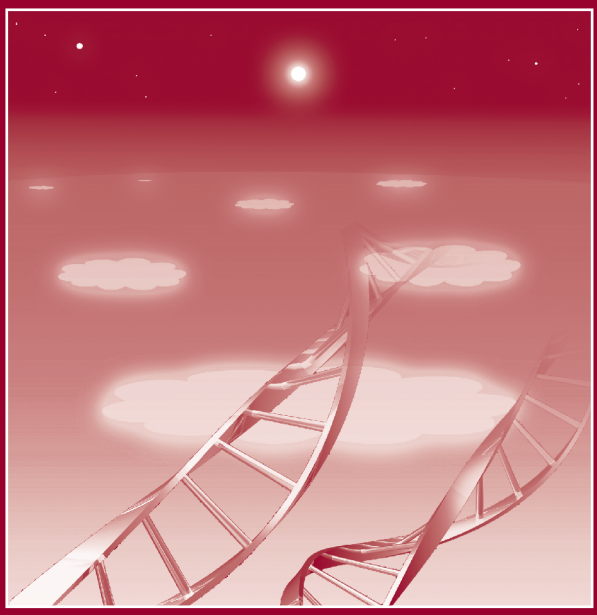
Proteins and Peptides

Pharmacokinetic, Pharmacodynamic, and Metabolic Outcomes



edited by

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Proteins and Peptides

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Proteins and Peptides

Pharmacokinetic, Pharmacodynamic, and Metabolic Outcomes

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Preface

The promise of biotechnology and an increased understanding of the human genome have resulted in an explosion of protein and peptide therapeutics entering research and development pipelines in biopharmaceutical as well as traditional pharmaceutical companies. Increasingly, these protein and peptide candidates are being designed to address previously untreatable diseases and conditions. To advance these molecules into clinical trials, however, an understanding of their pharmacokinetic, pharmacodynamic, and metabolic fate is required. The study of these events represents emerging disciplines with issues and challenges distinct from those of small molecules, on which many of the principles of these fields were initially developed.

That many of the protein and peptide therapeutics being evaluated are endogenous or emulate an endogenous material potentially defines preestablished pharmacokinetic, pharmacodynamic, and metabolic parameters for these molecules in the human model. Unfortunately, or fortunately, initial preclinical testing of potential protein and peptide therapeutics requires obtaining information on safety and preclinical efficacy in (typically) several nonhuman animal models. Such studies are complicated, or rather compromised, by the fact that nonhuman models may not express critical elements such as receptors, binding proteins, and enzyme activities that function to define pharmacokinetic, pharmacodynamic, and metabolic parameters in humans. Additionally, human disease states being emulated, but never fully recapitulated, in nonhuman animal models may or may not faithfully describe conditions that will be confronted in the clinic. All of these issues are further complicated by the fact that these peptide and protein therapeutic candidates must be formulated for long-term storage stability and delivered at concentrations and in locations that are likely very different from endogenous events.

Most protein and peptide therapeutics are administered by injection, usually being formulated with a strategy to minimize the frequency of these injections. In this regard, recent studies have identified several alternative routes of administration for proteins and peptides that were previously not considered a viable option for delivery. Although the size and labile nature of protein and peptide therapeutic candidates typically impede their passage across most biological barriers, intranasal and pulmonary delivery for therapeutic proteins and peptides is now a commercial reality. Additionally, tremendous progress has been made for the delivery of proteins and peptides via transdermal and oral routes as well as delivery to the eye and brain. All of these routes pose unique pharmacokinetic, pharmacodynamic, and metabolic challenges for the protein or peptide being delivered, each of which might be altered in the human model of disease relative to the nonhuman models initially examined.

