Dragons ’Round the Fleece Again: STI571 Versus α1 Acid Glycoprotein

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Ovid recounts the story of Jason and his Argonauts (1), who, after dealing with jealous harpies, wandering rocks, spectral armies, and fire-snorting bulls, approach the Golden Fleece only to find it guarded by a sleepless dragon who complicates the ease with which their prize might be grasped. In the current age, we hope to revolutionize cancer therapeutics by defining drug molecules that target the pathophysiologic basis of cancer: activated oncogenes, deregulated tumor suppressor genes, and the ubiquitously relevant processes of angiogenesis and apoptosis. Drugs bound specifically to these or their related targets are the Fleece of our quest. STI571 is a selective p110BCR-ABL oncogene tyrosine kinase inhibitor (2). BCR-ABL-related molecules are etiologic for adult chronic myeloid leukemia (CML) (3) and a fraction of acute lymphoblastic leukemias. Therefore, STI571 treatment of BCR-ABL-expressing neoplasms is prototypic in a way that we hope to emulate by use of target-directed drugs in other diseases that are driven by other oncogene-derived kinases.

Noteworthy features in STI571’s preclinical development, presented previously in these pages (4), were the curative activity in certain animal models of CML and the lack of activity in tumor models not dependent on this target kinase. Initial clinical returns with the agent have been concordant with those expectations, with evidence of clinical activity in patients with chronic-phase CML even in early phase I testing (5) and with little evidence of serious toxicity at dose levels where benefit has been seen. A few clouds have appeared on this otherwise rather sunny horizon. In initial clinical testing, patients with more advanced blast-phase CML, in an as yet not rigorously quantitated sense, seem to have fewer responses of shorter duration, in comparison to patients with chronic-phase disease (6).

Gambacorti-Passerini et al. (7) undertook further animal model experiments, reported in this issue of the Journal, to address the potentially related phenomenon that mice with a large CML tumor burden had greater resistance to STI571 than mice with a smaller tumor burden. Surprisingly, in vitro, CML cells explanted from the larger, resistant tumors were as sensitive to STI571 as parental cells. In contrast, cells exposed in vivo in large tumors did not show inhibition of growth or p110BCR-ABL kinase activity. This result suggested a problem in target “access” by drug in vivo in animals with large, resistant tumors. The culprit was found to be the plasma α1 acid glycoprotein (AGP): Mice with larger tumors had increased AGP concentrations; exogenously added AGP could confer resistance to STI571 in vitro; and erythromycin, a drug that also binds AGP, could restore sensitivity to STI571 in the previously resistant, in vivo, large tumor models presumably by displacing STI571 from AGP. The striking result in this study is that drug resistance occurs on an organismic rather than a cellular basis, in a way that varies with tumor burden.

AGP as a modulator of drug effects in humans is certainly not news (8). AGP, also known as orosomucoid, is a plasma protein that is an acute-phase reactant. It is produced by the liver in response to inflammatory cytokines, stress, and other still poorly defined stimuli, including host neoplasms. It is distinctive in that approximately 40% by weight of each molecule is carbohydrate, including sialic acid. The latter negative charges are thought to contribute to its propensity to bind a number of cationic drugs, including propranolol, haloperidol, methadone, tricyclic antidepressants, among others. A capacity to bind acidic and neutral drugs by distinct binding modes has been described previously (9). In humans, there are two AGP genes, AGP1 and AGP2, thought to have arisen by a gene duplication, and a third AGP gene identical to AGP2 is present in some individuals (10). The existence of polymorphisms in the AGP gene sequence, along with variable states of carbohydrate addition and processing, means that there is really not one AGP species circulating in plasma but rather a population of molecules, all likely able to bind candidate drugs with various affinities around some population average and to have various concentrations owing to the state of a patient’s disease and “underlying” condition.

