ficient use of donors will hinder the implementation of islet transplantation into health care delivery systems.

Health care delivery continues to be redefined toward end points such as efficacy, cost-containment, equitable allocation of resources, and satisfied health care customers. Given their resource-intensive and expensive nature, islet transplants will face ever-increasing scrutiny by health care professionals and payers. Documentation of substantial evidence of efficacy will be needed for regulatory approval of transplanting human islets and should also facilitate third-party reimbursements of islet transplants. To justify allocation of more pancreases from deceased donors to islet recipients, insulin independence must be achieved with islets from a single donor pancreas, as with pancreas transplants.

To restore insulin independence, state-of-the-art islet processing techniques and recipient treatment protocols, as well as selection of suitable donors and recipients, are required. Transplantation of islets isolated from young donors[1] with high body mass index[2] into lean and insulin-sensitive recipients facilitates restoration of insulin independence post-transplantation. Accordingly, most islet transplants performed recently met these criteria.[3] We believe that all islet transplant programs should seek to perform transplantation in patients for whom the risk-benefit ratio is most favorable and for whom success is most likely.

Doing so would maximize the use of the limited number of suitable donor organs while controlling health care resources. In 2004, 1466 pancreases were recovered for whole-pancreas transplantation from 3899 deceased donors aged 18 to 49 years.[4] Of the remaining 2233 pancreases, about 45%, or 1000 per year, are available from donors with a body mass index of 26 or greater; of these, only about one third meet all medical criteria. Transplanting islets pooled from multiple donors in a single transplant procedure, as suggested by Dr Smith, should be considered in selected cases when logistics are favorable, but this increases the risk of sensitization,[5] and the sheer tissue mass increases the risk of portal hypertension and thrombosis.[6]

Thus, we believe our basic premise is not flawed. We will continue to refine single-donor protocols so that transplantation of islets from a larger pool of donor pancreases into a larger subgroup of recipents with type 1 diabetes becomes a reimbursable practice of medicine.

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Clinical Factors and Recurrent Venous Thrombotic Events

To the Editor: In their study of thrombophilia, Dr Christiansen and colleagues[1] examine the comparative rates of thrombosis in patients with idiopathic and provoked clots, as well as the presence or absence of prothrombotic characteristics in these groups. When considering provoked thrombotic events, particularly in those patients who are in the hospital and are at high risk for clotting, the use of prophylactic measures other than oral anticoagulants (such as subcutaneous heparin or intermittent pneumatic compression devices) will notably influence the outcome of interest. While not mentioned in the protocol, it would be helpful to know if the authors obtained this information and considered this potential bias.

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In Reply: We followed up 474 patients with a first deep vein thrombosis for a mean (SD) of 7.3 (2.7) years and found a recurrence rate of 25.9 per 1000 patient-years—33.2 per 1000 patient-years for those with an idiopathic first thrombotic event and 17.7 per 1000 patient-years for those with a provoked first thrombotic event. Of all 90 recurrences, 61 were idiopathic and 29 were provoked (defined as pregnancy, puerperium, use of oral contraceptives within 30 days, or trauma, surgery, immobilization, or use of plaster casts within 3 months before the event).

As Dr Flansbaum suggests, the proportion of provoked events would undoubtedly be higher in the absence of prophylactic measures, such as anticoagulants after surgery. Prophylaxis preventing first thrombotic events would not affect the recurrence rates for provoked and idiopathic events. However, a concern would be whether patients with an idiopathic first thrombotic event were monitored differently than those with a provoked first thrombotic event, which might have affected recurrence risk. If so, it would probably have attenuated the difference between the 2 groups because we had found an increased risk of recurrence in those with idiopathic first thrombotic events.

However, we believe differential treatment to be unlikely. Our national guidelines are unambiguous for patients with a history of thrombosis, who receive subcuta-

neous heparin and oral anticoagulation for 4 to 6 weeks after surgery, postpartum, and during long-term immobilization. It is unlikely that less prophylaxis would be given to those with a history of a provoked thrombotic event. Although not advised, patients with idiopathic thrombosis, particularly those with prothrombotic defects, may receive more frequent or long-term anticoagulation.

Our main finding was no excess risk of recurrent thrombosis in those patients with prothrombotic defects. This finding did not change when we adjusted for anticoagulant use or even excluded all periods of increased risk, as well as all periods of anticoagulant use. Therefore, our main finding cannot be explained by more frequent anticoagulant use in these patients. Nevertheless, as our study shows the recurrence risks given the current standard of care, it is possible that in the complete absence of thromboprophylaxis the estimates would have been different.