The chapter topics that follow were selected to provide an overall roadmap for understanding our current understanding of parameters that define the pharmacokinetic, pharmacodynamic, and metabolic challenges for the delivery

of protein or peptide therapeutics. In general, these chapters recite lessons learned for the major areas of proteins and peptide therapeutics that have been successfully taken to market, for example, antibodies, interleukins, interferons, growth factors, and peptide hormones. Additionally, chapters have been included that explore innovations for protein and peptide delivery that include needle-less delivery and strategies to deliver these molecules to locations such as the eye and brain. Although all of the chapters were written with a forward-looking perspective, with the goal of identifying issues that are likely to become increasingly important in the future. It is hoped that the information shared in these chapters will provide the reader with an increased understanding of issues critical for successfully guiding a protein or peptide therapeutic candidate through the maze of issues that define the pharmacokinetics, pharmacodynamics, and metabolism of these molecules.

We would like to take this opportunity to again thank our authors, who represent key contributors in these areas, for the expertise that they have shared. It is our sincere wish that the knowledge put forth in the following chapters will have a positive impact on the development of new drugs that will improve health and alleviate suffering.

Randall J. Mrsny
Ann Daugherty

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1 In Vitro/In Vivo Correlations of Pharmacokinetics, Pharmacodynamics, and Metabolism for Hematologic Growth Factors and Cytokines

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HEMATOPOIETIC LINEAGES AND THE CONTROL OF CELL PRODUCTION

Blood comprises approximately 55% liquid and 45% cellular material and fulfills many recognized functions in mammalian physiology. The most important of these is oxygenation of bodily tissues followed by an important secondary function in combating disease, particularly infectious disease, via both cell-based and humoral mechanisms.

Blood has been the subject of scientific inquiry from prehistory and because of its ready accessibility and liquid nature has lent itself to early dissection of both organization and function. In the early part of the 20th century, Carnot pioneered the idea that blood composition was controlled by a humoral factor (1), which was ultimately identified as erythropoietin (EPO). This work was founded on the observations made by Viault (2), who followed changes in red blood cell count as he and his traveling companions (human and animal) ascended to altitude. From early in the last century it was thus suspected that blood composition may be subject to change in response to environmental variation and that humoral factors may be the mediators of this effect.

The cellular constituents of blood had, of course, been observed by Anthony van Leeuwenhoek in the 17th century in one of the first applications of his newly invented microscope. Hence, the idea that there are various types of blood cells and that their production is under humoral control is not really new, nor is it confined to the era of recombinant proteins, which began in the 1970s. However, that epoch did provoke unprecedented advances in understanding cytokines in general and hematopoietic cytokines in particular, culminating in the cloning of the first hematopoietic cytokine [interleukin-3 (IL-3)] in 1984 (3).

Understanding the basis of cellular diversity in blood had meanwhile undergone equally important advances with the description of the first quantitative assays for murine hematopoietic "stem" cells in 1961 (4). Although spleen colony-forming units (CFU-S) first described by Till and McCulloch were ultimately demonstrated not to exhibit all of the hallmark properties that characterize the most primitive hematopoietic stem cells (i.e., most CFU-S lacked lymphoid differentiation potential and exhibited only a limited capacity for self-renewal), this assay and the cell type it detected is viewed by many to have ushered in the modern era of stem cell biology. The first in vitro colony formation assays for hematopoietic progenitor cells were described in 1965 and 1966 (5,6). In these assays, bone marrow cells that were otherwise unrecognizable were cultured in semisolid medium in the presence of crude preparations of body fluids, tissue extracts, or medium "conditioned" by various cells. Since

these extracts (and later their components) stimulated the formation of blood cell colonies, they acquired the descriptive name of "colony-stimulating factors" (CSFs) and their cell targets, the equally unsurprising epithet "colony-forming cells."

