things 'Wall Street'. In that case it would be inundated with mountains of regulatory red tape and multiagency oversight that would make its daily operations either excessively costly or practically impossible. For this reason, early governmental buy-in and involvement of the appropriate regulatory and scientific agencies in the fund's inception and design are critical to its viability. Effective public relations and marketing of the concept, focused attention on government-relations strategies and high-quality political lobbying are likely to be essential contributors to the megafund's ultimate success.

The fourth and final consideration is the perception of the megafund by the academic and scientific community. Like all large institutions, particularly those that are not directly influenced by production demands, shareholder concerns, market forces or profit motive, a portion of the scientific establishment retains a vested interest in maintaining the status quo with regard to research funding. This is true even in the face of clear evidence (as presented by Lo and colleagues) that some elements of the current funding system are underproductive, operationally inefficient and ill-suited for facilitating actionable translational innovation. The small but vocal sector of the academic research community that has the most to gain by maintenance of the funding status quo is not only unlikely to support the fund's conceptual foundation but may also, in fact, actively resist its development on the grounds that it inappropriately comingles business and research or that it diverts funds away from the traditional research establishment. An effective prospective strategy must be developed to counteract this opposition, which, although not universal, is likely to be conspicuous.

Conversely, many researchers and scientific administrators, including many early-career investigators, recognize that the current research-funding system is often bureaucratic, inefficient, unsustainable and in need of alternatives. To be successful, the megafund's designers should consider actively engaging members of this scientific contingent to work collaboratively on shaping the fund into an appealing vehicle for research investment that preserves academic rigor and research ethics without sacrificing the unique, market-driven strengths of the fund. If these efforts are successful, a megafund could even emerge as attractive and viable alternate investment avenues for government dollars, including but not limited to those specifically earmarked for research funding.

I applaud the innovative thinking that Lo and colleagues have applied to the problem of financing translational research, and I believe that the mechanism that they have presented represents an economically viable supplement to the current research-funding system. This is particularly true because it creates an instrument that harnesses the strengths of the free market and ties long-term profit to tangible success. If this financial instrument can successfully provide a comprehensive funding architecture that bridges the finance gap between basic and late-stage research, if the research projects comprising its portfolio can be appropriately selected and adequately diversified, if issues related to governmental compliance and regulations can be successfully navigated and if forward-thinking members of the scientific community can be appropriately engaged, then I believe that a cancer megafund has the potential to be a transformative force in the translational research world.

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The cancer megafund: mathematical modeling needed to gauge risk

To the Editor:

As a CEO and former investment banker specializing in securitization, I noted with interest the paper by Andrew Lo and colleagues[1] proposing the application of securitization techniques to fund biopharmaceutical R&D. Such an approach promises to both enlarge the investor base willing to back breakthrough research and create a new asset class, thereby increasing diversification across the financial system.

Before embarking on such a path, however, we should all heed Bernard Munos's cautionary note: no financial engineering shall fix the root cause of the industry's failed innovation model[2]. The creation of an efficient market requires the ability for investors to gauge the quality of the underlying assets to be securitized. Failure to gauge such quality may result in the swift drying up of liquidity, as was observed during the 2008 credit crunch in the market for securitized mortgages.

Furthermore, Lo and colleagues[1] provide expectations for returns and the ability to service the debt on the basis of data about past attrition rates, costs and revenues. The payer-driven market's shift away from buying products to buying outcomes will increase commercial risk in a way that may take years to measure and understand. Additionally, default risk is highly sensitive to correlation assumptions between R&D programs, which are notoriously hard to pin down.

For megafunds to become a staple of the biopharmaceutical industry's landscape, a rethink of R&D is necessary.

New approaches based on mathematical modeling of diseases to predict a compound's efficacy over carefully characterized target populations should be encouraged as a way for investors to gauge assets' risk-return profiles. Appropriate methodological tools to measure outcomes in real life, such as the Effect Model Law[3], must be implemented. Finally, mathematical models have the potential to vastly expand the field of potential druggable targets, thereby reducing correlation risk and making it possible to reap the benefits of diversification.

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