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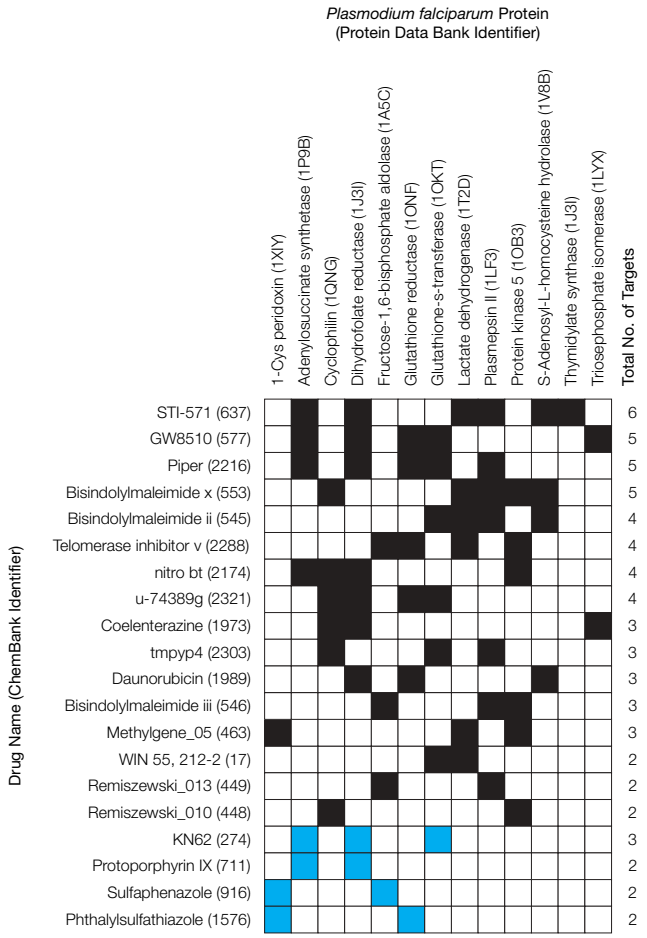
RESEARCH LETTER

Identification of Potential Multitarget Antimalarial Drugs

To the Editor: Malaria is one of the deadliest tropical diseases, causing more than 300 million infections yearly.[1] Successful clearance of the malarial parasites, *Plasmodium* species, from a patient's body by antimalarial drugs is impeded by the emergence of drug-resistant strains. Drugs that effectively eliminate *Plasmodium* with short treatment duration reduce risk of treatment failure and emergence of drug-resistant strains.[1]

Antimalarial drugs currently target single *Plasmodium* proteins. Effective therapeutic regimens require a combination of drugs that have different mechanisms of action during the same stage of the parasite's life cycle.[1] However, malaria is a disease that occurs mostly in tropical and subtropical areas, where patients have limited access to drugs, and combination drug regimens may not succeed due to poor adherence.[2] Multitarget drugs are currently being used extensively to treat both infectious and inherited diseases.[3] New antimalarial therapies that include multitarget drugs may have higher efficacy than single-target drugs and provide a simpler regimen for antimalarial therapy.[4] Our purpose in this study was to predict a list of drugs that will bind to the active site of multiple *Plasmodium falciparum* proteins with high affinity.

Figure. Binding Patterns of 4 Approved (Blue) and 16 Experimental (Black) Multitarget Drugs to 13 *Plasmodium falciparum* Proteins



These drugs target the active site of 2-6 proteins with high affinity.

Methods. We used a computational protein-inhibitor docking with dynamics protocol[5] to calculate the binding affinities of 1105 approved and 1239 experimental drugs (obtained from ChemBank[6]) against 13 *Plasmodium* proteins whose structures have been determined by x-ray crystallography. Binding affinity calculations were carried out using AutoDock version 3.0.5 with a Lamarckian genetic algorithm (The Scripps Research Institute, La Jolla, Calif). We first placed each drug into the active site of the protein to find the most stable binding mode. The protein-drug complexes were consequently solvated in a water shell with sodium and chloride ions. We applied 100 steps of energy minimization followed by 0.1 ps of molecular dynamics simulation to each complex using XPLOR version 3.851 (Yale University, New Haven, Conn). The conformations at 0.1 ps were used for the protein-drug binding affinity calculations.

For each protein, a given drug was docked into the active site and allowed to move in an exhaustive manner to find the most stable binding conformation. The protein-