Although spectacular progress had been made in the three previous decades, work in the early 1990s provided a remarkable leap in our insight into the organization and control of hematopoiesis; an understanding that to date has still to be equaled for any other tissue in the body. The hematopoietic cell hierarchy, as it was defined at that time and as it is still understood today, is represented by, at its root, a self-sustaining stem cell pool. Maintenance and selected expansion of this pool occurs through processes of asymmetric cell division, and some would say deterministic, others would say stochastic, cell fate decisions that yield a heterogeneous pool of differentially committed progenitor cells. At one extreme, these precursor cells may have the potential to develop into any of the six blood cell lineages, and at the other extreme, they may be capable of responding in one of only two ways—either by dying (a process referred to as apoptosis) or by developing into a single type of mature blood cell. Stem cell self-renewal is largely regulated by intracellular transcription factors that control the expression of an array of "stemness" genes. Oppositely, later processes of hematopoietic development are under the control of extracellular humoral regulators—variously called the CSFs, growth factors, interleukins, or cytokines. These cytokines act either alone or in concert to control the number and type of blood cells that are produced. Some of them act on relatively primitive cells with multilineage differentiation potential [e.g., IL-3 or stem cell factor (SCF)], while others act only on more committed cells in the later stages of blood cell production (e.g., EPO).

Many of these cytokines have been purified and cloned and are available in pharmaceutically useful quantities in recombinant form. Since they are large molecules that cannot be absorbed intact through the gut or skin, recombinant cytokines must be administered via intravenous or subcutaneous injection. While some of these cytokines have been deployed as therapeutics used in millions of patients, others have found little application in medicine and have thus far remained useful only as laboratory reagents or research tools. Of those that have found clinical utility, several have been reengineered to enhance their drug-like attributes, while others remain essentially identical to the native proteins purified from tissue sources.

RECOMBINANT HEMATOPOIETIC CYTOKINES OF THERAPEUTIC IMPORTANCE

The discovery of hematopoietic cytokines, predominantly in the 1970s and 1980s, followed the development of assays to detect their activity like the in vitro colony-forming cell assays introduced above. However, the larger challenge at that time was purifying proteins with separate activities from the complex biological fluids used as the starting material. Macrophage (M)-CSF (also known as CSF-1) was the first hematopoietic growth factor to be purified, initially from human urine and later from medium conditioned by a murine fibroblast cell line (7). This was followed in the same year by the discovery of granulocyte-macrophage (GM)-CSF in medium conditioned by tissues from the lungs of mice previously treated with bacterial lipopolysaccharide (8). A few years later, a

third myeloid growth factor was identified: granulocyte (G)-CSF (9). It was after some years that the genes that encoded these proteins were cloned—cloning was a relatively nascent technology at that time; thus, 1985 saw the cloning of human M-CSF (10), EPO (11,12), and GM-CSF (13,14), and 1986 saw the cloning of G-CSF (15,16), IL-3 (17), and IL-5 (18).

The natural versions of most hematopoietic cytokines are glycosylated, for example, IL-3 (17), IL-5 (19), IL-6 (20), IL-7 (21), GM-CSF (13), G-CSF (22), M-CSF (23), SCF (24), and EPO (25). In several cases, however, the carbohydrate has been shown not to be required to maintain activity, for example, the O-linked carbohydrate at threonine 133 on natural G-CSF. In one celebrated case however, that of EPO, the carbohydrate component was found to be not only obligatory for in vivo action but also amenable to manipulation to therapeutic advantage (26). Endogenous cytokines are frequently heterogeneous at some level, often because of posttranslational modifications such as glycosylation, sulfation, proteolytic cleavage, etc. Recombinant forms may not therefore be identical to the natural prototype and will vary markedly depending on the host cell in which they are produced, method of purification, and a number of other factors. Overall, the precise biochemical nature and activity of endogenous cytokines remain largely unknown as does their comparability with recombinant preparations. Comparisons can be made to define relative potency, but other aspects of product performance, for example, pharmacokinetics, safety, etc., must be studied carefully in animals or humans and often in large numbers of subjects and over extended periods before their safety and efficacy can be definitively established.