AGP has also long been proposed as a modulator of drug clinical effect in a variety of settings [e.g., (11)]. Recently, AGP came to the fore in cancer developmental therapeutics because it avidly binds staurosporine-related compounds UCN-01 and PKC412, interestingly, in a species-dependent fashion. Mouse AGP binds UCN-01 far less avidly than does human AGP (12,13). This difference changes the handling of UCN-01, from a drug with terminal half-lives in various animal species of 5–12 hours to a drug in humans that persists for hundreds to thousands of hours after a single dose. This behavior renders much of the animal model work on which the development of UCN-01 and PKC412 was predicated to be of questionable relevance to humans. In addition (and as pointed out by Gambacorti-Passerini et al. in this issue of the Journal), the predictive power of animal toxicology may diminish because human toxicity may emerge only after drug has bound to all circulating AGP. At the very least, one must now relate clinical phenomena to levels of free drug and not simply to levels of total drug. One must also be concerned that the patient population one studies is normalized with respect to AGP concentration. Although the clinical impact of the present results of Gambacorti-Passerini et al. (7) on humans remains to be clarified, STI571’s use in blast-phase CML patients must take into account that these patients are, on average, more ill than patients with chronic-phase disease. Thus, they may have higher AGP concentrations than chronic-phase...
patients. AGP thus emerges as a “dragon” potentially preventing STI571 from the p210BCR-ABL “Fleece.”

Many other issues also loom on consideration of this outcome. First, although the science behind the design of agents targeted to the “molecular determinants” of cancer pathogenesis described above is emerging and will undoubtedly get better as more crystal structures of target molecules become available (14), the “rules” for expecting a compound to have an interaction with AGP or indeed any plasma protein component are poorly defined or nonexistent. Such scientific pursuits may not be as glamorous as defining a new lead structure against oncogene targets but may be critical if the true promise of oncogene target-directed lead compounds is to be realized. Cancer therapy needs molecules that do not simply recognize a target but that are crafted to deal with the target in the context of an organism.

Second, the study by Gambacorti-Passerini et al. (7) offers one more example of the caution that must greet experiments in animals. Clearly, differences in animal plasma handling of drug could lead to widely different expectations of eventual efficacy in humans, a concept forcefully illustrated by the human experience with camptothecin analogues, where human albumin preferentially binds the inactive carboxylate forms of camptothecin and 9-aminocamptothecin, in comparison to mouse albumin (15). This circumstance likely contributes in part to the markedly different clinical efficacy in humans of such agents as 9-aminocamptothecin in comparison to in vivo activity in mice (16).

Third, the mere fact that a drug interacts with AGP or albumin is not necessarily cause for alarm; numerous clinically effective agents have this property to various degrees. The difference in chemical affinity between the plasma protein and the drug’s intended target is the key issue and calls for careful assessment of human pharmacology with molecular pharmacodynamics of targeted agents in early clinical trials. If we know the target is being favorably affected, any degree of plasma protein binding is thus not relevant or is being supervised. Animal models to address these issues, e.g., engineered to express different human drug-metabolizing enzymes and plasma proteins, would clearly be of value and have begun to be constructed.

Fourth, strategies to capitalize on the observation presented by Gambacorti-Passerini et al., that erythromycin might be able to displace STI571 from AGP and modulate its activity in vivo, represent one potential way to deal with the problem of AGP binding: displace the therapeutic drug by a clinically well-tolerated agent (a Trojan horse approach?). However, the concentrations of erythromycin targeted by these authors (approximately 20 μM) are eightfold to 10-fold higher than is commonly achieved by oral administration of usual doses. In humans, these concentrations likely would require sustained intravenous administration with all the concerns related to adverse effects from the modulator compound. The ideal modulator for such an approach, if there is one, would take considerable effort to define in its own right.

Where should our efforts be directed for STI571? Continued clinical development is clearly warranted, with more widespread trials in the hematologic neoplasms known to depend on p210BCR-ABL and its variants, as well as diseases, such as small-cell lung carcinoma, which express c-kit, or gliomas, which express platelet-derived growth factor receptor, kinases for which STI571 also has selective activity (17,18). Such trials must carefully consider these new data in their design and implementation.

As we all know, Jason got his Fleece. This goal was achieved only with the help of the sorceress (and his paramour) Medea, who concocted a “soporific” potion for application to the dragon’s eyelids, allowing the hero to “go for the gold”—quite literally. Concern must be expressed that many of the protein kinase inhibitors that are directed toward the ATP (i.e., adenosine triphosphate) site, under development by academic and commercial laboratories, may bind to AGP. The quest will be to find a way to circumvent the AGP dragon and thus permit these molecules to get to their targets. How to do this in an informed fashion without Medea’s assistance remains a quest of heroic dimensions.

References