With respect to the clinical development and subsequent consideration of therapeutic proteins by regulatory agencies, it has been suggested that the protein product is in essence the process used to manufacture it. This perspective presents a considerable hurdle in comparing related products like, for example, follow-on biologics (FOBs), subsequent entry biologics, or biosimilars intended to offer alternative products after innovator patent expiry. Thus, the term "generic" is difficult to apply given the likely nonidentity of proteins produced in different host cell systems that are purified and formulated using different methods—presenting an interesting challenge for regulatory authorities for which differing solutions are being developed in different countries.

From a drug development perspective, the general observation that has emerged from the medical exploitation of hematopoietic cytokines is that pleiotropy is an undesirable property for such agents. More lineage-restricted cytokines have, in general, proven more useful (27), as exemplified by the clinical utility of EPO (28), G-CSF (29), and GM-CSF (30) and the promise of a thrombopoietin (TPO) mimetic. In the following sections, the discovery and development of these hematopoietic growth factors with demonstrated clinical utility, and their pharmacokinetic (PK) and pharmacodynamic (PD) properties, will be discussed.

STEM CELL FACTOR (STEMGEN®)

Also known as mast cell growth factor (MGF), kit ligand (KL), and steel factor, SCF is the ligand for the cognate tyrosine kinase receptor c-kit. It is approved for clinical use in limited countries as a coadministration with G-CSF for hematopoietic stem and progenitor cell mobilization based on phase 3 clinical trial data in breast cancer patients (31). Despite its use in stem cell mobilization, all

patients require prophylactic administration of H1 and H2 antihistamines and a bronchodilator to ameliorate the collateral effects of SCF in stimulating mast cells.

The PK parameters of SCF in humans have not been extensively studied but appear relatively unremarkable. A phase 1 trial in cancer patients indicated a predose serum SCF level of around 1 μg/mL, with a C_{max} 12 to 17 hours after first administration, reducing with subsequent injections (32). Clearance was linear, with a half-life of approximately 35 hours. More intriguing were the data obtained for recombinant SCF administered to mice. Following intravenous administration, radiolabeled material distributed very quickly to the lungs of treated mice and was then eliminated via the kidney and liver with a half-life of around two hours. Sl/Sl^d mice, which lack mast cells because of a genetic lesion in the SCF gene, also accumulated SCF in the lungs but did not suffer the effects of mast cell degranulation seen in their wild-type littermates (33).

The link between the PK and PD of SCF is not particularly clear. The major PD endpoint measured in phase 3 trials was the mobilization of $CD34^+$ cells. However, mobilization is an indirect result of neutrophil-derived proteases cleaving adhesion molecules that tether stem and progenitor cells to the bone marrow stroma (34). Thus, mobilization is mechanistically related to the granulocyte *response* rather than a direct effect of SCF. Since SCF has been shown to interact with intracellular G-CSF signaling (35), the phenomenon observed and exploited in patients is understandable. This outcome may not be directly linked to SCF, and so it may be causally distinct from the PK. In contrast, the side effects (or at least unintended effects) on mast cells are better understood and more satisfactorily linked to drug exposure.

GRANULOCYTE-MACROPHAGE COLONY-STIMULATING FACTOR (LEUKINE®)

GM-CSF is one of two myeloid cytokines approved for clinical use in cancer patients in the European Union and the United States, the other being G-CSF. GM-CSF does not have the breadth of application that G-CSF has, with its approved clinical uses being confined to acute leukemia and in transplant settings. As the name implies, GM-CSF is more pleiotropic than G-CSF. Among the documented effects of GM-CSF are stimulation of progenitor cell proliferation (36), neutrophil function (37,38), monocyte activation (39), and dendritic cell function (40), especially, as a vaccine adjuvant.

In a recent study (41), GM-CSF was administered daily for 10 days to cancer patients; PK analysis showed a dose-dependent increase in drug level several hours after the first administration when none had been detectable beforehand. By the time of the next daily dose, about half the patients still had low but detectable GM-CSF in their blood. In common with many cytokines, SC administration prolonged the half-life of GM-CSF, possibly via delayed absorption, with nonlinear clearance for escalating doses (42). With repeated administration, clearance of GM-CSF gradually increases (41,43,44). Though the mechanism for this effect is not well defined, it may include target cell–mediated clearance as will be discussed later for M-CSF, G-CSF, and TPO. Intravenous administration of GM-CSF illustrates two distinct phases of disposition: the first, presumably representing initial distribution, is quick ($T_{1/2}$ less than five minutes); the second phase is slower, with $T_{1/2}$ of two to three hours (45) representing clearance.

Hematological (PD) responses to administration of GM-CSF include increases in circulating lymphocytes, monocytes, neutrophils, and eosinophils, with small or no changes in erythrocytes and platelets (41). Though these effects, especially on neutrophils, may be used to define the PK/PD relationship in, for example, neutropenia after bone marrow transplantation, the desired PD in other settings may not be so clear. For instance, in the deployment of GM-CSF for immunotherapy applications, the increased leukocyte count, which relates to both dose and duration of GM-CSF treatment, correlated positively with the absolute number of putative immune effector (GM-CSFRα^+/CD14$^+$, GM-CSFRα^+/CD66b$^+$) cells. In contrast, high doses of GM-CSF impaired antibody-dependent cellular cytotoxicity (ADCC) in in vitro assays of harvested cells. This suggests that dose and schedule need to be optimized for this application, but the predictable PK of GM-CSF should make this relatively straightforward as long as the nature of the desired biological effect is well defined. In practice, the cell types required to elicit optimal immune function are not fully understood and will require further study to define the desired PD of GM-CSF in what would appear to be its most useful application.

MACROPHAGE COLONY-STIMULATING FACTOR

M-CSF is approved for clinical use in some countries under the name Leukoprol® (mirimostim). It was originally cloned in 1985 but was one of the first cytokines studied in the 1960s and had been purified from urine by 1975(46). As the name would suggest, M-CSF was first shown to stimulate the growth of bone marrow–derived monocyte/macrophage cells in vitro (7) but was subsequently found to play a role in inflammation (47), bone remodeling (48), reproduction (49), the central nervous system (50–52), and cancer (53–56).

PK studies using M-CSF created a new paradigm for understanding the relationship between the PK and PD of hematopoietic cytokines. This new understanding centers on the ability of these cytokines to stimulate the production of their appropriate target cells, in this case monocytes/macrophages, only then to have those very cells consume and ultimately clear the stimulator from the serum as their numbers increase. This model has been extended to TPO (57,58), EPO (59,60), G-CSF (61), and perhaps even GM-CSF (41,43,44), but rests on insight gained from the study of M-CSF (62).

Mice normally have detectable levels of M-CSF in their serum, and studies performed using radiolabeled M-CSF demonstrated the serum half-life of this cytokine to be about 10 minutes. Approximately 96% of the cleared M-CSF could be accounted for by splenic or hepatic macrophages, the remainder was eliminated in the urine. Upon analysis of a number of parameters, including the effect of lysosomal protease inhibitors, it was apparent that internalization and degradation in macrophages via the cell surface M-CSF receptor, c-fms, was the predominant mechanism of M-CSF clearance.

The implications of this mechanism are clear. First, the clearance of physiological amounts of cytokines can be quite rapid, being mediated by the normal population of receptor positive cells. Second, pharmacological levels of exogenous cytokine can quickly saturate this clearance mechanism, leading to prolonged exposure and increasing the relative contribution of nonspecific clearance mechanisms, for example, renal filtration. Third, as the PD response to the cytokine accumulates over time, the capacity of the selective clearance

mechanism will increase, reducing the relative role of nonspecific pathways. Fourth, in the absence of a target cell response, the clearance of a cytokine might be rather slow, increasing as the response mounts. This model is very attractive to explain homeostatic regulation of cytokine levels and target cell populations, and has ramifications for therapeutic administration of recombinant cytokines that share much of their biology with their endogenous prototypes. Indeed, this exact mechanism was used to develop therapeutically enhanced versions of G-CSF, as is outlined later.

GRANULOCYTE COLONY-STIMULATING FACTOR (NEUPOGEN®, FILGRASTIM)

G-CSF was one of the earliest cytokines to be biologically and biochemically characterized by the Australian CSF pioneers at the Walter and Eliza Hall Institute of Medical Research in Melbourne under the guidance of such giants in the field as Don Metcalf and Richard Stanley. It is due only to the insight of these pioneers that human G-CSF could be purified (22) and cloned (15,16) elsewhere and subsequently developed into a major therapeutic drug that has been administered to several million cancer patients since its launch in 1991.

Some of the early studies were confounded by incomplete separation of GM-CSF and G-CSF, and the seminal paper describing the activity of purified human G-CSF referred to it as a pluripotent factor (22), possibly in error because of assaying it on impure cell preparations. Nevertheless, from the early days, experiments where G-CSF was used as a single activity showed that although it was a modest CSF, it was highly selective in its actions on neutrophilic progenitor cells (9,63). As it turned out, the modesty of its in vitro actions was misleading, but its selectivity was probably not (for review see Ref. 29). The dominant clinical effect of G-CSF action is neutrophilia, though minor or sporadic effects on other blood cells have been reported. Most notably, G-CSF is well documented to increase monocyte proliferation (64,65), which may be linked also to reports of increased osteoclast-mediated bone turnover (66,67). These data illustrate that increased bone turnover, at least in rodents, results from expanded osteoclast activity after treatment (68). Whether this is related to the profound effects of G-CSF on monocyte production kinetics awaits definition of the relationship between these monocytes and osteoclast development.

Humans injected with G-CSF can expect a neutrophil response within one to two days (69–71). However, this is not the case after cancer chemotherapy where G-CSF is normally used to treat neutropenia, because the marrow is often not capable of responding on that timescale (69). This PD response is driven by a rapid absorption of typically SC administered G-CSF, wherein peak concentrations are noted within two to eight hours. The elimination half-life after either SC or IV administration is two to four hours depending on dose and neutrophil count (61,72). As G-CSF is administered daily, the neutrophil count increases, and in parallel, the clearance time of G-CSF is shortened; a relationship that was correlated even in early studies with receptor number on neutrophils (73). As noted above, this appears to be a very similar mechanism to that suggested for the M-CSF PK/PD relationship, that is, the cellular response to a cytokine in turn selectively clears that very cytokine, while in parallel a less saturable pathway (renal clearance) accounts for the balance of the elimination.

In an extension of this very satisfying model, a novel form of G-CSF was engineered specifically to evade the nonselective clearance pathway, yielding a new drug tailored to effect a neutrophil response that could only be cleared by those very neutrophils once they accumulate to a sufficient level (74–78). This form (pegfilgrastim) was designed for use in patients undergoing cancer chemotherapy and in whom support for neutrophil production was required. The underlying hypothesis in designing a form of G-CSF that would not be cleared by the kidney yet would remain sensitive to neutrophil-mediated clearance was that a degree of self-regulation would be an intrinsic feature of the molecule. This was proven to be correct first in animal and then in clinical studies. During neutropenia, the drug has an extended half-life; upon neutrophil recovery clearance is reactivated (75). Thus, for the first time, a drug that offered "automated" control of neutrophil counts was developed. This exciting mechanism of action has led to the broad uptake of pegfilgrastim in medical practice, but has yet to be applied to other therapeutics.

ERYTHROPOIETIN (EPOGEN®, EPOETIN ALFA)

EPO is widely used in the treatment of anemia since it is the central regulator of erythropoiesis. The major quantitative site of EPO production is the kidney, so patients with declining renal function were the first and are still the most obvious candidates for EPO therapy (79). Use in anemia associated with cancer treatment is also common. Although controversial, a number of other experimental uses have emerged since EPO was approved for use in 1989 (80), including stroke, nerve crush injury, heart failure, myocardial infarction, immunomodulation, and for improving cognitive function. It remains unclear how these latter effects work in the absence of EPO receptor on many of the target tissues (see Ref. 81 for a critique of methods used to claim otherwise).

Confining our discussion to the effects of EPO on erythropoiesis, it must be borne in mind how highly dynamic is the process of red blood cell production. A normal 70-kg human produces on the order of 2.5×10^{11} erythrocytes per day, and this rate of production is maintained by a basal EPO level of around 10 to 20 mU/mL (82,83). Pharmacological administration of EPO at a dose intended to sustain a three times per week dosing cycle (150 U/kg) or a weekly treatment cycle (40,000 U/kg) leads to a C_{max} of 150 or 850 mU/mL, respectively (84). Reticulocytes are released earlier than normal from the bone marrow and reside for a disproportionately longer fraction of their life span in the blood following EPO therapy. Despite this being the first PD readout of EPO administration, the more important result is a change in hemoglobin concentration. In the same study (84), the reticulocyte shift could be clearly seen in the blood by five days and a readily discernable change in hemoglobin by day 8—the two dosing regimens being approximately the same despite the 30% dose increment with the weekly regimen. This inefficiency is suggested to be driven by the nonlinearity of EPO PK, which seems to lean toward reduced clearance at higher doses. In this case, it is likely that the similar PD response was driven by the accumulated time above the concentration threshold required for pharmacological action, which was similar between the two regimens.

A model was expounded in the early 1990s (85,86) that still yields a satisfactory explanation of the relationship between EPO exposure and response. Furthermore, this model has to date proven satisfactory to explain the PD response

to all erythropoiesis-stimulating agents (ESAs). The model states, in essence, that the time between administrations during which the ESA serum level exceeds the threshold for response is the sole driver of efficacy. Of course, the details of the model parameters change with intrinsic potency of the ESA, dose, and clearance parameters, but the model remains the same across all ESAs. The implication is that all ESAs perform similarly when matched for the time above this threshold level. Inefficiency does become a factor as the interval between injections gets longer—explaining the 30% dose penalty with EPO administered once versus three times per week, as shown in the above study. Longer-acting analogs of EPO specifically engineered to improve half-life [darbepoetin alfa (87)] and pegylated EPO [e.g., PEG-EPOβ (88)] are not hampered by this inefficiency until after a longer interval and are, therefore, able to sustain a desired clinical outcome for up to three or four weeks between injections. It remains to be seen how dosing of a non-EPO-based ESA may be approved by regulatory authorities (89), but initial observations suggest adherence to the same PK/PD model.

THROMBOPOIETIN

Despite being named in 1958 (90), TPO was not isolated until 1994 when this was achieved simultaneously by five groups (91–95). TPO is the seminal regulator of platelet production, which, like M-CSF and G-CSF, is consumed by its target cells (megakaryocytes and platelets) that express the c-mpl receptor (57,58). Two forms of recombinant human TPO were initially examined in clinical studies: a full-length and glycosylated molecule that is equivalent to the native growth factor (rHuTPO) and a truncated and pegylated version known as megakaryocyte growth and development factor (MGDF). None of these "first-generation" agents attained regulatory approval mainly because of the production of antibodies by the human immune system that were directed against the administered therapeutic (96,97). These antibodies were also capable of neutralizing endogenous TPO causing extended-term refractory thrombocytopenia. This spurred the creation of novel mpl ligands, seven of which have been recently discussed (98) and all of which have the feature of no overlap in amino acid sequence with endogenous TPO.

The PK of MGDF is reflected in a predictable absorption and elimination profile (99), with C_{max} being observed three to four days after a single SC administration. Elimination is, as mentioned above, affected by the PD response to the drug (57,58). In monkeys, the C_{max} is attained in about 3 hours and MGDF is eliminated with a half-life of around 8 to 13 hours (100). The PK and PD characteristics of full-length recombinant human TPO and MGDF are similar (101). Elimination half-lives are 24 to 40 hours for rHuTPO and 31 hours for MGDF in humans.

The platelet response to administered MGDF is not immediate (102), taking three to four days before even reticulated platelets (a controversial though acceptable measure of early platelet increases) are detected in the circulation, with platelet counts peaking only after around 13 to 15 days. This probably reflects the indirect nature of mpl agonism on thrombocytopoiesis, the main action being confined to an increase in megakaryocyte ploidy and maturation rather than platelet formation (99). Similar kinetics are also exhibited by AMG 531 (Nplate®, romiplostim), one of the third-generation synthetic peptide mpl agonists (103). The medical exploitation of mpl ligands is not yet complete,

with several third-generation molecules being developed for the treatment of immune thrombocytopenic purpura (ITP). As with many biopharmaceuticals, it is still unclear for which diseases they will finally be used and how the disease setting will affect their PK/PD.

SUMMARY

Emerging from the confusion of the early days of hematopoietic cytokine discovery was a simple view that for each type of blood cell there would be a single lineage-specific regulator and for each cytokine there would be a specific and defined function. This has not turned out to be the case—blood cell lineages are affected by many different cytokines throughout their development. In addition, all cytokines have been found to have a diverse array of actions, some direct, others indirect, even for the most selective of agents, EPO and G-CSF. Other cytokines have very complex actions, especially as part of overlapping cytokine networks with hereto unforeseen interactions and interdependencies.

In general, most hematopoietic cytokines are short lived in the blood and require repeated frequent injections to clearly see their actions. To improve their utility as therapeutics, the exposure profile of some have been modified by relatively simple pegylation, for example, G-CSF [pegfilgrastim (76)] and EPO [PEG-EPOβ (88)] and that of others by more complex glycoengineering, for example, EPO [darbepoetin alfa (104)]. Some have been mimicked by peptides, for example, EPO [hematide (89)], TPO (AMG 531), or even small molecules, for example, TPO [eltrombopag (98)], while others have been conjugated into chimeric molecules, for example, G-CSF and Flt-3 ligand [progenipoietin (105)].

The field of hematopoietic cytokine biology continues to develop as complex pathways are deconvoluted, and surprises continue to emerge (27). For a number of these factors, end-cell regulation has emerged as a common method of homeostatic control of cellular pathways, with cytokines serving as the central humoral mediators. It remains to be seen how this will be exploited further for the development of cytokine therapeutics with utility in human medicine.

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X t ¼ 0 w < x < þw %F@ ¼ %F@ 0 %FH@ ¼ 0 %H@ ¼ 0 w > x >þ w %F@ ¼ 0 %FH@ ¼ 0 %H@ ¼ %H@ 0 ð9Þ t > 0 x ¼ @1 %F@ ¼ %FH@ ¼ 0 ð10Þ @ 2 %F@ @x 2 ¼ %F@ mþ1 i@1 2%F@ mþ1 i þ %F@ mþ1 iþ1 Dx 2 ð11Þ @%F@ @t ¼ %F@ mþ1 i %F@ m i Dt ð12Þ @%FH@ @t ¼ %FH@ mþ1 i %FH@ m i Dt ð13Þ D eff Dt Dx 2 %F@ mþ1 i@1 þ 1þ 2D eff Dt Dx 2 %F@ mþ1 i þ D eff Dt Dx 2 %F@ mþ1 iþ1 ¼ %F@ m i þ Dtðk on %F@ m i %FH@ m i k on %H@ 0 %F@ m i þ k off %FH@ m i Þ ð14Þ %FH@ mþ1 i ¼ %FH@ m i þ Dtðk on %H@ 0 %F@ m i k on %F@ m i %FH@ m i k off %FH@ m i Þ ð15Þ

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